Modulator Treatments for Cystic Fibrosis: Effectiveness and Value

Final Evidence Report and Meeting Summary

September 23, 2020

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Data are available upon request through the Cystic Fibrosis Foundation Patient Registry/ Comparative Effectiveness Research Committee. You can contact the committee at datarequests@cff.org. Restrictions on access to data are to ensure patient privacy for all persons in the CF Foundation Patient Registry.

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In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers, and other stakeholders. The following clinical experts provided input that helped guide the ICER team as we shaped our scope and report. None of these individuals is responsible for the final contents of this report or should be assumed to support any part of this report, which is solely the work of the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit: https://icer-review.org/material/cystic-fibrosis-2-stakeholder-list/

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Cystic Fibrosis Foundation

- *Contributions: CFF has received charitable contributions and/or fees for service >$5,000 from health care companies, including Vertex Pharmaceuticals.*
- *Equity Interests: CFF has the option to acquire equity interests >$10,000 from a pharmaceutical company unrelated to this report.*
- *Intellectual Property: CFF has entered into therapeutic development award agreements that may result in intellectual property and royalty rights from various pharmaceutical companies.*
- *Research Support: CFF provides financial support to the Therapeutics Development Network (TDN) which delivers high-quality clinical trials to CF patients in the search for better therapies and a cure. CFF provides financial support to the Data Safety Monitoring Board whose primary responsibility is to protect the safety and welfare of people with CF who participate in TDN-approved studies.*
- *Other Relationships: CFF facilitated, but did not participate in, the development of the CFF Pulmonary Guidelines: Use of CFTR Modulator Therapy in Patients with CF.*
- *For more information on CFF's interactions, see www.cff.org/industry.*

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List of Acronyms and Abbreviations Used in this Report

AHRQ	Agency for Healthcare Research and Quality
AE	Adverse event
AER	Annualized event rate
AHRQ	Agency for Healthcare Research and Quality
AR	Annualized rate
BID	Twice a day (bis in die)
BMI	Body mass index
BSC	Best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CF	Cystic fibrosis
CFF	Cystic fibrosis foundation
CFFPR	Cystic Fibrosis Foundation Patient Registry
CFQ-R	Cystic fibrosis questionnaire-revised
CFRD	Cystic fibrosis-related diabetes
CFTR	Cystic fibrosis transmembrane conductance regulator gene
Cm	Centimeter
D/C	Discontinuation
ELX	Elexacaftor
EQ-5D-5L	EuroQol 5-dimensions 5-level questionnaire
ER/PY	Event rate per patient year
evLYG	Equal value life years gained
FDA	Food and Drug Administration
FVC	Forced vital capacity
GI	Gastrointestinal
HIV	Human immunodeficiency virus
Hosp.	Hospitalization
HRQOL	Health related quality of life
IQR	Interquartile range
ITT	Intention to treat
IV	Intravenous
IVA	Ivacaftor
Kg	Kilogram
Kg/m2	Kilogram per meter squared
LCI	Lung clearance index
LUM	Lumacaftor
m^2	Square meter
MCID	Minimum clinically important difference
Mg	Milligram
mITT	Modified intention to treat
mmol/L	Millimoles per liter
MMRM	Mixed model repeated measure
MOCA	Montreal Cognitive Assessment Tool,
n	Number

N	Total number
N/A	Not applicable
NIH	National Institute of Health
NICE	National Institute for Health and Care Excellence (UK agency)
NR	Not reported
N.S.	Not significant
OLE	Open label extension
PERT	Pancreatic enzyme replacement therapy
PEx	Pulmonary exacerbation
ppFEV$_1$	Percent predicted forced expiratory volume in 1 second
PO	By mouth (per os)
PY	Patient year
Q	every
Resp.	Respiratory
RR	Risk ratio
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SNOT-20	20-item Sino-Nasal Outcome Test
SOC	Standard of care
TEAE	Treatment-emergent adverse event
TEZ	Tezacaftor
TMT	Trail Making Test
USPSTF	United States Preventive Services Task Force
VAS	Visual analog Scale
VC	Vital Capacity
VO2Max	Maximal oxygen uptake
WAC	Wholesale acquisition cost
WPAI	Work Productivity Activity and Impairment Questionnaire
95%CI	95% Confidence Interval
Δ	Difference

Executive Summary

Background

Cystic fibrosis (CF) is an autosomal recessive condition caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. The CFTR protein is an ion channel at the cell surface that primarily transports chloride ions across the cell membrane. According to the Cystic Fibrosis Foundation Annual Report, the overall prevalence of CF in the US in 2016 was 30,775.[2]

The impact of the disease on patients is profound. The thick secretions cause chronic lung infections, reduced lung function, poor weight gain (due to gastrointestinal dysfunction), diabetes (due to pancreatic damage), and fertility problems.[3] Patients suffer frequent acute pulmonary exacerbations, leading to repeated hospitalizations and long courses of intravenous (IV) antibiotics that require invasive procedures like the placement of ports for IV access and repeated absence from school and work. Because of decreased lung function, patients may have reduced ability to participate in sports and other daily activities. Patients and their families frequently spend several hours every day on treatments intended to help clear the lungs of secretions and thus reduce the likelihood of infections and the risk of declines in pulmonary function. The disease is progressive over time, and patients who become eligible and can obtain one may require lung transplantation to live. Although CF is uncommon, it represents a substantial economic burden. In 2013, CF-related hospital costs alone were estimated to exceed $1.1 billion.[4]

This review focuses on the oral triple therapy, Trikafta® (elexacaftor/tezacaftor/ivacaftor, Vertex Pharmaceuticals, Inc.). In addition, we updated our prior review of the three other FDA-approved modulator therapies, all of which are made by the same manufacturer: Kalydeco® (ivacaftor), Orkambi® (lumacaftor/ivacaftor), and Symdeko® (tezacaftor/ivacaftor). The United States Food and Drug Administration (FDA) approved Trikafta on October 21, 2019 for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least one copy of the *F508del* mutation in the *CFTR* gene (see Table ES1).[5] The majority (90%) of patients with CF carry at least one copy of the *F508del* mutation. This mutation leads to the expression of a protein that folds improperly and is not transported to the cell membrane, where it functions. Two of the components of Trikafta, tezacaftor and elexacaftor, help to correct the folding of the protein product from this mutation, thus increasing the amount of the CFTR protein in the cell membrane. The third component of Trikafta, ivacaftor (aka Kalydeco when given alone), increases the flow of ions across the CFTR protein, which helps to alleviate the symptoms of CF. Approximately 27,000 individuals in the United States have CF with genetic mutations that are eligible for treatment with Trikafta (90% of individuals with CF). Of these patients, approximately 17,000 are eligible for treatment under the current FDA label, which limits treatment to patients ages 12 years and older.[5]

Table ES1. FDA Approved CFTR Modulator Drugs and Their Indications

Drug	Dose	Indication
Kalydeco (Ivacaftor)	150 mg PO BID with fat containing food if 6 years and older Weight based oral dosing for younger children	Patients age 6 months and older who have one mutation in the *CFTR* gene that is responsive to ivacaftor based on clinical and/or in vitro assay data.
Orkambi (Lumacaftor/ Ivacaftor)	Two tablets (each containing lumacaftor 200 mg/ivacaftor 125 mg) PO q 12 hours with fat-containing food if 12 years and older Weight based oral dosing for younger children	Patients age 2 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene.
Symdeko (Tezacaftor/ Ivacaftor)	One tablet (containing tezacaftor 100 mg/ivacaftor 150 mg) PO in the morning and one tablet (containing ivacaftor 150 mg) in the evening with fat-containing food, approximately 12 hours apart if 12 years or 6 years and older weighing 30 kg or more. Weight based oral dosing for younger, lighter children.	Patients age 6 years and older who are homozygous for the *F508del* mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that is responsive to tezacaftor/ivacaftor based on *in vitro* data and/or clinical evidence.
Trikafta (Elexacaftor/ Tezacaftor/ Ivacaftor)	Morning dose: two elexacaftor 100 mg, tezacaftor 50 mg and ivacaftor 75 mg tablets PO Evening dose: one ivacaftor 150 mg tablet PO Morning and evening dose should be taken approximately 12 hours apart with fat-containing food.	Patients aged 12 years and older who have at least one *F508del* mutation in the *CFTR* gene.

BID: twice a day, CFTR: Cystic fibrosis transmembrane conductance regulator, kg: kilogram, mg: milligram, PO: by mouth, q: every

Patient Perspectives

From the beginning of this assessment, we sought input from patients, caregivers, and representatives from patient advocacy organizations on the research design of this review (e.g., the PICOTS framework; population, intervention, comparators, outcomes, timing, and setting). We also sought insight on the patient experience of CF and its treatment, including benefits of treatment that may not be described in the clinical literature, any broader potential other benefits or disadvantages associated with treatments, and contextual consideration related to CF. These are summarized in the Executive Summary and discussed in greater detail in Sections 2 and 6 of the full report.

Patients, family members, and caregivers described how CF impacts all aspects of their lives, and emphasized how its clinical manifestations extend beyond the pulmonary effects that are most commonly associated with CF. These effects included pancreatic manifestations (CF-related diabetes), mood (anxiety and depression), and nasal symptoms such as loss of sense of smell. Due to their condition, patients are frequently unable to participate in desired activities, including

exercise, travel, educational and professional opportunities, and planning for the future (e.g., marriage, having children, retirement). Many patients also reported spending several hours per day on their CF care regimens.

Patients who have taken Trikafta reported substantial and rapid improvements in their health, often within hours to days of treatment initiation. This included the elimination of cough, a symptom that many patients reported as causing social stigma and negative impacts on the quality and length of sleep. Patients also noted that they have decreased the use of some supportive treatments such as insulin, laxatives, and hypertonic saline, and have had fewer pulmonary events that require medical attention. Many patients also reported that they are now able to participate in activities that would have previously been unthinkable, including exercise, social events, and planning for the future.

The Cystic Fibrosis Research, Inc. (CFRI) Voice of the Patient report summarizes patient and caregiver perspectives on the burden posed by CF.[6] The top three symptoms having the greatest impact on quality of life for patients living with CF were:

1. Acute pulmonary exacerbations / infections
2. Excessive cough
3. GI issues

In addition, the top three life activities that are challenging because of CF were:

1. Time with friends / social activities
2. Work / School attendance
3. Participation in sports / extracurricular activities

Finally, the top three key benefits that patients hope to receive from new treatments were:

1. Fewer lung infections / exacerbations
2. Improved breathing
3. Improved GI symptoms / digestion

These results closely aligned with the feedback ICER heard during its own patient engagement efforts, and patients shared with us how treatment impacted many of these symptoms. These are described in detail in the full report as well as additional details from the Voice of the Patient report.

Comparative Clinical Effectiveness

We updated our prior review of the comparative clinical effectiveness of CFTR modulators in patients with cystic fibrosis, focusing on the evidence of the safety and efficacy of the new CFTR modulator Trikafta in comparison with other CFTR modulators or best supportive care in subgroups of patients with CF that define their eligibility for specific CFTR modulator therapy. The new, real-world data on Kalydeco, Orkambi, and Symdeko are summarized in the full report, but not in the Executive Summary as they did not change our prior assessment and because most patients will be treated with Trikafta, rather than the earlier therapies.

Clinical Benefits

The most common outcome when evaluating therapies for CF is the percent predicted forced expiratory volume in one second ($ppFEV_1$), which is measured as a percentage of the normal amount of air that a healthy, non-smoking individual of the same age, sex, race, and height can blow out in one second.[7] By definition, normal should be 100%. However, in CF the $ppFEV_1$ declines over time with lower $ppFEV_1$ representing more severe disease. A $ppFEV_1 \geq 90\%$ is normal, while a $ppFEV_1 < 40\%$ represents severe disease. The rate of decline varies between patients due to many factors, including age, the patients' combination of mutations, body mass index (BMI), chronic infection with *Pseudomonas aeruginosa*, pancreatic insufficiency and CF-related diabetes (CFRD).

The other commonly reported outcome is the respiratory domain of the Cystic Fibrosis Questionnaire-Revised (CFQ-R). Scores range from 0 to 100 with higher scores representing higher quality of life. A typical score in children is about 75, which declines to about 60 in adults. The score decreases with increased coughing or wheezing and with acute pulmonary exacerbations. The minimal clinically-important difference is estimated to be a 4 point change.

Trikafta versus Symdeko for Patients Homozygous for the F508del *Mutation: Head-to-Head Results*

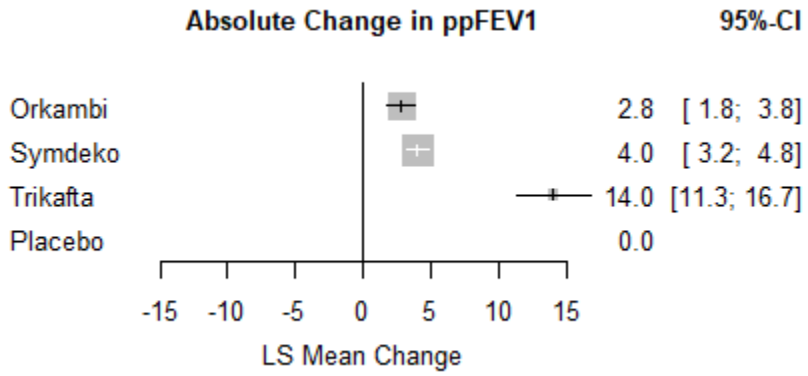
There was one pivotal head-to-head study comparing Trikafta to Symdeko in the population of patients who are homozygous for the *F508del* mutation.[8] All patients underwent a 4-week run in period with Symdeko. Compared to Symdeko, the $ppFEV_1$ in patients randomized to Trikafta was 10.0 points higher at four weeks (95% CI 7.4 to 12.6, $p<0.001$). Quality of life as assessed by the respiratory domain of the CFQ-R was 17.4 points higher in the Trikafta group (95% CI 11.8 to 23, $p<0.001$). The rate of acute pulmonary exacerbations was not a primary or secondary outcome in the trial because of the short follow-up period. However, they were reported as AEs without statistical results (Trikafta 2%, Symdeko 12%).

This good-quality trial demonstrated a marked improvement in pulmonary function and respiratory quality of life through 4 weeks of follow-up with Trikafta compared to Symdeko with a good safety profile. The primary limitation of the study is its short follow-up time of only 4 weeks.

Trikafta versus other CFTR Modulators for Patients Homozygous for the* F508del *Mutation: Network Meta-Analysis Results

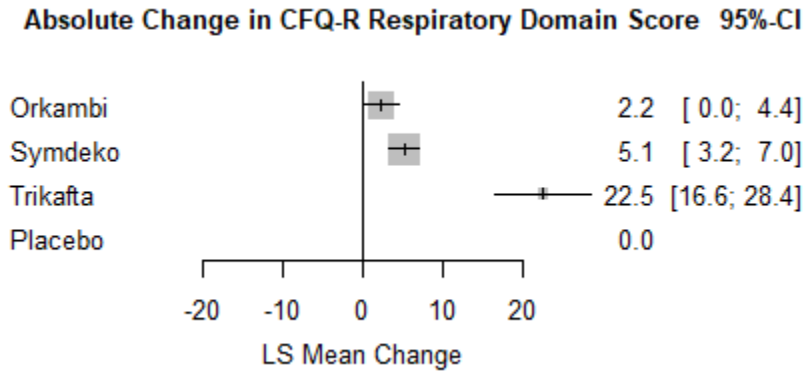
The forest plots for the network meta-analysis results comparing each of the three CF modulator therapies that have been studied in the same population illustrates the marked improvement of Trikafta compared with the other therapies.

Figure ES1. NMA Results for ppFEV$_1$ Comparing CF Modulator Therapy to Placebo



The results are similar for the respiratory domain of the CFQ-R (Figure 4.2). The improvements with Trikafta are substantially larger than those of Orkambi and Symdeko.

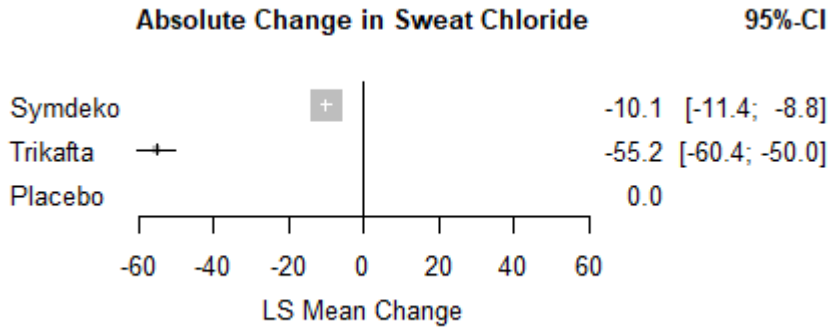
Figure ES2. NMA Results for CFQ-R Respiratory Domain Comparing CF Modulator Therapy to Placebo



Sweat chloride data were only available for Symdeko and Trikafta (Figure ES3). Sweat chloride levels are often used to aid in the diagnosis of CF. Normal levels in patients without CF are typically

less than 30 mmol/L, while levels ≥ 60 mmol/L are typical in patients with CF. It is unclear how improvements in sweat chloride levels correlate with changes in CF symptoms and disease progression over time.

Figure ES3. NMA Results for Sweat Chloride Level Comparing CF Modulator Therapy to Placebo



Trikafta for Patients Heterozygous for the* F508del *Mutation and a Residual Function Mutation

There are no published studies evaluating the safety and efficacy of Trikafta in this population. However, Trikafta is comprised of Symdeko plus another modulator (elexacaftor) and it primarily targets the abnormal protein formed by the *F508del* mutation. Unless elexacaftor interferes with the mechanism of action of ivacaftor and/or tezacaftor or introduces new, significant AEs, Trikafta should be at least as effective as Symdeko in this population. In randomized trials versus placebo, Symdeko increased $ppFEV_1$ by 6.8%, reduced acute pulmonary exacerbations by 46%, and improved the respiratory domain of the CFQ-R by 11.1 points.

Trikafta in Patients Heterozygous for the* F508del *Mutation and a Minimal Function Mutation

In the pivotal trial, compared to placebo, the $ppFEV_1$ of patients on Trikafta was 13.8 points higher at four weeks and 14.3 points higher at 24 weeks ($p<0.001$ for both comparisons). There were no differences in relative outcomes across prespecified subgroups based on sex, age, baseline $ppFEV_1$, or region. The rate of acute pulmonary exacerbations was 63% lower in the Trikafta group (RR 0.37, 95% CI 0.25 to 0.63). Quality of life as assessed by the respiratory domain of the CFQ-R was 20.2 points higher in the Trikafta group ($p<0.001$) and sweat chloride concentrations were 41.8 mmol/L lower ($p<0.001$).

Harms

Serious adverse events (SAEs), as defined by the studies, commonly occurred at the same or *lower* rates among those taking the CFTR modulators, including Trikafta, than those taking placebo, including AEs ascribed to the drugs. No deaths during CFTR modulator trials were related to the

drugs. Rash was the only SAE ascribed to Trikafta and that patient did not discontinue therapy. Trikafta appears to have minimal harms.

Controversies and Uncertainties

CF is a chronic disease that impacts patients every day of their lives. The two pivotal clinical trials of Trikafta lasted 4 and 24 weeks respectively, which is not long enough to provide stable estimates for the long-term impact of Trikafta. In addition, there are likely differences in the long-term benefits of Trikafta based on the patient's age at initiation of therapy and the severity of their CF symptoms at that time. Finally, in patients heterozygous for the *F508del* mutation and a residual function mutation, there are no data on Trikafta, though we do have data on Symdeko, which includes two of the 3 drugs in Trikafta.

$ppFEV_1$ is a surrogate measure of CF disease severity. Despite its wide use as the primary outcome in clinical trials and clinical practice, both the absolute $ppFEV_1$ level and changes in $ppFEV_1$ cannot fully capture disease severity or the clinical impact of modulator therapy on the many organ systems impacted by CF and the life experiences of patients.

Summary and Comment

Trikafta for Patients who are Homozygous for the F508del Mutation

Given that Trikafta is Symdeko plus an additional modulator, the consistent evidence in controlled trials of lung function improvement, with clinically significant improvements and associated reductions in acute pulmonary exacerbations, and with no evidence of significant harms, we have high certainty Trikafta provides a substantial (moderate-large) net health benefit relative to best supportive care and to Symdeko. We therefore assign a rating of "superior" (A) to the comparative clinical effectiveness of Trikafta in this population, both versus best supportive care and versus Symdeko.

Trikafta for Patients who are Heterozygous for the **f508del** *Mutation and a Residual Function Mutation*

There are no published randomized trial or observational data for Trikafta in this population. However, because Trikafta is Symdeko plus an additional CFTR modulator drug it should be at least as effective unless there are interactions that decrease the effectiveness of Symdeko. In the population of patients homozygous for the *F508del* mutation, Trikafta was significantly more effective than Symdeko and there was no evidence of additional toxicity with Trikafta. Thus, we judge that Trikafta will be at least as effective as Symdeko versus best supportive care (B+). Using similar logic, we judge that we have moderate certainty that Trikafta has a comparable, small, or substantial net heath benefit compared with Symdeko, with high certainty of at least a comparable net health benefit (C++).

Trikafta for Patients who are Heterozygous for the* f508del *Mutation With a Minimal Function Mutation

The single 24-week randomized controlled trial of Trikafta in this population demonstrated clinically-significant improvements in lung function improvement and respiratory quality of life, with clinically-significant improvements and associated reductions in acute pulmonary exacerbations, and no evidence of significant harms. Thus, we have high certainty Trikafta provides a substantial (moderate-large) net health benefit relative to best supportive care. We therefore assign a rating of "superior" (A) to the comparative clinical effectiveness of Trikafta in this population.

These ICER Evidence Ratings for Trikafta and the other CFTR modulators are summarized in Table ES2 below. The ICER Evidence ratings for Kalydeco, Orkambi, and Symdeko have not changed from the prior report.

Table ES2. ICER Evidence Ratings for CFTR Modulator Therapies for Cystic Fibrosis.

Intervention	ICER Evidence Rating
Population 1: Eligible for Kalydeco	
Kalydeco vs. BSC	A
Population 2: Homozygous *F508del*	
Orkambi vs. BSC	B
Symdeko vs. BSC	B+
Trikafta vs. BSC	A
Trikafta vs. Symdeko	A
Population 3: Heterozygous *F508del* / Residual Function Mutation	
Symdeko vs. BSC	B+
Trikafta vs. BSC	B+
Trikafta vs. Symdeko	C++
Population 4: Heterozygous *F508del* / Minimal Function Mutation	
Trikafta vs. BSC	A

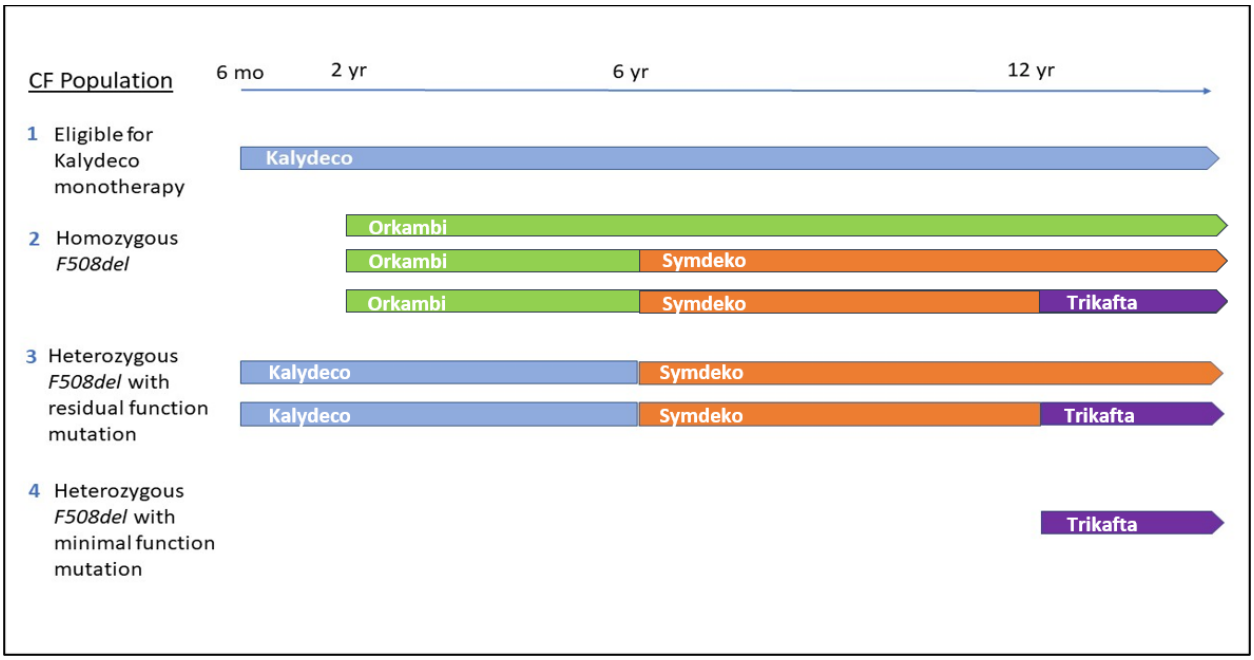
BSC: Best supportive care

Long-Term Cost Effectiveness

We estimated the lifetime effectiveness and cost-effectiveness of CFTR modulator treatments plus best supportive care for CF patients. We modeled four different populations based on mutation status. For patients who are candidates for Kalydeco only based on current indications, we compared Kalydeco plus best supportive care to best supportive care alone. For patients who are homozygous for the *F508del* mutation and patients who are heterozygous for the *F508del* mutation with a residual function mutation, we compared Trikafta plus best supportive care, Symdeko plus best supportive care, Orkambi plus best supportive care (for base-case results and threshold price only) and best supportive care alone. For patients who are heterozygous for the *F508del* mutation with a minimal function mutation, we compared Trikafta plus best supportive care to best

supportive care alone. Because the recommended start age varies by drug, we model sequential drugs in relevant populations (Figure ES4).

Figure ES4. Schematic of the CFTR Modulator Strategies



Computer models are commonly used to project the long-term outcomes for a population. The model structure reflects the possible outcomes that patients may experience over their lifetimes, based on the disease and the impacts of treatment. When assumptions were made, we chose those that favored better cost-effectiveness findings for CFTR modulator therapy and we assessed the potential impact of each assumption by varying the assumption widely in sensitivity analyses. Patient heterogeneity is simulated in the model (e.g., it assumes that some CF patients have a slower lung function decline than others), but the output of the model describes the *average* outcomes for a *population*. These results are intended to inform understanding at the population level and not individual patient decision-making.

Three of the treatments for CF, Kalydeco, Orkambi, and Symdeko, fall under ICER's framework for therapies for ultra-rare diseases.[9] Therefore, we considered dual base-case analyses that reflect both health care system and societal perspectives if the impact of the treatment on patient and caregiver productivity, education, disability and nursing home costs were large relative to health care costs. Because we did not find this to be the case, we present the societal perspective as scenario analyses for Kalydeco, Orkambi, and Symdeko. For scenarios where the ultra-rare framework did not apply (i.e., Trikafta, which has an eligible patient population of greater than 10,000 individuals), productivity losses and other indirect effects were considered in a scenario analysis.

The key assumptions used in the model are described in Table ES3 below.

Table ES3. Key Model Assumptions

Assumption	Rationale
ppFEV$_1$ does not increase over time in the absence of CFTR modulator therapy.	Lung function declines with age in healthy patients and those with CF.
Best supportive care is assumed to be the same in all treatment arms, though the intensity of therapy increases with decreasing lung function category (≥70%, 40%-69%, <40%).	Modulator therapy will have an impact on costs associated with acute pulmonary exacerbations and lung transplantation, but whether other costs of care not associated with lung function will be affected by modulator therapies within a given lung function category is not known. We evaluated this assumption in a scenario analysis.
The CFTR modulator drug effect is modeled as an increase in ppFEV$_1$, and increase in weight for age *z*-score, and a decrease in the annual number of acute pulmonary exacerbations.	These are well-documented effects of CFTR modulator drugs from clinical trials. We acknowledge that there are other non-pulmonary effects that were not studied in the clinical trials.
There is no CFTR modulated drug effect on weight for age *z*-score for patients who are heterozygous for the *F508del* mutation with a residual function mutation.	This is consistent with these patients having minimal pancreatic insufficiency. The clinical trials in this population do not report change in weight for age *z*-score.
CFTR modulator drugs decrease the annual number of acute pulmonary exacerbations through the increase in ppFEV$_1$ (i.e., the risk of exacerbations depends on lung function) as well as an additional reduction in acute pulmonary exacerbations, independent of the lung function effect.	We do not observe the rate ratio reported in the clinical trials by assuming that the reduction in the number of acute pulmonary exacerbations is only due to the increase in ppFEV$_1$ associated with the drug. This assumption is needed to match the risk reductions observed in the clinical trials.
We 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.
We start patients on a CFTR modulator drug at the age that they are first eligible and then they switch to a more effective drug when becoming age eligible. The increase in ppFEV$_1$ will be determined by the difference in the effectiveness of the new drug relative to the original drug.	It is reasonable to assume that patients will start on a modulator drug as soon as they are eligible but that they will switch to a more effective one over time. We do not assume that drugs will be given off label.

Drug Acquisition Costs

The wholesale acquisition cost (WAC) was used as the annual net drug acquisition cost for each medication in the model (Table ES4).

Table ES4. Drug Cost Inputs

Intervention	WAC per Day*[10]	Annual Drug Cost
Kalydeco	$853.40	$311,704
Orkambi	$746.40	$272,623
Symdeko	$800.00	$292,200
Trikafta	$853.50	$311,741

*WAC as of December 2, 2019

Base-Case Results

The models found that all of the CFTR modulators were very effective and that they increased total costs when compared with best supportive care alone. For example, Trikafta added about 5 to 6 discounted total life years and $5.3 to $6.7 million discounted total costs compared with best supportive care across the three populations in which it was modeled. The base-case results for the drugs in their relevant patient populations are summarized in Table ES5 below.

Table ES5. Results for the Base-Case Costs and Effectiveness Measures for CFTR Modulators Plus Best Supportive Care (BSC) Compared to BSC Alone, By Study Population (Discounted at 3% per Year)

Population and Treatment	Total Costs	Total QALYs	Total Life Years	Equal Value Life Years*
Population 1 - Eligible for Kalydeco Monotherapy Only				
BSC	$2,319,000	15.83	21.63	15.83
Kalydeco Plus BSC	$8,765,000	20.54	26.06	21.30
Population 2 - Homozygous for the *F508del* Mutation				
BSC	$2,088,000	15.77	21.46	15.87
Orkambi Plus BSC	$7,508,000	19.43	25.22	19.85
Symdeko Plus BSC	$7,962,000	20.04	25.66	20.77
Trikafta Plus BSC	$8,473,000	21.26	26.66	22.02
Population 3 - Heterozygous *F508del* with Residual Function Mutation				
BSC	$2,214,000	16.33	22.12	16.41
Symdeko Plus BSC	$8,367,000	20.93	26.53	22.01
Trikafta Plus BSC	$8,901,000	22.41	27.66	23.44
Population 4 - Heterozygous *F508del* with Minimal Function Mutation				
BSC	$2,224,000	11.48	17.05	11.69
Trikafta Plus BSC	$7,541,000	16.52	22.42	17.75

QALY: quality adjusted life year; BSC: best supportive care

*Note that equal value life years do not always exactly equal QALYs because of patient to patient variations in a microsimulation

Table ES6 summarizes the cost-effectiveness results for each of the drugs compared to best supportive care in each of the populations for which the drug has an FDA indication. In all cases, the cost per QALY gained is greater than $1 million, which is substantially higher than cost-effectiveness thresholds in the US and the rest of the world. Table ES6 also shows the added cost for every acute pulmonary exacerbation averted through treatment, varying across patient subpopulations from a low of $539,000 per acute pulmonary exacerbation averted to a high of $737,000 per acute pulmonary exacerbation averted.

Table ES6. Incremental Cost-Effectiveness Ratios Compared to Best Supportive Care (BSC) for the Base Case (Discounted at 3% per Year)

Treatment vs. BSC	Cost Per QALY Gained	Cost Per evLYG	Cost Per LY Gained	Cost Per PEx Averted
Population 1 - Eligible for Kalydeco Monotherapy Only				
Kalydeco Plus BSC	$1,370,000	$1,180,000	$1,450,000	$737,000
Population 2 - Homozygous for the *F508del* Mutation				
Orkambi Plus BSC	$1,480,000	$1,360,000	$1,440,000	$614,000
Symdeko Plus BSC	$1,380,000	$1,200,000	$1,400,000	$621,000
Trikafta Plus BSC	$1,160,000	$1,040,000	$1,230,000	$675,000
Population 3 - Heterozygous *F508del* with Residual Function Mutation				
Symdeko Plus BSC	$1,340,000	$1,100,000	$1,390,000	$549,000
Trikafta Plus BSC	$1,100,000	$951,000	$1,210,000	$539,000
Population 4 - Heterozygous *F508del* with Minimal Function Mutation				
Trikafta Plus BSC	$1,050,000	$877,000	$990,000	$565,000

BSC: best supportive care; QALY: quality adjusted life year; evLYG: equal value life year gained; LY: life year; PEx: acute pulmonary exacerbation

Sensitivity Analyses

We performed sensitivity analyses to assess the impact of the uncertainly about the inputs to the model including costs, natural history of CF, and the impact of treatments. The detailed results are presented in Section 5 of the full report, but they do not materially differ from the results of the base-case analyses. For example, varying the estimates for utilities, reduction in acute pulmonary exacerbations, costs of acute pulmonary exacerbations, gains in $ppFEV_1$, transplant costs, and the costs of best supportive care across a reasonable range of estimates did not decrease the cost per QALY of Trikafta in the population of patients homozygous for the *F508del* mutation below $1 million. We did not conduct these analyses for cost per evLYG as they would show the same inputs were key drivers of variability in results.

Scenario Analyses

We performed a scenario analysis using a modified societal perspective that incorporated lost productivity in patients unable to work full time as well as lost productivity due to acute pulmonary

exacerbations (Table 5.13 in the full report). Including productivity losses in the analysis yielded incremental cost-effectiveness ratios that were similar to those in the base-case analysis. For example, in the population of patients homozygous for the *F508del* mutation, the ICER for Trikafta was $1.15 million per QALY using the societal perspective and $1.16 million per QALY in the base case.

We also performed an extreme scenario analysis in which we assumed that Trikafta cured patients with CF. In this analysis, we assumed that patients had a normal quality of life, no further acute pulmonary exacerbations and no need for ongoing supportive care or monitoring for CF and its complications. The only cost was that of Trikafta at its current price. In this analysis the discounted lifetime cost of Trikafta was approximately $7.1 million and the incremental cost per QALY was $612,000. The incremental cost per evLYG would be the same since patients are restored to full health in this scenario.

Annual prices necessary to reach cost-effectiveness thresholds of $50,000, $100,000, $150,000, $200,000, $300,000, and $500,000 per QALY are listed in Table ES7 for each CF population and CFTR modulator. Threshold prices for Trikafta are calculated only for cost-effectiveness thresholds less than $200,000 per QALY because it does not qualify for the ultra-rare disease framework.

Table ES7. Annual Price Required for CFTR Modulator Therapies to Reach Cost per QALY Thresholds

	Annual WAC	Price to Achieve $50,000 per QALY	Price to Achieve $100,000 per QALY	Price to Achieve $150,000 per QALY	Price to Achieve $200,000 per QALY	Price to Achieve $300,000 per QALY	Price to Achieve $500,000 per QALY
Population 1 - Eligible for Kalydeco Monotherapy							
Kalydeco	$311,700	$48,600	$58,600	$68,600	$78,600	$98,500	$138,500
Population 2 - Homozygous for the *F508del* Mutation							
Orkambi	$272,600	$42,800	$50,800	$58,900	$66,900	$83,000	$115,100
Symdeko	$292,200	$46,500	$55,800	$65,000	$74,300	$92,900	$129,900
Trikafta	$311,700	$52,300	$64,000	$75,600	$87,300	N/A	N/A
Population 3 - Heterozygous *F508del* with Residual Function Mutation							
Symdeko	$292,200	$48,400	$57,900	$67,300	$76,800	$95,700	$133,600
Trikafta	$311,700	$54,700	$67,000	$79,200	$91,400	N/A	N/A
Population 4 - Heterozygous *F508del* with Minimal Function Mutation							
Trikafta	$311,700	$61,500	$74,000	$86,400	$98,900	N/A	N/A

WAC: wholesale acquisition cost; QALY: quality adjusted life year gained; N/A: not applicable because drug does not qualify for the ultra-rare disease framework

Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental Appendix materials). We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. We also reviewed the literature for other economic models of modulator therapy for CF and found that our results were consistent with their results.

Summary and Comment

Our models estimated that CFTR modulator therapies dramatically improve both the length and quality of life of patients with CF. However, because of their high cost and the need for lifetime use, the incremental cost-effectiveness ratios of CFTR drugs plus best supportive care compared with best supportive care ranged between $1.1 to $1.5 million per QALY, and between $877,000 to $1.4 million per evLYG (Trikafta in Population 4 and Orkambi in Population 2, respectively). Even if we assume that Trikafta cures CF (normal life expectancy, normal quality of life, no costs due to CF other than Trikafta), at the current price, the incremental cost-effectiveness ratio is still $612,000 per QALY, which is well above commonly-accepted cost-effectiveness thresholds. Our results were robust to variations to parameter estimates except for annual drug costs, including adopting a societal perspective or using life years gained as the health outcome.

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 Tables ES8 and ES9 below and are accompanied by descriptions of whether Trikafta may impact them.

Potential Other Benefits

Table ES8. Potential Other Benefits of Trikafta

Other Benefits	Description
This intervention offers reduced complexity that will significantly improve patient outcomes.	N/A
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.	N/A
This intervention will significantly reduce caregiver or broader family burden.	Potentially, if patients are able to reduce or stop some of the complex and time-consuming aspects of best supportive care. However, the studies are in progress so there are no data yet.
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.	Yes
This intervention will have a significant impact on improving return to work and/or overall productivity.	Yes, this is likely.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.	Potentially, if patients are able to reduce or stop some of the complex and time-consuming aspects of best supportive care. However, the studies are in progress so there are no data yet.

Contextual Considerations

Table ES9. Potential Contextual Considerations

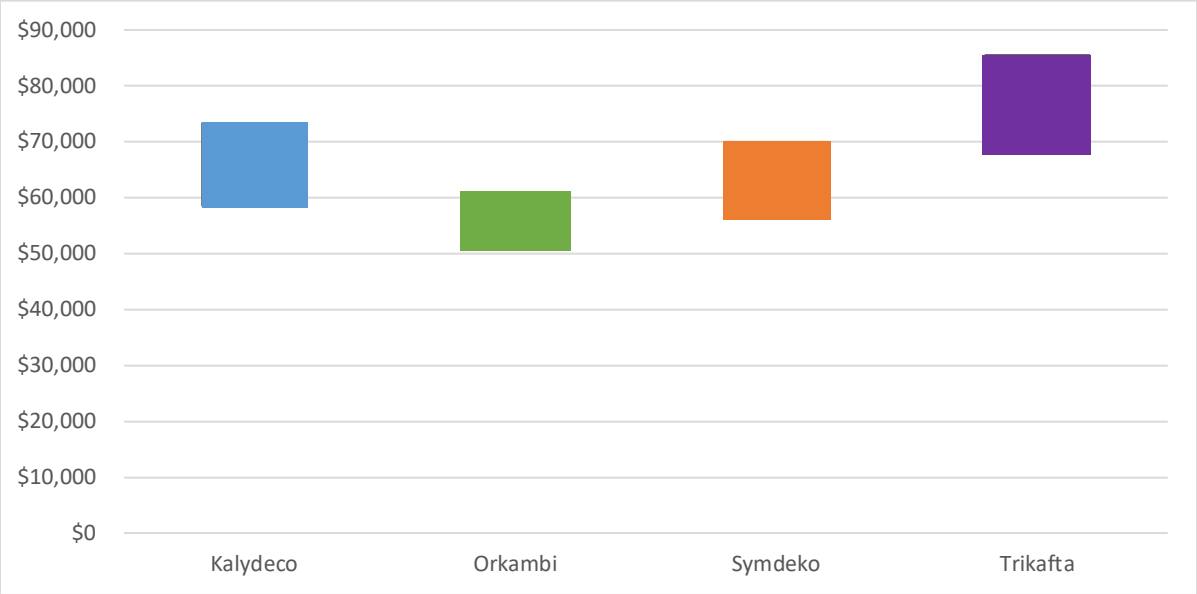
Contextual Consideration	Description
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	Yes
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	Yes
This intervention is the first to offer any improvement for patients with this condition.	Yes, for those heterozygous for the *F508del* mutation and a minimal function mutation.
Compared to "the comparator", there is significant uncertainty about the long-term risk of serious side effects of this intervention.	Yes, the longest follow-up is 24 weeks for a drug that requires lifelong treatment.
Compared to "the comparator", there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	Yes, the longest follow-up is 24 weeks for a drug that requires lifelong treatment.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.	N/A

Health-Benefit Price Benchmarks

The ICER health benefit price benchmark (HBPB) is a price range suggesting the highest price a manufacturer should charge for a treatment, based on the amount of improvement in overall health patients receive from that treatment, when a higher price would cause disproportionately greater losses in health among other patients in the health system due to rising overall costs of health care and health insurance. In short, it is the top price range at which a health system can reward innovation and better health for patients without doing more harm than good.

The HBPB ranges for each drug are shown in Figure ES5. The HBPB range would require 76% to 81% discounts from WAC for both Kalydeco and Symdeko, with the HBPB range at $58,600 to $73,400 per year for Kalydeco, and $56,200 to $69,900 per year for Symdeko. The HBPB range for Orkambi is $50,800 to $61,000 (78% to 81% discount from WAC). For Trikafta, the HBPB range is $67,900 to $85,500 per year, requiring 73% to 78% discounts from WAC. The HBPB ranges for the drugs follow the pattern we would expect given the cost-effectiveness analysis results, with Trikafta highest, followed by Kalydeco, Symdeko, and Orkambi.

Figure ES5. Health Benefit Price Benchmark Ranges per Year for Kalydeco, Orkambi, Symdeko, and Trikafta



Potential Budget Impact

We used the cost-effectiveness model to estimate the potential total budgetary impact over five years of the recently approved Trikafta for prevalent individuals in the United States (US) with CF aged 12 years and older who have at least one *F508del* mutation in the *CFTR* gene (following the FDA label indication). Potential budget impact was defined as the total differential cost of using this new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. In our estimates of potential budget impact, we used the wholesale acquisition cost (WAC) as the base case price, and the blended $50,000, $100,000, and $150,000 cost-effectiveness threshold prices across the three populations eligible for Trikafta, as well as the five-year annualized potential budget impact threshold of $819 million per year for new drugs.

We estimated the number of individuals with CF in the US who would be eligible for treatment with Trikafta (Populations 2, 3, and 4 above), using estimates from the CF Foundation Patient Registry (CFFPR) of individuals with CF in the US greater than 12 years old with any *F508del* mutation[11] and assuming that all eligible patients would add or switch to Trikafta upon reaching 12 years of age. This resulted in estimates of 8,870 CF patients in population 2 (homozygous for *F508del* mutation) or 1,774 patients each year over five years; 1,925 patients in population 3 (heterozygous for *F508del* mutation with residual function mutation) or 385 per year; and 6,070 patients in population 4 (heterozygous for *F508del* mutation with minimal function mutation) or 1,214 per year. Using data[2] on the proportion of eligible patients currently prescribed CFTR modulators, we estimated that Trikafta plus best supportive care would displace a mix of Symdeko plus best supportive care for 68.5%, and best supportive care alone for 31.5%, of patients eligible for both Trikafta and Symdeko (populations 2 and 3. For patients in population 4, we assumed Trikafta treatment would be added to best supportive care alone. Note that our assumption that 20% of these patients would initiate Trikafta in each of the first five years may be conservative, as clinical experts predicted that uptake would be much more rapid than 20% per year.

The annual potential budget impact of treating the combined Trikafta-eligible populations using list price (WAC) compared to the $819 million threshold is shown in Table ES10. When considering all eligible patients, the annualized potential budget impact of Trikafta at list price would exceed the potential budget impact threshold by 71%, even though the total number of patients eligible for Trikafta under its current labeled indication is relatively low (n = 16,865).

Table ES10. Estimated Annualized Potential Budget Impact of Trikafta for Treatment of Eligible Populations Using List Price Over a Five-year Time Horizon

	Eligible Population	N Treated per Year	Annual BI per Patient	Total Annual BI (millions)	Percent of Threshold
Homozygous *F508del* (Population 2)					
Trikafta	8,870	1,774	$79,000	$416.2	51%
Heterozygous *F508del* with Residual Function Mutation (Population 3)					
Trikafta	1,925	385	$74,000	$85.0	10%
Heterozygous *F508del* with Minimal Function Mutation (Population 4)					
Trikafta	6,070	1,214	$250,000	$896.7	109%
Total Trikafta-Eligible US CF Population*					
Trikafta	16,865	3,373	$140,000	$1,397.9	**171%**

Numbers may not sum due to rounding.

BI: budget impact

*Annual BI per patient for total eligible US CF population weighted by percentage contribution.

Access and Affordability Alert

Assuming all eligible patients in populations 2 and 3 transitioned from an older CFTR modulator to Trikafta, an additional 35% of eligible patients in population 4 could be treated with Trikafta at its list price without exceeding ICER's potential budget impact threshold of $819 million. This would represent approximately 77% of the overall eligible population for Trikafta. Discussions with clinical experts suggested that uptake could approach or exceed this level given the unmet need for patients in this population. Given that the clinical goal for uptake would exceed the potential budget impact threshold at the national level, ICER is issuing an access and affordability alert. The purpose of an ICER affordability and access alert is to signal to stakeholders and policy makers that the amount of added health care costs associated with a new service may be difficult for the health system to absorb over the short term without displacing other needed services or contributing to rapid growth in health care insurance costs that threaten sustainable access to high-value care for all patients.

CTAF Votes

The CTAF Panel deliberated on key questions raised by ICER's report at a public meeting on August 27, 2020. The results of these votes are presented below, and additional information on the deliberation surrounding the votes can be found in the full report.

Comparative Clinical Effectiveness

Patient Population 2 (Questions 1-2): *Individuals with CF who are homozygous for the* F508del *mutation*

1. ***Is the evidence adequate to demonstrate that the net health benefit of treatment with Trikafta with best supportive care is greater than that of best supportive care alone?***

Yes: 14 votes	No: 0 votes

2. ***Is the evidence adequate to demonstrate that the net health benefit of treatment with Trikafta and best supportive care is greater than that of treatment with Symdeko and best supportive care?***

Yes: 14 votes	No: 0 votes

Patient Population 3 (Questions 3-4): *Individuals with CF who are heterozygous for the* F508del *mutation with a residual function mutation.*

3. ***Is the evidence adequate to demonstrate that the net health benefit of treatment with Trikafta with best supportive care is greater than that of best supportive care alone?***

Yes: 13 votes	No: 1 votes

4. ***Is the evidence adequate to demonstrate that the net health benefit of treatment with Trikafta and best supportive care is greater than that of treatment with Symdeko and best supportive care?***

Yes: 6 votes	**No: 8 votes**

Patient Population 4: *Individuals with CF who are heterozygous for the* F508del *mutation with a minimal function mutation.*

5. ***Is the evidence adequate to demonstrate that the net health benefit of treatment with Trikafta with best supportive care is greater than that of best supportive care alone?***

Yes: 14 votes	No: 0 votes

Potential Other Benefits and Contextual Considerations

6. ***When compared to best supportive care, does treating patients with Trikafta offer one or more of the following potential "other benefits?" (select all that apply)***

This intervention will significantly reduce caregiver or broader family burden.	13/13*
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.	12/13*
This intervention will have a significant impact on improving patients' ability to return to work and/or their overall productivity.	13/13*
This intervention will have a significant positive impact outside the family, including on schools and/or communities.	11/13*
There are other important benefits or disadvantages that should have an important role in judgments of the value of this intervention	6/13*

*Only 13 CTAF panelist votes were tallied due to a malfunction with the voting technology

7. ***Are any of the following contextual considerations important in assessing Trikafta's long-term value for money? (select all that apply)***

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.	14/14
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	14/14
This intervention is the first to offer any improvement for patients with this condition.	8/14
Compared to best supportive care, there is significant uncertainty about the long-term risk of serious side effects of this intervention.	11/14
Compared to best supportive care, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	10/14
There are additional contextual considerations that should have an important role in judgments of the value of this intervention	1/14

Long-Term Value For Money at Current Prices

As described in ICER's Value Assessment Framework, questions on long-term value for money are subject to a value vote when incremental cost-effectiveness ratios for the interventions of interest are between $50,000 and $175,000 per QALY in the primary "base case" analysis. The base case estimates of the cost per QALY for Trikafta in all populations exceeded the higher end of this range, and therefore the treatment was deemed "low long-term value for money at current prices" without a vote unless CTAF determined in its discussion that the Evidence Report base case analysis did not adequately reflect the most probable incremental cost-effectiveness ratio for Trikafta.

Key Policy Implications

Following its deliberation on the evidence, the CTAF Panel engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on Trikafta for patients with at least one *F508del* mutation to policy and practice. The policy roundtable members included one patient with CF, one family member of an individual with CF, a representative from a patient advocacy organization, two practicing CF clinical experts, and two payer representatives. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The top-line policy implications are presented below, and additional information can be found in the full report.

Manufacturers

1. ***The manufacturer should lower the price of Trikafta to align fairly with its demonstrated benefits. Pricing treatments within a proportional level to their benefits allows a health system to reward innovation and improve access to patients. Pricing far beyond this reasonable level causes harm to patients – some with CF and some with other diseases – who are forced to delay or forego care or even to drop health insurance entirely.***

2. ***Benefiting from monopoly pricing power, the manufacturer of Trikafta and the other available CFTR modulators bears a significant social responsibility to change its pricing approach by exercising restraint in the use of its monopoly pricing power and by committing to engaging in public deliberations in which independent evaluations of the evidence will be discussed and integrated with broader considerations of value through input from patients and other key stakeholders.***

Payers

3. ***Prior authorization criteria for Trikafta should be based on clinical evidence, specialty society guidelines, and input from clinical experts and patient groups. The process for authorization should be clear and efficient for providers. Options for specific elements of coverage criteria within insurance coverage policy are discussed in the full report.***

4. ***Public and private payers should continue to affirm their commitment to provide access to the CFTR modulators and should remove superfluous requirements for coverage approval and continuation.***

Patient Advocacy Organizations

5. ***Patient organizations that have a leading role in funding, organizing, promoting, and otherwise fostering innovative research on new treatments should demand commitments from manufacturers for sustainable pricing of the products patients helped bring to the market.***

Specialty Societies

6. ***Professional societies should fully exercise their responsibility by bearing witness to the impact on their patients of failed pricing and insurance policies and by demanding to be part of the public process that should guide pricing to balance the needs for affordability and for investments in future innovation.***

Researchers

7. ***Leading journals should refuse to publish manuscripts based on clinical trials that redact portions of their trial protocols.***

8. ***The groundbreaking studies initiated and funded by the Cystic Fibrosis Foundation should be applauded and may serve as a model for other patient organizations seeking to generate evidence. Future studies should measure and report a broad set of outcomes to better assess the health and economic impact of CF interventions to patients, their caregivers, and their health system.***

9. ***Large studies with long term follow-up are needed to complement the short-term results observed in the pivotal randomized trials.***

10. ***Patients who are heterozygous of the* F508del *mutation and a residual function mutation should be prioritized in future research.***

1. Introduction

1.1 Background

Cystic fibrosis (CF) is an autosomal recessive condition caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. The CFTR protein is an ion channel at the cell surface that primarily transports chloride ions across the cell membrane. Children born with CF inherit two pathogenic mutations, one from each parent. 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. In the US approximately 1 in 3,000 Whites are born with CF; it is the most common fatal genetic disease in Caucasian populations, but it is less common among Latinos (1 in 4,000-10,000) and African Americans (1 in 10,000-20,000).[12-15] According to the Cystic Fibrosis Foundation Annual Report, the overall prevalence of CF in the US in 2016 was 30,775.[2] Although rare, CF represents a substantial economic burden. In 2013, CF-related hospital costs alone were estimated to exceed $1.1 billion.[4]

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.[16] 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.[2] They are often grouped into five classes (Table 1.1 below) based on the effect of the mutation on the CFTR protein and, as noted above, each patient with CF carries two of these mutations. 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.[16] This leads to thick secretions that can block passages in the lungs, pancreas, skin and reproductive organs. Changes in the skin lead to elevations in the concentration of chloride ions in the skin, which is sometimes used to screen for CF and to evaluate the impact of the new therapies on CFTR function. More importantly, the thick secretions cause chronic lung infections, reduced lung function, poor weight gain (due to gastrointestinal dysfunction), diabetes (due to pancreatic damage), and fertility problems.[3] These symptoms dramatically impact the lives of affected patients. Patients suffer frequent acute pulmonary exacerbations, leading to repeated hospitalizations and long courses of IV antibiotics that require invasive procedures like the placement of ports for IV access and repeated absence from school and work. The chronic cough from the thick secretions is noticeable to everyone surrounding the patient leading to self-consciousness, stigmatization, anxiety, and depression. The decreased lung function impacts their ability to participate in sports and other daily activities. Seeing their lung function steadily decline leads patients to dread the future and may preclude planning for a long life with family, a rewarding career, and eventual retirement.

Table 1.1. Mutation Classes for the *CFTR* Gene and Potential Treatments

Class / Examples of Mutations	Impact on CFTR Protein	Approved Drug Therapies*
Class I – **nonsense mutations** – **splice mutations** – **deletions** ***22% of people with CF have at least one mutation in this class***	No functional CFTR protein is produced	None (no CFTR protein to be modulated)
Class II – **F508del†** – **N1303K** – **I507del** ***88% of people with CF have at least one mutation in this class***	CFTR protein is produced, but misfolds, which prevents transport of CFTR protein to apical membrane	– Lumacaftor/ivacaftor (Orkambi) combination therapy – Tezacaftor/ivacaftor (Symdeko) combination therapy – Elexacaftor/tezacaftor/ivacaftor (Trikafta) triple therapy
Class III – **G551D** – **S549N** ***6% of people with CF have at least one mutation in this class***	CFTR protein is produced and transported to apical membrane, but channel gate does not react properly	– Ivacaftor (Kalydeco) monotherapy
Class IV – **D1152H** – **R347P** – **R117H** ***6% of people with CF have at least one mutation in this class***	CFTR protein is produced and transported to apical membrane, but channel does not function properly	– Ivacaftor (Kalydeco) monotherapy
Class V – **3849+10kbC → T** – **2789+5G → A** – **A455E** ***5% of people with CF have at least one mutation in this class***	Insufficient amounts of CFTR protein are created and move to apical membrane	– Ivacaftor (Kalydeco) monotherapy

*Potentially effective therapy for at least one mutation in the class
†Most common mutation in CF
Adapted from the Cystic Fibrosis Foundation website: https://www.cff.org/What-is-CF/Genetics/Know-Your-CFTR-Mutations-Infographic.pdf

Management

Best supportive care for CF includes chest physical therapy, airway clearance devices, bronchodilators, inhaled and systemic antibiotics as needed or chronically, inhaled hypertonic saline, and aerosolized DNase, which reduces sputum thickness. In addition, patients often require pancreatic enzyme replacement to treat pancreatic insufficiency and insulin for CF-related diabetes.

Routine daily treatment typically takes one to three hours[17], but can take up to 6 hours per day.[6] Patients with end-stage CF become eligible for lung transplantation.

While supportive care has improved the prognosis for patients, these treatments do not address the underlying cause of CF. Recently introduced agents directly target the CFTR protein.

CFTR Modulator Drugs

There are two classes of modulator drugs. The first, known as potentiators, increase the probability that the CFTR ion channel remains open. Ivacaftor (Kalydeco®, Vertex Pharmaceuticals, Inc.) is the only FDA-approved drug in this category. CFTR correctors, such as lumacaftor, tezacaftor, and elexacaftor help to correct folding of the CFTR protein and its transportation to the cell surface. For the most part the drugs are more effective in combination. The FDA has approved three combinations: Orkambi® (lumacaftor/ivacaftor, Vertex Pharmaceuticals, Inc.), Symdeko® (tezacaftor/ivacaftor, Vertex Pharmaceuticals, Inc.), and Trikafta® (elexacaftor/tezacaftor/ivacaftor, Vertex Pharmaceuticals, Inc.). We use trade names in this report for simplicity.

Table 1.2. FDA Approved CFTR Modulator Drugs and their Indications

Drug	Dose	Indication
Kalydeco (Ivacaftor)	150 mg PO BID with fat containing food if 6 years and older Weight based oral dosing for younger children	Patients age 6 months and older who have one mutation in the *CFTR* gene that is responsive to ivacaftor based on clinical and/or in vitro assay data.
Orkambi (Lumacaftor/ Ivacaftor)	Two tablets (each containing lumacaftor 200 mg/ivacaftor 125 mg) PO q 12 hours with fat-containing food if 12 years and older Weight based oral dosing for younger children	Patients age 2 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene.
Symdeko (Tezacaftor/ Ivacaftor)	One tablet (containing tezacaftor 100 mg/ivacaftor 150 mg) PO in the morning and one tablet (containing ivacaftor 150 mg) in the evening with fat-containing food, approximately 12 hours apart if 12 years or 6 years and older weighing 30 kg or more. Weight based oral dosing for younger, lighter children.	Patients age 6 years and older who are homozygous for the *F508del* mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that is responsive to tezacaftor/ivacaftor based on *in vitro* data and/or clinical evidence.
Trikafta (Elexacaftor/ Tezacaftor/ Ivacaftor)	Morning dose: two elexacaftor 100 mg, tezacaftor 50 mg and ivacaftor 75 mg tablets PO Evening dose: one ivacaftor 150 mg tablet PO Morning and evening dose should be taken approximately 12 hours apart with fat-containing food.	Patients aged 12 years and older who have at least one *F508del* mutation in the *CFTR* gene.

BID: twice a day, CFTR: Cystic fibrosis transmembrane conductance regulator, kg: kilogram, mg: milligram, PO: by mouth, q: every

This review focuses on the triple therapy, Trikafta. The United States Food and Drug Administration (FDA) approved Trikafta on October 21, 2019.[5] Approximately 27,000 individuals in the United States have CF with genetic mutations that are eligible for treatment with Trikafta (90% of individuals with CF). Of these patients, approximately 17,000 are eligible for treatment under the current FDA label, which limits treatment to patients ages 12 years and older.[5] In addition, we updated our 2018 review of Kalydeco, Orkambi, and Symdeko.[18]

The use of these CFTR modulator therapies 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 both through improved efficacy in patients currently eligible for dual therapy (Orkambi, Symdeko) and those with mutations that are not eligible for treatment with the current generation of modulator therapies (patients who are heterozygous for the *F508del* mutation and a minimal function mutation).

Patients with a good response to CFTR modulator therapy may be able to discontinue some of the standard daily symptomatic treatments such as hypertonic saline and dornase alfa. In addition, if the patient can clear pseudomonas, they could stop their inhaled antibiotics. Patients dependent on nocturnal tube feeding may be able to stop the treatment. There may also be significant time savings for patients if some of their therapies can be reduced. However, to date none of these changes have been demonstrated in clinical trials or observational studies and it is unclear if discontinuing standard therapies may be detrimental to long term health. A randomized trial evaluating the impact of the withdrawal of some supportive care for patients on CFTR modulator therapy is underway.[19]

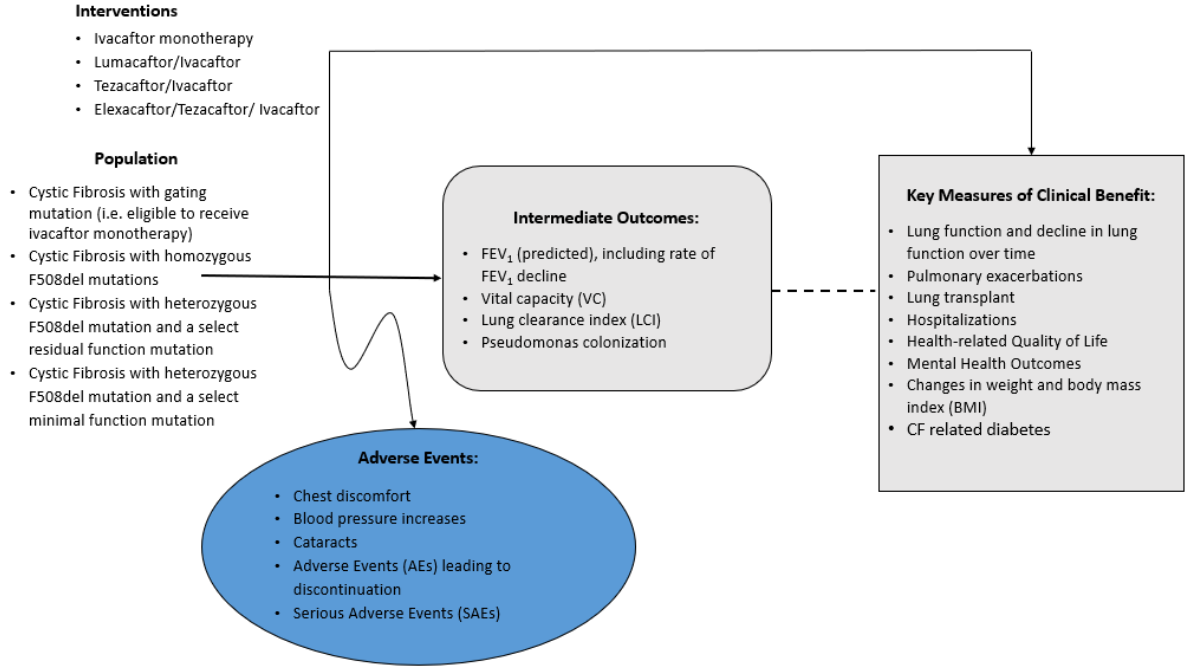
1.2 Scope of the Assessment

The scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence was abstracted from randomized controlled trials as well as high-quality observational studies, particularly for long-term outcomes and uncommon adverse events (AEs). Our evidence review included input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature that met ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework-2/grey-literature-policy/).

Analytic Framework

The analytic framework for this assessment is depicted in Figure 1.1.

Figure 1.1 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., changes in lung clearance index), and those within the squared-off boxes are key measures of benefit (e.g., health-related quality of life). 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 AE of treatment which are listed within the blue ellipse.[20]

Populations

We reviewed the 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 Kalydeco.
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.

Interventions

Population 1: Patients Eligible Only for Kalydeco

- Ivacaftor plus best supportive care

Population 2: Homozygous F508del

- Lumacaftor/ivacaftor plus best supportive care
- Tezacaftor/ivacaftor plus best supportive care
- Elexacaftor/tezacaftor/ivacaftor plus best supportive care

Population 3: Heterozygous F508del *with a Residual Function Mutation*

- Ivacaftor plus best supportive care
- Tezacaftor/ivacaftor plus best supportive care
- Elexacaftor/tezacaftor/ivacaftor plus best supportive care

Population 4: Heterozygous F508del *with a Minimal Function Mutation*

- Elexacaftor/tezacaftor/ivacaftor plus best supportive care

Comparators

The comparator for each population is best supportive care and, where applicable, the other interventions with an indication for that population.

Outcomes

Key Outcomes

- Lung function and decline in lung function over time
- Acute pulmonary exacerbations
- Lung transplant
- Hospitalizations
- Mortality
- Health-related quality of life (HRQoL)
- Mental health including depression and anxiety
- Weight, body mass index (BMI), and growth
- CF-related diabetes (CFRD)

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
- Hemoptysis
- Pneumothorax
- Gall stones
- Kidney stones
- Sinus / nasal polyp surgeries
- Fertility in women

Intermediate Outcomes

- Percent predicted FEV_1 ($ppFEV_1$), including rate of $ppFEV_1$ decline
- Sweat chloride
- Vital capacity
- Lung clearance index
- Pseudomonas colonization
- Fasting glucose and related measures of glucose control

Adverse Events

- Chest discomfort
- Increased blood pressure
- Liver function / injury
- Cataracts
- AEs leading to treatment discontinuation
- Serious adverse events (SAEs)

Timing

Studies of all follow-up durations were eligible.

Settings

All settings were considered. Studies conducted in any country were included. However, the primary interest was in outpatient settings in the United States.

1.3 Definitions

Disease and Pathophysiology

Heterozygous (for a genetic variation): The state of carrying the genetic variation only in one chromosome.

Homozygous (for a genetic variation): The state of carrying the genetic variation in both chromosomes in a chromosome pair.

Mutations: Heritable changes in the DNA, here, of the *CFTR* gene. More than 2,000 different *CFTR* mutations at different loci (places) of the *CFTR* gene have been identified,[2,21] with varying effects on the quantity and function of the CFTR protein.[22] A subset of these mutations are known to be pathogenic (see below).

Pathogenic mutations: Mutations that substantially affect the quantity of functional CFTR protein on the cell membrane, causing CF. Based on the Clinical and Functional Translation of *CFTR* repository, more than 1800 mutations are known to cause CF.[23] A patient manifests CF and its complications if they have pathogenic mutations in both copies of the *CFTR* gene.

Outcomes

Absolute change: the numeric difference between the endpoint value (however defined) and the baseline (starting) value.

Forced expiratory volume in one second (FEV_1): the volume of air a person can exhale during a forced breath after a full inhalation, measured in the first second of the breath.[24] FEV_1 is reported in liters and measures the capacity of a person's lungs. Lower FEV_1 values indicate increasing lung impairment or damage. FEV_1 is measured via spirometry.

Percent predicted forced expiratory volume in one second ($ppFEV_1$): measured FEV1 as a percentage of the predicted FEV1 value for a healthy individual of the same age, sex, race, and height.[7] A clinically-relevant change in absolute percent predicted FEV_1 has been considered to be three to five points, although this is controversial.[25]

CF-related diabetes (CFRD): We accepted each study's definition of CFRD. While we may refer to CF-related diabetes as "diabetes" in this report, CFRD does not have the same pathophysiology as type I or II diabetes mellitus in people without CF. During a period of stable baseline health CFRD is

diagnosed with standard diabetes criteria. However, modified criteria are used to diagnose CFRD during acute illness or continuous feedings.[26]

Cystic Fibrosis Questionnaire-Revised (CFQ-R): A validated survey which measures HRQoL in CF patients.[27] The CFQ-R measures quality of life and physical disease symptoms using the following scales: physical functioning, emotional functioning, social functioning, body image, eating problems, treatment burden, respiratory symptoms, and digestive symptoms, among other domains specific to older patients. Scores range from 0-100 with an increasing score indicating better quality of life. In general, a four-point change is considered clinically meaningful (the minimum clinically-important difference, or MCID) for the respiratory domain.[28] This report primarily focuses on the CFQ-R respiratory domain score since it was reported in the pivotal trials of the CFTR modulators.

Lung Clearance Index (LCI): A novel outcome that assesses the uneven distribution of lung ventilation, an indicator of obstructive lung disease and is typically used in those with a milder lung disease. It represents the number of lung volume turnovers required for the lungs to clear a tracer gas to reach 2.5% of starting tracer gas concentration.[29]. Reductions from baseline indicate an improvement.

Pulmonary exacerbations (PEx): New or change in antibiotic therapy (IV, inhaled, or oral) for any four or more of the signs/symptoms: change in sputum; new or increased hemoptysis; increased cough; increased dyspnea; malaise, fatigue, or lethargy; temperature above 38 degrees Celsius; anorexia or weight loss; sinus pain or tenderness; change in sinus discharge; change in physical examination of the chest; decrease in pulmonary function by 10%; and radiographic changes indicative of pulmonary infection).[30] The CFTR modulators' manufacturer informed us that the same definition was used in all clinical trials, but different sub-definitions were reported in studies (e.g., acute pulmonary exacerbation requiring hospitalization or requiring antibiotics). Real world research may not use the same definition.

Weight for age *z*-score: A score that corresponds to the weight percentile of a child considering the distribution of weights of healthy children of the same age. For example, a weight for age *z*-score of -1.3 corresponds to the 10th percentile of age specific weight values. An increase in the *z*-score from -1.3 to -1.2 corresponds to climbing from the 10th to the 12th weight percentile among children of the same age. An increase in the *z*-score from -0.3 to -0.2 would correspond to climbing 4 percentiles (from the 38th to the 42nd percentile).

1.4 Research, Development, and Manufacturing Costs

As described in ICER's modified framework for assessing value of treatments for ultra-rare diseases, ICER invites manufacturers to submit relevant information on research, development, and manufacturing costs that may impact pricing of a drug. Vertex did not submit information on these costs, as it declined to participate in the review process.

1.5 Potential Cost-Saving Measures in Cystic Fibrosis

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/final-vaf-2017-2019/). These services are ones that would not be directly affected by therapies for CF (e.g., reduction in use of treatment for acute pulmonary exacerbation), 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. During stakeholder engagement and public comment periods, ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with CF that could be reduced, eliminated, or made more efficient. No suggestions have been received.

2. Patient Perspectives

2.1. Methods

From the beginning of this assessment, we sought input from patients, caregivers, and representatives from patient advocacy organizations on the research design of this review (e.g., the PICOTS framework; population, intervention, comparators, outcomes, timing, and setting). We also sought insight on the patient experience of CF and its treatment, including clinical benefits of treatment that may not be described in the literature, any broader potential other benefits or disadvantages associated with treatments, and contextual consideration related to CF, details of which are reported in this section and Section 6. We also built upon the insights that these stakeholders shared with ICER during its 2018 review of Kalydeco, Orkambi, and Symdeko,[18] as well as existing sources of information on patient perspectives such as the Voice of the CF Patient report produced by Cystic Fibrosis Research Incorporated (CFRI) under the FDA Externally-Led Patient Focused Drug Development program.[6]

We heard from patients, caregivers, and advocacy organizations in the following ways during this review. Additional details regarding how this input informed ICER's research approach can be found below the list.

- **Open Input**
  - 32 responses to ICER's Patient Input Questionnaire from patients and caregivers, 21 letters from patients and caregivers, and two letters from patient advocacy organizations with whom we also held conference call discussions.
  - 2 discussion calls with patient advocacy organization representatives
- **Draft Scope**
  - Two letters from patient advocacy organizations, one letter from the caregiver of a teenager with CF
- **Draft Report**
  - ICER presented the preliminary modeling approach to one patient organization and considered feedback
  - We held two group discussions with a total of 15 patients and caregivers, including several leaders from patient-run advocacy organizations.
  - CF Foundation reviewed a pre-publication draft of this report
  - ICER received 9 public comments from patient advocacy organizations and 45 comments from individuals with CF and caregivers/family members.

Input received during the Open Input period informed the initial selection of population, interventions, comparators, and outcomes measures for which we sought evidence described in a

draft scoping document that was open to public comment for three weeks. As compared to ICER's previous report, we added CFRD, HRQoL, pill burden and correlation to adherence with medication regimen, pseudomonas infection, and vital capacity as outcomes, increased blood pressure, and SAEs to the draft scope.

We revised the draft scope to reflect feedback from patient advocacy organizations, most notably to expand the list of outcomes and AEs for which we sought evidence. We added mortality, hemoptysis, pneumothorax, gall stones, kidney stones, sinus / nasal polyp surgeries, and sweat chloride as outcomes, and liver function / injury as AEs. We also removed the combination therapy Orkambi from consideration in the population of patients who are heterozygous for the *F508del* mutation with a residual function mutation, as it does not have an FDA indication in that population. Although we received some suggestions to focus only on triple therapy, we elected to update our prior review of the three older drugs to incorporate new real-world data and to help provide context for the additional benefits of triple therapy. We retained FEV_1 as an intermediate outcome despite it being a primary outcome in many of the trials because the key outcomes that matter to patients are their quality of life and functional improvements that flow from the improvement in FEV_1 as well as the longer-term reductions in pulmonary exacerbations, hospitalizations, transplants, and mortality.

In response to the feedback we received during the preliminary model presentation, we have modified the presentation of economic modeling results to separate best supportive care cost outcomes into more granular categories, and have conducted a scenario analysis in which we assumed increasing levels of cost offsets related to best supportive care.

ICER made multiple revisions to the draft report in response to public comments from patients, caregivers, and patient advocacy organizations. Detailed responses, including rationale for why changes were or were not made, can be found in a response document located here: https://icer-review.org/material/cystic-fibrosis-2-response-to-public-comments/.

2.2 Impact on Patients and Caregivers

Several themes emerged from our conversations, and we have organized them in three sections below: first, the impacts of disease and the ways in which treatments improve symptoms; second, the burden to patients and families of their CF care regimen; and finally, insights related to accessing and affording CF treatment.

Patients, caregivers, and advocacy organizations highlighted the heterogeneity of the disease, emphasizing that no two patients are alike. 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.

Disease Burden and Experience with Modulator Treatments

We reviewed the CFRI Voice of the Patient report to better understand patient and caregiver perspectives on the burden posed by CF.[6] The report summarizes the proceedings at an October 29, 2018 public meeting that featured panel discussions among CF patients, caregivers, and clinical experts, as well as live polling of attendees (polling responses were also accepted for 30 days after the event). The nine symptoms identified by polls as having the greatest impact on quality of life for patients living with CF are listed below.

1. Pulmonary exacerbations / infections
2. Excessive cough
3. GI issues
4. Fatigue
5. Shortness of breath
6. Mental health issues
7. Sinus disease
8. CF-related diabetes
9. Chronic pain

In addition, the report highlighted important key life activities that are challenging because of CF:

1. Time with friends / social activities
2. Work / School attendance
3. Participation in sports / extracurricular activities
4. Financial stability

Finally, the report identified six key benefits that patients hope to receive from new treatments:

1. Fewer lung infections / exacerbations
2. Improved breathing
3. Improved GI symptoms / digestion
4. Reduced fatigue
5. More time for non-CF activities
6. Relief from depression/anxiety

These results closely aligned with the feedback ICER heard during its own patient engagement efforts, and patients shared with us how treatment impacted many of these symptoms. When we spoke with patients who had started Trikafta, the first thing that they noticed was that either their cough stopped or was greatly diminished. There was often an initial purge of mucus — one patient reported expulsion of nearly 12 ounces of mucus in an evening — and then patients felt like they could take deeper breaths for the first time in their life. Patients emphasized that reducing or

eliminating their cough brought numerous benefits, especially the ability to sleep through the night without waking due to coughing attacks, which brought increased energy levels and improvements in mood. One patient shared that she ran a 5k before and after starting Trikafta, and was able to complete the second race without coughing nearly 10 minutes faster than her previous time. Patients on modulator therapy for several years (i.e., Kalydeco, Orkambi, and/or Symdeko) reported a reduction in the frequency of pulmonary exacerbations and the need for IV antibiotics. Patients and their caregivers noted a meaningful increase in energy. One patient told us that "I haven't been able to do any exercise in years. Now I can snowboard, swim, hike at high elevations, and even run a little bit."

Nasal symptom improvements were also important, including a marked reduction in nasal polyps, reduced need to visit the ear, nose, and throat (ENT) clinic, a reduction in nasal surgery, and perhaps most important for quality of life: regaining a sense of smell. Patients spoke of getting a good night's sleep for the first time in their lives and how much more energy it gave them. GI complaints decreased significantly with less constipation and less pain, and several patients reported that they could reduce or stop taking laxative supplements. Musculoskeletal pain from coughing and arthritis also decreased. The overall experience was summarized by one patient, who said "My quality of life has increased exponentially."

We spoke with several patients who had been on Orkambi and/or Symdeko and switched to Trikafta upon its approval. Among these patients, there was agreement that they all experienced additional improvements beyond those they received from their earlier therapies. This included some patients who were intolerant to Orkambi due to side effects, those whose lung function was stabilized but not improved, and others who had clinical benefits while on either drug.

Another theme was 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. One parent reported that her daughter "had an underlying sadness, but [after starting Trikafta] now sees the world through a completely different lens." Her daughter, who had been an avid horse-back rider before she could no longer participate due to her disease progression is now able to ride three days a week. Another patient reported that "my biggest mental change has been my calmness." Another patient reported that after starting Trikafta "I have stopped weekly therapy for depression. I no longer think about death all of the time."

A common thread in these remarks was the ability to plan for the future, which for many had been unthinkable due to the dire prognosis of the disease. Parents shared with us that their children are imagining future educational and professional opportunities, while adults spoke about re-entering the workforce, planning for retirement, vacations, and entering into long-term relationships with less concern about how CF might impact their longevity. Parents who have CF themselves are able to spend more time with their children as they grow up, and may live long enough to have

grandchildren as well. Patients expressed hope that currently-available treatments would provide substantial benefits, with one patient stating that "we have been waiting for a miracle and the triple combo is the closest thing." Patients commonly used the word "transformative" to describe Trikafta. Patients who had already started therapy with Trikafta spoke about the transformation in their outlook about the future from one of dreading the inevitable decline associated with CF to planning for the future. One patient, who had not had a good response to another modulator therapy said that starting Trikafta "felt like a miracle to me." Patients also reported hope for their community – in particular the hope that children with CF who start on modulator therapy early in their lives might be able to avoid the pulmonary, pancreatic, and other complications of CF and thus live normal or near-normal lives.

Hope was also expressed by caregivers: "Our hope is that it will make her close to normal, if not normal, while taking the triple combo." One mother said that her son "has so much less anxiety and both her and her husband's mental health dramatically improved" after her son started taking Trikafta. She had stopped working to care for her son, but now has gone back to work.

Treatment Burden

Patients and caregivers described the immense 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; the CFRI report notes that this can be up to 6 hours per day.[6] 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.

One patient who is ineligible for current treatments, which do not treat her specific mutations, spoke about the difficulties of traveling with CF beyond the vigilance required to reduce the risk of catching a contagious illness. She described having to bring three carry-on bags of CF treatments, including IV antibiotics, and breathing tubes, and of her hope that an effective treatment would reduce this burden.

Treatment burden for caregivers was also discussed. Parents of CF patients may have to permanently leave their job to make time for the daily treatments associated with CF. One patient discussed that during his hospitalizations, his spouse would either have to take significant time off work, or feel guilty if unable to do so, thus increasing stress and negatively impacting both their quality of life.

Patients expressed hope that the new triple therapy would alleviate some of this daily load, and for some patients this daily load was already improving. Some reported that they have reduced or stopped using other treatments such as hypertonic saline, inhaled medications, laxatives, or insulin.

Patients also spoke of their desire to spend less time in the hospital, and how modulator treatments have reduced the number of pulmonary exacerbations and other health events that require doctor's visits or hospital stays. One mother wrote that four year old daughter has been able to eliminate her pancreatic enzymes and is breathing essentially normally on ivacaftor. She noted that this means she can hire babysitters, and her daughter can participate in school programs (lunch) and spend time at friends' houses without the need to train others on CF care.

Access and Costs

During both ICER reviews of CF therapies, patients and caregivers shared their fears related to insurance-related access barriers. Examples include requirements for repeated submission of genetic test results despite the fact that no available treatments permanently modify the *CFTR* gene and delays related to prior authorization policies.

Another theme we heard was 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.

The financial burden imposed by the disease was frequently borne by the caregivers. Caregivers often forego job opportunities, switch from full- to part-time employment, or stop working altogether in order to care for their loved one who has CF. "It can't be underestimated how much caregivers do in terms of time off of work," said one caregiver.

Some patients also stated that the were "deeply concerned about the staggering price of drugs." One patient on Medicare wrote that "I am extremely worried about how much out of pocket I can afford. My Part D Plan has not covered other specialty drugs thoroughly, so I can imagine that I will have to rely on outside health grants." Others voiced concern that regulations regarding pre-existing conditions and lifetime cost caps would be repealed, noting that these could lead insurance to only partially cover the cost of therapy or not cover it at all. These patients noted that they could not afford the cost of modulator therapies on their own. One patient told us that she postponed marrying her now-husband out of concern that his insurer would no longer cover her off-label Kalydeco prescription. She wrote, "I am worried about the costs on the whole health care system and the costs of these drugs driving up premiums for everyone in the health group. My husband's company is self-insured so I am worried that by having me on the plan he could get targeted for driving up everyone's premium costs." Patients also expressed concern with the cost of treatments beyond the modulators, noting that bills for hospital stays, medical devices, and treatments such as insulin can be staggering. Another patient relayed stories of others in her CF network who self-rationed their medications (CFTR modulators and otherwise) due to unaffordable costs. Another acquaintance lost her eligibility for grant funding for copay assistance because her husband got a new job that paid more.

3. Summary of Coverage Policies and Clinical Guidelines

3.1 Coverage Policies

We reviewed the Tufts Medical Center Specialty Drug Evidence and Coverage (SPEC) Database for US commercial health plan coverage policies for Trikafta, Kalydeco, Orkambi, Symdeko, and. Developed by the Center for Evaluation of Value and Risk in Health, the SPEC database features data more than 290 specialty drugs, more than 175 disease areas, and more than 25,000 decisions from 17 of the largest US national and regional commercial payers: Aetna, Anthem, Blue Cross Blue Shield (BCBS) of Florida (FL), Massachusetts (MA), Michigan (MI), North Carolina (NC), New Jersey (NJ), and Tennessee (TN), CareFirst, Centene, Cigna, Emblem, Health Care Service Corporation (HCSC), Highmark, Humana, Independence Blue Cross (IndepBC), and UnitedHealthcare (UHC).[31]

We also searched for National or Local Coverage Determinations (NCDs or LCDs) from the Centers for Medicare and Medicaid Services (CMS) and from the California Department of Health Care Services, but were unable to locate any policies pertaining to CFTR modulator therapies.

Trikafta

At the time this report was published and as of the last update of the SPEC database, six of the surveyed payers had issued coverage policies for Trikafta (Anthem, BCBSFL, BCBSMI, BCBSNC, Centene, UHC). Of the surveyed plans, 3 were equivalent to the FDA label while 3 were more restrictive. All plans required documentation of at least one *F508del* mutation for authorization. One payer, BCBSNC, covered Trikafta as a second-line therapy and required that patients have an inadequate response or contraindication/intolerance to Orkambi or Symdeko. Centene and UHC required prescription to be by or in consultation with a pulmonologist, and UHC also required the specialist to be affiliated with a CF care center.

Table 3.1. Summary of Representative Commercial Coverage Policies for Trikafta

Payer	Comparison to FDA Label	Line of Therapy	Prescriber Criteria	Other Approval Criteria	Renewal Criteria	Authorization Period
Anthem	Equivalent	1	N/A	May not be approved for individuals with severe hepatic impairment (Child-Pugh Class C)	N/A	N/A
BCBSFL	Equivalent	1	N/A	N/A	NS	6 months
BCBSMI	Equivalent	1	N/A	N/A	N/A	N/A
BCBSNC	More restrictive	2 (Orkambi or Symdeko)	N/A	N/A	N/A	N/A
Centene	More restrictive	1	By/consultation with pulmonologist	$ppFEV_1$ between 40-90%	NS	6 months
UHC	More restrictive	1	By/consultation with pulmonologist affiliated with CF center	N/A	NS	6 months

$ppFEV_1$: percent predicted forced expiratory volume in 1 second, N/A: not applicable, NS: not specified

Kalydeco

We identified publicly available coverage policies for Kalydeco for all but five of the surveyed payers (BCBSNJ, BCBSTN, Emblem, HCSC, and Highmark); policies from the payers whose policies we found are described in Table 3.2. All plans required documentation of a genetic mutation responsive to treatment with Kalydeco. Seven of 12 policies (58%) were consistent with the FDA label, while the remaining 5 (42%) were more restrictive with regards to either prescriber restrictions or age requirements. Aetna and BCBSFL required patients to be 12 months of age or older, which did not reflect the FDA label expansion on April 30, 2019,[32] while CareFirst set a minimum age of two years, which did not reflect the label expansion on August 15, 2018.[33]

Cigna required re-authorization after six months with documentation of a clinical response (i.e., improvement in $ppFEV_1$, reduction in pulmonary exacerbations, improvement in BMI, or improvement in the respiratory domain of the CFQ-R). BCBSFL required re-authorization every six months and BCBSMI every 12 months to assess treatment response, though neither payer listed requirements for re-authorization.

Table 3.2. Summary of Representative Commercial Coverage Policies for Kalydeco

Payer	Comparison to FDA Label	Line of Therapy	Prescriber Criteria	Age	Renewal Criteria	Authorization Period
Aetna	More restrictive	1	N/A	≥ 12 months	N/A	N/A
Anthem	Equivalent	1	N/A	≥ 6 months	N/A	N/A
BCBSFL	More restrictive	1	N/A	≥ 12 months	NS	6 months
BCBSMA	Equivalent	1	N/A	≥ 6 months	N/A	N/A
BCBSMI	Equivalent	1	N/A	≥ 6 months	NS	12 months
BCBSNC	Equivalent	1	N/A	≥ 6 months	N/A	N/A
CareFirst	More restrictive	1	N/A	≥ 2 years	N/A	N/A
Centene	Equivalent	1	N/A	≥ 6 months	N/A	N/A
Cigna	Equivalent	1	N/A	≥ 6 months	Clinical improvement	12 months
Humana	Equivalent	1	N/A	≥ 6 months	N/A	N/A
IndepBC	More restrictive	1	Pulmonologist	≥ 6 months	N/A	N/A
UHC	More restrictive	1	By/consultation with pulmonologist	≥ 6 months	N/A	N/A

N/A: not applicable, NS: not specified

Orkambi

We identified publicly available coverage policies for Orkambi for all but five of the above payers (BCBSNJ, BCBSTN, Emblem, HCSC, and Highmark). Policies for the remaining 12 payers are described in Table 3.3. All plans required documentation that the patient is homozygous for the *F508del* mutation, and Aetna's policy required re-confirmation of mutation status for renewal. Of these plans, 8 (67%) follow the FDA label, while 4 (33%) were more restrictive. As above, more restrictive policies focused on age limits or prescriber criteria. CareFirst's policy requires patients to be at least 6 years old, the labeled age range prior to August 7, 2018.[34] Two plans included renewal criteria for demonstration of clinical benefit (BCBSMI) or demonstration of benefit or stabilization (Aetna)

Table 3.3. Summary of Representative Commercial Coverage Policies for Orkambi

Payer	Comparison to FDA Label	Line of Therapy	Prescriber Criteria	Age	Renewal Criteria	Authorization Period
Aetna	Equivalent	1	N/A	≥ 2 years	Clinical response or stabilization	N/A
Anthem	Equivalent	1	N/A	≥ 2 years	N/A	N/A
BCBSFL	Equivalent	1	N/A	≥ 2 years	NS	6 months
BCBSMA	Equivalent	1	N/A	≥ 2 years	N/A	N/A
BCBSMI	More restrictive	1	Pulmonologist in CF center	≥ 2 years	Clinical improvement	N/A
BCBSNC	Equivalent	1	N/A	≥ 2 years	N/A	N/A
CareFirst	More restrictive	1	N/A	≥ 6 years	N/A	N/A
Centene	Equivalent	1	N/A	≥ 2 years	N/A	N/A
Cigna	Equivalent	1	N/A	≥ 2 years	N/A	N/A
Humana	Equivalent	1	N/A	≥ 2 years	N/A	N/A
IndepBC	More restrictive	1	Pulmonologist	≥ 2 years	N/A	N/A
UHC	More restrictive	1	By/consultation with pulmonologist affiliated with CF center	≥ 2 years	NS	6 months

N/A: not applicable, NS: not specified

Symdeko

We identified publicly available coverage policies for Symdeko for all but five of the above payers (BCBSNJ, BCBSTN, Emblem, HCSC, and Highmark). All plans required documentation that the patient is homozygous for the *F508del* mutation or has another *CFTR* gene mutation responsive to treatment with Symdeko. As with Orkambi, Aetna required re-confirmation of mutation status for renewal. Of the 12 plans with publicly available policies, 5 (42%) aligned with the FDA label and 7 (58%) were more restrictive (Table 3.4). Plan restrictions came in the form of age restrictions or provider criteria. Anthem, CareFirst, Cigna, and IndepBC required patients to be aged 12 or older, which did not reflect the FDA label expansion from June 21, 2019.[35] Two plans included renewal criteria for clinical response or stabilization (Aetna) or clinical improvement (BCBSMI)

Notably, all but one payer covered Symdeko as a first-line therapy, with Humana requiring patients to have previously attempted treatment with or have a contraindication or intolerance to Kalydeco or Orkambi.

Table 3.4. Summary of Representative Commercial Coverage Policies for Symdeko

Payer	Comparison to FDA Label	Line of Therapy	Prescriber Criteria	Age	Renewal Criteria	Authorization Period
Aetna	Equivalent	1	N/A	≥ 6 years	Clinical response or stabilization	NS
Anthem	More restrictive	1	N/A	≥ 12 years	N/A	N/A
BCBSFL	Equivalent	1	N/A	≥ 6 years	NS	6 months
BCBSMA	Equivalent	1	N/A	≥ 6 years	N/A	N/A
BCBSMI	More restrictive	1	CF expert	≥ 6 years	Clinical improvement	1 year
BCBSNC	Equivalent	1	N/A	≥ 6 years	N/A	N/A
CareFirst	More restrictive	1	N/A	≥ 12 years	N/A	N/A
Centene	Equivalent	1	N/A	≥ 6 years	N/A	N/A
Cigna	More restrictive	1	N/A	≥ 12 years	NS	6 months
Humana	More restrictive	2 (Kalydeco or Orkambi)	N/A	≥ 6 years	N/A	N/A
IndepBC	More restrictive	1	Pulmonologist	≥ 12 years	N/A	N/A
UHC	More restrictive	1	By/consultation with pulmonologist affiliated with CF center	≥ 6 years	NS	6 months

N/A: not applicable, NS: not specified

3.2 Clinical Guidelines

We searched for guidelines on the use of CFTR modulators from major US and ex-US organizations. Given that the modulator therapies are the focus of this report, we have not summarized guidance related to other aspects of CF care, but have included references to such guidance statements from CFF and the UK National Institute for Heath and Care Excellence to reflect that CF is a disease that affects multiple organ systems and requires multidisciplinary care.

Cystic Fibrosis Foundation (CFF), 2018[36]

The CF Foundation guidelines on the use of CFTR modulators offer recommendations in two categories: strong and conditional. Broadly, strong recommendations indicate that most individuals in a given situation would prefer the recommended action, while conditional recommendations

indicate that the majority of individuals would prefer the recommended action, but acknowledges that many would not. Importantly, these guidelines have not yet been updated to reflect the recent label expansions for Kalydeco (changing the youngest indicated age range from 2 years to 6 months) and Orkambi (changing the youngest indicated age range from 12 to 2 years), which occurred after their publication. They have also not yet been updated to include guidance related to Symdeko and Trikafta, which were approved after their publication.

Kalydeco

The guidelines strongly recommend the use of Kalydeco versus no modulator therapy in children ages 2-5 years with gating mutations other than *G551D* or *R117H* (i.e., *G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P*, or *G1349D*). In a separate 2016 guidelines statement for preschool-aged individuals (2-5 years), the CF Foundation strongly recommends the use of Kalydeco in individuals with a *G551D* mutation and that its use be considered in individuals with a *R117H* mutation.[37] Another 2012 guideline statement regarding the use of chronic medication to maintain lung function includes a strong recommendation for the use of Kalydeco for all individuals ages 6 and older with at least one copy of a *G551D* mutation.[38]

Conditional recommendations in favor of treatment are given for patients with the same mutations who are ages 6-11, 12-17, and 18+ at any baseline $ppFEV_1$ level, primarily due to the existence of less (or no) direct clinical evidence in these populations. The guidelines note that the ultimate decision may vary due to insurance coverage and out-of-pocket costs to the patient. The guidelines note that children in the 6-11 age range with $ppFEV_1$ below 40% will have rapidly progressing disease and will be likely to benefit from therapy; children in the same age range with greater than 90% $ppFEV_1$ may experience a smaller absolute benefit, but will be more likely to maintain their current lung function with modulator therapy.

The guideline includes conditional recommendations for the use of Kalydeco versus no modulator treatment for individuals with the *R117H* mutation between the ages of 6-17 with $ppFEV_1$ below 90% and for all individuals over the age of 18 regardless of pulmonary function levels. A conditional recommendation against treatment (very low certainty) is included for individuals between the age of 0-5 with an R177H mutation due to the substantial costs of therapy and potential for side effects weighed against the potential for foregone benefits in patient-important outcomes. Similarly, the CF Foundation conditionally recommends against Kalydeco for individuals ages 6-17 with an *R117H* mutation and $ppFEV_1$ greater than 90% (low to very low certainty), noting that some data in the 6-11 age range suggest a decline in $ppFEV_1$ with Kalydeco treatment.

Orkambi

The CF Foundation strongly recommends the use of Orkambi versus no modulator treatment for individuals homozygous for the *F508del* mutation older than 12 years of age with $ppFEV_1$ below

90% (moderate certainty). Conditional recommendations in favor of treatment (low to very low certainty) are included for individuals ages 6-11 regardless of lung function levels and for individuals ages 12-18+ with greater than 90% ppFEV$_1$, though they note concerns regarding treatment intolerance among patients with less than 40% ppFEV$_1$. Additional considerations for all age groups included potential drug-drug interactions, insurance coverage, and out-of-pocket costs. The guidelines do not include a recommendation regarding the use of Orkambi in patients younger than 5.

Guidelines for Other Aspects of CF Care

The CF Foundation has produced guidelines statements regarding all aspects of CF care, including diagnosis, nutrition/gastrointestinal care, respiratory care, infection prevention and control, CF-related conditions (CF-related diabetes, liver disease, and bone disease), and for the screening and treatment of depression and anxiety.[39]

National Institute for Health and Care Excellence (NICE), 2019[40]

In October 2019, NICE reached an interim access agreement with Vertex Pharmaceuticals Inc. to provide eligible patients with access to Kalydeco, Orkambi, and Symdeko during a data collection period to address several uncertainties raised by the NICE appraisal committee. These uncertainties related to long-term effects on ppFEV$_1$, treatment impacts on lung function decline, discontinuation, compliance, BMI, height, and weight for patients younger than 18, use of IV antibiotics, CFRD, mortality, pancreatic insufficiency, sweat chloride, and quality of life. Details of any price concessions made as part of this agreement are not publicly available.

Kalydeco

Under the agreement, NICE will provide Kalydeco to patients who are 1 year of age or older and have a gating mutation amenable to treatment with Kalydeco (at least one copy of *G551D*, *G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N* and *S549R*) or who are 18 years of age or older and have at least one copy of the *R117H* mutation.

Orkambi

Under the same agreement, all patients 2 years of age or older who are homozygous for the *F508del* mutation will be eligible for treatment with Orkambi.

Symdeko

Patients who are at least 12 years of age or older, are homozygous for the *F508del* mutation, and who have one of the following gene mutations will be eligible for treatment with Symdeko: *P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272 26A→G,* and *3849+10kbC→T*.

Trikafta

Trikafta is not included in the above arrangement for the other three modulator therapies. NICE is in the preliminary stages of its appraisal of the treatment.[41]

Guidelines for Other Aspects of CF Care

NICE provides guidance for the treatment of CF beyond modulator therapy, including diagnosis; support; management of complications; pulmonary and "other" monitoring assessment, and management; and preventing cross-infection.[42]

Canadian Agency for Drugs and Technology in Health (CADTH)

CADTH has not issued a recommendation for Symdeko and Trikafta, as they have yet to be submitted for review by the manufacturer.

Kalydeco

CADTH has issued three separate recommendations regarding the use of Kalydeco, each of which included a recommendation for coverage conditional on substantial price reductions. Across the three guidance documents, CADTH recommended coverage for patients ages 6 and older with *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R*, or *G970R* mutations; and for patients ages 18 and older with a *R117H* mutation and chronic sinopulmonary disease. In addition to the requirement for price reductions, CADTH also requested the development of clinical criteria by CF clinics for treatment discontinuation in patients with *G551D* and *R117H* mutations who do not respond to therapy.[43-45]

Orkambi

In September 2018, CADTH issued a recommendation against reimbursement of Orkambi for patients 6 years of age and older who are homozygous for the *F508del* mutation.[46] In their rationale for the negative recommendation, CADTH cited concerns related to the clinical and statistical significance of trial outcomes, as well as cost-effectiveness.

4. Comparative Clinical Effectiveness

4.1 Overview

We updated our prior review of the comparative clinical effectiveness of CFTR modulators in patients with cystic fibrosis, focusing on the evidence of the efficacy and safety of the new CFTR modulator Trikafta in comparison with other CFTR modulators or best supportive care. We defined four target populations of interest based on combinations of genetic mutations for which a CFTR modulator has been approved (see Appendix D). Our review focused on the intermediate and long-term outcomes and harms assessed in available studies. We sought evidence on the outcomes specified in Section 1.2, including pulmonary exacerbations, $ppFEV_1$, weight/BMI, and quality of life measures.

The most common outcome when evaluating therapies for CF is the percent predicted forced expiratory volume in one second ($ppFEV_1$), which is measured as a percentage of the normal amount of air that a healthy, non-smoking individual of the same age, sex, race, and height can blow out in one second.[7] By definition, normal should be 100%. However, in CF the $ppFEV_1$ declines over time with lower $ppFEV_1$ representing more severe disease. A $ppFEV_1$ ≥90% is normal, while a $ppFEV_1$<40% represents severe disease. The rate of decline varies between patients due to many factors, including age, the patients' combination of mutations, BMI, chronic infection with *Pseudomonas aeruginosa*, pancreatic insufficiency and CFRD.

The other commonly reported outcome is the respiratory domain of the Cystic Fibrosis Questionnaire-Revised (CFQ-R). Scores range from 0 to 100 with higher scores representing higher quality of life. A typical score in children is about 75, which declines to about 60 in adults. The score decreases with increased coughing or wheezing and with pulmonary exacerbations. The minimal clinically-important difference is estimated to be a 4 point change.

4.2 Methods

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on CFTR modulators followed established research methods.[47,48] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[49] The PRISMA guidelines include a list of 27 checklist items, which are described further in Appendix Table A1.

We updated our prior literature searches in Ovid-Medline and EMBASE and added search terms for Trikafta. No limitations were placed on the searches regarding publication date, language, age,

country, study design, or publication type (e.g., peer-reviewed or conference proceeding). All search strategies were generated utilizing the Population and Intervention criteria described in Section 1.2. The search strategies included a combination of indexing terms (MeSH terms in MEDLINE, searched through PubMed, and EMTREE terms in EMBASE), as well as free-text terms, and are presented in Appendix Tables A2- A5. The date of the most recent search was November 8, 2019.

To supplement the database searches, we performed a manual check of the reference lists of included trials and reviews and invited any interested stakeholder to share references germane to the scope of this project. Further details of the search algorithms, methods for study selection, quality assessment, and data extraction are available in Appendix Tables A2-5 and Appendix D.

Study Selection

Subsequent to the literature search and removal of duplicate citations using both online and local software tools, study selection was accomplished through two levels of screening, at the abstract and full-text level. Two reviewers independently screened the titles and abstracts of all publications using DistillerSR (Evidence Partners, Ottawa, Canada) and resolved any issues of disagreement through consensus. No study was excluded at abstract level screening due to insufficient information. For example, an abstract that did not report an outcome of interest in the abstract would be accepted for further review in full text.

Citations accepted during abstract-level screening were retrieved in full text for review. Reasons for exclusion were categorized according to the PICOTS elements during full-text review.

Data Extraction and Quality Assessment

Data were extracted into evidence tables (Appendix Tables D1-D15).

Data extraction was performed in the following steps:

1) Two reviewers extracted information from the full articles.
2) Extracted data was reviewed for logic, and data were validated by a third investigator for additional quality assurance.

We used criteria employed by the US Preventive Services Task Force ([USPSTF] see Appendix D) to assess the quality of clinical trials, using the categories "good," "fair," or "poor."[50]

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus (see Appendix D).[51]

Assessment of Publication Bias

Given the emerging nature of the evidence base for these newer treatments, we scanned the ClinicalTrials.gov website to identify studies completed more than two years ago. None were identified.

Data Synthesis and Statistical Analyses

As in the prior review, we conducted meta-analyses for outcomes that had data from at least two studies that were similar in population, intervention, and other characteristics including length of follow-up. Meta-analyses carried over from the prior report were conducted with random effects model restricted maximum likelihood analyses. Harms were analyzed as arcsine transformed data.[52] Estimates of indirect comparisons were obtained as linear combinations of the direct estimates, following Bucher et al.[53] For this review we performed random effects component network meta-analyses (CNMA) for key outcomes (ppFEV$_1$, CFQ-R, and sweat chloride) in patients homozygous for the *F508del* mutation (Population 2) in order to allow indirect comparisons between treatments that lacked head to head trials. We followed the frequentist CNMA approach for disconnected networks described by Rucker et al (2019).[54]

4.3 Results

The results are organized by the four populations of interest:

1. Individuals with CF Eligible Only For Kalydeco.
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 each population, the results are summarized by drug. We summarized the findings from the prior review for each therapy and describe any new results.

Study Selection

Our literature search yielded 1,103 potentially relevant references (Figure A1) of which 27 met our eligibility criteria. The primary reasons for study exclusion for this review included studies captured in the prior review, duplicates, and non-comparative study designs with either follow-up less than one month or study size less than 100 participants. We made an exception for one study that included only 96 participants because it was close to 100 and reported 5 year outcomes.[55]

Key Studies

There are two key studies of Trikafta.[8,56] The first randomized 107 patients homozygous for the *F508del* mutation (Population 2) to Trikafta or Symdeko with a primary outcome of change in $ppFEV_1$ at 4 weeks. The second randomized 403 patients heterozygous for the *F508del* mutation and a minimal function mutation (Population 4) to Trikafta or placebo with a primary outcome of change in $ppFEV_1$ at 24 weeks. Both studies were good quality. The results are summarized in the sections below for the relevant populations.

Quality of Individual Studies

As noted in the Key Studies section the pivotal randomized trials for Trikafta[8,56] were of good quality as was the earlier dose finding study.[57] There were no other new randomized trials, but there were a number of additional publications of the randomized trials that were judged to be of good quality in our prior review. The new publications from these studies either reported additional outcomes not reported in the initial publication or presented open label, long-term follow-up data. There were several cohort studies with matched concurrent or historical controls that we rated as fair quality because of concerns about residual confounding. Uncontrolled case series were rated as poor quality. We did not rate the quality of the thirteen new studies that were available only as abstracts.

Clinical Benefits

Population 1: Individuals with CF Eligible Only For Kalydeco

Key Findings: Children, adolescents, and adults with G551D *and non-*G551D *gating mutations experienced statistically-significant and clinically-meaningful gains in* $ppFEV_1$ *and reductions in the rate of pulmonary exacerbations with Kalydeco compared to placebo in 24-week studies. Longer-term follow-up suggests lung function improvements, including reduced rates of pulmonary exacerbations, are durable through five years. Studies also demonstrated statistically-significant improvements in body weight and the respiratory domain of the CFQ-R in populations aged 12 and older. Significant improvements in lung function or weight were not observed in adult patients with* R117H *residual function mutations. Observational studies with up to five years of follow-up reported significant reductions in rates of death, organ transplantation, CF related diabetes and hospitalizations for patients treated with Kalydeco, but there was significant selection bias in the control groups that may explain much of these reductions. Contrary to expectations, a small study of children aged 6 to 11 years with* R117H *residual function mutations, reported that those on Kalydeco had significant decreases in lung function and trends towards worse quality of life on the respiratory domain of the CFQ-R.*

Since our prior review, two abstracts and one publication extending the results of trials described in the prior report.[58-60] In addition, there are eight new observational studies (five full text, three

abstracts only).[21,55,61-66] See Appendix Tables D1 to D15 and our prior report[18] for detailed analyses of the clinical trials of Kalydeco in patients with mutations that respond to Kalydeco. The prior report summarized four RCTs (STRIVE, ENVISION, KONNECTION, and KONDUCT) that evaluated the safety and efficacy of Kalydeco in patients with at least one *G551D*, non-*G551D* gating, or *R117H* mutation.[67-70] The prior review also summarized three noncomparative studies: KIWI,[71] a Phase III single-arm study that included children aged 2-5 with a *G551D* gating mutation; GOAL,[72] a longitudinal cohort study of individuals aged 6 years and older with at least on *G551D* mutation; and PERSIST,[73] which followed eligible STRIVE and ENVISION participants for an additional 96 weeks on Kalydeco.

Table 4.1 below summarizes the prior results as well as the new studies. For patients ages 6 years and older with gating mutations (*G551D*), the studies reported an absolute improvement of 10.4 percentage points (95% CI 8.6 to 12.3) in $ppFEV_1$ compared to placebo, significant reductions in risk of pulmonary exacerbations (34% vs. 56%, hazard ratio 0.455, p=0.001), increases in weight and BMI (2.8 kg and 0.7 kg/m^2 respectively), and clinically significant improvements in the respiratory domain of the CFQ-R quality of life instrument of about 10 points. The improvement in the CFQ-R difference was not statistically significant for the subgroup of patients 6 to 11 year of age in one study.[70] Long-term follow-up of patients who continued Kalydeco treatment reported sustained improvements in $ppFEV_1$ through 96 weeks.[73]

A study of patients with the *R117H* gating mutation reported that Kalydeco improved their $ppFEV_1$ by 5% and the respiratory domain of the CFQ-R by 12.6 points those aged 18 years and older. However, in the subgroup ages 6 to 11 years, Kalydeco was not more effective than placebo. Children on Kalydeco decreased their $ppFEV_1$ by 6.3% compared to placebo and had worse scores on the respiratory domain of the CFQ-R. This is a subgroup analysis from a small study, so it may be a chance finding. In both age groups of patients with the *R117H* mutation, there were no significant differences in pulmonary exacerbation rates or BMI.

Table 4.1. Summary of Kalydeco (150 mg 2x/day) on Clinical Efficacy Outcomes for *G551D*-, non-*G551D* Gating Mutations, and *R117H*-*CFTR* Mutations

Trial, Study Design & Follow-Up duration	Age (N)	Absolute Diff. in $ppFEV_1$, % (95%CI)	Pulmonary Exacerbation	Diff. in Weight, kg (95%CI)	Diff. in CFQ-R Respiratory Domain, points (95%CI)	Other, RR (95%CI)
***G551D* Mutation**						
STRIVE[67] ENVISION[68] Randomized Controlled Trial 48 Weeks	≥6 years (N=213)	**10.4 (8.6, 12.3)***	**HR 0.455 (0.29, 0.73)† NR†**	**2.8 (1.8, 3.8)***	**9.7 (6.5, 13.0)***	
Non-*G551D* Mutation						
KONNECTION[69] Randomized Controlled Trial 8 Weeks	≥6 years (N=39)	**10.7 (7.3, 14.1)**	NR	**BMI (kg/m^2): 0.7 (95%CI: 0.3, 1.0)**	**9.6 (4.5, 14.7)**	
***R117H* Mutation**						
KONDUCT[70] Randomized Controlled Trial 24 weeks	≥6 years (N=69)		HR 0.93 (NR)	BMI (kg/m^2): 0.3 (95%CI: −1.6, 2.1)		
	6-11 years(N=17)‡	**−6.3 (−12.0, −0.7)§**			−6.1 (−15.7, 3.4)§	
	≥18 years(N=50)‡	**5.0 (1.2, 8.8)**			**12.6 (5.0, 20.3)**	
Observational Studies for All Indicated Mutations (Implied)						
US cohort[21] *Nonrandomized Comparative Study*	≥6 years # (N=1256 / 6,200 controls)	**+1.4 vs. -5.3, p<0.001**	**RR 0.64 (95%CI: 0.58, 0.70)**	NR	NR	**Death: 0.41 (0.20, .84)**

3 years						
UK cohort[21] ***Nonrandomized Comparative Study*** **2 years**	≥6 years # (N=411 / 2,069 controls)	**+6.6 vs. -1.5, p<0.001**	**RR 0.61 (95%CI: 0.53, 0.70)**	NR	NR	Death: 0.52 (0.16, 1.7)
US cohort[66] ***Nonrandomized Comparative Study*** **5 years**	≥6 years # (N=635 / 1,874 controls)	-0.7 vs. -8.3, p NR	**0.58 (0.51-0.67) in year 5**	BMI +2.4 kg/m2 vs. +1.6 kg/m2, p NR		
UK cohort[66] ***Nonrandomized Comparative Study*** **4 years**	≥6 years # (N=247 / 1,230 controls)	+4.9 vs. -4.3, p NR	**0.57 (0.47-0.67) in year 4**	BMI +1.9 kg/m2 vs. +0.9 kg/m2, p NR		
GOAL study **5-year extension study** **5.5 years**	≥6 years (N=96)	0.8 (-2.0 to +3.6) at 5.5 years compared with baseline		**BMI 2.5 kg/m2 (2.0 to 3.1) at 5.5 years**.	**6.7 (2.5 to 10.9) at 5.5 years**	

Results in bold font are statistically significant.
95%CI: 95% Confidence Interval, BMI: body mass index, CFQ-R: Cystic Fibrosis Questionnaire-Revised, Diff: difference between Kalydeco and placebo, HR: hazard ratio, NR: not reported, $ppFEV_1$: predicted percent forced expiratory volume in one second, RR: risk ratio, Txp: transplantation

* Pooled (meta-analyzed). † Pulmonary exacerbations reported only in STRIVE study.
‡ Inconsistent results for different age groups. Only two participants were between 12 and 17 years and were excluded from subgroup analyses.
§ Favoring placebo. # Implied

New Randomized Trial Data for Kalydeco

One small randomized cross-over trial of Kalydeco in twenty adults with the *G551D* mutation suggested that cognitive function, as assessed by the Montreal Cognitive Assessment tool, improved slightly with 4 weeks on treatment.[60]

The second report described the impact of Kalydeco withdrawal in the same 20 patient crossover trial. Both $ppFEV_1$ and sweat chloride levels rapidly rebounded to near baseline levels.[58]

Finally, an open-label extension trial in 33 children between the ages of 2 and 5 years found that the improvements in sweat chloride and growth parameters observed in the 24 week randomized trial were maintained through an additional 84 weeks.[59] One child discontinued Kalydeco because of persistently elevated liver enzymes. No new AEs were identified.

New Observational Data for Kalydeco

There were eight observational studies on long term use of Kalydeco.[21,55,61-66] The two largest and longest are from the same populations (US and UK Registries), but report complementary outcomes.[21,66] These ongoing post-approval safety studies evaluate clinical outcomes and disease progressions in all those in the UK and US registries following commercial availability. Analyses compared Kalydeco-treated patients with untreated controls. Based on commercial availability in both countries, 5 year follow-up data are available for 685 Kalydeco users (and 1874 comparators) in the US and 4 year follow-up data are available for 247 UK participants on Kalydeco (and 1,230 comparators). An additional US study used claims data to evaluate the impact of Kalydeco on inpatient admissions.[62] Two additional studies (one in Ireland and one in France) published in abstract form provided limited additional follow up information about long term use of Kalydeco and clinical outcomes and measures of pulmonary function.[63,64]

Pulmonary Function and Exacerbations

Several studies measured $ppFEV_1$, which was also reported in clinical trials. In all of the studies, $ppFEV_1$ was higher in Kalydeco-treated patients. In the US and UK registry studies, which included the most patients, the increase ranged from 1.4 to 6.6% compared with a decrease of 1.5 to 5.3% in the control groups.[21,66] Similar trends were seen in the smaller Kalydeco studies.

Two- to 5-year outcomes were reported for the US and UK registries. For the US cohort at 2 year follow up, the rate of pulmonary exacerbations was lower in Kalydeco-treated patients than in matched untreated comparator patients (RR 0.64, 95% CI 0.58 to 0.70). At 5 years of follow up, the rate of pulmonary exacerbations per year during the fifth year was lower in the Kalydeco-treated group (0.5 per person per year vs. 0.9 per person per year; RR 0.58, 95% CI 0.51 to 0.67). In the UK cohort, which was followed for 4 years, the rate of hospitalization for pulmonary exacerbations was significantly lower in the Kalydeco-treated group; in addition, the rate of acute pulmonary

exacerbations per patient per year was decreased in the Kalydeco-treated group (0.7 vs. 1.4 per patient per year; RR 0.57, 95% CI 0.47 to 0.67). These outcomes were not reported in the other Kalydeco observational studies. Although it is difficult to directly compare the rates in the trials with those of the observational studies, the relative risks reported in the observational studies (range of 0.57-0.64) are comparable to those seen in the trials (0.4-0.7), suggesting that the benefits are maintained over time.

CF-Related Diabetes

In both the US and the UK cohorts, the rates of CF were lower in the Kalydeco-treated group than in the untreated comparators.[66] The relative risk of CFRD was between 13 and 35% lower in both cohorts at various time points between 2 and 5 years. In the US cohort, at 5 years of follow-up, the rate was 35.7% in the Kalydeco group, compared with 40.9% in the untreated group (RR 0.87, 95% CI 0.77 to 0.98). In the UK cohort at 4 years of follow up, the pattern was similar. The rate in the Kalydeco group was 18.6% compared with the rate in the untreated group of 29.1% (RR 0.64, 95% CI 0.49 to 0.84). This outcome was not reported in the other studies.

Body Mass Index

The impact of Kalydeco on BMI was measured by percent increase in BMI. BMI percent increase was higher in Kalydeco treated individuals in all studies where it was measured.[55,64,66] BMI percentage increase ranged from 1.9-3.6% in Kalydeco-treated individuals compared with 0.9-1.6% in comparator patients. The main outcome used in the trials was not percentage increase in BMI but rather absolute increase in BMI which was on average about 0.7 kg/m^2. Although the exact outcomes cannot be compared, the increase in BMI does appear to persist over longer term follow up.

Sweat Chloride Concentration

One US prospective study evaluated changes in sweat chloride concentration among individuals on CFTR modulators for at least 3 months. They report a reduction in sweat chloride concentration comparable to that seen in the clinical trials.[74]

Quality of Life

Only two studies reported on quality of life related to Kalydeco. Bell and colleagues conducted a cross-sectional study comparing users of Kalydeco with those receiving standard of care and awaiting Orkambi availability. Kalydeco users had improved scores on several aspects of the CFQ-R questionnaire, although this does not provide any long term evidence of the impact of quality of life outcomes.[61] McCormick and colleagues evaluated the impact of Kalydeco on chronic rhinosinusitis symptoms in patients with CF at 1, 2, and 6 month intervals. They found improvement in the several dimensions measured on the SNOT (Sino-Nasal Outcome Test) questionnaire.[65] These

included rhinologic, psychologic, and sleep related outcomes. How these compare over the long term with the QOL outcomes measured in the clinical trials is unclear.

Methodologic Concerns

Confounding by indication leading to selection bias was a significant concern in these observational studies. Patients receiving Kalydeco had gating mutations (predominantly Class II orIII3) while those in the control groups had other mutations. As noted in the background section, patients with one class of mutations often have different clinical manifestations than those with other mutation classes. For example, the prevalence and incidence of CFRD varies by mutation class (see Table 4.2 below).[75]

Table 4.2. CFRD Rates by Mutation Class

Mutation Class	No CFRD recorded	Prevalence	Incidence	Total
I	115 (50.9%)	111 (49.1%)	9 (7.3%)	226
II	4,365 (54.9%)	3,585 (45.1%)	357 (7.6%)	7,950
III	386 (63.3%)	224 (36.7%)	21 (5.2%)	610
IV	549 (86.9%)	83 (13.1%)	10 (1.8%)	632
V	644 (87.0%)	96 (13.0%)	12 (1.8%)	740
Other	1,456 (67.6%)	698 (32.4%)	80 (5.2%)	2,154
Total	7,515 (61.0%)	4,797 (39.0%)	489 (6.1%)	12,312

CFRD: Cystic Fibrosis related Diabetes

Using the observational data comparing patients on Kalydeco to those not on Kalydeco, Bessonova reported a 23% reduction in CFRD in the US Cohort (RR 0.77, 95% CI 0.70 to 0.84).[21] However, patients in the untreated group predominantly (87.6%) had Class I or II mutations, which have a high incidence and prevalence of CFRD. Patients in the Kalydeco group predominantly (81.2%) had Class III mutations, which have a lower incidence and prevalence of CFRD. Thus, part of the difference in the incidence of CFRD is due to the differences in the distribution of mutation classes. Using data from Table 4.2 above, we estimate that the difference in CFRD expected due to the class distribution differences is 15% (RR 0.85),[21] which means that the estimated effect of Kalydeco would be a RR of 0.91 or a reduction of 9% rather than 23%. Similar concerns may explain some of the other results reported in the observational studies. For example mortality is markedly different by mutation class: 21.2 per 1,000 person-years for patients with Class II mutations compared to 7.8 per 1000 person-years for patients with Class IV mutations.[76] Pancreatic insufficiency, *P. aeruginosa* colonization, $ppFEV_1$, and sweat chloride levels also vary by mutation class.[76]

Population 2. Orkambi, Symdeko, and Trikafta for Patients Homozygous for the *F508del* Mutation

Key Findings: Orkambi and Symdeko both provided small but statistically-significant improvements in absolute $ppFEV_1$ compared to placebo after 24 weeks of treatment; however, the magnitude of

effect varied by age, dose, and baseline lung function. Over 96 weeks, patients on Orkambi had slower decline in ppFEV$_1$ than matched controls. Neither Orkambi nor Symdeko provided statistically-significant short-term improvement in BMI or BMI-for-age z-score compared with placebo. Patients randomized to both Orkambi and Symdeko had improved quality of life on the respiratory domain of the CFQ-R compared with placebo. Orkambi and Symdeko reduced acute pulmonary exacerbations over 24 weeks, including those requiring intravenous antibiotics and hospitalizations, compared with placebo. Indirect comparisons yielded no meaningful differences between Orkambi and Symdeko. In a four-week head to head trial with Symdeko, Trikafta had large improvements in ppFEV$_1$ and quality of life on the respiratory domain of the CFQ-R compared with Symdeko. The differences between Trikafta and Symdeko were larger than those for either Orkambi or Symdeko compared with placebo.

We identified two randomized trials of Trikafta versus Symdeko in this population.[8,57] Our updated search did not identify any additional RCTs for Orkambi or Symdeko in this population, but there were four updates of the RCTs for Orkambi[77-80] and two updates of RCTs of Symdeko.[81,82] In addition, the search identified four observational studies of Orkambi.[74,83-85] See Appendix Tables D1 to D15, Appendix F, and our prior report[18] for detailed analyses of the clinical trials of Orkambi and Symdeko in patients homozygous for the *F508del* mutation considered in the 2018 review.

The key studies from the prior review included four randomized controlled trials, one single-arm trial and one long-term, open-label extension study (see Table 4.3).[30,86-89] Two randomized trials of Orkambi (TRAFFIC and TRANSPORT) were analyzed together, with a subsequent open-label extension study.[30,88] Study findings are described by therapeutic comparison below and summarized in Table 4.3 below. This section of the report summarizes the randomized trial data for each treatment comparison, including the randomized trial covered in the prior report and the additional results published since the prior report. We then present the results of our network meta-analyses of the randomized trials. Finally, we summarize the new observational data for Orkambi in this population.

Table 4.3. Summary of Orkambi, Symdeko and Trikafta in Patients Homozygous for the *F508del CFTR* Mutation

Trial, Study Design & Follow-Up duration	Age (N)	Absolute Difference in $ppFEV_1$, Percentage Points (95%CI)	Pulmonary Exacerbation, Rate Ratio (95%CI)	Difference in BMI, kg/m^2 (95%CI)	Difference in CFQ-R Respiratory Domain, points (95%CI)
Orkambi* vs. Placebo					
Ratjen 2017[86] **Randomized Controlled Trial** **24 weeks**	6-11 years (N=204)	**2.4 (0.4, 4.4)**	NR	−0.1 (−0.1, 0.3) *BMI z-score: 0.0 (−0.2, 0.2)*	2.5 (−0.4, 5.4)
TRAFFIC and TRANSPORT[30] **Randomized Controlled Trial** **24 Weeks**	≥12 years (N=1,108)	**2.8 (1.8, 3.8)**	**0.61 (0.49, 0.76)**	**0.24 (0.11, 0.37)** *BMI z-score: NR*	**2.2 (0.0, 4.5)**
TRAFFIC and TRANSPORT[90] **(Extension Study vs. Matched Controls)** **96 weeks**	≥12 years (N=2,043)†	**42% slower rate of decline†**			
Orkambi Real World Registry Data					
French CF Registry[83] **Real world uncontrolled observational study** 52 weeks	≥12 years (n=845) 154 (18.2%) discontinued treatment during the 1st year	**+2.7 increase from baseline**	**IV antibiotic courses 1.18 year prior vs. 0.77, p<0.001, 35% reduction**	0.5 increase from baseline	NR

	641 (75.6%) received continuous treatment.				
Irish CF Registry[84] **Real world uncontrolled observational study** **52 weeks**	≥12 years (n=308) 66%≥18 years	**Adults 1.1 (0.4-1.8)** Adolescents 1.3 (-0.2 to 2.7) increase from baseline.	**Percent reduction in days of IV antibiotics compared with the prior year** **Adults 51% (48-53)** **Adolescents 43% (39-46)**	**Adults 0.43 (0.30-0.56)** **Adolescents BMI z-score 1.6 (0.8-2.3) increase from baseline**	NR
Australian CF Registry[85] **Real world controlled observational study** **52 weeks**	≥12 years with ppFEV$_1$ <40% N=72 Orkambi, 43% discontinued N=30 age and sex matched controls with other mutations	No differences at any timepoint	**0.485 (0.32-0.74)**	NR	NR
Symdeko (100/500 mg) vs. Placebo					
EVOLVE[87] **Randomized Controlled Trial** **24 weeks**	Mean 26 years (N=504)	**4.0 (3.1, 4.8)**	**0.65 (0.48 to 0.88) all** **0.53 (0.34, 0.82) leading to hospitalization or IV antibiotics**	0.06 (−0.08, 0.20) *BMI z-score: 0.04 (−0.15, 0.07)*	**5.1 (3.2, 7.0)**
Network Meta-Analysis (Symdeko vs. Orkambi)					
EVOLVE[87] vs. Tr/Tr[30]		1.2 (−0.1, 2.5)	0.87 (0.53, 1.42)		2.9 (0.0, 5.8)
EVOLVE[87] vs. Ratjen 2017[86] **Indirect comparison**				*BMI z-score: −0.04 (−0.29, 0.21)*	

Trikafta vs. Symdeko					
Heijerman 2019[8] **Randomized Controlled Trial** **4 weeks**	≥12 years (N=107)	**10.0 (7.4, 12.6)**	NR	**0.60 (0.41, 0.79)** *BMI z-score: NR*	**17.4 (11.8, 23.0)**
Keating 2018[57] – homozygous population **RCT** **29 days**	≥12 years (n=28)	**11.0 vs.** 0.4	**NR** **Percent of participants:** **24% vs. 14%**	**NR**	**20.7 vs.** 5.2

Results in bold font are statistically significant.

95%CI: 95% Confidence Interval, BMI: body mass index, CFQ-R: Cystic Fibrosis Questionnaire-Revised, Diff: difference between Kalydeco and placebo, NR: not reported, $ppFEV_1$: predicted percent forced expiratory volume in one second, Tr/Tr: TRAFFIC/TRANSPORT, vs: versus.

* Data are presented for the now-approved dosages of lumacaftor (400 mg/day for children 6-11 years old and 800 mg/day for older patients).

† Open label extension study of TRAFFIC/TRANSPORT (n=455) compared with 1588 matched controls.

Orkambi Versus Best Supportive Care

Patients randomized to Orkambi had modest improvements in lung function over 6 months compared to placebo. Both adults and adolescents 12 and older and children 6 to 11 years had net increases in $ppFEV_1$ of 2.8 (95% CI 1.8 to 3.8) and 2.4 (95% CI 0.4 to 4.4) percentage points compared to placebo.[30,86] Similarly, patients in the Orkambi group had modest improvements in the respiratory domain of the CFQ-R (2.2 points; 95% CI 0.0 to 4.5). A similar, non-significant effect was found in children (2.5 points; 95% CI -0.4 to 5.4).[86]

The TRAFFIC/TRANSPORT study reported a significant reduction in acute pulmonary exacerbations among those randomized to Orkambi (rate ratio 0.61, 95% CI 0.49 to 0.76).[30] The 96-week extension of TRAFFIC/TRANSPORT demonstrated that the reduced rate of acute pulmonary exacerbations was maintained (0.65 events/year, 95% CI 0.56 to 0.75).[90]

An additional report from the pooled TRAFFIC/TRANSPORT extension study reported that there was a reduction in the acute pulmonary exacerbation rate for patients treated with Orkambi even if they did not have an initial increase in $ppFEV_1$.[79] Specifically, the rate ratio was 0.53 (95% CI 0.40 to 0.69) for those with an change in $ppFEV_1>0$ and 0.74 (95% CI 0.55 to 0.99) in those with a change in $ppFEV_1\leq0$. This post-hoc analysis suggests that change in $ppFEV_1$ may not fully capture even the respiratory benefits of Orkambi.

The two new clinical trial results examined the long-term safety and efficacy of Orkambi in younger patients. The first reported 96 week outcomes for 239 patients 6 to 11 years of age.[77] Treatment was discontinued due to AEs in 3.8% of patients. No new safety concerns were identified. The initial improvements were sustained for the respiratory domain of the CFQ-R (+7.4 points), BMI (+1.8 kg/m^2), and sweat chloride (-22.9 mmol/L). The second study reported on 60 patients ages 2 to 5 years with Orkambi for 24 weeks.[80] Three patients (5%) discontinued treatment because of elevated liver enzymes. Sweat chloride levels decreased by 31.7 mmol/L and markers of pancreatic function improved. In addition, the BMI for age Z-score increased by 0.29 (0.14 to 0.45) over 24 weeks.

New Observational Studies of Orkambi

There is less long-term observational evidence available for Orkambi than for Kalydeco. The largest study, from French CF centers provides one year of follow up on 845 individuals using Orkambi. There was no comparison group.[83] Three additional reports in abstract form provide follow-up information from a registry in Ireland and from the US and Australia. Duration of follow up ranged from 12-23 months.[74,84,85]

Pulmonary Outcomes

In the French observational study, ppFEV$_1$% increased by 2.7% (±8.9).[83] In the Irish study, published in abstract form, the increase was 1.1%.[84] In the clinical trials of Orkambi, the ppFEV$_1$% increased by 4.6-5.4%. Limited observational follow up evidence suggests that long term use may be associated with a continued small increase in ppFEV$_1$%.

None of the studies reported on the rate of acute pulmonary exacerbations per patient per year. Wark et al reported a reduction in acute pulmonary exacerbations among Orkambi treated individuals (RR 0.49, 95% CI 0.32 to 0.74) although absolute rates were not reported, Burgel and colleagues reported a reduction in IV antibiotic courses on Orkambi compared with before (0.77 per year compared with 1.18 per year), consistent with a 35% reduction.[83,85] In trials, the rate of acute pulmonary exacerbations were 0.7 to 0.8/48 weeks compared with 1.14/48 weeks in the placebo group. The longer term observational evidence although limited, suggests that the decrease in acute pulmonary exacerbations may persist.

Sweat Chloride Concentrations

One US prospective study presented as an abstract, evaluated changes in sweat chloride concentration among individuals on CFTR modulators for at least 3 months. They report a reduction in sweat chloride concentration among those on Orkambi comparable to that seen in the clinical trials.[74]

Symdeko Versus Best Supportive Care

The randomized trial of Symdeko in adolescents and adults reported modest but significant improvements in ppFEV$_1$ compared to placebo after 24 weeks (4.0%, 95% CI 3.1 to 4.8).[87] Symdeko resulted in a clinically and statistically significant improvement in the respiratory domain of CFQ-R (5.1 units; 95% CI 3.2 to 7.0) compared to placebo and significantly lower rate of pulmonary exacerbations (rate ratio 0.65; 95% CI 0.48 to 0.88). However, BMI and BMI z-score were not significantly different between drug and placebo (0.06 BMI units, 95% CI -0.08 to 0.20; -0.04 z score units, 95% CI -0.15 to 0.07]).

An abstract[82] reported the impact of Symdeko on domains of the CFQ-R other than the respiratory domain in the EVOLVE study. There were statistically-significant improvements in the physical functioning, treatment burden, health perceptions, and vitality domains for Symdeko compared with placebo at 24 weeks. The improvement in the social functioning domain was of borderline clinical significance (1.5 points, 95% CI 0.0 to 3.0). The differences in role functioning, eating problems, emotional functioning, weight, digestive symptoms, and body image domains were not significant.

The EXTEND trial followed 613 patients for a mean of 86 weeks primarily for safety.[81] SAEs related to treatment occurred in 2% of patients and 3 patients (0.5%) stopped treatment due AEs. No new safety concerns were identified. The pulmonary exacerbation rate per year was 0.72, which was similar to that observed in the EVOLVE trial (0.64). The respiratory domain of the CFQ-R and the improvement in $ppFEV_1$ remained stable.

Orkambi Versus Symdeko

No study has compared the two CFTR modulators approved for this population. However, by indirect comparison (network meta-analysis) of the two studies of adolescents and adults, we found no statistically significant differences in effects on $ppFEV_1$, pulmonary exacerbations, BMI z-score, or quality of life as assessed using the respiratory domain of the CFQ-R. Detailed results are available in the prior report (see Section 3).

Trikafta Versus Symdeko

As described above in the Key Studies section, we identified one pivotal head-to-head study comparing Trikafta to Symdeko in the population of patients who are homozygous for the *F508del* mutation.[8] Patients ages 12 years and older with a $ppFEV_1$ between 40% and 90% who were homozygous for the *F508del* mutation were eligible for the trial. All patients underwent a 4-week run in period with Symdeko. Then the investigators randomized 107 patients to Trikafta or continued treatment with Symdeko. The primary outcome was the absolute change in $ppFEV_1$ at 4 weeks. The study was of good quality. Approximately half of the participants were female, and the mean age was 29 years. Compared to Symdeko, the $ppFEV_1$ was 10.0 points higher at four weeks (95% CI 7.4 to 12.6, $p<0.001$). There were no differences in prespecified subgroups based on sex, age, baseline $ppFEV_1$, or prior CFTR modulator use. Quality of life as assessed by the respiratory domain of the CFQ-R was 17.4 points higher in the Trikafta group (95% CI 11.8 to 23, $p<0.001$). The trial was only 4 weeks long, but there was already a statistically significant change in BMI (0.60 kg/m2, 95% CI 0.41 to 0.79) in the Trikafta group compared with the Symdeko group. In addition, sweat chloride concentrations were 45.1 mmol/L lower (95 % CI 50.1 to -40.1, $p<0.001$). The rate of acute pulmonary exacerbations was not a primary or secondary outcome in the trial because of the short follow-up period. However, they were reported as AEs without statistical results (Trikafta 2%, Symdeko 12%). No patients in either group discontinued therapy due to AEs (0%). SAEs were higher in the Trikafta group (4% vs. 2%). One serious AE (rash) was thought to be related to Trikafta.

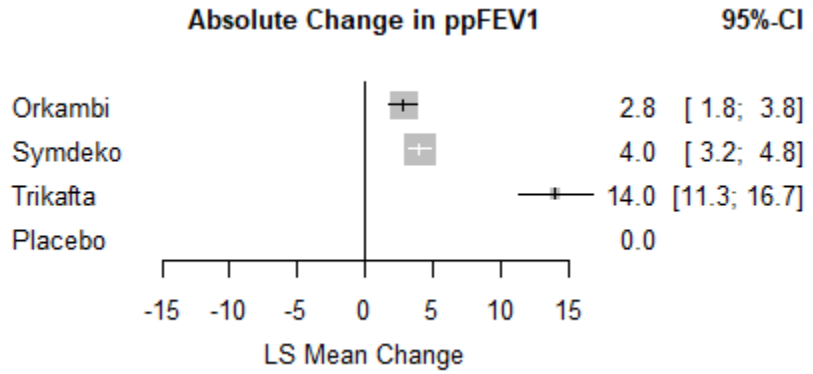
This good-quality trial demonstrated a marked improvement in pulmonary function and respiratory quality of life through 4 weeks of follow-up with Trikafta compared to Symdeko with a good safety profile. The primary limitation of the study is its short follow-up time of only 4 weeks.

In addition, there was a small, Phase II randomized study of similar design that compared 21 patients on Trikafta to 7 patients on Symdeko following a four-week run in period on Symdeko.[57] The study only reported within-group comparisons and no between-group comparisons. One patient in each group discontinued due to AEs. At 29 days, the $ppFEV_1$ increased by 11.0% (95% CI 7.9 to 14.0) in the Trikafta group versus 0.4% (95% CI -5.4 to 6.2 in the Symdeko group. Similarly, the respiratory domain of the CFQ-R improved by 20.7 points (95% CI 12.5 to 29.0) in the Trikafta group and 5.2 points (95% CI -9.5 to 19.9) in the Symdeko group. Finally, the sweat chloride levels decreased by 39.6 mmol/L (95% CI -45.6 to -33.8) in the Trikafta group and increased by 0.8 mmol/L (95% CI -9.3 to 11.0) in the Symdeko group. In the reported AEs there were 5 pulmonary exacerbations in the Trikafta group (24%) and 1 in the Symdeko group (14%). The primary limitations of this study are the small size of the trial, the short follow-up, and the lack of between group comparisons.

Network Meta-Analysis Results in Patients who are Homozygous for the* F508del *mutation

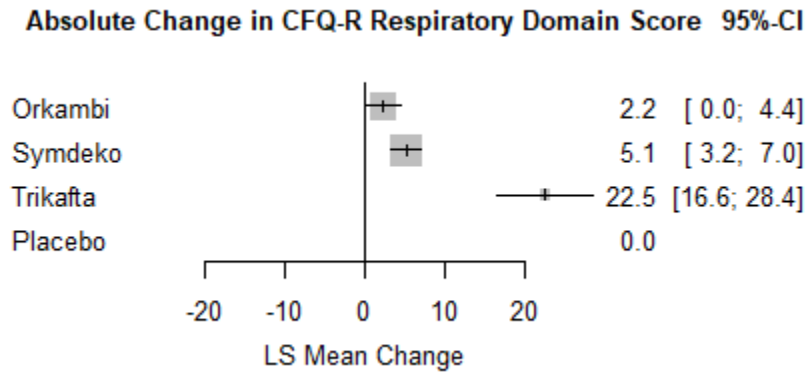
The forest plots for the network meta-analysis results comparing each of the three CF modulator therapies that have been studied in the same population illustrates the marked improvement of Trikafta compared with the other therapies. Additional results are reported in Appendix Tables D16-D18. In Figure 4.1 below, the estimated absolute increase in $ppFEV_1$ compared to placebo for Trikafta, 14.0% is markedly greater than the estimates for Orkambi (2.8%). and Symdeko (4.0%).

Figure 4.1. NMA Results for $ppFEV_1$ Comparing CF Modulator Therapy to Placebo



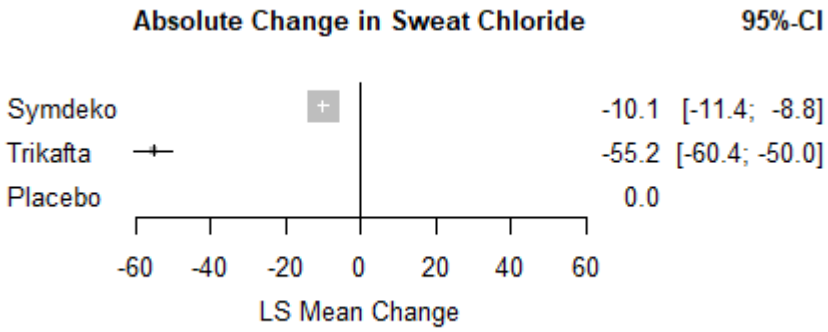
The results are similar for the respiratory domain of the CFQ-R (Figure 4.2). The improvements with Trikafta dwarf those of Orkambi and Symdeko.

Figure 4.2. NMA Results for CFQ-R Respiratory Domain Comparing CF Modulator Therapy to Placebo



Sweat chloride data were only available for Symdeko and Trikafta (Figure 4.3).

Figure 4.3. NMA Results for Sweat Chloride Level Comparing CF Modulator Therapy to Placebo



Population 3. Kalydeco, Symdeko, and Trikafta in Patients Heterozygous for the *F508del* Mutation and a Residual Function Mutation

Key Findings: Based on a single short-term (8 week) cross-over trial (EXPAND), Symdeko and Kalydeco both improved absolute and relative $ppFEV_1$ compared with placebo. Symdeko also improved $ppFEV_1$ more that Kalydeco. Clinically-important and statistically-significant improvements in respiratory symptom-related quality of life were observed for both Symdeko and Kalydeco compared with placebo. At 8 weeks, neither drug increased BMI nor reduced pulmonary exacerbations compared with placebo and each other; however, the follow-up duration was likely too short to adequately evaluate these outcomes. Although there is currently no published clinical trial evidence for Trikafta in this population, it should be at least as effective as Symdeko because Trikafta adds an additional modulator to Symdeko and when Trikafta was compared to Symdeko in patients homozygous for the F508del *mutation, it significantly improved outcomes like $ppFEV_1$ and CFQ-R without causing any new AEs.*

Since our prior review, there is one new case series in children between the ages of 6 and 11 years in this population and one abstract reporting additional quality of life data from EXPAND that was not reported in the original publication.[91,92] See Appendix Tables D1-15, Appendix F, and our prior report[18] for detailed analyses of the clinical trials of Orkambi and Symdeko in patients heterozygous for the *F508del* mutation and a residual function mutation. A single trial, EXPAND, evaluated both Symdeko (100/300 mg daily) and Kalydeco (300 mg daily) monotherapy compared to placebo in patients heterozygous for the *F508del* mutation with a second mutation amenable to Symdeko. EXPAND was a crossover trial in which participants took one of the drugs for 8 weeks (n=234). Participants were 12 years or older with $ppFEV_1$ between 40% and 90%, and stable lung disease.[93]

Kalydeco and Symdeko

The primary results are summarized in Table 4.4 below. Compared to placebo, both Kalydeco (4.7%, 95% CI 3.7 to 5.8) and Symdeko (6.8%, 95% CI 5.7 to 7.8) improved $ppFEV_1$. Symdeko improved $ppFEV_1$ more than Kalydeco (absolute difference 2.1%; 95% CI 1.2 to 2.9). Studies demonstrated that both Kalydeco and Symdeko had significant improvements in quality of life on the respiratory domain CFQ-R score compared with placebo (Kalydeco 9.7 points, 95% CI, 7.2 to 12.2; Symdeko 11.1 points, 95% CI 8.7 to 13.6). There were no significant quality of life differences seen between the two drugs. The rate of acute pulmonary exacerbations for patients randomized to Kalydeco and Symdeko was about half that of the placebo group, but the differences were not statistically significant.

In addition to the primary results summarized in Table 4.4, EXPAND reported subgroup analyses for ppFEV1 Symdeko by age group.[18] Patients less than 18 years old had a 12.0% increase in $ppFEV_1$ (95% CI 9.3 to 14.8) and those 18 years and older had a 6.0% increase (95% CI 4.9 to 7.0). However, these results should be interpreted with caution given only 11 patients under the age of 18 received Symdeko.

The new case series[92] included 9 children ages 6 to 11 years who were heterozygous for the *F508del* mutation and a residual function mutation. The remaining 61 participants were homozygous for the *F508del* mutation. The results are not reported separately by mutation status. The participants were followed for 24 weeks and their $ppFEV_1$ remained stable and in the normal range (from 91.1% to 92.0%) . Compared to baseline, there was a decrease in sweat chloride levels (-14.5 mmol/L, 95% CI -17.4 to -11.6) and a small improvement in the respiratory domain of the CFD-R (3.4 points, 95% CI 1.4 to 5.5).

The new abstract[91] reported that patients on Symdeko had significant improvements in the following domains of the CFQ-R: health perceptions, vitality, physical functioning, role functioning, social functioning, weight, treatment burden and emotional functioning compared with placebo.

Trikafta for Patients Heterozygous for the F508del CFTR *Mutation and a Residual Function Mutation*

There are no published studies evaluating the efficacy and safety of Trikafta in this population. However, Trikafta is Symdeko plus another modulator, elexacaftor, and it primarily targets the abnormal protein formed by the *F508del* mutation. Unless elexacaftor interferes with the mechanism of action of ivacaftor and/or tezacaftor or introduces new, significant AEs, Trikafta should be at least as effective as Symdeko. In fact, we have evidence that Trikafta is more effective than Symdeko in a randomized trial of patients homozygous for the *F508del* mutation (Population 2, results described above).[8] In that population, the effect size on ppFEV$_1$ and the respiratory domain of the CFQ-R for Trikafta compared with Symdeko was much larger than that of Symdeko versus placebo in the same population. Furthermore, there was no evidence that the addition of elexacaftor introduced new AEs. Thus, despite the lack of clinical trial evidence in this population, we expect Trikafta to be at least as effective as Symdeko for patients heterozygous for the *F508del* mutation and a residual function mutation.

Since the release of the draft report, Vertex announced the results of the 445-104 study.[94] In a subgroup of participants in the study, patients ages 12 years and older who were homozygous for the *F508del* mutation and a residual function mutation received Symdeko for a 4 week run in period, and then were randomized to continue on Symdeko or Trikafta. The outcomes for this subgroup were not reported in the press release.

Table 4.4. Summary of Symdeko and Kalydeco for Patients Heterozygous for the *F508del CFTR* Mutation and a Residual Function Mutation

Trial Study Design Follow-Up	Age (N)	Absolute Diff. in $ppFEV_1$, (95%CI)	Pulmonary Exacerbation, Rate Ratio	Difference in BMI, kg/m^2	Difference in CFQ-R Respiratory Domain, points (95%CI)
EXPAND[93] 8 weeks (cross-over)	≥12 years (N=234)	**Symdeko (100/300 mg) vs. Placebo**			
		6.8 (5.7, 7.8)	0.54 (0.26, 1.13)	0.34 vs. 0.18 (NR*)	**11.1 (8.7, 13.6)**
		Kalydeco (300 mg) vs. Placebo			
		4.7 (3.7, 5.8)	0.46 (0.21, 1.01)	0.47 vs. 0.18 (NR*)	**9.7 (7.2, 12.2)**
		Symdeko (100/300 mg) vs. Kalydeco (300 mg)			
		2.1 (1.2, 2.9)	1.18 (0.49, 2.87)	0.34 vs. 0.47 (NR*)	1.4 (−1.0, 3.9)

Results in bold font are statistically significant.

95%CI: 95% Confidence Interval, BMI: body mass index, CFQ-R: Cystic Fibrosis Questionnaire-Revised, Diff: difference between Kalydeco and placebo, NR: not reported, $ppFEV_1$: predicted percent forced expiratory volume in one second, vs: versus.

* Insufficient data to allow calculation of confidence interval; implied nonsignificant.

Population 4. Trikafta in Patients Heterozygous for the *F508del* Mutation and a Minimal Function Mutation

Key Findings: Based on a single 24-week randomized trial, Trikafta both improved absolute and relative ppFEV$_1$ compared with placebo. Clinically-important and statistically-significant improvements in respiratory symptom-related quality of life were observed for Trikafta compared with placebo. At 24 weeks, acute pulmonary exacerbations were significantly reduced, and BMI was significantly increased compared with placebo.

There are two randomized clinical trials of Trikafta in this population[56,57] and no observational studies. See Appendix Tables D1- D12 for details of the randomized trials. The key findings are summarized in Table 4.5 below and described below. We reported the results for the FDA approved dose of Trikafta only in the dose-ranging Phase II study.[57]

In the pivotal trial, patients ages 12 years and older with a ppFEV$_1$ between 40% and 90% who have the *F508del* mutation and a minimal function mutation were eligible for the trial.[56] The investigators randomized 403 patients to Trikafta or identical placebo pills. The primary outcome was the absolute change in ppFEV$_1$ at 24 weeks. The study was of good quality. Approximately half of the participants were female, and the mean age was 26 years. Compared to placebo, the ppFEV$_1$ was 13.8 points higher at four weeks and 14.3 points higher at 24 weeks ($p<0.001$ for both comparisons). There were no differences in prespecified subgroups based on sex, age, baseline ppFEV$_1$, or region. The rate of pulmonary exacerbations was 63% lower in the Trikafta group (RR 0.37, 95% CI 0.25 to 0.63). Quality of life as assessed by the respiratory domain of the CFQ-R was 20.2 points higher in the Trikafta group ($p<0.001$) and sweat chloride concentrations were 41.8 mmol/L lower ($p<0.001$).

This good-quality trial demonstrated a marked improvement in pulmonary function and respiratory quality of life through 24 weeks of follow-up with Trikafta compared to placebo, with a good safety profile.[56] The primary limitation of the study is its relatively short follow-up time.

The Phase II, dose ranging, randomized study compared three different doses of elexacaftor added to Symdeko to placebo in 65 patients.[57] We report here only the results from the group who received the FDA-approved dose (200 mg elexacaftor, n=21) and the placebo group (n=12). The study only reported within-group comparisons and no between-group comparisons. There were no SAEs and no discontinuations due to AEs for patients in the Trikafta group during the 29 day trial. There was a significant increase in ppFEV$_1$ compared to baseline for the Trikafta group (13.8%, 95% CI 10.9 to 16.6), but not in the placebo group (0.0%, 95% CI -3.9 to 4.0). Similarly, there was a significant increase in the respiratory domain of the CFQ-R compared to baseline for the Trikafta group (25.7 points 95% CI 18.3 to 33.1), but not in the placebo group (4.2 points, 95% CI -5.6 to 14.0). Finally, there was a significant decrease in sweat chloride levels compared to baseline for the Trikafta group (-39.1 mmol/L, 95% CI -44.9 to -33.3), but not in the placebo group (0.0%, 95% CI -3.9

to 4.0). In the reported AEs there were 2 acute pulmonary exacerbations in the Trikafta group (10%) and 4 in the placebo group (33%). The primary limitations of this study are the small size of the trial, the short follow-up, and the lack of between group comparisons.

Table 4.5. Summary of Trikafta for Patients Heterozygous for the *F508del CFTR* Mutation and a Minimal Function Mutation

Trial Study Design Follow-Up	Age (N)	Absolute Diff. in $ppFEV_1$, % (95%CI)	Pulmonary Exacerbation, Rate Ratio (95%CI)	Diff. in BMI, kg/m^2	Diff. in CFQ-R Respiratory Domain, points (95%CI)
Trikafta vs. Placebo					
Middleton 2019[56] **Randomized Controlled Trial** **24 weeks**	≥12 years (N=403)	**14.3 (12.7 to 15.8)**	**0.37 (0.25 to 0.55)**	**1.04 (0.85 to 1.23)**	**20.2 (17.5 to 23.0)**
Keating 2018[57] **RCT** **29 days**	≥12 years (n=33)	**13.8 vs. 0.0**	**NR** **10% vs. 33%**	**NR**	**25.7 vs. 4.2**

Results in bold font are statistically significant.
95%CI: 95% Confidence Interval, BMI: body mass index, CFQ-R: Cystic Fibrosis Questionnaire-Revised, Diff: difference between Kalydeco and placebo, kg: kilogram, m^2: square meter, NR: not reported, $ppFEV_1$: predicted percent forced expiratory volume in one second
* Insufficient data to allow calculation of confidence interval; implied nonsignificant.

Harms

For all three CFTR modulators approved prior to Trikafta, harms were mild and generally uncommon. A detailed description of the AEs can be found in our prior report.[18] They are summarized here along with the results for Trikafta.

SAEs, as defined by the studies, commonly occurred at the same or *lower* rates among those taking the CFTR modulators, including Trikafta, than those taking placebo, including AEs ascribed to the drugs. No deaths during CFTR modulator trials were related to the drugs. The primary reasons that patients discontinued CFTR modulator therapy were elevated liver enzymes, elevated creatinine kinase levels, hemoptysis, bronchospasm, dyspnea, pulmonary exacerbation, and rash. Rash was the only SAE thought to be due to Trikafta (n=1) and that patient did not discontinue therapy.

From meta-analyses in the prior report, the summary rates of discontinuation due AEs in the randomized trials were:

- Kalydeco 1.2% (95% CI 0.3 to 2.5)
- Orkambi 6.3% (95% CI 3.7 to 9.6)
- Symdeko 2.5% (95% CI 0.1 to 8.3)
- Placebo 2.1% (95% CI 1.1 to 3.4)

In the two pivotal trials of Trikafta[8,56] the discontinuation rates due to AEs were 1.0% (2/202 over 24 weeks) and 0% (0/55 over four weeks).

Chest tightness ("abnormal respiration") has noted by some patients and clinicians as linked to Orkambi, however, it was not commonly reported in the clinical trials. The symptom appears to be more common in patients with lower baseline ppFEV$_1$.[95] A real-world cohort study reported that nearly 20% of patients reported chest tightness with Orkambi.[96]

Uncertainty and Controversies

Cystic fibrosis is a chronic disease that impacts patients every day of their lives. The two pivotal clinical trials of Trikafta lasted 4 and 24 weeks respectively, which is not nearly long enough to provide stable estimates for the long-term impact of Trikafta. In addition, there are likely differences in the long-term benefits of Trikafta based on the age of initiation of therapy and the severity of CF symptoms at the time of initiation. Finally, in some populations, such as patients heterozygous for the F508 del mutation and a residual function mutation, there are no data on the effects of Trikafta.

The complexity of CF genetics, which directly affects disease severity and progression, is another important source of uncertainty when generalizing the results of the pivotal trials. Each population

that we reviewed has genetic and disease variability within members of the population, which means that clinical trial outcomes from relatively small samples over short periods of time may not accurately capture the clinical benefits and harms for patients.

$ppFEV_1$ is a surrogate measure of CF disease severity. Despite its wide use as the primary outcome in clinical trials and clinical practice, both the absolute $ppFEV_1$ level and changes in $ppFEV_1$ cannot fully capture disease severity or the clinical impact of modulator therapy on the many organ systems affected by CF and the life experiences of patients. Furthermore, the impact of an absolute increase of 5% in a patient with a baseline $ppFEV_1$ of 40% likely differs from that of a 5% increase in a patient with a baseline of 90%.

Stakeholders highlighted uncertainties around CFTR modulator treatment decisions based on their personal experiences. One parent, for example, shared that their child experienced beneficial weight gains while on Orkambi but simultaneously experienced lung function deterioration. Not only does this patient's experience provide an example of often difficult decision making needed regarding tradeoffs on the apparent effects of the drugs (here, weight gain vs. lung function), but it also highlights that individual patients will respond to CFTR modulator treatment in unique ways.

Nearly 85% of people with CF in the US receive care at an accredited CF center, which provide multidisciplinary clinical care. This high-quality, specialized approach to care has improved survival for people with CF. Many of the CF trials discussed in this report were conducted in such accredited CF centers, and these trials demonstrated improvements in health outcomes among those receiving best supportive care (BSC) are likely with the addition of appropriate CFTR modulators. BSC is burdensome for patients and many hope to decrease the intensity of BSC after starting disease modulating therapy, even though patients in the clinical trials were encouraged to continue their supportive care. There are no data to guide patients on which supportive therapies are essential to continue and which may be reduced or stopped, although at least one trial is underway to answer this question. The answer may vary by age, mutation status, underlying severity of disease, and response to therapy.

Finally, CF is a multisystem disease, yet many aspects of the disease have not been systematically evaluated in the randomized trials of modulator therapies. Thus, our rating of the impact of CFTR modulators is highly dependent on the outcomes reported in the clinical trials.

4.4 Summary and Comment

Population 1: Patients Eligible Only for Kalydeco

Given the consistent evidence in randomized trials and observational studies up to 5 years of improved lung function and clinically significant improvements in pulmonary exacerbations and quality of life, with no evidence of significant harms, we have high certainty Kalydeco provides a

substantial (moderate-large) net health benefit relative to best supportive care. We therefore assign a rating of "superior" (A) to the comparative clinical effectiveness of Kalydeco in this population (Table 4.6 below).

Population 2: Homozygous for the *F508del* Mutation

Orkambi

In two large Phase III trials, an accompanying 96-week open-label extension study, and additional real-world observational studies Orkambi provided a consistent 3% improvement in ppFEV$_1$ as well as a reduced rate of decline in lung function over time. However, patients also reported drug-drug interactions and side effects leading to discontinuation. Thus, for patients homozygous for the *F508del* mutation, we have high certainty Orkambi provides a small net health benefit relative to placebo (i.e. best supportive care), and therefore assess the evidence to be "incremental" (B).

Symdeko

A single, parallel-arm, Phase III trial demonstrated a moderate improvement in ppFEV$_1$ compared with placebo. However, the trial was relatively short in duration (24 weeks). For patients homozygous for the *F508del* mutation, we have moderate certainty that Symdeko provides a small or substantial net health benefit, with high certainty of at least a small net health benefit relative to placebo (i.e., best supportive care). Therefore, we assess the evidence to be "incremental or better" ("B+").

Trikafta

Given that Trikafta is Symdeko plus an additional modulator, the consistent evidence in controlled trials of lung function improvement, with clinically-significant improvements and associated reductions in pulmonary exacerbations, and with no evidence of significant harms, we have high certainty Trikafta provides a substantial (moderate-large) net health benefit relative to best supportive care and to Symdeko. We therefore assign a rating of "superior" (A) to the comparative clinical effectiveness of Trikafta in this population, both versus best supportive care and versus Symdeko (Table 4.6).

Population 3: Heterozygous *F508del* With a Residual Function Mutation

Symdeko

A single 8-week cross-over trial provided demonstrated clinically-significant improvement in lung function compared with placebo. Long-term studies to confirm these data are required. For patients heterozygous for the *F508del* mutation with an approved residual function mutation, we have moderate certainty that Symdeko provides a small or substantial net health benefit, with high

certainty of at least a small net health benefit relative to placebo (i.e., best supportive care). Therefore, we assess the evidence to be "incremental or better" ("B+").

Trikafta

There are no published randomized trial or observational data for Trikafta in this population. However, Trikafta is Symdeko plus an additional CFTR modulator drug, so it should be at least as effective unless there are interactions that decrease the effectiveness of Symdeko. In the population of patients homozygous for the *F508del* mutation, Trikafta was significantly more effective than Symdeko and there was no evidence for additional toxicity with Trikafta. Thus, we judge that Trikafta will be at least as effective as Symdeko versus best supportive care (B+). Using similar logic, we judge that we have moderate certainty that Trikafta has a comparable, small, or substantial net heath benefit compared with Symdeko, with high certainty of at least a comparable net health benefit (C++) (Table 4.6 below).

Population 4: Heterozygous F508del with a Minimal Function Mutation

Trikafta

The single 24-week randomized controlled trial of Trikafta in this population demonstrated clinically significant improvements in lung function improvement and respiratory quality of life, with clinically significant improvements and associated reductions in pulmonary exacerbations, and no evidence of significant harms. Thus, we have high certainty Trikafta provides a substantial (moderate-large) net health benefit relative to best supportive care. We therefore assign a rating of "superior" (A) to the comparative clinical effectiveness of Trikafta in this population (Table 4.6 below).

Table 4.6. ICER Evidence Ratings for CFTR Modulator Therapies for Cystic Fibrosis.

Intervention	ICER Evidence Rating
Population 1: Eligible for Kalydeco	
Kalydeco vs. BSC	A
Population 2: Homozygous *F508del*	
Orkambi vs. BSC	B
Symdeko vs. BSC	B+
Trikafta vs. BSC	A
Trikafta vs. Symdeko	A
Population 3: Heterozygous *F508del* / Residual Function Mutation	
Symdeko vs. BSC	B+
Trikafta vs. BSC	B+
Trikafta vs. Symdeko	C++
Population 4: Heterozygous *F508del* / Minimal Function Mutation	
Trikafta vs. BSC	A

BSC: Best supportive care

5. Long-Term Cost Effectiveness

5.1 Overview

The objective of this analysis was to estimate the lifetime effectiveness and cost-effectiveness of CFTR modulator treatments plus best supportive care for CF patients. We modeled four different populations based on mutation status, and four different CFTR modulators or combinations of modulators that have indications in one or more CF populations. For patients who are candidates for Kalydeco only based on current indications, we compared Kalydeco plus best supportive care to best supportive care alone. For patients who are homozygous for the *F508del* mutation, we compared Orkambi plus best supportive care, Symdeko plus best supportive care, Trikafta plus best supportive care, and best supportive care alone. We report only a subset of results for lifetime treatment with Orkambi for this population (i.e., base-case results and threshold prices). For patients who are heterozygous for the *F508del* mutation with a residual function mutation, we compared Symdeko plus best supportive care, Trikafta plus best supportive care, and best supportive care alone. We did not consider lifetime treatment with ivacaftor monotherapy for this population because Symdeko has been shown to be clinically superior in trials. For patients who are heterozygous for the *F508del* mutation with a minimal function mutation we compared Trikafta plus best supportive care and best supportive care alone.

We updated previously developed *de novo* microsimulation models to capture improvements in both quality of life and length of life associated with CFTR modulator therapies.[18] Computer models are commonly used to project the long-term outcomes for a population. The model structure reflects the possible prognoses that a population of simulated individuals may experience over their lifetimes, based on our knowledge of the disease and how treatments may impact the prognoses. These projections are informed by the available evidence but also rely on clinically reasonable assumptions, the impacts of which were evaluated in scenario analyses. When assumptions were made, we chose those that favored better cost-effectiveness findings for CFTR modulator therapy, and we assessed the potential impact of each assumption by varying the assumption widely in sensitivity analyses. However, we were often faced with limitations in the available data. Although we incorporate heterogeneity across simulated individuals (e.g., assume that some CF patients have a slower lung function decline than others), this model is meant to inform *average* outcomes for a *population*. CF affects many organ systems, although much of its morbidity and mortality are associated with its impact on the respiratory system. While the quality-of-life impacts of the disease will be captured to some degree by the quality-of-life measures used in the model, it is important to note that economic models such as the ones used in this analysis cannot completely capture the full range of quality-of-life effects associated with the disease or the improvements in quality of life experienced by CF patients taking CFTR modulator therapy.

Health and economic outcomes were estimated over a lifetime time horizon from treatment initiation until death. The primary health outcome was quality-adjusted life years (QALYs) but we also report life expectancy in life years (LYs), equal value life years gained (evLYGs), and the lifetime number of acute pulmonary exacerbations. QALYs are a measure that combines both length of life and quality of life into a single measure, and are the recommended metric for use in cost-effectiveness analyses.[97] evLYG is a measure that counts quality of life gains pre-life extension but does not penalize a year of life gained if that year of life is of a lower quality of life than a comparable person without CF (i.e., it evenly measures any gains in length of life, regardless of quality of life).

Three of the treatments for CF, Kalydeco, Orkambi, and Symdeko, fall under ICER's framework for therapies for ultra-rare diseases.[9] Therefore, we considered dual base-case analyses that reflect both health care system and societal perspectives if the impact of the treatment on patient and caregiver productivity, education, disability and nursing home costs were large relative to health care costs. Because we did not find this to be the case, we present the societal perspective as scenario analyses for Kalydeco, Orkambi, and Symdeko. Because we did not find this to be the case, we present the societal perspective as scenario analyses for Kalydeco, Orkambi, and Symdeko. For scenarios where the ultra-rare framework did not apply (i.e., Trikafta, which has an eligible patient population of greater than 10,000 individuals), productivity losses and other indirect effects were considered in a scenario analysis. The impact inventory is provided in Appendix Table E1. Costs and health outcomes were discounted at 3% per year in the base-case analysis; undiscounted results are presented in Appendix Table E2. The models were developed in TreeAge software version 2019 (Williamstown, MA).

We made several updates to the models that were developed for the 2018 report.[18] First the start ages for which CF patients were eligible to initiate CFTR modulators are different for the 2020 analysis. In the current model, patients started on a CFTR modulator when they were first eligible and then switch to a more effective modulator when they become age eligible. We also modified the annual risk of developing diabetes and allowed the risk to vary across populations. Lastly, we modified the disutility for experiencing an acute pulmonary exacerbation to apply for six months and not for one year, as concerns were raised by clinical experts about the one-year assumption.

In addition, we made three changes to our analysis since the draft report. First, we incorporated age-specific utilities that reflect the overall decrease in HRQoL as populations age. This is a recommended component of economic models[97] and we felt it was important as CF patients are living longer with CFTR modulator therapy. Second, we incorporated CF-related costs following lung transplantation. Our prior assumption was that there were no CF-related costs, but we now include disease management costs that pertain to non-pulmonary costs. Lastly, we changed our disease management costs to reflect costs to private payers only. Our prior cost estimates were a blend of costs to private and public payers. The overall impact of these changes were to increase

the incremental cost-effectiveness ratios (i.e., they became less favorable), which was driven by the incorporation of age-specific utilities (i.e., the other two assumptions slightly decreased the incremental ratios).

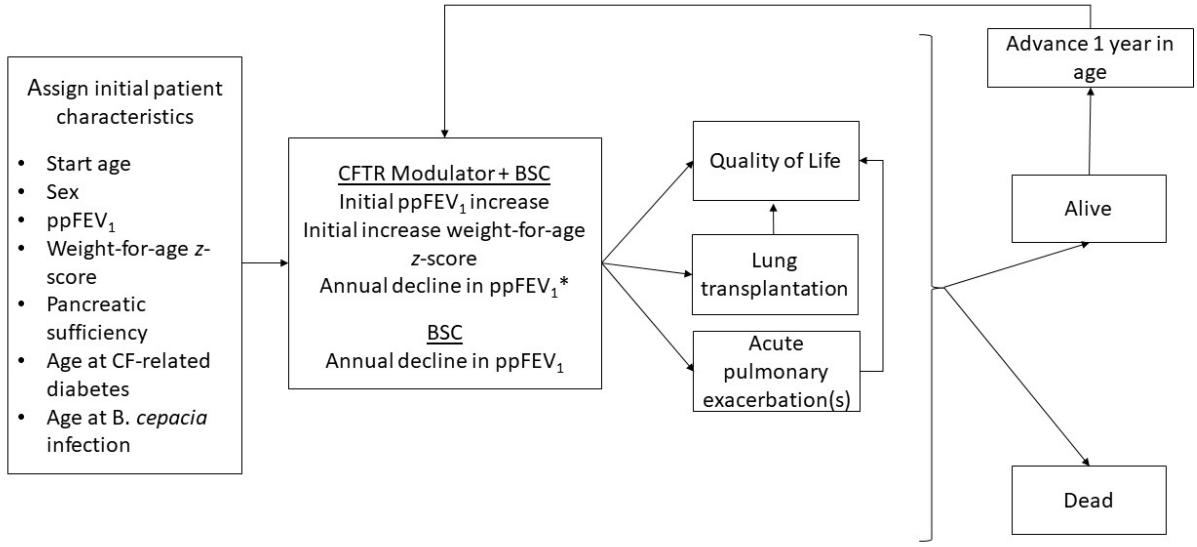
5.2 Methods

Model Structure

The primary model variable was $ppFEV_1$, modeled as a continuous variable. A microsimulation model was chosen to account for the continuous nature of $ppFEV_1$ and to capture the primary effect of the CFTR modulator drugs (i.e., increase in $ppFEV_1$ or slowing the decline of $ppFEV_1$ over the longer term). For each population, a hypothetical cohort of CF patients begins the model at the age of CFTR modulator initiation. We assigned a gender distribution based on the current prevalent CF population.[2] Each simulated patient is assigned a $ppFEV_1$ value drawn from a distribution and then experiences annual age-specific declines in lung function. The means and standard deviations (SD) of the initial $ppFEV_1$ distributions were set so that when the cohort reached the average ages reported in the relevant clinical trials, the means, and ranges of the $ppFEV_1$ matched those observed in the relevant trials. As an example, for individuals with a *G551D* mutation (representing those patients who are candidates for Kalydeco only) we set the starting distribution so that the $ppFEV_1$ mean and range of the cohort as they were followed over time was similar to the $ppFEV_1$ mean and range (84.2%; 44.0%-133.8%) of the ENVISION trial at age nine (mean age) and the mean and range (63.3%; 31.6%-98.2%) of the STRIVE trial at age 26 (mean age).[67,68] In addition to $ppFEV_1$, the model tracked the values of other variables for each simulated person that were important for determining the annual risk of dying from CF: weight-for-age *z*-score, number of acute pulmonary exacerbations per year (defined as exacerbations requiring intravenous antibiotics), pancreatic sufficiency, lung transplantation, and diagnosis of CFRD or *B. cepacia* infection. During any given year, a simulated person may experience a change in their $ppFEV_1$, experience one or more acute pulmonary exacerbations, be diagnosed with CFRD or *B. cepacia* infection, or undergo lung transplantation if their $ppFEV_1$ falls to 30% or below. Figure 5.1 shows a diagram of the model, with the annual risks of acute pulmonary exacerbation and lung transplantation dependent on the value of $ppFEV_1$ at the beginning of each year. Persons were simulated for their lifetime, accumulating life years, QALYs (i.e., life years weighted by a quality-of-life value), equal value life years, and costs each year.

For the treatment arms, we allowed the initial $ppFEV_1$ and weight-for-age *z*-score values to increase based on trial results, or by assumption if no trial evidence existed. In addition, treatment slowed the decline in $ppFEV_1$ over the lifetime of the patient. The annual risk of acute pulmonary exacerbation decreased with treatment, both because of the increase in $ppFEV_1$ and due to an added effect, that is independent of the improvement in $ppFEV_1$.

Figure 5.1 Model Framework



*Annual decline in ppFEV1 begins two years after treatment with CFTR modulator arm and is half that of BSC

Target Populations

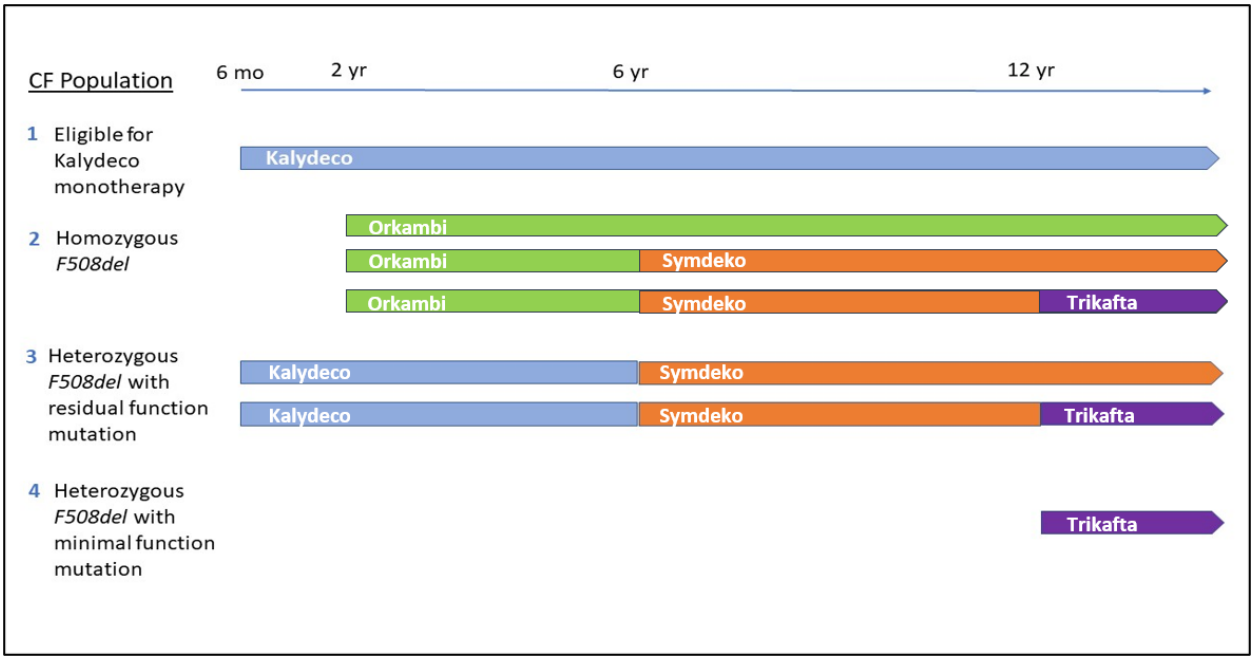
We evaluate four possible therapeutic options for four CF populations as follows. Some analyses were updates of our prior analysis[18] and some were new, as noted below.

1. For patients who are candidates for Kalydeco only based on current indications, we compared Kalydeco plus best supportive care to best supportive care alone (updated analysis).
2. For patients who are homozygous for the *F508del* mutation, we compared Orkambi plus best supportive care, Symdeko plus best supportive care, Trikafta plus best supportive care, and best supportive care alone as competing alternatives (updated and new analyses). Patients in the second and third treatment strategies were treated with Orkambi starting at age 2 years until they turn 6 (Figure 5.2).
3. For patients who are heterozygous for the *F508del* mutation with a residual function mutation, we compared Symdeko plus best supportive care, Trikafta plus best supportive care, and best supportive care alone (updated and new analyses). Patients in the first two treatment strategies were treated with Kalydeco monotherapy starting at age 6 months until they turn 6 years old (Figure 5.2). We used the efficacy for Trikafta from the population who are heterozygous for the *F508del* mutation with a minimal function mutation to model Trikafta in this population, which differs from the study populations of the clinical trials.

4. For patients who are heterozygous for the *F508del* mutation with a minimal function mutation, we compared Trikafta plus best supportive care and best supportive care alone (new analysis).

Because the recommended start age varies by drug, we model sequential drugs in relevant populations (Figure 5.2). For example, for patients who are homozygous for the *F508del* mutation we assume that all patients on a CFTR modulator strategy will start with Orkambi at age 2 and then switch to Symdeko at age 6 if not on lifetime Orkambi. Patients assigned to lifetime Trikafta therapy will switch to this therapy at age 12. At switching we will allow for an improvement in lung function based on the difference in efficacy between the two drugs. Although individual patients may not follow these fixed trajectories in practice, our assumption is that simulated patients will receive the most effective available therapy at all ages.

Figure 5.2 Schematic of the CFTR Modulator Strategies



The target populations vary in terms of their prognosis .[98] On average, CF patients who are homozygous for *F508del* or have two minimal function mutations have a more severe prognosis than patients with one or no minimal function mutation. McKone et al. classified patients into high-risk and low-risk groups based on the effects of the functional class of their phenotype.[98] They found that the median age of death was much younger 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.*[99] We adjusted the lung function declines in our model to represent these different subgroups of patients. In general, individuals heterozygous for the *F508del* mutation with a

residual function mutation have a higher likelihood of maintaining pancreatic sufficiency[93,99] and a lower risk of developing CFRD.[75]

We assumed that best supportive care consists of the following pulmonary and pancreatic therapies (percent utilization overall): dornase alfa (91.9%), inhaled tobramycin (70.2%), inhaled aztreonam (43.3%), azithromycin (64.2%), hypertonic saline (73.4%), oxygen (10.8%), non-invasive ventilation (3.2%), pancreatic enzyme replacement therapy (84.9%) and supplemental feeding (tube or oral, 54.6%).[2] Individuals with CF-related diabetes were assumed to require oral hyperglycemic agents (4.0%), intermittent insulin (6.1%), and chronic insulin (73.2%), and to require diabetes-specific follow-up care (e.g., HbA1c measurements). We assumed that best supportive care applied to all individuals, whether on CFTR modulators or not, but that the intensity of therapy varied by lung function category. In addition, we allowed the intensity of best supportive therapy to be reduced by Trikafta, independent of lung function, in a scenario analysis. Acute pulmonary exacerbations were defined as those that involve treatment with IV antibiotics either in the hospital or with home treatment. We chose this definition for acute pulmonary exacerbations because it is the definition used in the mortality equation we employed.[100] We assumed that acute pulmonary exacerbations treated with oral therapy in an ambulatory setting would be included in the disease management costs. Disease management costs included all costs except those for acute pulmonary exacerbations requiring IV antibiotics and lung transplantation and varied by level of $ppFEV_1$. Acute pulmonary exacerbations requiring IV antibiotics and lung transplantation were costed separately. We assumed that disease management costs for a given level of $ppFEV_1$ would be the same for patients in both arms (modulator therapy vs. no modulator therapy). Disease management costs will vary as individuals who live longer will have higher management costs, although individuals on modulator therapy will also have better lung function, resulting in reductions in these costs. There are likely other reductions in costs related to fewer sinus or abdominal surgeries. Although we do not have direct evidence on these reductions, we evaluate the potential impact on disease management costs in a scenario analysis.

Treatment Strategies

For each population, we compared the eligible CFTR modulator treatment(s) plus best supportive care to best supportive care alone. We did not compare CFTR modulator treatments directly with each other.

Key Model Characteristics and Assumptions

We made several assumptions for this analysis (Table 5.1).

Table 5.1. Key Model Assumptions

Assumption	Rationale
ppFEV$_1$ does not increase over time in the absence of CFTR modulator therapy.	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, though the intensity of therapy increases with decreasing lung function category (≥70%, 40%-69%, <40%).	Modulator therapy will have an impact on costs associated with acute pulmonary exacerbations and lung transplantation, but whether other costs of care not associated with lung function will be affected by modulator therapies within a given lung function category is not known. We evaluated this assumption in a scenario analysis.
The weight for-age *z*-score is constant over the lifetime of a patient, with a one-time increase with CFTR modulator therapy.	The limited evidence for how weight for-age *z*-score changes over time indicates that weight for age *z*-score gains seen in trials are sustained but not further elevated. This assumption applies to the population of patients on average and not to individual patients.
The risk of *B. cepacia* infection over time does not depend on lung function severity.	The occurrence of *B. cepacia* infection is incorporated because it is part of the CF-specific mortality risk.
The CFTR modulator drug effect is modeled as an increase in ppFEV$_1$ and increase in weight for age *z*-score, and a decrease in the annual number of acute pulmonary exacerbations.	These are well-documented effects of CFTR modulator drugs from clinical trials. We acknowledge that there are other non-pulmonary effects that were not studied in the clinical trials.
There is no CFTR modulated drug effect on weight for age *z*-score for patients who are heterozygous for the *F508del* mutation with a residual function mutation.	This is consistent with these patients having minimal pancreatic insufficiency. The clinical trials in this population do not report change in weight for age *z*-score.
CFTR modulator drugs decrease the annual number of acute pulmonary exacerbations through the increase in ppFEV$_1$ (i.e., the risk of exacerbations depends on lung function) as well as an additional reduction in acute pulmonary exacerbations, independent of the lung function effect.	We do not observe the rate ratio reported in the clinical trials by assuming that the reduction in the number of acute pulmonary exacerbations is only due to the increase in ppFEV$_1$ associated with the drug. This assumption is needed to match the risk reductions observed in the clinical trials.
We assumed 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.
We started patients on a CFTR modulator drug at the age that they are first eligible and then they switch to a more effective drug when becoming age eligible. The increase in ppFEV$_1$ will be determined by the difference in the effectiveness of the new drug relative to the original drug.	It is reasonable to assume that patients will start on a modulator drug as soon as they are eligible but that they will switch to a more effective one over time. We do not assume that drugs will be given off label.

Model Inputs

Clinical Inputs

We modeled the $ppFEV_1$ trajectories through age-specific annual declines.[101,102] To match the mean $ppFEV_1$ values observed in the drug trials, we allowed the decline for ages under nine to be slightly higher than reported in the literature for CF individuals with a gating mutation (representing those patients who are candidates for Kalydeco), who are homozygous for the *F508del* mutation, or who are heterozygous for the *F508del* mutation with a minimal function mutation. The annual risk of having acute pulmonary exacerbation was modeled as a function of $ppFEV_1$, age, and the number of acute pulmonary exacerbations the previous year.[103-105] The annual risk of lung transplant was 0% for individuals with $ppFEV_1$ >30%, as per guidelines.[106] The annual risk of diabetes was modeled as a function of age, sex, and mutation class.[75] CF patients who are homozygous for the *F508del* mutation, or who are heterozygous for the *F508del* mutation with a minimal function mutation had the highest annual risk of CFRD, and patients who are heterozygous for the *F508del* mutation with a residual function mutation had the lowest risk. We assumed that 5% of CF individuals who are candidates for Kalydeco only, who are homozygous for the *F508del* mutation, or who are heterozygous for the *F508del* mutation with a minimal function mutation (i.e., Populations 1, 2, and 4) had pancreatic sufficiency at diagnosis and that this proportion was stable over lifetime.[107] For CF individuals heterozygous for the *F508del* mutation with a residual function mutation (Population 3), we estimated that 84% had pancreatic sufficiency at diagnosis based on the EXPAND trial population.[93] Similarly, we assumed that weight-for-age *z*-score is constant for each person throughout life (in the absence of modulator therapy), which was set to -0.23.[108] The risk of *B. cepacia* infection over time was derived from age-specific prevalence values from the CF Foundation Registry and does not depend on lung function severity. [2] Base-case values are listed Table 5.2.

Table 5.2. Key Model Inputs

	Baseline Value	Source
Annual Decline in $ppFEV_1$		
Age 6-8 years (applied to age 0-6 years)	-1.12 (-2.00 for gating or *F508del* homozygous or *F508del* heterozygous with minimal function mutation*)	Konstan, 2007;Konstan, 2012[101,102]
Age 9-12 years	-2.39	
Age 13-17 years	-2.34	
Age 18-24 years	-1.92	
Age ≥25 years	-1.45	
Annual Rate of Acute Pulmonary Exacerbation by Age and $ppFEV_1$		
Age <18	$8.5938*\exp(-0.035*ppFEV_1)$	Goss, 2007; Whiting, 2014[103,104]
Age ≥18	$3.7885*\exp(-0.026*ppFEV_1)$	
Hazard Ratio for Increase in Rate of Pulmonary Exacerbation (Relative to 0 Exacerbations the Prior Year)		
1 Exacerbation the Prior Year	1.6	VanDevanter, 2016[105]
2 Exacerbations the Prior Year	2.4	
3+ Exacerbations the Prior Year	4.0	
Number of Pulmonary Exacerbations Per Year: 1 / 2/ 3+ (Conditional On 1+)		
Age < 5	0.76 / 0.19 / 0.05	Goss, 2007[103]
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		
$ppFEV_1$ >30	0	Thabut, 2013[109]
$ppFEV_1$ ≤30	0.647	
Annual Risk of CF-Related Diabetes (Male, Female) x (Pop 2&4 / Pop 1 / Pop3)		
Age 0-9	0.008, 0.016 / 0.006, 0,013 / 0.002, 0.004	Adler, 2008[75]
Age 10-19	0.039, 0.060 / 0.031, 0.048 / 0.009, 0.014	
Age 20-29	0.049, 0.071 / 0.039, 0.057 / 0.011, 0.016	
Age 30-39	0.065, 0.072 / 0.052, 0.058 / 0.015, 0.016	
Age 40+	0.051, 0.029 / 0.041, 0.023 / 0.012, 0.007	

*Assumed higher declines for youngest age group for individuals with a gating mutation or who are homozygous for the *F508del* mutation to fit trial-specific means for each population.

Clinical Probabilities/Response to Treatment

We first ran the microsimulation models for each population under conditions of best supportive care alone. Specifically, we generated lifetime trajectories for 10,000 simulated patients where we tracked the health events that occurred each year and generated summary measures such as life expectancy (i.e., average life spans) or average number of acute pulmonary exacerbation over a

lifetime. These runs provided lifetime estimates of health and economic outcomes for patients not treated with a CFTR modulator. To model the treatments' effects, we implemented several changes to the model to represent what we know about, or made reasonable assumptions about, how CFTR modulators impact patients' prognoses. First, we assumed that there is an immediate increase in $ppFEV_1$ and improvement in weight-for-age *z*-score (with the exception of patients who are heterozygous for the *F508del* mutation with a residual function mutation), as observed in the trials or by assumption if no trial evidence existed (Table 5.3). If a cohort switches CFTR drugs, we assumed that they experience the net increase in $ppFEV_1$ between the two drugs based on what was observed in the trials, or by assumption if no trial evidence existed (Table 5.3). The improvement in lung function in turn decreased the risk of experiencing acute pulmonary exacerbations and ultimately lung transplantation, increased a person's HRQOL, and decreased annual mortality risk. If we only allowed acute pulmonary exacerbation to decrease based on the increase in $ppFEV_1$, we would be unable to match the risk ratios reported in the clinical trials. To be consistent with the trial evidence, we incorporated an *additional* decrease in the risk of acute pulmonary exacerbation, independent of the effect of lung function improvement. Following the initial increase in $ppFEV_1$ we assumed $ppFEV_1$ would not decline for two years. After that time, we needed to make long-term assumptions about the impact of treatment on the trajectory of lung function over time. We modeled three assumptions about the treatment effect after two years: 1) no $ppFEV_1$ decline as long as the patient is on drug (favorable assumption), 2) no $ppFEV_1$ decline on drug for 2 years and then a decline that is 50% of the standard care rate thereafter (plausible assumption), 3) no $ppFEV_1$ decline on drug for 2 years and then a decline that is equal to the standard care rate thereafter (unfavorable assumption). We used the second assumption in the base-case analysis, where 50% is in the range of the CFTR modulator effect on lung function decline.[66,110] We assumed that same long-term effect for all CFTR modulator drugs, even though they had different initial effects on $ppFEV_1$. This was because of a lack of evidence on long-term effectiveness and because the estimates of decline with Kalydeco and Orkambi – two CFTR modulators with very different initial $ppFEV_1$ effects – had very similar long-term effect estimates (47% of standard of care rate for Kalydeco and 42% of standard of care rate for Orkambi).[88,110] We assumed that the increase in weight-for-age *z*-score would persist for a patient's lifetime.[59,110]

The drug trials reported reductions in acute pulmonary exacerbation rates (e.g., rate ratios). When available we used the rate ratios for acute pulmonary exacerbations that required IV antibiotics. We assumed that part of the decline in number of acute pulmonary exacerbations was due to the increase in $ppFEV_1$. However, we also allowed for an independent effect of the drugs on reducing the acute pulmonary exacerbation rates. For example, the rate ratio for Kalydeco plus best supportive care versus best supportive care alone was 0.56.[67] The model-generated rate ratio for a population similar to STRIVE was 0.83 when we assumed that the decline in acute pulmonary exacerbations with drug was *only* due to the increase in $ppFEV_1$. When we assumed that Kalydeco also reduced the risk of exacerbation and the number of multiple exacerbations (given at least one)

by 22%, the model-generated risk ratio was similar to that shown in the clinical trial. This approach assumes that the reduction in exacerbation rate was a combination of a lower percentage of patients experiencing any exacerbations in a year as well as fewer exacerbations among those who do experience at least one.

Table 5.3. Treatment Effectiveness Inputs

	Increase in ppFEV$_1$ (Mean, 95% CI)	Acute Pulmonary Exacerbation RR	Change in Weight-For Age *Z*-Score (Mean, 95% CI)*	Source
Population 1 - Eligible for Kalydeco Monotherapy Only				
Kalydeco	10.0 (4.5-15.5)	0.56	0.35 (0.20-0.51)	Davies, 2013;Ramsey, 2011;Borowitz, 2016;McKone, 2014[67,68,73,108]
Population 2 - Homozygous for the *F508del* Mutation				
Orkambi	2.8 (1.8-3.8)	0.44	Same as above (assumed)	Wainwright, 2015;Konstan, 2017;Taylor-Cousar, 2017; NICE, 2016; Heijerman, 2019[8,30,87,88,111,112]
Symdeko	4.0 (3.1-4.8)	0.54†	Same as above	
Symdeko vs. Orkambi	1.2*			
Trikafta vs. Symdeko	10.0	NR	Same as above (assumed)	
Population 3 - Heterozygous *F508del* with Residual Function Mutation				
Kalydeco	4.7 (3.7-5.8)	0.46 (0.21-1.01)‡	0 (assumed)	Rowe, 2017[93]
Symdeko	6.8 (5.7-7.8)	0.54 (0.26-1.13)‡	0	
Symdeko vs. Kalydeco	2.1 (calculated)		0	
Trikafta	13.8 (assumed same as for Pop 4)		0	
Trikafta vs. Symdeko	7.0 (calculated)		0	
Population 4 - Heterozygous *F508del* with Minimal Function Mutation				
Trikafta	14.3	0.37	BMI effect reported	Middleton, 2019[56]

*Change in weight-for-age *z*-score reporting is variable and not consistent. We assumed that all drugs would achieve the same effect on weight-for-age *z*-score as observed in Borowitz et al., 2016[108] except for Population 3. The BMI effect reported in Population 4 was consistent with the change in weight-for-age *z*-score reported in Population 1.

†Rate ratio (RR) is for acute pulmonary exacerbations with either IV antibiotics or hospitalization (or both). We assume that all hospitalizations would involve IV antibiotics.

‡RR reported for acute pulmonary exacerbations defined by modified Fuchs criteria (not necessarily requiring IV antibiotics).

Mortality

Each year, simulated individuals face a risk of dying. We modeled this probability as a combination of their age-specific mortality rate based on the US life tables [113] and a CF-specific rate. CF-specific mortality rates were a function of sex, $ppFEV_1$, weight-for-age *z*-scores, number of acute pulmonary exacerbations, diagnosis of CF-related diabetes, pancreatic sufficiency, and *B. cepacia* infection.[100] The mortality equation derived by Liou et al. has been used extensively in decision models of CF, including a model developed by Vertex Pharmaceuticals, Inc.[114]. Incorporating the annual risks of dying over the lifetime of the patient cohort allowed us to calculate life expectancy for the population (mean number of remaining life years). More details about the mortality equation are provided in Appendix E. Survival after lung transplant was a function of time since transplant and was better than prior to transplant.[109]

Utilities

To calculate QALYs, we multiplied each year of life by a HRQoL weight (i.e., utility) meant to reflect the HRQoL experienced for that year. We derived joint utilities by multiplying the average utility weights specific to CF patients by average age-specific utility weights for the general population.[115]. Age-specific utilities are provided in Appendix Table E3. This allows the model to account for the decline in HRQoL as individuals age, as well as the HRQoL impacts of CF. We used EQ-5D utilities as the HRQoL weights because we had data on EQ-5D by $ppFEV_1$ categories and because EQ-5D is a valid measure widely used for generating QALYs. Specifically, we used the linear interpolation of EQ-5D utilities by $ppFEV_1$ conducted by Schechter et al. (Table 5.4).[116] The extrapolation was based on EQ-5D values estimated for $ppFEV_1$ groups (0.86 for >70%, 0.81 for 40%-69%, and 0.64 for <40%) among CF patients that were provided to Tappenden et al. for a NICE economic evaluation.[117] Because we modeled $ppFEV_1$ as a continuous variable, we used a linear function to assign utilities based on $ppFEV_1$ (utility = 0.593047 + $ppFEV_1$*0.003476). We used similar assumptions as Tappenden et al. and applied a short-term utility decrement of 0.17 over 6 months for each acute pulmonary exacerbation experienced.[117] We used the same utility used by Schechter et al.[116] for the first year after lung transplantation (0.32) based on a study of quality of life for lung transplantation in patients with CF.[118] Subsequent years after transplantation were set to a utility equivalent to a $ppFEV_1$ of 70%-79%: 0.838.

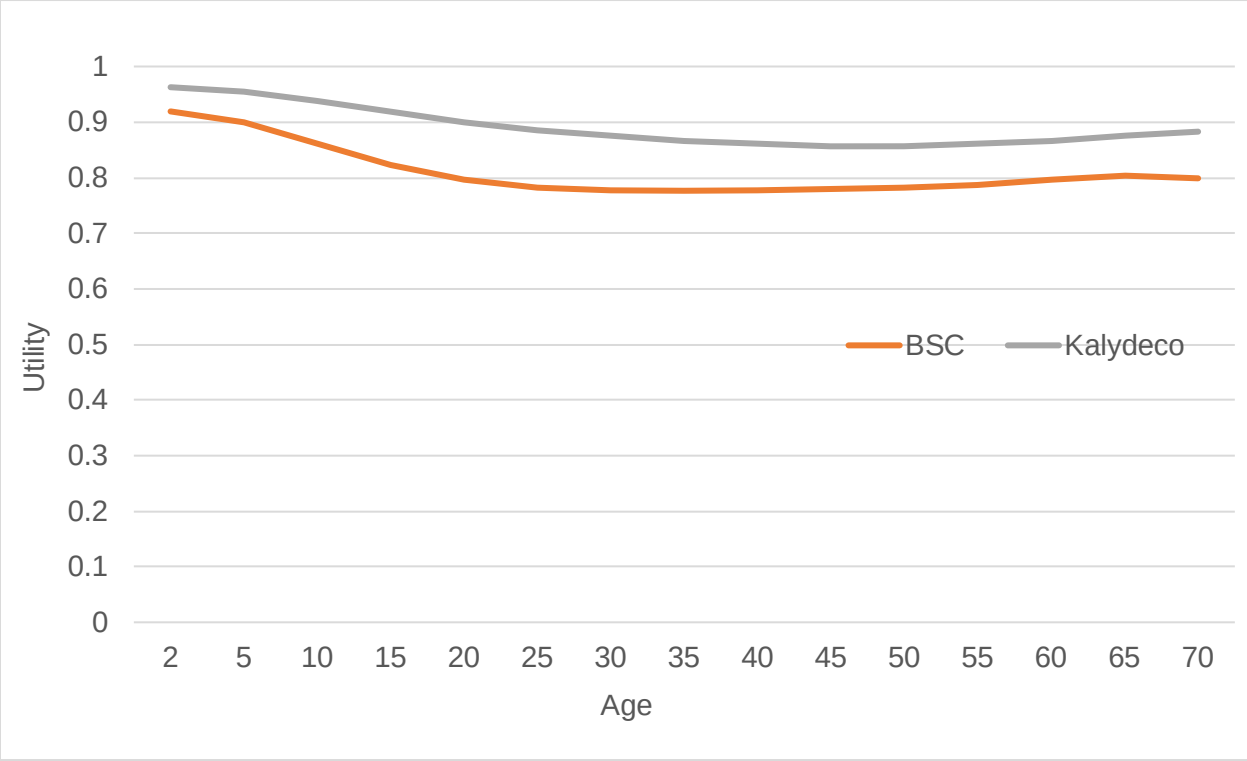
Table 5.4. Utility Values by Level of $ppFEV_1$ (Derived from Schechter et al.)

$ppFEV_1$ (%)	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
<20	0.625

$ppFEV_1$: Percent predicated forced expiratory volume in 1 second

We were able to conduct a validation exercise for these utility estimates, using a study conducted by Bell et al[61]That study compared EQ-5D measures between CF patients with a *G551D* mutation who were treated with Kalydeco and comparable patients (i.e., homozygous for the *F508del* mutation) who were treated with standard of care alone.[61] Patients in the Kalydeco treatment group had a significantly greater mean EQ-5D score than patients in the standard of care treatment group (0.90 vs. 0.81, $p < 0.01$).[61] These mean utilities represent a range of attributes that inform HRQoL improvements with Kalydeco and are not specific to lung function improvements. We sought to determine whether our utility estimates that were based on lung function would produce similar findings as the Bell study. To do this, we simulated a cohort of patients treated with Kalydeco and a cohort receiving best supportive care alone. Each year of the simulation, we calculated the mean EQ-5D utility among those simulated people in each group who were still alive and had not undergone lung transplantation. We only modeled CF-specific utilities for this exercise and not age-specific utilities. In our validation exercise we found that, at age 25 (similar age as the patients in the Bell study), modeled patients on Kalydeco plus best supportive care and best supportive care alone had mean utility values of 0.88 and 0.78, respectively (Figure 5.3).

Figure 5.3. Cystic Fibrosis Patients Eligible for Kalydeco Monotherapy, Mean Utility by Age



Adverse Events

Serious and severe AEs were generally comparable across treatment groups and often higher in the placebo arms. Therefore, we did not explicitly model AEs in terms of added costs or disutilities but assumed that patients who experienced a bothersome AE would discontinue the drug. As the discontinuation rates typically reported in the trials were greater than the reported discontinuation rates due to AEs, we assumed that the reported discontinuation rates included discontinuation due to AEs.

Economic Inputs

Drug Acquisition Costs

Annual net drug acquisition costs for each medication were used in the model. We could not calculate net prices for all drugs using our standard source (SSR Health, LLC), as this source did not include consistent publicly disclosed net sales figures for the specialty drugs in this review. As no discount was observed in the Federal Supply Schedule (FSS) prices for these drugs, we used wholesale acquisition cost (WAC) as the net price for each drug (Table 5.5).[119] As Trikafta was only recently approved by the FDA, information on its net pricing was not yet available; we therefore assumed its net pricing will be as for the other CFTR drugs, and used the WAC in our analyses.

Lower doses (for younger patients) have the same price as adult doses, so no age adjustments were done. We assumed that there were no additional costs associated with the administration and monitoring of the CFTR drugs above best supportive care.

Table 5.5. Drug Cost Inputs

Intervention	WAC per Day*[10]	Annual Drug Cost
Kalydeco	$853.40	$311,704
Orkambi	$746.40	$272,623
Symdeko	$800.00	$292,200
Trikafta	$853.50	$311,741

*WAC as of December 2, 2019

Some prior cost-effectiveness analyses in CF have attempted to account for possible price changes over time, by assuming that the drug prices will decrease upon loss of patent exclusivity.[104,120,121] For example, Dilokthornsakul et al. assumed that the prices of Kalydeco and Orkambi would drop to 10% of WAC after patent expiration.[120,121] We chose not to make such an assumption in our current analysis, because attempts to model price changes over time would add an additional layer of uncertainty and speculation to our analysis, and while there have been calls to include price changes in cost-effectiveness analysis, the current convention is not to include estimates of changes in drug price throughout the life cycle.[122,123] The assumption of a large price drop at patent expiry was considered to be a limitation and not appropriate In CADTH's Common Drug Reviews of the economic models submitted for Kalydeco and Orkambi, and was not recommended as a base case assumption for the UK NICE appraisal committee's assessment of Orkambi.[43-46,124] Estimating such changes may be especially difficult in the US market, where drug prices are mostly unregulated, and changes in prices occur relatively frequently. The timing of entry of other competitors (branded or generic) is difficult to predict, due to the possibility of patent litigation and "pay for delay" agreements. Generic drugs are generally expected to have discounted pricing relative to branded competitors, but the size of that future discount is difficult to estimate, particularly for rare diseases with limited to no competition. This was seen, for example, with the introduction of a new generic version of trientine hydrochloride (Syprine®), which entered with a 14% discount off a brand price that had increased by a factor of 30 in recent years.[125] Finally, even products with historically stable pricing may be sold to or acquired by another manufacturer, who could decide to change pricing in dramatic and unpredictable fashion.

Administration and Monitoring Costs

We assumed that there were no additional costs associated with the administration and monitoring of the CFTR modulator drugs above best supportive care.

Health Care Utilization Costs

We assumed that annual CF-related health care costs over an individual's lifetime consisted of three components (not including the cost of the CFTR modulator drugs): disease management, acute pulmonary exacerbations requiring IV antibiotics, and lung transplant-related costs. We used an approach similar to that taken by Dilokthornsakul et al. in their cost-effectiveness analyses.[120,121] Both disease management and acute pulmonary exacerbation components incorporated a gradient cost structure that was derived from Lieu et al. to reflect increasing costs with increasing disease severity categories (≤40% ppFEV$_1$, severe; between 40% and 70% ppFEV$_1$, moderate; ≥70% pp FEV$_1$, mild).[126] An age-related adjustment (<18 or 18+) was included in the exacerbation component. The 2018 CF Foundation Patient Registry data were used to calculate the adjustment, reflecting a higher proportion of total treatment duration spent in the hospital versus home IV treatment for children with a pulmonary exacerbation than for adults.[2] This resulted in a lower cost per exacerbation for adults.

Average cost estimates based on 1996 data[126] do not include all currently-available CF treatments and therefore do not reflect current best supportive care costs. Because the Lieu study reported a gradient cost structure by lung function (e.g., costs among patients with ≤40% ppFEV$_1$ is greater that costs among patients with ≥70% pp FEV$_1$) we assumed that this cost gradient applied to current costs. Because patients with better lung function incur fewer costs than those with poorer lung function, this results in additional cost savings with CFTR modulators over the short term due to slowing down lung function decline. To derive current best supportive care costs, we used an average annual cost estimate from an analysis of 2016 commercial payer claims data, excluding CFTR-related costs,[127] and updated to 2019 US dollars using the personal consumption expenditure (PCE) price index. This resulted in an average annual cost estimate of $93,301 (2019 US dollars), which includes disease management costs and acute pulmonary exacerbation costs. We have received confidential confirmation from two private payers that this annual cost is in line with their observed costs.

Transplant-related costs include the one-time cost of receiving a lung transplant followed by an annual cost associated with post-transplantation care. Estimates for the cost of a lung transplant and initial year following a transplant were derive from a 2017 Milliman Research Report.[128] Annual costs were reduced for all subsequent years following the first year post-transplant based on estimates from a study of inpatient and outpatient billing services of lung transplantation patients at the University of Washington.[129] The CF-related disease management costs were assumed to be 41% of the costs prior to transplant (i.e., costs associated with the lowest lung function category) to represent non-pulmonary CF-related costs,[127] and exacerbation costs were assumed to be zero (i.e., exacerbations do not occur) for individuals in post-transplant years.

Cost estimates are shown in Table 5.6 and are reported in 2019 US dollars.

Table 5.6. Direct Costs by Disease Severity

	$ppFEV_1 \geq 70\%$	$ppFEV_1$ 40%-69%	$ppFEV_1 < 40\%$
Disease Management	$30,258	$39,914	$68,240
PEx* (age <18)	$63,204	$100,143	$148,368
PEx* (age 18+)	$57,273	$91,037	$130,460
Lung Transplant	$948,437		
Post-Transplant (Year 1)	$365,773		
Post-Transplant (Year 2+)	$131,738		

*PEx = acute pulmonary exacerbation requiring IV antibiotics

Productivity Costs

For the societal perspective, we used an analysis provided by the CF Foundation regarding employment status among two groups of CF patients: those treated with Kalydeco and a matched group who were not treated with a CFTR modulator. The analysis showed that treated patients were more likely to be employed full time compared with untreated patients. Reported absolute differences in full-time employment- varied from 3% among persons aged 18-24 years to 14.5% among persons aged 35-39 years. We used the reported differences in the employment rates to incorporate the productivity gains associated with the CFTR modulators, assuming that they all had the same impact as observed with Kalydeco. We used an average weekly wage of $971 (Bureau of Labor Statistics) plus a fringe rate. We also added productivity losses to the cost of acute pulmonary exacerbations. Because we did not find a substantial impact of treatment on indirect costs relative to direct health care costs, we present the societal perspective as a scenario analysis and not as dual base-case analyses.

A large impact on caregiver costs from CFTR modulator treatment would require that caregiver burden be associated with lung function (e.g., the primary characteristic which modulator treatments change) or have direct evidence that the CFTR modulators reduce caregiver burden. However, Neri et al. 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 exacerbations.[130] Angelis et al. did find that direct non-health care costs in the United Kingdom were of the same magnitude as direct health care costs, not including CFTR modulators, but did not report societal costs by lung function category.[131] Any assumptions about how CFTR modulator drugs affect caregiver burden would be speculative. Therefore, we did not include impacts on caregiver costs in this analysis. The addition of direct non-health care costs that are not affected by CFTR modulator treatments would result in an increase in total societal costs due to the substantial increase in life expectancy with modulator therapy.

Model Analyses

The models, based on each of the four CF populations, were used to calculate average survival (remaining number of years of life), quality-adjusted survival, numbers of acute pulmonary exacerbations, number of lung transplantations, and costs (CFTR modulator, disease management, acute pulmonary exacerbation, and lung transplantation). We calculated the incremental results for each CFTR modulator therapy versus best supportive care alone as the incremental cost per LY, evLYG, QALY, and acute pulmonary exacerbation. Outcomes were discounted at 3% per year for the cost-effectiveness analysis, but not for the outcome's analysis.

Sensitivity Analyses

We ran one-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, as described in the model inputs section above. Probabilistic sensitivity analyses were also performed by jointly varying all model parameters over 1,000 simulations, then calculating 95% credible interval estimates for each model outcome based on the results and reporting the percent of the simulations where the drug was cost-effective for a given threshold (varying from $50,000 per QALY to $500,000 per QALY for Kalydeco and Symdeko, and from $50,000 per QALY to $200,000 per QALY for Trikafta). We use normal distributions for parameters in the mortality model and drug effect parameters, beta distributions for utilities and probabilities, and truncated normal distributions for costs. Additionally, we performed a threshold analysis by systematically altering the price of CFTR modulators to estimate the maximum prices that would correspond to a set of given cost-effectiveness thresholds. We did not conduct these analyses for cost per evLYG as they would show the same inputs were drivers of variability in estimates.

Scenario Analyses

We performed five scenario analyses. In the first, we present our results that used a societal perspective. In the second, we varied our assumption about long-term effectiveness of the CFTR modulator drugs. In our base case, we assume that after two years individuals on CFTR modulator therapies would experience 50% of the annual $ppFEV_1$ decline that those receiving best supportive care alone would experience. In scenario analyses, we assume that the annual decline in lung function with the CFTR modulator drugs varied between 0% long-term decline (i.e., no long-term lung function decline experienced with drug) to 100% (i.e., long-term decline with drug is the same as best supportive care after two years). This range was supported by the simulated standard error of the long-term percent decline (99% credible interval 1%-99%). In a third scenario analysis, when patients experience a pulmonary exacerbation, we incorporate an additional decrease in $ppFEV_1$ that is not recovered. This effect is supported by a study,[132] although the magnitude of this effect is unclear, and it is uncertain the degree to which this effect is already captured in the other benefits

of CFTR drugs (e.g., decrease in long-term decline in lung function). In a scenario analysis, we varied the additional absolute decline in $ppFEV_1$ due to a pulmonary exacerbation between 0% (i.e., no additional decline in $ppFEV_1$ due to pulmonary exacerbation) to 5% (i.e., a 5% absolute decline in $ppFEV_1$ for each pulmonary exacerbation experienced). In a final scenario analysis, we explored the assumption that CFTR modulator therapies have a quality-of-life benefit in addition to respiratory improvements. An analysis of STRIVE CFQ-R findings reported scores for domains other than the respiratory domain and found clinically significant improvements in certain domains (e.g., physical functioning, health perception, vitality, weight). [133] Although a CFQ-R score does not directly translate into a utility, we varied an independent utility effect (i.e., using a multiplier to the lung-function-informed utility) due to CFTR therapy from 1 (no independent effect) to 1.05 (a 5% increase in utility with drug), above that due to lung function improvement. Bell et al. reported mean EQ-5D values of 0.90 for cystic fibrosis patients with a *G551D* mutation who were treated with Kalydeco and 0.81 for patients homozygous for the *F508del* mutation who were treated with standard of care alone, indicating an overall quality-of-life effect due to the Kalydeco treatment.[61] A 5% increase in utility for someone with a base of 0.90 represents an absolute gain of 0.045, which is half of the overall observed effect reported by Bell et al. and would reflect quality-of-life impacts not measured by EQ-5D. In a fifth scenario analysis we incorporated a CFTR modulator benefit on the annual risk of CFRD. We used an adjusted relative risk from an observational study,[21] adjusted for the differential risk of CFRD by mutation class,[75] and varied the risk reduction between 5% and 23%.

We conducted three additional analyses for Trikafta. First, we assumed a start age of 6 years instead of 12 years, anticipating that younger patients will be eligible for this drug in the near future. Second, we assumed that Trikafta reduces the intensity of best supportive therapy needed by reducing disease management costs by 75%. Last, we evaluated a "curative scenario" for Trikafta. In this scenario we assumed patients would live to a normal life expectancy with no CF-related decrements in quality of life and no CF-related costs outside of the cost of Trikafta at its current price. In this analysis we allowed Trikafta treatment to begin at age 6 months and assumed people would be 100% adherent to the medication. This analysis provides an extreme lower bound for the potential cost-effectiveness of this drug at its current price.

Model Validation

We used several approaches to validate the model. First, we provided preliminary methods and results to representatives from a patient group and clinical experts. Based on feedback from these groups, we refined data inputs used in the model and ran additional scenario analyses (e.g., varying the costs of best supportive care among patients treated with Trikafta, and modeling a younger population for Trikafta). Second, we varied model input parameters to evaluate face validity of changes in results. Simulated individuals were compared 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.[2] We also performed model verification for model calculations using internal reviewers. Finally, we compared results to other cost-effectiveness models in this therapy area.

5.3 Results

Base Case Outcomes Results

All CFTR modulators were compared to best supportive care and were found to be very effective (Table 5.7). Note that the difference in total life years for Population 4 (heterozygous *F508del* and a minimal function mutation) versus Population 2 (homozygous *F508del*) is because the cohorts begin treatment at different ages (12 vs. 2 years of age, respectively). Also note that a higher percentage of patients who reach ppFEV$_1$ of less than 40% does not necessarily translate into a greater chance of experiencing lung transplantation, as those at higher risk of dying (due to reasons other than their ppFEV$_1$) may die prior to getting lung transplantation.

Table 5.7. Results for the Base Case Outcomes for CFTR Modulators Plus Best Supportive Care (BSC) Compared to BSC Alone, By Study Population (Undiscounted)

Population and Treatment	Total Life Years	Average Number of PEx	Percent With Lung Transplants	Percent Experiencing $ppFEV_1$ 40%-69%	Percent Experiencing $ppFEV_1$ <40%
Population 1 - Eligible for Kalydeco Monotherapy Only (age 6 months)					
BSC	37.77	31.95	33.5%	87.4%	49.6%
Kalydeco Plus BSC	54.10	18.55	4.9%	53.8%	11.7%
Difference	16.33	13.40	28.6%	33.6%	37.9%
Population 2 - Homozygous for the *F508del* Mutation (age 2 years)					
BSC	37.05	21.13	32.9%	88.9%	50.1%
Orkambi Plus BSC	49.94	12.30	7.4%	65.9%	15.8%
Difference	12.89	8.83	25.5%	23.0%	34.3%
Symdeko Plus BSC	51.84	11.67	5.4%	59.3%	12.4%
Difference	14.79	9.46	27.5%	29.6%	37.7%
Trikafta Plus BSC	56.36	10.51	3.2%	44.1%	8.0%
Difference	19.31	10.62	29.7%	44.8%	42.1%
Population 3 - Heterozygous *F508del* with Residual Function Mutation (age 6 months)					
BSC	39.47	23.99	36.8%	87.5%	52.8%
Symdeko Plus BSC	57.58	12.44	6.0%	52.2%	12.2%
Difference	18.11	11.55	30.8%	35.3%	40.6%
Trikafta Plus BSC	63.59	11.20	3.1%	35.1%	7.1%
Difference	24.12	12.79	33.7%	52.4%	45.7%
Population 4 - Heterozygous *F508del* with Minimal Function Mutation (age 12 years)					
BSC	26.22	18.31	32.5%	93.5%	53.3%
Trikafta Plus BSC	40.32	8.90	5.9%	70.4%	15.2%
Difference	14.10	9.41	26.6%	23.1%	38.1%

PEx: acute pulmonary exacerbations; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; BSC: best supportive care

Base Case Cost-Effectiveness Results

The base-case results are shown in Tables 5.8, 5.9, and 5.10. All CFTR modulators were compared to best supportive care. We did not compare the drugs with each other for CF populations with two CFTR modulator alternatives because of the lack of substantive differences between them in the meta-analysis results and in the modeling results. In all cases, the cost per QALY gained is greater than $1 million, which is substantially higher than cost-effectiveness thresholds in the US and the rest of the world. Table ES5 also shows the added cost for every pulmonary exacerbation averted through treatment, varying across patient subpopulations from a low of $539,000 per acute pulmonary exacerbation averted to a high of $737,000 per acute pulmonary exacerbation averted.

For individuals eligible for Kalydeco monotherapy only, the total discounted lifetime costs for Kalydeco plus best supportive care and best supportive care only were approximately $8,765,000 and $2,319,000, respectively. The total discounted QALYs (and life years) for Kalydeco plus best supportive care and best supportive care alone were 20.54 (26.06) and 15.83 (21.63), respectively. The incremental cost-effectiveness ratios for Kalydeco in this population were approximately $1,370,000 per QALY gained, $1,180,000 per evLYG, and $1,450,000 per life year gained.

For individuals who are homozygous for the *F508del* mutation the total discounted lifetime costs for Orkambi, Symdeko, Trikafta and best supportive care were approximately $7,508,000, $7,962,000, $8,470,000, and $2,088,000, respectively. The total discounted QALYs (and life years) for Orkambi, Symdeko, Trikafta, and best supportive care were 19.43 (25.22), 20.04 (25.66), 21.26 (26.66) and 15.77 (21.46), respectively. Note that despite the larger increase in $ppFEV_1$ with Trikafta compared to Symdeko, the benefit is not proportional to the $ppFEV_1$ increase due to the other benefits that are not related to $ppFEV_1$ (i.e., independent effect on acute pulmonary exacerbations, effect on weight-for-age *z*-score, and long-term decline in lung function – assumed to be the same for both drugs). The incremental cost-effectiveness ratios for Orkambi, Symdeko, and Trikafta versus best supportive care in this population were approximately $1,480,000 per QALY, $1,380,000 per QALY and $1,160,000 per QALY, respectively; $1,360,000 per evLYG, $1,200,000 per evLYG and $1,040,000 per evLYG, respectively; and $1,440,000, $1,400,000 and $1,230,000 per life year gained, respectively.

For individuals who are heterozygous for the *F508del* mutation with a residual function mutation, the total discounted lifetime costs for Symdeko, Trikafta and best supportive care were approximately $8,367,000, $8,901,000, and $2,214,000, respectively. The total discounted QALYs (and life years) for Symdeko, Trikafta and best supportive care were 20.93 (26.53), 22.41 (27.66) and 16.33 (22.12), respectively. The incremental cost-effectiveness ratios for Symdeko and Trikafta in this population were approximately $1,340,000 per QALY and $1,100,000 per QALY, respectively; $1,100,000 per evLYG and $951,000 per evLYG, respectively; and $1,390,000 and $1,210,000 per life year gained, respectively.

For individuals who are heterozygous for the *F508del* mutation with a minimal function mutation, the total discounted lifetime costs for Trikafta plus best supportive care and best supportive care alone were approximately $7,541,000 and $2,224,000, respectively. The total discounted QALYs (and life years) for Trikafta plus best supportive care and best supportive care alone were 16.52 (22.42) and 11.48 (17.05), respectively. The incremental cost-effectiveness ratios for Trikafta in this population were approximately $1,050,000 per QALY gained, $877,000 per evLYG and $990,000 per life year gained.

Note that the costs for disease management were higher in patients treated with CFTR modulator therapy compared to those treated with best supportive care alone (Table 5.9). The increased costs

are due to patients treated with CFTR modulators living longer and incurring disease management costs associated with the extra years of life.

Table 5.8. Outcome Results for the Base-Case Effectiveness Measures for CFTR Modulators Plus Best Supportive Care (BSC) Compared to BSC Alone, By Study Population (Discounted at 3% per Year)

Population and Treatment	Total QALYs	Total Life Years	Equal Value Life Years*
Population 1 - Eligible for Kalydeco Monotherapy Only			
BSC	15.83	21.63	15.83
Kalydeco Plus BSC	20.54	26.06	21.30
Population 2 - Homozygous for the *F508del* Mutation			
BSC	15.77	21.46	15.87
Orkambi Plus BSC	19.43	25.22	19.85
Symdeko Plus BSC	20.04	25.66	20.77
Trikafta Plus BSC	21.26	26.66	22.02
Population 3 - Heterozygous *F508del* with Residual Function Mutation			
BSC	16.33	22.12	16.41
Symdeko Plus BSC	20.93	26.53	22.01
Trikafta Plus BSC	22.41	27.66	23.44
Population 4 - Heterozygous *F508del* with Minimal Function Mutation			
BSC	11.48	17.05	11.69
Trikafta Plus BSC	16.52	22.42	17.75

QALY: quality adjusted life year; BSC: best supportive care

*Note that equal value life years do not always exactly equal QALYs because of patient to patient variations in a microsimulation

Table 5.9. Cost Results for the Base-Case Cost Measures for CFTR Modulators Plus Best Supportive Care (BSC) Compared to BSC Alone, By Study Population (Discounted at 3% per Year)

	Cost Source				
Population and Treatment	CFTR Drug	Disease Management	Acute Pulmonary Exacerbation	Lung Transplantation	Total
Population 1 - Eligible for Kalydeco Monotherapy Only					
BSC	$0	$755,000	$1,224,000	$339,000	$2,319,000
Kalydeco Plus BSC	$7,358,000	$832,000	$538,000	$37,000	$8,765,000
Population 2 - Homozygous for the *F508del* Mutation					
BSC	$0	$755,000	$991,000	$342,000	$2,088,000
Orkambi Plus BSC	$6,212,000	$822,000	$418,000	$55,000	$7,508,000
Symdeko Plus BSC	$6,732,000	$821,000	$370,000	$38,000	$7,962,000
Trikafta Plus BSC	$7,339,000	$811,000	$302,000	$20,000	$8,473,000
Population 3 - Heterozygous *F508del* with Residual Function Mutation					
BSC	$0	$774,000	$1,077,000	$363,000	$2,214,000
Symdeko Plus BSC	$7,099,000	$845,000	$379,000	$44,000	$8,367,000
Trikafta Plus BSC	$7,743,000	$835,000	$304,000	$19,000	$8,901,000
Population 4 - Heterozygous *F508del* with Minimal Function Mutation					
BSC	$0	$663,000	$1,142,000	$419,000	$2,224,000
Trikafta Plus BSC	$6,310,000	$784,000	$396,000	$51,000	$7,541,000

BSC: best supportive care

Table 5.10. Incremental Cost-Effectiveness Ratios Compared to Best Supportive Care (BSC) for the Base Case (Discounted at 3% per Year)

Treatment vs. BSC	Cost Per QALY Gained	Cost Per evLYG	Cost Per LY Gained	Cost Per PEx Averted
Population 1 - Eligible for Kalydeco Monotherapy Only				
Kalydeco Plus BSC	$1,370,000	$1,180,000	$1,450,000	$737,000
Population 2 - Homozygous for the *F508del* Mutation				
Orkambi Plus BSC	$1,480,000	$1,360,000	$1,440,000	$614,000
Symdeko Plus BSC	$1,380,000	$1,200,000	$1,400,000	$621,000
Trikafta Plus BSC	$1,160,000	$1,040,000	$1,230,000	$675,000
Population 3 - Heterozygous *F508del* with Residual Function Mutation				
Symdeko Plus BSC	$1,340,000	$1,100,000	$1,390,000	$549,000
Trikafta Plus BSC	$1,100,000	$951,000	$1,210,000	$539,000
Population 4 - Heterozygous *F508del* with Minimal Function Mutation				
Trikafta Plus BSC	$1,050,000	$877,000	$990,000	$565,000

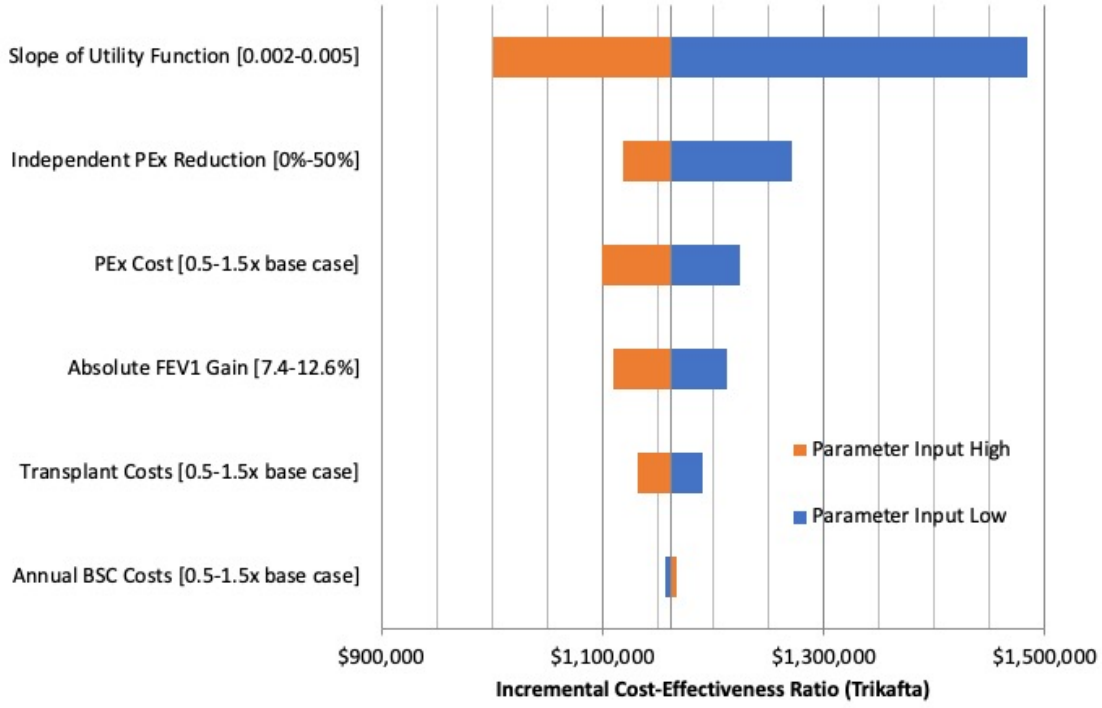
BSC: best supportive care; QALY: quality adjusted life year; evLYG: equal value life year gained; LY: life year; PEx: acute pulmonary exacerbation

Sensitivity Analysis Results

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (e.g., standard errors) or reasonable ranges to evaluate changes in cost per additional QALY for CFTR modulators plus best supportive care versus best supportive care alone. Because utilities depending on the $ppFEV_1$ value were a linear equation, we varied the slope of the line (base case, 0.003476). For example, for a $ppFEV_1$ of 70% we varied the utility from 0.73 to 0.94 (base case, 0.84). Drug cost variation is described as part of threshold analyses (see below).

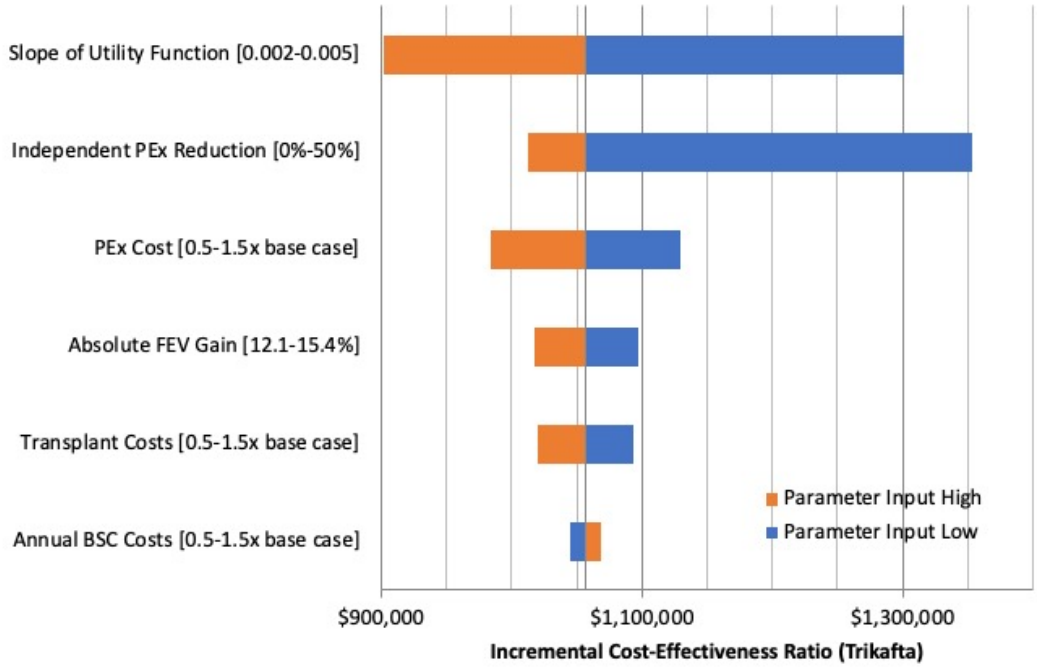
The impacts of variations in input values on cost-per-QALY estimates are shown for Trikafta in CF individuals homozygous for *F508del* mutation in Figure 5.4, and in individuals heterozygous for *F508del* mutation and minimal function mutation in Figure 5.5. The analyses were most sensitive to assumptions about the lung function-specific utilities, assumptions about the independent effect of the CFTR modulator on the risk of acute pulmonary exacerbations, and the costs associated with acute pulmonary exacerbations. While changes in these parameters resulted in large variations in cost-effectiveness estimates, they did not approach commonly cited thresholds. Also, while not shown in the figures, we recognize that the difference in resource intensity and costs by level of lung function might have changed over time (our source for this differential was published in 1996), and so varied the differential in background costs across $ppFEV_1$ categories by multiplying costs by a factor of 0.5-1.5 times the base-case values (with the higher value resulting in larger absolute cost differences across the three categories), and again found that the cost per QALY estimates did not approach commonly used thresholds. Results were similar for the other drugs in each population, with results shown in Appendix Figures E1-E4.

Figure 5.4. Tornado Diagram for One-Way Sensitivity Analyses of Cost per QALY Gained for Trikafta Plus Best Supportive Care Versus Best Supportive Care Alone in CF Individuals Homozygous for *F508del* Mutation



PEx: acute pulmonary exacerbation; BSC: best supportive care

Figure 5.5. Tornado Diagram for One-Way Sensitivity Analyses of Cost per QALY Gained for Trikafta Plus Best Supportive Care Versus Best Supportive Care Alone in CF Individuals Heterozygous for *F508del* Mutation and Minimal Function Mutation



PEx: acute pulmonary exacerbation; BSC: best supportive care

We also evaluated the uncertainty in the model parameters simultaneously by conducting a probabilistic sensitivity analysis (Table 5.11). For all CFTR modulators in all CF populations evaluated, the number of iterations in which the CFTR modulators were cost-effective at a threshold of $500,000 per QALY or lower (or $200,000 per QALY or lower for Trikafta) was approximately 0%. Scatterplots showing the incremental costs and incremental effectiveness results from the probabilistic sensitivity analyses, with various cost-effectiveness thresholds, can be found in Figures E5-E8 in Appendix E.

Table 5.11. Probabilistic Sensitivity Analysis Results: CFTR Modulators Versus Best Supportive Care (Probability of Being Cost-Effective at Different Cost-Effectiveness Thresholds)

CF Population and CFTR Modulator	Cost-Effective at $50,000 per QALY	Cost-Effective at $100,000 per QALY	Cost-Effective at $150,000 per QALY	Cost-Effective at $200,000 per QALY	Cost-Effective at $300,000 per QALY	Cost-Effective at $500,000 per QALY
Population 1 - Eligible for Kalydeco Monotherapy Only						
Kalydeco plus BSC	0%	0%	0%	0%	0%	0%
Population 2 - Homozygous for the *F508del* Mutation						
Symdeko plus BSC	0%	0%	0%	0%	0%	0%
Trikafta plus BSC	0%	0%	0%	0%	--	--
Population 3 - Heterozygous *F508del* with Residual Function Mutation						
Symdeko plus BSC	0%	0%	0%	0%	0%	0%
Trikafta plus BSC	0%	0%	0%	0%	--	--
Population 4 - Heterozygous *F508del* with Minimal Function Mutation						
Trikafta plus BSC	0%	0%	0%	0%	--	--

CFTR: cystic fibrosis transmembrane conductance regulator gene; QALY: quality-adjusted life year; BSC: best supportive care

Table 5.12 shows the 95% credible intervals for each probabilistic sensitivity analysis. These intervals would include the incremental ratio from 95% of the simulations done in the sensitivity analysis. For example, the 95% credible interval for the incremental cost-effectiveness ratios for Kalydeco compared with best supportive care for CF patients eligible for Kalydeco only was $863,600 to $2,474,300 per QALY.

Table 5.12. Probabilistic Sensitivity Analysis Results: CFTR Modulators Versus Best Supportive Care (95% Credible Intervals)

CF Population and CFTR Modulator	95% Credible Interval from Probabilistic Sensitivity Analyses
Population 1 - Eligible for Kalydeco Monotherapy Only	
Kalydeco plus BSC	$863,600 - $2,474,300 per QALY gained
Population 2 - Homozygous for the *F508del* Mutation	
Symdeko plus BSC	$821,400 - $2,464,000 per QALY gained
Trikafta plus BSC	$797,500 - $1,850,300 per QALY gained
Population 3 - Heterozygous *F508del* with Residual Function Mutation	
Symdeko plus BSC	$854,100 - $2,654,500 per QALY gained
Trikafta plus BSC	$733,900 - $1,886,200 per QALY gained
Population 4 - Heterozygous *F508del* with Minimal Function Mutation	
Trikafta plus BSC	$749,000 - $1,511,000 per QALY gained

Scenario Analyses Results

Modified Societal Perspective

We incorporated the costs associated with lost productivity in individuals with CF as a result of not being able to work full time in the absence of CFTR modulator therapies as well as lost productivity due to acute pulmonary exacerbations (Table 5.13). For individuals eligible only for Kalydeco monotherapy only we projected that the difference in lifetime (discounted) indirect costs was $73,200. We acknowledge that the indirect costs are likely an underestimate due to the lack of data on the impact of caregiver burden with CFTR modulators. In addition, the indirect costs due to employment are realized in the future and thus the gains are diminished by discounting. For example, including productivity losses in the analysis resulted in incremental cost-effectiveness ratios for Kalydeco very similar to those seen in the base case ($1,352,000 per QALY societal vs. $1,367,000 per QALY base case). However, the impact on indirect costs would need to be substantial in order for the cost-effectiveness ratios from a societal perspective to reach commonly-used thresholds. Estimates for the incremental cost-effectiveness ratios for the CFTR modulators for the other three populations also tracked very closely with base case estimates (Table 5.13). Modified societal estimates for cost per evLYG were similar to those for cost per QALY. For example, for Trikafta in the homozygous *F508del* population, the cost per evLYG was $1,025,000 (compared with $1,148,000 per QALY). Other cost per evLYG results are shown in Appendix Table E4.

Table 5.13. Incremental Cost-Effectiveness Ratios Compared to Best Supportive Care (BSC) for the Societal Perspective

Treatment vs. BSC	Incremental Costs	Incremental QALYs	Cost Per QALY Gained
Population 1 - Eligible for Kalydeco Monotherapy Only			
Kalydeco plus BSC	$6,373, 000	4.72	$1,352,000
Population 2 - Homozygous for the *F508del* Mutation			
Symdeko plus BSC	$5,796,000	4.27	$1,357,000
Trikafta plus BSC	$6,302,000	5.49	$1,148,000
Population 3 - Heterozygous *F508del* with Residual Function Mutation			
Symdeko plus BSC	$6,069,000	4.60	$1,319,000
Trikafta plus BSC	$6,601,000	6.08	$1,087,000
Population 4 - Heterozygous *F508del* with Minimal Function Mutation			
Trikafta plus BSC	$5,234,000	5.04	$1,038,000

BSC: best supportive care; QALY: quality adjusted life year

Long-Term Effectiveness Assumptions

In the base case we assumed that CFTR modifiers would result in 50% of the annual declines in $ppFEV_1$ as for best supportive care, after the first two years without any decline. In this scenario analysis we varied that assumption from 0% (i.e., no decline in $ppFEV_1$ over an individual's lifetime) to 100% (i.e., the same annual decline as those on best supportive care after the first two years on drug) (Table 5.14). For CF individuals eligible only for Kalydeco monotherapy only, the incremental cost-effectiveness ratio for Kalydeco was $856,000 per QALY when we assumed that there was no long-term decline in $ppFEV_1$ (i.e., the drug increased $ppFEV_1$ at the start of therapy and individuals' lung function remained constant for the remainder of their lifetime). Similar declines in incremental cost-effectiveness ratios were found with other drugs and populations (Table 5.14). Long-term effectiveness scenario estimates for cost per evLYG were similar to those for cost per QALY and are shown in Appendix Table E5.

Table 5.14. Incremental Cost-Effectiveness Ratios ($ per QALY) Compared to Best Supportive Care for the Long-Term Effectiveness Assumption

Treatment vs. BSC	0% Decline	25% Decline	75% Decline	100% Decline
Population 1 - Eligible for Kalydeco Monotherapy Only				
Kalydeco plus BSC	$856,000	$1,060,000	$1,835,000	$2,578,000
Population 2 - Homozygous for the *F508del* Mutation				
Symdeko plus BSC	$866,000	$1,068,000	$2,041,000	$2,623,000
Trikafta plus BSC	$817,000	$965,000	$1,431,000	$1,810,000
Population 3 - Heterozygous *F508del* with Residual Function Mutation				
Symdeko plus BSC	$820,000	$991,000	$1,614,000	$2,183,000
Trikafta plus BSC	$763,000	$886,000	$1,148,000	$1,559,000
Population 4 - Heterozygous *F508del* with Minimal Function Mutation				
Trikafta plus BSC	$784,000	$903,000	$1,225,000	$1,445,000

BSC: best supportive care

$ppFEV_1$ Recovery After Acute Pulmonary Exacerbation Assumptions

In the base case we assumed that CF individuals' $ppFEV_1$ would fully recover to baseline following acute pulmonary exacerbations, allowing only for the natural decline in lung function and the impact of the CFTR drugs on that natural decline. In this scenario analysis we varied that assumption from 0% (i.e., no additional decline in $ppFEV_1$ due to pulmonary exacerbation) to 5% (i.e., a 5% absolute decline in $ppFEV_1$ for each pulmonary exacerbation experienced) (Table 5.15). For CF individuals eligible for Kalydeco monotherapy only, the incremental cost-effectiveness ratio

for Kalydeco was $1,122,000 per QALY when we assumed that there was a 5% absolute decline in $ppFEV_1$ for each pulmonary exacerbation experienced. Similar declines in ICERs were found with other drugs and populations (Table 5.15). Recovery after acute pulmonary exacerbation scenario estimates for cost per evLYG were similar to those for cost per QALY and are shown in Appendix Table E6.

Table 5.15. Incremental Cost-Effectiveness Ratios ($ per QALY) Compared to Best Supportive Care for the Lung Function Recovery After Pulmonary Exacerbation Assumption

Treatment vs. BSC	1% Decline	3% Decline	5% Decline
Population 1 - Eligible for Kalydeco Monotherapy Only			
Kalydeco plus BSC	$1,242,000	$1,152,000	$1,122,000
Population 2 - Homozygous for the *F508del* Mutation			
Symdeko plus BSC	$1,205,000	$1,082,000	$1,035,000
Trikafta plus BSC	$1,027,000	$924,000	$883,000
Population 3 - Heterozygous *F508del* with Residual Function Mutation			
Symdeko plus BSC	$1,094,000	$975,000	$923,000
Trikafta plus BSC	$933,000	$841,000	$802,000
Population 4 - Heterozygous *F508del* with Minimal Function Mutation			
Trikafta plus BSC	$943,000	$856,000	$824,000

BSC: best supportive care

Independent Utility Effect

In the base case, we assumed that CF individuals' utility was based only on lung function (i.e., $ppFEV_1$, acute pulmonary exacerbations, lung transplantations). In this scenario analysis we varied an independent utility effect (i.e., using a multiplier to the lung-function-informed utility) due to CFTR therapy from 1 (no independent effect) to 1.05 (a 5% increase in utility with drug), above that due to lung function improvement (Table 5.16). For CF individuals eligible only for Kalydeco, the incremental cost-effectiveness ratio for Kalydeco was $1,141,000 per QALY when we assumed that there was a 5% increase in utility due to drug that is independent of lung function improvement. Similar declines in incremental ratios were found with other drugs and populations (Table 5.16). Independent utility effect scenario estimates for cost per evLYG were similar to those for cost per QALY and are shown in Appendix Table E7.

Table 5.16. Incremental Cost-Effectiveness Ratios ($ per QALY) Compared to Best Supportive Care for the Non-Respiratory Utility Assumption

Treatment vs. BSC	1% Increase	2% Increase	4% Increase	5% Increase
Population 1 - Eligible for Kalydeco Monotherapy Only				
Kalydeco plus BSC	$1,315,000	$1,266,000	$1,178,000	$1,141,000
Population 2 - Homozygous for the *F508del* Mutation				
Symdeko plus BSC	$1,317,000	$1,261,000	$1,165,000	$1,123,000
Trikafta plus BSC	$1,122,000	$1,082,000	$1,011,000	$980,000
Population 3 - Heterozygous *F508del* with Residual Function Mutation				
Symdeko plus BSC	$1,195,000	$1,149,000	$1,064,000	$1,027,000
Trikafta plus BSC	$1,015,000	$983,000	$921,000	$894,000
Population 4 - Heterozygous *F508del* with Minimal Function Mutation				
Trikafta plus BSC	$1,023,000	$990,000	$934,000	$909,000

BSC: best supportive care

CFTR Effect on Risk of CFRD

In the base case we assumed that CFTR modulator therapy did not reduce an individual's risk of developing CFRD. In this scenario analysis we allowed CFTR modulator treatment to reduce the annual risk of CFRD between 5% and 23% (Table 5.17). For CF individuals eligible only for Kalydeco, the incremental cost-effectiveness ratio for Kalydeco was $1,364,000 per QALY when we assumed that there was a 23% reduction in the annual risk of CFRD due to the drug. Similar declines in incremental ratios were found with other drugs and populations (Table 5.17). CFTR effect on the risk of CFRD scenario estimates for cost per evLYG were similar to those for cost per QALY and are shown in Appendix Table E8.

Table 5.17. Incremental Cost-Effectiveness Ratios ($ per QALY) Compared to Best Supportive Care for the Assumption of Drug Effect on CF-Related Diabetes

Treatment vs. BSC	5% Decrease	23% Decrease
Population 1 - Eligible for Kalydeco Monotherapy Only		
Kalydeco plus BSC	$1,367,000	$1,364,000
Population 2 - Homozygous for the *F508del* Mutation		
Symdeko plus BSC	$1,378,000	$1,364,000
Trikafta plus BSC	$1,162,000	$1,156,000
Population 3 - Heterozygous *F508del* with Residual Function Mutation		
Symdeko plus BSC	$1,244,000	$1,239,000
Trikafta plus BSC	$1,051,000	$1,049,000
Population 4 - Heterozygous *F508del* with Minimal Function Mutation		
Trikafta plus BSC	$1,055,000	$1,052,000

Eligibility Age of 6 Years Old for Trikafta

Anticipating that the eligibility age for Trikafta will soon be lowered to age 6, we conducted an analysis where we started CFTR modulator therapy at that age (assuming the same treatment effects as ages 12+). Table 5.18 shows the cost-effectiveness results in the three eligible populations. CFTR effect on the risk of CFRD scenario estimates for cost per evLYG were similar to those for cost per QALY and are shown in Appendix Table E9.

Table 5.18. Incremental Cost-Effectiveness Ratios Compared to Best Supportive Care (BSC) for Starting Trikafta at Age 6 Years of Age (Discounted at 3% per Year)

Treatment vs. BSC	Total cost	QALYs	Cost Per QALY Gained
Population 2 - Homozygous for the *F508del* Mutation			
BSC	$2,088,000	15.77	--
Trikafta Plus BSC	$8,449,000	20.81	$1,262,000
Population 3 - Heterozygous *F508del* with Residual Function Mutation			
BSC	$2,210,000	16.31	--
Trikafta Plus BSC	$8,901,000	22.06	$1,164,000
Population 4 - Heterozygous *F508del* with Minimal Function Mutation			
BSC	$2,178,000	14.01	--
Trikafta Plus BSC	$8,206,000	19.30	$1,139,000

BSC: best supportive care; LY: life year; QALY: quality adjusted life years; PEx: pulmonary exacerbation

Reduced Need for Best Supportive Care Therapies with Trikafta

Our results were not sensitive to variations in the best supportive care (e.g., disease management) costs when varied by a factor of 0.5-1.5 of the base-case values, though those analyses assume that the best supportive care costs varied for both CFTR treated and untreated patients. The results were slightly more sensitive when we allowed best supportive care costs to decrease only for the Trikafta treated patients (under the assumption that Trikafta will alleviate the need for other supportive treatments). For example, when we reduced the cost of best supportive care by 75%, the incremental ratio for Trikafta in CF individuals homozygous for *F508del* mutation changed from $1,163,000 per QALY to $1,052,000 per QALY. The incremental cost-effectiveness ratio for Trikafta in CF individuals heterozygous for *F508del* mutation with a residual function mutation changed from $1,101,000 per QALY to $998,000 per QALY. The incremental cost-effectiveness ratio for Trikafta in CF individuals heterozygous for *F508del* mutation with a minimal function mutation changed from $1,055,000 per QALY to $938,000 per QALY.

Curative Scenario

Even though Trikafta is not considered curative, to estimate an extreme lower bound (i.e., extreme favorable estimate) for its potential cost-effectiveness at the current price, we examined an extreme-case scenario for Trikafta for eligible CF patients who are either homozygous for the *F508del* mutation or who are heterozygous for the *F508del* mutation and a minimal function mutation. Expected lifetime costs and QALYs for these two populations are the same starting at birth so we grouped them together as the comparator. For patients treated with Trikafta, we assumed that the only costs were due to Trikafta and derived the benefit using the QALYs of the general population starting from birth (with drug beginning at 6 months and full adherence to therapy). The discounted QALYs gained for Trikafta under this scenario were approximately 11.62 (27.79 minus 16.17). The discounted cost associated with Trikafta – net of costs associated with those not receiving Trikafta – was an estimated $7,109,000 ($9,172,000 minus $2,063,000), yielding an incremental cost-effectiveness ratio of $612,000 per QALY for Trikafta in this scenario at its current price.

Threshold Analysis Results

Annual prices necessary to reach cost-effectiveness thresholds of $50,000, $100,000, $150,000, $200,000, $300,000, and $500,000 per QALY are listed in Table 5.19 for each CF population and CFTR modulator. Threshold prices for Trikafta are calculated only for cost-effectiveness thresholds less than $200,000 per QALY because it does not qualify for the ultra-rare disease framework.

Threshold prices were higher for the CF population heterozygous for *F508del* mutation and residual function mutation for Symdeko, and higher for CF individuals heterozygous for *F508del* mutation for Trikafta. A discount of 54% to 58% would be necessary to reach a cost-effectiveness threshold of

$500,000/QALY for Kalydeco, Orkambi, and Symdeko. A discount of 68% to 72% would be necessary to reach a cost-effectiveness threshold of $200,000/QALY for Trikafta.

Table 5.19. Threshold Analysis Results Presented as Annual Prices

	Annual WAC	Price to Achieve $50,000 per QALY	Price to Achieve $100,000 per QALY	Price to Achieve $150,000 per QALY	Price to Achieve $200,000 per QALY	Price to Achieve $300,000 per QALY	Price to Achieve $500,000 per QALY
Population 1 - Eligible for Kalydeco Monotherapy							
Kalydeco	$311,700	$48,600	$58,600	$68,600	$78,600	$98,500	$138,500
Population 2 - Homozygous for the *F508del* Mutation							
Orkambi	$272,600	$42,800	$50,800	$58,900	$66,900	$83,000	$115,100
Symdeko	$292,200	$46,500	$55,800	$65,000	$74,300	$92,900	$129,900
Trikafta	$311,700	$52,300	$64,000	$75,600	$87,300	N/A	N/A
Population 3 - Heterozygous *F508del* with Residual Function Mutation							
Symdeko	$292,200	$48,400	$57,900	$67,300	$76,800	$95,700	$133,600
Trikafta	$311,700	$54,700	$67,000	$79,200	$91,400	N/A	N/A
Population 4 - Heterozygous *F508del* with Minimal Function Mutation							
Trikafta	$311,700	$61,500	$74,000	$86,400	$98,900	N/A	N/A

WAC: wholesale acquisition cost; QALY: quality adjusted life year gained; N/A: not applicable because drug does not qualify for the ultra-rare disease framework

Note that Symdeko and Trikafta are each used for treatment in multiple populations. Therefore, we also calculated population-weighted threshold prices using estimated numbers of patients in each population. (We assumed approximately 8,870 CF individuals homozygous for *F508del* mutation, 1,926 CF individuals heterozygous for *F508del* mutation with a residual function mutation, and 6,070 CF individuals heterozygous for *F508del* mutation with a minimal function mutation.) The blended annual prices for Symdeko across the two relevant populations at the $50,000, $100,000, and $150,000 per QALY threshold prices were approximately $46,900, $56,200, and $65,500, respectively, and at the $500,000 per QALY threshold price was approximately $130,100. The blended annual prices for Trikafta across the three relevant populations at the $50,000, $100,000, and $150,000 per QALY threshold prices were approximately $55,900, $67,900, and $79,900, respectively, and at the $200,000 per QALY threshold price was approximately $91,900.

Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental Appendix materials). We also conducted sensitivity analyses with null input values to ensure the model was producing

findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

Model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments.

Prior Economic Models

We identified one prior published, US-based cost-effectiveness analysis of Kalydeco conducted by Dilokthornsakul and colleagues, who modeled the long-term costs and outcomes of Kalydeco treatment of CF patients with the *G551D* mutation.[121] They developed a Markov model with a lifetime horizon and US payer perspective, comparing each treatment to usual care. Our models were informed by these prior models, and therefore share some similarities, including time horizon, perspective, and the base-case assumption of 50% decline in efficacy two years after treatment initiation. The prior model included health states for three categories defined by lung function (mild: $ppFEV_1 \geq 70\%$, moderate: $40\% \leq ppFEV_1 < 70\%$, and severe: $ppFEV_1 < 40\%$), while the ICER analysis models $ppFEV_1$ as a continuous value.

Although base-case outcomes in the 2016 analysis[121] were undiscounted, results were also presented using an annual discount rate of 3%. Discounted incremental QALYs were 5.21, incremental lifetime costs approximately $3,658,000, and the base-case incremental cost–effectiveness ratio was approximately $705,000 per QALY (2013 US$ converted to 2019 using the personal consumption expenditure [PCE] price index). Our current analysis estimated incremental QALYs of 4.72, incremental costs of $6,446,000, and an incremental cost-effectiveness ratio of approximately $1,367,000 per QALY. Starting age for treatment in the prior Kalydeco model was 25 years old, while we modeled treatment initiation at six months old. Dilokthornsakul et al. also assumed that the drug price would drop to 10% of that amount after patent expiration in 2027 and did not incorporate age-specific utilities. These assumptions, along with the later age of treatment initiation, may have led to the lower ICER observed in the analysis by Dilokthornsakul and colleagues.

Prior to the Dilokthornsakul et al analysis, Whiting and colleagues modeled the cost-effectiveness of Kalydeco treatment of CF patients aged six years or older (with median age = 20 years) with *G551D* mutation in the United Kingdom.[104] They modified a deterministic simulation model developed by Vertex Pharmaceuticals, Inc. to add lung transplantations. That analysis was conducted from the UK National Health Service perspective, with a lifetime horizon and 3.5% discount rate for costs and outcomes. For long-term effects of Kalydeco treatment on $ppFEV_1$ decline, they modeled three different scenarios: conservative, with same rate of decline as for standard care; intermediate, with 66% rate of decline; and optimistic, with stable $ppFEV_1$ over lifetime. The cost of Kalydeco used in

the model was £182,000 (approximately $317,000 in 2019 US$), with the assumption that it would decline to £20,000 in 14 years, due to loss of patent exclusivity. They used UK-based utility values and costs for usual care, making these results less comparable to our US-based analysis. This model led to estimated QALY gains of 1.27 (in the conservative scenario), 2.16 (in the intermediate scenario), and 5.26 (in the optimistic scenario), the latter being closest to our current model estimate of 4.72 incremental QALYs. The incremental cost-effectiveness ratio was estimated to vary between £335,000 and £1,274,000 per QALY (approximately $584,000 to $2,221,000 in 2019 US$).

5.4 Summary and Comment

We developed individual-level microsimulation models to project the lifetime benefits and costs of CFTR modulator therapies for four different CF cohorts. The drugs increased lung function, decreased lung function decline over time, increased weight-for-age *z*-scores, and decreased the number of acute pulmonary exacerbations and lung transplantations over the lifetime of populations. The base-case models did not account for non-lung (or weight) aspects of the disease, nor did they decrease the need for CF-related supportive care. However, we did address these limitations by conducting several relevant scenario analyses. Overall, all drugs (plus best supportive care) evaluated were very effective compared with best supportive care alone in all populations studied, with life expectancy gains ranging from 12.9 years for Orkambi to 19.3 years for Trikafta (undiscounted). Discounted QALY gains ranged from 3.66 to 6.08, discounted CFTR drug-related costs ranged from $6.2 million to $7.7 million, and the incremental cost-effectiveness ratios of CFTR drugs plus best supportive care compared with best supportive care alone were $1,370,000 per QALY for Kalydeco, $1,480,000 per QALY for Orkambi, $1,340,000 to $1,138,000 per QALY for Symdeko, and $1,050,000 to $1,160,000 per QALY for Trikafta. Using evLYG, the incremental cost-effectiveness ratios of CFTR drugs plus best supportive care compared with best supportive care alone were $1,180,000 per evLYG for Kalydeco, $1,360,000 per evLYG for Orkambi, $1,100,000 to $1,200,000 per evLYG for Symdeko, and $877,000 to $1,040,000 per evLYG for Trikafta. For Trikafta, we also evaluated a scenario where we assumed no CF-related costs beyond the cost of the drug and assumed no CF-related mortality or HRQoL effects. This analysis provided an extreme lower bound (i.e., extreme favorable estimate) on the cost-effectiveness of Trikafta at its current price and still resulted in an ICER of $612,000 per QALY, which is well above commonly-used thresholds for cost effectiveness. Our results were robust to variations in parameter estimates, adopting a societal perspective, or using life years gained as the health outcome, with the exception of decreases in annual drug costs.

Limitations

There are several limitations to our analysis that deserve mention. We used $ppFEV_1$ as the primary marker of lung function to characterize the progression of CF over time. Trials generally did not

include patients with either very low or very high lung function, which may impact the generalizability of our results. Furthermore, based on available evidence, only the effect of the CFTR modulators on lung function, weight, and acute pulmonary exacerbations were included in the model. As any surrogate marker of disease, it is not a perfect marker for progression. We conducted a scenario analysis and found that a 5% increase in non-respiratory-related utility would decrease the incremental cost-effectiveness ratios by approximately 13% to 23% for all drugs and populations. In addition, limited evidence exists about the CFTR modulators' impact on individuals' ability to work or attend school, or the degree to which caregiver burden is reduced by CFTR modulator treatment. Such information would better inform our analysis from a societal perspective. More importantly, we only had short-term measures of drug effect and had to make assumptions about their effect over the lifetime of the patient. In addition, we used trial-based estimates of discontinuation of these therapies to be consistent with the efficacy estimates; real-world patterns of discontinuation may differ from these.

Conclusions

We found that CFTR modulator therapies plus best supportive care substantially improves patient health outcomes compared to best supportive care. Because of the high cost of these drugs, however, the cost effectiveness of CFTR modulator therapies exceeds commonly used cost-effectiveness thresholds. For ultra-rare diseases, decision-makers often give special weighting to other benefits and to contextual considerations that may lead to coverage and funding decisions at higher cost-effectiveness thresholds than applied to decisions about other treatments. We evaluated thresholds up to $500,000 per QALY for Kalydeco, Orkambi, and Symdeko (with total eligible populations below 10,000) and still found that drug prices would need to be substantially reduced to be considered cost effective at this threshold. For Trikafta, which does not qualify for the ultra-rare disease framework, discounts greater than 70% would be necessary to reach commonly used cost-effectiveness thresholds.

6. 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. We also recognize that there may be broader contextual issues related to the severity of the condition, whether other treatments are available, and ethical, legal, or other societal priorities that influence the relative value of illnesses and interventions. These general elements are listed in the table below, and the subsequent text provides detail about the elements that are applicable to the comparison of adding versus not adding CFTR modulators to standard care for CF patients. We sought input from stakeholders, including individual patients, patient advocacy organizations, and clinicians to inform the contents of this section.

Each ICER review culminates in a public meeting of an independent voting Council of clinicians, patients, and health services researchers. As part of their deliberations, Council members will judge whether a treatment may substantially impact the considerations listed in Table 6.1. The presence of substantial other benefits or contextual considerations may shift a council member's vote on an intervention's long-term value for money to a different category than would be indicated by the clinical evidence and cost-effectiveness analyses alone. For example, a council member may initially consider a therapy with an incremental cost-effectiveness ratio of $150,000 per QALY to represent low long-term value for money. However, the Council member may vote for a higher value category if they consider the treatment to bring substantial other benefits or contextual considerations. Conversely, disadvantages associated with a treatment may lead a Council member to vote for a lower value category. A Council member may also determine that there are no other benefits or contextual considerations substantial enough to shift their vote. All factors that are considered in the voting process are outlined in ICER's value assessment framework. The content of these deliberations is described in the last chapter of ICER's Final Evidence Report, which is released after the public meeting.

This section, as well as the Council's deliberation, provides stakeholders with information to inform their decisions on a range of issues, including shared decision-making between patients and clinicians, coverage policy development, and pricing negotiations.

Table 6.1. 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 the patient's ability to return to work or school and/or their overall productivity.
This intervention will have a significant positive impact outside the family, including on schools and/or communities.
This intervention will have a significant impact on the entire "infrastructure" of care, including effects on screening for affected patients, on the sensitization of clinicians, and on the dissemination of understanding about the condition, that may revolutionize how patients are cared for in many ways that extend beyond the treatment itself.
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 best supportive treatment, there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to best supportive treatment, 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.

6.1 Potential Other Benefits

CF represents a major and lifelong burden to patients and their caregivers. As described in Section 2, important aspects of the lived experience of CF patients and their informal caregivers are not captured by quality of life instruments or by the typically used outcomes in trials and registries. It is likely that there are improvements in the quality of life (for instance, improved sleep, energy, hope for the future and a reduction in anxiety and depression) with CFTR modulator treatment that may not be fully reflected in our model estimate.

We heard from many patients and caregivers who reported that individuals who experience large clinical benefits from modulator therapy are able to spend less time on other aspects of their care regimen and in some cases have reduced or eliminated the use of some supportive care (e.g., hypertonic saline, insulin, laxatives), while others need to continue full best supportive care. Similarly, reducing the number of non-modulator treatments patients take would translate to less caregiver time spent on treatment, thus reducing the impact of CF on family and caregivers. However, as mentioned in Section 4, there are currently no data to inform individual decision-making around which treatments are essential versus those that may be reduced or stopped. There is a randomized trial, SIMPLIFY, that is currently recruiting participants to answer this question.[19] Improved health and symptom control may also translate to caregiver benefits by decreasing anxiety associated with a loved one having a severe condition.

The time costs associated with CF and its complications are large and lifelong. While the time costs of patients are partially accounted for in the analyses from a societal perspective, the time costs for their informal caregivers are difficult to estimate from the available literature.

The approval of Trikafta, more specifically its elexacaftor component, represents a new treatment approach that will provide an option to patients whose mutations were not amenable to treatment with the other modulator therapies (those who are heterozygous for the *F508del* mutation and a minimal function mutation), and may also benefit patients for whom existing therapies were not successful (i.e., those who are homozygous for the *F508del* mutation, and those heterozygous for the *F508del* mutation with a residual function mutation).

6.2 Contextual Considerations

CF is a condition with major impacts on both length and quality of life, and represents a high lifetime burden of disease.

However, other than for Kalydeco, the evidence is sparse, especially for the long-term effects of CFTR modulators on disease progression. Our modeling analyses assumes that there are reductions in the rate of CF progression, which may be overly optimistic. The magnitude and sustainability of such effects remain uncertain.

Currently, the CFTR modulators are the only available interventions that target the primary pathophysiology of the disease. Short of a cure for CF, modulators have the potential to dramatically alter the course of this disease, particularly for those who start treatment at a young age.

7. Health-Benefit Price Benchmarks

Annual prices of each CFTR modulator that would achieve incremental cost-effectiveness ratios of $100,000 and $150,000 per QALY or evLYG are presented in Table 7.1, with corresponding prices per day shown in Appendix Table E10. These are blended threshold prices that reflect the population-weighted average of the threshold prices across the relevant populations for each drug. The cost per evLYG price ranges are slightly higher than the cost per QALY ranges because each of these treatments was estimated to result in slightly higher evLYG than QALYs gained in the base-case analysis.

The ICER health benefit price benchmark (HBPB) is a price range suggesting the highest price a manufacturer should charge for a treatment, based on the amount of improvement in overall health patients receive from that treatment, when a higher price would cause disproportionately greater losses in health among other patients due to rising overall costs of health care and health insurance. In short, it is the top price range at which a health system can reward innovation and better health for patients without doing more harm than good.

Table 7.1. Annual Cost-Effectiveness Threshold Prices for Kalydeco, Orkambi, Symdeko, and Trikafta

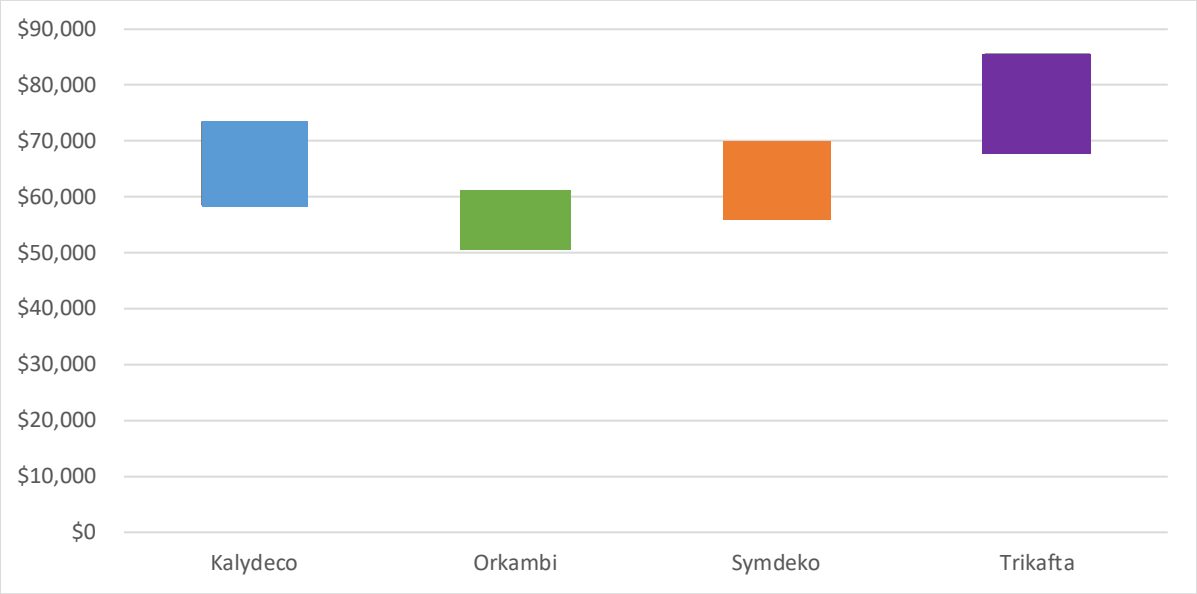
Annual Prices Using…	Annual WAC	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold	Discount from WAC to Reach Threshold Prices
Kalydeco				
QALYs Gained	$311,700	$58,600	$68,600	78% to 81%
evLYG		$61,800	$73 400	76% to 80%
Orkambi				
QALYs Gained	$272,600	$50,800	$58,900	78% to 81%
evLYG		$52,300	$61,000	78% to 81%
Symdeko				
QALYs Gained	$292,200	$56,200	$65,500	78% to 81%
evLYG		$59,100	$69,900	76% to 80%
Trikafta				
QALYs Gained	$311,700	$67,900	$79,900	74% to 78%
evLYG		$71,600	$85,500	73% to 77%

WAC: wholesale acquisition cost; evLYG: equal value life year gained; QALY: quality-adjusted life year

The HBPB ranges for each drug are shown in Figure 7.1. The HBPB range would require 76% to 81% discounts from WAC for both Kalydeco and Symdeko, with the HBPB range at $58,600 to $73,400 per year for Kalydeco, and $56,200 to $69,900 per year for Symdeko. The HBPB range for Orkambi is $50,800 to $61,000 (78% to 81% discount from WAC). For Trikafta, the HBPB range is $67,900 to

$85,500 per year, requiring 73% to 78% discounts from WAC. The HBPB ranges for the drugs follow the pattern we would expect given the cost-effectiveness analysis results, with Trikafta highest, followed by Kalydeco, Symdeko, and Orkambi.

Figure 7.1. Health Benefit Price Benchmark Ranges per Year for Kalydeco, Orkambi, Symdeko, and Trikafta



8. Potential Budget Impact

8.1 Overview

We used the cost-effectiveness model to estimate the potential total budgetary impact of the recently approved Trikafta for prevalent individuals in the United States (US) with CF aged 12 years and older who have at least one *F508del* mutation in the *CFTR* gene (following the FDA label indication). In our estimates of potential budget impact, we used the wholesale acquisition cost (WAC) as the base case price, and the blended $50,000, $100,000, and $150,000 cost-effectiveness threshold prices across the three populations eligible for Trikafta. We did not include the other therapies modeled above in this potential budget impact analysis, given their established presence on the market.

8.2 Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over a five-year time horizon, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy.

This potential budget impact analysis includes the estimated number of individuals with CF in the US who would be eligible for treatment with Trikafta (populations 2, 3, and 4 above). To estimate the size of the potential candidate populations for treatment, we used estimates from the CF Foundation Patient Registry (CFFPR) of individuals with CF in the US who were greater than 12 years old and had any *F508del* mutation.[11] We assumed that all eligible patients would add or switch to Trikafta upon reaching 12 years of age. The CFFPR in 2018 reports 8,870 CF patients homozygous for the *F508del* mutation aged 12 and older (population 2), all of whom were assumed to be eligible for Trikafta. We assumed that 20% of these patients (1,774) would initiate Trikafta in each of the five years for population 2. We also assumed that all patients over the age of 12 and heterozygous for an *F508del* mutation with a residual function mutation (population 3) were eligible for Trikafta. To calculate the number in this population, we used estimates of the number of patients aged 12 and older with heterozygous *F508del* mutation multiplied by the proportions of patients with residual versus minimal function mutations in patients with Class IV-V mutations (79%) or other mutations (29%). Applying these proportions, our potential budget impact model assumes 1,925 cystic fibrosis patients heterozygous for *F508del* mutation with residual function mutations in the United States will be eligible for Trikafta. We assumed that 20% of these patients would initiate

Trikafta in each of the five years, or 385 patients per year. Similarly, we also assumed that all patients over the age of 12 and heterozygous for an *F508del* mutation with a minimal function mutation (population 4) were eligible for Trikafta. To calculate the number in this population, we used estimates of the number of patients aged 12 and older with heterozygous *F508del* mutation multiplied by the proportions of patients with minimal function mutations in patients with Class IV-V mutations (21%) or other mutations (71%). Applying these proportions, our potential budget impact model assumes 6,070 cystic fibrosis patients heterozygous for *F508del* mutation with minimal function mutations in the United States will be eligible for Trikafta. We assumed that 20% of these patients would initiate Trikafta in each of the five years, or 1,214 patients per year. Note that our assumption that 20% of these patients would initiate Trikafta in each of the first five years may be conservative, as clinical experts predicted that uptake would be much more rapid than 20% per year.

For patients eligible for Trikafta who were also eligible for Symdeko (Populations 2 and 3), we used data from the CF Foundation Patient Registry Annual Data Report for 2018,[2] which reported that 68.5% of eligible patients were prescribed CFTR modulators, to estimate the proportion of patients eligible for Trikafta who would currently be treated with Symdeko. For patients who are homozygous for the *F508del* mutation (population 2) and patients who are heterozygous for the *F508del* mutation with a residual function mutation (population 3), we assumed that Trikafta plus best supportive care would displace a mix of Symdeko plus best supportive care (for 68.5% of eligible patients) and best supportive care alone (for 31.5% of eligible patients). For patients who are heterozygous for the *F508del* mutation with a minimal function mutation (population 4), we assumed Trikafta treatment would be added to best supportive care alone.

ICER's methods for estimating potential budget impact are described in detail elsewhere[134] and have been recently updated. The intent of our revised approach to potential budgetary impact is to document the percentage of patients who could be treated at selected prices without crossing a potential budget impact threshold that is aligned with overall growth in the U.S. economy. For 2019-2020, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to be approximately $819 million per year for new drugs.

8.3 Results

The tables below illustrate the five-year annualized per-patient potential budget impact of Trikafta in the relevant populations. The results in each table are based on the list price ($311,741 per year) and the blended annual threshold prices for cost-effectiveness thresholds of $150,000, $100,000, and $50,000 per QALY versus best usual care ($79,900, $67,900, and $55,900, respectively). We used the blended threshold prices across the three eligible populations as these seemed more policy relevant than the use of separate threshold prices for each population. Note that this

analysis uses results from the cost-effectiveness model, which account for treatment discontinuation and impact of treatments on best supportive care costs.

Tables 8.1 illustrates the five-year annualized per-patient potential budget impact of Trikafta compared to best usual care in the population homozygous for the *F508del* mutation (population 2). For population 2, the average annualized potential budgetary impact when using Trikafta's list price was an additional per-patient cost of approximately $79,000 versus the mix of Symdeko and best supportive care. Its average annualized potential budget impacts at the threshold prices for $50,000 to $150,000 per QALY were estimated to be cost-saving relative to a mix of Symdeko and best supportive care alone. Note that we estimate cost-savings for Trikafta at these prices because of the high cost offset from the comparator mix ($243,000 per patient), which includes the cost of Symdeko at its current price for the majority of patients.

Table 8.1. Annualized Per-Patient Potential Budget Impact Over a Five-year Time Horizon for Trikafta in the Population Aged 12 and Older Homozygous for *F508del* Mutation (Population 2)

	Average Annual Per Patient Budget Impact			
	At List Price	**At $150,000/ QALY Price**	**At $100,000/ QALY Price**	**At $50,000/ QALY Price**
Trikafta+BSC	$322,000	$111,000	$100,000	$89,000
Symdeko+BSC (68.5%) & BSC (31.5%)	$243,000			
Net Impact	$79,000	-$132,000	-$143,000	-$153,000

All annualized costs include drug and non-drug health care costs. Numbers may not sum due to rounding.
QALY: quality-adjusted life year

Table 8.2 illustrates the five-year annualized per-patient potential budget impact of Trikafta compared to the mix of Symdeko and best supportive care in the population over the age of 12 and heterozygous for an *F508del* mutation with a residual function mutation (population 3). For population 3, the average annualized potential budgetary impact when using Trikafta's list price was an additional per-patient cost of approximately $74,000 versus the mix of Symdeko and best supportive care. Its average annualized potential budget impacts at the threshold prices for $50,000 to $150,000 per QALY were estimated to be cost-saving relative to a mix of Symdeko and best supportive care alone. As in population 2, note that we estimate cost-savings for Trikafta at these prices because of the high cost offset from the comparator mix ($244,000 per patient), which includes the cost of Symdeko at its current price.

Table 8.2. Annualized Per-Patient Potential Budget Impact Over a Five-year Time Horizon for Trikafta in the Population Aged 12 and Older Heterozygous for *F508del* Mutation with Residual Function Mutation (Population 3)

	Average Annual Per Patient Budget Impact			
	At List Price	At $150,000/ QALY Price	At $100,000/ QALY Price	At $50,000/ QALY Price
Trikafta+BSC	$318,000	$109,000	$98,000	$88,000
Symdeko+BSC (68.5%) & BSC (31.5%)	$244,000			
Net Impact	$74,000	-$135,000	-$145,000	-$156,000

All annualized costs include drug and non-drug health care costs. Numbers may not sum due to rounding.
QALY: quality-adjusted life year

Table 8.3 illustrates the five-year annualized per-patient potential budget impact of Trikafta compared to best usual care in the population heterozygous for the *F508del* mutation with minimal function mutation (population 4). For Trikafta, the average annualized potential budgetary impact when using its list price was an additional per-patient cost of approximately $250,000 versus best supportive care. Its average annualized potential budget impact versus best supportive care at the threshold prices for $50,000 to $150,000 per QALY ranged from approximately $17,000 to approximately $39,000 per patient. Note that the cost offset for this population is much smaller ($82,000 per patient) because it includes costs for best supportive care alone.

Table 8.3. Annualized Per-Patient Potential Budget Impact Over a Five-year Time Horizon for Trikafta in the Population Aged 12 and Older Heterozygous for *F508del* Mutation with Minimal Function Mutation (Population 4)

	Average Annual Per Patient Budget Impact			
	At List Price	At $150,000/ QALY Price	At $100,000/ QALY Price	At $50,000/ QALY Price
Trikafta+BSC	$332,000	$121,000	$111,000	$100,000
BSC	$82,000			
Net Impact	$250,000	$39,000	$28,000	$17,000

All annualized costs include drug and non-drug health care costs. Numbers may not sum due to rounding.
QALY: quality-adjusted life year

The annual potential budgetary impacts of treating the combined Trikafta-eligible populations using list price (WAC) compared to the $819 million threshold is shown in Table 8.4. For Populations 2 and 3, the annualized potential budget impact of treating all patients with Trikafta would not exceed the $819 million ICER potential budget impact threshold at list price (again, assuming cost offsets from a mix of Symdeko and best supportive care alone). However, for Population 4, the annualized potential budget impact of treating with Trikafta at list price would exceed the $819 million ICER potential budget impact threshold by 9%. Only approximately 90% of the 6,070 patients in Population 4 could be treated before exceeding the potential budget impact threshold at this price. When combined for all populations, the annualized potential budget impact of treating the entire eligible population with Trikafta at list price would exceed the $819 million ICER potential budget impact threshold by 71%. While the total number of patients eligible for treatment with Trikafta is relatively low (n = 16,865), the increased cost per patient from using Trikafta over current treatment mix leads to a total estimate exceeding the potential budget impact threshold.

Table 8.4. Estimated Annualized Potential Budget Impact of Trikafta for Treatment of Eligible Populations Using List Price Over a Five-year Time Horizon

	Eligible Population	N Treated per Year	Annual BI per Patient	Total Annual BI (millions)	Percent of Threshold
Homozygous *F508del* (Population 2)					
Trikafta	8,870	1,774	$79,000	$416.2	51%
Heterozygous *F508del* with Residual Function Mutation (Population 3)					
Trikafta	1,925	385	$74,000	$85.0	10%
Heterozygous *F508del* with Minimal Function Mutation (Population 4)					
Trikafta	6,070	1,214	$250,000	$896.7	109%
Total Trikafta-Eligible US CF Population*					
Trikafta	16,865	3,373	$140,000	$1,397.9	**171%**

Numbers may not sum due to rounding.

BI: budget impact

*Annual BI per patient for total eligible US CF population weighted by percentage contribution.

8.4 Access and Affordability Alert

Assuming all eligible patients in populations 2 and 3 transitioned from an older CFTR modulator to Trikafta, an additional 35% of eligible patients in population 4 could be treated with Trikafta at its list price without exceeding ICER's potential budget impact threshold of $819 million. This would represent approximately 77% of the overall eligible population for Trikafta. Discussions with clinical experts suggested that uptake could approach or exceed this level given the unmet need for patients in this population. Given that the clinical goal for uptake would exceed the potential budget impact threshold at the national level, ICER is issuing an access and affordability alert. The purpose of an ICER affordability and access alert is to signal to stakeholders and policy makers that

the amount of added health care costs associated with a new service may be difficult for the health system to absorb over the short term without displacing other needed services or contributing to rapid growth in health care insurance costs that threaten sustainable access to high-value care for all patients.

9. Summary of the Votes and Considerations for Policy

9.1 About the CTAF Process

During CTAF public meetings, the CTAF Panel deliberates and votes on key questions related to the systematic review of the clinical evidence, an economic analysis of the applications of treatments under examination, and the supplementary information presented. Panel members are not pre-selected based on the topic being addressed and are intentionally selected to represent a range of expertise and diverse perspectives.

Acknowledging that any judgment of evidence is strengthened by real-life clinical and patient perspectives, subject matter experts are recruited for each meeting topic and provide input to CTAF Panel members before the meeting to help clarify their understanding of the different interventions being analyzed in the evidence review. The same clinical experts serve as a resource to the CTAF Panel during their deliberation, and help to shape recommendations on ways the evidence can apply to policy and practice.

After the CTAF Panel votes, a policy roundtable discussion is held with the CTAF Panel, clinical experts, patient advocates, payers, and when feasible, manufacturers. The goal of this discussion is to bring stakeholders together to apply the evidence to guide patient education, clinical practice, and coverage and public policies. Participants on policy roundtables are selected for their expertise on the specific meeting topic, are different for each meeting, and do not vote on any questions.

At the August 27, 2020 meeting, the CTAF Panel discussed issues regarding the application of the available evidence to help patients, clinicians, and payers address important questions related to the use of Trikafta for individuals with CF. Following the evidence presentation and public comments (public comments from the meeting can be accessed here), the CTAF Panel voted on key questions concerning the comparative clinical effectiveness and potential other benefits and contextual considerations related to Trikafta for CF. These questions are developed by the ICER research team for each assessment to ensure that the questions are framed to address the issues that are most important in applying the evidence to support clinical practice, medical policy decisions, and patient decision-making. The voting results are presented below, along with specific considerations mentioned by CTAF Panel members during the voting process.

In its deliberations and votes related to value, the CTAF Panel considered the individual patient benefits, and incremental costs to achieve such benefits, from a given intervention over the long term.

There are four elements to consider when deliberating on long-term value for money (see Figure 9.1 below):

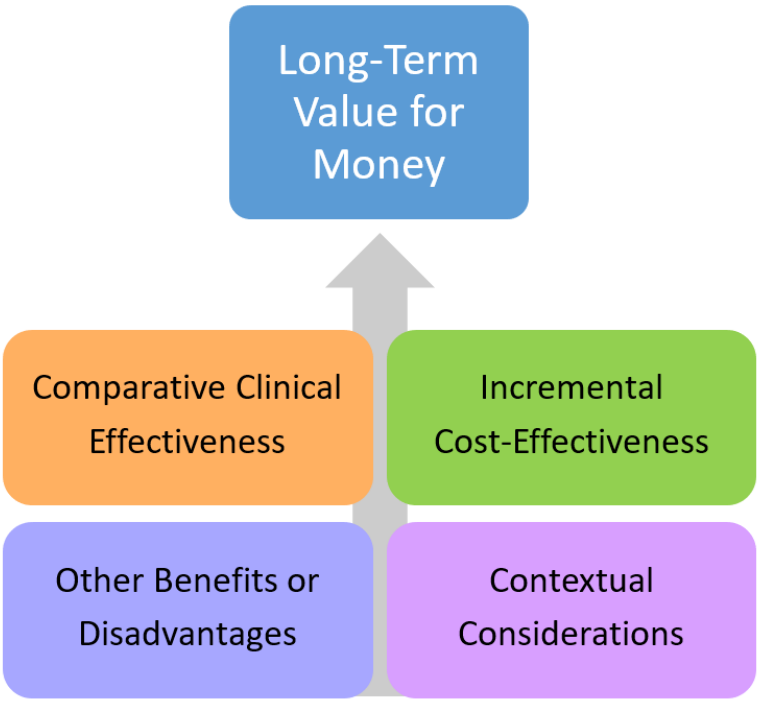
1. Comparative clinical effectiveness is a judgment of the overall difference in clinical outcomes between two interventions (or between an intervention and placebo), tempered by the level of certainty possible given the strengths and weaknesses of the body of evidence. CTAF uses the ICER Evidence Rating Matrix as its conceptual framework for considering comparative clinical effectiveness.

2. Estimated incremental cost-effectiveness is the average incremental cost per patient of one intervention compared to another to achieve a desired "health gain," such as an additional stroke prevented, case of cancer diagnosed, or gain of a year of life. Alternative interventions are compared in terms of cost per unit of effectiveness, and the resulting comparison is presented as a cost-effectiveness ratio. Relative certainty in the cost and outcome estimates continues to be a consideration. As a measure of cost-effectiveness, the CTAF voting panel follows common academic and health technology assessment standards by using cost per quality-adjusted life year (QALY), with formal voting on "long-term value for money" when the base case incremental cost-effectiveness ratio is between $50,000 per QALY and $175,000 per QALY.

3. Potential other benefits refer to any significant benefits or disadvantages 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. Examples of potential other benefits include better access to treatment centers, mechanisms of treatment delivery that require fewer visits to the clinician's office, treatments that reduce disparities across various patient groups, and new potential mechanisms of action for treating clinical conditions that have demonstrated low rates of response to currently available therapies. Other disadvantages could include increased burden of treatment on patients or their caregivers. For each intervention evaluated, it will be open to discussion whether potential other benefits or disadvantages such as these are important enough to factor into the overall judgment of long-term value for money. There is no quantitative measure for potential other benefits or disadvantages.

4. Contextual considerations include ethical, legal, or other issues (but not cost) that influence the relative priority of illnesses and interventions. Examples of contextual considerations include whether there are currently any existing treatments for the condition, whether the condition severely affects quality of life or not, and whether there is significant uncertainty about the magnitude of benefit or risk of an intervention over the long term. There is no quantitative measure for contextual considerations.

Figure 9.1. Conceptual Structure of Long-term Value for Money



9.2 Voting Results

Comparative Clinical Effectiveness

Patient Population 2 (Questions 1-2): *Individuals with CF who are homozygous for the* F508del *mutation*

1. ***Is the evidence adequate to demonstrate that the net health benefit of treatment with Trikafta with best supportive care is greater than that of best supportive care alone?***

Yes: 14 votes	No: 0 votes

Comments: CTAF unanimously judged that the evidence demonstrates that Trikafta plus best supportive care provides superior net health benefit to patients than best supportive care alone. The council was persuaded by evidence demonstrating substantial benefits on ppFEV$_1$ and quality of life as measured by the CFQ-R, as well as negligible harms

2. ***Is the evidence adequate to demonstrate that the net health benefit of treatment with Trikafta and best supportive care is greater than that of treatment with Symdeko and best supportive care?***

Yes: 14 votes	No: 0 votes

Comment: CTAF's unanimous vote was driven by the same considerations highlighted during discussion of question 1, as evidence from clinical trials demonstrated substantial benefits for Trikafta over Symdeko.

Patient Population 3 (Questions 3-4): *Individuals with CF who are heterozygous for the* F508del *mutation with a residual function mutation.*

3. ***Is the evidence adequate to demonstrate that the net health benefit of treatment with Trikafta with best supportive care is greater than that of best supportive care alone?***

Yes: 13 votes	No: 1 votes

Comment: A majority of the CTAF panel judged that the evidence was adequate to demonstrate that Trikafta plus best supportive care provides superior net health benefit to best supportive care alone. Although no published evidence was available at the time of the public meeting, Trikafta is Symdeko plus another modulator, elexacaftor, and the evidence for Symdeko plus best supportive was sufficient to demonstrate benefit versus best supportive care alone. Clinical experts noted that *in vitro* evidence suggests that elexacaftor would provide additional benefit for patients in this population.

4. ***Is the evidence adequate to demonstrate that the net health benefit of treatment with Trikafta and best supportive care is greater than that of treatment with Symdeko and best supportive care?***

Yes: 6 votes	**No: 8 votes**

Comment: A slight majority of CTAF found the evidence was inadequate to demonstrate that Trikafta provides greater net health benefits to patients than Symdeko, both with best supportive care. This was primarily due to a lack of published data in this population comparing Trikafta to Symdeko.

Patient Population 4: *Individuals with CF who are heterozygous for the* F508del *mutation with a minimal function mutation.*

5. ***Is the evidence adequate to demonstrate that the net health benefit of treatment with Trikafta with best supportive care is greater than that of best supportive care alone?***

Yes: 14 votes	No: 0 votes

Comment: CTAF unanimously judged Trikafta to provide superior net health benefits versus best supportive care alone based on evidence demonstrating substantial lung function and quality of life improvements.

Potential Other Benefits and Contextual Considerations

Votes for questions 6 and 7 applied to all eligible patient populations except where otherwise noted in comments.

6. ***When compared to best supportive care, does treating patients with Trikafta offer one or more of the following potential "other benefits?" (select all that apply)***

This intervention will significantly reduce caregiver or broader family burden.	13/13*
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.	12/13*
This intervention will have a significant impact on improving patients' ability to return to work and/or their overall productivity.	13/13*
This intervention will have a significant positive impact outside the family, including on schools and/or communities.	11/13*
There are other important benefits or disadvantages that should have an important role in judgments of the value of this intervention	6/13*

*Only 13 CTAF panelist votes were tallied due to a malfunction with the voting technology

Comment: CTAF recognized that Trikafta is likely to provide several important other benefits not captured by the clinical and economic data. Patient experts at the meeting highlighted that Trikafta is the first treatment for patients who are heterozygous for the *F508del* mutation and a minimal function mutation. Individuals on Trikafta spoke about how their health had improved since starting Trikafta, leading to less time spent in the hospital and, for some, on other elements of their daily CF self-care. A patient expert on the roundtable noted that she had not missed work since starting Trikafta and, for the first time, had a positive balance of sick hours when she previously had a negative balance. Similarly, she is now able to be a more active and engaged in member of her community. These benefits extend to families and caregivers who often spend considerable time assisting their loved ones with hospital visits and their daily CF care regimen and have more peace of mind knowing that their family member or friend with CF's health is improving. CTAF also noted that successful treatment with Trikafta may reduce the need for lung transplants, making them available for individuals with other conditions. CTAF members also recognized the substantial improvements in anxiety and depression that patients reported, noting that they may not have been adequately captured by the clinical trials.

7. ***Are any of the following contextual considerations important in assessing Trikafta's long-term value for money? (select all that apply)***

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.	14/14
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	14/14
This intervention is the first to offer any improvement for patients with this condition.	8/14
Compared to best supportive care, there is significant uncertainty about the long-term risk of serious side effects of this intervention.	11/14
Compared to best supportive care, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	10/14
There are additional contextual considerations that should have an important role in judgments of the value of this intervention	1/14

Comment: CTAF unanimously acknowledged that CF is condition of high severity with substantial impacts on length of life, quality of life, and that patients experience a high lifetime burden of illness. They also noted that significant uncertainty remains about the magnitude or durability of long-term benefits, as well as the long-term risks associated with Trikafta, as it was recently approved, and currently-available clinical trials were not long enough to provide greater certainty. One CTAF member's vote for additional considerations was intended to highlight that CF is an often-fatal illness with no cure.

Long-Term Value For Money at Current Prices

As described in ICER's Value Assessment Framework, questions on long-term value for money are subject to a value vote when incremental cost-effectiveness ratios for the interventions of interest are between $50,000 and $175,000 per QALY in the primary "base case" analysis. The base case estimates of the cost per QALY for Trikafta in all populations exceeded the higher end of this range, and therefore the treatment was deemed "low long-term value for money at current prices" without a vote unless CTAF determined in its discussion that the Evidence Report base case analysis did not adequately reflect the most probable incremental cost-effectiveness ratio for Trikafta

9.3 Roundtable Discussion and Key Policy Implications

Following its deliberation on the evidence, the CTAF Panel engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on Trikafta for patients with at least one *F508del* mutation to policy and practice. The policy roundtable members included one patient with CF, one family member of an individual with CF, a representative from a patient advocacy organization, two practicing CF clinical experts, and two payer representatives. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The names of the Policy Roundtable participants are shown below, and conflict of interest disclosures for all meeting participants can be found in Appendix H.

Table 9.1. Policy Roundtable Members

Name	Title and Affiliation
Mary Dwight	Senior Vice President of Policy and Advocacy, Cystic Fibrosis Foundation
Janet Zachary-Elkind	Deputy Director, NY State Department of Health, Office of Health Insurance Programs
Mariah Hanley, JD,	Individual with CF
Manu Jain, MD, MSc	Professor, Department of Medicine (Pulmonary and Critical Care); Department of Pediatrics, Northwestern University
Don Maurice Kreis, JD, MS	Parent of Individual with CF
Carlos Milla, MD,	Professor of Pediatrics, Pulmonology, Stanford University School of Medicine
Jeff White, PharmD, MS	Staff Vice President, Clinical Pharmacy Services, IngenioRX (Anthem)

The roundtable discussion was facilitated by Dr. Steven Pearson, MD, MSc, President of ICER. Much of the policy roundtable discussion centered on the impact that the high costs for CFTR modulators, and Trikafta in particular, on coverage policy. The ensuing discussion allowed a deeper exploration of the perspectives of patients and their families, of CF advocacy groups, and of public and private insurers wrestling with these challenges.

The main themes and recommendations from the discussion are organized by audience and summarized below.

Manufacturers

1. ***The manufacturer should lower the price of Trikafta to align fairly with its demonstrated benefits. Pricing treatments within a proportional level to their benefits allows a health system to reward innovation and improve access to patients. Pricing far beyond this reasonable level causes harm to patients – some with CF and some with other diseases – who are forced to delay or forego care or even to drop health insurance entirely.***

Trikafta represents a major clinical advance for the care of CF and provides superior benefits compared to other modulators. However, our report's findings and discussion at the public meeting indicate that its price set too high in relation to its clinical benefits. When treatments are priced too high, they contribute to higher insurance premiums, copayments, and restrictions on access. Studies have shown that as insurance costs increase patients may delay care, forego care entirely, or even drop their health insurance. This leads to increased suffering and mortality. We heard stories of CF patients in these exact circumstances in the public comments on our draft report.

Despite this disconnect, we are confident that no insurer in the United States will even briefly entertain the option of non-covering Trikafta. The experience with our last report may serve as a reassurance. To our knowledge no insurer, including New York Medicaid, who used our report as part of their identification of a price target for negotiation over the price of Orkambi, even whispered about possible non-coverage. In fact, New York Medicaid made explicit that in no way would its negotiation include any possibility of erecting increased barriers to access in any way. We too, at our first public meeting on CFTR modulators, started by asserting that payers will cover these drugs (see video, 20:00-21:00).

To be entirely clear, in all cases we support actions to achieve fair prices that maintain the ability of patients to get the treatments they will benefit from. When we as a nation give a company a monopoly on a treatment and, instead of "wrestling" with them over coverage, tacitly agree that coverage will be provided because we want all patients to benefit, we need some mechanism to suggest an upper limit to the price that a company feels it can charge. It is precisely because access to Trikafta is not and should not be viewed as negotiable that we believe it is essential to use evidence of how much its benefits patients as a guide for its price. When the price of any service throughout the health system is way out of proportion to its ability to improve lives, it can cause more harm to other patients -- some with CF, some with other diseases – who can no longer afford their health care.

2. ***Benefiting from monopoly pricing power, the manufacturer of Trikafta and the other available CFTR modulators bears a significant social responsibility to change its pricing approach by exercising restraint in the use of its monopoly pricing power and by committing to engaging in public deliberations in which independent evaluations of the evidence will be discussed and integrated with broader considerations of value through input from patients and other key stakeholders.***

The first CFTR modulator was approved eight years ago, so changes to the treatment pathway and adjustments to clinical practice are therefore reasonably mature. The manufacturer should no longer make vague justifications for the high prices of the CFTR modulators based on general statements about research and development costs or prospects for future innovation and continued investment in new treatments for CF. These arguments increasingly ring hollow in the absence of any quantification or further details to contextualize them. The manufacturer bears further responsibility to change their approach to justifying their pricing during a phase when they have enjoyed sustained company growth, rising profits and stock values, and have funded substantial stock repurchase programs. In addition, any benefit of the doubt given by payers when Kalydeco was first approved for a small subset of the CF population has vanished with the introduction of newer treatments for much larger groups of patients. The manufacturer should therefore be fully transparent about the calculus made for pricing of the CFTR modulators and be willing to engage in processes intended to produce independent judgments of what fair pricing and sustainable access look like for CF innovations.

Finally, the manufacturer no longer can point to a small patient population in an orphan disease as the reason for exorbitant pricing. More than 27,000 patients are potentially eligible for Trikafta in the US alone. The company reported net revenue of $1.8 billion from Trikafta alone during the first 6 months of 2020 – it classifies as a blockbuster drug. The annual price for Trikafta is far above that of other drugs with a modest number of potentially eligible patients.

Payers

3. ***Prior authorization criteria for Trikafta should be based on clinical evidence, specialty society guidelines, and input from clinical experts and patient groups. The process for authorization should be clear and efficient for providers. Options for specific elements of coverage criteria within insurance coverage policy are discussed below.***

Coverage Criteria Considerations: Trikafta

1) **Diagnosis:**
   a) Proof of CFTR mutation status (at least one *F508del* mutation) should be required for initial coverage, but not for requalification as CFTR modulator treatments do not permanently modify the genome.

2) **Clinical Eligibility Criteria:**
   a) 12 years of age or older is the age threshold supported by direct clinical evidence and codified at the time Trikafta was first approved by the FDA. Given that there is no *a priori* clinical rationale that younger patients would not benefit, and that more recent evidence suggests that the FDA may soon expand the label to a younger population, payers should establish clear pathways for exceptions and consider coverage for younger patients meeting other clinical criteria. It is reasonable for payers to require these exception requests be made by a practicing CF expert, as the potential side effects of using the approved dose in a pediatric population are not yet known.

   b) Baseline ppFEV1 level should not be a consideration for coverage. Clinical experts indicated that, although trials excluded patients with ppFEV1 <40% and >90%, there is no clinical reason to suspect that patients outside of these ranges would not have comparable risks and benefits to those of the study population.

   c) It is reasonable for insurers to require physician attestation that the patient is receiving best supportive care.

   d) Sweat chloride levels should not be used for eligibility or renewal criteria, as expert opinion indicated that it is not predictive of clinical response.

   e) Patients who have had a liver transplant should not be excluded from coverage. Although these patients were excluded from the clinical trial, expert input indicated that they are still likely to receive benefit from Trikafta.

3) **Concomitant use of other therapies**: There is no evidence to support combination therapy with another currently-available CFTR modulator treatment (Kalydeco, Symdeko, or Orkambi).

4) **Step Therapy:** In general step therapy should not be required for patients who qualify for Trikafta because Trikafta is clearly superior to Symdeko and Orkambi in most patients who carry the *F508del* mutation. It may be clinically reasonable to consider Symdeko in patients heterozygous for *F508del* with a residual function mutation if Symdeko becomes much less expensive, although insurers should be prepared to rapidly update these policies once data on the effectiveness of Trikafta in this population become available.

5) **Renewal Criteria:**
   a) Provider attestation of clinical benefit is sufficient given that there is no defined standard for clinical response to treatment. Clinical expert input indicated that modulator therapy may improve, maintain, or slow the decline of respiratory function, which all represent important health benefits for CF patients.
   b) Repeat genetic testing should not be required for renewal, as CFTR modulator treatments do not permanently modify the genome.

6) **Provider Criteria:** Given the complexity of managing CF and of ensuring appropriate overall care for patients, it is reasonable for insurers to require that Trikafta be prescribed by a CF clinical expert.

4. Public and private payers should continue to affirm their commitment to provide access to the CFTR modulators and should remove superfluous requirements for coverage approval and continuation.

For the CFTR drugs, it is important for payers to seek to control costs without using access restrictions as a key feature of negotiation. Patients and their families need to know that insurers will help them receive these new drugs. Testimony provided at the policy roundtable highlighted that most payers have dropped unnecessary, and at times illogical, requirements for documentation prior to approval of insurance coverage for both Kalydeco and Trikafta. Two examples were the removal of requirements for periodic genetic testing and requirements that supportive care fail patients before they can access modulator treatment. However, some barriers remain, such as step therapy protocols that require patients eligible for Trikafta to try Symdeko or Orkambi first. Discussion at the meeting indicated that such barriers are less prevalent for highly-effective modulator therapies like Kalydeco and Trikafta, and more prevalent for other supportive treatments for CF. One roundtable participant praised the many public and private insurers who provided access to Trikafta through case-by-case decisions before it was added to their formularies, noting that this type of response to an early approval by the FDA reflected the strength of the clinical evidence and was beneficial for individuals with CF.

A CF patient expert on the roundtable noted that many individuals with CF have difficulty finding their insurer's coverage policy for Trikafta, an issue that is suspected to be more common among smaller regional insurers. It is essential that all insurers make their coverage criteria readily available and that policies are clearly written.

Patient Advocacy Organizations

5. ***Patient organizations that have a leading role in funding, organizing, promoting, and otherwise fostering innovative research on new treatments should demand commitments from manufacturers for sustainable pricing of the products patients helped bring to the market.***

It is likely that without the CF Foundation's efforts, the drug developers would have prioritized other diseases and the innovations that resulted in CFTR modulator therapies may not have been realized. However, the CF Foundation has not had a "seat at the table" to discuss the pricing of these innovations. While other patient organizations should hold the CF Foundation up as an example of how to fund research and development in an underserved area, they must also couple this with a requirement of the developers to commit to sustainable pricing practices.

Specialty Societies

6. ***Professional societies should fully exercise their responsibility by bearing witness to the impact on their patients of failed pricing and insurance policies and by demanding to be part of the public process that should guide pricing to balance the needs for affordability and for investments in future innovation.***

There is considerable excitement in the clinical community about the potential for both short-term and sustained clinical benefit with the CFTR modulators, but physicians also have a front-row seat to the inequities and access challenges posed by the pricing of these drugs. The oncology community is an important model for physician activism, having highlighted the financial toxicity associated with new cancer regimens. The CF clinical community should consider a similar effort, given the financial challenges posed by CFTR modulators and other supportive-care treatments for CF.

Researchers

7. ***Leading journals should refuse to publish manuscripts based on clinical trials that redact portions of their trial protocols.***

The protocol for the pivotal trial of Trikafta in patients heterozygous for the *F508del* mutation was made available electronically with the publication of the results of the trial in the New England

Journal of Medicine but it was heavily redacted, raising questions about the fidelity of the methods and results of the trial. Transparency is an essential component in randomized clinical trials. Clinicians, guideline committees, and patients depend on the integrity of those designing, performing, and reporting clinical trials. Concerns that this process was not always performed ethically have led to the requirement that clinical trials be registered in public, online databases, such as clinicaltrials.gov prior to the recruitment of trial participants. More recently, high impact journals have published the clinical trials protocol as supplement to the results of pivotal trials. Sharing study protocols makes the critical appraisal of the trial more robust including the assessment of selective reporting of trial results and identifying when the pre-specified primary outcome and analytic methods are changed.

8. ***The groundbreaking studies initiated and funded by the Cystic Fibrosis Foundation should be applauded and may serve as a model for other patient organizations seeking to generate evidence. Future studies should measure and report a broad set of outcomes to better assess the health and economic impact of CF interventions to patients, their caregivers, and their health system.***

The CF Foundation played a central role in fostering the development of CFTR modulators as well as convincing manufacturers of the benefits of investing in CF innovation. Part of their strength is the development of a registry that includes the majority of patients with CF in the United States. They continue to innovate through randomized trials like SIMPLIFY, which seeks to identify which therapies included in the current best standard care can be safely stopped for patients on Trikafta. However, ICER's review identified a paucity of evidence on patient-centered outcomes pertaining to extrapulmonary manifestations of the disease, including but not limited to: mental health and affect, quality of life beyond the respiratory domain, impact on the endocrine, gastrointestinal, and functional effects of CF; impact on caregivers, including quality of life, affect, and time costs; and information on costs, including out of pocket costs, informal caregiver time, and transportation costs. Patients, clinicians, insurers, and other stakeholders need this information to make fully-informed decisions about their treatment and to ensure that the health system is spending its limited resources wisely. At a minimum, the full CFQ-R should be reported and the EQ-5D should be measured and reported. Specifically, a CF core outcomes set (COS) should be developed and applied. A CF-specific COS is under development (see http://www.comet-initiative.org/studies/details/882; http://www.comet-initiative.org/studies/details/120) that is considering many of these measures.

9. ***Large studies with long term follow-up are needed to complement the short-term results observed in the pivotal randomized trials.***

The randomized trials of the CFTR modulators demonstrated a short-term improvement in $ppFEV_1$. However, the impact of the CFTR inhibitors on the rate of decline in $ppFEV_1$ with ongoing treatment

remains uncertain. Need long term studies, particularly on the impact of Trikafta on the decline in $ppFEV_1$ over time, the incidence of CFRD, and the ability to drop some of the standard therapies used to maintain the health of patients with CF. We applaud the efforts of the CF Foundation-sponsored PROMISE study, which is enrolling patients on Trikafta for a cohort study, but encourage them to extend follow-up beyond the planned two years.

10. ***Patients who are heterozygous of the* F508del *mutation and a residual function mutation should be prioritized in future research.***

The population of patients homozygous for the *F508del* mutation and a residual function mutation vary significantly in their clinical manifestations and thus may have variable responses to CFTR modulators like Trikafta. This population should be a priority for future research and should be encouraged to participate in studies like PROMISE.

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This is the second ICER review of Kalydeco, Orkambi, and Symdeko, and the first review of Trikafta for cystic fibrosis.

References

1. Knapp EA, Fink AK, Goss CH, et al. The Cystic Fibrosis Foundation Patient Registry. Design and Methods of a National Observational Disease Registry. *Annals of the American Thoracic Society.* 2016;13(7):1173-1179.
2. Cystic Fibrosis Foundation. Cystic Fibrosis Foundation Patient Registry 2018 Annual Data Report. 2019; https://www.cff.org/Research/Researcher-Resources/Patient-Registry/2018-Patient-Registry-Annual-Data-Report.pdf.
3. 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.
4. Agrawal A, Mehta D, Sikachi R, Du D, Wang J. Nationwide trends of hospitalizations for cystic fibrosis in the United States from 2003 to 2013. *Intractable Rare Dis Res.* 2017;6(3):191-198.
5. US Food and Drug Administration (FDA). FDA approves new breakthrough therapy for cystic fibrosis. 2019; https://www.fda.gov/news-events/press-announcements/fda-approves-new-breakthrough-therapy-cystic-fibrosis.
6. Cystic Fibrosis Research Inc. Voice of the Cystic Fibrosis Patient: A Summary Report of the Externally-Led Patient-Focused Drug Development Meeting on Cystic Fibrosis. 2018; http://cfri.org/wp-content/uploads/2019/03/EL-PFDD.CFRI_.VoiceofCFPatientReport.pdf. Accessed February 4, 2020.
7. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *American journal of respiratory and critical care medicine.* 1999;159(1):179-187.
8. Heijerman H, McKone E, Downey D, et al. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blink, randomised, phase 3 trial. *Lancet (London, England).* 2019;394(10212):1940-1948.
9. Institute for Clinical and Economic Review. Modifications to the ICER value assessment framework for treatments for ultra-rare diseases. 2017; https://icer-review.org/wp-content/uploads/2017/11/ICER-Adaptations-of-Value-Framework-for-Rare-Diseases.pdf. Accessed April 4, 2020.
10. Red Book Online® Search. Truven Health Analytics; 2018. http://www.micromedexsolutions.com.ezp-prod1.hul.harvard.edu/micromedex2/librarian/CS/E7F89E/ND_PR/evidencexpert/ND_P/evidencexpert/DUPLICATIONSHIELDSYNC/A4E796/ND_PG/evidencexpert/ND_B/evidencexpert/ND_AppProduct/evidencexpert/ND_T/evidencexpert/PFActionId/redbook.FindRedBook?navitem=topRedBook&isToolPage=true. Accessed January 15th, 2018.
11. Cystic Fibrosis Foundation. Cystic Fibrosis Foundation Patient Registry (Unpublished Data). In. Bethesda, MD2018.
12. 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.
13. Scotet V, Dugueperoux 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. Parad RB, Comeau AM. Newborn screening for cystic fibrosis. *Pediatric annals.* 2003;32(8):528-535.
15. 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. *MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports.* 2004;53(Rr-13):1-36.
16. O'Sullivan BP, Freedman SD. Cystic fibrosis. *The Lancet.* 2009;373(9678):1891-1904.
17. Sawicki GS, Sellers DE, Robinson WM. High treatment burden in adults with cystic fibrosis: challenges to disease self-management. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society.* 2009;8(2):91-96.
18. Balk E, Trikalinos T, Kuntz K, et al. *Modulator Treatments for Cystic Fibrosis: Effectiveness and Value; Final Evidence Report and Meeting Summary.* Boston, MA: Institute for Clinical and Economic Review; June 7 2018.
19. Cystic Fibrosis Foundation. Research We Fund. 2019.
20. Woolf S, Schünemann HJ, Eccles MP, Grimshaw JM, Shekelle P. Developing clinical practice guidelines: types of evidence and outcomes; values and economics, synthesis, grading, and presentation and deriving recommendations. *Implementation Science : IS.* 2012;7:61-61.
21. Bessonova L, Volkova N, Higgins M, et al. Data from the US and UK cystic fibrosis registries support disease modification by CFTR modulation with ivacaftor. *Thorax.* 2018;73:731-740.
22. Cystic Fibrosis Foundation. What is Cystic Fibrosis. 2017; https://www.cff.org/What-is-CF/About-Cystic-Fibrosis/. Accessed October 24, 2017.
23. Clinical and Functional Translation of CFTR. CFTR2.org. 2018; https://www.cftr2.org/.
24. Lung Institute. What is FEV1? Here's what you need to know. 2016; https://lunginstitute.com/blog/what-is-fev1-heres-what-you-need-to-know/. Accessed March 6, 2018.
25. National Institute for Health and Care Excellence (NICE). *Lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation.* nice.org June 2016 2016.
26. Moran A, Brunzell C, Cohen RC, et al. Clinical care guidelines for cystic fibrosis-related diabetes: a position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. *Diabetes Care.* 2010;33(12):2697-2708.
27. Quittner AL, Buu A, Messer MA, Modi AC, Watrous M. Development and validation of The Cystic Fibrosis Questionnaire in the United States: a health-related quality-of-life measure for cystic fibrosis. *Chest.* 2005;128(4):2347-2354.
28. Quittner AL, Modi AC, Wainwright C, Otto K, Kirihara J, Montgomery AB. Determination of the minimal clinically important difference scores for the Cystic Fibrosis Questionnaire-Revised respiratory symptom scale in two populations of patients with cystic fibrosis and chronic Pseudomonas aeruginosa airway infection. *Chest.* 2009;135(6):1610-1618.
29. Robinson PD, Latzin P, Verbanck S, et al. Consensus statement for inert gas washout measurement using multiple- and single- breath tests. *The European respiratory journal.* 2013;41(3):507-522.
30. Wainwright CE, Elborn JS, Ramsey BW, et al. Lumacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR. *The New England journal of medicine.* 2015;373(3):220-231.
31. Center for Evaluation of Value and Risk in Health (CEVR). Tufts Medical Center Specialty Drug Evidence and Coverage (SPEC) Database. 2020; https://cevr.tuftsmedicalcenter.org/databases/spec-database. Accessed January 14, 2020.

32. FDA Approves KALYDECO® (ivacaftor) as First and Only CFTR Modulator to Treat Eligible Infants with CF as Early as Six Months of Age [press release]. April 30 2019.
33. FDA Approves KALYDECO® (ivacaftor) as First and Only Medicine to Treat the Underlying Cause of CF in Children Ages 12 to <24 Months with Certain Mutations in the CFTR Gene [press release]. August 15 2018.
34. FDA Approves ORKAMBI® (lumacaftor/ivacaftor) as First Medicine to Treat the Underlying Cause of Cystic Fibrosis for Children Ages 2-5 Years with Most Common Form of the Disease [press release]. August 7 2018.
35. FDA Approves SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) to Treat the Underlying Cause of CF in Children Ages 6-11 Years with Certain Mutations in the CFTR Gene [press release]. June 21 2019.
36. Ren CL, Morgan RL, Oermann C, et al. Cystic Fibrosis Foundation Pulmonary Guidelines. Use of Cystic Fibrosis Transmembrane Conductance Regulator Modulator Therapy in Patients with Cystic Fibrosis. *Annals of the American Thoracic Society.* 2018;15(3):271-280.
37. Lahiri T, Hempstead SE, Brady C, et al. Clinical Practice Guidelines From the Cystic Fibrosis Foundation for Preschoolers With Cystic Fibrosis. *Pediatrics.* 2016:peds.2015-1784.
38. Mogayzel PJ, Jr., Naureckas ET, Robinson KA, et al. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. *American journal of respiratory and critical care medicine.* 2013;187(7):680-689.
39. Cystic Fibrosis Foundation. Clinical Care Guidelines. 2019; https://www.cff.org/Care/Clinical-Care-Guidelines/.
40. National Institute for Health and Care Excellence (NICE). Data Collection Agreement. 2019; https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/data-collection-agreement.
41. National Institute for Health and Care Excellence (NICE). Elexacaftor, tezacaftor and ivacaftor fixed dose combination therapy for treating cystic fibrosis with the F508del mutation [ID1661]. 2019; https://www.nice.org.uk/guidance/proposed/gid-ta10566.
42. National Institute for Health and Care Excellence (NICE). Cystic fibrosis: diagnosis and management. 2017.
43. Canadian Agency for Drugs and Technology in Health (CADTH). Final CDEC Recommendation - Ivacaftor (Kalydeco - Vertex Pharmaceuticals (Canada) Incorporated); Indication: Cystic Fibrosis with G551D Mutation. 2013; https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_Kalydeco_March-25-13_e.pdf.
44. Canadian Agency for Drugs and Technology in Health (CADTH). CDEC Final Recommendation - Ivacaftor (Kalydeco - Vertex Pharmaceuticals Inc.); Indication: Cystic Fibrosis with G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or G970R mutation. 2014; https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_SR0379_Kalydeco_Dec-23-14.pdf.
45. Canadian Agency for Drugs and Technology in Health (CADTH). CADTH Canadian Drug Expert Commmittee Final Recommendation: Ivacaftor (Kalydeco - Vertex Pharmaceuticals Inc.); Indication: Cystic Fibrosis with R117H Mutation. 2015; https://www.cadth.ca/sites/default/files/cdr/complete/SR0430_complete_Kalydeco_R117H_Nov-23-15_e.pdf.
46. Canadian Agency for Drugs and Technology in Health (CADTH). Lumacaftor/ivacaftor (Orkambi - Vertex Pharmaceuticals (Canada) Incorporated). 2018.

47. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Ann Intern Med.* 1997;126(5):376-380.
48. Higgins J, Green S,. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0.* The Cochrane Collaboration; 2011.
49. Moher D, Liberati A, Tetzlaff J, DG A. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Annals of Internal Medicine.* 2010;8(5):336-341.
50. Agency for Healthcare Research and Quality. *U.S. Preventive Services Task Force Procedure Manual.* 2008.
51. Ollendorf DA, Pearson SD. ICER Evidence Rating Matrix: A User's Guide. 2020; https://icer-review.org/methodology/icers-methods/icer-evidence-rating-matrix/. Accessed January 31, 2020.
52. Rucker G, Schwarzer G, Carpenter J, Olkin I. Why add anything to nothing? The arcsine difference as a measure of treatment effect in meta-analysis with zero cells. *Statistics in medicine.* 2009;28(5):721-738.
53. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *Journal of clinical epidemiology.* 1997;50(6):683-691.
54. Rucker G, Petropoulou M, Schwarzer G. Network meta-analysis of multicomponent interventions. *Biometrical journal Biometrische Zeitschrift.* 2019.
55. Guimbellot JS, Baines A, Khan U, et al. Long Term Effects of Ivacaftor in G551D Patients: Five Year Follow-up Data in GOAL-E2. *Pediatric Pulmonology.* 2018;53(2):232-232.
56. Middleton PG, Mall M, Drevinek P, et al. Elexacaftor-Tezacaftor-Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele. *New England Journal of Medicine.* 2019;381(19):1809-1819.
57. Keating D, Marigowda G, Burr L, et al. VX-445–Tezacaftor–Ivacaftor in Patients with Cystic Fibrosis and One or Two Phe508del Alleles. *New England Journal of Medicine.* 2018;379(17):1612-1620.
58. Keating D, Wilson L, Williams E, Kotsimbos T, Wilson J. Ivacaftor withdrawal syndrome during a randomised placebo-controlled cross-over study. *Journal of Cystic Fibrosis.* 2019;18(S1):S130-130.
59. Rosenfeld M, Cunningham S, Harris WT, et al. An open-label extension study of ivacaftor in children with CF and a CFTR gating mutation initiating treatment at age 2-5years (KLIMB). *Journal of Cystic Fibrosis.* 2019;18(6):838-843.
60. Wilson J, Allen-Graham J, Talbot A, et al. Treatment with ivacaftor in CF patients with the G551D mutation is associated with improvement in cognition. *Journal of Cystic Fibrosis.* 2018;17:S57-57.
61. Bell S, Mainz J, MacGregor G, et al. Patient-reported outcomes in patients with cystic fibrosis with a G551D mutation on ivacaftor treatment: results from a cross-sectional study. *BMC Pulmonary Medicine.* 2019;19(146):1-9.
62. Feng L, Grosse SD, Green R, Fink A, Sawicki GS. Precision Medicine in Action: The Impact of Ivacaftor on Cystic Fibrosis-Related Hospitalizations. *Health Affairs.* 2018;37(5):773-779.
63. Hubert D, Fajac I, Munck A, et al. An Observational Study of Ivacaftor in Patients with Cystic Fibrosis in France: First Interim Analysis of Health Care Resource Utilization from the BRIO Study. *Value in Health.* 2018;21(3):342-342.
64. Kirwan L, Fletcher G, Harrington M, et al. Temporal trends in key outcome measures in cystic fibrosis patients treated with ivacaftor: real-world data from the Irish CF registry. *Journal of Cystic Fibrosis.* 2017;16:S48-48.

65. McCormick J, Cho D, Lampkin B, et al. Ivacaftor improves rhinologic, psychologic, and sleep-related quality of life in G551D cystic fibrosis patients. *International Forum of Allergy & Rhinology.* 2019;9(3):292-297.
66. Volkova N, Moy K, Evans J, et al. Disease progression in patients with cystic fibrosis treated iwth ivacaftor: Data from national US and UK registries. *Journal of Cystic Fibrosis.* 2019;19:68-79.
67. Ramsey BW, Davies J, McElvaney NG, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *The New England journal of medicine.* 2011;365(18):1663-1672.
68. Davies JC, Wainwright CE, Canny GJ, et al. Efficacy and safety of ivacaftor in patients aged 6 to 11 years with cystic fibrosis with a G551D mutation. *American journal of respiratory and critical care medicine.* 2013;187(11):1219-1225.
69. De Boeck K, Munck A, Walker S, et al. Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society.* 2014;13(6):674-680.
70. Moss RB, Flume PA, Elborn JS, et al. Efficacy and safety of ivacaftor in patients with cystic fibrosis who have an Arg117His-CFTR mutation: a double-blind, randomised controlled trial. *The Lancet Respiratory medicine.* 2015;3(7):524-533.
71. Davies JC, Cunningham S, Harris WT, et al. Safety, pharmacokinetics, and pharmacodynamics of ivacaftor in patients aged 2-5 years with cystic fibrosis and a CFTR gating mutation (KIWI): an open-label, single-arm study. *The Lancet Respiratory medicine.* 2016;4(2):107-115.
72. Rowe SM, Heltshe SL, Gonska T, et al. Clinical mechanism of the cystic fibrosis transmembrane conductance regulator potentiator ivacaftor in G551D-mediated cystic fibrosis. *American journal of respiratory and critical care medicine.* 2014;190(2):175-184.
73. McKone EF, Borowitz D, Drevinek P, et al. Long-term safety and efficacy of ivacaftor in patients with cystic fibrosis who have the Gly551Asp-CFTR mutation: a phase 3, open-label extension study (PERSIST). *The Lancet Respiratory medicine.* 2014;2(11):902-910.
74. Mayer-Hamblett N, Zemanick ET, Odem-Davis K, VanDevanter DR, Rowe S, Konstan M. CFTR Modulator-Induced Sweat Chloride Changes Across the Cystic Fibrosis Population: First Results from the CHEC-SC Study. *Pediatric Pulmonology.* 2019;54(S2):229-229.
75. Adler A, Shine B, Chamnan P, Haworth C, Bilton D. Genetic determinants and epidemiology of cystic fibrosis-related diabetes: results from a British cohort of children and adults. *Diabetes care.* 2008;31(9):1789-1794.
76. McKone EF, Emerson SS, Edwards KL, Aitken ML. Effect of genotype on phenotype and mortality in cystic fibrosis: a retrospective cohort study. *Lancet (London, England).* 2003;361(9370):1671-1676.
77. Chilvers M, Davies JC, Ratjen F, et al. Long-term safety and efficacy of lumacaftor/ivacaftor therapy in patients aged 6-11 years with cystic fibrosis homozygous for the F508del-CFTR mutation. *Journal of Cystic Fibrosis.* 2019;18(S1):S23-23.
78. Chilvers M, Owen C, G M, et al. Safety and Efficacy of Lumacaftor/Ivacaftor in patients aged ≥6 years with CF homozygous for f508del-CFTR (phase 3 extension study). *Pediatric Pulmonology.* 2017;52(Suppl 47):319-320.
79. McColley SA, Konstan MW, Ramsey BW, et al. Lumacaftor/Ivacaftor reduces pulmonary exacerbations in patients irrespective of initial changes in FEV1. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society.* 2019;18(1):94-101.
80. McNamara JJ, McColley SA, Marigowda G, et al. Safety, pharmacokinetics, and pharmacodynamics of lumacaftor and ivacaftor combination therapy in children aged 2-5 years with cystic fibrosis homozygous for F508del-CFTR: an open-label phase 3 study. *The Lancet Respiratory medicine.* 2019;7(4):325-335.

81. Flume P, Lekstrom-Himes J, Fischer Biner R, et al. A phase 3, open-label study of tezacaftor/ivacaftor (TEZ/IVA) therapy: interim analysis of pooled safety, and efficacy in patients homozygous for F508del-CFTR. *Journal of Cystic Fibrosis.* 2018;17:S64-S65.
82. Yang Y, Rizio A, Chuang C-C, et al. Effects of tezacaftor/ivacaftor (TEZ/IVA) treatment in patients with cystic fibrosis homozygous for F508del-CFTR: patient-reported outcomes in a phase 3 randomized, controlled trial (EVOLVE). *Thorax.* 2018;73(Suppl 4):A42-A42.
83. Burgel P, Munck A, Durieu I, et al. Real-Life Safety and Effectiveness of Lumacaftor–Ivacaftor in Patients with Cystic Fibrosis. *American journal of respiratory and critical care medicine.* 2020;201(2):188-197.
84. Kirwan L, Rice M, Babu S, Zhou S, Fletcher G, Jackson AD. Key outcomes in cystic fibrosis patients treated with Orkambi for 12 months: real-world data from the Irish Cystic Fibrosis Registry. *Journal of Cystic Fibrosis.* 2019;18:S131-131.
85. Wark PA, Tong K, Dorahy D, et al. A multicentre, observational case-control study to determine the effect of lumacaftor/ivacaftor in patients with severe lung disease and cystic fibrosis. *Pediatric Pulmonology.* 2019;54(S2):432-432.
86. Ratjen F, Hug C, Marigowda G, et al. Efficacy and safety of lumacaftor and ivacaftor in patients aged 6-11 years with cystic fibrosis homozygous for F508del-CFTR: a randomised, placebo-controlled phase 3 trial. *The Lancet Respiratory medicine.* 2017;5(7):557-567.
87. Taylor-Cousar JL, Munck A, McKone E, et al. Tezacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del. *The New England journal of medicine.* 2017;377(21):2013-2023.
88. Konstan MW, McKone EF, Moss RB, et al. Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase 3, extension study. *The Lancet Respiratory medicine.* 2017;5(2):107-118.
89. Milla CE, Ratjen F, Marigowda G, Liu F, Waltz D, Rosenfeld M. Lumacaftor/Ivacaftor in Patients Aged 6-11 Years with Cystic Fibrosis and Homozygous for F508del-CFTR. *American journal of respiratory and critical care medicine.* 2017;195(7):912-920.
90. Konstan M, McKone E, Moss R, et al. Evidence of reduction in annual rate of fev1 decline and sustained benefits with lumacaftor and ivacaftor (LUM/IVA) in patients (PTS) with CF homozygous for f508del-cftr. *Pediatric Pulmonology.* 2016;51:260.
91. Chuang C, Rizio A, Loop B, et al. Effects of tezacaftor/ivacaftor (TEZ/IVA) treatment in patients heterozygous for F508del-CFTR and a residual function mutation: patient-reported outcomes in a phase 3 randomized, controlled trial (EXPAND). *Thorax.* 2018;73(Suppl 4):A41-A41.
92. Walker S, Flume P, McNamara J, et al. A phase 3 study of tezacaftor in combination with ivacaftor in children aged 6 through 11years with cystic fibrosis. *Journal of Cystic Fibrosis.* 2019;18(5):708-713.
93. Rowe SM, Daines C, Ringshausen FC, et al. Tezacaftor–Ivacaftor in Residual-Function Heterozygotes with Cystic Fibrosis. *New England Journal of Medicine.* 2017;377(21):2024-2035.
94. Positive Phase 3 Study Results for TRIKAFTA(R) (elexacaftor/tezacaftor/ivacaftor and ivacaftor) in People Ages 12 and Older With Cystic Fibrosis Who Have One Copy of the F508del Mutation and One Gating or Residual Function Mutation [press release]. July 20 2020.
95. Elborn JS, Ramsey BW, Boyle MP, et al. Efficacy and safety of lumacaftor/ivacaftor combination therapy in patients with cystic fibrosis homozygous for Phe508del CFTR by pulmonary function subgroup: a pooled analysis. *The Lancet Respiratory medicine.* 2016;4(8):617-626.
96. Jennings MT, Dezube R, Paranjape S, et al. An Observational Study of Outcomes and Tolerances in Patients with Cystic Fibrosis Initiated on Lumacaftor/Ivacaftor. *Annals of the American Thoracic Society.* 2017.

97. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: Second panel on cost-effectiveness in health and medicine. *JAMA.* 2016;316(10):1093-1103.
98. McKone E, Goss CH, Aitken ML. Genotype as a Predictor of Prognosis in Cystic Fibrosis. *Chest.* 2006;130(5):1441-1447.
99. Sawicki GS, Konstan MW, McKone EF, et al. Rate of Lung Function Decline in Patients with Cystic Fibrosis (CF) Having a Residual Function Gene Mutation. *American journal of respiratory and critical care medicine.* 2017;195:A4847.
100. Liou T, Adler F, FitzSimmons S, Cahill B, Hibbs J, Marshall B. Predictive 5-Year Survivorship Model of Cystic Fibrosis. *American Journal of Epidemiology.* 2001;153(4):345-352.
101. Konstan MW, Morgan WJ, Butler SM, et al. Risk factors for rate of decline in forced expiratory volume in one second in children and adolescents with cystic fibrosis. *J Pediatr.* 2007;151(2):134-139, 139.e131.
102. Konstan M, Wagener J, VanDevanter D. Risk factors for rate of decline in FEV1 in adults with cystic fibrosis. *Journal of Cystic Fibrosis.* 2012;11(5):405-411.
103. Goss CH, Burns JL. Exacerbations in cystic fibrosis: epidemiology and pathogenesis (part 1). *Thorax.* 2007;62(4):8.
104. Whiting P, Al M, Burgers L, et al. Ivacaftor for the treatment of patients with cystic fibrosis and the G551D mutation: a systematic review and cost-effectiveness analysis. *Health technology assessment (Winchester, England).* 2014;18(18):1-106.
105. VanDevanter DR, Kahle JS, O'Sullivan AK, Sikirica S, Hodgkins PS. Cystic fibrosis in young children: A review of disease manifestation, progression, and response to early treatment. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society.* 2016;15(2):147-157.
106. Lynch Jr, Sayah D, Belperio J, Weigt S. Lung transplantation for cystic fibrosis: results, indications, complications, and controversies. *Seminars in Respiratory and Critical Care Medicine.* 2015;36(2):299-320.
107. Ahmed N, Corey M, Forstner G, et al. Molecular consequences of cystic fibrosis transmembrane regulator (CFTR) gene mutations in the exocrine pancreas. *Gut.* 2003;52(8):1159-1164.
108. Borowitz D, Lubarsky B, Wilschanski M, et al. Nutritional Status Improved in Cystic Fibrosis Patients with the G551D Mutation After Treatment with Ivacaftor. *Digestive diseases and sciences.* 2016;61(1):198-207.
109. Thabut G, Christie J, Mal H, et al. Survival benefit of lung transplant for cystic fibrosis since lung allocation score implementation. *American journal of respiratory and critical care medicine.* 2013;187(12):1335-1340.
110. Sawicki GS, McKone EF, Pasta DJ, et al. Sustained Benefit from ivacaftor demonstrated by combining clinical trial and cystic fibrosis patient registry data. *American journal of respiratory and critical care medicine.* 2015;192(7):836-842.
111. The National Institute for Health and Care Excellence. NICE Committee Papers. 2016.
112. The National Institute for Health and Care Excellence. Lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation. 2016.
113. Arias E, Xu J. United States Life Tables, 2017. *National vital statistics reports.* 2019;68(7).
114. Rubin J, O'callaghan L, Pelligra C, et al. Modeling long-term health outcomes of patietns with cystic fibrosis homozygous for F508del-CFTR treated with lumacaftor/ivacaftor. *Therapeutic Advances in Respiratory Disease.* 2019;13.
115. Hanmer J, Lawrence W, Anderson J, Kaplan R, DG F. Report of Nationally Representative Values for the Noninstitutionalized US Adult Population for 7 Health-Related Quality-of-Life Scores. *Medical Decision Making.* 2006;26(4):391-400.

116. Schechter MS, Trueman D, Farquharson R, Higuchi K, Daines CL. Inhaled aztreonam versus inhaled tobramycin in cystic fibrosis. An economic evlaution. *Annals of the American Thoracic Society.* 2015;12(7):1030-1038.
117. Tappenden P, Harnan S, Uttley L, et al. The cost effectiveness of dry powder antibiotics for treatment of Pseudomonas aeruginosa in patients with cystic fibrosis. *PharmacoEconomics.* 2014;32:159-172.
118. Busschbach JJ, Horikx PE, van den Bosch JM, Brutel de la Riviere A, de Charro FT. Measuring the quality of life before and after bilateral lung transplantation in patients with cystic fibrosis. *Chest.* 1994;105(3):911-917.
119. Pharmaceutical Pricing. U.S. department of Veterans Affairs; 2018. Accessed January 16th, 2018.
120. Dilokthornsakul P, Patidar M, Campbell JD. Forecasting the Long-Term Clinical and Economic Outcomes of Lumacaftor/Ivacaftor in Cystic Fibrosis Patients with Homozygous phe508del Mutation. *Value in Health.* 2017.
121. 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.
122. Moreno SG, Ray JA. The value of innovation under value-based pricing. *Journal of Market Access & Health Policy.* 2016;4:10.3402/jmahp.v3404.30754.
123. Garrison LP, Jr., Mansley EC, Abbott TA, 3rd, Bresnahan BW, Hay JW, Smeeding J. Good research practices for measuring drug costs in cost-effectiveness analyses: a societal perspective: the ISPOR Drug Cost Task Force report--Part II. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2010;13(1):8-13.
124. National Institute for Health and Care Excellence. Lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation: Technology appraisal guidance [TA398]. 2016; https://www.nice.org.uk/guidance/ta398/chapter/4-Committee-discussion#cost-effectiveness-2. Accessed February 28, 2020.
125. Dagoni R. Outrage as Teva Charges $18,275 for Generic Drug in US. *Jerusalem Post*2018.
126. Lieu TA, Ray GT, Farmer G, Shay GF. The cost of medical care for patients with cystic fibrosis in a health maintenance organization. *Pediatrics.* 1999;103(6):e72.
127. Grosse SD, Do T, Vu M, Feng L, Berry J, Sawicki GS. Healthcare expenditures for privately insured US patients with cystic fibrosis, 2010-2016. *Pediatric Pulmonology.* 2018;53(12):1611-1618.
128. Bentley TS, Phillips SJ. *2017 U.S. organ and tissue transplant cost estimates and discussion.* Milliman;2017.
129. Ramsey SD, Patrick DL, Albert RK, Larson EB, Wood DE, Raghu G. The cost-effectiveness of lung transplantation. A pilot study. University of Washington Medical Center Lung Transplant Study Group. *Chest.* 1995;108(6):1594-1601.
130. Neri L, Lucidi V, Catastini P, Colombo C. Caregiver burden and vocational participation among parents of adolescents with CF. *Pediatr Pulmonol.* 2015.
131. Angelis A, Kanavos P, Lopez-Bastida J, Nicod E, Serrano-Aquilar P. Social and economic costs and health-related quality of life in non-institutionalised patients with cystic fibrosis in the United Kingdom. *BMC Healt5h Serv Res.* 2015.
132. Sanders DB, Bittner RC, Rosenfeld M, Hoffman LR, Redding GJ, Goss CH. Failure to recover to baseline pulmonary function after cystic fibrosis pulmonary exacerbation. *American journal of respiratory and critical care medicine.* 2010;182(5):627-632.
133. Quittner A, Suthoff E, Rendas-Baum R, et al. Effect of ivacaftor treatment in patients with cystic fibrosis and the G551D-CFTR mutation: patient-reported outcomes in the STRIVE randomized, controlled trial. *Health and quality of life outcomes.* 2015;13:93.

134. Pearson S. The ICER Value Framework: Integrating Cost Effectiveness and Affordability in the Assessment of Health Care Value. *Value in Health.* 2018;21(3):258-265.
135. Cystic Fibrosis Foundation, Borowitz D, Parad RB, et al. Cystic Fibrosis Foundation practice guidelines for the management of infants with cystic fibrosis transmembrane conductance regulator-related metabolic syndrome during the first two years of life and beyond. *Journal of Paediatrics.* 2009;155(6):S106-116.
136. Ollendorf DA, Pearson SD. An integrated evidence rating to frame comparative effectiveness assessments for decision makers. *Medical care.* 2010;48(6 Suppl):S145-152.
137. ClinicalTrials.gov. A Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of VX-661/Ivacaftor in Pediatric Subjects With Cystic Fibrosis (CF). 2019; https://clinicaltrials.gov/ct2/show/results/NCT02953314. Accessed 01/22/2020.
138. ClinicalTrials.gov. A Study to Evaluate the Safety and Efficacy of Long Term Treatment With VX-661 in Combination With Ivacaftor in Subjects With Cystic Fibrosis Who Have an F508del-CFTR Mutation. 2019; https://clinicaltrials.gov/ct2/show/NCT02565914.
139. ClinicalTrials.gov. Rollover Study to Evaluate the Safety and Efficacy of Long-term Treatment With Lumacaftor in Combination With Ivacaftor. 2019; https://clinicaltrials.gov/ct2/show/NCT02544451.
140. Nick JA, St Clair C, Jones MC, Lan L, Higgins M. Ivacaftor in cystic fibrosis with residual function: Lung function results from an N-of-1 study. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society.* 2020;19(1):91-98.
141. McColley SA, Konstan MW, Ramsey BW, et al. Association between changes in percent predicted fev1 and incidence of pulmonary exacerbations, including those requiring hospitalization and/or iv antibiotics, in patients with CF treated with lumacaftor in combination with ivacaftor. *Pediatric Pulmonology.* 2015;50:282.
142. Food and Drug Administration. Ivacaftor Prescribing Information. In:2017.
143. Food and Drug Administration. U.S. Prescribing Information - Symdeko. In: HHS, ed. www.fda.gov2018.
144. Pickard AS, Law EH, Jiang R, et al. United States Valuation of EQ-5D-5L Health States Using an International Protocol. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2019;22(8):931-941.
145. Cystic Fibrosis Foundation. *Cystic Fibrosis Foundation Patient Registry 2016 Annual Data Report.* cff.org2017.
146. 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.
147. Konstan MW, Ramsey BW, Elborn J, et al. Safety and efficacy of treatment with lumacaftor in combination with ivacaftor in patients with CF homozygous for F508DELCFTR. *Pediatric Pulmonology.* 2015;50:269-270.
148. Taylor-Cousar JL, Jain M, Barto TL, et al. Lumacaftor/ivacaftor in patients with cystic fibrosis and advanced lung disease homozygous for F508del-CFTR. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society.* 2017.
149. Boyle MP, Bell SC, Konstan MW, et al. A CFTR corrector (lumacaftor) and a CFTR potentiator (ivacaftor) for treatment of patients with cystic fibrosis who have a phe508del CFTR mutation: a phase 2 randomised controlled trial. *The Lancet Respiratory medicine.* 2014;2(7):527-538.
150. Flume PA, Wainwright CE, Elizabeth Tullis D, et al. Recovery of lung function following a pulmonary exacerbation in patients with cystic fibrosis and the G551D-CFTR mutation treated

with ivacaftor. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society.* 2017.
151. Accurso FJ, Rowe SM, Clancy JP, et al. Effect of VX-770 in persons with cystic fibrosis and the G551D-CFTR mutation. *The New England journal of medicine.* 2010;363(21):1991-2003.
152. 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.
153. Konstan MW, Plant BJ, Elborn JS, et al. Efficacy response in CF patients treated with ivacaftor: post-hoc analysis. *Pediatr Pulmonol.* 2015;50(5):447-455.
154. Heltshe SL, Mayer-Hamblett N, Burns JL, et al. Pseudomonas aeruginosa in cystic fibrosis patients with G551D-CFTR treated with ivacaftor. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2015;60(5):703-712.
155. Bai Y, Higgins M, Volkova N, et al. Real-world outcomes in young (6-to 12-year-old) patients (pts) with cystic fibrosis (CF) treated with ivacaftor (IVA): Analysis of 2014 US and UK CF registries data. *Journal of Cystic Fibrosis.* 2016;15:S57-S58.
156. Bai Y, Higgins M, Volkova N, et al. Real-world outcomes in patients (PTS) with cystic fibrosis (CF) treated with ivacaftor (IVA): Analysis of 2014 US and UK CF registries. *Journal of Cystic Fibrosis.* 2016;15:S41.
157. Barry PJ, Plant BJ, Simmonds NJ, et al. Ivacaftor decreases mortality in G551D patients with severe lung disease. *Pediatric Pulmonology.* 2015;50:275-276.
158. Volkova N, Bai Y, Higgins M, et al. Disease progression in patients (pts) with cystic fibrosis (CF) treated with ivacaftor (IVA): Analysis of real-world data from the UK CF Registry. *Journal of Cystic Fibrosis.* 2016;15:S41.
159. Elborn S, Wainwright C, Sermet-Gaudelus I, et al. Pulmonary effects of the investigational CFTR potentiator, ivacaftor, in two phase 3 trials in subjects with CF who have the G551D-CFTR mutation. *American journal of respiratory and critical care medicine.* 2012;185.
160. Flume P, Wainwright C, Tullis E, Rodriguez S, Davies J, Wagener J. Pulmonary exacerbations in CF patients with the G551D-CFTR mutation treated with ivacaftor. *Journal of Cystic Fibrosis.* 2013;12:S63.
161. Bai Y, Higgins M, Volkova N, et al. Ivacaftor long-term safety study: Analysis of 2013 us CF foundation patient registry data. *Pediatric Pulmonology.* 2015;50:284.
162. Mainz J, Narayanan S, Suthoff ED, et al. Patient-reported outcomes among patients (pts) with cystic fibrosis and the G551D-CFTR mutation treated with ivacaftor (IVA) compared with those homozygous for the F508del-CFTR mutation. *Journal of Cystic Fibrosis.* 2016;15:S115.
163. Accurso FJ, Ratjen F, Altes T, et al. Effect of withdrawal of ivacaftor therapy on CFTR channel activity and lung function in patients with cystic fibrosis. *Journal of Cystic Fibrosis.* 2013;12:S62.
164. Davies JC, Sheridan H, Lee PS, Song T, Stone A, Ratjen F. Effect of ivacaftor on lung function in subjects with CF who have the G551D-CFTR mutation and mild lung disease: A comparison of lung clearance index (LCI) vs. spirometry. *Journal of Cystic Fibrosis.* 2012;11:S15.
165. Elborn JS, Rodriguez S, Lubarsky B, Gilmartin G, Bell S. Effect of ivacaftor in patients with cystic fibrosis and the G551D-CFTR mutation who have baseline FEV1 >90% of predicted. *Pediatric Pulmonology.* 2013;48:298.
166. Plant BJ, Konstan M, Aherns R, et al. Lung function, weight, and sweat chloride responses in patients with cystic fibrosis and the G551D-CFTR mutation treated with ivacaftor: A secondary analysis. *Journal of Cystic Fibrosis.* 2013;12:S62.
167. Suthoff E, Rendas-Baum R, Vera-Llonch M, Bayliss M, Sermet-Gaudelus I, Quittner AL. Patient-reported treatment effects of ivacaftor beyond respiratory symptoms in patients with cystic fibrosis (CF). *Pediatric Pulmonology.* 2014;49:250.

168. Hathorne H, Brand KM, Britton LJ, et al. The investigation of quality of life and adherence in patients with the G551D mutation receiving ivacaftor therapy. *Pediatric Pulmonology.* 2015;50:427.
169. Wainwright C, Bell S, Morton J, et al. The effect of ivacaftor in individuals with CF and severe lung disease. *Pediatric Pulmonology.* 2014;49:376-377.
170. Barry PJ, Plant BJ, Nair A, et al. Effects of ivacaftor in patients with cystic fibrosis who carry the G551D mutation and have severe lung disease. *Chest.* 2014;146(1):152-158.
171. Davies J, Sheridan H, Bell N, et al. Assessment of clinical response to ivacaftor with lung clearance index in cystic fibrosis patients with a G551D-CFTR mutation and preserved spirometry: a randomised controlled trial. *The Lancet Respiratory medicine.* 2013;1(8):630-638.
172. Edgeworth D, Keating D, Ellis M, et al. Improvement in exercise duration, lung function and well-being in G551D-cystic fibrosis patients: a double-blind, placebo-controlled, randomized, cross-over study with ivacaftor treatment. *Clinical science (London, England : 1979).* 2017;131(15):2037-2045.
173. Stalvey MS, Pace J, Niknian M, et al. Growth in Prepubertal Children With Cystic Fibrosis Treated With Ivacaftor. *Pediatrics.* 2017;139(2).
174. Fink A, Sawicki GS, Morgan WJ, Schechter MS, Rosenfeld M, Marshall BC. Treatment response to ivacaftor in clinical practice: Analysis of the us CF foundation patient registry. *Pediatric Pulmonology.* 2015;50:361.
175. Heltshe SL, Godfrey EM, Josephy T, Aitken ML, Taylor-Cousar JL. Pregnancy among cystic fibrosis women in the era of CFTR modulators. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society.* 2017.

APPENDICES

Appendix A. Search Strategies and Results

Table A1. PRISMA 2009 Checklist

	#	Checklist Item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured Summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and Registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility Criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information Sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study Selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data Collection Process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data Items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of Bias in Individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary Measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of Results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.
Risk of Bias Across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional Analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study Selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.

Study Characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of Bias within Studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of Individual Studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of Results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of Bias Across Studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional Analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of Evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.
From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097		

Search Strategy of MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present and Cochrane Register of Controlled Trials via Ovid (11/08/2019)

Table A2. Elexacaftor/tezacaftor/ivacaftor

#	Search Terms
1	Exp cystic fibrosis/ OR cystic fibrosis.ti,ab.
2	(deltaF508-CFTR OR deltaF508-CFTR protein OR f508del).mp.
3	Exp cystic fibrosis transmembrane conductance regulator/ OR (cystic fibrosis transmembrane conductance regulator OR CFTR).ti,ab.
4	(cystic fibrosis transmembrane conductance regulator potentiator OR CFTR potentiator).ti,ab.
5	(cystic fibrosis transmembrane conductance regulator corrector OR CFTR corrector).ti,ab.
6	(cystic fibrosis transmembrane conductance regulator modulator OR CFTR modulator).ti,ab.
7	OR/1-6
8	(Elexacaftor OR VX 445 OR VX-445 OR VX445 OR Trikafta).mp.
9	7 AND 8
10	(animals not (humans and animals)).sh.
11	9 NOT 10
12	Limit 11 to English Language

Table A3. Updated Search for ivacaftor, lumacaftor/ivacaftor, and tezacaftor/ivacaftor

#	Search Terms
1	Exp cystic fibrosis/ OR cystic fibrosis.ti,ab.
2	Exp cystic fibrosis transmembrane conductance regulator/ OR (cystic fibrosis transmembrane conductance regulator OR CFTR).ti,ab.
3	(cystic fibrosis transmembrane conductance regulator potentiator OR CFTR potentiator).ti,ab.
4	(cystic fibrosis transmembrane conductance regulator corrector OR CFTR corrector).ti,ab.
5	(cystic fibrosis transmembrane conductance regulator modulator OR CFTR modulator).ti,ab.
6	OR/1-5
7	(Ivacaftor OR Kalydeco OR VX-770 OR VX 770 OR VX770).ti,ab.
8	(Lumacaftor OR Orkambi OR VX-809 OR VX 809 OR VX809).ti,ab.
9	(Tezacaftor OR Symdeko OR VX-661 OR VX 661 OR VX661).ti,ab.
10	OR/7-9
11	6 AND 10
12	(addresses or autobiography or bibliography or biography or clinical trial, phase I or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or video audio media).pt.
13	11 NOT 12
14	(animals not (humans and animals)).sh.
15	13 NOT 14

16	Limit 15 to yr=2017-Current
17	Remove duplicates from 16

Search strategy of EMBASE (11/08/2019)

Table A4. Elexacaftor/tezacaftor/ivacaftor

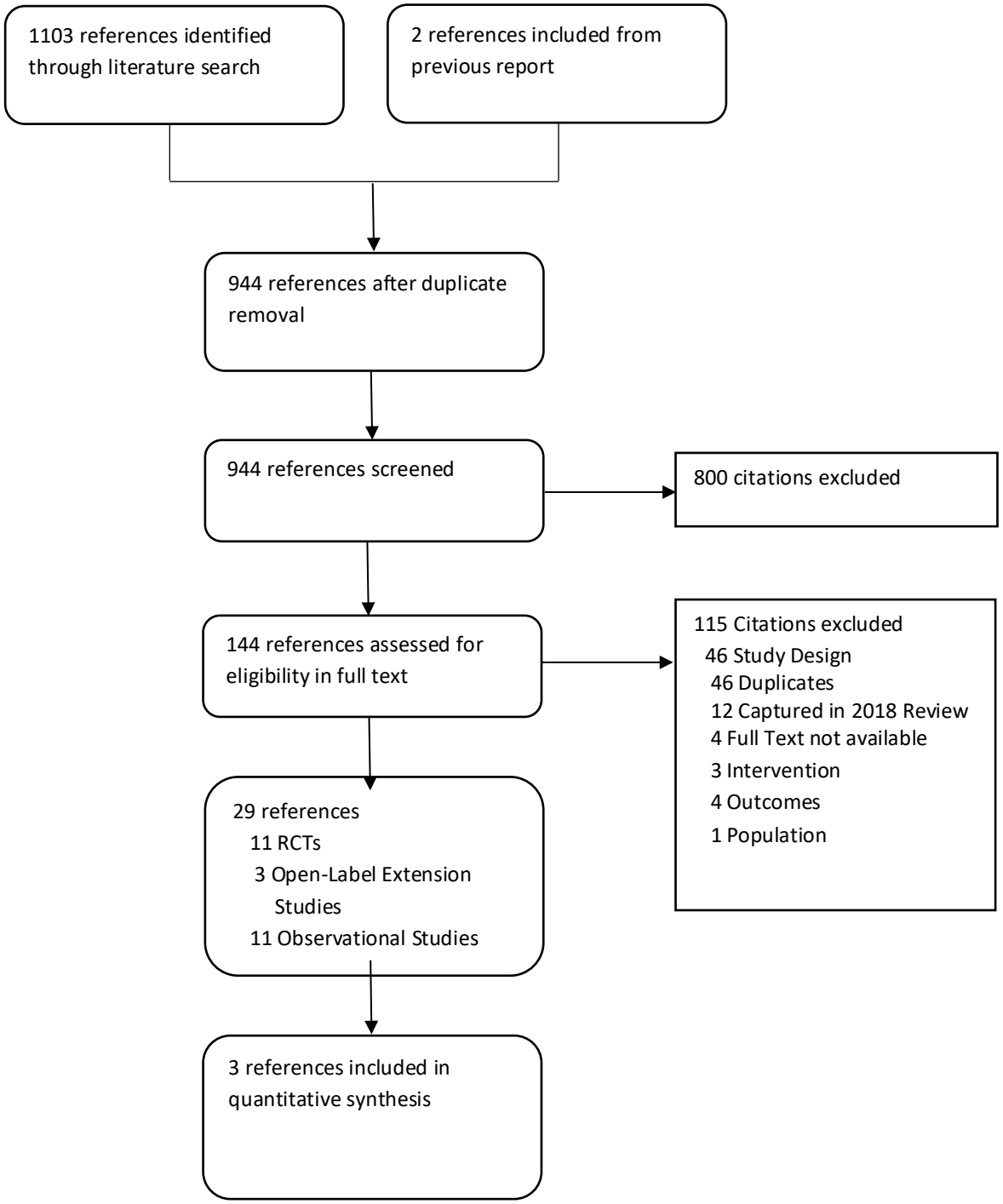
#	Search Terms
#1	'cystic fibrosis'/exp OR 'cystic fibrosis':ti,ab
#2	(deltaF508-CFTR OR deltaF508-CFTR protein OR f508del):ti,ab
#3	'cystic fibrosis transmembrane conductance regulator'/exp OR ('cystic fibrosis transmembrane conductance regulator' OR 'CFTR'):ti,ab
#4	'cystic fibrosis transmembrane conductance regulator potentiator':ti,ab OR 'CFTR potentiator':ti,ab
#5	'cystic fibrosis transmembrane conductance regulator corrector':ti,ab OR 'CFTR corrector':ti,ab
#6	'cystic fibrosis transmembrane conductance regulator modulator':ti,ab OR 'CFTR modulator':ti,ab
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
#8	'elexacaftor'/exp OR "elexacaftor plus ivacaftor plus tezacaftor'/exp OR ('elexacaftor' OR 'vx-445' OR 'vx 445' OR 'vx445' OR 'trikafta'):ti,ab OR ('elexacaftor' AND 'ivacaftor' AND 'tezacaftor'):ti,ab
#9	#7 AND #8
#10	'animal'/exp or 'nonhuman'/exp or 'animal experiment'/exp NOT 'human'/exp
#11	#9 NOT #10
#12	#11 AND [English]/lim

Table A5. Updated Search for ivacaftor, lumacaftor/ivacaftor, and tezacaftor/ivacaftor

#	Search Terms
#1	'cystic fibrosis'/exp OR 'cystic fibrosis':ti,ab
#2	'cystic fibrosis transmembrane conductance regulator'/exp OR ('cystic fibrosis transmembrane conductance regulator' OR 'CFTR'):ti,ab
#3	('cystic fibrosis transmembrane conductance regulator potentiator' OR 'CFTR potentiator'):ti,ab
#4	('cystic fibrosis transmembrane conductance regulator corrector' OR 'CFTR corrector'):ti,ab
#5	('cystic fibrosis transmembrane conductance regulator modulator' OR 'CFTR modulator'):ti,ab
#6	#1 OR #2 OR #3 OR #4 OR #5
#7	'ivacaftor'/exp OR ('ivacaftor' OR 'VX-770' OR 'VX770' OR 'VX 770' OR 'Kalydeco'):ti,ab
#8	'lumacaftor'/exp OR 'ivacaftor plus lumacaftor'/exp ('lumacaftor' OR 'ivacaftor plus lumacaftor' OR 'VX-809' OR 'VX 809' OR 'VX809' OR 'Orkambi'):ti,ab
#9	'tezacaftor'/exp OR 'ivacaftor plus tezacaftor'/exp OR ('tezacaftor' OR 'ivacaftor plus tezacaftor' OR 'VX-661' OR 'VX 661' OR 'VX661' OR 'Symdeko'):ti,ab
#10	#7 OR #8 OR #9
#11	#6 AND #10
#12	'animal'/exp or 'nonhuman'/exp or 'animal experiment'/exp NOT 'human'/exp
#13	#11 not #12
#14	#13 NOT ('case report'/de OR 'human tissue'/de OR 'nonhuman'/de OR 'practice guideline'/de OR 'questionnaire'/de OR 'chapter'/it OR 'conference review'/it OR

	'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
#15	#14 AND (2017:py OR 2018:py OR 2019:py)
#16	#15 AND [English]/lim

Figure A1. PRISMA Flow Chart Showing Results of Literature Search for CFTR Modulators



Appendix B. Previous Systematic Reviews and Technology Assessments

We identified one ongoing health technology assessment (HTA) of Trikafta conducted by the National Institute for Health and Care Excellence (NICE), three HTAs for Orkambi (two by NICE and one by the Canadian Agency for Drugs and Technologies in Health (CADTH)), two reviews of Symdeko (one by NICE and CADTH each), and two CADTH assessments for Kalydeco. These reviews are summarized below.

Technology Assessments

NICE

Elexacaftor, tezacaftor and ivacaftor fixed dose combination therapy for treating cystic fibrosis with the F508del mutation [ID1661]

NICE is currently conducting an appraisal of the clinical and cost effectiveness of Trikafta for treating CF in patients with at least one *F508del* CFTR mutation. The expected publication date is to be confirmed.

Tezacaftor and ivacaftor combination therapy for treating cystic fibrosis with the F508del mutation [ID1303] (Suspended)

NICE's appraisal of the clinical and cost effectiveness of Symdeko for the treatment of CF patients with at least one *F508del* CFTR mutation was suspended because the manufacturer did not submit evidence required for the assessment.

In October 2019, National Health Service (NHS) England and the manufacturer reached an interim access agreement for Symdeko, which includes the collection of further data through an interim data collection agreement.

Lumacaftor with ivacaftor for treating cystic fibrosis in children aged 2 to 11 years old homozygous for the F508del mutation [ID1486] (Suspended)

NICE has suspended its appraisal of Orkambi for the treatment of children ages 2-11 years old who are homozygous for the *F508del* CFTR mutation as a result of the manufacturer's refusal to participate in the appraisal.

National Health Service (NHS) England and the manufacturer reached an interim access agreement for Orkambi, which includes the collection of further data through an interim data collection agreement.

Lumacaftor-ivacaftor for treating cystic fibrosis homozygous for the F508del mutation [TA398] (July 27, 2016)

NICE performed a clinical and economic review of Orkambi in 2016 and concluded that Orkambi is not recommended for the treatment of CF in patients 12 years or older who are homozygous for the *F508del* CFTR mutation. NICE based its decision on the clinical evidence from two Phase III randomized controlled trials (RCTs), TRAFFIC and TRANSPORT, and one extension study, PROGRESS. While Orkambi was generally well tolerated and was found to result in statistically significant effects on key outcomes in comparison to usual care alone, the clinical significance of these improvements wasn't clear. Furthermore, these results might not be generalizable to patients with very mild or severe forms of CF and the clinical evidence was deemed insufficient to determine the long-term effect of Orkambi. NICE assessed the cost effectiveness of Orkambi based on the manufacturer's microsimulation model and concluded the manufacturer's model might overestimate the benefits of Orkambi treatment and substantially underestimate the costs.

In November 2019, NHS England and the manufacturer reached an interim access agreement for Orkambi, which includes the collection of further data through an interim data collection agreement.

CADTH

Tezacaftor/Ivacaftor - Cystic fibrosis, F508del mutation(s) [Not filed] (August 15, 2019)

CADTH does not recommend reimbursement for Symdeko for the treatment of patients with CF and an *F508del* mutation, as the manufacturer has not filed a data submission.

Lumacaftor/Ivacaftor - Cystic Fibrosis, F508del CFTR mutation in patients 6 years and older [SR0559-000] (October 12, 2018)

Following its appraisal of Orkambi for the treatment of CF patients 6 years and older who are homozygous for the *F508del* CFTR mutation, CADTH does not recommend Orkambi for reimbursement. This decision was based on the findings that while treatment with Orkambi was found to lead to statistically significant improvements in $ppFEV_1$ when compared to placebo, the clinical significance of the magnitude of improvement was considered uncertain. Furthermore, statistically significant improvements in rates of pulmonary exacerbations, BMI, body weight, or height were not observed in either clinical trial (TRAFFIC or TRANSPORT).

Kalydeco - Cystic Fibrosis With R117H Mutation [SR0430-000,]

CADTH recommends Kalydeco for the treatment of CF in patients ages 18 years and older with the *R117H* CFTR mutation if the following clinical criteria and condition are met 1) Confirmed CF diagnosis that is accompanied by chronic sinopulmonary disease and 2) in consultation with clinical experts, discontinuation criteria should be developed for non-responders. Furthermore, CADTH stipulated that the price of Kalydeco should be substantially decreased.

Kalydeco - Cystic fibrosis with G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or G970R mutation [SR0379-000]

CADTH recommends Kalydeco for the treatment of CF in patients ages 6 years and older who have one of the following CFTR gene mutations: *G551D*, *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N*, *S549R*, or *G970R*. This recommendation is contingent on a substantial price reduction, as Kalydeco is currently not considered cost-effective.

Previous Systematic Reviews

Habib AR, Kajbafzadeh M, Desai S, Yang CL, Skolnik K, Quon BS. A Systematic Review of the Clinical Efficacy and Safety of CFTR Modulators in Cystic Fibrosis. Scientific reports. 2019;9(1):7234.

The investigators performed a systematic review to evaluate the clinical efficacy and safety of CFTR modulators (Kalydeco, Symdeko, and Orkambi) in individuals with CF, specifically in patients with at least one *G551D* mutation, *F508del* homozygous individuals, and *F508del*/*G551D* heterozygotes. A total of 14 placebo-controlled, parallel-group studies were included in the analysis. Efficacy was assessed based on the CFTR modulators impact on percent-predicted forced expiratory volume in one second ($ppFEV_1$), pulmonary exacerbations (PEx), hospitalizations due to PEx, CFQ-R respiratory domain scores, as well as nutrition status. Safety was evaluated based on adverse events (AEs), AEs leading to treatment discontinuation, as well as the prevalence of elevated liver function tests. The reviewers concluded that patients with gating mutations such as *G551D* currently benefit the most from CFTR modulator treatment, while individuals homozygous for *F508del* mutations only experience moderate benefits in comparison. CFTR modulators were not effective in individuals heterozygous for the *F508del* mutation. The CFTR modulator therapies were found to have a safety profile that is generally comparable to placebo, except for Orkambi which led to higher rates of treatment discontinuation due to respiratory adverse events.

Wu HX, Zhu M, Xiong XF, Wei J, Zhuo KQ, Cheng DY. Efficacy and Safety of CFTR Corrector and Potentiator Combination Therapy in Patients with Cystic Fibrosis for the F508del-CFTR Homozygous Mutation: A Systematic Review and Meta-analysis. Advances in therapy. 2019;36(2):451-461.

This systematic review and meta-analysis was conducted to examine the efficacy and safety of Orkambi and Symdeko combination therapy in the treatment of CF patients who are homozygous for the *F508del*-CFTR mutation. Five randomized controlled trials (RCTs) were included in the quantitative analysis. Efficacy was evaluated based on lung function, nutritional status, and CFQR respiratory domain scores. Safety was assessed based on the occurrence of adverse events and the number of AEs that led to treatment discontinuation. The two combination therapies were found to significantly improve $ppFEV_1$, CFQ-R respiratory domain score, as well as BMI when compared to placebo. Orkambi and Symdeko were found to have a safety profile comparable to placebo, although the proportion of discontinuations due to AEs was significantly higher for the combination therapies when compared to placebo.

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.

This review included four randomized control trials: one Phase II dose-ranging study (n=19), one adult (n=167) and one pediatric (n=52) Phase III trial with *G551D* mutation populations and one trial with homozygous *F508del* participants (n=140). The trial evaluating Kalydeco among the *F508del* population was also included. No clinical differences were reported for CFQ-R, lung function, pulmonary exacerbations, or weight outcomes.

Adults treated with Kalydeco reported significantly higher CFQ-R respiratory domain scores through 48 weeks compared to those taking placebo. Children on Kalydeco did not report similar improvements compared to placebo. Children and adults treated with Kalydeco both reported significant improvements in relative change from baseline in FEV_1 at 24 weeks, and adults reported similarly significant improvement in FEV_1 through 48 weeks. Pooled data showed significant improvements in absolute change from baseline in $ppFEV_1$ at both 24 and 48 weeks for Kalydeco groups compared to placebo. Both studies reported improvement in weight and decreased rates of pulmonary exacerbations among ivacaftor groups.

Pooled data from both Phase III studies showed increased rates of coughing and episodes of decreased pulmonary function in the placebo group. Adults treated with Kalydeco reported dizziness more frequently than placebo recipients. Neither trial reported a difference in study drug interruptions or discontinuations between placebo and Kalydeco groups.

Overall, the authors concluded the Phase III trials in *G551D* populations showed sufficient efficacy and safety compared to placebo through 48 weeks of treatment, supporting the use of Kalydeco in children and adults at least six years old.

Cystic Fibrosis Foundation, Borowitz D, Parad RB, et al. Cystic Fibrosis Foundation practice guidelines for the management of infants with cystic fibrosis transmembrane conductance

regulator-related metabolic syndrome during the first two years of life and beyond. Journal of Pediatrics. 2009;155(6):S106-116.

We identified one systematic review and guidline document from the Cystic Fibrosis Foundation for the use of Kalydeco and Orkambi.[135] The guideline was designed to advise clinicians, CF patients, and their families on the use of Kalydeco and Orkambi. A multidisciplinary committee was assembled to develop clinical questions using the Patient-Intervention-Comparison-Outcome (PICO) format. A systematic review of evidence for Kalydeco and Orkambi was conducted to identify relevant publications that met the PICO criteria.

The guideline panel made a conditional recommendation for treatment with Kalydeco in adults and children ages six and older with CF due to gating mutations other than *G551D* or *R117H.* For individuals with two copies of *F508del*, the guideline panel made a strong recommendation for treatment with Orkambi for adults and children ages 12 and older with $ppFEV_1$ <90%. A conditional recommendation was made for treatment with Orkambi in (1) patients ages 12 or older with $ppFEV_1$ >90% and (2) children ages six to 11.

Appendix C. Ongoing Studies

Trial	Study Design	Study Arms	Patient Population	Key Outcomes	Estimated Completion
Elexacaftor (ELX) / Tezacaftor (TEZ) / Ivacaftor (IVA)					
Evaluation of VX-445/ TEZ/ IVA in Cystic Fibrosis Subjects 6 Through 11 Years of Age NCT03691779 **Vertex Pharmaceuticals**	Phase 3, open-label, non-randomized, sequential assignment Estimated N: 56	**Experimental** Part A: - Morning: VX-445/ IVA - Evening: IVA Part B: - Morning: VX-445/ TEZ/ IVA - Evening: IVA (dose to be based on the outcome of Part A)	**Inclusions** - Ages 6 – 11 years - Homozygous or heterozygous for F508del mutation (F/F or F/MF genotypes) - $ppFEV_1$ value ≥40% for age, sex, and height **Exclusions** - Clinically significant cirrhosis with or without portal hypertension - Glucose-6-phosphate dehydrogenase (G6PD) deficiency - Lung infection with organisms associated with a more rapid decline in pulmonary status - Solid organ or hematological transplantation	**Primary Outcomes** *[Day 1 through 15]* Part A: - Observed pre-dose concentration of VX-445, TEZ, and IVA - Maximum Observed Concentration of VX-445, TEZ, and IVA - Area under the concentration versus time curve during a dosing interval of VX-445, TEZ, and IVA Part B: Safety and tolerability as assessed by number of subjects with AEs and SAEs *[Time Frame: from baseline through safety follow-up (28 Weeks)]* **Secondary Outcomes** Part A *[Day 1 through 15]* - Maximum observed concentration of VX-445, TEZ, and IVA metabolites - Observed pre-dose concentration of VX-445, TEZ, and IVA metabolites - Area under the concentration versus time curve during a dosing interval of VX-445, TEZ, and IVA metabolites - Safety and tolerability as assessed by number of subjects with AEs and [from baseline through safety follow-up (28 Weeks)] Part B *[Baseline through Weeks 12 and 24]* - Absolute change in $ppFEV_1$ - Absolute change in sweat chloride - Absolute change in CFQ-R respiratory domain score - Absolute change in BMI and BMI for age-z-score	July 2020

				- Absolute change in weight and weight for age-z-score - Absolute change in height and height for age-z-score - Absolute change in the Modified Facial Hedonic Scale - Trough of VX-445/TEZ/IVA, and IVA metabolites - Absolute change in LCI2.5	
Clinical Outcomes of Triple Combination Therapy in Severe Cystic Fibrosis Disease NCT04038710 **National Jewish Health**	Observational, prospective study, cases only Estimated N: 7	Patients that are eligible to enroll in Vertex's triple combination therapy through the expanded access program	**Inclusions** - Ages ≥12 years - Confirmed CF diagnosis - Ability to reproducibly perform spirometry - Physician decision to treat with TCT through the EAP program **Exclusions** - Any acute lower respiratory symptoms treated with oral, inhaled, or intravenous antibiotics or systemic corticosteroids within the 2 weeks prior - Major or traumatic surgery within 12 weeks - Initiation of any new chronic therapy within 4 weeks - Use of an investigational agent within 28 days - History of lung or liver transplantation or listing for organ transplantation	**Primary Outcomes** *[Baseline up to 52 weeks]* - Pulmonary Function (FEV1 values) **Secondary Outcomes** *[Baseline up to 52 weeks]* CFQ-R score	March 2020
A Study Evaluating the Efficacy and Safety of VX445/ Tezacaftor/ Ivacaftor in Cystic Fibrosis Subjects, Homozygous for F508del	Phase 3b, randomized, double-blind, parallel assignment Estimated N: 158	**Experimental** - Morning: ELX/TEZ/IVA - Evening: IVA **Comparator** - Morning: TEZ/IVA or IVA - Evening: IVA	**Inclusions** - Ages ≥12 years - Homozygous for F508del mutation (F/F) - FEV1 value ≥40% and ≤90% of predicted mean for age, sex, and height **Exclusions** - Clinically significant cirrhosis with or without portal hypertension	**Primary Outcomes** *[Baseline through Week 24]* - Absolute change in CFQ-R respiratory domain score **Secondary Outcomes** *[Baseline through Week 24]* - Absolute change in $ppFEV_1$ - Absolute change in sweat chloride (SwCl) - Safety and tolerability as assessed by number of subjects with AEs and SAEs *[Baseline through Week 28]*	September 2020

NCT04105972 **Vertex Pharmaceuticals**			- Lung infection with organisms associated with a more rapid decline in pulmonary status - Solid organ or hematological transplantation		
A Phase 3 Study of VX-445 Combination Therapy in Cystic Fibrosis (CF) Subjects Heterozygous for F508del and a Gating or Residual Function Mutation (F/G and F/RF Genotypes) NCT04058353 **Vertex Pharmaceuticals**	Phase 3, randomized, double-blind, parallel assignment Estimated N: 250	**Experimental** Morning: ELX/TEZ/IVA Evening: IVA **Comparator** Morning: TEZ/IVA or IVA Evening: IVA	**Inclusions** - Ages ≥12 years - Confirmed CF diagnosis - Heterozygous for F508del and either a gating or residual function mutation (F/G and F/RF genotypes) - FEV1 value ≥40% and ≤90% of predicted mean for age, sex, and height **Exclusions** - Clinically significant cirrhosis with or without portal hypertension - Lung infection with organisms associated with a more rapid decline in pulmonary status - Solid organ or hematological transplantation	**Primary Outcomes** *[Baseline through Week 8]* - Absolute change in $ppFEV_1$ for ELX/TEZ/IVA arm **Secondary Outcomes** *[Baseline through Week 8]* - Absolute change in sweat chloride (SwCl) for ELX/TEZ/IVA group (and compared to control group) - Absolute change in $ppFEV_1$ for ELX/TEZ/IVA group compared to the control group - Absolute change from baseline in CFQ-R respiratory domain score for ELX/TEZ/IVA group (and compared to control group) - Safety and tolerability as assessed by number of subjects with AEs and SAEs	October 2020
Impact of Triple Combination CFTR Therapy on Sinus Disease NCT04056702 **Jennifer Taylor-Cousar / CFF**	Observational, prospective cohort study Estimated N: 70	**Cohort 1** - ELX/TEZ/IVA **Cohort 2** - No treatment (patients ineligible for treatment)	**Inclusions** - 18 – 89 years - CF and comorbid chronic sinus disease **Exclusions** - Sinus surgery within the last 6 months or planned sinus surgery during the study period - Recent pulmonary exacerbation or viral infection within two weeks of initial visit	**Primary Outcomes** *[From baseline up to 6 months]* - Change in Sinus CT opacification **Secondary Outcomes** *[From baseline up to 6 months]* - Change in 22-item Sino-Nasal Outcome Test (SNOT-22) score - Change in Questionnaire for Olfactory Disorders (QOD) score	April 2021

A Study Evaluating the Long-term Safety and Efficacy of VX-445 Combination Therapy NCT03525574 **Vertex Pharmaceuticals**	Phase 3, open-label, single group assignment Estimated N: 507	**Experimental** - Morning: VX-445/ TEZ/ IVA - Evening: IVA	**Inclusions** - Completed study drug treatment in a parent study (VX17-445-102, VX17-445-103); or had study drug interruption(s) in a parent study but completed study visits up to the last scheduled visit of the Treatment Period in the parent study. **Exclusions** - History of drug intolerance in a parent study that would pose an additional risk to the subject - Current participation in an investigational drug trial (other than a parent study)	**Primary Outcomes** *[Baseline up to 100 weeks]* - Safety and tolerability as assessed by number of subjects with AEs and SAEs **Secondary Outcomes** *[Baseline up to 96 weeks]* - Absolute change from baseline in ppFEV$_1$ - Absolute change in sweat chloride (SwCl) - Number of pulmonary exacerbations (PEx) - Time to first PEx - Absolute change in BMI and BMI z-score - Absolute change in body weight - Absolute change from baseline in CFQ-R respiratory domain score	June 2021
A Study Evaluating the Long-term Safety of VX-445 Combination Therapy NCT04043806 **Vertex Pharmaceuticals**	Phase 3, open-label, single group assignment Estimated N: 480	**Experimental** - Morning: ELX/TEZ/IVA - Evening: IVA	**Inclusions** - 12 years and older - Currently participating in NCT03447262 **Exclusions** - History of drug intolerance in study NCT03447262 that would pose an additional risk to the subject - Current participation in an investigational drug trial (other than study NCT03447262)	**Primary Outcome** [*Baseline through Week 100*] - Safety and tolerability as assessed by number of subjects with AEs and SAEs	May 2022
Study Evaluating the Long-term Safety and Efficacy of VX-445 Combination Therapy NCT04058366 **Vertex Pharmaceuticals**	Phase 3, open-label, single group assignment Estimated N: 250	**Experimental** - Morning: ELX/ TEZ/ IVA - Evening: IVA	**Inclusions** - 12 years and older - Completed study drug treatment in parent study (VX18-445-104; NCT04058353); or had study drug interruption(s) in parent study but completed study visits up to the last scheduled visit of the Treatment Period in the parent study **Exclusions** - History of study drug intolerance in parent study that would pose an additional risk to the subject	**Primary Outcomes** *[From Baseline up to Week 100]* - Safety and tolerability as assessed by number of subjects with AEs and SAEs **Secondary Outcomes** *[From Baseline up to Week 96]* - Absolute change in ppFEV$_1$ - Absolute change in sweat chloride (SwCl) - Absolute change in BMI - Absolute change in BMI z-score - Absolute change in body weight - Absolute change in CFQ-R respiratory domain score	August 2022

A Prospective Study to Evaluate Biological and Clinical Effects of Significantly Corrected CFTR Function (PROMISE) NCT04038047 **David Nichols, MD (Seattle Children's Hospital) / CFF**	Observational, prospective, Cohort Study Estimated N: 400	**Cohort** ELX/TEZ/IVA	**Inclusions** - Ages ≥12 years - CF diagnosis with CFTR mutations consistent with the FDA approved indication - Willing to fast for 8 hours prior to study visits - Enrolled in the CFF Patient Registry - Clinically stable with no significant changes in health status within the 14 days prior **Exclusions** - Use of Trikafta within the 180 days prior - Acute use of oral, inhaled, or intravenous antibiotics, or systemic corticosteroids for lower respiratory tract symptoms within 2 weeks prior - Initiation of any new chronic therapy within the 4 weeks prior - Use of an investigational agent within the 28 days prior - Use of chronic oral corticosteroids (equivalent to 10 mg. or more per day of prednisone) within the 28 days prior - Treatment for nontuberculous mycobacterial infection, consisting of ≥ two antibiotics (oral, IV, and/or inhaled) within 28 days prior	**Primary Outcomes** *[Baseline through 6 and 24 months]* - Change in sweat chloride - Change in FEV1 **Secondary Outcomes** *[Baseline through 6 and 24 months]* - Change in weight - Change in BMI - Change in CFQ-R	November 2022

			- History of lung or liver transplantation or listing for organ transplantation		
VX-445/TEZ/IVA Expanded Access Program for Cystic Fibrosis (CF) Patients Heterozygous for F508del Mutation and a Minimal Function Mutation (F/MF Genotypes) NCT04058210 **Vertex Pharmaceuticals**	Expanded Access	**Experimental** - Morning: ELX/TEZ/IVA - Evening: IVA	**Inclusions** Patients who have F/MF genotypes AND who meet at least 1 of the following criteria: - $ppFEV_1$ <40% for ≥2 months before; OR - Documentation of being active on a lung transplant waiting list or of being evaluated for lung transplantation, but deemed unsuitable because of contraindications **Exclusions** - Patients with severe hepatic impairment (Child-Pugh Class C) - History of any other comorbidity that might pose undue risk in administering ELX/ TEZ/ IVA to the patient	N/A	Expanded Access Program
Tezacaftor (TEZ) / Ivacaftor (IVA)					
TRANSITION: An Observational Study of Transition From Lumacaftor/Ivacaftor to Tezacaftor/Ivacaftor (Tez/Iva) NCT03445793 **National Jewish Health**	Single center, Observational, prospective cohort study Estimated N: 28	Transition from LUM/IVA to TEZ/IVA	**Inclusions** - Confirmed CF diagnosis with two copies of F508del mutation - Ages ≥12 years - Ability to reproducibly perform spirometry testing - Continuous use of Orkambi for at least 1 month prior to visit 1 **Exclusions** - History of hypersensitivity to TEZ and/or IVA - Presence of a condition or abnormality that would compromise the safety of the patient or the quality of the data - Any acute lower respiratory symptoms treated with oral, inhaled, or IV	**Primary Outcomes** *[Baseline through 6 months]* - Change in sweat chloride concentration in mmol/L **Secondary Outcomes** *[Baseline through 6 months]* - Rationale for transition per physician questionnaire and per subject questionnaire *[First visit on day 1]* - Number of pulmonary exacerbations - Spirometry measurements in liters - CFQ-R respiratory domain score in whole numbers - CFQ-R Gastro-Intestinal score in whole numbers - Weight in kilograms - BMI - Fecal elastase - Measure of pancreatic function	March 2020

			antibiotics, or systemic corticosteroids within the 2 weeks prior - Major or traumatic surgery within 12 weeks - Unable or unwilling to fast (including no enteric tube feedings) for at least 6 hours prior each visit - Initiation of any new chronic therapy within 4 weeks - Use of an investigational agent and/or oral corticosteroids within 28 days prior to Visit 1 - Treatment for nontuberculous mycobacterial infection, consisting of greater than or equal to two antibiotics (oral, IV, and/or inhaled) within 28 days prior to Visit 1 - History of lung or liver transplantation, or listing for organ transplantation	- Transaminase measurements - Bronchodilator requirements in doses/day - Determination of changes in bronchodilator use following transition - Insulin requirements in units/day	
Gut Imaging for Function & Transit in Cystic Fibrosis Study 2 (GIFT-CF2) NCT04006873 **Nottingham University Hospitals NHS Trust**	Phase 2, randomized, triple-blind, crossover assignment Estimated N: 12	**Experimental** - Morning: TEZ/IVA - Evening: IVA **Comparator** - Placebo	**Inclusions** - Confirmed diagnosis of CF, either by sweat test or genetic testing **Exclusions** - Currently taking CFTR modulator drug - ppFEV$_1$ <40% - Contra-indication to MRI scanning - Unable to stop medications directly prescribed to alter bowel habit, such as laxatives or anti-diarrheas, on the study day - Previous resection of any part of the GI tract apart from appendicectomy or cholecystectomy. Surgical relief of meconium ileus or DIOS will be permitted unless clinical records show excision of intestine >20cm in length. - Intestinal stoma - Diagnosis of inflammatory bowel disease or coeliac disease confirmed by biopsy	**Primary Outcomes** *[1 day of scanning]* - Oro-caecal Transit Time **Secondary Outcomes** *[1 day of scanning]* - Gastric volume - Small bowel water content - Colonic volume - Gastrointestinal symptoms **Other Outcomes** *[1 day of scanning]* - Sigmoid colon volume - T1 relaxation of ascending colon chyme - Fat fraction of ascending colon chyme - Faecal elastase - Sputum and faecal microbiome - Faecal calprotectin	August 2020

			- Gastrointestinal malignancy		
Novel Therapeutic Approaches for Treatment of CF Patients With W1282X Premature Termination Codon Mutations NCT03624101 **University of Alabama at Birmingham**	Phase 4, open-label, single group assignment Estimated N: 5	**Experimental** - Morning: TEZ/IVA - Evening: IVA *(Subjects will receive Symdeko in 3 intermittent four-week intervals, followed by a 4-week follow-up period (for safety and to detect efficacy changes upon washout))*	**Inclusions** - Ages ≥18 years - Body weight ≥16kg - CF diagnosis and documentation of the presence of a nonsense mutation of the CFTR gene, as determined by historical genotyping - FEV1 ≥30% and ≤ 90% of predicted for age, gender, and height **Exclusions** - Any change in a chronic treatment/prophylaxis regimen for CF or for CF-related conditions within 2 weeks prior to screening - Ongoing participation in any other therapeutic clinical trial - Evidence of pulmonary exacerbation or acute upper or lower respiratory tract infection within 2 weeks - History of solid organ or hematological transplantation; positive hepatitis B surface antigen test; hepatitis C antibody test; or HIV - Major complication of lung disease within 4 weeks prior to screening - Current smoker or a smoking history of ≥ 10 pack-years - Prior or ongoing medical condition, medical history, physical findings, electrocardiogram findings, or laboratory abnormality that could adversely affect the safety of the subject, makes it unlikely that the course of treatment or follow-up would be completed, or could impair the assessment of study results	**Primary Outcomes** - Lung function (change in FEV_1) at 24 weeks	November 2020
A Study to Evaluate the	Phase 3, open-label, single	**Experimental**	**Inclusions** - Ages ≥6 years	**Primary Outcomes** *[From baseline up to 28 days after Last Dose]*	December 2020

Safety and Efficacy of Long-term Treatment With TEZ/IVA in CF Subjects With an F508del CFTR Mutation NCT03537651 **Vertex Pharmaceuticals**	group assignment Estimated N: 130	- Subjects <40 kg: Morning: TEZ/ IVA - Evening: IVA Subjects ≥40 kg: - Morning: TEZ/ IVA - Evening: IVA	- Completed the Week 24 Visit in Study 113 Part B or the Week 8 Visit in Study 115 - Eligible CFTR Mutation **Exclusions** - Ongoing participation in another study with investigational drug	- Safety and tolerability of long-term TEZ/IVA treatment based on AEs and SAEs **Secondary Outcomes** *[Baseline through 96 weeks]* - Absolute change in lung clearance index2.5 - Absolute change in sweat chloride - Absolute change in CFQ-R respiratory domain score - Absolute change in BMI	
A Study to Evaluate the Safety and Efficacy of Long-Term Treatment With VX-661 in Combination With Ivacaftor in Subjects With Cystic Fibrosis Who Have an F508del-CFTR Mutation NCT02565914 **Vertex Pharmaceuticals**	Phase 3, open-label, parallel assignment Estimated N: 1116	**Experimental** Part A-C: Morning: VX-661 / IVA Evening: IVA **Comparator** Part A: Observational Control Group (no intervention)	**Inclusion** - Ages ≥12 years - Subjects entering the treatment cohort must have completed study drug Treatment Period in a parent study - Subjects re-enrolling in the Part A treatment cohort must have received ≥4 weeks of treatment - Subjects entering the Part A Observational Cohort must be <18 years old, received at least 4 weeks of treatment and completed visits up to the last scheduled visit of the Treatment Period of a parent study (and the Safety Follow up Visit for subjects from NCT02508207), but do not meet eligibility criteria for enrollment into the Treatment Cohort **Exclusion** - History of any comorbidity that might confound the results of the study or pose an additional risk to the subject - History of drug intolerance in the parent study that would pose an additional risk to the subject - Participation in an investigational drug trial other than the parent studies of	**Primary Outcomes** *[Baseline up to 3 years]* Part A: Safety and tolerability of long-term treatment of VX-661 in combination with ivacaftor based on AEs, ophthalmologic exams, clinical laboratory values, standard digital electrocardiograms, vital signs, and pulse oximetry **Secondary Outcomes** *[Baseline through Week 96]* Part A: - Relative change from baseline in ppFEV$_1$ - Absolute change from baseline in CFQ-R respiratory domain score - Absolute change from baseline in body weight and in body weight z-score for subjects aged <20 years - Absolute change from baseline in height z-score for subjects aged <20 years - Time-to-first pulmonary exacerbation - Pharmacokinetic (PK) parameters: trough concentrations of VX-661, a VX-661 metabolite (M1-661), ivacaftor, ivacaftor metabolite (M1-ivacaftor) - Observational Cohort: Safety, as determined by related SAEs *[Baseline up to 3 years]* Parts A and B: - Absolute change from baseline in % ppFEV$_1$	March 2023

			NCT02565914 or other eligible Vertex studies investigating VX-661 in combination with ivacaftor, or use of a commercially available CFTR modulator	- Number of pulmonary exacerbations - Absolute change from baseline in BMI and in BMI z-score for subjects aged <20 years Part B and C: - Safety and tolerability assessments including number of subjects with AEs and SAEs events *[Baseline through safety follow-up visit]*	
iPS Cell Response to CFTR Modulators: Study of Symdeko in CF Patients Carrying Partial Function Mutations NCT03506061 **Emory University / NHLBI**	Phase 2, open-label, single group assignment Estimated N: 22	**Experimental** - TEZ/IVA	**Inclusion** - Ages ≥12 years - A clinical diagnosis of CF and a partial function mutation not currently covered or likely to be covered for FDA treatment with a CFTR modulator. - Sweat chloride < 70 mmol/L - Pancreatic sufficiency as indicated by no exogenous pancreatic enzyme supplement therapy - FEV1% predicted ≥40 to ≤ 90% post bronchodilator - Clinically stable in the past 4 weeks with no evidence of CF exacerbation - BMI > 18 kg/m2 **Exclusion** - SUD within the last year - Pulmonary exacerbation or changes in therapy for pulmonary disease in the 4 weeks prior to screening - Cirrhosis or elevated liver transaminases > 3 times the ULN - Inhibitors or inducers of CYP3A4, or other medicines known to negatively influence Symdeko administration - History of solid organ transplant - History of non-TB mycobacterial infection (any positive culture in the past 18 months) or active therapy for these infections.	**Primary Outcomes** *[From baseline to Week 4]* - Change in FEV1 **Secondary Outcomes** *[From baseline to Week 4]* - Change in sweat chloride - Change in nasal potential difference (NPD) measurements - Change in CFQ-R Score	May 2023

			- Treatment in the last 6 months with either Kalydeco or Orkambi - Treatment with another investigational drug or other intervention within one month prior to enrollment, throughout the duration of study participation, and for an additional four weeks following final drug administration		
Functional Respiratory Imaging (FRI) to Assess the Short-term Effect of the Product ORKAMBI (Lumacaftor/ Ivacaftor) on Lung Function in ORKAMBI naive Patients With Cystic Fibrosis Homozygous for Phe508del NCT03956589 **University Hospital, Antwerp**	Phase 4, open-label, single group assignment Estimated N: 20	**Experimental** - TEZ/IVA	**Inclusions** - Documented diagnosis of CF (homozygous for F508del mutation) - Age ≥ 12 years - ppFEV$_1$ > 50% - Patient must be on a stable regimen of CF medication for 4 weeks prior to Visit **Exclusions** - Anticipated requirement for hospitalization within the next three weeks - History of pneumothorax within the past 6 months - History of hemoptysis requiring embolization within the past 12 months - IV antibiotics within the past 4 weeks - Ongoing exacerbation or Allergic bronchopulmonary aspergillosis - Posttransplant patients - Patients with severe hepatic impairment	**Primary Outcomes** *[Baseline and at 3 months]* - Change in specific image-based airway resistance - Change in specific image-based airway volumes (siVaw) **Secondary Outcomes** *[Baseline and at 3 months]* - Internal Airflow Distribution - Air Trapping - Airway Wall Volume - Aerosol Deposition - Dynamic lung volumes - Static lung volumes - Airway resistances - Lung clearance index - 6-minute walking test - Sweat chloride test - CFQ-R - Digital lung auscultation - Exacerbation frequency	December 2019
Lumacaftor (LUM) / Ivacaftor (IVA)					
Validation of Respiratory Epithelial Functional Assessment to Predict Clinical Efficacy of	Open-label, single group assignment Estimated N: 104	**Experimental** LUM/IVA	**Inclusions** - Ages ≥12 years - Homozygous for F508del Mutation - Patient never received Orkambi® in the past **Exclusions**	**Primary Outcomes** *[Baseline and at 24 week]* - Percentage of FEV$_1$ **Secondary Outcomes** - Z-score of FEV$_1$ *[Baseline, week 24 and 48]* - Percentage of FEV$_1$ *[Week 48]* - % of FVC; RFC *[Baseline, Week 24 and 48]* - Lung clearance index *[Baseline and Week 48]*	

Orkambi®. (PREDICT-CF) NCT03894657 **Assistance Publique - Hôpitaux de Paris**			- Homozygous F508del patients who do not meet the treatment indications according to the marketing authorization application - Active smoker - Severe nasal mucosa disrepair - Contraindications to xylocaine anesthesia, - Participation with another interventional study with drug	- Height; Weight *[Baseline, Week 24 and 48]* - Colony forming unit (CFU) *[Baseline, Week 24 and 48]* - Number of exacerbations *[Baseline and Week 48]* - Sweat Chloride *[Baseline and Week 48]* - Level in Forskolin/ IBMXdependant Short Circuit Current *[At Baseline]* - Percentage of cells displaying apical staining *[At baseline]* - Area under the curve of LUM/IVA *[Week 24 and 48]* - Drug concentrations of LUM/IVA *[At Week 24 and 48]*	
Gastrointestinal Study at Orkambi Therapy in CF Patients NCT03859531 **Karolinska University Hospital**	Observational, Prospective cohort Study Estimated N: 20	**Cohort** LUM/IVA	**Inclusions** - CF Patients who are homozygous for F508del - Ages > 12 years **Exclusions** - Patients who the patency capsule does not pass within 48 hours - FEV1 < 30% - Liver function blood tests >3 xULN - Bilirubin >2 xULN - AST or ALT alone >5 xULN - Previous lung transplant	**Primary Outcomes** *[Change from baseline at 6 months]* - Concentration of fecal calprotectin - Concentration of fecal elastase-1 - Change in small bowel capsule endoscopy (SBCE) **Secondary Outcomes** *[Change from baseline at 6 months]* - Change in CRP - Change in sedimentation rate - Concentration of serum electrophoresis - Change in liver function tests - Change in bilirubin	June 2020
Orkambi Treatment in 2 to 5 Year Old Children With CF NCT03795363 **Children's Hospital of Philadelphia**	Observational, Prospective Cohort Study Estimated N: 32	**Cohort** LUM/IVA	**Inclusions** - CF and homozygous for F508del mutations, approved for treatment - Ages 2 to <6 years **Exclusions** - On parenteral nutrition - Use of any medications that inhibit or induce cytochrome P450 (CYP) 3A - Liver function tests elevated above 3x the reference range for age and sex - Severe lung disease	**Primary Outcomes** *[At 24 weeks]* - Sleeping or Resting Energy Expenditure - Anthropometric Assessment **Secondary Outcomes** *[At 24 weeks]* - Fecal Elastase/Pancreatic Function - Fecal Calprotectin/Gut Inflammation - Plasma Total Fatty Acids **Other Outcome Measures** *[At 24 weeks]* - Dietary Intake - Serum fat soluble vitamin levels	May 2020

				- Changes in bile acid concentration levels - Changes in concentration levels of serum calprotectin - Muscle-fat Stores - Growth Status Changes	
Orkambi Exercise Study (Orkambi) NCT02821130 **University of British Columbia**	Observational Prospective Cohort Study Estimated N: 11	**Cohort** LUM/IVA	**Inclusions** - Confirmed CF diagnosis and homozygous for F508del mutation - Ages ≥19 years - Stable clinical status - FEV1 < 90% predicted - BMI > 16 or <30 kg/m2 - Non-smoking or past smoking history of less than 20 pack-years **Exclusions** - A disease other than CF that could importantly contribute to dyspnea or exercise limitation - Chronic airway infection - Contraindications to clinical exercise testing - Use of supplemental oxygen or desaturation less than 85% with exercise - Diagnosis of pneumothorax in past 4 weeks - History of organ transplantation	**Primary Outcomes** - Change in iso-time dyspnea rating from baseline to visit 3 and 4 during constant load exercise tests **Secondary Outcomes** *[At 1 and 3 months]* - Change from baseline cardio-respiratory responses during constant-load exercise tests - Change from baseline chronic activity-related dyspnea - Change from baseline QoL - Change from baseline physical activity - Change from baseline pulmonary function measures	December 2019
Monitoring Response to Orkambi in Cystic Fibrosis Lung Disease by Inhaled Xenon MRI NCT02848560 **Children's Hospital Medical**	Prospective, observational, Case-Control Estimated N: 38	**Treatment Group** - LUM/IVA **Control Group** - Not eligible for Orkambi Prescription	**Inclusions** Treatment Group: - Ages 6 – 12 - Homozygous F508del mutation - Anticipated to be a candidate for treatment with Orkambi Control Group: - Ages 6 – 12 at enrollment - Two non-functional CFTR mutations with one of them being F508del CFTR mutation - Not eligible for CFTR modulation therapy	**Primary Outcomes** - Hyperpolarized 129Xe magnetic resonance imaging (MRI) Image Analysis at year 3	December 2020

Center, Cincinnati			**Exclusions** - FEV_1% predicted <60% - Standard MRI exclusions (metal implants, claustrophobia)		
Impact of the Introduction of ORKAMBI on Anxiety, Depression, Quality of Life and Adherence of Adolescents and Young Adults (ORK-AJA) NCT03659214 **Assistance Publique - Hôpitaux de Paris**	Retrospective Cohort Study Estimated N: 60	**Treatment Group** - LUM/IVA **Control Group** - Not treated with Orkambi or treated with Kalydeco	**Inclusions** Treatment Group: - Patients with proven CF Control Group: - Patients not carrying 2 DF508 causing mutations - Patients not treated with Orkambi or treated with Kalydeco - Patients not carrying to G551D, G178R, S549N, S549R, G551S, G1244E, S1251N. S1255P or G1349D mutation **Exclusions** - Transplanted patients - Ages <12 or > 20 years	**Primary Outcome** *[At 24 months]* - Score of Generalized Anxiety Disorder (GAD-7) **Secondary Outcomes** *[At 24 months]* - Score of Patient Health Questionnaire (PHQ-9) - Scores of Cystic Fibrosis Questionnaire (CFQ 14+) - GIRERD Scale	December 2018
Longitudinal Assessment of Exercise Capacity and Vascular Function in Patients With CF NCT03338595 **Augusta University**	Longitudinal Cohort Study Estimated N: 30	**Cohort** LUM/IVA	**Inclusions** - Patients diagnosed with CF - Homozygous for F508del mutation - Prescribed Orkambi - Ages ≥7 years - $ppFEV_1$ > 40% - Resting oxygen saturation > 85% - Patients with or without CFRD - Traditional CF-treatment medications **Exclusions** - $ppFEV_1$ < 40% - Resting oxygen saturation <85% - Clinical diagnosis of heart disease - Pulmonary artery hypertension - Use of VX-770 within 6 months prior	**Primary Outcome** - Maximal exercise capacity at year 1 **Secondary Outcome** - Flow mediated dilation at year 1	May 2020

Observational Study of Glucose Tolerance Abnormalities in Patient With Cystic Fibrosis Homozygous for Phe 508 Del CFTR Treated by Lumacaftor-Ivacaftor (GLUCORRECTOR) NCT03512119 **University Hospital, Strasbourg, France**	Observational Cohort Study Estimated N: 100	**Cohort** LUM/IVA	**Inclusions** - Patients with CF homozygous F508del mutation aged 12 years and older - Combined LUMA/IVA treatment scheduled or already started - Glucose intolerance in oral glucose tolerance test (OGTT) (ADA criteria) or newly diabetes diagnosed at the OGTT (ADA criteria) or diabetic patients with insulin requirement ≤ 0.3 unit/kg/day or without insulin treatment - Signed informed consent of patient and of one parent OR legal representative for minor subject **Exclusions** - Hypersensitivity to the active substances or to any of the excipients of LUM/IVA - Lung and/or liver transplant - Known diabetes with insulin treatment > 0.3 unit/kg/day	**Primary Outcome** - Measure of 2 hours plasma glucose value (mmol/l) of OGTT, change from baseline at 1 year **Secondary Outcomes** *[Time Frame: Day 0 and Year 1]* - Fasting and one hour glucose value of OGTT (mmol/l) - C peptide and insulin values at T0, 1,2 hours of OGTT - Glucose, insulin, and C peptide AUC of OGTT - HOMA-R, HOMA-S - Mean glucose value per day and 2 h after meal (mg/dl)	October 2018
Safety and Pharmacokinetic Study of Lumacaftor/Ivacaftor in Subjects 1 to Less Than 2 Years of Age With Cystic Fibrosis, Homozygous for F508del NCT03601637 **Vertex Pharmaceuticals**	Phase 3, 2-part, open-label, non-randomized, single group assignment Estimated N: 40	**Experimental** Part A: LUM/IVA - Cohort 1 [18 to <24 months] - Cohort 2 [12 to <18 months] Part B: LUM/IVA	**Inclusions** - Ages 1 to < 2 years - Homozygous for F508del (F/F) **Exclusions** - Any clinically significant laboratory abnormalities at the Screening Visit that would interfere with the study assessments or pose an undue risk for the subject - Solid organ or hematological transplantation	**Primary Outcome** *[From baseline to safety follow-up; up to 10 days after last dose]* Part A: Area under the concentration versus time curve during a dosing interval (AUCtau) of LUM/IVA Part B: safety and tolerability as assessed by number of subjects with AEs and SAEs **Secondary Outcome** *[From baseline to safety follow-up; up to 10 days after last dose]* Part A: safety and tolerability as assessed by number of subjects with AEs and SAEs Part A: average observed pre-dose concentrations Part B: absolute change in sweat chloride from baseline at week 24 Part B: average observed pre-dose concentration (Trough) of LUM/IVA and their respective metabolites from baseline to safety follow-up (up to 2 weeks after last dose)	September 2020

A Study to Explore the Impact of Lumacaftor/Ivacaftor on Disease Progression in Subjects Aged 2 Through 5 Years With Cystic Fibrosis, Homozygous for F508del NCT03625466 **Vertex Pharmaceuticals**	Phase 2, randomized, placebo-controlled, double-blind to open-label, trial Estimated N: 50	**Experimental** - LUM/IVA	**Inclusions** - Confirmed CF F508del Homozygous diagnosis - Weight ≥ 8kg **Exclusions** - Solid organ or hematological transplantation - Clinically significant lab abnormalities or comorbidities that would pose a risk for study	**Primary Outcome** *[From baseline at week 48]* - Absolute change in MRI global chest score **Secondary Outcomes** *[From baseline at week 48]* - Absolute change in lung clearance index, weight-for-age z-score, stature-for-are z-score, BMI-for-age z-score	November 2020
Effect of Lumacaftor/Ivacaftor in Children With Cystic Fibrosis Homozygote for F508del on Small Airway Function (ROOTS) NCT04138589 **University Medical Center Groningen**	Multi-center observational study Estimated N: 30	**Cohorts** - LUM/IVA - TEZ/IVA	**Inclusions** - Ages 6-18 years - CF F508del homozygous diagnosis **Exclusions** - Unable to perform acceptable, repeatable lung function tests	**Primary Outcome** - Change in lung clearance index (LCI) at 12 months **Secondary Outcome** - Change in PRAGMA-CF score at 12 months	February 2021
Ivacaftor (IVA)					
A Phase 3, 2 Part, Open-Label Study to Evaluate the Safety, Pharmacokinetic	Phase 3, Open-label extension, single group assignment	**Experimental:** IVA (Part A) - Group 1: Participants 12 to < 24 months	**Inclusions** - Ages up to 24 months - Confirmed CF diagnosis with 1 of the following 9 CFTR mutations on at least 1 allele: G551D, G178R, S549N, S549R,	**Primary Outcomes** Part A: - Safety, as determined by number of subjects with AEs, clinically relevant abnormal laboratory values, standard 12 lead electrocardiograms,	June 2020

s, and Pharmacodynamics of Ivacaftor in Subjects With Cystic Fibrosis Who Are Less Than 24 Months of Age and Have a CFTR Gating Mutation NCT02725567 **Vertex Pharmaceuticals**	Estimated N: 35	- Group 2: Participants 6 to < 12 months - Group 3: Participants 3 to < 6 months - Group 4: Participants 0 to < 3 months IVA (Part B) - Group 5: Participants 12 to < 24 months - Group 6: Participants 6 to < 12 months - Group 7: Participants 0 to < 6 months	G551S, G1244E, S1251N, S1255P, or G1349D **Exclusions** - History of any illness or condition that might confound the results of the study or pose an additional risk in administering study drug to the subject - Colonization with organisms associated with a more rapid decline in pulmonary status at screening - History of abnormal liver function or abnormal liver function at screening - History of solid organ or hematological transplantation - Use of any moderate or strong inducers or inhibitors of cytochrome P450 (CYP) 3A within 2 weeks prior - Participation in a clinical study involving administration of either an investigational or a marketed drug within 30 days or 5 terminal half-lives before screening - Hemoglobin (Hgb) <9.5 g/dL at screening - Chronic kidney disease of ≥Stage 3 - Non-congenital or progressive lens opacity or cataract at Screening	vital signs, and ophthalmologic examinations *[Day 1 up to Day 70]* - Peak concentrations (C3-6h) of IVA, M1 IVA, and M6 IVA *[After 4 days]* - Trough concentrations (Ctrough) of IVA, M1 IVA, and M6 IVA *[After 4 days]* Part B: - Safety, as determined by number of subjects with AEs, clinically relevant abnormal laboratory values, standard 12 lead ECGs, vital signs, and ophthalmologic examinations *[Day 1 up to Week 24]* **Secondary Outcomes** *[Through Week 24]* - Peak concentrations (C3-6h) of IVA, M1 IVA, and M6 IVA - Trough concentrations (Ctrough) of IVA, M1 IVA, and M6 IVA - Absolute change from baseline in sweat chloride using quantitative pilocarpine iontophoresis	
A Study to Evaluate the Safety of Long-term Ivacaftor Treatment in Subjects With Cystic Fibrosis Who Are Less Than 24 Months of Age at Treatment Initiation and Have an	Phase 3, open-label, parallel assignment Estimated N: 75	**Experimental** - IVA **Comparator** - No intervention (observational arm)	**Inclusions** - Ages ≤24 months - Subjects transitioning from Study 124 Part B must have completed the last study visit of Study 124 Part B - Subjects Not from Study 124 Part B: Confirmed diagnosis of CF, or 2 CF-causing mutations; IVA-responsive CFTR mutation on at least 1 allele **Exclusions** Subjects from Study 124 Part B:	**Primary Outcomes** - Safety assessments based on the number of subjects with AEs and SAEs *[Baseline through safety follow-up; up to 24 weeks after last dose]* **Secondary Outcomes** - Absolute change in sweat chloride *[Baseline through Week 96]*	June 2021

Approved Ivacaftor-Responsive Mutation NCT03277196 **Vertex Pharmaceuticals**			- History of any illness or condition that might confound the results of the study or pose an additional risk in administering IVA to the subject. - Subjects receiving commercially available IVA treatment <u>Subjects Not from Study 124 Part B:</u> - History of any illness or condition that might confound the results of the study or pose an additional risk in administering IVA to the subject - An acute upper or lower respiratory infection, or pulmonary exacerbation, or changes in therapy for pulmonary disease within 4 weeks - Abnormal liver function at screening - Hemoglobin <9.5 g/dL at screening - History of solid organ or hematological transplantation - Use of any moderate or strong inducers or inhibitors of CYP3A within 2 weeks		
Observational Study of Outcomes in Cystic Fibrosis Patients With Selected Gating Mutations on a CFTR Allele (The VOCAL Study) NCT02445053 **Vertex Pharmaceuticals**	Observational, prospective cohort study <u>Estimated N</u>: 90	**Cohort** - IVA	**Inclusions** - Ages ≥6 years - CF diagnosis with 1 of the following CFTR mutations on at least 1 allele: G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, or G1349D **Exclusions** - Previously exposed to Kalydeco, except currently treated patients who started Kalydeco treatment within 6 months of enrollment - Currently enrolled in a Kalydeco interventional study or other interventional therapeutic clinical study directed at CFTR modulation - History of organ transplantation	**Primary Outcomes** *[48 Months]* - Number of pulmonary exacerbations and duration of treatment for pulmonary exacerbations during compared to the period before IVA treatment - Percentage of patients with cultures positive for Pseudomonas aeruginosa during compared to the period before IVA treatment - Percentage of patients with cultures positive for bacteria other than Pseudomonas aeruginosa and for fungi during compared to the period before IVA treatment - Absolute change in $ppFEV_1$ - Absolute change in weight, weight-for-age Z score, BMI, and BMI-for-age Z-score - Incidence and prevalence of comorbidities during compared to the period before IVA treatment	December 2020

				- Incidence and cause of deaths - Incidence and reason for organ transplantations **Other Outcomes** *[48 Months]* - Effect of IVA treatment on HRQoL in patients with CF and in caregivers of pediatric patients enrolled	
A Study to Confirm the Long-term Safety and Effectiveness of Kalydeco in Patients With Cystic Fibrosis Who Have an R117H-CFTR Mutation, Including Pediatric Patients NCT02722057 **Vertex Pharmaceuticals**	Observational Cohort Study Estimated N: 150	**Cohort 1** Intervention (Cohort will not be utilized) **Cohort 2** Non-interventional (IVA) **Cohort 3** Historical participants who have never been exposed to IVA (matched on age, gender, and lung function to patients in cohort 2)	**Inclusions** - Ages ≥6 years Cohort 2: - Confirmed CF diagnosis with at least 1 allele of the R117H-CFTR mutation - Enrolled in the US CFF Patient Registry - With a record of Kalydeco treatment initiation from 01 January 2015 through 31 December 2016 Cohort 3: - Patients with CF in CFF Patient Registry as of January 1, 2009 - At least one R117H-CFTR mutation - No prior exposure to IVA	**Primary Outcomes** *[36 Months]* - Lung function measurements (ppFEV$_1$ and FVC) - Pulmonary exacerbations, use of IV antibiotics - Nutritional parameters (BMI, BMI-for-age z-score, weight, and weight-for-age z-score) - Death or transplantation - Hospitalizations - Selected Complications (Symptomatic sinus disease, Pulmonary complications, CF-related diabetes (CFRD) and distal intestinal obstruction syndrome (DIOS), Hepatobiliary complications, Pancreatitis)	December 2019
Nutritional Impact of Ivacaftor Treatment in 6 Month to 2 Year Old Children With CF Gating Mutations NCT03783286 **Children's Hospital of Philadelphia**	Observational, prospective cohort study Estimated N: 18	**Cohort** - IVA	**Inclusions** - Ages 1 – 2 years - CF with at least one CFTR gating mutation of these ten (G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1439D, or R117H) - Usual state of good health **Exclusions** - On parenteral nutrition - Use of any medications which are as inhibitors or inducers of cytochrome P450 (CYP) 3A	**Primary Outcomes** *[12 Weeks]* - Change from baseline of Sleeping Energy Expenditure - Change from baseline in BMI, BMI z scores **Secondary Outcomes** *[12 Weeks]* - Fecal Elastase I/Pancreatic Function - Fecal Calprotectin/Gut Inflammation - Plasma Total Fatty Acids *[4 to 6 months]* **Other Outcomes** - Dietary measure - Serum fat soluble vitamins A, D, E and K, bile acids, and serum calprotectin	June 2020

			- Liver function tests elevated above 3x the reference range for age and sex - Other illness affecting growth or nutritional status	- Muscle/fat stores - Growth Status/Growth Velocity	

AE: adverse event, BMI: body mass index, CF: cystic fibrosis, CFF: cystic fibrosis foundation, CFQ-R: cystic fibrosis questionaire-revised, CFTR: cystic fibrosis transmembrane conductance regulator, FDA: food and drug administration, FVC: forced vital capacity, GI: gastrointestinal, HIV: human immunodeficiency virus, kg: kilogram, mmol/L: millimoles per liter, n: number, N: total number, PEx: pulmonary exacerbation, $ppFEV_1$: percent predicted forced expiratory volume in 1 second, SAE: serious advese event
Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

Appendix D. Comparative Clinical Effectiveness Supplemental Information

We performed screening at both the abstract and full-text level. A single investigator screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor" (see Appendix Table F2)[50] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.

Fair: Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.

Poor: Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.

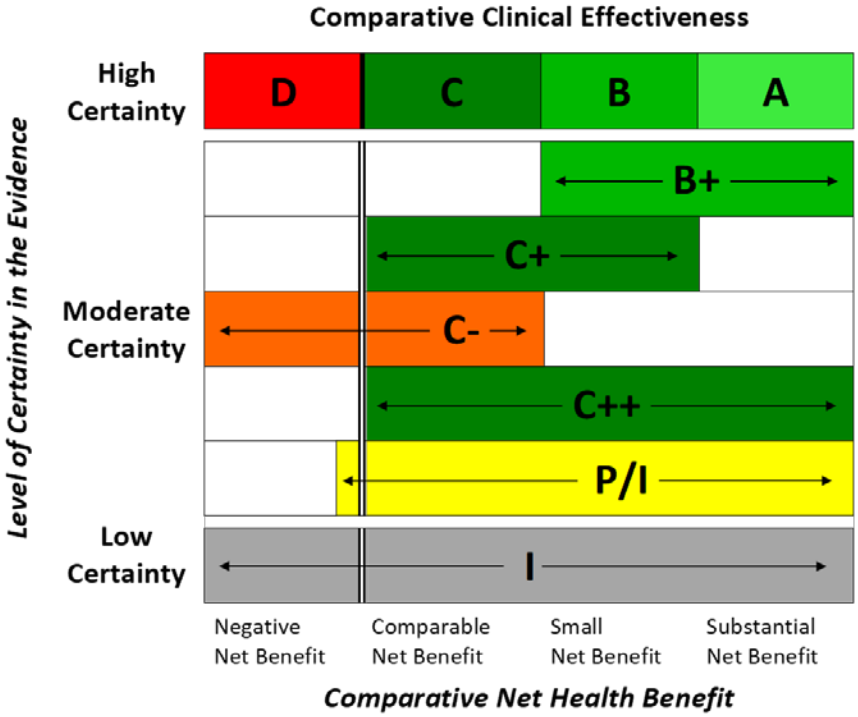
Note that case series are not considered under this rating system–because of the lack of comparator, these are generally considered to be of poor quality.

ICER Evidence Rating

We used the ICER Evidence Rating Matrix (see Figure D1) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

- The **magnitude** of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND
- The level of **certainty** in the best point estimate of net health benefit.[51,136]

Figure D1. ICER Evidence Rating Matrix



A = "Superior" - High certainty of a substantial (moderate-large) net health benefit
B = "Incremental" - High certainty of a small net health benefit
C = "Comparable"- High certainty of a comparable net health benefit
D= "Negative"- High certainty of an inferior net health benefit
B+= "Incremental or Better" – Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit
C+ = "Comparable or Incremental" - Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit
C- = "Comparable or Inferior" – Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit
C++ = "Comparable or Better" - Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit
P/I = "Promising but Inconclusive" - Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit
I = "Insufficient" – Any situation in which the level of certainty in the evidence is low

Abstraction Tables – Randomized Controlled Trials (RCTs) and Open Label Extension Studies (OLEs)

Table D1. Study Design

Trial & Author	Design & duration of follow-up	Population, Total N	Interventions and dosing procedures	Inclusion Criteria	Exclusion Criteria
Elexacaftor (ELX) / Tezacaftor (TEZ) / Ivacaftor (IVA)					
Trial 1 **Middleton 2019**[56]	Phase 3, multicenter, randomized, double-blind, placebo-controlled trial Follow-Up: - 4-week screening period - 24-week intervention period - 4-week safety follow-up (OLE)	**Heterozygous** (F508del/minimal function mutation) N=403	Intervention: ELX 200 mg / TEZ 100 mg / IVA150 mg (AM) + IVA 150mg (PM) Comparator: Placebo (AM) + Placebo (PM)	- 12 years or older with confirmed CF diagnosis - F508del/minimal function genotype (heterozygous) - ppFEV$_1$ between 40-90% - Stable CF disease	- History of any illness or clinical condition that might confound the study results or pose an additional risk in administering study drug(s) to the patient - Abnormal laboratory values - Acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy for sinopulmonary disease within 28 days - Lung infection with organisms associated with a more rapid decline in pulmonary status - Participation in a study of an investigational treatment within 28 days or 5 terminal half-lives (whichever is longer) before screening

Trial 2 **Heijerman 2019[8]**	Phase 3, multicenter, randomized, double-blind, active-controlled trial Follow-Up: - 4-week run-in period (TEZ/IVA treatment) - 4-week treatment period - 4-week safety follow-up	**Homozygous** (F508del/ F508del) N=107	**Run-in Period** Intervention: TEZ 100mg / IVA 150mg (AM) + IVA 150mg (PM) **Treatment Period** Intervention: ELX 200 mg / TEZ 100 mg / IVA150 mg (AM) + IVA 150mg (PM) Comparator: Placebo / TEZ 100mg / IVA 150mg (AM) + IVA 150mg (PM)	- 12 years or older with confirmed CF diagnosis - Homozygous for the F508del mutation (F/F) - $ppFEV_1$ between 40-90% - Stable CF disease	- History of any illness or clinical condition that might confound the study results or pose an additional risk in administering study drug(s) to the patient - Abnormal laboratory values - Acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy for sinopulmonary disease within 28 days - Lung infection with organisms associated with a more rapid decline in pulmonary status - Participation in a study of an investigational treatment within 28 days or 5 terminal half-lives (whichever is longer) before screening
Keating 2018[57]	Phase 2, randomized, double-blind, placebo- or active-controlled, parallel group assignment, dose-ranging study	**Homozygous** (F508del/ F508del) N=33	Intervention: ELX 200 mg / TEZ 100 mg / IVA 150 mg (AM) + IVA 150mg (PM) Comparator: Triple placebo	- 18 years or older with CFTR genotypes of F508del/minimal function (heterozygous) or homozygous F508del - $ppFEV_1$ between 40-90% - Stable disease	- Respiratory infection or change in therapy for sinopulmonary disease within 28 days before first dose of study drug - Lung infection with organisms associated with more rapid decline in pulmonary status - History of clinically significant cirrhosis, hemolysis, solid organ, or hematological transplantation

	Follow-Up: - 4-week run-in period (TEZ/IVA treatment) - 4-week treatment period	**Heterozygous** (F508del/minimal function mutation) N=28	Intervention: ELX 200 mg / TEZ 100 mg / IVA 150 mg (AM) + IVA 150mg (PM) Comparator: Placebo / TEZ 100 mg / IVA 150 mg (AM) + IVA 150mg (PM)		- Participation in an investigational treatment study other than a CFTR modulator within 28 days
Tezacaftor (TEZ) / Ivacaftor (IVA)					
EVOLVE **Taylor-Cousar 2017[87]** **Yang 2018[82]**	Phase 3, placebo-controlled, double-blind, parallel group assignment Follow-Up: 24 weeks	**Homozygous** (F508del/ F508del) N=504	Intervention: TEZ 100 mg / IVA 150 mg (AM) + IVA 150mg (PM) Comparator: Placebo (AM) + Placebo (PM)	- 12 years or older with confirmed F508del homozygous diagnosis of CF - $ppFEV_1$ at time of screening = 40- 90% - Stable disease	- History of any comorbidity that might pose an additional risk or confound the study results - Clinically significant abnormalities at screening - Acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy for pulmonary disease within 28 days prior to study - History of transplantation - Participation in previous phase 3 trials of LUM/IVA; or had received LUM/IVA through an early- or extended-access program

Iker 2019[92] **ClinicalTrials.gov 2019**[137]	Phase 3, open-label, multicenter study <u>Part A Follow-Up</u>: - 14 days treatment - 14 days wash-out and safety follow-up <u>Part B Follow-Up:</u> - 24 weeks treatment period - Either 4 weeks of safety follow-up or enrolment in 96-week OLE study	<u>Part A</u>: **Homozygous** (F508del/F508del) **or heterozygous** (F508del + residual function, or F508del + gating mutation) N=13 <u>Part B</u>: **Homozygous** (F/F genotype) **or heterozygous** (F508del + residual function mutation) N=70	**<u>Part A</u>** <u>Intervention:</u> - **Cohort 1** (<25 kg): TEZ 50 mg / IVA 75 mg (AM) + IVA 75mg (PM) - **Cohort 2** (≥25 kg): TEZ 50 mg / IVA 150 mg (AM) + IVA 150mg (PM) **<u>Part B</u>** <u>Intervention:</u> - **Cohort 1** (<40 kg): TEZ 50 mg / IVA 75 mg (AM) + IVA 75mg (PM) - **Cohort 2** (≥40 kg): TEZ 100 mg / IVA 150 mg (AM) + IVA 150mg (PM)	- Children ages 6 - 11 years with confirmed CF diagnosis - Weight ≥ 15 kg at screening - Stable CF disease - ppFEV$_1$ ≥ 40% at screening - 28 days wash-out period for investigational LUM/IVA or physician prescribed Orkambi before start of study required - Physician prescribed Kalydeco could be taken up until day 1 of study <u>Eligible mutations – Part A</u>: Homozygous (F508del/F508del), F508del + residual function mutation, or F508del + gating mutation <u>Eligible mutations – Part B</u>: F/F genotype, or F508del + residual function mutation	- History of comorbidities that might confound results or pose additional risks to the participant; - Clinically significant laboratory abnormalities at screening - Acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy for pulmonary disease within 28 days of study - Colonization with organisms associated with a more rapid decline in pulmonary status at screening - History of solid-organ or hematologic transplant

EXTEND **Flume J CF 2018**[81] **ClinicalTrials.gov**[138]	Phase 3, open-label extension study (interim analysis) Follow-Up: - Safety: 86 weeks - Efficacy: 48 weeks *(Results of interim analysis present efficacy data at 24 weeks)*	**Heterozygous** (F508del-CFTR + residual function mutation) **or homozygous** (F508del/ F508del) N=613	Intervention: TEZ 100 mg / IVA 150 mg (AM) + TEZ 100 mg / IVA 150 mg (PM)	**Part A:** Completed study drug treatment period in a parent study (NCT02070744, NCT02347657, NCT02516410, NCT02392234, NCT02412111) or study drug treatment and the Safety Follow up Visit for subjects from NCT02508207 **Part B**: Completed study drug treatment during the Treatment Period in Part A **Part C**: Did not withdraw consent from Part B and completed drug treatment	- History of any comorbidity that might confound the results of the study or pose an additional risk to the subject - History of drug intolerance in the parent study - Participation in an investigational drug trial (including studies investigating VX-661/ivacaftor or lumacaftor/ivacaftor) other than the parent studies of NCT02565914 or other eligible Vertex studies investigating VX-661 in combination with ivacaftor, or use of a commercially available CFTR modulator

Lumacaftor (LUM) / Ivacaftor (IVA)					
TRAFFIC and TRANSPORT **Wainwright 2015[30]**	TRAFFIC: Phase 3, multinational, randomized, double-blind, placebo-controlled, parallel-group study TRANSPORT: Phase 3, multinational, randomized, double-blind, placebo-controlled, parallel-group study Follow-Up: - TRAFFIC: 24 weeks - TRANSPORT: 24 weeks - Rollover Safety Study (PROGRESS)	**Homozygous** (F508del/ F508del) N=1108	Intervention: - **Arm I**: LUM 600 mg / IVA 250 mg (AM) + IVA 250mg (PM) - **Arm II**: LUM 400 mg / IVA 250 mg (AM) + LUM 400 mg / IVA 250 mg (PM) Comparator: Placebo (AM) + Placebo (PM)	- 12 years or older with confirmed f508del homozygous diagnosis of CF - $ppFEV_1$ = 40- 90% of the predicted normal values at time of screening - Stable disease	- Any comorbidity that increases risk in the study - Abnormal lab values - Respiratory event within 4 weeks of first day on drug - Colonization with certain bacteria - Prolonged QT interval - History of transplant - Use of strong inhibitors, moderate inducers, or strong inducers of CYP3A within 14 days

TRAFFIC and TRANSPORT – subgroup analysis **McColley 2019[79]**	Post hoc analysis of pooled data from TRAFFIC and TRANSPORT studies **Subgroups of LUM 400 mg /IVA 250 mg (AM) + LUM 400 mg/IVA 250 mg (PM):** - Absolute change of $ppFEV_1 \leq 0$ - Absolute change of $ppFEV_1 > 0$ - Relative change of $ppFEV_1 < 5\%$ - Relative change of $ppFEV_1 \geq 5\%$	**Homozygous** (F508del/ F508del) N=1108	Intervention: LUM 400 mg / IVA 250 mg (AM) + LUM 400 mg / IVA 250 mg (PM) Comparator: Placebo (AM) + Placebo (PM)	See TRAFFIC and TRANSPORT (Wainwright 2015)	See TRAFFIC and TRANSPORT (Wainwright 2015)

McNamara 2019[80]	Phase 3, open-label, multicentre, two-part study Follow-Up (Part A - Safety): - 15 days treatment period - 10 days follow-up after last dose Follow-Up (Part B - Efficacy and Safety): - 24 weeks treatment period - 2 weeks wash-out period - Option to roll over into long-term OLE	**Homozygous** (F508del/ F508del) Part A: N=12 Part B: N=60	Intervention - **Cohort 1** (<14kg): LUM 100mg / IVA 125mg (AM) + LUM 100mg / IVA 125mg (PM) - **Cohort 2** (≥14kg): LUM 150 mg / IVA 188 mg (AM) + LUM 150 mg / IVA 188 mg (PM)	- Children ages 2-5 years - Weight ≥ 8kg - Confirmed F508del homozygous diagnosis of CF	- History of any comorbidity that would confound the results of the study or posed an additional risk to the patient - Clinically significant laboratory abnormalities - Acute upper or lower respiratory infection, pulmonary exacerbation, or change in therapy for pulmonary disease within 28 days - History of solid organ or hematological transplantation
Chilvers 2017[78] **Chilvers 2019**[77] **ClinicalTrials.gov**[139]	Open-label extension, non-randomized, parallel assignment, two-part study (only results for treatment period 1 are reported) Follow-Up: - 96 weeks	**Homozygous** (F508del/ F508del) N=239	Intervention - LUM/IVA (Part A) → LUM/IVA (Part B) - Placebo (Part A) → LUM/IVA (Part B) Comparator Observational Cohort (Patients who completed parent study but were not eligible/ elected OLE)	Participants from Parent Studies 109 (NCT02514473) and 011B (NCT01897233)	For treatment cohort only - History of a comorbidity or laboratory abnormality that might confound results of the study or add risk for the patient - History of drug intolerance in prior study - History of poor compliance with study drug and/or procedure in prior study

					- Participation in an investigational drug trial
Ivacaftor (IVA)					
KLIMB **Rosenfeld 2019**[59]	Open-label extension study in children who completed Part B of the KIWI study (a 24-week Phase 3, open-label, single arm study) <u>Follow-up:</u> - 84 weeks	**Heterozygous** (F508del + gating mutation) N=33	<u>Weight-based granules of IVA twice daily</u> - **Weight < 14kg**: IVA 50 mg (AM) + IVA 50 mg (PM) - **Weight ≥ 14 kg**: IVA 75 mg (AM) + IVA 75 mg (PM) - Children (n=1) who turned 6 years of age during KLIMB received IVA 150 mg (AM) + IVA 150 mg (PM) as tablets	Children who completed Part B of the KIWI study	- Participants who prematurely discontinued from previous study - Participants who received commercially available ivacaftor treatment - History of study treatment intolerance or history of illness that may confound results.

Nick 2020[140]	Phase 2, randomized, double-blind, placebo-controlled, multiple, within-patient, crossover study Follow-Up: - 2-week screening period - Segmented crossover period (two 4-week cycles followed by 4 to 8-week washout period) - 8-week open label period	Heterozygous (F508del and a residual function mutation) – included missense mutations N=24	During each 4-week crossover cycle, patients received 2 weeks of IVA and PBO in 1 of 4 randomly assigned treatment sequences. In the 8-week open-label period, after second crossover washout, all patients received IVA.	- 12 years or older with confirmed CF diagnosis - $ppFEV_1 \geq 40\%$ - Sweat chloride concentration $\leq$80 mmol/L - Clinical evidence of residual CFTR function	- Inability to perform spirometry - Acute upper or lower respiratory infection - Pulmonary exacerbation - Change in therapy for pulmonary disease within 4 weeks - Use of IVA within 30 days of screening

CF: cystic fibrosis, CFTR: cystic fibrosis transmembrance conductance regulator, kg: kilogram, mg: milligram, n: number, N: total number NR: not reported, OLE: open label extension, $ppFEV_1$: percent predicted forced expiratory volume in 1 second

Table D2. Baseline Characteristics I

Trial & Author	Arms	N	Female, n (%)	Age			ppFEV$_1$					Sweat Chloride Concentration, mean mmol/L (SD)
				Mean years (SD)	12 to <18 years, n (%)	≥18 years, n (%)	Mean % (SD)	<40%, n (%)	40 to <70%, n (%)	70 to 90%, n (%)	>90%, n (%)	
Elexacaftor (ELX) / Tezacaftor (TEZ) / Ivacaftor (IVA)												
Trial 1 Middleton 2019[56]	ELX/TEZ/IVA	200	96 (48.0)	25.6 (9.7)	56 (28.0)	144 (72.0)	61.6 (15.0)	18 (9.0)	114 (57.0)	66 (33.0)	2 (1.0)	102.3 (11.9)
	Placebo	203	98 (48.3)	26.8 (11.3)	60 (29.6)	143 (70.4)	61.3 (15.5)	16 (7.9)	120 (59.1)	62 (30.5)	5 (2.5)	102.9 (9.8)
Trial 2 Heijerman 2019[8]	ELX/TEZ/IVA	55	31 (56.4)	28.8 (11.5)	16 (29.1)	39 (70.9)	61.6 (15.4)†	6 (10.9)	31 (56.4)	18 (32.7)	0 (0)	91.4 (11.0)
	Placebo/TEZ/IVA	52	28 (53.8)	27.9 (10.8)	14 (26.9)	38 (73.1)	60.2 (14.4)†	4 (7.7)	34 (65.4)	14 (26.9)	0 (0)	90.0 (12.3)
Keating 2018[57]	ELX/TEZ/IVA	21	11 (52.4)	33.3 (10.3)	0 (0)	21 (100)*	59.4 (18.0)	4 (19.0)	11 (52.4)	5 (23.8)	1 (4.8)	103.9 (9.7)
heterozygous population	Placebo	12	2 (16.7)	29.7 (7.5)	0 (0)	12 (100)*	59.0 (14.9)	2 (16.7)	7 (58.3)	3 (25.0)	0 (0)	103.1 (8.2)
Keating 2018[57]	ELX/TEZ/IVA	21	9 (42.9)	29.9 (7.6)	0 (0)	21 (100)*	60.0 (15.1)	1 (4.8)	15 (71.4)	4 (19.0)	1 (4.8)	92.7 (11.1)
homozygous population	Placebo/TEZ/IVA	7	1 (14.3)	27.9 (8.0)	0 (0)	7 (100)*	62.8 (13.2)	0 (0)	4 (57.1)	3 (42.9)	0 (0)	99.5 (9.0)
Tezacaftor (TEZ) / Ivacaftor (IVA)												
EVOLVE Taylor-Cousar 2017[87] Yang, 2018[82]	TEZ/IVA	248	121 (48.8)	26.9 (11.2)	58 (23.4)	190 (76.6)	59.6 (14.7)	23 (9.3)	157 (63.3)	65 (26.2)	2 (0.8)	101.3 (10.9)
	Placebo	256	125 (48.8)	25.7 (9.5)	58 (22.7)	198 (77.3)	60.4 (15.7)	24 (9.4)	152 (59.4)	73 (28.5)	7 (2.7)	100.5 (10.2)
Walker 2019[92]	TEZ/IVA (Part A)	13	7 (53.8)	8.1 (1.8)	N/A		89.1 (14.8)	NR				NR
	TEZ/IVA (Part B)	70	34 (48.6)	8.1 (1.8)	N/A		91.1 (12.3)	NR				99.1 (19.2), n=64

EXTEND Flume 2018[81]	TEZ/IVA	613	NR									
Lumacaftor (LUM) / Ivacaftor (IVA)												
TRAFFIC and TRANSPORT Wainwright 2015[30]	LUM600/IVA	368	182 (49.5)	24.5 (Range: 12-54)	96 (26.1)	272 (73.9)	60.8 (Range: 31.1–92.3)	24 (6.5)	241 (65.5)	98 (26.6)	3 (0.8)	NR
	LUM400/IVA	369	182 (49.3)	25.3 (Range: 12-57)	98 (26.6)	271 (73.4)	60.5 (Range: 31.3–96.5)	29 (7.9)	233 (63.1)	100 (27.1)	3 (0.8)	NR
	Placebo	371	181 (48.8)	25.4 (Range: 12-64)	96 (25.9)	275 (74.1)	60.4 (Range: 33.9–99.8)	28 (7.5)	238 (64.2)	97 (26.1)	3 (0.8)	NR
TRAFFIC and TRANSPORT - sub-group analysis McColley 2019[141]	LUM/IVA Absolute ppFEV$_1$ change ≤ 0	146	73 (50.0)	NR	34 (23.3)	112 (76.7)	NR	8 (5.5)	≥ 40: 134 (91.8)			NR
	LUM/IVA Absolute ppFEV$_1$ change > 0	223	109 (48.9)	NR	64 (28.2)	159 (71.3)	NR	21 (9.4)	≥ 40: 202 (90.6)			NR
	LUM/IVA Relative ppFEV$_1$ change < 5%	228	110 (48.2)	NR	59 (25.9)	169 (74.1)	NR	13 (5.7)	≥ 40: 211 (92.5)			NR
	LUM/IVA Relative ppFEV$_1$ change ≥ 5%	141	72 (51.1)	NR	39 (27.7)	102 (72.3)	NR	16 (11.3)	≥ 40: 125 (88.7)			NR
	Placebo	371	181 (48.8)	NR	96 (25.9)	275 (74.1)	NR	28 (7.5)	≥ 40: 338 (91.1)			NR
McNamara 2018[80] (Part A)	LUM200/IVA250	4	2 (50.0)	2.3 (0.5)	N/A		NR					NR
	LUM300/IVA376	8	2 (25.0)	4.0 (0.9)	N/A		NR					NR
	LUM200/IVA250	19	9 (47.4)	2.6 (0.4)	N/A			NR				105.5 (8.0)

McNamara 2018[80] (Part B)	LUM300/IVA376	41	20 (48.8)	4.2 (0.9)	N/A		83.8 (10.9)	NR		106.0 (7.2), n=37
Chilvers 2017[78] Chilvers 2019[77] *BL reported are pooled BL at the beginning of the parent studies*	LUM/IVA → LUM/IVA	143	83 (58.0)	8.9 (1.6) §	NR		89.7 (13.8)	NR		103.8 (10.4), n=160
	Placebo → LUM/IVA‡	96	56 (58.3)		NR		88.9 (11.7)	NR		103.4 (9.8), n=98
Ivacaftor (IVA)										
KLIMB Rosenfeld 2019[59]	Weight-based IVA	33	6 (18.2)	3.7 (1.0)	0 (0)*	0 (0)*	NR	NR		51.6 (22.9)
Nick 2020[140]	IVA	24	12 (50.0	37.3 (13.9)	24 (100)		67.8 (22.6)	<70%: 15 (62.5)	3 (12.5)	6 (25.0)	64.7 (25.7)
	Placebo									

mmol/L: millimoles per liter, n: number, N: total number, NR: not reported, ppFEV$_1$: percent predicted forced expiratory volume in 1 second, SD: standard deviation

* Assumption made based on study protocol, † after 4-week open-label run-in period with TEZ/IVA, ‡patients received Placebo in parent study and LUM/IVA treatment in extension study, §at baseline of parent study

Table D3. Baseline Characteristics II

Trial	Arms	N	BMI, mean (SD)	Weight, mean kg (SD)	Height, mean cm (SD)	CFQ-R Respiratory Domain Score, mean (SD)	Lung Clearance Index 2.5, mean (SD)	*Pseudomonas aeruginosa* – positive, n (%)
Elexacaftor (ELX) / Tezacaftor (TEZ) / Ivacaftor (IVA)								
Trial 1 Middleton 2019[56]	ELX/TEZ/IVA	200	21.5 (3.1)	NR	NR	68.3 (16.9)	NR	150 (75.0)*
	Placebo	203	21.3 (3.1)	NR	NR	70.0 (17.8)	NR	142 (70.0)*
Trial 2 Heijerman 2019[8]	ELX/TEZ/IVA	55	21.8 (3.2)	NR	NR	70.6 (16.2)	NR	39 (71.0)*
	Placebo/TEZ/IVA	52	21.9 (4.1)	NR	NR	72.6 (17.9)	NR	31 (59.6)*
Keating 2018[57]	ELX/TEZ/IVA	21	22.1 (1.7)	60.5 (8.8)	165.1 (10.0)	61.1 (17.5)	NR	19 (90.5)
heterozygous population	Placebo	12	22.9 (2.9)	69.6 (8.2)	174.7 (12.4)	57.4 (14.1)	NR	10 (83.3)
Keating 2018[57]	ELX/TEZ/IVA	21	22.3 (2.8)	65.2 (12.0)	170.5 (10.4)	71.2 (17.3)	NR	15 (71.4)

homozygous population	Placebo/TEZ/IVA	7	24.0 (4.1)	74.7 (16.0)	175.9 (13.1)	73.0 (22.3)	NR	5 (71.4)
Tezacaftor (TEZ) / Ivacaftor (IVA)								
EVOLVE **Taylor-Cousar 2017[87]** **Yang 2018[82]**	TEZ/IVA	248	21.0 (3.0)	NR	NR	70.1 (16.8)	NR	185 (74.6)
	Placebo	256	21.1 (2.9)	NR	NR	69.9 (16.6)	NR	182 (71.1)
Walker 2019[92]	TEZ/IVA (Part A)	13	17.1 (2.4)	30.5 (8.5)	NR	NR	NR	NR
	TEZ/IVA (Part B)	70	17.4 (2.7)	30.7 (10.0)	131.0 (13.0)	81.8 (13.8)	NR	NR
EXTEND **Flume 2018[81]**	TEZ/IVA	613	NR					
Lumacaftor (LUM) / Ivacaftor (IVA)								
TRAFFIC and TRANSPORT **Wainwright 2015[30]**	LUM600/IVA	368	21.0 (Range: 14.2, 35.1)	NR	NR	NR	NR	NR
	LUM400/IVA	369	21.5 (Range: 14.6, 31.4)	NR	NR	NR	NR	NR
	Placebo	371	21 .0 (Range: 14.1,32.2)	NR	NR	NR	NR	NR
TRAFFIC and TRANSPORT – subgroup analysis **McColley 2019[79]**	LUM/IVA Absolute ppFEV$_1$ change ≤ 0	146	NR	NR	NR	NR	NR	120 (82.2)
	LUM/IVA Absolute ppFEV$_1$ change > 0	223	NR	NR	NR	NR	NR	166 (74.4)
	LUM/IVA Relative ppFEV$_1$ change < 5%	228	NR	NR	NR	NR	NR	179 (78.5)

	LUM/IVA Relative ppFEV$_1$ change ≥ 5%	141	NR	NR	NR	NR	NR	107 (75.9)
	Placebo	371	NR	NR	NR	NR	NR	276 (74.4)
McNamara 2019[80] (Part A)	LUM200/IVA250	4	16.9 (0.6)	12.5 (0.9)	86.0 (4.6)	NR	NR	NR
	LUM300/IVA376	8	15.9 (1.0)	16.4 (1.5)	101.7 (6.0)	NR	NR	NR
McNamara 2019[80] (Part B)	LUM200/IVA250	19	16.0 (1.1)	12.7 (1.0)	89.1 (3.4)	NR	7.6 (0.9), n=5	NR
	LUM300/IVA376	41	16.0 (1.0)	17.1 (2.3)	103.4 (6.1)	NR	9.3 (2.0), n=32	NR
Chilvers 2017[78] **Chilvers 2019[77]** ***BL reported are pooled BL at the beginning of the parent studies***	LUM/IVA → LUM/IVA	143	16.6 (1.8), n=101	NR	NR	78.5 (14.3), n=135	10.2 (2.4), n=128	NR
	Placebo → LUM/IVA	96	16.6 (2.0), n=101	NR	NR	77.1 (15.5), n=78	10.3 (2.2), n=101	NR
Ivacaftor (IVA)								
KLIMB **Rosenfeld 2019[59]**	Weight-based IVA	33	NR	Weight z-score, mean (SD): 0.07 (0.83)	Height z-score, mean (SD): -0.31 (0.95)	NR	NR	NR
Nick 2020[140]	IVA	24	24.2 (4.8)	70.5 (13.9)	171.1 (9.5)	NR	10.6 (3.1)	NR
	Placebo							

BMI: body mass index, CFQ-R: cystic fibrosis questionnaire-revised, cm: centimeters, kg: kilogram, n: number, N: total number, NR: not reported, SD: standard deviation

* within previous two years

Table D4. Efficacy at 4 weeks I

Trial	Arms	N	ppFEV$_1$		Sweat Chloride		CFQ-R Respiratory Domain Score	
			Absolute Change, Points (95%CI)	Treatment Δ (95%CI), p-value	Absolute Change, mmol/L (95%CI)	Treatment Δ (95%CI), p-value	Absolute Change, points (95%CI)	Treatment Δ (95%CI), p-value
Elexacaftor (ELX) / Tezacaftor (TEZ) / Ivacaftor (IVA)								
Trial 1 **Middleton 2019[56]**	ELX/TEZ/IVA	200	13.6 (12.4, 14.8)	13.8 (12.1, 15.4), p<0.001	-41.2 (-43.1, -39.2)	-41.2 (-44.0, -38.5), p<0.001	18.1 (15.9, 20.4)	20.1 (16.9, 23.2), p<0.001
	Placebo	203	-0.2 (-1.3, 1.0)		0.1 (-1.9, 2.0)		-1.9 (-4.2, 0.3)	
Trial 2 **Heijerman 2019[8]**	ELX/TEZ/IVA	55	10.4 (8.6, 12.2)	10.0 (7.4, 12.6), p<0.0001	-43.4 (-46.9, -40.0)	-45.1 (-50.1, -40.1), p<0.0001	16.0 (12.1, 19.9)	17.4 (11.8, 23.0), p<0.0001
	Placebo/TEZ/IVA	52	0.4 (-1.4, 2.3)		1.7 (-1.9, 5.3)		-1.4 (-5.4, 2.6)	
Keating 2018[57] ***heterozygous population***	ELX/TEZ/IVA	21	13.8 (10.9, 16.6)	13.8 (NR), NR	-39.1 (-44.9, -33.3)	36.9 (NR), NR	25.7 (18.3, 33.1)	21.5 (NR), NR
	Placebo	12	0.0 (-3.9, 4.0)		-2.2 (-9.9, 5.6)		4.2 (-5.6, 14.0)	
Keating 2018[57] ***homozygous population***	ELX/TEZ/IVA	21	11.0 (7.9, 14.0)	10.6 (NR), NR	-39.6 (-45.3, -33.8)	40.4 (NR), NR	20.7 (12.5, 29.0)	15.5 (NR), NR
	Placebo/TEZ/IVA	7	-0.4 (-5.4, 6.2)		0.8 (-9.3, 11.0)		5.2 (-9.5, 19.9)	
Tezacaftor (TEZ) / Ivacaftor (IVA								
EVOLVE **Taylor-Cousar 2017[87]** **Yang, 2018[82]**	TEZ/IVA	248	3.4 (2.6, 4.1)*	3.5 (NR), NR	-9.6 (-10.8, -8.4)*	-9.2 (NR), NR	5.6 (3.7, 7.5)*	4.6 (NR), NR
	Placebo	256	-0.1 (-0.8, 0.5)*		-0.4 (-1.8, 0.7)*		1.1 (-0.9, 2.9)*	
Walker 2019[92]	TEZ/IVA (Part B)	70	NR		-13.0 (-16.2, -9.9)	N/A	NR	
Lumacaftor (LUM) / Ivacaftor (IVA)								
TRAFFIC and TRANSPORT **Wainwright 2015[30]**	LUM600/IVA	368	2.5 (1.7, 3.1)*	2.4 (NR), NR	NR		5.4 (3.8, 6.9)*	3.4 (NR), p<0.025
	LUM400/IVA	369	2.6 (1.7, 3.2)*	2.5 (NR), NR	NR		6.2 (4.6, 7.9)*	4.2 (NR), p<0.025
	Placebo	371	0.1 (-0.7, 0.8)*	---	NR		2.0 (0.4, 3.5)*	---

TRAFFIC and TRANSPORT – subgroup analysis **McColley 2019[79]**	LUM/IVA	1108	4 Weeks data NR					
McNamara 2019[80] (Part B)	LUM/IVA (pooled)	60	NR		-24.7 (-20.7, -28.4)*	N/A	NR	
Ivacaftor (IVA)								
Nick 2020[140]	IVA	24	Crossover cycle 1: 2.1 (SD: 4.6) Crossover cycle 2: 3.7 (SD: 6.1) Open-label period: 4.7 (SD: 4.2)	NR	Open Label: -15.7 (14.8)†	N/A	NR	NR
	PBO	24	Crossover cycle 1: 0.6 (SD: 3.7) Crossover cycle 2: 0.8 (SD:4.2) Open label period: N/A	NR		N/A	NR	NR

95%CI: 95% Confidence Interval, BMI: body mass index, CFQ-R: cystic fibrosis questionaire-revised, kg: kilograms, mmol/L: millimoles per liter, n: number, N: total number, N/A: not applicable, NR: not reported, ppFEV$_1$: percent predicted forced expiratory volume in 1 second, SD: standard deviation, Δ: difference

*numbers are digitized and should be interpreted with caution

† At 8-weeks

Table D5. Efficacy at 4 weeks II

Trial	Arms	N	BMI		Weight		Height		LCI2.5	
			Absolute Change, kg/m2 (95%CI)	Treatment Δ (95%CI), p-value	Absolute Change, kg (95%CI)	Treatment Δ (95%CI), p-value	Absolute Change, cm (95%CI)	Treatment Δ (95%CI), p-value	Absolute Change, points (95% CI)	Treatment Δ (95%CI), p-value
Elexacaftor (ELX) / Tezacaftor (TEZ) / Ivacaftor (IVA)										
Trial 1 **Middleton 2019[56]**	ELX/TEZ/IVA	200	0.54 (0.50, 0.58)*	0.44 (NR), NR	NR		NR		NR	
	Placebo	203	0.10 (0.05, 0.15)*		NR		NR		NR	
Trial 2 **Heijerman 2019[8]**	ELX/TEZ/IVA	55	NR	0.60 (0.41, 0.79), p<0.0001	NR	1.6 (1.0, 2.1), p<0.0001	NR		NR	
	Placebo/TEZ/IVA	52	NR		NR		NR		NR	
Keating 2018 heterozygous population	ELX/TEZ/IVA	21	NR		NR		NR		NR	
	Placebo	12	NR		NR		NR		NR	
Keating 2018 homozygous population	ELX/TEZ/IVA	21	NR		NR		NR		NR	
	Placebo/TEZ/IVA	7	NR		NR		NR			
Tezacaftor (TEZ) / Ivacaftor (IVA)										
EVOLVE **Taylor-Cousar 2017** **Yang 2018**	TEZ/IVA	248	0.11 (0.04, 0.17)*	-0.03 (NR), NR	NR		NR		NR	
	Placebo	256	0.14 (0.07, 0.20)*		NR		NR		NR	
Walker 2019	TEZ/IVA (Part B)	70	NR		NR		NR		NR	
Lumacaftor (LUM) / Ivacaftor (IVA)										
TRAFFIC and TRANSPORT (Wainwright 2015)	LUM600/IVA	368	0.12 (0.06, 0.17)*	(NR), n.s.	NR		NR		NR	
	LUM400/IVA	369	0.10 (0.06, 0.17)*	(NR), n.s.	NR		NR		NR	

	Placebo	371	0.11 (0.06, 0.17)*	---	NR	NR	NR	
McColley 2019	LUM/IVA	1108	4-week data not reported					
McNamara 2018 (Part B)	LUM/IVA (pooled)	60	NR		NR	NR	-0.6 (-1.1, -0.1)*	N/A
Ivacaftor (IVA)								
Nick 2020[140]	IVA	24	NR		NR	NR	-1.6 (2.3)	NR
	PBO	24	NR		NR	NR		

95%CI: 95% Confidence Interval, BMI: body mass index, CI: confidence interval, cm: centimeter, kg: kilograms, kg/m^2: kilogram per meter squared, LCI: lung clearance index, n: number, N: total number, N/A: not applicable, NR: not reported, n.s.: not significant, Δ: difference

* numbers are digitized and should be interpreted with caution

Table D6. Efficacy at 24 weeks I

Trial	Arms	N	ppFEV$_1$		Sweat Chloride		Pulmonary Excacerbations (PE)			
			Absolute Change, % (95%CI)	Treatment Δ (95%CI), p-value	Absolute Change, mmol/L (95%CI)	Treatment Δ (95%CI), p-value	Events, n (AER)	Δ RR (95%CI), p-value	Number of PE leading to hosp., ER/PY	Δ hosp., RR (95%CI), p-value
Trial 1	ELX/TEZ/IVA	200	13.9 (12.8, 15.0)	14.3 (12.7, 15.8), p<0.001	-42.2 (-44.0, -40.4)	-41.8 (-44.4, -39.3), p<0.001	41 (0.4)	0.4 (0.3, 0.6), p<0.001	0.1	0.3 (0.1, 0.6), NR
Middleton 2019[56]	Placebo	203	-0.4 (-1.5, 0.7)		-0.4 (-2.2, 1.4)		113 (1.0)		0.2	
Tezacaftor (TEZ) / Ivacaftor (IVA)										
EVOLVE 2017 Taylor-Cousar 2017[87] Yang, 2018[82]	TEZ/IVA	248	3.4 (2.7, 4.0)	4.0 (3.1, 4.8), p<0.001	-9.9 (-10.9, -8.9)	-10.1 (-11.4, -8.8), NR	78 (0.6)	0.7 (0.5, 0.9) p=0.005	0.3	0.5 (0.3, 0.8), NR
	Placebo	256	-0.6 (-1.3, 0.0)		0.2 (-0.8, 1.2)		122 (1.0)		0.5	
Walker 2019[92]	TEZ/IVA (Part B)	70	0.9 (- 0.6, 2.3)	N/A	-14.5 (-17.4, -11.6)	N/A	NR			
EXTEND (interim analysis at 24 weeks - homozygous population) Flume 2018[81]	Placebo → TEZ/IVA	231	4.3 (3.3, 5.4)	0.9 (NR), NR	NR		NR (0.65)†	NR		
	TEZ/IVA → TEZ/IVA*	228	3.4 (2.3, 4.5)		NR		NR (0.72)†	NR		
Lumacaftor (LUM) / Ivacaftor (IVA)										
TRAFFIC and TRANSPORT Wainwright 2015[30]	LUM600/IVA	368	2.6 (1.8, 3.4)‡	3.3 (2.3, 4.3) p<0.001	NR		173 (0.8)	0.7 (0.6, 0.9) p=0.001	0.3‡	0.2 (NR), p<0.001
	LUM400/IVA	369	2.3 (1.4, 3.1)‡	2.8 (1.8, 3.8) p<0.001			152 (0.7)	0.6 (0.5, 0.8) p<0.001	0.2‡	0.3 (NR), p=0.003
	Placebo	371	-0.3 (-1.1, 0.5)‡	---			251 (1.1)	---	0.5‡	---

TRAFFIC and TRANSPORT - sub-group analysis **McColley 2019[79]**	LUM/IVA Absolute $ppFEV_1$ change ≤ 0	146	NR		NR		NR (0.9) ‡	0.7 (0.6, 1.0), p=0.0441	0.2	0.4 (0.2, 0.7), p=0.0009
	LUM/IVA Absolute $ppFEV_1$ change > 0	223	NR		NR		NR (0.6) ‡	0.5 (0.4, 0.7), p<0.0001	0.2	0.4 (0.2, 0.6), p<0.0001
	LUM/IVA Relative $ppFEV_1$ change < 5%	228	NR		NR		NR (0.7) ‡	0.6 (0.5, 0.8), p=0.0003	0.1	0.3 (0.2, 0.5), p<0.0001
	LUM/IVA Relative $ppFEV_1$ change ≥ 5%	141	NR		NR		NR (0.7) ‡	0.6 (0.4, 0.8), p=0.0013	0.2	0,5 (0.3, 0.8), p=0.0053
	Placebo	371	NR		NR		NR (1.1) ‡	---	0.5	---
McNamara 2019[80] (Part B)	LUM/IVA (pooled)	60	0.5 (-6.9, 7.9)	N/A	-31.7 (-35·7, -27.6), n=52	N/A	NR			
Chilvers 2017[78]	LUM/IVA → LUM/IVA	143	2.8 (0.7, 4.9), n=134	NR	-24.2 (-27.0, -21.4), n=127	NR	NR			
	Placebo → LUM/IVA	96	2.0 (-0.8, 4.9), n=86		-29.0 (-32.8, 25.2), n=85	NR	NR			
Ivacaftor (IVA)										
KLIMB **Rosenfeld 2019[59]**	IVA	33	NR		-4.5 (NR)	N/A	NR			

95%CI: 95% Confidence Interval, AER: annualized event rate, ER/PY: event rate per patient year, hosp.: hospitalization, kg: kilograms, LCI: lung clearance index, mmol/L: millimoles per liter, n: number, N: total number, N/A: not applicable, NR: not reported, $ppFEV_1$: percent predicted forced expiratory volume in 1 second, RR: risk ratio, SD: standard deviation, Δ: difference

* change from baseline in parent study (EVOLVE), † time period: from baseline of parent study (EVOLVE) up to 24-weeks in EXTEND study, ‡numbers are digitized and should be interpreted with caution

Table D7. Efficacy at 24 Weeks II

Trial	Arms	N	BMI		Weight		Height		CFQ-R Respiratory Domain Score		$LCI_{2.5}$	
			Absolute Change, kg/m^2 (95%CI)	Treatment Δ (95%CI), p-value	Absolute Change, kg (95% CI)	Treatment Δ (95%CI), p-value	Absolute Change, cm (95%CI)	Treatment Δ (95%CI), p-value	Absolute Change, points (95% CI)	Treatment Δ (95%CI), p-value	Absolute Change, mean (95%CI)	Treatment Δ (95%CI), p-value
Elexacaftor (ELX) / Tezacaftor (TEZ) / Ivacaftor (IVA)												
Trial 1 **Middleton 2019[56]**	ELX/TEZ/IVA	200	1.13 (0.99, 1.26)	1.04 (0.85, 1.23), p<0.001	3.4 (3.0, 3.8)	2.9 (2.3, 3.4)	NR		17.5 (15.6, 19.5)	20.2 (17.5, 23.0), p<0.001	NR	
	Placebo	203	0.09 (−0.05, 0.22)		0.5 (0.2, 0.9)		NR		-2.7 (-4.6, -0.8)		NR	
Tezacaftor (TEZ) / Ivacaftor (IVA)												
EVOLVE 2017 **Taylor-Cousar 2017[87]** **Yang 2018[82]**	TEZ/IVA	248	0.2 (0.1, 0.3)	0.1 (-0.1, 0.2), p=0.41	NR		NR		5.0 (3.5, 6.5)	5.1 (3.2, 7.0), NR	NR	
	Placebo	256	0.1 (0.03, 0.2)		NR		NR		-0.1 (-1.6, -1.4)		NR	
Walker 2019[92]	TEZ/IVA (Part B)	70	0.2 (0.1, 0.4)	N/A	1.7 (1.3, 2.0), n=67	N/A	2.7 (2.4, 2.9), n=67	N/A	3.4 (1.4, 5.5)	N/A	NR	N/A
EXTEND (interim analysis at 24	Placebo → TEZ/IVA	231	0.25 (0.13, 0.38)	0.02 (NR), NR	NR	NR	NR	NR	3.7 (1.5, 6.0)	0.6 (NR), NR	NR	

weeks - homozygous population) **Flume 2018[81]**	TEZ/IVA → TEZ/IVA	228	0.23 (0.11, 0.36)		NR	NR	NR	NR	3.1 (0.8, 5.3)		
Lumacaftor (LUM) / Ivacaftor (IVA)											
TRAFFIC and TRANSPORT **Wainwright 2015[30]**	LUM600/IVA	368	0.4 (0.31, 0.50)*	0.3 (0.2, 0.4) p<0.001	NR		NR		4.9 (3.5, 6.5)*	3.1 (0.8, 5.3) p=0.007	NR
	LUM400/IVA	369	0.3 (0.26, 0.46)*	0.2 (0.1, 0.4) p<0.001	NR		NR		4.1 (2.5, 5.7)*	2.2 (0.0, 4.5) p=0.05	NR
	Placebo	371	0.1 (0.05, 0.23)*	---	NR		NR		1.9 (0.3, 3.5)*	---	NR
TRAFFIC and TRANSPORT - sub-group analysis **MColley 2019[79]**	LUM/IVA Absolute $ppFEV_1$ change ≤ 0	146	NR		NR		NR		NR		NR
	LUM/IVA Absolute $ppFEV_1$ change > 0	223	NR		NR		NR		NR		NR
	LUM/IVA Relative $ppFEV_1$ change < 5%	228	NR		NR		NR		NR		NR
	LUM/IVA Relative $ppFEV_1$ change ≥ 5%	141	NR		NR		NR		NR		NR
	Placebo	371	NR		NR		NR		NR		NR
McNamara 2019[80] (Part B)	LUM/IVA (pooled)	60	0.3 (0.1, 0.5), n=57	N/A	1.4 (1.2, 1.7)	N/A	3.6 (3.3, 3.9)	N/A	NR	-0.6	N/A

											(-1.2, 0.0), n=21	
Chilvers 2017[78]	LUM/IVA → LUM/IVA	143	0.8 (0.6, 1.0), n=139	NR	NR		NR		7.7 (5.2, 10.3), n=112	NR	-1.1 (-1.5, -0.7), n=78	NR
	Placebo → LUM/IVA	96	0.4 (0.2, 0.6), n=93	NR	NR		NR		3.0 (-0.2, 6.2), n=88	NR	-1.0 (-1.5, -0.5), n=68	NR
Ivacaftor (IVA)												
KLIMB **Rosenfeld 2019[59]**	IVA	33	-0.2 (NR)*†	N/A	NR		NR		NR		NR	

95%CI: 95% Confidence Interval, BMI: body mass index, CFQ-R: cystic fibrosis questionaire-revised, CI: confidence interval, cm: centimeter, kg: kilogram, kg/m^2: kilogram per meter squared, LCI: lung clearance index, m^2: square meter, N: total number, N/A: not applicable, NR: not reported, $ppFEV_1$: percent predicted forced expiratory volume in 1 second, Δ: difference

* numbers are digitized and should be interpreted with caution, † measured from baseline of parent study (KLIMB)

Table D8. Long-term Efficacy Outcomes I

Trial	Arms	N	Follow-Up Duration	Absolute Change in $ppFEV_1$, % (SE)	Absolute Change in Sweat Chloride, mmol/L (SE)	Pulmonary Excacerbations (PE)		Absolute Change in CFQ-R Respiratory Domain Score, points (95% CI)
						Number of events (AER)	Number of PE leading to hospitalization, ER/PY	
Chilvers 2019[77]	LUM/IVA → LUM/IVA	143	96 weeks	3.1 (1.0, 5.1)	-22.9 (-25.5, -20.3), n=122	0.5 (0.3, 0.6)	NR	7.4 (4.8, 10.0), n=108
	Placebo → LUM/IVA	96		0.0 (-2.7, 2.7)	-22.8 (-26.3, -19.3), n=78	0.3 (0.2, 0.4)	NR	6.6 (3.1, 10.0), n=65
KLIMB **Rosenfeld 2019[59]**	IVA	33	84 weeks	NR	-8.5 (-18.9, 1.8), n=20	n (%): 10 (30.3)	n (%): 6 (18.2)	NR

95%CI: 95% Confidence Interval, AER: annualized event rate, CFQ-R: cystic fibrosis questionairre-revised, ER/PY: event rate per patient year, mmol/L: millimole per liter, n: number, NR: not reported, $ppFEV_1$: percent predicted forced expiratory volume in 1 second, SE: standard error

Table D9. Long-term Efficacy Outcomes II

Trial	Arms	N	Follow-Up Duration	BMI		Weight		Height		Absolute Change in LCI2.5, points (95% CI)
				Absolute Change in BMI, kg/m2 (SE)	Absolute Change in BMI z score (SE)	Absolute Change in Weight, kg (SE)	Absolute Change in Weight z score (SE)	Absolute Change in Height, cm (SE)	Absolute Change in Height z score (SE)	
Chilvers 2019[77]	LUM/IVA → LUM/IVA	143	96 weeks	1.8 (1.6, 2.0), n=130	0.2 (0.1, 0.3)	10.3 (9.6, 11.0)*	0.1 (0.04, 0.2)	13.4 (12.9, 14.0)*	-0.01 (-0.1, 0.1)	-0.9 (-1.3, -0.5), n=88
	Placebo → LUM/IVA	96		2.0 (1.8, 2.3), n=83	0.3 (0.2, 0.4)	11.0 (10.1, 11.8)*	0.2 (0.1, 0.3)	13.5 (12.8, 14.1)*	0.02 (-0.1, 0.1)	-0.9 (-1.3, -0.4), n=69
KLIMB **Rosenfeld 2019[59]**	IVA	33	84 weeks	NR	-0.1 (-0.3, 0.2)	NR	0.0 (-0.2, 0.2)	NR	0.1 (0.0, 0.3)	NR

95%CI: 95% confidence interval, BMI: body mass index, cm: centimeter, kg: kilogram, LCI: lung clearance index, m^2: square meter, NR: not reported, SE: standard error

* measured from baseline in parent study

Table D10. Patient Reported Outcomes

Trial	Arms	N	Follow-Up (weeks)	Treatment Burden, treatment effect vs placebo (95%CI), p-value	Health Perception, treatment effect vs placebo (95%CI), p-value	Physical Functioning, treatment effect vs placebo (95%CI), p-value	Social Functioning, treatment effect vs placebo (95%CI), p-value	Emotional Functioning, treatment effect vs placebo (95%CI), p-value	Role Functioning, treatment effect vs placebo (95%CI), p-value	Vitality, treatment effect vs placebo (95%CI), p-value
Tezacaftor (TEZ) / Ivacaftor (IVA)										
EVOLVE **Taylor-Cousar 2017[87]** **Yang 2018[82]**	TEZ/IVA	481	24 weeks	3.4 (1.6, 5.1), p<0.05	3.2 (1.2, 5.2), n.s.*	3.8 (1.9, 5.8), p<0.05	1.5 (0.0, 3.0), n.s.	0.6 (-1.0, 2.2), n.s.*	1.5 (-0.3, 3.4), n.s.	2.3 (0.1, 4.5), n.s.

95%CI: 95% Confidence Interval, N: total number, n.s.: not significant, vs: versus

* In the post hoc CDF analyses differences favoring TEZ/IVA were observed

Table D11. Harms I

Trial	Arms	N	Any AE, n (%)	SAEs		TEAE, n (%)	AE leading to D/C, n (%)	Death, n (%)	Infective Pulmonary Exacerbations of CF, n (%)
				Any SAE, n (%)	Rash Events, n (%)				
Elexacaftor (ELX) / Tezacaftor (TEZ) / Ivacaftor (IVA)									
Trial 1 **Middleton 2019[56]**	ELX/TEZ/IVA	202	188 (93.1)	28 (13.9)	3 (1.5)	NR	2 (1.0)	0 (0)	44 (21.8)
	Placebo	201	193 (96.0)	42 (20.9)	1 (0.5)	NR	0 (0)	0 (0)	95 (47.3)
Trial 2 **Heijerman 2019[8]**	ELX/TEZ/IVA	55	32 (58.1)	2 (3.6)	1 (1.8)	12 (21.8)	0 (0)	0 (0)	1 (1.8)
	Placebo/TEZ/IVA	52	33 (63.5)	1 (1.9)	0 (0)	9 (17.3)	0 (0)	0 (0)	6 (11.5)
Keating 2018[57] ***heterozygous population***	ELX/TEZ/IVA	21	18 (85.7)	0 (0)	NR	NR	0 (0)	0 (0)	2 (9.5)
	Placebo	12	12 (100)	2 (16.7)	NR	NR	0 (0)	0 (0)	4 (33.3)
Keating 2018[57] ***homozygous population***	ELX/TEZ/IVA	21	19 (90.5)	0 (0)	NR	NR	1 (4.8)	0 (0)	5 (23.8)
	Placebo/TEZ/IVA	7	5 (71.4)	1 (14.3)	NR	NR	1 (14.3)	0 (0)	1 (14.3)
Tezacaftor (TEZ) / Ivacaftor (IVA)									

EVOLVE **Taylor-Cousar 2017[87]** **Yang, 2018[82]**	TEZ/IVA	251	227 (90.4)	31 (12.4)	NR	64 (25.5)	7 (2.8)	0 (0)	75 (29.9)
	Placebo	258	245 (95.0)	47 (18.2)	NR	66 (25.6)	8 (3.1)	0 (0)	96 (37.2)
Walker 2019[92]	TEZ/IVA (Part A)	13	12 (92.3)	0 (0)	0 (0)*	NR	0 (0)	0 (0)	0 (0)
	TEZ/IVA (Part B)	70	65 (92.9)	6 (8.6)	NR	1 (1.4)	1 (1.4)	0 (0)	16 (22.9)
EXTEND † **Flume 2018[81]**	TEZ/IVA	613	601 (98.0)	194 (31.6)	NR	NR	3 (0.5)	0 (0)	331 (54.0)
Lumacaftor (LUM) / Ivacaftor (IVA)									
TRAFFIC and TRANSPORT **Wainwright 2015[30]**	LUM600/IVA	369	356 (96.5)	84 (22.8)	NR	NR	14 (3.8)	0 (0)	145 (39.3)
	LUM400/IVA	369	351 (95.1)	64 (17.3)	NR	NR	17 (4.6)	0 (0)	132 (35.8)
	Placebo	370	355 (95.9)	106 (28.6)	NR	NR	6 (1.6)	0 (0)	182 (49.2)
TRAFFIC and TRANSPORT – sub-group analysis **McColley 2019[79]**	LUM/IVA	1108	Safety Data NR						
McNamara 2019[80]	LUM/IVA Part A (pooled)	12	10 (83)	0 (0)	NR	NR	1 (8.3)	NR	NR
	LUM/IVA Part B (pooled)	60	59 (98.3)	4 (6.7)	NR	NR	NR	NR	2 (3.3)
Chilvers 2019[77]‡	LUM/IVA → LUM/IVA	143	141 (98.6)	43 (30.1)	NR	NR	9 (3.8)	0 (0)	59 (41.3)
	Placebo → LUM/IVA	96	93 (96.9)	29 (30.2)	NR	NR		0 (0)	34 (35.4)
Ivacaftor (IVA)									
KLIMB **Rosenfeld 2019[59]**	Weight-based IVA	33	33 (100)	11 (33.3)	NR	NR	1 (3.0)	NR	NR
Nick 2020[140]	IVA	24	23 (95.8)	1 (4.2)	NR	NR	NR	NR	3 (12.5)

AE: adverse event, CF: cystic fibrosis, D/C: discontinuation, n: number, N: total number, NR: not reported, SAE: serious adverse event, TEAE: treatment-emergent adverse

* assumption made based on SAEs: 0 (0), † at 86 weeks, ‡time frame: from day 1 up to 100 weeks

Table D12. Harms II

Trial	Arms	N	Sputum increased, n (%)	Headache, n (%)	Cough, n (%)	Rash, n (%)	Diarrhea, n (%)	Upper Resp. Tract Infection, n (%)	Nasopharyngitis, n (%)	Oropharyngeal pain, n (%)	Hemoptysis, n (%)	Fatigue, n (%)	Pyrexia, n (%)	Nausea, n (%)	Vomiting, n (%)
Elexacaftor (ELX) / Tezacaftor (TEZ) / Ivacaftor (IVA)															
Trial 1 **Middleton 2019[56]**	ELX/TEZ/IVA	202	40 (19.8)	35 (17.3)	34 (16.8)	22 (10.9)	26 (12.9)	24 (11.9)	22 (10.9)	20 (9.9)	11 (5.4)	9 (4.5)	NR	NR	NR
	Placebo	201	39 (19.4)	30 (14.9)	77 (38.3)	13 (6.5)	14 (7.0)	22 (10.9)	26 (12.9)	25 (12.4)	28 (13.9)	20 (10.0)	NR	NR	NR
Trial 2 **Heijerman 2019[8]**	ELX/TEZ/IVA	55	NR	3 (5.5)	8 (14.5)	2 (3.6)	NR	4 (7.3)	4 (7.3)	4 (7.3)	2 (3.6)	NR	NR	NR	NR
	Placebo/TEZ/IVA	52	NR	4 (7.7)	4 (7.7)	2 (3.8)	NR	2 (3.8)	2 (3.8)	0 (0)	5 (9.6)	NR	NR	NR	NR
Keating 2018[57] ***heterozygous population***	ELX/TEZ/IVA	21	5 (23.8)	2 (9.5)	7 (33.3)	NR	0 (0)	NR	4 (19.0)	NR	2 (9.5)	NR	1 (4.8)	1 (4.8)	NR
	Placebo	12	3 (25.0)	2 (16.7)	1 (8.3)	NR	1 (8.3)	NR	0 (0)	NR	2 (16.7)	NR	1 (8.3)	2 (16.7)	NR
Keating 2018[57] ***homozygous population***	ELX/TEZ/IVA	21	8 (38.1)	0 (0)	7 (33.3)	NR	0 (0)	NR	1 (4.8)	NR	3 (14.3)	NR	3 (14.3)	1 (4.8)	NR
	Placebo/TEZ/IVA	7	0 (0)	1 (14.3)	1 (14.3)	NR	0 (0)	NR	1 (14.3)	NR	0 (0)	NR	1 (14.3)	1 (14.3)	NR

Tezacaftor (TEZ) / Ivacaftor (IVA)															
EVOLVE **Taylor-Cousar 2017[87]** **Yang, 2018[82]**	TEZ/IVA	251	36 (14.3)	44 (17.5)	66 (26.3)	4 (1.6)	17 (6.8)	NR	42 (16.7)	22 (8.8)	26 (10.4)	16 (6.4)	28 (11.2)	23 (9.2)	NR
	Placebo	258	42 (16.3)	37 (14.3)	84 (32.6)	13 (5.0)	23 (8.9)	NR	39 (15.1)	29 (11.2)	35 (13.6)	31 (12.0)	32 (12.4)	18 (7.0)	NR
Walker 2019[92]	TEZ/IVA (Part A)	13	1 (7.7)	3 (23.1)	3 (23.1)	1 (7.7)	NR	0 (0)	1 (7.7)	1 (7.7)	NR	NR	1 (7.7)	NR	0 (0)
	TEZ/IVA (Part B)	70	3 (4.3)	6 (8.6)	25 (35.7)	0 (0)	NR	6 (8.6)	6 (8.6)	6 (8.6)	NR	NR	13 (18.6)	NR	7 (10.0)
EXTEND † **Flume 2018[81]**	TEZ/IVA	613	NR	NR	240 (39.2)	NR	NR	NR	156 (25.4)	NR	NR	NR	NR	NR	NR
Lumacaftor (LUM) / Ivacaftor (IVA)															
TRAFFIC and TRANSPORT **Wainwright 2015[30]**	LUM600/IVA	369	55 (14.9)	58 (15.7)	121 (32.8)	NR	36 (9.8)	24 (6.5)	23 (6.2)	44 (11.9)	52 (14.1)	NR	NR	29 (7.9)	NR
	LUM400/IVA	369	54 (14.6)	58 (15.7)	104 (28.2)	NR	45 (12.2)	37 (10.0)	48 (13.0)	24 (6.5)	50 (13.6)	NR	NR	46 (12.5)	NR
	Placebo	370	70 (18.9)	58 (15.7)	148 (40.0)	NR	31 (8.4)	20 (5.4)	40 (10.8)	30 (8.1)	50 (13.5)	NR	NR	28 (7.6)	NR
TRAFFIC and TRANSPORT – sub-group analysis **McColley 2019[79]**	LUM/IVA	1108	Safety Data NR												
McNamara 2019[80]	LUM/IVA Part A (pooled)	12	NR	NR	5 (41.7)	NR	NR	NR	NR	NR	NR	NR	NR	NR	2 (16.7)

	LUM/IVA Part B (pooled)	60	NR	NR	38 (63.3)	NR	NR	10 (16.7)	NR	NR	NR	NR	17 (28.3)	NR	17 (28.3)
Chilvers 2019[77]‡	LUM/IVA → LUM/IVA	143	18 (12.6)	29 (20.3)	91 (63.6)	10 (7.0)	16 (11.2)	36 (25.2)	21 (14.7)	32 (22.4)	8 (5.6)	10 (7.0)	45 (31.5)	13 (9.1)	30 (21.0)
	Placebo → LUM/IVA	96	7 (7.3)	26 (27.1)	64 (66.7)	10 (10.4)	8 (8.3)	13 (13.5)	16 (16.7)	18 (18.8)	1 (1.0)	11 (11.5)	27 (28.1)	11 (11.5)	15 (15.6)
Ivacaftor (IVA)															
KLIMB **Rosenfeld 2019[59]**	Weight-based IVA	33	NR	NR	24 (72.7)	4 (12.1)	NR	5 (15.2)	NR	NR	NR	NR	13 (39.4)	NR	13 (39.4)
Nick 2020[140]	IVA	24	3 (12.5)	NR	8 (33.3)	NR	NR	8 (33.3)	NR	NR	NR	4 (16.7)	3 (12.5)	NR	NR

n: number, N: total number, NR: not reported, resp.: respiratory

† at 86 weeks, ‡time frame: from day 1 up to 100 weeks

Table D13. Study Quality

Trial	Comparable Groups	Non-differential Follow-up	Patient/ Investigator Blinding (Double-Blind)	Clear Definition of Outcomes	Selective outcome reporting	Measurements Valid	Intention to treat analysis	Approach to Missing Data	USPSTF Rating
Middleton 2019[56]	yes	yes	yes	yes	no	yes	ITT	MMRM	good
Heijerman 2019[8]	yes	yes	yes	yes	no	yes	mITT	MMRM	good
Keating 2018[57]	yes	yes	yes	yes	no	yes	ITT	MMRM	good
Taylor-Cousar 2017[87]	yes	yes	yes	yes	no	yes	ITT	MMRM	good
Walker 2019[92]	N/A	N/A	N/A	yes	no	yes	ITT	MMRM	poor
Wainwright 2015[30]	yes	yes	yes	yes	no	yes	mITT	MMRM	good
McNamara 2019[80]	N/A	yes	N/A	yes	no	yes	ITT	?	poor
Nick 2020[140]	N/A	N/A	yes	yes	no	yes	mITT	MMRM	good

ITT: intention to treat, mITT: modified intention to treat, MMRM: mixed model repeated measure, N/A: not applicable, USPSTF: U.S. preventive services task force

Table D14. New Evidence of Trials Captured in the 2018 Cystic Fibrosis Review

Trial & Author	Intervention & N	Follow-Up Duration	Baseline Characteristics	Efficacy Outcomes	Safety Data
EXPAND **Chuang 2018[91]**	- Tezacaftor/ Ivacaftor - Placebo N=240	Average of 4 and 8 weeks	See EXPAND abstraction table in 2018 cystic fibrosis review	Patient Reported Outcomes *(Treatment effect vs placebo (95%CI), p-value)* Treatment Burden: 2.8 (0.8, 4.8), p<0.05 Health Perception: 9.2 (6.7, 11.7), p<0.05 Physical Functioning: 7.1 (4.5, 9.7), p<0.05 Social Functioning: 3.1 (1.3, 4.9), p<0.05 Emotional Functioning: 2.6 (0.8, 4.3), n.s. Role Functioning: 3.3 (1.0, 5.6), p<0.05 Vitality: 8.3 (5.6, 10.9), p<0.05	NR
NCT01937325 **Post-hoc analysis** **Wilson 2018[60]**	- Ivacaftor - Placebo N=20	4 weeks followed by a 3-month open-label extension	Age, mean years (Range): 32.5 (18-65) Female, n (%): 8 (40.0) MOCA score, mean (SD): 27.2 (5.4)	**At 4 Weeks** MOCA score, mean change (Range): - IVA: 3.95 (−3.70, 18.18), p=0.042 - Placebo: 0.41 (-10.0, 11.54), p=0.675 TMT, mean time change (SD): No statistically significant improvement **At 3 Months**	NR

			TMT, mean time (SD): 34.0 sec (8.7)	MOCA score, mean change (Range): - IVA: 5.69 (-10.00, 21.74) p=0.006 TMT, mean time change (SD): No statistically significant improvement	
NCT01937325 **Post-hoc analysis** **Keating 2019[58]**	No treatment (Ivacaftor withdrawal) N=20	4 weeks	*After 4 weeks of treatment (before withdrawal)* $ppFEV_1$, mean % (SD): 73.0 (24.0) Sweat Chloride, mean mmol/L (SD): 103.8 mmol/L (14.0)	$ppFEV_1$, mean % change (SD): 10.1 (NR), p<0.05 Sweat Chloride, mean mmol/L change (SD): 41.1 (NR), p<0.001 VO2Max: -2.7 (NR), n.s.	NR

95%CI: 95% Confidence Interval, MOCA: Montreal Cognitive Assessment Tool, mmol/L: millimoles per liter, N: total number, NR: not reported, $ppFEV_1$: percent predicted forced expiratory volume in 1 second, SD: standard deviation, TMT: Trail Making Test, VO2Max: maximal oxygen uptake

Table D15. Observational Studies

Study	Study Design, Data Source (Year) & Duration of Follow-Up	Intervention(s) & Dosing Schedule	Inclusions & Exclusion Criteria	Baseline Characteristics	Outcomes	Harms / Complications
Ivacaftor						
Bessonova 2018[21]	Ongoing, observational, post-approval safety study U.S. Cystic Fibrosis Foundation Registry (CFFR) 2014 <u>Follow-Up</u>: 3 years following commercial availability (2011-2014); average length of IVA exposure: 2.0 years	- IVA (n=1256) - Matched comparator group (patients who had never received IVA treatment; n=6200) N=7456	**Inclusions** All patients included in US CFFR in 2014	**Female, n (%)** - IVA: 630 (50.2) - Comparator Group: 3092 (49.9) **ppFEV$_1$ Categories (%)** <u>IVA:</u> - <40%: 90 (7.2) - 40 to <70%: 290 (23.1) - ≥70%: 639 (50.9) - Missing: 237 (18.9) <u>Comparator:</u> - <40%: 435 (7.0) - 40 to <70%: 1330 (21.5) - ≥70%: 3191 (51.5) - Missing: 1244 (20.1) **PEx, n (%)** - IVA: 444 (28.5) - Comparator: 2187 (37.4) **Hospitalizations, n (%)** - IVA: 443 (38.4) - Comparator: 2294 (39.3)	**Organ Transplantation, n (AR%)** - IVA: 2 (0.2) - Comparator: 68 (1.1) - RR (95%CI), p-value: 0.15 (0.04, 0.59), p=0.0017 **PEx, n (AR%)** - IVA: 349 (27.8) - Comparator: 2684 (43.3) - RR (95%CI), p-value: 0.64 (0.58, 0.70), p<0,0001 **Hospitalization (for any reason), n (AR%)** - IVA: 346 (27.5) - Comparator: 2671 (43.1) - RR (95%CI), p-value: 0.64 (0.58, 0.70), p<0.0001 **ppFEV$_1$, mean %-change (SE)** - IVA (n=636): 1.4 (1.3) - Comparator (n=2854): -5.3 (0.4) - p-value: p<0.0001 **CFRD, n (%)** - IVA: 382 (30.4) - Comparator: 2449 (39.5)	**Death, n (AR%)** - IVA: 8 (0.6) - Comparator: 97 (1.6) - RR (95%CI), p-value: 0.41 (0.20, 0.84), p=0.0110 **Gastrointestinal Complications, n (%)** - IVA: 467 (37.2) - Comparator: 2474 (39.9) - RR (95%CI): 0.93 (0.86, 1.01) **Pulmonary Complications, n (%)** - IVA: 431 (34.3) - Comparator: 2207 (35.6) - RR (95%CI): 0.96 (0.89, 1.05) **Hepatobiliary, n (%)** - IVA: 58 (4.6) - Comparator: 484 (7.8) - RR (95% CI): 0.59 (0.45, 0.77) **Bone/Joint, n (%)** - IVA: 222 (17.7) - Comparator: 1389 (22.4) - RR (95%CI): 0.79 (0.69, 0.90)

					- RR (95%CI), p-value: 0.77 (0.70, 0.84), p<0.0001 **Depression, n (%)** - IVA: 178 (14.2) - Comparator: 1060 (17.1) - RR (95%CI), p-value: 0.83 (0.71, 0.96), p=0.0099	
	Ongoing, observational, post-approval safety study UK Cystic Fibrosis Registry 2014 <u>Follow-Up</u>: 2 years following commercial availability (2012-2014); average length of IVA exposure: 1.3 years	- IVA (n=411) - Matched comparator group (patients who had never received IVA treatment; n=2069) N=2,480	**Inclusions** All patients included in UK CFR in 2014	**Female, n (%)** - IVA: 195 (47.4) - Comparator Group: 986 (47.1) **ppFEV$_1$ Categories, n (%)** <u>IVA:</u> - <40%: 46 (12.0) - 40 to <70%: 100 (26.2) - ≥70%: 193 (50.5) - Missing: 43 (11.3) <u>Comparator:</u> - <40%: 204 (10.2) - 40 to <70%: 603 (30.3) - ≥70%: 981 (49.2) - Missing: 205 (10.3) **PEx, n (%)** - IVA: 207 (54.2) - Comparator: 1061 (53.2) **Hospitalizations, n (%)** - IVA: 173 (45.3)	**Organ Transplantation, n (AR%)** - IVA: 2 (0.5) - Comparator: 18 (0.9) - RR (95%CI), p-value: 0.56 (NR), p=0.5586 **PEx, n (AR%)** - IVA: 140 (34.1) - Comparator: 1157 (55.9) - RR (95%CI), p-value: 0.61 (0.53, 0.70), p<0.001 **Hospitalization (for PEx only), n (AR%)** - IVA: 107 (26.0) - Comparator: 937 (45.3) - RR (95%CI), p-value: 0.57 (0.48, 0.68), p<0.0001 **ppFEV$_1$, mean %-change (SE)** - IVA (n=250): 6.6 (1.6) - Comparator (n=1211): -1.5 (0.7) - p-value: p<0.001 **CFRD, n (%)**	**Death, n (AR%)** - IVA: 3 (0.7) - Comparator: 29 (1.4) - RR (95%CI), p-value: 0.52 (0.16, 1.70), p=0.3882 **Gastrointestinal Complications, n (%)** - IVA: 83 (20.2) - Comparator: 484 (23.4) - RR (95%CI): 0.86 (0.70, 1.06) **Pulmonary Complications, n (%)** - IVA: 256 (62.3) - Comparator: 1363 (65.9) - RR (95%CI): 0.95 (0.88, 1.03) **Hepatobiliary, n (%)** - IVA: 92 (22.4) - Comparator: 579 (28.0) - RR (95% CI): 0.80 (0.66, 0.97) **Bone/Joint, n (%)** - IVA: 75 (18.2)

				- Comparator: 862 (43.3)	- IVA: 85 (20.7) - Comparator: 602 (29.1) - RR (95%CI), p-value: 0.71 (0.58, 0.87), p<0.0007 **Depression, n (%)** - IVA: 18 (4.4) - Comparator: 122 (5.9) - RR (95%CI), p-value: 0.74 (0.46, 1.20), p=0.26	- Comparator: 573 (27.7) - RR (95%CI): 0.66 (0.53, 0.82)
Volkova 2019[66]	Observational, post-approval safety study US Cystic Fibrosis Foundation Registry (CFFR) 2016 Follow-Up: 5 years (2012-2016)	- IVA (n=635) - Comparator (patients without IVA use during first year of market availability; n=1874) N=2,509	**Inclusions** All patients with a record of IVA use during first calendar year of market availability who were still on treatment in 2016, and who had not received a lung transplant *No inclusion/ exclusion criteria based on patient age or genotype were applied*	**Female, n (%)** - IVA: 328 (51.7) - Comparator: 915 (48.8) **BMI, mean kg/m^2 (95%CI)** - IVA: 20.3 (20.0, 20.6) - Comparator: 20.0 (19.8, 20.2) **ppFEV$_1$, mean % (SD)** - IVA: 79.0 (25.3) - Comparator: 81.7 (23.7) **ppFEV$_1$ Categories, n (%)** IVA: - <40%: 38 (6.0) - 40 to <70%: 146 (23.0) - ≥70%: 393 (61.9) - Missing: 58 (9.1) Comparator:	**ppFEV$_1$, mean %-change (95%CI)** - IVA: -0.7 (-1.6, 0.2) - Comparator: -8.3 (-9.0, -7.7) - RR (95%CI): NR **Hospitalizations, n (%)** - IVA: 167 (26.3) - Comparator: 830 (44.3) - RR (95%CI): 0.59 (0.52, 0.68) **BMI, mean kg/m^2 change (95%CI)** - IVA: 2.4 (2.1, 2.6) - Comparator: 1.6 (1.5, 1.7) - RR (95%CI): NR **PEx, n (%)** - IVA: 163 (25.7) - Comparator: 825 (44.0) - RR (95%CI): 0.58 (0.51, 0.67) **CFRD, n (%)** - IVA: 227 (35.7) - Comparator: 766 (40.9)	See Bessonova 2018

				- <40%: 66 (3.5) - 40 to <70%: 351 (18.7) - ≥70%: 1184 (63.2) - Missing: 273 (14.6) **PEx, n (%)** - IVA: 230 (37.5) - Comparator: 592 (33.1) **Hospitalizations, n (%)** - IVA: 232 (37.8) - Comparator: 644 (36.0) **P. Aeruginosa, n (%)** - IVA: 359 (56.5) - Comparator: 937 (50.0)	- RR (95%CI): 0.87 (0.77, 0.98) **P. Aeruginosa, n (%)** - IVA: 286 (45.1) - Comparator: 1044 (55.7) - RR (95%CI): 0.81 (0.73, 0.89)	
	Observational, post-approval safety study UK CFR 2016 <u>Follow-Up</u>: 4 years (2013-2016)	- IVA (n=247) - Comparator (n=1230) N=1,477		**Female, n (%)** - IVA: 113 (45.7) - Comparator: 588 (47.8) **BMI, mean (95%CI)** - IVA: 20.6 (20.1, 21.1) - Comparator: 20.5 (20.3, 20.7) **ppFEV$_1$, mean (SD)** - IVA: 73.0 (23.6) - Comparator: 73.4 (22.4)	**ppFEV$_1$, mean %-change (95%CI)** - IVA: 4.9 (3.3,6.6) - Comparator: -4.3 (-5.1, -3.4) - RR (95%CI): NR **Hospitalizations, n (%)** - IVA: 65 (26.3) - Comparator: 549 (44.6) - RR (95%CI): 0.59 (0.47, 0.73) **BMI, mean kg/m^2 change (95%CI)** - IVA: 1.9 (1.6, 2.1) - Comparator: 0.9 (0.8, 1.0) - RR (95%CI): NR	See Bessonova 2018

				ppFEV$_1$ Categories, n (%) IVA: - <40%: 26 (10.5) - 40 to <70%: 69 (27.9) - ≥70%: 132 (53.4) - Missing: 20 (8.1) Comparator: - <40%: 93 (7.6) - 40 to <70%: 388 (31.5) - ≥70%: 646 (52.5) - Missing: 103 (8.4) **PEx, n (%)** - IVA: 133 (53.8) - Comparator: 556 (45.2) **Hospitalizations, n (%)** - IVA: 116 (47.0) - Comparator: 505 (41.1) **P. Aeruginosa, n (%)** - IVA: 156 (63.2) - Comparator: 704 (57.2)	**PEx, n (%)** - IVA: 81 (32.8) - Comparator: 707 (57.5) - RR (95%CI): 0.57 (0.47, 0.67) **CFRD, n (%)** - IVA: 46 (18.6) - Comparator: 358 (29.1) - RR (95%CI): 0.64 (0.49, 0.84) **P. Aeruginosa, n (%)** - IVA: 96 (38.9) - Comparator: 688 (55.9) - RR (95%CI): 0.70 (0.59, 0.82)	
Feng 2018[62]	Retrospective cohort, single center study MarketScan Research Database (Treatment Pathways 4.0	IVA (N=143)	**Inclusions** - ICD-9-CM or ICD-10-CM diagnosis for CF on ≥ one inpatient claims or on ≥two	**Age, n (%)** - Children (6-17 years): 53 (37.0) - Adults (18-65 years): 90 (63.0)	**All-cause Hospitalizations, n (rate/PY)** - Overall: 37 (0.26) - Children: 13 (0.25) - Adults: 24 (0.27) **CF-related Hospitalizations, n (rate/PY)**	NR

	including Commercial and Medicare Supplemental databases) Follow-Up: 12 months prior to IVA treatment (baseline) compared to 12 months post-IVA treatment (within group comparison		outpatient claims at least 30 days apart - At least 1 prescription claim for monotherapy, between ages 6-65 - 12 months of continuous enrollment before and after first filled prescription **Exclusions** NR	**All-cause Hospitalizations, n (rate/PY)** - Overall: 82 (0.57) - Children: 32 (0.60) - Adults: 50 (0.56) **CF-related Hospitalizations, rate/PY** - Overall: 42 (0.29) - Children: 17 (0.32) - Adults: 25 (0.28) **Effect of Medication Adherence on All-cause Hospitalizations, n (rate/PY)** - 3 to 9 fills: 20 (0.38) - 10 to 12 fills: 28 (0.31)	- Overall: 8 (0.006) - Children: 3 (0.006) - Adults: 5 (0.006) **All-cause Hospitalizations based on Medication Adherence, n (rate/PY)** - 3 to 9 fills: 11 (0.21) - 10 to 12 fills: 9 (0.10)	
BRIO Study **Hubert 2018[63]**	Prospective, ongoing, multi-centre observational study 33 French Cystic Fibrosis Centers Follow-Up: Interim analysis of health care resource utilization for 12 months pre- and 12	IVA (N=107)	**Inclusions** - Patients with CF - ≥ 6 years old - ivacaftor-responsive mutations **Exclusions** NR	**Age, mean years (SD)** 21.1 (14.3) **Female, n (%)** 47 (44.0) **Hospitalization days/PY** 5.3 **Days of Antibiotic use/PY** 20.9	**Change in All-Cause Hospitalizations/PY, RR (95%CI)** 0.40 (0.26, 0.61) **Hospitalization days/PY (RR; 95%CI)** 2.5 (0.46; 0.22, 0.95) **Number of antibiotics/PY for PEx Treatment, RR (95%CI)** 0.47 (0.32, 0.68)	NR

	months post-ivacaftor initiation				**Days of Antibiotic use/PY (RR; 95%CI)** 11.4 (0.54; 0.40, 0.72)	
GOAL Study **McCormick 2019[65]** **Extension of GOAL Study** **Guimbellot 2018[55]**	Multicenter, prospective, longitudinal cohort-study Long-term, Observational Extension to the GOAL Study Cystic Fibrosis Foundation Registry <u>Follow-Up</u>: - GOAL: 6 months - Extension: 5 years	IVA - GOAL: N= 153 - Extension: N=96	**Inclusions** - ≥ 6 years of age - ≥ 1 copy of G551D mutation	**<u>GOAL Study</u>** **SNOT-20, subset mean score (SD)** - Rhinology: 1.04 (0.99) - Ear/Face: 0.31 (0.56) - Sleep: 1.13 (1.34) - Psychological: 0.80 (0.92) **<u>Extension</u>** **Age, mean years (SD)** - Overall: 19.8 (NR) - < 18 years (n=52): 11.6 (NR) - ≥ 18 years (n=44): 29.5 (NR) **Female, n (%)** 43 (44.8) **ppFEV$_1$, mean % (SD)** - Mean ppFEV$_1$: 82.0 - < 18 years: 94.7 - ≥ 18 years: 67.0 **BMI, mean kg/m^2** - < 18 years: 17.9 - ≥ 18 years: 23.4	**<u>GOAL Study (at 6 months)</u>** **SNOT-20, subset mean score change, p-value** - Rhinology: -0.25, p<0.01 - Ear/Face: 0.03, p=0.608 - Sleep: -0.18, p=0.074 - Psychological: -0.26, p<0.01 **ppFEV$_1$, mean % change (95%CI)** 7.9 (5.8, 10.1), p<0.0001 **BMI, mean kg/m^2 change (95%CI)** NR **CFQR-R score, mean change (95%CI):** 8.8 (4.8, 12.8), p<0.0001 **Sweat Chloride, mean mEq/L change (95%CI)** NR **<u>Extension (at 5.5 years)</u>** **ppFEV$_1$, mean % change (95%CI)** - Overall: 0.8 (-2.0, 3.6), n.s. - < 18 years: -2.0 (-5.9, 2.0), p=0.3228 - ≥ 18 years: 4.3 (0.6, 8.1), p=0.0237	NR

					BMI, mean kg/m^2 change (95%CI) - Overall: 2.5 (2.0, 3.1), p<0.0001 - < 18 years: 3.6 (2.9, 4.3), p<0.0001 - ≥ 18 years: 1.2 (0.4, 2.0), p=0.003 **CFQR-R score, mean change (95%CI):** 6.7 (2.5, 10.9), p=0.002 **Sweat Chloride, mean mEq/L change (95%CI)** - Overall: -49.5 (-55.0, -44.1), p<0.0001 - < 18 years: -47.3 (-54.9, -39.8), p<0.0001 - ≥ 18 years: -52.4 (-60.6, -44.3), p<0.0001	
Bell 2019[61]	Cross-sectional observational study 5 countries (France, UK< Germany, Australia, and Ireland) Follow-up: mean duration of IVA exposure was 21.8 months	- IVA (n=72) - Standard of care (n=137)	**Inclusions** IVA - Patients with a CF diagnosis with CF with ≥ 1 G551D mutation - Received IVA for >3 month SOC	**Age, mean years (SD)** - IVA: 23.9 (13.9) - SOC: 24.6 (11.1) **Female, n (%)** - IVA: 41 (60.3) - SOC: 44 (35.2) **ppFEV$_1$, mean % (SD)** - IVA: 79.8 (25.6) - SOC: 70.7 (28.8) **BMI, mean kg/m^2 (SD)**	**CFQ-R Domains** Body Image, LSM (SE) - IVA: 74.9 (2.9) - SOC: 67.8 (2.2) - n.s. Digestive Symptoms, LSM (SE) - IVA: 85.5 (2.2) - SOC: 78.0 (1.7) - p < 0.05 Eating Problems, LSM (SE) - IVA: 91.1 (2.1) - SOC: 84.2 (1.6) - p < 0.05	

			- homozygous for F508del mutation **Exclusions** - Participation in a clinical trial - Experiencing pulmonary exacerbation at clinic visit	- ≥ 19 years old: 22.2 (3.2) - < 19 years old, z-score: 0.001 (0.87) <u>Weight</u> (6-11 and ≥14-year versions only) G551D/IVA: 80.7 F508del/SOC: 64.2 P < 0.01	<u>Emotional Functioning, LSM (SE)</u> - IVA: 78.8 (2.8) - SOC: 75.0 (1.9) - n.s. <u>Health perceptions, LSM (SE)*</u> - IVA: 67.6 (2.6) - SOC: 58.6 (1.8) - p < 0.01 <u>Physical Functioning, LSM (SE)</u> - IVA: 74.6 (2.6) - SOC: 66.6 2.0) - p < 0.05 <u>Respiratory Symptoms, LSM (SE)</u> - IVA: 75.4 (2.4) - SOC: 62.5 (1.8) - p < 0.001 <u>Role Functioning, LSM (SE)†</u> - IVA: 77.0 (2.9) - SOC: 73.5 (2.3) - n.s. <u>School Functioning, LSM (SE)¥</u> - IVA: 83.1 (8.7) - SOC: 82.7 (9.7) - n.s. <u>Social Functioning, LSM (SE)‡</u> - IVA: 70.2 (2.1) - SOC: 68.6 (1.5) - n.s. <u>Treatment Burden, LSM (SE)</u> - IVA: 65.3 (2.7) - SOC: 54.8 (1.6) - p < 0.01	

					Vitality, LSM (SE)* - G551D/IVA: 63.5 (3.1) - F508del/SOC: 55.9 (1.9) - p < 0.05 **EQ-5D-5L** Index Score (0-1), LSM (SE) - IVA (n=72): 0.90 (0.02) - SOC (n=137): 0.81 (0.02) - p < 0.01 VAS Score (0-100), n; LSM (SE) - IVA (n=72): 75.7 (1.8) - SOC (n=135): 70.0 (1.4) - p = 0.0136 **WPAI** Productivity loss, LSM (SE) - IVA (n=27) 24.62 (6.69) - SOC (n=32): 34.57 (6.73) - p = 0.3242 Activity Impairment, LSM (SE) - IVA (n=70): 21.63 (2.95) - SOC (n=135): 28.30 (2.19) - p = 0.08	
Kirwan 2017[64]	Observational Cohort Study Irish Cystic Fibrosis Registry Follow-up: 30 months pre and post ivacaftor treatment	IVA (N=114)	**Inclusions** CF patients treated with IVA **Exclusions** NR	**Age groups, n (%)** - <18 years: 54 (47) - ≥18 years: 60 (53) **Female, n (%)** 51 (45)	**ppFEV$_1$%** 7.7% increase (p < 0.001) **PEx, n** - Pre-IVA: 820 - Post-IVA: 523 **Duration of PEx, days**	NR

					43 fewer days per patient post commencement of treatment (p < 0.001) **Hospitalization (for PEx), n** Pre-IVA: 158 Post-IVA: 109 **Total days of Hospitalization, days** - Pre-IVA: 16.8 - Post-IVA: 13.0 - p=0.0301 **Mean BMI and BMI z score** Increased over treatment period (p < 0.001)	
Lumacaftor/Ivacaftor						
Burgel 2020[83]	Multicenter Observational Study French Cystic Fibrosis Reference Network <u>Follow-Up:</u> 52 weeks	LUM/IVA (N=845) - Adults ≥18 years (n=553) - Adolescents 12-17 years (n=292) <u>Dosing</u>: - Twice daily LUM 400mg/ IVA 250mg (n=744) - reduced doses (not	**Inclusions** - CF patients ≥ 12 years - homozygous for the F508del CFTR mutation - started LUM/IVA in 2016 **Exclusions** - Patients who received a lung transplant	**Age, median years [IQR]** 22.0 [16, 30] **Female, n (%)** 377 (44.6) **ppFEV$_1$, median % [IQR]** 65 [47, 80] **ppFEV$_1$ < 40%, n (%)** 124 (14.8) **BMI, median kg/m^2 [IQR]** 19 [17, 21]	*LUM/IVA (N=821)* - *Contin. Treatment, n=631* - *Intermit. Treatment, n=45* - *Discount. Treatment, n=145* **ppFEV$_1$, absolute % change (SD)** - Overall: 2.7 (8.9) - Contin. treatment: 3.7 (8.6) - Intermit. treatment: 2.4 (8.5) - Discont. treatment: -1.4 (9.0) - Adolescents with cont. treatment (n=258): 4.76 (8.17) - Adults with cont. treatment (n=373): 2.91 (8.85) **Weight gain, mean kg**	**TEAEs, n (%)** 494 (59.4) **AEs leading to Discont., n (%)** 154 (18.2) **Death, n (%)** 2 (1.3) **Respiratory AEs, n (%)** 316 (38.0) **Digestive AEs, n (%)** 181 (21.8) **Menstrual Abnormality, n (%)**

		specified; n=101)	- Patients ineligible for LUM/IVA		- Overall: 2.1 **BMI increase, mean kg/m²** - Overall: 0.5	53 (6.4) **Fatigue, n (%)** 37 (4.4) **Headache, n (%)** 19 (3.3) *AEs were more prevalent in patients with diabetes (65.4% v. 56.8%; p=0.024)*
Wark 2019[85]	Retrospective cohort study 7 Australian CF centers Follow-Up: 52 weeks	- LUM/IVA (n=72) - Untreated Control Group (ineligible for LUM/IVA treatment; n=30)	**Inclusions** - CF patients > 12 years - homozygous for f508del CFTR mutation - $ppFEV_1$ < 40% **Exclusions** NR	NR	**Mean rate of change in $ppFEV_1$, slope (95% CI)** - LUM/ IVA: 0.34 (-0.29, 1.03) - Control: -0.34 (-0.72, -0.04) **Reduction in PEx (95% CI)** LUM/IVA vs. Control: 0.49 (0.3, 0.7), p=0.001 No differences in $ppFEV_1$ at weeks 4, 12, 24, and 52 when 2 groups were compared	Harms not reported but mention of high rate of side effects **Treatment Discont., n/N (%)** 44/102 (43%)
Kirwan 2019[84]	Observational Cohort Study Irish Cystic Fibrosis Registry Follow-up: 12 months pre and post lumacaftor/ivacaftor treatment	- LUM/IVA (N=308)	**Inclusions** - CF Patients aged 12+ **Exclusions** NR	**Male, n (%)** 179 (58) **≥ 18 years old, n (%)** 203 (66)	**Mean $ppFEV_1$ increase** - Adults: 1.10% (95%CI: 0.4, 1.8) - Children: 1.26% (95% CI: -0.2, 2.7) **Mean BMI increase** - Adults: 0.43 (95%CI: 0.30, 0.56) **Mean BMI z-score increase** - Children: 0.16 (95%CI: 0.08, 0.23)	NR

					Reduction in number of IV antibiotics for PEx, % (95% CI) - Adults: 47% (95%CI: -55, -37) - Children: 40% (95% CI: -53, -23) **Reduction in total number of days on IV antibiotics** - Adults: 51% (95% CI: -53, -48) - Children: 43% (95%CI: -46,-39)	
Multiple Treatment Regimens						

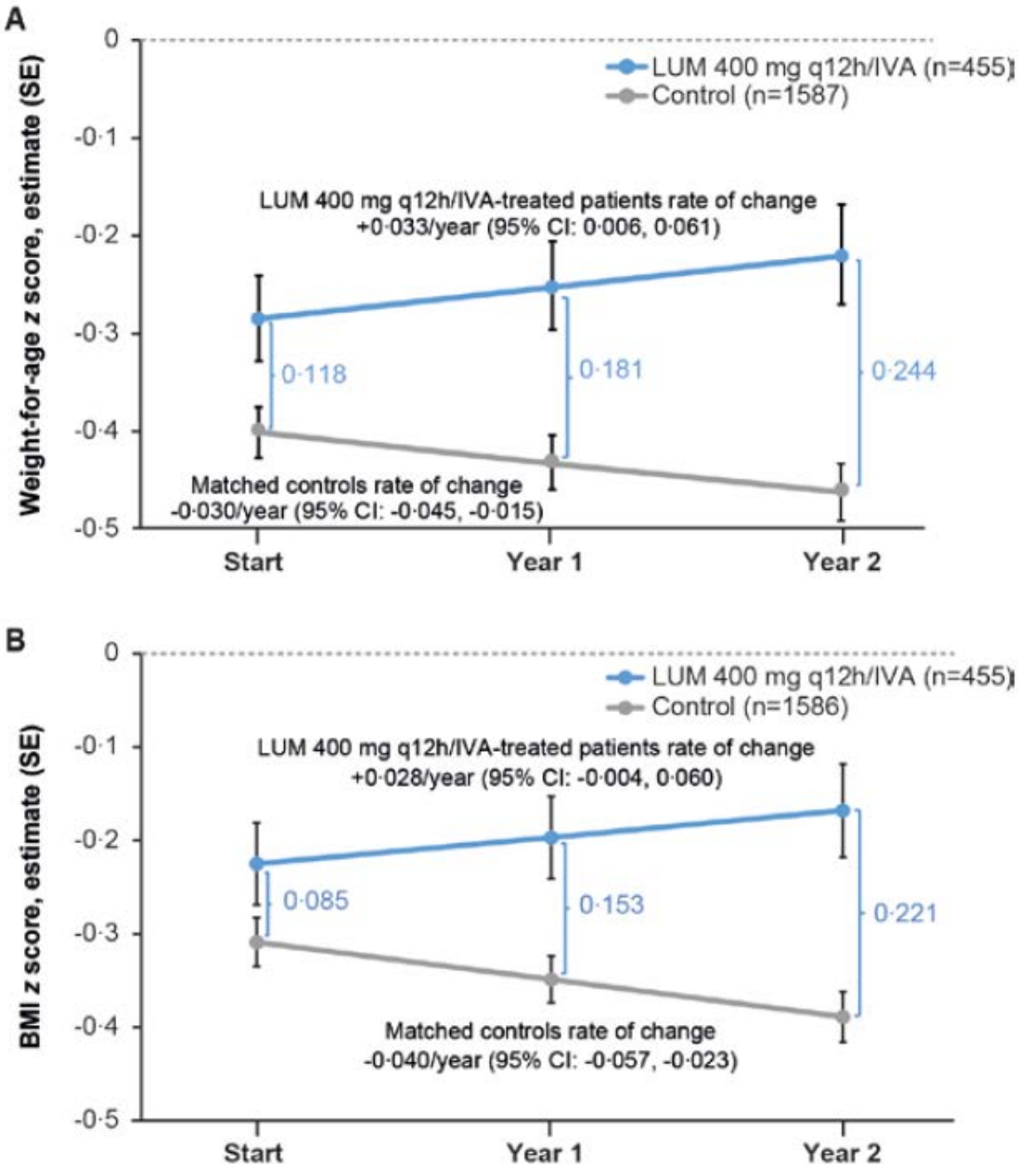
Mayer-Hamblett 2019[74]	Population-based Epidemiologic Study (CHEC-SC) CF Foundation Patient Registry (CFFPR) <u>Follow-up:</u> - 12 months	- IVA (n=319) - LUM/IVA (n=661) - TEZ/IVA (n=285)	**Inclusions** CF patients who have been prescribed commercially approved CFTR modulator for over 3 months **Exclusions** NR	**Age, n (%)** <u>IVA</u> - 2-5 years: 32 (10) - 6-11 years: 62 (19) - 12-17 years: 61 (19) - 18-25 years: 57 (18) - ≥26 years: 106 (33) <u>LUM/IVA</u> - 2-5 years: 0 (0) - 6-11 years: 171 (26) - 12-17 years: 208 (32) - 18-25 years: 156 (24) - ≥26 years: 125 (19) <u>TEZ/IVA</u> - 2-5 years: 0 (0) - 6-11 years: 0 (0) - 12-17 years: 103 (36) - 18-25 years: 80 (28) - ≥26 years: 102 (36) **Genotype, n(%)** <u>IVA</u> - Gating: 167 (52) - R117H: 54 (17) - Splice: 52 (16) - Missense: (42 (13) - F508del Homozygous: 0 (0) - Other: 4 (1) <u>LUM/IVA</u> - Gating: 1 (0.2) - R117H: 0 (0)	**Sweat Chloride, mean change (SD)** <u>IVA</u> - G511D: -51.4 (26.1) - R117H: -24.1 (19.9) <u>F508del Homozygous</u> - LUM/IVA: -20.5 (19.3) - TEZ/IVA: -12.6 (18.9)	NR

				- Splice: 0 (0) - Missense: 0 (0) - F508del Homozygous: 660 (99) - Other: 1 (0.2) <u>TEZ/IVA</u> - Gating: 0 (0) - R117H: 0 (0) - Splice: 20 (7) - Missense: 9 (3) - F508del Homozygous: 253 (88) - Other: 3 (1)		

95%CI: 95% Confidence Interval, AE: adverse event, AR: annualized rate, BMI: body mass index, CF: cystic fibrosis, CFRD: cystic fibrosis related diabetes, EQ-5D-5L: EuroQol 5-dimensions 5-level questionnaire, IQR: interquartile range, IVA: ivacaftor, kg: kilogram, kg/m^2: milogram per meter squared, LSM: least squares mean, LUM/IVA: lumacaftor/ivacaftor, n: number, N: total number, NR: not reported, n.s.: not significant, PEx: pumonary exacerbation, $ppFEV_1$: percent predicted forced expiratory volume in 1 second, PY: patient year, RR: risk ratio, SD: standard deviation, SE: standard error, SNOT-20: 20-item Sino-Nasal Outcome Test, TEAE: treatment-emergent adverse event, TEZ/IVA: tezacaftor/ivacaftor, SOC: Standard of Care, VAS: Visual analog Scale, WPAI: Work Productivity Activity and Impairment Questionnaire

* 6-11 and ≥14-year versions only, † ≥14-year versions only, ‡ 12-13-year and ≥14-year version only, ¥ 6-11 years version only

Figure D1. Effect of 400 mg Lumacaftor Twice Daily with Ivacaftor Compared to Matched Controls on Weight-for-Age and BMI Z-score

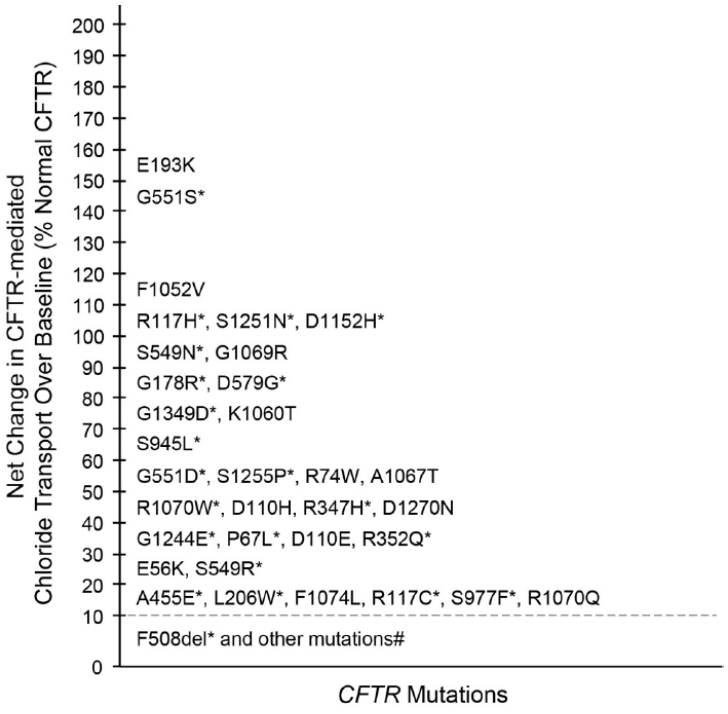


Genetic Specific Data on CFTR Modulators

Ivacaftor

The effect of ivacaftor differs by mutation.[142] Below are the in vitro response thresholds and stratified efficacy data from clinical trials, adapted from the FDA label (prescribing information).[142]

Figure D2. Net Change Over Baseline (% of untreated normal) in CFTR-Mediated Chloride Transport Following Addition of Ivacaftor from FDA Label[142]



*Clinical data exist for these mutations

Figure D3. Efficacy Outcomes of Ivacaftor by Genetic Mutation from FDA Label[142]

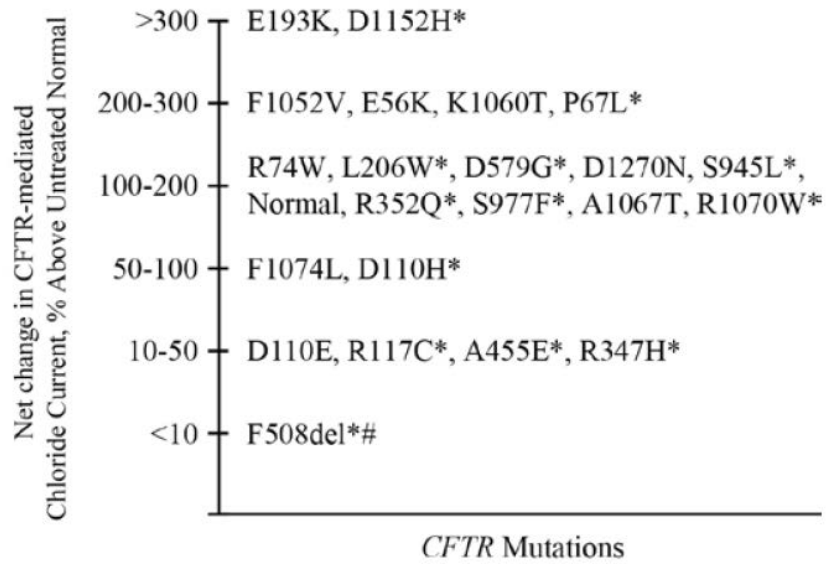
Mutation (n)	Absolute Change in percent predicted FEV_1*†	Absolute Change in CFQ-R Respiratory Domain Score (Points)*§	Absolute Change in Sweat Chloride (mmol/L)*§
3272-26A→G (23)	3.5 (-9.1, 16.0)	8.0 (-11.1, 27.8)	-2.3 (-25.0, 11.8)
3849+10kBc→T (40)	5.1 (-6.8, 16.2)	7.5 (-30.6, 55.6)	-4.6 (-80.5, 23.0)
711+3A→G (2)	9.2 (8.9, 9.6)	-8.3 (-13.9, -2.8)	-9.9 (-13.5, -6.3)
E831X (1)	7.1 (7.1, 7.1)	0.0 (0.0, 0.0)	-7.8 (-7.8, -7.8)
Missense mutations (n=62 for IVA and n=63 for PBO) Results shown as difference in mean (95% CI) change from study baseline for KALYDECO vs. placebo-treated patients:			
	3.6 (1.9, 5.2)	11.5 (7.5, 15.4)	-7.8 (-11.2, -4.5)
By individual missense mutation (n). Results shown as mean (minimum, maximum) for change from study baseline for KALYDECO-treated patients			
D579G (2)	13.3 (12.4, 14.1)	15.3 (-2.8, 33.3)	-30.8 (-36.0, -25.5)
D1152H (15)	2.4 (-5.0, 10.2)	13.7 (-16.7, 50.0)	-4.8 (-22.0, 3.0)
A455E (14)	3.7 (-6.6, 19.7)	6.8 (-13.9, 33.3)	7.5 (-16.8, 16.0)
L206W (2)	4.2 (2.5, 5.9)	12.5 (-5.6, 30.6)	3.9 (-8.3, 16.0)
P67L (12)	4.3 (-2.5, 25.7)	10.8 (-12.5, 36.1)	-10.5 (-34.8, 9.8)
R1070W (1)	2.9 (2.9, 2.9)	44.4 (44.4, 44.4)	0.3 (0.3, 0.3)
R117C (1)	3.5 (3.5, 3.5)	22.2 (22.2, 22.2)	-36.0 (-36.0, -36.0)
R347H (3)	2.5 (-0.6, 6.9)	6.5 (5.6, 8.3)	-19.2 (-25.8, -7.0)
R352Q (2)	4.4 (3.5, 5.3)	9.7 (8.3, 11.1)	-21.9 (-45.5, 1.8)
S945L (9)	8.8 (-0.2, 20.5)	10.6 (-25.0, 27.8)	-30.8 (-50.8, -17.3)
S977F (1)	4.3 (4.3, 4.3)	-2.8 (-2.8, -2.8)	-19.5 (-19.5, -19.5)

*Average of Week 4 and 8 values
†Absolute change in $ppFEV_1$ by individual mutations is an ad hoc analysis.
§Absolute change in CFQ-R respiratory domain score and absolute change in sweat chloride by mutation subgroups and by individual mutations are ad hoc analyses.

Symdeko[143]

The effect of Symdeko differs by mutation.[142] Below are the in vitro response thresholds and stratified efficacy data from clinical trials, adapted from the FDA label (prescribing information).[142]

Figure D4. Net Change Over Baseline (% of Untreated Normal) in CFTR-Mediated Chloride Transport Following Addition of Symdeko from FDA Label[143]



*Clinical data exist for these mutations; #*F508del* represents data from one allele

Figure D5. Efficacy Outcomes of Symdeko by Genetic Mutation from FDA Label[143]

Mutation (n)	Absolute Change in percent predicted FEV_1*†	Absolute Change in CFQ-R Respiratory Domain Score (Points)*§	Absolute Change in Sweat Chloride (mmol/L)*§
Splice mutations (n= 93 for TEZ/IVA, n=97 for PBO) Results shown as difference in mean (95% CI) change from study baseline for SYMDEKO vs. placebo-treated patients:			
	7.4 (6.0, 8.7)	9.5 (6.3, 12.7)	-5.4 (-8.0, -2.7)
By individual splice mutation (n). Results shown as mean (minimum, maximum) for change from study baseline for SYMDEKO-treated patients			
2789+5G→A (25)	8.6 (-1.5, 23.4)	12.0 (-8.3, 38.9)	-3.2 (-16.5, 9.0)
3272-26A→G (23)	5.7 (-2.1, 25.9)	5.7 (-22.2, 44.4)	-3.8 (-22.3, 16.5)
3849+10kBc→T (43)	5.8 (-7.2, 22.3)	8.2 (-25.0, 47.2)	-5.6 (-27.0, 8.5)
711+3A→G (2)	4.3 (2.0, 6.7)	-4.2 (-5.6, -2.8)	-15.4 (-21.0, -9.8)
E831X± (0)	NA	NA	NA
Missense mutations (n=66 for TEZ/IVA, n=63 for PBO) Results shown as difference in mean (95% CI) change from study baseline for SYMDEKO vs. placebo-treated patients:			
	5.9 (4.2, 7.5)	13.4 (9.6, 17.3)	-16.3 (-19.7, -12.9)
By individual missense mutation (n). Results shown as mean (minimum, maximum) for change from study baseline for SYMDEKO-treated patients			
D579G (2)	8.1 (-0.2, 16.4)	11.1 (5.6, 16.7)	-23.1 (-24.8, -21.5)
D110H (1)	-1.0 (-1.0, -1.0)	-11.1 (-11.1, -11.1)	-22.5 (-22.5, -22.5)
D1152H (21)	3.8 (-2.5, 12.5)	15.2 (-8.3, 55.6)	-4.1 (-15.0, 11.5)
A455E (11)	8.5 (2.6, 16.1)	11.6 (-11.1, 44.4)	-0.3 (-8.8, 14.0)

Mutation (n)	Absolute Change in percent predicted FEV_1*†	Absolute Change in CFQ-R Respiratory Domain Score (Points)*§	Absolute Change in Sweat Chloride (mmol/L)*§
L206W (4)	3.0 (-4.5, 10.2)	12.5 (-2.8, 38.9)	-36.1 (-44.5, -27.5)
P67L (11)	9.4 (0.0, 31.9)	11.7 (-12.5, 72.2)	-29.3 (-50.0, 0.8)
R1070W (2)	6.1 (2.0, 10.1)	29.2 (16.7, 41.7)	-13.8 (-26.8, -0.8)
R117C (1)	2.9 (2.9, 2.9)	16.7 (16.7, 16.7)	-38.8 (-38.8, -38.8)
R347H (2)	-0.5 (-2.8, 1.7)	5.6 (-5.6, 16.7)	-13.8 (-19.0, -8.5)
R352Q (2)	4.9 (2.6, 7.1)	8.3 (8.3, 8.3)	-43.3 (-49.8, -36.8)
S945L (7)	9.6 (0.7, 19.5)	11.3 (-4.2, 25.0)	-29.0 (-42.5, -8.0)
S977F (2)	10.1 (5.5, 14.7)	-1.4 (-8.3, 5.6)	-13.9 (-22.3, -5.5)

*Average of Week 4 and 8 values
†Absolute change in $ppFEV_1$ by individual mutations is an ad hoc analysis.
§Absolute change in CFQ-R Respiratory Domain Score and absolute change in sweat chloride by mutation subgroups and by individual mutations are ad hoc analyses.
(n=) patient numbers analysed
±Patients enrolled did not receive tezacaftor/ivacaftor treatment.

League Tables from Network Meta-Analysis (NMA) in Population Homozygous for the F508del Mutation

Table D16. NMA Results for Absolute Change from Baseline in $ppFEV_1$, Mean (95% Confidence Interval)

Trikafta			
10.0 (7.4, 12.6)	Symdeko		
11.2 (8.3, 14.1)	1.2 (-0.1, 2.5)	Orkambi	
14.0 (11.3, 16.7)	**4.0 (3.2, 4.8)**	**2.8 (1.8, 3.8)**	Placebo

Each box represents the estimated mean change and 95% confidence interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% confidence interval does not contain zero.

Table D17. NMA Results for Absolute Change from Baseline in CFQ-R Respiratory Domain Score, Mean mmol/liter (95% Confidence Interval)

Trikafta			
17.4 (11.8, 23.0)	Symdeko		
20.3 (14.0, 26.6)	2.9 (0.0, 5.8)	Orkambi	
22.5 (16.6, 28.4)	**5.1 (3.2, 7.0)**	2.2 (0.0, 4.4)	Placebo

Each box represents the estimated mean change and 95% confidence interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% confidence interval does not contain zero.

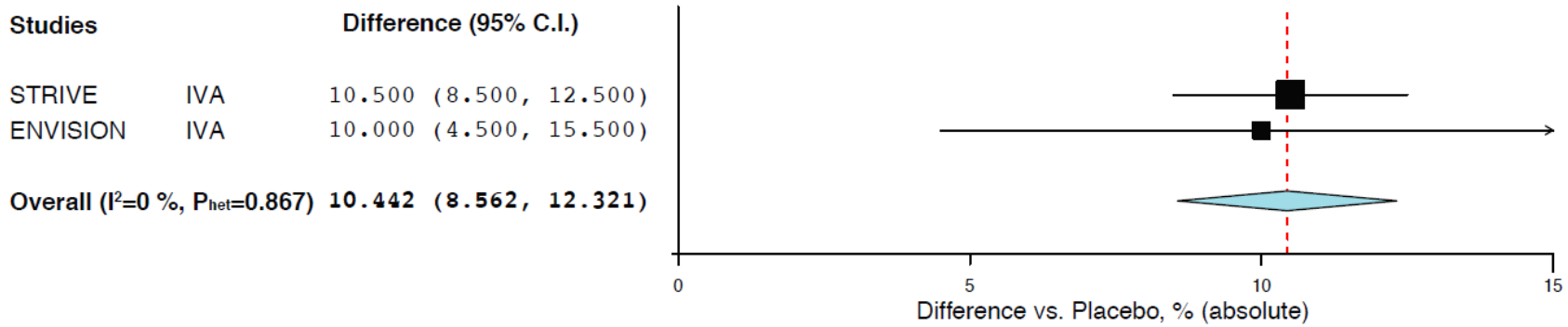
Table D18. NMA Results for Absolute Change from Baseline in Sweat Chloride, Mean (95% Confidence Interval)

Trikafta		
-45.1 (-50.1, -40.1)	Symdeko	
-55.2 (-60.4, -50.0)	**-10.1 (-11.4, -8.8)**	Placebo

Each box represents the estimated mean change and 95% confidence interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% confidence interval does not contain zero.

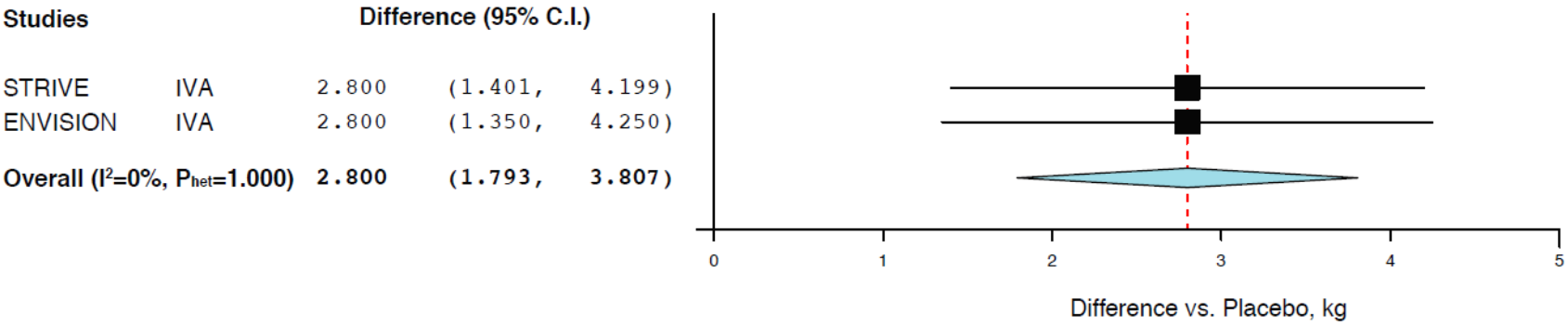
Forest Plots from Meta-Analysis

Figure D6. A Meta-Analysis of ppFEV$_1$ for Ivacaftor Versus Placebo in Patients with Gating and Residual Function Mutations (Difference in Change in Absolute Percentage Points Between Study Arms)



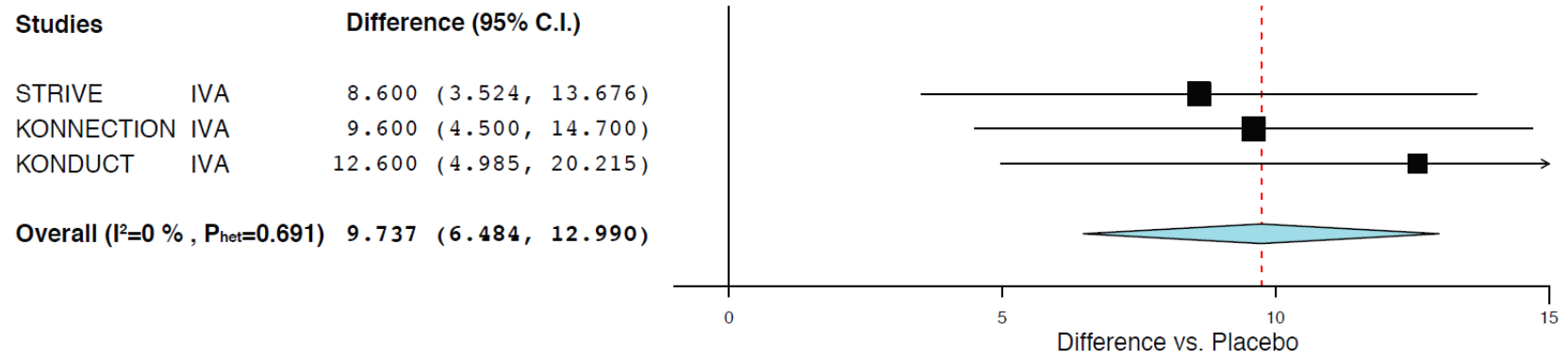
C.I: confidence interval, IVA: ivacaftor, Phet: chi-square P value for heterogeneity

Figure D7. Meta-Analysis of Weight for Ivacaftor Versus Placebo in Patients with Gating and Residual Function Mutations (Difference in Change in Weight, in kg, Between Study Arms)



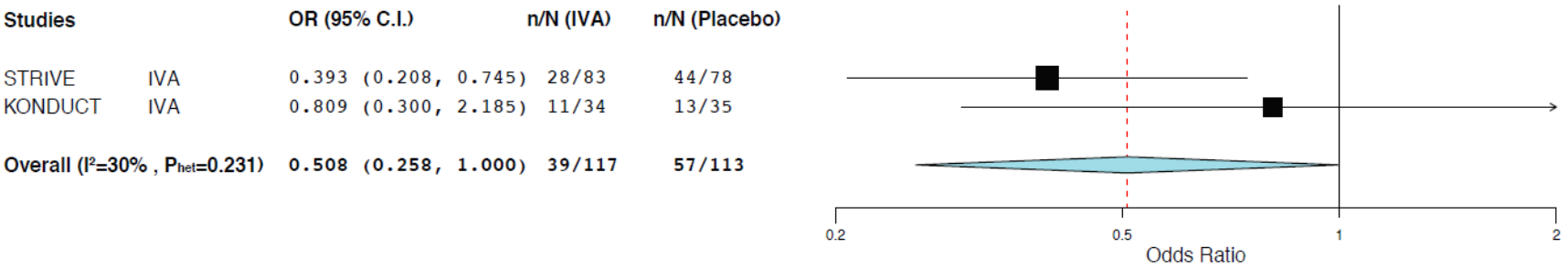
C.I.: confidence interval, IVA: ivacaftor, Phet: chi-square P value for heterogeneity

Figure D8. Meta-Analysis of CFQ-R Respiratory Domain for Ivacaftor Versus Placebo in Patients with Gating and Residual Function Mutations (Difference in Change in Scores Between Study Arms)



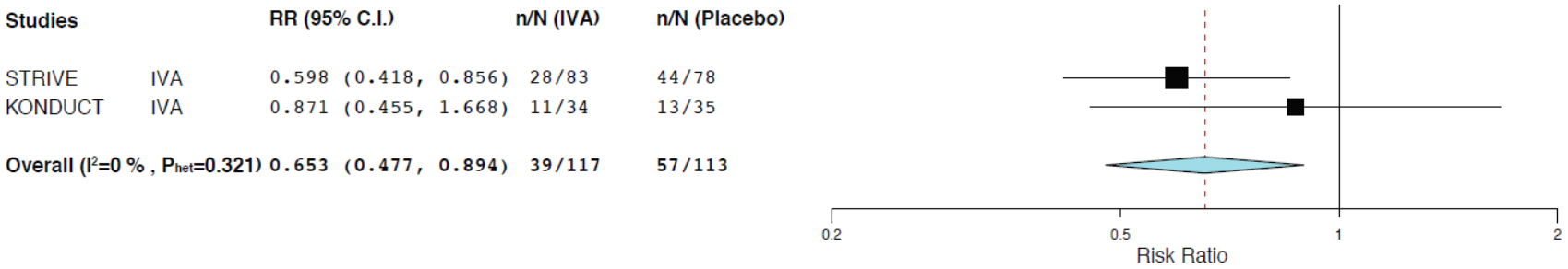
C.I.: confidence interval, CFQ-R: Cystic Fibrosis Questionnaire-Revised, IVA: ivacaftor, Phet: chi-square P value for heterogeneity.

Figure D9. Meta-Analysis of Odds Ratio of Pulmonary Exacerbations for Ivacaftor Versus Placebo in Patients with Gating and Residual Function Mutations



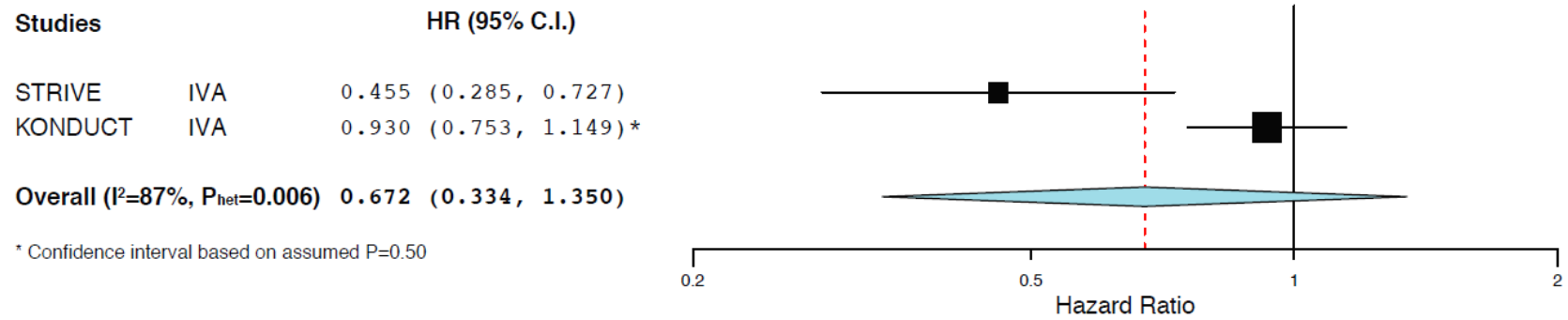
Abbreviations: C.I.: confidence interval, IVA: ivacaftor, OR: odds ratio, P_{het} = chi-square P value for heterogeneity.

Figure D10. Meta-Analysis of Risk Ratio of Pulmonary Exacerbations for Ivacaftor Versus Placebo in Patients with Gating and Residual Function Mutations



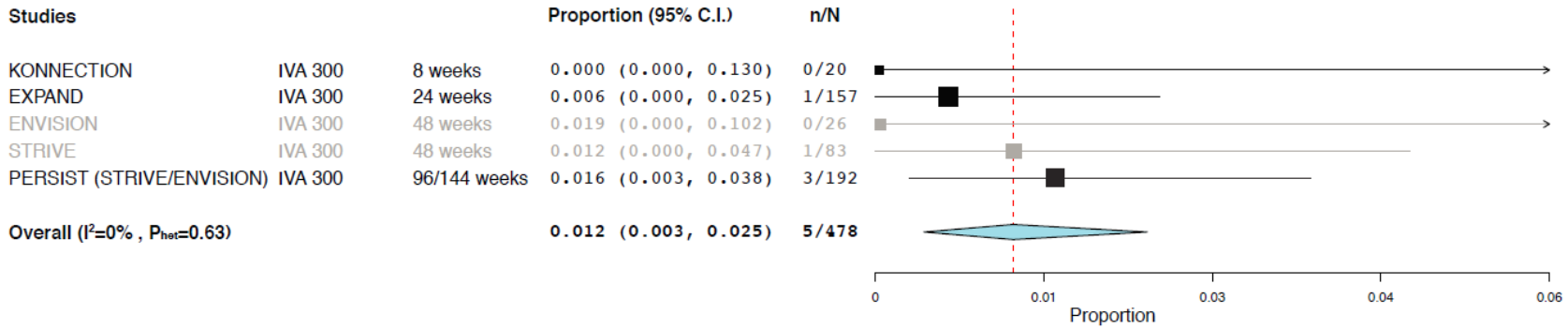
C.I.: confidence interval, IVA: ivacaftor, Phet = chi-square P value for heterogeneity, RR: risk ratio.

Figure D11. Meta-Analysis of Hazard Ratio Pulmonary Exacerbations for Ivacaftor Versus Placebo in Patients with Gating and Residual Function Mutations



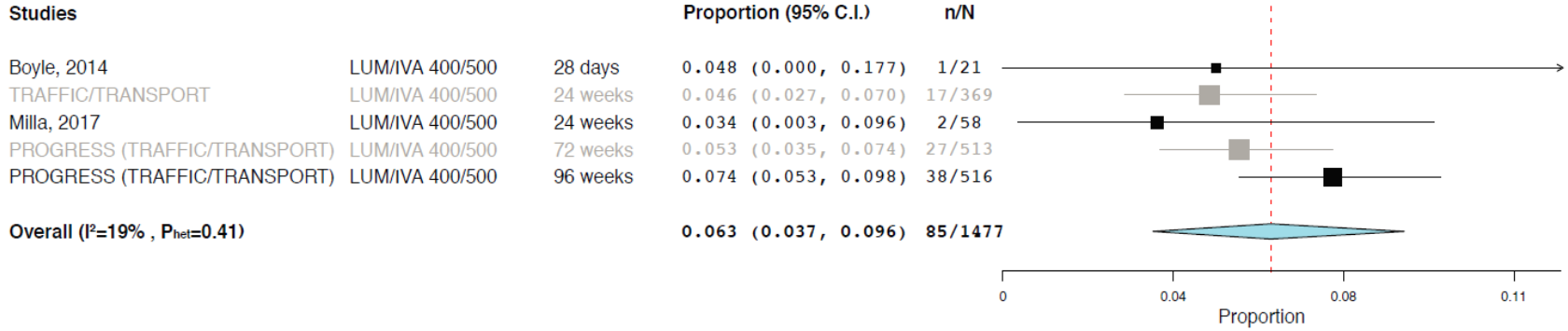
C.I.: confidence interval, HR: hazard ratio, IVA: ivacaftor, Phet = chi-square P value for heterogeneity.

Figure D12. Meta-Analysis of Proportion of Patients Who Discontinued Ivacaftor Due to Adverse Events



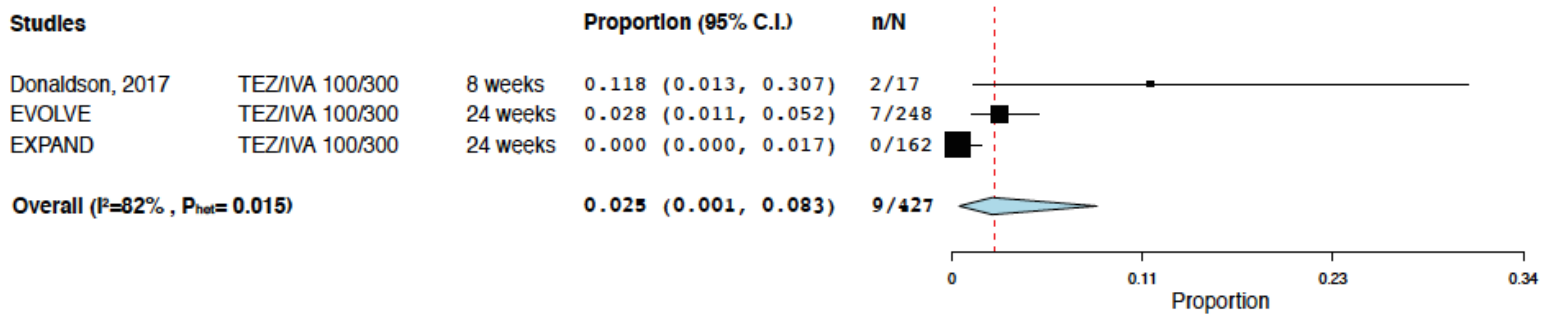
Studies in grey provide shorter-term results than subsequent studies and are not included in the meta-analysis
C.I.: confidence interval, IVA: ivacaftor, P_{het}: chi-square P value for heterogeneity.

Figure D13. Meta-Analysis of Proportion of Patients Who Discontinued Lumacaftor/Ivacaftor Due to Adverse Events



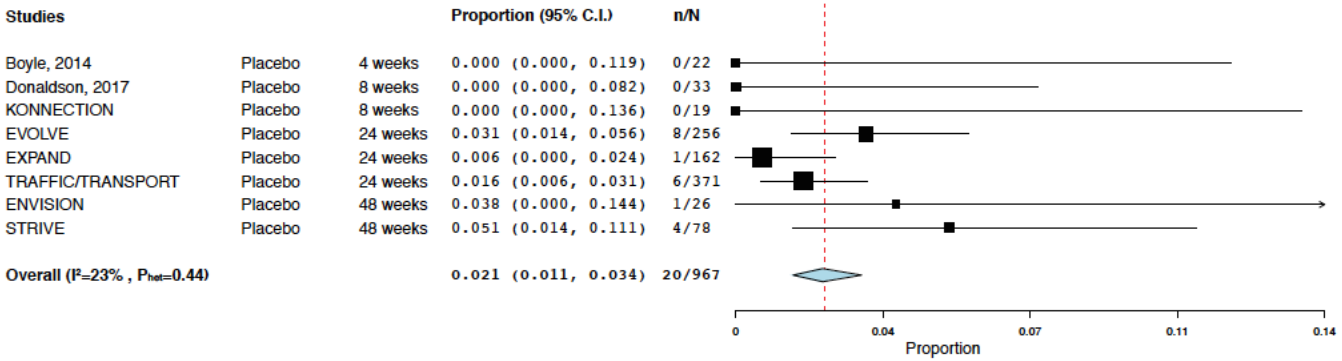
Studies in grey provide shorter-term results than subsequent studies and are not included in the meta-analysis
C.I.: confidence interval, LUM/IVA: lumacaftor/ivacaftor (with daily dosage in mg per drug), P_{het} : chi-square P value for heterogeneity

Figure D14. Meta-Analysis of Proportion of Patients Who Discontinued Tezacaftor/Ivacaftor Due to Adverse Events



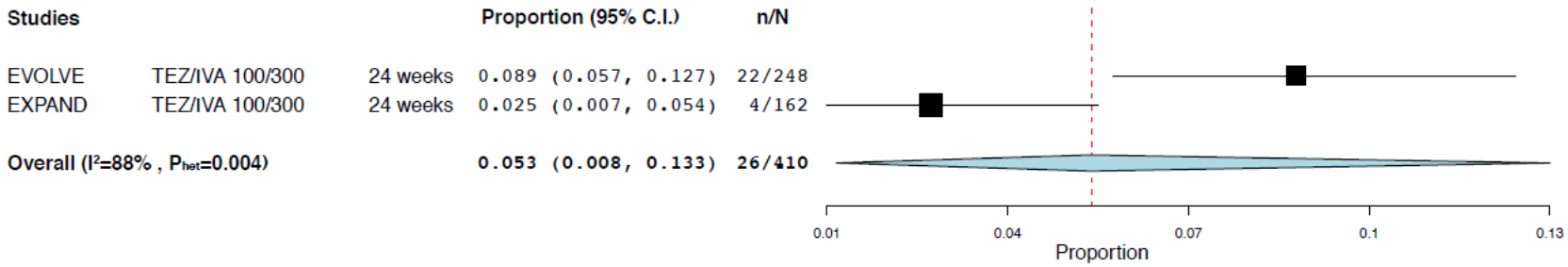
C.I.: confidence interval, Phet: chi-square P value for heterogeneity, TEZ/IVA: tezacaftor/ivacaftor (with daily dosage in mg per drug)

Figure D15. Meta- Analysis of Proportion of Patients Who Discontinued Placebo Due to Adverse Events



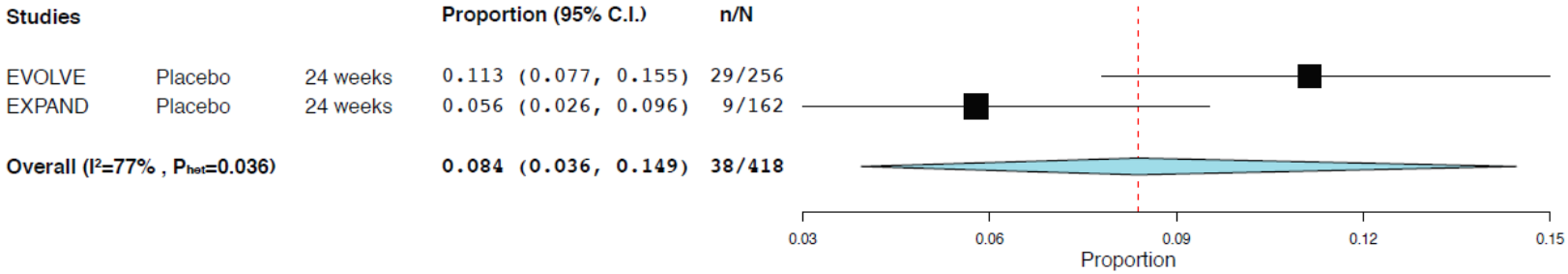
C.I.: confidence interval, P_{het}: chi-square P value for heterogeneity

Figure D16. Meta-Analysis of Proportion of Patients with Grade 3 or 4 Adverse Events on Tezacaftor/Ivacaftor



C.I.: confidence interval, Phet: chi-square P value for heterogeneity, TEZ/IVA: tezacaftor/ivacaftor (with daily dosage in mg per drug)

Figure D17. Meta-Analysis of Proportion of Patients with Grade 3 or 4 Adverse Events on Placebo



Abbreviations: C.I.: confidence interval, Phet: chi-square P value for heterogeneity

Appendix E. Comparative Value Supplemental Information

Description of evLYG Calculations

The cost per evLYG considers any extension of life at the same "weight" no matter what treatment is being evaluated. Below are the stepwise calculations used to derive the evLYG.

1. First, we attribute a utility representing the age- and gender-adjusted utility of the general population in the US that are considered healthy. We generally use a value of 0.851 for the age- and gender-adjusted utility of the general population in the US that are considered healthy.[144] However, the younger CF population included in these analyses had a higher average utility; we therefore used a utility value of 0.92 to represent the general population utility for this analysis.

2. For each cycle (Cycle I) in the model where using the intervention results in additional years of life gained, we multiply this general population utility with the additional life years gained (ΔLYG).

3. We sum the product of the life years and average utility (cumulative LYs/cumulative QALYs) for Cycle I in the comparator arm with the value derived in Step 2 to derive the equal value of life years (evLY) for that cycle.

4. If no life years were gained using the intervention versus the comparator, we use the conventional utility estimate for that Cycle I.

5. The total evLY is then calculated as the cumulative sum of QALYs gained using the above calculations for each arm.

6. We use the same calculations in the comparator arm to derive its evLY.

Finally, the evLYG is the incremental difference in evLY between the intervention and the comparator arms.

Table E1. Impact Inventory

Sector	Type of Impact	Included in This Analysis from… Perspective?		Notes on Sources
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	☒	☒	
	Health-related quality of life effects	☒	☒	
	Adverse events	☒	☒	Modeled through discontinuation rate.
Medical Costs	Paid by third-party payers	☒	☒	
	Paid by patients out-of-pocket	☒	☒	
	Future related medical costs	☒	☒	
	Future unrelated medical costs	☐	☐	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	☐	
Non-Health Care Sectors				
Productivity	Labor market earnings lost	NA	☒	
	Cost of unpaid lost productivity due to illness	NA	☒	
	Cost of uncompensated household production	NA	☒	
Consumption	Future consumption unrelated to health	NA	☐	
Social services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

Description of Mortality Equation

CF-specific mortality rates were a function of sex, ppFEV$_1$, weight-for-age *z*-scores, number of acute pulmonary exacerbations, diagnosis of CF-related diabetes, pancreatic sufficiency, and *B. cepacia* infection as derived by Liou et al.[100] 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*[145], we opted to not include this characteristic in the mortality rate function. The following equation was used to model the annual mortality rate for age *a* (h_a) for non-transplanted patients[100]:

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

$$K = 0.15(SEX - 0.47) - 0.042(ppFEV_1 - 67.7) - 0.0280(WFA + 0.85) + 0.350(\#PE - 1.1) + 0.440(DIAB - 0.061) - 0.140(PS - 0.053) + 1.410(BAI - 0.032) - 0.280(\#PE - 1.1)(BAI - 0.032)$$

The patient-specific parameters that affect mortality among non-transplanted patients were *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 pancreatic sufficiency, 1 yes), *BAI* (0 no *B. cepacia* infection, 1 yes). The age-specific baseline hazard (b_a) was a product of the age-specific rates from the US life tables [113] and an adjustment factor that was needed to match the life expectancy targets of a CF cohort.

Table E2. Undiscounted Results for the Base-Case Effectiveness Measures for CFTR Modulators Plus Best Supportive Care (BSC) Compared to BSC Alone, By Study Population

Population and Treatment	Total Life Years	Total QALYs	Total Cost
Population 1 - Eligible for Kalydeco Monotherapy Only			
BSC	37.77	25.98	$4,406,000
Kalydeco Plus BSC	54.10	39.22	$18,182,000
Population 2 - Homozygous for the *F508del* Mutation			
BSC	37.05	25.79	$3,910,000
Symdeko Plus BSC	51.84	37.74	$16,214,000
Trikafta Plus BSC	56.36	41.90	$18,119,000
Population 3 - Heterozygous *F508del* with Residual Function Mutation			
BSC	39.47	27.38	$4,338,000
Symdeko Plus BSC	57.58	41.17	$17,768,000
Trikafta Plus BSC	63.59	46.85	$20,117,000
Population 4 - Heterozygous *F508del* with Minimal Function Mutation			
BSC	26.22	17.21	$3,449,000
Trikafta Plus BSC	40.32	28.38	$13,455,000

PEx: pulmonary exacerbations; QALY: quality adjusted life year; BSC: best supportive care

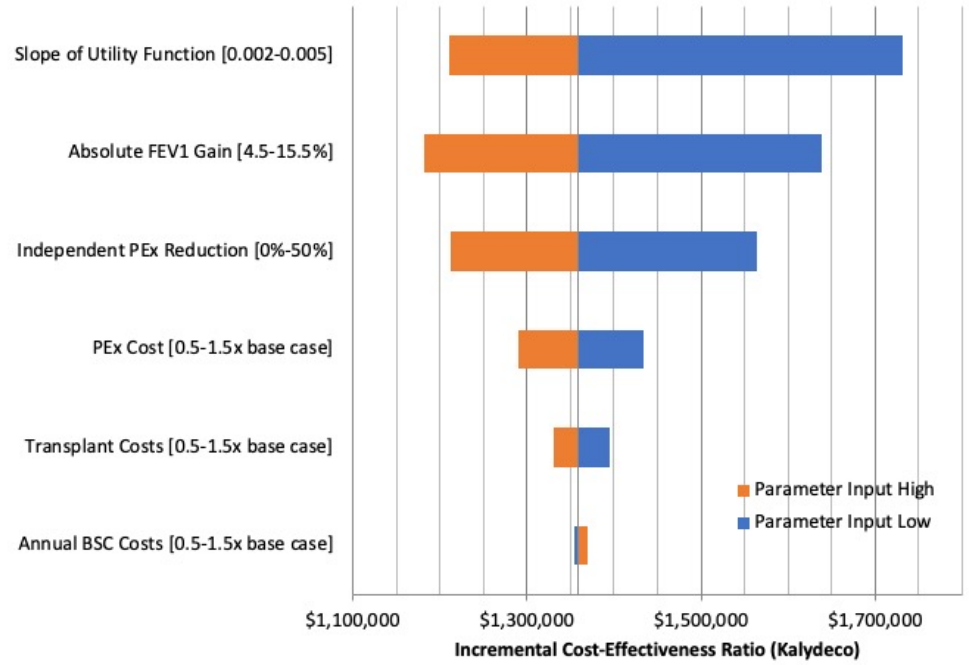
Table E3. Age-Specific Utilities Associated with Aging Population[115]

Age Range	Utility*
0-9	1.00
10-19	0.950
20-29	0.921
30-39	0.906
40-49	0.875
50-59	0.849
60-69	0.826
70-79	0.787
80-89	0.753
90+	0.725

*Extrapolation assumptions were made for ages less than 20 years.

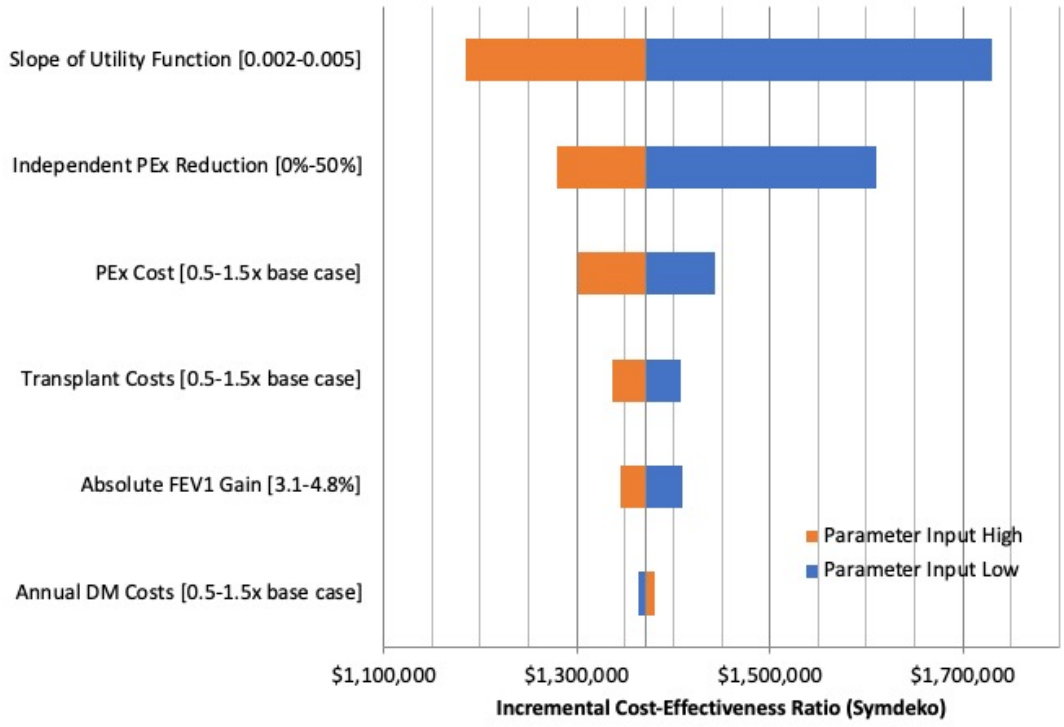
One-Way Sensitivity Analyses

Figure E1. Tornado Diagram for One-Way Sensitivity Analyses of Cost per QALY Gained for Ivacaftor Plus Best Supportive Care Versus Best Supportive Care Alone in CF Individuals Eligible for Kalydeco Monotherapy Only



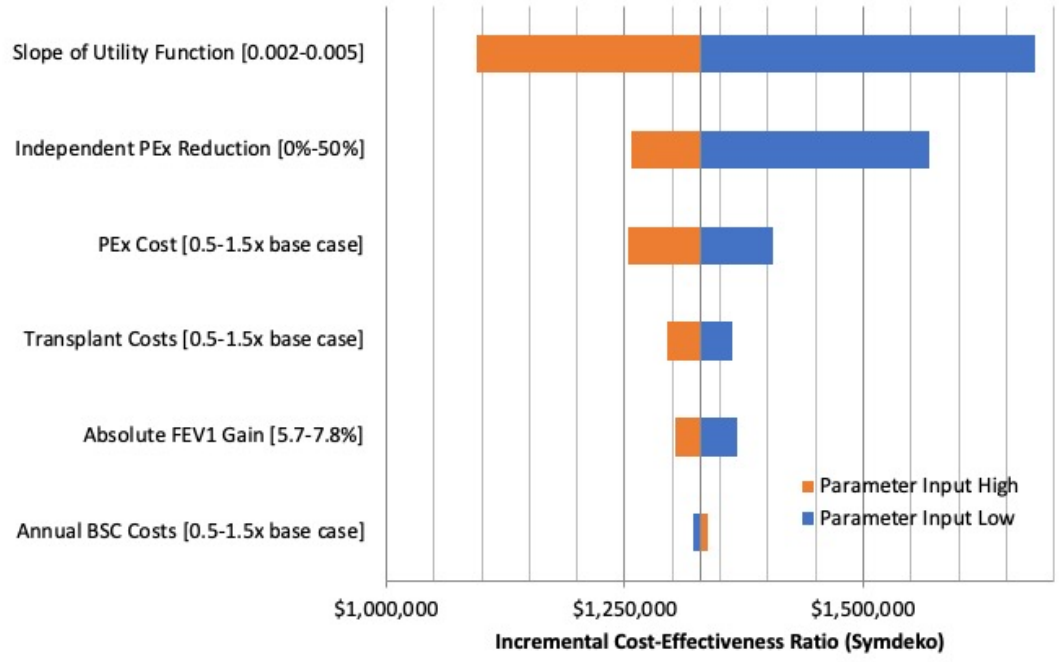
PEx: acute pulmonary exacerbation; BSC: best supportive care

Figure E2. Tornado Diagram for One-Way Sensitivity Analyses of Cost per QALY Gained for Symdeko Plus Best Supportive Care Versus Best Supportive Care Alone in CF Individuals Homozygous for *F508del* Mutation



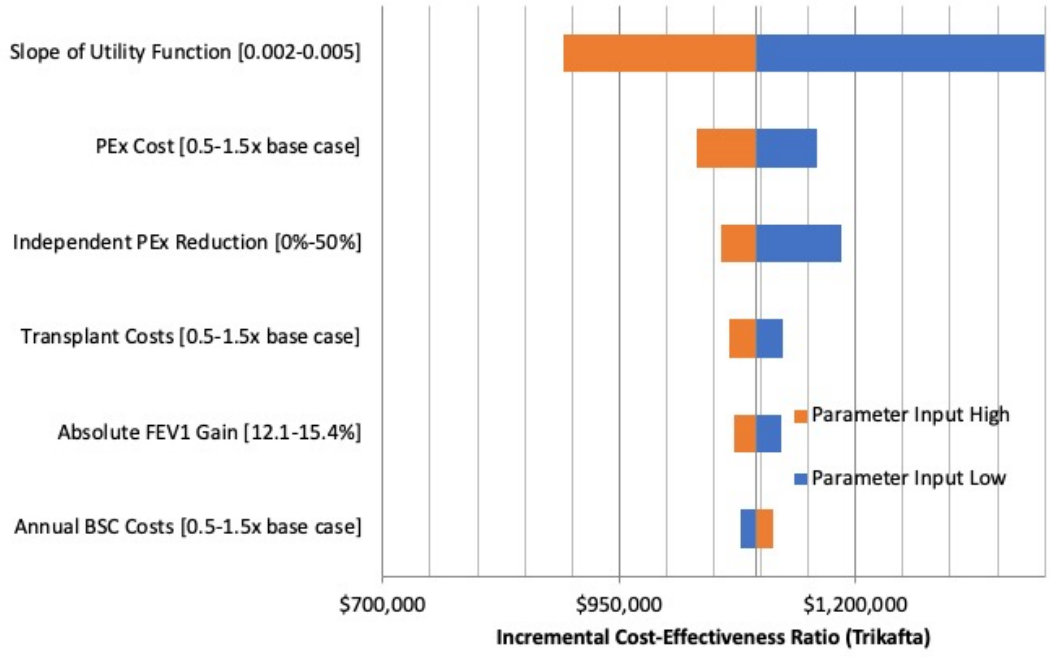
PEx: acute pulmonary exacerbation; BSC: best supportive care

Figure E3. Tornado Diagram for One-Way Sensitivity Analyses of Cost per QALY Gained for Symdeko Plus Best Supportive Care Versus Best Supportive Care Alone in CF Individuals Heterozygous for *F508del* Mutation and Residual Function Mutation



PEx: acute pulmonary exacerbation; BSC: best supportive care

Figure E4. Tornado Diagram for One-Way Sensitivity Analyses of Cost per QALY Gained for Trikafta Plus Best Supportive Care Versus Best Supportive Care Alone in CF Individuals Heterozygous for *F508del* Mutation and Residual Function Mutation



PEx: acute pulmonary exacerbation; BSC: best supportive care

Probabilistic Sensitivity Analyses

Figure E5. Incremental Costs and Incremental Effectiveness for Kalydeco Plus Best Supportive Care Versus Best Supportive Care Alone in CF Individuals Eligible for Kalydeco Monotherapy Only (1,000 Iterations)

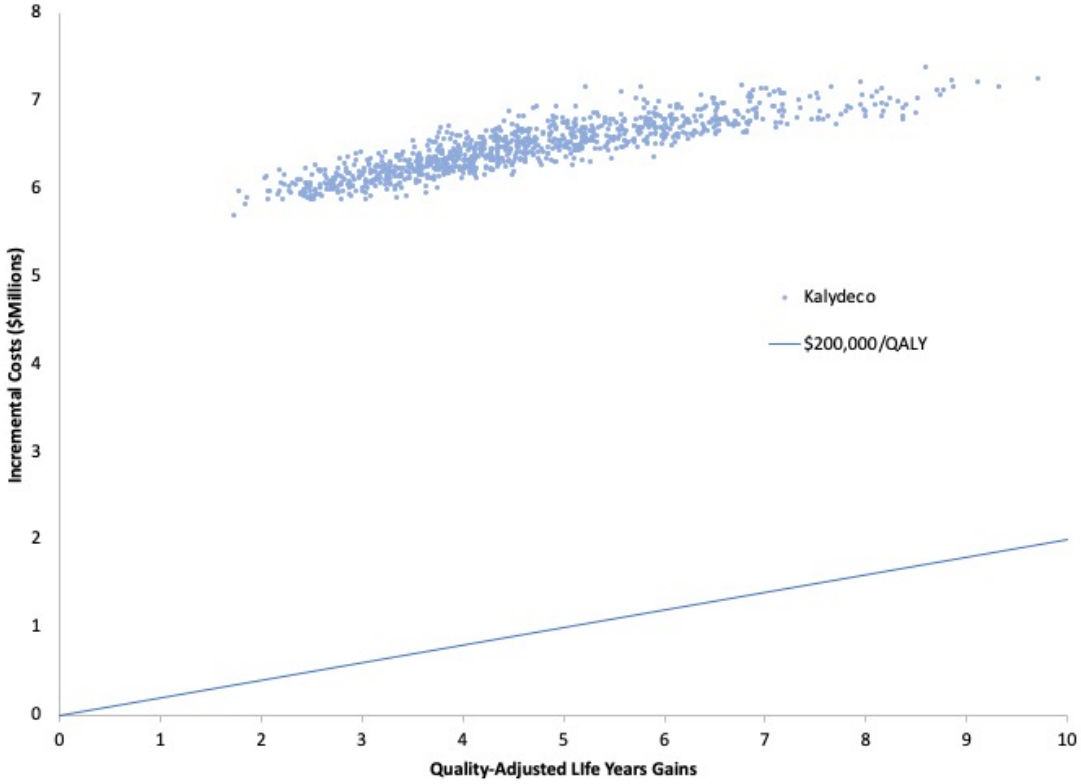


Figure E6. Incremental Costs and Incremental Effectiveness for Symdeko Plus Best Supportive Care Versus Best Supportive Care Alone and Trikafta plus Best Supportive Care Versus Best Supportive Care Alone in CF Individuals Homozygous for *F508del* Mutation (1,000 Iterations)

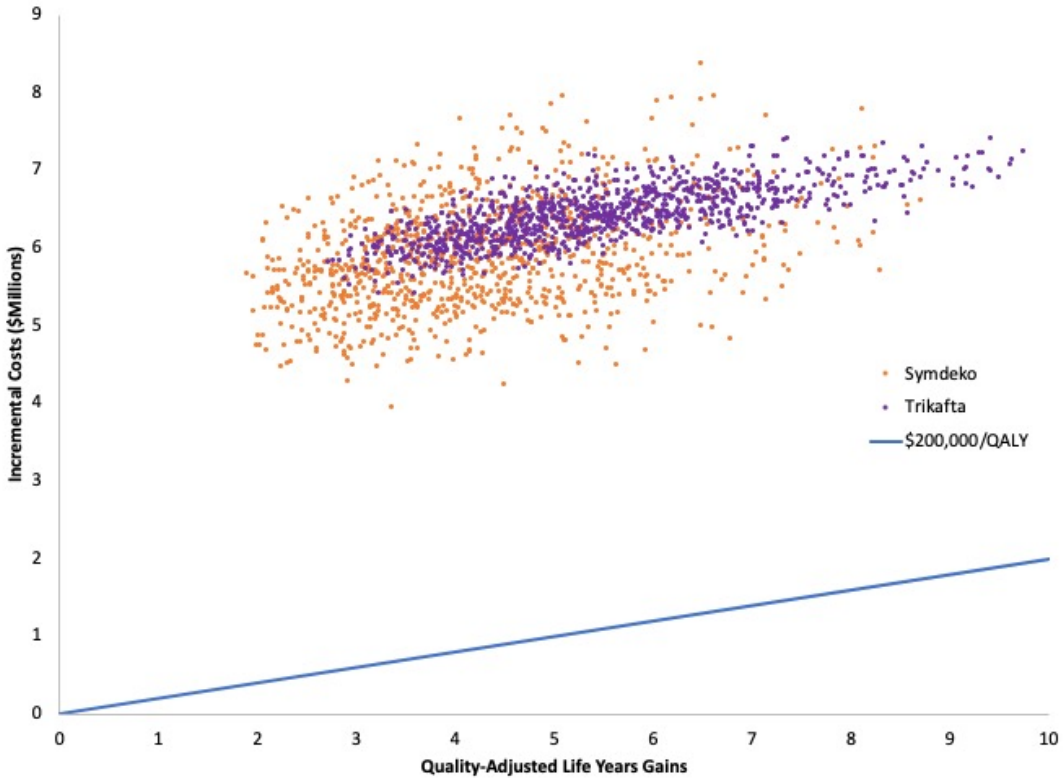


Figure E7. Incremental Costs and Incremental Effectiveness for Symdeko Plus Best Supportive Care Versus Best Supportive Care Alone and Trikafta plus Best Supportive Care Versus Best Supportive Care Alone in CF Individuals Heterozygous for *F508del* Mutation and Residual Function Mutation (1,000 Iterations)

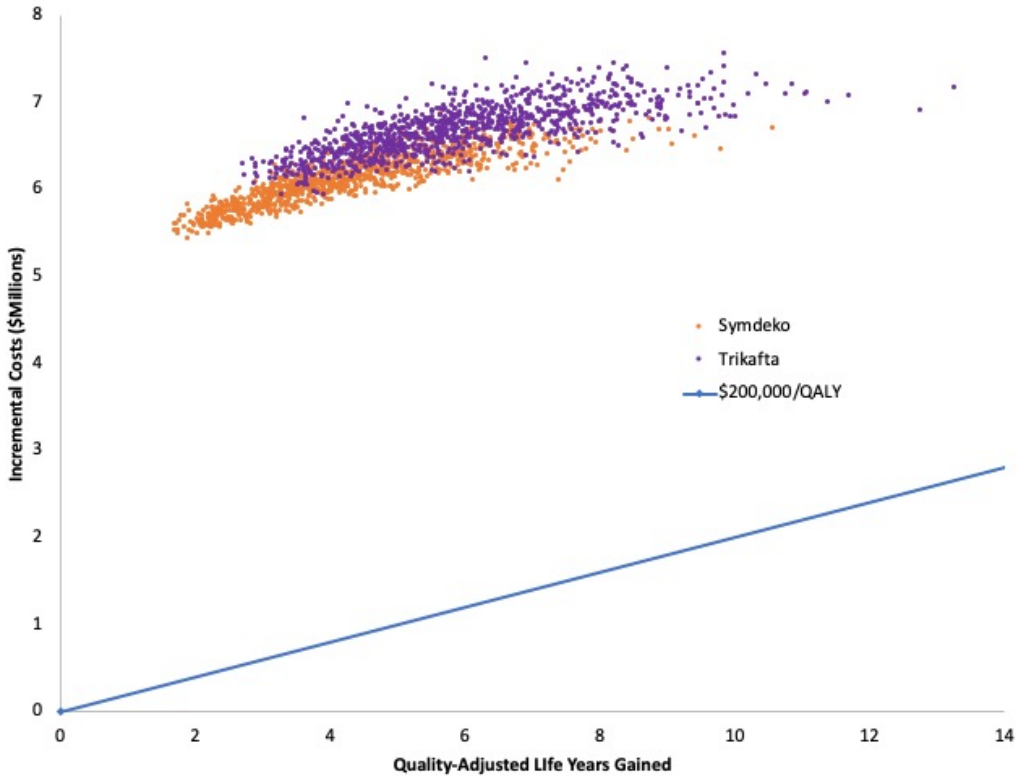


Figure E8. Incremental Costs and Incremental Effectiveness for Trikafta plus Best Supportive Care Versus Best Supportive Care Alone in CF Individuals Heterozygous for *F508del* Mutation and Minimal Function Mutation (1,000 Iterations)

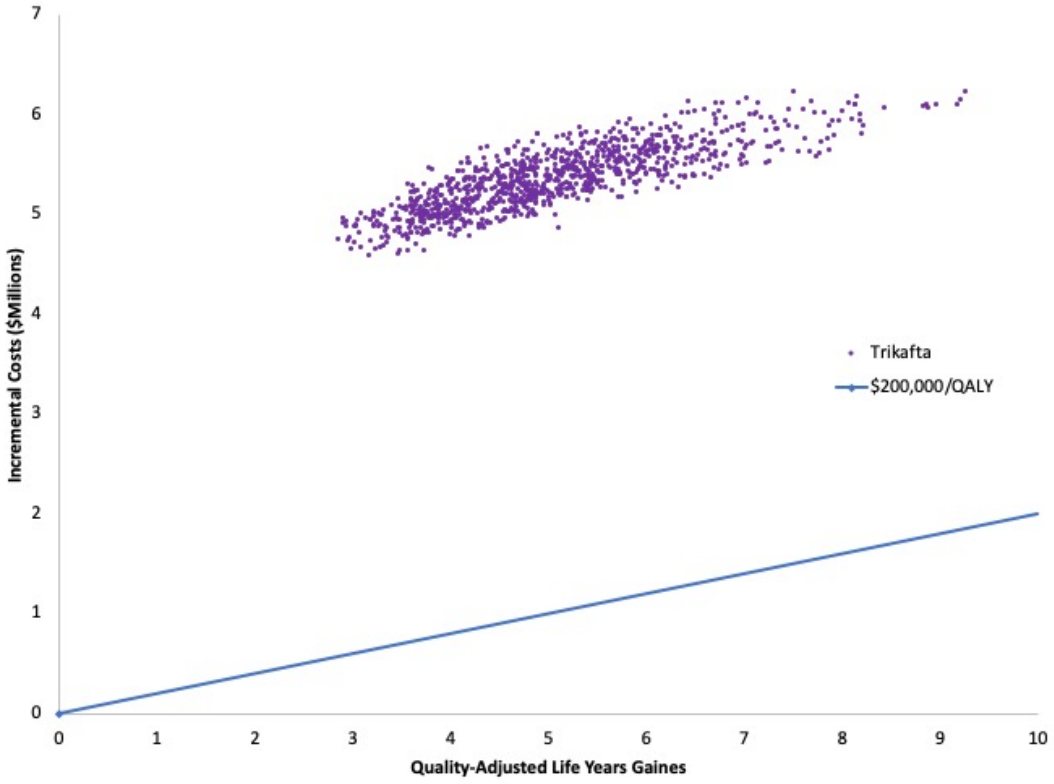

Incremental Costs ($Millions)
Quality-Adjusted Life Years Gaines
Trikafta
$200,000/QALY
0
1
2
3
4
5
6
7
8
9
10

Table E4. Incremental Cost-Effectiveness Ratios Compared to Best Supportive Care (BSC) for the Societal Perspective

Treatment vs. BSC	Incremental Costs	Incremental evLYGs	Cost Per evLYG Gained
Population 1 - Eligible for Kalydeco Monotherapy Only			
Kalydeco plus BSC	$6,373, 000	5.47	$1,165,000
Population 2 - Homozygous for the *F508del* Mutation			
Symdeko plus BSC	$5,796,000	4.90	$1,183,000
Trikafta plus BSC	$6,302,000	6.15	$1,025,000
Population 3 - Heterozygous *F508del* with Residual Function Mutation			
Symdeko plus BSC	$6,069,000	5.60	$1,084,000
Trikafta plus BSC	$6,601,000	7.03	$939,000
Population 4 - Heterozygous *F508del* with Minimal Function Mutation			
Trikafta plus BSC	$5,234,000	6.06	$864,000

BSC: best supportive care; evLYG: equal value life years gained

Table E5. Incremental Cost-Effectiveness Ratios ($ per evLYG) Compared to Best Supportive Care for the Long-Term Effectiveness Assumption

Treatment vs. BSC	0% Decline	25% Decline	75% Decline	100% Decline
Population 1 - Eligible for Kalydeco Monotherapy Only				
Kalydeco plus BSC	789,000	$950,000	$1,622,000	$2,349,000
Population 2 - Homozygous for the *F508del* Mutation				
Symdeko plus BSC	$784,000	$941,000	$1,601,000	$2,318,000
Trikafta plus BSC	$755,000	$873,000	$1,275,000	$1,627,000
Population 3 - Heterozygous *F508del* with Residual Function Mutation				
Symdeko plus BSC	$760,000	$893,000	$1,427,000	$1,950,000
Trikafta plus BSC	$724,000	$821,000	$1,149,000	$1,421,000
Population 4 - Heterozygous *F508del* with Minimal Function Mutation				
Trikafta plus BSC	$667,000	$757,000	$1,024,000	$1,222,000

Table E6. Incremental Cost-Effectiveness Ratios ($ per evLYG) Compared to Best Supportive Care for the Lung Function Recovery After Pulmonary Exacerbation Assumption

Treatment vs. BSC	1% Decline	3% Decline	5% Decline
Population 1 - Eligible for Kalydeco Monotherapy Only			
Kalydeco plus BSC	$1,083,000	$1,008,000	$994,000
Population 2 - Homozygous for the *F508del* Mutation			
Symdeko plus BSC	$1,036,000	$924,000	$889,000
Trikafta plus BSC	$905,000	$806,000	$771,000
Population 3 - Heterozygous *F508del* with Residual Function Mutation			
Symdeko plus BSC	$959,000	$850,000	$810,000
Trikafta plus BSC	$840,000	$750,000	$716,000
Population 4 - Heterozygous *F508del* with Minimal Function Mutation			
Trikafta plus BSC	$771,000	$696,000	$677,000

Table E7. Incremental Cost-Effectiveness Ratios ($ per evLYG) Compared to Best Supportive Care for the Non-Respiratory Utility Assumption

Treatment vs. BSC	1% Increase	2% Increase	4% Increase	5% Increase
Population 1 - Eligible for Kalydeco Monotherapy Only				
Kalydeco plus BSC	$1,176,000	$1,145,000	$1,086,000	$1,061,000
Population 2 - Homozygous for the *F508del* Mutation				
Symdeko plus BSC	$1,161,000	$1,125,000	$1,062,000	$1,032,000
Trikafta plus BSC	$1,011,000	$985,000	$939,000	$917,000
Population 3 - Heterozygous *F508del* with Residual Function Mutation				
Symdeko plus BSC	$1,072,000	$1,041,000	$985,000	$959,000
Trikafta plus BSC	$934,000	$911,000	$870,000	$852,000
Population 4 - Heterozygous *F508del* with Minimal Function Mutation				
Trikafta plus BSC	$860,000	$844,000	$813,000	$800,000

Table E8. Incremental Cost-Effectiveness Ratios ($ per evLYG) Compared to Best Supportive Care for the Assumption of Drug Effect on CF-Related Diabetes

Treatment vs. BSC	5% Decrease	23% Decrease

Population 1 - Eligible for Kalydeco Monotherapy Only		
Kalydeco plus BSC	$1,204,000	$1,205,000
Population 2 - Homozygous for the *F508del* Mutation		
Symdeko plus BSC	$1,197,000	$1,185,000
Trikafta plus BSC	$1,037,000	$1,030,000
Population 3 - Heterozygous *F508del* with Residual Function Mutation		
Symdeko plus BSC	$1,104,000	$1,098,000
Trikafta plus BSC	$958,000	$956,000
Population 4 - Heterozygous *F508del* with Minimal Function Mutation		
Trikafta plus BSC	$877,000	$874,000

Table E9. Incremental Cost-Effectiveness Ratios ($ per evLYG) Compared to Best Supportive Care (BSC) for Starting Trikafta at Age 6 Years of Age (Discounted at 3% per Year)

Treatment vs. BSC	Total cost	evLYGs	Cost Per evLYG Gained
Population 2 - Homozygous for the *F508del* Mutation			
BSC	$2,088,000	15.86	--
Trikafta Plus BSC	$8,449,000	21.54	$1,120,000
Population 3 - Heterozygous *F508del* with Residual Function Mutation			
BSC	$2,210,000	16.40	--
Trikafta Plus BSC	$8,901,000	22.77	$1,050,000
Population 4 - Heterozygous *F508del* with Minimal Function Mutation			
BSC	$2,178,000	14.13	--
Trikafta Plus BSC	$8,206,000	20.21	$991,000

Table E10. Per-Day Cost-Effectiveness Threshold Prices for Kalydeco, Symdeko, and Trikafta

Daily Prices Using…	WAC/Day	Price/Day at $100,000 Threshold	Price/Day at $150,000 Threshold	Discount from WAC to Reach Threshold Prices
Kalydeco				
QALYs Gained	$853.40	$160.39	$187.74	78% to 81%
evLYG		$169.15	$200.87	76% to 80%
Orkambi				
QALYs Gained	$746.40	$139.18	$161.17	78% to 81%
evLYG		$143.14	$167.11	78% to 81%
Symdeko				
QALYs Gained	$800.00	$153.74	$179.20	78% to 81%
		$161.90	$191.45	76% to 80%
Trikafta				
QALYs Gained	$853.50	$185.90	$218.78	74% to 78%
evLYG		$196.11	$234.09	73% to 77%

WAC: wholesale acquisition cost; evLYG: equal value life year gained; QALY: quality-adjusted life year

Appendix F. Evidence Tables from 2018 Review

Author & Year of Publication, (Trial), Quality Rating	Study Design and Duration of Follow-up, (Sites & geographical location)	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Symdeko						
Taylor-Cousar [87] ***NEJM*** **2017** **EVOLVE - Homozygous F508d** **Good**	Phase 3, randomized, double-blind, multicenter, placebo-controlled, parallel-group trial Trial conducted in 91 sites in the United States, Canada, and Europe from January 30, 2015, to January 20, 2017. Duration of follow-up: 24 weeks	**N=504** (1) TEZ/IVA: 100 mg of tezacaftor once daily and 150 mg of ivacaftor twice daily (n=248) (2) Placebo (n=256)	**Inclusion** • 12 years of age or older • Confirmed diagnosis of CF • Two Phe508del alleles • Percentage of the predicted FEV_1 between 40% and 90% at screening Stable disease **Exclusion**	**Age** **Mean, years (SD)** (1) 26.9 (11.2) (2) 25.7 (9.5) **Female, n (%)** (1) 121 (48.8) (2) 125 (48.8) **Percent predicted FEV_1 ($ppFEV_1$)** **Mean, percentage points (SD)** (1) 59.6 (14.7) (2) 60.4 (15.7) **BMI** **Mean, kg (SD)** (1) 20.96 (2.95) (2) 21.12 (2.88) ***CFQ-R respiratory domain** **Mean, score (SD)** (1) 70.1 (16.8) (2) 69.9 (16.6)	**$ppFEV_1$** **Mean absolute change from baseline, percentage points (95% CI)** (1) 3.4 (2.7 to 4.0) (2) -0.6 (-1.3 to 0.0) Difference=4.0 (3.1 to 4.8) **$ppFEV_1$** **Mean relative change from baseline, % (95% CI)** (1) 6.3 (5.1 to 7.4) (2) −0.5 (−0.7 to 0.6) Difference =6.8 (5.3 to 8.3) **Pulmonary exacerbation (PEx), no. of events (annualized estimated event rate)** (1) 78 (0.64)	**Any AE, n (%)** (1) 227 (90.4) (2) 245 (95.0) **Grade 3/4 AE, n (%)** (1) 22 (8.8) (2) 29 (11.2) **SAE, n (%)** (1) 31 (12.4) (2) 47 (18.2) **Discontinuation d/t AE, n (%)** (1) 7 (2.8) (2) 8 (3.1) **Infective PEx of CF, n (%)** (1) 75 (29.9) (2) 96 (37.2) **Cough, n (%)** (1) 66 (26.3) (2) 84 (32.6)

				* Scores on (CFQ-R) range from 0-100, higher scores indicating a higher patient-reported QoL with regard to respiratory status.	(2) 122 (0.99) **BMI** **Mean absolute change from baseline, kg/m² (95% CI)** (1) 0.18 (0.08 to 0.28) (2) 0.12 (0.03 to 0.22) Difference=0.06 (−0.08 to 0.19) **CFQ-R Respiratory domain** **Mean absolute change from baseline, points (95% CI)** (1) 5.0 (3.5 to 6.5) (2) −0.1 (−1.6 to 1.4) Difference=5.1 (3.2 to 7.0)	**Headache, n (%)** (1) 44 (17.5) (2) 37 (14.3)
Rowe [93] ***NEJM*** **2017** **EXPAND - Heterozygous F508d** **Good**	Phase 3, randomized, double-blind, multicenter, placebo-controlled, two-period, three-intervention crossover trial Trial conducted at 86 sites from March 27, 2015, to Feb 16, 2017.	**N=248** (1) Placebo (n=162) (2) IVA: Kalydeco, 150 mg every 12 hours (n=157) (3) TEZ/IVA; tezacaftor 100 mg once daily with ivacaftor 150 mg every 12 hours (n=162)	**Inclusion** • 12 years of age or older • Confirmed diagnosis of CF • One Phe508del allele and one allele with a residual-function mutation • Percentage of the predicted FEV_1 between 40% and 90% at screening • Stable disease	**Age** **Mean, years (SD)** (1) 32.6 (13.9) (2) 36.3 (15.2) (3) 35.6 (13.5) **Sex** **Female, n (%)** (1) 46 (58) (2) 40 (49) (3) 48 (58)	**$ppFEV_1$** **Mean absolute change from baseline** Within-group, L (SD) (1) −0.02 (0.21) (2) 0.17 (0.23) (3) 0.23 (0.25) Between-group, least-squared mean differences, L (95% CI)	**Any AE, n (%)** (1) 126 (78) (2) 114 (73) (3) 117 (72) **Grade 3/4 AE, n (%)** (1) 9 (6) (2) 8 (5) (3) 4 (2) **SAE, n (%)** (1) 14 (9)

	Duration of follow-up: 24 weeks	Incomplete block design Randomized 1:1:1:1:1:1 to 6 blocks each containing two interventions of 8 weeks with an 8-week washout period between. Participants were randomized to receive two of three interventions studied for 8 weeks each with an 8-week washout period between.	**Exclusion** • Any comorbidity or lab abnormality that may confound study results or increase potential harm to participant • PE or change in treatment within 14 days first dose • Prolonged QT/QTc interval • Solid organ transplant • Used inhibitors or inducers of CYP3A4 • Participation in another trial in last 3 months • Pregnancy or breast-feeding • History or evidence of cataracts or lens opacity • Use of restricted medications or foods in specified window before first dose • Unwilling to take contraceptives during study if of reproductive potential • Colonization with organisms associated	**Type of Residual Function Mutation, n (%)** Class V (1) 48 (60) (2) 48 (59) (3) 50 (60) Class II-IV (1) 32 (40) (2) 33 (41) (3) 33 (40) **$ppFEV_1$ Mean, percentage points (SD)** (1) 62.1 (14.0) (2) 62.8 (14.6) (3) 61.8 (14.9) **BMI Mean, kg (±SD)** (1) 24.6 (5.0) (2) 24.5 (5.5) (3) 23.6 (4.6) **CFQ-R Respiratory domain Mean, mean (±SD)** (1) 67.8 (17.5) (2) 70.0 (17.7) (3) 66.5 (17.9) **Pancreatic insufficiency, n (%)** Yes (1) 11 (14)	Iva v. Plac: 4.7 (3.7 to 5.8) Tez/Iva v. Plac: 6.8 (5.7 to 7.8) Tez/Iva v. Iva: 2.1 (1.2 to 2.9) **$ppFEV_1$ Mean relative change from baseline, %** Within-group, % (SD) (1) -0.16 (9.45) (2) 8.40 (10.76) (3) 11.17 (12.39) Between-group, least-squared mean differences, % (95% CI) Iva v. Plac: 8.1 (6.3 to 9.9) Tez/Iva v. Plac: 11.4 (9.6 to 13.2) Tez/Iva v. Iva: 3.3 (1.8 to 4.8) **CFQ-R Mean change from baseline, points** Within-group: NR Between-group, least-squares mean difference, points (95% CI): Iva vs. Plac: 9.7 (7.2 to 12.2) Tez/Iva vs. Plac: 11.1 (8.7 to 13.6)	(2) 10 (6) (3) 8 (5) **Discontin d/t AE, n (%)** (1) 1 (<1) (2) 2 (<1) (3) 0 **Infective PEx of CF, n (%)** (1) 31 (19) (2) 20 (13) (3) 21 (13) **Cough, n (%)** (1) 30 (19) (2) 17 (11) (3) 23 (14) **Headache, n (%)** (1) 13 (8) (2) 11 (7) (3) 19 (12) **Hemoptysis, n (%)** (1) 14 (9) (2) 17 (11) (3) 12 (7) **Increase in creatinine, n (%)** (1) 5 (3)

			with more rapid decline in pulmonary status	(2) 11 (14) (3) 11 (13) • <u>No</u> (1) 56 (70) (2) 61 (75) (3) 60 (72) <u>Missing</u> (1) 13 (16) (2) 9 (11) (3) 12 (14)	Tez/Iva vs. Iva: 1.4 (−1.0 to 3.9) **PExs** <u>Number of events</u> (1) 20 (2) 9 (3) 11 <u>Estimated event rate/year</u> (1) 0.63 (2) 0.29 (3) 0.34 <u>Rate ratio v. placebo (95% CI)</u> (2) (0.21 to 1.01) (3) (0.26 to 1.1.3)	(2) 8 (5) (3) 6 (4)
Donaldson [146] ***Am J Resp Crit Care Med*** **2017** **Phase 2** **Good**	Phase 2, randomized, placebo-controlled, multicenter, dose-escalation study 37 centers in US, Canada, Germany and UK. Enrollment: Feb 2012 to March 2014 Duration of follow-up: 56 days for safety; 28-days efficacy ***Only reporting on homozygous F508del, TEZ/IVA***	**N=41** Multiple doses in trial. Only reporting relevant dose (1) TEZ/IVA: 100 mg qd tezacaftor and 150 mg ivacaftor q 12 hours (n=17) (2) Placebo (n=24)	**Inclusion** • Confirmed diagnosis of CF • Homozygosity for the Phe-508del CFTR mutation • Age of 18 years or older • $ppFEV_1$ at the time of screening that was 40- 90% of the predicted normal values • Body weight of at least 40 kg and BMI of at least 18.5 kg/m2 • **Exclusion** • Any comorbidity or lab abnormality that	**Pooled Homozygous *F508del*** (1) N=17 (2) N=24 **Age** **Mean, years (±SD)** (1) 31.0 (9.3) (2) 30.2 (7.8) **Sex** **Female, n (%)** (1) 11 (64.7) (2) 8 (33.3) **$ppFEV_1$** **Mean, percentage points (SD)** (1) 58.7 (16)	**$ppFEV_1$** **Mean (least-squares) absolute change from baseline, percentage points (95% CI)** (1) 3.75 (NR) (2) -0.14 (NR) Difference=3.89 (0.94 to 6.83) **$ppFEV_1$** **Mean (least-squares) relative change from baseline, percent (95% CI)** (1) NR (NR) (2) NR (NR) Difference=7.04 (1.77 to 12.31)	**AE in all homozygous *F508del*** **Any AE, n (%)** (1) 92 (86.8) (2) 30 (90.9) **Any Serious AE, n (%)** (1) 8 (7.5) (2) 5 (15.2) **Serious PEx, n (%)** (1) 7 (6.6) (2) 5 (15.2)

	100/150mg combination and placebo		may confound study results or increase potential harm to participant • PE or change in treatment within 14 days first dose • Pregnancy or breast-feeding • Unwilling to take contraceptives during study if of reproductive potential • History of solid organ transplant • Participation in another trial in last 3 months • History of alcohol, medication, or illicit drug use within 1 year before screening •	(2) 57.8 (15.3) **BMI** **Mean, kg (SD)** (1) 23.0 (3.7) (2) 21.7 (2.4)	**CFQ-R Respiratory domain** **Mean absolute change from baseline, points (p-value)** (1) 3.79 (p=0.1679) (2) NR (NR) Difference=6.81 (p=0.2451)	**Discontinuation due to AE, n (%)** (1) 2 (11.8) (2) 0 (0) **Cough, n (%)** (1) 17 (16.0) (2) 6 (18.2)
Orkambi						
Wainwright [30] ***NEJM*** **2015** **TRAFFIC and TRANSPORT - Homozygous F508d**	Two phase 3, double-blind, placebo-controlled, randomized trial Duration of follow-up: 24 weeks	**N=1108** (1) LUM/IVA: 600 mg of lumacaftor once daily in combination with 250 mg of ivacaftor every 12 hours (n=368)	**Inclusion** • Confirmed diagnosis of CF • Homozygosity for the Phe-508del CFTR mutation • Age of 12 years or older • Percentage of predicted FEV_1 at the time of screening that	**Age** **Mean, years** (1) 24.5 (2) 25.3 (3) 25.4 **Sex** **Female, n (%)** (1) 182 (49.5) (2) 182 (49.3) (3) 181 (48.8)	**Pooled Analysis, least-squares means** **$ppFEV_1$** **Mean absolute change from baseline** Within-group, percentage points (p-value) (1) 3.0 (p < 0.001)	**Any AE, n (%)** (1) 356 (96.5) (2) 351 (95.1) (3) 355 (95.9) **Discontinuation d/t AE, n (%)** (1) 14 (3.8) (2) 17 (4.6) (3) 6 (1.6)

Good	187 centers in North America, Australia, and Europe Enrollment between April 2013 and April 2014 All data reported are pooled groups of two studies – TRAFFIC and TRANSPORT	(2) LUM/IVA: 400 mg of lumacaftor every 12 hours in combination with 250 mg of ivacaftor every 12 hours (n=369) (3) Placebo: Lumacaftor-matched placebo every 12 hours in combination with ivacaftor-matched placebo every 12 hours (n=371)	was 40- 90% of the predicted normal values • Stable cystic fibrosis disease **Exclusion** • Any comorbidity that increases risk in the study (cirrhosis, Torsades de Pointes) • Abnormal lab values • Respiratory event within 4 weeks of first day on drug • Colonization with certain bacteria • Prolonged QT interval • History of transplant • Using strong inhibitors, moderate inducers, or strong inducers of CYP3A within 14 days of first day on drug • History of cataract or lens opacity or evidence of cataract or lens opacity determined to be clinically significant	**$ppFEV_1$** **Mean, percentage points** (1) 60.8 (2) 60.5 (3) 60.4 **BMI** **Mean, kg/m^2** (1) 21.0 (2) 21.5 (3) 21.0	(2) 2.5 ($p < 0.001$) (3) -0.32 ($p = 0.40$) Between-group difference, percentage points (95% CI) (1) 3.3 (2.3 to 4.3) (2) 2.8 (1.8 to 3.8) (3) NA **$ppFEV_1$** **Mean relative change from baseline** Within-group, % (p-value) (1) 5.4 ($p < 0.001$) (2) 4.6 ($p < 0.001$) (3) -0.17 ($p = 0.80$) Between-group difference, % (95% CI) (1) 5.6 (3.8 to 7.3) (2) 4.8 (3.0 to 6.6) (3) NA **BMI** **Mean absolute change from baseline, kg/m^2 (p-value)** Within group (1) 0.41 ($p<0.001$) (2) 0.37 ($p<0.001$) (3) 0.13 ($p=0.007$)	**≥ One SAE, n (%)** (1) 84 (22.8) (2) 64 (17.3) (3) 106 (28.6) **Infective PEx of CF, n (%)** (1) 145 (39.3) (2) 132 (35.8) (3) 182 (49.2) **Cough, n (%)** (1) 121 (32.8) (2) 104 (28.2) (3) 148 (40.0) **Headache, n (%)** (1) 58 (15.7) (2) 58 (15.7) (3) 58 (15.7)

					CFQ-R Respiratory domain **Mean absolute change from baseline, points (p-value)** (1) 4.9 (p<0.001) (2) 4.1 (p<0.001) (3) 1.9 (p=0.02) **PEx** **No. of events; Rate Ratio (95%CI)** (1) 173; 0.70 (0.56 to 0.87) (2) 152; 0.61 (0.49 to 0.76) (3) 251; NA	
Elborn [95] ***Lancet Resp Med*** **2016** **TRAFFIC and TRANSPORT Subgroup analysis**	**See Wainwright** Prespecified subgroup analyses of pooled efficacy and safety data by lung function. **For Demographics data:** (1) Placebo n=371 (<40%ppFEV$_1$=28) LUM 400 mg q12 Iva 250 mg q12, n=731 (2) Baseline ppFEV$_1$ <40% n=53 (3) Baseline ppFEV$_1$ ≥40% n=687 (4) Screening ppFEV$_1$ <70% n=527	**See Wainwright**	**See Wainwright**	**Data reported are stratified – see Study design and follow-up** **Age** **Median, years (range)** (1) 23.0 (12–64) (2) 27.0 (13–44) (3) 23.0 (12–57) (4) 26.0 (12–57) (5) 18.5 (12–53) **Sex** **Female, n (%)** (1) 181 (49%) (2) 31 (58%) (3) 331 (49%) (4) 269 (51%) (5) 93 (46%) • **ppFEV$_1$** **Mean, percentage points (range)**	**Pooled Analysis < 40% vs. ≥40% ppFEV$_1$** **Lumacaftor 400mg q 12 hrs/ Ivacaftor 250 mg q 12hrs** **ppFEV$_1$** **Mean absolute change from baseline vs. placebo, percentage points (95% CI)** (1) reference (2) 3.3. (0.2 to 6.4) (3) 2.8 (1.7 to 3.8) **ppFEV$_1$** **Mean (least-squares) relative change from**	**Pooled Analysis < 40% vs. ≥40% ppFEV$_1$** **Both doses (600mg & 400mg)** **Any AE, n (%)** (1) 350 (96) (2) 52 (98) (3) 649 (96) **Infective PEx of CF, n (%)** (1) 182 (50) (2) 27 (51) (3) 248 (37) **Cough, n (%)** (1) 147 (40) (2) 21 (40) (3) 203 (30)

	(5) Screening $ppFEV_1$ • ≥70% n=204 • For Results at 24 weeks: (1) Placebo (2) LUM 400 mg q12 Iva 250 mg q12, • FEV1<40% (3) LUM 400 mg q 12 Iva 250 mg q 12, FEV1≥40%			(1) 60.4 (33.9–99.8) (2) 37.2 (31.1-39.9) (3) 62.5 (40.0-96.5) (4) 54.0 (31.1-69.8) (5) 77.9 (70.0–96.5) • **BMI** **Mean, kg/m² (SD)** (1) 21.0 (2.9) (2) 20.9 (3.4) (3) 21.3 (3.0) (4) 21.2 (2.9) (5) 21.4 (3.3)	**baseline vs placebo, % (95% CI)** (1) reference (2) 9.1 (0.7 to 17.4) (3) 4.5 (2.7 to 6.3) **BMI** **Least-squares mean vs. placebo, kg/m² (95% CI)** (1) reference (2) 0.3 (-0.2 to 0.8) (3) 0.2 (0.1 to 0.4) **CFQ-R Respiratory domain** **Least-squares mean vs. placebo, points (95% CI)** (1) reference (2) −4.2 (−12.0 to 3.7) (3) 2.9 (0.5 to 5.3) **PEx** **Event rate ratio (95%CI)** (1) reference (2) 0.59 (0.33 to 1.05) (3) 0.61 (0.48 to 0.77) **PEx** **No. events requiring IV antibiotics, rate ratio (95%CI)** (1) Reference	**Headache, n (%)** (1) 57 (16) (2) 10 (19) (3) 103 (15)

					(2) 0.56 (0.27 to 1.17) (3) 0.42 (0.30 to 0.58) **PEx** **No. events requiring hospitalization, rate ratio (95%CI)** (1) reference (2) 0.67 (0.27 to 1.65) (3) 0.36 (0.23 to 0.54)	
Konstan [88] ***Lancet Resp Med*** **2017** **PROGRESS - Homozygous F508d**	Phase 3, multicenter, parallel group, open-label trial. Patients who completed TRAFFIC or TRANSPORT participated in the study in 191 sites in 15 countries Duration of follow-up: 96 weeks; however, main efficacy outcomes reported at 72 weeks	**N=1030** (1) LUM/IVA: continued 400 mg of lumacaftor every 12 hours in combination with 250 mg of ivacaftor every 12 hours (n=340) (2) LUM/IVA: Placebo transitioned to 400 mg lumacaftor every 12 hours in combination with ivacaftor 250 mg every 12 hours (n=176) At 72 weeks (primary efficacy),	**Inclusion** • Confirmed diagnosis of CF • Homozygosity for the *F508del*-CFTR mutation • Age of 12 years or older **Exclusion** • Any comorbidity or lab abnormality that may confound study results or increase potential harm to participant • History of drug intolerance in the prior study • Pregnancy or breast-feeding • History of poor compliance with	**Age** **Mean, years (SD)** (1) 25.1 (9.3) (2) 24.9 (10.1) **Sex** **Female, n (%)** (1) 164 (48) (2) 86 (49) **$ppFEV_1$** **Mean, percentage points (SD)** (1) 60.4 (14.2) (2) 60.2 (13.8) **BMI** **Mean, kg/m² (SD)** (1) 21.4 (2.9) (2) 20.9 (2.8) ***Pseudomonas* positive, no.**	**Pooled Analysis, least-squares means** **$ppFEV_1$** **Mean absolute change from baseline, percentage points (95% CI) – Wang-Hankinson** 72 weeks (1) 0.5 (−0.4 to 1.5) (2) 1.5 (0.2 to 2.9) 96 weeks (1) 0.5 (−0.7 to 1.6) (2) 0.8 (−0.8 to 2.3) **$ppFEV_1$** **Mean absolute change from baseline, percentage points (95% CI) – GLI**	**Death, n (%)** (1) 2 (0.5) (2) 1 (0.5) **Discontinuations for two groups, n (%)** 170 (33) **Discontinuation d/t AE, n (%)** 38 (7) **Infective PEx of CF, %** 65 **Cough, %** 44 **Increased sputum, %**

		those on LUM/IVA in Traffic/Transport had received 96 weeks of active drug.	study drug or procedures • Participation in an investigational drug trial	(1) 261 (2) 126	72 weeks (1) 0.9 (0.0 to 1.9) (2) 1.9 (0.6 to 3.2) 96 weeks (1) 1.1 (0.0 to 2.2) (2) 1.1 (−0.5 to 2.6) **ppFEV$_1$** **Mean relative change from baseline, % (95% CI)** At 72 weeks (1) 1.4 (−0.3 to 3.2) (2) 2.6 (0.2 to 5.0) At 96 weeks (1) 1.2 (−0.8 to 3.3) (2) 1.1 (−1.7 to 3.9) **BMI** **Mean absolute change from baseline, kg/m^2** At 72 weeks (1) 0.69 (0.56 to 0.81) (2) 0.62 (0.45 to 0.79) At 96 weeks (1) 0.96 (0.81 to 1.11) (2) 0.76 (0.56 to 0.97)	22 **Hemoptysis, %** 20

					CFQ-R Respiratory domain **Mean absolute change from baseline, points (95% CI)** <u>At 72 weeks</u> (1) 5.7 (3.7 to 7.5) (2) 3.3 (0.7 to 5.9) <u>At 96 weeks</u> (1) 3.5 (1.3 to 5.8) (2) 0.5 (−2.7 to 3.6) **PEx,** **No. of events per patient-year (95%CI)** (1) 0.65 (0.56 to 0.75) (2) 0.69 (0.56 to 0.85) **PEx,** **No. of events requiring hospital admission per patient-year (95%CI)** (1) 0.24 (0.19 to 0.29) (2) 0.30 (0.22 to 0.40) **PEx,** **No. of events requiring intravenous antibiotics per patient-year (95%CI)**	

					(1) 0.32 (0.26 to 0.38) (2) 0.37 (0.29 to 0.49)	
Konstan [147] ***Pediatric Pulmonology*** **2015** **Abstract**	**See Konstan 2017** Interim analysis of PROGRESS at 24 weeks	**N=176** (1) LUM/IVA: 400 mg of lumacaftor every 12 hours in combination with 250 mg of ivacaftor every 12 hours (n=340) (2) LUM/IVA: Placebo transitioned to 400 mg lumacaftor every 12 hours in combination with ivacaftor 250 mg every 12 hours (n=176)	**See Konstan 2017**	**See Konstan 2017**	**$ppFEV_1$** **Mean (least-squares) relative change from baseline, percent (SE); p-value** 24 weeks of PROGRESS* (1) 2.6 (0.47); p<0.0001 (2) 3.5 (0.64); p<0.0001 **BMI** **Mean (least-squares) absolute change from baseline, kg/m^2 (SE); p-value** 24 weeks of PROGRESS* (1) 0.56 (0.06); p<0.0001 (2) 0.37 (0.08); p<0.0001 **CFQ-R Respiratory domain** **Mean absolute change from baseline, points (SE); p-value** 24 weeks of PROGRESS*	**Most commonly reported AEs:** Infective PEx of CF (48%) Cough (39%) Headache (17%) Dyspnea (17%) Abnormal respiration (14%)

					(1) 6.3 (0.85); p<0.0001 (2) 5.1 (1.17); p<0.0001 **PEx** **Event rate per year (95%CI)** (1) 0.6 (0.5 to 0.8) (2) 0.6 (0.5 to 0.8) *Interim analysis	
McColley [141] ***Pediatric Pulmonology*** **2015** **Abstract**	**See Wainwright 2015** Post hoc analysis TRAFFIC and TRANSPORT evaluating the association between changes in percent predicted FEV1 and PE rates	Stratified analysis by: • ≤0% or • >0% absolute improvement in $ppFEV_1$ AND • ≥5 or • <5% relative improvement in $ppFEV_1$ from baseline to Day 15 •	**See Wainwright 2015**	**See Wainwright 2015**	**Rate Ratio (95% CI), drug vs. placebo** **PEx** ≤0% absolute improvement: 0.74 (0.55 to 0.99) >0% absolute improvement: 0.53 (0.40 to 0.69) <5% relative improvement: 0.62 (0.47 to 0.80) ≥5% relative improvement: 0.60 (0.44 to 0.82) **PEx requiring hospitalization** ≤0% absolute improvement: 0.40 (0.23 to 0.69) >0% absolute improvement:	**NA**

					0.38 (0.24 to 0.59) <u><5% relative improvement:</u> 0.31 (0.19 to 0.51) <u>≥5% relative improvement:</u> 0.50 (0.31 to 0.82) **PEx requiring antibiotics** <u>≤0% absolute improvement:</u> 0.49 (0.33 to 0.74) >0% absolute improvement: 0.40 (0.28 to 0.58) <5% relative improvement: 0.37 (0.25 to 0.54) ≥5% relative improvement: 0.54 (0.37 to 0.80)	
Taylor-Cousar[148] ***Journal of Cystic Fibrosis*** **2017**	Open-label prospective study of LUM/IVA in patients homozygous for *F508del* with $ppFEV_1$<40% Six centers in United States	**N=46** LUM/IVA 400 mg q 12 hours with IVA 250 mg q 12 hours (n=28) ½ dose necessary for 39% of patients at start of study (n=18)	**Inclusion** • Confirmed diagnosis of CF • Homozygosity for the *F508del*-CFTR mutation • Age of 12 years or older • $ppFEV_1$<40%, adjusted for age, gender and height **Exclusion**	**Mean age, years (range)** 32.1 (17 to 56) **Sex: Male, n (%)** 30 (65) **$ppFEV_1$** **Mean, percentage points (range)** **29.1 (18.3 to 42.0)** **BMI** **Mean, kg/m² (range)** 21.4 (15.7 to 28.5)	**Primary endpoint: safety and tolerability** Secondary outcomes: **Mean absolute change in $ppFEV_1$ (least-squares) from baseline (95% CI):** Day 15: -1.7pp (-3.2 to -0.1)	Any AE, n (%): 43 (93) AE leading to treatment discontinuation: 8 (17) Serious AE: 18 (39) **AE leading to death: 1 (2)**

	Duration of follow-up: 24 weeks		• Current use of invasive mechanical ventilation • Any comorbidity that may confound study results or increase potential harm to participant • Abnormal liver or renal function	**Documentation of being on lung transplant list at screening, n** Yes: 2 No: 25 Unavailable: 19	Week 24: -0.4pp (-1.9 to 1.1) **Mean absolute change in CFQ-R respirator domain score (LS) from bassline (95% CI):** Week 24: 2.5 (-1.0 to 5.9) **BMI change from baseline, mean (SD):** Week 24: 0.29 kg/m^2 (0.17) Also measured: Annualized all-cause hospitalization event rate in the 24 weeks prior to study compared with the 24 weeks on LUM/IVA 1.15 events/year compared with 2.78 events/year prior to study start IV antibiotic duration (days) in the 24 weeks prior to study compared with the 24 weeks on study drug. Found LUM/IVA led to decreased normalized total	AE with incidence >10%: Infective PE: 27 (59) **Respiration abnormal: 26 (57)** Cough 21 (46) Dyspnea 20 (43)

					duration (11.38 days) vs. prior 24 weeks (19.89 days). Mean difference of -8.52 (3.67), p=0.0369	
Jennings [96] ***Annals ATS*** **2017**	Retrospective observational study, pre/post treatment with LUM/IVA One center: Johns Hopkins Duration of follow-up: 11 months Subgroup by age and FEV_1	**N=116** (1) Pre-LUM/IVA (2) Post-LUM/IVA	**Exclusion:** • Previous exposure to LUM/IVA • Participation in a clinical trial	**Homozygous *F508del*** 100% **Sex** **M:F** 54:62 **Age** **Mean, years (range)** 24.7 (12-59) **$ppFEV_1$** **Mean, percentage points (range)** 67.4 (20-115) **CF-related diabetes (CFRD), No. (%)** 26 (22.4) ***Pseudomonas* positive No. (%)** 71 (61.2) **MRSA positive** **No. (%)** 35 (30.2) ***B. cepacia* complex positive, No. (%)** 8 (6.9)	**$ppFEV_1$** **Mean change from baseline, percentage points (range)** 0.11 (−39 to 20)	**Reported Side Effects, n (%)** 46 (39.7) **Discontinuation** 20 (17.2) **Chest tightness/discomfort** 23 (19.8) **Dyspnea** 12 (10.3) **Increased cough/congestion** 10 (8.6) **Diarrhea** 5 (4.3) **Nausea** 3 (2.6) **Decreased appetite** 2 (1.7) **Rash** 2 (1.7)

				Proton-pump inhibitor use, No. (%) 51 (44) **Anti-depressant use, No. (%)** 21 (18.1) **Azole use, No. (%)** 6 (5.2)		**Discontinuation by subgroup, adjusted odds ratio (95% CI):** **Age**: 1.00 (0.95 to 1.06) **Female**: 3.12 (1.04 t0 9.34) **Baseline** $ppFEV_1$ <40%: 2.35 (0.74 to 7.50)
Ratjen [86] ***Lancet Resp Med*** **2017** **Homozygous *F508del***	Phase III, randomized, double-blind, placebo-controlled, multinational trial Nine countries: USA, Australia, Belgium, Canada, Denmark, France, Germany, Sweden, and the UK Duration of follow-up: 24 weeks Enrollment: July 23, 2015 to Sept 20, 2016	**N=206** (1) LUM/IVA: Lumacaftor 200 mg and ivacaftor 250 mg q 12 (n=104) (2) Placebo (n=102)	**Inclusion:** • Age 6-11 • Confirmed diagnosis of cystic fibrosis • Weight at least 15 kg • ppFEV1≥70% and lung clearance index (LCI) ≥ 7.5 • homozygous *F508del* **Exclusion:** • Any comorbidity or lab abnormality that may confound study results or increase potential harm to participant • Acute respiratory tract infection, PE, or changes in therapy for pulmonary disease within 28 days of treatment initiation	**Mean age, years (SD)** (1) 8.7 (1.6) (2) 8.9 (1.6) **Sex** **Female, n (%)** (1) 63 (61) (2) 58 (57) **$ppFEV_1$** **Mean, percentage points (SD)** (1) 88.8 (13.7) (2) 90.7 (10.8) **Weight** **Mean, kg (SD)** (1) 29.4 (6.5) (2) 30.2 (6.8) **LCI** **Mean (SD)** (1) 10.3 (2.4) (2) 10.3 (2.2)	**LCI** **Mean (least-squares) absolute change from baseline, score (95% CI)*** 24 weeks (1) −1.0 (−1.3 to −0.8) (2) 0.1 (−0.2 to 0.3) Difference: −1·1 (−1.4 to −0.8) p<0·0001 **BMI** **Mean (least-squares) absolute change from baseline, kg/m^2 (95% CI)** 24 weeks (1) 0.4 (0.3 to 0.5) (2) 0.3 (0.1 to 0.4) Difference: 0·1 (−0.1 to 0.3) p=0.2522 **$ppFEV_1$**	**Any AE, n (%)** (1) 98 (95) (2) 98 (97) **Any SAE, n (%)** (1) 13 (13) (2) 11 (11) **Study discontinuation, n (%)** (1) 1 (1)* respiration abnormal (2) 0 (0) **Elevated liver enzymes of clinical significance, n (%):** (1) 13 (13) (2) 8 (8) **Cough, n (%)** (1) 46 (45) (2) 47 (47)

			• History of solid organ transplant		**Mean (least-squares) absolute change from baseline, percentage points (95% CI)** 24 weeks (1) 1.1 (−0.4 to 2.6) (2) −1.3 (−2.8 to 0.2) Difference: 2.4 (0.4 to 4.4) p=0.0182 **CFQ-R** **Mean (least-squares) absolute change from baseline, points (95% CI)** 24 weeks (1) 5.5 (3.4 to 7.6) (2) 3.0 (1.0 to 5.0) Difference: 2.5 (−0.1 to 5.1) p=0.0628 *Decreases in LCI reflect improvements in lung function while increases in LCI indicate lung function decline	**Infective PEx of CF, n (%)** (1) 20 (19) (2) 18 (18) **Oropharyngeal pain, n (%)** (1) 15 (15) (2) 10 (10) • **Pyrexia, n (%)** (1) 15 (15) (2) 20 (20) **Acute change in ppFEV$_1$ immediately after study drug administration @ day 1, mean absolute change (SD)** **< 2 hours post-dose** (1) -5.5 (8.2) (2) -0.1 (5.1) **4-6 hours post-dose** (1) -7.7 (7.3) (2) -1.4 (7.1) **24 hours post-dose** (1) -4.1 (10.1) (2) -1.7 (6.8)

Milla [89] ***Am J Respir Crit Care Med*** **2017** **Homozygous *F508del***	Open-label, phase III Duration of follow-up: 24 weeks active med with 2 week washout	**N=58** (54 completed 24 weeks) Lumacaftor 200 mg q 12 hours with 250 mg of ivacaftor q 12 hours	**Inclusion**: • Age 6-11 at screening • Confirmed diagnosis of cystic fibrosis • ppFEV1≥40% • Homozygous *F508del* • Stable disease **Exclusion**: • Any comorbidity or lab abnormality that may confound study results or increase potential harm to participant	**Mean age, years (SD)** 9.1 (1.53) **Sex Female, n (%)** 31 (53.4) **$ppFEV_1$** **Mean, percentage points (SD)** 91.4 (13.7) **Weight** **Mean, kg (SD)** 31.5 (6.1) **Weight-for-age z-score** **Mean (SD)** -0.03 (1.03) **BMI-for-age z-score** **Mean (SD)** 0.01 (0.90)	**$ppFEV_1$** **Mean (least-squares) absolute change from baseline, percentage points (95% CI)** 24 weeks 2.5 (-0.2 to 5.2) **BMI** **Mean (least-squares) absolute change from baseline, kg/m^2 (95% CI)** 24 weeks 0.64 (0.46 to 0.83) **BMI-for-age z-score** **Mean (least-squares) absolute change from baseline (95% CI)** 24 weeks 0.15 (0.08 to 0.22) **Weight-for-age Z score** **Mean (least-squares) absolute change from baseline (95% CI)** 24 weeks 0.13 (0.07 to 0.19) **CFQ-R** **Mean (least-squares) absolute change from**	**All adverse events n (%):** 55 (94.8) **Serious adverse event n (%):** 4 (6.9) **Interruption of treatment due to an adverse event, n (%):** 6 (10.3) **Discontinuation due to an adverse event, n (%):** 2 (3.4) **Elevated liver enzymes of clinical significance, n (%):** 11 (19.3) **Serious events, n (%):** Infective PEx: 2 (3.4) Ileus: 1 (1.7) Elevated liver transaminase levels: 1 (1.7) **Respiratory events n (%):** Dyspnea: 1 (1.7)

					baseline, points (95% CI) 24 weeks 5.4 (1.4 to 9.4) **LCI (exploratory endpoint; n=30) Mean (least-squares) absolute change from baseline, score (95% CI)*** 24 weeks -0.88 (-1.40 to -0.37) *Decreases in LCI reflect improvements in lung function while increases in LCI indicate lung function decline	Respiration abnormal: 1 (1.7) Wheezing: 2 (3.4) **Common adverse events, n (%):** Cough: 29 (50) Nasal congestion: 12 (20.7) Infective PEx: 12 (20.7) Headache: 12 (20.7) **Cataract, n (%):** 1 (1.7)
Boyle [149] ***Lancet Respiratory*** **2014** **Homozygous *F508del***	Double-blind, placebo-controlled, phase 2 trial with 3 cohorts 24 centers in Australia, Belgium, Germany, New Zealand or US Enrollment: Oct 2010 to May 2012	**N=35** Three cohorts: only reporting on cohort 3, days 28-56 (combo) (1) LUM/IVA: 400 mg lumacaftor q 12 hours with 250 mg ivacaftor q 12 hours (n=11)	**Inclusion**: • Age 18+ • Confirmed diagnosis of cystic fibrosis • ppFEV$_1$≥40% • At least one *F508del* (we only report on two copies) **Exclusion**: • Any comorbidity or lab abnormality that may confound study results or increase	**Only LUM/IVA group baseline provided - placebo pooled (mixed hetero and homozygous)** **Age** **Mean, years (SD)** (1) 25.5 (6.7) (2) 30.8 (12.4) **Sex** **Female, n (%)** (1) 5 (45) (2) 9 (33)	**ppFEV$_1$** **Mean (least-squares) absolute change from baseline, percentage points (95%CI)** (1) 6.1 (2.0 to 10.2) (2) −1.6 (−4.2 to 1.1) Difference: 7.7 (2.7 to 12.6) **ppFEV$_1$** **Mean (least-squares) relative change from**	**Any AE, n (%)** (1) 10 (91) (2) 20 (74) • **SAE, n subjects (%)** (1) 1 (9); 2 events (1 PE) (2) 4 (15); 6 events (4 PE) **PEx of CF, n (%)** (1) 2 (18) (2) 7 (26)

	Duration of follow-up: 28 days	(2) Placebo (n=24; pooled across cohort 2 and 3)	potential harm to participant • PE or change in treatment within 14 days first dose • Prolonged QT/QTc interval • Solid organ transplant • Used inhibitors or inducers of CYP3A4 • In another trial in last 3 months	**BMI** **Mean, kg/m² (SD)** (1) 21.7 (2.9) (2) 22.6 (2.7) **Weight** **Mean, kg (SD)** (1) 60.7 (10.3) (2) 66.0 (10.6)	**baseline, percentage points (95%CI)** (1) 8.2 (1.8 to 14.7) (2) −2.1 (−6.3 to 2.2)	**Discontinuation d/t AE, n** 1/15 **Cough, n (%)** (1) 3 (27) (2) 6 (22) **Headache, n (%)** (1) 2 (18) (2) 5 (19)
Ivacaftor						
Ramsey [67] ***NEJM*** **2011** **STRIVE – *G551D*** **Good**	Phase 3, randomized, double-blind, placebo-controlled international trial Duration of follow-up: 48 weeks	**N=161** (1) IVA: 150 mg of ivacaftor twice daily (n=83) (2) Matched Placebo (n=78)	**Inclusion** • 12 years of age or older • Confirmed CF diagnosis • *G551D* mutation on at least one *CFTR* allele • FEV_1 between 40-90% of predicted value for persons of their age, sex, and height **Exclusion** • History of illness or condition that may confound results or pose safety risk • Acute respiratory infection, PE, or changes in therapy for pulmonary	**Age** **Mean, years (range)** (1) 26.2 (12-53) (2) 24.7 (12-53) **Sex** **Female, n (%)** (1) 44 (53) (2) 40 (51) **$ppFEV_1$** **Mean, percentage points** (1) 63.5 (2) 63.7 **Weight** **Mean, kg** (1) 61.7 (2) 61.2 **BMI** **Mean, kg/m²**	**$ppFEV_1$** **Mean absolute change from baseline, percentage points (95% CI)** (1) 10.1 (2) −0.4 Difference=10.5 (8.5 to 12.5) **PEx** **No. of events (rate per subject)** (1) 47 (0.59) (2) 99 (1.38) **PEx** **No. of subjects** (1) 28 (2) 44	**Any AE, n (%)** (1) 82 (99) (2) 78 (100) **SAE, n (%)** (1) 20 (24) (2) 33 (42) **Interruption d/t AE, n (%)** (1) 11 (13) (2) 5 (6) **Discontinuation d/t AE, n (%)** (1) 1 (1) (2) 4 (5) **PEx, n (%)** (1) 11 (13) (2) 26 (33)

			disease within 4 weeks of enrollment • Abnormal liver and renal function • History of solid organ or hematological transplant • Pregnancy, breast-feeding, or planning pregnancy • On-going participation in another clinical trial • Using inhaled hypertonic saline treatment • Concomitant use of CPY3A4 inhibitors or inducers	(1) 21.7 (2) 21.9 ***CFQ-R Respiratory domain** (1) NR (2) NR * Scores on (CFQ-R) range from 0-100, higher scores indicating a higher patient-reported QoL with regard to respiratory status.	RR (95% CI): 0.43 (0.27 to 0.68) **Weight** **Mean change from baseline, kg (95% CI)** (1) 3.1 (2) 0.4 Difference=2.7 (1.3 to 4.1) **CFQ-R Respiratory domain** **Absolute change from baseline, points** (1) 5.9 (2) −2.7 Difference=8.6	**Hemoptysis, n (%)** (1) 1 (1) (2) 4 (5)
Davies [68] ***Am J Respir Care Med*** **2013** **ENVISION – *G551D*** **Good**	Phase 3, randomized, double-blind, placebo-controlled trial Duration of follow-up: 48 weeks	**N=52** (1) IVA: 150 mg of ivacaftor twice daily (n=26) (2) Matched Placebo (n=26)	**Inclusion** • 6-11 years of age • Confirmed CF diagnosis • *G551D* mutation on at least one *CFTR* allele • FEV_1 of 40-105% of the predicted value for persons of their age, sex, and height • Body weight ≥15kg **Exclusion** • History of illness or condition that may confound results or pose safety risk • Acute respiratory infection, PE, or changes in therapy	**Age** **Mean, years (range)** (1) 8.9 (6-12) (2) 8.9 (6-12) **Sex** **Female, n (%)** (1) 17 (65) (2) 10 (38) **$ppFEV_1$** **Mean, percentage points (range)** (1) 84.7 (52.4-133.8) (2) 83.7 (44.0-116.3) **Weight** **Mean, kg (range)** (1) 31.8 (18.8-62.6) (2) 30.0 (17.8-46.3)	**$ppFEV_1$** **Mean adjusted* change from baseline, percentage points (95% CI)** (1) 10.7 (2) 0.7 Difference= 10.0 (4.5 to 15.5) **Weight** **Mean adjusted* change from baseline, kg (95% CI)** (1) 5.9 (2) 3.1 Difference=2.8 (1.3 to 4.2)	**Any AE, n (%)** (1) 26 (100) (2)25 (96.2) **SAE, n (%)** (1) 5 (19) (2) 6 (23) **Interruption d/t AE, n (%)** (1) 1 (4) (2) 3 (12) **Discontinuation d/t AE, n (%)** (1) 0 (2) 1 (4) **PEx of CF, n (%)** (1) 8 (31)

			for pulmonary disease within 4 weeks of enrollment • Abnormal liver and renal function • History of solid organ or hematological transplant • On-going participation in another clinical trial • Using inhaled hypertonic saline treatment • Concomitant use of CPY3A4 inhibitors or inducers	**BMI** **Mean, kg/m^2 (range)** (1) 17.1 (14.2-26.0) (2) 16.8 (13.8-22.1) **CFQ-R Respiratory domain** **Mean, points** (1) 78 (2) 80	**CFQ-R Respiratory domain** **Mean adjusted* change from baseline, (95% CI)** (1) 6.1 (2) 1.0 Difference=5.1 (−1.6 to 11.8) **PExs†** **No. reported** (1) 4 (2) 3 * Least squares mean and mixed-effects model for repeated measures. Adjusted for all available. † Protocol-defined exacerbations. Additional exacerbations were reported as AEs, but difference in definitions were not available.	(2) 8 (31) **Cough, n (%)** (1) 13 (50) (2) 19 (73) **Headache, n (%)** (1) 7 (27) (2) 4 (15)
McKone [73] ***Lancet Respir Med*** **2014** **PERSIST – *G551D*** **Good**	Phase 3, open-label extension Duration of follow-up: 96 weeks	**N=192** (1) IVA: 150 mg of ivacaftor twice daily a.) STRIVE IVA (n=77) b.) STRIVE placebo (n=67) c.) ENVISION IVA (n=26) d.) ENVISION	**Inclusion** • *G551D* mutation on at least one *CFTR* allele • Had completed either STRIVE or ENVISION study • Negative urine pregnancy test for women of child-bearing potential had	**Age** **Mean, years (SD)** (1) a.) 27.7 (9.8) b.) 26.0 (9.6) c.) 9.8 (1.9) d.) 9.8 (1.8) **Sex** **Female, n (%)** (1)	**ppFEV$_1$** **Mean absolute change from baseline, percentage points (SD)** (1) a.) 9.4 (10.8) b.) 9.5 (11.2) c.) 10.3 (12.4) d.) 10.5 (11.5)	**Any AE, n (%)** STRIVE and ENVISION placebo groups: Week 1-48: 82 (92%) Week 48-96: 81 (92%)

		placebo (n=22) Note: Groups a) and c) on IVA for 48 weeks prior to PERSIST start, then followed for additional 96 weeks on ivacaftor (144 weeks total); Groups b) and d) on ivacaftor for 96 weeks of PERSIST after 48 weeks of placebo in prior trial (96 weeks total). All patients in PERSIST received ivacaftor	• Participants of child-bearing potential and who are sexually active must meet contraceptive requirements **Exclusion** • History of illness or condition that may confound results or pose safety risk • History of study treatment intolerance • Pregnancy, breast-feeding, or planning pregnancy • Concomitant use of CPY3A4 inhibitors or inducers	a.) 41 (53) b.) 35 (52) c.) 17 (65) d.) 9 (41) **$ppFEV_1$** **Mean, percentage points (SD)** (1) a.) 71.9 (18.5) b.) 62.2 (18.7) c.) 94.9 (14.5) d.) 83.6 (17.4) **BMI** **Mean, kg/m² (SD)** (1) a.) 23.0 (4.0) b.) 21.9 (3.5) c.) 18.6 (2.9) d.) 16.8 (2.2) **Weigh** **Mean, kg (SD)** (1) a.) 66.0 (14.9) b.) 61.4 (13.1) c.) 37.9 (11.7) d.) 32.4 (8.9)	**BMI** **Mean absolute change from baseline, kg/m² (SD)** (1) a.) 1.2 (2.2) b.) 1.0 (1.6) c.) 0.30 (0.6) d.) 0.37 (0.5) **Weight** **Mean absolute change from baseline, kg (SD)** (1) a.) 4.1 (7.1) b.) 3.0 (4.7) c.) 14.8 (5.7) d.) 10.1 (4.1) **CFQ-R Respiratory domain** **Mean absolute change from baseline, points (SD)** (1) a.) 6.8 (19.6) b.) 9.8 (16.2) c.) 10.6 (18.9) d.) 10.8 (12.8)	STRIVE and ENVISION ivacaftor groups: Week 48-96: 100 (97%) Week 96-144: 95 (92%) **SAE, n (%)** All SAEs: 82 (43%) Week 1-48: 38 (20%) Week 48-96: 44 (23%) STRIVE and ENVISION placebo groups: Week 1-48: 15 (17%) Week 48-96: 19 (21%) STRIVE and ENVISION ivacaftor groups: Week 48-96: 23 (22%) Week 96-144: 25 (24%) **Deaths, n (%)** (1) 2 **Discontinuation d/t AE, n (%)** (1) 3 (2)

						PEx, no. of events (%) (1) STRIVE and ENVISION placebo groups: Week 1-48: 30 (34%) Week 48-96: 35 (39%) STRIVE and ENVISION ivacaftor groups: Week 48-96: 46 (45%) Week 96-144: 46 (45%) **Cough, n (%)** (1) STRIVE and ENVISION placebo groups: Week 1-48: 27 (30%) Week 48-96: 16 (18%) STRIVE and ENVISION ivacaftor groups: Week 48-96: 32 (31%) Week 96-144: 27 (26%)

						Headache, n (%) (1) <u>STRIVE and ENVISION placebo groups</u>: Week 1-48: 11 (12%) Week 48-96: 7 (8%) <u>STRIVE and ENVISION ivacaftor groups</u>: Week 48-96: 14 (14%) Week 96-144: 17 (17%)
De Boeck [69] ***J Cyst Fibros*** **2014** **KONNECTION – non-G551D gating mutations** **Fair**	Two-part, double blind, randomized, controlled, crossover study Trial conducted in 12 sites in the United States, France, and Belgium. Duration of follow-up: 8 weeks	**N=39** (1) IVA-Placebo: 150 mg of ivacaftor every 12 hours for 8 weeks followed by placebo q12 hours for 8 weeks (n=20) (2) Placebo-IVA: Placebo q12 hours for 8 weeks followed by ivacaftor 150 mg q12 hours for 8 weeks (n=19) Both treatment groups observed a	**Inclusion** • Confirmed diagnosis of CF • A non-G51D gating mutation on at least one allele • Age of 6 years or older **Exclusion** • History of illness or condition that may confound results or pose safety risk • Acute respiratory infection, PE, or changes in therapy for pulmonary	**Age** **Mean, years** (1) 23.8 (2) 21.7 **Sex** **Female, n (%)** (1) 7 (35.0) (2) 10 (52.6) **$ppFEV_1$** **Mean, percentage points** (1) 77.7 (2) 79.1 **BMI-for-age z-score** **Mean, score** (1) 0.50 (2) 0.23	**$ppFEV_1$** **Mean absolute change* from baseline, percentage points (95% CI)** (1) 7.5 (2) −3.2 Difference=10.7 (7.3 to 14.1) **BMI** **Mean absolute change from baseline, kg/m^2 (95% CI)** (1) 0.7 (2) 0.02 Difference=0.7 (0.34 to 0.99)	**Any AE, n (%)** Ivacaftor: 28 (73.7) Placebo: 31 (83.8) **SAE, n (%)** Ivacaftor: 4 (10.5) Placebo: 7 (18.9) **Infective PEx of CF, n (%)** (1) 9 (23.7) (2) 11 (29.7) **Cough, n (%)** (1) 6 (15.8) (2) 7 (18.9)

		4-8 week washout between placebo and ivacaftor	disease within 4 weeks of enrollment • History of solid organ or hematological transplant • On-going participation in another clinical trial within 30 days of screening • Using inhaled hypertonic saline treatment • Concomitant use of CPY3A4 inhibitors or inducers • Evidence of cataracts or lens opacity at screening		**CFQ-R respiratory domain** **Mean absolute change from baseline, points (95% CI)** (1) 8.9 (2) −0.7 Difference= 9.62 (4.5 to 14.7) *Mixed-effects model for repeated measures.	**Headache, n (%)** (1) 5 (25) (2) 7 (39) **Discontinuation d/t AE, n (%)** (1) 0 (2) 0
Moss [70] ***NEJM*** **2015** **KONDUCT – R117H** **Good**	Phase 3, multicenter, placebo controlled, double blind, parallel group trial Duration of follow-up: 24 weeks	**N=69** (1) IVA: 150 mg of ivacaftor every 12 hours for 24 weeks (n=34) (2) Placebo (n=35)	**Inclusion** • 6 years of age or older • Confirmed diagnosis of CF • Arg117His-CFTR mutation • $ppFEV_1$ of at least 40 **Exclusion** • Gating mutation (1 or more) • History of illness or condition that may confound results or pose safety risk • Acute respiratory infection, PE, or changes in therapy	**Age** **Mean, years (SD)** (1) 29.2 (16.6) (2) 32.7 (17.4) **Sex** **Female, n (%)** (1) 19 (56.0) (2) 20 (57.0) **$ppFEV_1$** **Mean, percentage points (SD)** (1) 75.7 (19.3) (2) 70.2 (18.9) **BMI** **Mean, kg (SD)** (1) 24.5 (6.3) (2) 23.1 (6.0)	**$ppFEV_1$** **Mean absolute change from baseline, percentage points (SD)** (1) 2.6 (1.2) (2) 0.5 (1.1) Difference=2.1 (95% CI:-1.13 to 5.35) **$ppFEV_1$** **Mean relative change from baseline % (SD)** (1) 4.8 (1.9) (2) -0.2 (1.8)	**Protocol-defined PEx of CF, n patients (%)** (1) 11 (32.3) (2) 13 (37) **Protocol-defined PEx of CF, n events (event rate)** (1) 13 (0.249) (2) 17 (0.295) **SAE, n patients (%)** (1) 4 (12) (2) 6 (17.5)

			for pulmonary disease within 4 weeks of enrollment • Abnormal liver function at screening • History of solid organ or hematological transplant • History or alcohol, medication, or illicit drug abuse within 1 year of study initiation • On-going participation in another clinical trial within 30 days of screening • Any "non-CF-related" illness within 2 weeks of study initiation • Concomitant use of CPY3A4 inhibitors or inducers	**CFQ-R Respiratory domain Mean, points (SD)** (1) 75.3 (20.1) (2) 66.4 (24.4)	Difference= 5.0 (95% CI:-0.24 to 10.31) **BMI** **Mean absolute change from baseline, kg/m^2 (SD)** (1) 0.49 (0.67) (2) 0.23 (0.65) Difference=0.26 (95% CI:-1.57 to 2.10) **CFQ-R respiratory domain** **Mean absolute change from baseline, points (SD)** (1) 7.6 (2.2) (2) -0.8 (2.2) Difference=8.4 (95% CI:2.17 to 14.61)	**Needing admission to hospital, n patients (events)** (1) 2 (2) (2) 6 (7) **Needing intravenous antibiotic therapy, n patients (events)** (1) 2 (2) (2) 6 (8)
Davies [71] ***Lancet Respiratory*** **2016** **KIWI – gating mutations**	Two-part, open-label, single-arm, phase 3 study 15 hospitals in the USA, UK, and Canada Part B enrolled June 28, 2013 to Sept 26, 2013	**N=34 (Part B, only)** Part A: 4-day ivacaftor q 12 hours for pharmacokinetic and safety (two doses) - 50 mg if they weighed <14 kg (n=4), and 75 mg if they weighed ≥14 kg (n=5)	**Inclusion** • Children aged 2–5 years • Weight 8 kg or more • Confirmed diagnosis of CF • *CFTR* gating mutation on at least one allele (Gly551Asp, Gly178Arg, Ser549Asn, Ser549Arg, Gly551Ser, Gly970Arg, Gly1244Glu,	**Part B reported (only)** **Age** **N (%)** Age 2: 9 (26%) Age 3: 11 (32%) Ages 4 and 5: 14 (41%) **Sex** **Female, n (%)** 6 (18) **Weight-for-age z-score** **Mean, score (SD)**	**Part A results not reported** **Part B results:** **Mean weight-for age z-scores, mean (SD) – across both doses** Difference between 24 weeks and baseline: 0.2 (0.3), p<0.001	**Harms Part A not reported** **Harms Part B: Patients with any AE, n (%)** (1) 10 (100) (2) 23 (96) **SAE, no. events (no. pts, %)** (1) 4 (3, 30)

		Part B: 24-week safety (1) 50 mg (n=10) (2) 75 mg (n=24)	Ser1251Asn, Ser1255Pro, or Gly1349Asp) **Exclusion** • History of illness or condition that may confound results or pose safety risk • Acute respiratory infection, PE, or changes in therapy for pulmonary disease within 4 weeks of enrollment • Abnormal liver function at screening • History of solid organ or hematological transplant • Use of moderate or strong inducers or inhibitors of CPY3A4 • Participation in a clinical study of investigational or marketed drug within 30 days of screening	-0.2 (0.8) **Height-for-age z-score, Mean, score (SD)** -0.3 (0.8) **Mutations, n (%)** G551D homozygous: 1(3) G551D heterozygous with *F508del*: 26 (76) G551D heterozygous not *F508del*: 5 (15) Ser549Asn heterozygous: 2 (6)	**Mean BMI-for-age z-scores, mean (SD) – across both doses** Difference between 24 weeks and baseline – 0.4 (0.4), p<0.001 **Mean height-for-age z-scores, mean (SD) – across both doses** Difference between 24 weeks and baseline: -0.1 (0.3), p=0.84 **IRT, ng/mL (marker of pancreatic stress), mean (SD)** baseline to week 24 – 20.7 (24) p=0.002 FEV_1 not reported since spirometry is not a reliable measure in very young children	(2) 3 (3, 13) **SAE: Infective PEx of CF, n (%)** (1) 1 (10) (2) 1 (4) **AE: Infective PEx of CF, n (%)** (1) 1 (10) (2) 4 (17) **Cough, n (%)** (1) 4 (40) (2) 15 (63) **Vomiting, n (%)** (1) 3 (30) (2) 7 (29) **Hepatic enzyme elevation, n (%)** (1) 3 (30) (2) 2 (8)

Rowe [72] ***Am J Respir Care Med*** **2014** **GOAL**	Longitudinal cohort, single arm, observational study Duration of follow-up: 6 months	**N=153** (1) IVA: 150 mg of ivacaftor twice daily	**Inclusion:** • Male or female ≥ 6 years of age at Visit 1 • Must have a clinical diagnosis of cystic fibrosis and the following CFTR mutations: • Included mutations: G551D on at least 1 allele with any known or unknown mutations allowed on second allele; R117H on at least 1 allele with any known or unknown mutation on the second allele except G551D; a non-G551D gating mutation on one allele: (G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, G1349D) with any known or unknown mutation on the second allele except G551D or R117H **Exclusion** NR	**Age** **Mean, years (SD)** 21 (11.3) **Age categories, n (%)** Ages 6-11:38 (25) Ages 12-17: 33 (22) Ages 18-29: 52 (34) Ages 30+: 30 (20) **Sex** **Female, n (%)** 70 (46) **ppFEV$_1$** **Mean, percentage points (SD)** 82.4 (25.9) <u>By age</u> Ages 6-11: 104.3 (16.2) Ages 12-17: 91.2 (18.3) Ages 18+: 69.1 (23.3) **Weight** **Mean, kg (SD)** Pooled not reported <u>By age</u> Ages 6-11: 30.6 (7.7) Ages 12-17: 56.1 (15.7) Ages 18+: 66.5 (13.7) **BMI** **Mean, kg/m^2 (SD)** 21.3 (4.5)	**ppFEV$_1$** **Absolute change from baseline, percentage points (95% CI)** 1 mo: 6.7 (5.2 to 8.3) 3 mo: 5.4 (4.0 to 6.7) 6 mo: 6.7 (4.9 to 8.5) <u>6 mo, by age group (SD)</u> Ages 6-11: 4.3 (11.1) Ages 12-17: 8.1 (8.2) Ages 18+: 7.4 (10.7) **Weight** **Mean absolute change from baseline, kg (95%CI)** 1 mo: 1.2 (0.9 to 1.4) 3 mo: 1.7 (1.3 to 2.1) 6 mo: 2.5 (1.9 to 3.1) <u>6 mo, by age group (SD)</u> Ages 6-11: 3.7 (2.9) Ages 12-17: 3.3 (3.3) Ages 18+: 1.5 (3.5)	**Not reported**

				By age Ages 6-11: 17.2 (2.4) Ages 12-17: 21.0 (4.1) Ages 18+: 23.3 (4.1) **CFQ-R Respiratory domain Mean, points (SD)** Pooled not reported By age Ages 6-11: 83.6 (12.2) Ages 12-17: (76.2) (15.6) Ages 18+: 62.4 (20.5)	**BMI** **Mean absolute change from baseline, kg/m² (95% CI)** 1 mo: 0.4 (0.3 to 0.5) 3 mo: 0.6 (0.4 to 0.7) 6 mo: 0.8 (0.6 to 1.0) 6 mo, by age group (SD) Ages 6-11: 1.1 (1.2) Ages 12-17: 0.9 (1.0) Ages 18+: 0.5 (1.3) **CFQ-R Respiratory domain** **Mean absolute change from baseline, (95% CI)** 1 mo: 9.7 (7.1 to 12.4) 3 mo: 10.9 (8.1 to 13.7) 6 mo: 7.4 (4.1 to 10.7) 6 mo, by age group (SD) Ages 6-11: -0.7 (16.7) Ages 12-17: 7.6 (14.6)	

					Ages 18+: 11.7 (20.7)	
Flume [150] ***J Cyst Fibros*** **2017** **STRIVE** **Good**	Post-hoc analysis of participants who experienced PExs from STRIVE randomized clinical trial (Ramsey, 2011) This study analyzed only those who reported a PEx during STRIVE Duration of follow-up: 48 weeks (STRIVE)	**N=See STRIVE** (1) IVA: 150 mg of ivacaftor twice daily (n=83) (2) Matched placebo (n=78)	**See STRIVE**	**See STRIVE** **Characteristics of participants who had ≥1 protocol-defined PEx during study (baseline data prior to PEx)** (1) n=2 (2) n=44 **Age** **Mean, years (SD)** (1) 26.9 (7.81) (2) 24.4 (9.29) **Age, n (%)** (1) • <18: 4 (14.3) • ≥18: 24 (85.7) (2)	**PEx** **No. subjects (%)** (1) 28 (33.7) (2) 44 (56.4) **No. of PExs (event rate)** (1) 47 (0.589) (2) 99 (1.382) **No. of days per pt with event, mean (SD)** (1) 13.54 (27.27) (2) 36.67 (49.54) **No. of pts treated with IV antibiotics for PEx, n (%)** (1) 15 (18.1) (2) 27 (34.6) **No. of events treated with IV antibiotics, n (event rate)**	**See STRIVE**

				• <18: 11 (25.0) • ≥18:33 (75.0) **Weight** **Mean, kg (SD)** (1) 63.01 (13.95) (2) 59.33 (14.7) **BMI** **Mean, kg/m^2 (SD)** (1) 21.94 (3.42) (2) 21.68 (3.92) **BMI-for-age z-score** **Mean, score (SD)** (1) −0.95 (0.94) (2) −0.54 (0.95) **ppFEV$_1$ prior to first PEx** **Mean, percentage points (SD)** (1) 68.36 (20.67) (2) 61.64 (16.75)	(1) 28 (0.397) (2) 47 (0.711) **No. subjects hospitalized for PEx (%)** (1) 11 (13.3) (2) 23 (29.5) **No. of PExs treated by hospitalization (event rate)** (1) 21 (0.311) (2) 21 (0.489) **No. of subjects reporting increased cough during a PEx (%)** (1) 46/47 (97.9) (2) 95/99 (96.0) **No. of subjects reporting PEx with full long-term functional recovery* (%)** (1) 13/28 (46.4) (2) 21/44 (47.7) * Full long-term recovery=return to ≥100% of ppFEV$_1$ measurement most closely preceding PEx.	
Accurso [151] ***NEJM***	Multicenter phase 2 double-blind, placebo-controlled, two-part dose-ranging study (N=39).	**Part 1** **N=20** (1) IVA: ivacaftor every 12 hours in	**Inclusion** • 18 years of age or older • Diagnosed with CF	**Sex** **Females, n (%)** Part 1: 11 (55) Part 2: 9 (47)	**ppFEV$_1$** **Mean relative change from baseline,**	**All AEs, no. reported (%)** Part 1: 7 (88) Part 2: 6 (86)

2010 **Phase 2**	Part 1: Participants randomly assigned to receive 25, 75, or 150mg of ivacaftor, or placebo, every 12 hours for two 14-day periods separated by a washout period. Part 2: New participants randomly assigned to receive either 150 or 250mg of ivacaftor, or placebo, every 12 hours for 28 consecutive days. Duration of follow-up: 28 days	25, 75 or 150mg dosage for 14 days, then 25, 75, or 150mg dosage for 14 days post-washout period (n=4 per group) (2) Placebo (n=4) **Part 2** **N=19** (1) IVA: 150 (n=8) or 250mg (n=7) of ivacaftor every 12 hours for 28 consecutive days (2) Placebo (n=4)	• G551D mutation on at least one *CFTR* allele • ppFEV$_1$≥40 **Exclusion** • History of illness or condition that may confound results or pose safety risk • Acute respiratory infection, PE, or changes in therapy for pulmonary disease within 4 weeks of enrollment • Abnormal liver or renal function at screening • History of solid organ or hematological transplant • Pregnancy or breast-feeding • Ongoing participation in another therapeutic clinical trial, or prior participation in an investigational study without appropriate washout	**Age** **Median, years (range)** Part 1: 30 (19-51) Part 2: 21(18-42) **BMI** **Median, kg/m^2 (range)** Part 1: 23 (17-29) Part 2: 22 (20-25) **ppFEV$_1$** **Median, percentage points (range)** Part 1: 56 (42-109) Part 2: 69 (40-122) **CFQ-R Respiratory domain** **Median, score (range)** Part 1: NA Part 2: 72.2 (16.7-88.9)	**percentage points (95% CI)** Part 1 25mg: 4.9 (-2.6 to 12.5) 75mg: 10.0 (4.5 to 15.6) 150mg: 10.5 (3.3 to 17.7) Placebo: 0.7 (-8.8 to 10.2) Difference: 25mg vs placebo: p=0.45 75mg vs. placebo: p=0.09 150mg vs placebo: p=0.10 **ppFEV$_1$** **Median relative change from baseline, percentage points (range)** Part 2 150mg: 8.7 (2.1 to 31.3) 250mg: 4.4 (0 to 18.3) Placebo: 7.3 (5.2 to 8.2) Difference 150mg vs. placebo: p=0.56 250mg vs. placebo: p=0.78	**Mild AEs, no. reported (%)** Part 1: 5 (63) Part 2: 5 (71) **Moderate AEs, no. reported (%)** Part 1: 0 Part 2: 1 (14) **Severe AEs, no. reported (%)** Part 1: 2 (25) Part 2: 0 **Discontinuation in Part 2:** 0

					CFQ-R Respiratory domain **Median change from baseline, points (range)** <u>Part 2 at 28 days</u> 150mg: 8.3 (0 to 16.7) 250mg: 11.1 (-5.6 to 33.3) Placebo: 0 <u>Difference</u> 150mg vs. placebo: p=0.46 250mg vs. placebo: p=0.47	
Guigui [152] ***Respir Med Case Rep*** **2016**	Non-randomized comparative study of ivacaftor effectiveness in individuals with residual function mutations at a single CF center Duration of follow-up: 3 years (one month after initiating ivacaftor treatment and every three months after)	**N=11** (1) Ivacaftor (n=7) (2) Regular care (n=4)	**Inclusion:** • Ivacaftor provided by insurance company (at time of study, ivacaftor was not approved to treat those with residual function mutations).	**$ppFEV_1$** **Mean, percentage points** (1) 50 (2) NR **BMI** **Mean, kg (SD)** (1) 19.5 (2) (2) 22 (3) **CFQ-R Respiratory domain** **Mean, score (SD)** (1) 50 (5) (2) 48 (6) **No. of PEs per year (SD)** (1) 4.4 (2) (2) 4.6 (2)	**$ppFEV_1$** **Mean, percentage points (SD)** <u>Year 1</u> (1) NR (2) 61 (15) <u>Year 3</u> (1) 60 (NR) (2) 54 (14) **BMI** **Mean, kg/m^2 (SD)** <u>Year 3</u> (1) 22.3 (3) (2) 21 (3) **CFQ-R** **Mean, points (SD)** <u>Year 3</u> (1) 95 (5) (2) 50 (4)	**NR**

					No. of PEs per year (SD) Year 3 (1) 2 (2) (2) 5.5 (3)	
Sawicki [110] ***Am J Respir Crit Care Med*** **2015**	Non-randomized comparative study; G551D individuals 6+ years of age who received ivacaftor during a phase 3 study (STRIVE, ENVISION, and/or PERSIST) were matched to up to 5 *F508del* homozygous individuals using the Cystic Fibrosis Foundation Patient Registry (CFFPR). Individuals were matched by propensity score which included sex, baseline age, year of CF diagnosis, sweat chloride value, CF-related diabetes, weight-for-age z score, BMI, use of inhaled medications and $ppFEV_1$ (among others) Duration of follow-up: up to 3 years	**N=1,075** (1) Ivacaftor (n=189), G551D only (2) Regular care (n=886), *F508del* homozygous only	**Inclusion:** **G551D** • Participation in STRIVE, ENVISION, and/or PERSIST • Have at least 3 FEV_1 measures over ≥6 months after 30 days on ivacaftor ***F508del* homozygous** • 2010 baseline during a clinically stable encounter and matching by propensity score to a G551D individual participating in one of the Phase 3 studies	**$ppFEV_1$** **Mean, percentage points (SD)** (1) 65.7 (19.5) (2) 67.5 (20.4) **BMI-for-age z-score Mean, score (SD)** (1) -0.16 (0.90) (2) -0.12 (0.92) **Weight-for-age z-score Mean, score (SD)** (1) -0.21 (0.96) (2) -0.17 (0.92)	**$ppFEV_1$** **Annualized rate of decline, percent (SE)** Year 3 (1) -0.91 (0.34) (2) –1.72 (0.16) Difference = 0.80 (95% CI: 0.06 to 1.55)* **ppFEV1** **Treatment difference** Year 3 10.70 (p<0.001) **BMI** **Mean BMI-for-age z-score (SE)*** Year 3 (1) 0.087 (0.08) (2) -0.23 (0.04) **BMI-for-age z score, estimated rate of change*** (1) -0.016 (2) -0.024 p=0.72 **Weight** **Mean weight-for-age z-score (SE)** Year 3 (1) 0.08 (0.08)	**NR**

					(2) -0.22 (0.04) p<0.001 **Weight-for-age z score, estimated rate of change*** (1) NR (2) NR p=0.29 *Estimation and significance of rate change differences done by mixed model.	
Borowitz [108] ***Dig Dis Sci*** **2016**	Pooled and stratified data from STRIVE and ENVISION randomized clinical trials	**See STRIVE and ENVISION**	**See STRIVE and ENVISION**	**Age** **Mean, years (SD)** Ages ≤20 (1) 12 (4.2) (2) 12 (4.3) Ages >20 (1) 31 (8.4) (2) 29 (8.0) **ppFEV$_1$** **Mean, percentage points (SD)** Ages ≤20 (1) 77.5 (17.64) (2) 77.9 (19.01) Ages >20 (1) 60.3 (15.03) (2) 59.1 (15.57) **BMI** **Mean, kg (SD)** Ages ≤20 (1) 18.5 (2.92)	**Weight** **Mean (least-squares) change from baseline, kg*** Ages ≤20 (1) 4.9 (2) 2.2 Difference=2.7 (95% CI:1.14 to 4.29) Ages >20 (1) NR (2) NR **Weight** **Mean weight-for-age z-score, change from baseline*** Ages ≤20 (1) 0.29 (2) -0.06 Difference=0.35 (95%CI: 0.202 to 0.508)	**Not reported**

				(2) 18.2 (2.38) Ages >20 (1) 22.6 (3.73) (2) 23.1 (3.42) **BMI-for-age z-score Mean, score (SD)** Ages ≤20 (1) -0.179 (0.9533) (2) -0.220 (0.8516) Ages >20 (1) NR (2) NR **Mean weight at baseline, kg (SD)** Ages ≤20 (1) 43.3 (16.18) (2) 41.8 (15.12) Ages >20 (1) 64.9 (13.87) (2) 65.4 (13.26)	Ages >20 (1) NR (2) NR **BMI** **Mean change from baseline, kg/m²*** Ages ≤20 (1) NR (2) NR Ages >20 (1) 0.9 (2) -0.1 Difference=1.0 (95% CI: 0.44 to 1.49) **BMI** **Mean BMI-for-age z score change from baseline*** Ages ≤20 (1) 0.26 (2) -0.13 Difference=0.39 (95% CI: 1.35 to 0.573) Ages >20 (1) 2.7 (2)-0.2 Difference=2.9 (95%CI: 1.35 to 4.47) *At 48 weeks.	
Konstan [153]	Post-hoc analysis of STRIVE and ENVISION looking at ivacaftor	**See STRIVE and ENVISION**	**See STRIVE and ENVISION**	**Tertiles, by absolute change in $ppFEV_1$, percentage points:**	**$ppFEV_1$** **Mean absolute change from**	**PEx, mean no. of days**

Pediatr Pulmonol **2015**	efficacy on an individual-response level. Subgroups were defined by tertiles (thirds) of FEV_1 response. Patients were assigned to a tertile within treatment groups based on the absolute change from baseline in $ppFEV_1$ through 48 weeks of treatment.			Ivacaftor (n=109) Lower tertile: FEV ≤5.56 (n=37) Middle tertile: FEV >5.56 and ≤13.5 (n=36) Upper tertile: FEV>13.59 (n=36) Placebo (n=100) Lower: FEV ≤−2.65 (n=34) Middle: FEV >−2.65 and ≤1.74 (n=33) Upper: FEV<1.74 (n=33) **Age** **Mean, years (SD)** Ivacaftor Lower: 23.1 (13.7) Middle: 24.9 (10.6) Upper: 18.3 (8.3) Placebo Lower: 22.1 (11.2) Middle: 23.4 (11.4) Upper: 18.0 (8.7) **$ppFEV_1$** **Mean, percentage points (SD)** Ivacaftor Lower: 72.1 (23.0) Middle: 64.5 (18.2) Upper: 68.9 (11.7) Placebo Lower: 73.1 (19.7) Middle: 66.7 (18.7)	**baseline, percentage points (95% CI)*** Lower Tertile Ivacaftor: 1.58 Placebo: -6.39 Difference=7.97† (6.48 to 9.47) Lower ivacaftor vs. pooled placebo difference=2.29† (0.40 to 4.19) Middle Tertile Ivacaftor: 9.37 Placebo: -0.29 Difference=9.66† (8.77 to 10.55) Upper Tertile Ivacaftor: 21.19 Placebo: 5.59 Difference=15.60† (13.00 to 18.19) **Weight** **Mean change from baseline, kg (95% CI)*** Lower tertile difference= 0.62 (2.10 to 5.13)† Middle tertile difference= 1.89 (-0.18 to 3.97) Upper tertile difference= 2.65 (0.39 to 4.91)† **CFQ-R**	**experienced (SD)** Lower ivacaftor: 15.61 (30.57) Lower placebo: 29.79 (50.63) Difference=14.18 Middle ivacaftor: 14.59 (26.45) Middle placebo: 33.64 (49.67) Difference=19.05 Upper ivacaftor: 5.83 (15.94) Upper placebo: 28.02 (40.24) Difference=22.19 (p=0.0019)

				Upper: 64.6 (18.8) **Weight** **Mean, kg (SD)** Ivacaftor Lower: 56.5 (22.5) Middle: 58.3 (15.1) Upper: 48.8 (15.8) Placebo Lower: 53.1 (21.4) Middle: 57.0 (15.9) Upper: 50.7 (17.8)	**Mean absolute change from baseline, points (95% Ci)** Lower tertile difference: 4.42 (-1.04 to 9.89) Middle tertile difference: 11.3 (6.85 to 15.74)† Upper tertile difference: 6.26 (1.06 to 11.47)† *Through 48 weeks of treatment †Significant difference vs. placebo	
Quittner [133] ***Health Qual Life Outcomes*** **2015**	Analysis of STRIVE CFQ-R data broken down by individual survey scales: Body Image, Digestive Symptoms, Eating Problems, Emotional Functioning, Health Perceptions, Physical Functioning, Respiratory Symptoms, Role Functioning, Social Functioning, Treatment Burden, Vitality, and Weight. Participants ages 14+ completed the Teen/Adult version;	**See STRIVE**	**See STRIVE**	**See STRIVE**	**CFQ-R treatment difference (ivacaftor vs. placebo)** Body Image* 2.7 (p=0.086) Digestive Symptoms 0.5 (p=0.732) Eating Problems* 3.3 (p=0.002) Emotional Functioning* 2.1 (p=0.096) Health Perceptions* 7.6 (p<0.001) Physical Functioning* 4.4 (p=0.006) Respiratory Symptoms*	**Not reported**

	those under 14 at baseline completed the Child version. Parents of 12 and 13 year-olds completed the Parent/Caregiver CFQ-R. Minimal clinically important difference (MCID) defined as 4 points for CFQ-R scores.				8.6 (p<0.001) Role Functioning -0.6 (p=0.651) Social Functioning* 4.3 (p=0.003) Treatment Burden 3.3 (p=0.042) Vitality 5.5 (p=0.002)* Weight 5.3 (p=0.053) *Placebo reported decrease in CFQ-R score between baseline and 48 weeks.	
Heltshe [154] ***Clin Infect Dis*** **2015**	Combination data from GOAL and Cystic Fibrosis Foundation Patient Registry analyzing *Pseudomonas aeruginosa* (PA) incidence, prevalence, and association with clinical outcomes during treatment with ivacaftor. GOAL data (6 mos. of ivacaftor) supplemented with CFFPR data from year before and year after ivacaftor treatment initiation for comparison.	**See GOAL**	**See GOAL**	**PA infection duration in year prior to treatment with ivacaftor, n/N (%)** Persistent* 59/145 (40%) Intermittent 30/148 (20%) Infection-free 59/148 (40%) *Note: participants with persistent infection tended to be older, had lower FEV_1, and higher hospitalization rates at baseline.	**PA culture positivity, odds ratio*** 0.65 (35% reduction) **PA prevalence after ivacaftor initiation by baseline category, n/N infection free (%)*** Persistent 5/48 (10%) Intermittent 21/30 (70%) **Frequency of PA isolation after ivacaftor initiation, n/N (%)*** More frequent 7/143 (5%) Less frequent	**Not reported**

	Duration of follow-up: 2 years (Median follow-up in the CFFPR=12.5 mos.)				36/134 (27%) No change 91/143 (68%) Reduction in PA frequency was not significantly associated with improvements in FEV_1, BMI, hospitalization, or exacerbation rate. *On ivacaftor vs. before ivacaftor.	
Bai [155] ***J Cyst Fibros*** **2016** **Abstract**	Non-randomized comparative long-term post-approval observational safety study using data from UK and US CF patient registries. Comparators not receiving ivacaftor were matched to ivacaftor recipients based on age, sex, and genotype severity. Duration of follow-up: 1 year (2014)	**N=1,324** (1) IVA (n=215) (2) Standard of care (n=1,109)	**NR**	**NR**	**US data only** **Deaths, n/N (%)** (1) 0/215 (0) (2) 2/1109 (0.2) **Organ transplants, n (%)** (1) 0 (0) (2) 1 (0.1) **Hospitalizations, n (%)** (1) 25 (11.6) (2) 338 (30.5) RR (95% CI)=0.38 (0.26 to 0.56) **PEx, n (%)** (1) 20 (9.3) (2) 307 (27.7) RR (95% CI)=0.34 (0.22 to 0.52)	**See Outcomes**

					Cystic fibrosis related diabetes (CFRD), n (%) (1) 16 (7.5) (2) 131 (11.9) RR (95% CI)=0.63 (0.38 to 1.03) **Hepatobiliary complications, n (%)** (1) 3 (1.4) (2) 62 (5.6) RR (95% CI) =0.25 (0.08 to 0.79) **Pulmonary complications, n (%)** (1) 61 (28.4) (2) 392 (35.4) RR (95% CI)=0.80 (0.64 to 1.01)	
Bai [156] ***J Cyst Fibros*** **2016** **Abstract**	Non-randomized comparative long-term post-approval observational safety study using data from UK and US CF patient registries. Only US data is reported Comparators not receiving ivacaftor were matched to ivacaftor recipients based on age, sex, and genotype severity.	**N=7,456** (1) IVA (n=1,256) (2) Standard of care (6,200)	**NR**	**NR**	**US data only** **Deaths, n/N (%)** (1) 8/1256 (0.6) (2) 97/6200 (1.6) RR (95% CI)=0.41 (0.20 to 0.84) **Organ transplants, n (%)** (1) 2 (0.2) (2) 68 (1.1) RR (95% CI)=0.15 (0.04 to 0.59) **Hospitalizations, n (%)**	**See Outcomes**

	Duration of follow-up: 1 year (2014)				(1) 346 (27.6) (2) 2671 (43.1) RR (95% CI)=0.64 (0.58 to 0.70) **PE, n (%)** (1) 349 (27.8) (2) 2684 (43.3) RR (95% CI)=0.64 (0.58 to 0.70)	
Barry [157] ***J Cyst Fibros*** **2015** **Abstract**	Non-randomized comparative prospective cohort study measuring effects of ivacaftor on death and transplantation among CF patients with FEV_1 <40. Duration of follow-up: Median = 1126 days	**N=56** (1) Ivacaftor (n=21) (2) Standard of care (n=35)	**NR**	**NR** Ivacaftor group received drug in prior multi-center cohort study and had baseline FEV_1 <40 and continued treatment during prospective cohort study.	**Deaths, n/N** (1) 5/21 (2) 12/21 **Lung transplant, n/N** (1) 1/21 (2) 8/21 **Mulivariate model, all subjects:** Ivacaftor therapy associated with improved survival (HR=0.24, p=0.047) Male sex associated with improved survival (HR=0.13, p=0.012)	**See Outcomes**
Volkova [158] ***J Cyst Fibros*** **2016** **Abstract**	Non-randomized comparative long-term post-approval observational safety study using a United Kingdom CF registry. 2012 registry data served as baseline. Patients with a	**N=1,642** (1) Ivacaftor (n=277) (2) Standard of care (n=1365)	**NR**	**$ppFEV_1$** **Mean, percentage points (SD)** (1) 70.6 (24.8) (2) 71.4 (23.6) **PEx** **Annual risk, %** (1) 51.6	**$ppFEV_1$** **Mean, percentage points (SD)** <u>2013</u> (1) 75.8 (25.7) (2) 70.6 (24.3) <u>2014</u> (1) 77.8 (25.6) (2) 70.8 (24.2)	**PEx** **Annual risk, %** <u>2013</u> (1) 49.5 (2) 56.8 <u>2014</u> (1) 34.3 (2) 57.0

	record of ivacaftor in 2013 and 2014 were matched about 1:5 to comparator patients without a history of ivacaftor use with comparable age, sex, and genotype severity.			(2) 44.3 **Annual risk of hospitalization for PEx, %** (1) 48.0 (2) 43.4 **CFRD, %** (1) 17.3 (2) 23.2 **Distal intestinal obstruction syndrome, %** (1) 6.5 (2) 7.4		**Annual risk of hospitalization for PEx, %** 2013 (1) 38.3 (2) 44.3 2014 (1) 24.6 (2) 45.6 **Annual risk of Cystic fibrosis-related diabetes, %** 2013 (1) 18.8 (2) 25.6 2014 (1) 20.6 (2) 28.4 **Annual risk of distal intestinal obstruction syndrome (DIOS), %** 2013 (1) 5.1 (2) 7.5 2014 (1) 4.7 (2) 8.1
Elborn [159]	Subgroup analysis of STRIVE and ENVISION ivacaftor treatment effect on mean	**N=213** (1) Ivacaftor (See	**See STRIVE and ENVISION**	**Age** **N ivacaftor/n placebo** STRIVE <18: 19/17	**ppFEV$_1$** **Mean absolute change from baseline,**	**See STRIVE and ENVISION**

Am J Resp Crit Care Med **2012** **Abstract**	absolute change from baseline ppFEV$_1$ at 24 weeks by baseline age and FEV$_1$. Duration of follow-up: 24 weeks	STRIVE and ENVISION) (2) Placebo (See STRIVE and ENVISION)		18+: 64/61 ENVISION <18: 26/26 18+: 0 **Low FEV$_1$** **N ivacaftor/n placebo** STRIVE (ppFEV$_1$<70%) (1) 49 (2) 45 ENVISION (ppFEV$_1$<70%) (1) 4 (2) 8 **Mid FEV$_1$** **N ivacaftor/n placebo** STRIVE (ppFEV$_1$≥70) (1) 34 (2) 33 ENVISION (ppFEV$_1$ 70-90%) (1) 12 (2) 6 **High FEV$_1$** **N ivacaftor/n placebo** STRIVE (Not defined) (1) 4 (2) 5 ENVISION (ppFEV$_1$>90%) (1) 10 (2) 11	**percentage points (p-value)** STRIVE <18: 11.9 (p=0.0003) 18+: 9.9 (p<0.0001) ENVISION <18: 12.5 (p<0.0001) 18+: NA Low FEV$_1$ STRIVE: 10.7 (p<0.0001) ENVISION: NA Mid FEV$_1$ STRIVE: 10.6 (p<0.0001) ENVISION: 9.3 (p=0.1322) High FEV$_1$ STRIVE: NA ENVISION: 6.9 (p=0.1920)	
Flume [160] ***J Cyst Fibros***	Analysis of PEx incidence and incidence of protocol-defined PEx	**N= 213**	**See STRIVE and ENVISION**	**See STRIVE and ENVISION**	**Incidence of protocol-defined signs and symptoms of a PEx,**	**Not reported**

2013 **Abstract**	signs and symptoms reported in STRIVE.	(1) IVA: ivacaftor group from STRIVE (n=83) (2) Placebo (n=78)			**no. times reported (% of total events)** Increased cough (1) 99 (26.7) (2) 145 (23.3) Change in sputum (1) 73 (19.7) (2) 110 (17.7) Malaise, fatigue, lethargy (1) 45 (12.1) (2) 76 (12.2) Dyspnea (1) 33 (8.9) (2) 64 (10.3)	
Bai [161] ***Pediatr Pulmonol*** **2015** **Abstract**	5-year observational post-authorization safety study Analyzed results of the US CF Foundation Patient Registry (CFFPR) data in 2013 Average duration of ivacaftor exposure was 1.4 years Duration of follow-up: 5 years	**N=5,931** (1) IVA (n=999) (2) Comparator (n=4,932)	Not reported	Patients treated with ivacaftor were matched 1:5 with patients in the CFFPR who never received ivacaftor on age, gender, and CFTR genotype.	**No. of deaths, annual risk (%)** (1) 5 (0.5) (2) 66 (1.3) Unadjusted relative risks* (95% CI) = 0.37 (0.15 to 0.93) **No. of organ transplantation, annual risk (%)** (1) 2 (0.2) (2) 53 (1.1) Unadjusted relative risks (95% CI) = 0.19 (0.05 to 0.76) **No. of hospitalization, annual risk (%)** (1) 247 (24.7) (2) 2055 (41.7)	**See Outcomes**

					Unadjusted relative risks (95% CI) = 0.59 (0.53 to 0.66) **No. of PEx, annual risk (%)** (1) 256 (25.6) (2) 2037 (41.3) Unadjusted relative risks (95% CI) = 0.62 (0.56 to 0.69) *Unadjusted relative risks for ivacaftor vs comparator cohort as well as their 95% CIs based on normal approximation were calculated by the authors.	
Mainz [162] ***J Cyst Fibros*** **2016** **Abstract**	Compared CFQ-R scores of G551D patients on IVA (≥ 3 months) to homozygous *F508del* on standard of care in a real-world setting (prior to LUM/IVA availability). Clinical data was collected from patient medical records.	**N=209** (1) IVA* (n=72) (2) Caregiver, standard of care (n=137) *The mean duration of patients on ivacaftor was 22 months.	**Inclusion** • 12 years of age or older • G551D-CFTR mutation • Caregivers of pts aged 6-11 completed a one-time survey comprising the CFQ-R, EQ-5D-5L, and WPAI	**Sex** **Female, n (%)** (1) 43 (60.3) (2) 73 (35.2) **Mean no. of comorbidities, n** (1) 1.5 (2) 2.0 p<0.01	**CFQ-R Respiratory domain** **Mean (least-squares) score, points*** (1) 75.4 (2) 62.5 **CFQ-R Digestive Symptoms domain** **Mean (least-squares) score*** (1) 85.4 (2) 78.0 **CFQ-R Eating domain**	

	Duration of follow-up: survey administered once				**Mean (least-squares) score*** (1) 91.1 (2) 84.2 **CFQ-R Health Perceptions domain** **Mean (least-squares) score*** (1) 67.6 (2) 58.6 **CFQ-R Physical Functioning domain** **Mean (least-squares) score*** (1) 74.6 (2) 66.6 **CFQ-R Treatment Burden domain** **Mean (least-squares) score** (1) 65.3 (2) 54.8 **CFQ-R Vitality domain** **Mean (least-squares) score*** (1) 63.5 (2) 55.9 **CFQ-R Weight domain** **Mean (least-squares) score*** (1) 80.7	

					(2) 64.2 **EQ-5D-5L index score*** (1) 0.90 (2) 0.81 **VAS score (p-value)*** (1) 75.7 (2) 70.0 **School productivity loss (%)** (1) 24.6 (2) 33.6 **Activity impairment (%)** (1) 21.6 (2) 28.3 *Statistically significant difference between ivacaftor and standard of care	
Accurso [163] ***J Cyst Fibros*** **2013** **Abstract**	3 randomized, blinded, phase 2 studies in G551D patients had cross-over designs.	**N=** (1) Study 101: Ivacaftor treatment lasted 14 days (n=4) (2) Study 106: Ivacaftor treatment lasted 28 days (n=18)	**Not reported**	**Not reported**	**$ppFEV_1$** **Mean change from baseline, percentage points (SE); p-value** (1) 5.2 (2.0); NR (2) 7.1 (2.7); p=0.0104 (3) 8.8 (2.7); p=0.0313	**Not reported**

		(3) Study 107: Ivacaftor treatment lasted 28 days (n=8)				
Davies [164] ***J of Cyst Fibros*** **2012** **Abstract**	Phase 2, randomized, double-blind, placebo-controlled, crossover, multicenter study. Duration of follow-up: 12 weeks (2 four-week treatment periods with four-week washout between)	**N=7** (interim analysis) Participants were randomized to one of two treatment orders: (1) 150mg of ivacaftor every 12 hours for 4 weeks, washout for 4 weeks, and 150mg placebo every 12 hours for 4 weeks OR (2) 150mg of placebo every 12 hours for 4 weeks, washout for 4 weeks, and 150mg	**Inclusion** • 6 years of age or older • Confirmed diagnosis of CF, with GG551D-CFTR mutation • FEV_1 of at least 90% LCI of at least 7.4	**Age** **Mean, years (SD)** 14.0 (8.6) **LCI** **Mean (SD)** 9.2 (1.9) **$ppFEV_1$** **Mean, percentage points (SD)** 98.5 (6.4)	**$ppFEV_1$** **Treatment difference for the mean change from baseline, percentage points (p-value)** 7.2 (p=0.1264) **LCI** **Mean change from baseline treatment difference (p-value)** −2.22 (p=0.0097)	**Any AE, n/N** During placebo: 5/7 During ivacaftor: 6/7 **SAE, n/N** 1/7

		ivacaftor every 12 hours for 4 weeks				
Elborn [165] ***Pediatr Pulmonol*** **2013** **Abstract**	Post-hoc analyses on STRIVE, ENVISION (and Study 106 which not reported here) randomized, placebo controlled, double-blind, multicenter studies. Duration of follow-up: 48 weeks	**N=31** (1) STRIVE IVA (n=4) (2) STRIVE Placebo (n=5) (3) ENVISION IVA (n=10) (4) ENVISION Placebo (n=12)	**Inclusion** • FEV_1 of at least 90% at baseline in STRIVE, ENVISION	**$ppFEV_1$** **Mean, percentage points (SD)** (1) 95.6 (2.7) (2) 93.8 (3.0) (3) 99.3 (12.4) (4) 101.7 (6.5) **Weight** **Mean, kg (SD)** (1) 59.2 (20.1) (2) 58.8 (2.2) (3) 37.4 (12.5) (4) 29.8 (7.3)	48 Week Data: **$ppFEV_1$** **Absolute change from baseline, percentage points (SD)** (1) 9.1 (3.0) (2) −7.7 (13.7) (3) 1.5 (13.5) (4) −4.4 (8.3) **Weight** **Absolute change from baseline, kg (SD)** (1) 8.2 (7.6) (2) −1.6 (2.7) (3) 7.0 (3.7) (4) 3.0 (2.3)	Not reported
Plant [166] ***J Cyst Fibros*** **2013** **Abstract**	Secondary analyses of STRIVE and ENVISION, including analysis of $ppFEV_1$ and body weight by FEV_1 response (<5% and ≥5% improvement). Duration of follow-up: 48 weeks (see STRIVE and ENVISION)	**N=209** (1) IVA: 48 weeks of ivacaftor (n=109) (2) Placebo: 48 weeks of placebo (n=100)	**See STRIVE, ENVISION**	**See STRIVE, ENVISION**	**$ppFEV_1$** **Treatment difference in mean change from baseline, percentage points (p-value)** STRIVE <5% FEV_1 improvement: 4.2 (p<0.0001) ≥5%: 6.2 (p=0.0023) ENVISION	**Not reported**

					<u>≤5%:</u> 1.6 (p=0.5093) <u>≥5%:</u> 9.8 (p=0.0522) **Weight Treatment difference in absolute change from baseline, kg (p-value)** <u>STRIVE</u> <u>≤5%:</u> 3.3 (p<0.0001) <u>≥5%:</u> 1.7 (p=0.3313) <u>ENVISION</u> <u>>5%:</u> 2.0 (p=0.0582) <u>≥5%:</u> 3.4 (p=0.0094)	
Suthoff [167] ***Pediatr Pulmonol*** **2014** **STRIVE** **Abstract**	Analysis of patient-reported quality of life outcomes, via CFQ-R, from STRIVE. Duration of follow-up: 48 weeks	(1) IVA: 150 mg of ivacaftor twice daily (2) Matched placebo	**See STRIVE**	**See STRIVE**	**CFQ-R Respiratory domain** **Percent of subjects reporting*** <u>Improvement (p-value)</u> (1) 57 (2) 25 <u>Decline</u> (1) 29 (2) 54 **CFQ-R Social Functioning domain** **Percent of subjects reporting*** <u>Improvement (p-value)</u> (1) 49 (2) 29	**Not reported**

					Decline (1) 30 (2) 50 **CFQ-R Vitality domain** **Percent of subjects reporting*** Improvement (p-value) (1) 49 (2) 23 Decline (1) 36 (2) 50 **CFQ-R Treatment Burden domain** **Percent of subjects reporting*** Improvement (p-value) (1) 44 (2) 22 Decline (1) 26 (2) 41 **CFQ-R Health Perceptions domain** **Percent of subjects reporting*** Improvement (p-value) (1) 44 (2) 17	

					Decline (1) 28 (2) 45 **CFQ-R Physical Functioning domain** **Percent of subjects reporting*** Improvement (p-value) (1) 35 (2) 12 Decline (1) 13 (2) 40 **CFQ-R Eating Problems domain** **Percent of subjects reporting*** Improvement (p-value) (1) 25 (2) 10 Decline (1) 12 (2) 27 **CFQ-R Weight Problems** **Percent of subjects reporting*** Improvement (p-value) (1) 19 (2) 13	

					<u>Decline</u> (1) 9 (2) 28 *p<0.05 for difference between treatment groups in the percent improved and declined	
Hathorne [168] ***Pediatr Pulmonol*** **2015** **GOAL** **Abstract**	Quality of life analysis using GOAL study data. Data was measured before and 6 months after initiation of ivacaftor.	**N=151** Ivacaftor (single arm)	**See GOAL**	**See GOAL**	**Statistical significance of improvement in CFQ-R domains after 6 mo of treatment by sex (p-value)*** <u>Treatment Burden domain</u> (1) females (p=0.0002) (2) males (p=0.0034) <u>Health Perceptions domain</u> (1) females (p=0.0292) (2) males (p=0.0121) <u>Physical Functioning domain</u> (1) females (p=0.0429) (2) males (p=0.0110) <u>Role Functioning domain</u>	**Not reported**

					(1) females (p=0.0001) (2) males (p=0.0061) * Authors do not define whether changes in quality of life (CFQ-R scores) meet a minimum clinically important difference. Unclear whether statistical significance of improvement meets threshold for clinical importance.	
Wainwright [169] ***Pediatr Pulmonol*** **2014** **Abstract**	12 months data from the Australian CF Data Registry (ACFDR). Duration of follow-up: 24 weeks	**N=331** (1) IVA: n=17 (2) Matched placebo: n=314 Patients were assessed every 2-3 months post-treatment. (n=17) Data were collected retrospectively from patient records and the physician declaration form required every 3	**Inclusion** • 15-54 years of age • Confirmed diagnosis of CF • Pancreatic insufficient patients with G551D mutation • FEV1 < 70%	**Age** **Mean, years (SD)** (1) 29 (7.3) (2) 27 (8) **ppFEV$_1$** **Mean, percentage points (SD)** (1) 38.3 (12.4) (2) 45.4 (14.5) **BMI** **Mean, kg (SD)** (1) 20.4 (2.6) (2) 20.5 (2.8)	**Median hospital admission count (IQR)** (1) 0.6 (0.0 to 1.8) (2) 2.4 (0.6 to 3.5) Difference: p=0.007 **Length of stay in hospital, days (IQR)** (1) 2.9 (0.0 to 27.5) (2) 23.5 (8.2 to 45.2) Difference: p=0.015	Not Reported

		months for supply/resupply of ivacaftor.				
Barry [170] ***Chest*** **2014**	Retrospective case-control study of patients receiving ivacaftor on the compassionate use program in the UK and Ireland. Duration of follow-up: 1-1.75 years (1 year before ivacaftor treatment and 90-270 days on ivacaftor) Median time on ivacaftor: 237 days	**N=56** (1) IVA: cases had at least 3 months treatment with ivacaftor by the time of data collection (n=21) (2) Matched control subjects: each case was matched up to 2 control subjects (n=35)	**Inclusion** • Confirmed diagnosis of CF • At least one G551D allele • $ppFEV_1$ < 40% • Minimum of 3 months treatment with ivacaftor **Exclusion** • Patients with FEV1 <40% were excluded from phase 3 clinical trials	**Age** **Mean, years (range)** (1) 22 (20-31) (2) 23 (21-27) **$ppFEV_1$** **Mean, percentage points (SD)** (1) 26.5 (7.2) (2) 30.3 (7.5) **Weight** **Median, kg (IQR)** (1) 49.8 (44.4-60.7) (2) 54 (49.0-62.4) **BMI** **Mean, kg/m^2** (1) 19.1 (2.9) (2) 20.2 (5.2) **Sex** **Female, %** (1) 52 (2) 49	**$ppFEV_1$** **Mean, percentage points (SD)** (1) 30.7 (9.9) (2) NR **$ppFEV_1$** **Median absolute change from baseline, percentage points (IQR)** (1) 3.8 (0.2 to 7.7) (2) 0.6 (-2.1 to 2.8) **Weight** **Median, kg (IQR)** (1) 51.6 (48.6 to 66.8) (2) NR **Weight** **Median change from baseline, kg (IQR)** (1) 2.3 (-0.4 to 4.2) (2) 0.6 (-0.5 to 3.2) **BMI** **NR, kg/m^2** (1) 20.2 (2) NR **BMI** **Median change from baseline, kg/m^2 (IQR)**	No adverse events reported in the treatment group. 2 previously listed control subjects underwent lung transplantation.

					(1) 0.84 (NR) (2) 0.2 (NR)	
Davies [171] ***Lancet Respir Med*** **2013**	Phase 2, multicenter, placebo-controlled, double-blind 2x2 crossover study. Duration of follow-up: 28 days	**N=20** **Demographics:** (1) Placebo → IVA: 28 days of placebo twice daily, 28-day washout period, and 28 days of 150 mg ivacaftor twice daily (n=10) (2) IVA → Placebo: 28 days of 150 mg ivacaftor twice daily, 28-day washout period, 28 days of placebo twice daily (n=10) **Results, at 28 days** (1) IVA (n=18) (2) Placebo (n=17)	**Inclusion** • Confirmed diagnosis of CF • At least one G551D-CFTR allele • $ppFEV_1$ > 90% • Age of 6 years or older • Weight ≥ 15 kg • LCI > 7.4	**By arm (treatment order 1 or 2)** **Age** **Mean, years (SD)** (1) 19.8 (13.35) (2) 13.4 (7.12) **$ppFEV_1$** **Mean, percentage points (SD)** (1) 92.6 (7.43) (2) 101.8 (11.59) **BMI** **Mean, kg (SD)** (1) 22.7 (6.96) (2) 19.4 (3.71) **Sex** **Female, n (%)** (1) 4 (40) (2) 6 (60) **CFQ-R Respiratory domain** **Mean, score (SD)** (1) 71.7 (13.4) (2) 75.6 (18.2) **LCI** **Mean (SD)** (1) 8.88 (1.46) (2) 9.17 (1.66)	**Results are pooled for all subjects during ivacaftor and placebo weeks.** **$ppFEV_1$** **Mean, percentage points (95% CI)** Ivacaftor: 104.97 Placebo: 94.85 Difference= 8.67 (2.36 to 14.97) **CFQ-R Respiratory domain** **Mean, points (95% CI)** Ivacaftor: 83.33 Placebo: 79.97 Difference= 3.99 (−5.32 to 1.33) **LCI (95% CI)** Ivacaftor: 8.13 Placebo: 9.40 Difference= −2.16 (−2.88 to 1.44)	**Any AE, n (%)** Ivacaftor: 13 (72%) Placebo: 15 (79%) **SAE, n** Ivacaftor: 3 Placebo: 1
Edgeworth [172]	Single-center, double-blind, placebo-controlled,	**N=20**	**Inclusion** • Aged between 16 and 75 years	**All participants** **Age** **Mean, years (range)**	**Results are pooled for all subjects during ivacaftor and placebo weeks.**	**All participants**

Clin Sci (London) **2017**	randomized, crossover study. Duration of follow-up: 84 days; 28 days of treatment; 28 days of washout; 28 days of other treatment	(1) IVA: ivacaftor 150 mg twice daily for 28 days (n=10) (2) Matched Placebo: 150 mg of placebo twice daily for 28 days (n=10)	• Confirmed diagnosis of CF • At least one G551D-CFTR allele • $ppFEV_1 \geq 25\%$ **Exclusion** • Known adverse reaction to ivacaftor • Deemed unlikely to physically complete a CPET study	32 (18-65)* **$ppFEV_1$** **Mean, percentage points (range)** 54 (23-110) **BMI** **Mean, kg/m^2 (SD)** 25.8 (18-36.4) **Sex** **Female, n (%)** 8 (40)	**$ppFEV_1$** **Mean absolute change from baseline, percentage points (95% CI)** (1) 14.1 (9.4 to 18.8) (2) 0.4 (-4.3 to 5.1) Difference = 13.7 (7.0 to 20.3) **BMI** **Mean absolute change from baseline, kg/m^2 (95% CI)** (1) 1.9 (1.1 to 2.7) (2) 0.7 (-0.2 to 1.5) Difference = 1.2 (0.1 to 2.3) **CFQ-R Respiratory domain** **Mean absolute change from baseline (95% CI)** (1) 16.1 (−29.9–62.0) (2) −6.1 (−41.0 to 28.8) Difference: 22.2 (−26.3 to 70.6)	**No. hospitalizations for PEs** 5 **Abdominal discomfort, n** 3 **Elevated creatinine kinase, n** 1
Stalvey [173]	Post-hoc analysis on GOAL and ENVISION	**N=83**	**See GOAL and ENVISION**	**Weight-for-age z-score** **Mean, score (p-value)** (1) 0	**Weight**	Not reported

Pediatr Pulmonol **2017** **GOAL and ENVISION**	Duration of follow-up: GOAL: 6 mo ENVISION: 48 weeks	GOAL: (1) IVA: n=35 ENVISION: (2) IVA: n=25 (3) Placebo: n=23		(2) 0.08 (3) -0.16 **Age** **Mean, years (SD)** (1) 8.7 (1.6) (2) 8.5 (1.8) (3) 8.8 (1.8) **ppFEV$_1$** **Mean, percentage points (SD)** (1) 106.4 (14.6) (2) 87.3 (14.6) (3) 83.8 (20.8) **BMI** **Mean, kg/m^2 (SD)** (1) 17.1 (2.4) (2) 17.2 (2.7) (3) 16.8 (1.8) **Sex** **Female, n (%)** (1) 16 (45.7) (2) 14 (56) (3) 9 (39.1)	**Mean weight-for-age z-score at endpoint (p-value)** (1) 0.27 (p<0.0001 vs. baseline) (2) 0.44 (p<0.001 vs. placebo) (3) -0.36 (p<0.001 vs. baseline)	
Fink [174] ***Pediatr Pulmonol*** **2015** **Abstract**	Retrospective observational cohort study using US Cystic Fibrosis Foundation Patient Registry comparing nutritional and pulmonary outcomes in the 12 months preceding and 12 months on ivacaftor.	**N=403** Ivacaftor (single arm)	**NR**	**Mean age at treatment start, years (median)** 21.4 (18.5) **Females, %** 49	**ppFEV$_1$** **Mean change from baseline, percentage points (SD)** 5.4 (9.1) **Mean difference in no. PEx's reported (SD)** -2.1 (1.1)	**Not reported**

					Weight **Mean change in from baseline, kg (SD)** 4.3 (4.7) **Percent without change in weight or lung function** 13 **Percent with change in weight and lung function** 42 **Percent with change in only weight** 37 **Percent with change in only lung function** 8 **Percent with FEV_1 response and baseline FEV_1 of:** ≥80: 43 40-79: 60 <40: 48 **Percent with weight response and baseline FEV_1 of**: ≥80: 84 <80: 72	
Multiple Regimens						

Heltshe [175] ***J Cyst Fibros*** **2017** **Manuscript**	Retrospective, observational, epidemiologic analysis using the US CF Foundation Patient Registry between 2005-2014	Pre-and post-phase III trials of ivacaftor (2009-2013) and lumacaftor/ivacaftor (2013-2014)	Women with cystic fibrosis between the ages of 15-44 (childbearing years)	**Genotype, N (%)** Homozygous *F508del*: 31,989 (46.7) Heterozygous *F508del*: 22,533 (32.9) G551D: 2,860 (4.2) R117H: 1,182 (1.7) Other: 9,884 (14.4) Pregnancy rate per 100 woman-years (all years): 25.5	The number of women with CF in the childbearing years increased annually from 5,335 in 2005 to 7,164 in 2014 Slight downward trend in pregnancy rates (2% reduction per year) consistent with national trends. Pregnancy rates were lower during years of clinical trials (compared to pre-trial) but rebounded post-approval for ivacaftor (no data on lumacaftor/ivacaftor). Number of live births grew from 2005-2009 (70.1%) to 2013-2014 (73.4%) in registry population. Percent live births were higher in the CF population than the overall US population (64.6%)	NA

Appendix G. Public Comments

This section includes summaries of the public comments prepared for the CTAF Public Meeting on August 27, 2020. These summaries were prepared by those who delivered the public comments at the meeting and are presented in order of delivery. Three speakers did not submit summaries of their public comments.

A video recording of all comments can be found here. Conflict of interest disclosures are included at the bottom of each statement for each speaker who is not employed by a pharmaceutical manufacturer.

JP Clancy, MD
Vice President of Clinical Research
Cystic Fibrosis Foundation

I have been a member of the cystic fibrosis (CF) care and research community for more than 25 years, intimately involved in the science of CF and the development of new therapies. This perspective has allowed me to directly witness the impact of new CF therapies on the disease. Historically, all of these were treatments for disease manifestations secondary to lost CFTR function. These symptomatic treatments, while effective were typically one dimensional and had limited impact. This all changed in 2012 with the approval of Kalydeco®, the first modulator therapy that targets the underlying cause of CF. Modulators are unique in that they improve the function of mutant CFTR proteins in CF cells. Treating the fundamental CF defect substantially delays progressive and irreversible organ damage and may even prevent onset of CF symptoms.

Approved modulators have been shown to provide significant benefits to eligible patients. Kalydeco® and Trikafta® are unique in that they demonstrate a high magnitude of benefit across numerous CF manifestations. Thus, we consider them "highly effective modulator therapies" (HEMTs). These modulators improve numerous key clinical outcomes including lung function, growth, risk of pulmonary exacerbations, sweat chloride concentrations, and quality of life. Clinical trial results show that for patients on Trikafta with only one copy of the most common genetic mutation, *F508del*, lung function improved on average by 14 percentage points compared to controls. This level of benefit is unparalleled in CF. Trikafta also reduced pulmonary exacerbations by 63%, improved weight, and dramatically improved respiratory symptoms. Similar benefits were seen in those with two copies of *F508del* using a different study design. These improvements translate into real life benefits described by patients, benefits that we cannot easily quantify with a dataset.

Access to other approved modulators (Orkambi® and Symdeko®) is still critical for the CF community. Individual modulator therapy response varies, and availability of modulator options ensures that patients who do not have a strong response to, or do not tolerate HEMTs have access to other modulators. They are also essential for preserving lung and other organ function in children not yet eligible for Trikafta. Indeed, published studies have demonstrated that modulators like Orkambi have long-term benefits, including reduction in lung function decline over time. These effects predict a dramatically improve long-term survival.

Modulators have the potential to fundamentally alter the course of this chronic, life-shortening disease, particularly for those who start treatment at a young age. Patients starting modulator treatment early have the greatest life-long potential to benefit. This preventive use could lead to fundamental changes in how we care for patients, like using symptomatic therapies less frequently and reducing treatment burden. Data also suggests that long-term modulator use will fundamentally alter the course of CF. Because CFTR modulators restore mutant CFTR activity, all downstream consequences of lost CFTR activity could be prevented, reducing the need for future chronic therapies. As an example, the Cystic Fibrosis Foundation is leading the PROMISE study for patients 12 and older on Trikafta to understand its impact on all facets of CF, including patient reported outcomes and quality of life measures. This study will extend to younger children pending FDA approval. The CF Foundation is also supporting studies to inform us about wholistic benefits of Trikafta therapy, including impact on lung infection, CF-related diabetes, liver disease, bone health, sinus disease, fertility, GI symptoms and mental health. This 360-degree examination of Trikafta will be critical to understanding its full-scale benefits.

Trikafta received FDA approval only 10 months ago. ICER's review so close to approval does not allow enough time to collect long-term data. Without sufficient data, these therapies might be significantly undervalued. Long-term data are also essential to any model used to assess cost effectiveness. As noted, there are concerted efforts underway to understand the long-term and real-world impacts of modulators on health status, quality of life, health care resource utilization, and other factors. By not including these results, this analysis risks significantly undervaluing Trikafta.

CFTR modulators have great potential to dramatically change the trajectory of an individual's life. I recently was contacted by a young adult patient that I cared for ten years ago. She has been on Kalydeco since its phase 3 trial in 2011. She is now in graduate school, maintains lung function in the 90s and generally takes only Kalydeco and enzymes to remain well. While this is an individual instance, her experience is a glimpse into the near-term future for many in the CF community treated with highly effective modulators.

- ***Contributions: CFF has received charitable contributions and/or fees for service >$5,000 from health care companies, including Vertex Pharmaceuticals.***
- ***Equity Interests and Intellectual Property: CFF has entered into therapeutic development award agreements that have and may continue to provide CFF with intellectual property, equity interests, and royalty and milestone payment rights from various pharmaceutical companies.***
- ***Research Support: CFF provides financial support to the Therapeutics Development Network (TDN) which delivers high-quality clinical trials to CF patients in the search for better therapies and a cure. CFF provides financial support to the Data Safety Monitoring Board whose primary responsibility is to protect the safety and welfare of people with CF who participate in TDN approved studies.***
- ***Other Relationships: CFF facilitated, but did not participate in, the development of the CFF Pulmonary Guidelines: Use of CFTR Modulator Therapy in Patients with CF.***

Siri Vaeth, MSW
Executive Director
Cystic Fibrosis Research, Inc.

I address you on behalf of many: my daughter who lives with cystic fibrosis; Cystic Fibrosis Research, Inc.

(CFRI) and my organizational peers in the Cystic Fibrosis Engagement Network; and the thousands of members of the national CF community we serve. We are deeply concerned by the conclusions reached in ICER's evidence report regarding elexacaftor/tezacaftor/ivacaftor (Trikafta) as a CF therapy. While our organizations are listed as stakeholders whose input impacted the report, we reject its conclusions. The devastating impacts of cystic fibrosis cannot be fully conveyed until you experience them, or watch your loved one suffer them. Last year, half the individuals with CF who died were under 31 years old, largely from respiratory failure. Diabetes, sinus disease, pancreatitis, osteoporosis, liver disease, diabetes, male infertility, fatigue, and pain are additional complications. Advanced lung disease may cause a chronic sense of smothering and fear of a catastrophic hemoptysis or pneumothorax. Life extending transplants are fraught with their own tremendous risks. The report greatly minimizes the pain and suffering experienced by those with CF.

We are opposed to ICER's use of Quality Adjusted Life Year (QALY) measures. This discriminatory methodology will always penalize individuals with disabilities, most especially those with incurable chronic diseases. The concept of the QALY was developed specifically to ration medical care and has nothing to do with patients having access to the most appropriate drug for their condition. The use of a QALY-based threshold to determine benefits and coverage is banned by the Affordable Care Act and Medicare and violates the Americans with Disabilities Act. The use of QALY is

especially problematic with CF due to multiple CFTR mutations and varied disease expression. The utility weights used to determine a person with CF's QALY, based on FEV1, are simplistic. A more accurate measure requires a patient-centered analysis that includes multiple disease symptoms.

By placing a numerical value on one's quality of life and health utility, you have taken a disturbing step towards placing greater value on the healthy, and lower value on the disabled. We do not agree with the claim that ICER's use of QALY to determine drug price value is not inextricably related to placing a value on the lives of those needing the drugs. The report's economic analysis leads to an overprediction of Trikafta's cost over time due to the use of static pricing with a projected lifetime use. Your report found Trikafta exceeds cost-effectiveness thresholds "even under the assumption that it maintained individuals with CF in normal health..." The CF therapeutic pipeline is robust: others are developing CFTR modulators, mRNA therapies, and genomic editing techniques. It is unlikely that Trikafta will remain the only therapeutic option.

We remain concerned that ICER did not assess the full array of medical costs associated with CF and its complications and failed to include projected loss of income for adults with CF and CF caregivers. A therapy that reduces medical costs while enabling people to work has far broader financial implications. Of course, we cannot put a price on the savings in physical and emotional suffering. Who knew that shortly after Trikafta's approval and availability we would face a pandemic? We are relieved we had access to the drug before the pandemic hit; I know Individuals with CF who survived COVID and strongly believe it is thanks to Trikafta. A woman with end-stage CF was literally prepped for transplant surgery, when it was determined the donor lungs were not viable. Put on Trikafta to buy time, she was soon off supplemental oxygen and removed from the transplant list. Clearly this was an economic benefit, but no price can sum up Trikafta's impact upon her and those who love her. We believe that despite input from patients and advocacy groups, the value of Trikafta is not accurately conveyed, potentially giving credence to payers who seek to reduce costs by denying coverage for this drug and other new therapies. We are concerned that this flawed analysis will be embraced by payers to deny access to Trikafta, with a resulting negative impact on innovation. Approximately 10% of those with CF cannot benefit from CFTR therapies. Only 7% of 7,000 identified rare diseases have approved therapies. It is incredibly difficult to incentivize research and drug development when the numbers who will benefit are so low. For those without new therapies, facing an early death is a tragic reality. ICER very rarely finds rare disease drugs to have adequate cost effectiveness ratios. We fear this consistent – and inaccurate - assessment will serve to suppress research, and discourage investment in drug development. This would be catastrophic for the CF community and other rare disease groups. We strongly object to the methodology used to evaluate this therapy, and as such, reject the report's conclusions.

CFRI receives educational grants to support our services to the CF community from Vertex Pharmaceuticals, Genentech, Gilead Sciences, AbbVie, Chiesi USA, and Ionis Pharmaceuticals. These grants represent > 25% CFRI's total budget.

Juliana Keeping, Parent of Individual with CF
Communications Director, Patients for Affordable Drugs

My name is Juliana Keeping, and my son Eli is 7-years-old, diagnosed with cystic fibrosis at two weeks old.

Thanks for having me to speak today on behalf of myself and son. Eli has the most common version of CF and takes Symdeko to treat his illness, along with other drugs, inhaled treatments, and physical therapies. Eli is among the 90 percent of people living with CF for whom our latest modulator, Trikafta, can make a difference — potentially, a big one. Yet 10 percent of the estimated 100,000 people in the world living with rarer variations of my son's genetic, life-shortening illness have no modulator. My family remains dedicated to finding treatments and cures for every person with CF, and continues to fundraise for research, as our community has for decades. Trikafta gives me hope that one day my son will not only be able to breathe like me, but to outlive me. But consider that Trikafta costs nearly $312,000 per year. This is a drug that treats the vast majority of individuals with this rare disease. What, then, would an acceptable price be for a drug that treats the remaining 10 percent? It's a question that should give us pause. Drug makers like Vertex take advantage of patients like my son by pricing drugs based not on what makes a fair and reasonable return for their investment, but what they can get away with. Today, Americans with cystic fibrosis are being forced off of the very modulators they fundraised to create . Drugs don't work if people can't afford them. My son could just as easily become a victim of unrestrained drug pricing as he could his disease.

Bottom line: our modulators cost too much

ICER's 2018 report concluded prices of Orkambi, Symdeko, and Kalydeco, — between $272,623 to 311,701 per year — would need to be slashed by about half to be considered cost effective. I agree. So does the latest draft report, which also states, and I do not quarrel with this conclusion, that a discount of up to 66 percent would be necessary for Trikafta — which lists at nearly $312k/year — to be considered cost effective . My reasons for concluding the prices are too high are different from — but complement — the ICER analysis. As patients and loving caregivers we must stand guard against unjustifiable price gouging wherever it arises.

The CF community's charity dollars and taxpayers played an outsize role in the creation of our modulators.

The pharmaceutical industry wants to compensate investors for the high risk involved in bringing a drug to market. Without massive price tags, new life-saving treatments will not be invented and made available to people who need them, or so they say. But in the case of all CFTR modulator drugs, the CF community and taxpayers took the early, critical risk by investing money into the research and clinical trials. Vertex moved to acquire the IP only after the treatments were shown to be viable.

Today, Vertex continues to exploit its monopoly to gouge patients and payers

It says it needs to charge these prices to continue to invest in new drugs. Yet Vertex has, since 2018, relied on a tax bonanza to repurchase hundreds of millions of dollars its own shares , money that could have been used to lower drug prices. So far, its stock buybacks total more.

No conflicts of interest to disclose.

Laura Rogers
Parent of an Individual with CF

My name is Laurie Rogers, and I am from Deadwood, South Dakota. My husband and I have been married for 25 years and have raised 4 children, including our youngest, Madelaine, who is 17 and will be starting her senior year of high school this coming week. At just over one month of age on May 19, and while seemingly healthy, we received a phone call, that one of Madelaine's newborn screenings had indicated the possibility of Cystic Fibrosis. In 2003 when Madelaine was born, the life expectancy for a child born with CF was 32 years old. Although she has had to endure some hefty antibiotics, sometimes through IV, for respiratory infections, her biggest battle from a young age was her digestive system. We tried many strategies to maintain her weight and decrease the amount of daily stomach discomfort she was experiencing. Despite our efforts, she experienced several hospitalizations over her first 14 years related to her digestive dysfunction. Ultimately, we made the decision to have a feeding tube placed. This was primarily to help maintain her weight, but also to help assist in administering the medications she was needing for her persistent unpredictable, and uncomfortable digestive issues. Aside from these challenges, Madelaine has had relatively healthy lungs and comparatively to some others with CF, we have been lucky.

In 2015 when Madelaine was 12, she was eligible for Orkambi. Although her health was well maintained with this modulator, we were still eagerly awaiting some of the therapies in the CF Pipeline. In the summer of 2018, Madelaine was enrolled in the "triple trial". After the initial 8 weeks, which was in early September, that involved possible study drug or possible placebo, she was officially switched to study drug, aka "the triple". While in this trial, the clinical outcomes and measurements are kept confidential, even from the patient and family, so we really had no idea what, if any measurable clinical effect the drug might be having. By January of 2019, at our 10th research visit, we were to have a routine CF clinic visit as well. Mad had had a good winter, no

illness, or anything adverse to report. Finally, we would get some feedback, and some numbers to look at after 4 months in the trial. To our surprise Madelaine's weight was up 2 lbs. and her lung function was over 100%. This had risen 14% in 4 months, numbers we had not seen since age 4 or 5. It was about this time, after a year of monitoring, it was agreed that her feeding tube could be removed as well.

At this point, I started to pay even more attention to all her symptoms. After returning home from this visit, Madelaine developed a minor cough. She increased treatments, got a little extra rest and in about 3 days, the cough was gone. Madelaine had NEVER in 16 years gotten over a cough without antibiotic treatment. I also noticed that her sleeping position had changed. Many mornings, she would be asleep on her back with her knees bent and drawn up to her stomach with her feet flat on her bed. She always said her stomach was just more comfortable when she slept in that position. For years, even in her sleep she was managing her CF. I now noticed she was no longer sleeping with her knees bent, instead she looked relaxed. Not only did she look relaxed while sleeping, her mood was noticeably improved. Her family and friend relationships improved. One of her sisters speaks of this regularly, and even close family friends have commented how much Madelaine has really "grown up" in the past year or so. This very much could be true, but we all believe she has lost some of her edginess simply because much of her discomfort and fatigue is finally relieved. I don't know if any of us, including Madelaine ever knew how affected her mood and personality had been all this time. Since Trikafta's approval, Madelaine is still participating in a roll over study, and has now been taking it for almost 2 years. She feels great, her measurable symptoms are improving, and has only had the need for antibiotics once during this time.

I don't think Madelaine has ever thought CF held her back, that being said, she is at the age that post high school plans are needing to be made. She has always wanted to further her education, and for a long time she has said she was going to stay close to home to attend college. Over the past year, those plans have changed, and she now hopes to at least move across the state for school. Maybe it is just her maturing, but because of her comments, I really think she is more confident in her health. She is looking forward to planning her future knowing that her health has become more manageable. Quite possibly even decreasing the number of medicines she takes each day, and or decreasing the hours she spends doing treatments. Madelaine has had her dreams and future plans reassured through Trikafta. She knows she has a long bright future, and many others in the CF community have literally gotten their lives back. I don't know how anyone can put a price tag on that. In 2017 the median life expectancy of a child with born with CF had grown to 47 years old. That is a 15 year improvement over the course of Madelaine's short life. It has been said that CF is the BEST STORY IN MEDICINE.

Madelaine, and our entire family are living by that statement. There is no doubt in my mind that there will be a cure in the near future. Near enough, that Madelaine could very much benefit from

it. If Trikafta is the answer to assisting her, and many more, in sustaining and improving their health until that day comes, then there should be nothing standing their way.

Laura's daughter has been enrolled with the Vertex Trikafta trial(s) since July of 2018. There has been appointment, travel, and meal reimbursement throughout the trial, and she is currently still enrolled.

Chad Riedy, National Advocacy Chair
Cystic Fibrosis Foundation

My name is Chad Riedy and in 1984, at the age of 3, I was diagnosed with cystic fibrosis. Upon my diagnosis my parents were told that they shouldn't expect me to live to see my 12th birthday. I am now 39 years old and living in Alexandria, VA with my wife, Julie, and our two boys. It's hard to imagine that at the time of my diagnosis, the cf gene would not be discovered for another 5 years and that it would be 10 years until the first targeted therapy would be approved.

36 years later, we have moved beyond simply managing the symptoms and damage caused by infections to actually being able to correct the underlying defect in the gene. The data demonstrates the impact these modulators, specifically Trikafta are having on lung function, hospitalizations, and exacerbations, but this is not the whole story.

Through data and quality adjusted life years, you cannot hear the laughter of my boys as we run around together. You cannot hear the joy in my wife's voice as we take a walk and actually have a conversation while doing it. You cannot feel the elation in my heart as I carry full laundry ham-pers up two flights of stairs without stopping. You cannot see the sweat that drips from my forehead as I carry and pour 50 pound bags of sand for our new walkway and patio. You cannot see the tears in our eyes as our world opens up with possibility. While these might not be a big deal to many, they are to our family. It was just 5 short years ago when my lung function dropped to 24% because of an infection.

I could not walk 10 feet across my living room floor. I could not pick up my kids and hold them when they got hurt or carry them upstairs to bed. I struggled to read to them and speak in full sentences. For 38 years I have watched and felt cystic fibrosis slowly take away my lung function, the time with my family and my ability to be the person and parent that I truly want to be.

Fortunately, I have been able to try three different modulators over the past 5 years. I was involved in the Phase 3 study for Orkambi, which ultimately I had to stop because of side effects and rapidly declining lung function. I then waited for Symdeko with high hopes that this would be the one that would return some of my lost lung function and allow me more time with my family. While it initially provided a little bump, I still had the thick sticky mucus, 2 to 4 hours of treatments every day, IV antibiotics and fear. Fear that the next exacerbation would be the one that would either require a transplant or take my life. And then came Trikafta. 287 days ago I took my first dose and

within minutes it began working. I was experiencing, what has affectionately be-come known as, 'the purge'. And for the next two days I would continue to cough up mucus that I didn't know I had. My lungs would crackle and pop as mucus was finally thin enough to leave.

This was a new sensation, previously, when I would feel and hear those same sounds it meant my lungs were bleeding. But this time it was different. For the first time, my mucus no longer reminds me of Slimmer from the Ghostbusters, instead it is thin, clear and comes out easily.

My lung function has risen to the highest it has been since the beginning of 2015. I run with my kids, exercise harder and am finishing those pro-jects around the house that I have put off. Even my voice sounds different, all because I can take a deep breath. The numbers do not show you the joy, the happy tears, the sweat and the love that has come from the simple fact that I now can breathe a little easier. They do not show you the hope that my family has for a future where I grow old and grayer with my wife. Where I get to witness my children grow up and accomplish the milestones that so many take for granted. This is the impact beyond the numbers that Trikafta has had on my life and so many others. This is an impact that we need to foster and make sure that all those with cf get to experience.

Chad is the National Advocacy Co-Chair for the Cystic Fibrosis Foundation.

Appendix H. Conflict of Interest Disclosures

Tables H1 through H3 contain conflict of interest (COI) disclosures for all participants at the CTAF public meeting on August 27.

Table H1. ICER Staff and Consultants and COI Disclosures

Name	Organization	Disclosures
Avery McKenna, BS, Research Assistant	ICER	*
David Rind, MD, MSc, Chief Medical Officer	ICER	*
Jeffrey A. Tice, MD, Professor of Medicine	University of California, San Francisco	*
Kael Wherry, PhD	University of Minnesota, School of Public Health	*
Karen M. Kuntz, ScD, Professor	University of Minnesota School of Public Health	*
Matt Seidner, BS, Program Director	ICER	*
Monica Frederick, BS, Program and Event Coordinator	ICER	*
Noemi Fluetsch, MPH, Research Assistant	ICER	*
Rick Chapman, PhD, MS, Director of Health Economics	ICER	*
Steven D. Pearson, MD, MSc, President	icer	*

*No conflicts of interest to disclose, defined as individual health care stock ownership in any health plan or pharmaceutical, biotechnology, or medical device manufacturers, or any health care consultant income or honoraria from health plans or manufacturers.

Table H2. CTAF Panel Member Participants and COI Disclosures

Name	Organization	Disclosures
Ann Raldow, MD, MPH	Assistant Professor, Department of Radiation Oncology, University of California, Los Angeles	*
Brian O'Sullivan, MD	Professor of Pediatric Pulmonology, Geisel School of Medicine at Dartmouth College	*
Felicia Cohn, PhD	Bioethics Director, Kaiser Permanente, Orange County	*
Jeffrey Klingman, MD	Chief of Neurology, The Permanente Medical Group	*
Joy Melnikow, MD, MPH	Director of the Center for Healthcare Policy and Research and Professor of Family and Community Medicine, University of California, Davis	*
Kimberly Gregory, MD, MPH	Vice Chair, Women's Healthcare Quality and Performance Improvement, Cedars-Sinai Medical Center	*
Neal Kohatsu, MD, MPH, FACPM	Chief Health Strategist, Population Health Group, Center for Healthcare Policy and Research, University of California, Davis	*
Paul Heidenreich, MD, MS (Chair)	Professor and Vice-Chair for Quality, Stanford University	*

Ralph G. Brindis, MD, MPH, MACC, FSCAI, FAHA	Clinical Professor of Medicine, University of California, San Francisco	*
Rena K. Fox, MD	Professor of Medicine, University of California, San Francisco	*
Richard Seiden, JD	Patient Advocate, Retired Partner, Foley & Lardner LLP	*
Rita Redberg, MD, MSc, FACC	Cardiologist and Professor of Medicine, and Director of Women's Cardiovascular Services, University of California, San Francisco	*
Robert Collyar	Patient Advocate	*
Sei Lee, MD	Associate Professor of Medicine, University of California San Francisco	*

* No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Table H3. Policy Roundtable Participants and COI Disclosures

Policy Roundtable Participant	Conflict of Interest
Carlos Milla, MD, Professor of Pediatrics, Pulmonology, Stanford University School of Medicine	Dr. Milla has received in excess of $5,000 in advisory fees and research funding from Vertex Pharmaceuticals, Proteostasis Inc., and Eloxx Pharma. He also receives advisory board honorarium from Vertex Pharmaceuticals.
Don Maurice Kreis, JD, MS, Parent of Individual with CF	No financial conflicts of interest to disclose.
Janet Zachary-Elkind, Deputy Director, NY State Department of Health, Office of Health Insurance Programs	Janet Zachary-Elkind is an employee of the NY State Department of Health (Medicaid).
Jeff White, PharmD, MS, Staff Vice President, Clinical Pharmacy Services, IngenioRX (Anthem)	Dr. White is an employee of IngenioRX (Anthem) and owns stock in Anthem.
Manu Jain, MD, MSc, Professor, Department of Medicine (Pulmonary and Critical Care); Department of Pediatrics, Northwestern University	Dr. Jain has received in excess of $5,000 in advisory fees and research funding from Vertex Pharmaceuticals. He is also on the Speaker's Bureau of Vertex Pharmaceuticals and Gilead Sciences
Mariah Hanley, JD, Individual with CF	No financial conflicts of interest to disclose.
Mary Dwight, Senior Vice President of Policy and Advocacy, Cystic Fibrosis Foundation	CFF has received charitable contributions and/or fees for service in excess of $5,000 from health care companies including Vertex Pharmaceuticals. CFF has the option to acquire equity interests >$10,000 from a pharmaceutical company unrelated to this report. CFF has entered into therapeutic development award agreements that may result in intellectual property and royalty rights from various pharmaceutical companies