Modulator Treatments for Cystic Fibrosis: Effectiveness and Value

Final Evidence Report and Meeting Summary

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Ethan Balk and Tom Trikalinos served as the lead authors for the report. Geri Cramer and Kristin Mickle led the systematic review and authorship of the comparative clinical effectiveness section. Rick Chapman was responsible for oversight of the cost-effectiveness analyses. Geri Cramer and Rick Chapman developed the budget impact model. Sonya Khan authored the section on coverage policies and clinical guidelines. Dan Ollendorf and Steven Pearson provided methodologic guidance on the clinical and economic evaluations. The role of the University of Minnesota (UMN) School of Public Health Modeling Group is limited to the development of the cost-effectiveness model, and the resulting ICER reports do not necessarily represent the views of the UMN. We would also like to thank Ariel Jurmain, Erin Lawler, Molly Morgan, David Whitrap, and Leslie Xiong for their contributions to this report.

About ICER

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The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

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/cf-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.*

Table of Contents

List of Acronyms Used in this Report

AHRQ	Agency for Healthcare Research and Quality
AE	Adverse event
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
CI	Confidence interval
GI	Gastrointestinal
HRQOL	Health related quality of life
IV	Intravenous
LCI	Lung clearance index
MCID	Minimum clinically important difference
NIH	National Institute of Health
NICE	National Institute for Health and Care Excellence (UK agency)
PEx	Pulmonary exacerbation
PERT	Pancreatic enzyme replacement therapy
ppFEV$_1$	Percent predicted forced expiratory volume in 1 second
SAE	Serious adverse event
USPSTF	United States Preventive Services Task Force
VC	Vital capacity
WAC	Wholesale acquisition cost
WTP	Willingness to pay

Executive Summary

Background

Cystic fibrosis (CF) is a progressive genetic disease that affects many organ systems, though most of its morbidity and mortality is associated with its impact on the respiratory system. According to the Cystic Fibrosis Foundation Annual Report, there were 30,000 individuals living with CF in the US in 2016.[1] Given that the eligible patient populations for treatment with the drugs under review in this assessment were under 10,000 for each drug, we performed this review using ICER's framework for treatments of ultra-rare disorders (https://icer-review.org/wp-content/uploads/2017/11/ICER-Adaptations-of-Value-Framework-for-Rare-Diseases.pdf).

The pathogenesis of CF is linked to the cystic fibrosis transmembrane conductance regulator (CFTR) gene. In epithelial cells, the CFTR gene is transcribed and translated to produce the CFTR protein, which is in turn, transported to the apical membrane, the part of the membrane that faces inwards towards the open lumina of an organ, such as the airways within the lung. There the protein acts as a chloride ion gate and contributes to the regulation of salt transport in and out of the cell. Mutations to the CFTR gene lead to thickened secretions in the lung, gastrointestinal tract, pancreas, and other organs. Due in part to the thickened lung secretions, people with CF commonly have frequent acute pulmonary infections requiring antibiotic treatment and hospitalization. Ultimately, most people with CF suffer progressive damage to their airways, leading to bronchiectasis and ultimately to respiratory failure, which is responsible for the majority of CF-related deaths.

A little over 300 different mutations are known to cause CF.[2] Patients with CF carry pathogenic mutations in both copies of the *CFTR* gene. The most common pathogenic mutation is the *F508del* mutation. About 86% of all patients have at least one copy of the mutation; these patients are approximately evenly split between homozygous (two copies of the mutation) and heterozygous (one copy of *F508del* and another mutation).[3,4] Another relatively common mutation is *G551D*, which is found in approximately 5% of CF patients.[3] In patients with at least one copy of *G551D* some of the protein folds correctly, but when it reaches the apical membrane it does not open appropriately to let chloride ions flow normally.

The impact of CF and the complexity of its management are associated with multiple physical and social challenges as well as economic insecurity, which can severely affect the quality of life of CF patients, their caretakers, and the rest of their families.

Management

The core treatment regimen for CF has historically aimed to control symptoms. It includes aggressive airway hygiene with chest physiotherapy, airway clearance devices, bronchodilators, inhaled and systemic antibiotics, inhaled hypertonic saline, and aerosolized recombinant human DNase to reduce sputum thickness. Also helpful is management of the diet, with pancreatic enzyme replacement therapy and insulin if necessary. The treatment burden for CF patients is high, with patients reporting that they spend upwards of two hours a day completing treatment activities.[5] Lung transplantation remains the last-line intervention for CF patients with end-stage disease. Patients who undergo successful lung transplantation no longer suffer from CF in their lungs but continue to have symptoms related to CF in other organ systems.

While improvements in supportive care have improved the prognosis for CF patients, these treatments are directed only at symptom management. Recently introduced agents known as CFTR modulators directly address the pathophysiology of the disease and are the focus of this review.

CFTR modulator drugs

Modulator drugs increase CFTR-mediated ion transport. Two types of modulator drugs have been developed, with complementary modes of action. The effectiveness of modulators depends on the CF-causing mutation.

CFTR potentiators, such as Kalydeco® (ivacaftor monotherapy), increase the likelihood that the CFTR channel will transport ions through the cell membrane, i.e., they increase the channel's "open probability". Kalydeco has been approved for patients with various "gating" (e.g. *G551D*) and other mutations that result in residual CFTR protein function in the cell membrane (e.g., *R117H*).

CFTR correctors, such as lumacaftor and tezacaftor, increase the amount of normal or mutated CFTR protein that gets transported to the apical (luminal) membrane, thereby increasing the amount of CFTR protein on the cell surface. Orkambi® (lumacaftor/ivacaftor) and Symdeko™ (tezacaftor/ivacaftor) are considered in patients homozygous for the *F508del* mutation. While Symdeko has also been studied in patients who are heterozygous for the *F508del* allele with a residual function mutation, it was approved by the FDA in February 2018 not only for these populations but for other mutations potentially responsive to Symdeko based on laboratory assessments.[6]

For the purposes of this report we use trade names to facilitate ease of interpretation of the data, with the exception of unapproved doses of lumacaftor with ivacaftor.

Insights Gained from Discussions with Patients and Patient Groups

We held semi-structured discussions via teleconference with parents of children with CF as well as with adult patients with CF and identified several cross-cutting themes.

The first theme identified from these discussions pertained to aspects of the CF experience that have a strong impact on quality of life from the patient's and family's perspective. First, daily care is demanding. Aggressive airway hygiene, a mainstay of standard CF management, is a time-consuming process. Additionally, patients routinely take many pills and inhalation treatments as part of standard care and are concerned by the prospect of even more interventions (e.g., more pills for the modulator treatments, or additional medications to manage emerging complications of CF, such as CF-related diabetes). The high daily demands of standard care take a toll on patients and caregivers. Second, CF patients often endure frequent and severe complications from their disease. Hospitalizations typically last for many days or weeks leading to substantial time lost from school, work, and leisure for both patients and caregivers. Hospitalizations and specialized care can be associated with additional logistical hindrances and expenses if it is necessary to travel to a facility with experience in CF management. Third, even so-called minor complications of CF are pervasive and reduce quality of life. For example, chronic sinusitis can be accompanied by the inability to smell or taste foods, which reduces appetite and contributes to malnutrition. All of the above can greatly limit the ability of CF patients to participate in the social, athletic, work, and other functions that their peers engage in.

Another theme in our discussions with patients and caregivers reflected the challenges of adhering to CF management. The daily management of CF is demanding; skipping airway hygiene for a day creates time for other activities and may not have an immediately perceptible negative impact on clinical function. Thus, children or young adults who move on to the next stage of their lives (e.g., leaving home to go to college) may be tempted to lapse in terms of adherence.

A third theme was related to financial insecurity due to management of the disease. While all patients we spoke with had insurance coverage, their co-payments varied for CF-related treatment. Uncertainty about future insurance coverage for treatments was also commonly raised. Additional expenses are associated with hospitalizations including travel, accommodation, arranging for care of other children, and other concerns. Further, parents with inflexible work schedules risk losing their jobs after exhausting their sick time.

Comparative Clinical Effectiveness

We evaluated evidence of the efficacy, safety, and effectiveness of CFTR modulators in comparison with other CFTR modulators or placebo in our target population of individuals with cystic fibrosis. We included any age group with a genetic mutation for which a CFTR modulator had been or was expected to be approved. Comparative trials of CFTR modulators (vs. other intervention or

placebo) were typically powered to detect differences in the change from baseline in percent predicted forced expiratory volume in 1 second ($ppFEV_1$), a measure of respiratory function. While we abstracted both change from baseline and differences between treatment groups, we note that there is no universally agreed-upon definition of a clinically-important difference given the substantial heterogeneity in respiratory function inherent in CF.[7]

We also captured data on the following additional outcomes: mortality, pulmonary exacerbation, weight and body mass index (BMI), and quality of life. We also sought patient-reported outcome data and incorporated it in the review if available. We sought evidence on harms from any study design.

We evaluated treatment in three distinct populations:

1. Kalydeco for patients with gating and residual function mutations. This included individuals with *G551D* and non-*G551D* gating mutations and those with *R117H* residual function mutations.

2. Orkambi and Symdeko for individuals homozygous for the *F508del* mutation.

3. Symdeko and Kalydeco for individuals heterozygous for the *F508del* mutation with a second mutation amenable to Symdeko.

We first describe the evidence regarding clinical benefits for each population. Next, we describe the evidence on harms for the CFTR modulators collectively.

1. Kalydeco for patients with gating and residual function mutations

Clinical Benefits

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 three years. Limited evidence also suggests one-year reductions in rates of death, organ transplantation, and hospitalizations. Statistically significant gains in body weight and respiratory symptom-related quality of life with Kalydeco were reported for G551D and non-G551D gating mutation populations aged 12 and older compared to placebo. Statistically significant improvements in lung function or weight were not observed in adult patients with R117H residual function mutations. In a small sample of children aged 6 to 11 years with R117H residual function mutations, those on Kalydeco experienced statistically significant worsening of lung function and trended towards decreased respiratory symptom-related quality of life scores compared to placebo.

Four randomized controlled trials (RCTs) – STRIVE, ENVISION, KONNECTION, and KONDUCT – evaluated the safety and efficacy of Kalydeco in individuals with at least one *G551D*, non-*G551D* gating, or *R117H* mutation.[8-11] All four studies required a baseline ppFEV$_1$ ≥40%. All four trials randomized participants to receive either 150 mg of Kalydeco or placebo twice daily for 24 weeks. A fifth comparative study compared over 1,600 people (implicitly with any relevant mutation) taking Kalydeco with over 8000 matched controls not taking Kalydeco; the conference abstract reported one-year follow-up data.[12] We also evaluated three noncomparative studies: KIWI,[13] a Phase III single-arm study that included children aged 2-5 with a *G551D* gating mutation; GOAL,[14] a longitudinal cohort study of individuals aged 6 years and older with at least on *G551D* mutation; and PERSIST,[15] which followed eligible STRIVE and ENVISION participants for an additional 96 weeks on Kalydeco.

Study findings are summarized in Table ES 1 below. For people 6 years and older with gating mutations (*G551D* and non-*G551D*), studies have mostly found improvements in the primary pulmonary, weight, and quality of life outcomes with Kalydeco compared to placebo over 24 to 48 weeks. Studies have reported significant improvements in ppFEV$_1$ compared to placebo of 10.4 percentage points (95% CI 8.6 to 12.3, by meta-analysis) over 24 to 48 weeks, significant reductions in risk of pulmonary exacerbations (34% vs. 56%, hazard ratio 0.455, P=0.001), increases in weight (2.8 kg or 0.7 kg/m^2), and clinically significant improvements in the respiratory domain of the CFQ-R quality of life instrument of about 5 to 10 points, although the difference with placebo was nonsignificant in the study of 6 to 11 year olds with the *G551D* mutation. Long-term follow-up (96 weeks) of these people on continued Kalydeco treatment found maintenance of their improvements in ppFEV$_1$ (10.7 percentage points, 95% CI 7.3 to 14.1). Other long-term follow-up studies found continued lowered risk of pulmonary exacerbations compared to matched controls on best supportive care (RR 0.64, 95% CI 0.58 to 0.70) and lowered annual risk of death (RR 0.41, 95% CI 0.20 to 0.84).

Based on a single study of people with the *R117H* gating mutation, Kalydeco improved respiratory function and quality of life in people aged 18 years and older; however, among the small subset of study participants 6 to 11 years old, Kalydeco was not more effective than placebo. For those 18 and older, ppFEV$_1$ improved by 5 percentage points and the respiratory domain of CFQ-R improved by 12.6 points. For the 17 children aged 6 to 11 years, ppFEV$_1$ worsened on Kalydeco, going down 6.3 percentage points compared to placebo; the respiratory domain of CFQ-R was also reduced, but not significantly so. In both age groups there were no differences in risk of pulmonary exacerbation (hazard ratio 0.93) or change in BMI.

Table ES1. Summary of Kalydeco (150 mg 2x/day) on Clinical Efficacy Outcomes for *G551D*-, non-*G551D* Gating Mutations, and *R117H*-CFTR Mutations

Age Duration (N)	Studies	ppFEV$_1$ (Absolute Diff), Percentage Points	Pulmonary Exacerbation	Weight (Diff)	CFQ-R Respiratory Domain (Diff)	Other (RR)
G551D Mutation						
	Randomized Controlled Trials					
≥6 yr 48 wk (N=213)	STRIVE ENVISION	**10.4 (8.6, 12.3)***	**HR 0.455 (0.29, 0.73)†** **nd†**	**Weight (kg): 2.8 (1.8, 3.8)***	**9.7 (6.5 to 13.0)***	
Non-*G551D* Mutation						
	Randomized Controlled Trial					
≥6 yr 8 wk (N=39)	KONNECTION	**10.7 (7.3, 14.1)**	nd	**BMI (kg/m^2): 0.7 (0.3, 1.0)**	**9.6 (4.5, 14.7)**	
R117H Mutation						
	Randomized Controlled Trial					
≥6 yr 24 wk (N=69)	KONDUCT		HR 0.93 (nd)	BMI (kg/m^2): 0.3 (−1.6, 2.1)		
6-11 yr (N=17)‡		**−6.3 (−12.0, −0.7)**§			−6.1 (−15.7, 3.4)§	
≥18 yr (N=50)‡		**5.0 (1.2, 8.8)**			**12.6 (5.0, 20.3)**	
Any Indicated Mutations (Implied)						
	Nonrandomized Comparative Study					
≥6 yr #	US cohort	nd	**RR 0.64 (0.58, 0.70)**	nd	nd	**Death: 0.41 (0.20, .84)**
1 yr (N=1256 **)						**Organ Txp: 0.15 (0.04, 0.59)**
						Hospitalization: 0.64 (0.58, 0.70)

Results in bold font are statistically significant.

Abbreviations: BMI: body mass index, CFQ-R: Cystic Fibrosis Questionnaire-Revised, Diff: difference between Kalydeco and placebo, HR: hazard ratio, nd: no data (not reported), ppFEV$_1$: predicted percent forced expiratory volume in one second, RR: risk ratio, Txp: transplantation, wk: weeks, yr: year.

* 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. ** On Kalydeco, matched with 6000 controls

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2. Orkambi and Symdeko for patients with homozygous *F508del* mutation

Clinical Benefits

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 varies by age, dose, and baseline lung function. In longer-term follow-up (96 weeks), those 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. Both Orkambi and Symdeko provide improved respiratory-related quality of life compared with placebo. Orkambi and Symdeko reduced pulmonary exacerbation events over 24 weeks, including those requiring intravenous antibiotics and hospitalizations, compared with placebo. Indirect comparisons yielded no material differences between Orkambi and Symdeko in key clinical outcomes.

Six key studies including four randomized controlled trials, one single arm trial and one long-term, open-label extension study were identified (see Table ES 2).[16-20] Two randomized trials of Orkambi (TRAFFIC and TRANSPORT) were analyzed together, with a subsequent open-label extension study.[16,19] Three of the trials (and the open-label extension study) evaluated Orkambi in people 12 years or older (mean age 25 years) or children aged 6 to 11 years old. The single arm study also evaluated Orkambi in children aged 6 to 11 years old. The single randomized trial of Symdeko included mostly adults (mean age 26 years). All primary studies evaluated 24 weeks of therapy; the open-label extension followed people for an additional 96 weeks of therapy. TRAFFIC, TRANSPORT and EVOLVE, included people with ppFEV$_1$ between 40% and 90% (mean 60%); the other trial of Orkambi, Ratjen et al., included younger children who had lung function closer to normal (ppFEV$_1$ >70%; mean 90%).

The trials evaluated various doses of lumacaftor (all used the same dose of Kalydeco, 250 mg twice daily). TRAFFIC/TRANSPORT evaluated both lumacaftor 600 and 800 mg total daily; the FDA approved dosage for adults is 800/500 mg daily (Orkambi). As study reporting allows, we focus on data for the FDA approved dose. The Orkambi trial of children 6 to 11 years old used the FDA approved dosage of 400/500 mg daily for this age range. The Symdeko trial also used the FDA approved dosage for adults (100/300 mg daily).

Study findings are described by therapeutic comparison below and summarized in Table ES 2 on page ES9.

Orkambi

People taking Orkambi had modest, but statistically significant, improvements in lung function over six 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, respectively, compared to placebo.

The effect of Orkambi on weight was inconsistent across trials. TRAFFIC found no significant difference in weight change compared with placebo, but the identically designed TRANSPORT study found significant weight gain on the drug; pooled analysis found a small, but statistically significant weight increase of 0.24 kg/m^2 (95% CI, 0.11 to 0.37) compared to placebo. The open-label extension study found continued weight gain of about 0.75 to 1 kg/m^2 over 96 weeks. The randomized trial of children 6 to 11 years old found no differences in weight measures.

The respiratory domain of the quality of life measure CFQ-R was statistically significantly different in adolescents and adults between Orkambi and placebo (2.2 points; 95% CI 0.0 to 4.5), although this did reach the recognized clinically important difference of 4.0.[21] A similar, though statistically nonsignificant effect was found in the trial of children (2.5 points; 95% CI -0.4 to 5.4).

TRAFFIC/TRANSPORT reported a significant reduction in risk of pulmonary exacerbations among those taking Orkambi (rate ratio 0.61, 95% CI 0.49 to 0.76). Similarly decreased rates of pulmonary exacerbations were found in the 96-week extension study (0.65 events/year, 95% CI 0.56 to 0.75). The pediatric trial did not report on pulmonary exacerbations.

Symdeko

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). 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]).

Orkambi vs. 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 full report (see Section 3).

Table ES2. Summary of Orkambi and Symdeko on Clinical Efficacy Outcomes for Homozygous *F508del* CFTR Mutations

Age Duration (N)	Studies	$ppFEV_1$ (Absolute Diff), Percentage Points	Pulmonary Exacerbation, Rate Ratio	Weight (Diff)	CFQ-R Respiratory Domain (Diff)
Orkambi* vs. Placebo					
		Randomized Controlled Trials			
6-11 yr 24 wk (N=204)	Ratjen et al.	**2.4 (0.4, 4.4)**	nd	BMI: −0.1 kg/m^2 (−0.1, 0.3) *BMI z-score: 0.0 (−0.2, 0.2)*	2.5 (−0.4, 5.4)
≥12 yr 24 wk (N=1108)	TRAFFIC TRANSPORT	**2.8 (1.8, 3.8)**	**0.61 (0.49, 0.76)**	**BMI: 0.24 kg/m^2 (0.11, 0.37)** *BMI z-score: nd*	**2.2 (0.0, 4.5)**
		Extension Study (vs. Matched Controls)			
≥12 yr 96 wk (N=2043)†	TRAFFIC TRANSPORT	**42% slower** rate of decline†			
Symdeko (100/500 mg) vs. Placebo					
		Randomized Controlled Trial			
Mean 26 yr 24 wk (N=504)	EVOLVE	**4.0 (3.1, 4.8)**	**0.53 (0.34, 0.82)**	BMI: 0.06 kg/m^2 (−0.08, 0.20) *BMI z-score: 0.04 (−0.15, 0.07)*	**5.1 (3.2, 7.0)**
Symdeko vs. Orkambi					
		Network Meta-Analysis			
Indirect comparison	EVOLVE vs. Tr/Tr	1.2 (−0.1, 2.5)	0.87 (0.53, 1.42)		2.9 (0.0, 5.8)
	EVOLVE vs. Ratjen			*BMI z-score: −0.04 (−0.29, 0.21)*	

Results in bold font are statistically significant.

Abbreviations: BMI: body mass index, CFQ-R: Cystic Fibrosis Questionnaire-Revised, Diff: difference between Kalydeco and placebo, nd: no data (not reported), $ppFEV_1$: predicted percent forced expiratory volume in one second, Tr/Tr: TRAFFIC/TRANSPORT, wk: weeks, yr: year.

* 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.

3. Symdeko and Kalydeco for patients with heterozygous *F508del* mutation and a second mutation amenable to Symdeko

Clinical Benefits

Key Findings: Based on a single short-term (8 week) cross-over trial, Symdeko and Kalydeco both improved absolute and relative ppFEV$_1$ compared with placebo. Symdeko provides a statistically significant benefit over 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, BMI and pulmonary exacerbations were not significantly different between the two drugs and compared with placebo, however; the follow-up duration was likely too short to adequately evaluate these outcomes.

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 cross-over trial in which participants took drug for only 8 weeks (n=234). Participants were 12 years or older with ppFEV$_1$ between 40% and 90%, and stable lung disease.[22]

Findings are summarized in Table ES3 on the following page. Compared to placebo, both interventions provided statistically significant improvement in absolute ppFEV$_1$: 6.8 percentage points for Symdeko (95% CI 5.7 to 7.8) and 4.7 percentage points for Kalydeco (95% CI 3.7 to 5.8). While the clinical significance of these improvements is unknown, these are larger in absolute terms than those seen in the homozygous population. Symdeko also resulted in statistically superior improvement compared to Kalydeco (difference 2.1 percentage points; 95% CI 1.2 to 2.9). Symdeko and Kalydeco both yielded clinically and statistically significant improvements in quality of life using the CFQ-R respiratory domain score as compared to placebo (Symdeko 11.1 points, 95% CI 8.7 to 13.6; Kalydeco 9.7 points, 95% CI, 7.2 to 12.2), with no significant difference seen in comparisons between the two drugs. While taking either CFTR modulator, patients had fewer episodes of pulmonary exacerbation (11 and 9 events, respectively) than while taking placebo (20 events), but the differences were not statistically significant.

In addition to the randomized trial data reported in Table ES3, EXPAND reported subgroup differences in effects of Symdeko on ppFEV$_1$ based on age. Those less than 18 years old showed a 12.0 percentage point improvement in absolute ppFEV$_1$ (95% CI, 9.3 to 14.8), whereas those 18 years and older saw a 6.0 percentage point increase (4.9 to 7.0); however, data should be interpreted with caution given only 11 patients under the age of 18 received Symdeko.

Table ES3. Summary of Symdeko and Kalydeco on Clinical Efficacy Outcomes for Heterozygous *F508del* CFTR Mutation

Age N Duration	Study	$ppFEV_1$ (Absolute Diff), Percentage Points	Pulmonary Exacerbation, Rate Ratio	Weight (Diff) BMI, kg/m^2	CFQ-R Respiratory Domain (Diff)
≥12 yr	EXPAND	**Symdeko (100/300 mg) vs. Placebo** *(Randomized Controlled Trial)*			
N=234		**6.8 (5.7, 7.8)**	0.54 (0.26, 1.13)	0.34 vs. 0.18 (nd*)	**11.1 (8.7, 13.6)**
8 wk (cross-over)		**Kalydeco (300 mg) vs. Placebo** *(Randomized Controlled Trial)*			
		4.7 (3.7, 5.8)	0.46 (0.21, 1.01)	0.47 vs. 0.18 (nd*)	**9.7 (7.2, 12.2)**
		Symdeko (100/300 mg) vs. Kalydeco (300 mg) *(Randomized Controlled Trial)*			
		2.1 (1.2, 2.9)	1.18 (0.49, 2.87)	0.34 vs. 0.47 (nd*)	1.4 (−1.0, 3.9)

Results in bold font are statistically significant.

Abbreviations: BMI: body mass index, CFQ-R: Cystic Fibrosis Questionnaire-Revised, Diff: difference between Kalydeco and placebo, nd: no data (not reported), $ppFEV_1$: predicted percent forced expiratory volume in one second, wk: weeks, yr: year.

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

Harms

For all three CFTR modulators, harms were nonserious and generally uncommon. Serious adverse events, as defined by the studies, commonly occurred at the same or *lower* rates among those taking the CFTR modulators than those taking placebo, including adverse events ascribed to the drugs. No deaths during CFTR modulator trials were related to the drugs. However, reasons for CFTR modulator discontinuation included elevated liver enzymes, creatinine kinase levels, hemoptysis, bronchospasm, dyspnea, pulmonary exacerbation, and rash.

Across studies, summary (i.e., meta-analyzed) rates of discontinuation due to adverse events were:

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

Chest tightness ("abnormal respiration") is a concern that we heard from patients and clinicians, however, the adverse event was only sparsely reported in the literature. In TRAFFIC and TRANSPORT, abnormal respiration was more common with Orkambi (800/500 mg) than placebo (8.7% vs. 5.9%); in the open-label extension study, reported rates of abnormal respiration were between 10-17% over 96 weeks.[16,19] Of note, those with baseline ppFEV$_1$ <70% reported more chest tightness than those with baseline ppFEV$_1$ ≥70% (11-20% vs. 6-8%).[23] A real-world cohort study reported that nearly 20% of patients reported chest tightness.[24] Abnormal respiration was not reported to be a concern for Symdeko and clinical data showed no to low reporting of this side effect.[18,22] Symdeko also has fewer drug interactions than Orkambi.[6,25]

Controversies and Uncertainties

CFTR modulator data is unfolding, with the evidence base for some regimens limited to a few published studies. Outcomes of interest, particularly related to weight changes and pulmonary exacerbations, are not consistently reported across studies. Thus, conclusions on individual outcomes are based mostly on one or two trials. Evidence of the comparative effects of CFTR modulators (versus placebo) beyond six months is sparse and largely inconclusive; however, with non-comparative data out to three years, Kalydeco effectiveness has been widely accepted in the clinical community for certain mutations. For the homozygous *F508del* mutation population, there are no trials that directly compare the two treatment options, Symdeko and Orkambi. For the heterozygous *F508del* mutation population, there is only a very short-term (8 week) crossover trial comparing treatment options to each other or to placebo.

A key uncertainty relates to the relationship between improvements in lung function (as measured by ppFEV$_1$) and reductions in the rate of pulmonary exacerbations. While some level of benefit in

lung function was seen in all studies, exacerbations were not measured consistently and benefit was not uniformly seen. While there are structural explanations in some cases (e.g., the 8-week crossover EXPAND study may have been too short to capture differences in exacerbations), the degree to which reductions in exacerbation rates are contingent on or independent from effects on lung function remains uncertain.

In addition, data on the durability and nature of CFTR modulator effects on lung function are only just emerging. Specifically, there is evidence indicating that these agents provide *improvements* in lung function over the short term (albeit to varying degrees depending on agent and population), but information on slowing of the rate of lung function *decline* over the longer term is not yet mature and still developing.

Research on CFTR modulators is hampered by a number of factors inherent to the population of people with CF. CF genetics are highly complex and variable, and the disease affects relatively small populations when considered by type of mutation. In addition, the recent FDA approval of Symdeko was not limited to the population studied in the EXPAND trial, which required at least one *F508del* mutation. Therefore, we cannot state with any certainty how generalizable the results from EXPAND are to patients with other mutations, for whom outcomes data are currently unavailable. Additionally, where two drugs for the same population are available, there are little head-to-head data. For example, in the homozygous *F508del* population, we do not have randomized studies looking at Symdeko versus Orkambi.

Other patient characteristics are also likely to impact the effectiveness of the drugs. Limited evidence suggests that, in contrast with adults, children with the *R117H* mutation do not receive a benefit with Kalydeco, while adolescents heterozygous for the *F508del* mutation may have a greater benefit with Symdeko than adults.

Additionally, variation within and across studies in the care delivered as part of CF symptom management increases the difficulty in interpreting the findings regarding added benefits of CFTR modulators. Even within studies, there was wide variation in the concomitant therapies being used by study participants. It is unknown whether there are any interactions between the effect of the CFTR modulators and any of the concomitant therapies. It is possible that the modulators have little incremental benefit when used with some standard of care therapies or, alternatively, that some of the concomitant therapies may enhance their effects. It is also likely that this variability makes even general indirect comparisons between active therapies that we conducted somewhat problematic to interpret.

Nearly 85% of people with CF in the United States receive care at accredited CF centers, 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, thus improvements in health outcomes seen among these patients (those

assumed to be receiving best supportive care) likely reflect added benefits of CFTR modulators. We identified uncertainties, however, regarding whether beneficial gains in survival are distributed unequally due to differences in access to US CF care centers. For example, Canadian CF patients have been living longer since the mid-1990s and currently live, on average, 10 years longer than American CF patients despite higher usage of mucolytics.[26,27] When comparing the US and Canada, the difference between Canadian and US survival disappeared when US patients receiving Medicare and Medicaid were excluded from survival data, suggesting CF patients receiving care through public health insurance are missing out on 10 years of life.[26,28] It is unclear whether patients are receiving different care depending on their insurance type or whether American CF patients with public insurance are more likely to have important socioeconomic disadvantages that affect their CF management. While long-term studies are underway to evaluate the impact of CFTR modulators on long-term survival, ensuring access to the highest quality CF care in the interim may improve the survival of all CF patients.

Percent predicted FEV_1 was the primary outcome for most studies. However, it important to note that $ppFEV_1$ is a surrogate measure of disease severity that attempts to measure lung function relative to what is predicted in healthy persons of the same age and sex. Additionally, it remains unclear what magnitude of change in $ppFEV_1$ is clinically relevant.

Evaluation of adverse events among people with CF is challenging because the most frequently reported events may be due to the underlying disease, as evidence by the higher rates of adverse events among those taking placebo than CFTR modulators.

Finally, cystic fibrosis is a multisystem disease, yet many aspects of the disease have not been systematically researched. Our evaluation of the impact of CFTR modulators is highly dependent on those outcomes measured in the trial data, namely pulmonary function, weight, respiratory symptom-related quality of life and the number, type and annualized rate of pulmonary exacerbations.

Summary and Comment

Kalydeco for patients with cystic fibrosis caused by gating and residual function mutations:

- Kalydeco provides improvements in $ppFEV_1$ (5.0 to 10.7 percentage points in different populations), weight, and respiratory-symptom-related quality of life (9.6 to 12.6 points) for children, adolescents, and adults (over 24 weeks). Longer-term follow-up (up to three years) shows lung function, weight, and quality of life gains are durable across all gating mutations.
- However, limited data suggest 6 to 11 year olds with the *R117H* mutation may not have improved respiratory function and quality of life with Kalydeco treatment.
- Pulmonary exacerbations were less frequent (HR=0.46), shorter, and required fewer hospitalizations and intravenous antibiotics for patients taking Kalydeco.

- Fewer patients (across populations) discontinued Kalydeco due to adverse events (1.2%) than with placebo (2.1%).

Across all subpopulations, rates of discontinuation due to adverse events and severe adverse events were similar for Kalydeco and placebo.

Given the relatively consistent evidence arising from 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 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.

Orkambi for patients with cystic fibrosis caused by two copies of the F508del mutation:

- Orkambi improved $ppFEV_1$; however, changes in absolute $ppFEV_1$ were relatively modest (2.4 to 2.8 percentage points).
- At 24 weeks, BMI increases with Orkambi among those aged 12 years and older (0.61 kg/m^2), which was maintained over the subsequent 96 weeks; but no significant difference was found in a study of younger children.
- Treatment improved respiratory symptom-related quality of life in patients age 12 and older (2.2 points); a similar improvement was found in a smaller study of children 6-11 years old, but the effect was not statistically significant.
- The rate of pulmonary exacerbation was lower for patients aged 12 and older taking Orkambi (rate ratio = 0.61); data were not reported in the study of younger children.
- Chest tightness (abnormal respiration) was reported as a side effect for those taking Orkambi ranging from 8% in the Phase III trials to 20% in a real-world post-approval study.
- Rates of discontinuation due to adverse events were higher for Orkambi (4.6%) than for placebo (1.6%) within a trial in this population. Similar results were seen among all studies across populations (6.3% vs. 2.1%, respectively).

In two large Phase III trials and an accompanying 96-week open-label extension study, Orkambi provided improvements in $ppFEV_1$ as well as a reduced rate of decline in lung function; however, lung function improvements were modest, and patients also reported drug-drug interactions as well as abnormal respiration and other 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 for patients with cystic fibrosis caused by two copies of the F508del mutation:

- Treatment with Symdeko improved absolute ppFEV$_1$ (4.0 percentage points) and respiratory-related quality of life (5.1 points) compared to placebo over 24 weeks. No significant differences in weight were reported.
- Treatment reduced the rate of pulmonary exacerbation over 24 weeks (rate ratio = 0.53).
- In this population, rates of discontinuation due to adverse events were similar for Symdeko (2.8%) and placebo (3.1%). Similar results were seen among all studies across populations (2.5% vs. 2.1%, respectively).

A single, parallel-arm, Phase III trial showed a moderate improvement in ppFEV$_1$ with Symdeko, and reductions in the rate of pulmonary exacerbation; however, the trial was relatively short in duration. Discontinuation due to adverse events was lower than seen in the trial of Orkambi. While a single, short-duration trial only provides moderate certainty, for patients homozygous for the *F508del* mutation, we judge the net health benefit of Symdeko to be "incremental or better" ("B+"), indicating moderate certainty of a small or substantial net health benefit and high certainty of at least a small benefit.

Symdeko for patients with cystic fibrosis caused by one copy of the F508del mutation and a second mutation amenable to Symdeko:

- Treatment with Symdeko resulted in improvement in absolute ppFEV$_1$ (6.8 percentage points) and respiratory sympton-related quality of life (11.1 points).
- The treatment effect on pulmonary exacerbations and BMI was exploratory only, due to small patient numbers and short trial duration (8 weeks).

While a single trial showed evidence of improvement in lung function for Symdeko compared with placebo, the study was of short duration (eight weeks) and used a crossover design. Longer-term studies to confirm effects on pulmonary exacerbation and weight gain are necessary. As above, the current trial evidence provides only moderate certainty, but the level of benefit demonstrated suggests 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+") in patients heterozygous for the *F508del* mutation with an approved residual function mutation.

Long-Term Cost Effectiveness

We conducted a cost-effectiveness analysis using a *de novo* microsimulation model comparing CFTR modulator treatments plus best supportive care to best supportive care alone for CF patients. We modeled the same three populations described in the project scope (i.e., those with gating mutations, homozygous for *F508del*, and heterozygous for *F508del* with a residual function mutation potentially responsive to treatment). The CFTR modulators of interest for these three populations were:

1. Gating mutations: Kalydeco (with patients initiating treatment at two years old).
2. Homozygous for the *F508del* mutation: Orkambi or Symdeko (with patients initiating treatment at six years old).
3. Heterozygous for the *F508del* mutation and a residual function mutation that are potentially responsive to treatment: Symdeko or Kalydeco (for patients initiating treatment at 12 years old).

CF is a condition which falls under ICER's ultra-rare disease framework. Therefore, we considered whether to adopt dual base-case analyses based on health system and societal perspectives. However, while the impact of this disease can be substantial on patient and caregiver productivity, and informal caregiver time, the impact of treatment with the CFTR modulators on societal costs is not expected to be substantial in proportion to the health system costs, because the drugs do not greatly reduce the daily burdens associated with usual CF supportive care. We therefore present the results from a societal perspective as a scenario analysis rather than as part of a dual base case.

Outcomes were estimated over a lifetime time horizon using one-year time increments from treatment initiation until death. The primary health outcome was quality-adjusted life years (QALYs) but we also report life expectancy and the lifetime number of acute pulmonary exacerbations. Costs and health outcomes were discounted at 3% per year. A comprehensive list of model assumptions, along with the rationale for each, is available in Section 4 of the report.

The primary model variable was percent predicted forced expiratory volume in one second ($ppFEV_1$), modeled as a continuous variable. For each population, a cohort of CF patients begins the model at the age of drug initiation. Each simulated patient is assigned a $ppFEV_1$ value drawn from a distribution and then experiences annual age-specific declines in lung function. In addition to $ppFEV_1$, the model tracked the values of other variables for each simulated person: 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 CF-related diabetes or *B. cepacia* infection. During any given year, a simulated person may experience a change in their $ppFEV_1$, experience one or more pulmonary exacerbations, be diagnosed with diabetes mellitus or *B. cepacia* infection, or undergo lung transplantation. The annual risk of death is influenced by all of these variables. EQ-5D utility values derived from a sample of cystic fibrosis

patients were assigned based on lung function or receipt of lung transplantation; disutilities were assigned for acute pulmonary exacerbations. For the treatment arms, we allowed the initial ppFEV$_1$ and weight-for-age *z*-score values to change based on trial results or assumptions in the absence of data. We also allowed the risk of acute pulmonary exacerbation to decrease with treatment, independent of the improvement in ppFEV$_1$.

All costs were adjusted to 2017 US dollars using the personal consumption expenditure (PCE) price index. Annual net drug acquisition costs for each was derived from the Federal Supply Schedule (FSS) to determine discounted (net) prices of Kalydeco and Orkambi (Table 4.5).[29] As Symdeko was only recently approved by the FDA, information on its net pricing was not yet available. We therefore applied the FSS discount rate for Orkambi (3.2%) to the wholesale acquisition cost (WAC) of Symdeko to arrive at an estimated net price.

We assumed that annual CF-related healthcare 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 transplant-related costs. Both disease management and pulmonary exacerbation components incorporated a gradient cost structure that was derived from Lieu et al. to reflect increasing costs with increasing disease severity categories (mild, moderate, and severe ppFEV$_1$ categories).[30] An age-related adjustment (<18 or 18+) was included in the exacerbation component. To derive current best supportive care costs, we used two average annual cost estimates based on an unpublished analysis of 2016 commercial payer and Medicaid claims data ($130,879 and $83,173 in 2016 US dollars) (S. Grosse, personal communication, April 12, 2018). Transplant-related costs include the one-time cost of receiving a lung transplant followed by an annual cost associated with post-transplantation care.

Base-Case Results

Overall, all three CFTR modulator therapies provided substantial health benefits (range of 5.0-6.1 gain in discounted QALYs; 3.5-4.3 gain in discounted life years) at a substantial increase in direct medical costs (range of $4.1-$6.3 million in discounted costs) (Table ES4).

The incremental cost-effectiveness ratios for Kalydeco for individuals with a gating mutation were approximately $1.5 million and $960,000 per life year and QALY gained respectively (Table ESY). For individuals who are homozygous for the *F508del* mutation the incremental cost-effectiveness ratios for Orkambi and Symdeko versus best supportive care were approximately $891,000 per QALY and $974,000 per QALY, respectively, and approximately $1.3 million and $1.4 million per life year gained, respectively. For individuals who are heterozygous for the *F508del* mutation with a residual function mutation, the incremental cost-effectiveness ratios for Kalydeco and Symdeko in this population were approximately $940,000 QALY and $841,000 per QALY, respectively, and approximately $1.3 million and $1.2 million per life year gained, respectively.

Table ES4. Results for the Base Case for CFTR Modulators Plus Best Supportive Care (BSC) Compared to BSC Alone, By Study Population (Discounted at 3% per Year)

Population and Treatment	CFTR Drug Cost	Total Cost	Average Number of PEx	Total Life Years	Total QALYs
CF Individuals with A Gating Mutation					
BSC	$0	$2,227,765	32.75	22.16	15.92
Kalydeco Plus BSC	$7,443,121	$8,666,308	18.86	26.52	22.65
CF Individuals Homozygous for *F508del* Mutation					
BSC	$0	$2,108,199	26.02	20.77	14.74
Orkambi Plus BSC	$5,847,893	$6,983,336	11.45	24.57	20.21
Symdeko Plus BSC	$6,290,005	$7,478,684	13.36	24.70	20.25
CF Individuals Heterozygous for *F508del* Mutation with Residual Function Mutation					
BSC	$0	$2,081,180	25.51	18.98	12.92
Kalydeco Plus BSC	$6,447,156	$7,557,596	10.85	23.07	18.74
Symdeko Plus BSC	$5,934,935	$7,091,919	12.68	23.25	18.88

CFTR: Cystic fibrosis transmembrane conductance regulator; PEx: pulmonary exacerbations; QALYS: quality adjusted life years; BSC: best supportive care

Table ES5. Incremental Cost-Effectiveness Ratios Compared to Best Supportive Care (BSC) for the Base Case

Treatment vs. BSC	Cost Per LY Gained	Cost Per QALY Gained	Cost Per PEx Averted
CF Individuals with a Gating Mutation			
Kalydeco Plus BSC	$1,476,543	$956,762	$463,571
CF Individuals Homozygous for *F508del* Mutation			
Orkambi Plus BSC	$1,280,892	$890,739	$334,495
Symdeko Plus BSC	$1,367,400	$974,348	$424,212
CF Individuals Heterozygous for *F508del* Mutation and Residual Function Mutation			
Kalydeco Plus BSC	$1,340,171	$941,110	$373,541
Symdeko Plus BSC	$1,174,508	$840,568	$390,600

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

Sensitivity and Scenario Analysis Results

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e. standard errors) or reasonable ranges to evaluate changes in cost per addition QALY for CFTR modulators plus best supportive care versus best supportive care alone. All analyses were most sensitive to assumptions about lung function-specific utilities, the independent effect of the drugs on the reduction of acute pulmonary exacerbations, and the discount rate; while changes some of these changes resulted in large variation in cost-effectiveness estimates, in no case did the results approach commonly cited thresholds.

We also evaluated the uncertainty in the model parameters simultaneously by conducting a probabilistic sensitivity analysis. For all CFTR modulators in all CF populations evaluated, the number of iterations in which the CFTR modulators were cost-effective at a WTP threshold of $500,000 per QALY or less was 0%. For example, the 95% credible interval for the incremental cost-effectiveness ratios for Kalydeco compared with best supportive care was $669,500 to $1,591,500 per QALY for CF individuals with gating mutations.

In a scenario analysis we incorporated the costs associated with lost productivity in individuals with CF. For individuals with a gating mutation we projected that the difference in lifetime (discounted) indirect costs was $31,600. Including productivity losses in the analysis resulted in incremental cost-effectiveness ratios for Kalydeco very similar to those seen in the base case ($952,100 per QALY societal vs. $956,800 per QALY base case). Estimates for the incremental cost-effectiveness ratios for the CFTR modulators for the other two populations also tracked very closely with base case estimates. We did not include impacts on patient educational levels or caregiver costs in this analysis, given the lack of evidence that this varies by lung function or is impacted by CFTR modulators. The addition of direct non-health care costs that are not affected by CFTR modulator treatments would likely result in an increase in total societal costs, due to our modeled increase in life expectancy with modulator therapy.

In the base case we assumed that CFTR modifiers would result in 50% of the annual decline in $ppFEV_1$ that would be seen for best supportive care, after a 2-year period without any decline. In another scenario analysis we varied that assumption from 0% (i.e., no declines in $ppFEV_1$ over the individual's lifetime) to 100% (i.e., the same annual declines as those on best supportive care after the first two years on drug). As an example, for CF individuals with a gating mutation, the incremental cost-effectiveness ratio for Kalydeco was $620,400 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 ICERs were found with other drugs and populations, but again did not approach commonly-accepted thresholds.

Two other scenarios were explored. In one scenario we explored the impact of assuming that $ppFEV_1$ would not fully recover after a pulmonary exacerbation. Assuming a 5% absolute decline in $ppFEV_1$ for each pulmonary exacerbation experienced reduces the cost-effectiveness ratios by approximately 25%. We also examined the impact of allowing an independent increase in utility above that due to lung function improvement. Assuming a 5% increase in utility with CFTR modulator drugs reduced base-case cost-effectiveness ratios by approximately 15%.

Threshold Analyses

The annual price for each drug at which the drug for CF individuals with relevant mutations would be cost-effective at thresholds of $50,000, $100,000, $150,000, $200,000, $300,000, and $500,000 per QALY is shown in Table ES6.

Table ES6. Threshold Analysis Results

	Estimated Annual WAC	Estimated Annual Net Price	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
CF Individuals with A Gating Mutation								
Kalydeco	$311,719	$309,842	$55,145	$69,142	$83,146	$97,142	$125,149	$181,149
CF Individuals Homozygous for *F508del* Mutation								
Orkambi	$272,886	$264,090	$55,562	$67,820	$80,063	$92,321	$116,822	$165,824
Symdeko	$292,258	$282,850	$53,210	$65,467	$77,718	$89,976	$114,484	$163,501
CF Individuals Heterozygous for *F508del* Mutation and Residual Function Mutation								
Kalydeco	$311,719	$309,842	$60,295	$74,175	$88,054	$101,934	$129,693	$185,211
Symdeko	$292,258	$282,850	$57,921	$71,969	$86,016	$100,071	$128,166	$184,356

WAC: wholesale acquisition cost; QALY: quality adjusted life year gained

Since Kalydeco and Symdeko are each used for treatment in two different populations, we also calculated population-weighted threshold prices using estimated numbers of patients in each population (3,000 CF individuals with gating mutations, 8,464 CF individuals homozygous for *F508del* mutation, and 6,195 CF individuals heterozygous for *F508del* mutation and residual function mutation). For Kalydeco, the blended annual price across the two relevant populations ranged from approximately $58,600 at the $50,000 per QALY threshold to approximately $183,900 at the $500,000 per QALY threshold. For Symdeko, the blended annual price across the two relevant populations ranged from approximately $55,200 at the $50,000 per QALY threshold to approximately $172,300 at the $500,000 per QALY threshold.

Summary and Comment

We developed an individual-level microsimulation model to project the lifetime benefits and costs of CFTR modulator therapies for three different CF populations. The drugs increased lung function, increased weight-for-age z-scores, and decreased the number of acute pulmonary exacerbations and lung transplantations over the lifetime of individuals. The drugs did not impact non-lung aspects of the disease, nor did they decrease the need for CF-related supportive care. Overall, all

drugs (plus best supportive care) evaluated were very effective compared with best supportive care alone in all populations studied, with quality-adjusted life year gains ranging from 5.47 to 6.73 (discounted). With (discounted) CFTR drug-related costs ranging from $4.9 million to $7.4 million, the incremental cost-effectiveness ratios of drugs plus best supportive care compared with best supportive care alone were approximately $0.9 million per QALY for all drugs in all populations considered. Our results were robust to variations to parameter estimates, adopting a modified societal perspective, or using life years gained as the health outcome, except for unit drug costs.

Other Benefits and Contextual Considerations

Our reviews seek to provide information on other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These elements are listed in the table below. As CFTR modulators were evaluated under ICER's framework for a serious ultra-rare condition (https://icer-review.org/wp-content/uploads/2017/11/ICER-Adaptations-of-Value-Framework-for-Rare-Diseases.pdf) additional elements appear in the table that are assessed for such conditions.

Other Benefits

Table ES7. Potential Other Benefits and Contextual Considerations (Not Specific to Any Disease or Therapy)

Potential Other Benefits	
This intervention offers reduced complexity that will significantly improve patient outcomes.	CFTR modulator treatment is often additive to current treatment regimens, and may therefore increase complexity of daily, routine CF care. However, reductions in the rate and/or intensity of pulmonary exacerbations may reduce patient and caregiver burden over time.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.	No impact identified
This intervention will significantly reduce caregiver or broader family burden.	As described above, CFTR modulators are not likely to reduce the daily burden of managing CF, but may reduce patient/caregiver burden with regard to managing exacerbations.
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.	CFTR modulators are the first and only treatments that target the underlying defect in the CFTR protein caused by specific mutations in the *CFTR* gene.
This intervention will have a significant impact on improving the patient's ability to return to work or school and/or their overall productivity.	In patients with FEV1<40%, CFTR modulators may increase the patient's ability to work and improve overall productivity.
This intervention will have a significant positive impact outside the family, including on schools and/or communities.	No impact identified
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.	No impact identified
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.	No impact identified

Contextual Considerations

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.	Cystic fibrosis significantly impacts both length and quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	Patients with cystic fibrosis have a high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.	While CFTR modulators are the first to target disease pathology, advancements in supportive care have also greatly improved prognosis for CF patients.
Compared to best supportive treatment, there is significant uncertainty about the long-term risk of serious side effects of this intervention.	Serious side effects of CFTR modulators appear to be minimal compared to the effects of the underlying disease; however, long-term data are not yet available.
Compared to best supportive treatment, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	The long-term effects of CFTR modulators on the rate of disease progression are starting to develop but remain sparse. The magnitude and durability of CTFR modulator benefit has not been reliably quantified at this time.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.	No impact identified

Potential Budget Impact

We used results from the same model employed for the cost-effectiveness analyses to estimate the total potential budget impact of Symdeko in cystic fibrosis, specifically for those heterozygous or homozygous for the *F508del* mutation. Potential budget impact was defined as the total differential cost of using Symdeko plus best supportive care, 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. We estimated the eligible prevalent population in the United States, derived from the 2016 Cystic Fibrosis Foundation Patient Registry Annual Data Report,[1] at 8,464 cystic fibrosis patients over the age of 6 with two copies of the *F508del* mutation, and 6,195 cystic fibrosis patients over the age of 12 with one copy of the *F508del* mutation.

Table ES8 shows the per-patient budget impact calculations for Symdeko in those homozygous for the *F508del* mutation relative to current care assuming Orkambi plus best supportive care in 50% and only best supportive care in 50%, based on prescribing rates for Orkambi.[1] The average

potential budgetary impact when using the WAC ($292,258) was an additional per-patient cost of approximately $117,300 and approximately $109,100 using the discounted WAC ($282,850). At the three cost-effectiveness threshold prices (at $50,000, $100,000 and $150,000 per QALY), there would be estimated cost savings, because while there would be increased costs from using Symdeko in addition to best supportive care, these additional costs would be more than offset by the replacement of Orkambi at net price by Symdeko at the much lower assumed threshold prices.

Table ES8. Per-Patient Budget Impact Calculations Over a Five-year Time Horizon for Individuals Homozygous for *F508del* Mutation

	Average Annual Per Patient Budget Impact				
	WAC	Discounted WAC	$150,000/ QALY	$100,000/ QALY	$50,000/ QALY
Symdeko+BSC	$300,749	$292,545	$113,699	$98,765	$92,331
Orkambi+BSC (50%) & BSC (50%)	$183,418				
Difference	$117,331	$109,128	($69,719)*	($84,653)*	($91,078)*

WAC: wholesale acquisition cost; QALY: quality adjusted life year; BSC: best supportive care
*Indicates cost-saving

Table ES8 shows the per-patient budget impact calculations for Symdeko in those with one *F508del* mutation and a residual function mutation, compared to current care assuming Kalydeco plus best supportive care in 50% and best supportive care in 50%. The average potential budgetary impact when using the WAC ($292,258) was an additional per-patient cost of approximately $92,800 and approximately $84,600 using the discounted WAC ($282,850). At the three cost-effectiveness threshold prices (at $50,000, $100,000 and $150,000 per QALY), there would be estimated cost savings, again because the increased costs from using Symdeko in addition to best supportive care would be more than offset by the replacement of Kalydeco at net price by Symdeko at the much lower assumed threshold prices.

Table ES9. Per-Patient Budget Impact Calculations Over a Five-year Time Horizon for Individuals with *F508del* Mutation and Residual Function Mutation

	Average Annual Per Patient Budget Impact				
	WAC	Discounted WAC	$150,000/ QALY	$100,000/ QALY	$50,000/ QALY
Symdeko+BSC	$301,966	$293,776	$122,441	$110,212	$97,983
Kalydeco +BSC (50%) & BSC (50%)	$209,185				
Difference	$92,781	$84,591	($86,744)*	($98,973)*	($111,202)*

WAC: wholesale acquisition cost, QALY: quality-adjusted life year, BSC: best supportive care
*Indicates cost-saving

For the combined populations of interest, the annual potential budgetary impact of treating the entire eligible population with Symdeko at the net price over five years is 95% of the $915 million threshold, but exceeded the threshold by 2% using WAC. While the total number of patients eligible for treatment with Symdeko is relatively low (n = 14,659), the increased cost per patient from using Symdeko over the current treatment mix leads to a total estimate approaching the budget impact threshold. Note that this number may actually be understated, because the approved FDA label for Symdeko allows treatment beyond those having at least one copy of the *F508del* mutation, so long as the mutation is responsive to Symdeko (through *in vitro* or clinical data).[6]

Table ES10. Estimated Total Potential Budget Impact of Symdeko for Treatment of Eligible Populations Using Net Prices Over a Five-year Time Horizon

	Eligible Population	N Treated per Year	Annual BI per Patient	Total BI (millions)	Percent of Threshold
Homozygous *F508del*					
Symdeko	8,464	1,693	$109,128	$552,527,040	60%
Heterozygous *F508del* with Residual Function Mutation					
Symdeko	6,195	1,239	$84,591	$312,510,796	34%
Total Eligible US CF Population*					
Symdeko	14,659	2,932	$172,274	$865,037,837	95%

BI: budget impact

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

Value-Based Price Benchmarks

Our value-based benchmark prices for Kalydeco, Orkambi, and Symdeko are presented in Table ES11. As Kalydeco and Symdeko are each used for treatment in two different populations, we calculated blended threshold prices weighted by estimated numbers of patients in each population. For each drug, the discounts required to meet both threshold prices (>70%) are much greater than the currently assumed discount from WAC.

Table ES11. Value-Based Benchmark Prices for Kalydeco, Orkambi, and Symdeko

	Annual WAC	Annual Net Price (with Mark-Up)	Annual Price to Achieve $100,000 per QALY	Annual Price to Achieve $150,000 per QALY	Discount from WAC to Reach Threshold Prices
Kalydeco	$311,719	$309,842	$72,533	$86,453	72% to 77%
Orkambi	$272,886	$264,090	$67,820	$80,063	71% to 75 %
Symdeko	$292,258	$282,850	$68,215	$81,225	72% to 77%

QALY: quality-adjusted life year

Midwest CEPAC Votes

The Midwest CEPAC Panel deliberated on key questions raised by ICER's report during the public meeting on May 17, 2018. 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

1) **For individuals with approved gating, non-gating, and residual function mutations (including but not limited to G551D and R117H), is the evidence adequate to demonstrate that the net health benefit of treatment with Kalydeco (ivacaftor) with best supportive care is greater than that of best supportive care alone?**

Yes: 12 votes	No: 0 votes

2) **For individuals who are homozygous for the F508del mutation, is the evidence adequate to demonstrate that the net health benefit of treatment with Orkambi (lumacaftor/ivacaftor) with best supportive care is greater than that of best supportive care alone?**

Yes: 11 votes	No: 1 votes

3) **For individuals who are homozygous for the F508del mutation, is the evidence adequate to demonstrate that the net health benefit of treatment with Symdeko (tezacaftor/ivacaftor) with best supportive care is greater than that of best supportive care alone?**

Yes: 12 votes	No: 0 votes

4) **For individuals who are homozygous for the F508del mutation, is the evidence adequate to distinguish the net health benefit between treatment with Symdeko with best supportive care and Orkambi with best supportive care?**

Yes: 1 votes	***No: 11 votes***

5) **For individuals who are candidates for Symdeko combination therapy because they carry one F508del mutation and residual function mutation that is potentially responsive to Symdeko, is the evidence adequate to demonstrate that the net health benefit of treatment with Symdeko with best supportive care is greater than that of best supportive care alone?**

Yes: 11 votes	No: 1 votes

Other Benefits and Contextual Considerations

When compared to best supportive care, does Kalydeko, Orkambi, or Symdeko offer one or more of the following "other benefits"? (yes, no, uncertain)

Potential Other Benefits	# of votes
This intervention offers reduced complexity that will significantly improve patient outcomes.	4 / 12
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.	0 / 12
This intervention will significantly reduce caregiver or broader family burden.	8 / 12
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.	10 / 12
This intervention will have a significant impact on improving the patient's ability to return to work or school and/or their overall productivity.	7 / 12
This intervention will have a significant positive impact outside the family, including on schools and/or communities.	3 / 12
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.	2 / 12
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.	7 / 12

Are any of the following contextual considerations important in assessing Kalydeco's, Orkambi's, or Symdeko's long-term value for money in patients? (yes, no, uncertain)

Potential Other Contextual Considerations	# of votes
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.	12 / 12
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	12 / 12
This intervention is the first to offer any improvement for patients with this condition.	5 / 12
Compared to best supportive treatment, there is significant uncertainty about the long-term risk of serious side effects of this intervention.	3 / 12
Compared to best supportive treatment, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	10 / 12
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.	7 / 12

Long-Term Value for Money

1) **For individuals with approved gating, non-gating, and residual function mutations (including but not limited to G551D and R117H), given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits and contextual considerations, what is the long-term value for money of Kalydeco with best supportive care compared with best supportive care alone?**

Low: 10 votes	Intermediate: 2 votes	High: 0 votes

2) **For individuals who are homozygous for the F508del mutation, given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits and contextual considerations, what is the long-term value for money of Orkambi with best supportive care compared with best supportive care alone?**

Low: 11 votes	Intermediate: 1 votes	High: 0 votes

3) **For individuals who are homozygous for the F508del mutation, given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits and contextual considerations, what is the long-term value for money of Symdeko with best supportive care compared with best supportive care alone?**

Low: 11 votes	Intermediate: 1 votes	High: 0 votes

4) **For individuals who are candidates for Symdeko combination therapy because they carry one F508del mutation and residual function mutation that is potentially responsive to Symdeko, given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits and contextual considerations, what is the long-term value for money of Symdeko with best supportive care compared with supportive care alone?**

Low: 11 votes	Intermediate: 1 votes	High: 0 votes

Key Policy Implications

Following its deliberation on the evidence, the Midwest CEPAC Panel engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on modulator treatments for cystic fibrosis to policy and practice. The policy roundtable members included one patient advocate, one caregiver, two clinical experts, and two payers. 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.

Key Recommendations on Pricing and Access

- The prices for CFTR modulators are too high, harming patients and families today while threatening the health care system's ability to maintain access for all patients to important future clinical advances. Benefiting from monopoly pricing power, the company bears a significant social responsibility to change its pricing approach by committing to the following two actions:
    - Abandon vague claims that prices are justified by the need to invest in future research and instead join the growing number of biotech innovators who provide a transparent, explicit justification for their prices based on the ability of treatments to improve the length and quality of patients' lives;
    - Accept that the process for determining a reasonable price for new drugs requires innovators, especially those with monopoly pricing power at their disposal, to exercise restraint and be open to an independent process to evaluate fair pricing that includes the full engagement of the innovator, patients, patient advocacy groups, clinical experts, insurers, and other stakeholders.
- Public and private payers should continue to affirm their commitment to provide access to important clinical advances for CF and should remove superfluous requirements for coverage approval and continuation.

- Since insurance coverage denial for CF drugs is off the table, payers should be willing to develop and adopt new approaches to moderate the impact of monopolistic pricing power.
- 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.
- 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.

Recommendations to Improve Future Research

- 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.
- Manufacturer-sponsored research should enroll patients who are often encountered in clinical practice, but who are routinely excluded from clinical trials.
- Leverage all available resources to maximize the evidence base.
  Because CF is relatively rare, effort should be made to maximize use of all existing data, including routinely collected information.

1. Introduction

1.1 Background

Cystic fibrosis (CF) is the most common life-shortening genetic disease in Caucasian populations. Its birth prevalence varies by ethnic descent. In the US approximately 1 in 3,000 Whites are born with CF, but it is less common among in Latinos (1 in 4,000-10,000) and African Americans (1 in 10,000-20,000). According to the Cystic Fibrosis Foundation Annual Report, the overall prevalence of CF in the US in 2016 was 30,000.[1] Although rare, CF represents a substantial economic burden. In 2013, CF-related hospital costs alone were estimated to exceed $1.1 billion.[31]

Pathogenesis

Over 1800 cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations have been described to be associated with CF, but the functional significance of only a subset is known. Based on the Clinical and Functional Translation of *CFTR* repository, a little over 300 mutations have been characterized in detail.[2] CF-causing mutations result in absent, not functioning, or abnormally functioning CFTR protein. Patients with CF carry pathogenic mutations in both copies of the *CFTR* gene. People with pathogenic mutations in only one copy of the *CFTR* gene do not manifest CF but are carriers of the disease. The most common pathogenic mutation is the *F508del* mutation. This mutation (a loss of phenylalanine at the 508th position) causes the protein to misfold and become marked for degradation. About 86% of all CF patients have at least one copy of the mutation; of these patients, approximately 41% are heterozygous and 46% are homozygous.[3,4] Another common mutation is *G551D*, which is found in approximately 5% of CF patients.[3] In patients with at least one copy of *G551D* some of the protein folds correctly, but when it reaches the apical membrane it does not open appropriately to let chloride ions flow normally.

The following is an oft-used classification scheme for mutations that are known to cause CF. A classification system for the most common pathogenic mutations of the *CFTR* gene describes five classes:

- Class I (transcription-stopping or "X-group") mutations result in no CFTR protein being produced.
- Class II mutations ("folding mutations") result in protein formation (folding) and trafficking defects that hinder the transport of the CFTR to the apical membrane of cells. This group includes the most common CF-causing mutation, *F508del*.
- Class III mutations ("gating mutations") result in a non-functioning CTFR protein on the apical membrane of cells. An example is the aforementioned *G551D* mutation, which is responsible for approximately 5% of CF cases.

- Class IV and V mutations are associated with residual function (reduced functionality) of CFTR.

CF is a progressive disease that affects many organ systems, though most of its morbidity and mortality are associated with its impact on the respiratory system. In epithelial cells, the CFTR gene is transcribed and translated to produce the CFTR protein, which is in turn, transported to the apical membrane, the part of the membrane that faces inwards towards the lumen of an organ. There it acts as a chloride ion gate and contributes to the regulation of salt transport in and out of the cell. Mutations to the CFTR gene can affect the amount of CFTR protein that is produced and transferred to the apical membrane or the CFTR protein's ability to regulate chloride and sodium ion flow.[32] Failure to express normally-functioning CFTR protein in the apical (luminal) membrane of epithelial cells leads to thickened secretions in the lung, gastrointestinal tract, pancreas, and other organs. These thickened secretions are an integral part of the cascade that cause the primary manifestations of CF.

In the lungs, the thickened secretions lead to decreased mucociliary clearance and chronic bronchial infection, which result in lung destruction over time. Daily aggressive pulmonary hygiene (i.e., nebulized medications and chest physiotherapy) are necessary to maintain health. Recurrent pulmonary exacerbations occur despite best care and require antibiotic treatment, increased pulmonary hygiene, and often hospitalization. Infections are associated with bacteria expected in bronchiectasis of other causes and tend to occur early in CF. The bronchi of many CF patients are eventually colonized with *Pseudomonas aeruginosa*, *Burkholderia cepacia* complex and other pathogens which are commonly resistant to most antibiotics. Chronic and repeated lung infections contribute to progressive damage in the airways, leading to bronchiectasis and ultimately to respiratory failure, which is responsible for the majority of CF-related deaths.

CF affects all epithelia, and thus also affects other organ systems. Dysfunction in the epithelia of the intestine, pancreas, and liver can cause intestinal malabsorption, pancreatic insufficiency and CF-related diabetes, as well as biliary cirrhosis. Most men with CF are infertile because the vas deferens is not fully developed, but women with CF are subfertile, in part due to changes in cervical mucus, but are usually able to become pregnant and give birth. The disease and its management are therefore associated with multiple physical and psychosocial problems and economic insecurity, which can severely affect the quality of life of CF patients, their caretakers, and the rest of their families.

Diagnosis

All 50 US states and the District of Columbia now provide newborn screening for CF. Most states use some combination of blood testing for pancreatic injury and *CFTR* gene mutation analysis for screening. Patients who carry CF-causing mutations in each copy of the *CFTR* gene manifest CF. The diagnosis of CF is made by measuring the concentration of chloride ions in sweat following an

established protocol. CF diagnosis is definitive in patients with sweat chloride concentrations above 60 mEq/L (as measured with established protocols in certified labs) and who have a clinical picture consistent with CF.

Most CF patients have been diagnosed in childhood, although some patients with milder presentations have been diagnosed as adults. In the US in 2016, the median age at diagnosis for all patients was four months of age; 62% of new CF diagnoses were detected through newborn screening.[1] Early diagnosis before symptom onset allows early treatment and, thus, is associated with better lung and nutritional outcomes later in life.[33]

Clinical Presentation

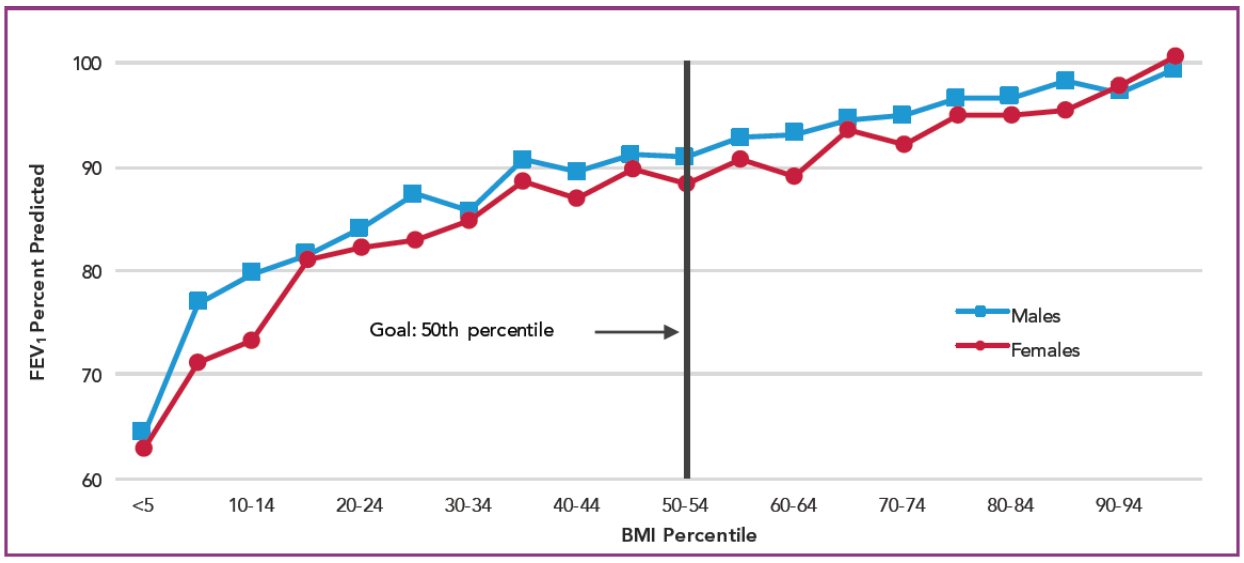
While lung function is normal at birth, lung infections tend to occur early in life. Repeated and chronic infections can lead to bronchiectasis at a young age. Acute pulmonary infections requiring antibiotic treatment (pulmonary exacerbations) occur and can rapidly deteriorate pulmonary function. Pulmonary exacerbations are associated with increased lung damage, earlier mortality, higher healthcare costs, and lower quality of life.[34,35] End-stage lung disease results in respiratory failure and death. CF patients with Class I, II, and III mutations tend to have somewhat lower lung function compared to those with Class IV and V mutations.[1]

The gastrointestinal (GI) system is also commonly affected in CF patients. Malabsorption of fat due to insufficient pancreatic enzymes, known as pancreatic insufficiency, affects an estimated 85% of CF patients and makes reaching a normal weight difficult for CF patients.[36] Pancreatic damage that leads to an insufficiency of pancreatic enzymes often occurs within a few months after birth.[36] Similarly to lung function, pancreatic sufficiency and weight are influenced by genotype; *F508del* homozygous individuals are typically the most underweight, and *F508del* heterozygotes with G551D and *R117H* mutations showing slightly better nutrition.[37] Over 80% of Cystic Fibrosis Foundation Patient Registry (CFFPR) patients are prescribed pancreatic enzyme replacement therapy (PERT) as part of their CF regimen to aid in fat metabolism and weight gain.[1]

Children born today show significant improvements in reaching and maintaining sufficient weight compared to CF patients born in 1987.[1] As children mature into adulthood, clinical guidelines aim for adults 20 years and older to have a body mass index (BMI) at or above 22 for women and 23 for men.[1]

Lung function and weight are also closely related for CF patients, as shown in Figure 1.2.

Figure 1.2. FEV_1 Percent Predicted Versus BMI Percentile for Children Six to 19 Years in 2016[1]



Management

The core treatment regimen for CF has historically aimed to control symptoms. It includes aggressive airway hygiene with chest physiotherapy, airway clearance devices, bronchodilators, inhaled and systemic antibiotics as needed or chronically, inhaled hypertonic saline, and aerosolized recombinant human DNase to reduce sputum thickness by breaking down free inflammatory cell DNA, as well as nutritional support through pancreatic enzyme replacement therapy, insulin, and diet. The treatment burden for CF patients is high, with patients reporting that they spend upwards of two hours a day completing treatment activities.[5] Organ transplantation remains the last-line intervention for CF patients with end-stage disease.

Advances in the early diagnosis and management of CF have led to longer survival than in earlier eras. In the 2016 annual report of the US Cystic Fibrosis Foundation Patient Registry, 53% of CF patients in the US were adults. The median predicted survival of CF patients born in 2016 is estimated to be 47.7 years.[1] According to an NIH fact sheet "In 1962, the predicted median survival for CF patients was about 10 years, with few surviving into their teenage years."[38] Today, nearly 75% of those registered in the CFFPR over 18 years old were considered to have normal lung function or mild lung impairment; in 1987, this proportion was only about one-third.[1] Likewise, lung function was severely impaired in about one-third of patients in 1987; today that number is 4%.[1]

While improvements in supportive care have improved the prognosis for CF patients, these treatments are directed only at symptom management. Recently introduced agents that modulate the pathophysiology of the disease, namely, Kalydeco®, Orkambi® and Symdeko™ represent a new class of treatments, and are the focus of this review.

CFTR modulator drugs

Modulator drugs increase CFTR-mediated ion transport. Two types of modulator drugs have been developed, with complementary modes of action. The effectiveness of modulators depends on the CF-causing mutation. For example, patients who are homozygous for class I mutations cannot respond to modulator-based treatments because there is no CFTR protein to be modulated. A full list of mutations for which each drug is approved is available in Appendix D.

CFTR potentiators, such as ivacaftor (Kalydeco), increase the likelihood that the CFTR channel will transport ions through the cell membrane, i.e., they increase the channel's "open probability". Kalydeco has been approved for patients with various "gating" (e.g. G551D, a Class III mutation) and other mutations that result in residual CFTR protein function in the cell membrane (e.g., *R117H*).

CFTR correctors, such as lumacaftor and tezacaftor, increase the amount of normal or mutated CFTR protein that gets transported to the apical (luminal) membrane, thereby increasing the amount of CFTR protein on the cell surface. Combinations of CFTR correctors and potentiators are considered in patients with "folding" (e.g., *F508del,* a Class II mutation) and/or residual function mutations. Orkambi (lumacaftor/ivacaftor) and Symdeko (tezacaftor/ivacaftor) are considered in patients homozygous for the *F508del* mutation. Symdeko is also considered in patients who are heterozygous for the *F508del* allele and carry a residual function mutation.

For the purposes of this report we use trade names to facilitate ease of interpretation of the data, with the exception of unapproved doses of lumacaftor with ivacaftor.

The use of these agents has generated great interest on the part of clinicians, patients, and their families. These drugs are the first of their kind to address the underlying genetic deficiencies leading to CF. Added to best supportive care, these drugs have been shown to improve respiratory function and weight, and they may slow the rate of decline of respiratory function over time. While generally safe, there may be some tolerability issues in some populations. Uncertainties around the use of modulators exist because most data are relatively short-term (or at best up to only about 3 years) and on surrogate endpoints, and evidence about longer-term benefit and increased survival does not yet exist. In addition, currently marketed CFTR modulators are very expensive, and alignment of their cost to patient benefit is not well understood, especially considering that these regimens will be incremental costs on top of current treatments comprising best supportive care. All stakeholders will therefore benefit from a comprehensive review of the clinical evidence and potential economic impact of adding CFTR modulator treatments to best supportive care.

1.2 Scope of the Assessment

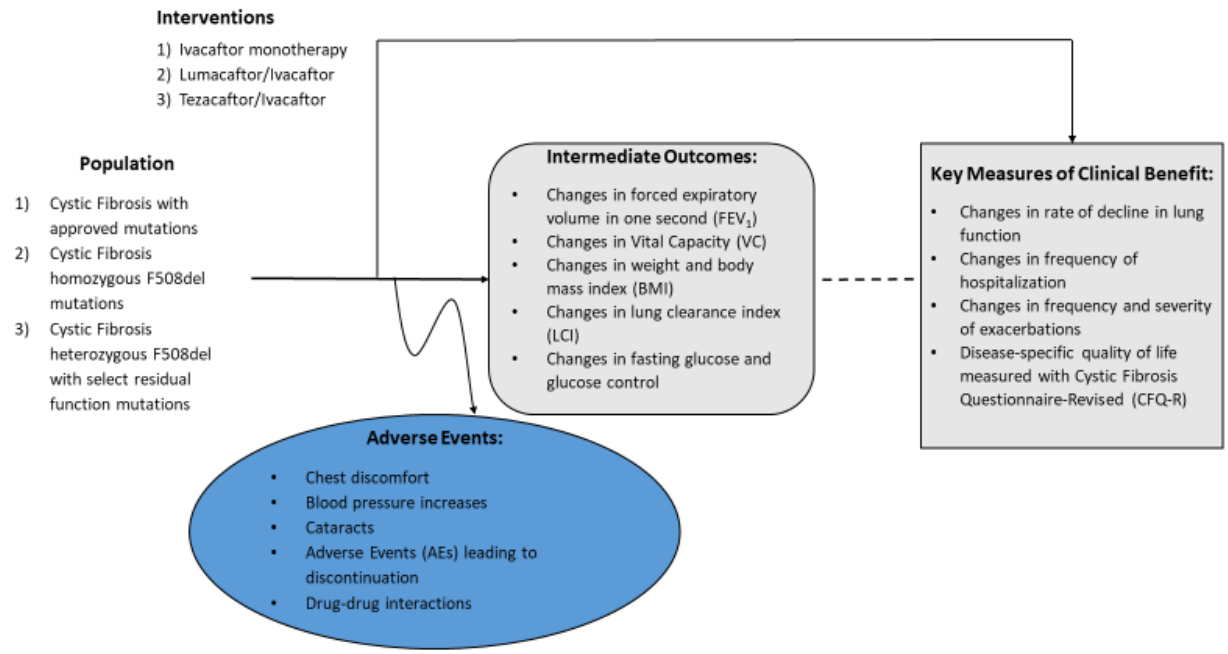
The scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence was collected from available randomized controlled trials and observational studies.

Our evidence review included input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Analytic Framework

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

Figure 1.1 Analytic Framework



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 adverse events of treatment which are listed within the blue ellipse.[39]

Populations

We reviewed evidence in three distinct populations:

1) The first population included individuals with CF and mutations consistent with the FDA-approved indications for Kalydeco. In this population, we reviewed evidence on Kalydeco. We included studies of individuals with mutations that have either gating or other (residual) functional implications (e.g., *R117H*).
2) The second population included individuals with CF who are homozygous for the *F508del* mutation. In this population we reviewed evidence on both Orkambi and Symdeko.
3) The third population included individuals with CF who are heterozygous for the *F508del* mutation and a residual function mutation that is potentially responsive to Symdeko. In this population we reviewed evidence on Symdeko and Kalydeco.

Within these populations, subgroups of interest were defined according to presence of advanced nonreversible lung disease (e.g., patients who have predicted FEV_1 below 40%, between 40-90%, or above 90%) and age (groups as defined in each study). Predicted FEV_1 is a measure of lung function defined as the forced expiratory volume during the first second of expiration, adjusted for age, height, sex, and race.[40,41] Other subgroups of interest were people with advanced non-pulmonary disease, such as recurrent pancreatitis, diabetes, liver transplantation, poor growth, and infertility.

We included studies of individuals of any age, regardless of their past medical history, comorbidities, or the severity of their CF; however, we sought to exclude studies conducted in individuals after lung transplantation (for whom CFTR modulation therapy would not affect lung function). We imposed no other restrictions regarding population eligibility.

Interventions and Comparators

We examined the following comparisons in the following three appropriate populations:

1. For individuals who are candidates for Kalydeco, we compared adding Kalydeco to best supportive care versus best supportive care alone and placebo.
2. For individuals who are homozygous for the *F508del* mutation, we compared adding Orkambi or Symdeko to best supportive care versus best supportive care alone. We also compared Orkambi to Symdeko.
3. For individuals who are candidates for Symdeko because they carry one *F508del* mutation and residual function mutation that is potentially responsive to Symdeko, we compared adding Symdeko to best supportive care versus adding Kalydeco to best supportive care versus best supportive care alone.

We excluded studies of lumacaftor and tezacaftor monotherapy, based on stakeholder feedback, neither is intended to be used as monotherapy. We excluded studies of Kalydeco, Orkambi, or Symdeko conducted in populations for whom the drugs are not approved or are not anticipating approval based on their genetic mutations. We also excluded studies of composite treatment strategies that, for example, start with Kalydeco and shift to a combination regimen after a period of time – if they were conducted in populations in which at least one of the regimens is not approved.

Settings

All settings were considered. Studies conducted in any country were considered.

Outcomes

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

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

- Mortality
- Pulmonary exacerbations (acute and severe worsening of pulmonary symptoms)
- Hospitalizations
- Lung transplantation
- Acute pancreatitis
- Fertility

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

- FEV_1 (predicted), including rate of FEV_1 decline
- Lung clearance index (LCI)
- Weight, BMI, and growth (surrogate measures of nutrition status)
- Fasting glucose and related measures of glucose control or diabetes

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

- Disease-specific quality of life (specifically, as measured with the Cystic Fibrosis Questionnaire-Revised [CFQ-R] respiratory domain or other measures where available.[42]
- Mental health and affect, including depression, worry, and anxiety (as measured with validated instruments)
- Functional status, including work, social/family, emotional, physical, etc. (as measured with validated instruments)
- Time lost from school or work
- Ability to participate in athletic activities and social functions
- Financial insecurity
- Caregiver burden

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

- Liver dysfunction
- Upper respiratory infections
- Gastrointestinal complaints (e.g., nausea, diarrhea, abdominal pain)
- Headache
- Rash
- Chest discomfort
- Dyspnea
- Cataracts
- Adverse events leading to treatment discontinuation

Other outcomes were considered and reviewed depending on relevance to patients and availability of data.

Evidence on drug-drug interactions from eligible studies was also included.

We excluded measures of cellular (as opposed to organ) function and other blood, serum, or urine laboratory measures (other than glucose), such as sweat chloride, fecal elastase, sputum inflammatory measures, and nasal potential difference. While these outcomes may help to demonstrate whether the modulators address the basic defects in CF, they are not directly pertinent to clinical outcomes. We also excluded novel or "candidate" measures, such as metrics based on high resolution computerized tomography.

Timing

Randomized controlled and non-randomized comparative studies of all follow-up durations were eligible. Observational studies had to report outcomes at least one month following treatment.

Single-dose studies of any type were excluded. Our focus was on studies in which patients are prescribed a course of treatment.

Potential Major Advance for a Serious Ultra-Rare Condition

ICER is assessing CFTR modulator treatments under an adaptation of the ICER value framework focused on treatments for serious, ultra-rare conditions because we believe the assessment meets the following proposed criteria:

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

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

1.3 Definitions

Disease and Pathophysiology

Cystic Fibrosis (CF): We relied on each study's definition of CF. However, the diagnostic criteria are standard. The diagnosis of CF is definitive in patients who have sweat chloride concentrations above 60 mEq/L (as measured with established protocols in certified labs) and who have a clinical picture consistent with CF. See Section 2, for a summary of current diagnosis guidelines.

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 1,700 different *CFTR* mutations at different loci (places) of the *CFTR* gene have been identified, with varying effects on the quantity and function of the CFTR protein.[3] 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, a little over 300 mutations are known to cause CF.[2] 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.[43] 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 (FEV_1): measured FEV_1 as a percentage of the predicted FEV_1 value for a healthy individual of the same age, sex, and height.[41] A clinically relevant change in absolute percent predicted FEV_1 has been considered to be three to five points or greater.[7]

CF-related diabetes: We accepted each study's definition of CF-related diabetes. While we may refer to CF-related diabetes as "diabetes" in this report, CF-related diabetes does not have the same pathophysiology as type I or II diabetes mellitus in people without CF. During a period of stable baseline health CF-related diabetes is diagnosed with standard diabetes criteria. However, modified criteria are used to diagnose CF-related diabetes during acute illness or continuous feedings.[44]

Cystic Fibrosis Questionnaire-Revised (CFQ-R): A validated survey which measures health-related quality of life (HRQOL) in CF patients.[45] 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).[21] 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 surrogate outcome that assesses the uneven distribution of lung ventilation, an indicator of obstructive 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.[46] Technical issues limit the feasibility of its use to adults and older children. 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).[16] 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., PEx requiring hospitalization or requiring antibiotics).

Pulmonary abnormality or chest tightness: An adverse effect that has been associated with modulator therapy (primarily Orkambi) often leading to discontinuation.

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 10-th 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 Insights Gained from Discussions with Patients and Patient Groups

We held semi-structured discussions via teleconference with parents of children with CF as well as with adult patients with CF, and identified cross-cutting themes, as described in further detail below.

The first theme pertained to aspects of the CF experience that have a strong impact on quality of life from the patient's and family's perspective. First, daily care is demanding. Aggressive airway hygiene, a mainstay of standard CF management, is a time-consuming process. Additionally, patients routinely take many pills and inhalation treatments as part of standard care and are concerned by the prospect of even more interventions (e.g., more pills for the modulator treatments, or additional medications to manage emerging complications of CF, such as CF-related diabetes). The high daily demands of standard care take a toll on patients and caregivers. Second, CF patients often endure frequent and severe complications from their disease. Hospitalizations (e.g., secondary to pulmonary exacerbations), typically last for many days or weeks leading to substantial time lost from school, work, and leisure for both patients and caregivers. Hospitalizations and specialized care can be associated with additional logistical hindrances and expenses if it is necessary to travel to a facility with experience in CF management. Third, even minor complications of CF are pervasive and cannot be discounted in terms of reduced quality of life. For example, chronic sinusitis can be accompanied by the inability to smell or taste foods, which reduces appetite and contributes to malnutrition. All of the above can greatly limit the ability of CF patients to participate in the social, athletic, work, and other functions that their peers engage in.

Another theme referred to the challenges of adhering to CF management. The daily management of CF is demanding, and a main goal of treatment is to delay the progression of the disease;

skipping airway hygiene on a day both releases precious time for other activities and may not have an immediately perceptible negative impact on clinical function. Thus, children or young adults who move on to the next stage of their lives (e.g., leaving home to go to college) may be tempted to lapse in terms of adherence.

A third theme was related to financial insecurity induced by the management of the disease. While all patients with whom we spoke have insurance coverage, their co-payments vary for CF-related treatment. Uncertainty about future insurance coverage of all treatments was also commonly raised. Additional expenses are associated with hospitalizations including travel, accommodation, arranging for care of other children, and other concerns. Further, parents with inflexible work schedules risk losing their jobs after exhausting their sick time.

1.5. Potential Cost-Saving Measures in Cystic Fibrosis

As described in its Final Value Assessment Framework for 2017-2019, ICER will now include in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/final-vaf-2017-2019/). ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) currently used for people with CF that could be reduced, eliminated, or made more efficient.

Some patients and caregivers we spoke with expressed concern about the very large cost associated with some CF treatments, including CFTR modulators, for what may be a modest gain in quality of life.

In responses to the draft scoping document, stakeholders focused on potential ways in which CFTR modulators could offset costs by reducing pulmonary exacerbations and prolonging the decline in lung function leading to lung transplant. These potential changes in healthcare resources were captured in ICER's economic models of the modulators themselves. We did not receive any suggestions on low-value services, but we heard from patient groups that randomized withdrawal studies are currently being planned to help inform possible changes to the current CF care regimen.

2. Summary of Coverage Policies and Clinical Guidelines

2.1 Coverage Policies

To understand the insurance landscape for modulators treatments for cystic fibrosis, we reviewed publicly available 2017 coverage policies and formularies for Midwestern state Medicaid programs (Missouri), Centers for Medicare and Medicaid Services (CMS) policies, and major commercial plans in individual marketplaces across Missouri and other Midwestern states, including Anthem Blue Cross Blue Shield, Aetna, Blue Cross Blue Shield Kansas City, and Cigna Missouri. We surveyed each plan's coverage policies for the three modulator treatments: Kalydeco, Orkambi, and Symdeko. No coverage policies were found for Symdeko as it was recently approved in February 2018.

All the plans surveyed provided prior authorization criteria for the coverage of Orkambi or Kalydeco. Specifically, for Orkambi, all plans required a documented diagnosis of CF, as well as a CF mutation test documenting that the patient is homozygous for the *F508del* mutation.[47-50] Plans varied on age requirements, some, like Cigna, allowing in patients six years or older, while other plans, like Anthem, required patients to be 12 years or older.[49,50]

For Kalydeco, all plans also required patients be over the age of two and have a definitive documented diagnosis of CF, as well as a CF mutation test documenting that the patient has one mutation that is responsive to Kalydeco based on its label (i.e. any of the following mutations: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R*, or *R117H*).[47,50-52] Some plans also specifically call out that Kalydeco is not approved for any CF patients with a homozygous *F508del* mutation without the concurrent treatment with lumacaftor.

We received anecdotal reports from patient advocacy groups and clinical experts that some patients have experienced difficulty accessing modulator treatments prescribed to them. Several of the examples of coverage denials appeared to be errors in the administration of the policy – for example, denial of coverage despite the patient having a covered mutation. One example of a coverage policy that went beyond current FDA labeling was Florida Medicaid's prior authorization criteria for Orkambi, requiring that patients age 6-18 must have undergone a baseline ophthalmic examination to monitor for lens opacities and cataracts.[53]

2.2 Clinical Guidelines

There are a number of guidelines on the treatment and management of cystic fibrosis. These guidelines focus on different aspects of disease management, including diagnosis, care delivery, nutritional considerations, respiratory care guidelines, infection prevention, and management of other comorbid conditions like CF-related diabetes, liver disease and bone disease. Below, we have summarized guidelines from the Cystic Fibrosis Foundation, the National Institute for Health and Care Excellence, and the European Cystic Fibrosis Society.

Cystic Fibrosis Foundation (CFF)

Diagnosis[54]

The CFF guidelines recommend that diagnosis of CF begin with the clinical presentation of CF, followed by a sweat chloride test. Guidelines suggest that a sweat chloride test result greater than or equal to 60 mmol/L results in a CF diagnosis. A result less than or equal to 29 mmol/L suggests that CF is unlikely. For test results between 30 and 59 mmol/L, CFF recommends genetic testing to determine if any CFTR mutations are present. This is then followed by a clinical evaluation at a CFF-accredited care center for physiologic testing to make a more definitive diagnosis.

Nutritional and GI Care Guidelines[55]

In the care and management of patients with CF, CFF recommends a focus on the patient's nutritional status as a key component of clinical care for all patients, outlining guidelines for the caloric intake for patients, monitoring of growth and weight status of patients, and dosing of pancreatic enzyme replacement therapy (PERT). CFF recommends that for patients older than two years of age, energy intake should be 110-200% above those of healthy patients with similar age, sex, and size in order to see weight gain. It also recommends that the maintenance of normal weight, for both children and adults, was associate with better FEV_1, as well as survival. CFF recommends that children and adolescents maintain a BMI at or above the 50^{th} percentile in order to see benefit in FEV_1 measurements. Finally, CFF recommends that PERT dosing should be 500-2500 units lipase per kg body weight per meal in order to help bolster absorption of dietary fat and prevent macro- and micronutrient deficiencies.

Respiratory Care Guidelines[56]

CFF has a series of guidelines relating to respiratory care for patients with CFF. These include chronic medications to maintain lung health, pulmonary exacerbations clinical care, CF airway clearance therapies, and pneumothorax and hemoptysis care guidelines.

CFF lists a series of chronic medications that can be used in the management of respiratory care of CF patients. CFF recommends the use of some inhaled antibiotics, such as tobramycin and

aztreonam, for all patients. It recommends mucolytics such as dornase alfa in patients at all stages of the disease, and hypertonic saline in all patients. CFF also suggests that anti-inflammatories, such as ibuprofen and azithromycin, may be beneficial for some patients. Finally, CFF recommends the use of Kalydeco in patients with at least one copy of the *G551D* mutation. CFF acknowledges that the guidelines were published prior to the label expansion for Kalydeco and the approval of Kalydeco and lumacaftor for patients with the homozygous *F508del* mutation.

Pulmonary Exacerbations[57]

For the treatment of acute pulmonary exacerbations, which the guidelines describe as an increase in respiratory symptoms accompanied by an acute decrease in lung function, CFF lists a series of treatment recommendations, as well as a series of treatments it does not recommend. CFF recommends the continuation of chronic medications for maintenance of lung health during exacerbations. It recommends that airway clearance therapy techniques be increased during exacerbations. CFF recommends daily dosing of aminoglycosides rather than dosing three times a day during exacerbations. CFF states there is insufficient evidence to recommend the following treatments: delivery of IV antibiotics in a non-hospital setting, the continuation of inhaled antibiotics in patients being treated with the same antibiotics via IV, and the routine use of corticosteroids in the treatment of exacerbations, among others.

Airway Clearance Therapy (ACT)[58]

CFF recommends the use of airway clearance for clearance of sputum, augmentation of cough, maintenance of lung function and improved quality of life in patients with CF. They do not recommend one form of ACT over another form, and rather suggest that each individual patient may have unique factors that would make one form of ACT more beneficial than another for that individual. CFF recommended aerobic exercise as well due to its overall health benefits.

Infection Prevention and Control[59]

In order to better prevent the spread of infection in patients with CF, these guidelines recommend a series of precautions and policies, particularly for use in health care settings. These precautions include hand hygiene, contact precautions, mask use by CF patients, minimizing wait times in outpatient waiting rooms/common areas, and placement of patients with CF in single-patient rooms in inpatient settings.

National Institute for Health and Care Excellence (NICE)[60]

Diagnosis

NICE guidelines, which are written primarily for the United Kingdom, recommend diagnosis using a sweat test or a cystic fibrosis gene test in people with a series of qualifications, including family

history, recurrent and chronic pulmonary disease, persistent chest X-ray changes among others. For individuals with a positive sweat test result, a clinical assessment that suggests CF, or a gene test that suggests one or more CF mutations, NICE recommends referral to specialist CF centers.

Provision of Care to CF Patients:

NICE outlines extensive guidelines around appropriate and comprehensive care to patients with CF and their families. NICE recommends the provision of adequate information and support to newly diagnosed individuals and their families, particularly information around local support and advocacy services, how to manage the risks of cross-infection, and transition to adult care. Care delivery itself should be provided by a multidisciplinary team made up of clinicians, dietitians, pharmacists, psychologists and physiotherapists, as well as social workers that are based at specialist cystic fibrosis centers. NICE recommends that these centers should plan patient care, minimizing the risk of cross-infection and maintain patient registries that track condition, treatments, and outcomes. Other recommendations include considering the use of telemedicine and home visits to minimize risk of infections.

Annual and Routine Reviews

NICE recommends that patients with CF undergo a comprehensive annual review that includes assessments of pulmonary function, nutritional and intestinal absorption, liver disease, CF-related diabetes, psychological status, and the patient's exercise program. NICE states that these reviews should occur regularly for patients with CF and should occur more frequently in newly diagnosed or very young patients.

Airway Clearance Techniques

NICE recommends offering individualized airway clearance technique plans to patients based on their ability to clear mucus from their lungs, their (and their family or caregiver's) preference, as well as any other factors that may impact adherence to the plan. NICE specifically recommends against offering high-frequency chest wall oscillation as a technique for patients with CF except in exceptional circumstances, as evidence does not demonstrate that it is a more effective technique than others.

Mucoactive Agents

NICE recommends the use of mucoactive agents for patients with CF with clinical evidence of lung disease. The first choice should be dornase alfa. If the patient does not respond, clinicians should consider the use of dornase alfa with hypertonic saline, or hypertonic saline alone. For those patients who cannot use dornase alfa, clinicians should consider mannitol dry powder for inhalation, particularly for children. NICE does not recommend Orkambi for the treatment of patients who are homozygous for the *F508del* mutation.

Infection and Nutrition

NICE has extensive guidelines on the management of a series of bacterial infections through the use of oral, inhaled or intravenous antibiotics, depending on the strain.

In addition, NICE outlines guidelines for the management of patient's nutritional needs through caloric intake, nutritional needs and pancreatic enzyme replacement therapy, where appropriate.

3. Comparative Clinical Effectiveness

3.1 Overview

To inform our review of the comparative clinical effectiveness of CFTR modulators in patients with cystic fibrosis, we extracted evidence from available clinical studies, whether in published or unpublished form (e.g., conference abstracts or presentations, FDA review documents). We focused on evidence of the efficacy, safety, and effectiveness of CFTR modulators in comparison with other CFTR modulators or placebo in our target population of individuals with cystic fibrosis of any age with a genetic mutation for which a CFTR modulator has been approved (see Appendix D). Our review focused on assessing the intermediate and long-term outcomes and harms assessed in available studies. We sought evidence on the following outcomes primarily: pulmonary exacerbation, percent predicted FEV_1, weight/BMI, and quality of life measures.

When reviewing clinical evidence in ultra-rare populations, ICER acknowledges the challenges of study design, recruitment, and availability of data on long-term outcomes. As such, when possible we aim to add to our findings specific context regarding areas of challenges in study design.

3.2 Methods

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on CFTR modulators followed established best research methods.[61,62] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[63] The PRISMA guidelines include a list of 27 checklist items, which are described further in Appendix Table A1.

We conducted the literature searches in PubMed and EMBASE. 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 Interventions described above. 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- A3. The date of the most recent search is December 19, 2017.

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 A2-3, Figure A2, and F1.

Study Selection

We included all relevant randomized clinical trials and nonrandomized comparative studies of any size and duration. We also included single-arm (i.e., non-comparative) studies with at least 100 participants and at least one month of follow-up. We excluded studies evaluating Kalydeco and Orkambi combination therapy in populations outside their respective FDA-approved indications, as well as studies of composite treatment strategies that started with Kalydeco and later shifted to a combination regimen. *In vitro* and non-human studies were excluded, as were single-dose and pharmacokinetic studies. We excluded conference proceedings and abstracts reporting data also available in full-text peer-reviewed publications.

We supplemented our review of published studies with data from known conference proceedings (within the last five years), regulatory documents, information submitted by manufacturers, ClinicalTrials.gov, and other grey literature when the evidence meets ICER standards and is not duplicative (for more information, see http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Data Extraction and Quality Assessment

Main trial data was extracted directly into SRDR™ (https://srdr.ahrq.gov). All eligible citations were extracted into Microsoft Word tables. Elements included a description of patient populations, sample size, duration of follow-up, funding source, study design features (e.g., open-label or cross-over periods), interventions (drug, dosage, frequency, schedules), outcome assessments (e.g., timing, definitions, and methods of assessment), results, and quality assessment for each study.

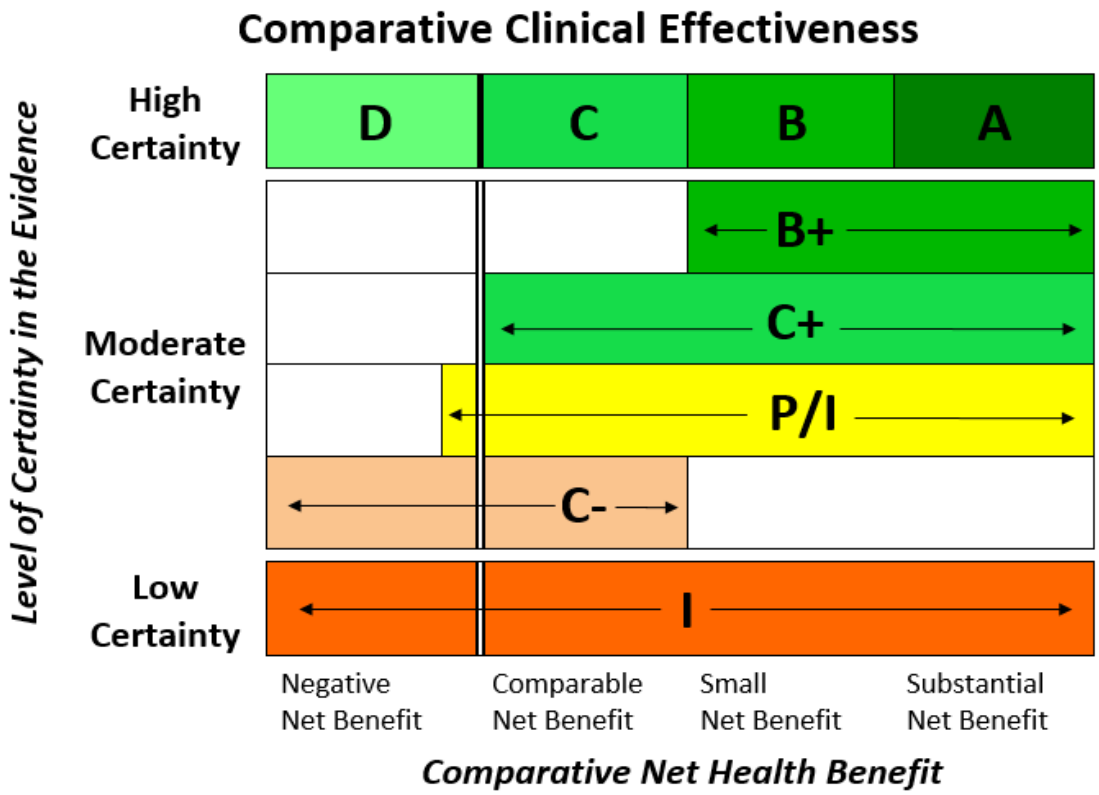
Data were extracted from the full articles by a single reviewer and validated by a second reviewer.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix (see Figure 3.1) 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.[64]

Figure 3.1. 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 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 comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit*
*C- = **"Comparable or Inferior"** - Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior*
*I = **"Insufficient"** - Any situation in which the level of certainty in the evidence is low*

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for newer treatments, we performed an assessment of publication bias for CFTR modulators using the clinicaltrials.gov database of trials. We scanned the site to identify studies completed more than two years ago that would have met our inclusion criteria and for which no findings have been published. Any such studies may indicate whether there is bias in the published literature. For this review, we did not find evidence of any study completed more than two years ago that that has not subsequently been published. We did learn of one study in patients with one copy of the *F508del* mutation and

another mutation that results in no residual CFTR function, but this study was stopped early for futility.[6]

Quality of Individual Studies

We rated all identified randomized control trials to be good quality using criteria from the US Preventive Services Task Force (USPSTF).[65] See Appendix F Table for full trial ratings. Trials of good quality had study arms that were comparable at baseline, authors employed valid instruments to evaluate outcomes, and differential attrition was not observed. Fair-quality studies reported slight imbalances in baseline characteristics, showed some differences in follow-up between trial arms, and used less reliable measurement instruments to assess outcomes. We did not assign a quality rating to non-comparative studies or references that were obtained from grey literature sources (e.g., conference proceedings).

Meta-Analysis

We conducted meta-analysis for each outcome of interest, including harms, for which there were data from at least two studies that were sufficiently similar in population, intervention (e.g., dose), and other characteristics. From comparative studies, we meta-analyzed data on clinical, physiologic, and patient-centered outcomes. In part based on which outcomes had enough data to meta-analyze from sufficiently similar studies, we conducted meta-analyses of percent predicted FEV_1, weight (in kg, BMI or as a BMI normalized to age and sex [z score]), CFQ-R respiratory domain, and pulmonary exacerbations. For harms outcomes, we combined data from single-arm studies and individual arms of comparative studies. We conducted meta-analyses of the proportion of participants receiving each drug (and placebo) who experienced severe adverse events (Grade 3 or 4) as well as drug discontinuation due to adverse events. Pulmonary abnormalities (chest tightness) were too infrequently reported to allow meaningful meta-analysis. Where data were reported for the same study participants at multiple time points (e.g., in both the RCT and the extension study), we included data from the longest duration of follow-up (i.e., the extension study) in the meta-analysis. When feasible, we also conducted meta-regression with study duration as a covariate; for these analyses we used all available data. All meta-analyses were conducted with random effects model restricted maximum likelihood analyses. Harms were analyzed as arcsine transformed data.[66] Estimates of indirect comparisons were obtained as linear combinations of the direct estimates, following Bucher et al.[67]

3.3 Results

We evaluated treatment in three distinct populations:

I. Kalydeco in gating and residual function mutation populations. This included individuals with *G551D* and non-*G551D* gating mutations and those with *R117H* residual function mutations.

II. Orkambi and Symdeko in individuals homozygous for the *F508del* mutation.

III. Symdeko and Kalydeco in individuals heterozygous for the *F508del* mutation with a second mutation amenable to Symdeko.

Study Selection

Our literature search yielded 1,897 potentially relevant references (Figure A1) of which 49 met eligibility criteria. The primary reasons for study exclusion included regimens for CFTR modulators outside the scope of the review (i.e. studies in other CF genetic populations or assessing other CF therapy regimens), non-clinical outcomes (e.g., *in vitro* studies), lack of outcomes of interest, and non-comparative study designs with either follow-up less than one month or study size less than 100 participants. Abstracts presented before 2012 were also excluded.

Kalydeco: We included 35 articles on Kalydeco treatment in gating and residual function mutations; 19 articles were peer-reviewed publications and 16 were abstracts without associated peer-reviewed publications. Seven Phase III clinical trials were included, four of which were randomized clinical trials and three of which were single-arm studies; these were reported in ten included publications and seven conference abstracts. All randomized controlled trials were considered good quality. Seventeen references (10 publications, seven conference abstracts) reported randomized controlled trials data. An additional ten non-randomized controlled studies were reported in four publications and six conference abstracts, and four single-arm studies were reported by four publications and three abstracts. Three of the single-arm citations reported results from the GOAL study. One additional publication reporting on GOAL and a randomized control trial was included.

Orkambi: We included ten articles on Orkambi treatment in individuals who are homozygous for the *F508del* mutation (seven peer-reviewed publications and two abstracts). Of the ten citations, four were randomized controlled trials and six were single-arm studies. All randomized controlled trials were considered good quality.

Symdeko: We included three articles on Symdeko treatment, all of which were peer-reviewed randomized controlled trials (one Phase II, two Phase III). All randomized controlled trials were considered good quality, although parallel arm design is more impactful than short-term, crossover design.

We report the results for the CFTR modulators by population of interest in the sections that follow, given the genetic specificity of the disease. We were unable to locate evidence in the following subgroups of interest: people with recurrent pancreatitis, diabetes, or liver transplantation. Some outcomes (e.g., pregnancy) were reported for CFTR modulators in general, without sufficient details to outline results by genetic subpopulation or drug regimen.

Clinical Benefits

Clinical Benefits of Kalydeco in Gating and Residual Function Mutation Populations

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 three years. Limited evidence also suggests one-year reductions in rates of death, organ transplantation, and hospitalizations. Statistically significant gains in body weight and respiratory symptom-related quality of life with Kalydeco were reported for G551D and non-G551D gating mutation populations aged 12 and older compared to placebo. Statistically significant improvements in lung function or weight were not observed in adult patients with R117H residual function mutations. In a small sample of children aged 6 to 11 years with R117H residual function mutations, those on Kalydeco experienced statistically significant decreases in lung function and trended towards decreased respiratory symptom-related quality of life scores compared to placebo. Harms associated with Kalydeco are discussed separately, below.

Four key randomized controlled trials – STRIVE, ENVISION, KONNECTION, and KONDUCT – evaluated the safety and efficacy of Kalydeco in individuals with at least one *G551D*, non-*G551D* gating, and *R117H* mutations (Table 3.1).[8-11] All four studies required a baseline ppFEV$_1$ ≥ 40%; upper limits were 90% for ages 12 and up and 105% for ages 6-11. All four trials randomized participants to receive either 150 mg of Kalydeco or placebo twice daily for 24 weeks. STRIVE, ENVISION, and KONDUCT were parallel group studies that assessed the mean absolute change from baseline in ppFEV$_1$ through 24 weeks of treatment as the primary outcome, with additional data collection through 48 weeks in STRIVE and ENVISION. KONNECTION was a two-part, cross-over trial that randomly assigned participants to receive either Kalydeco twice daily for eight weeks followed by eight weeks of matched placebo or eight weeks of matched placebo followed by eight weeks of Kalydeco. The short-term duration of this study is an important limitation. Primary and secondary outcomes were the same as STRIVE, ENVISION, and KONDUCT except these were reported at eight weeks.

KIWI, a Phase III single-arm study that included children aged 2-5 with a *G551D* gating mutation, assessed change from baseline in weight and BMI z-scores (difference in standardized deviations

from normal population, for age and sex) as secondary efficacy endpoints (Table 3.1).[13] Lung function measures were not included in this study because children under five years cannot perform spirometry reproducibly. Children were required to weigh at least 8 kg and to have at least one gating mutation at screening to qualify for enrollment.

Long-term safety of Kalydeco was assessed in two open-label studies: PERSIST and GOAL. PERSIST followed eligible STRIVE and ENVISION participants for an additional 96 weeks, during which all participants received 150 mg of Kalydeco twice daily (Table 3.1).[15] GOAL was a longitudinal cohort study of individuals aged six years and older with at least on *G551D* mutation and without prior history of Kalydeco use; participants received 150mg of Kalydeco twice daily.[14] Key outcomes of GOAL included spirometry ($ppFEV_1$), weight, CFQ-R scores, and hospitalizations.

Additional details for the studies described above are summarized in Appendix F.

Table 3.1. Key Trials of Kalydeco Efficacy Conducted in *G551D*, non-*G551D* Gating Mutations, and *R117H* Residual Function Mutation Populations

Study Quality and Study Design						
	STRIVE[8] RCT, Phase III Good	**ENVISION**[9] RCT, Phase III Good	**PERSIST**[15] Single-arm, open-label extension Good	**KIWI**[13] Single-arm, open-label trial Good	**KONNECTION***[10] RCT, Phase III cross-over design Good	**KONDUCT**[11] RCT, Phase III Good
Follow-up Duration	48 weeks	48 weeks	96 weeks	24 weeks	8 weeks	24 weeks
Mutations Included	*G551D*	*G551D*	*G551D*	*G551D*	non-*G551D* gating	*R117H*
Ages Included	12+	6-11	6+	2-5	6+	6+
Treatment Groups	Kalydeco Placebo	Kalydeco Placebo	Kalydeco	Kalydeco	Kalydeco Placebo	Kalydeco Placebo
No. of participants	161	52	144	34	39	69
% Female	52%	52%	53%	18%	44%	57%
Age, mean (range)	25.5 (12-53)	8.9 (6-12)	NR†	NR (2-5)	22.8 (6-57)	31 (NR)
ppFEV$_1$, mean	63.6%	84.2%	NR†	N/A	78.4%	72.9%
Weight, mean	61.5 kg	30.9 kg	NR†	NR	NR	NR†
Weight z-score‡	NR	NR	NR†	−0.2	0.084	NR†
BMI z-score‡	NR	0.08	NR†	NR	0.359	NR

RCT: randomized controlled trial; BMI: body mass index; ppFEV$_1$: percent predicted forced expiratory volume in one second

*All participants received both Kalydeco and placebo; randomization determined one of two treatment orders: eight weeks of Kalydeco followed by eight weeks of placebo OR eight weeks of placebo followed by eight weeks of Kalydeco. A four- to eight-week washout period bridged the two treatment periods.

†Data reported by treatment arm but not for overall trial population

‡Z-score = 0 indicates average weight for age and sex

Percent Predicted Forced Expiratory Volume (ppFEV$_1$)

Treatment differences (between-group differences comparing Kalydeco and placebo groups) in mean absolute and relative ppFEV$_1$ changes are shown in Table 3.2.

Table 3.2. Summary of Kalydeco Clinical Efficacy Outcomes for *G551D*-, non-*G551D* Gating Mutations, and *R117H*-CFTR Mutations Versus Placebo

Population	FEV$_1$, Mean Absolute Change from Baseline, Percentage Points (95% CI)	Weight, Mean Absolute Change from Baseline, Kg (95% CI)	BMI, Mean Absolute Change from Baseline, Kg/m^2 (95% CI)	CFQ-R Respiratory Domain, Mean Absolute Change from Baseline, Points (95% CI)
G551D				
Ages 6-11[†9] (n=52)	10.0[‡] (4.5 to 15.5)	2.8[§] (1.3 to 4.2)	NR	5.1 (−1.6 to 11.8)
Ages 12+[†8] (n=161)	10.5 (8.5 to 12.5)	2.8 (1.3 to 4.1)	NR	8.6 (NR) p<0.001
Non-*G551D* gating mutations				
Ages 6+[#10] (n=39)	10.7 (7.3 to 14.1)	NR	0.70 (0.34 to 0.99)	9.6 (4.5 to 14.7)
R117H				
Ages 6+[¤ 11] (n=69)	2.1[‡] (−1.13 to 5.35)	NR	0.26[‡] (−1.57 to 2.10)	8.4[‡] (2.17 to 14.6)
Ages 6-11 (n=17)	*−6.3 (−12.0 to −0.7)*	*NR*	*−0.18[‡] (−2.38 to 2.01)*	*−6.1[‡] (−15.7 to 3.4)*
Ages 18+ (n=50)	*5.0 (1.2 to 8.8)*	*NR*	*0.31[‡] (−1.90 to 2.51)*	*12.6[‡] (5.0 to 20.3)*

N/A: not applicable for trial; NR: not reported

*Ages 2-5 (KIWI), a single-arm study where all participants received Kalydeco (50 or 75 mg, based on weight)

†Ages 6-11 (ENVISION) and ages 12+ (STRIVE) show treatment difference (Kalydeco vs. placebo) at 48 weeks

‡Adjusted, least squares mean and mixed-effects model for repeated measures

§ Adjusted, least squares mean and linear mixed model

#Cross-over study design (8 weeks) followed by a 16-week open label extension (KONNECTION); treatment difference (Kalydeco vs. placebo) at 8 weeks

¤Ages 6+ (KONDUCT), treatment difference (Kalydeco vs. placebo) at 24 weeks. Treatment differences by age group shown in italics; age 12-17 subgroup (n=2) was too small for subgroup analysis

All randomized controlled trials reported mean absolute change from baseline ppFEV$_1$ (Table 3.2). Differences between Kalydeco and placebo groups' mean absolute change from baseline after 48 weeks of treatment showed significant gains on Kalydeco in ppFEV$_1$ for *G551D* individuals aged 6-11 (treatment difference: 10.0 percentage points; 95% CI 4.5 to 15.5; baseline ppFEV$_1$ 84%) [9] and 12 and older (treatment difference: 10.5 percentage points; 95% CI 8.5 to 12.5; baseline ppFEV$_1$:

64%).[8] Lung function outcomes at 24 and 48 weeks were comparable. Meta-analysis of the two RCTs comparing Kalydeco to placebo in patients with *G551D* mutations yielded a difference in $ppFEV_1$ of 10.4 percentage points (95% CI 8.6 to 12.3), favoring Kalydeco (Appendix D, Figure D6).[8,9] Results from the GOAL observational study show similar $ppFEV_1$ gains for non-*G551D* gating mutations before and after Kalydeco treatment initiation (treatment difference: 10.7 percentage points; 95% CI 7.3 to 14.1).[14]

Lung function effects depended on age for *R117H* individuals in the KONDUCT study. Analysis of all participants showed a non-significant 2.1 percentage point difference (95% CI −1.13 to 5.35 percentage points) in $ppFEV_1$ between Kalydeco and placebo groups.[11] When stratified by age, however, children aged 6-11 on Kalydeco had significant declines in absolute $ppFEV_1$ (difference: −6.3 percentage points, 95% CI −11.96 to −0.71 percentage points, p=0.03) compared to those on placebo, though the trial authors note the overall group's lung function was stable except for one child who experienced a pulmonary exacerbation.[11] In contrast, those aged 18 and older experienced significant gains in $ppFEV_1$ (difference: 5.0%; 95% CI 1.15 to 8.78) compared to those on placebo. Only two participants in the study were aged 12-17, which precluded statistical analysis.

Two publications explored long-term $ppFEV_1$ outcomes: one Phase III single-arm open-label extension (PERSIST) and one non-randomized comparative study. PERSIST enrolled *G551D* individuals who completed STRIVE or ENVISION and assessed long-term safety and efficacy over an additional 96 weeks of Kalydeco use.[15] Absolute change from baseline $ppFEV_1$ was evaluated as a secondary outcome. Gains were similar for patients originally randomized to Kalydeco and placebo in both studies and averaged 9-10 percentage points over 96 weeks. This magnitude of effect is similar to what was observed in STRIVE over 24 weeks.

Additional post-PERSIST analyses matched *G551D* individuals aged six and older who received Kalydeco during STRIVE, ENVISION, and/or PERSIST with up to five age-, sex-, weight-, and $ppFEV_1$-comparable *F508del* homozygous individuals using the Cystic Fibrosis Foundation Patient Registry (CFFPR).[68] Treatment differences showed *G551D* participants on Kalydeco during a Phase III trial gained a mean absolute 10.7 percentage points (p<0.001) compared to *F508del* receiving only standard care. The annualized rate of $ppFEV_1$ decline showed those on Kalydeco experienced a modest but statistically significant difference in the rate of lung function decline (0.8 percentage points; 95% CI 0.06 to 1.55%) over three years compared to those receiving only standard care (Appendix F).[68]

Weight and BMI

Outcomes related to nutrition were reported using a variety of measures, ultimately limiting direct comparisons of nutritional outcomes (Table 3.2). STRIVE and ENVISION both reported mean absolute changes from baseline weight, while KONNECTION and KONDUCT reported mean absolute changes in BMI. ENVISION and KONNECTION also reported absolute changes in BMI-for-age z-scores.

Overall, participants with *G551D* mutations in STRIVE and ENVISION receiving Kalydeco experienced a statistically significant mean 2.8 kg weight gain from baseline compared to those on placebo after 48 weeks (STRIVE 95% CI 1.3 to 4.1; ENVISION 95% CI 1.3 to 4.2).[8,9] These effects represent about a 10% weight gain in children aged 6-11 years and about a 5% weight gain in adults. Meta-analysis of the two trials yielded the same estimate, with a tighter confidence interval: 2.8 kg (95% CI 1.8 to 3.8) (Appendix D, Figure D7).

Age-stratified analysis (≤20 and >20 years old) showed a similar trend of weight gain for those on Kalydeco compared to placebo (Appendix F).[69] Those under 20 years of age benefitted to a greater magnitude compared to those aged 20 and older (4.9 kg, 95% CI: NR vs. 2.9 kg, 95% CI 1.35 to 4.47 kg). Individual-level response analysis in this study suggested weight gain and increased lung function were not correlated, though both outcomes improved with Kalydeco treatment.

The 34 children ages 2-5 years receiving Kalydeco in the single arm, open-label KIWI study showed a statistically significant mean increase in weight z-score (0.2, SD 0.3; p<0.0001) and BMI z-score (0.4, SD 0.4; p<0.0001).

Non-*G551D* gating mutation individuals on Kalydeco experienced a statistically-significant 0.7 kg/m^2 (95% CI 0.34 to 0.99 kg/m^2) BMI increase after eight weeks of treatment compared to placebo.[10] *R117H* individuals again had mixed results in subgroup analyses by age, and Kalydeco treatment effects were non-significant in all groups analyzed.[11] Based on the data reported in the article, there was no statistically significant difference in weight change among younger and older participants, though most *R117H* participants (87%) were pancreatic sufficient and at a normal body mass at baseline.

Quality of Life using Cystic Fibrosis Questionnaire– Revised (CFQ-R)

All four randomized controlled trials collected CFQ-R respiratory domain scores, as shown in Table 3.2. Three of four trials reported significant, clinically meaningful increases from baseline CFQ-R respiratory domain scores for Kalydeco groups compared to placebo.

Participants aged 12 and older reported significant improvements in quality of life regarding respiratory symptoms. STRIVE, KONNECTION, and the subset of KONDUCT participants who were aged 18 and older reported a mean absolute increase of 8.6 (95% CI NR, p<0.001), 9.6 (95% CI 4.5 to

14.7), and 12.6 (95% CI 5.02 to 20.25) points on the CFQ-R Respiratory domain compared to placebo, respectively.[8,10,11] The KONNECTION study included children as young as six years, but the study average age was 22.8 years; therefore, we assume most participants were aged 12 or older. Meta-analysis of these three trials yielded a summary estimate of the difference between Kalydeco and placebo of 9.7 units (95% CI 6.5 to 13.0) (Appendix D, Figure D8).

Participants aged 6-11 years (*G551D* and *R177H*), however, showed conflicting results in CFQ-R respiratory domain score improvement. *G551D* participants reported a non-significant 5.1 (95% CI −1.6 to 11.8) point improvement compared to placebo [9], while *R117H* participants reported a −6.1 (95% CI −15.68 to 3.41) point change [11]; *R117H* findings may have been impacted by the small sample size, however (n=17). These studies were not meta-analyzed.

One additional analysis of STRIVE CFQ-R outcomes reported scores for all domains included in the questionnaire (Appendix F).[70] Treatment differences in health perceptions (7.6 points, p<0.001), physical functioning (4.4 points, p=0.006), respiratory symptoms (8.6 points, p<0.001), social functioning (4.3, p=0.003), vitality (5.5 points, p=0.002), and weight (5.3 points, p=0.053) domains exceeded the MCID threshold of four points. Treatment differences in the other domains also favored Kalydeco over placebo, though effects were not clinically meaningful. For the respiratory domain, 57% of those taking Kalydeco reported improvement in CFQ-R scores versus 25% on placebo (p<0.05). Likewise, 29% of Kalydeco recipients versus 54% of those on placebo reported a CFQ-R respiratory domain score decrease (p<0.05).

Pulmonary Exacerbations

Pulmonary exacerbations reported in randomized clinical trials are shown in Table 3.3. Pulmonary exacerbations were generally reported as either an outcome or adverse event, and in some cases as both, complicating in-depth understanding and analysis. Our meta-analysis and summary results for pulmonary exacerbations use the "outcome" data, not the adverse event data.

Table 3.3. Pulmonary Exacerbations in *G551D* Gating and *R117H* Residual Function Populations, by Reported Outcome Definition

	STRIVE[8]		KONDUCT[11]	
Follow-up Duration	**48 weeks**		**24 weeks**	
	Placebo (n=78)	Kalydeco (n=83)	Placebo (n=35)	Kalydeco (n=34)
Modified Fuch's Criteria				
No. PEx	99 (1.3/subject)	47 (0.6/subject)	17 (0.5/subject)	13 (0.4/subject)
No. Subjects with PEx	44	28	13	11
Hazard ratio (p value)	0.455 (0.001)		0.93 (NR)	
Required IV Antibiotics				
No. PEx (% of all PEx)	47 (47)	28 (60)	7 (41)	2 (15)
No. Subjects with PEx	NR	NR	6	2
Required Hospitalization				
No. PEx (% of all PEx)	31 (31)	21 (45)	8 (47)	2 (15)
No. Subjects with PEx	NR	NR	6	2

PEx: pulmonary exacerbations; NR: not reported

In addition, pre-specified definitions of pulmonary exacerbation were not always available in published studies, appendices, or protocols. During conversations with the manufacturer, however, we heard all published clinical trials used the same protocol definition of a pulmonary exacerbation (modified Fuch's criteria).

We noted two discrepancies in pulmonary exacerbations reported as adverse events and outcomes. ENVISION reported four exacerbations in the Kalydeco group and three in the placebo group as outcomes; however, eight exacerbations are reported for each group when categorized as adverse events.[9] Second, the KONDUCT study reported 13 and 11 exacerbations in the Kalydeco and placebo groups, respectively, and report three additional exacerbations (one in placebo, two in the Kalydeco group) as adverse events.[11]

STRIVE was the only randomized comparative study showing a treatment effect on the incidence of pulmonary exacerbations (Table 3.3). STRIVE participants receiving Kalydeco experienced approximately half as many pulmonary exacerbations compared to the placebo group over 48 weeks (55% risk reduction, p<0.001).[8] ENVISION reported exacerbations among 4 of 26 (15%) Kalydeco and 3 of 26 (12%) placebo recipients over 48 weeks.[71] The frequency of pulmonary exacerbations was similar (33-46%) during the additional 96 weeks of Kalydeco treatment during.[15]

Exacerbations during KONNECTION were reported by cross-over period with short-term intervention (8 weeks): 9 of 38 (24%) and 11 of 39 (28%) of participants experienced a pulmonary exacerbation during the eight-week Kalydeco and placebo periods, respectively.[10]

Among the different definitions of pulmonary exacerbation explicitly or implicitly used by studies, we were most interested in pulmonary exacerbations requiring IV antibiotics and hospitalization because these are often associated with additional financial costs and reduced quality of life. STRIVE and KONDUCT were the only two studies to explicitly report these outcomes. The rate of exacerbations requiring IV antibiotics through 48 weeks was 0.71 for Kalydeco and 0.40 for placebo recipients. Thus, our calculations provide a rate ratio of 0.56 (NS).[8] As shown in Table 3.3, there was no consistent trend in the Kalydeco and placebo groups in the rate of exacerbations requiring hospitalization or IV antibiotics.

Meta-analysis of pulmonary exacerbations per modified Fuch's criteria in STRIVE and KONDUCT yielded a summary odds ratio of 0.51 (95% CI 0.26 to 1.00) and a summary relative risk of 0.65 (95% CI 0.48 to 0.89) (Appendix D, Figures D9 and D10). KONDUCT did not report a p-value or confidence interval for the hazard ratio, implying statistical nonsignificance. However, assuming a nonsignificant p-value of either 0.10 or 0.50 yielded almost identical summary hazard ratios of about 0.67 (95% CI 0.33 to 1.35) (Appendix D, Figure D11). The two studies, though, had very different estimates of hazard ratios and the meta-analysis is statistically heterogeneous.

A *post hoc* analysis of STRIVE participants assessed post-exacerbation lung function recovery.[72] Lung function recovery, defined as returning to ≥100% of pre-exacerbation ppFEV$_1$, was assessed two-to eight-weeks ("short-term recovery") after antibiotic treatment for an exacerbation and again using the end-of-study ppFEV$_1$ measurement ("long-term recovery"). Short-term (53.7% vs. 57.1%), and long-term recovery rates (46.6% vs. 47.7%) were similar for the placebo and Kalydeco groups. However, other related outcomes favored Kalydeco over placebo: 57% lower rate of pulmonary exacerbations (RR: 0.43; 95% CI 0.29 to 0.68); statistically significantly shorter pulmonary exacerbations (mean normalized days per patient: 13.5 [SD 27.3] vs. 36.7 [SD 49.5], respectively; p<0.001); fewer patients treated with IV antibiotics for an exacerbation (patients treated with IV antibiotics: 18.1% vs. 34.6%, respectively; p=0.02); and shorter antibiotic treatments (mean normalized days per patient of IV antibiotic therapy: 6.7 [SD 19.4] vs. 11.0 [SD 20.3], respectively; p=0.02) compared to placebo.

A large, non-randomized, comparative, long-term study also reported significantly lower risks of pulmonary exacerbations associated with Kalydeco (N=1667 on Kalydeco).[12,73] The study implicitly included all people with available data receiving Kalydeco, regardless of mutation. The annual risk of an exacerbation was assessed by matching individuals on Kalydeco to similar patients on best supportive care (US 6200, UK 2069).[12] Over a one year period 6 to 12 year-old US children taking Kalydeco experienced a significantly lower annual risk of pulmonary exacerbation compared to those on best supportive care (RR: 0.34, 95% CI 0.22 to 0.52).[73] Analysis of all ages (not reported in the abstract) showed those on Kalydeco also experienced a statistically significant decrease in the annual risk of pulmonary exacerbation (RR: 0.64, 95% CI 0.58 to 0.70) in the US cohort of 1256 participants on Kalydeco; similar results were seen in a UK cohort of 411 patients.[12] The annual risk of other clinical outcomes in the US cohort were also lower for patients on Kalydeco compared to

placebo, including death (RR: 0.41, 95% CI 0.20 to 0.84), organ transplant (RR: 0.15, 95% CI 0.04 to 0.59), and hospitalization (RR: 0.64, 95% CI 0.58 to 0.70), with similar but nonsignificant results for death and organ transplantation.[12]

Clinical Benefits of Orkambi and Symdeko in Individuals 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 varies by age, dose, and baseline lung function. In longer-term follow-up (96 weeks), those 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. Both Orkambi and Symdeko provide improved respiratory-related quality of life compared with placebo. Orkambi and Symdeko reduced pulmonary exacerbation events over 24 weeks, including those requiring intravenous antibiotics and hospitalizations, compared with placebo. Indirect comparisons yielded no material differences between Orkambi and Symdeko in key clinical outcomes. Harms associated with Orkambi and Symdeko are discussed separately, below.

Two treatment regimens were reviewed for individuals homozygous for the *F508del* mutation: Orkambi and Symdeko. Across these two treatments, we identified six key trials including four Phase III randomized controlled trials, one single arm trial and one long-term, open-label extension trial. Five of the six trials were of Orkambi.

Two placebo-controlled, parallel-arm Phase III RCTs of Orkambi, TRAFFIC and TRANSPORT, enrolled patients ages 12 and older with two copies of the *F508del* mutation.[16] Inclusion criteria included a screening FEV$_1$ between 40-90% predicted and stable disease.[16] Two doses of lumacaftor were tested against placebo (lumacaftor 600 mg daily or 400 mg twice a day, both with ivacaftor 250 mg twice a day).[16] Study design was identical in both trials, so data were pooled by the author and are presented here. A subgroup analysis by baseline ppFEV$_1$ is also reviewed in this section where data are available.

A single placebo-controlled, parallel-arm Phase III randomized controlled trial evaluated 200 mg of lumacaftor twice daily in combination with 250 mg ivacaftor twice daily in children ages 6-11 years with two copies of the *F508del* mutation. Inclusion criteria specified a minimum weight of 15 kg, ppFEV$_1$ > 70% and lung clearance index (LCI$_{2.5}$) of 7.5 or more lung volume turnovers at screening.[17] Exclusion criteria were similar to TRAFFIC/TRANSPORT.

One randomized, placebo-controlled, parallel-arm trial of Symdeko, EVOLVE, enrolled 510 cystic fibrosis patients ages 12 and older who were homozygous for the *F508del* mutation for 24 weeks of follow-up.[18] Inclusion and exclusion criteria were similar to TRAFFIC/TRANSPORT.

The long-term safety of Orkambi was assessed in two open-label continuation studies. PROGRESS followed eligible TRAFFIC and TRANSPORT participants for an additional 96 weeks, during which all participants received either 600 mg of lumacaftor daily (combined with 250 mg of ivacaftor twice daily) or 400 mg of lumacaftor twice daily (combined with 250 mg of ivacaftor twice daily).[19] Milla et al. reported on 58 children ages 6-11 years old receiving 200 mg of lumacaftor twice daily in combination with 250 mg ivacaftor twice daily during follow-up of 24 weeks.[20] The primary endpoint of both open-label studies was based on treatment-emergent adverse events and other physiologic measures.

Across all studies, outcomes of interest included $ppFEV_1$ (as both absolute and relative changes), weight or BMI (or BMI Z score), CFQ-R respiratory domain, and number or rate of pulmonary exacerbations. See Table 3.4 for a comparison of baseline patient characteristics and outcome measures across key trials and Table 3.5 for a summary of results across trials.

For simplicity, results present outcomes by the differing doses of lumacaftor only, as the dose of Kalydeco did not differ.

Table 3.4. Included Trials in the Homozygous *F508del* Population

Study Design and Study Quality	TRAFFIC/TRANSPORT*[16] RCT, Phase III, Ages 12+ Good	Ratjen et al.[17] RCT, Phase III, Good	PROGRESS[19] Single-arm, open-label extension	Milla et al.[20] Single-arm study	EVOLVE[18] RCT, Phase III, Good
Follow-up Duration	24 weeks	24 weeks	96 weeks	24 weeks	24 weeks
Treatment Groups	Orkambi* Placebo	Orkambi Placebo	Orkambi*	Orkambi	Symdeko Placebo
No. of Participants	1108	204	1029	58	504
% Female	49%	59%	48%	53%	49%
Age, mean (range)	25.1 (12-64)	8.8 (6-11)	25.0 (SD~10)	9.1 (6-11)	26.3 (SD~10)
$ppFEV_1$, mean	60.6%	89.8%	60.3%	91.4%	60.0%
BMI, mean	21.2 kg/m^2	16.4 kg/m^2	21.2 kg/m^2	16.89 kg/m^2	21.04 kg/m^2

*An additional arm, 600 mg daily lumacaftor with ivacaftor was studied; Pooled analysis
$ppFEV_1$: percent predicted forced expiratory volume in 1 second; BMI: body mass index

Table 3.5. Summary of Clinical Efficacy Outcomes from Randomized Controlled Trials for Patients Homozygous for *F508del*

	Orkambi					Symdeko	
	TRAFFIC and TRANSPORT*[16]			Ratjen et al.[17]		EVOLVE[18]	
	Lumacaftor 600 mg qd w/ivacaftor	Orkambi (400 mg q 12 hrs)	Placebo	Orkambi (200 mg q 12)	Placebo	Symdeko (100 mg daily)	Placebo
FEV_1, Absolute Change†, Percentage Points (p-value or 95% CI)	3.0 (p<0.001)	2.5 (p<0.001)	-0.32 (p=0.40)	1.1 (-0.4 to 2.6)	-1.3 (-2.8 to 0.2)	3.4 (2.7 to 4.0)	-0.6 (-1.3 to 0.0)
FEV_1, Relative Change†, % (p-value or 95% CI)	5.4 (p<0.001)	4.6 (p<0.001)	-0.17 (p<0.001)	NR	NR	6.3 (5.1 to 7.4)	-0.5 (-1.7 to 0.6)
Lung Clearance Index (LCI), Absolute Change (95% CI)	NR	NR	NR	-1.0 (-1.3 to -0.8)	0.1 (-0.2 to 0.3)	NR	NR
BMI, Absolute Change†, kg/m^2 (P-Value or 95% CI)	0.41 (p<0.001)	0.37 (p<0.001)	0.13 (p<0.007)	0.4 (0.3 to 0.5)	0.3 (0.1 to 0.4)	0.18 (0.08 to 0.28)	0.12 (0.03 to 0.22)
BMI-For-Age Z Score, Absolute Change, (95% CI)	NR	NR	NR	0.1 (0.0 to 0.2)	0.1 (0.0 to 0.1)†	-0.06 (-0.14 to 0.02)	-0.02 (-0.10 to 0.06)
CFQ-R, Respiratory Domain Absolute Change†, Points (P-Value Or 95% CI)	4.9 (p<0.001)	4.1 (p<0.001)	1.9 (p=0.02)	5.5 (3.4 to 7.6)	3.0 (1.0 to 5.0)	5.0 (3.5 to 6.5)	-0.1 (-1.6 to 1.4)
Pulmonary Exacerbation, No. (Rates)	173± (0.80 per 48 wk)	152± (0.70 per 48 wk)	251± (1.14 per 48 wk)	NR	NR	78‡ (0.64 per yr)	122‡ (0.99 per yr)

All data change from baseline to follow-up; q=every, qd=daily

CI: confidence interval

*Pooled results †least-square means ‡Number of events (annualized estimated event rate)

† Nonsignificant (P-value >0.05).

Percent Predicted Forced Expiratory Volume (ppFEV$_1$) and Lung Clearance Index (LCI)

Orkambi

The key Orkambi randomized controlled trials reported absolute and relative changes in ppFEV$_1$ between baseline and 24 weeks.[16,17] For individuals ages 12 and older enrolled in TRAFFIC and TRANSPORT, least-squares mean absolute change in ppFEV$_1$ was 3.0 percentage points 600 mg/day lumacaftor/ivacaftor arm, 2.5 percentage points in the Orkambi arm, and -0.32 percentage points in the placebo arm between baseline and 24 weeks (Table 3.5).[16] The differences compared to placebo were 3.3 (95% CI, 2.3 to 4.3) percentage points for 600 mg daily lumacaftor/ivacaftor arm and 2.8 (95% CI, 1.8 to 3.8) percentage points for Orkambi.[16]

Konstan et al. performed a *post hoc* analysis by matching participants from TRAFFIC/TRANSPORT taking Orkambi with controls from the US CFFPR (homozygous *F508del*) to assess changes to the annual rate of ppFEV$_1$ decline.[74] Based on 455 patients taking Orkambi and 1,588 matched controls, the authors found Orkambi produced a 42% slower rate of decline in ppFEV$_1$ (1.33 vs. 2.29 percentage points per year; p-value < 0.001).[74]

Although changes in ppFEV$_1$ in the randomized trials were positive and significant, a post-approval study at a single hospital (n=116, mean age=24.7 years (range 12-59), 62% female, baseline ppFEV$_1$=67.4) found no benefit of Orkambi after an average of four months use in a real-world cohort of children and adults (n=116; mean change in ppFEV$_1$ 0.11%; 95% CI, -39% to 20%).[24]

The ppFEV$_1$ was reported as a secondary endpoint in the two trials in the 6-11 year old population, as lung function is often preserved in younger children.[17] Milla et al. reported no statistically significant difference in absolute change in ppFEV$_1$ from baseline to 24 weeks in an open-label Phase III trial.[20] A randomized placebo-controlled trial of 206 children found participants taking 200 mg of lumacaftor twice a day in combination with 250 mg of ivacaftor twice a day (Orkambi) experienced a statistically significant absolute change in ppFEV$_1$ of 2.4 percentage points (95% CI 0.4 to 4.4) compared with placebo; however, this was primarily driven by decreases in ppFEV$_1$ in the placebo group between baseline and 24 weeks.[17] The within-group change in the Orkambi arm did not show a statistically significant improvement.[17] Relative changes in ppFEV$_1$ were not reported in either trial.

In an effort to capture the respiratory benefit of Orkambi, lung clearance index (LCI$_{2.5}$) was used as the primary efficacy endpoint in the trial. LCI is a novel surrogate outcome that measures the number of lung volume turnovers required for the lungs to clear a tracer gas to reach 2.5% of starting tracer gas concentration.[17] Reductions from baseline indicate an improvement. In both trials of Orkambi in the 6-11 year old population, Orkambi provided a statistically significant improvement from baseline with a change of -0.88 (95% CI, -1.40 to -0.37) and -1.0 (95% CI, -1.3 to -

0.8).[17,20] In the RCT, the difference between Orkambi and placebo was also statistically significant (difference of -1.1, 95% CI -1.4 to -0.8).[17]

Subgroup analysis

In TRAFFIC and TRANSPORT, similar changes in absolute $ppFEV_1$ over 24 weeks compared with placebo were found for Orkambi (400 mg twice daily) for patients with baseline $ppFEV_1 < 40\%$ (3.3%, 95% CI 0.2 to 6.4, n=29) and patients with baseline $ppFEV_1 \geq 40\%$ (2.8%, 95% CI 1.7 to 3.8, n=336), as well as for patients with baseline $ppFEV_1 < 70\%$ (3.3%, 95% CI 2.1 to 4.4, n=245) and patients with baseline $ppFEV_1 \geq 70\%$ (1.9%, 95% CI −0.2 to 4.0, n=114).[23]

A 24-week, open-label Phase IIIb study of individuals with advanced lung disease ($ppFEV_1<40\%$) reported a statistically significant decline in $ppFEV_1$ (-1.7%; 95% CI, -3.2 to -0.1) for the first 15 days followed by a return to baseline at week four, remaining stable until study completion.[75]

Symdeko

In the homozygous population, one RCT (EVOLVE) reported absolute and relative changes in $ppFEV_1$ for Symdeko.[18] The primary efficacy endpoint, absolute change from baseline in percentage of predicted FEV_1 through 24 weeks, showed a statistically significant improvement in absolute $ppFEV_1$ of 3.4 percentage points (95% CI, 2.7 to 4.0).[18] Compared with placebo, Symdeko provided 4.0 percentage point improvement (95% CI 3.1 to 4.8).[18]

Relative change from baseline in percentage of predicted FEV_1 through week 24 showed a statistically significant improvement both within the active drug arm (6.3%, 95% CI, 5.1 to 7.4) and between Symdeko and placebo (6.8%, 95% CI, 5.3 to 8.3).[18]

Orkambi versus Symdeko

No study has directly compared Orkambi and Symdeko. As shown in Table 3.6, the absolute change in $ppFEV_1$ was significantly greater with both drugs than with placebo. By indirect comparison (network meta-analysis), the difference in absolute change in $ppFEV_1$ between the two drugs is nonsignificant: 1.2 percentage points (95% CI -0.1 to 2.5, p=0.073).

Table 3.6. Absolute Change in ppFEV$_1$ in Patients Homozygous for the *F508del* Mutation

	Orkambi vs. Placebo*	Symdeko vs. Placebo†	Symdeko vs. Orkambi‡
FEV$_1$, Absolute Change, Percentage Points (95% CI)	2.8 (1.8 to 3.8)	4.0 (3.1 to 4.8)	1.2 (-0.1 to 2.5)

*Two studies included (TRAFFIC and TRANSPORT); data for lumacaftor 400 mg twice daily with ivacaftor 250 mg twice daily only

†One study included (EVOLVE; n=504)

‡ TRAFFIC, TRANSPORT and EVOLVE (n=1612); the comparison of Symdeko and Orkambi is an indirect comparison between the two placebo-controlled trials

Weight and BMI

Orkambi

BMI was reported as absolute change from baseline in all Orkambi trials (Table 3.5). In trials with younger patients, BMI-for-age z-score was also reported. Results in BMI varied across trials. In the TRAFFIC trial (n=549), neither active treatment dose arm showed a difference in BMI compared to placebo.[16] However, in TRANSPORT, an identically designed trial of 559 participants, least-squares mean absolute change in BMI was significantly higher in the two active comparator arms compared to placebo.[16] It is not clear why the effect of Orkambi on weight differed in the two trials except to note that the increases in BMI were only about 1-2% from participants' baseline BMIs. In a pooled analysis, lumacaftor 600 mg daily with ivacaftor showed a statistically significant increase of 0.28 kg/m^2 (95% CI, 0.15 to 0.41 kg/m^2) compared to placebo and Orkambi showed a statistically significant increase of 0.24 kg/m^2 (95% CI, 0.11 to 0.37) versus placebo.[16] After 96-weeks on Orkambi, individuals in PROGRESS (open-label extension of TRAFFIC and TRANSPORT) had an absolute change in BMI of 0.76 to 0.96 kg/m^2 (95% CI, 0.56 to 0.97 kg/m^2 and 95% CI, 0.81 to 1.11 kg/m^2 depending on original assignment arm).[19] Both BMI-for-age z-score and weight-for-age z-score in participants under the age of 20 in TRAFFIC/TRANSPORT showed improvement with Orkambi versus matched controls (see Appendix Figure D1).[16]

Results of absolute change in BMI in children 6-11 years old also varied between studies. In the open-label, single-arm, Phase III study, children saw an absolute change in BMI of 0.64 kg/m^2 (95% CI, 0.46 to 0.83 kg/m^2) at 24 weeks (a 3.8% increase from baseline).[20] However, in the randomized controlled trial, there was no difference in absolute BMI between Orkambi and placebo.[17] BMI-for-age z-scores also showed a significant increase from baseline to 24-weeks in the single-arm study (0.15 kg/m^2; 95% CI, 0.08 to 0.22 kg/m^2) yet showed no difference compared to placebo in the RCT.[17,20] Weight-for-age z-scores changed from a baseline mean of -0.03 (1.03) to 0.13 (95% CI, 0.07 to 0.19) at 24 weeks (least-squares mean using mixed-effects model for repeated measures).[20]

Subgroup analysis

In TRAFFIC and TRANSPORT, similar changes in BMI over 24 weeks compared with placebo were found for Orkambi (400 mg twice daily) for patients with baseline $ppFEV_1$ < 40% (0.3, 95% CI −0.2 to 0.8, n=29) and patients with baseline $ppFEV_1$ ≥ 40% (0.2, 95% CI 0.1 to 0.4, n=336), as well as for patients with baseline $ppFEV_1$ < 70% (0.2, 95% CI 0.0 to 0.3, n=245) and patients with baseline $ppFEV_1$ ≥ 70% (0.3, 95% CI 0.1 to 0.6, n=114).[23]

Symdeko

Absolute change in BMI from baseline to 24 weeks in the EVOLVE trial showed within-person improvement of 0.18 kg/m^2 (95% CI, 0.08 to 0.28) in the Symdeko arm and 0.12 kg/m^2 (95% CI, 0.03 to 0.22) in the placebo arm (<1% increases from baseline).[18] The difference in absolute change in BMI between treatment and placebo was non-significant.[18] BMI-for-age z-score change from baseline to 24 weeks was non-significant for both arms (see Table 3.5).[18] Long-term data on the effect of Symdeko on BMI or BMI-for-age z-score is not available yet.

Orkambi versus Symdeko

No study has directly compared Orkambi and Symdeko. As shown in Table 3.7, the absolute change in BMI Z score was similar for both drugs versus placebo; thus, by indirect comparison (network meta-analysis), the difference in Z score between the two drugs is nonsignificant: -0.04 z score units (95% CI -0.29 to 0.07)

Table 3.7. Meta-analysis of Change in BMI-for-age Z score in Patients Homozygous for the *F508del* Mutation

	Orkambi vs. Placebo*	Symdeko vs. Placebo†	Symdeko vs. Orkambi‡
BMI-for-age Z score, (95% CI)	0.0 (-0.2 to 0.2)	-0.04 (-0.15 to 0.07)	-0.04 (-0.29 to 0.21)

*One study included (Ratjen et al.; n=204).
†One study included (EVOLVE; n=504)
‡Ratjen et al. and EVOLVE (n=708)

Quality of Life using Cystic Fibrosis Questionnaire– Revised (CFQ-R)

Orkambi

Adolescents and adults receiving Orkambi in TRAFFIC and TRANSPORT reported improved respiratory symptoms on the CFQ-R after 24 weeks as compared to individuals randomized to placebo (2.2 points; 95% CI 0.0 to 4.5, see Table 3.8; individual arm results in Table 3.5).[16] While statistically significant, this value did not meet the MCID of 4.[21] These benefits lasted through 72

weeks for all participants who enrolled in the open-label extension study, PROGRESS.[19] At 96 weeks, patients continued to report improved symptoms, however, the benefits did not statistically differ from baseline in most patients.[19]

Respiratory symptom quality of life was mixed in children ages 6-11 years. Milla et al. reported a statistically and clinically significant improvement in CFQ-R between baseline and 24 weeks in an open-label trial (5.4 points; 95% CI, 1.4 to 9.4).[20] These findings were similar in the randomized controlled trial where children randomized to Orkambi reported an absolute change from baseline to 24 weeks of 5.5 points (95% CI, 3.4 to 7.6), however, children randomized to placebo also reported fewer respiratory symptoms (3.0 points; 95% CI, 1.0 to 5.0).[17] Orkambi was not found to confer a statistically significant benefit when compared to placebo.[17]

Other domains of the CFQ-R were not reported in the key studies.

Subgroup analysis

In TRAFFIC and TRANSPORT, estimates of relative effects of Orkambi compared with placebo on CFQ-R over 24 weeks varied based on baseline ppFEV$_1$ category, but because of high variability in the score across the study, differences across subgroups were not statistically significant.[23]

Symdeko

Individuals enrolled in the Symdeko arm of the EVOLVE study showed a clinically and statistically significant improvement in respiratory symptoms from baseline to 24 weeks (5.0 points; 95% CI, 3.5 to 6.5) while individuals randomized to placebo showed a slight but nonsignificant decline.[18] Compared with placebo, Symdeko improved respiratory domain quality of life (difference of 5.1 points; 95% CI, 3.2 to 7.0).[18]

Other domains of the CFQ-R were not reported in the key studies.

Orkambi versus Symdeko

No study has directly compared Orkambi and Symdeko. As shown in Table 3.8, both drugs resulted in statistically significant improvements in respiratory symptom-related quality of life, but the effect was larger with Symdeko. By indirect comparison (network meta-analysis), Symdeko was just nonsignificantly more effective to improv CFQ-R respiratory domain score than Orkambi: difference 2.9 units (95% CI -0.0 to 5.8, p=0.054).

Table 3.8. Meta-analysis of Quality of Life in Patients Homozygous for the *F508del* Mutation (CFQ-R) Respiratory Domain Score

	Orkambi vs. Placebo*	Symdeko vs. Placebo†	Symdeko vs. Orkambi‡
CFQ-R, absolute change, score (95% CI)	2.2 (0.0 to 4.5)	5.1 (3.2 to 7.0)	2.9 (-0.0 to 5.8)

*Two studies included (TRAFFIC and TRANSPORT); lumacaftor 400 mg twice daily with ivacaftor 250 mg twice daily only

†One study included (EVOLVE; n=504)

‡ TRAFFIC, TRANSPORT and EVOLVE (n=1612)

Pulmonary Exacerbations

Table 3.9. Reported Annualized Pulmonary Exacerbation Rates Per Patient Year in Patients Homozygous for the *F508del* Mutation

	TRAFFIC/TRANSPORT		PROGRESS	EVOLVE	
Follow-up Duration	24 weeks		96 weeks	24 weeks	
	Placebo	Orkambi	Orkambi*	Placebo	Symdeko
No. Subjects	371	369	369	256	248
Modified Fuch's Criteria					
No. PEx	251	152	NR	NR	NR
No. PEx per Pt Yr (95% CI)	1.14 (0.97 to 1.34)	0.70 (0.57 to 0.84)	0.65 (0.56 to 0.75)	0.99 NR	0.64 NR
Required IV Antibiotics					
No. PEx per Pt Yr	0.58 (0.47 to 0.72)	0.25 (0.19 to 0.33)	0.32 (0.26 to 0.38)	Either IV antibiotics or hospitalizations (or both) 0.54 events/yr	Either IV antibiotics or hospitalizations (or both) 0.29 events/yr
Required Hospitalization					
No. PEx per Pt Yr	0.45 (0.36 to 0.57)	0.17 (0.12 to 0.25)	0.24 (0.19 to 0.29)	Either IV antibiotics or hospitalizations (or both) 0.54 events/yr	Either IV antibiotics or hospitalizations (or both) 0.29 events/yr

PEx: pulmonary exacerbations

*Lumacaftor 400 mg twice daily with ivacaftor 250 mg twice daily, ±total 120 weeks data (96 weeks after 24 in TRAFFIC/TRANSPORT

Orkambi

Patients receiving Orkambi in TRAFFIC and TRANSPORT reported fewer pulmonary exacerbation events (modified Fuch's criteria) from baseline to 24 weeks than patients randomized to placebo (Table 3.9).[16] The rate ratio between active drug and placebo was 0.65 (95% CI, 0.55 to 0.77) with the greatest reduction in the Orkambi arm (0.61, 95% CI 0.49 to 0.76).[16] Orkambi provided statistically significant reductions in pulmonary exacerbations requiring antibiotics (56% fewer than placebo) and hospitalizations (61% fewer than placebo).[16]

Pulmonary exacerbations reported during TRAFFIC/TRANSPORT are also shown in Table 3.9. After 96 weeks, those who continued on Orkambi maintained a stable reduction (Table 3.9).[19] The number of events requiring hospitalization per patient-year increased slightly after an additional 96 weeks. Similarly, the number of events requiring intravenous antibiotics per patient-year also increased slightly from 0.25 (95% CI, 0.19 to 0.33) at the end of the randomized clinical trial to 0.32 (95% CI, 0.26 to 0.38) at the end of the open-label extension study (Table 3.9).

Pulmonary exacerbation events were not reported as an outcome in studies of children 6-11 years old.

Symdeko

Pulmonary exacerbations reported during EVOLVE are shown in Table 3.9. Patients in the EVOLVE trial randomized to Symdeko showed a statistically significantly lower rate of pulmonary exacerbation compared to those randomized to placebo (RR 0.65; 95% CI 0.48 to 0.88).[18] The rate of pulmonary exacerbations requiring antibiotics or hospitalization was also significantly lower in the Symdeko arm compared to the placebo arm (RR 0.53; 95% CI, 0.34 to 0.82).[18]

Orkambi versus Symdeko

As shown in Table 3.10, both drugs significantly reduce the rate of pulmonary exacerbations to a similar extent. Indirect comparison (network meta-analysis) between Symdeko and Orkambi found no statistically significant difference in pulmonary exacerbations between the two drugs, with an estimated rate ratio of 0.87 (95% CI 0.53 to 1.42).

Table 3.10. Meta-analysis of Pulmonary Exacerbations in Patients Homozygous for the *F508del* Mutation

	Orkambi vs. Placebo*	Symdeko vs. Placebo†	Symdeko vs. Orkambi‡
Pulmonary Exacerbations, Rate Ratio, Score (95% CI)Ł	0.61 (0.49 to 0.76)	0.53 (0.34 to 0.82)	0.87 (0.53 to 1.42)

*Two studies included (TRAFFIC and TRANSPORT), 400 mg dose only †One study included (EVOLVE; n=504)
‡Pulmonary exacerbations defined as infective or requiring intravenous antibiotics or hospitalization

Clinical Benefits of Symdeko and Kalydeco in Individuals Heterozygous for the F508del Mutation

Key Findings: Based on a single short-term (8 week) cross-over trials, Symdeko and Kalydeco both improve absolute and relative ppFEV$_1$ compared with placebo. Symdeko provides a statistically significant benefit over Kalydeco. Respiratory symptom-related quality of life was statistically significantly improved by both Symdeko and Kalydeco compared with placebo. At 8 weeks, BMI and pulmonary exacerbations are not significantly different between the two drugs and compared with placebo, however, the follow-up duration was likely too short to adequately evaluate these outcomes. Harms associated with Symdeko and Kalydeco are discussed separately, below.

There is one key trial of Symdeko and Kalydeco in patients heterozygous for the *F508del* mutation with a second mutation that is responsive to Kalydeco (see Appendix D for list of secondary genes and gene specific efficacy outcomes). The EXPAND trial is a Phase III, randomized, double-blind, placebo-controlled, three intervention crossover trial in which each patient received two of the three interventions for eight-week periods separated by an eight-week washout period.[22] The three interventions included Symdeko (tezacaftor 100 mg daily with ivacaftor 150 mg twice daily), Kalydeco (ivacaftor 150 mg twice daily) or placebo. Individuals were included if they were aged 12 or older, had a percentage of predicted FEV$_1$ at screening between 40-90%, a diagnosis of cystic fibrosis and stable lung disease. Exclusion criteria included laboratory values in the abnormal range, acute respiratory infections or changes in pulmonary disease 28 days prior to first drug, had a history of transplant or recently used other CFTR modulators. Individuals were randomized to one of six intervention sequences.[22] The quality of the study was good, although it provided short-term (eight week) data relative to the parallel-arm RCTs in patients homozygous for the *F508del* mutation (i.e., 24 weeks in EVOLVE and TRAFFIC/TRANSPORT).

The primary efficacy endpoint was absolute change in ppFEV$_1$ from baseline to an average of the four-week and eight-week measurements in the first intervention and was compared to the same timepoints in the second assigned intervention. Key secondary endpoints included CFQ-R respiratory domain score and relative change in ppFEV$_1$. Exploratory endpoints included the rate of pulmonary exacerbations and BMI.[22]

Of the 246 patients who received treatment, 95% (n=234) completed both intervention periods and provided efficacy data. The average age at screening across all subjects was 34.8 (SD 14.2) years, 55% of subjects were female, average ppFEV$_1$ was 62.3% (SD 14.5), average BMI was 24.2 (SD 5.1) kg/m^2, and average baseline CFQ-R score was 68.1 (SD 17.7).[22]

While all patients had one *F508del* mutation, the second mutation varied. Table 1 of the EXPAND manuscript describes the cohort as being 60% class V noncanonical splice and 40% class II to IV residual function mutations in the second allele at baseline.[22]

Table 3.11. Summary of Results in the EXPAND Trial in Patients Heterozygous for a *F508del* Mutation[22]

	Symdeko (N=161) vs. Placebo (N=161)	Kalydeco (N=156) vs. Placebo (N=161)	Symdeko (N=161) vs. Kalydeco (N=156)
ppFEV$_1$, Absolute Change‡, Percentage Points (95% CI)	6.8 (5.7 to 7.8)	4.7 (3.7 to 5.8)	2.1 (1.2 to 2.9)
FEV$_1$, Relative Change, % (95% CI)	11.4 (9.6 to 13.2)	8.1 (6.3 to 9.9)	3.3 (1.8 to 4.8)
BMI, Absolute Change‡, kg/m^2 (Variance Data Not Reported)	0.34 Symdeko 0.18 placebo	0.47 Kalydeco 0.18 placebo	0.34 Symdeko 0.47 Kalydeco
CFQ-R, Absolute Change‡, Points (95% CI)	11.1 (8.7 to 13.6)	9.7 (7.2 to 12.2)	1.4 (-1.0 to 3.9)
Pulmonary Exacerbation, Rate Ratio vs. Placebo (95% CI)	0.54 (0.26 to 1.13)	0.46 (0.21 to 1.01)	1.18 (0.49 to 2.87)

CI: confidence interval

Percent Predicted Forced Expiratory Volume (ppFEV$_1$)

Change in ppFEV$_1$ was measured as an average of the results at four weeks and eight weeks compared to baseline.[22] Compared to placebo, both interventions provided statistically significant improvement in absolute ppFEV$_1$: 6.8 percentage points for Symdeko (95% CI 5.7 to 7.8) and 4.7 percentage points for Kalydeco (95% CI 3.7 to 5.8)(Table 3.11).[22] The difference between Symdeko and Kalydeco was also statistically significant but clinically modest, favoring Symdeko (2.1 percentage points; 95% CI 1.2 to 2.9).[22] These changes compared to baseline ppFEV$_1$ of 62%.

Subgroup Analysis

The EXPAND trial analyzed the difference in absolute change in ppFEV$_1$ by age, baseline ppFEV$_1$, class of residual function mutation, sex, use of concomitant medications and colonization of pseudomonas aeruginosa. Most of the subgroups showed similar relatively consistent treatment effects for Symdeko versus placebo; however, age < 18 vs. ≥ 18 years seemed to modify the effect. Those less than 18 years old showed a 12.0 percentage point improvement in absolute ppFEV$_1$ (95% CI, 9.3 to 14.8) whereas those 18 years and older saw a 6.0 percentage point increase (4.9 to 7.0).[22] The confidence intervals were wider in the under 18 subgroup due to small numbers (< 15% of each arm).[22]

Similar results were seen in the same subgroups with Kalydeco compared with placebo.

Body Mass Index

BMI was a non-powered exploratory endpoint in the EXPAND trial given the short time frame on each intervention sequence. BMI increased 0.34 kg/m^2 for Symdeko (1.4% increase from baseline), 0.47 kg/m^2 for ivacaftor (1.9%), and 0.18 kg/m^2 for placebo (0.7%) (Table 3.11).[22] No data were reported to allow an estimate of statistical significance.

Quality of Life using Cystic Fibrosis Questionnaire– Revised (CFQ-R)

Symdeko provided significantly better quality of life using the CFQ-R respiratory domain score compared to placebo (11.1 points; 95% CI 8.7 to 13.6) (Table 3.11).[22] Kalydeco also provided significantly better respiratory symptom-related quality of life compared to placebo (9.7 points; 95% CI, 7.2 to 12.2).[22] No significant benefit was found between Symdeko and Kalydeco on CFQ-R.[22]

The proportion of patients that received a clinically significant improvement in CFQ-R was 65% in the Symdeko group, 58% in the Kalydeco group and 33% in the placebo group.[22]

Pulmonary Exacerbations

The placebo group in the EXPAND trial reported the greatest number of pulmonary exacerbations overall (n=20 events; estimated event rate per year of 0.63) (Table 3.12). The Symdeko group reported 11 events (0.34 estimated event rate per year) and the Kalydeco group reported 9 events (0.29 estimated event rate per year) (Table 3.12). The rate ratio versus placebo was not statistically significant for either drug. Estimated indirect analysis of Symdeko compared to Kalydeco showed no significant differences between the drugs; however, this is not unexpected since pulmonary exacerbation was an exploratory endpoint and the study was of a limited duration (8 weeks). Data on the number of events or event rates of pulmonary exacerbations requiring IV antibiotics or hospitalization were not reported.

Table 3.12. Reported Annualized Pulmonary Exacerbation Rates in Patients Heterozygous for the *F508del* Mutation

EXPAND*[22]			
Follow-Up Duration	**8 weeks**		
	Placebo	**Kalydeco**	**Symdeko**
Modified Fuch's Criteria			
No. Subjects	161	156	161
No. PEx's	20	9	11
Estimated Event Rate per Year	0.63	0.29	0.34
Rate Ratio vs. Placebo	-	0.46	0.54
95% CI	-	(0.21 to 1.01)	(0.26 to 1.13)

PEx: pulmonary exacerbation; CI: confidence interval

*Pulmonary exacerbations requiring IV or hospitalization not reported

Harms

Frequencies of adverse events for all three CFTR modulators are reported in Table 3.13. Serious adverse events occurred less frequently in all modulators compared to placebo. Reasons for CFTR modulator discontinuation included elevated liver enzymes, creatinine kinase levels,[76] hemoptysis, bronchospasm, dyspnea, pulmonary exacerbation and rash.[16] No deaths during CFTR modulator trials were related to the drugs.

Table 3.13. Percent of Patients Reporting Adverse and Serious Adverse Events from RCTs

	Kalydeco				Orkambi		Symdeko			
	STRIVE[8]		KONDUCT[11]		TRAFFIC/TRANSPORT±[16]		EVOLVE[18]		EXPAND[22]	
	G551D		*R117H*		Homozygous *F508del*		Homozygous *F508del*		Heterozygous *F508del*	
	48 weeks		24 weeks		24 weeks		24 weeks		8 weeks	
	Active	Placebo	Active	Placebo	Active	Placebo	Active	Placebo	Active	Placebo
N	83	71	34	35	369	370	251	258	162	162
Any Adverse Event (AE)	82 (99%)	78 (100%)	32 (94%)	35 (100%)	351 (95.1%)	355 (95.9%)	227 (90.4%)	245 (95.0%)	117 (72%)	126 (78%)
Any AE Grade ≥3	NR	NR	NR	NR	NR	NR	22 (8.8%)	29 (11.2%)	4 (2%)	9 (6%)
Any Serious Adverse Event (SAE)	20 (24%)	33 (42%)	4 (12%)	6 (17%)	64 (17.3%)	106 (28.6%)	31 (12.4%)	47 (18.2%)	8 (5%)	14 (9%)
Any AE Leading to Discontinuation	1 (1%)	4 (5%)	0	0	17 (4.6%)	6 (1.6%)	7 (2.8%)	8 (3.1%)	0	1 (1%)
AE Resulting in Death	0	0	0	0	0	0	0	0	0	0
Most Common Adverse Events										
ALT Increased	3 (3.6%)	3 (3.9%)	NR	NR	10 (2.8%)	16 (4.4%)	8 (3.2%)	13 (5.0%)	1 (0.6%)	1 (0.6%)
AST Increased	3 (3.6%)	3 (3.9%)	NR	NR	11 (2.9%)	11 (3.0%)	NR	NR	1 (0.6%)	0
Infective PEx of CF	34 (41%)	50 64.1%)	13 (38%)	14 (40%)	132 (35.8%)	182 (49.2%)	75 (29.9%)	96 (37.2%)	21 (13%)	31 (19%)
Cough	27 (32.5%)	33 (42.3%)	10 (29%)	9(26%)	104 (28.2%)	148 (40%)	66 (26.3%)	84 (32.6%)	23 (14%)	16 (10%)
Increased Sputum	NR	NR	5 (15%)	4 (11%)	54 (14.6%)	70 (18.9%)	36 (14.3%)	42 (16.3%)	14 (9%)	11 (7%)
Dyspnea	NR	NR	NR	NR	48 (13%)	29 (7.8%)	16 (6.4%)	18 (7.0%)	9 (6%)	11 (7%)
Abnormal Respiration/Chest Tightness	NR	NR	NR	NR	32 (8.7%)	22 (5.9%)	11ǂ (4.4%)	11ǂ (4.3%)	2 (1.2%)	0
Hemoptysis	9 (10.8%)	17 (21.8%)	0*	6* (23%)	50 (13.6%)	50 (13.5%)	26 (10.4%)	35 (13.6%)	12 (7%)	14 (9%)
Diarrhea	11 (13.3%)	10 (12.8%)	5 (15%)	4 (11%)	45 (12.2%)	31 (8.4%)	17 (6.8%)	23 (8.9%)	13 (8%)	10 (6%)
Nausea	13 (15.7%)	9 (11.5%)	NR	NR	46 (12.5%)	28 (7.6%)	23 (9.2%)	18 (7.0%)	9 (6%)	10 (6%)
Fatigue	NR	NR	NR	NR	NR	NR	16 (6.4%)	31 (12.0%)	12 (7%)	16 (10%)

NR: not reported ± TRAFFIC/TRANSPORT, 400 mg only; ALT/AST: alanine aminotransferase/aspartate aminotransferase

ǂ Chest discomfort=0%,

*Participants>18 years (24 ivacaftor; 26 placebo)

Common side effects of CFTR modulators include rash, dizziness, headache, and upper respiratory tract infection,[76] and nasopharyngitis.[6] Additional side effects are reported in Table 3.13. FDA labels for all three modulators include monitoring for elevated liver enzymes (alanine and aspartate transaminase) and cataracts, as these have been reported with CFTR modulator use.[76,6,25] Concomitant use of CFTR modulators with CYP3A inhibitors is not recommended due to drug interactions.

Through stakeholder input, ICER was told that chest discomfort (often reported as chest tightness or abnormal respiration), was one of the primary reasons for Orkambi discontinuation. In TRAFFIC and TRANSPORT, abnormal respiration was reported in 8.7% of individuals receiving 400 mg lumacaftor twice daily compared to 5.9% of individuals receiving placebo.[16] The long-term follow-up study, PROGRESS, reported rates of abnormal respiration between 10-17%.[19] Individuals in the placebo arm in TRAFFIC/TRANSPORT reported higher rates of chest tightness than those originally randomized to active drug out to 96-weeks.[19] Additionally, individuals with baseline ppFEV$_1$ < 70% predicted reported more chest tightness than those with baseline ppFEV$_1$ ≥ 70% (11-20% vs. 6-8%, respectively in the 400 mg lumacaftor twice daily arm).[19] A real world cohort study at the Johns Hopkins Cystic Fibrosis Center after Orkambi approval (n=116) showed that nearly 20% of patients reported chest tightness.[24]

For Symdeko, chest discomfort was reported as zero in the *F508del* homozygous population and 1.2% in the heterozygous population.[18,22]

Orkambi is reported to have significant drug interactions that are not seen with Symdeko.[6,25]

Meta-Analyses of Harms Across Interventions

Eleven publications provided data on rates of discontinuation due to adverse events. [4,8-10,15,16,18-20,22,77] The studies evaluated ivacaftor 300 mg/day (five studies), Orkambi 800/500 mg/day (five studies), Symdeko 100/300 mg/day (three studies), and placebo (eight studies). Studies or study arms of nonstandard doses were omitted from analysis. With one exception, described below, across studies, duration of intervention did not correlate with drug discontinuation rates by metaregression. Summary rates of discontinuation due to adverse events were: Kalydeco 1.2% (95% CI 0.3, 2.5), Orkambi 6.3% (95% CI 3.7, 9.6), Symdeko 2.5% (95% CI 0.1, 8.3), and placebo 2.1% (95% CI 1.1, 3.4) (Appendix D, Figures D12-15). The three Symdeko studies were heterogeneous, with a small study having a higher discontinuation rate (2/17, 11.8%) than the other two studies (0 and 2.8%) resulting in a wide confidence interval.[4] A crude comparison across interventions suggests that discontinuation due to adverse events is significantly more likely to occur with Orkambi than Kalydeco, Symdeko, or placebo, which all had similar rates of drug discontinuation due to adverse events. For Orkambi, no correlation with treatment duration was evident (by meta-regression) from four to 72 weeks (P=0.37); however, inclusion of the study arm of people on drug

for 96 weeks (with a discontinuation rate of 7.4%) yielded a significant correlation of 0.4% per month (95% CI 0.1, 0.7; P=0.018).

Two publications provided data on grade 3 or 4 severe adverse events.[18,22] The studies evaluated ivacaftor 300 mg/day (1 study), Symdeko 100/300 mg/day (2 studies), and placebo (2 studies). In both studies, the drugs were taken for 24 weeks. Summary rates of grade 3 or 4 severe adverse events were: Kalydeco 5.1% (95% CI 2.6, 9.9), Symdeko 5.3% (95% CI 0.8, 13.3), and placebo 8.4% (95% CI 3.6, 14.9) (Appendix D, Figures D16- 17).[18] However, for both Symdeko and placebo, the reported rates of grade 3 or 4 severe adverse events were considerably lower in EXPAND than in EVOLVE; this resulted in statistical heterogeneity between the two studies. Nevertheless, within and across studies, all interventions had similar rates of grade 3 or 4 severe adverse events.

Controversies and Uncertainties

Many factors limit or complicate our ability to interpret the clinical benefits of CFTR modulators. Perhaps the largest limitation is the complexity of CF genetics, which directly impact disease severity and progression. Each population reviewed–gating and residual function mutations (Class III), heterozygous *F508del*, and homozygous *F508del* (Class II)–has unique genetic and disease variability marked by a general deterioration in lung and pancreatic function. As such, interpreting clinical trial outcomes from relatively small samples in short periods of time (one year or less), may provide a limited picture of clinical benefit. In addition, the FDA approval of Symdeko was not limited to the population studied in the EXPAND trial which required at least one *F508del* mutation. Therefore, we cannot state with any certainty, how generalizable the results from EXPAND are to patients with different genetic makeup.

Additionally, the myriad therapies employed in best-practice CF symptom management may increase the uncertainties of the benefits of CFTR modulators. Standard-of-care treatments include dornase alfa and hypertonic saline; azithromycin, tobramycin, and aztreonam are also used in those with *Pseudomonas aeruginosa* infections. Data from the CFFPR indicate 88% of registry patients use dornase alfa and 70% use hypertonic saline; of those who are *Pseudomonas aeruginosa*-positive, two-thirds or more use inhaled tobramycin and azithromycin (69% and 66%, respectively), 43% use inhaled aztreonam, and most participants in CFTR modulator trials were concurrently taking some or all these standard-of-care treatments during study treatment. As expected, these interventions positively impact pulmonary status in many or most patients. Both dornase alfa and tobramycin have been shown to improve FEV_1 in children with CF (3-6% and 8-20%, respectively).[8,71] In contrast, hypertonic saline use, which was shown to decrease the risk of pulmonary exacerbations by 66% compared to placebo[8], was not permitted during Kalydeco Phase III trials, a restriction which may limit the applicability of the study to typical care. The open-label extension study allowed the use of hypertonic saline; however, no data was available for our review. These interactions should be systematically evaluated in future studies.

Interpreting lung function using FEV_1 comes with numerous uncertainties. FEV_1 is a surrogate measure of disease severity that attempts to measure lung function relative to what is predicted in healthy persons of the same age and sex. Despite being well-defined in literature and widely used in clinical trials and clinical practice, it remains unclear what magnitude of change in FEV_1 is clinically relevant. While there is precedent for FDA approval based on 2-3% absolute change in ppFEV1, it is unclear how this translates to improved survival and/or quality of life. Similarly, the lung clearance index is a new surrogate outcome that has had limited long-term use. While validation studies are ongoing, there have also been debates about which tracer gas is most optimal and adequate training and diffusion of the procedure. There are also few direct correlation studies between lung function surrogates such as ppFEV1 and lung clearance index in people with CF and hard clinical endpoints such as lung transplant or death.[12]

Stakeholders identified uncertainties around CFTR modulator treatment decisions considering 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 not all patients will respond to CFTR modulator treatment the same or as predicted based on the study evidence.

Nearly 85% of people with CF in the United States 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 are likely with the addition of appropriate CFTR modulators. We identified uncertainties, however, regarding whether beneficial gains in survival are distributed unequally due to differences in access to US CF care centers. For example, Canadian CF patients have been living longer since the mid-1990s and currently live, on average, 10 years longer than American CF patients.[26,27] When comparing the US and Canada, the difference between Canadian and US survival disappeared when US patients receiving Medicare and Medicaid were excluded from survival data, suggesting CF patients receiving care through US public health insurance have a survival disadvantage.[26,28] It is unclear whether patients are receiving different care depending on their insurance type or whether American CF patients with public insurance are more likely to have important socioeconomic disadvantages that affect their CF management. While long-term studies are underway to evaluate the impact of CFTR modulators on long-term survival, ensuring access to the highest quality CF care in the interim may improve the survival of all CF patients.

Evaluating "adverse events" in studies of people with CF is challenging because the most frequently reported events in studies are likely not side effects due to the drugs, but instead are adverse outcomes due to the underlying disease that occur while patients are taking the drugs. The "adverse events" reported across all trials included outcomes expected with CF, like cough or

increased sputum production. For example, pulmonary exacerbation, a very common event for people with CF, was reported as both a clinical outcome and an adverse event, sometimes in the same study. Furthermore, across studies, specific adverse events commonly occurred more frequently among those taking placebo than those taking CFTR modulators; this was even found for adverse events that were ascribed to the drugs. For example, in STRIVE, serious adverse events were about twice as common with placebo than with ivacaftor;[8] in EXPAND, more patients taking placebo had adverse events considered by the investigator to be related or possibly related to the trial regimen with placebo than with Symdeko.[22]

Finally, cystic fibrosis is a multisystem disease, yet many aspects of the disease have not been systematically researched. Thus, our rating of the impact of CFTR modulators is highly dependent on those outcomes measured in the trial data, namely pulmonary function, weight, respiratory symptom-related quality of life and the number, type and annualized rate of pulmonary exacerbations.

3.4 Summary and Comment

Table 3.14. ICER Evidence Rating for Use of Kalydeco for Cystic Fibrosis Caused by the *G551D*, non-*G551D* Gating, and *R117H* Residual Function Mutations.

Population/Genetic Group	ICER Evidence Rating
***G551D,* Other Gating, Non-*G551D* Gating Mutations, And *R117H* Residual Function Mutations**	
Kalydeco	A

Kalydeco for patients with cystic fibrosis caused by gating and residual function mutations:

- Kalydeco provides improvements in $ppFEV_1$ (5.0 to 10.7 percentage points in different populations), weight, and respiratory-symptom-related quality of life (9.6 to 12.6 points) for children, adolescents, and adults (over 24 weeks). Longer-term follow-up (up to three years) shows lung function, weight, and quality of life gains are durable across all gating mutations.
- However, limited data suggest 6-11 year olds with the *R117H* mutation may not have improved respiratory function and quality of life with Kalydeco treatment.
- Pulmonary exacerbations were less frequent (HR=0.46), shorter, and required fewer hospitalizations and intravenous antibiotics for patients taking Kalydeco.
- Fewer patients (across populations) discontinued Kalydeco due to adverse events (1.2%) than with placebo (2.1%).

Across all subpopulations, rates of discontinuation due to adverse events and severe adverse events were similar for Kalydeco and placebo.

Given the relatively consistent evidence arising from 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 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.

Homozygous F508del mutations

Table 3.15. Evidence Rating for the Use of Orkambi for Cystic Fibrosis Caused by Two Copies of the *F508del* Mutation

Population/Genetic Group	ICER Evidence Rating
Homozygous F508del Mutation	
Orkambi	B
Symdeko	B+

Orkambi for patients with cystic fibrosis caused by two copies of the F508del mutation:

- Orkambi improved $ppFEV_1$; however, changes in absolute $ppFEV_1$ may not be considered clinically important (2.4 to 2.8 percentage points).
- At 24 weeks, BMI increases with Orkambi among those aged 12 years and older (0.61 kg/m^2), which was maintained over the subsequent 96 weeks; but no significant difference was found in a study of younger children.
- Treatment improved respiratory symptom-related quality of life in patients age 12 and older (2.2 points); a similar improvement was found in a smaller study of children 6-11 years old, but the effect was not statistically significant.
- The rate of pulmonary exacerbation was lower for patients aged 12 and older taking Orkambi (rate ratio = 0.61); data were not reported in the study of younger children.
- Chest tightness (abnormal respiration) was reported as a side effect for those taking Orkambi ranging from 8% in the Phase III trials to 20% in a real-world post-approval study.
- Rates of discontinuation due to adverse events were higher for Orkambi (4.6%) than for placebo (1.6%) within a trial in this population. Similar results were seen among all studies across populations (6.3% vs. 2.1%, respectively).

In two large Phase III trials and an accompanying 96-week open-label extension study, Orkambi provided a consistent magnitude of approximately 3 percentage point 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 for patients with cystic fibrosis caused by two copies of the F508del mutation:

- Treatment with *Symdeko* improved absolute ppFEV$_1$ (4.0 percentage points) and respiratory-related quality of life (5.1 points) compared to placebo over 24 weeks. No significant differences in weight were reported.
- Treatment reduced the rate of pulmonary exacerbation over 24 weeks (rate ratio = 0.53).
- In this population, rates of discontinuation due to adverse events were similar for Symdeko (2.8%) and placebo (3.1%). Similar results were seen among all studies across populations (2.5% vs. 2.1%, respectively).

A single, parallel-arm, Phase III trial showed a moderate improvement in ppFEV$_1$ however, the trial was relative short in duration. 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+").

Heterozygous F508del with a residual function mutation

Table 3.16. Evidence Rating for The Use of Symdeko For Cystic Fibrosis Caused by a Single Copy of The *F508del* Mutation with An Approved Residual Function Mutation

Population/Genetic Group	ICER Evidence Rating
Heterozygous F508del with Residual Function Mutation	
Symdeko	B+

Symdeko for patients with cystic fibrosis caused by one copy of the F508del mutation and a second mutation amenable to Symdeko:

- Treatment with Symdeko resulted in clinically relevant improvement in absolute ppFEV$_1$ (6.8 percentage points) and respiratory symptom-related quality of life (11.1 points).
- The treatment effect on pulmonary exacerbations and BMI was exploratory only due to small numbers and short duration

A single 8-week cross-over trial provided evidence of the 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+").

4. Long-Term Cost Effectiveness

4.1 Long-Term Cost Effectiveness

Overview

The objective of this analysis was to estimate the cost-effectiveness of CFTR modulator treatments plus best supportive care for CF patients. We modeled three different populations based on mutation status, and three different CFTR modulators or combinations of modulators that have indications in one or more CF populations. We evaluated Kalydeco for individuals with gating mutations, and Orkambi and Symdeko for individuals who are homozygous for the *F508del* mutation. For patients who are heterozygous for the *F508del* mutation with a residual function mutation, we evaluated Symdeko and Kalydeco as possible CFTR modulator treatments.

The model structure for this assessment is described below. CF is a condition which falls under ICER's ultra-rare disease framework. Therefore, we considered dual base-case analyses that reflect both health system and societal perspectives. While the impact of this disease on patient and caregiver productivity, informal caregiver time, education, and disability costs can be substantial, the impact of treatment with the CFTR modulators on societal costs is not expected to be as substantial, because the drugs do not greatly reduce the daily burdens associated with usual CF supportive care. We therefore present the results from a modified societal perspective as a scenario analysis rather than as part of the base case.

Outcomes were estimated over a lifetime time horizon using one-year time increments from treatment initiation until death. The primary health outcome was quality-adjusted life years (QALYs) but we also report life expectancy 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.[78] The impact inventory is provided in Appendix Table E1. Costs and health outcomes were discounted at 3% per year. The model was developed in TreeAge software version 2017 (Williamstown, MA). A preliminary version of the results in this section of the report were presented publicly on April 26, 2018 and included some data inputs based on 2016 costs; this version includes results generated from re-running the models with those data inputs updated to 2017 values.

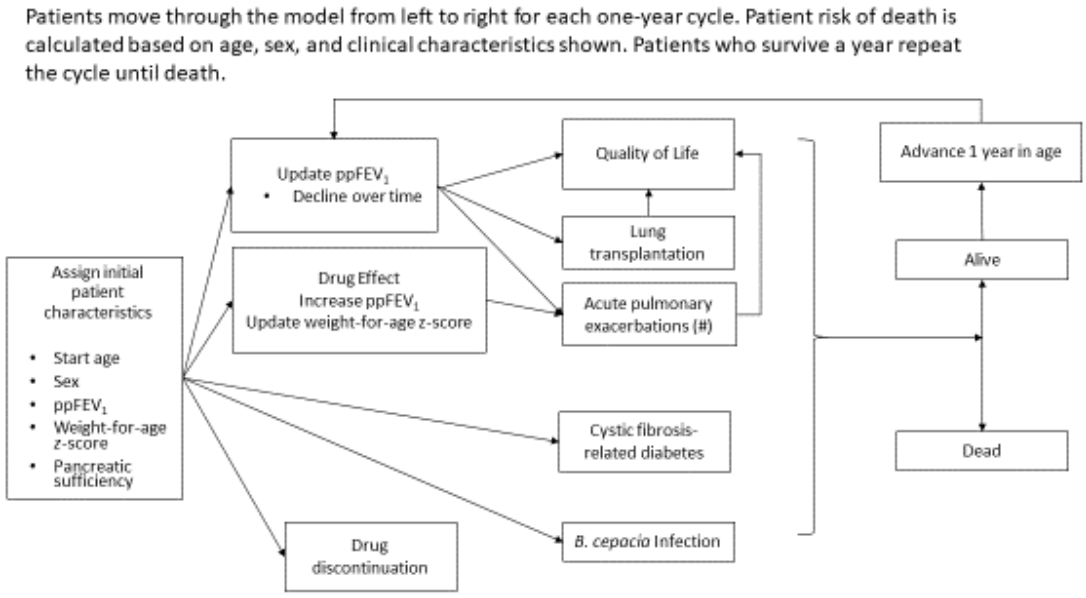
Cost-Effectiveness Model: Methods

Model Structure

We developed a *de novo* discrete-time microsimulation model. The primary model variable was percent predicted forced expiratory volume in one second ($ppFEV_1$), modeled as a continuous variable. This model type was chosen to account for the continuous nature of $ppFEV_1$ and to capture the primary effect of the CFTR modulator drugs (i.e., increase in $ppFEV_1$ or slowing the decline of $ppFEV_1$ over the longer term). For each population, a cohort of CF patients begins the model at the age of drug initiation. We assigned a gender distribution based on the current prevalent CF population.[1] 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. For example, for individuals with a *G551D* mutation we set the starting distribution so that the population 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).[8,9] In addition to $ppFEV_1$, the model tracked the values of other variables for each simulated person: 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 CF-related diabetes or *B. cepacia* infection. During any given year, a simulated person may experience a change in their $ppFEV_1$, experience one or more pulmonary exacerbations, be diagnosed with diabetes mellitus or *B. cepacia* infection, or undergo lung transplantation if their $ppFEV_1$ falls to 30% or below. The annual risk of death is influenced by all of these variables. Figure 4.1 shows a diagram of the model, with the risk of pulmonary exacerbation and lung transplantation dependent on the $ppFEV_1$ value. Persons are simulated for their lifetime, accumulating life years, QALYs (i.e., life years weighted by a quality-of-life value) and costs each year.

For the treatment arms, we allowed the initial $ppFEV_1$ and weight-for-age *z*-score values to change based on trial results or by assumption if no trial evidence existed. We also allowed the risk of acute pulmonary exacerbation to decrease with treatment, independent of the improvement in $ppFEV_1$.

Figure 4.1 Model Framework



Target Population

We considered three distinct populations for this analysis. The first population includes individuals with CF and gating mutations, such as the *G551D* mutation, consistent with the FDA-approved indications for Kalydeco. The age of treatment initiation is two years old, consistent with FDA labeling. The initial distribution of $ppFEV_1$ in this population was assumed to be normal with a mean (SD) of 96.37 (12.02). The second population includes individuals with CF who are homozygous for the *F508del* mutation. This population is eligible for treatment with Orkambi or Symdeko, and we assumed that the age of treatment initiation was six years old for both treatments given that recommended age for Symdeko will likely be lowered with additional trials, as was the case for Orkambi. The initial distribution of ppFEV1 in this population was assumed to be normal with a mean (SD) of 88.09 (13.39). The third population includes individuals with CF who are heterozygous for the *F508del* mutation and a residual function mutation that is potentially responsive to Symdeko. This population is eligible for treatment with Symdeko combination or Kalydeco, and the age of treatment initiation is 12 years old. The initial distribution of ppFEV1 in this population was assumed to be normal with a mean (SD) of 81.93 (15.41). For all populations, we truncated the $ppFEV_1$ distributions at a mimimum of 44 and maximum of 134. We did not evaluate treating individuals with CF and the *R117H* mutation (although evidence is summarized in Section 3) because this is a small population with very limited trial evidence and a substantially different prognosis compared with individuals with gating mutations.

We found that individuals with gating mutations or who are homozygous for the *F508del* mutation are similar in terms of their expected $ppFEV_1$ trajectories and in terms of other variables (e.g., pancreatic sufficiency). In general, individuals heterozygous for the *F508del* mutation with a residual function mutation have a better prognosis, and have a higher percentage with pancreatic sufficiency.[22,79]

We assumed that best supportive care consists of the following pulmonary and pancreatic therapies (percent utilization): dornase alfa (87.5%), inhaled tobramycin (69.4%), inhaled aztreonam (43.2%), azithromycin (65.5%), hypertonic saline (70.7%), oxygen (10.4%), non-invasive ventilation (2.8%), pancreatic enzyme replacement therapy (86.5%) and supplemental feeding (tube or oral, 56.4%).[1] Individuals with or developing CF-related diabetes were assumed to require oral hyperglycemic agents (3.9%), intermittent insulin (5.9%) and chronic insulin (76.3%), 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. Acute pulmonary exacerbations were defined as those that involve treatment with IV antibiotics either in the hospital or with home treatment. We estimated disease management costs for all CF individuals, including annual clinic visits and all other costs except those for acute pulmonary exacerbations and lung transplantation; the disease management costs varied by level of $ppFEV_1$. Acute pulmonary exacerbations and lung transplantation were costed separately. The rationale for this approach was that the disease management costs for a given level of $ppFEV_1$ will 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.

Treatment Strategies

For each population, we compared the eligible CFTR modulator treatment(s) plus best supportive care 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 4.1).

Table 4.1. Key Model Assumptions

Assumption	Rationale
ppFEV$_1$ does not increase over time.	We made this assumption because average lung function generally declines with age.
Best supportive care is the same in all treatment arms, given the same ppFEV$_1$ category.	We only assume that CFTR modulator therapy will have an impact on costs associated with acute pulmonary exacerbations, lung transplantation, and ppFEV$_1$-specific disease management. All other costs of supportive care not associated with lung function (e.g., pancreatic insufficiency, CF-related diabetes)will not be affected by CFTR modulator therapies, which has been supported by limited data.
The weight-for-age *z*-score is constant over the lifetime of a patient.	There is limited evidence for how weight-for-age z-score changes over time and this assumption has been used in other CF economic evaluations.
The risk of *B. cepacia* infection over time does not depend on lung function severity.	The occurrence of *B. cepacia* infection was incorporated only because it impacts CF-specific mortality risk and was modeled only as a function of age.
The drug effects are modeled as an increase in ppFEV$_1$, an increase in weight-for-age *z*-score, and a decrease in the annual number of acute pulmonary exacerbations relative to best supportive care alone.	These are the well-documented effects of CFTR modulator drugs.
CFTR drugs decrease the annual number of acute pulmonary exacerbations through the increase in ppFEV1 (the risk of exacerbations depends on lung function). There is also an independent effect of drugs on acute pulmonary exacerbation, independent of the lung function effect.	Modeling the impact of ppFEV$_1$ changes and an independent effect of drug treatment on acute pulmonary exacerbation rates allowed us to calibrate to the reductions in exacerbations observed in clinical trials.
Treatment discontinuation rates are the same as those reported in the trials. There is no further drug discontinuation after the end of the trial time horizon.	Because we used trial effectiveness estimates, we assumed the same percentage of patients are taking the drug in the model as in the trials, irrespective of available data on real-world discontinuation.

Model Inputs

Clinical Inputs

We modeled the ppFEV$_1$ trajectories through age-specific annual declines.[35,80] 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 or who are homozygous for the *F508del* 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.[81-83] The annual risk of lung transplant was 0% for individuals with ppFEV$_1$ >30% as

per guidelines.[84] The annual risk of diabetes was modeled as a function of age and sex.[85] We assumed that 5% of CF individuals with a gating mutation or who are homozygous for the *F508del* mutation had pancreatic sufficiency at diagnosis and that this proportion was stable over lifetime.[86] For CF individuals heterozygous for the *F508del* mutation with a residual function mutation, we estimated that 84% had pancreatic sufficiency at diagnosis based on the EXPAND trial population.[22] 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.[69] The risk of *B. cepacia* infection over time was derived from age-specific prevalence values from the CFF Registry and does not depend on lung function severity.[1] Base-case values are listed Table 4.2.

Table 4.2. Key Model Inputs

	Baseline Value	Source
Annual Decline in ppFEV$_1$		
Age 6-8 years	-1.12 (-2.00 for gating or *F508del* homozygous mutation*)	Konstan, 2007;Konstan, 2012[35,80]
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[81,82]
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[83]
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[81]
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[87]
ppFEV$_1$ ≤30	0.647	
Annual Risk of CF-Related Diabetes (Male, Female)		
Age 0-9	0.008, 0.016	Adler, 2008[85]
Age 10-19	0.039, 0.060	
Age 20-29	0.049, 0.071	
Age 30-39	0.065, 0.072	
Age 40+	0.051, 0.029	

*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

To model the treatments' effects, we assumed that there is an immediate increase in $ppFEV_1$ and improvement in weight-for-age *z*-score, as observed in the trials or by assumption if no trial evidence existed (Table 4.3). We assumed no $ppFEV_1$ decline on drug for the first two years and then a decline that is 50% of the best supportive care rate thereafter.[68,74] We assumed that the increase in weight-for-age *z*-score would persist for a patient's lifetime.[68]

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 + best supportive care versus best supportive care alone was 0.56.[8] 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 $ppFEV_1$. We assumed that Kalydeco also had an independent effect on the reduction in acute pulmonary exacerbations by reducing the chance that an individual will experience an exacerbation and reducing the number of multiple acute pulmonary exacerbations among those patients experiencing at least one exacerbation. We varied these assumptions until the model-generated rate ratio was 0.56. The independent effect from Kalydeco for CF individuals with gating mutations was to reduce the risk of exacerbation and the number of multiple exacerbations (given at least one) by 22%. This approach assumes that the reduction in exacerbation rate was a combination of a lower percentage of patients experiencing an exacerbation in a year and fewer exacerbations among those who do experience at least one.

Table 4.3. 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
CF Individuals with a Gating Mutation				
Kalydeco	10.0 (4.5-15.5)	0.56	0.35 (0.20-0.51)	Davies, 2013;Ramsey, 2011;Borowitz, 2016;McKone, 2014[8,9,15,69]
CF Individuals Who are Homozygous for the *F508del* Mutation				
Orkambi	2.8 (1.8-3.8)	0.44	Same as above	Wainwright, 2015;Konstan, 2017;Taylor-Cousar, 2017; NICE, 2016[16,18,19,88,89]
Symdeko	4.0 (3.1-4.8)	0.54†	Same as above	
CF Individuals Who are Heterozygous for the *F508del* Mutation with a Residual Function Mutation				
Symdeko	6.8 (5.7-7.8)	0.54 (0.26-1.13)‡	Same as above	Rowe, 2017[22]
Kalydeco	4.7 (3.7-5.8)	0.46 (0.21-1.01)‡	Same as above	

*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.

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

‡RR reported for pulmonary exacerbations defined by modified Fuch's 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[90] 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.[91] The Liou analysis also found that *S. aureus* infection was an independent predictor of mortality; however, the impact of infection was to decrease the mortality rate. Because we found no explanation as to why infection with *S. aureus* would be associated with better survival, and because of the recent rise in methicillin resistant *S. aureus*[1], we opted to not include this characteristic in the mortality rate function. The following equation was used to model the annual mortality rate for age *a* (h_a) for non-transplanted patients[91]:

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

$$K = 0.15(SEX - 0.47) - 0.042(ppFEV_1 - 67.7) - 0.0280(WFA + 0.85) + 0.350(\#PE - 1.1) + 0.440(DIAB - 0.061) - 0.140(PS - 0.053) + 1.410(BAI - 0.032) - 0.280(\#PE - 1.1)(BAI - 0.032)$$

The patient-specific parameters that affect mortality among non-transplanted patients were *SEX* (0 male, 1 female), *ppFEV₁* (%), *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 () was a product of the age-specific rates from the US life tables[90] and an adjustment factor that was needed to match the life expectancy targets of a CF cohort. Survival after lung transplant was a function of time since transplant and was better than prior to transplant.[87]

Utilities

We used the linear interpolation of EQ-5D utilities by $ppFEV_1$ conducted by Schechter et al. (Table 4.4).[92] These utilities were used to weight each year of life to accumulate QALYs over an individual's lifetime. 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 cystic fibrosis patients provided to Tappenden et al. for a NICE economic evaluation.[93] 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 during the year in which an acute pulmonary exacerbation occurred.[93] We used the same utility used by Schechter et al.[92] for the first year after lung transplantation (0.32) based on quality of life study of lung transplantation in patients with cystic fibrosis.[94] Subsequent years after transplantation were set to a utility equivalent to a $ppFEV_1$ of 70%-79%: 0.838.

Table 4.4. 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

Adverse Events

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

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. We therefore used data from the Federal Supply Schedule (FSS) to determine discounted (net) prices of Kalydeco and Orkambi (Table 4.5).[29] The FSS is a price schedule set forth by the U.S. General Services Administration (GSA) that is used in negotiation with manufacturers of drugs, medical equipment, and supplies and service contracts for the VA and other federal organizations. As Symdeko was only recently approved by the FDA, information on its net pricing was not yet available. We therefore applied the FSS discount rate for Orkambi (3.2%) to the wholesale acquisition cost (WAC) of Symdeko to arrive at an estimated net price.

Table 4.5. Drug Cost Inputs

Intervention	Administration	Unit	WAC per Unit/Dose*[95]	Net price per Unit†	Annual Drug Cost
Kalydeco	Oral twice daily	150mg tablet	$426.72	$424.15	$309,841.58
Orkambi					
Age 6-11 years	Oral, 2 tablets twice daily	100mg/125mg	$186.78	$180.76	$264,085.53
Age 12+ years	Oral, 2 tablets twice daily	200mg/125mg	$186.78	$180.76	$264,085.53
Symdeko	Oral (once/twice) daily	100mg/150mg	$400.08	$387.20	$282,656.00

*WAC as of January 12, 2018

†FSS prices as of January 2, 2018

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.[82,96,97] For

example, Dilokthornsakul et al. assumed that the prices of Kalydeco and Orkambi would drop to 10% of WAC after patent expiration.[96,97] 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.[98,99] 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 recently evidenced by 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.[100] 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 healthcare 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 transplant-related costs. We used an approach similar to that taken by Dilokthornsakul et al. in their cost-effectiveness analyses.[96,97] Both disease management and 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).[30] An age-related adjustment (<18 or 18+) was included in the exacerbation component. The 2016 CFF 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.[1] This resulted in a lower cost per exacerbation for adults.

Average cost estimates based on 1996 data[30] do not include all currently available CF treatment and therefore are not likely reflective of current best supportive care costs. Several other studies have found higher average annual medical costs even after adjusting for inflation[101];[102]. To derive current best supportive care costs, we used two average annual cost estimates provided by Scott

Grosse from the CDC based on his analysis of 2016 commercial payer and Medicaid claims data ($130,879 and $83,173 in 2016 US dollars) (S. Grosse, personal communication, April 12, 2018). We applied a 5% reduction to account for transplant-related costs, excluded CFTR-related costs, and updated to 2017 US dollars using the personal consumption expenditure (PCE) price index. We then calculated a weighted average based on health insurance information reported in the 2016 CFFPR showing a 60%/40% insurance mix (private/other).[1] This resulted in an average annual cost estimate of $77,143, which was used to calibrate the best supportive care cost estimates.

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 transplant and initial year following a transplant were derive from a 2017 Milliman Research Report.[103] 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.[104] The CF-related disease management and exacerbation costs were assumed to be zero for individuals in post-transplant years.

Cost estimates are shown in Table 4.6 and are reported in 2017 US dollars.

Table 4.6. Direct Costs by Disease Severity

	$ppFEV_1 \geq 70\%$	$ppFEV_1$ 40%-69%	$ppFEV_1 < 40\%$
Disease Management	$25,367	$33,462	$57,210
PEx* (age <18)	$52,988	$83,956	$124,386
PEx* (age 18+)	$48,015	$76,322	$109,372
Lung Transplant	$905,191		
Post-Transplant (Year 1)	$273,665		
Post-Transplant (Year 2+)	$103,913		

*PEx = acute pulmonary exacerbation requiring IV antibiotics

Productivity Costs

For the societal perspective, we used data provided by CFF regarding employment status as a function of age and lung function. The data provided showed that employment rates for patients with $ppFEV_1 \geq 40\%$ were similar to the general population. However, employment rates were lower for patients with $ppFEV_1 < 40\%$. We estimated a 50% increase in the loss of productivity for patients with $ppFEV_1 < 40\%$ and assumed an average weekly wage of $857 (Bureau of Labor Statistics) plus a fringe rate. Thus, we assumed that changes in lung function increase the chance that a person is employed. We also added productivity losses to the cost of acute pulmonary exacerbations. Because there is no evidence on the impact the CFTR modulator therapies have on employment and education status, we were only able to model these effects through $ppFEV_1$.

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.[105] Angelis et al. did find that direct non-health care costs were of the same magnitude as direct health care costs (in the United Kingdom) but did not report societal costs by lung function category.[106] Therefore, we did not include impacts on caregiver costs in this analysis, given the lack of evidence that it varies by lung function or is impacted by CFTR modulators. 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.

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-effectiveness for a given willingness to pay (WTP) threshold (varying from $50,000 per QALY to $500,000 per QALY). 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 WTP thresholds.

Scenario Analyses

We performed four 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 we incorporated an additional decrease in $ppFEV_1$ that is not recovered when individuals experience a pulmonary exacerbation. This effect is supported by a study,[107] 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). [70] 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.

Model Validation

We used several approaches to validate the model. First, we provided preliminary methods and results to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we refined data inputs used in the model. 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.[1] We also performed model verification for model calculations using internal reviewers. Finally, we compared results to other cost-effectiveness models in this therapy area.

Cost-Effectiveness Model: Results

Base Case Results

The base case results are shown in Tables 4.7 and 4.8. All CFTR modulators are 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.

For individuals with a gating mutation, the total discounted lifetime costs for Kalydeco plus best supportive care and best supportive care only were approximately $8,666,300 and $2,227,800, respectively. The total discounted QALYs (and life years) for Kalydeco plus best supportive care and best supportive care alone were 22.65 (26.52) and 15.92 (22.16), respectively. The incremental cost-effectiveness ratios for Kalydeco in this population were approximately $956,800 per QALY gained and $1,476,500 per life year gained.

For individuals who are homozygous for the *F508del* mutation the total discounted lifetime costs for Orkambi, Symdeko and best supportive care were approximately $6,983,300, $7,478,700 and $2,108,200, respectively. The total discounted QALYs (and life years) for Orkambi, Symdeko and best supportive care were 20.21 (24.57), 20.25 (24.70) and 14.74 (20.77), respectively. The

incremental cost-effectiveness ratios for Orkambi and Symdeko versus best supportive care in this population were approximately $890,700 per QALY and $974,300 per QALY, respectively, and approximately $1,280,900 and $1,367,400 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 Kalydeco, Symdeko and best supportive care were approximately $7,557,600, $7,091,900 and $2,081,200, respectively. The total discounted QALYs (and life years) for Kalydeco, Symdeko and best supportive care were 18.74 (23.07), 18.88 (23.25) and 12.92 (18.98), respectively. The incremental cost-effectiveness ratios for Kalydeco and Symdeko in this population were approximately $941,100 per QALY and $840,600 per QALY, respectively, and approximately $1,340,200 and $1,174,500 per life year gained, respectively.

Table 4.7. Results for the Base Case for CFTR Modulators Plus Best Supportive Care (BSC) Compared to BSC Alone, By Study Population (Discounted at 3% per Year)

Population and Treatment	CFTR Drug Cost	Total Cost	Average Number of PEx	Total Life Years	Total QALYs
CF Individuals with A Gating Mutation					
BSC	$0	$2,227,765	32.75	22.16	15.92
Kalydeco Plus BSC	$7,443,121	$8,666,308	18.86	26.52	22.65
CF Individuals Homozygous for *F508del* Mutation					
BSC	$0	$2,108,199	26.02	20.77	14.74
Orkambi Plus BSC	$5,847,893	$6,983,336	11.45	24.57	20.21
Symdeko Plus BSC	$6,290,005	$7,478,684	13.36	24.70	20.25
CF Individuals Heterozygous for *F508del* Mutation with Residual Function Mutation					
BSC	$0	$2,081,180	25.51	18.98	12.92
Kalydeco Plus BSC	$6,447,156	$7,557,596	10.85	23.07	18.74
Symdeko Plus BSC	$5,934,935	$7,091,919	12.68	23.25	18.88

CFTR: cystic fibrosis-related diabetes; PEx: pulmonary exacerbations; QALYS: quality adjusted life years; BSC: best supportive care

Table 4.8. Incremental Cost-Effectiveness Ratios Compared to Best Supportive Care (BSC) for the Base Case

Treatment vs. BSC	Cost Per LY Gained	Cost Per QALY Gained	Cost Per PEx Averted
CF Individuals with a Gating Mutation			
Kalydeco Plus BSC	$1,476,543	$956,762	$463,571
CF Individuals Homozygous for *F508del* Mutation			
Orkambi Plus BSC	$1,280,892	$890,739	$334,495
Symdeko Plus BSC	$1,367,400	$974,348	$424,212
CF Individuals Heterozygous for *F508del* Mutation and Residual Function Mutation			
Kalydeco Plus BSC	$1,340,171	$941,110	$373,541
Symdeko Plus BSC	$1,174,508	$840,568	$390,600

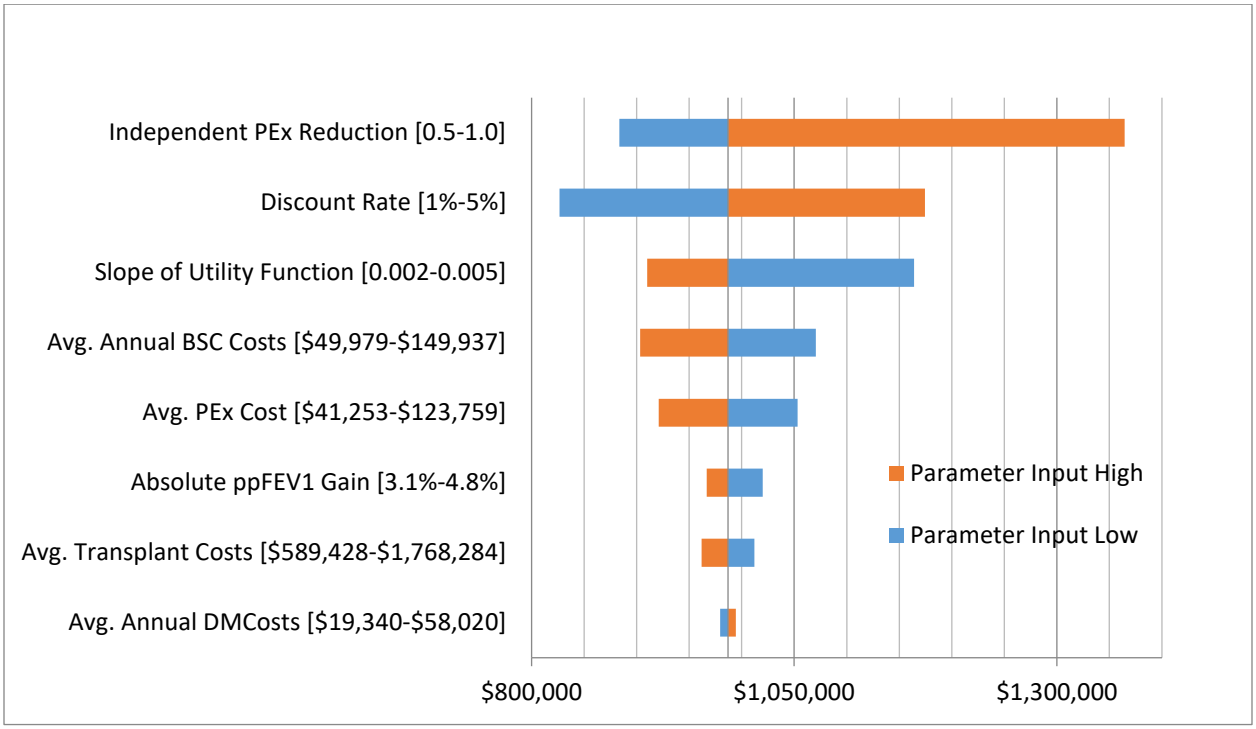
SBSC: best supportive care; LY: life year; QALY: quality adjusted life years; PEx: pulmonary exacerbation

Sensitivity Analysis Results

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e. 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). Drug cost variation is described more completely as part of threshold analyses (see below).

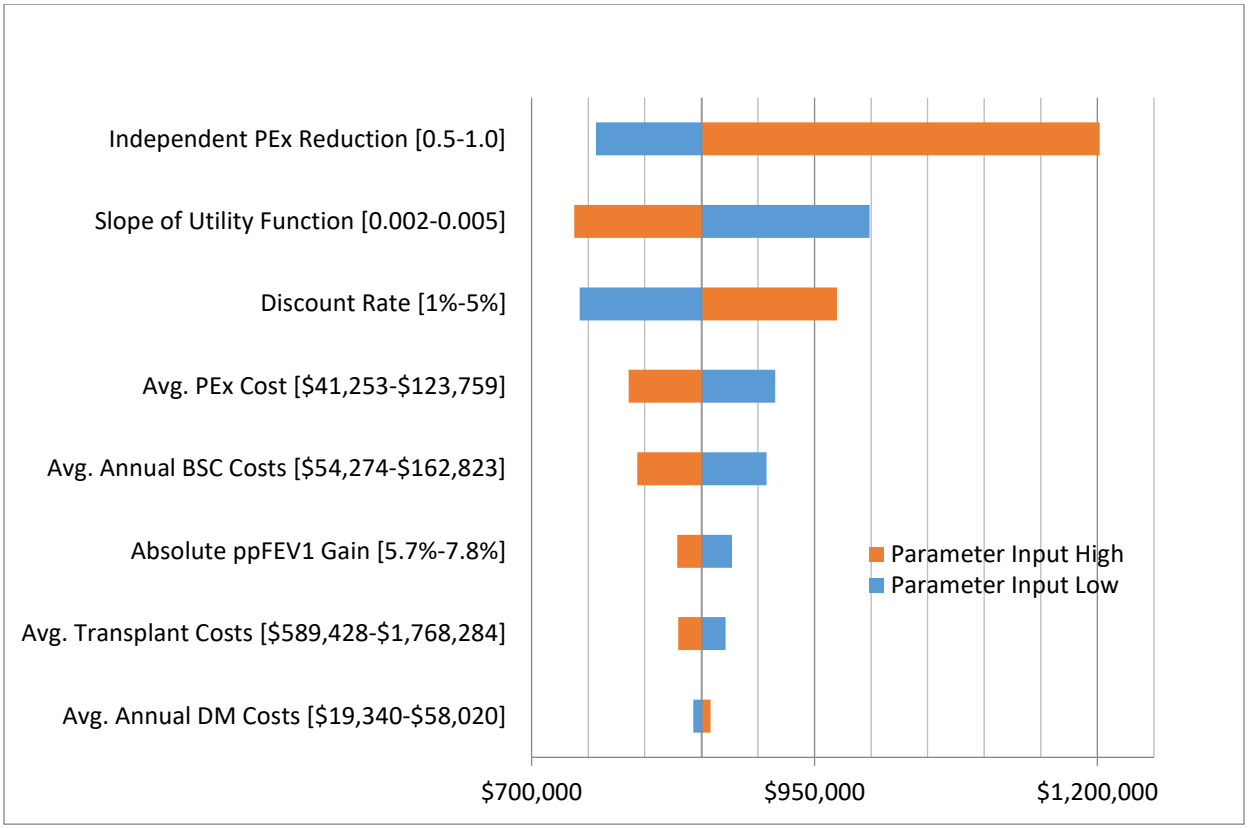
The impacts of variations in input values on cost-per-QALY estimates are shown for Symdeko in CF individuals homozygous for *F508del* mutation in Figure 4.2, and in individuals heterozygous for *F508del* mutation and residual function mutation in Figure 4.3. The analyses were most sensitive to assumptions about the independent effect of drugs on the reduction of acute pulmonary exacerbations, the discount rate, and lung function-specific utilities; while changes in the former resulted in large variation in cost-effectiveness estimates, these did not approach commonly cited thresholds. Also, while not shown in the Figure, 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 value (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 Figures E1-E3 in Appendix E.

Figure 4.2. 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; DM: disease management; Probability of transplant among individuals with $ppFEV_1$<30%.

Figure 4.3. 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, DM = disease management, Probability of transplant among individuals with $ppFEV_1$<30%.

We also evaluated the uncertainty in the model parameters simultaneously by conducting a probabilistic sensitivity analysis (Table 4.9). For all CFTR modulators in all CF populations evaluated, the number of iterations in which the CFTR modulators were cost-effective at a WTP threshold of $500,000 per QALY or less was approximately 0%. For example, the 95% credible interval for the incremental cost-effectiveness ratios for Kalydeco compared with best supportive care was $669,500 to $1,591,500 per QALY for CF individuals with gating mutations. Scatterplots showing the cost and effectiveness results from the probabilistic sensitivity analyses can be found in Figures E4-E6 in Appendix E.

Table 4.9. Probabilistic Sensitivity Analysis Results: CFTR Modulators Versus Best Supportive Care

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
CF Individuals with a Gating Mutation						
Kalydeco plus BSC	0%	0%	0%	0%	0%	0%
CF Individuals Homozygous for *F508del* Mutation						
Orkambi plus BSC	0%	0%	0%	0%	0%	0%
Symdeko plus BSC	0%	0%	0%	0%	0%	0%
CF Individuals Heterozygous for *F508del* Mutation and Residual Function Mutation						
Kalydeco plus BSC	0%	0%	0%	0%	0%	0%
Symdeko plus BSC	0%	0%	0%	0%	0%	0.2%

CFTR: cystic fibrosis transmembrane conductance regulator gene; BSC: best supportive care;

Scenario Analyses Results

Modified Societal Perspective

We incorporated the costs associated with lost productivity in individuals with CF (Table 4.10). For individuals with a gating mutation we projected that the difference in lifetime (discounted) indirect costs was $31,600. Including productivity losses in the analysis resulted in incremental cost-effectiveness ratios for Kalydeco very similar to those seen in the base case ($952,100 per QALY societal vs. $956,800 per QALY base case). Estimates for the incremental cost-effectiveness ratios for the CFTR modulators for the other two populations also tracked very closely with base case estimates (Table 4.10).

Table 4.10. Incremental Cost-Effectiveness Ratios Compared to Best Supportive Care (BSC) for the Societal Perspective

Treatment vs. BSC	Incremental Costs (Direct)	Incremental Costs (Indirect)	Cost Per QALY Gained
CF Individuals with a Gating Mutation			
Kalydeco plus BSC	$6,438,543	-$31,635	$952,061
CF Individuals Homozygous for *F508del* Mutation			
Orkambi plus BSC	$4,875,137	-$30,639	$885,140
Symdeko plus BSC	$5,370,485	-$30,891	$968,744
CF Individuals Heterozygous for *F508del* Mutation and Residual Function Mutation			
Kalydeco plus BSC	$5,476,416	-$26,054	$936,633
Symdeko plus BSC	$5,010,739	-$27,306	$835,987

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 declines in $ppFEV_1$ over an individual's lifetime) to 100% (i.e., the same annual declines as those on best supportive care after the first two years on drug) (Table 4.11). For CF individuals with a gating mutation, the incremental cost-effectiveness ratio for Kalydeco was $620,400 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 ICERs were found with other drugs and populations (Table 4.11).

Table 4.11. 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
CF Individuals with a Gating Mutation				
Kalydeco plus BSC	$620,428	$751,624	$1,271,535	$1,772,535
CF Individuals Homozygous for *F508del* Mutation				
Orkambi plus BSC	$566,976	$698,108	$1,191,460	$1,647,556
Symdeko plus BSC	$615,966	$761,672	$1,314,815	$1,886,539
CF Individuals Heterozygous for *F508del* Mutation and Residual Function Mutation				
Kalydeco plus BSC	$651,429	$774,607	$1,152,209	$1,443,267
Symdeko plus BSC	$580,459	$688,044	$1,038,188	$1,289,044

BSC: best supportive care

ppFEV$_1$ Recovery After Pulmonary Exacerbation Assumptions

In the base case we assumed that CF individuals' ppFEV$_1$ would fully recover to baseline following 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 4.12). For CF individuals with a gating mutation, the incremental cost-effectiveness ratio for Kalydeco was $737,900 per QALY when we assumed that there was a 5% absolute decline in ppFEV$_1$ for each pulmonary exacerbation experienced. Similar declines in ICERs were found with other drugs and populations (Table 4.12).

Table 4.12. 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
CF Individuals with a Gating Mutation			
Kalydeco plus BSC	$826,217	$749,865	$737,931
CF Individuals Homozygous for *F508del* Mutation			
Orkambi plus BSC	$732,581	$608,234	$569,114
Symdeko plus BSC	$827,295	$706,465	$678,570
CF Individuals Heterozygous for *F508del* Mutation and Residual Function Mutation			
Kalydeco plus BSC	$772,962	$641,731	$606,196
Symdeko plus BSC	$700,135	$595,378	$570,023

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., $ppFEV_1$, 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 4.13). For CF individuals with a gating mutation, the incremental cost-effectiveness ratio for Kalydeco was $836,500 per QALY when we assumed that there was a 5% increase in utility due to drug that in independent of lung function improvement. . Similar declines in ICERs were found with other drugs and populations (Table 4.13).

Table 4.13. 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
CF Individuals with a Gating Mutation				
Kalydeco plus BSC	$927,566	$901,055	$855,659	$836,511
CF Individuals Homozygous for *F508del* Mutation				
Orkambi plus BSC	$859,468	$830,519	$778,983	$756,152
Symdeko plus BSC	$940,146	$908,528	$852,381	$827,580
CF Individuals Heterozygous for *F508del* Mutation and Residual Function Mutation				
Kalydeco plus BSC	$911,513	$883,952	$833,545	$810,438
Symdeko plus BSC	$814,291	$789,831	$745,070	$724,539

BSC: best supportive care

Threshold Analysis Results

Unit and 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 Tables 4.14 and 4.15 respectively, for each CF population and CFTR modulator. Threshold prices were higher for the CF population heterozygous for *F508del* mutation and residual function mutation, and slightly higher for Orkambi compared with Symdeko for CF individuals homozygous for *F508del* mutation on an annual cost basis. A discount of approximately 37%-44% would be necessary to reach a cost-effectiveness threshold of $500,000/QALY. Larger discounts would be needed to achieve cost-effectiveness thresholds of $300,000 or less per QALY.

Table 4.14. Threshold Analysis Results Presented as Price per Unit

	WAC per Unit	Net Price per Unit	Unit Price to Achieve $50,000 per QALY	Unit Price to Achieve $100,000 per QALY	Unit Price to Achieve $150,000 per QALY	Unit Price to Achieve $200,000 per QALY	Unit Price to Achieve $300,000 per QALY	Unit Price to Achieve $500,000 per QALY
CF Individuals with A Gating Mutation								
Kalydeco	$426.72	$424.15	$75.49	$94.65	$113.82	$132.98	$171.32	$247.98
CF Individuals Homozygous for *F508del* Mutation								
Orkambi	$186.78	$180.76	$38.03	$46.42	$54.80	$63.19	$79.96	$113.50
Symdeko	$400.08	$387.20	$72.84	$89.62	$106.39	$123.17	$156.72	$223.82
CF Individuals Heterozygous for *F508del* Mutation and Residual Function Mutation								
Kalydeco	$426.72	$424.15	$82.54	$101.54	$120.54	$139.54	$177.54	$253.54
Symdeko	$400.08	$387.20	$79.29	$98.52	$117.75	$136.99	$175.45	$252.37

WAC: wholesale acquisition cost; QALY: quality adjusted life year gained

Table 4.15. Threshold Analysis Results Presented as Annual Prices

	Annual WAC	Annual Net Price	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
CF Individuals with A Gating Mutation								
Kalydeco	$311,719	$309,842	$55,145	$69,142	$83,146	$97,142	$125,149	$181,149
CF Individuals Homozygous for *F508del* Mutation								
Orkambi	$272,886	$264,090	$55,562	$67,820	$80,063	$92,321	$116,822	$165,824
Symdeko	$292,258	$282,850	$53,210	$65,467	$77,718	$89,976	$114,484	$163,501
CF Individuals Heterozygous for *F508del* Mutation and Residual Function Mutation								
Kalydeco	$311,719	$309,842	$60,295	$74,175	$88,054	$101,934	$129,693	$185,211
Symdeko	$292,258	$282,850	$57,921	$71,969	$86,016	$100,071	$128,166	$184,356

WAC: wholesale acquisition cost; QALY: quality adjusted life year gained

Note that Kalydeco and Symdeko are each used for treatment in two different populations. Therefore, we also calculated population-weighted threshold prices using estimated numbers of patients in each population. (We assumed approximately 3,000 CF individuals with gating mutations, 8,464 CF individuals homozygous for *F508del* mutation, and 6,195 CF individuals heterozygous for *F508del* mutation and residual function mutation.) The blended unit price for Kalydeco across both relevant populations varied from $80.24 at $50,000 per QALY, $99.29 at $100,000 per QALY, $118.35 at $150,000 per QALY and $251.73 at $500,000 per QALY. The blended annual prices across the two relevant populations at the $50,000, $100,000 and $150,000 per QALY threshold prices were approximately $58,600, $72,500 and $86,500, respectively, and at the

$500,000 per QALY threshold price was approximately $183,900. Blended unit prices for Symdeko across both of its relevant populations were $75.57 at $50,000 per QALY, $93.38 at $100,000 per QALY, $111.19 at $150,000 per QALY, and $235.89 at $500,000 per QALY. The blended annual prices across the two relevant populations at the $50,000, $100,000 and $150,000 per QALY threshold prices were approximately $55,200, $68,200 and $81,200, respectively, and at the $500,000 per QALY threshold price was approximately $172,300.

Prior Published Evidence on Costs and Cost-Effectiveness

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.

We identified two prior published, US-based cost-effectiveness analyses of CFTR modulator drugs, both from the same group. Dilokthornsakul and colleagues have modeled the long-term costs and outcomes of Kalydeco treatment of CF patients with the *G551D* mutation (2016)[97] and, more recently, Orkambi treatment of CF patients with homozygous *F508del* mutation (2017).[96] They developed a Markov model with a lifetime horizon and US payer perspective, comparing each treatment to usual care. Our model in the current analysis was informed by these prior models, and therefore shares some similarities, including time horizon, perspective, and the base-case assumption of 50% decline in efficacy two years after treatment initiation. The prior models 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[97] were undiscounted, results were also presented using a discount rate of 3%. Discounted incremental QALYs were 5.21, incremental lifetime costs approximately $3,527,000, and the base-case incremental cost–effectiveness ratio was approximately $680,000 per QALY (2013 US$ converted to 2017 using the personal consumption expenditure [PCE] price index). Our current model estimated incremental QALYs of 6.73, incremental costs of $6,438,543, and an incremental cost-effectiveness ratio of approximately $956,800 per QALY. Starting age for treatment in the earlier Kalydeco model was 25 years old, while we modeled treatment initiation at two years old. Kalydeco WAC was $426.72 per tablet, which was only slightly higher than the net price used in our analysis ($424.15), but Dilokthornsakul et al. assumed that the drug price would drop to 10% of that amount after patent expiration in 2027. This assumption, along with the later age of treatment initiation, may have led to the lower lifetime costs observed in the analysis by Dilokthornsakul and colleagues.

The same model was later adapted by Dilokthornsakul and colleagues to examine the lifetime costs and outcomes of Orkambi combination treatment of CF patients with homozygous *F508del* mutation.[96] Starting age for treatment with Orkambi was 25 years old, while the ICER analysis

modeled treatment initiation at six years old. The WAC for Orkambi was $117.88 per tablet, which was lower than the net price used in our analysis ($180.76). Dilokthornsakul et al. again assumed that the drug price would drop to 10% of WAC after patent expiration. Their analysis estimated a gain of 2.42 QALYs with an incremental lifetime cost of approximately $2,698,000, or approximately $1,115,000 per QALY (all discounted; costs converted to 2017 dollars). Our current model for Orkambi estimated incremental QALYs of 5.47, incremental lifetime costs of $4,875,137, and an incremental cost-effectiveness ratio of $890,739 per QALY. Again, the later age of treatment initiation and the assumption of a lower future price may have led to the lower lifetime costs calculated in this analysis than those from our current model.

Prior to these analyses, Whiting and colleagues had 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.[82] They modified a deterministic simulation model developed by Vertex Pharmaceuticals, adding in lung transplantations. This 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 $306,000 in 2017 US$), 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) to 5.26 (in the optimistic scenario), the latter being closest to our current model estimate of 6.73 incremental QALYs. The incremental cost-effectiveness ratio was estimated to vary between £335,000 and £1,274,000 per QALY (approximately $563,000 to $2,141,000 in 2017 US$).

4.4 Summary and Comment

We developed an individual-level microsimulation model to project the lifetime benefits and costs of CFTR modulator therapies for three different CF cohorts. The drugs increased lung function, increased weight-for-age *z*-scores, and decreased the number of acute pulmonary exacerbations and lung transplantations over the lifetime of individuals. The drugs did not impact non-lung aspects of the disease, nor did they decrease the need for CF-related supportive care. Overall, all drugs (plus best supportive care) evaluated were very effective compared with best supportive care alone in all populations studied, with quality-adjusted life year gains ranging from 5.47 to 6.73 (discounted). With (discounted) CFTR drug-related costs ranging from $4.9 million to $7.4 million, the incremental cost-effectiveness ratios of drugs plus best supportive care compared with best supportive care alone were approximately $0.9 million per QALY for all drugs in all populations considered. Our results were robust to variations to parameter estimates, adopting a societal perspective, or using life years gained as the health outcome, except for unit 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 are included in the model. As any surrogate marker of disease, it is not a perfect marker for progression. We did not have direct measures of CFTR modulator benefit on EQ-5D utilities above that associated with $ppFEV_1$. We conducted a scenario analysis to examine the potential impact of this and found that a 5% increase in non-respiratory-related utility would increase the ICER by approximately 13% for all drugs and populations. In addition, limited evidence exists about the drugs' impact on individual's ability to work or attend school, or the degree to which caregiver burden is reduced by CFTR modulator drugs. 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 improve patient health outcomes compared to best supportive care. Because of the high cost of these drugs, however, the cost of CFTR modulator therapies exceed commonly used cost-effectiveness thresholds. For ultra-rare diseases, decision-makers often give special considerations that lead to coverage and funding decisions at higher willingness-to-pay thresholds. We evaluated thresholds up to $500,000 per QALY and still found that drug prices would need to be reduced by about 40% to be considered cost effective at this threshold.

5. Other Benefits and Contextual Considerations

Our reviews seek to provide information on 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 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.

Table 5.1. Potential Other Benefits or Contextual Considerations (Not Specific to Any Disease or Therapy)

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.

5.1 Other Benefits

CF represents a major and lifelong burden to patients and their caregivers. As described in Section 1.5, 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 possible that there are improvements in the quality of life with CFTR modulator treatment that may not be fully reflected in our model estimate. However, we also heard from individual patients and their caregivers that use of CFTR modulators is typically additive to their daily burden of disease management, thereby increasing (rather than reducing) the complexity of managing the disease.

The time costs associated with CF and its complications are very large and extend over a lifetime. While the time costs of patients are, theoretically, accounted for when estimating QALYs, the time costs of their informal caregivers are very difficult to estimate.

5.2 Contextual Considerations

The major contextual consideration pertains to the fact that the evidence is sparse, especially for the long-term effects of CFTR modulators on the rate of progression of the disease. Our modeling analyses suggest that reductions in the rate of CF progression with these medications may improve both unadjusted and quality-adjusted life expectancy relative to supportive care alone. The magnitude and sustainability of such effects have yet to be reliably quantified.

Currently, the CFTR modulators are the only available intervention that targets the basic pathophysiology of the disease. Novel treatments, e.g., a triple combination of VX-445 and VX-659 (novel CFTR corrector) with tezacaftor and ivacaftor, and treatment advances that are likely to be realized in the next decade may be associated with better outcomes and may eventually substantially change the typical course of the disease.

With the uptake of systematic newborn screening in the last several years, an increasing number of CF patients are diagnosed early, before the onset of symptoms or the establishment of irreversible lung, pancreatic, liver, and other complications. Early and aggressive management of CF, with or without CFTR modulator therapy, is expected to change the course of the disease in these patients.

While CFTR modulator therapies may play a role in improving health, overall improvements in the management of care of the disease have substantially improved the prognosis for the CF population, possibly to the detriment of new therapies trying to prove a significant clinical response. However, even with these gains in longevity and quality of life over the last few decades, the United States still lags other comparable countries in terms of health benefits in the CF population.

6. Value-Based Price Benchmarks

Our value-based benchmark prices for Kalydeco, Orkambi, and Symdeko are presented in Table 6.1. As Kalydeco and Symdeko are each used for treatment in two different populations, we calculated blended threshold prices weighted by estimated numbers of patients in each population. For each drug, the discounts required to meet both threshold prices (>70%) are much greater than the currently assumed discount from WAC.

Table 6.1. Value-Based Benchmark Prices for Kalydeco, Orkambi, and Symdeko

	Annual WAC	Annual Net Price (with Mark-Up)	Annual Price to Achieve $100,000 per QALY	Annual Price to Achieve $150,000 per QALY	Discount from WAC to Reach Threshold Prices
Kalydeco	$311,719	$309,842	$72,533	$86,453	72% to 77%
Orkambi	$272,886	$264,090	$67,820	$80,063	71% to 75 %
Symdeko	$292,258	$282,850	$68,215	$81,225	72% to 77%

QALY: quality-adjusted life year

7. Potential Budget Impact

7.1 Overview

We used results from the same model employed for the cost-effectiveness analyses to estimate the total potential budgetary impact of Symdeko in cystic fibrosis, specifically for those heterozygous or homozygous for the *F508del* mutation. We used the WAC for Symdeko, an estimate of discounted WAC, and the cost-effectiveness threshold prices at $50,000, $100,000, and $150,000 per QALY in our estimates of budget impact. We did not include the other therapies modeled above in this potential budget impact analysis, given their established presence on the market.

7.2 Methods

Potential budget impact was defined as the total differential cost of using Symdeko plus best supportive care, 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.

The potential budget impact analysis included the candidate populations eligible for treatment: those patients with cystic fibrosis who may be eligible for Symdeko. To estimate the size of the potential candidate populations for treatment, we used inputs from the Cystic Fibrosis Foundation Patient Registry Annual Data Report (2016), which includes prevalence and treatment estimates from the Cystic Fibrosis Foundation Patient Registry.[1] In this analysis, we assumed that all CF patients homozygous for the *F508del* mutation over the age of six would be eligible for Symdeko. We also assumed that all patients over the age of 12 and heterozygous for an *F508del* mutation with an allowed residual function mutation were eligible for Symdeko. Note that while the approved FDA label for Symdeko allows treatment beyond those having one *F508del* mutation with a second mutation amenable to Symdeko, we did not include such patients because of the lack of published data on the number of individuals with less frequently occurring mutations, making it infeasible to calculate a reliable number of additional patients likely to be treated.

To calculate the number in the first population, we used the estimate of *F508del* mutation prevalence (24,901) multiplied by the percent who are homozygous (41%) as described by the CFFPR Annual Data Report (2016).[1] We then estimated the proportion of patients over the age of six years in the overall cystic fibrosis population (82.9%). Applying these proportions to the prevalent population, our budget impact model assumes 8,464 cystic fibrosis patients with two copies of the *F508del* mutation in the United States will be eligible for Symdeko. We assumed that 20% of these patients (1,693) would initiate Symdeko in each of the five years.

To calculate the population with heterozygous *F508del* mutation, we used the same estimate of *F508del* mutation prevalence (24,901) multiplied by the percent who are heterozygous (45.8%) as described by the Cystic Fibrosis Foundation Patient Registry Annual Data Report (2016).[1] We then multiplied by the proportion of patients over the age of 12 (66.9%) and subtracted the number of *G551D* and *R117H* patients (2,145) as defined in the 2016 CFF Patient Registry Annual Data Report (because these two mutations are not included on the Symdeko label).[1] Administration, 2018, 113} In total, our budget impact model assumes 6,195 cystic fibrosis patients with one copy of the *F508del* mutation will be eligible for Symdeko in the United States. This number may be understated because the approved FDA label for Symdeko allows treatment beyond those having one *F508del* mutation, so long as the mutation is responsive to Symdeko (through *in vitro* or clinical data).[6] We assumed that 20% of the patients (1,239) would initiate Symdeko in each of the five years.

ICER's methods for estimating potential budget impact are described in detail here and have recently been updated. The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

Briefly, we evaluate a new drug that would take market share from one or more drugs and calculate the blended budget impact associated with displacing use of existing therapies with the new intervention. For this analysis, in the population homozygous for the *F508del* mutation, we assumed that Symdeko (plus best supportive care) would replace Orkambi in 50% of eligible patients and would be added to best supportive care in 50% of the eligible patients being treated. According to the CFFPR Annual Data Report (2016), prescribing rates for Orkambi are 52.5% across all eligible patients.[1] For the population heterozygous for an *F508del* mutation with an allowed residual function mutation, we assumed that Symdeko (plus best supportive care) would replace Kalydeco in 50% of eligible patients and would be added to best supportive care in 50% of the eligible patients being treated. In the absence of data on treatment mix in this specific population, we based our assumption on the prescribing rate of Kalydeco in the *R117H* mutation population as a surrogate (approximately 50% of eligible patients).[1]

Using this approach to estimate potential budget impact, we then compared our estimates to an updated budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation (http://icer-review.org/wp-content/uploads/2018/03/ICER-value-assessment-framework-update-FINAL-062217.pdf), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent two-year period, and the contribution of spending

on retail and facility-based drugs to total health care spending. Calculations are performed as shown in Table 7.1.

For 2017-18, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $915 million per year for new drugs.

Table 7.1. Calculation of Potential Budget Impact Threshold

Item	Parameter	Estimate	Source
1	Growth in US GDP, 2017 (est.) +1%	3.20%	World Bank, 2016
2	Total health care spending, 2016 ($)	$2.71 trillion	CMS NHE, 2014
3	Contribution of drug spending to total health care spending (%)	17.7%	CMS National Health Expenditures (NHE), 2016; Altarum Institute, 2014
4	Contribution of drug spending to total health care spending ($) (Row 2 x Row 3)	$479 billion	Calculation
5	Annual threshold for net health care cost growth for ALL new drugs (Row 1 x Row 4)	$15.3 billion	Calculation
6	Average annual number of new molecular entity approvals, 2015-2016	33.5	FDA, 2017
7	Annual threshold for average cost growth per individual new molecular entity (Row 5 ÷ Row 6)	$457.5 million	Calculation
8	Annual threshold for estimated potential budget impact for each individual new molecular entity (doubling of Row 7)	$915 million	Calculation

7.3 Results

Table 7.2 illustrates the per-patient budget impact calculations for Symdeko in those homozygous for the *F508del* mutation, compared to current care assuming Orkambi plus best supportive care in 50% and only best supportive care in 50%. Potential budget impact is presented based on WAC ($292,258 per year), discounted WAC ($282,850 per year), and the prices to reach $150,000, $100,000, and $50,000 per QALY in this population ($75,166, $63,315, and $51,463 per year, respectively).

Table 7.2. Per-Patient Budget Impact Calculations Over a Five-year Time Horizon for Individuals Homozygous for *F508del* Mutation

	Average Annual Per Patient Budget Impact				
	WAC	Discounted WAC	$150,000/ QALY	$100,000/ QALY	$50,000/ QALY
Symdeko+BSC	$300,749	$292,545	$113,699	$98,765	$92,331
Orkambi+BSC (50%) & BSC (50%)	$183,418				
Difference	$117,331	$109,128	($69,719)*	($84,653)*	($91,078)*

WAC: wholesale acquisition cost, QALY: quality adjusted life year, BSC: best supportive care
*Indicates cost-saving

The average potential budgetary impact when using the WAC ($292,258) was an additional per-patient cost of approximately $117,300 and approximately $109,100 using the discounted WAC ($282,850). At the three cost-effectiveness threshold prices (at $50,000, $100,000 and $150,000 per QALY), there would be estimated cost savings, ranging from approximately $69,700 per patient using the annual price ($75,166) to achieve $150,000 per QALY to approximately $91,000 using the annual price ($51,463) to achieve a $50,000 per QALY cost-effectiveness threshold. Note that we estimate overall savings because while there would be increased costs from using Symdeko in addition to best supportive care, these additional costs would be more than offset by the replacement of Orkambi at net price by Symdeko at the much lower assumed threshold prices.

Table 7.3 illustrates the per-patient budget impact calculations for those with one *F508del* mutation and a residual function mutation, compared to current care assuming Kalydeco plus best supportive care in 50% and best supportive care in 50% of patients. We present the potential budget impact results based on WAC ($292,258 per year), discounted WAC ($282,850 per year), and the prices to reach $150,000, $100,000, and $50,000 per QALY for Symdeko in this population ($85,960, $71,922, and $57,883 per year, respectively).

Table 7.3. Per-Patient Budget Impact Calculations Over a Five-year Time Horizon for Individuals with *F508del* Mutation and Residual Function Mutation

	Average Annual Per Patient Budget Impact				
	WAC	**Discounted WAC**	**$150,000/ QALY**	**$100,000/ QALY**	**$50,000/ QALY**
Symdeko+BSC	$301,966	$293,776	$122,441	$110,212	$97,983
Kalydeco +BSC (50%) & BSC (50%)	$209,185				
Difference	$92,781	$84,591	($86,744)*	($98,973)*	($111,202)*

WAC: wholesale acquisition cost, QALY: quality-adjusted life year, BSC: best supportive care
*Indicates cost-saving

The average potential budgetary impact when using the WAC ($292,258) was an additional per-patient cost of approximately $92,800 and approximately $84,600 using the discounted WAC ($282,850). Importantly, at the three cost-effectiveness threshold prices (at $50,000, $100,000 and $150,000 per QALY), there would be estimated cost savings, ranging from approximately $86,700 per patient using the annual price ($85,960) to achieve $150,000 per QALY to approximately $111,200 using the annual price ($57,883) to achieve a $50,000 per QALY cost-effectiveness threshold. Again, it should be noted that these overall savings would result from the mix of increased costs from using Symdeko in addition to best supportive care as well as the potential savings from replacement of Kalydeco at net price by Symdeko at the much lower assumed cost-effectiveness threshold prices.

For the combined populations of interest, the annual potential budgetary impact of treating the entire eligible population with Symdeko over five years did not exceed the $915 million ICER budget impact threshold at discounted WAC and the three cost-effectiveness threshold prices for $50,000, $100,000, and $150,000 per QALY, but barely exceeded the threshold (by 2%) at WAC. The annual potential budgetary impacts of treating the entire eligible populations using net prices (discounted WAC) are compared to the $915 million threshold in Table 7.4. The potential annual budget impact we estimated for Symdeko in the combined populations is 95% of the $915 million annual budget impact threshold at the net price. While the total number of patients eligible for treatment with Symdeko is relatively low (n = 14,659), the increased cost per patient from using Symdeko over current treatment mix leads to a total estimate approaching the budget impact threshold.

Table 7.4. Estimated Total Potential Budget Impact of Symdeko for Treatment of Eligible Populations Using Net Prices Over a Five-year Time Horizon

	Eligible Population	N Treated per Year	Annual BI per Patient	Total BI (millions)	Percent of Threshold
Homozygous *F508del*					
Symdeko	8,464	1,693	$109,128	$552,527,040	60%
Heterozygous *F508del* with Residual Function Mutation					
Symdeko	6,195	1,239	$84,591	$312,510,796	34%
Total Eligible US CF Population*					
Symdeko	14,659	2,932	$172,274	$865,037,837	95%

BI: budget impact

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

8. Summary of the Votes and Considerations for Policy

8.1 About the Midwest CEPAC Process

During Midwest CEPAC public meetings, the Midwest CEPAC 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 Midwest CEPAC 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 Midwest CEPAC Panel during their deliberation, and help to shape recommendations on ways the evidence can apply to policy and practice.

After the Midwest CEPAC Panel votes, a policy roundtable discussion is held with the Midwest CEPAC 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 May 17, 2018 meeting, the Midwest CEPAC Panel discussed issues regarding the application of the available evidence to help patients, clinicians, and payers address important questions related to the use of CFTR modulator treatments for cystic fibrosis. Following the evidence presentation and public comments (public comments from the meeting can be accessed here, starting at minute 1:50:20), the Midwest CEPAC Panel voted on key questions concerning the comparative clinical effectiveness, comparative value, and other benefits and contextual considerations related to CFTR modulators. 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 Midwest CEPAC Panel members during the voting process.

In its deliberations and votes related to value, the Midwest CEPAC 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 X 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. Midwest CEPAC uses the ICER Evidence Rating Matrix as its conceptual framework for considering comparative clinical effectiveness.

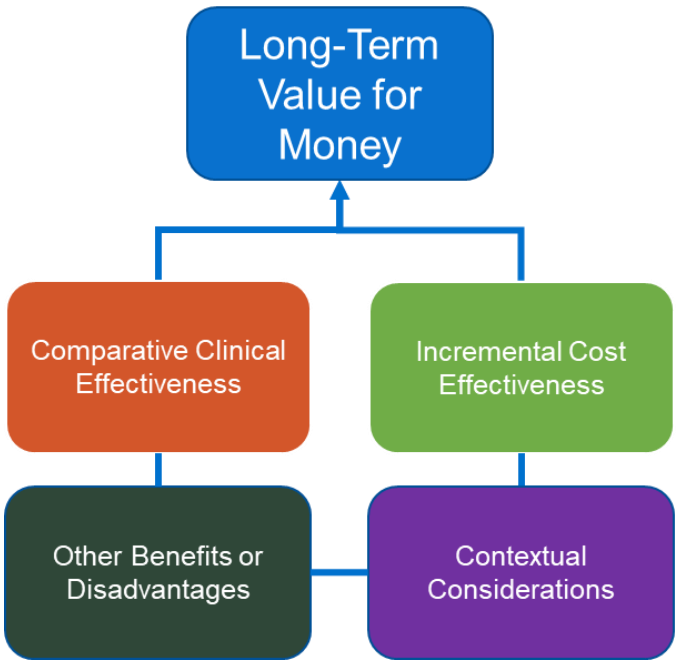
2. Estimated incremental cost-effectiveness is the average incremental cost per patient of one intervention compared to another to achieve a desired "health gain," such as an additional stroke prevented, case of cancer diagnosed, or gain of a year of life. Alternative interventions are compared in terms 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 Midwest CEPAC 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. 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 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 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 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 8.1 Conceptual Structure of Long-term Value for Money



8.2 Voting Results

Comparative Clinical Effectiveness

1) **For individuals with approved gating, non-gating, and residual function mutations (including but not limited to G551D and R117H), is the evidence adequate to demonstrate that the net health benefit of treatment with Kalydeco (ivacaftor) with best supportive care is greater than that of best supportive care alone?**

Yes: 12 votes	No: 0 votes

Comments: After some discussion of the relatively small sample sizes available for the Kalydeco trials, the panel voted unanimously in the affirmative, based primarily on the sizable improvements in lung function observed.

2) **For individuals who are homozygous for the F508del mutation, is the evidence adequate to demonstrate that the net health benefit of treatment with Orkambi (lumacaftor/ivacaftor) with best supportive care is greater than that of best supportive care alone?**

Yes: 11 votes	No: 1 votes

Comments: Prior to voting on this question, patient and clinical experts described some of the perceived differences between Orkambi and Kalydeco – for example, while Orkambi produces clinical benefit, the size of the benefit is modest in comparison to Kalydeco, which had already been on the market. However, Orkambi is available to a much broader set of patients, and for a different type of mutation with a different prognosis. Some panel members voiced hesitation about Orkambi's net health benefits due to adherence concerns due to the chest tightness sensations some patients experience.

3) **For individuals who are homozygous for the F508del mutation, is the evidence adequate to demonstrate that the net health benefit of treatment with Symdeko (tezacaftor/ivacaftor) with best supportive care is greater than that of best supportive care alone?**

Yes: 12 votes	No: 0 votes

Comments: The panel voted unanimously in the affirmative. Several panelists noted that Symdeko's clinical effectiveness was similar to that of Orkambi, but with a lower discontinuation rate due to adverse events.

4) **For individuals who are homozygous for the F508del mutation, is the evidence adequate to distinguish the net health benefit between treatment with Symdeko with best supportive care and Orkambi with best supportive care?**

Yes: 1 votes	***No: 11 votes***

Comments: While clinical experts mentioned that side effects and current stability on treatment might determine whether to choose Symdeko or Orkambi, the panelists' vote was driven by a lack of head-to-head comparisons of the two agents and the results of the indirect comparison, which were not statistically significant.

5) **For individuals who are candidates for Symdeko combination therapy because they carry one F508del mutation and residual function mutation that is potentially responsive to Symdeko, is the evidence adequate to demonstrate that the net health benefit of treatment with Symdeko with best supportive care is greater than that of best supportive care alone?**

Yes: 11 votes	No: 1 votes

Comments: Most of the panelists voted in the affirmative, noting a moderately-sized level clinical benefit. One panelist felt that the study design (8-week crossover trial) and small sample size precluded definitive conclusions at this time.

Other Benefits and Contextual Considerations

When compared to best supportive care, does Kalydeko, Orkambi, or Symdeko offer one or more of the following "other benefits"? (yes, no, uncertain)

Potential Other Benefits	# of votes
This intervention offers reduced complexity that will significantly improve patient outcomes.	4 / 12
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.	0 / 12
This intervention will significantly reduce caregiver or broader family burden.	8 / 12
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.	10 / 12
This intervention will have a significant impact on improving the patient's ability to return to work or school and/or their overall productivity.	7 / 12
This intervention will have a significant positive impact outside the family, including on schools and/or communities.	3 / 12
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.	2 / 12
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.	7 / 12

Comments: Panel members voted that modulator treatments for CF provide several other benefits that are not necessarily captured in the clinical data. There was some discussion over whether modulator treatments will reduce or increase complexity of treatment. One one hand, it is an additional pill to take and does not replace any existing treatments. However, a clinical expert noted that some patients who have been successful on Orkambi have been able to stop inhaled

antibiotics, which simplified their drug regimen. Four panelists voted that modulator treatments offer reduced complexity that will improve patient outcomes.

Ten panelists felt that modulator treatments provide a new mechanism of action, although a panelist who did not vote for this other benefit mentioned that it is unknown whether this new mechanism will actually allow for the successful treatment of patients who have been failed by other therapies.

Another benefit that several panelists noted was potential reductions in caregiver or broader family burden, based on a lower rate of pulmonary exacerbations and associated reductions in hospital days. These same benefits were also felt to have the potential effect of improving a patient's ability to return to work or school, and to have a positive impact outside the family.

Seven panelists voted that other benefits not listed above were also important. For example, one panelist said that modulator-related benefits like weight gain were inconsistently measured in clinical trials. Another panelist noted the potential for improved mental health of patients and caregivers the reduction in pulmonary exacerbations.

Are any of the following contextual considerations important in assessing Kalydeco's, Orkambi's, or Symdeko's long-term value for money in patients? (yes, no, uncertain)

Potential Other Contextual Considerations	# of votes
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.	12 / 12
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	12 / 12
This intervention is the first to offer any improvement for patients with this condition.	5 / 12
Compared to best supportive treatment, there is significant uncertainty about the long-term risk of serious side effects of this intervention.	3 / 12
Compared to best supportive treatment, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	10 / 12
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.	7 / 12

Comments: The panel unanimously voted that CF patients have a condition of particularly high severity and a high lifetime burden of illness. There was some discussion about whether this intervention is the first to offer improvement for patients with this condition. Modulator treatments are the first type of treatment to modify the disease mechanism itself, rather than addressing symptoms only. On the other hand, a clinical expert noted there are many treatment options available to patients with CF, and best supportive care for CF patients has improved greatly over the past few decades. Five panelists voted that this intervention is the first to offer

improvement, and several noted that they voted this way due to the modulators' novel mechanism of action.

Ten panelists voted that there is uncertainty about the long-term benefits of this intervention. Several panelists noted that, while there is early evidence that modulator treatments may slow the rate of decline of lung function over the long run, the magnitude of effect is currently very uncertain.

Long-Term Value for Money

Comments: When considering the long-term value for money of modulator treatments, the CEPAC panel discussed the treatment development process. The Cystic Fibrosis Foundation (CFF) played an integral role in funding the early research that led to CFTR modulator development. One panelist asked a representative from CFF if they attempted to exert control or influence over the price. The response was that the Foundation had concerns about sustainable pricing, but did not "have a seat at the table" when pricing decisions were made.

Following this discussion, the Midwest CEPAC panel voted on the long-term value for money of CFTR modulator treatments. In all cases, a majority of the panel voted that the long-term value of these therapies was low.

6) **For individuals with approved gating, non-gating, and residual function mutations (including but not limited to G551D and R117H), given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits and contextual considerations, what is the long-term value for money of Kalydeco with best supportive care compared with best supportive care alone?**

Low: 10 votes	Intermediate: 2 votes	High: 0 votes

7) **For individuals who are homozygous for the F508del mutation, given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits and contextual considerations, what is the long-term value for money of Orkambi with best supportive care compared with best supportive care alone?**

Low: 11 votes	Intermediate: 1 votes	High: 0 votes

8) **For individuals who are homozygous for the F508del mutation, given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits and contextual considerations, what is the long-term value for money of Symdeko with best supportive care compared with best supportive care alone?**

Low: 11 votes	Intermediate: 1 votes	High: 0 votes

9) **For individuals who are candidates for Symdeko combination therapy because they carry one F508del mutation and residual function mutation that is potentially responsive to Symdeko, given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits and contextual considerations, what is the long-term value for money of Symdeko with best supportive care compared with supportive care alone?**

Low: 11 votes	Intermediate: 1 votes	High: 0 votes

8.3 Roundtable Discussion and Key Policy Implications

Following its deliberation on the evidence, the Midwest CEPAC Panel engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on modulator treatments for cystic fibrosis to policy and practice. The policy roundtable members included one patient advocate, one caregiver, two clinical experts, and two payers. 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 8.1 Policy Roundtable Members

Name	Title and Affiliation
Mary Dwight	Senior VP of Policy and Advocacy, Cystic Fibrosis Foundation
Jeremy Olimb	Pastor, and father of children with cystic fibrosis
David Orenstein, MD, MA	Antonio J and Janet Palumbo Professor of Cystic Fibrosis, Children's Hospital of Pittsburgh
Manu Jain, MD, MS	Professor of Medicine and Pediatrics, Director of Adult CF; Feinberg School of Medicine, Northwestern University
Erik Schindler, PharmD, BCPS	Manager, Clinical Pharmacy; UnitedHealthcare Pharmacy
Jane Horvath, MHSA	Senior Policy Fellow, National Academy for State Health Policy

The roundtable discussion was facilitated by Dr. Steven Pearson, MD, MSc, President of ICER. The main themes and recommendations from the discussion are organized by type and summarized below.

Much of the policy roundtable discussion centered on the difficulty in balancing the very real benefits realized by patients and families from the advent of CFTR modulators, including the hope that future innovation will bring even more effective treatments to a broader segment of the CF community, with the concern that the high costs for these drugs contribute not only to the financial toxicity experienced by CF patients but to the rising difficulties in maintaining access to affordable care for everyone. At the root of this discussion were the high prices for CFTR modulators, prices that the ICER analysis and subsequent votes of the Midwest CEPAC found to be far too high to align in reasonable fashion with the benefits and cost-offsets of these drugs. 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. Key policy themes and recommendations for future action are highlighted below.

Key Recommendations on Pricing and Access

1. ***The prices for CFTR modulators are too high, harming patients and families today while threatening the health care system's ability to maintain access for all patients to important future clinical advances. Benefiting from monopoly pricing power, the company bears a significant social responsibility to change its pricing approach by committing to the following two actions:***
    - ***Abandon vague claims that prices are justified by the need to invest in future research and instead join the growing number of biotech innovators who provide a transparent, explicit justification for their prices based on the ability of treatments to improve the length and quality of patients' lives;***
    - ***Accept that the process for determining a reasonable price for new drugs requires innovators, especially those with monopoly pricing power at their disposal, to exercise restraint and be open to an independent process to evaluate fair pricing that includes the full engagement of the innovator, patients, patient advocacy groups, clinical experts, insurers, and other stakeholders.***

    The first CFTR modulator was approved six 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.

2. ***Public and private payers should continue to affirm their commitment to provide access to important clinical advances for CF and should remove superfluous requirements for coverage approval and continuation.***
   Payers need to strive to provide broad access to treatments that improve patients' lives while also seeking to control costs so that health care can be affordable for all. In the case of the CF 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 some payers impose unnecessary, and at times illogical, requirements for documentation prior to approval of insurance coverage. Examples include requirements for periodic genetic testing or other re-affirmation that a patient continues to have CF, a disease with immutable mutations and no current cure, or requiring that patients must be failed by supportive care medications before trying CFTR modulators, which are intended as *add-on* treatment to best supportive care rather than as a replacement. Such requirements pose an unnecessary burden, have no benefit for the patient, and do not engender trust in the payer by the treating clinician.

3. ***Since insurance coverage denial for CF drugs is off the table, payers should be willing to develop and adopt new approaches to moderate the impact of monopolistic pricing power.***
   Historically, both public and private payers have had limited bargaining power in situations where a single manufacturer exercises its pricing power in a rare and underserved disease. Depending on the degree of engagement by the manufacturer in efforts to determine a value-based price, it may be necessary for payers to develop new approaches that can give them the ability to reign in excessive pricing. One prominent example is the recent program implemented by the New York Medicaid program. Under its new budget law, the program is empowered to highlight medications that contribute to growth in pharmaceutical spending above a designated budget cap. Selected medications can be relegated to a public process in which New York's Drug Utilization Review Board (DURB) uses a variety of data points, including the results of independent drug value assessments, to determine a target price for supplemental rebate negotiation by Medicaid. If negotiations fail to reach at least 75% of the targeted rebate, the state has the right to require disclosure of research and development information from the manufacturer, along with other potential penalties.

Orkambi was the subject of the New York Medicaid meeting on April 26, 2018 and the DURB unanimously selected as a target price the price from the ICER report needed to meet a cost-effectiveness threshold of $150,000 per QALY. Further negotiations are ongoing, but the New York example already demonstrates how payers should explore additional tools that may give them additional leverage in moderating the health-system impact of excessively priced medications.

4. ***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.***
   In the policy roundtable discussion, the CF Foundation described its central role in fostering the development of CFTR modulators as well as convincing manufacturers of the benefits of investing in CF innovation. 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.

5. ***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.***
   Clinical experts on the roundtable agreed that the physician community could do more to advocate for fair and aligned pricing for the products they prescribe to their patients. 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.

Recommendations to Improve Future Research

1. ***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 evidence review showed 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. 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.

2. ***Manufacturer-sponsored research should enroll patients who are often encountered in clinical practice, but who are routinely excluded from clinical trials.***
   Clinical trials have often excluded patients who have a very high or very low ppFEV1, the very young, or those who have CF-related diabetes. Conducting studies in a broader set of populations can help assess hypothesized benefits of CFTR modulators across the spectrum of the disease, and allow payers to more readily accept the FDA's increasingly broad decisions regarding indicated populations for treatment. Evidence suggests that CFTR modulators slow the rate of progression of the disease; thus, it is reasonable (and some might argue more ethical) to conduct studies in younger patients or, more generally, in patients who do not yet have extensive irreversible organ damage. Finally, targeting patients with extra-pulmonary manifestations such as CF related diabetes can measure the effects of outside of the respiratory system.

3. ***Leverage all available resources to maximize the evidence base.***
   Because CF is relatively rare, effort should be made to maximize use of all existing data, including routinely collected information. There was considerable discussion of the CF Foundation's registry at the policy roundtable, which collects a considerable amount of data on approximately 95% of the CF patients in the U.S. While research on some of the evidence gaps discussed above is ongoing and publications are forthcoming, the CF Foundation should consider broadening researcher access to the underlying data, using innovative designs (e.g., nested clinical trials, N-of-1 studies), and other measures to speed the generation of publicly-available information on these important topics.

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This is the first ICER review of modulator treatments for cystic fibrosis.

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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

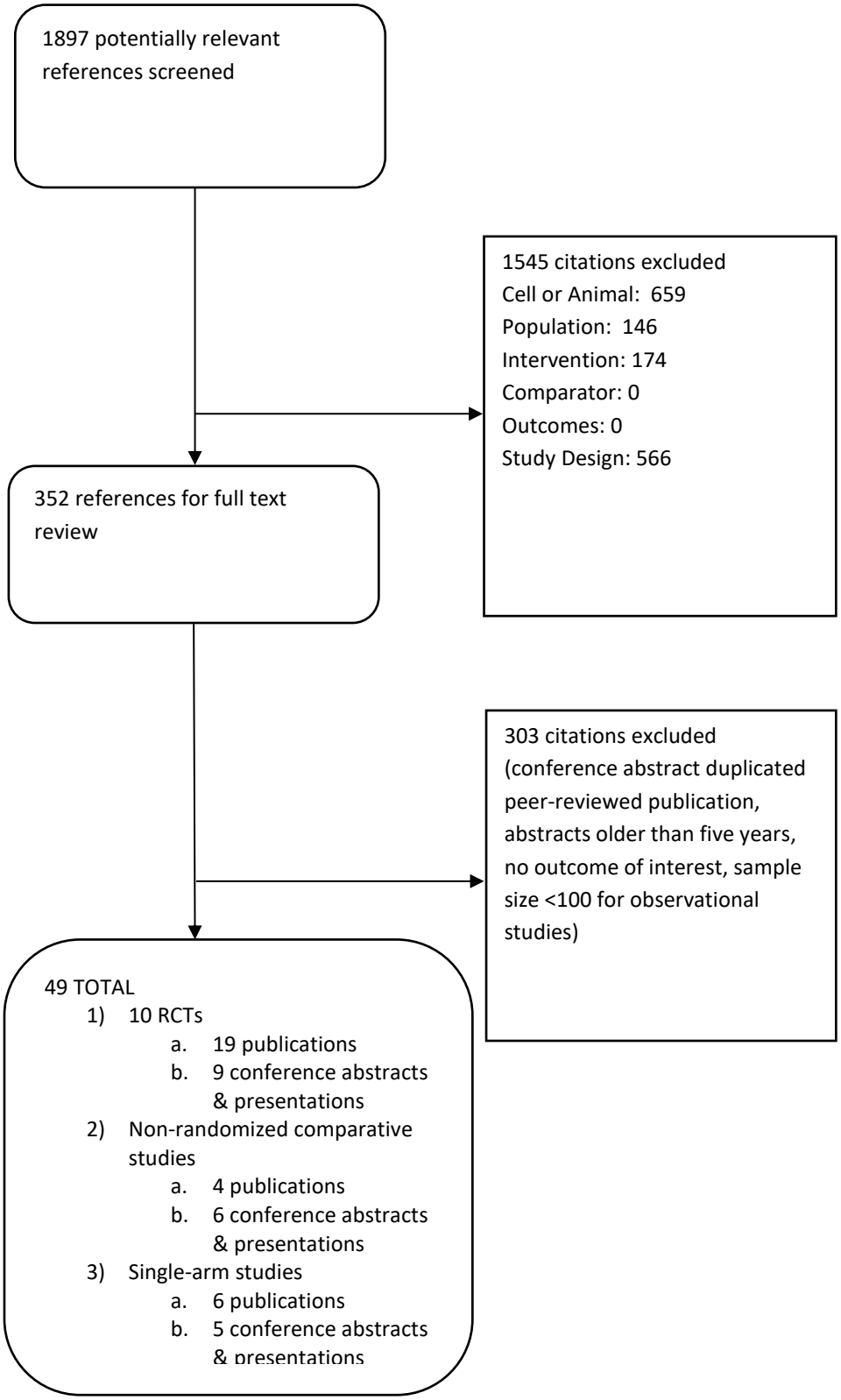
Table A2. Search Strategies of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled trials using PubMed®

#1	**Search cystic fibrosis[MeSH Terms]**
#2	Search cystic fibrosis transmembrane conductance regulator[MeSH Terms]
#3	#1 or #2
#4	Search cystic fibrosis transmembrane conductance regulator (CFTR) potentiator
#5	Search cystic fibrosis transmembrane conductance regulator (CFTR) corrector
#6	Search cystic fibrosis transmembrane conductance regulator (CFTR) modulator
#7	Search CFTR potentiator
#8	Search CFTR corrector
#9	Search CFTR modulator
#10	Search ivacaftor
#11	Search lumacaftor
#12	Search tezacaftor
#13	Search VX-770
#14	Search VX-809
#15	Search VX-661
#16	Search Kalydeco
#17	Search Orkambi®
#18	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17
#19	#3 and #18

Table A3. Embase Search Strategy

#1	**'**cystic fibrosis transmembrane conductance regulator (CFTR) potentiator'
#2	'cystic fibrosis transmembrane conductance regulator (CFTR) corrector'
#3	'cystic fibrosis transmembrane conductance regulator (CFTR) modulator'
#4	'CFTR potentiator'
#5	'CFTR corrector'
#6	'CFTR modulator'
#7	'ivacaftor':de OR 'ivacaftor':ab,ti
#8	'lumacaftor':de OR 'lumacaftor':ab,ti
#9	'tezacaftor':de OR 'tezacaftor':ab,ti
#10	'ivacaftor plus lumacaftor':de OR 'ivacaftor plus lumacaftor':ab,ti
#11	'ivacaftor plus tezacaftor':de OR 'ivacaftor plus tezacaftor':ab,ti
#12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11

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



Appendix B. Previous Systematic Reviews and Technology Assessments

We identified two completed technology assessments on ivacaftor and two assessments on Orkambi, one from the National Institute for Health and Care Excellence (NICE) in the UK and three from the Canadian Agency for Drugs and Technologies in Health (CADTH). These reviews are summarized below. Of note, NICE expects to publish a proposing an appraisal document on Symdeko treatment for treating cystic fibrosis in people with the F508del mutation.

Technology Assessments

NICE Technology Assessment Report:

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

https://www.nice.org.uk/guidance/ta398/chapter/1-Recommendationsksjhdf;alskjnef;awnefaw

The National Institute for Health and Care Excellence (NICE) performed a review of Orkambi in 2016. NICE did not recommend treatment for CF patients 12 years or older who are homozygous for the *F508del* mutation. The decision was based on the clinical evidence and cost-effective analysis. For clinical effectiveness, NICE examined the TRAFFIC, TRANSPORT, and PROGRESS clinical trials. Despite the general good quality of these trials, the results might not be generalizable to patients with mild or severe CF due to the inclusion criteria. Furthermore, the clinical evidence was insufficient to determine the long-term effect of Orkambi, since the treatment period in the main trials was 24 weeks. NICE noted that reporting the average of week 16 and week 24 results, rather than week 24 data alone, was more favorable to Orkambi. Concerning safety, NICE concluded that Orkambi was generally well tolerated.

NICE assessed cost effectiveness of Orkambi based on the manufacturer's microsimulation model. NICE concluded the manufacturer's model might overestimate the benefits of Orkambi treatment and substantially underestimate the costs.

NICE is currently developing guidance on Symdeko combination therapy for treating cystic fibrosis with the *F508del* mutation. The review is now on the scoping stage, and the publication date is to be announced.

CADTH:

Ivacaftor

CADTH Canadian Drug Expert Committee Final Recommendation (November, 19, 2015)

https://www.cadth.ca/sites/default/files/cdr/complete/SR0430_complete_Kalydeco_R117H_Nov-23-15_e.pdf

Common Drug Review – Clinical Review Report (March, 13, 2015)

https://www.cadth.ca/sites/default/files/cdr/clinical/SR0430_KalydecoR117H_CL_Report.pdf

Orkambi

CADTH Canadian Drug Expert Committee Final Recommendation (October, **28, 2016)**

https://www.cadth.ca/sites/default/files/cdr/complete/SR0471_complete_Orkambi-Oct-28-16.pdf

This review from the Canadian Agency for Drugs and Technologies in Health (CADTH) focused on assessing ivacaftor in the treatment for cystic fibrosis in patients 18 years and older with the CFTR R117H mutation. CADTH recommended ivacaftor for treating cystic fibrosis in adult patients with the CFTR R117H mutation if the following criteria and condition are met: first, patients have confirmed diagnosis of CF with chronic sinopulmonary disease; second, discontinuation criteria should be developed for non-responders in consultation with physicians; third, there is a substantial reduction in price.

CADTH assessed the clinical effectiveness of ivacaftor in the *R117H* residual function mutation population, which showed ivacaftor was associated with modest, clinically relevant changes in $ppFEV_1$ and respiratory symptoms compared to placebo. No significant treatment effect was observed in the time to pulmonary exacerbations. Ivacaftor was associated with few serious adverse events or withdrawals due to adverse events in trials. Considering the limited sample size (n=69, KONDUCT) and short duration of the studies, CADTH concluded additional data are needed to determine the long-term safety of ivacaftor. After assessing the manufacturer's economic model and conducting a Common Drug Review Reanalysis (CDR), CADTH concluded that for ivacaftor to be cost-effective, a price reduction of at least 98% would be necessary.

Following ivacaftor, CADTH reviewed Orkambi. CADTH recommended that Orkambi not be reimbursed for the treatment of CF in patients aged 12 years and older who are homozygous for the *F508del* mutation. The clinical evidence suggested that the magnitude of $ppFEV_1$, BMI, and pulmonary exacerbations improvement with Orkambi compared to placebo was of uncertain clinical significance.

Previous Systematic Reviews

We identified one systematic review on ivacaftor.[108]

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 ivacaftor among the *F508del* population was also included. No clinical differences were reported for CFQ-R, lung function, pulmonary exacerbations, or weight outcomes.

Adults taking ivacaftor reported significantly higher CFQ-R respiratory domain scores through 48 weeks compared to those taking placebo. Children on ivacaftor did not report similar improvements compared to placebo. Children and adults receiving ivacaftor 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 ivacaftor 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 among placebo recipients. Adults taking ivacaftor reported dizziness more frequently than placebo recipients. Neither trial reported a difference in study drug interruptions or discontinuations between placebo and ivacaftor 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 ivacaftor in children and adults at least six years old.

We identified one systematic review and guidline document from the Cystic Fibrosis Foundation for the use of ivacaftor and Orkambi.[33]

The guideline was designed to advise the use of these medications for clinicians, CF patients, and their families. A multidisciplinary committee was assembled to develop clinical questions using the Patient-Intervention-Comparison-Outcome format. A systematic review on ivacaftor and Orkambi was conducted to find relevant publications. The published peer-reviewed literature was from database inception through April 2016 in Ovid, EMBASE, PubMed, Cochrane Library, and Google Scholar. RCTs reflecting PICO criteria were included in the meta-analysis. The evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach, and recommendations were based on the results.

In summary, for adults and children age six and older with CF due to gating mutations other than *G551D* or *R117H*, the guideline panel made a conditional recommendation for treatment with

ivacaftor. For those with two copies of *F508del*, the guideline panel made a strong recommendation for treatment with Orkambi for adults and children age 12 and older with an $ppFEV_1$ <90%; and made a conditional for treatment with Orkambi for (1) adults and children age 12 or older with $ppFEV_1$ >90% and (2) children age six to 11.

Appendix C. Ongoing Studies

Title, Trial Sponsor, ClinicalTrials.gov Identifier	Study Design	Treatment Arms	Patient Population	Key Outcomes	Estimated Completion Date
Ivacaftor					
A Phase 3, 2 Part, Open-Label Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Ivacaftor in Subjects With Cystic Fibrosis Who Are Less Than 24 Months of Age and Have a CFTR Gating Mutation Vertex Pharmaceuticals Incorporated NCT02725567	Phase III Open label Non-randomized Single group assignement Estimated enrollment: 35	1. Experimental: Part A- Ivacaftor Group 1: Participants 12 to < 24 months Group 2: Participants 6 to < 12 months Group 3: Participants 3 to < 6 months) Group 4: Participants 0 to < 3 months 2. Experimental: Part B – Ivacaftor Group 5: Participants 12 to < 24 months Group 6: Participants 6 to < 12 months Group 7: Participants 0 to < 6 months	Inclusion Criteria • Confirmed diagnosis of CF by sweat chloride value or CF mutation criteria. • Must have 1 of the following 9 CFTR mutations on at least 1 allele: *G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P*, or *G1349D*. • No clinically significant abnormalities in hematology, serum chemistry, and vital signs Exclusion Criteria • History of abnormal liver function or abnormal liver function at screening • History of solid organ or hematological transplantation • Hemoglobin (Hgb) <9.5 g/dL at screening • Chronic kidney disease of Stage 3 or above • Presence of a non-congenital or progressive lens opacity or cataract at Screening	Primary Outcome Measures • Part A: AEs, serum chemistry and hematology abnormal lab values, standard 12 lead ECGs, vital signs, and ophthalmologic examinations [Time Frame: Day 1 - Day 70] • Part B: Same as above [Time Frame: Day 1 - Week 24] • Part A: Peak concentrations (C3-6h) of ivacaftor, M1 ivacaftor, and M6 ivacaftor [Time Frame: after 4 days of IVA treatment] • Part A: Ctrough of IVA, M1 IVA, and M6 IVA [Time Frame: after 4 days of IVA treatment] Secondary Outcome Measures • Part B: Peak concentrations (C3-6h) of IVA, M1 IVA, and M6 IVA [Time Frame: through Week 24] • Part B: Ctrough of IVA, M1 IVA, and M6 IVA [Time Frame: through Week 24] • Part B: Absolute change from baseline in sweat chloride [Time Frame: through Week 24]	June 2020
A Phase 3, 2-Arm, Open-label Study to Evaluate the Safety and Pharmaco-dynamics of Long-term Ivacaftor Treatment in Subjects With Cystic Fibrosis Who Are Less Than 24 Months of Age at Treatment Initiation	Phase III 2-Arm Open label Non-randomized	1. Experimental: Ivacaftor will be administered every 12 hours from Day 1 through the morning dose of the Week 104 Visit. 3. No Intervention: Observational Arm	Inclusion Criteria **Ivacaftor Arm: Subjects From Study 124 (above) Part B:** • Must have completed the last study visit of Study 124 Part B. **Ivacaftor Arm: Subjects Not From Study 124 Part B:**	Primary Outcome Measures • Safety assessments based on the number of subjects with AEs and SAEs [Time Frame: Baseline - safety follow-up (up to 24 weeks after last dose)] Secondary Outcome Measures Absolute change in sweat chloride [Time Frame: Baseline - Week 104]	June 7, 2021

and Have a CFTR Gating Mutation Vertex Pharmaceuticals Incorporated NCT03277196	Parallel assignement Estimated enrollment: 75		• Confirmed diagnosis of CF, or 2 CF-causing mutations. • One of the following CFTR mutations on at least 1 allele: *G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, or G1349D.* Exclusion Criteria **Ivacaftor Arm: Subjects Not From Study 124 Part B:** • History of any illness or condition that might pose an additional risk in administering ivacaftor to the subject An acute upper or lower respiratory infection, or pulmonary exacerbation, or changes in therapy for pulmonary disease within 4 weeks of Day 1		
Phase 3b, Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Assess the Safety, Efficacy, and Tolerability of Symdeko (TEZ/IVA) in an Orkambi-experienced Population Who Are Homozygous for the ***F508del*** CFTR Mutation Vertex Pharmaceuticals Incorporated NCT03150719	Phase III 2-Arm Randomized Double-blind Parallel assignement Estimated enrollment: 90	1. Experimental: TEZ 100 mg/IVA 150 mg fixed-dose combination tablet in the morning; IVA 150 mg tablet in the evening. 2. Interventions: Drug: TEZ/IVA; IVA Placebo matched to TEZ/IVA fixed-dose combination tablet in the morning; placebo matched to IVA tablet in the evening. Interventions: Placebo 2.	Inclusion Criteria: • Prior discontinuation of lumacaftor/ivacaftor, with at least 1 respiratory sign or symptom considered related to therapy. • Resolution or stabilization of qualifying event(s) >28 days prior to Screening. • Discontinuation of lumacaftor/ivacaftor therapy must have occurred <8 weeks from the first dose of lumacaftor/ivacaftor. • Homozygous for *F508del* mutation in the CFTR gene • FEV1 ≥25% and ≤90% of predicted normal for age, sex, and height. Exclusion Criteria:	Primary Outcome Measures • Incidence of respiratory adverse events (AEs) [Time Frame: At Day 56] Number and proportion of subjects with respiratory AEs will be reported Secondary Outcome Measures • Absolute change in ppFEV1 [Time Frame: from baseline to the average of the Day 28 and Day 56 measurements] • Relative change in ppFEV1 • Absolute change in CFQ-R score • Tolerability, defined as the number and proportion of study participants who discontinue treatment [Time Frame: through Day 56] • Number and proportion of subjects who discontinued TEZ/IVA will be reported.	June 30, 2018

			• Recent rapid or progressive deterioration in respiratory status. • Receiving continuous oxygen at >2L/min or on face-mask ventilation. • An acute upper or lower respiratory infection, pulmonary exacerbation, or change in therapy for pulmonary disease within 28 days before Day 1. • Documentation of colonization with organisms associated with a more rapid decline in pulmonary status. • History of lung transplantation since most recent initiation of lumacaftor/ivacaftor. • Participation in an investigational drug study or use of a CFTR modulator within 28 days or 5 terminal half-lives of the investigational drug or modulator (whichever is longer).	Safety assessments based on the number of subjects with adverse events (AEs) and serious adverse events (SAEs)	
A Phase 1/2 Study of VX-445 in Healthy Subjects and Subjects With Cystic Fibrosis Vertex Pharmaceuticals Incorporated NCT03227471	Phase II 2-Arm Randomized Parallel assignement Estimated enrollment: 224	1. Experimental Part A: VX-445 in Healthy Subjects (HS) Part A includes single dose escalation. 2. Experimental: Part B: VX-445 in HS Part B includes multiple-dose escalation. 3. Experimental: Part C: VX-445 in Triple Combination (TC) with TEZ/IVA in HS Multiple-dose escalation of VX-445 in TC with TEZ/IVA	Inclusion Criteria: Parts A, B, and C: •Female subjects must be of non-childbearing potential. •Between the ages of 18 and 55 years, inclusive. •BMI of 18.0 to 32.0 kg/m2, inclusive, and a total body weight >50 kg Parts D, E, and F: •Body weight ≥35 kg. •Parts D and F: Heterozygous for F508del and an MF mutation •Part E: Homozygous for F508del •FEV1 value ≥40% and ≤90% of predicted mean for age, sex, and height.	Primary Outcome Measures • Absolute change in sweat chloride concentrations [Parts C, D, E, and F only] [Time Frame: from baseline through Day 29] • Relative change in ppFEV1 [Parts D, E, and F only] • Absolute change in CFQ-R score [Parts D, E, and F only] • Maximum observed concentration (Cmax) of VX-445,TEZ and metabolites (M1-TEZ and M2-TEZ), IVA and metabolites (M1-IVA and M6-IVA) and VX-561 [Time Frame: from Day 1 through Day 43]	April 6, 2018

		4. Experimental: Part D1: F/MF genotypes TC 100 mg VX-445 qd in TC with TEZ and IVA for 4 weeks. 5. Experimental: Part D2: F/MF genotypes TC-High Subjects will receive VX-445 in TC with TEZ and IVA for 4 weeks. F/MF genotypes TC-Mid VX-445 in TC with TEZ and IVA for 4 weeks. Experimental: Part D2: F/MF genotypes TC-Low VX-445 in TC with TEZ and IVA for 4 weeks. Experimental: Part E: F/F genotype - TC VX-445 in TC with TEZ and IVA for 4 weeks Active Comparator: TEZ/IVA TEZ and IVA for 4 weeks. Experimental: Part F: F/MF genotypes - TC VX-445 in TC with TEZ and VX-561 for 4 weeks.	Exclusion Criteria: Parts A, B, and C: • History of febrile illness within 14 days before the first study drug dose. • Glucose-6-phosphate dehydrogenase (G6PD) deficiency. Parts D, E, and F: • History of 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. • History of solid organ or hematological transplantation.	• Area under the concentration versus time curve during a dosing interval (AUCtau) of VX-445, TEZ and metabolites (M1-TEZ and M2-TEZ), IVA and metabolites (M1-IVA and M6-IVA) and VX-561 • Observed pre-dose concentration (Ctrough) of VX-445, TEZ and metabolites (M1-TEZ and M2-TEZ), IVA and metabolites (M1-IVA and M6-IVA) and VX-561 Secondary Outcome Measures • Absolute change in sweat chloride concentrations [Parts C, D and E only] • Relative change in ppFEV1 [Parts D and E only] • Absolute change in CFQ-R score [Parts D and E only] • Maximum observed concentration (Cmax) of VX-445,TEZ and metabolites (M1-TEZ and M2-TEZ), and IVA and metabolites (M1-IVA and M6-IVA) [Time Frame: from Day 1 through Day 43] • Area under the concentration versus time curve during a dosing interval (AUCtau) of VX-445, TEZ and metabolites (M1-TEZ and M2-TEZ), and IVA and metabolites (M1-IVA and M6-IVA) Observed pre-dose concentration (Ctrough) of VX-445, TEZ and metabolites (M1-TEZ and M2-TEZ), and IVA and metabolites (M1-IVA and M6-IVA)	
A Phase 2, Randomized, Double-blind, Controlled Study to Evaluate the Safety and Efficacy of VX-659 Combination Therapy in Subjects Aged 18 Years and Older With Cystic Fibrosis	Phase II 2-Arm Randomized Parallel assignement	1. Experimental: Part 1: F/MF genotype -TC Low 80 mg of VX-659 qd in TC with TEZ and IVA for 4 weeks F/MF genotype - TC Mid 240 mg of VX-659 qd in TC with TEZ and IVA for 4 weeks. F/MF genotype - TC High 400 mg VX-659 qd in TC with TEZ and IVA for 4 weeks.	Inclusion Criteria • Body weight ≥35 kg. • Subjects must have an eligibleCFTR genotype. • Part 1 and Part 3: Heterozygous for F508del and an MF mutation (F/MF) • Part 2: Homozygous for F508del (F/F)	Primary Outcome Measures • Safety and tolerability as assessed by number of subjects with adverse events (AEs) and serious adverse events (SAEs) [From baseline through safety follow-up (20 Weeks)] • Absolute change in percent predicted forced expiratory volume in 1 second (ppFEV1) [Baseline through Day 29]	March 20, 2018

Vertex Pharmaceuticals Incorporated NCT03224351	Estimated enrollment: 105	Comparator: F/MF genotype - placebo for 4 weeks. 2. Experimental: Part 2: F/F genotype – TC 400 mg of VX-659 qd in TC with TEZ and IVA for 4 weeks Comparator: F/F genotype - TEZ/IVA 3. Experimental: Part 3: F/MF genotype - TC 400 mg of VX-659 qd in TC with TEZ and VX-561 for 4 weeks Comparator: F/MF genotype - Placebo	• FEV1 value ≥40% and ≤90% of predicted mean for age, sex, and height Exclusion Criteria **Ivacaftor Arm: Subjects Not From Study 124 Part B:** • History of 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. History of solid organ or hematological transplantation.	Secondary Outcome Measures • Absolute change in sweat chloride concentrations [From baseline through Day 29] • Relative change in ppFEV1 • Absolute change in CFQ-R • Maximum observed concentration of VX-659, TEZ, M1-TEZ, IVA, M1-IVA, and VX-561 [Day 1 through Day 29] • Area under the concentration vs time curve during a dosing interval of VX-659, TEZ, M1-TEZ, IVA, M1-IVA, and VX-561 • Observed pre-dose concentration of drugs above	
A Phase 3, Open Label Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of VX-661 in Combination With Ivacaftor in Subjects 6 Through 11 Years of Age With Cystic Fibrosis, Homozygous or Heterozygous for the ***F508del*** CFTR Mutation Vertex Pharmaceuticals Incorporated NCT02953314	Phase III 2-Arm Open label Non-randomized Parallel assignement Estimated enrollment: 72	1. Experimental Part A: Cohort 1 VX-661 50 mg qd + IVA 75 mg q12h Interventions: Drug: VX-661 Drug: Ivacaftor Cohort 2 VX-661 50 mg qd + IVA 150 mg q12h Interventions: Drug: VX-661 Drug: Ivacaftor 2. Experimental: Part B: VX-661 + IVA VX-661 + IVA 75 mg q 12h or IVA 150 mg q 12h Interventions: Drug: VX-661 Drug: Ivacaftor	Inclusion Criteria • Subjects who weigh ≥15 kg without shoes at the screening • All genotypes as specified by the study protocol are eligible in Part A. • The following genotypes are eligible in Part B: ○ homozygous for the *F508del* CFTR mutation ○ heterozygous for the *F508del* CFTR mutation and with a second allele with a CFTR mutation predicted to have residual function. ○ heterozygous for the *F508del* CFTR mutation and with a second CFTR allele with a gating defect that is clinically demonstrated to be ivacaftor responsive • A sweat chloride value ≥60 mmol/L or chronic sinopulmonary and/or gastrointestinal disease consistent with a diagnosis of CF	Primary Outcome Measures • Part A: Maximum observed concentration of VX-661 and ivacaftor [Day 1 and Day 14] • Part A: Area under the concentration versus time curve during a dosing interval of VX-661 and ivacaftor • Part B: Safety and tolerability of VX-661 in combination with ivacaftor as determined by adverse events and serious adverse events [Time Frame: from baseline through 29 Weeks] Secondary Outcome Measures • Part A: Cmax of selected metabolites for VX-661 and Ivacaftor [Time Frame: Day 1 and Day 14] • Part A: AUCτ of selected metabolites for VX-661 and Ivacaftor • Part A: Safety and tolerability of VX-661 in combination with ivacaftor as determined by adverse events (AEs) and serious adverse events (SAEs) [From baseline through Day 31]	September 2018

			• Subjects who are homozygous for the *F508del*-CFTR mutation must have a sweat chloride value ≥60 mmol/L. • Subjects with ppFEV1 of ≥40% • Subjects who are willing to remain on their stable CF medication regimen through Day 14 (Part A) or through Week 24 (Part B) or, if applicable, through the Safety Follow up Visit. • Female subjects of childbearing potential must have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at the Day 1 Visit before receiving the first dose of study drug. • Subjects of childbearing potential who are sexually active must meet the contraception requirements <u>Exclusion Criteria</u> • An acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy for pulmonary disease within 28 days before Day 1 • A standard 12 lead ECG demonstrating QTc >450 msec at the Screening Visit. • Ongoing or prior participation in an investigational drug study or use of commercially available CFTR modulator (except physician-prescribed ivacaftor for approved indications) within 30 days of screening. Pregnant and nursing females	• Part B: Cmax of VX-661, M1-661, M2-661, ivacaftor, M1-ivacaftor, and M6-ivacaftor [Time Frame: Day 1 through Week 16] • Part B: AUCτ of VX-661, M1-661, M2-661, ivacaftor, M1-ivacaftor, and M6-ivacaftor • Part B: Absolute change in ppFEV1 • Part B: Relative change in ppFEV1 • Part B: Absolute change in weight • Part B: Absolute change in weight for age z-score • Part B: Absolute change in height • Part B: Absolute change in height for age z-score • Part B: Absolute change in body mass index (BMI) • Part B: Absolute change in BMI for age z-score • Part B: Absolute change in sweat chloride Part B: Absolute change in CFQ-R score	

Intestinal Current Measurements (ICM) to Evaluate the Activation of Mutant CFTR in Subjects With Cystic Fibrosis Aged 12 Years and Older, Homozygous for the p.Phe508del-CFTR Mutation, Treated With Lumacaftor in Combination With Ivacaftor Hannover Medical School NCT02807415	Oberservational Case-only Estimated enrollment: 125	1. Baseline measurements will be performed within a 4-week interval prior to the start of oral treatment with lumacaftor + ivacaftor. According to the phase 3 study results by week 4 the gain of FEV1 levels off, drug levels are in steady state and all reversible initial reductions of lung function are resolved. Thus the second assessment will be performed during the initial steady state at a day 10 - 14 weeks after the initiation of oral treatment with lumacaftor + ivacaftor. 2. Study participants will be requested to record the administration of Orkambi® by date and time for 7 days before the scheduled visit to perform functional CFTR assays. The local patient databases at the three sites will be searched for all subjects who fulfil the inclusion criteria. After all subjects have been removed from the list who fulfill one or more exclusion criteria, the eligible subjects will be randomly assigned to rank numbers. Subjects will then be contacted in the sequence as they appear in the rank number list.	<u>Inclusion Criteria</u> • Phe508del homozygous subjects aged 12 years and older with cystic fibrosis • FEV1 ≥ 40% of predicted normal for age, gender and height (Knudson standards) or FEV1 > 35% of predicted normal for age, gender and height at baseline, stable lung function during the preceding three months and no acute upper or lower respiratory infection or pulmonary exacerbation during the preceding four weeks <u>Exclusion Criteria</u> • An acute upper or lower respiratory infection or pulmonary exacerbation at baseline • Advanced liver disease as documented by sonography • Abnormal liver function at baseline, defined as ≥ 3 upper limit of normal in minimum 3 of the following: serum aspartate transaminase, serum alanine transaminase, gamma-glutamyl transpeptidase, or total bilirubin • Abnormal blood creatine phosphokinase at baseline • Creatinine clearance < 60 mL/min • Co-medication with strong CYP3A inhibitors and inducers • Non-congenital lens opacities • Haemorrhoids (bleeding risk when taking rectal suction biopsies for ICM)	<u>Primary Outcome Measures</u> • ICM Absolute change from baseline of the cumulative chloride secretory ion current response to forskolin/IBMX and carbachol in rectal tissue as a CFTR biomarker [Measurement at the baseline visit within a 4-week interval prior to the start of oral treatment with lumacaftor and ivacaftor; second measurement at a day 10 - 14 weeks after the initiation of oral treatment with lumacaftor and ivacaftor] <u>Secondary Outcome Measures</u> • Spirometry Absolute change from baseline in percent predicted FEV1 [Measurement at the baseline visit within a 4-week interval prior to the start of oral treatment with lumacaftor and ivacaftor; second measurement at a day 10 - 14 weeks after the initiation of oral treatment with lumacaftor and ivacaftor] • NPD Absolute change from baseline of the Sermet score of nasal transepithelial potential difference measurements (NPD) as a CFTR biomarker [Measurement at the baseline visit within a 4-week interval prior to the start of oral treatment with lumacaftor and ivacaftor; second measurement at a day 10 - 14 weeks after the initiation of oral treatment with lumacaftor and ivacaftor] Sweat chloride testing Absolute change from baseline of the chloride concentration in Gibson-Cooke pilocarpine iontophoresis sweat test as a CFTR biomarker [Measurement at the baseline visit within a 4-week interval prior to the start of oral treatment with lumacaftor and ivacaftor; second measurement at a day 10 - 14	June 2019

			• History of nasal surgery that removed the respiratory epithelium • Topical treatment of nostrils in the 3 days prior to baseline Disturbing nasal aspects of secretions, erythema, crustae, ulcera, edema at baseline	weeks after the initiation of oral treatment with lumacaftor and ivacaftor]	
A Study of the Effect of Combination Lumacaftor and Ivacaftor on Markers of Hyperglycemia in Persons With Cystic Fibrosis Massachusetts General Hospital NCT02858843	Single center Open label Single-group assignement Estimated enrollment: 50	1. The participants will have been previously screened to make sure they are candidates for the study. These patients will be contacted prior to their first visit to discuss enrollment in the study. 2. At the study visit the participant will come to the CRC or DRC for a research visit. The following will occur at this study visit: informed consent; brief medical history; weight and height; vital signs and blood pressure; blood draw for DNA extraction, A1c and an extra research tube for storage. This will be scheduled at a time that is convenient to the patient.	Inclusion Criteria • Age 18 years old or greater • Patients diagnosed with cystic fibrosis (CF), genotype homozygous Phe508del • Subject has been started on lumacaftor/ivacaftor for clinical reasons, with no contraindication for starting the drug • Contraindications for taking drug include abnormal liver enzyme tests, renal dysfunction, pregnancy or nursing mothers Exclusion Criteria • Does not have a HgbA1c within 1 year prior to starting medication. • Has not been on the combination therapy for at least 2 months	Primary Outcome Measures • Change in glycated hemoglobin (hemoglobin A1C) [Time Frame: 1 year] • A blood test will be used to determine the hemoglobin A1c change while on the medication. • Change in units of insulin used over a period of 6 months to 1 year. [Time Frame: 1 year] Secondary Outcome Measures • Change in glycemia contingent on genetic risk score [Time Frame: 1 year] • The investigators will examine how change in glycemia is dependent on genotype at variants associated with type 2 diabetes and insulin secretion using genetic risk scores. • Pulmonary function test (PFT) forced expiratory volume at one second (FEV1) measurements [Time Frame: 1 year] The investigators will compare how PFT measurement of FEV1 are related to changes in glycemia	June 2018
Effects of Orkambi on Exertional Dyspnea, Exercise Performance, and Ventilatory Responses in Adults With Cystic Fibrosis University of British Columbia	Obeservational Case-only Estimated enrollment: 16	1. Experimental: Part 1: F/MF genotype -TC Low 80 mg of VX-659 qd in TC with TEZ and IVA for 4 weeks F/MF genotype - TC Mid 240 mg of VX-659 qd in TC with TEZ and IVA for 4 weeks. F/MF genotype - TC High	Inclusion Criteria • Confirmed diagnosis of CF and homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene • Aged 19 years or older • Forced Expiratory Volume in 1 second (FEV1.0) < 90% predicted	Primary Outcome Measures • Change in iso-time dyspnea rating from baseline (visit 2) to visit 3 and 4 during constant-load exercise tests. [Parameters will be measured during 3 visits. Visit 2 will occur before the participants go on Orkambi. Visit 3 and 4 will occur at 1 month and 3 months after initiating full dose of	December 2019

NCT02821130		400 mg VX-659 qd in TC with TEZ and IVA for 4 weeks. Comparator: F/MF genotype - placebo for 4 weeks. 2. Experimental: Part 2: F/F genotype – TC 400 mg of VX-659 qd in TC with TEZ and IVA for 4 weeks Comparator: F/F genotype - TEZ/IVA 3. Experimental: Part 3: F/MF genotype - TC 400 mg of VX-659 qd in TC with TEZ and VX-561 for 4 weeks Comparator: F/MF genotype - Placebo	• Body mass index greater than 16 or less than 30 kg/m2 • Currently non-smoking or a past smoking history of less than 20 pack-years Exclusion Criteria • Chronic airway infection with Mycobacterium abscessus, Burkholderia cepacia complex, or other organisms with infection control implications based on the treating physicians • Use of supplemental oxygen or desaturation less than 85% with exercise Diagnosis of pneumothorax in the past 4 weeks	drug, respectively. All visits will be completed within 4 months.] Secondary Outcome Measures • Cardio-respiratory responses • Chronic activity-related dyspnea • Quality of life measured using the St. George's Respiratory Questionnaire. Physical activity measured using the International Physical Activity Questionnaire (long version) and Recent Physical Activity Questionnaire.	
Personalized Therapy of Cystic Fibrosis: Set-up of Response Markers Hôpital Necker-Enfants Malades NCT02965326	2-Arm Non-randomized Parallel assignement Estimated enrollment: 75	1. Cystic fibrosis, treated Cystic fibrosis patients treated either by Ivacaftor or by the association Ivacaftor-Lumacaftor Procedure: Nasal swab; rectal biopsy. 2. Cystic fibrosis, non treated Cystic fibrosis patients, non treated by a CFTR modulator Procedure: Nasal swab; rectal biopsy. 3. Non-Cystic fibrosis Patients in whom cystic fibrosis diagnosis has been suspected, but excluded by physiological and genetic investigations Procedure: Nasal swab; rectal biopsy.	Inclusion Criteria • Cystic fibrosis patients treated by CFTR modulators (Ivacaftor or the association Ivacaftor-Lumacaftor) • Cystic fibrosis patients non treated by CFTR modulators • Patients in whom cystic fibrosis diagnosis has been suspected, but excluded by physiological and genetic investigations Exclusion Criteria • Pregnant or lactating women • Contraindication to nasal swab • Contraindication to rectal biopsy	Primary Outcome Measures • Correlation between biological markers and clinical and physiological outcome [Time Frame: 6 months] Secondary Outcome Measures Correlation between biological markers and clinical and physiological outcome [Time Frame: 12 months]	October 2020
A Randomized, Double-blind, Placebo-controlled, Crossover Study to Evaluate the Efficacy	Randomized Double-blind	Experimental Sequence 1: Ivacaftor → Placebo	Inclusion Criteria • Confirmed diagnosis of CF and at least one of the following:	Primary Outcome Measures	September 25, 2018

of Ivacaftor in Subjects With Cystic Fibrosis Who Are 6 Years of Age and Older and Have Either a 3849 + 10KB C→T or D1152H-CFTR Mutation Vertex Pharmaceuticals Incorporated NCT03068312	Placebo-controlled Single group assignement Crossover study Estimated enrollment: 50	Subjects will be randomized to receive Ivacaftor, 150 mg every 12 hours (q12h) for 8 weeks in Treatment Period 1 followed by Placebo matching Ivacaftor for 8 weeks in Treatment Period 2. A washout period of 8 weeks will be maintained between the 2 periods. Experimental: Sequence 2: Placebo → Ivacaftor Subjects will be randomized to receive Placebo matching to Ivacaftor for 8 weeks in Treatment Period 1 followed by Ivacaftor 150 mg q12h for 8 weeks in Treatment Period 2. A washout period of 8 weeks will be maintained between the 2 periods.	increased sweat chloride level, identification of 2 CF causing mutations, or demonstration of abnormal nasal epithelial ion transport. • A 3849 + 10KB C→T or D1152H mutation on at least 1 CFTR allele. • FEV1 ≥40% of predicted and ≤105% of predicted at screening. Exclusion Criteria • A *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R*, or *R117H* mutation. • For subjects <18 years of age at the Screening, evidence of cataract/lens opacity determined to be clinically significant by the ophthalmologist. Use of any moderate or strong inducers or inhibitors of cytochrome P450 (CYP) 3A, including consumption of certain herbal medications and certain fruit and fruit juices, within 14 days before Day 1.	• Correlation between biological markers and clinical and physiological outcome [Time Frame: 6 months] Secondary Outcome Measures Correlation between biological markers and clinical and physiological outcome [Time Frame: 12 months]	
A Phase 3, Open-label, Rollover Study to Evaluate the Safety and Efficacy of Long Term Treatment With VX-661 in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous or Heterozygous for the ***F508del***-CFTR Mutation Vertex Pharmaceuticals Incorporated NCT02565914	Phase III Open label Non-randomized Parallel assignment Estimated enrollment: 1116	1. Experimental Part A: VX-661/ivacaftor VX-661 100 mg/ ivacaftor 150 mg fixed dose combination (FDC) tablet daily (qd) in the morning and ivacaftor 150 mg tablet qd in the evening 2. No Intervention Part: A Observational Cohort Long-term Follow-up 3. Experimental Part B: VX-661/ivacaftor	Inclusion Criteria 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. • Previously received at least 4 weeks of study drug before discontinuing in Part A of Study NCT02565914 to participate in another qualified Vertex study.	Primary Outcome Measures Part A: Safety and tolerability of long-term treatment of VX-661 in combination with ivacaftor based on adverse events (AEs), ophthalmologic exams, clinical laboratory values, standard digital electrocardiograms (ECGs), vital signs, and pulse oximetry [Time Frame: from baseline through Study Completion (up to 3 years)] Secondary Outcome Measures • Parts A and B: Absolute change from baseline in ppFEV1 [Time Frame: from baseline through Week 96]	September 2019

		VX-661 100 mg/ ivacaftor 150 mg fixed dose combination (FDC) tablet daily (qd) in the morning and ivacaftor 150 mg tablet qd in the evening	• Completed the last required visit of another qualified Vertex study before or during the Returning Visit in Part A Study NCT02565914. • <18 years of age (age on the date of informed consent/assent in the parent study) • Completed study drug Treatment Period in a parent study or study drug treatment and the Safety Follow up Visit for subjects from NCT02508207, but do not elect to enroll in the NCT02565914 Treatment Cohort; or • Received at least 4 weeks of study drug 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 <u>Part B:</u> • Did not withdraw consent from the parent study or Part A of Study NCT02565914. • Completed study drug treatment during the Treatment Period in Part A of NCT02565914, Studies NCT02730208 or NCT03150719, or other eligible Vertex studies. • Previously received at least 4 weeks of study drug before discontinuing Study NCT02565914 to participate in another qualified Vertex study, which is defined as a Vertex study of investigational CFTR modulators that allows	• Part A: Relative change from baseline in ppFEV1 • Parts A and B: Number of pulmonary exacerbations • Parts A and B: Absolute change from baseline in body mass index (BMI) • Parts A and B: Absolute change from baseline in BMI z-score for subjects aged <20 years • Part A: Absolute change from baseline in CFQ-R score • Part A: Absolute change from baseline in body weight • Part A: Absolute change from baseline in body weight z-score for subjects aged <20 years • Part A: Absolute change from baseline in height z-score for subjects aged <20 years • Part A: Time-to-first pulmonary exacerbation • Part A: Pharmacokinetic (PK) parameters: trough concentrations of VX-661 , a VX-661 metabolite (M1-661), ivacaftor, ivacaftor metabolite (M1-ivacaftor) • Part A: Observational Cohort: Safety, as determined by related serious adverse events (SAEs) [Time Frame: from baseline through study Completion (up to 3 years)] Part B: Safety and tolerability assessments including number of subjects with adverse events (AEs) and serious adverse events [Time Frame: from baseline through safety follow-up visit]	

			participation of subjects in Study NCT02565914. Exclusion Criteria: • History of drug intolerance in the parent study that would pose an additional risk to the subject. 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.		
A Phase 2, Randomized, Placebo-Controlled, Double-blind Study to Evaluate the Effect of VX-661 in Combination With Ivacaftor on Chest Imaging Endpoints in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous for the ***F508del*** CFTR Mutation Vertex Pharmaceuticals Incorporated NCT02730208	Phase II Randomized Double-blind Placebo-controlled Estimated enrollment: 40	1. Experimental: VX-661/ivacaftor Fixed-dose combination tablet of VX-661 100-mg/ivacaftor 150-mg and an evening dose of ivacaftor 150-mg to be taken approximately 12 hours after the morning dose 2. Experimental: Placebo visually-matched tablets to be taken on the same schedule as the active treatment.	Inclusion Criteria • Homozygous for the *F508del* CFTR mutation • Confirmed diagnosis of CF • Percent predicted forced expiratory volume (ppFEV1) ≥70% of predicted normal for age, sex, and height during screening. • Stable CF disease as judged by the investigator Exclusion Criteria • An acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 28 days before Day 1 (first dose of study drug) • Pregnant or nursing females. • Sexually active subjects of reproductive potential who are not willing to follow the contraception requirements.	Primary Outcome Measures • Change in CT imaging score from baseline at Week 72 [Time Frame: from baseline at Week 72] Secondary Outcome Measures • Safety and tolerability assessments including number of subjects with adverse events (AEs) and serious adverse events (SAEs) [Time Frame: Through week 72]	September 2018

			Any contraindication to undergoing chest imaging, as per the site's institutional guidelines		
A Phase 3, Rollover Study to Evaluate the Safety of Long-term Treatment With Lumacaftor/Ivacaftor Combination Therapy in Subjects Aged 2 Years and Older With Cystic Fibrosis, Homozygous for the ***F508del***-CFTR Mutation Vertex Pharmaceuticals Incorporated NCT03125395	Phase III Non-randomized Open label Parallel assignment Actual enrollment: 50	1. Experimental: Subjects <6 years of age and <14 kg at enrollment: LUM 100 mg/IVA 125 mg q12h. Subjects <6 years of age and ≥14 kg at enrollment: LUM 150 mg/IVA 188 mg q12h. Subjects ≥6 years of age at enrollment, regardless of weight: LUM 200 mg/IVA 250 mg q12h.	Inclusion Criteria • Completed 24 weeks of LUM/IVA treatment and the Safety Follow-up Visit in Study VX15-809-115 Part B (Study 115B, NCT02797132) • Completed 24 weeks of LUM/IVA treatment and the Safety Follow-up Visit in Study 115B, but do not want to enroll in the Treatment Cohort. • Received at least 4 weeks of LUM/IVA treatment and completed visits up to Week 24 and the Safety Follow-up Visit, if required, of Study 115B but are not taking LUM/IVA at the end of the Study 115B Treatment Period because of a drug interruption and either did not receive Vertex approval to enroll in the Treatment Cohort or do not want to enroll in the Treatment Cohort. • Permanently discontinued LUM/IVA in Study 115B after receiving at least 4 weeks of treatment and remained in the study from the time of treatment discontinuation through the Week 24 Visit and Safety Follow-up Visit, if required. Exclusion Criteria • Prematurely discontinued LUM/IVA treatment in Study 115B. • Subjects with a history of allergy or hypersensitivity to LUM/IVA. • Liver function test (LFT) abnormality meeting criteria for	Primary Outcome Measures Safety and tolerability assessments based on the number of subjects with adverse events (AEs) and serious adverse events (SAEs) [Time Frame: From baseline through safety follow-up (up to 98 weeks).] Secondary Outcome Measures • Absolute change from baseline in sweat chloride [From baseline through 96 weeks] • Absolute change from baseline in body mass index • Absolute change in BMI-for-age Z-score • Absolute change from baseline in weight • Absolute change in weight-for-age Z-score • Absolute change from baseline in stature (height) • Absolute change from baseline in stature-for-age Z-score • Time-to-first pulmonary exacerbation • Number of pulmonary exacerbations • Number of Cystic Fibrosis (CF)-related hospitalizations • Absolute change from baseline in fecal elastase-1 (FE-1) levels • Absolute change from baseline in serum levels of immunoreactive trypsinogen (IRT) • Change from baseline in sputum microbiology cultures • Absolute change from baseline in lung clearance index (LCI)2.5 Absolute change from baseline in LCI5.0	July 26, 2019

			LUM/IVA treatment interruption at the completion of Study 115B, for which no convincing alternative etiology is identified. • QTc value at the completion of Study 115B that would pose an additional risk to the subject in the opinion of investigator, and which should be discussed with the Vertex medical monitor Participation in an investigational drug trial (including studies investigating LUM and/or IVA) other than Study 115B.		
A Phase 3, Rollover Study to Evaluate the Safety and Efficacy of Long-term Treatment With Lumacaftor in Combination With Ivacaftor in Subjects Aged 6 Years and Older With Cystic Fibrosis, Homozygous for the ***F508del***-CFTR Mutation Vertex Pharmaceuticals Incorporated NCT02544451	Phase III Non-randomized Open label Parallel assignment Estimated enrollment: 240	1. Experimental: Experimental: Treatment Cohort: lumacaftor/ivacaftor (6 through 11) Lumacaftor (LUM) 200 mg every 12 hours (q12h)/ivacaftor (IVA) 250 mg q12h (subjects aged 6 through 11 years) 2. Experimental: Treatment Cohort: lumacaftor/ivacaftor (12 and older) LUM 400 mg q12h/IVA 250 mg q12h (subjects aged 12 years and older) 3. No intervention: Observational cohort Long-term follow-up	Inclusion Criteria Subjects entering the Treatment Cohort must meet both of the following criteria: • Completed study visits up to Week 24 of Study 109 or Week 26 of Study 011B and did not permanently discontinue treatment Subjects entering the Observational Cohort must meet 1 of the following criteria: • Completed 24 weeks of study drug treatment in Study 109 or completed 24 weeks of study drug treatment and the Week 26 Safety Follow up in Study 011B. Received at least 4 weeks of study drug and completed visits up to Week 24 of Study 109 or Week 26 of Study 011B.	Primary Outcome Measures • Treatment Cohort: Assess safety and tolerability of long term treatment of lumacaftor in combination with ivacaftor, based on adverse events and changes in clinical laboratory values, vital signs, and spirometry [Time Frame: up to 4 weeks after last dose [last dose = Week 96]] Secondary Outcome Measures • Treatment Cohort: Absolute change in Lung Clearance Index 2.5 (LCI2.5) (subjects from Study 109 and the Study 011B LCI Substudy only) [From baseline to Week 96] • Absolute change in sweat chloride • Absolute change in body mass index • Absolute change in CFQ-R score • Observational Cohort: Safety, as determined by serious adverse events [Time Frame: 2 years] • Treatment Cohort: Absolute change in Lung Clearance Index 5.0 (LCI5.0) • Absolute change in ppFEV1 • Relative change in ppFEV1 • Absolute change in body mass index (BMI)-for-age-z-score	August 2018

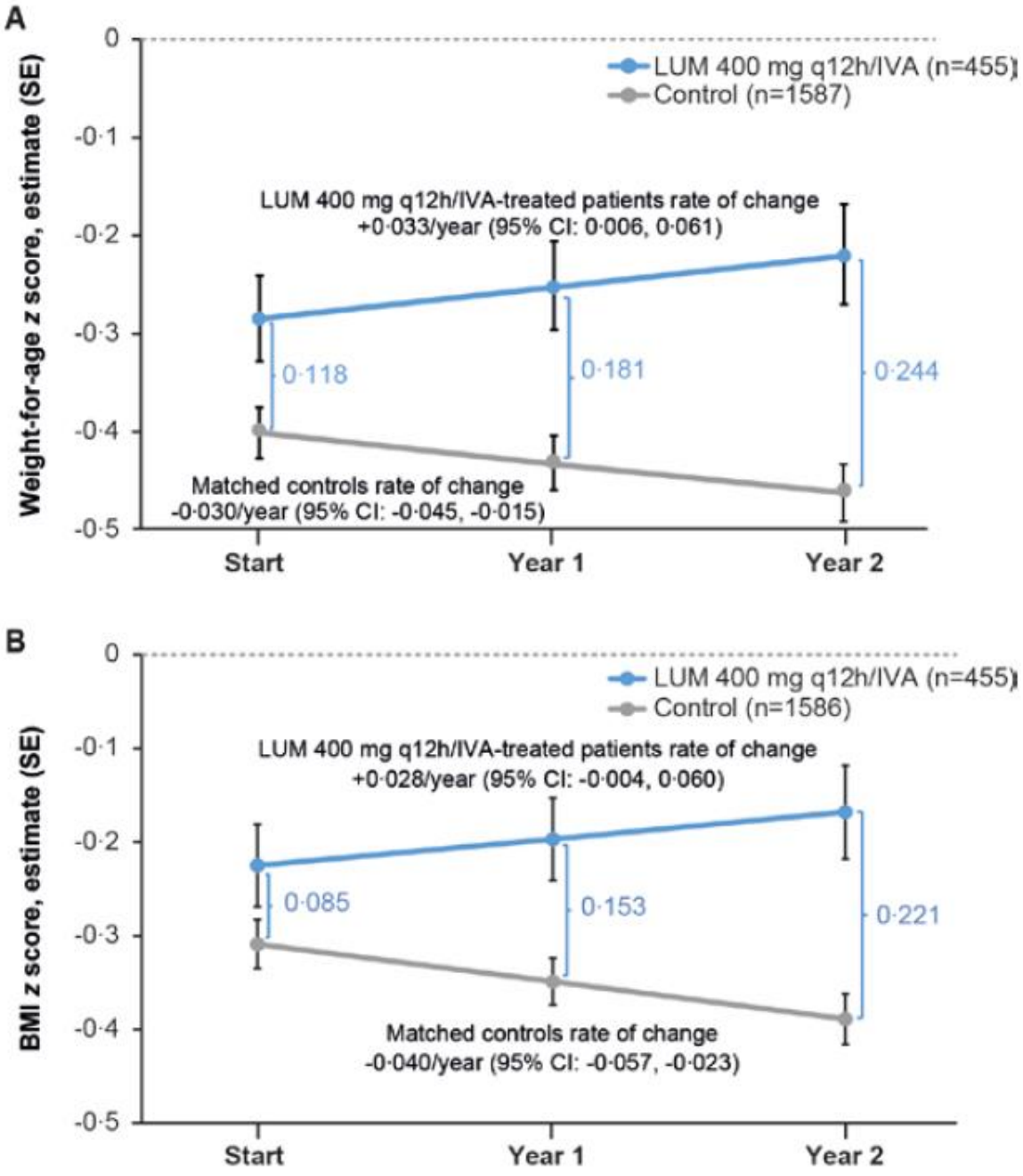
				• Absolute change in weight • Absolute change in weight-for-age-z-score • Absolute change in height • Absolute change in height-for-age-z-score • Absolute change in Treatment Satisfaction Questionnaire for Medication (TSQM) domains • Time-to-first pulmonary exacerbation (subjects from Study 109 only) • Event of having at least 1 pulmonary exacerbation • Number of pulmonary exacerbations • Rate of change in LCI2.5 (subjects from Study 109 and the Study 011B LCI Substudy only) • Rate of change in LCI5.0 Rate of change in ppFEV1	
Observational Study of Outcomes in Cystic Fibrosis Patients With Selected Gating Mutations on a CFTR Allele (The VOCAL Study) Vertex Pharmaceuticals Incorporated NCT02445053	Observational Cohort study Estimated enrollment: 90	1. Experimental: Ivacaftor Observational model: cohort	Inclusion Criteria • Male or female with confirmed diagnosis of CF16 • At least 1 allele with 1 of the following CFTR mutations: G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D • Six years of age or older Exclusion Criteria • Previously exposed to ivacaftor, except currently treated patients who started ivacaftor treatment within 6 months of enrollment • Currently enrolled in a ivacaftor interventional study or other interventional therapeutic clinical study directed at CFTR modulation • History of organ transplantation	Primary Outcome Measures • Number of pulmonary exacerbations and duration of treatment for pulmonary exacerbations [Time Frame: 48 Months] • Percentage of patients with cultures positive for Pseudomonas aeruginosa • Percentage of patients with cultures positive for bacteria other than Pseudomonas aeruginosa and for fungi • Absolute change in percent predicted FEV1 • Absolute change in weight, weight-for-age Z score, body mass index (BMI), and BMI-for-age Z-score • Incidence and prevalence of comorbidities during ivacaftor treatment compared to the period before ivacaftor treatment • Incidence and cause of deaths Incidence and reason for organ transplantations	December 2020

A Study in US Cystic Fibrosis Patients With the R117H-CFTR Mutation to Confirm the Long-term Safety and Effectiveness of Kalydeco, Including Patients <18 Years of Age, Combining Data Captured in the Cystic Fibrosis Foundation Registry From an Interventional Cohort and a Non-Interventional Cohort Vertex Pharmaceuticals Incorporated NCT02722057	Observational Cohort study Estimated enrollment: 150	1. Cohort 1: Intervention The Interventional cohort will not be utilized. 2. Cohort 2: Non Intervention A Non-Interventional Cohort comprising pediatric (<18 years of age) and adult R117H-CFTR patients treated with commercially-available ivacaftor. 3. Cohort 3 - Historical A Historical Cohort comprising data from an earlier time period for pediatric (<18 years of age) and adult patients with the R117H-CFTR mutation who have never been exposed to ivacaftor and matched on age, gender, and lung function to patients in the Non-Interventional Cohort.	Inclusion Criteria Non Interventional Cohort • Male or female with confirmed diagnosis of CF • Must have at least 1 allele of the R117H-CFTR mutation • Enrolled in the US CFF Patient Registry • With a record of ivacaftor treatment initiation from 01 January 2015 through 31 December 2016 Historical Cohort • Patients with CF in the CFF Patient Registry as of 01 January 2009 • Must have at least 1 allele of the R117H-CFTR mutation • Patients with no evidence of any prior ivacaftor exposure	Primary Outcome Measures • FEV1 and forced vital capacity [FVC]) [Time Frame: 36 Months] • Pulmonary exacerbations, use of IV antibiotics • Height and weight measurements. BMI, BMI-for-age z-score, and weight-for-age z-score • Death or transplantation • Hospitalizations • Symptomatic sinus disease, Pulmonary complications, CF-related diabetes and distal intestinal obstruction syndrome, Hepatobiliary complications, Pancreatitis • Information for the above shown CF-related complications as recorded in the registry will be evaluated Select pulmonary microorganisms	December 2019

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

Appendix D. Comparative Clinical Effectiveness Supplemental Information

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

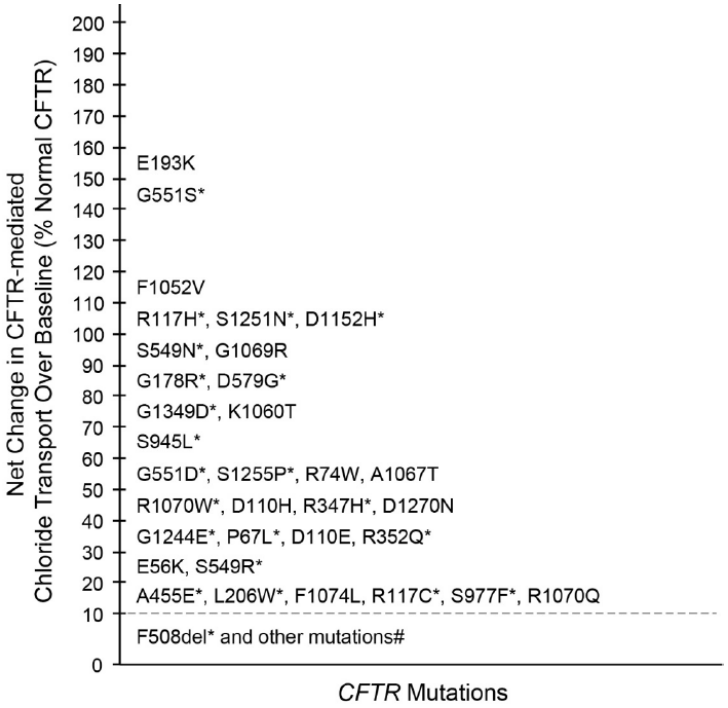


Genetic Specific Data on CFTR Modulators

Ivacaftor

The effect of ivacaftor differs by mutation.[76] Below are the in vitro response thresholds and stratified efficacy data from clinical trials, adapted from the FDA label (prescribing information).[76]

Figure D2. Net Change Over Baseline (% of untreated normal) in CFTR-Mediated Chloride Transport Following Addition of Ivacaftor from FDA Label[76]



*Clinical data exist for these mutations

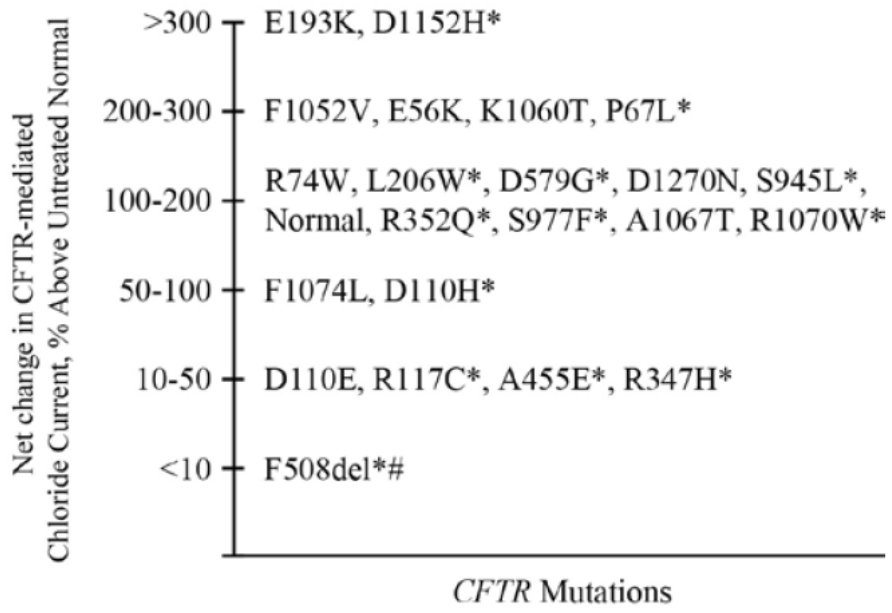
Figure D3. Efficacy Outcomes of Ivacaftor by Genetic Mutation from FDA Label[76]

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[6]

The effect of Symdeko differs by mutation.[76] Below are the in vitro response thresholds and stratified efficacy data from clinical trials, adapted from the FDA label (prescribing information).[76]

Figure D4. Net Change Over Baseline (% of Untreated Normal) in CFTR-Mediated Chloride Transport Following Addition of Symdeko from FDA Label[6]



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

Figure D5. Efficacy Outcomes of Symdeko by Genetic Mutation from FDA Label[6]

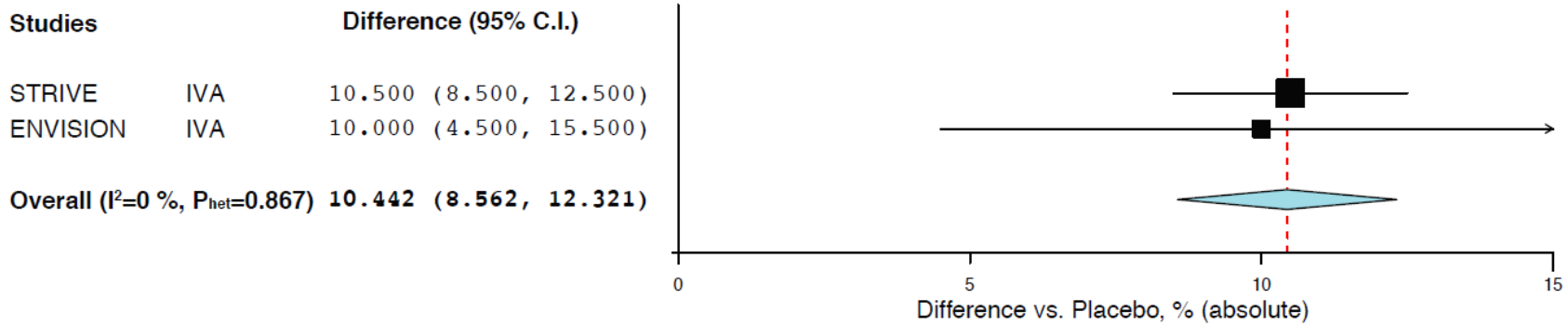
Mutation (n)	Absolute Change in percent predicted FEV_1*†	Absolute Change in CFQ-R Respiratory Domain Score (Points)*§	Absolute Change in Sweat Chloride (mmol/L)*§
Splice mutations (n= 93 for TEZ/IVA, n=97 for PBO) Results shown as difference in mean (95% CI) change from study baseline for SYMDEKO vs. 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.

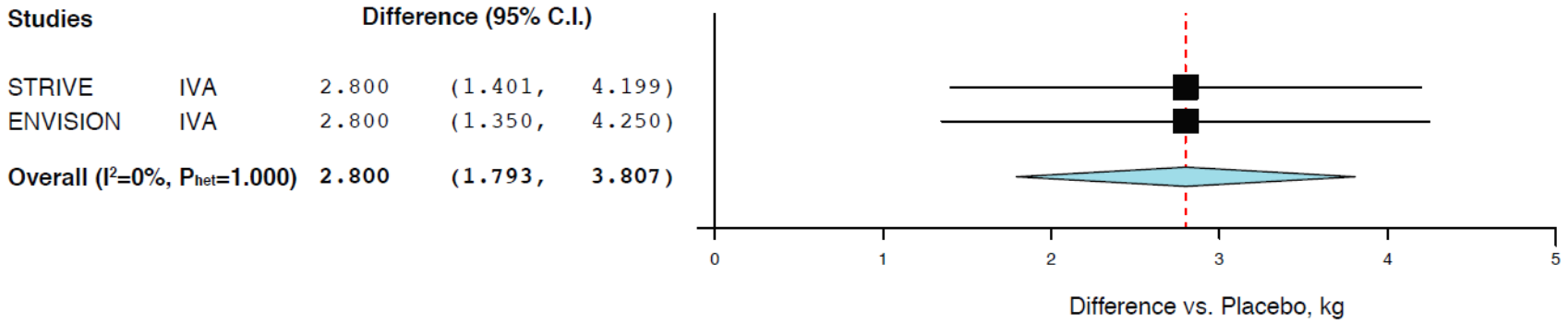
Forest Plots from Meta-Analysis

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)



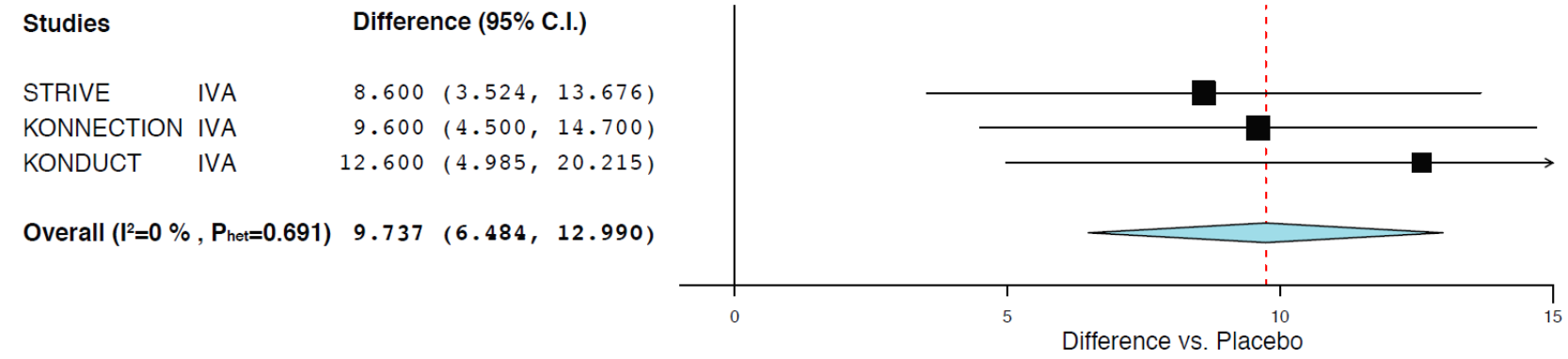
C.I: confidence interval, IVA: ivacaftor, Phet: chi-square P value for heterogeneity

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)



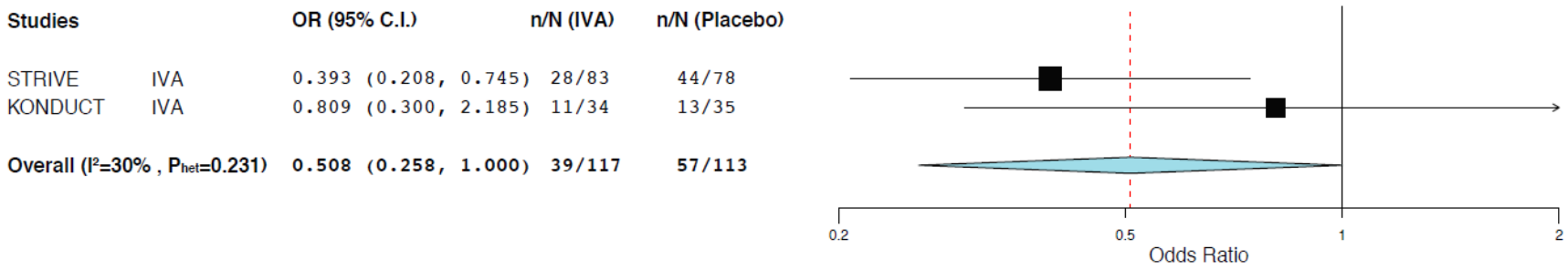
C.I.: confidence interval, IVA: ivacaftor, Phet: chi-square P value for heterogeneity

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)



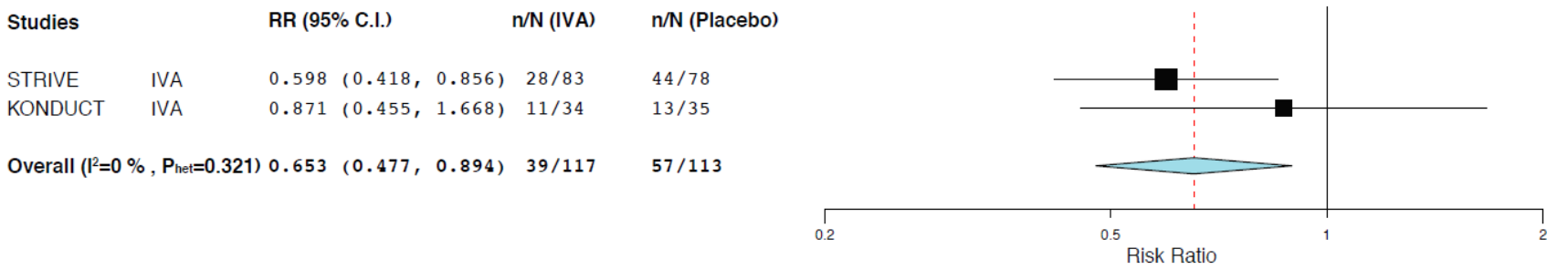
C.I.: confidence interval, CFQ-R: Cystic Fibrosis Questionnaire-Revised, IVA: ivacaftor, Phet: chi-square P value for heterogeneity.

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



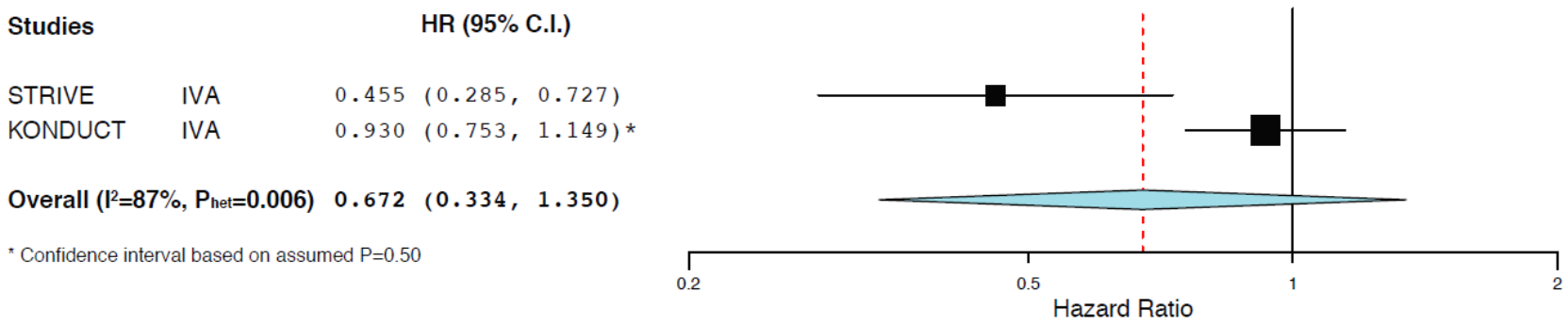
Abbreviations: C.I.: confidence interval, IVA: ivacaftor, OR: odds ratio, P_{het} = chi-square P value for heterogeneity.

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



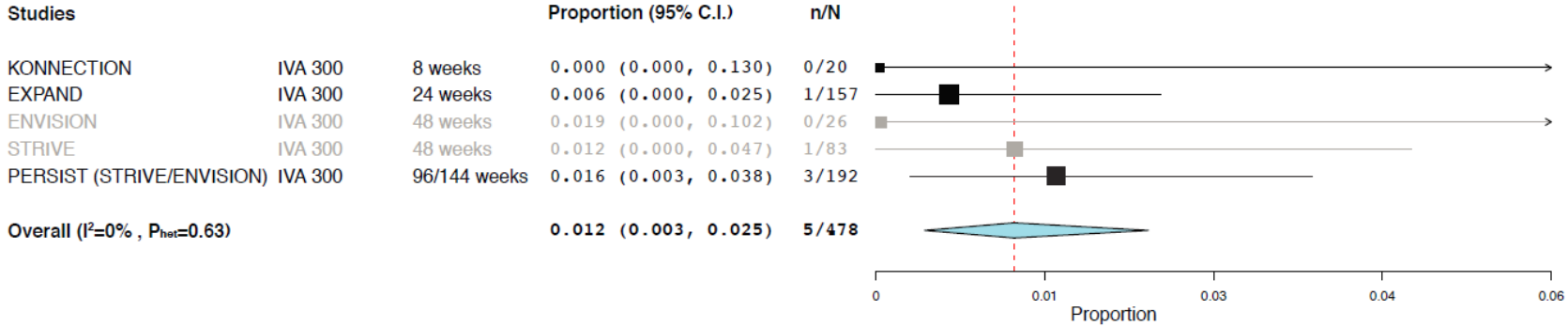
C.I.: confidence interval, IVA: ivacaftor, Phet = chi-square P value for heterogeneity, RR: risk ratio.

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



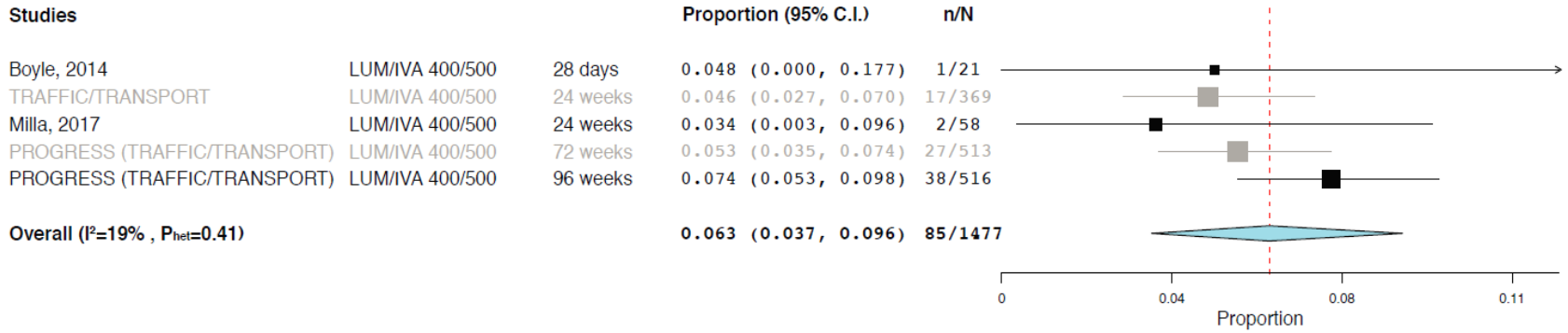
C.I.: confidence interval, HR: hazard ratio, IVA: ivacaftor, Phet = chi-square P value for heterogeneity.

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



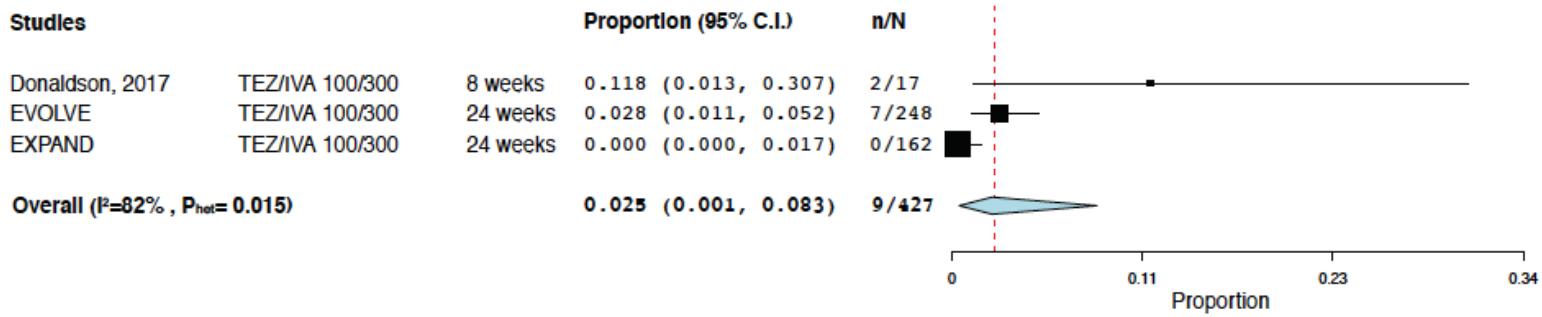
Studies in grey provide shorter-term results than subsequent studies and are not included in the meta-analysis
C.I.: confidence interval, IVA: ivacaftor, P_{het}: chi-square P value for heterogeneity.

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



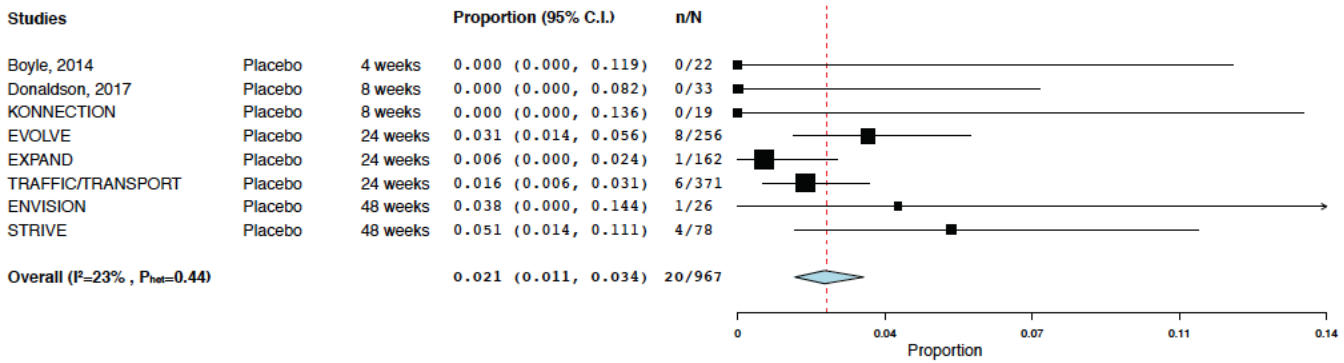
Studies in grey provide shorter-term results than subsequent studies and are not included in the meta-analysis
C.I.: confidence interval, LUM/IVA: lumacaftor/ivacaftor (with daily dosage in mg per drug), P_{het} : chi-square P value for heterogeneity

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



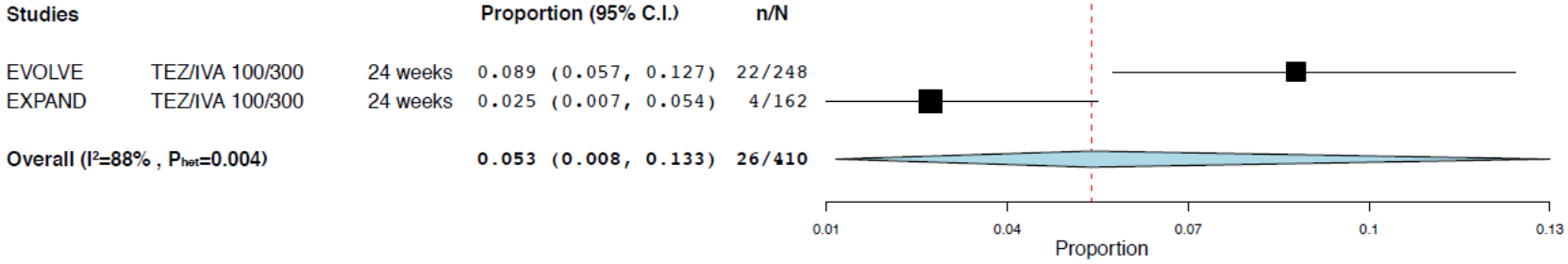
C.I.: confidence interval, Phet: chi-square P value for heterogeneity, TEZ/IVA: tezacaftor/ivacaftor (with daily dosage in mg per drug)

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



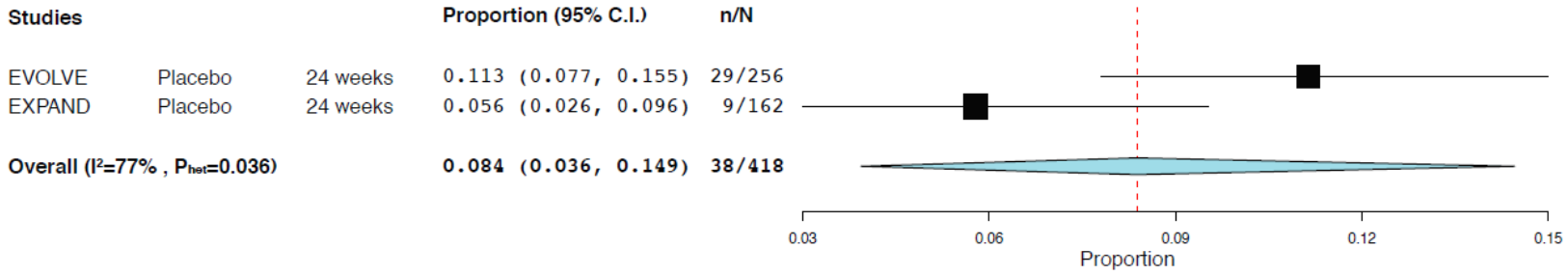
C.I.: confidence interval, P_{het}: chi-square P value for heterogeneity

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

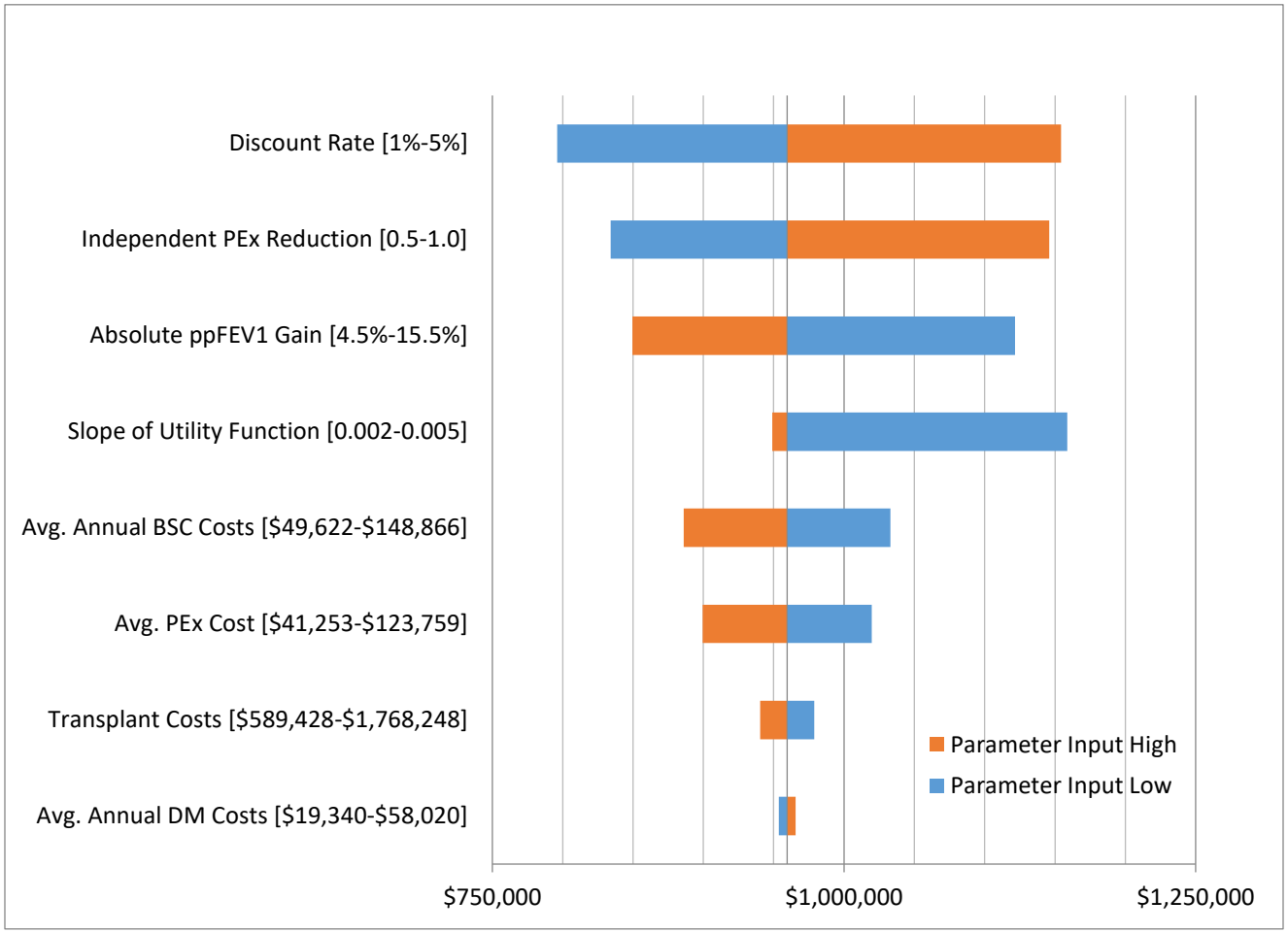
Appendix E. Comparative Value Supplemental Information

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	☐	

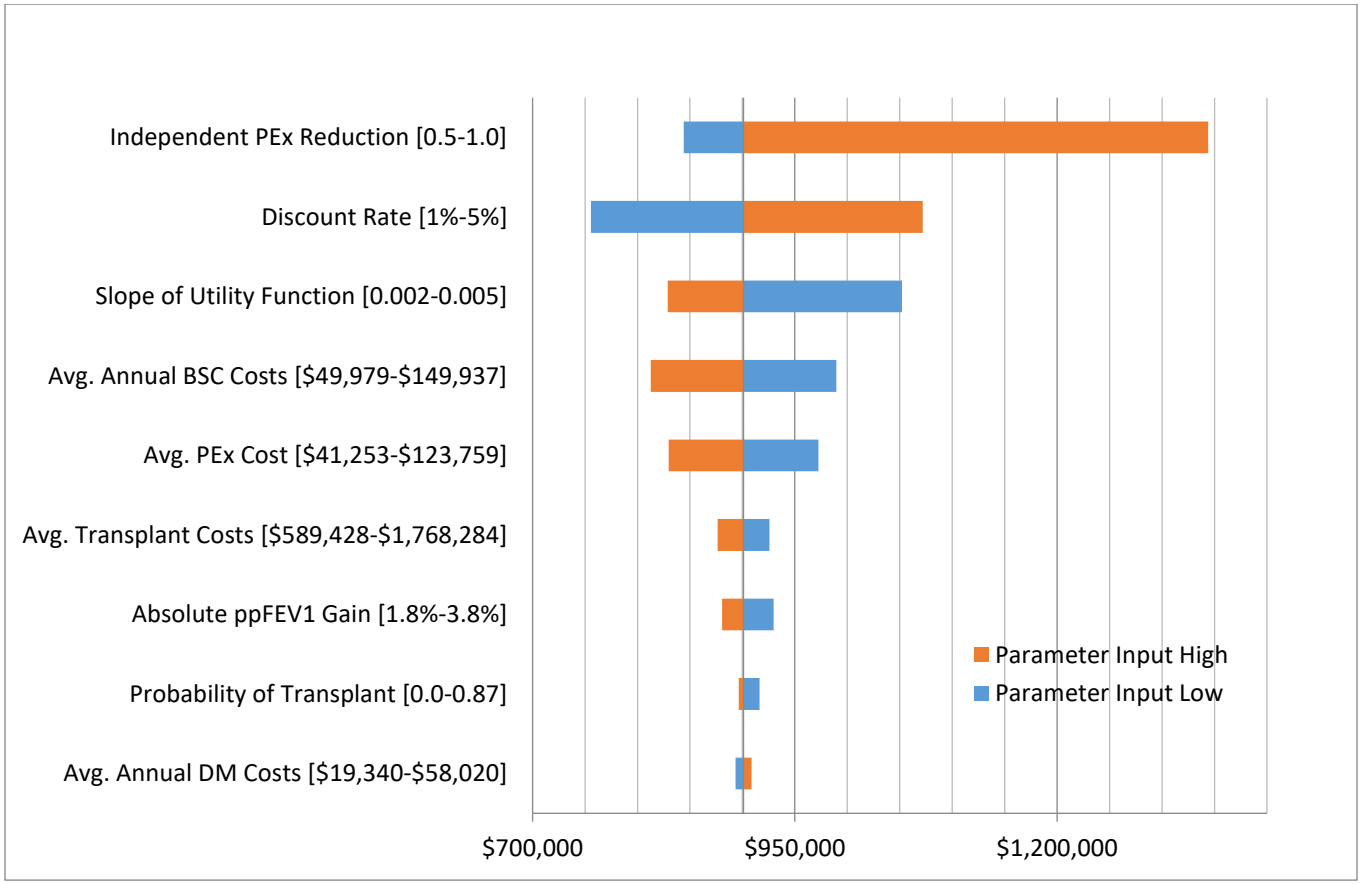
One-Way Sensitivity Analyses

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 with Gating Mutations



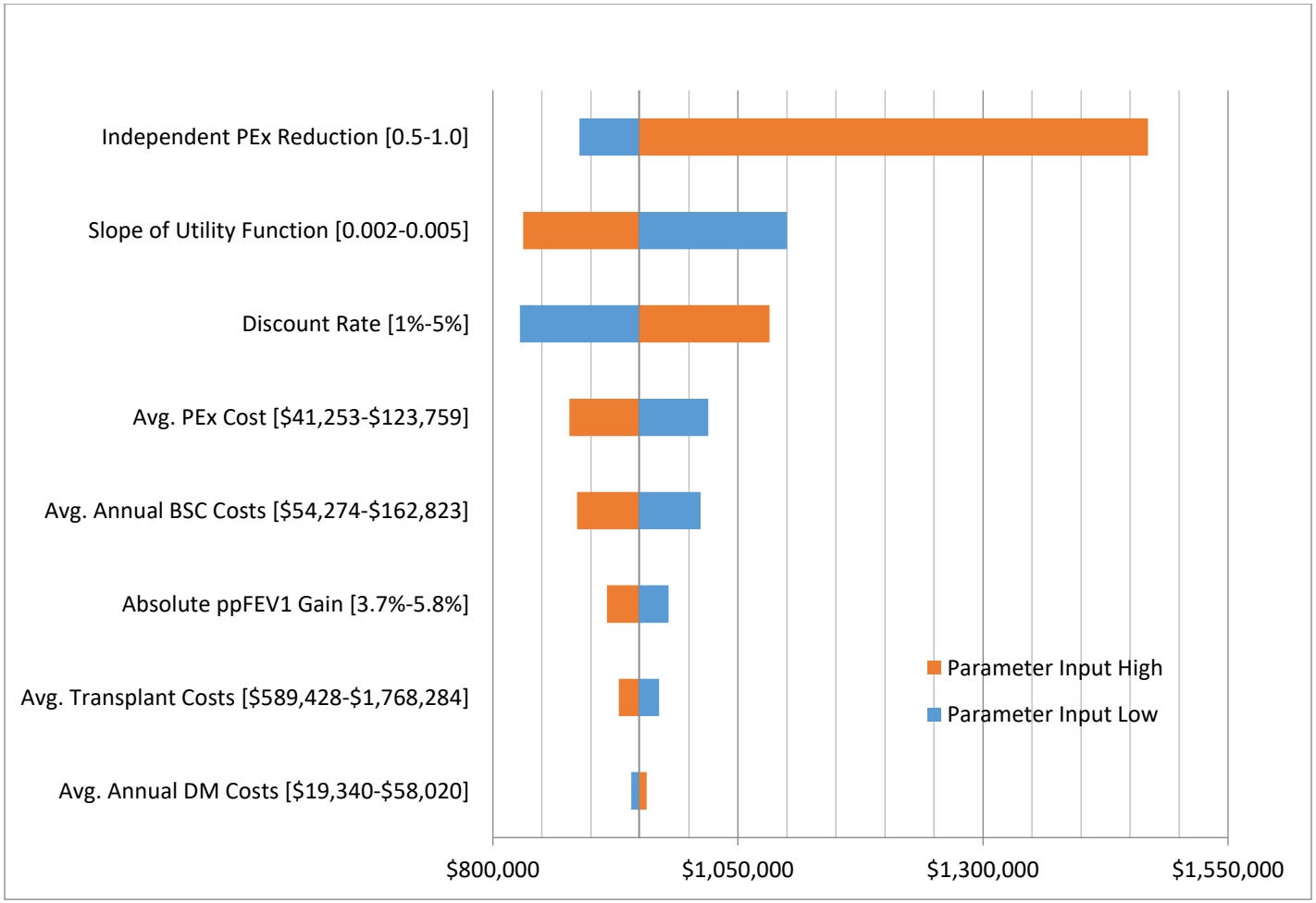
PEx: acute pulmonary exacerbation; BSC: best supportive care; DM: disease management
Probability of transplant among individuals with $ppFEV_1$<30%

Figure E2. Tornado Diagram for One-Way Sensitivity Analyses of Cost per QALY Gained for Orkambi Plus Best Supportive Care Versus Best Supportive Care Alone in CF Individuals Homozygous for *F508del* Mutation



PEx: acute pulmonary exacerbation; BSC: best supportive care; DM: disease management
Probability of transplant among individuals with $ppFEV_1$<30%

Figure E3. Tornado Diagram for One-Way Sensitivity Analyses of Cost per QALY Gained for Kalydeco 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; DM: disease management
Probability of transplant among individuals with $ppFEV_1$<30%

Probabilistic Sensitivity Analyses

Figure E4. Scatterplot of Cost and Effectiveness for Ivacaftor Plus Best Supportive Care and Best Supportive Care Alone in CF Individuals with Gating Mutations (1,000 Iterations)

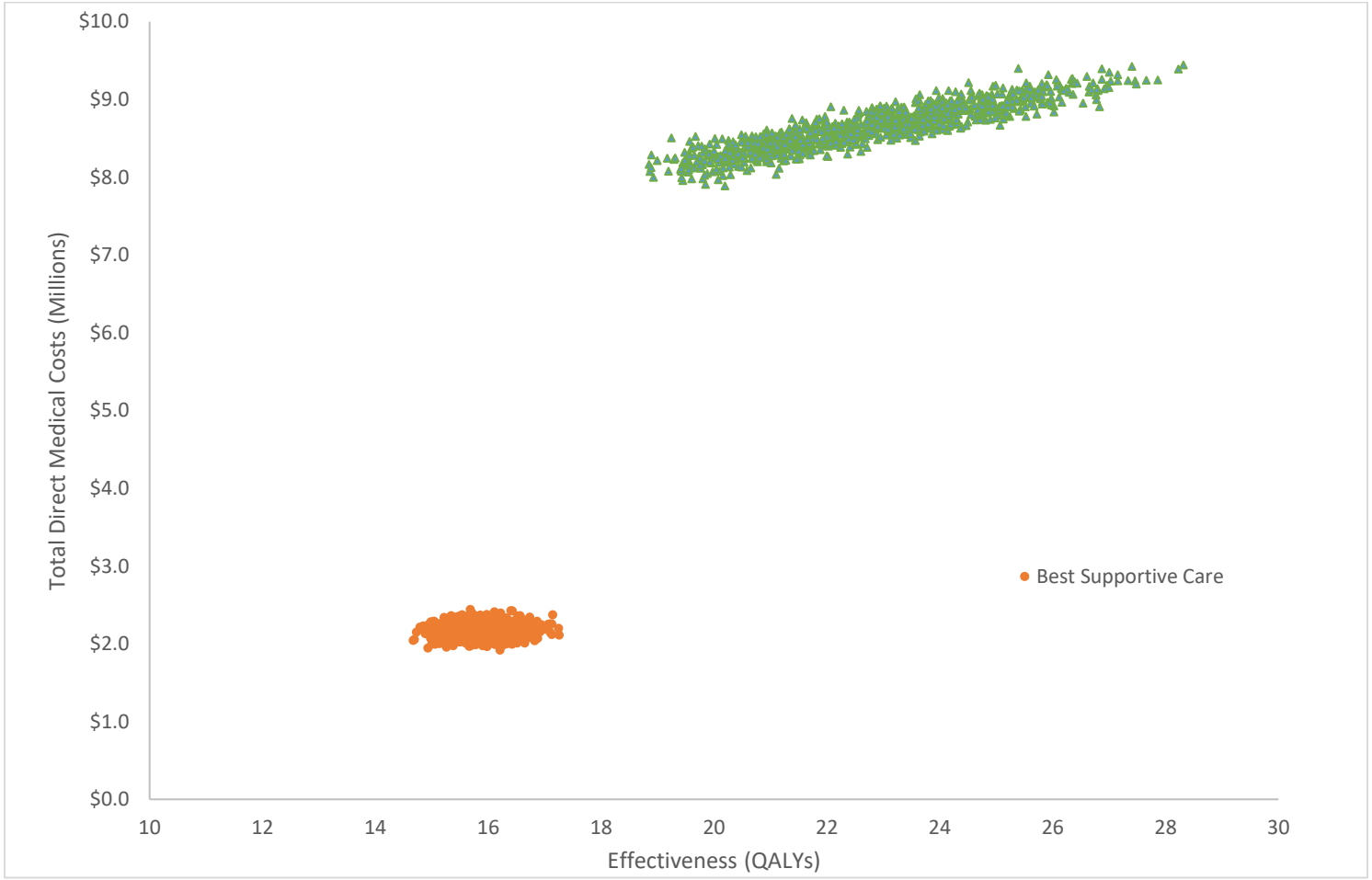


Figure E5. Scatterplot of Cost and Effectiveness for Lumacaftor/Ivacaftor Plus Best Supportive Care, Tezacaftor/Ivacaftor plus Best Supportive Care, and Best Supportive Care Alone in CF Individuals Homozygous for *F508del* Mutation (1,000 Iterations)

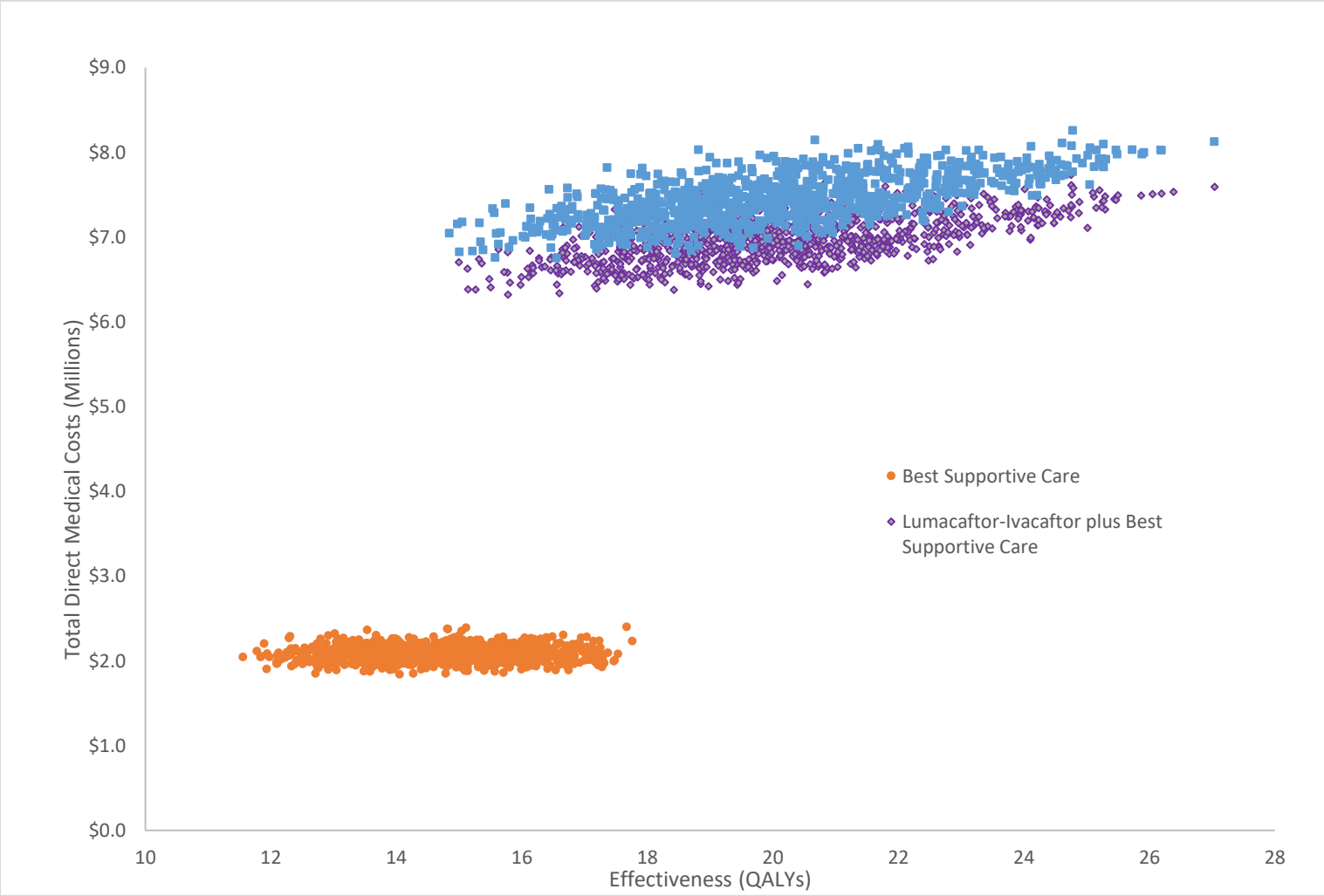
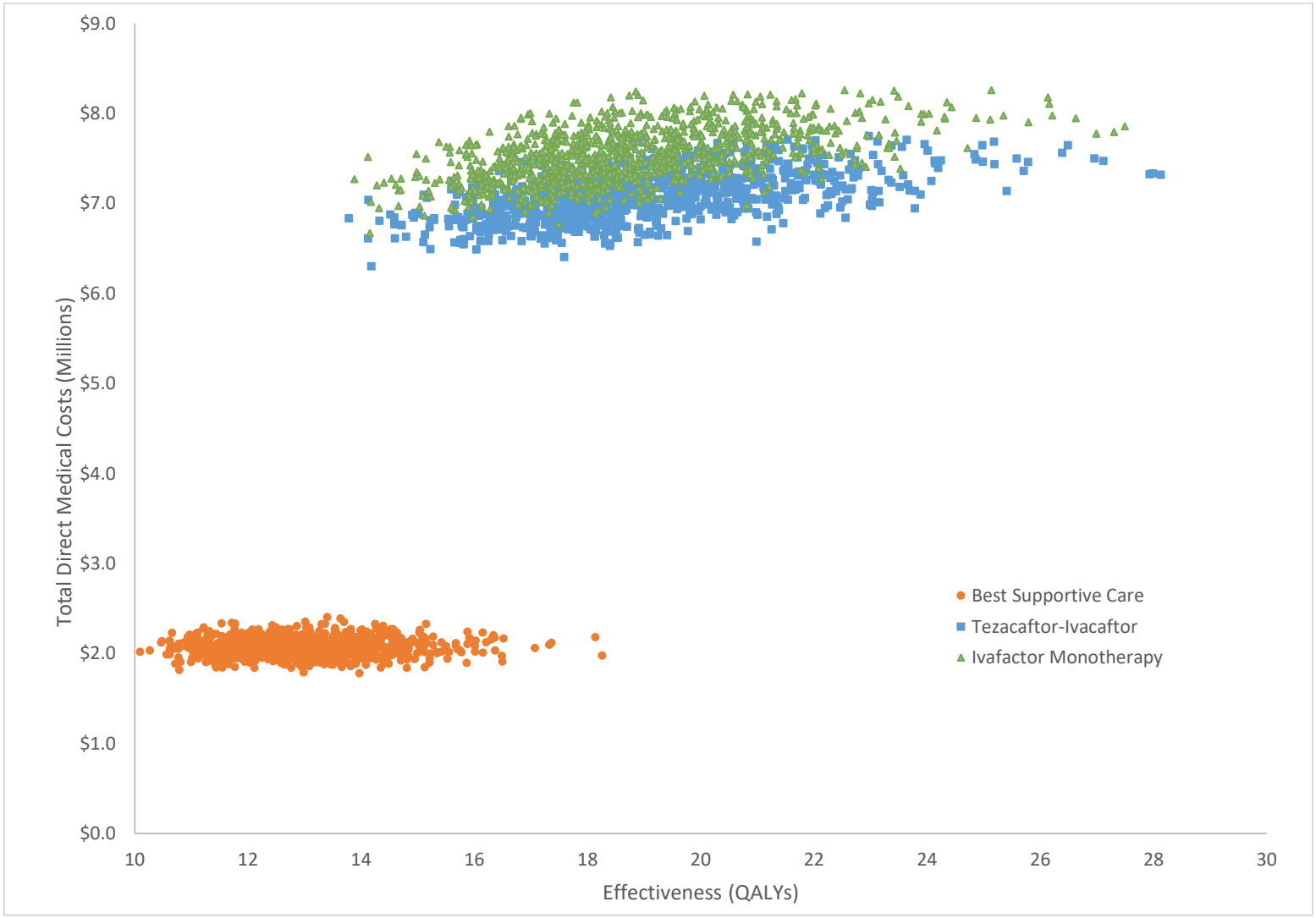


Figure E6. Scatterplot of Cost and Effectiveness for Kalydeco Plus Best Supportive Care, Tezacaftor/ivacaftor plus Best Supportive Care, and Best Supportive Care Alone in CF Individuals Heterozygous for *F508del* Mutation and Residual Function Mutation (1,000 Iterations)



Appendix F. Evidence Tables

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 [18] ***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) (2) 122 (0.99) **BMI** **Mean absolute change from baseline, kg/m^2 (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)	**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) **Headache, n (%)** (1) 44 (17.5)

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
				* Scores on (CFQ-R) range from 0-100, higher scores indicating a higher patient-reported QoL with regard to respiratory status.	**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)	(2) 37 (14.3)
Rowe [22] ***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. Duration of follow-up: 24 weeks	**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) 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	**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 **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	**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) **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)	**$ppFEV_1$** **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) 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)	**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) (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)

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
		interventions studied for 8 weeks each with an 8-week washout period between.	• 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 with more rapid decline in pulmonary status	(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) (2) 11 (14) (3) 11 (13) • No (1) 56 (70)	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) Tez/Iva vs. Iva: 1.4 (−1.0 to 3.9) **PExs** Number of events (1) 20 (2) 9 (3) 11 Estimated event rate/year (1) 0.63 (2) 0.29 (3) 0.34 Rate ratio v. placebo (95% CI) (2) (0.21 to 1.01) (3) (0.26 to 1.1.3)	(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) (2) 8 (5) (3) 6 (4)

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
				(2) 61 (75) (3) 60 (72) Missing (1) 13 (16) (2) 9 (11) (3) 12 (14)		
Donaldson [4] ***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 100/150mg combination and placebo***	**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 may confound study results or increase potential harm to participant • PE or change in treatment within 14 days first dose	**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) (2) 57.8 (15.3) **BMI** **Mean, kg (SD)** (1) 23.0 (3.7) (2) 21.7 (2.4)	**$ppFEV_1$** **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) **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)	**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) **Discontinuation due to AE, n (%)** (1) 2 (11.8) (2) 0 (0) **Cough, n (%)** (1) 17 (16.0) (2) 6 (18.2)

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
			• 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 •			
Orkambi						
Wainwright [16] ***NEJM*** **2015** **TRAFFIC and TRANSPORT - Homozygous F508d** **Good**	Two phase 3, double-blind, placebo-controlled, randomized trial Duration of follow-up: 24 weeks 187 centers in North America, Australia, and Europe Enrollment between April 2013 and April 2014	**N=1108** (1) LUM/IVA: 600 mg of lumacaftor once daily in combination with 250 mg of ivacaftor every 12 hours (n=368) (2) LUM/IVA: 400 mg of lumacaftor every 12 hours in combination with 250 mg of ivacaftor every 12 hours (n=369)	**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 was 40- 90% of the predicted normal values • Stable cystic fibrosis disease	**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) **$ppFEV_1$** **Mean, percentage points**	**Pooled Analysis, least-squares means** **$ppFEV_1$** **Mean absolute change from baseline** Within-group, percentage points (p-value) (1) 3.0 (p < 0.001) (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	**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) **≥ One SAE, n (%)** (1) 84 (22.8) (2) 64 (17.3) (3) 106 (28.6)

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
	All data reported are pooled groups of two studies – TRAFFIC and TRANSPORT	(3) Placebo: Lumacaftor-matched placebo every 12 hours in combination with ivacaftor-matched placebo every 12 hours (n=371)	**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	(1) 60.8 (2) 60.5 (3) 60.4 **BMI** **Mean, kg/m²** (1) 21.0 (2) 21.5 (3) 21.0	**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/m² (p-value)** Within group (1) 0.41 (p<0.001) (2) 0.37 (p<0.001) (3) 0.13 (p=0.007) **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)	**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)

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
					(2) 152; 0.61 (0.49 to 0.76) (3) 251; NA	
Elborn [23] ***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%ppFEV1=28) LUM 400 mg q12 Iva 250 mg q12, n=731 (2) Baseline ppFEV1 <40% n=53 (3) Baseline ppFEV1 ≥40% n=687 (4) Screening ppFEV1 <70% n=527 (5) Screening ppFEV1 • ≥70% n=204 •	**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)** (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)	**Pooled Analysis** **< 40% vs. ≥40% ppFEV1** **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 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/m^2 (95% CI)** (1) reference (2) 0.3 (-0.2 to 0.8)	**Pooled Analysis** **< 40% vs. ≥40% ppFEV1** **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) **Headache, n (%)** (1) 57 (16) (2) 10 (19) (3) 103 (15)

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
	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%			(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)	(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 (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 [19] ***Lancet Resp Med*** **2017**	Phase 3, multicenter, parallel group, open-label trial.	**N=1030** (1) LUM/IVA: continued 400 mg of lumacaftor every 12 hours in	**Inclusion** • Confirmed diagnosis of CF • Homozygosity for the *F508del*-CFTR mutation • Age of 12 years or older	**Age** **Mean, years (SD)** (1) 25.1 (9.3) (2) 24.9 (10.1)	**Pooled Analysis, least-squares means** **$ppFEV_1$**	**Death, n (%)** (1) 2 (0.5) (2) 1 (0.5)

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
PROGRESS - Homozygous F508d	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	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), those on LUM/IVA in Traffic/Transport had received 96 weeks of active drug.	**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 study drug or procedures • Participation in an investigational drug trial	**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/m^2 (SD)** (1) 21.4 (2.9) (2) 20.9 (2.8) ***Pseudomonas* positive, no.** (1) 261 (2) 126	**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** 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)	**Discontinuations for two groups, n (%)** 170 (33) **Discontinuation d/t AE, n (%)** 38 (7) **Infective PEx of CF, %** 65 **Cough, %** 44 **Increased sputum, %** 22 **Hemoptysis, %** 20

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
					BMI **Mean absolute change from baseline, kg/m²** 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) **CFQ-R Respiratory domain** **Mean absolute change from baseline, points (95% CI)** At 72 weeks (1) 5.7 (3.7 to 7.5) (2) 3.3 (0.7 to 5.9) At 96 weeks (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)	

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
					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 [109] ***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/m² (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* (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)	**Most commonly reported AEs:** Infective PEx of CF (48%) Cough (39%) Headache (17%) Dyspnea (17%) Abnormal respiration (14%)

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
					(2) 0.6 (0.5 to 0.8) *Interim analysis	
McColley [110] ***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 ppFEV1 AND • ≥5 or • <5% relative improvement in ppFEV1 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: 0.38 (0.24 to 0.59) <5% relative improvement: 0.31 (0.19 to 0.51) ≥5% relative improvement: 0.50 (0.31 to 0.82) **PEx requiring antibiotics** ≤0% absolute improvement:	**NA**

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
					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[75] ***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 Duration of follow-up: 24 weeks	**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** • Current use of invasive mechanical ventilation • Any comorbidity that may confound study results or increase potential harm to participant • Abnormal liver or renal function	**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) **Documentation of being on lung transplant list at screening, n** Yes: 2 No: 25 Unavailable: 19	**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) 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/m² (0.17) Also measured: Annualized all-cause hospitalization event rate in	Any AE, n (%): 43 (93) AE leading to treatment discontinuation: 8 (17) Serious AE: 18 (39) **AE leading to death: 1 (2)** AE with incidence >10%: Infective PE: 27 (59) **Respiration abnormal: 26 (57)** Cough 21 (46) Dyspnea 20 (43)

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
					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 duration (11.38 days) vs. prior 24 weeks (19.89 days). Mean difference of -8.52 (3.67), p=0.0369	
Jennings [24] ***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)	**$ppFEV_1$** **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)

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
				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) **Proton-pump inhibitor use, No. (%)** 51 (44) **Anti-depressant use, No. (%)** 21 (18.1) **Azole use, No. (%)** 6 (5.2)		**Diarrhea** 5 (4.3) **Nausea** 3 (2.6) **Decreased appetite** 2 (1.7) **Rash** 2 (1.7) **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 [17] ***Lancet Resp Med*** **2017** **Homozygous *F508del***	Phase III, randomized, double-blind, placebo-controlled, multinational trial Nine countries: USA, Australia, Belgium, Canada, Denmark,	**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*	**Mean age, years (SD)** (1) 8.7 (1.6) (2) 8.9 (1.6) **Sex** **Female, n (%)** (1) 63 (61) (2) 58 (57) **$ppFEV_1$**	**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	**Any AE, n (%)** (1) 98 (95) (2) 98 (97) **Any SAE, n (%)** (1) 13 (13) (2) 11 (11) **Study discontinuation, n (%)**

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
	France, Germany, Sweden, and the UK Duration of follow-up: 24 weeks Enrollment: July 23, 2015 to Sept 20, 2016		**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 • History of solid organ transplant	**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)	**BMI** **Mean (least-squares) absolute change from baseline, kg/m² (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 **$ppFEV_1$** **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	(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) **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 ppFEV1 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)

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
					decline	**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 [20] ***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)	**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)

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
					CFQ-R **Mean (least-squares) absolute change from 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 [77] ***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 • ppFEV1≥40% • At least one *F508del* (we only report on two copies) **Exclusion**: • Any comorbidity or lab abnormality that may confound study results	**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**	**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 baseline, percentage points (95%CI)**	**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) **Discontinuation d/t AE, n**

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
	Duration of follow-up: 28 days	(2) Placebo (n=24; pooled across cohort 2 and 3)	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 • In another trial in last 3 months	**Female, n (%)** (1) 5 (45) (2) 9 (33) **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)	(1) 8.2 (1.8 to 14.7) (2) −2.1 (−6.3 to 2.2)	1/15 **Cough, n (%)** (1) 3 (27) (2) 6 (22) **Headache, n (%)** (1) 2 (18) (2) 5 (19)
Ivacaftor						
Ramsey [8] ***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 disease	**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	**$ppFEV_1$** **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 RR (95% CI): 0.43 (0.27 to 0.68)	**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)

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
			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	**BMI** **Mean, kg/m²** (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.	**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 [9] ***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	**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**	**$ppFEV_1$** **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) **CFQ-R Respiratory domain**	**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)

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
			• Acute respiratory infection, PE, or changes in therapy 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	**Mean, kg (range)** (1) 31.8 (18.8-62.6) (2) 30.0 (17.8-46.3) **BMI** **Mean, kg/m² (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	**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.	**PEx of CF, n (%)** (1) 8 (31) (2) 8 (31) **Cough, n (%)** (1) 13 (50) (2) 19 (73) **Headache, n (%)** (1) 7 (27) (2) 4 (15)
McKone [15] ***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 placebo (n=22) Note: Groups a) and c) on IVA for 48 weeks	**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 • Participants of child-bearing potential and who are sexually active must meet	**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) a.) 41 (53) b.) 35 (52) c.) 17 (65)	**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) **BMI** **Mean absolute change from baseline, kg/m² (SD)** (1)	**Any AE, n (%)** STRIVE and ENVISION placebo groups: Week 1-48: 82 (92%) Week 48-96: 81 (92%) 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%)

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
		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	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	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/m^2 (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)	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)	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%)

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
						Week 48-96: 16 (18%) STRIVE and ENVISION ivacaftor groups: Week 48-96: 32 (31%) Week 96-144: 27 (26%) **Headache, n (%)** (1) STRIVE and ENVISION placebo groups: Week 1-48: 11 (12%) Week 48-96: 7 (8%) STRIVE and ENVISION ivacaftor groups: Week 48-96: 14 (14%) Week 96-144: 17 (17%)
De Boeck [10] ***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 4-8 week	**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 disease	**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**	**$ppFEV_1$** **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/m² (95% CI)** (1) 0.7 (2) 0.02 Difference=0.7 (0.34 to 0.99) **CFQ-R respiratory domain** **Mean absolute change from baseline, points (95% CI)**	**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) **Headache, n (%)** (1) 5 (25)

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
		washout between placebo and ivacaftor	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	(1) 0.50 (2) 0.23	(1) 8.9 (2) −0.7 Difference= 9.62 (4.5 to 14.7) *Mixed-effects model for repeated measures.	(2) 7 (39) **Discontinuation d/t AE, n (%)** (1) 0 (2) 0
Moss [11] ***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	**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)	**$ppFEV_1$** **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) Difference= 5.0 (95% CI:-0.24 to 10.31)	**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)

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
			• 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 • 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	**BMI** **Mean, kg (SD)** (1) 24.5 (6.3) (2) 23.1 (6.0) **CFQ-R Respiratory domain** **Mean, points (SD)** (1) 75.3 (20.1) (2) 66.4 (24.4)	**BMI** **Mean absolute change from baseline, kg/m² (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 [13] ***Lancet Respiratory*** **2016** **KIWI – gating mutations**	Two-part, open-label, single-arm, phase 3 study 15 hospitals in the USA, UK, and Canada	**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	**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,	**Part B reported (only)** **Age** **N (%)** Age 2: 9 (26%) Age 3: 11 (32%) Ages 4 and 5: 14 (41%) **Sex**	**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)

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
	Part B enrolled June 28, 2013 to Sept 26, 2013	they weighed ≥14 kg (n=5) Part B: 24-week safety (1) 50 mg (n=10) (2) 75 mg (n=24)	Gly551Ser, Gly970Arg, Gly1244Glu, 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	**Female, n (%)** 6 (18) **Weight-for-age z-score Mean, score (SD)** -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	**SAE, no. events (no. pts, %)** (1) 4 (3, 30) (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)

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
Rowe [14] ***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) By age 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 By age Ages 6-11: 30.6 (7.7) Ages 12-17: 56.1 (15.7)	**$ppFEV_1$** **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) 6 mo, by age group (SD) 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) 6 mo, by age group (SD) Ages 6-11: 3.7 (2.9) Ages 12-17: 3.3 (3.3) Ages 18+: 1.5 (3.5) **BMI** **Mean absolute change from baseline, kg/m^2 (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)	**Not reported**

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
				Ages 18+: 66.5 (13.7) **BMI** **Mean, kg/m² (SD)** 21.3 (4.5) <u>By age</u> 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 <u>By age</u> Ages 6-11: 83.6 (12.2) Ages 12-17: (76.2) (15.6) Ages 18+: 62.4 (20.5)	**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) <u>6 mo, by age group (SD)</u> Ages 6-11: -0.7 (16.7) Ages 12-17: 7.6 (14.6) Ages 18+: 11.7 (20.7)	
Flume [72] ***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	**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)**	**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)	**See STRIVE**

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
	Duration of follow-up: 48 weeks (STRIVE)			(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) • <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)	**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)** (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	

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				(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)	ppFEV$_1$ measurement most closely preceding PEx.	
Accurso [111] ***NEJM*** **2010** **Phase 2**	Multicenter phase 2 double-blind, placebo-controlled, two-part dose-ranging study (N=39). 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:	**Part 1** **N=20** (1) IVA: ivacaftor every 12 hours in 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)	**Inclusion** • 18 years of age or older • Diagnosed with CF • 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	**Sex** **Females, n (%)** Part 1: 11 (55) Part 2: 9 (47) **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)	**ppFEV$_1$** **Mean relative change from baseline, 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	**All AEs, no. reported (%)** Part 1: 7 (88) Part 2: 6 (86) **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

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
	28 days		• Ongoing participation in another therapeutic clinical trial, or prior participation in an investigational study without appropriate washout		250mg vs. placebo: p=0.78 **CFQ-R Respiratory domain Median change from baseline, points (range)** Part 2 at 28 days 150mg: 8.3 (0 to 16.7) 250mg: 11.1 (-5.6 to 33.3) Placebo: 0 Difference 150mg vs. placebo: p=0.46 250mg vs. placebo: p=0.47	
Guigui [112] ***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)** Year 1 (1) NR (2) 61 (15) Year 3 (1) 60 (NR) (2) 54 (14) **BMI** **Mean, kg/m^2 (SD)** Year 3 (1) 22.3 (3) (2) 21 (3) **CFQ-R** **Mean, points (SD)** Year 3 (1) 95 (5) (2) 50 (4)	**NR**

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
					No. of PEs per year (SD) Year 3 (1) 2 (2) (2) 5.5 (3)	
Sawicki [68] ***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)	**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**

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
	Duration of follow-up: up to 3 years				(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 [69] ***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	**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) Ages >20	**Not reported**

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
				(1) 18.5 (2.92) (2) 18.2 (2.38) <u>Ages >20</u> (1) 22.6 (3.73) (2) 23.1 (3.42) **BMI-for-age z-score Mean, score (SD)** <u>Ages ≤20</u> (1) -0.179 (0.9533) (2) -0.220 (0.8516) <u>Ages >20</u> (1) NR (2) NR **Mean weight at baseline, kg (SD)** <u>Ages ≤20</u> (1) 43.3 (16.18) (2) 41.8 (15.12) <u>Ages >20</u> (1) 64.9 (13.87) (2) 65.4 (13.26)	(1) NR (2) NR **BMI** **Mean change from baseline, kg/m²*** <u>Ages ≤20</u> (1) NR (2) NR <u>Ages >20</u> (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*** <u>Ages ≤20</u> (1) 0.26 (2) -0.13 Difference=0.39 (95% CI: 1.35 to 0.573) <u>Ages >20</u> (1) 2.7 (2)-0.2 Difference=2.9 (95%CI: 1.35 to 4.47) *At 48 weeks.	
Konstan [113]	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 experienced (SD)** Lower ivacaftor:

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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)	**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**	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)

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
				Middle: 64.5 (18.2) Upper: 68.9 (11.7) <u>Placebo</u> Lower: 73.1 (19.7) Middle: 66.7 (18.7) Upper: 64.6 (18.8) **Weight** **Mean, kg (SD)** <u>Ivacaftor</u> Lower: 56.5 (22.5) Middle: 58.3 (15.1) Upper: 48.8 (15.8) <u>Placebo</u> 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 [70] ***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.	**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* 8.6 (p<0.001)	**Not reported**

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
	Participants ages 14+ completed the Teen/Adult version; 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.				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 [114] ***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	**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%)	**Not reported**

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	ivacaftor treatment initiation for comparison. Duration of follow-up: 2 years (Median follow-up in the CFFPR=12.5 mos.)				<u>Less frequent</u> 36/134 (27%) <u>No change</u> 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 [73] ***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**

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
					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 [12] ***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,	**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**

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
	and genotype severity. 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 [115] ***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 [116] ***J Cyst Fibros*** **2016** **Abstract**	Non-randomized comparative long-term post-approval observational safety study using a United Kingdom CF registry.	**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, %**	**$ppFEV_1$** **Mean, percentage points (SD)** 2013 (1) 75.8 (25.7) (2) 70.6 (24.3) 2014	**PEx** **Annual risk, %** 2013 (1) 49.5 (2) 56.8 2014 (1) 34.3

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
	2012 registry data served as baseline. Patients with a 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.			(1) 51.6 (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	(1) 77.8 (25.6) (2) 70.8 (24.2)	(2) 57.0 **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 [117]	Subgroup analysis of STRIVE and ENVISION	**N=213**	**See STRIVE and ENVISION**	**Age** **N ivacaftor/n placebo**	**ppFEV$_1$** **Mean absolute change from**	**See STRIVE and ENVISION**

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
Am J Resp Crit Care Med **2012** **Abstract**	ivacaftor treatment effect on mean absolute change from baseline ppFEV1 at 24 weeks by baseline age and FEV_1. Duration of follow-up: 24 weeks	(1) Ivacaftor (See STRIVE and ENVISION) (2) Placebo (See STRIVE and ENVISION)		STRIVE <18: 19/17 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	**baseline, 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)	

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
				ENVISION (ppFEV$_1$>90%) (1) 10 (2) 11		
Flume [118] ***J Cyst Fibros*** **2013** **Abstract**	Analysis of PEx incidence and incidence of protocol-defined PEx signs and symptoms reported in STRIVE.	**N= 213** (1) IVA: ivacaftor group from STRIVE (n=83) (2) Placebo (n=78)	**See STRIVE and ENVISION**	**See STRIVE and ENVISION**	**Incidence of protocol-defined signs and symptoms of a PEx, 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)	**Not reported**
Bai [119] ***Pediatr Pulmonol*** **2015** **Abstract**	5-year observational post-authorization safety study Analyzed results of the US CF Foundation Patient Registry (CFFPR) data in 2013	**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)	**See Outcomes**

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
	Average duration of ivacaftor exposure was 1.4 years Duration of follow-up: 5 years				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) 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 [120] ***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).	**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	

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
	Clinical data was collected from patient medical records. Duration of follow-up: survey administered once				**CFQ-R Eating domain** **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	

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
					(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 [121] ***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) (3) Study 107: Ivacaftor treatment lasted 28 days (n=8)	**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**

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
Davies [122] ***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 ivacaftor every 12 hours for 4 weeks	**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

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
Elborn [123] ***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 [124] ***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 <5%: 1.6 (p=0.5093) ≥5%: 9.8 (p=0.0522) **Weight**	**Not reported**

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
					Treatment difference in absolute change from baseline, kg (p-value) STRIVE <5%: 3.3 (p<0.0001) ≥5%: 1.7 (p=0.3313) ENVISION >5%: 2.0 (p=0.0582) ≥5%: 3.4 (p=0.0094)	
Suthoff [125] ***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*** Improvement (p-value) (1) 57 (2) 25 Decline (1) 29 (2) 54 **CFQ-R Social Functioning domain** **Percent of subjects reporting*** Improvement (p-value) (1) 49 (2) 29 Decline (1) 30 (2) 50 **CFQ-R Vitality domain**	**Not reported**

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
					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	

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
					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 Decline (1) 9 (2) 28	

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
					*p<0.05 for difference between treatment groups in the percent improved and declined	
Hathorne [126] ***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> (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.	**Not reported**

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
Wainwright [127] ***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 months for supply/resupply of ivacaftor.	**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
Barry [128] ***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)	**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 • ppFEV1 < 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)	**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)**	No adverse events reported in the treatment group. 2 previously listed control subjects underwent lung transplantation.

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
	Median time on ivacaftor: 237 days			(2) 54 (49.0-62.4) **BMI** **Mean, kg/m²** (1) 19.1 (2.9) (2) 20.2 (5.2) **Sex** **Female, %** (1) 52 (2) 49	(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/m²** (1) 20.2 (2) NR **BMI** **Median change from baseline, kg/m² (IQR)** (1) 0.84 (NR) (2) 0.2 (NR)	
Davies [71] ***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,	**Inclusion** • Confirmed diagnosis of CF • At least one G551D-CFTR allele • ppFEV1 > 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)	**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	**Any AE, n (%)** Ivacaftor: 13 (72%) Placebo: 15 (79%) **SAE, n** Ivacaftor: 3 Placebo: 1

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
		28 days of placebo twice daily (n=10) **Results, at 28 days** (1) IVA (n=18) (2) Placebo (n=17)		(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)	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)	
Edgeworth [129] ***Clin Sci (London)*** **2017**	Single-center, double-blind, placebo-controlled, randomized, crossover study. Duration of follow-up: 84 days; 28 days of treatment; 28 days of washout; 28 days of other treatment	**N=20** (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)	**Inclusion** • Aged between 16 and 75 years • Confirmed diagnosis of CF • At least one G551D-CFTR allele • ppFEV1 ≥ 25% **Exclusion** • Known adverse reaction to ivacaftor • Deemed unlikely to physically complete a CPET study	**All participants** **Age** **Mean, years (range)** 32 (18-65)* **$ppFEV_1$** **Mean, percentage points (range)** 54 (23-110) **BMI** **Mean, kg/m² (SD)** 25.8 (18-36.4) **Sex** **Female, n (%)**	**Results are pooled for all subjects during ivacaftor and placebo weeks.** **$ppFEV_1$** **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/m² (95% CI)** (1) 1.9 (1.1 to 2.7) (2) 0.7 (-0.2 to 1.5)	**All participants** **No. hospitalizations for PEs** 5 **Abdominal discomfort, n** 3 **Elevated creatinine kinase, n** 1

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
				8 (40)	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)	
Stalvey [130] ***Pediatr Pulmonol*** **2017** **GOAL and ENVISION**	Post-hoc analysis on GOAL and ENVISION Duration of follow-up: GOAL: 6 mo ENVISION: 48 weeks	**N=83** GOAL: (1) IVA: n=35 ENVISION: (2) IVA: n=25 (3) Placebo: n=23	**See GOAL and ENVISION**	**Weight-for-age z-score** **Mean, score (p-value)** (1) 0 (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/m² (SD)** (1) 17.1 (2.4)	**Weight** **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)	Not reported

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
				(2) 17.2 (2.7) (3) 16.8 (1.8) **Sex** **Female, n (%)** (1) 16 (45.7) (2) 14 (56) (3) 9 (39.1)		
Fink [131] ***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) **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	**Not reported**

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
					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 [132] ***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	NA

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
					2013-2014 (73.4%) in registry population. Percent live births were higher in the CF population than the overall US population (64.6%)	

Appendix G. Summaries of Public Comments Delivered at Public Meeting

This section includes summaries of the public comments prepared for the Midwest CEPAC Public Meeting on May 17, 2018 in St. Louis, Missouri. These summaries were prepared by those who delivered the public comments at the meeting and are presented in order of delivery. A video recording of all comments can be found here (https://youtu.be/fw-FHQWNvfE), beginning at minute 1:50:20. Conflict of interest disclosures are included at the end of the statement. Two speakers did not submit a written public comment summary.

1. **Michael Boyle, MD, Senior Vice President of Theraputics Development, Cystic Fibrosis Foundation**

At time of publication, ICER has not received a summary of public comment from Dr. Boyle.

Dr. Boyle is an employee of Cystic Fibrosis Foundation (CFF), which provides research and clinical trial support to health care companies, including Vertex Pharmaceuticals, that results in the Foundation's receipt of payments, equity interests, and/or fees for service >$5,000 from Vertex Pharmaceuticals and other healthcare companies. Dr. Boyle is also an uncompensated Adjunct Professor of Medicine at Johns Hopkins University.

2. **Siri Vaeth, MSW, Associate Director, Cystic Fibrosis Research, Inc. (CFRI)**

I speak on behalf of my daughter with cystic fibrosis, CFRI, the Cystic Fibrosis Engagement Network, and the thousands of people whose lives were quantified in this shocking cost benefit analysis. We share collective outrage with the methodology and outcome of this report.

Emily's Entourage, Rock CF Foundation and the Bonnell Foundation join CFRI in rejecting your assertion that ICER engaged with us as stakeholders.

The report radically downplays the life-threatening, horrifying complications of CF. Individuals with CF are suffering. Previously there was no way to stop declining lung function, regardless of adherence to medical regimen. For many who have benefitted from CFTR-modulating drugs, it is the first time they have genuine hope that they will survive.

Your report only benefits those seeking to avoid paying for life-saving drugs - not those who are living with, and dying from, this disease. As a rare disease, CF has few therapeutic options. This report has alarming implications, providing payers with justification to refuse coverage of these

therapies, making them inaccessible to patients and discouraging investment in and development of new drugs for the CF and rare disease communities.

CF is not a manageable disease. An exacerbation is not a minor event. Lung transplants are only life extending and fraught with their own extreme risks. You did not conduct due diligence to understand our experience. You crunched numbers to determine that life-saving therapies which reduce pain and suffering are not cost effective. You bear responsibility for the impact of this deeply flawed report.

CFRI provides a broad range of educational, psychosocial, and advocacy programs that receive grant funding from several pharmaceutical companies, including Vertex.

3. **Chad Riedy, National Advocacy Co-Chair, Cystic Fibrosis Foundation**

Being diagnosed with cystic fibrosis in 1984 at the age of three years old, I was not expected live to see my twelfth birthday and for a good portion of my life we did not have therapies like hypertonic saline, inhaled antibiotics, or the vest. I have seen how they have changed the way cf is treated and the difference they have made, but they are the not the answer. They simply help us manage our disease but do not treat the root cause of our disease. CFTR modulators are much closer to the answer and, while not perfect, they are a vital piece.

Since being on Symdeko for the past five months, I can carry my kids up the stairs to bed. I can help a neighbor move his couch. I can bike with my family and take a walk to the farmer's market without fear. While taking it has not lessened the amount of time I still have to spend on treatments and other cf related responsibilities, it has provided a better quality of life right now and real hope for the days to come. Hope that with decreased exacerbations and lung function deterioration I will be able to grow old and gray with my wife, Julie, see Liam and Tate grow up and have many more days enjoying life.

You can't quantify these impacts in data and you can't quantify time with family. Symdecko has been life-changing for me and my family. CF Fighters deserve to have every medicine and every therapy in their playbook and CFTR modulators are the best play yet. We are fighters. We are hopeful.

Mr. Riedy is the National Advocacy Co-Chair at CFF, a volunteer position. CFF paid for Mr. Riedy's travel expenses to this meeting.

4. **Mike Price, Parent of a Child with Cystic Fibrosis**

At time of publication, ICER has not received a summary of public comment from Mr. Price.

No relevant conflicts of interest to report.

5. **Juliana Keeping, Parent of a Child with Cystic Fibrosis; Communications Director, Patients for Affordable Drugs**

My name is Juliana Keeping, and my 5-year-old son, Elijah, has cystic fibrosis.

I'm the communications director for Patients For Affordable Drugs, a nonprofit patient advocacy organization that formed in response to soaring prescription drug costs in the U.S.

I support ICER's conclusion that CF drugs are overpriced. Drugs don't work if people can't afford them.

To demonstrate that point, I've brought with me the story of a 40-year-old CF patient named Lora Moser from Austin, Texas.

Lora Moser family and friends raised $750,000 for the development of Orkambi, Kalydeco and Symdeko.

She has a prescription for Orkambi she can't fill as the co-pay is $4,400 per month..

Not only is Lora not receiving her medicines, people with CF all over the world are not getting our charity-funded drugs, because these drugs are priced out of reach.

The federal government and the Cystic Fibrosis Foundation took on all the risk in creating these medicines, but Vertex priced the drugs as if it alone took on the risk.

CF drugs have made multi-millionaires out of Vertex executives like Jeffrey Leiden. According to Axios, his compensation in 2017 alone was $78.5 million.

Vertex has also bought back a half billion in its own stock. Instead of buying its shares to enrich investors and paying executives like Leiden tens of millions, Vertex should use its corporate tax breaks to lower the prices of its medicines.

The problem is the price.

Orkambi, Kalydeco and Symdeko cost far too much.

Ms. Keeping owns shares of stock in Vertex Pharmaceuticals. Patients for Affordable Drugs is funded in part by the Laura and John Arnold Foundation, which also provides funding to ICER.

Appendix H. Conflict of Interest Disclosure

Table H1. ICER Staff and Consultant COI Disclosures

Name	Organization	Disclosures
Ethan Balk, MD, MPH	Brown University	None
Rick Chapman, PhD, MS	ICER	None
Geri Cramer, BSN, MBA	ICER	None
Ariel Jurmain, BA	ICER	None
Sonya Khan, MPH	ICER	None
Karen Kuntz, ScD	University of Minnesota	None
Kristin Mickle, MPH	ICER	None
Daniel Ollendorf, PhD	ICER	None
Steven Pearson, MD, MSc	ICER	None
Thomas Trikalinos, MD, PhD	Brown University	None
Kael Wherry, MS	University of Minnesota	None
Ian Williamson, MBA	University of Minnesota	None

Table H2. Midwest CEPAC Panel Member COI Disclosures

Name	Organization	Disclosures
Eric Armbrecht, PhD	St. Louis University	*
Ralph Brindis, MD, MPH, MACC, FSCAI, FAHA	UCSF	*
Don Casey, MD, MPH, MBA	Medecision, IPO4Health	*
Rena Conti, PhD	University of Chicago	*
Stacie Dusetzina, PhD	Vanderbilt University	*
Elbert Huang, MD, MPH	University of Chicago	*
Jill Johnson, PharmD	University of Arkansas	*
Timothy McBride, PhD	Washington University in St. Louis	*
Scodd Micek, PharmD	St. Louis College of Pharmacy	*
Reem Mustafa, MD, MPH, MhD	University of Kansas	*
Rachel Sachs, JD, MPH	Washington University in St. Louis	*
Stuart Winston, DO	St. Joseph Mercy Health System	*

* 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.

Name	Title	COI Declaration
Mary Dwight	Senior Vice President of Policy and Advocacy Cystic Fibrosis Foundation	CFF provides research and clinical trial support to health care companies, including Vertex Pharmaceuticals. CFF has received charitable contributions and/or fees for service >$5,000 from Vertex Pharmaceuticals and other health care companies.
Jane Horvath, MHSA	Senior Policy Fellow National Academy for State Health Policy	Employee of the National Academy for State Health Policy.
Manu Jain, MD, MS	Professor of Medicine and Pediatrics, and Director of Adult CF Feinberg School of Medicine, Northwestern University	Member of the Vertex Pharmaceuticals Advisory Board, and Site PI for Vertex Phase 2 and 3 studies. Has received more than $5,000 in honoraria or consultancies during the previous year.
Jeremy Olimb	Pastor and father of children with cystic fibrosis	No conflicts of interest to report.
David Orenstein, MD, MA	Antonio J and Janet Palumbo Professor of Cystic Fibrosis Children's Hospital of Pittsburgh	No conflicts of interest to report.
Erik Schindler, PharmD, BCPS	Manager, Clinical Pharmacy UnitedHealthcare Pharmacy	Employee of UnitedHealthCare.