Modulator Treatments for Cystic Fibrosis: Effectiveness and Value

Draft Evidence Report

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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.*

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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 Preventative Services Task Force
VC	Vital capacity
WAC	Wholesale acquisition cost
WTP	Willingness to pay

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.[2]

Pathogenesis

Over 1800 cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations have been described, 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 are known to cause CF.[3] 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. Approximately 87% of CF patients are heterozygous and 46% of patients are homozygous for the *F508del* mutation.[4,5] Another common mutation is G551D, which is found in approximately 5% of CF patients.[4] 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.[6] 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 toilet (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. Initially, infections are associated with bacteria expected in bronchiectasis of other causes (e.g., *Streptococcus pneumoniae*). However, infections by *Staphylococcus aureus* and *Pseudomonas* species 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 is associated with better lung and nutritional outcomes later in life.[7]

Clinical Presentation

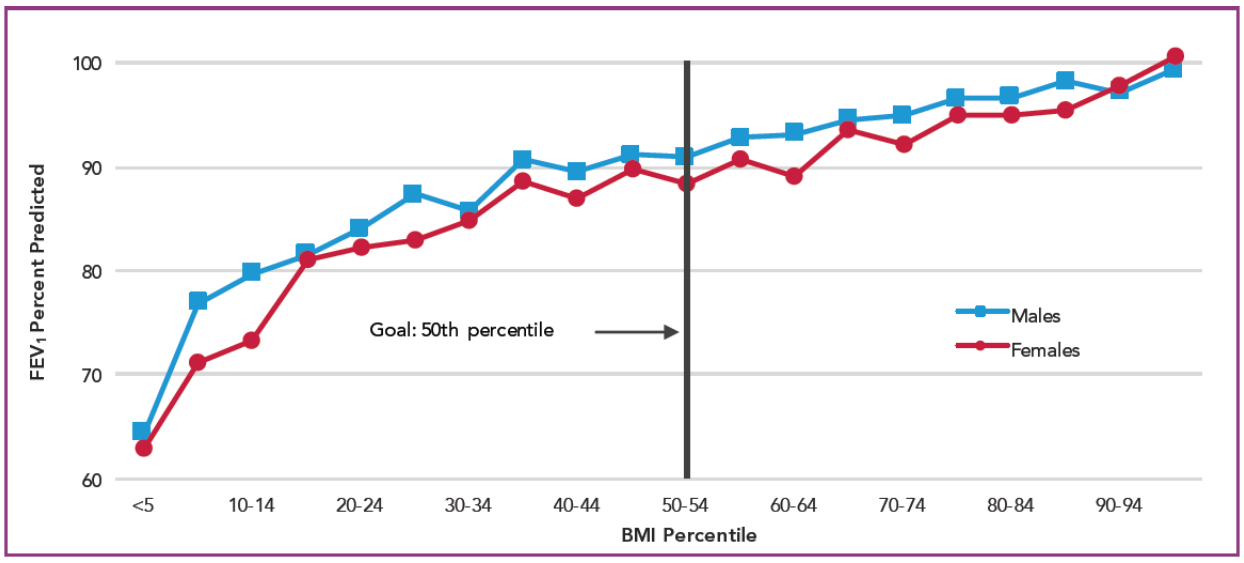
The most remarkable aspects of the clinical presentation are from the respiratory system. While lung function is normal at birth, lung infections tend to occur early in life. Repeated and chronic infections can lead to bronchiectasis at a young age. Acute pulmonary infections requiring antibiotic treatment (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.[8,9] 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.[10] Pancreatic damage that leads to an insufficiency of pancreatic enzymes often occurs within a few months after birth.[10] 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.[11] 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 aims to control symptoms. It includes aggressive airway hygiene with chest physiotherapy, 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.[12] 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."[13] 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, ivacaftor (Kalydeco®), lumacaftor, and tezacaftor, 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 these 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, increase the likelihood that the CFTR channel will transport ions through the cell membrane, i.e., they increase the channel's "open probability". Ivacaftor monotherapy 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. For example, lumacaftor/ivacaftor (Orkambi®) as well as tezacaftor/ivacaftor and ivacaftor (Symdeko™; hereinafter referred to as tezacaftor/ivacaftor) combinations are considered in patients homozygous for the *F508del* mutation. Tezacaftor/ivacaftor is also considered in patients who are heterozygous for the *F508del* allele and carry a residual function mutation.

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 short-term 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

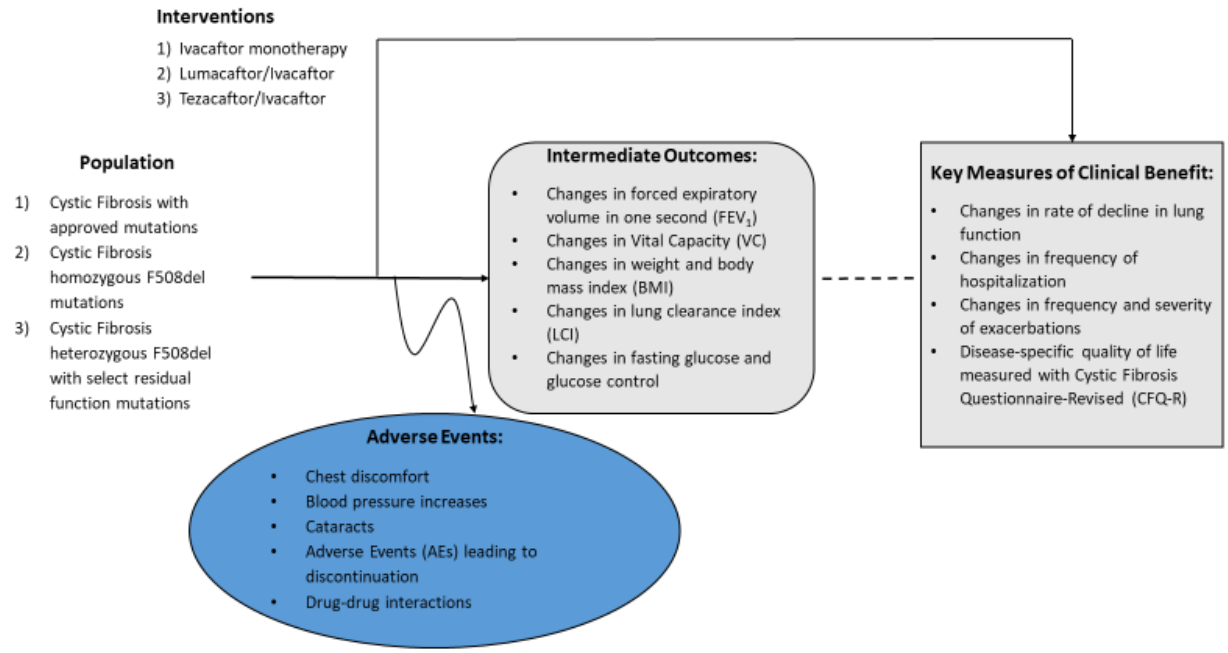
The scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence was collected from available randomized controlled trials and observational studies.

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.[14]

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 ivacaftor. In this population, we reviewed evidence on ivacaftor monotherapy. 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 lumacaftor/ivacaftor and tezacaftor/ivacaftor combination therapy.
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 tezacaftor/ivacaftor. In this population we reviewed evidence on tezacaftor/ivacaftor combination and ivacaftor monotherapy.

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.[15,16] 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 appropriate populations:

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

lumacaftor/ivacaftor, or tezacaftor/ivacaftor 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 ivacaftor monotherapy 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.

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
- 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.[17]
- 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. 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.

Settings

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

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 ivacaftor monotherapy) 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.[4] 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.[3] 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.[18] 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.[16] A clinically relevant change in absolute percent predicted FEV_1 has been considered to be three to five points or greater.[19]

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.[20]

Cystic Fibrosis Questionnaire-Revised (CFQ-R): A validated survey which measures health-related quality of life (HRQOL) in CF patients.[21] 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.[22] 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.[23] 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).[24] 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 lumacaftor/ivacaftor). It may require discontinuation of its cause modulator treatment.

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 are not fully captured by quality of life instruments. To start, 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. Rather, we are looking for information on low-value services used in the management of cystic fibrosis beyond the potential offsets that arise from a new treatment. We did not receive additional suggestions in response to the final scoping document but continue to welcome such input.

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: ivacaftor, lumacaftor/ivacaftor, and tezacaftor/ivacaftor. No coverage policies were found for tezacaftor/ivacaftor as it was recently approved, in February 2018.

All the plans surveyed provided prior authorization criteria for the coverage of lumacaftor/ivacaftor or ivacaftor. Specifically, for lumacaftor/ivacaftor, 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.[25-28] 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.[27,28]

For ivacaftor, 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 ivacaftor based on its label (i.e. any of the following mutations: G551d, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or R117H).[25,28-30] Some plans also specifically call out that ivacaftor is not approved for any CF patients with a homozygous *F508del* mutation without the concurrent treatment with lumacaftor.

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[31]

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[32]

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[33]

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 tobramysin and aztreonam, particularly in patients with moderate to severe lung disease. It recommends mucolytics such as dornase alfa in patients with severe 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 ivacaftor in patients with at least one copy of the G551 mutation. CFF acknowledges that the guidelines were published prior to the label expansion for ivacaftor and the approval of ivacaftor and lumacaftor for patients with the homozygous *F508del* mutation.

Pulmonary Exacerbations[34]

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 does not recommend the following treatments due to lack of evidence: 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)[35]

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[36]

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)[37]

Diagnosis

NICE guidelines 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 lumacaftor/ivacaftor 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.[38,39] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[40] 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 ivacaftor monotherapy and lumacaftor/ivacaftor combination therapy in populations outside their respective FDA-approved indications, as well as studies of composite treatment strategies that started with ivacaftor monotherapy 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.

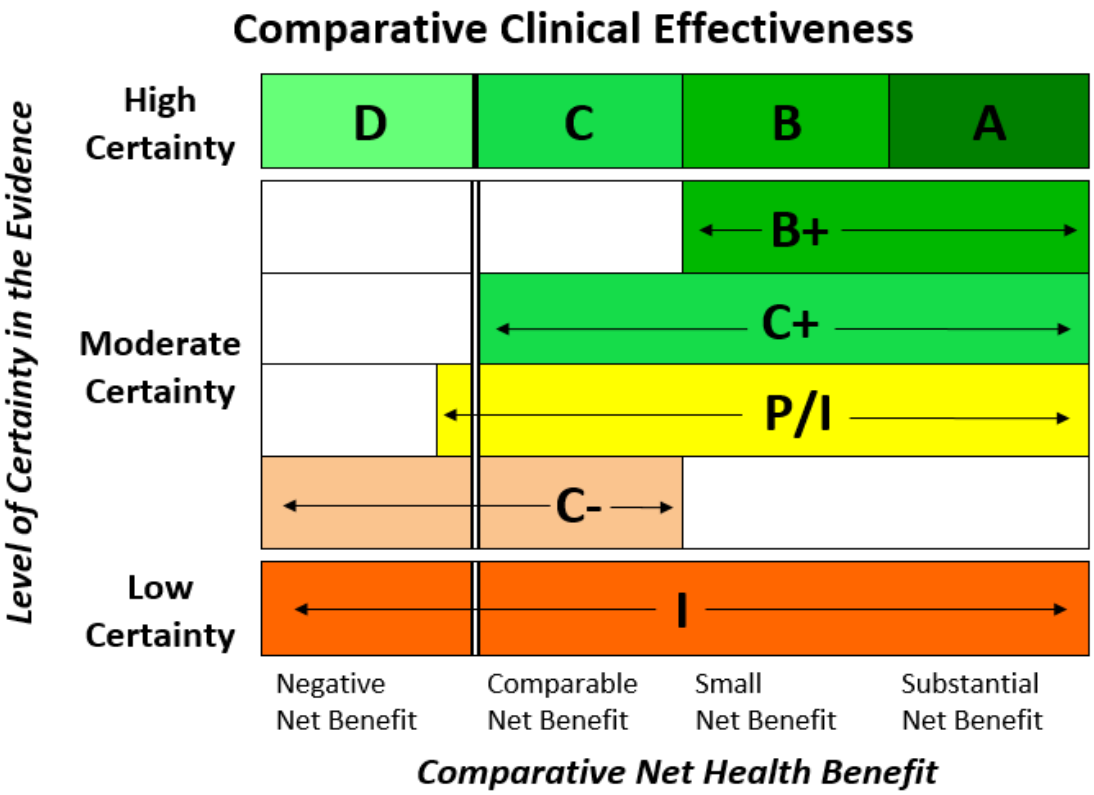
Data were extracted from the full articles by a single reviewer and validated by a second reviewer.

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.[40]

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.[41]

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).[42] 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.[43] Estimates of indirect comparisons were obtained as linear combinations of the direct estimates, following Bucher et al.[44]

3.3 Results

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.

Ivacaftor monotherapy: We included 35 articles on ivacaftor treatment in gating and residual function mutations; 19 articles were peer-reviewed publications and 16 were abstracts that do not have 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, which 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 "*G551D* Observational Study" (GOAL) study. One additional publication reporting on GOAL and a randomized control trial was included.

Lumacaftor/ivacaftor: We included ten articles on lumacaftor/ivacaftor 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.

Tezacaftor/ivacaftor: We included three articles on tezacaftor/ivacaftor 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 Ivacaftor in Gating and Residual Function Mutation Populations

Children, adolescents, and adults with G551D and non-G551D gating mutations experienced significant and clinically meaningful gains in ppFEV$_1$ and reductions in rate of pulmonary exacerbations with ivacaftor compared to placebo. Long-term follow-up suggests lung function improvements are durable. Significant gains in body weight and respiratory symptom-related quality of life with ivacaftor were reported for G551D and non-G551D gating mutation

populations aged 12 and older compared to placebo. Significant improvement 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 ivacaftor experienced significant decreases in lung function and trended towards decreased respiratory symptom-related quality of life scores compared to placebo.

Four key randomized controlled trials – STRIVE, ENVISION, KONNECTION, and KONDUCT – evaluated the safety and efficacy of ivacaftor in individuals with at least one *G551D*, non-*G551D* gating, and *R117H* mutations (Table 3.1).[45-48] 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 ivacaftor or placebo twice daily. 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 ivacaftor twice daily for eight weeks followed by eight weeks of matched placebo or eight weeks of matched placebo followed by eight weeks of ivacaftor. 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 absolute change from baseline in weight and BMI as secondary efficacy endpoints (Table 3.1).[49] 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 ivacaftor 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 ivacaftor twice daily (Table 3.1).[50] GOAL was a longitudinal cohort study of individuals aged six years and older with at least on *G551D* mutation and without prior history of ivacaftor use; participants received 150mg of ivacaftor twice daily.[51] 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 Ivacaftor Efficacy Conducted in *G551D*, non-*G551D* Gating Mutations, and *R117H* Residual Function Mutation Populations

Study Quality and Study Design						
	STRIVE[45] RCT, Phase III Good	**ENVISION[46]** RCT, Phase III Good	**PERSIST[50]** Single-arm, open-label extension Good	**KIWI[49]** Single-arm, open-label trial Good	**KONNECTION*[47]** RCT, Phase III cross-over design Good	**KONDUCT[48]** 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	Ivacaftor Placebo	Ivacaftor Placebo	Ivacaftor	Ivacaftor	Ivacaftor Placebo	Ivacaftor 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 ivacaftor and placebo; randomization determined one of two treatment orders: eight weeks of ivacaftor followed by eight weeks of placebo OR eight weeks of placebo followed by eight weeks of ivacaftor. 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 ivacaftor and placebo groups) in mean absolute and relative ppFEV$_1$ changes are shown in Table 3.2.

Table 3.2. Summary of Ivacaftor 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 2-5* **(n=9)**	N/A	N/A	N/A	N/A
Ages 6-11†[46] (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+†[45] (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+#[47] (n=39)	10.7 (7.3 to 14.1)	NR	0.7 (0.34 to 0.99)	9.6 (4.5 to 14.7)
R117H				
Ages 6+¤ [48] (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 (-11.96 to −0.71)*	*NR*	*−0.18‡ (−2.38 to 2.0)*	*−6.1‡ (-15.68 to 3.41)*
Ages 18+ (n=50)	*5.0 (1.15 to 8.78)*	*NR*	*0.31‡ (−1.90 to 2.51)*	*12.6‡ (5.02 to 20.25)*

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

*Ages 2-5 (KIWI), a single-arm study where all participants received ivacaftor

†Ages 6-11 (ENVISION) and ages 12+ (STRIVE) show treatment difference (ivacaftor 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 (ivacaftor vs. placebo) at 8 weeks

¤Ages 6+ (KONDUCT), treatment difference (ivacaftor vs. placebo) at 24 weeks. Treatment differences by age group shown in italics; ages 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 ivacaftor and placebo groups' mean absolute change from baseline after 48 weeks of treatment showed significant gains on ivacaftor 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%) [46] and 12

and older (treatment difference: 10.5 percentage points; 95% CI 8.5 to 12.5; baseline ppFEV$_1$: 64%).[45] Lung function outcomes at 24 and 48 weeks were comparable. Meta-analysis of the two RCTs comparing ivacaftor 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 ivacaftor (Appendix D, Figure D6).[45,46] Results from the GOAL observational study show similar ppFEV$_1$ gains for non-G551D gating mutations before and after ivacaftor treatment initiation (treatment difference: 10.7 percentage points; 95% CI 7.3 to 14.1 percentage points).[51]

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 ivacaftor and placebo groups.[48] When stratified by age, however, children aged 6-11 on ivacaftor 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.[48] 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 ivacaftor use.[50] Absolute change from baseline ppFEV$_1$ was evaluated as a secondary outcome. Gains were similar for patients originally randomized to ivacaftor 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 ivacaftor 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).[52] Treatment differences showed *G551D* participants on ivacaftor during a Phase III trial gained a mean absolute 10.70 percentage points (p<0.001) compared to *F508del* receiving only standard care. The annualized rate of ppFEV$_1$ decline showed those on ivacaftor 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).[52]

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 ivacaftor 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).[45,46] 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 ivacaftor compared to placebo (Appendix F).[53] 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 ivacaftor treatment.

Non-*G551D* gating mutation individuals on ivacaftor 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.[47] *R117H* individuals again had mixed results in subgroup analyses by age, and ivacaftor treatment effects were non-significant in all groups analyzed.[48] 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 ivacaftor 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.[45,47,48] 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 ivacaftor 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 [46], while *R117H* participants reported a −6.1 (95% CI −15.68 to 3.41) point change [48]; *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).[54] 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 ivacaftor over placebo, though effects were not clinically meaningful. For the respiratory domain, 57% of those taking ivacaftor reported improvement in CFQ-R scores versus 25% on placebo (p<0.05). Likewise, 29% of ivacaftor 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[45]		KONDUCT[48]	
Follow-up Duration	**48 weeks**		**24 weeks**	
	Placebo (n=78)	Ivacaftor (n=83)	Placebo (n=35)	Ivacaftor (n=34)
Modified Fuch's Criteria				
No. PEx's	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's (% of all PEx's)	47 (47)	28 (60)	7 (41)	2 (15)
No. Subjects with PEx	NR	NR	6	2
Required Hospitalization				
No. PEx's (% of all PEx's)	31 (31)	21 (45)	8 (47)	2 (15)
No. Subjects with PEx	NR	NR	6	2

PEx: Pulmonary exacerbations

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 ivacaftor group and three in the placebo group as outcomes; however, eight exacerbations are reported for each group when categorized as adverse events.[46] Second, the KONDUCT study reported 13 and 11 exacerbations in the ivacaftor and placebo groups, respectively, and report three additional exacerbations (one in placebo, two in the ivacaftor group) as adverse events.[48]

STRIVE was the only randomized comparative study showing a treatment effect on the incidence of pulmonary exacerbations (Table 3.3). STRIVE participants receiving ivacaftor experienced approximately half as many pulmonary exacerbations compared to the placebo group over 48 weeks (55% risk reduction, $p<0.001$).[45] ENVISION reported exacerbations among 4 of 26 (15%) ivacaftor and 3 of 26 (12%) placebo recipients over 48 weeks.[55] The frequency of pulmonary exacerbations was similar (33-46%) during the additional 96 weeks of ivacaftor treatment during.[50]

Exacerbations during KONNECTION were reported by cross-over period: 9 of 38 (24%) and 11 of 39 (28%) of participants experienced a pulmonary exacerbation during the eight-week ivacaftor and placebo periods, respectively.[47]

We were also 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 ivacaftor and 0.40 for placebo recipients. Thus, our calculations provide a rate ratio of 0.56 (NS).[45] As shown in Table 3.3, there was no consistent trend in the ivacaftor 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.[56] 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 ivacaftor groups. However, other related outcomes favored ivacaftor 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.

Two non-randomized, comparative, long-term studies also reported significantly lower risks of pulmonary exacerbations associated with ivacaftor.[57,58] The annual risk of an exacerbation was assessed by matching individuals on ivacaftor to similar patients on best supportive care.[57,58] Over a one year period six-to twelve year-old children taking ivacaftor 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).[57] Analysis of all ages showed those on ivacaftor also experienced a statistically significant decrease in the annual risk of pulmonary exacerbation (RR: 0.64; 95% CI 0.58 to 0.70).[58] The annual risk of death was also lower for patients on ivacaftor compared to placebo (RR: 0.41, 95% CI 0.20 to 0.84).[58]

Clinical Benefits of Lumacaftor/Ivacaftor and Tezacaftor/Ivacaftor in Individuals Homozygous for the F508del Mutation

Lumacaftor/ivacaftor and tezacaftor/ivacaftor both provide small but statistically-significant improvements in absolute ppFEV$_1$ compared to placebo; however, the magnitude of effect varies by age, dose, and baseline lung function. Neither lumacaftor/ivacaftor nor tezacaftor/ivacaftor provide significant short-term improvement in BMI-for-age z score compared with placebo; however, lumacaftor/ivacaftor appears to show an improvement in BMI with long-term use. Both lumacaftor/ivacaftor and tezacaftor/ivacaftor provide improved respiratory-related quality of life compared with placebo. Lumacaftor/ivacaftor and tezacaftor/ivacaftor reduced pulmonary exacerbation events, including those requiring intravenous antibiotics and hospitalizations, compared with placebo. Indirect comparisons yielded no material differences between lumacaftor/ivacaftor and tezacaftor/ivacaftor in key clinical outcomes.

Two treatment regimens were reviewed for individuals homozygous for the *F508del* mutation: lumacaftor/ivacaftor and tezacaftor/ivacaftor. 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 lumacaftor/ivacaftor.

Two placebo-controlled, parallel-arm Phase III RCTs of lumacaftor/ivacaftor, TRAFFIC and TRANSPORT, enrolled patients ages 12 and older with two copies of the *F508del* mutation.[24] Inclusion criteria included a screening FEV_1 between 40-90% predicted and stable disease.[24] Two doses of lumacaftor/ivacaftor were tested against placebo (lumacaftor 600 mg daily or 400 mg twice a day, both with ivacaftor 250 mg twice a day).[24] 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.[59] Exclusion criteria were similar to TRAFFIC/TRANSPORT.

One randomized, placebo-controlled, parallel-arm trial of tezacaftor/ivacaftor, EVOLVE, enrolled 510 cystic fibrosis patients ages 12 and older who were homozygous for the *F508del* mutation for 24 weeks of follow-up.[60] Inclusion and exclusion criteria were similar to TRAFFIC/TRANSPORT.

The long-term safety of lumacaftor/ivacaftor 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).[61] 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.[62] 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 ivacaftor did not differ.

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

Study Design and Study Quality	TRAFFIC/TRANSPORT*[24] RCT, Phase III, Ages 12+ Good	Ratjen et al.[59] RCT, Phase III, Good	PROGRESS[61] Single-arm, open-label extension	Milla et al.[62] Single-arm study	EVOLVE[60] RCT, Phase III, Good
Follow-up Duration	24 weeks	24 weeks	96 weeks	24 weeks	24 weeks
Treatment Groups	Lumacaftor / ivacaftor* Placebo	Lumacaftor / ivacaftor Placebo	Lumacaftor / ivacaftor*	Lumacaftor / ivacaftor	Tezacaftor / ivacaftor 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

*Two lumacaftor/ivacaftor arms (600 mg/daily and 400 mg/twice daily lumacaftor); 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*

	Lumacaftor/Ivacaftor					Tezacaftor/Ivacaftor	
	TRAFFIC and TRANSPORT*[24]			Ratjen et al.[59]		EVOLVE[60]	
	LUM-IVA (600 mg daily)	LUM-IVA (400 mg q 12 hrs)	Placebo	LUM-IVA (200 mg q 12)	Placebo	TEZ-IVA (100 mg daily)	Placebo
FEV_1, Absolute Change†, Percentage Points (p-value or 95%)	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

CI: confidence interval

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

Percent Predicted Forced Expiratory Volume ($ppFEV_1$) and Lung Clearance Index (LCI)

Lumacaftor/ivacaftor

The key lumacaftor/ivacaftor randomized controlled trials reported absolute and relative changes in $ppFEV_1$ between baseline and 24 weeks.[24,59] 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 400 mg twice a day arm, and -0.32 percentage points in the placebo arm between baseline and 24 weeks (Table 3.5).[24] The differences compared to placebo were 3.3 (95% CI, 2.3 to 4.3) percentage points for 600 mg daily and 2.8 (95% CI, 1.8 to 3.8) percentage points for 400 mg twice a day.[24]

Konstan et al. performed a *post hoc* analysis by matching participants from TRAFFIC/TRANSPORT taking 400 mg lumacaftor twice daily with controls from the US CFFPR (homozygous *F508del*) to assess changes to the annual rate of $ppFEV_1$ decline.[63] Using 455 LUM-IVA patients and 1,588 matched controls, the authors found lumacaftor/ivacaftor produced a 42% slower rate of decline in $ppFEV_1$ (1.33 vs. 2.29 percentage points per year; p-value < 0.001).[63]

Although changes in $ppFEV_1$ in the randomized trials were positive and significant, a post-approval study at a single hospital found no benefit of lumacaftor/ivacaftor 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%).[64]

The $ppFEV_1$ was reported as a secondary endpoint in the two trials in the six-11 year old population, as lung function is often preserved in younger children.[59] 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.[62] 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 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.[59] The within-group change in the lumacaftor/ivacaftor arm did not show a statistically significant improvement.[59] Relative changes in $ppFEV_1$ were not reported in either trial.

In an effort to capture the respiratory benefit of lumacaftor/ivacaftor, 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.[59] Reductions from baseline indicate an improvement. In both trials of lumacaftor/ivacaftor in the six-11 year old population, lumacaftor/ivacaftor 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).[59,62] In the RCT, the difference between lumacaftor/ivacaftor and placebo was also statistically significant (difference of -1.1; 95% CI, -1.4 to -0.8).[59]

Subgroup analysis

In TRAFFIC and TRANSPORT, similar changes in absolute $ppFEV_1$ over 24 weeks compared with placebo were found for lumacaftor/ivacaftor (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).[65]

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.[66]

Tezacaftor/Ivacaftor

In the homozygous population, one RCT (EVOLVE) reported absolute and relative changes in $ppFEV_1$ for tezacaftor/ivacaftor.[60] 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).[60] Compared with placebo, tezacaftor/ivacaftor provided 4.0 percentage point improvement (95% CI, 3.1 to 4.8).[60]

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 tezacaftor/ivacaftor and placebo (6.8%, 95% CI, 5.3 to 8.3).[60]

Lumacaftor/Ivacaftor versus Tezacaftor/Ivacaftor

No study has directly compared lumacaftor/ivacaftor and tezacaftor/ivacaftor. 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

	Lumacaftor/Ivacaftor vs. Placebo*	Tezacaftor/Ivacaftor vs. Placebo†	Tezacaftor/Ivacaftor vs. Lumacaftor/Ivacaftor‡
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 tezacaftor/ivacaftor and lumacaftor/-ivacaftor is an indirect comparison between the two placebo-controlled trials

Weight and BMI

Lumacaftor/Ivacaftor

BMI was reported as absolute change from baseline in all lumacaftor/ivacaftor 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 lumacaftor/ivacaftor dose arm showed a difference in BMI compared to placebo.[24] 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.[24] It is not clear why the effect of lumacaftor/ivacaftor 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 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 lumacaftor 400 mg twice a day showed a statistically significant increase of 0.24 kg/m^2 (95% CI, 0.11 to 0.37 kg/m^2) versus placebo.[24] After 96-weeks on 400 mg twice daily lumacaftor, individuals in PROGRESS (open-label extension of TRAFFIC and TRANSPORT) had an absolute change in BMI of 0.76-0.96 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).[61] 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 lumacaftor/ivacaftor versus matched controls (see Appendix Figure D1).[24]

Results of absolute change in BMI in children six-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).[62] However, in the randomized controlled trial, there was no difference in absolute BMI between lumacaftor/ivacaftor and placebo.[59] 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.[59,62] 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).[62]

Subgroup analysis

In TRAFFIC and TRANSPORT, similar changes in BMI over 24 weeks compared with placebo were found for lumacaftor/ivacaftor (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).[65]

Tezacaftor/ivacaftor

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 tezacaftor/ivacaftor arm and 0.12 kg/m^2 (95% CI, 0.03 to 0.22) in the placebo arm (<1% increases from baseline).[60] The difference in absolute change in BMI between treatment and placebo was non-significant.[60] BMI-for-age z-score change from baseline to 24 weeks was non-significant for both arms (see Table 3.5).[60] Long-term data on the effect of tezacaftor/ivacaftor on BMI or BMI-for-age z-score is not available yet.

Lumacaftor/Ivacaftor versus Tezacaftor/Ivacaftor

No study has directly compared lumacaftor/ivacaftor and tezacaftor/ivacaftor. 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

	Lumacaftor/Ivacaftor vs. Placebo*	Tezacaftor/Ivacaftor vs. Placebo†	Tezacaftor/Ivacaftor vs. Lumacaftor/Ivacaftor‡
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)

Lumacaftor/ivacaftor

Adolescents and adults receiving lumacaftor/ivacaftor 400 mg twice a day 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).[24] While statistically significant, this value did not meet the MCID of 4.[22] These benefits lasted through 72 weeks for all participants who enrolled in the open-label extension study, PROGRESS.[61] At 96 weeks, patients continued to report improved symptoms, however, the benefits did not statistically differ from baseline in most patients.[61]

Respiratory symptom quality of life was mixed in children ages six-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).[62] These findings were similar in the randomized controlled trial where children randomized to lumacaftor/ivacaftor 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).[59] Lumacaftor/ivacaftor was not found to confer a statistically significant benefit when compared to placebo.[59]

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

Subgroup analysis

In TRAFFIC and TRANSPORT, estimates of relative effects of lumacaftor/ivacaftor (400 mg twice daily 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.[65]

Tezacaftor/Ivacaftor

Individuals enrolled in the tezacaftor/ivacaftor 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.[60] Compared with placebo, tezacaftor/ivacaftor improved respiratory domain quality of life (difference of 5.1 points; 95% CI, 3.2 to 7.0).[60]

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

Lumacaftor/Ivacaftor versus Tezacaftor/Ivacaftor

No study has directly compared lumacaftor/ivacaftor and tezacaftor/ivacaftor. 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 tezacaftor/ivacaftor. By indirect comparison (network meta-analysis), tezacaftor/ivacaftor was just nonsignificantly more effective to improv CFQ-R respiratory domain score than lumacaftor/ivacaftor: 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

	Lumacaftor/Ivacaftor vs. Placebo*	Tezacaftor/Ivacaftor vs. Placebo†	Tezacaftor/Ivacaftor vs. Lumacaftor/Ivacaftor‡
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	**Lumacaftor / Ivacaftor**	**Lumacaftor / Ivacaftor***	**Placebo**	**Tezacaftor / Ivacaftor**
No. Subjects	371	369	369	256	248
Modified Fuch's Criteria					
No. Pex's	251	152	NR	NR	NR
No. Pex's 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's 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's 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

Pexs: Pulmonary exacerbation

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

<u>Lumacaftor/Ivacaftor</u>

Patients receiving lumacaftor/ivacaftor 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).[24] The rate ratio between active drug and placebo was 0.65 (95% CI, 0.55 to 0.77) with the greatest reduction in the 400 mg twice daily arm (0.61, 95% CI, 0.49 to 0.76).[24] Lumacaftor 400 mg twice daily provided statistically significant reductions in pulmonary exacerbations requiring antibiotics (56% fewer than placebo) and hospitalizations (61% fewer than placebo).[24]

Pulmonary exacerbations reported during TRAFFIC/TRANSPORT are also shown in Table 3.9. After 96 weeks, those who continued on lumacaftor/ivacaftor 400 mg twice daily maintained a stable reduction (Table 3.9).[61] 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 six-11 years old.

Tezacaftor/Ivacaftor

Pulmonary exacerbations reported during EVOLVE are shown in Table 3.9. Patients in the EVOLVE trial randomized to tezacaftor/ivacaftor 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,).[60] The rate of pulmonary exacerbations requiring antibiotics or hospitalization was also significantly lower in the tezacaftor/ivacaftor arm compared to the placebo arm (RR 0.53; 95% CI, 0.34 to 0.82).[60]

Lumacaftor/Ivacaftor versus Tezacaftor/Ivacaftor

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 tezacaftor/ivacaftor and lumacaftor/ivacaftor (400 mg) 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

	Lumacaftor/Ivacaftor vs. Placebo*	Tezacaftor/Ivacaftor vs. Placebo†	Tezacaftor / Ivacaftor vs. Lumacaftor / Ivacaftor‡
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 Tezacaftor/Ivacaftor and Ivacaftor in Individuals Heterozygous for the F508del Mutation

Tezacaftor/ivacaftor and ivacaftor monotherapy both improve absolute and relative ppFEV$_1$ compared with placebo. Tezacaftor/ivacaftor provides a significant benefit over ivacaftor monotherapy. Respiratory symptom-related quality of life was improved by both tezacaftor/ivacaftor and ivacaftor monotherapy compared with placebo. It is unknown whether tezacaftor/ivacaftor or ivacaftor monotherapy will improve BMI or significantly reduce pulmonary exacerbations in the heterozygous F508del with residual function mutation population because a long-term, adequately powered cohort is not yet available.

There is one key trial of tezacaftor/ivacaftor in patients heterozygous for the *F508del* mutation with a second mutation that is responsive to ivacaftor (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.[67] The three interventions included combination therapy (tezacaftor 100 mg daily with ivacaftor 150 mg twice daily), ivacaftor monotherapy (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.[67] 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.[67]

Of the 246 patients that 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).[67]

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.[67]

Table 3.11. Summary of Results in the EXPAND Trial in Patients Heterozygous for a *F508del* Mutation[67]

	Tezacaftor/ivacaftor (N=161) vs. Placebo (N=161)	Ivacaftor Monotherapy (N=156) vs. Placebo (N=161)	Tezacaftor/ivacaftor (N=161) vs. Ivacaftor Monotherapy (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 tezacaftor/ivacaftor 0.18 placebo	0.47 ivacaftor monotherapy 0.18 placebo	0.34 tezacaftor/ivacaftor 0.47 ivacaftor monotherapy
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.[67] Compared to placebo, both interventions provided statistically significant improvement in absolute $ppFEV_1$: 6.8 percentage points for tezacaftor/ivacaftor (95% CI 5.7 to 7.8) and 4.7 percentage points for ivacaftor monotherapy (95% CI 3.7 to 5.8)(Table 3.11).[67] The difference between tezacaftor/ivacaftor and ivacaftor monotherapy was also statistically significant but clinically modest, favoring tezacaftor/ivacaftor (2.1 percentage points; 95% CI 1.2 to 2.9).[67] 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 tezacaftor/ivacaftor 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) where those 18 years and older saw a 6.0 percentage point increase (4.9 to 7.0).[67] The confidence intervals were wider in the under 18 subgroup due to small numbers (< 15% of each arm).[67]

Similar results were seen in the same subgroups with ivacaftor monotherapy 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 tezacaftor/ivacaftor (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).[67] No data were reported to allow an estimate of statistical significance.

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

Tezacaftor/ivacaftor 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).[67] Ivacaftor monotherapy also provided significantly better respiratory symptom-related quality of life compared to placebo (9.7 points; 95% CI, 7.2 to 12.2).[67] No significant benefit was found between tezacaftor/ivacaftor and ivacaftor monotherapy on CFQ-R.[67]

The proportion of patients that received a clinically significant improvement in CFQ-R was 65% in the tezacaftor/ivacaftor group, 58% in the ivacaftor monotherapy group and 33% in the placebo group.[67]

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 tezacaftor/ivacaftor group reported 11 events (0.34 estimated event rate per year) and the ivacaftor monotherapy group reported nine 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 tezacaftor/ivacaftor compared to ivacaftor monotherapy 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 (eight 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*[67]			
Follow-Up Duration	**8 weeks**		
	Placebo	**Ivacaftor**	**Tezacaftor/ivacaftor**
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)

PExs: 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,[68] hemoptysis, bronchospasm, dyspnea, pulmonary exacerbation and rash.[24] 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

	Ivacaftor				Lumacaftor/ivacaftor				Tezacaftor/ivacaftor	
	STRIVE[45]		KONDUCT[48]		TRAFFIC/TRANSPORT±[24]		EVOLVE[60]		EXPAND[67]	
	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 Discontin.	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,[68] and nasopharyngitis.[41] 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.[68,41,69] 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 lumacaftor/ivacaftor 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.[24] The long-term follow-up study, PROGRESS, reported rates of abnormal respiration between 10-17%.[61] 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.[61] 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).[61] A real world cohort study at the Johns Hopkins Cystic Fibrosis Center after lumacaftor/ivacaftor approval (n=116) showed that nearly 20% of patients reported chest tightness.[64]

For tezacaftor/ivacaftor, chest discomfort was reported as zero in the *F508del* homozygous population and 1.2% in the heterozygous population.[60,67]

Meta-Analyses of Harms Across Interventions

Eleven publications provided data on rates of discontinuation due to adverse events. [5,24,45-47,50,60-62,67,70] The studies evaluated ivacaftor 300 mg/day (five studies), lumacaftor/ivacaftor 400/500 mg/day (five studies), tezacaftor/ivacaftor 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: ivacaftor monotherapy 1.2% (95% CI 0.3, 2.5), lumacaftor/ivacaftor 6.3% (95% CI 3.7, 9.6), tezacaftor/ivacaftor 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 tezacaftor/ivacaftor 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.[5] A crude comparison across interventions suggests that discontinuation due to adverse events is significantly more likely to occur with lumacaftor/ivacaftor than ivacaftor monotherapy, tezacaftor/ivacaftor, or placebo, which all had similar rates of drug discontinuation due to adverse events. For lumacaftor/ivacaftor, 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.[60,67] The studies evaluated ivacaftor 300 mg/day (1 study), tezacaftor/ivacaftor 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: ivacaftor monotherapy 5.1% (95% CI 2.6, 9.9), tezacaftor/ivacaftor 5.3% (95% CI 0.8, 13.3), and placebo 8.4% (95% CI 3.6, 14.9) (Appendix D, Figures D16- 17).[60] However, for both tezacaftor/ivacaftor 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.

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).[45,55] In contrast, hypertonic saline use, which was shown to decrease the risk of pulmonary exacerbations by 66% compared to placebo[45], was not permitted during ivacaftor 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, it remains unclear what magnitude of change in FEV_1 is clinically relevant, i.e. what percent decrease should cause concern, how much of the change is due to measurement variability,

and what is due to day-to-day fluctuation in lung function. A Dutch study aiming to discern the difference between these three underlying causes of FEV_1 changes suggested a 13% change represents a clinically important change – that is, a change not due to measurement error or regular fluctuations.(Taylor-Robinson, Thorax 2011) Such a cut-off has not been carried over into clinical use. If a threshold for clinically meaningful FEV_1 changes was defined, it would be easier to assess the risk/benefit equation. 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 $ppFEV_1$ and lung clearance index in people with CF and hard clinical endpoints such as lung transplant or death.[58]

Stakeholders identified uncertainties around CFTR modulator treatment decisions considering their personal experiences. One parent, for example, shared that their child experienced beneficial weight gains on lumacaftor/ivacaftor but simultaneously experienced lung function deterioration. For these parents and patients, it was difficult to decide whether weight gain at the expense of lung function decline made it worthwhile to stay on the modulator.

It is uncertain whether expanding access to the highest quality CF standard-of-care centers could provide equally beneficial gains in clinical outcomes like lung function, weight and nutrition, pulmonary exacerbations, hospitalizations, transplants, and survival. Evidence from Canada's health system suggests important health improvements when patients access the highest quality treatment centers and when insurance coverage is guaranteed.[71] Canadian CF patients have been living longer than American CF patients since the mid-1990s and currently live, on average, 10 years longer.[71] When US patients receiving Medicare and Medicaid were excluded from survival data, however, the difference between Canadian and US survival disappeared. It is unclear whether people 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. Expanding equitable access to the highest quality of care to all CF patients would likely go long way to improving CF-related health outcomes, and ultimately improve population-level survival. Available studies do not provide evidence regarding the effect of the CFTR modulators in people not receiving best supportive care, as provided in the trials. Nevertheless, based on the trial data, further improvements in health outcomes among those receiving best supportive care are likely with the addition of appropriate CFTR modulators.

Adverse events in this space are challenging because the most frequently reported events may be due to the underlying disease. The often-long lists of 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.

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 Ivacaftor 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 Mutation**	
Ivacaftor	A

G511D and non-*G551D* gating populations

- Provides significant improvements in $ppFEV_1$, weight, and respiratory-symptom-related quality of life compared to placebo for children, adolescents, and adults. Long-term follow-up shows lung function, weight, and quality of life gains are durable across all gating mutations.
- Lung function decline was slower in those taking ivacaftor compared to best supportive care.
- Pulmonary exacerbations were less frequent, shorter, and required fewer hospitalizations and intravenous antibiotics for CF patients taking ivacaftor compared to placebo.

R117H residual function populations

- The overall trial population did not experience a statistically significant change in lung function, BMI, or time to first pulmonary exacerbation between ivacaftor and placebo, though respiratory symptoms significantly improved.
- Children aged six-11 showed significant declines in $ppFEV_1$ compared to those on best supportive care (placebo), though this subgroup included only 17 patients and may have been influenced by an outlier.
- Adults aged 18 and older experienced significant absolute gains in $ppFEV_1$, weight, and respiratory symptom-related quality of life compared to placebo, though the magnitude was smaller compared to that seen in the gating mutation populations. Differences in pulmonary exacerbations were not observed.

Rates of discontinuation due to adverse events and severe adverse events were similar for ivacaftor as for placebo.

We have high certainty ivacaftor provides a substantial (moderate-large) net health benefit relative to placebo (i.e. best supportive care), and therefore assess the evidence to be "superior" (A).

Homozygous F508del mutations

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

Population/Genetic Group	ICER Evidence Rating
Homozygous F508del Mutation	
Lumacaftor/ivacaftor	B
Tezacaftor/ivacaftor	B+

Evidence of lumacaftor/ivacaftor for cystic fibrosis caused by two copies of the F508del mutation showed:

- Improvement in absolute ppFEV$_1$ and preserved lung function compared to placebo; however, changes in absolute ppFEV$_1$ may not be considered clinically important
- No difference in BMI from placebo in short term studies. At 96-weeks, patients 12 and older taking lumacaftor/ivacaftor showed increased BMI compared to baseline
- Improved respiratory symptom-related quality of life compared to placebo in patients age 12 and older but mixed in children six-11 years old
- The rate of pulmonary exacerbation was lower for patients aged 12 and older taking lumacaftor/ivacaftor than those taking placebo
- Chest tightness (abnormal respiration) was reported as a side effect for those taking lumacaftor/ivacaftor
- Rates of discontinuation due to adverse events were significantly higher for lumacaftor/ivacaftor (6.0%) than for placebo

For patients homozygous for the *F508del* mutation, we have high certainty lumacaftor/ivacaftor provides a small net health benefit relative to placebo (i.e. best supportive care), and therefore assess the evidence to be "incremental" (B).

Evidence of tezacaftor/ivacaftor for cystic fibrosis caused by two copies of the F508del mutation showed:

- Improvement in absolute ppFEV$_1$ compared to placebo; although the magnitude may not be considered clinically important
- Reduced the rate of pulmonary exacerbation compared to placebo, including pulmonary exacerbations requiring IV antibiotics and hospitalization

- Rates of discontinuation due to adverse events (2.3%) and of severe adverse events (5.3%) were similar for tezacaftor/ivacaftor as for lumacaftor/ivacaftor and for placebo.

For patients homozygous for the *F508del* mutation, we have moderate certainty that tezacaftor/ivacaftor provides at least a small, or substantial net health benefit, with high certainty of at least a comparable net health benefit relative to placebo (i.e., best supportive care). Therefore, we assess the evidence to be "comparable or better" ("B+").

Heterozygous F508del with a residual function mutation

Table 3.16. Evidence Rating for The Use of Tezacaftor/Ivacaftor 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	
Tezacaftor/ivacaftor	B+

Evidence of tezacaftor/ivacaftor for cystic fibrosis caused by one copy of the F508del mutation:

- Included a single Phase III crossover trial
- Trial population showed a clinically relevant improvement in absolute ppFEV$_1$ and respiratory sympton-related quality of life compared to placebo
- The treatment effect on pulmonary exacerbations and BMI was exploratory only due to small numbers and short duration

For patients heterozygous for the *F508del* mutation with an approved residual function mutation, we have moderate certainty that tezacaftor/ivacaftor provides at least a small, or substantial net health benefit, with high certainty of at least a comparable net health benefit relative to placebo (i.e., best supportive care). Therefore, we assess the evidence to be "comparable 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 ivacaftor for individuals with gating mutations, and lumacaftor/ivacaftor and tezacaftor/ivacaftor 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 tezacaftor/ivacaftor and ivacaftor monotherapy 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 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. 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).

Cost-Effectiveness Model: Methods

Model Structure

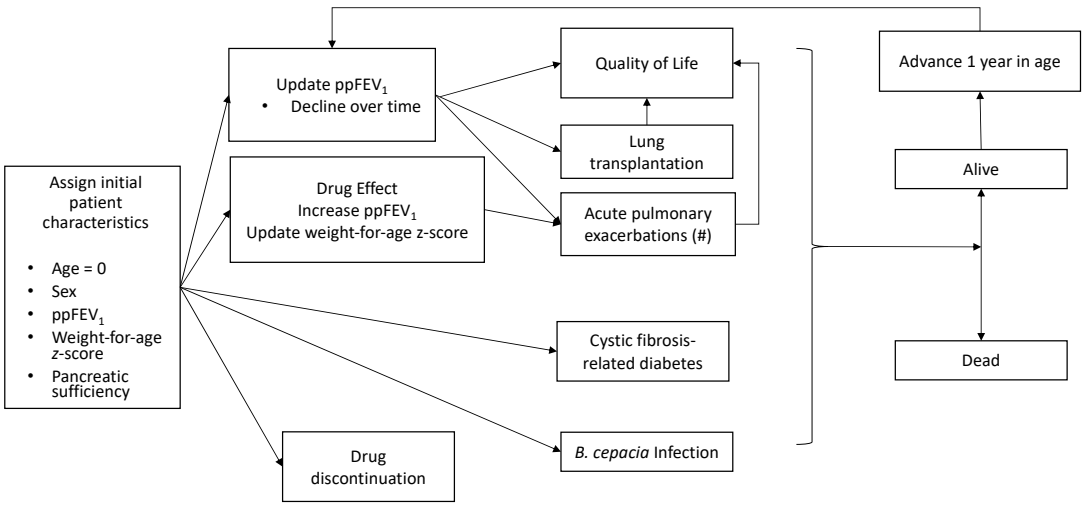
We developed a *de novo* discrete-time microsimulation model. The primary model variable was percent predicted forced expiratory volume in one second ($ppFEV_1$), modeled as a continuous variable. This model type was chosen to account for the continuous nature of $ppFEV_1$ and to capture the primary 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).[45,46] 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. 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 QALYs 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. 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

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



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 ivacaftor monotherapy. The age of treatment initiation is two years and older, consistent with FDA labeling. The second population includes individuals with CF who are homozygous for the *F508del* mutation. This population is eligible for treatment with lumacaftor/ivacaftor or tezacaftor/ivacaftor, and we assumed that the age of treatment initiation was six years and older for both treatments given that recommended age for tezacaftor/ivacaftor will likely be lowered with additional trials, as was the case for lumacaftor/ivacaftor. The third population includes individuals with CF who are heterozygous for the *F508del* mutation and a residual function mutation that is potentially responsive to tezacaftor/ivacaftor. This population is eligible for treatment with tezacaftor/ivacaftor combination or ivacaftor monotherapy, and the age of treatment initiation is 12 years and older. 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.[67,72]

We assumed that best supportive care consists of the following pulmonary therapies (percent utilization): dornase alfa (87.5%), inhaled tobramycin (69.4%), inhaled aztreonam (43.2%), azithromycin (65.5%), hypertonic saline (70.7%), oxygen (10.4%), non-invasive ventilation (2.8%), 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. 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 higher 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 with other eligible CFTR modulator treatments plus best supportive care (when available) and with best supportive care alone.

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.	We only assume that CFTR modulator therapy will have an impact on costs associated with acute pulmonary exacerbations and lung transplantation, but all other costs of supportive care not associated with lung function will not be affected by CFTR modulator therapies.
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.
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.[9,73] 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.[74-76] The annual risk of lung transplant was 0% for $ppFEV_1$ >30% as per guidelines; the risk estimate for those with reduced lung function is presented in Table 4.2.[77] The annual risk of diabetes was modeled as a function of age and sex.[78] 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.[79] 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.[67] 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.[53] 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[9,73]
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[74,75]
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[76]
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[74]
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[80]
$ppFEV_1$ ≤30	0.647	
Annual Risk of CF-Related Diabetes (Male, Female)		
Age 0-9	0.008, 0.016	Adler, 2008[78]
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.[52,63] We assumed that the increase in weight-for-age *z*-score would persist for a patient's lifetime.[52]

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 ivacaftor + best supportive care versus best supportive care alone was 0.56.[45] 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 ivacaftor 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 ivacaftor 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				
Ivacaftor Monotherapy	10.0 (4.5-15.5)	0.56	0.35 (0.20-0.51)	Davies, 2013;Ramsey, 2011;Borowitz, 2016;McKone, 2014[45,46,50,53]
CF Individuals Who are Homozygous for the *F508del* Mutation				
Lumacaftor/Ivacaftor	2.8 (1.8-3.8)	0.44	Same as above	Wainwright, 2015};Konstan, 2017;Taylor-Cousar, 2017; NICE, 2016[24,60,61,81,82]
Tezacaftor/ivacaftor	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				
Tezacaftor/ivacaftor	6.8 (5.7-7.8)	0.54 (0.26-1.13)‡	Same as above	Rowe, 2017[67]
Ivacaftor Monotherapy	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.[53]

†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[83] 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.[84] 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[84]:

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

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

The patient-specific parameters that affect mortality among non-transplanted patients were *SEX* (0 male, 1 female), *$ppFEV_1$* (%), *WFA* (weight-for-age *z* score), *#PE* (number of acute pulmonary exacerbations in the current year), *DIAB* (0 no diagnosis of diabetes, 1 yes), *PS* (0 no pancreatic sufficiency, 1 yes), *BAI* (0 no *B. cepacia* infection, 1 yes). The age-specific baseline hazard (b_a) was a product of the age-specific rates from the US life tables[83] 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.[80]

Utilities

We used the linear interpolation of EQ-5D utilities by $ppFEV_1$ conducted by Schechter et al. (Table 4.4).[85] 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%) provided to Tappenden et al. for a NICE economic evaluation.[86] 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.[86] We used the same utility used by Schechter et al.[85] for the first year after lung transplantation (0.32) based on quality of life study of lung transplantation in patients with cystic fibrosis.[87] (Subsequent years after transplantation were set to a utility equivalent to a $ppFEV_1$ of 70%-79%.)

Table 4.4. Utility Values by Level of $ppFEV_1$

$ppFEV_1$ (%)	Utility
>90	0.920
80-89	0.873
70-79	0.838
60-69	0.801
50-59	0.765
40-49	0.729
30-39	0.692
20-29	0.653
<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 ivacaftor and lumacaftor/ivacaftor (Table 4.5).[88] The FSS supports the acquisition of pharmaceutical drugs, medical equipment, and supplies and service contracts for the VA and other federal organizations. As tezacaftor/ivacaftor was only recently approved by the FDA, information on its net pricing was not yet available. We therefore applied the FSS discount rate for lumacaftor/ivacaftor (3.2%) to the wholesale acquisition cost (WAC) of tezacaftor/ivacaftor to arrive at an estimated net price.

Table 4.5. Drug Cost Inputs

Intervention	Administration	Unit	WAC per Unit/Dose*[89]	Net price per Unit†	Annual Drug Cost
Ivacaftor	Oral twice daily	150mg tablet	$426.72	$424.15	$309,841.58
Lumacaftor/ Ivacaftor					
Age 6-11 years	Oral, 2 tablets twice daily	100mg/125mg	$186.78	$180.76	$264,085.53
Age 12+ years	Oral, 2 tablets twice daily	200mg/125mg	$186.78	$180.76	$264,085.53
Tezacaftor/ Ivacaftor	Oral (once/twice) daily	100mg/150mg	$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 cystic fibrosis have attempted to account for possible price changes over time, by assuming that the drug prices will decrease upon loss of patent exclusivity.[75,90,91] For example, Dilokthornsakul et al. assumed that the prices of ivacaftor and lumacaftor/ivacaftor would drop to 10% of WAC after patent expiration.[90,91] 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 there is at present no well-developed methodology for estimating changes in drug price throughout the life cycle. This is especially true 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. 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.[90,91] Both

disease management and pulmonary exacerbation components incorporate separate cost structures that were derived from to reflect increasing costs with increasing disease severity categories (mild, moderate, and severe).[92] 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.

Original estimates, because they were derived from HMO data[92], resulted in an average annual cost that is lower, after adjusting for inflation, than two other studies conducted using private insurance fee-for-service data[93];[94]. Based on health insurance information reported in the 2016 CFFPR, we assumed a 60%/40% insurance mix (private/other) and applied a multiplier to our base estimates to model the higher private payer costs.[1]

Transplant-related costs include the one-time cost of receiving a lung transplant followed by an annual cost associated with post-transplantation care. Estimates were derived from Ramsey et al. (1995) based on inpatient and outpatient billing services of lung transplantation patients at the University of Washington.[95] 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. All costs were adjusted to 2017 dollars using the medical care component of the Consumer Price Index.

Table 4.6. Direct Costs by Disease Severity

	$ppFEV_1 \geq 70\%$	$ppFEV_1$ 40%-69%	$ppFEV_1 < 40\%$
Disease Management	$14,824	$19,555	$33,433
PEx* (age <18)	$30,966	$49,063	$72,691
PEx* (age 18+)	$28,060	$44,602	$63,917
Lung Transplant	$389,438		
Post-Transplant (Year 1)	$337,545		
Post-Transplant (Year 2+)	$128,169		

*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.

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.[96] 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.[97] 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 $500,00 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 two 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%).

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 matched to observed statistics of CF patients: median age of survival, percent in lung function categories (≤40% $ppFEV_1$, severe; between 40% and 70% $ppFEV_1$, moderate; ≥70% pp FEV_1, mild) by age, and median $ppFEV_1$ by age.[1] 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 ivacaftor plus best supportive care and best supportive care only were approximately $7,514,000 and $1,197,000, respectively. The total discounted QALYs (and life years) for ivacaftor plus best supportive care and best supportive care alone were 21.3 (25.3) and 15.2 (21.0), respectively. The incremental cost-effectiveness ratios for ivacaftor in this population were approximately $1,029,000 per QALY gained and $1,462,000 per life year gained.

For individuals who are homozygous for the F508del mutation the total discounted lifetime costs for lumacaftor/ivacaftor, tezacaftor/ivacaftor and best supportive care were approximately $5,941,000, $6,177,000 and $1,093,000, respectively. The total discounted QALYs (and life years) for lumacaftor/ivacaftor, tezacaftor/ivacaftor and best supportive care were 19.4 (23.3), 19.4 (23.4) and 14.4 (19.8), respectively. The incremental cost-effectiveness ratios for lumacaftor/ivacaftor and tezacaftor/ivacaftor versus best supportive care in this population were approximately $970,000 per QALY and $1,017,000 per QALY, respectively, and approximately $1,394,000 and $1,431,000 per life year gained, respectively.

For individuals who are heterozygous for the F508del mutation with a residual function mutation, the total discounted lifetime costs for ivacaftor monotherapy, tezacaftor/ivacaftor and best supportive care were approximately $6,267,000, $5,861,000 and $1,078,000, respectively. The total discounted QALYs (and life years) for ivacaftor monotherapy, tezacaftor/ivacaftor and best supportive care were 17.3 (21.2), 17.5 (21.5) and 12.1 (17.6), respectively. The incremental cost-effectiveness ratios for ivacaftor monotherapy and tezacaftor/ivacaftor in this population were

approximately $966,000 per QALY and $886,000 per QALY, respectively, and approximately $1.4 and $1.2 million 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	$1,197,072	28.4	21.0	15.2
Ivacaftor Plus BSC	$6,852,668	$7,514,387	16.3	25.3	21.3
CF Individuals Homozygous for *F508del* Mutation					
BSC	$0	$1,092,974	22.1	19.8	14.4
Lumacaftor/Ivacaftor Plus BSC	$5,355,379	$5,941,498	9.4	23.3	19.4
Tezacaftor/ivacaftor Plus BSC	$5,567,649	$6,177,033	10.9	23.4	19.4
CF Individuals Heterozygous for *F508del* Mutation with Residual Function Mutation					
BSC	$0	$1,078,405	21.7	17.6	12.1
Ivacaftor Plus BSC	$5,696,801	$6,267,423	9.0	21.2	17.3
Tezacaftor/ivacaftor Plus BSC	$5,263,069	$5,860,791	10.5	21.5	17.5

CFTR: cystic fibrosis transmembrane conductance regulator; PEx: pulmonary exacerbations; QALY: quality adjusted life year; 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			
Ivacaftor Plus BSC	$1,461,577	$1,029,461	$518,931
CF Individuals Homozygous for *F508del* Mutation			
Lumacaftor/Ivacaftor Plus BSC	$1,394,475	$970,214	$381,990
Tezacaftor/ivacaftor Plus BSC	$1,430,504	$1,017,251	$455,063
CF Individuals Heterozygous for *F508del* Mutation and Residual Function Mutation			
Ivacaftor Plus BSC	$1,423,077	$996,171	$407,845
Tezacaftor/ivacaftor Plus BSC	$1,225,193	$886,083	$427,1235

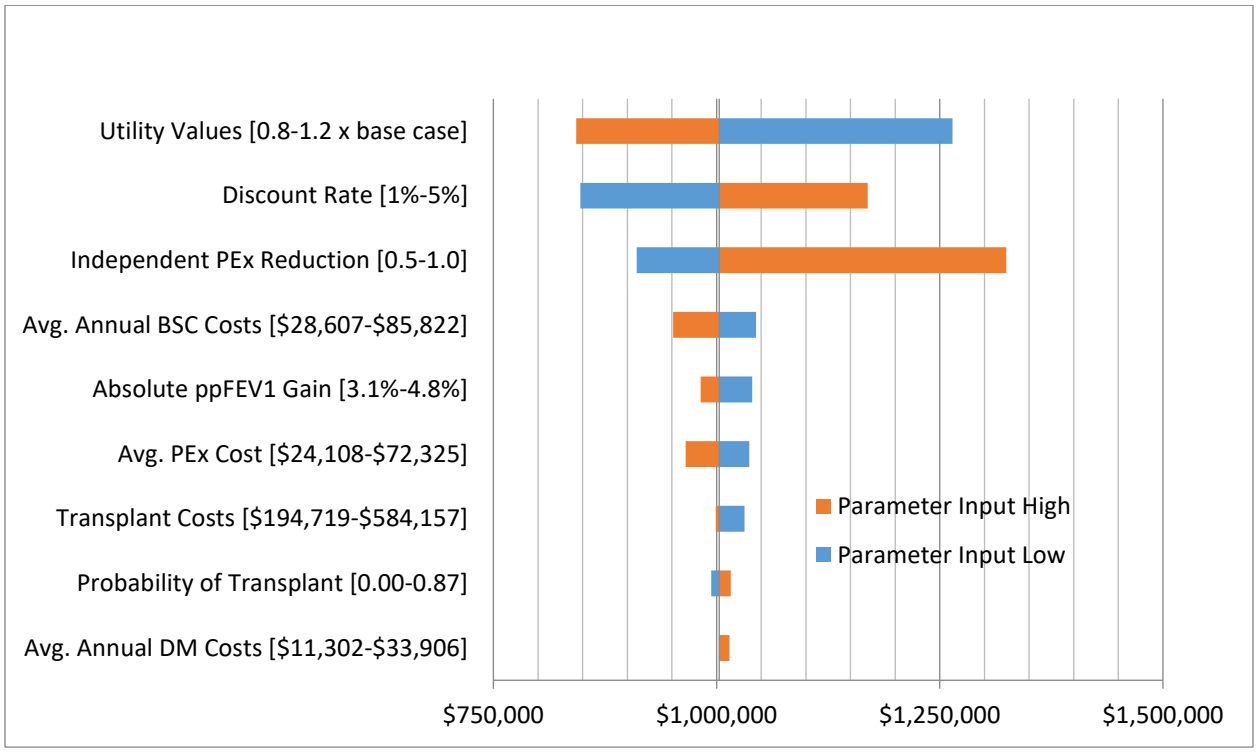
BSC: best supportive care; LY: life year; QALY: quality adjusted life years; Pex: pulmonary exacerbation

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 addition QALY for CFTR modulators plus best supportive care versus best supportive care alone. Because there were nine different values for utilities depending on the ppFEV$_1$ value, we varied these values simultaneously instead of one at a time. Specifically, we varied the utilities between 0.8 and 1.2 times the base-case values. Drug cost variation is described more completely as part of threshold analyses (see below).

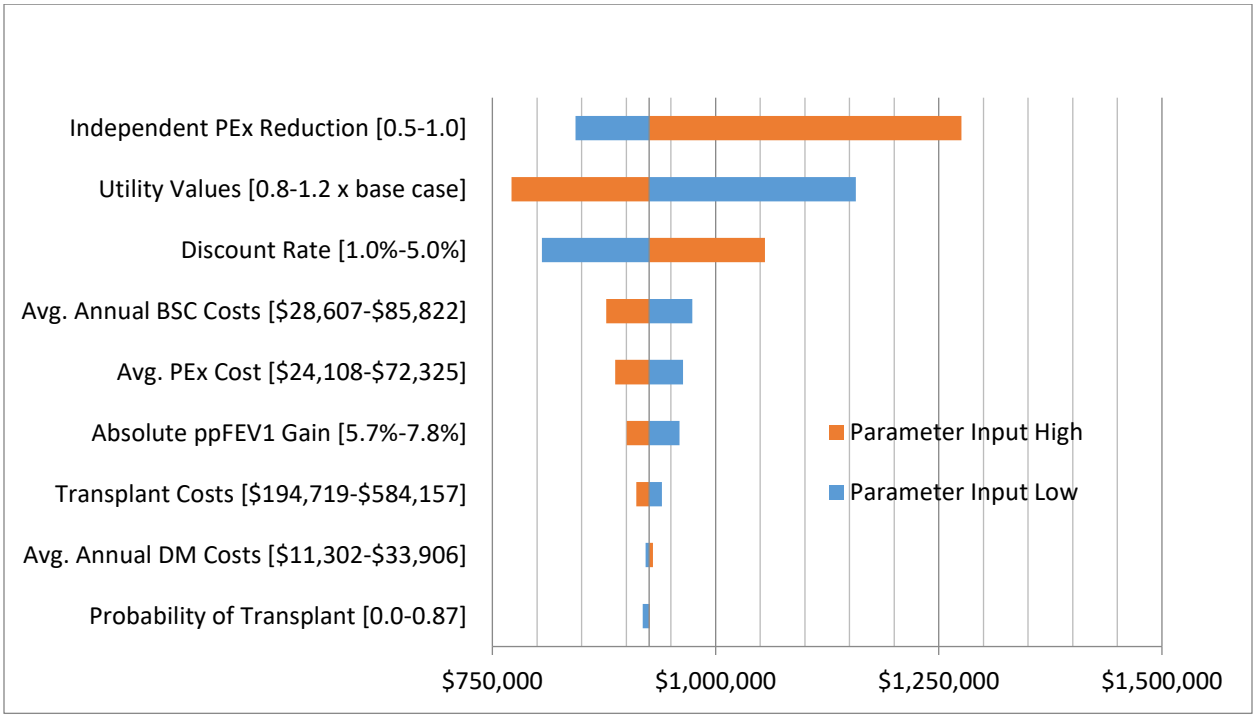
The impacts of variations in input values on cost-per-QALY estimates are shown for tezacaftor/ivacaftor in CF individuals homozygous for *F508del* mutation in Figure 4.2, and in individuals heterozygous for *F508del* mutation and residual function mutation in Figure 4.3. The analyses were most sensitive to assumptions about lung function-specific utilities, independent effect of drugs on the reduction of acute pulmonary exacerbations, and the discount rate; while changes in the former resulted in large variation in cost-effectiveness estimates, these did not approach commonly cited 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 Tezacaftor/ivacaftor 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 Tezacaftor/ivacaftor 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 0%. For example, the 95% credible interval for the incremental cost-effectiveness ratios for ivacaftor compared with best supportive care was $713,300 to $2.4 million 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						
Ivacaftor plus BSC	0%	0%	0%	0%	0%	0%
CF Individuals Homozygous for *F508del* Mutation						
Lumacaftor/Ivacaftor plus BSC	0%	0%	0%	0%	0%	0%
Tezacaftor/ivacaftor plus BSC	0%	0%	0%	0%	0%	0%
CF Individuals Heterozygous for *F508del* Mutation and Residual Function Mutation						
Ivacaftor plus BSC	0%	0%	0%	0%	0%	0%
Tezacaftor/ivacaftor plus BSC	0%	0%	0%	0%	0%	0%

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 $33,000. Including productivity losses in the analysis resulted in incremental cost-effectiveness ratios for ivacaftor very similar to those seen in the base case ($1,024,900 per QALY societal vs. $1,072,100 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			
Ivacaftor plus BSC	$6,317,315	-$27,739	$1,024,937
CF Individuals Homozygous for *F508del* Mutation			
Lumacaftor / Ivacaftor plus BSC	$4,848,524	-$25,748	$955,062
Tezacaftor/ivacaftor plus BSC	$5,084,059	-$26,071	$1,012,035
CF Individuals Heterozygous for *F508del* Mutation and Residual Function Mutation			
Ivacaftor plus BSC	$5,189,018	-$22,213	$991,906
Tezacaftor/ivacaftor plus BSC	$4,782,386	-$22,844	$881,850

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 the individuals 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 ivacaftor was $733,900 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).

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				
Ivacaftor plus BSC	$733,897	$848,410	$1,400,667	$1,917,473
CF Individuals Homozygous for *F508del* Mutation				
Lumacaftor / Ivacaftor plus BSC	$644,125	$786,394	$1,346,105	$1,938,365
Tezacaftor/ivacaftor plus BSC	$673,188	$823,907	$1,427,894	$2,099,607
CF Individuals Heterozygous for *F508del* Mutation and Residual Function Mutation				
Ivacaftor plus BSC	$729,329	$856,082	$1,290,938	$1,646,070
Tezacaftor/ivacaftor plus BSC	$653,745	$767,229	$1,154,900	$1,467,955

BSC: best supportive care

Threshold Analysis Results

Prices necessary to reach cost-effectiveness thresholds of $50,000, $100,000, $150,000, $200,000, $300,000 and $500,000 per QALY are listed in Table 4.12, for each CF population and CFTR modulator. Threshold prices were higher for the CF population heterozygous for *F508del* mutation and residual function mutation, and higher for tezacaftor/ivacaftor compared with lumacaftor/ivacaftor for CF individuals homozygous for *F508del* mutation. A discount of approximately 50% 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 4.12. Threshold Analysis Results

	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								
Ivacaftor Monotherapy	$426.72	$424.15	$52.13	$71.12	$90.11	$109.10	$147.09	$223.05
CF Individuals Homozygous for *F508del* Mutation								
Lumacaftor/ivacaftor	$186.78	$180.76	$25.55	$33.98	$42.42	$50.86	$67.73	$101.47
Tezacaftor/ivacaftor	$400.08	$387.20	$51.02	$68.40	$85.78	$103.17	$137.93	$207.46
CF Individuals Heterozygous for *F508del* Mutation and Residual Function Mutation								
Ivacaftor Monotherapy	$426.72	$424.15	$57.20	$76.59	$95.98	$115.37	$154.16	$231.73
Tezacaftor/ivacaftor	$400.08	$387.20	$55.23	$75.09	$94.94	$114.80	$154.52	$233.95

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

Note that ivacaftor and tezacaftor/ivacaftor are each used for treatment in two different populations in Table 4.12. 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 price for ivacaftor across both relevant populations varied from $55.54 at $50,000 per QALY to $94.07 for $150,000 per QALY and to $228.90 for $500,000 per QALY. Blended prices for tezacaftor/ivacaftor across both of its relevant populations were $52.80 at $50,000 per QALY, $89.65 at $150,000 per QALY, and $218.65 at $500,000 per QALY.

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 ivacaftor treatment of CF patients with the *G551D* mutation (2016)[91] and, more recently, lumacaftor/ivacaftor treatment of CF patients with homozygous *F508del* mutation (2017).[90] 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[91] were undiscounted, results were also presented using a discount rate of 3%. Discounted incremental QALYs were 5.21, incremental lifetime costs approximately $3,772,000, and the base-case incremental cost–effectiveness ratio was approximately $725,000 per QALY (2013 US$ converted to 2017 using the Consumer Price Index for Medical Care [CPI-M]). Our current model estimated incremental QALYs of 6.00, incremental costs of $6,389,598, and an incremental cost-effectiveness ratio of approximately $1,065,000 per QALY. Starting age for treatment in the earlier ivacaftor model was 25 years old, while we modeled treatment initiation at two years old. Ivacaftor 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 lumacaftor/ivacaftor combination treatment of CF patients with homozygous *F508del* mutation.[90] Starting age for treatment with lumacaftor/ivacaftor was 25 years old, while the ICER analysis modeled treatment initiation at six years old. The WAC for lumacaftor/ivacaftor 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 lumacaftor/ivacaftor estimated incremental QALYs of 4.89, incremental lifetime costs of $4,818,074, and an incremental cost-effectiveness ratio of $984,969 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 ivacaftor treatment of CF patients aged six years or older (with median age = 20 years) with *G551D* mutation in the United Kingdom.[75] 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 ivacaftor 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 ivacaftor 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 6.00 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 4.89 to 6.0 (discounted). With (discounted) CFTR drug-related costs ranging from $5.3 million to $6.9 million, the incremental cost-effectiveness ratios of drugs plus best supportive care compared with best supportive care alone were approximately $1 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. 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. 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 half to be considered cost effective.

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 who have failed other available treatments.
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

Value-based price benchmarks will be included in the revised Evidence Report that will be released on/about May 3, 2018.

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 tezacaftor/ivacaftor in cystic fibrosis, specifically for those heterozygous or homozygous for the *F508del* mutation. We used the WAC for tezacaftor/ivacaftor, 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 tezacaftor/ivacaftor 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 tezacaftor/ivacaftor. 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 tezacaftor/ivacaftor. 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 tezacaftor/ivacaftor.

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 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 tezacaftor/ivacaftor. We assumed that 20% of these patients (1,693) would initiate tezacaftor/ivacaftor 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 tezacaftor/ivacaftor 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 tezacaftor/ivacaftor in the United States. We assumed that 20% of the patients (1,239) would initiate tezacaftor/ivacaftor 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 tezacaftor/ivacaftor (plus best supportive care) would replace lumacaftor/ivacaftor 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 lumacaftor/ivacaftor 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 tezacaftor/ivacaftor (plus best supportive care) would replace ivacaftor 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 ivacaftor 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 tezacaftor/ivacaftor in those homozygous for the *F508del* mutation, compared to current care assuming lumacaftor/ivacaftor plus best supportive care in 50% and only best supportive care in 50%. Potential budget impact is presented based on WAC ($292,000 per year), discounted WAC ($282,656 per year), and the prices to reach $150,000, $100,000, and $50,000 per QALY in this population ($62,610, $49,924, and $37,237 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
Tezacaftor/ ivacaftor+BSC	$262,445	$254,852	$76,024	$65,714	$56,950
Lumacaftor/ ivacaftor+BSC (50%) & BSC (50%)	$147,752				
Difference	$114,693	$107,099	($71,728)	($82,038)	($90,802)

WAC: wholesale acquisition cost; QALY: quality adjusted life year; BSC: best supportive care

The average potential budgetary impact when using the WAC ($292,000) was an additional per-patient cost of approximately $114,700 and approximately $107,000 using the discounted WAC ($282,656). 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 $72,000 per patient using the annual price ($62,610) to achieve $150,000 per QALY to approximately $91,000 using the annual price ($37,237) 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 tezacaftor/ivacaftor in addition to best supportive care, these additional costs would be more than offset by the replacement of lumacaftor/ivacaftor at net price by tezacaftor/ivacaftor at the much lower assumed threshold prices.

Table 7.3 illustrates the per-patient budget impact calculations for those with one *F508de*l mutation and a residual function mutation, compared to current care assuming ivacaftor plus best supportive care in 50% and best supportive care in 50%. We present the potential budget impact results based on WAC ($292,000 per year), discounted WAC ($282,656 per year), and the prices to reach $150,000, $100,000, and $50,000 per QALY for tezacaftor/ivacaftor in this population ($69,294, $54,801, and $40,308 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
Tezacaftor/ ivacaftor+BSC	$269,453	$261,685	$83,974	$72,250	$60,200
Ivacaftor +BSC (50%) & BSC (50%)	$170,450				
Difference	$99,003	$91,234	($86,477)	($98,201)	($110,250)

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

The average potential budgetary impact when using the WAC ($292,000) was an additional per-patient cost of approximately $99,000 and approximately $91,200 using the discounted WAC ($282,656). 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 $86,500 per patient using the annual price ($69,294) to achieve $150,000 per QALY to approximately $110,000 using the annual price ($40,308) 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 tezacaftor/ivacaftor in addition to best supportive care as well as the potential savings from replacement of ivacaftor at net price by tezacaftor/ivacaftor 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 tezacaftor/ivacaftor over five years did not exceed the $915 million 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 (103%) using 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 tezacaftor/ivacaftor in the combined populations is 96% of the $915 million threshold at the net price.

Table 7.4. Estimated Total Potential Budget Impact of Tezacaftor/Ivacaftor 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*					
Tezacaftor/ivacaftor	8,464	1,693	$107,099	$541,450,027	59%
Heterozygous *F508del* with Residual Function Mutation					
Tezacaftor/ivacaftor	6,195	1,239	$91,234	$336,375,172	37%
Total US Population*					
Tezacaftor/ivacaftor	14,659	2,932	$100,395	$877,825,198	96%

BI: budget impact;

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

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

References

1. Cystic Fibrosis Foundation. *Cystic Fibrosis Foundation Patient Registry 2016 Annual Data Report.* cff.org2017.
2. Agrawal A, Mehta D, Sikachi RR, Du D, J. W. Nationwide trends of hospitalizations for cystic fibrosis in the United States from 2003 to 2013. *Intractable Rare Dis Res.* 2017;6(3):191-198.
3. Clinical and Functional Translation of CFTR. CFTR2.org. 2018; https://www.cftr2.org/.
4. Foundation CF. What is Cystic Fibrosis. 2017; https://www.cff.org/What-is-CF/About-Cystic-Fibrosis/. Accessed October 24, 2017.
5. Donaldson SH, Pilewski JM, Griese M, et al. Tezacaftor/Ivacaftor in Subjects with Cystic Fibrosis and F508del/F508del-CFTR or F508del/G551D-CFTR. *American journal of respiratory and critical care medicine.* 2017.
6. O'Sullivan BP, Freedman SD. Cystic fibrosis. *The Lancet.* 2009;373(9678):1891-1904.
7. Cystic Fibrosis Foundation, Borowitz D, Parad RB, et al. Cystic Fibrosis Foundation practice guidelines for the management of infants with cystic fibrosis transmembrane conductance regulator-related metabolic syndrome during the first two years of life and beyond. *Journal of Paediatrics.* 2009;155(6):S106-116.
8. Britto MT, Kotagal UR, Hornung RW, Atherton HD, Tsevat J, Wilmott RW. Impact of recent pulmonary exacerbations on quality of life in patients with cystic fibrosis. *Chest.* 2002;121(1):64-72.
9. Konstan MW, Morgan WJ, Butler SM, et al. Risk factors for rate of decline in forced expiratory volume in one second in children and adolescents with cystic fibrosis. *The Journal of pediatrics.* 2007;151(2):134-139, 139.e131.
10. Cystic fibrosis: Assessment and management of pancreatic sufficiency. UpToDate; 2017. https://www.uptodate.com/contents/cystic-fibrosis-assessment-and-management-of-pancreatic-insufficiency. Accessed March 6, 2018.
11. Comer DM, Ennis M, McDowell C, et al. Clinical phenotype of cystic fibrosis patients with the G551D mutation. *QJM : monthly journal of the Association of Physicians.* 2009;102(11):793-798.
12. Sawicki GS, Sellers DE, Robinson WM. High treatment burden in adults with cystic fibrosis: challenges to disease self-management. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society.* 2009;8(2):91-96.
13. National Institutes of Health. Cystic Fibrosis Fact Sheet. 2013; https://report.nih.gov/nihfactsheets/ViewFactSheet.aspx?csid=36.
14. Woolf S, Schünemann HJ, Eccles MP, Grimshaw JM, Shekelle P. Developing clinical practice guidelines: types of evidence and outcomes; values and economics, synthesis, grading, and presentation and deriving recommendations. *Implementation Science : IS.* 2012;7:61-61.
15. Wang X, Dockery DW, Wypij D, Fay ME, Ferris BG, Jr. Pulmonary function between 6 and 18 years of age. *Pediatric pulmonology.* 1993;15(2):75-88.
16. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *American journal of respiratory and critical care medicine.* 1999;159(1):179-187.
17. University of Miami. Cystic Fibrosis Questionnaire- Revised. 2017; http://www.psy.miami.edu/cfq_QLab/index.html. Accessed October 30, 2017.
18. Lung Institute. What is FEV1? Here's what you need to know. 2016; https://lunginstitute.com/blog/what-is-fev1-heres-what-you-need-to-know/. Accessed March 6, 2018.

19. National Institute for Health and Care Excellence (NICE). *Lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation.* nice.org June 2016 2016.
20. Moran A, Brunzell C, Cohen RC, et al. Clinical care guidelines for cystic fibrosis-related diabetes: a position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. *Diabetes Care.* 2010;33(12):2697-2708.
21. Quittner AL, Buu A, Messer MA, Modi AC, Watrous M. Development and validation of The Cystic Fibrosis Questionnaire in the United States: a health-related quality-of-life measure for cystic fibrosis. *Chest.* 2005;128(4):2347-2354.
22. Quittner AL, Modi AC, Wainwright C, Otto K, Kirihara J, Montgomery AB. Determination of the minimal clinically important difference scores for the Cystic Fibrosis Questionnaire-Revised respiratory symptom scale in two populations of patients with cystic fibrosis and chronic Pseudomonas aeruginosa airway infection. *Chest.* 2009;135(6):1610-1618.
23. Robinson PD, Latzin P, Verbanck S, et al. Consensus statement for inert gas washout measurement using multiple- and single- breath tests. *The European respiratory journal.* 2013;41(3):507-522.
24. Wainwright CE, Elborn JS, Ramsey BW, et al. Lumacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR. *N Engl J Med.* 2015;373(3):220-231.
25. Aetna. Specialty Pharmacy Clinical Policy Bulletins Aetna Non-Medicare Prescription Drug Plan: Cystic Fibrosis. 2015; http://www.aetna.com/products/rxnonmedicare/data/2015/MISC/cystic_fibrosis.html. Accessed February 2018.
26. City BCBSK. Orkambi (lumacaftor/ivacaftor) Medical Policy. 2017; http://medicalpolicy.bluekc.com/MedPolicyLibrary/Prescription%20Drugs/Standard%20Prescription%20Drugs%20Pharmacy%20Benefit/07-17%20Orkambi%20(lumacaftor-ivacaftor).pdf. Accessed February 2018.
27. Anthem. Orkambi (ivacaftor/lumacaftor). 2015; https://www11.anthem.com/provider/noapplication/f0/s0/t0/pw_e235679.pdf?na=pharminfo. Accessed February 2018.
28. Cigna. 2017 Cigna Prior Authorization Criteria. 2017; https://www.cigna.com/iwov-resources/medicare-2017/docs/prior-authorization-chs.pdf. Accessed February 2018.
29. City BCBSK. Kalydeco (ivacaftor) Medical Policy. 2017; http://medicalpolicy.bluekc.com/MedPolicyLibrary/Prescription%20Drugs/Standard%20Prescription%20Drugs%20Pharmacy%20Benefit/07-17%20Kalydeco%20(ivacaftor)%200817%20update.pdf. Accessed February 2018.
30. Anthem. Kalydeco (ivacaftor). 2015; https://www11.anthem.com/provider/noapplication/f0/s0/t0/pw_e181473.pdf?na=pharminfo. Accessed February 2018.
31. Farrell PM, White TB, Ren CL, et al. Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation. *The Journal of pediatrics.* 2017;181(Supplement):S4-S15.e11.
32. Stallings VA, Stark LJ, Robinson KA, Feranchak AP, Quinton H. Evidence-Based Practice Recommendations for Nutrition-Related Management of Children and Adults with Cystic Fibrosis and Pancreatic Insufficiency: Results of a Systematic Review. *Journal of the American Dietetic Association.*108(5):832-839.
33. Mogayzel PJ, Jr., Naureckas ET, Robinson KA, et al. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. *American journal of respiratory and critical care medicine.* 2013;187(7):680-689.

34. Flume PA, Mogayzel PJ, Jr., Robinson KA, et al. Cystic fibrosis pulmonary guidelines: treatment of pulmonary exacerbations. *American journal of respiratory and critical care medicine.* 2009;180(9):802-808.
35. Flume PA, Robinson KA, O'Sullivan BP, et al. Cystic Fibrosis Pulmonary Guidelines: Airway Clearance Therapies. *Respiratory Care.* 2009;54(4):522-537.
36. Saiman L, Siegel JD, LiPuma JJ, et al. Infection Prevention and Control Guideline for Cystic Fibrosis: 2013 Update. *Infection Control and Hospital Epidemiology.* 2014;35(S1):S1-S67.
37. National Institute for Health and Care Excellence. *Cystic Fibrosis: diagnosis and management (NICE Guideline).* NICE; October 25, 2017 2017.
38. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Annals of internal medicine.* 1997;126(5):376-380.
39. Higgins J, Green S,. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* The Cochrane Collaboration; 2011.
40. Moher D, Liberati A, Tetzlaff J, DG A. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Annals of internal medicine.* 2010;8(5):336-341.
41. Food and Drug Administration. U.S. Prescribing Information - Symdeko. In: HHS, ed. www.fda.gov2018.
42. Quality. AfHRa. *U.S. Preventive Services Task Force Procedure Manual.* 2008.
43. Rucker G, Schwarzer G, Carpenter J, Olkin I. Why add anything to nothing? The arcsine difference as a measure of treatment effect in meta-analysis with zero cells. *Statistics in medicine.* 2009;28(5):721-738.
44. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *Journal of clinical epidemiology.* 1997;50(6):683-691.
45. Ramsey BW, Davies J, McElvaney NG, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *N Engl J Med.* 2011;365(18):1663-1672.
46. Davies JC, Wainwright CE, Canny GJ, et al. Efficacy and safety of ivacaftor in patients aged 6 to 11 years with cystic fibrosis with a G551D mutation. *American journal of respiratory and critical care medicine.* 2013;187(11):1219-1225.
47. De Boeck K, Munck A, Walker S, et al. Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society.* 2014;13(6):674-680.
48. Moss RB, Flume PA, Elborn JS, et al. Efficacy and safety of ivacaftor in patients with cystic fibrosis who have an Arg117His-CFTR mutation: a double-blind, randomised controlled trial. *The Lancet Respiratory medicine.* 2015;3(7):524-533.
49. Davies JC, Cunningham S, Harris WT, et al. Safety, pharmacokinetics, and pharmacodynamics of ivacaftor in patients aged 2-5 years with cystic fibrosis and a CFTR gating mutation (KIWI): an open-label, single-arm study. *The Lancet Respiratory medicine.* 2016;4(2):107-115.
50. McKone EF, Borowitz D, Drevinek P, et al. Long-term safety and efficacy of ivacaftor in patients with cystic fibrosis who have the Gly551Asp-CFTR mutation: a phase 3, open-label extension study (PERSIST). *The Lancet Respiratory medicine.* 2014;2(11):902-910.
51. Rowe SM, Heltshe SL, Gonska T, et al. Clinical mechanism of the cystic fibrosis transmembrane conductance regulator potentiator ivacaftor in G551D-mediated cystic fibrosis. *American journal of respiratory and critical care medicine.* 2014;190(2):175-184.
52. Sawicki GS, McKone EF, Pasta DJ, et al. Sustained Benefit from ivacaftor demonstrated by combining clinical trial and cystic fibrosis patient registry data. *American journal of respiratory and critical care medicine.* 2015;192(7):836-842.

53. Borowitz D, Lubarsky B, Wilschanski M, et al. Nutritional Status Improved in Cystic Fibrosis Patients with the G551D Mutation After Treatment with Ivacaftor. *Digestive diseases and sciences.* 2016;61(1):198-207.
54. Quittner A, Suthoff E, Rendas-Baum R, et al. Effect of ivacaftor treatment in patients with cystic fibrosis and the G551D-CFTR mutation: patient-reported outcomes in the STRIVE randomized, controlled trial. *Health and quality of life outcomes.* 2015;13:93.
55. Davies J, Sheridan H, Bell N, et al. Assessment of clinical response to ivacaftor with lung clearance index in cystic fibrosis patients with a G551D-CFTR mutation and preserved spirometry: a randomised controlled trial. *The Lancet Respiratory medicine.* 2013;1(8):630-638.
56. Flume PA, Wainwright CE, Elizabeth Tullis D, et al. Recovery of lung function following a pulmonary exacerbation in patients with cystic fibrosis and the G551D-CFTR mutation treated with ivacaftor. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society.* 2017.
57. Bai Y, Higgins M, Volkova N, et al. Real-world outcomes in young (6-to 12-year-old) patients (pts) with cystic fibrosis (CF) treated with ivacaftor (IVA): Analysis of 2014 US and UK CF registries data. *Journal of Cystic Fibrosis.* 2016;15:S57-S58.
58. Bai Y, Higgins M, Volkova N, et al. Real-world outcomes in patients (PTS) with cystic fibrosis (CF) treated with ivacaftor (IVA): Analysis of 2014 US and UK CF registries. *Journal of Cystic Fibrosis.* 2016;15:S41.
59. Ratjen F, Hug C, Marigowda G, et al. Efficacy and safety of lumacaftor and ivacaftor in patients aged 6-11 years with cystic fibrosis homozygous for F508del-CFTR: a randomised, placebo-controlled phase 3 trial. *The Lancet Respiratory medicine.* 2017;5(7):557-567.
60. Taylor-Cousar JL, Munck A, McKone E, et al. Tezacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del. *The New England Journal of Medicine.* 2017.
61. Konstan MW, McKone EF, Moss RB, et al. Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase 3, extension study. *The Lancet Respiratory medicine.* 2017;5(2):107-118.
62. Milla CE, Ratjen F, Marigowda G, Liu F, Waltz D, Rosenfeld M. Lumacaftor/Ivacaftor in Patients Aged 6-11 Years with Cystic Fibrosis and Homozygous for F508del-CFTR. *American journal of respiratory and critical care medicine.* 2017;195(7):912-920.
63. Konstan M, McKone E, Moss R, et al. Evidence of reduction in annual rate of fev1 decline and sustained benefits with lumacaftor and ivacaftor (LUM/IVA) in patients (PTS) with CF homozygous for f508del-cftr. *Pediatric pulmonology.* 2016;51:260.
64. Jennings MT, Dezube R, Paranjape S, et al. An Observational Study of Outcomes and Tolerances in Patients with Cystic Fibrosis Initiated on Lumacaftor/Ivacaftor. *Annals of the American Thoracic Society.* 2017.
65. Elborn JS, Ramsey BW, Boyle MP, et al. Efficacy and safety of lumacaftor/ivacaftor combination therapy in patients with cystic fibrosis homozygous for Phe508del CFTR by pulmonary function subgroup: a pooled analysis. *The Lancet Respiratory medicine.* 2016;4(8):617-626.
66. Taylor-Cousar JL, Jain M, Barto TL, et al. Lumacaftor/ivacaftor in patients with cystic fibrosis and advanced lung disease homozygous for F508del-CFTR. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society.* 2017.
67. Rowe SM, Daines C, Ringshausen FC, et al. Tezacaftor–Ivacaftor in Residual-Function Heterozygotes with Cystic Fibrosis. *N Engl J Med.* 2017;377(21):2024-2035.
68. Food and Drug Administration. Ivacaftor Prescribing Information. In:2017.
69. Food and Drug Administration. Label- Orkambi. In: FDA; 2016.

70. Boyle MP, Bell SC, Konstan MW, et al. A CFTR corrector (lumacaftor) and a CFTR potentiator (ivacaftor) for treatment of patients with cystic fibrosis who have a phe508del CFTR mutation: a phase 2 randomised controlled trial. *The Lancet Respiratory medicine.* 2014;2(7):527-538.
71. Flume PA, VanDevanter DR. The Cystic Fibrosis Survival Gap: Why Do Canadians Fare Better Than Americans? *Annals of internal medicine.* 2017;166(8):599-600.
72. Sawicki GS, Konstan MW, McKone EF, et al. Rate of Lung Function Decline in Patients with Cystic Fibrosis (CF) Having a Residual Function Gene Mutation. *American journal of respiratory and critical care medicine.* 2017;195:A4847.
73. Konstan M, Wagener J, VanDevanter D. Risk factors for rate of decline in FEV1 in adults with cystic fibrosis. *Journal of Cystic Fibrosis.* 2012;11(5):405-411.
74. Goss CH, Burns JL. Exacerbations in cystic fibrosis: epidemiology and pathogenesis (part 1). *Thorax.* 2007;62(4):8.
75. Whiting P, Al M, Burgers L, et al. Ivacaftor for the treatment of patients with cystic fibrosis and the G551D mutation: a systematic review and cost-effectiveness analysis. *Health technology assessment (Winchester, England).* 2014;18(18):1-106.
76. VanDevanter DR, Kahle JS, O'Sullivan AK, Sikirica S, Hodgkins PS. Cystic fibrosis in young children: A review of disease manifestation, progression, and response to early treatment. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society.* 2016;15(2):147-157.
77. Lynch Jr, Sayah D, Belperio J, Weigt S. Lung transplantation for cystic fibrosis: results, indications, complications, and controversies. *Seminars in respiratory and critical care medicine.* 2015;36(2):299-320.
78. Adler A, Shine B, Chamnan P, Haworth C, Bilton D. Genetic determinants and epidemiology of cystic fibrosis-related diabetes: results from a British cohort of children and adults. *Diabetes care.* 2008;31(9):1789-1794.
79. Ahmed N, Corey M, Forstner G, et al. Molecular consequences of cystic fibrosis transmembrane regulator (CFTR) gene mutations in the exocrine pancreas. *Gut.* 2003;52(8):1159-1164.
80. Thabut G, Christie J, Mal H, et al. Survival benefit of lung transplant for cystic fibrosis since lung allocation score implementation. *American journal of respiratory and critical care medicine.* 2013;187(12):1335-1340.
81. The National Institute for Health and Care Excellence. NICE Committee Papers. 2016.
82. The National Institute for Health and Care Excellence. Lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation. 2016.
83. Arias E, Heron M, Xu J. United States life tables, 2014. *National vital statistics reports.* 2014;66(4).
84. Liou T, Adler F, FitzSimmons S, Cahill B, Hibbs J, Marshall B. Predictive 5-Year Survivorship Model of Cystic Fibrosis. *American Journal of Epidemiology.* 2001;153(4):345-352.
85. Schechter MS, Trueman D, Farquharson R, Higuchi K, Daines CL. Inhaled aztreonam versus inhaled tobramycin in cystic fibrosis. An economic evlaution. *Annals of the American Thoracic Society.* 2015;12(7):1030-1038.
86. Tappenden P, Harnan S, Uttley L, et al. The cost effectiveness of dry powder antibiotics for treatment of Pseudomonas aeruginosa in patients with cystic fibrosis. *PharmacoEconomics.* 2014;32:159-172.
87. Busschbach JJ, Horikx PE, van den Bosch JM, Brutel de la Riviere A, de Charro FT. Measuring the quality of life before and after bilateral lung transplantation in patients with cystic fibrosis. *Chest.* 1994;105(3):911-917.
88. Pharmaceutical Pricing. U.S. department of Veterans Affairs; 2018. Accessed January 16th, 2018.
89. Red Book Online® Search. Truven Health Analytics; 2018. http://www.micromedexsolutions.com.ezp-

prod1.hul.harvard.edu/micromedex2/librarian/CS/E7F89E/ND_PR/evidencexpert/ND_P/evidencexpert/DUPLICATIONSHIELDSYNC/A4E796/ND_PG/evidencexpert/ND_B/evidencexpert/ND_AppProduct/evidencexpert/ND_T/evidencexpert/PFActionId/redbook.FindRedBook?navitem=topRedBook&isToolPage=true. Accessed January 15th, 2018.
90. Dilokthornsakul P, Patidar M, Campbell JD. Forecasting the Long-Term Clinical and Economic Outcomes of Lumacaftor/Ivacaftor in Cystic Fibrosis Patients with Homozygous phe508del Mutation. *Value in Health.* 2017.
91. Dilokthornsakul P, Hansen RN, Campbell JD. Forecasting US ivacaftor outcomes and cost in cystic fibrosis patients with the G551D mutation. *The European respiratory journal.* 2016;47(6):1697-1705.
92. Lieu TA, Ray GT, Farmer G, Shay GF. The cost of medical care for patients with cystic fibrosis in a health maintenance organization. *Pediatrics.* 1999;103(6):e72.
93. Ouyang L, Grosse SD, Amendah DD, Schechter M. Healthcare expenditures for privately insured people with cystic fibrosis. *Pediatric pulmonology.* 2009;44(10):989-996.
94. O'Sullivan AK, Sullivan J, Higuchi K, Montgomery AB. Health care utilization & costs for cystic fibrosis patients with pulmonary infections. *Managed Care.* 2011;20(2):37-44.
95. Ramsey SD, Patrick DL, Albert RK, Larson EB, Wood DE, Raghu G. The cost-effectiveness of lung transplantation. A pilot study. University of Washington Medical Center Lung Transplant Study Group. *Chest.* 1995;108(6):1594-1601.
96. Neri L, Lucidi V, Catastini P, Colombo C. Caregiver burden and vocational participation among parents of adolescents with CF. *Pediatric pulmonology.* 2015.
97. Angelis A, Kanavos P, Lopez-Bastida J, Nicod E, Serrano-Aquilar P. Social and economic costs and health-related quality of life in non-institutionalised patients with cystic fibrosis in the United Kingdom. *BMC Healt5h Serv Res.* 2015.
98. Patel S, Sinha IP, Dwan K, Echevarria C, Schechter M, Southern KW. Potentiators (specific therapies for class III and IV mutations) for cystic fibrosis. *The Cochrane database of systematic reviews.* 2015(3):Cd009841.
99. Konstan MW, Ramsey BW, Elborn J, et al. Safety and efficacy of treatment with lumacaftor in combination with ivacaftor in patients with CF homozygous for F508DELCFTR. *Pediatric pulmonology.* 2015;50:269-270.
100. McColley SA, Konstan MW, Ramsey BW, et al. Association between changes in percent predicted fev1 and incidence of pulmonary exacerbations, including those requiring hospitalization and/or iv antibiotics, in patients with CF treated with lumacaftor in combination with ivacaftor. *Pediatric pulmonology.* 2015;50:282.
101. Accurso FJ, Rowe SM, Clancy JP, et al. Effect of VX-770 in persons with cystic fibrosis and the G551D-CFTR mutation. *N Engl J Med.* 2010;363(21):1991-2003.
102. Guigui S, Wang J, Cohen RI. The use of ivacaftor in CFTR mutations resulting in residual functioning protein. *Respiratory medicine case reports.* 2016;19:193-195.
103. Konstan MW, Plant BJ, Elborn JS, et al. Efficacy response in CF patients treated with ivacaftor: post-hoc analysis. *Pediatric pulmonology.* 2015;50(5):447-455.
104. Heltshe SL, Mayer-Hamblett N, Burns JL, et al. Pseudomonas aeruginosa in cystic fibrosis patients with G551D-CFTR treated with ivacaftor. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2015;60(5):703-712.
105. Barry PJ, Plant BJ, Simmonds NJ, et al. Ivacaftor decreases mortality in G551D patients with severe lung disease. *Pediatric pulmonology.* 2015;50:275-276.
106. Volkova N, Bai Y, Higgins M, et al. Disease progression in patients (pts) with cystic fibrosis (CF) treated with ivacaftor (IVA): Analysis of real-world data from the UK CF Registry. *Journal of Cystic Fibrosis.* 2016;15:S41.

107. Elborn S, Wainwright C, Sermet-Gaudelus I, et al. Pulmonary effects of the investigational CFTR potentiator, ivacaftor, in two phase 3 trials in subjects with CF who have the G551D-CFTR mutation. *American journal of respiratory and critical care medicine.* 2012;185.
108. Flume P, Wainwright C, Tullis E, Rodriguez S, Davies J, Wagener J. Pulmonary exacerbations in CF patients with the G551D-CFTR mutation treated with ivacaftor. *Journal of Cystic Fibrosis.* 2013;12:S63.
109. Bai Y, Higgins M, Volkova N, et al. Ivacaftor long-term safety study: Analysis of 2013 us CF foundation patient registry data. *Pediatric pulmonology.* 2015;50:284.
110. Mainz J, Narayanan S, Suthoff ED, et al. Patient-reported outcomes among patients (pts) with cystic fibrosis and the G551D-CFTR mutation treated with ivacaftor (IVA) compared with those homozygous for the F508del-CFTR mutation. *Journal of Cystic Fibrosis.* 2016;15:S115.
111. Accurso FJ, Ratjen F, Altes T, et al. Effect of withdrawal of ivacaftor therapy on CFTR channel activity and lung function in patients with cystic fibrosis. *Journal of Cystic Fibrosis.* 2013;12:S62.
112. Davies JC, Sheridan H, Lee PS, Song T, Stone A, Ratjen F. Effect of ivacaftor on lung function in subjects with CF who have the G551D-CFTR mutation and mild lung disease: A comparison of lung clearance index (LCI) vs. spirometry. *Journal of Cystic Fibrosis.* 2012;11:S15.
113. Elborn JS, Rodriguez S, Lubarsky B, Gilmartin G, Bell S. Effect of ivacaftor in patients with cystic fibrosis and the G551D-CFTR mutation who have baseline FEV1 >90% of predicted. *Pediatric pulmonology.* 2013;48:298.
114. Plant BJ, Konstan M, Aherns R, et al. Lung function, weight, and sweat chloride responses in patients with cystic fibrosis and the G551D-CFTR mutation treated with ivacaftor: A secondary analysis. *Journal of Cystic Fibrosis.* 2013;12:S62.
115. Suthoff E, Rendas-Baum R, Vera-Llonch M, Bayliss M, Sermet-Gaudelus I, Quittner AL. Patient-reported treatment effects of ivacaftor beyond respiratory symptoms in patients with cystic fibrosis (CF). *Pediatric pulmonology.* 2014;49:250.
116. Hathorne H, Brand KM, Britton LJ, et al. The investigation of quality of life and adherence in patients with the G551D mutation receiving ivacaftor therapy. *Pediatric pulmonology.* 2015;50:427.
117. Wainwright C, Bell S, Morton J, et al. The effect of ivacaftor in individuals with CF and severe lung disease. *Pediatric pulmonology.* 2014;49:376-377.
118. Barry PJ, Plant BJ, Nair A, et al. Effects of ivacaftor in patients with cystic fibrosis who carry the G551D mutation and have severe lung disease. *Chest.* 2014;146(1):152-158.
119. Edgeworth D, Keating D, Ellis M, et al. Improvement in exercise duration, lung function and well-being in G551D-cystic fibrosis patients: a double-blind, placebo-controlled, randomized, cross-over study with ivacaftor treatment. *Clinical science (London, England : 1979).* 2017;131(15):2037-2045.
120. Stalvey MS, Pace J, Niknian M, et al. Growth in Prepubertal Children With Cystic Fibrosis Treated With Ivacaftor. *Pediatrics.* 2017;139(2).
121. Fink A, Sawicki GS, Morgan WJ, Schechter MS, Rosenfeld M, Marshall BC. Treatment response to ivacaftor in clinical practice: Analysis of the us CF foundation patient registry. *Pediatric pulmonology.* 2015;50:361.
122. Heltshe SL, Godfrey EM, Josephy T, Aitken ML, Taylor-Cousar JL. Pregnancy among cystic fibrosis women in the era of CFTR modulators. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society.* 2017.

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

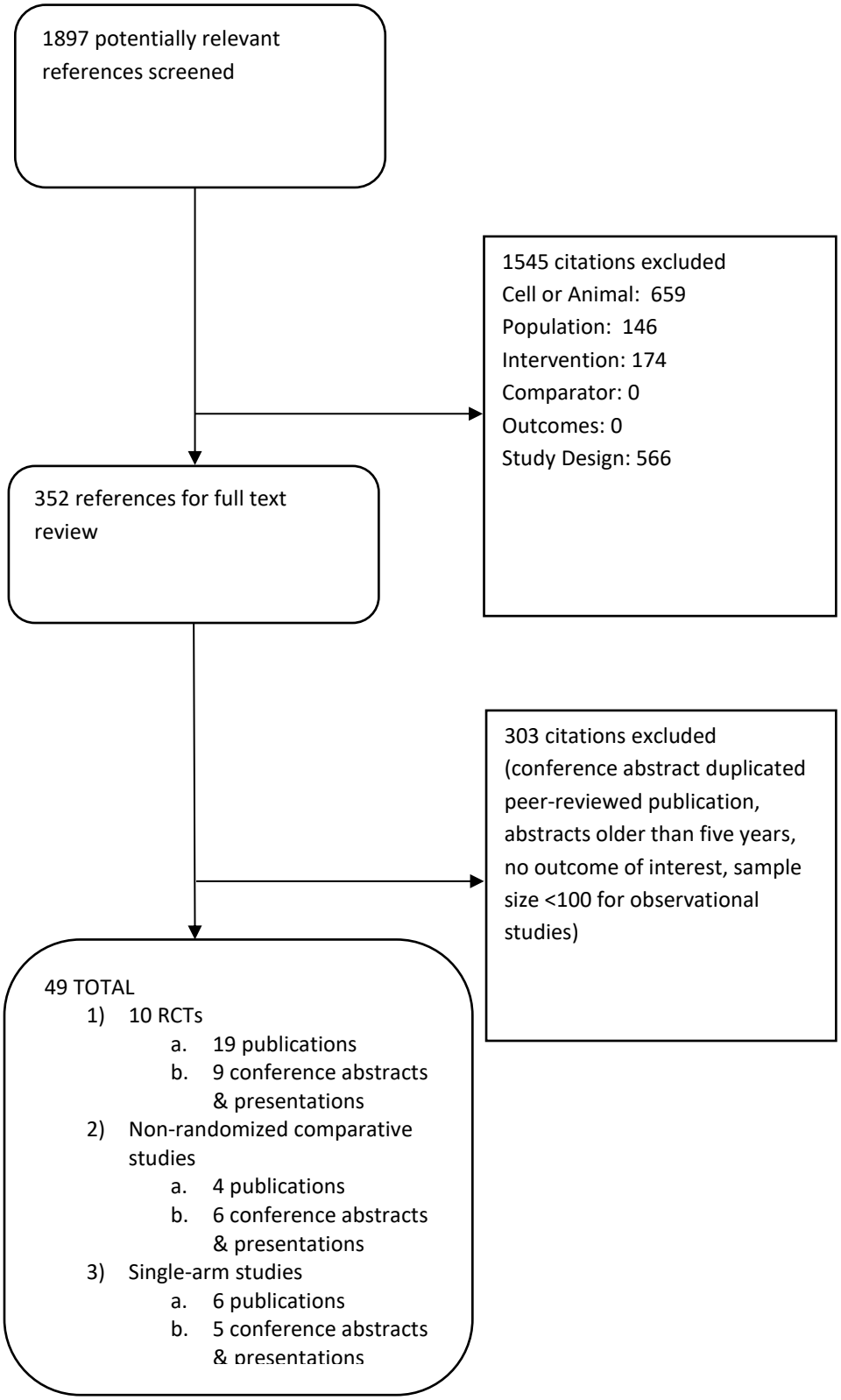
Table A2. Search Strategies of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled trials using PubMed®

#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 lumacaftor/ivacaftor, 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 tezacaftor/ivacaftor 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 lumacaftor/ivacaftor 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 lumacaftor/ivacaftor, 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 lumacaftor/ivacaftor. Concerning safety, NICE concluded that lumacaftor/ivacaftor was generally well tolerated.

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

NICE is currently developing guidance on tezacaftor/ivacaftor 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

Lumacaftor/ivacaftor

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 lumacaftor/ivacaftor. CADTH recommended that lumacaftor/ivacaftor 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 lumacaftor/ivacaftor compared to placebo was of uncertain clinical significance.

Previous Systematic Reviews

We identified one systematic review on ivacaftor.[98]

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 lumacaftor/ivacaftor.[7]

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 lumacaftor/ivacaftor 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 lumacaftor/ivacaftor for adults and children age 12 and older with an $ppFEV_1$ <90%; and made a conditional for treatment with lumacaftor/ivacaftor 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 Tezacaftor/Ivacaftor (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

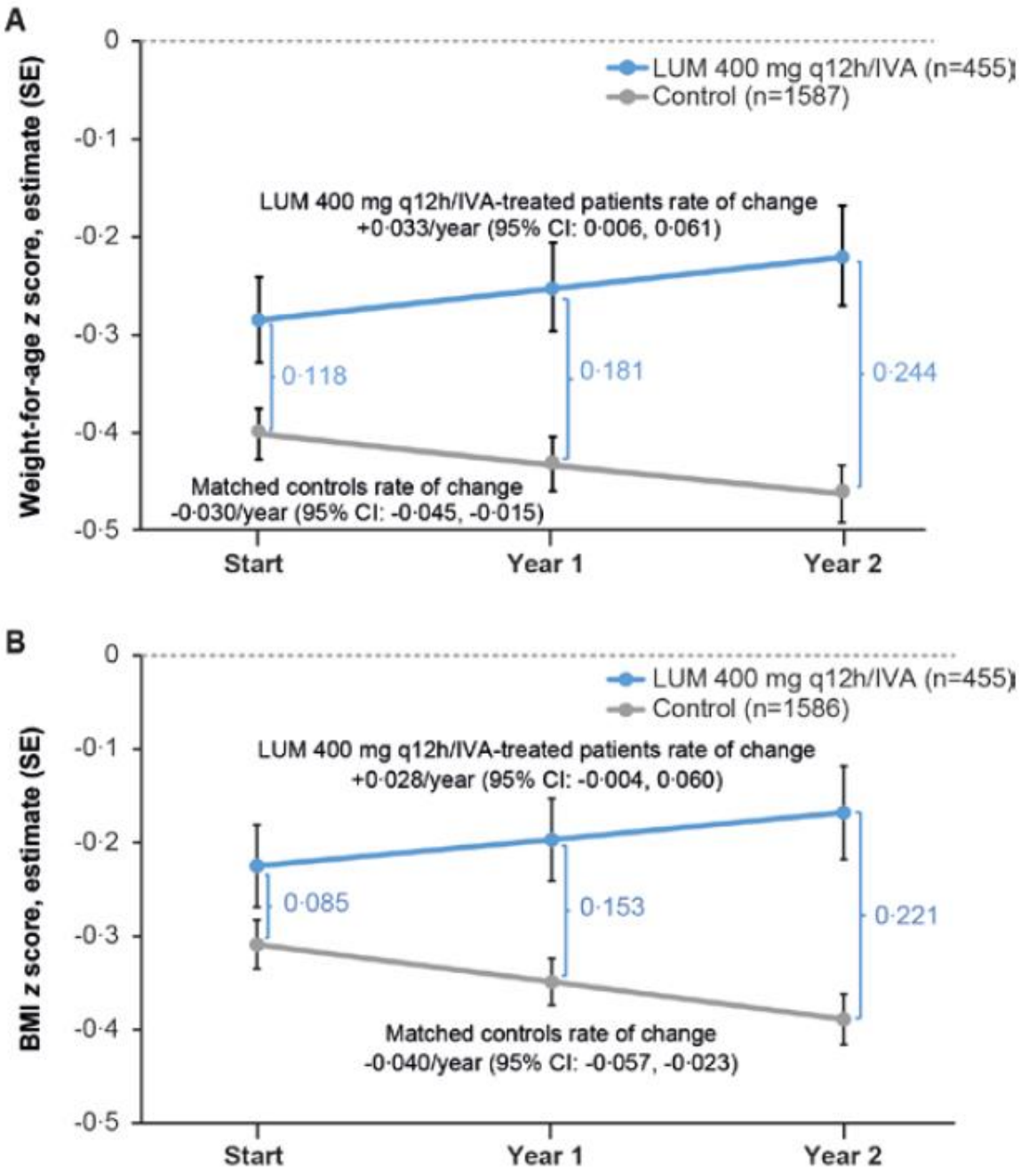
				• Absolute change in weight • Absolute change in weight-for-age-z-score • Absolute change in height • Absolute change in height-for-age-z-score • Absolute change in Treatment Satisfaction Questionnaire for Medication (TSQM) domains • Time-to-first pulmonary exacerbation (subjects from Study 109 only) • 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

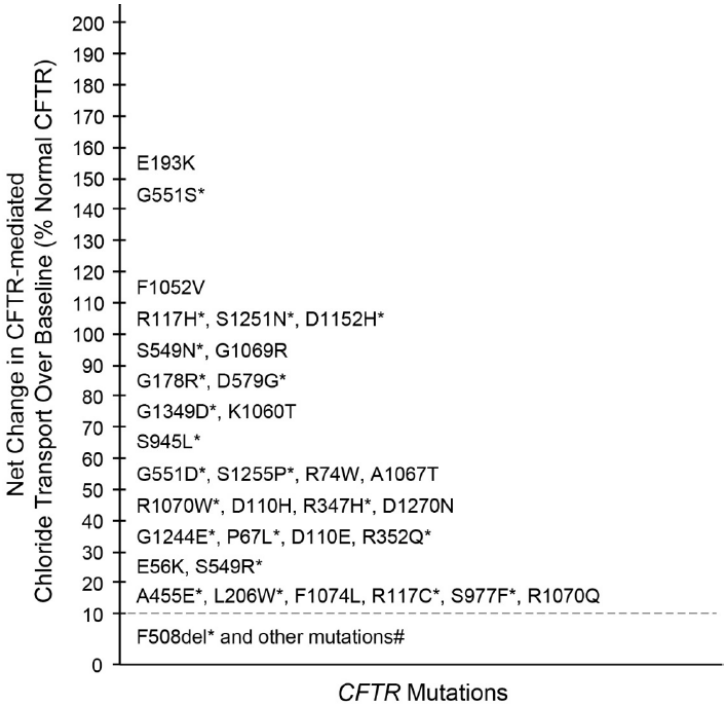


Genetic Specific Data on CFTR Modulators

Ivacaftor

The effect of ivacaftor differs by mutation.[68] Below are the in vitro response thresholds and stratified efficacy data from clinical trials, adapted from the FDA label (prescribing information).[68]

Figure D2. Net Change Over Baseline (% of untreated normal) in CFTR-Mediated Chloride Transport Following Addition of Ivacaftor from FDA Label[68]



*Clinical data exist for these mutations

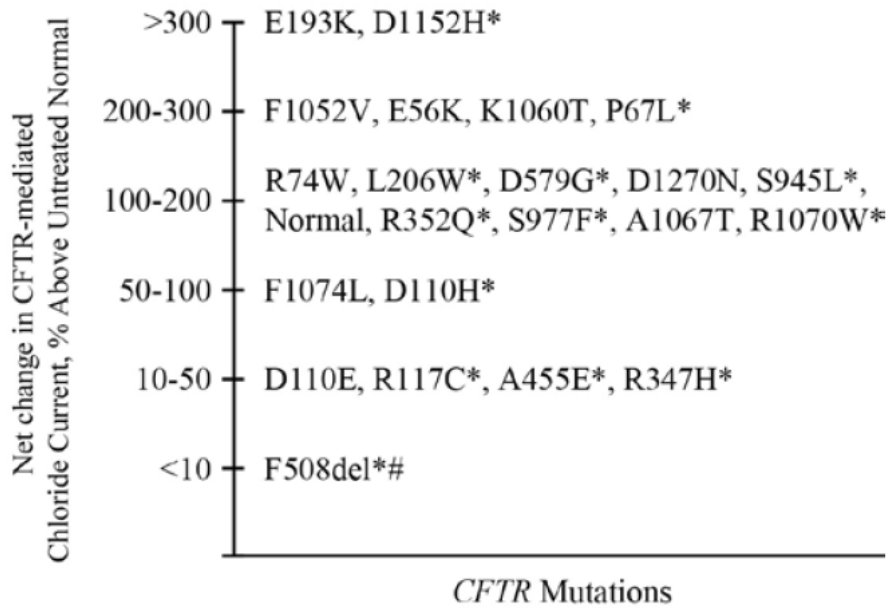
Figure D3. Efficacy Outcomes of Ivacaftor by Genetic Mutation from FDA Label[68]

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.			

***Tezacaftor/ivacaftor*[41]**

The effect of tezacaftor/ivacaftor differs by mutation.[68] Below are the in vitro response thresholds and stratified efficacy data from clinical trials, adapted from the FDA label (prescribing information).[68]

Figure D4. Net Change Over Baseline (% of Untreated Normal) in CFTR-Mediated Chloride Transport Following Addition of Tezacaftor/Ivacaftor from FDA Label[41]



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

Figure D5. Efficacy Outcomes of Tezacaftor/Ivacaftor by Genetic Mutation from FDA Label[41]

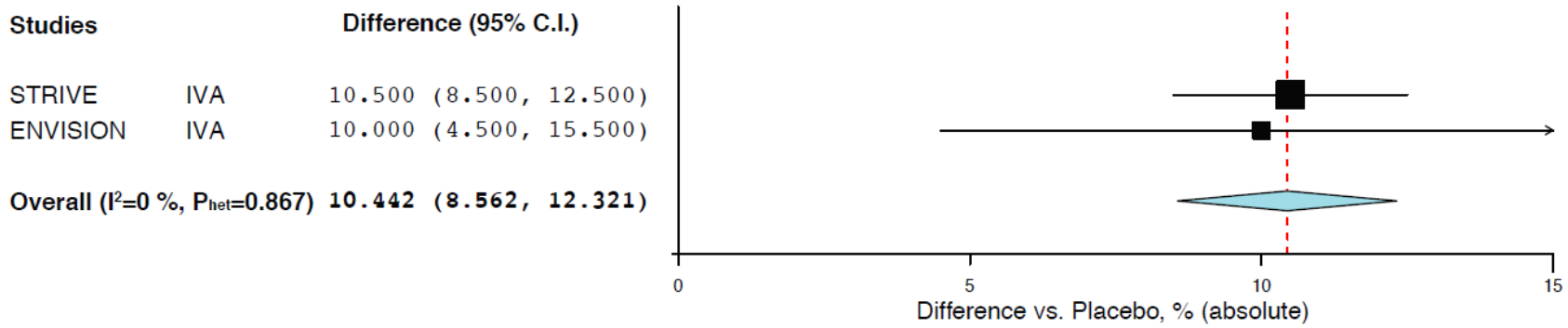
Mutation (n)	Absolute Change in percent predicted FEV_1*†	Absolute Change in CFQ-R Respiratory Domain Score (Points)*§	Absolute Change in Sweat Chloride (mmol/L)*§
Splice mutations (n= 93 for TEZ/IVA, n=97 for PBO) Results shown as difference in mean (95% CI) change from study baseline for SYMDEKO vs.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

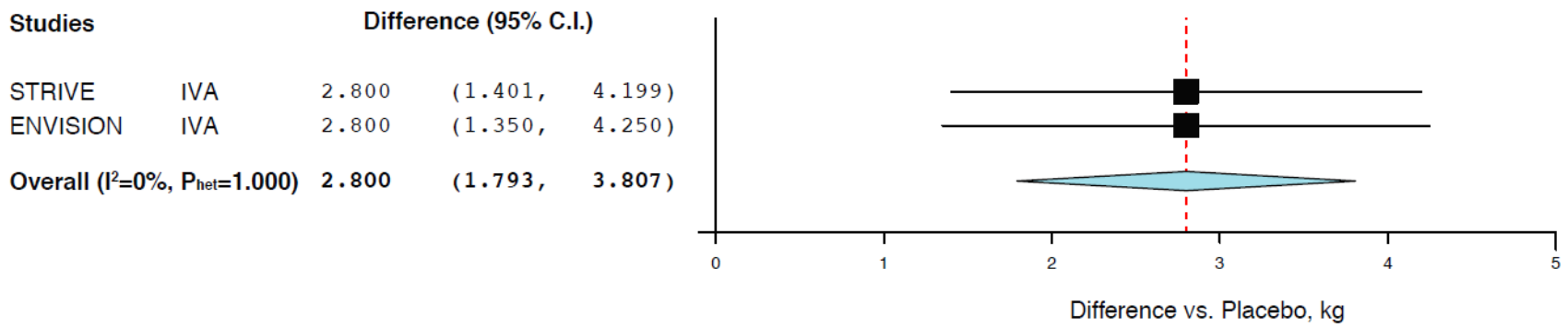
Forest Plots from Meta-Analysis

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)



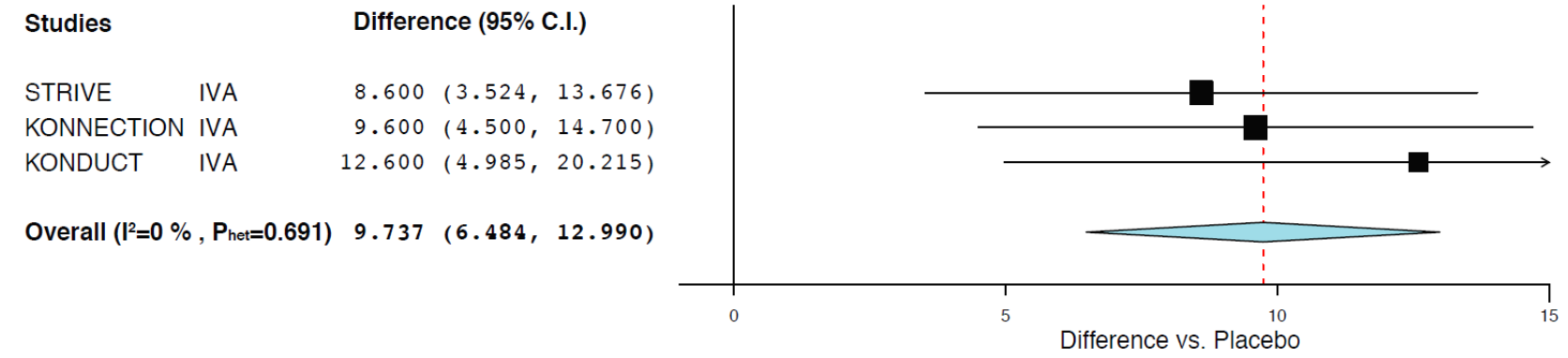
C.I: confidence interval, IVA: ivacaftor, Phet: chi-square P value for heterogeneity

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)



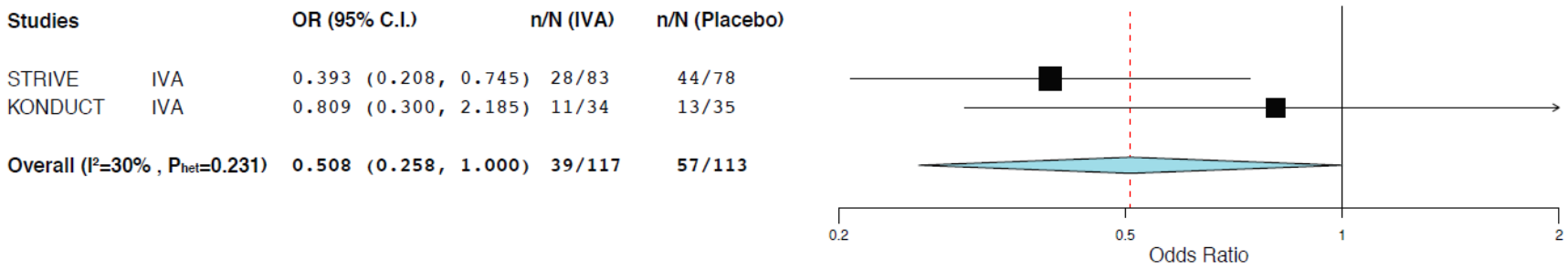
C.I.: confidence interval, IVA: ivacaftor, Phet: chi-square P value for heterogeneity

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)



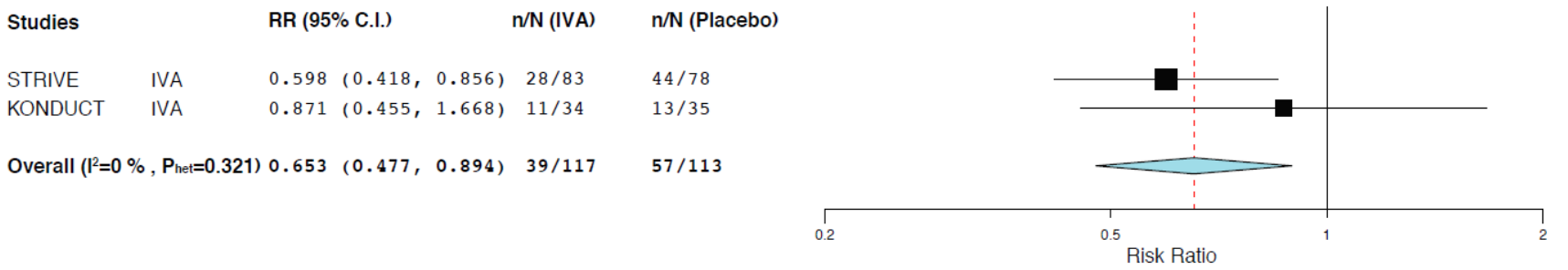
C.I.: confidence interval, CFQ-R: Cystic Fibrosis Questionnaire-Revised, IVA: ivacaftor, Phet: chi-square P value for heterogeneity.

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



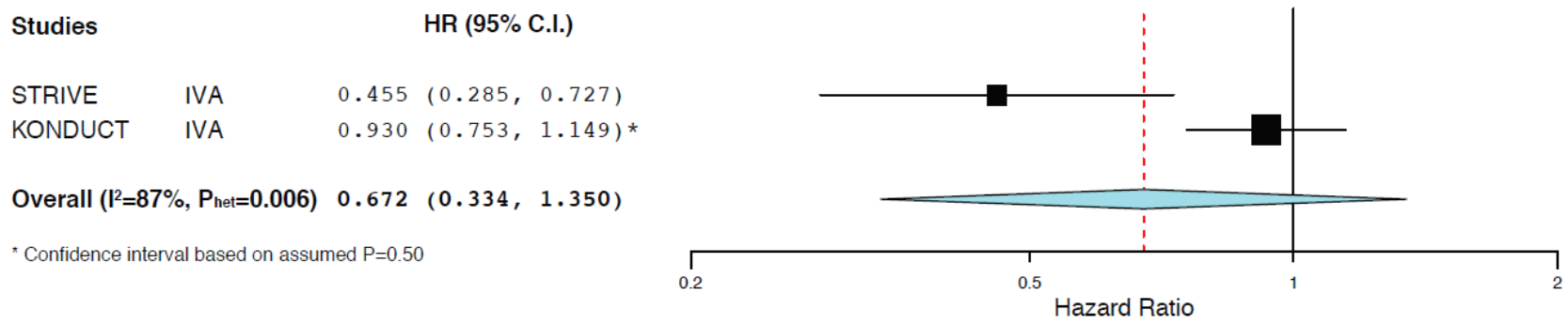
Abbreviations: C.I.: confidence interval, IVA: ivacaftor, OR: odds ratio, P_{het} = chi-square P value for heterogeneity.

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



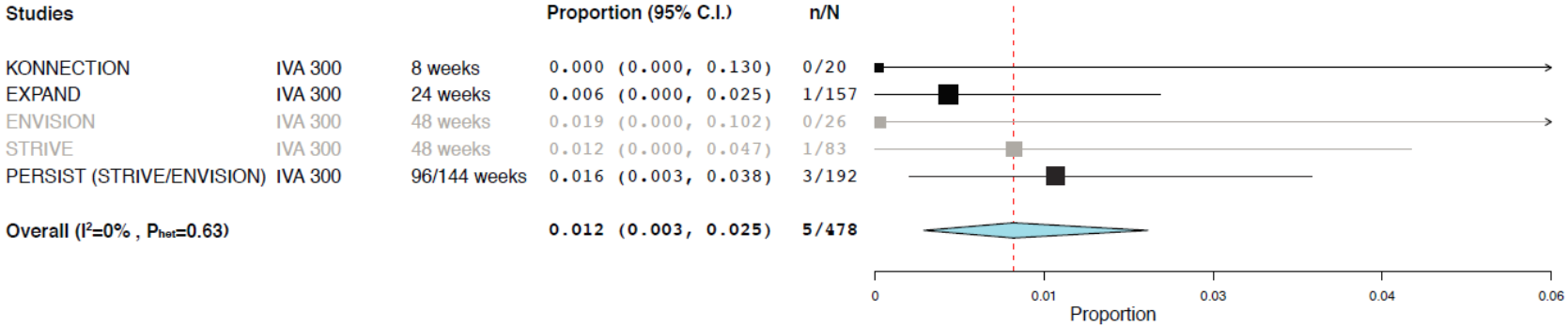
C.I.: confidence interval, IVA: ivacaftor, Phet = chi-square P value for heterogeneity, RR: risk ratio.

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



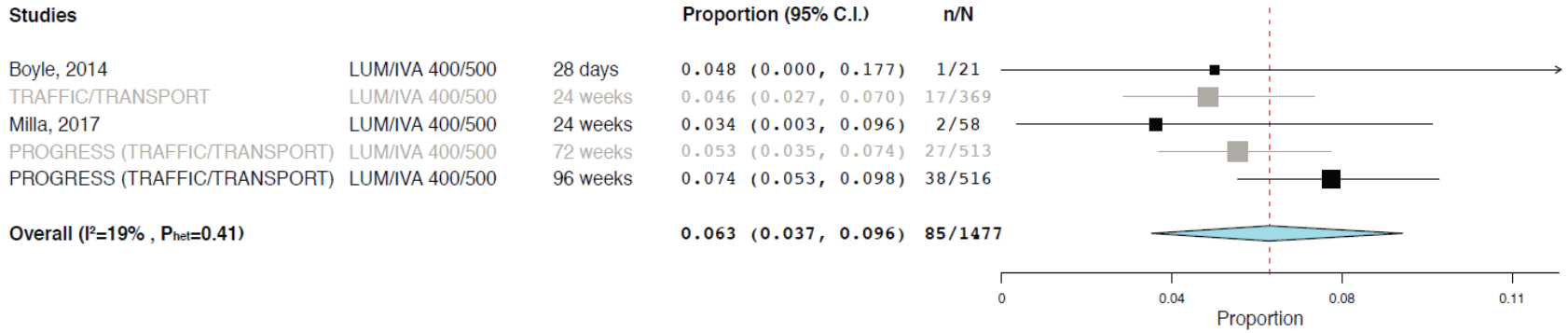
C.I.: confidence interval, HR: hazard ratio, IVA: ivacaftor, Phet = chi-square P value for heterogeneity.

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



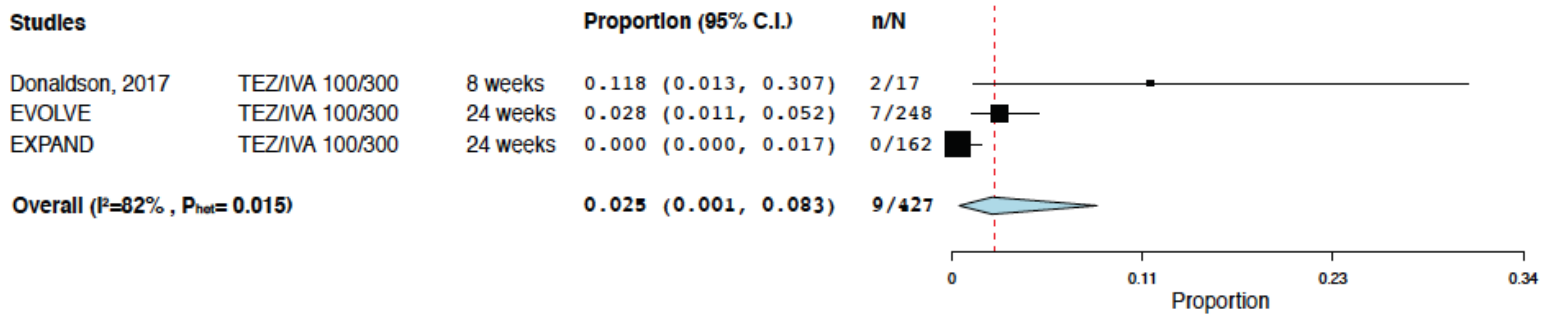
Studies in grey provide shorter-term results than subsequent studies and are not included in the meta-analysis
C.I.: confidence interval, IVA: ivacaftor, P_{het}: chi-square P value for heterogeneity.

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



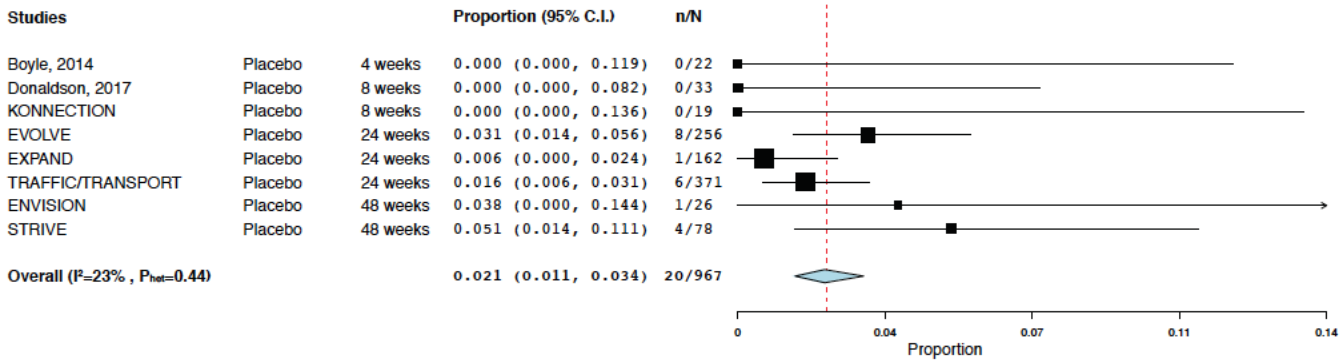
Studies in grey provide shorter-term results than subsequent studies and are not included in the meta-analysis
C.I.: confidence interval, LUM/IVA: lumacaftor/ivacaftor (with daily dosage in mg per drug), P_{het} : chi-square P value for heterogeneity

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



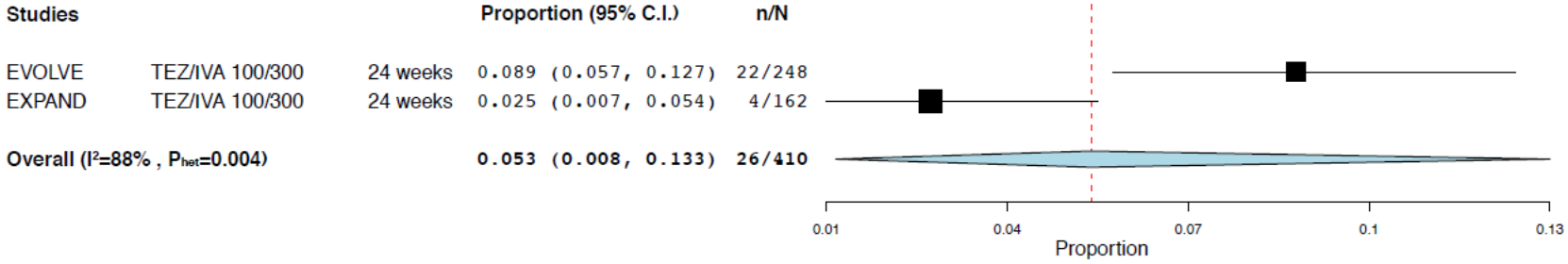
C.I.: confidence interval, Phet: chi-square P value for heterogeneity, TEZ/IVA: tezacaftor/ivacaftor (with daily dosage in mg per drug)

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



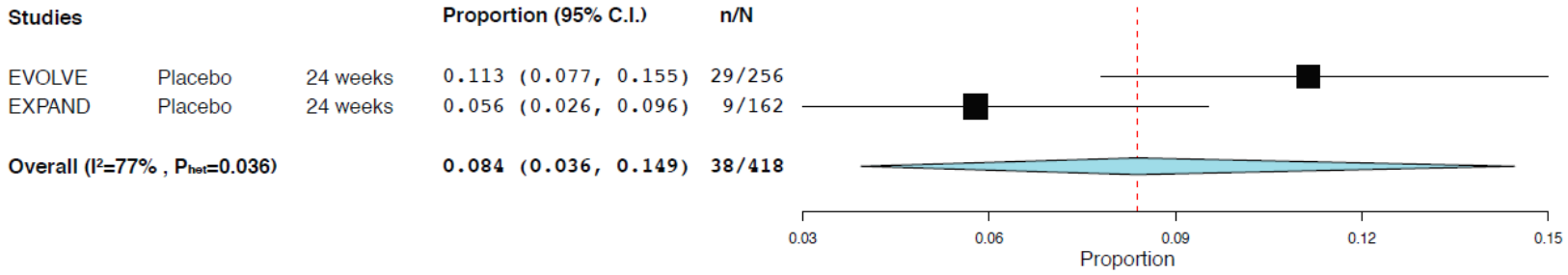
C.I.: confidence interval, P_{het}: chi-square P value for heterogeneity

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

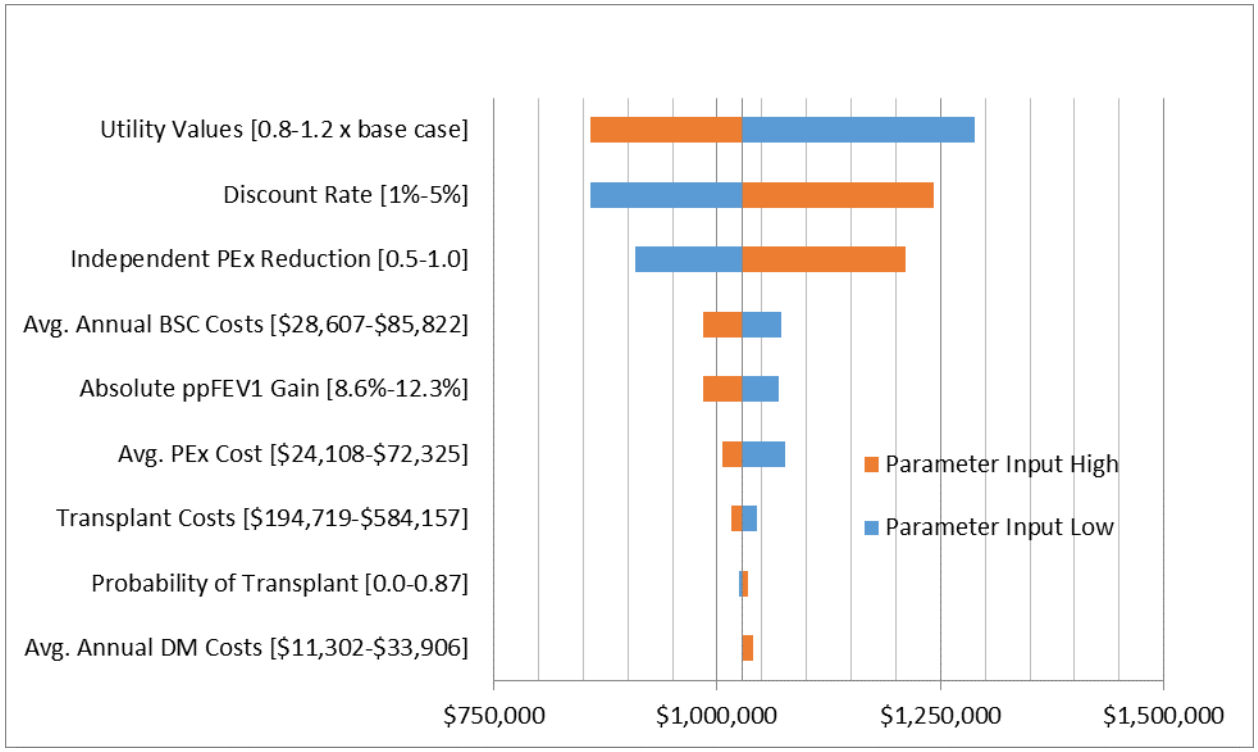
Appendix E. Comparative Value Supplemental Information

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	☐	

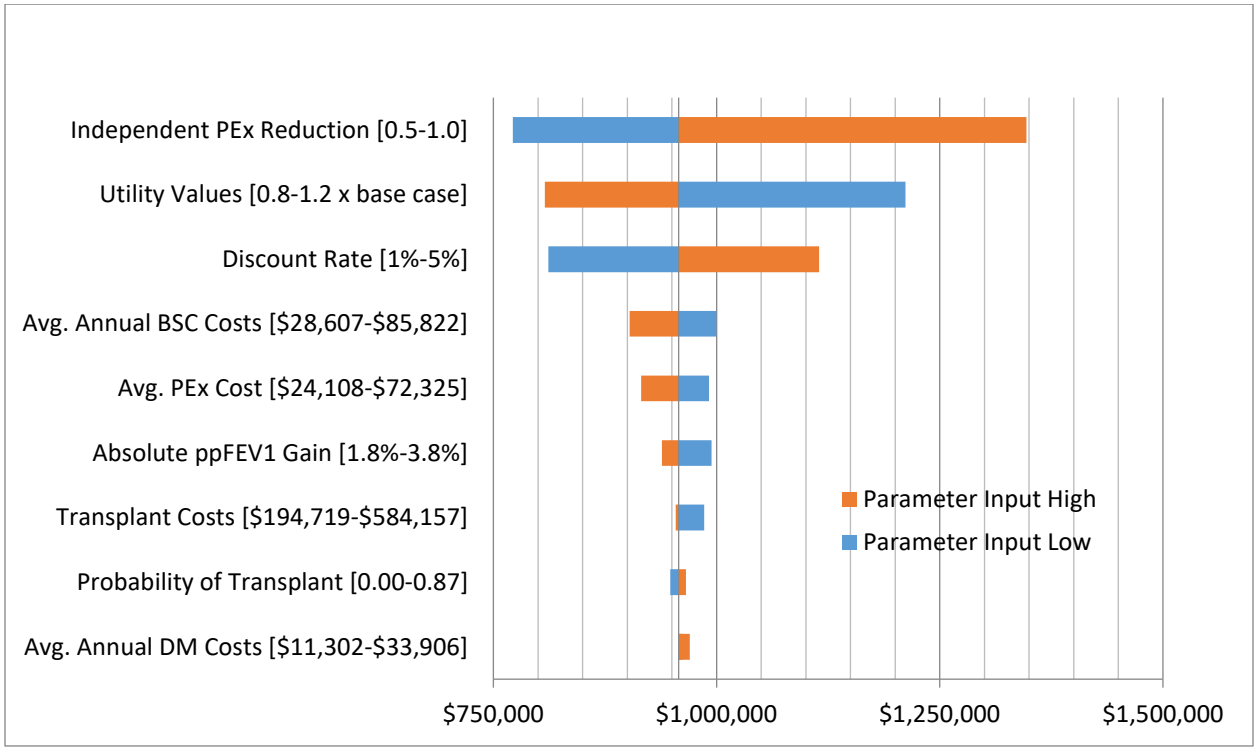
One-Way Sensitivity Analyses

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



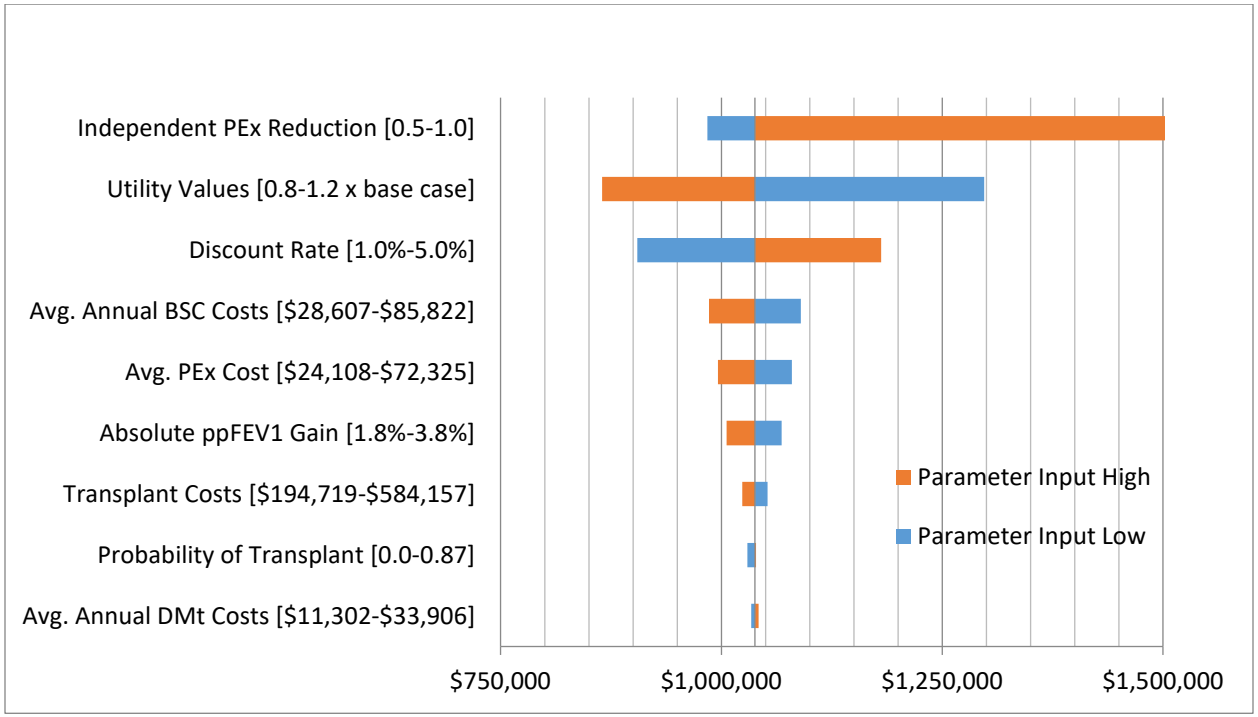
PEx: acute pulmonary exacerbation; BSC: best supportive care; DM: disease management
Probability of transplant among individuals with $ppFEV_1$<30%

Figure E2. Tornado Diagram for One-Way Sensitivity Analyses of Cost per QALY Gained for Lumacaftor/Ivacaftor 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 Ivacaftor Monotherapy 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)

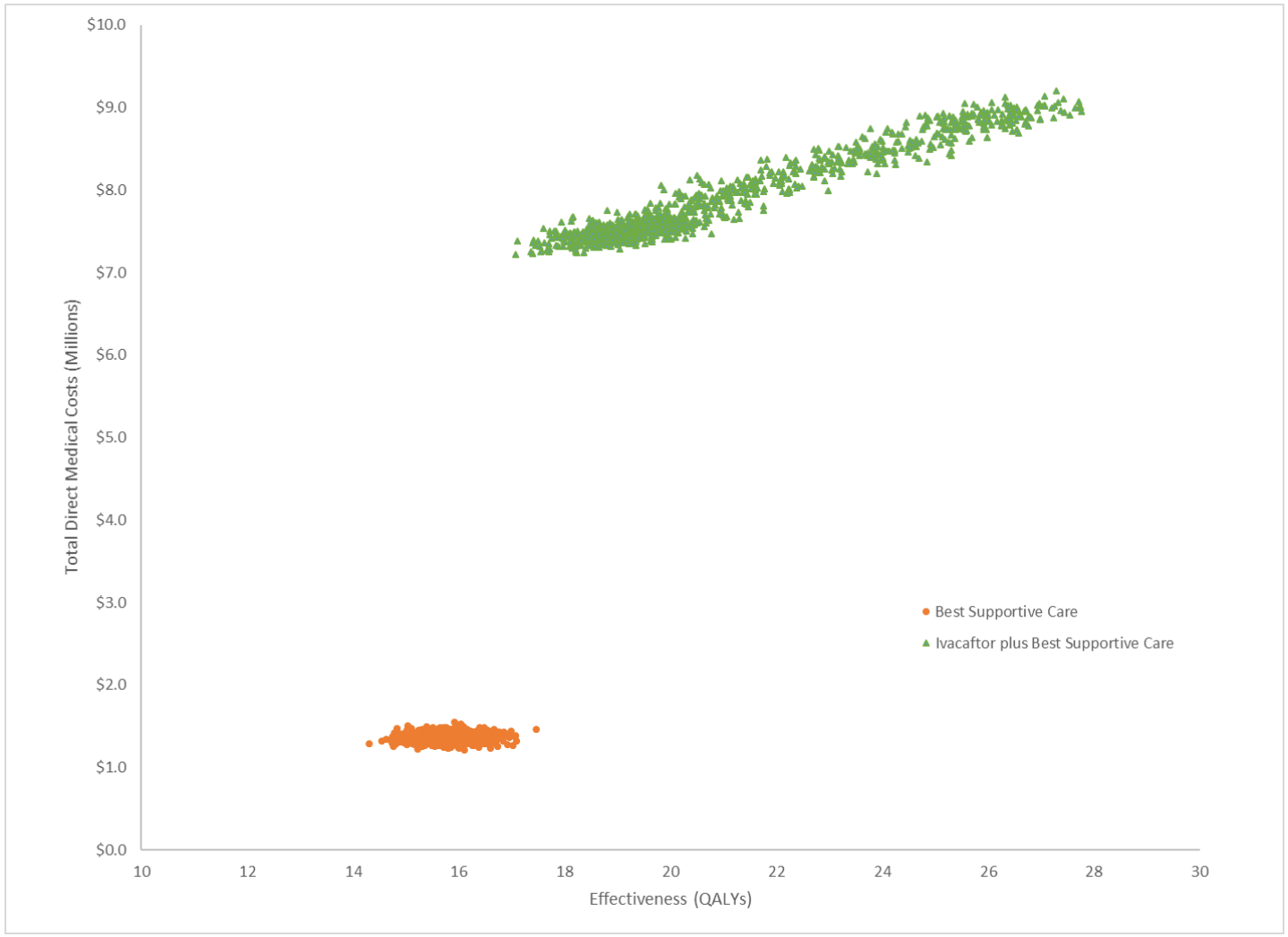


Figure E5. Scatterplot of Cost and Effectiveness for Lumacaftor/Ivacaftor Plus Best Supportive Care, Tezacaftor/Ivacaftor plus Best Supportive Care, and Best Supportive Care Alone in CF Individuals Homozygous for *F508del* Mutation (1,000 Iterations)

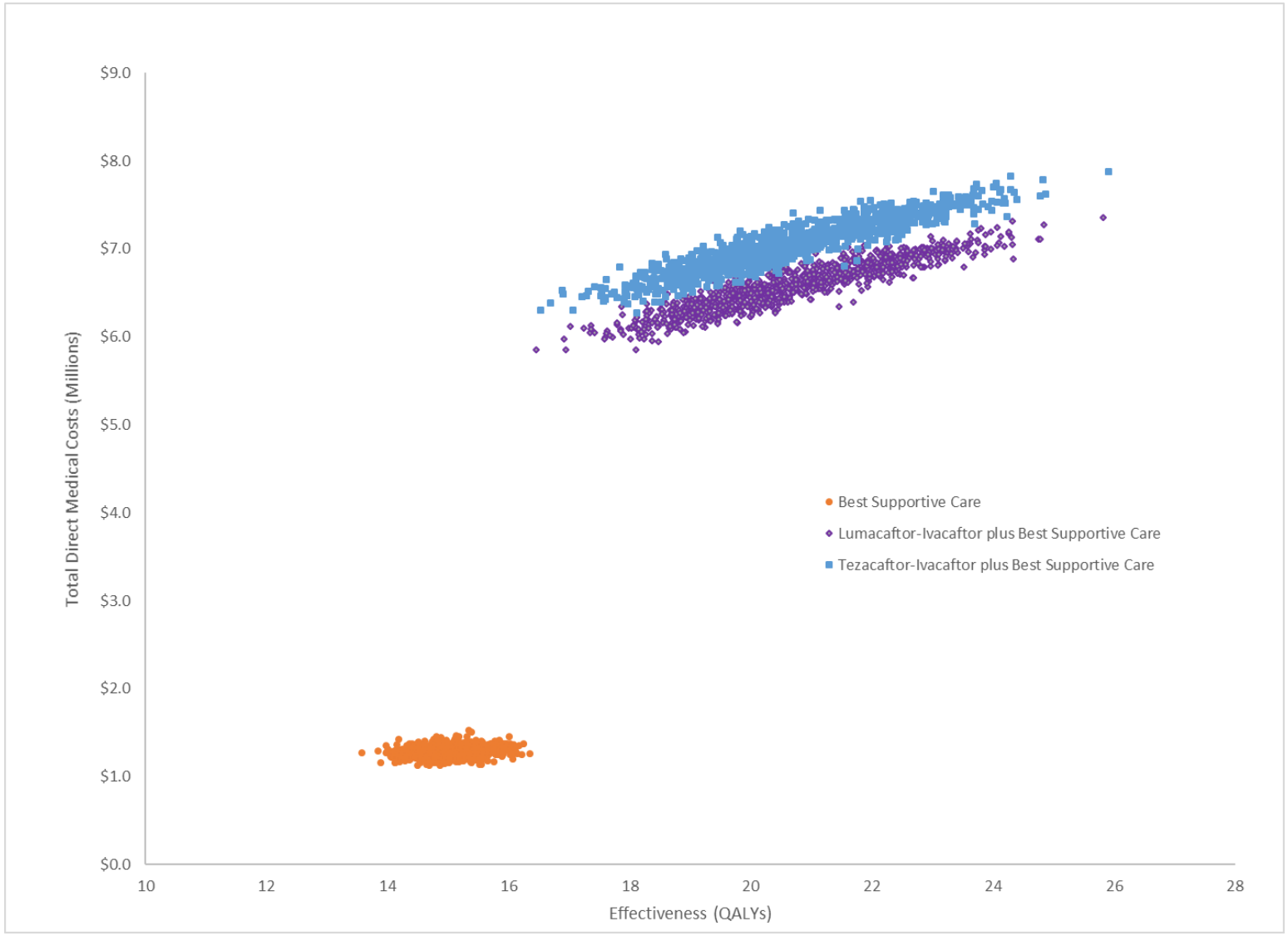
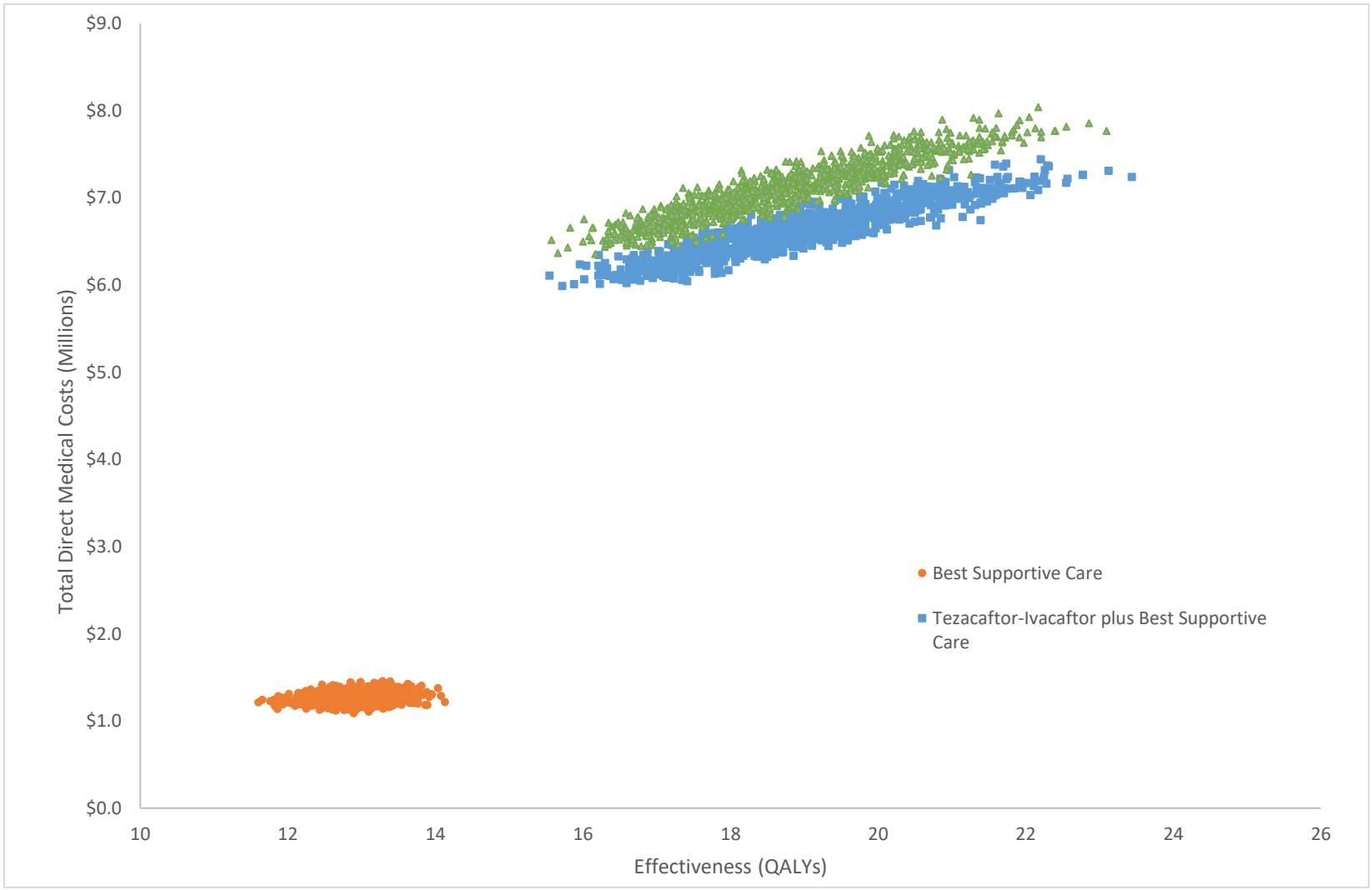


Figure E6. Scatterplot of Cost and Effectiveness for Ivacaftor Monotherapy Plus Best Supportive Care, Tezacaftor/ivacaftor plus Best Supportive Care, and Best Supportive Care Alone in CF Individuals Heterozygous for *F508del* Mutation and Residual Function Mutation (1,000 Iterations)



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
Tezacaftor/Ivacaftor						
Taylor-Cousar [60] ***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 [67] ***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: ivacaftor monotherapy, 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 [5] ***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 •			
Lumacaftor/Ivacaftor						
Wainwright [24] ***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 [65] ***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 [61] ***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 [99] ***Pediatric Pulmonology*** **2015** **Abstract**	**See Konstan 2017** Interim analysis of PROGRESS at 24 weeks	**N=176** (1) LUM/IVA: 400 mg of lumacaftor every 12 hours in combination with 250 mg of ivacaftor every 12 hours (n=340) (2) LUM/IVA: Placebo transitioned to 400 mg lumacaftor every 12 hours in combination with ivacaftor 250 mg every 12 hours (n=176)	**See Konstan 2017**	**See Konstan 2017**	**$ppFEV_1$** **Mean (least-squares) relative change from baseline, percent (SE); p-value** 24 weeks of PROGRESS* (1) 2.6 (0.47); p<0.0001 (2) 3.5 (0.64); p<0.0001 **BMI** **Mean (least-squares) absolute change from baseline, kg/m^2 (SE); p-value** 24 weeks of PROGRESS* (1) 0.56 (0.06); p<0.0001 (2) 0.37 (0.08); p<0.0001 **CFQ-R Respiratory domain** **Mean absolute change from baseline, points (SE); p-value** 24 weeks of PROGRESS* (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 [100] ***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[66] ***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 [64] ***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 [59] ***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 [62] ***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 [70] ***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 [45] ***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 [46] ***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/m^2 (range)** (1) 17.1 (14.2-26.0) (2) 16.8 (13.8-22.1) **CFQ-R Respiratory domain** **Mean, points** (1) 78 (2) 80	**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 [50] ***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/m^2 (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%) <u>STRIVE and ENVISION ivacaftor groups</u>: Week 48-96: 32 (31%) Week 96-144: 27 (26%) **Headache, n (%)** (1) <u>STRIVE and ENVISION placebo groups</u>: Week 1-48: 11 (12%) Week 48-96: 7 (8%) <u>STRIVE and ENVISION ivacaftor groups</u>: Week 48-96: 14 (14%) Week 96-144: 17 (17%)
De Boeck [47] ***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 [48] ***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 [49] ***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 [51] ***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 [56] ***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/m² (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	

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) −0.54 (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 [101] ***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 [102] ***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 [52] ***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 [53] ***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 [103]	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:

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
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 [54] ***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 [104] ***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**

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
	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 [57] ***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 [58] ***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 [105] ***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 [106] ***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 [107]	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 [108] ***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 [109] ***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 [110] ***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 [111] ***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 [112] ***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 [113] ***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 [114] ***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 [115] ***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 [116] ***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 [117] ***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 [118] ***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 [55] ***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 [119] ***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 [120] ***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 [121] ***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 [122] ***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%)	