Modulator Treatments for Cystic Fibrosis: Effectiveness and Value

Draft Evidence Report

February 20, 2020

Prepared for:

ICER Staff	University of Minnesota Modeling Group
Jeffrey A. Tice, MD Associate Professor of Medicine University of California, San Francisco **Rick Chapman, PhD, MS** Director of Health Economics ICER **Matt Seidner, BS** Program Director ICER **Steven D. Pearson, MD, MSc** President ICER **David M. Rind, MD, MSc** Chief Medical Officer ICER	**Karen M. Kuntz, ScD** Professor University of Minnesota School of Public Health **Kael Wherry, MS** Graduate Student University of Minnesota School of Public Health *The role of the University of Minnesota is limited to the development of the cost-effectiveness model, and the resulting ICER reports do not necessarily represent the views of the University of Minnesota.*

How to cite this document: Tice JA, Kuntz KM, Wherry K, Chapman R, Seidner M, Pearson SD, Rind DM. Modulator Treatments for Cystic Fibrosis: Effectiveness and Value; Draft Evidence Report. Institute for Clinical and Economic Review, February 20, 2020. https://icer-review.org/material/cystic-fibrosis-2-draft-evidence-report/

DATE OF PUBLICATION: February 20, 2020

Jeffrey Tice served as the lead author for the report and wrote the background, comparative clinical effectiveness, other benefits, and contextual considerations sections of the report; and co-authored the section on insights from patients with Matt Seidner. We would like to acknowledge the work of Patricia Synnott, Noemi Fluetsch, and Avery McKenna, who led the systematic review and contributed to the associated sections in the comparative clinical effectiveness chapter. Matt Seidner wrote the section on coverage policies and clinical guidelines, and provided editorial feedback. Karen Kuntz and Kael Wherry developed the cost-effectiveness model and authored the corresponding sections of the report. Rick Chapman provided methods guidance for the cost-effectiveness modeling effort and conducted the potential budget impact analysis. David Rind and Steven Pearson provided methodologic guidance on the clinical and economic evaluations. We would also like to thank Monica Frederick for her contributions to this report, as well as the authors and contributors who worked on 2018 ICER review of CF modulators.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at http://www.icer-review.org.

The funding for this report comes from government grants and non-profit foundations, with the largest single funder being the Laura and John Arnold Foundation. No funding for this work comes from health insurers, pharmacy benefit managers, or life science companies. ICER receives approximately 20% of its overall revenue from these health industry organizations to run a separate Policy Summit program, with funding approximately equally split between insurers/PBMs and life science companies. For a complete list of funders and for more information on ICER's support, please visit http://www.icer-review.org/about/support/.

About CTAF

The California Technology Assessment Forum (CTAF) – a core program of ICER – provides a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of all stakeholders. CTAF seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care.

The CTAF Panel is an independent committee of medical evidence experts from across California, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy. All Panel members meet strict conflict of interest guidelines and are convened to discuss the evidence summarized in ICER reports and vote on the comparative clinical effectiveness and value of medical interventions. More information about CTAF is available at https://icer-review.org/programs/ctaf/.

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.

The economic models used in ICER reports are intended to compare the clinical outcomes, expected costs, and cost-effectiveness of different care pathways for broad groups of patients. Model results therefore represent average findings across patients and should not be presumed to represent the clinical or cost outcomes for any specific patient. In addition, data inputs to ICER models often come from clinical trials; patients in these trials and provider prescribing patterns may differ in real-world practice settings.

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

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

Expert Reviewers

Manu Jain, MD, MSc
Professor, Department of Medicine (Pulmonary and Critical Care); Department of Pediatrics
Northwestern University
Dr. Jain has received in excess of $5,000 advisory fees and research funding from Vertex Pharmaceuticals. He is also on the Speaker's Bureau of Vertex Pharmaceuticals and Gilead Sciences.

Brian P. O'Sullivan, MD
Professor of Pediatric Pulmonology
Geisel School of Medicine, Dartmouth College
No relevant conflicts of interest to disclose, defined as more than $10,000 in health care company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Cystic Fibrosis Foundation

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

Table of Contents

List of Acronyms Used in this Report

AHRQ	Agency for Healthcare Research and Quality
AE	Adverse event
AER	Annualized event rate
AHRQ	Agency for Healthcare Research and Quality
AR	Annualized rate
BMI	Body mass index
BSC	Best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CF	Cystic fibrosis
CFF	Cystic fibrosis foundation
CFFPR	Cystic Fibrosis Foundation Patient Registry
CFQ-R	Cystic fibrosis questionnaire-revised
CFRD	Cystic fibrosis-related diabetes
CFTR	Cystic fibrosis transmembrane conductance regulator gene
Cm	Centimeter
D/C	Discontinuation
ELX	Elexacaftor
EQ-5D-5L	EuroQol 5-dimensions 5-level questionnaire
ER/PY	Event rate per patient year
FDA	Food and Drug Administration
FVC	Forced vital capacity
GI	Gastrointestinal
HIV	Human immunodeficiency virus
Hosp.	Hospitalization
HRQOL	Health related quality of life
IQR	Interquartile range
ITT	Intention to treat
IV	Intravenous
IVA	Ivacaftor
Kg	Kilogram
Kg/m2	Kilogram per meter squared
LCI	Lung clearance index
LUM	Lumacaftor
m^2	Square meter
MCID	Minimum clinically important difference
Mg	Milligram
mITT	Modified intention to treat
mmol/L	Millimoles per liter
MMRM	Mixed model repeated measure
MOCA	Montreal Cognitive Assessment Tool,
n	Number
N	Total number
N/A	Not applicable

NIH	National Institute of Health
NICE	National Institute for Health and Care Excellence (UK agency)
NR	Not reported
N.S.	Not significant
OLE	Open label extension
PERT	Pancreatic enzyme replacement therapy
PEx	Pulmonary exacerbation
$ppFEV_1$	Percent predicted forced expiratory volume in 1 second
PY	Patient year
Resp.	Respiratory
RR	Risk ratio
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SNOT-20	20-item Sino-Nasal Outcome Test
SOC	Standard of care
TEAE	Treatment-emergent adverse event
TEZ	Tezacaftor
TMT	Trail Making Test
USPSTF	United States Preventive Services Task Force
VAS	Visual analog Scale
VC	Vital Capacity
VO2Max	Maximal oxygen uptake
WAC	Wholesale acquisition cost
WPAI	Work Productivity Activity and Impairment Questionnaire
WTP	Willingness to pay
95%CI	95% Confidence Interval
Δ	Difference

1. Introduction

1.1 Background

Cystic fibrosis (CF) is an autosomal recessive condition caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. The CFTR protein is an ion channel at the cell surface that primarily transports chloride ions across the cell membrane. Children born with CF inherit two pathogenic mutations, one from each parent. CF is a progressive disease that affects many organ systems, but most of its morbidity and mortality are associated with its impact on the respiratory system. In the US approximately 1 in 3,000 Whites are born with CF; it is the most common fatal genetic disease in Caucasian populations, but it is less common among Latinos (1 in 4,000-10,000) and African Americans (1 in 10,000-20,000).[1-4] According to the Cystic Fibrosis Foundation Annual Report, the overall prevalence of CF in the US in 2016 was 30,775.[5] Although rare, CF represents a substantial economic burden. In 2013, CF-related hospital costs alone were estimated to exceed $1.1 billion.[6]

The life expectancy of patients with CF has increased substantially over the past 20 years, due in part to successes in the coordinated delivery of care and advances in CF management.[7] Until recently, treatment for CF focused on reducing symptoms and managing complications. New therapies target the abnormal proteins made by the mutated *CFTR* gene. More than 2,000 *CFTR* mutations have been identified that have different effects on the quantity and function of the CFTR protein.[5] They are often grouped into five classes (Table 1.1 below) based on the effect of the mutation on the CFTR protein. It is important to remember that each patient with CF carries two of these mutations. Mutations to the *CFTR* gene can affect the amount of CFTR protein that is produced, the amount of protein integrated into the cell membrane, or the CFTR protein's ability to regulate ion and water flow.[7] This leads to thick secretions that can block passages in the lungs, pancreas, skin and reproductive organs. Changes in the skin lead to elevations in the concentration of chloride ions in the skin, which is sometimes used to screen for CF and to evaluate the impact of the new therapies on CFTR function. More importantly, the thick secretions can cause chronic lung infections, reduced lung function, poor weight gain (due to gastrointestinal dysfunction), diabetes (due to pancreatic damage), and fertility problems.[8] These symptoms dramatically impact the lives of affected patients. The quality of life of patients with CF is often measured with the Cystic Fibrosis Questionnaire – Revised (CFQ-R), which assesses 13 domains relevant to patients living with CF. Patients suffer frequent pulmonary exacerbations, leading to repeated hospitalizations and long courses of IV antibiotics that require invasive procedures like the placement of ports for IV access and repeated absence from school and work. The chronic cough from the thick secretions is noticeable to everyone surrounding the patient leading to self-consciousness, stigmatization, anxiety, and depression. The decreased lung function impacts their ability to participate in sports and other daily activities. Seeing their lung function steadily decline leads patients to dread the

future and may preclude planning for a long life with family, a rewarding career, and eventual retirement.

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

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

*Potentially effective therapy for at least one mutation in the class

†Most common mutation in CF

Adapted from the Cystic Fibrosis Foundation website: https://www.cff.org/What-is-CF/Genetics/Know-Your-CFTR-Mutations-Infographic.pdf

The life expectancy of patients with CF has increased substantially over the past 20 years, due in part to successes in the coordinated delivery of care and advances in CF management.[7] Until recently, treatment for CF focused on reducing symptoms and managing complications. New

therapies target the abnormal proteins made by the mutated *CFTR* gene. More than 2,000 *CFTR* mutations have been identified that have different effects on the quantity and function of the CFTR protein.[5] Mutations to the *CFTR* gene can affect the amount of CFTR protein that is produced, the amount of protein integrated into the cell membrane, or the CFTR protein's ability to regulate ion and water flow.[7] This leads to thick secretions that can block passages in the lungs, pancreas, liver, intestines, and reproductive organs, which may result in frequent lung infections and reduced lung function, poor weight gain (due to gastrointestinal dysfunction), diabetes (due to pancreatic damage), and fertility problems.[8] These symptoms dramatically impact the lives of affected patients, who have a predicted life expectancy that is roughly half that of the rest of the United States population. Patients suffer frequent lung infections, leading to repeated hospitalizations and long courses of IV antibiotics that require invasive procedures like the placement of ports for IV access and repeated absence from school and work. Their daily treatment regimen is complex and burdensome and further impacts quality of life with up to 50 pills, five inhaled medications, and one hour of airway clearance every day. The high prevalence of mental health challenges within the CF population may represent in impact of the chronic illness. Patients report that the chronic cough from the thick secretions is noticeable to everyone surrounding the patient leading to self-consciousness, stigmatization, anxiety, and depression. The decreased lung function impacts their ability to participate in sports and other daily activities. Seeing their lung function steadily decline leads patients to dread the future and precludes planning for a long life with family, a rewarding career, and eventual retirement.

Management

Best supportive care for CF includes chest physical therapy, airway clearance devices, bronchodilators, inhaled and systemic antibiotics as needed or chronically, inhaled hypertonic saline, and aerosolized DNase, which reduces sputum thickness. In addition, patients often require pancreatic enzyme replacement to treat pancreatic insufficiency and insulin for CF-related diabetes. Routine daily treatment can take two to three hours.[9] Patients with end-stage CF become eligible for lung transplantation.

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

CFTR modulator drugs

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

(tezacaftor/ivacaftor, Vertex Pharmaceuticals, Inc.), and Trikafta™ (elexacaftor/tezacaftor/ivacaftor, Vertex Pharmaceuticals, Inc.). We are using trade names in this report for simplicity.

This review focuses on the triple therapy, Trikafta. The United States Food and Drug Administration (FDA) approved Trikafta on October 21, 2019.[10] In addition, we updated our 2018 review of Kalydeco, Orkambi, and Symdeko.[11]

The use of these agents has generated tremendous interest and hope on the part of clinicians, patients, and their families. The new triple therapy has the potential to improve the lives of patients with CF both through improved efficacy in patients currently eligible for dual therapy (Orkambi, Symdeko) and those with mutations that are not eligible for treatment with the current generation of modulator therapies (patients who are heterozygous for the *F508del* mutation and a minimal function mutation). In addition, there may be new data with longer follow-up for patients treated with currently-available therapies.

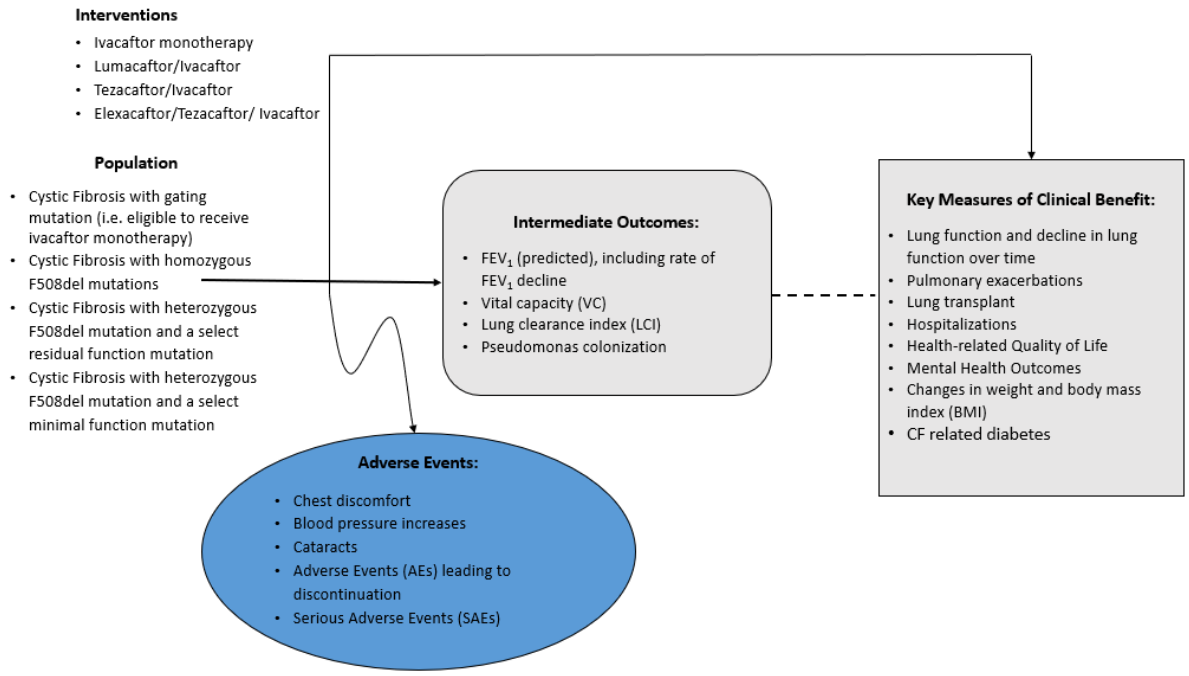
1.2 Scope of the Assessment

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

Analytic Framework

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

Figure 1.1 Analytic Framework: Modulator Therapies for Cystic Fibrosis



The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific health outcomes. Outcomes are listed in the shaded boxes: those within the rounded boxes are intermediate outcomes (e.g., changes in lung clearance index), and those within the squared-off boxes are key measures of benefit (e.g., health-related quality of life). The key measures of benefit are linked to intermediate outcomes via a dashed line, as the relationship

between these two types of outcomes may not always be validated. Curved arrows lead to the AE of treatment which are listed within the blue ellipse.[12]

Populations

We reviewed the CFTR modulator therapies in four distinct populations across all ages based on current FDA labeling and the clinical trial populations.

1. Individuals with CF who carry mutations included in the FDA-approved indications for ivacaftor.
2. Individuals with CF who are homozygous for the *F508del* mutation.
3. Individuals with CF who are heterozygous for the *F508del* mutation with a residual function mutation.
4. Individuals with CF who are heterozygous for the *F508del* mutation with a minimal function mutation.

Interventions

Population 1: Gating mutation

- Ivacaftor plus best supportive care

Population 2: Homozygous for *F508del*

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

Population 3: Heterozygous *F508del* and a residual function mutation

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

Population 4: Heterozygous *F508del* and a minimal function mutation

- Elexacaftor/tezacaftor/ivacaftor plus best supportive care

Comparators

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

Outcomes

Key Outcomes

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

Other Outcomes

- Time lost from school or work
- Pill burden and correlation to adherence with medication regimen
- Worry, stress, and anxiety about the disease or its financial impact
- Ability to participate in athletic activity and social functions
- Financial insecurity
- Caregiver burden
- Acute pancreatitis
- Fertility
- Liver transplant
- Hemoptysis
- Pneumothorax
- Gall stones
- Kidney stones
- Sinus / nasal polyp surgeries
- Fertility in women

Intermediate Outcomes

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

Adverse Events

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

Timing

Studies of all follow-up durations were eligible.

Settings

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

1.3 Definitions

Disease and Pathophysiology

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

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

Mutations: Heritable changes in the DNA, here, of the *CFTR* gene. More than 1,800 different *CFTR* mutations at different loci (places) of the *CFTR* gene have been identified,[13] with varying effects on the quantity and function of the CFTR protein.[14] A subset of these mutations are known to be pathogenic (see below).

Pathogenic mutations: Mutations that substantially affect the quantity of functional CFTR protein on the cell membrane, causing CF. Based on the Clinical and Functional Translation of *CFTR* repository, more than 1800 mutations are known to cause CF.[15] 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.[16] FEV_1 is reported in liters and measures the capacity of a person's lungs. Lower FEV_1 values indicate increasing lung impairment or damage. FEV_1 is measured via spirometry.

Percent predicted forced expiratory volume in one second ($ppFEV_1$): measured FEV_1 as a percentage of the predicted FEV_1 value for a healthy individual of the same age, sex, race, and height.[17] A clinically-relevant change in absolute percent predicted FEV_1 has been considered to be three to five points or greater.[18]

CF-related diabetes (CFRD): 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.[19]

Cystic Fibrosis Questionnaire-Revised (CFQ-R): A validated survey which measures health-related quality of life (HRQOL) in CF patients.[20] The CFQ-R measures quality of life and physical disease symptoms using the following scales: physical functioning, emotional functioning, social functioning, body image, eating problems, treatment burden, respiratory symptoms, and digestive symptoms, among other domains specific to older patients. Scores range from 0-100 with an increasing score indicating better quality of life. In general, a four-point change is considered clinically meaningful (the minimum clinically-important difference, or MCID).[21] This report primarily focuses on the CFQ-R respiratory domain score since it was reported in the pivotal trials of the CFTR modulators.

Lung Clearance Index (LCI): A novel outcome that assesses the uneven distribution of lung ventilation, an indicator of obstructive lung disease and is typically used in those with a milder lung disease. It represents the number of lung volume turnovers required for the lungs to clear a tracer gas to reach 2.5% of starting tracer gas concentration.[22]. 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).[23] 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). Real world research may not use the same definition.

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

1.4 Research, Development, and Manufacturing Costs

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

1.5 Potential Cost-Saving Measures in Cystic Fibrosis

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/final-vaf-2017-2019/). These services are ones that would not be directly affected by therapies for CF (e.g., reduction in use of treatment for pulmonary exacerbations), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of CF beyond the potential offsets that arise from a new intervention. During stakeholder engagement and public comment periods, ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with CF that could be reduced, eliminated, or made more efficient. To date, no suggestions have been received. However, the Cystic Fibrosis Foundation is sponsoring several studies – randomized clinical trials as well as real world research – to evaluate the safety and effectiveness of withdrawing symptomatic treatments, such as dornase alfa (Pulmozyme®, Genentech USA, Inc.), among individuals taking Trikafta

It has been suggested that patients with a good response to CFTR modulator therapy may be able to discontinue some of the standard daily symptomatic treatments such as hypertonic saline and dornase alfa. In addition, if the patient can clear pseudomonas, they could stop their inhaled antibiotics. Patients dependent on nocturnal tube feeding may be able to stop the treatment. There may also be significant time savings for patients if some of their therapies can be reduced. However, to date none of these changes have been demonstrated in clinical trials or observational studies and it is unclear if discontinuing standard therapies may be detrimental to long term health. A randomized trial of therapy withdrawal for patients on CFTR modulator therapy is underway.[24]

2. Patient Perspectives

2.1. Methods

From the beginning of this assessment, we sought input from patients, caregivers, and representatives from patient advocacy organizations on the research design of this review (e.g., the PICOTS framework; population, intervention, comparators, outcomes, timing, and setting). We also sought insight on the patient experience of CF and its treatment, including benefits of treatment that may not be described in the clinical literature, any broader potential other benefits or disadvantages associated with treatments, and contextual consideration related to CF, details of which are reported in this section and Section 6. We also built upon the insights that these stakeholders shared with ICER during its 2018 review of Kalydeco, Orkambi, and Symdeko,[11] as well as existing sources of information on patient perspectives such as the Voice of the CF Patient report produced by Cystic Fibrosis Research Incorporated (CFRI) under the FDA Externally-Led Patient Focused Drug Development program.[25]

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

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

Input received during the Open Input period informed the initial selection of population, interventions, comparators, and outcomes measures for which we sought evidence described in a draft scoping document that was open to public comment for three weeks. As compared to ICER's previous report, we added CF-related diabetes, health-related quality of life, pill burden and

correlation to adherence with medication regimen, pseudomonas infection, and vital capacity as outcomes, and increased blood pressure and serious adverse events (SAEs) as AE to the draft scope.

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

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

2.2 Impact on Patients and Caregivers

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

It is important to note that patients, caregivers, and advocacy organizations highlighted the heterogeneity of the disease, emphasizing that no two patients are alike. Patients with different combinations of *CFTR* mutations have variable disease courses and even patients with the same mutation type have different lived experiences with CF. There is no "typical" patient living with CF – the patients are unique individuals.

Disease Burden and Experience with Modulator Treatments

We reviewed the CFRI Voice of the Patient report to better understand patient and caregiver perspectives on the burden posed by CF.[25] The report summarizes the proceedings at an October 29, 2018 public meeting that featured panel discussions among CF patients, caregivers, and clinical experts, as well as live polling of attendees (polling responses were also accepted for 30 days after

the event). The nine symptoms identified by polls as having the greatest impact on quality of life for patients living with CF are listed below.

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

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

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

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

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

These results closely aligned with the feedback ICER heard during its own patient engagement efforts, and patients shared with us how treatment impacted many of these symptoms. When we spoke with patients who had started Trikafta, the first thing that they noticed was that either their cough stopped or was greatly diminished. There was often an initial purge of mucus — one patient reported expulsion of nearly 12 ounces of mucus in an evening — and then patients felt like they could take deeper breaths for the first time in their life. Patients emphasized that reducing or eliminating their cough brought numerous benefits, especially the ability to sleep through the night without waking due to coughing attacks, which brought increased energy levels and improvements in mood. One patient shared that she ran a 5k before and after starting Trikafta, and was able to complete the second race without coughing nearly 10 minutes faster than her previous time. Patients on modulator therapy for several years (i.e., Kalydeco, Orkambi, and/or Symdeko) reported a reduction in the frequency of pulmonary exacerbations and the need for IV antibiotics. Patients

and their caregivers noted a meaningful increase in energy. One patient told us that "I haven't been able to do any exercise in years. Now I can snowboard, swim, hike at high elevations, and even run a little bit."

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

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

Another theme was the psychosocial burden associated with living with a chronic, life-shortening illness. Depression and anxiety disorders contribute significantly to the overall burden of disease and are often insufficiently captured in measures of disease burden and quality of life. One parent reported that her daughter "had an underlying sadness, but [after starting Trikafta] now sees the world through a completely different lens." Her daughter, who had been an avid horse-back rider before she could no longer participate due to her disease progression is now able to ride three days a week. Another patient reported that "my biggest mental change has been my calmness." Another patient reported that after starting Trikafta "I have stopped weekly therapy for depression. I no longer think about death all of the time."

A common thread in these remarks was the ability to plan for the future, which for many had been unthinkable due to the dire prognosis of the disease. Parents shared with us that their children are imagining future educational and professional opportunities, while adults spoke about re-entering the workforce, planning for retirement, vacations, and entering into long-term relationships with less concern about how CF might impact their longevity. Parents who have CF themselves are able to spend more time with their children as they grow up, and may live long enough to have grandchildren as well. Patients expressed hope that currently-available treatments would provide substantial benefits, with one patient stating that "we have been waiting for a miracle and the triple combo is the closest thing." Patients commonly used the word "transformative" to describe Trikafta. Patients who had already started therapy with Trikafta spoke about the transformation in their outlook about the future from one of dreading the inevitable decline associated with CF to planning for the future. One patient, who had not had a good response to another modulator

therapy said that starting Trikafta "felt like a miracle to me." Patients also reported hope for their community – in particular the hope that children with CF who start on modulator therapy early in their lives might be able to avoid the pulmonary, pancreatic, and other complications of CF and thus live normal or near-normal lives.

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

Treatment Burden

Patients and caregivers described the immense daily burden required to manage CF. Airway clearance activities and taking dozens of pills and inhaled therapies consumes several hours of every day for patients; the CFRI report notes that this can be up to 6 hours per day.[25] This is exhausting and takes away time that would normally be spent on social activities, school, and family. It also contributes to the stigma associated with the disease. In addition, there is a substantial time burden from hospitalization for pulmonary exacerbations and the need for long-term IV antibiotic therapy.

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

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

Patients expressed hope that the new triple therapy would alleviate some of this daily load, and for some patients this daily load was already improving. Some reported that they have reduced or stopped using other treatments such as hypertonic saline, inhaled medications, laxatives, or insulin. Patients also spoke of their desire to spend less time in the hospital, and how modulator treatments have reduced the number of pulmonary exacerbations and other health events that require doctor's visits or hospital stays.

Access and Costs

Another theme we heard was the financial burden imposed by the disease. Many of the therapies are not completely covered by insurance, requiring substantial financial contributions by patients and their families. Patients miss school and work due to routine follow-up, disease exacerbations, and eventually the disability imposed by progressive disease.

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

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

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

3. Summary of Coverage Policies and Clinical Guidelines

3.1 Coverage Policies

We reviewed the Tufts Medical Center Specialty Drug Evidence and Coverage (SPEC) Database for US commercial health plan coverage policies for Trikafta, Kalydeco, Orkambi, Symdeko, and. Developed by the Center for Evaluation of Value and Risk in Health, the SPEC database features data more than 290 specialty drugs, more than 175 disease areas, and more than 25,000 decisions from 17 of the largest US national and regional commercial payers: Aetna, Anthem, Blue Cross Blue Shield (BCBS) of Florida (FL), Massachusetts (MA), Michigan (MI), North Carolina (NC), New Jersey (NJ), and Tennessee (TN), CareFirst, Centene, Cigna, Emblem, Health Care Service Corporation (HCSC), Highmark, Humana, Independence Blue Cross (IndepBC), and UnitedHealthcare (UHC).[26]

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

Trikafta

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

Table 3.1. Summary of Representative Commercial Coverage Policies for Trikafta

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

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

Kalydeco

We identified publicly available coverage policies for Kalydeco for all but five of the surveyed payers (BCBSNJ, BCBSTN, Emblem, HCSC, and Highmark); policies from the other payers are described in Table 3.2. All plans required documentation of a genetic mutation responsive to treatment with Kalydeco. Seven of 12 policies (58%) were consistent with the FDA label, while the remaining 5 (42%) were more restrictive with regards to either prescriber restrictions or age requirements. Aetna and BCBSFL required patients to be 12 months of age or older, which did not reflect the FDA label expansion on April 30, 2019,[27] while CareFirst set a minimum age of two years, which did not reflect the label expansion on August 15, 2018.[28]

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

Table 3.2. Summary of Representative Commercial Coverage Policies for Kalydeco

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

N/A: not applicable, NS: not specified

Orkambi

We identified publicly available coverage policies for Orkambi for all but five of the above payers (BCBSNJ, BCBSTN, Emblem, HCSC, and Highmark). Policies for the remaining 12 payers are described in Table 3.3. All plans required documentation that the patient is homozygous for the *F508del* mutation, and Aetna's policy required re-confirmation of mutation status for renewal. Of these plans, 8 (67%) follow the FDA label, while 4 (33%) were more restrictive. As above, more restrictive policies focused on age limits or prescriber criteria. CareFirst's policy requires patients to be at least 6 years old, the labeled age range prior to August 7, 2018.[29] Two plans included renewal criteria for demonstration of clinical benefit (BCBSMI) or demonstration of benefit or stabilization (Aetna)

Table 3.3. Summary of Representative Commercial Coverage Policies for Orkambi

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

N/A: not applicable, NS: not specified

Symdeko

We identified publicly available coverage policies for Symdeko for all but five of the above payers (BCBSNJ, BCBSTN, Emblem, HCSC, and Highmark). All plans required documentation that the patient is homozygous for the *F508del* mutation or has another *CFTR* gene mutation responsive to treatment with Symdeko. As with Orkambi, Aetna required re-confirmation of mutation status for renewal. Of the 12 plans with publicly available policies, 5 (42%) aligned with the FDA label and 7 (58%) were more restrictive (Table 3.4). Plan restrictions came in the form of age restrictions or provider criteria. Anthem, CareFirst, Cigna, and IndepBC required patients to be aged 12 or older, which did not reflect the FDA label expansion from June 21, 2019.[30] Two plans included renewal criteria for clinical response or stabilization (Aetna) or clinical improvement (BCBSMI)

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

Table 3.4. Summary of Representative Commercial Coverage Policies for Symdeko

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

N/A: not applicable, NS: not specified

3.2 Clinical Guidelines

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

Cystic Fibrosis Foundation (CFF), 2018[31]

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

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

Kalydeco

The guidelines strongly recommend the use of Kalydeco versus no modulator therapy in children ages 2-5 years with gating mutations other than *G551D* or *R117H* (i.e., *G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P*, or *G1349D*). In a separate 2016 guidelines statement for preschool-aged individuals (2-5 years), the CF Foundation strongly recommends the use of Kalydeco in individuals with a *G551D* mutation and that its use be considered in individuals with a *R117H* mutation.[32] Another 2012 guideline statement regarding the use of chronic medication to maintain lung function includes a strong recommendation for the use of Kalydeco for all individuals ages 6 and older with at least one copy of a *G551D* mutation.[33]

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

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

Orkambi

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

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

Guidelines for Other Aspects of CF Care

The CF Foundation has produced guidelines statements regarding all aspects of CF care, including diagnosis, nutrition/gastrointestinal care, respiratory care, infection prevention and control, CF-related conditions (CF-related diabetes, liver disease, and bone disease), and for the screening and treatment of depression and anxiety.[34]

National Institute for Health and Care Access (NICE), 2019[35]

In October 2019, NICE reached an interim access agreement with Vertex Pharmaceuticals Inc. to provide eligible patients with access to Kalydeco, Orkambi, and Symdeko during a data collection period to address several uncertainties raised by the NICE appraisal committee. These uncertainties related to long-term effects on ppFEV$_1$, treatment impacts on lung function decline, discontinuation, compliance, BMI, height and weight for patients younger than 18, use of IV antibiotics, CF-related diabetes, mortality, pancreatic insufficiency, sweat chloride, and quality of life. Details of any price concessions made as part of this agreement are unknown.

Kalydeco

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

Orkambi

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

Symdeko

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

Trikafta

Trikafta is not included in the above arrangement for the other three modulator therapies. NICE is in the preliminary stages of its appraisal of the treatment.[36]

Guidelines for Other Aspects of CF Care

NICE provides guidance for the treatment of CF beyond modulator therapy, including diagnosis; support; management of complications; pulmonary and "other" monitoring assessment, and management; and preventing cross-infection.[37]

Canadian Agency for Drugs and Technology in Health (CADTH)

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

Kalydeco

CADTH has issued three separate recommendations regarding the use of Kalydeco, each of which included a recommendation for coverage conditional on substantial price reductions. Across the three guidance documents, CADTH recommended coverage for patients ages 6 and older with *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R*, or *G970R* mutations; and for patients ages 18 and older with a *R117H* mutation and chronic sinopulmonary disease. In addition to the requirement for price reductions, CADTH also requested the development of clinical criteria by CF clinics for treatment discontinuation in patients with *G551D* and *R117H* mutations who do not respond to therapy.[38-40]

Orkambi

In September 2018, CADTH issued a recommendation against reimbursement of Orkambi for patients 6 years of age and older who are homozygous for the *F508del* mutation.[41] In their rationale for the negative recommendation, CADTH cited concerns related to the clinical and statistical significance of trial outcomes, as well as cost-effectiveness.

4. Comparative Clinical Effectiveness

4.1 Overview

We updated our prior review of the comparative clinical effectiveness of CFTR modulators in patients with cystic fibrosis, focusing on the evidence of the efficacy and safety of the new CFTR modulator Trikafta in comparison with other CFTR modulators or best supportive care (as estimated by the placebo are of clinical trials). We defined four target populations of interest in 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 several outcomes specified in Section 1.2, including pulmonary exacerbation, percent predicted FEV_1, weight/BMI, and quality of life measures.

4.2 Methods

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on CFTR modulators followed established research methods.[42,43] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[44] The PRISMA guidelines include a list of 27 checklist items, which are described further in Appendix Table A1.

We updated our prior literature searches in Ovid-Medline and EMBASE and added search terms for Trikafta. No limitations were placed on the searches regarding publication date, language, age, country, study design, or publication type (e.g., peer-reviewed or conference proceeding). All search strategies were generated utilizing the Population and Intervention criteria described in Section 1.2. The search strategies included a combination of indexing terms (MeSH terms in MEDLINE, searched through PubMed, and EMTREE terms in EMBASE), as well as free-text terms, and are presented in Appendix Tables A2- A5. The date of the most recent search was November 8, 2019.

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

Study Selection

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

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

Data Extraction and Quality Assessment

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

Data extraction was performed in the following steps:

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

We used criteria employed by the US Preventive Services Task Force ([USPSTF] see Appendix D) to assess the quality of clinical trials, using the categories "good," "fair," or "poor." [45 45 45 45 4546]

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus (see Appendix D).[47]

Assessment of Publication Bias

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

Data Synthesis and Statistical Analyses

As in the prior review, we sought to conduct meta-analyses for each outcome of interest, for which there were data from at least two studies that were sufficiently similar in population, intervention (e.g., dose), and other characteristics. Meta-analyses carried over from the prior report were conducted with random effects model restricted maximum likelihood analyses. Harms were

analyzed as arcsine transformed data.[48] Estimates of indirect comparisons were obtained as linear combinations of the direct estimates, following Bucher et al.[49] For this review we performed random effects component network meta-analyses (CNMA) for key outcomes (ppFEV$_1$, CFQ-R, and sweat chloride) in patients homozygous for the *F508del* mutation (Population 2) in order to allow indirect comparisons between treatments that lacked head to head trials. We followed the frequentist CNMA approach for disconnected networks described by Rucker et al (2019).[50]

4.3 Results

The results are organized by the four populations of interest:

1. Individuals with CF who carry mutations included in the FDA-approved indications for ivacaftor.
2. Individuals with CF who are homozygous for the *F508del* mutation.
3. Individuals with CF who are heterozygous for the *F508del* mutation with a residual function mutation.
4. Individuals with CF who are heterozygous for the *F508del* mutation with a minimal function mutation.

Within each population, the results are summarized by drug. We summarized the findings from the prior review for each therapy and describe any new results.

Study Selection

Our literature search yielded 876 potentially relevant references (Figure A1) of which 26 met our eligibility criteria. The primary reasons for study exclusion for this review included studies captured in the prior review, duplicates, and non-comparative study designs with either follow-up less than one month or study size less than 100 participants. We made an exception for one study that included only 96 participants because it was close to 100 and reported 5 year outcomes.[51]

Key Studies

There are two key studies of Trikafta.[52,53] The first randomized 107 patients homozygous for the *F508del* mutation (Population 2) to Trikafta or Symdeko with a primary outcome of change in ppFEV$_1$ at 4 weeks. The second randomized 403 patients heterozygous for the *F508del* mutation and a minimal function mutation (Population 4) to Trikafta or placebo with a primary outcome of change in ppFEV$_1$ at 24 weeks. Both studies were good quality. The results are summarized in the sections below for the relevant populations.

Quality of Individual Studies

As noted in the Key Studies section the pivotal randomized trials for Trikafta[52,53] were of good quality as was the earlier dose finding study.[54] There were no other new randomized trials, but

there were a number of additional publications of the randomized trials that were judged to be of good quality in our prior review. The new publications from these studies either reported additional outcomes not reported in the initial publication or presented open label, long-term follow-up data. There were several cohort studies with matched concurrent or historical controls that we rated as fair quality because of concerns about residual confounding. Uncontrolled case series were rated as poor quality. We did not rate the quality of the thirteen new studies that were available only as abstracts.

Clinical Benefits

Population 1: Kalydeco in Gating and Residual Function Mutation Populations

Key Findings: Children, adolescents, and adults with G551D *and non-*G551D *gating mutations experienced statistically significant and clinically meaningful gains in ppFEV$_1$ and reductions in the rate of pulmonary exacerbations with Kalydeco compared to placebo in 24-week studies. Longer-term follow-up suggests lung function improvements, including reduced rates of pulmonary exacerbations, are durable through five years. Statistically significant gains in body weight and respiratory symptom-related quality of life with Kalydeco were reported for* G551D *and non-*G551D *gating mutation populations aged 12 and older compared to placebo. Statistically significant improvements in lung function or weight were not observed in adult patients with* R117H *residual function mutations. In a small sample of children aged 6 to 11 years with* R117H *residual function mutations, those on Kalydeco experienced statistically significant decreases in lung function and trended towards decreased respiratory symptom-related quality of life scores compared to placebo. Observational studies with up to five years of follow-up report significant reductions in rates of death, organ transplantation, CF related diabetes and hospitalizations, but there is significant selection bias in the control groups that may explain much of these reductions.*

Since our prior review, two abstracts and one publication extending the results of trials described in the prior report.[55-57] In addition, there are eight new observational studies (five full text, three abstracts only).[13,51,58-63] See Appendix Tables D1 to D15 and our prior report[11] for detailed analyses of the clinical trials of Kalydeco in patients with mutations that respond to Kalydeco. The prior report summarized four RCTs (STRIVE, ENVISION, KONNECTION, and KONDUCT) that evaluated the safety and efficacy of Kalydeco in patients with at least one *G551D*, non-*G551D* gating, or *R117H* mutation.[64-67] The prior review also summarized three noncomparative studies: KIWI,[68] a Phase III single-arm study that included children aged 2-5 with a *G551D* gating mutation; GOAL,[69] a longitudinal cohort study of individuals aged 6 years and older with at least on *G551D* mutation; and PERSIST,[70] which followed eligible STRIVE and ENVISION participants for an additional 96 weeks on Kalydeco.

Table 4.1 below summarizes the prior results as well as the new studies. For patients ages 6 years and older with gating mutations (*G551D* and non-*G551D*), the studies reported an absolute

improvement of 10.4 percentage points (95% CI 8.6 to 12.3) in $ppFEV_1$ compared to placebo, significant reductions in risk of pulmonary exacerbations (34% vs. 56%, hazard ratio 0.455, p=0.001), increases in weight and BMI (2.8 kg and 0.7 kg/m^2 respectively), and clinically significant improvements in the respiratory domain of the CFQ-R quality of life instrument of 5 to 10 points, although the difference with placebo was non-significant in the study of patients 6 to 11 year of age with the *G551D* mutation. Long-term follow-up (96 weeks) of these people on continued Kalydeco treatment found maintenance of their improvements in $ppFEV_1$ (10.7 percentage points, 95% CI 7.3 to 14.1).

Based on a single study of people with the *R117H* gating mutation, Kalydeco improved respiratory function and quality of life in people aged 18 years and older. Their $ppFEV_1$ improved by 5% and the respiratory domain of CFQ-R improved by 12.6 points. However, among the subgroup ages 6 to 11 years, Kalydeco was not more effective than placebo. Their $ppFEV_1$ worsened on Kalydeco (-6.3%) compared to placebo and the respiratory domain of CFQ-R also worsened. Because this is a subgroup analysis from a small study, this may be a chance finding. In both age groups there were no significant differences in pulmonary exacerbation rates or BMI.

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

Trial, Study Design & Follow-Up duration	Age (N)	Absolute Diff. in $ppFEV_1$, % (95%CI)	Pulmonary Exacerbation	Diff. in Weight, kg (95%CI)	Diff. in CFQ-R Respiratory Domain, points (95%CI)	Other, RR (95%CI)
***G551D* Mutation**						
STRIVE[64] ENVISION[65] Randomized Controlled Trial 48 Weeks	≥6 years (N=213)	**10.4 (8.6, 12.3)***	**HR 0.455 (0.29, 0.73)† NR†**	**2.8 (1.8, 3.8)***	**9.7 (6.5, 13.0)***	
Non-*G551D* Mutation						
KONNECTION[66] Randomized Controlled Trial 8 Weeks	≥6 years (N=39)	**10.7 (7.3, 14.1)**	NR	**BMI (kg/m^2): 0.7 (95%CI: 0.3, 1.0)**	**9.6 (4.5, 14.7)**	
***R117H* Mutation**						
KONDUCT[67] Randomized Controlled Trial 24 weeks	≥6 years (N=69)		HR 0.93 (NR)	BMI (kg/m^2): 0.3 (95%CI: −1.6, 2.1)		
	6-11 years(N=17)‡	**−6.3 (−12.0, −0.7)§**			−6.1 (−15.7, 3.4)§	
	≥18 years(N=50)‡	**5.0 (1.2, 8.8)**			**12.6 (5.0, 20.3)**	
Observational Studies for All Indicated Mutations (Implied)						
US cohort[13] *Nonrandomized Comparative Study*	≥6 years # (N=1256 / 6200 controls)	**+1.4 vs. -5.3, p<0.001**	**RR 0.64 (95%CI: 0.58, 0.70)**	NR	NR	**Death: 0.41 (0.20, .84)**

3 years						
UK cohort[13] ***Nonrandomized Comparative Study*** **2 years**	≥6 years # (N=411 / 2069 controls)	**+6.6 vs. -1.5, p<0.001**	**RR 0.61 (95%CI: 0.53, 0.70)**	NR	NR	Death: 0.52 (0.16, 1.7)
US cohort[63] ***Nonrandomized Comparative Study*** **5 years**	≥6 years # (N=635 / 1874 controls)	-0.7 vs. -8.3, p NR	**0.58 (0.51-0.67) in year 5**	BMI +2.4 kg/m2 vs. +1.6 kg/m2, p NR		
UK cohort[63] ***Nonrandomized Comparative Study*** **4 years**	≥6 years # (N=247 / 1230 controls)	+4.9 vs. -4.3, p NR	**0.57 (0.47-0.67) in year 4**	BMI +1.9 kg/m2 vs. +0.9 kg/m2, p NR		
GOAL study **5-year extension study** **5.5 years**	≥6 years (N=96)	0.8 (-2.0 to +3.6) at 5.5 years compared with baseline		**BMI 2.5 kg/m2 (2.0 to 3.1) at 5.5 years**.	**6.7 (2.5 to 10.9) at 5.5 years**	

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

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

New Data From Randomized Trials of Kalydeco

One small randomized cross-over trial of Kalydeco in twenty adults with the *G551D* mutation suggested that cognitive function, as assessed by the Montreal Cognitive Assessment tool, improved slightly with 4 weeks on treatment.[57]

The second report described the impact of Kalydeco withdrawal in the same 20 patient crossover trial. Both $ppFEV_1$ and sweat chloride levels rapidly rebounded to near baseline levels.[55]

Finally, an open-label extension trial in 33 children between the ages of 2 and 5 years found that the improvements in sweat chloride and growth parameters observed in the 24 week randomized trial were maintained through an additional 84 weeks.[56] One child discontinued Kalydeco because of persistently elevated liver enzymes. No new AEs were identified.

New Observational Data for Kalydeco

There were eight observational studies on long term use of Kalydeco.[13,51,58-63] The two largest and longest are from the same populations (US and UK Registries), but report complementary outcomes.[13,63] These ongoing post-approval safety studies evaluate clinical outcomes and disease progressions in all those in the UK and US registries following commercial availability. Analyses compare Kalydeco-treated patients with untreated controls. Based on commercial availability in both countries, 5 year follow-up data are available for 685 Kalydeco users (and 1874 comparators) in the US and 4 year follow-up data is available for 247 UK participants on Kalydeco (and 1230 comparators). An additional US study used claims data to evaluate the impact of Kalydeco on inpatient admissions.[59] Two additional studies (one Ireland and one France) published in abstract form provided limited additional follow up information about long term use of Kalydeco and clinical outcomes and measures of pulmonary function.[60,61]

Pulmonary Function and Exacerbations

Several studies measured $ppFEV_1$, which was also reported in clinical trials. In all of the studies, $ppFEV_1$ was higher in Kalydeco treated patients. In the US and UK registry studies which included the most patients, the increase ranged from 1.4 to 6.6% compared with a decrease of 1.5 to 5.3% in the control groups.[13,63] Similar trends were seen in the smaller Kalydeco studies.

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

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

CF-Related Diabetes

In both the US and the UK cohorts, the rates of CF-related diabetes (CFRD) were lower in the Kalydeco treated group than in the non-treated comparators.[63] The relative risk of CFRD was between 13 and 35% lower in both cohorts at various time points between 2 and 5 years. In the US cohort, at 5 years of follow-up, the rate was 35.7% in the Kalydeco group, compared with 40.9% in the untreated group (RR 0.87, 95% CI 0.77 to 0.98). In the UK cohort at 4 years of follow up, the pattern was similar. The rate in the Kalydeco group was 18.6% compared with the rate in the untreated group of 29.1% (RR 0.64, 95% CI 0.49 to 0.84). This outcome was not reported in the other studies.

Body Mass Index

The impact of Kalydeco on BMI was measured by percent increase in BMI. BMI percent increase was higher in Kalydeco treated individuals in all studies where it was measured.[51,61,63] BMI percentage increase ranged from 1.9-3.6% in Kalydeco-treated individuals compared with 0.9-1.6% in comparator patients. The main outcome used in the trials was not percentage increase in BMI but rather absolute increase in BMI which was on average about 0.7 kg/m^2. Although the exact outcomes cannot be compared, the increase in BMI does appear to persist over longer term follow up.

Sweat Chloride Concentration

One US prospective study evaluated changes in sweat chloride concentration among individuals on CFTR modulators for at least 3 months. They report a reduction in sweat chloride concentration comparable to that seen in the clinical trials.[71]

Quality of Life

Only two studies reported on quality of life related to Kalydeco. Bell and colleagues conducted a cross-sectional study comparing users of Kalydeco with those receiving standard of care and awaiting Orkambi availability. Kalydeco users had improved scores on several aspects of the CFQ-R questionnaire, although this does not provide any long term evidence of the impact of quality of life outcomes.[58] McCormick and colleagues evaluated the impact of Kalydeco on chronic rhinosinusitis symptoms in patients with CF at 1, 2, and 6 month intervals. They found improvement in the

several dimensions measured on the SNOT (Sino-Nasal Outcome Test) questionnaire.[62] These included rhinologic, psychologic, and sleep related outcomes. How these compare over the long term with the QOL outcomes measured in the clinical trials is unclear.

Methodologic Concerns

Confounding by indication leading to selection bias is a significant concern in these observational studies. Patients receiving Kalydeco have gating mutations (predominantly Class III or IV) while those in the control groups have other mutations. As noted in the background, patients with one class of mutations often have different clinical manifestations than those with other mutation classes. For example, the prevalence and incidence of CFRD varies by mutation class (see Table 4.2 below).[72]

Table 4.2. CFRD Rates by Mutation Class

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

CFRD: Cystic Fibrosis related Diabetes

Using the observational data comparing patients on Kalydeco to those not on Kalydeco, Bessonova reported a 23% reduction in CFRD in the US Cohort (RR 0.77, 95% CI 0.70 to 0.84).[13] However, patients in the non-ivacaftor group predominantly (87.6%) had Class I or II mutations, which have a high incidence and prevalence of CFRD. Patients in the Kalydeco group predominantly (81.2%) had Class III mutations, which have a lower incidence and prevalence of CFRD. Thus, part of the difference in the incidence of CFRD is due to the differences in the distribution of mutation classes. Using data from Table 4.2 above, we estimate that the difference in CFRD expected due to the class distribution differences is 15% (RR 0.85),[13] which means that the estimated effect of Kalydeco would be a RR of 0.91 or a reduction of 9% rather than 23%. Similar concerns may explain some of the other results reported in the observational studies. For example mortality is markedly different by mutation class: 21.2 per 1,000 person-years for patients with Class II mutations compared to 7.8 per 1000 person-years for patients with Class IV mutations.[73] Pancreatic insufficiency, *P. aeruginosa* colonization, ppFEV$_1$, and sweat chloride levels also vary by mutation class.[73]

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

Key Findings: Orkambi and Symdeko both provided small but statistically significant improvements in absolute ppFEV$_1$ compared to placebo after 24 weeks of treatment; however, the magnitude of effect varies by age, dose, and baseline lung function. In longer-term follow-up (96 weeks), those on Orkambi had slower decline in ppFEV$_1$ than matched controls. Neither Orkambi nor Symdeko provided statistically significant short-term improvement in BMI or BMI-for-age z score compared with placebo. Both Orkambi and Symdeko provided improved respiratory-related quality of life compared with placebo. Orkambi and Symdeko reduced pulmonary exacerbation events over 24 weeks, including those requiring intravenous antibiotics and hospitalizations, compared with placebo. Indirect comparisons yielded no material differences between Orkambi and Symdeko in key clinical outcomes. In a four-week head to head trial with Symdeko, Trikafta had large improvements in ppFEV$_1$ and respiratory symptom-related quality of life compared with Symdeko. The differences between Trikafta and Symdeko were larger than those for either Orkambi or Symdeko compared with placebo.

We identified two randomized trials of Trikafta versus Symdeko in this population.[53,54] Our updated search did not identify any additional new RCTs for Orkambi or Symdeko in this population, but there were four updates of the RCTs for Orkambi[74-77] and two updates of RCTs of Symdeko.[78,79] In addition, the search identified four observational studies of Orkambi.[71,80-82] See Appendix Tables D1 to D15, Appendix F, and our prior report[11] for detailed analyses of the clinical trials of Orkambi and Symdeko in patients homozygous for the *F508del* mutation considered in the 2018 review.

The key studies from the prior review included four randomized controlled trials, one single-arm trial and one long-term, open-label extension study (see Table 4.3).[23,83-86] Two randomized trials of Orkambi (TRAFFIC and TRANSPORT) were analyzed together, with a subsequent open-label extension study.[23,85] Study findings are described by therapeutic comparison below and summarized in Table 4.3 below. This section of the report summarizes the randomized trial data for each treatment comparison, including the randomized trial covered in the prior report and the additional results published since the prior report. We then present the results of our network meta-analyses of the randomized trials. Finally, we summarize the new observational data for Orkambi in this population.

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

Trial, Study Design & Follow-Up duration	Age (N)	Absolute Difference in $ppFEV_1$, Percentage Points (95%CI)	Pulmonary Exacerbation, Rate Ratio (95%CI)	Difference in BMI, kg/m^2 (95%CI)	Difference in CFQ-R Respiratory Domain, points (95%CI)
Orkambi* vs. Placebo					
Ratjen 2017[83] **Randomized Controlled Trial** **24 weeks**	6-11 years (N=204)	**2.4 (0.4, 4.4)**	NR	−0.1 (−0.1, 0.3) *BMI z-score: 0.0 (−0.2, 0.2)*	2.5 (−0.4, 5.4)
TRAFFIC and TRANSPORT[23] **Randomized Controlled Trial** **24 Weeks**	≥12 years (N=1108)	**2.8 (1.8, 3.8)**	**0.61 (0.49, 0.76)**	**0.24 (0.11, 0.37)** *BMI z-score: NR*	**2.2 (0.0, 4.5)**
TRAFFIC and TRANSPORT[87] **(Extension Study vs Matched Controls)** **96 weeks**	≥12 years (N=2043)†	**42% slower rate of decline†**			
Orkambi Real World Registry Data					
French CF Registry[80] **Real world uncontrolled observational study** 52 weeks	≥12 years (n=845) 154 (18.2%) discontinued treatment during the 1st year	**+2.7 increase from baseline**	**IV antibiotic courses 1.18 year prior vs. 0.77, p<0.001, 35% reduction**	0.5 increase from baseline	NR

	641 (75.6%) received continuous treatment.				
Irish CF Registry[81] **Real world uncontrolled observational study** **52 weeks**	≥12 years (n=308) 66%≥18 years	**Adults 1.1 (0.4-1.8)** Adolescents 1.3 (-0.2 to 2.7) increase from baseline.	**Percent reduction in days of IV antibiotics compared with the prior year** **Adults 51% (48-53)** **Adolescents 43% (39-46)**	**Adults 0.43 (0.30-0.56)** **Adolescents BMI z-score 1.6 (0.8-2.3) increase from baseline**	NR
Australian CF Registry[82] **Real world controlled observational study** **52 weeks**	≥12 years with ppFEV1 <40% N=72 Orkambi, 43% discontinued N=30 age and sex matched controls with other mutations	No differences at any timepoint	**0.485 (0.32-0.74)**	NR	NR
Symdeko (100/500 mg) vs. Placebo					
EVOLVE[84] **Randomized Controlled Trial** **24 weeks**	Mean 26 years (N=504)	**4.0 (3.1, 4.8)**	**0.53 (0.34, 0.82)**	0.06 (−0.08, 0.20) *BMI z-score: 0.04 (−0.15, 0.07)*	**5.1 (3.2, 7.0)**
Network Meta-Analysis (Symdeko vs Orkambi)					
EVOLVE[84] vs. Tr/Tr[23]		1.2 (−0.1, 2.5)	0.87 (0.53, 1.42)		2.9 (0.0, 5.8)
EVOLVE[84] vs. Ratjen 2017[83] **Indirect comparison**				*BMI z-score: −0.04 (−0.29, 0.21)*	

Trikafta vs. Symdeko					
Heijerman 2019[53] **Randomized Controlled Trial** **4 weeks**	≥12 years (N=107)	**10.0 (7.4, 12.6)**	NR	**0.60 (0.41, 0.79)** *BMI z-score: NR*	**17.4 (11.8, 23.0)**
Keating 2018[54] – homozygous population **RCT** **29 days**	≥12 years (n=28)	**11.0 vs. 0.4**	**NR** **Percent of participants: 24% vs. 14%**	**NR**	**20.7 vs. 5.2**

Results in bold font are statistically significant.

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

* Data are presented for the now-approved dosages of lumacaftor (400 mg/day for children 6-11 years old and 800 mg/day for older patients).
† Open label extension study of TRAFFIC/TRANSPORT (n=455) compared with 1588 matched controls.

Orkambi Versus Best Supportive Care

Orkambi had modest, but statistically significant, improvements in lung function over 6 months compared to placebo. Both adults and adolescents 12 and older and children 6 to 11 years had net increases in $ppFEV_1$ of 2.8 (95% CI 1.8 to 3.8) and 2.4 (95% CI 0.4 to 4.4) percentage points compared to placebo.[23,83]

The respiratory domain of the quality of life measure CFQ-R was statistically significantly different in adolescents and adults between Orkambi and placebo (2.2 points; 95% CI 0.0 to 4.5), although this did reach the recognized minimal clinically important difference of 4.0.[21] A similar, though statistically non-significant effect was found in the trial of children (2.5 points; 95% CI -0.4 to 5.4).[83]

TRAFFIC/TRANSPORT reported a significant reduction in risk of pulmonary exacerbations among those taking Orkambi (rate ratio 0.61, 95% CI 0.49 to 0.76).[23] Similarly decreased rates of pulmonary exacerbations were found in the 96-week extension study (0.65 events/year, 95% CI 0.56 to 0.75).[87]

An additional report from the pooled TRAFFIC/TRANSPORT extension study reported that there was a reduction in the pulmonary exacerbation rate for patients treated with Orkambi even if they did not have an initial increase in $ppFEV_1$.[76] Specifically, the rate ratio was 0.53 (95% CI 0.40 to 0.69) for those with an change in $ppFEV_1>0$ and 0.74 (95% CI 0.55 to 0.99) in those with a change in $ppFEV_1\leq0$. This post-hoc analysis suggests that change in $ppFEV_1$ may not fully capture even the respiratory benefits of Orkambi.

The two new clinical trial results examined the long-term safety and efficacy of Orkambi in younger patients. The first reported 96 week outcomes for 239 patients 6 to 11 years of age.[88] Treatment was discontinued due to AEs in 3.8% of patients. No new safety concerns were identified. The initial improvements were sustained for the respiratory domain of the CFQ-R (+7.4 points), BMI (+1.8 kg/m^2), and sweat chloride (-22.9 mmol/L). The second study reported on 60 patients ages 2 to 5 years with Orkambi for 24 weeks.[77] Three patients (5%) discontinued treatment because of elevated liver enzymes. Sweat chloride levels decreased by 31.7 mmol/L and markers of pancreatic function improved. In addition, the BMI for age Z-score increased by 0.29 (0.14 to 0.45) over 24 weeks.

New Observational Studies of Orkambi

There is less long-term observational evidence available for Orkambi. The largest study, from French CF centers provides one year of follow up on 845 individuals using Orkambi. There was no comparison group.[80] Three additional reports in abstract form provide follow-up information from a registry in Ireland and from the US and Australia. Duration of follow up ranged from 12-23 months.[71,81,82]

Pulmonary Outcomes

In the French observational study, ppFEV$_1$% increased by 2.7% (±8.9).[80] In the Irish study, published in abstract form, the increase was 1.1%.[81] In the clinical trials of Orkambi, the ppFEV$_1$% increased by 4.6-5.4%. Limited observational follow up evidence suggests that long term use may be associated with a continued small increase in ppFEV$_1$%.

None of the studies reported on the rate of pulmonary exacerbations per patient per year. Wark et al reported a reduction in pulmonary exacerbations among Orkambi treated individuals (RR 0.49 (0.22, 0.74) although absolute rates were not reported Burgel and colleagues reported a reduction in IV antibiotic courses on Orkambi compared with before (0.77 per year compared with 1.18 per year), consistent with a 35% reduction.[80,82] In trials, the rate of pulmonary exacerbations were 0.7 to 0.8/48 weeks compared with 1.14/48 weeks in the placebo group. The longer term observational evidence although limited, suggests that the decrease in pulmonary exacerbations may persist.

Sweat Chloride Concentrations

One US prospective study presented as an abstract, evaluated changes in sweat chloride concentration among individuals on CFTR modulators for at least 3 months. They report a reduction in sweat chloride concentration among those on Orkambi comparable to that seen in the clinical trials.[71]

Symdeko Versus Best Supportive Care

The randomized trial of Symdeko in adolescents and adults reported modest but significant improvements in ppFEV$_1$ compared to placebo after 24 weeks (4.0%, 95% CI 3.1 to 4.8).[84] Symdeko resulted in a clinically and statistically significant improvement in the respiratory domain of CFQ-R (5.1 units; 95% CI 3.2 to 7.0) compared to placebo and significantly lower rate of pulmonary exacerbations (rate ratio 0.65; 95% CI 0.48 to 0.88). However, BMI and BMI z-score were not significantly different between drug and placebo (0.06 BMI units, [95% CI -0.08 to 0.20]; -0.04 z score units [95% CI -0.15 to 0.07]).

An abstract[79] reported the impact of Symdeko on domains of the CFQ-R other than the respiratory domain in the EVOLVE study. There were statistically significant improvements in the physical functioning, treatment burden, health perceptions, and vitality domains for Symdeko compared with placebo at 24 weeks. The improvement in the social functioning domain was of borderline clinical significance (1.5 points, 95% CI 0.0 to 3.0). The differences in role functioning, eating problems, emotional functioning, weight, digestive symptoms and body image domains were not significant.

The EXTEND trial followed 613 patients for a mean of 86 weeks primarily for safety.[78] SAEs related to treatment occurred in 2% of patients and 3 patients (0.5%) stopped treatment due AEs. No new safety concerns were identified. The pulmonary exacerbation rate per year was 0.72, which was similar to that observed in the EVOLVE trial (0.64). The respiratory domain of the CFQ-R and the improvement in $ppFEV_1$ remained stable.

Orkambi Versus Symdeko

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

Trikafta Versus Symdeko

As described above in the Key Studies section, we identified one pivotal head to head study comparing Trikafta to Symdeko in the population of patients who are homozygous for the *F508del* mutation.[53] Patients ages 12 years and older with a $ppFEV_1$ between 40% and 90% who were homozygous for the *F508del* mutation were eligible for the trial. All patients underwent a 4-week run in period with Symdeko. Then the investigators randomized 107 patients to Trikafta or continued treatment with Symdeko. The primary outcome was the absolute change in $ppFEV_1$ at 4 weeks. The study was of good quality. Approximately half of the participants were female, and the mean age was 29 years. Compared to Symdeko, the $ppFEV_1$ was 10.0 points higher at four weeks (95% CI 7.4 to 12.6, $p<0.001$). There were no differences in prespecified subgroups based on sex, age, baseline $ppFEV_1$, or prior CFTR modulator use. Quality of life as assessed by the respiratory domain of the CFQ-R was 17.4 points higher in the Trikafta group (95% CI 11.8 to 23, $p<0.001$). The trial was only 4 weeks long, but there was already a statistically significant change in BMI (0.60 kg/m2, 95% CI 0.41 to 0.79) in the Trikafta group compared with the Symdeko group. In addition, sweat chloride concentrations were 45.1 mmol/L lower (95 % CI 50.1 to -40.1, $p<0.001$). The rate of pulmonary exacerbations was not a primary or secondary outcome in the trial because of the short follow-up period. However, they were reported as AEs without statistical results (Trikafta 2%, Symdeko 12%). No patients in either group discontinued therapy due to AEs (0%). SAEs were higher in the Trikafta group (4% versus 2%). One serious AE (rash) was thought to be related to Trikafta.

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

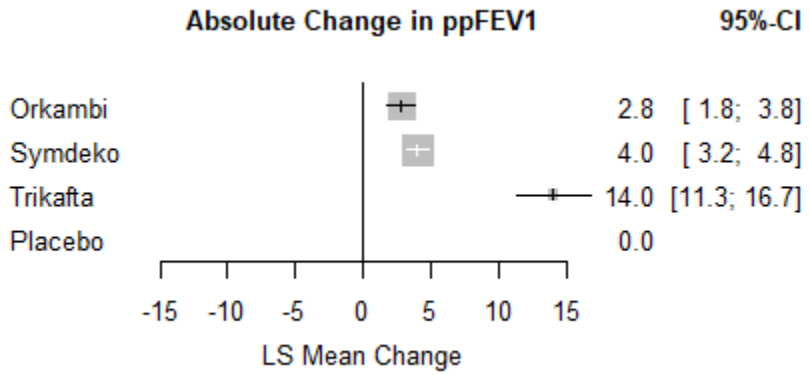
In addition, there was a small, Phase II randomized study of similar design that compared 21 patients on Trikafta to 7 patients on Symdeko following a four-week run in period on Symdeko.[54]

The study only reported within-group comparisons and no between-group comparisons. One patient in each group discontinued due to AEs. At 29 days, the $ppFEV_1$ increased by 11.0% (95% CI 7.9 to 14.0) in the Trikafta group versus 0.4% (95% CI -5.4 to 6.3) in the Symdeko group. Similarly, the respiratory domain of the CFQ-R improved by 20.7 points (95% CI 12.5 to 29.0) in the Trikafta group and 5.2 points (95% CI -9.5 to 19.9) in the Symdeko group. Finally, the sweat chloride levels decreased by 39.6 mmol/L (95% CI -45.6 to -33.8) in the Trikafta group and increased by 0.8 mmol/L (95% CI -9.3 to 11.0) in the Symdeko group. In the reported AEs there were 5 pulmonary exacerbations in the Trikafta group (24%) and 1 in the Symdeko group (14%). The primary limitations of this study are the small size of the trial, the short follow-up, and the lack of between group comparisons.

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

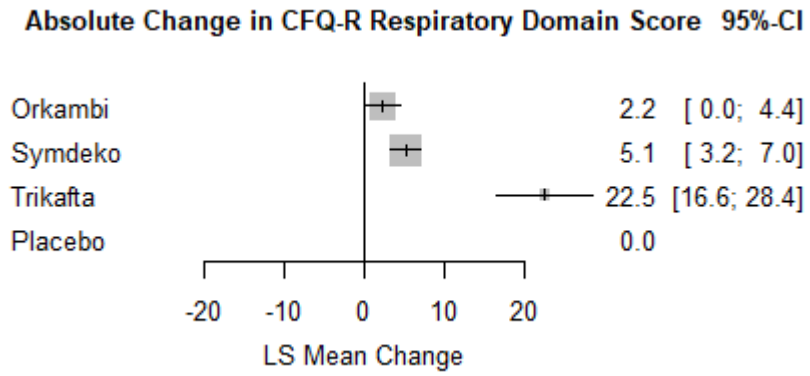
The forest plots for the network meta-analysis results comparing each of the three CF modulator therapies that have been studied in the same population illustrates the marked improvement of Trikafta compared with the other therapies. Additional results are reported in Appendix Tables D16-D18. In Figure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

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



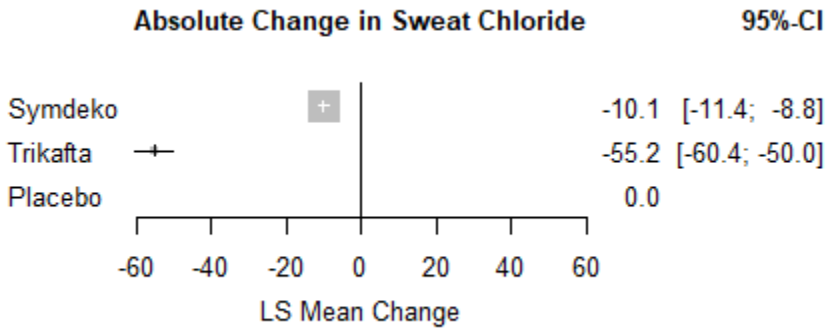
The results are similar for the respiratory domain of the CFQ-R (Figure 4.2). The improvements with Trikafta dwarf those of Orkambi and Symdeko.

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



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

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



There is less long-term observational evidence available for Orkambi. The largest study, from French CF centers provides one year follow up on 845 individuals using Orkambi. There was no comparison group.[80] Three additional reports in abstract form provide follow-up information from a registry in Ireland and from the US and Australia. Duration of follow up ranged from 12-23 months. [71,81,82]

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

Key Findings: Based on a single short-term (8 week) cross-over trial (EXPAND), Symdeko and Kalydeco both improved absolute and relative ppFEV$_1$ compared with placebo. Symdeko also improved ppFEV$_1$ more that Kalydeco. Clinically-important and statistically-significant improvements in respiratory symptom-related quality of life were observed for both Symdeko and Kalydeco compared with placebo. At 8 weeks, neither drug increased BMI nor reduced pulmonary exacerbations compared with placebo and each other, however; the follow-up duration was likely

too short to adequately evaluate these outcomes. Although there is currently no clinical trial evidence for Trikafta in this population, it should be at least as effective as Symdeko because Trikafta adds an additional modulator to Symdeko and when Trikafta was compared to Symdeko in patients homozygous for the F508del *mutation it significantly improved outcomes like ppFEV$_1$ and CFQ-R without causing any new AEs.*

Since our prior review, there is one new case series in children between the ages of 6 and 11 years in this population and one abstract reporting additional quality of life data from EXPAND that was not reported in the original publication.[91,92] See Appendix Tables D1-15, Appendix F, and our prior report[11] for detailed analyses of the clinical trials of Orkambi and Symdeko in patients heterozygous for the *F508del* mutation and a residual function mutation. A single trial, EXPAND, evaluated both Symdeko (100/300 mg daily) and Kalydeco (300 mg daily) monotherapy compared to placebo in patients heterozygous for the *F508del* mutation with a second mutation amenable to Symdeko. EXPAND was a crossover trial in which participants took one of the drugs for 8 weeks (n=234). Participants were 12 years or older with ppFEV$_1$ between 40% and 90%, and stable lung disease.[91]

Kalydeco and Symdeko

The primary results are summarized in Table 4.4 below. Compared to placebo, both interventions provided statistically significant improvements in ppFEV$_1$: 6.8 percentage points for Symdeko (95% CI 5.7 to 7.8) and 4.7 percentage points for Kalydeco (95% CI 3.7 to 5.8). Symdeko improved ppFEV$_1$ more than Kalydeco (absolute difference 2.1%; 95% CI 1.2 to 2.9). Symdeko and Kalydeco both yielded clinically and statistically significant improvements in quality of life using the CFQ-R respiratory domain score as compared to placebo (Symdeko 11.1 points, 95% CI 8.7 to 13.6; Kalydeco 9.7 points, 95% CI, 7.2 to 12.2), with no significant difference seen in comparisons between the two drugs. While taking either CFTR modulator, the rate of pulmonary exacerbations (11 and 9 events) was about half that observed while taking placebo (20 events), but the differences were not statistically significant.

In addition to the randomized trial data reported in Table 4.4, EXPAND reported subgroup differences in effects of Symdeko on ppFEV$_1$ based on age.[11] Those less than 18 years old showed a 12.0 percentage point improvement in absolute ppFEV$_1$ (95% CI 9.3 to 14.8), whereas those 18 years and older saw a 6.0 percentage point increase (95% CI 4.9 to 7.0); however, data should be interpreted with caution given only 11 patients under the age of 18 received Symdeko.

The new case series[90] included 9 children ages 6 to 11 years who were heterozygous for the *F508del* mutation and a residual function mutation. The remaining 61 participants were homozygous for the *F508del* mutation. The results are not reported separately by mutation status. The participants were followed for 24 weeks. The ppFEV$_1$ remained stable and in the normal range (from 91.1% to 92.0%) through 24 weeks. Compared to baseline, there was a decrease in sweat chloride levels (-14.5 mmol/L, 95% CI -17.4 to -11.6) and a small improvement in the respiratory domain of the CFD-

R (3.4 points, 95% CI 1.4 to 5.5). As described above in the homozygous population, the AEs were similar to those in older patients with CF and only 1 patient discontinued therapy due to an AE (constipation).

The new abstract[89] reported that patients on Symdeko had significant improvements in the following domains of the CFQ-R: health perceptions, vitality, physical functioning, role functioning, social functioning, weight, treatment burden and emotional functioning compared with placebo.

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

There are no studies evaluating the efficacy and safety of Trikafta in this population. However, Trikafta is Symdeko plus another modulator, elexacaftor, and it primarily targets the abnormal protein formed by the *F508del* mutation. Unless elexacaftor interferes with the mechanism of action of ivacaftor and/or tezacaftor or introduces new, significant AEs, Trikafta should be at least as effective as Symdeko. In fact, we have evidence that Trikafta is more effective than Symdeko in a randomized trial of patients homozygous for the *F508del* mutation (Population 2, results described above).[53] In that population, the effect size on ppFEV$_1$ and the respiratory domain of the CFQ-R for Trikafta compared with Symdeko was much larger than that of Symdeko versus placebo in the same population. Furthermore, there was no evidence that the addition of elexacaftor introduced new AEs. Thus, despite the lack of clinical trial evidence in this population, we expect Trikafta to be at least as effective as Symdeko for patients heterozygous for the *F508del* mutation and a residual function mutation.

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

Trial Study Design Follow-Up	Age (N)	Absolute Diff. in $ppFEV_1$, (95%CI)	Pulmonary Exacerbation, Rate Ratio	Difference in BMI, kg/m^2	Difference in CFQ-R Respiratory Domain, points (95%CI)
EXPAND[91] 8 weeks (cross-over)	≥12 years (N=234)	**Symdeko (100/300 mg) vs. Placebo**			
		6.8 (5.7, 7.8)	0.54 (0.26, 1.13)	0.34 vs. 0.18 (NR*)	**11.1 (8.7, 13.6)**
		Kalydeco (300 mg) vs. Placebo			
		4.7 (3.7, 5.8)	0.46 (0.21, 1.01)	0.47 vs. 0.18 (NR*)	**9.7 (7.2, 12.2)**
		Symdeko (100/300 mg) vs. Kalydeco (300 mg)			
		2.1 (1.2, 2.9)	1.18 (0.49, 2.87)	0.34 vs. 0.47 (NR*)	1.4 (−1.0, 3.9)

Results in bold font are statistically significant.

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

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

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

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

There are two randomized clinical trials of Trikafta in this population[52,54] and no observational studies. See Appendix Tables D1- D12 for details of the randomized trials. The key findings are summarized in Table 4.5 below and described below. We reported the results for the FDA approved dose of Trikafta only in the dose-ranging Phase II study.[54]

In the pivotal trial, patients ages 12 years and older with a ppFEV$_1$ between 40% and 90% who have the *F508del* mutation and a minimal function mutation were eligible for the trial.[52] The investigators randomized 403 patients to Trikafta or identical placebo pills. The primary outcome was the absolute change in ppFEV$_1$ at 24 weeks. The study was of good quality. Approximately half of the participants were female, and the mean age was 26 years. Compared to placebo, the ppFEV$_1$ was 13.8 points higher at four weeks and 14.3 points higher at 24 weeks ($p<0.001$ for both comparisons). There were no differences in prespecified subgroups based on sex, age, baseline ppFEV$_1$, or region. The rate of pulmonary exacerbations was 63% lower in the Trikafta group (RR 0.37, 95% CI 0.25 to 0.63). Quality of life as assessed by the respiratory domain of the CFQ-R was 20.2 points higher in the Trikafta group ($p<0.001$) and sweat chloride concentrations were 41.8 mmol/L lower ($p<0.001$).

This good-quality trial demonstrated a marked improvement in pulmonary function and respiratory quality of life through 24 weeks of follow-up with Trikafta compared to placebo, with a good safety profile.[52] The primary limitation of the study is its relatively short follow-up time.

The Phase II, dose ranging, randomized study compared three different doses of elexacaftor added to Symdeko to placebo in 65 patients.[54] We report here only the results from the group who received the FDA-approved dose (200 mg elexacaftor, n=21) and the placebo group (n=12). The study only reported within-group comparisons and no between-group comparisons. There were no SAEs and no discontinuations due to AEs for patients in the Trikafta group during the 29 day trial. There was a significant increase in ppFEV$_1$ compared to baseline for the Trikafta group (13.8%, 95% CI 10.9 to 16.6), but not in the placebo group (0.0%, 95% CI -3.9 to 4.0). Similarly, there was a significant increase in the respiratory domain of the CFQ-R compared to baseline for the Trikafta group (25.7 points 95% CI 18.3 to 33.1), but not in the placebo group (4.2 points, 95% CI -5.6 to 14.0). Finally, there was a significant decrease in sweat chloride levels compared to baseline for the Trikafta group (-39.1 mmol/L, 95% CI -44.9 to -33.3), but not in the placebo group (0.0%, 95% CI -3.9

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

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

Trial Study Design Follow-Up	Age (N)	Absolute Diff. in $ppFEV_1$, % (95%CI)	Pulmonary Exacerbation, Rate Ratio (95%CI)	Diff. in BMI, kg/m^2	Diff. in CFQ-R Respiratory Domain, points (95%CI)
Trikafta vs. Placebo					
Middleton 2019[52] **Randomized Controlled Trial** **24 weeks**	≥12 years (N=403)	**14.3 (12.7 to 15.8)**	**0.37 (0.25 to 0.55)**	**1.04 (0.85 to 1.23)**	**20.2 (17.5 to 23.0)**
Keating 2018[54] **RCT** **29 days**	≥12 years (n=33)	**13.8 vs. 0.0**	**NR** **10% vs. 33%**	**NR**	**25.7 vs. 4.2**

Results in bold font are statistically significant.

95%CI: 95% Confidence Interval, BMI: body mass index, CFQ-R: Cystic Fibrosis Questionnaire-Revised, Diff: difference between Kalydeco and placebo, kg: kilogram, m^2: square meter, NR: not reported, $ppFEV_1$: predicted percent forced expiratory volume in one second

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

Harms

For all three CFTR modulators approved prior to Trikafta, harms were mild and generally uncommon. A detailed description of the AEs can be found in our prior report.[11] They are summarized here along with the results for Trikafta.

SAEs, as defined by the studies, commonly occurred at the same or *lower* rates among those taking the CFTR modulators, including Trikafta, than those taking placebo, including AEs ascribed to the drugs. No deaths during CFTR modulator trials were related to the drugs. However, reasons for CFTR modulator discontinuation included elevated liver enzymes, creatinine kinase levels, hemoptysis, bronchospasm, dyspnea, pulmonary exacerbation, and rash. Rash was the only SAE ascribed to Trikafta and that patient did not discontinue therapy.

From the prior report, the summary (i.e., meta-analyzed) rates of discontinuation due AEs in the randomized trials were:

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

In the two pivotal trials of Trikafta[52,53] the discontinuation rates due to AEs were 1.0% (2/202 over 24 weeks) and 0% (0/55 over four weeks).

Chest tightness ("abnormal respiration"), particularly with Orkambi, was noted by patients and clinicians, however, the AE was only sparsely reported in the literature. This appears to be more common in patients with lower baseline $ppFEV_1$.[92] A real-world cohort study reported that nearly 20% of patients reported chest tightness with Orkambi.[93]

Uncertainty and Controversies

A major source of uncertainty is the complexity of CF genetics, which directly affects disease severity and progression. Each population that we reviewed has genetic and disease variability within members of the population, which means that clinical trial outcomes from relatively small samples over short periods of time may not accurately capture the clinical benefits and harms for patients.

$ppFEV_1$ is a surrogate measure of CF disease severity. Despite its wide use in clinical trials and clinical practice, both the absolute $ppFEV_1$ level and changes in $ppFEV_1$ cannot fully capture disease severity or the clinical impact of modulator therapy. Furthermore, the impact of an absolute increase of 5% in a patient with a baseline ppFEV1 of 40% likely differs from that of a 5% increase in a patient with a baseline of 90%.

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

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

Evaluating the AE data in studies of people with CF is challenging because the most frequently reported events are adverse outcomes due to the underlying disease (for example, pulmonary exacerbations) and not side effects of the therapy. Thus, SAE were often more common in the placebo group than in the modulator therapy group, which is paradoxical.

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

4.4 Summary and Comment

Population 1: Patients Eligible for Kalydeco

Given the consistent evidence in randomized trials and observational studies up to 5 years of improved lung function and clinically significant improvements in pulmonary exacerbations and quality of life, with no evidence of significant harms, we have high certainty Kalydeco provides a substantial (moderate-large) net health benefit relative to best supportive care. We therefore assign a rating of "superior" (A) to the comparative clinical effectiveness of Kalydeco in this population (Table 4.t below).

Population 2: Homozygous for the *F508del* Mutation

Orkambi for Patients With Cystic Fibrosis Caused by Two Copies of the F508del Mutation

In two large Phase III trials, an accompanying 96-week open-label extension study, and additional real-world observational studies Orkambi provided a consistent 3% improvement in $ppFEV_1$ as well as a reduced rate of decline in lung function over time. However, patients also reported drug-drug interactions and side effects leading to discontinuation. Thus, for patients homozygous for the *F508del* mutation, we have high certainty Orkambi provides a small net health benefit relative to placebo (i.e. best supportive care), and therefore assess the evidence to be "incremental" (B).

Symdeko for Patients With Cystic Fibrosis Caused by Two Copies of the F508del Mutation

A single, parallel-arm, Phase III trial demonstrated a moderate improvement in $ppFEV_1$ compared with placebo. However, the trial was relatively short in duration (24 weeks). For patients homozygous for the *F508del* mutation, we have moderate certainty that Symdeko provides a small or substantial net health benefit, with high certainty of at least a small net health benefit relative to placebo (i.e., best supportive care). Therefore, we assess the evidence to be "incremental or better" ("B+").

Trikafta for Patients With Cystic Fibrosis Caused by Two Copies of the F508del Mutation

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

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

Symdeko for Patients With Cystic Fibrosis Caused by One Copy of the F508del Mutation and a Second Mutation Amenable to Symdeko

A single 8-week cross-over trial provided demonstrated clinically-significant improvement in lung function compared with placebo. Long-term studies to confirm these data are required. For patients heterozygous for the *F508del* mutation with an approved residual function mutation, we have moderate certainty that Symdeko provides a small or substantial net health benefit, with high certainty of at least a small net health benefit relative to placebo (i.e., best supportive care). Therefore, we assess the evidence to be "incremental or better" ("B+").

Trikafta for Patients with Cystic Fibrosis Caused by One Copy of the F508del Mutation and a Second Mutation Amenable to Symdeko

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

Population 4: Heterozygous F508del With a Minimal Function Mutation

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

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

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

BSC: Best supportive care

5. Long-Term Cost Effectiveness

5.1 Overview

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

We updated previously developed *de novo* microsimulation models to capture improvements in both quality of life and length of life. CF affects many organ systems, though most of its morbidity and mortality are associated with its impact on the respiratory system. While the quality-of-life impacts of the disease will be captured to some degree by the quality-of-life measures used in the model, it is important to note that economic models such as the ones used in this analysis cannot capture the full range of quality-of-life effects associated with the disease, or the improvements in quality of life experienced by CF patients taking CFTR modulator therapy. Two of the treatments for CF, Kalydeco and Symdeko, fall under ICER's framework for therapies for ultra-rare diseases (Kalydeco and Symdeko). Therefore, we considered dual base-case analyses that reflect both health system and societal perspectives if the impact of the treatment on patient and caregiver productivity, education, disability and nursing home costs are large relative to health care costs. For scenarios where the ultra-rare framework did not apply (i.e., Trikafta, which has an eligible patient population of greater than 10,000 individuals), productivity losses and other indirect effects were considered in a scenario analysis.

Outcomes were estimated over a lifetime time horizon from treatment initiation until death. The primary health outcome was quality-adjusted life years (QALYs) but we also report life expectancy in life years (LYs), equal value life years gained (evLYGs) and the lifetime number of acute pulmonary exacerbations. QALYs are a measure that combines both length of life and quality of life into a single measure, and are the recommended metric for use in cost-effectiveness analyses.[94] The impact inventory is provided in Appendix Table E1. Costs and health outcomes were discounted

at 3% per year in the base-case analysis; undiscounted results are presented in Appendix Table E2. The models were developed in TreeAge software version 2018 (Williamstown, MA).

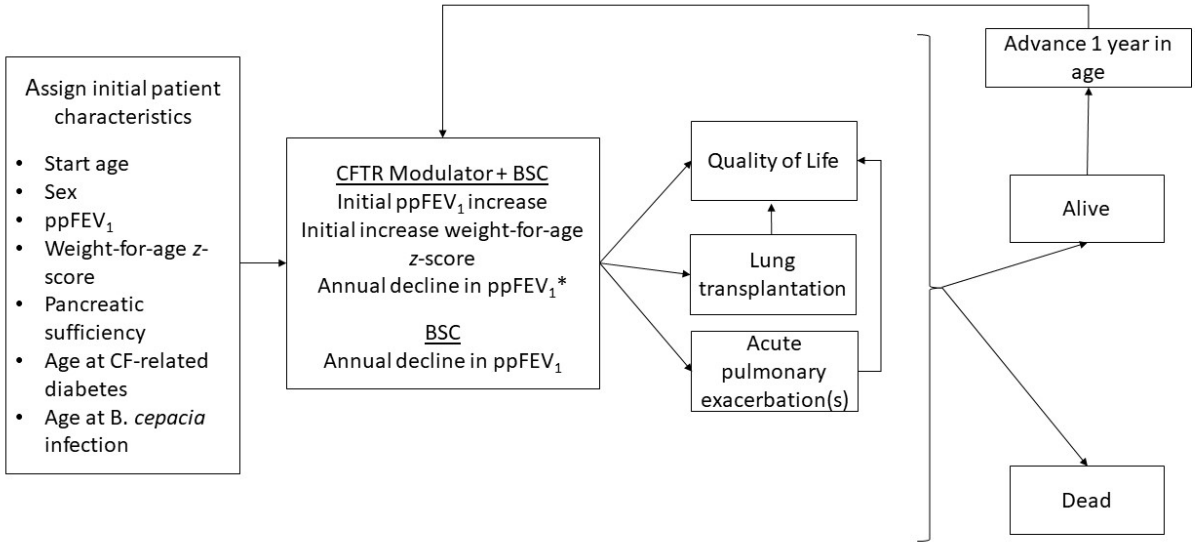
5.2 Methods

Model Structure

The primary model variable was $ppFEV_1$, modeled as a continuous variable. A microsimulation model was chosen to account for the continuous nature of $ppFEV_1$ and to capture the primary effect of the CFTR modulator drugs (i.e., increase in $ppFEV_1$ or slowing the decline of $ppFEV_1$ over the longer term). For each population, a 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.[5] 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 (representing those patients who are candidates for Kalydeco) 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).[64,65] 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 CFRD 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 CFRD or *B. cepacia* infection, or undergo lung transplantation if their $ppFEV_1$ falls to 30% or below. The annual risk of death is influenced by all of these variables. Figure 5.1 shows a diagram of the model, with the risk of pulmonary exacerbation and lung transplantation dependent on the $ppFEV_1$ value. Persons are simulated for their lifetime, accumulating life years, QALYs (i.e., life years weighted by a quality-of-life value) and costs each year.

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

Figure 5.1 Model Framework



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

Target Populations

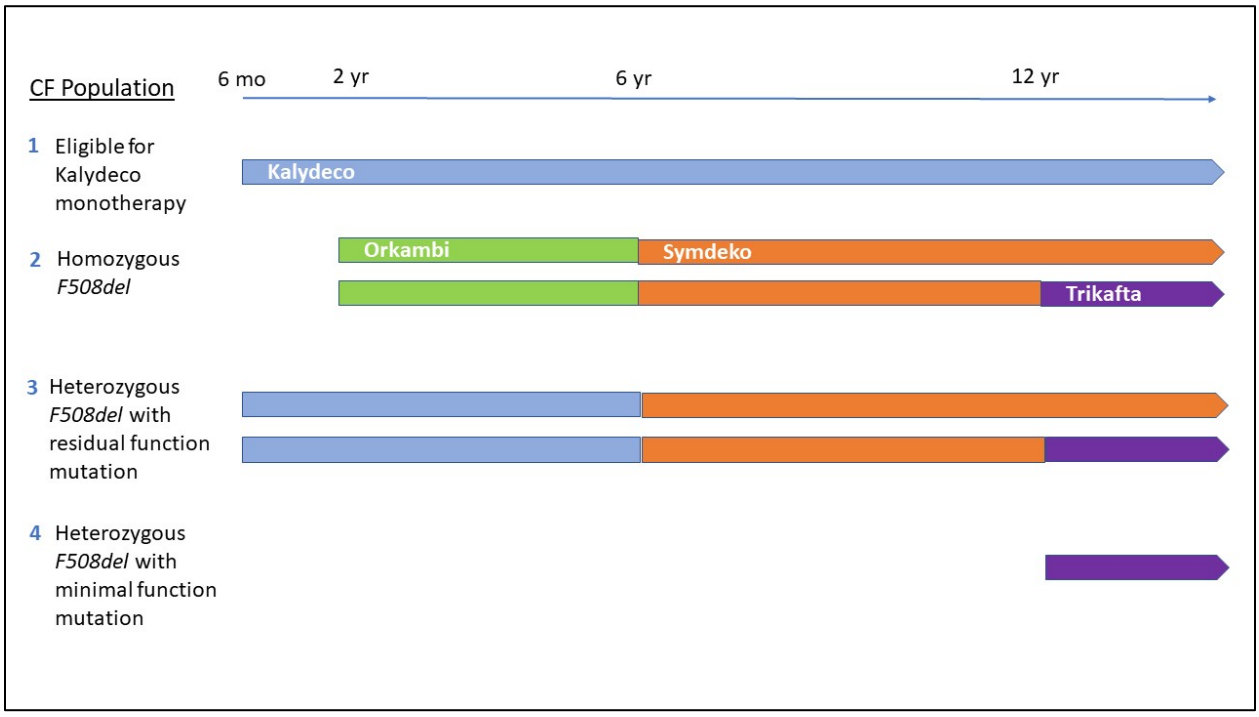
We evaluate four possible therapeutic options for four CF populations as follows. Some analyses were updates of our prior analysis[11] and some were new, as noted below.

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

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

Because the recommended start age varies by drug, we model sequential drugs in relevant populations (Figure 5.2). For example, for patients who are homozygous for the *F508del* mutation we assume that all patients on a CFTR modulator strategy will start with Orkambi at age 2 and then switch to Symdeko at age 6. Patients assigned to Trikafta therapy will switch to this therapy at age 12. At switching we will allow for an improvement in lung function based on the difference between the two drugs and will allow this improvement to be constant for two years.

Figure 5.2 Schematic of the CFTR Modulator Strategies



The target populations vary in terms of their prognosis.[95] On average, CF patients who are homozygous for *F508del* or have two minimal function mutations (such as *F508del*) have a more severe prognosis than patients with one or no minimal function mutation. McKone et al. classified patients into high-risk and low-risk groups based on the effects of the functional class of their phenotype.[95] They found that the median age of death was much younger for the high-risk genotypes (24.2 years vs. 37.6 years). Sawicki et al. showed that *F508del* homozygous patients had a faster rate of decline in their lung function compared with patients with a residual function mutation heterozygous for *F508del*.[96] We adjusted the lung function declines in our model to represent these different subgroups of patients. In general, individuals heterozygous for the

F508del mutation with a residual function mutation have a better prognosis, and have a higher percentage with pancreatic sufficiency.[93,99]

We assumed that best supportive care consists of the following pulmonary and pancreatic therapies (percent utilization overall): dornase alfa (91.9%), inhaled tobramycin (70.2%), inhaled aztreonam (43.3%), azithromycin (64.2%), hypertonic saline (73.4%), oxygen (10.8%), non-invasive ventilation (3.2%), pancreatic enzyme replacement therapy (84.9%) and supplemental feeding (tube or oral, 54.6%).[5] Individuals with CF-related diabetes were assumed to require oral hyperglycemic agents (4.0%), intermittent insulin (6.1%) and chronic insulin (73.2%), and to require diabetes-specific follow-up care (e.g., HbA1c measurements). We assumed that best supportive care applied to all individuals, whether on CFTR modulators or not, but that the intensity of therapy varied by lung function category. In addition, we allowed the intensity of best supportive therapy to be reduced by Trikafta independent of lung function in a scenario analysis. Acute pulmonary exacerbations were defined as those that involve treatment with IV antibiotics either in the hospital or with home treatment. We estimated disease management costs for all individuals with CF, including annual clinic visits and all other costs except those for acute pulmonary exacerbations and lung transplantation; the disease management costs varied by level of $ppFEV_1$. Acute pulmonary exacerbations and lung transplantation were costed separately. The rationale for this approach was that the disease management costs for a given level of $ppFEV_1$ will be the same for patients in both arms (modulator therapy vs. no modulator therapy). Disease management costs will vary as individuals who live longer will have higher management costs, although individuals on modulator therapy will also have better lung function, resulting in reductions in these costs. There are likely other reductions in costs related to fewer sinus or abdominal surgeries. Although we do not have direct evidence on these reductions, we evaluate the potential impact on disease management costs in a scenario analysis.

Treatment Strategies

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

Key Model Characteristics and Assumptions

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

Table 5.1. Key Model Assumptions

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

Model Inputs

Clinical Inputs

We modeled the $ppFEV_1$ trajectories through age-specific annual declines.[100,101] To match the mean $ppFEV_1$ values observed in the drug trials, we allowed the decline for ages under nine to be slightly higher than reported in the literature for CF individuals with a gating mutation (representing those patients who are candidates for Kalydeco), who are homozygous for the *F508del* mutation, or who are heterozygous for the *F508del* mutation with a minimal function mutation. The annual risk of having acute pulmonary exacerbation was modeled as a function of $ppFEV_1$, age, and the number of acute pulmonary exacerbations the previous year.[99-101] The annual risk of lung transplant was 0% for individuals with $ppFEV_1$ >30% as per guidelines.[102] The annual risk of diabetes was modeled as a function of age, sex, and mutation class.[72] CF patients who are homozygous for the *F508del* mutation, or who are heterozygous for the *F508del* mutation with a minimal function mutation had the highest annual risk of CFRD, and patients who are heterozygous for the *F508del* mutation with a residual function mutation had the lowest risk. We assumed that 5% of CF individuals who are candidates for Kalydeco, who are homozygous for the *F508del* mutation, or who are heterozygous for the *F508del* mutation with a minimal function mutation had pancreatic sufficiency at diagnosis and that this proportion was stable over lifetime.[103] 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.[91] 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.[104] The risk of *B. cepacia* infection over time was derived from age-specific prevalence values from the CF Foundation Registry and does not depend on lung function severity. [5] Base-case values are listed Table 5.2.

Table 5.2. Key Model Inputs

	Baseline Value	Source
Annual Decline in $ppFEV_1$		
Age 6-8 years (applied to age 0-6 years)	-1.12 (-2.00 for gating or *F508del* homozygous or *F508del* heterozygous with minimal function mutation*)	Konstan, 2007;Konstan, 2012[100,101]
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[102,103]
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[101]
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[99]
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[105]
$ppFEV_1$ ≤30	0.647	
Annual Risk of CF-Related Diabetes (Male, Female) x (Pop 2&4 / Pop 1 / Pop3)		
Age 0-9	0.008, 0.016 / 0.006, 0,013 / 0.002, 0.004	Adler, 2008[72]
Age 10-19	0.039, 0.060 / 0.031, 0.048 / 0.009, 0.014	
Age 20-29	0.049, 0.071 / 0.039, 0.057 / 0.011, 0.016	
Age 30-39	0.065, 0.072 / 0.052, 0.058 / 0.015, 0.016	
Age 40+	0.051, 0.029 / 0.041, 0.023 / 0.012, 0.007	

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

Clinical Probabilities/Response to Treatment

To model the treatments' effects, we assumed that there is an immediate increase in $ppFEV_1$ and improvement in weight-for-age *z*-score (with the exception of patients who are heterozygous for the *F508del* mutation with a residual function mutation), as observed in the trials or by assumption if no trial evidence existed (Table 5.3). When a person switches drugs we assumed that they

experience the net increase in $ppFEV_1$ between the two drugs (Table 5.3). The improvement in lung function will decrease the risk of experiencing pulmonary exacerbations and ultimately lung transplantation, increase a person's HRQOL, and decrease mortality risk. We also incorporated an additional decrease in the risk of pulmonary exacerbation, independent of the effect of lung function improvement in order to be consistent with the reported risk ratios from the clinical trials. We modeled various assumptions about the treatment effect beyond the time horizon of the trials: 1) no $ppFEV_1$ decline as long as the patient is on drug, 2) no $ppFEV_1$ decline on drug for 2 years and then a decline that is 50% of the standard care rate thereafter, 3) no $ppFEV_1$ decline on drug for 2 years and then a decline that is equal to the standard care rate thereafter. We used the second assumption in the base-case analysis, where 50% is in the range of the CFTR modulator effect on lung function decline.[109,110] We assumed that same long-term effect for all CFTR modulator drugs, even though they had different initial effects on $ppFEV_1$. This was because of a lack of evidence on long-term effectiveness and because the estimates of decline with Kalydeco and Orkambi – two CFTR modulator with very different initial $ppFEV_1$ effects – had very similar long-term effect estimates (47% of standard of care rate for Kalydeco and 42% of standard of care rate for Orkambi).[85,106] We assumed that the increase in weight-for-age *z*-score would persist for a patient's lifetime.[56,106]

The drug trials reported reductions in acute pulmonary exacerbation rates (e.g., rate ratios). When available we used the rate ratios for acute pulmonary exacerbations that required IV antibiotics. We assumed that part of the decline in number of acute pulmonary exacerbations was due to the increase in $ppFEV_1$. However, we also allowed for an independent effect of the drugs on reducing the acute pulmonary exacerbation rates. For example, the rate ratio for Kalydeco plus best supportive care versus best supportive care alone was 0.56.[64] The model-generated rate ratio for a population similar to STRIVE was 0.83 when we assumed that the decline in acute pulmonary exacerbations with drug was only due to the increase in $ppFEV_1$. We assumed that Kalydeco also had an independent effect on the reduction in acute pulmonary exacerbations by reducing the chance that an individual will experience an exacerbation and reducing the number of multiple acute pulmonary exacerbations among those patients experiencing at least one exacerbation. We varied these assumptions until the model-generated rate ratio was 0.56. The independent effect from Kalydeco for individuals with CF 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 5.3. Treatment Effectiveness Inputs

	Increase in $ppFEV_1$ (Mean, 95% CI)	Acute Pulmonary Exacerbation RR	Change in Weight-For Age *Z*-Score (Mean, 95% CI)*	Source
Population 1 - Eligible for Kalydeco Monotherapy				
Kalydeco	10.0 (4.5-15.5)	0.56	0.35 (0.20-0.51)	Davies, 2013;Ramsey, 2011;Borowitz, 2016;McKone, 2014[64,65,70,104]
Population 2 - Homozygous for the *F508del* Mutation				
Orkambi (ages 2-5)	2.8 (1.8-3.8)	0.44	Same as above (assumed)	Wainwright, 2015;Konstan, 2017;Taylor-Cousar, 2017; NICE, 2016; Heijerman, 2019[23,53,84,85,107,108]
Symdeko	4.0 (3.1-4.8)	0.54†	Same as above	
Symdeko vs. Orkambi	1.2*			
Trikafta vs. Symdeko	10.0	NR	Same as above (assumed)	
Population 3 - Heterozygous *F508del* with Residual Function Mutation				
Kalydeco	4.7 (3.7-5.8)	0.46 (0.21-1.01)‡	0 (assumed)	Rowe, 2017[91]
Symdeko	6.8 (5.7-7.8)	0.54 (0.26-1.13)‡	0	
Symdeko vs. Kalydeco	2.1 (calculated)		0	
Trikafta	13.8 (assumed same as for Pop 4)		0	
Trikafta vs. Symdeko	7.0 (calculated)		0	
Population 4 - Heterozygous *F508del* with Minimal Function Mutation				
Trikafta	14.3	0.37	BMI effect reported	Middleton, 2019[52]

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

†Rate ratio (RR) is for 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 [109] 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.[110] 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*[111], 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[110]:

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

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

The patient-specific parameters that affect mortality among non-transplanted patients were *SEX* (0 male, 1 female), *ppFEV₁* (%), *WFA* (weight-for-age *z* score), *#PE* (number of acute pulmonary exacerbations in the current year), *DIAB* (0 no diagnosis of diabetes, 1 yes), *PS* (0 no pancreatic sufficiency, 1 yes), *BAI* (0 no *B. cepacia* infection, 1 yes). The age-specific baseline hazard (b_a) was a product of the age-specific rates from the US life tables [109] 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.[105]

Utilities

We used the linear interpolation of EQ-5D utilities by $ppFEV_1$ conducted by Schechter et al. (Table 5.4).[112] These utilities were used to weight each year of life to accumulate QALYs over an individual's lifetime. The extrapolation was based on EQ-5D values estimated for $ppFEV_1$ groups (0.86 for >70%, 0.81 for 40%-69%, and 0.64 for <40%) among cystic fibrosis patients provided to Tappenden et al. for a NICE economic evaluation.[113] Because we modeled $ppFEV_1$ as a continuous variable, we used a linear function to assign utilities based on $ppFEV_1$ (utility = 0.593047 + $ppFEV_1$*0.003476). We used similar assumptions as Tappenden et al. and applied a short-term utility decrement of 0.17 during the year in which an acute pulmonary exacerbation occurred.[113] We used the same utility used by Schechter et al.[112] for the first year after lung transplantation (0.32) based on quality of life study of lung transplantation in patients with cystic fibrosis.[114] Subsequent years after transplantation were set to a utility equivalent to a $ppFEV_1$ of 70%-79%: 0.838.

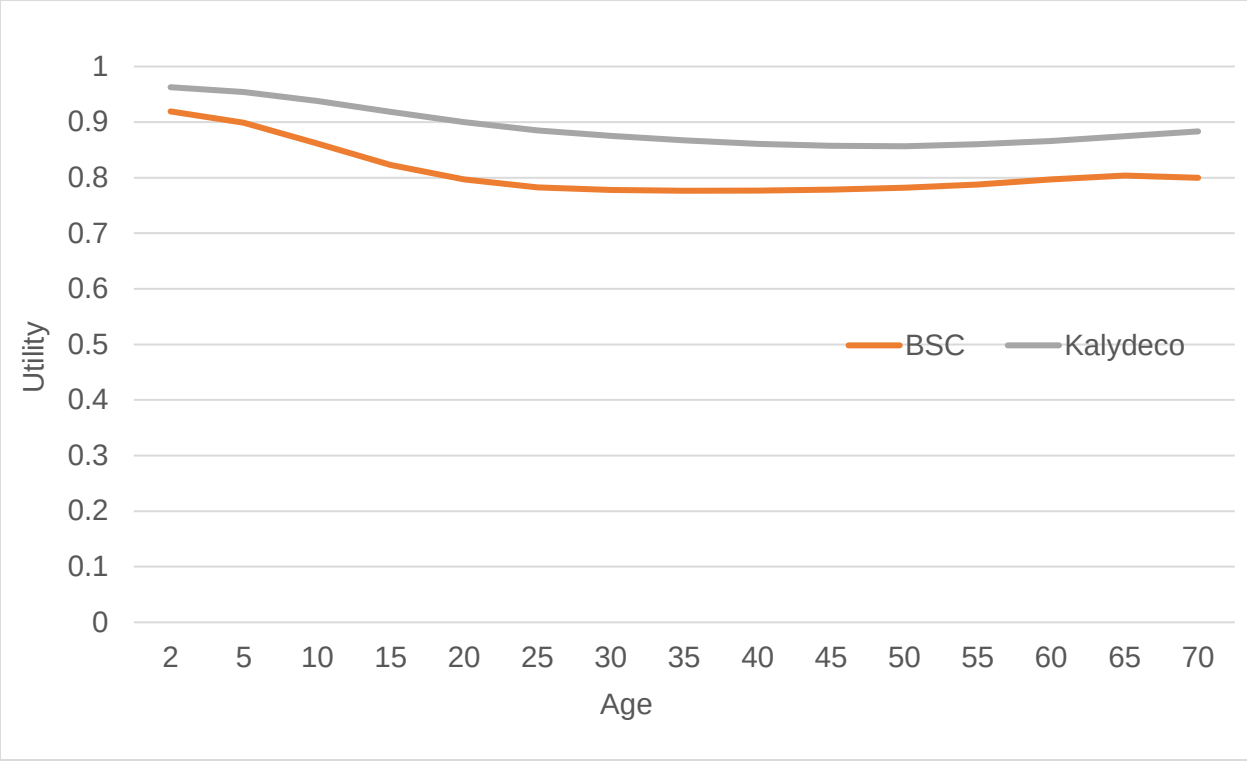
Table 5.4. Utility Values by Level of $ppFEV_1$ (Derived from Schechter et al.)

$ppFEV_1$ (%)	Utility
>90	0.920
80-89	0.873
70-79	0.838
60-69	0.801
50-59	0.765
40-49	0.729
30-39	0.692
20-29	0.653
<20	0.625

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

As validation for using these utility estimates, we simulated a cohort of patients treated with Kalydeco compared with a group receiving best supportive care only. Each year of the simulation, we calculated the mean EQ-5D utility among those simulated people who were still alive and had not undergone lung transplantation. We compared the simulated mean utilities to a study conducted by Bell et al. who compared HRQOL measures between cystic fibrosis patients with a *G551D* mutation who were treated with Kalydeco and patients homozygous for the *F508del* mutation who were treated with standard of care alone.[58] The mean age of patients who participated in the study was 23.9 years in the Kalydeco group and 24.6 years in the standard of care group.[58] Patients in the Kalydeco treatment group had a significantly greater mean EQ-5D score than patients in the standard of care treatment group (0.90 vs. 0.81, $p < 0.01$).[58] In our validation exercise we found that, at age 25, modeled patients on Kalydeco plus BSC and BSC alone had mean utility values of 0.88 and 0.78, respectively (Figure 5.3).

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



Adverse Events

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

Economic Inputs

Drug Acquisition Costs

Annual net drug acquisition costs for each medication were used in the model. We could not calculate net prices for all drugs using our standard source (SSR Health, LLC), as this source did not include consistent publicly-disclosed net sales figures for the specialty drugs in this review. In addition, there was no discount for the Federal Supply Schedule (FSS) prices, so we used wholesale acquisition cost (WAC) as net prices (Table 5.5).[115] The FSS is a price schedule set forth by the US General Services Administration (GSA) that is used in negotiation with manufacturers of drugs, medical equipment, and supplies and service contracts for the VA and other federal organizations. As Trikafta was only recently approved by the FDA, information on its net pricing is not yet

available; we assumed its net pricing will be as for the other CFTR drugs, and used the WAC in our analyses. Lower doses (for younger patients) have the same FSS price as adult doses, so no age adjustments were done. We assumed that there were no additional costs associated with the administration and monitoring of the CFTR drugs above best supportive care.

Table 5.5. Drug Cost Inputs

Intervention	WAC per Day*[116]	Annual Drug Cost
Kalydeco	$853.40	$311,704
Orkambi	$746.40	$272,623
Symdeko	$800.00	$292,200
Trikafta	$853.50	$311,741

*WAC as of December 2, 2019
†Costs for dosing for ages 2-5

Some prior cost-effectiveness analyses in CF have attempted to account for possible price changes over time, by assuming that the drug prices will decrease upon loss of patent exclusivity.[103,122,123] For example, Dilokthornsakul et al. assumed that the prices of Kalydeco and Orkambi would drop to 10% of WAC after patent expiration.[122,123] We chose not to make such an assumption in our current analysis, because attempts to model price changes over time would add an additional layer of uncertainty and speculation to our analysis, and while there have been calls to include price changes in cost-effectiveness analysis, the current convention is not to include estimates of changes in drug price throughout the life cycle.[124,125] The assumption of a large price drop at patent expiry was considered to be a limitation and not appropriate In CADTH's Common Drug Reviews of the economic models submitted for Kalydeco and Orkambi, and was not recommended as a base case assumption for the UK NICE appraisal committee's assessment of Orkambi.[38-41,121] Estimating such changes may be especially difficult in the US market, where drug prices are mostly unregulated, and changes in prices occur relatively frequently. The timing of entry of other competitors (branded or generic) is difficult to predict, due to the possibility of patent litigation and "pay for delay" agreements. Generic drugs are generally expected to have discounted pricing relative to branded competitors, but the size of that future discount is difficult to estimate, particularly for rare diseases with limited to no competition. This was seen, for example, with the introduction of a new generic version of trientine hydrochloride (Syprine®), which entered with a 14% discount off a brand price that had increased by a factor of 30 in recent years.[122] Finally, even products with historically stable pricing may be sold to or acquired by another manufacturer, who could decide to change pricing in dramatic and unpredictable fashion.

Administration and Monitoring Costs

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

Health Care Utilization Costs

We assumed that annual CF-related health care costs over an individual's lifetime consisted of three components (not including the cost of the CFTR modulator drugs): disease management, acute pulmonary exacerbations requiring IV antibiotics, and transplant-related costs. We used an approach similar to that taken by Dilokthornsakul et al. in their cost-effectiveness analyses.[122,123] Both disease management and pulmonary exacerbation components incorporated a gradient cost structure that was derived from Lieu et al. to reflect increasing costs with increasing disease severity categories (≤40% ppFEV$_1$, severe; between 40% and 70% ppFEV$_1$, moderate; ≥70% pp FEV$_1$, mild).[123] An age-related adjustment (<18 or 18+) was included in the exacerbation component. The 2018 CF Foundation Patient Registry data were used to calculate the adjustment, reflecting a higher proportion of total treatment duration spent in the hospital versus home IV treatment for children with a pulmonary exacerbation than for adults.[5] This resulted in a lower cost per exacerbation for adults.

Average cost estimates based on 1996 data[123] do not include all currently-available CF treatments and therefore are not likely reflective of current best supportive care costs. Several other studies have found higher average annual medical costs even after adjusting for inflation.[124,125] To derive current best supportive care costs, we used two average annual cost estimates provided by Scott Grosse from the CDC based on his analysis of 2016 commercial payer and Medicaid claims data ($130,879 and $83,173 in 2016 US dollars).[126] We applied a 5% reduction to account for transplant-related costs, excluded CFTR-related costs, and updated to 2019 US dollars using the personal consumption expenditure (PCE) price index. We then calculated a weighted average based on health insurance information reported in the 2016 CF Foundation Patient Registry Report (the same year as the data) showing a 60%/40% insurance mix (private/other).[111] This resulted in an average annual cost estimate of $77,143 (2016 US dollars), which was used to calibrate the best supportive care cost estimates prior to updating to 2019 US dollars.

Transplant-related costs include the one-time cost of receiving a lung transplant followed by an annual cost associated with post-transplantation care. Estimates for the cost of a transplant and initial year following a transplant were derive from a 2017 Milliman Research Report.[127] Annual costs were reduced for all subsequent years following the first year post-transplant based on estimates from a study of inpatient and outpatient billing services of lung transplantation patients at the University of Washington.[128] 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 5.6 and are reported in 2019 US dollars.

Table 5.6. Direct Costs by Disease Severity

	$ppFEV_1 \geq 70\%$	$ppFEV_1$ 40%-69%	$ppFEV_1 < 40\%$
Disease Management	$26,311	$34,708	$59,340
PEx* (age <18)	$54,960	$87,081	$129,016
PEx* (age 18+)	$49,802	$79,163	$113,443
Lung Transplant	$948,437		
Post-Transplant (Year 1)	$365,773		
Post-Transplant (Year 2+)	$131,738		

*PEx = acute pulmonary exacerbation requiring IV antibiotics

Productivity Costs

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

A large impact on caregiver costs from CFTR modulator treatment would require that caregiver burden be associated with lung function (e.g., the primary characteristic which modulator treatments change) or have direct evidence that the CFTR modulators reduce caregiver burden. However, Neri et al. found no relationship between caregiver burden, as measured by the General Strain Index, and patient factors such as $ppFEV_1$ or occurrence of acute pulmonary exacerbations.[129] Angelis et al. did find that direct non-health care costs in the United Kingdom were of the same magnitude as direct health care costs, not including CFTR modulators, but did not report societal costs by lung function category.[130] Any assumptions about how CFTR modulator drugs affect caregiver burden would be speculative. Therefore, we did not include impacts on caregiver costs in this analysis. The addition of direct non-health care costs that are not affected by CFTR modulator treatments would result in an increase in total societal costs due to the substantial increase in life expectancy with modulator therapy.

Model Analyses

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

Sensitivity Analyses

We ran one-way sensitivity analyses to identify the key drivers of model outcomes, using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges for each input, as described in the model inputs section above. Probabilistic sensitivity analyses were also performed by jointly varying all model parameters over 1,000 simulations, then calculating 95% credible interval estimates for each model outcome based on the results and reporting the percent of the simulations where the drug was cost-effectiveness for a given cost-effectiveness threshold (varying from $50,000 per QALY to $500,000 per QALY for Kalydeco and Symdeko, and from $50,000 per QALY to $200,000 per QALY for Trikafta). We use normal distributions for parameters in the mortality model and drug effect parameters, beta distributions for utilities and probabilities, and truncated normal distributions for costs. Additionally, we performed a threshold analysis by systematically altering the price of CFTR modulators to estimate the maximum prices that would correspond to a set of given WTP thresholds.

Scenario Analyses

We performed five scenario analyses. In the first, we present our results that used a societal perspective. In the second, we varied our assumption about long-term effectiveness of the CFTR modulator drugs. In our base case, we assume that after two years individuals on CFTR modulator therapies would experience 50% of the annual $ppFEV_1$ decline that those receiving best supportive care alone would experience. In scenario analyses, we assume that the annual decline in lung function with the CFTR modulator drugs varied between 0% long-term decline (i.e., no long-term lung function decline experienced with drug) to 100% (i.e., long-term decline with drug is the same as best supportive care after two years). This range was supported by the simulated standard error of the long-term percent decline (99% credible interval 1%-99%). In a third scenario analysis, when patients experience a pulmonary exacerbation, we incorporate an additional decrease in $ppFEV_1$ that is not recovered. This effect is supported by a study,[131] although the magnitude of this effect is unclear, and it is uncertain the degree to which this effect is already captured in the other benefits of CFTR drugs (e.g., decrease in long-term decline in lung function). In a scenario analysis, we varied the additional absolute decline in $ppFEV_1$ due to a pulmonary exacerbation between 0% (i.e., no

additional decline in ppFEV$_1$ due to pulmonary exacerbation) to 5% (i.e., a 5% absolute decline in ppFEV$_1$ for each pulmonary exacerbation experienced). In a final scenario analysis, we explored the assumption that CFTR modulator therapies have a quality-of-life benefit in addition to respiratory improvements. An analysis of STRIVE CFQ-R findings reported scores for domains other than the respiratory domain and found clinically significant improvements in certain domains (e.g., physical functioning, health perception, vitality, weight). [132] Although a CFQ-R score does not directly translate into a utility, we varied an independent utility effect (i.e., using a multiplier to the lung-function-informed utility) due to CFTR therapy from 1 (no independent effect) to 1.05 (a 5% increase in utility with drug), above that due to lung function improvement. Bell et al. reported mean EQ-5D values of 0.90 for cystic fibrosis patients with a *G551D* mutation who were treated with Kalydeco and 0.81 for patients homozygous for the *F508del* mutation who were treated with standard of care alone, indicating an overall quality-of-life effect due to the Kalydeco treatment.[58] A 5% increase in utility for someone with a base of 0.90 represents an absolute gain of 0.045, which is half of the overall observed effect reported by Bell et al. and would reflect quality-of-life impacts not measured by EQ-5D. In a fifth scenario analysis we incorporated a CFTR modulator benefit on the annual risk of CFRD. We used an adjusted relative risk from an observational study,[13] adjusted for the differential risk of CFRD by mutation class,[72] and varied the risk reduction between 5% and 23%.

We conducted three additional analyses for Trikafta. First, we assumed a start age of 6 years instead of 12 years, anticipating that younger patients will be eligible for this drug in the near future. Second, we assumed that Trikafta reduces the intensity of best supportive therapy needed by reducing disease management costs by 75%, Last, we evaluated a "curative scenario" for Trikafta. In this scenario we assumed patients would live to a normal life expectancy with no CF-related decrements in quality of life and no CF-related costs outside of the cost of Trikafta. In this analysis we allowed Trikafta treatment to begin at age 6 months and assumed people would be 100% adherent to the medication. We assigned average age-specific EQ-5D values for each year of life.[133] This analysis provides an extreme upper bound for the potential cost-effectiveness of this drug.

Model Validation

We used several approaches to validate the model. First, we provided preliminary methods and results to representatives from a patient group and clinical experts. Based on feedback from these groups, we refined data inputs used in the model and ran additional scenario analyses (e.g., varying the costs of best supportive care among patients treated with Trikafta, and modeling a younger population for Trikafta). Second, we varied model input parameters to evaluate face validity of changes in results. Simulated individuals were compared to observed statistics of CF patients: median age of survival, percent in lung function categories (≤40% ppFEV$_1$, severe; between 40% and 70% ppFEV$_1$, moderate; ≥70% pp FEV$_1$, mild) by age, and median ppFEV$_1$ by age.[5] We also

performed model verification for model calculations using internal reviewers. Finally, we compared results to other cost-effectiveness models in this therapy area.

5.3 Results

Base Case Outcomes Results

All CFTR modulators were compared to best supportive care and were found to be very effective (Table 5.7). Note that the difference in total life years for Population 4 (heterozygous *F508del* and a minimal function mutation) versus Population 2 (homozygous *F508del*) is because the cohorts begin treatment at different ages (12 vs. 2 years of age, respectively). Also note that a higher percentage of patients who reach $ppFEV_1$ of less than 40% does not necessarily translate into a greater chance of experiencing lung transplantation, as those at higher risk of dying (due to reasons other than their $ppFEV_1$) may die prior to getting lung transplantation.

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

Population and Treatment	Total Life Years	Average Number of PEx	Percent With Lung Transplants	Percent Experiencing $ppFEV_1$ 40%-69%	Percent Experiencing $ppFEV_1$ <40%
Population 1 - Eligible for Kalydeco Monotherapy (age 6 months)					
BSC	37.57	31.97	33.2%	87.5%	49.4%
Kalydeco Plus BSC	53.82	18.66	5.0%	53.8%	11.6%
Difference	16.25	13.31	28.3%	33.8%	37.8%
Population 2 - Homozygous for the *F508del* Mutation (age 2 years)					
BSC	37.09	25.44	32.7%	89.0%	49.3%
Symdeko Plus BSC	51.94	12.15	5.5%	59.0%	13.0%
Difference	14.85	13.29	27.2%	30.0%	36.4%
Trikafta Plus BSC	56.38	10.76	3.5%	43.8%	8.0%
Difference	19.29	14.68	29.2%	45.2%	41.4%
Population 3 - Heterozygous *F508del* with Residual Function Mutation (age 6 months)					
BSC	39.61	29.50	37.0%	88.5%	52.7%
Symdeko Plus BSC	56.19	13.24	6.4%	56.2%	13.8%
Difference	16.58	16.27	30.6%	32.2%	38.9%
Trikafta Plus BSC	62.17	11.84	3.1%	38.7%	7.3%
Difference	22.56	17.66	33.9%	49.8%	45.4%
Population 4 - Heterozygous *F508del* with Minimal Function Mutation (age 12 years)					
BSC	26.17	22.57	32.7%	93.5%	53.0%
Trikafta Plus BSC	40.10	9.10	5.2%	70.8%	14.8%
Difference	13.92	13.47	27.6%	22.8%	38.2%

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

Base Case Cost-Effectiveness Results

The base-case results are shown in Tables 5.8, 5.9, and 5.10. All CFTR modulators were compared to best supportive care. We did not compare the drugs with each other for CF populations with two CFTR modulator alternatives because of the lack of substantive differences between them in the meta-analysis results and in the modeling results.

For individuals eligible for Kalydeco monotherapy, the total discounted lifetime costs for Kalydeco plus best supportive care and best supportive care only were approximately $8,595,000 and $2,274,000, respectively. The total discounted QALYs (and life years) for Kalydeco plus best supportive care and best supportive care alone were 23.09 (26.05) and 17.13 (21.59), respectively. The incremental cost-effectiveness ratios for Kalydeco in this population were approximately $1,060,000 per QALY gained and $1,420,000 per life year gained.

For individuals who are homozygous for the *F508del* mutation the total discounted lifetime costs for Symdeko, Trikafta and best supportive care were approximately $7,825,000, $8,304,000 and $2,031,000, respectively. The total discounted QALYs (and life years) for Symdeko, Trikafta, and best supportive care were 22.63 (25.69), 24.13 (26.67) and 17.19 (21.47), respectively. Note that despite the larger increase in $ppFEV_1$ with Trikafta compared to Symdeko, the benefit is not proportional to the $ppFEV_1$ increase due to the other benefits that are not related to $ppFEV_1$ (i.e., independent effect on acute pulmonary exacerbations, effect on weight-for-age *z*-score, and long-term decline in lung function – assumed to be the same for both drugs). The incremental cost-effectiveness ratios for Symdeko and Trikafta versus best supportive care in this population were approximately $1,060,000 per QALY and $904,000 per QALY, respectively, and approximately $1,370,000 and $1,210,000 per life year gained, respectively.

For individuals who are heterozygous for the *F508del* mutation with a residual function mutation, the total discounted lifetime costs for Symdeko, Trikafta and best supportive care were approximately $8,152,000, $8,748,000 and $2,192,000, respectively. The total discounted QALYs (and life years) for Symdeko, Trikafta and best supportive care were 23.59 (26.51), 25.47 (27.64) and 17.76 (22.17), respectively. The incremental cost-effectiveness ratios for Symdeko and Trikafta in this population were approximately $1,020,000 per QALY and $850,000 per QALY, respectively, and approximately $1,370,000 and $1,200,000 per life year gained, respectively.

For individuals who are heterozygous for the *F508del* mutation with a minimal function mutation, the total discounted lifetime costs for Trikafta plus best supportive care and best supportive care only were approximately $7,372,000 and $2,200,000, respectively. The total discounted QALYs (and life years) for Trikafta plus best supportive care and best supportive care alone were 18.94 (22.35)

and 12.62 (17.03), respectively. The incremental cost-effectiveness ratios for Trikafta in this population were approximately $818,000 per QALY gained and $972,000 per life year gained.

Note that the costs for disease management were higher in patients treated with CFTR modulator therapy compared to those treated with best supportive care alone (Table 5.9). The increased costs are due to patients treated with CFTR modulators living longer and incurring disease management costs associated with the extra years of life.

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

Population and Treatment	Total QALYs	Total Life Years	Equal Value Life Years
Population 1 - Eligible for Kalydeco Monotherapy			
BSC	17.13	21.59	17.27
Kalydeco Plus BSC	23.09	26.05	23.39
Population 2 - Homozygous for the *F508del* Mutation			
BSC	17.19	21.47	17.26
Symdeko Plus BSC	22.63	25.69	22.89
Trikafta Plus BSC	24.13	26.67	24.29
Population 3 - Heterozygous *F508del* with Residual Function Mutation			
BSC	17.76	22.17	17.84
Symdeko Plus BSC	23.59	26.51	24.22
Trikafta Plus BSC	25.47	27.64	25.90
Population 4 - Heterozygous *F508del* with Minimal Function Mutation			
BSC	12.62	17.03	12.79
Trikafta Plus BSC	18.94	22.35	19.49

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

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

	Cost Source				
Population and Treatment	CFTR Drug	Disease Management	Acute Pulmonary Exacerbation	Lung Transplantation	Total
Population 1 - Eligible for Kalydeco Monotherapy					
BSC	$0	$629,000	$1,304,000	$341,000	$2,274,000
Kalydeco Plus BSC	$7,355,000	$724,000	$481,000	$36,000	$8,595,000
Population 2 - Homozygous for the *F508del* Mutation					
BSC	$0	$629,000	$1,062,000	$341,000	$2,031,000
Symdeko Plus BSC	$6,736,000	$712,000	$336,000	$41,000	$7,825,000
Trikafta Plus BSC	$7,339,000	$674,000	$269,000	$22,000	$8,304,000
Population 3 - Heterozygous *F508del* with Residual Function Mutation					
BSC	$0	$645,000	$1,178,000	$369,000	$2,192,000
Symdeko Plus BSC	$7,092,000	$675,000	$342,000	$43,000	$8,152,000
Trikafta Plus BSC	$7,740,000	$685,000	$304,000	$19,000	$8,748,000
Population 4 - Heterozygous *F508del* with Minimal Function Mutation					
BSC	$0	$542,000	$1,237,000	$422,000	$2,200,000
Trikafta Plus BSC	$6,299,000	$675,000	$352,000	$45,000	$7,372,000

BSC: best supportive care

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

Treatment vs. BSC	Cost Per QALY Gained	Cost Per evLYG	Cost Per LY Gained	Cost Per PEx Averted
Population 1 - Eligible for Kalydeco Monotherapy				
Kalydeco Plus BSC	$1,060,000	$1,030,000	$1,420,000	$475,000
Population 2 - Homozygous for the *F508del* Mutation				
Symdeko Plus BSC	$1,060,000	$1,030,000	$1,370,000	$436,000
Trikafta Plus BSC	$904,000	$892,000	$1,210,000	$472,000
Population 3 - Heterozygous *F508del* with Residual Function Mutation				
Symdeko Plus BSC	$1,020,000	$934,000	$1,370,000	$366,000
Trikafta Plus BSC	$850,000	$813,000	$1,200,000	$371,000
Population 4 - Heterozygous *F508del* with Minimal Function Mutation				
Trikafta Plus BSC	$818,000	$772,000	$972,000	$384,000

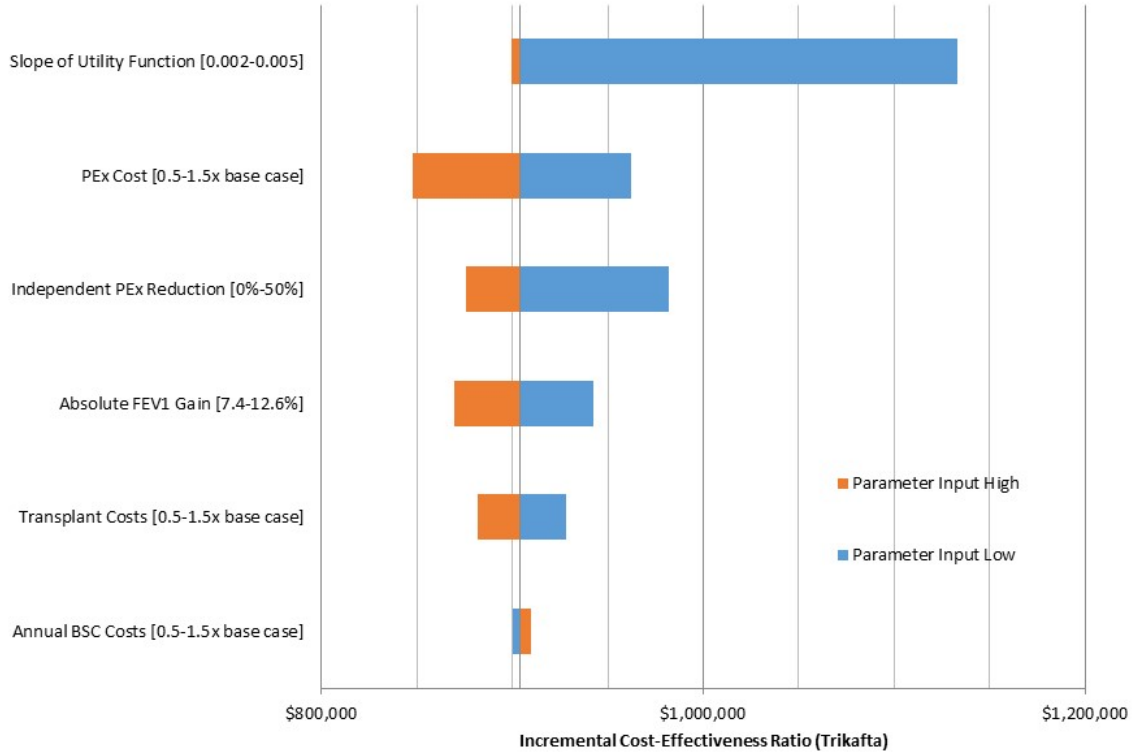
BSC: best supportive care; QALY: quality adjusted life year; evLYG: equal value life year gained; LY: life year; PEx: pulmonary exacerbation

Sensitivity Analysis Results

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

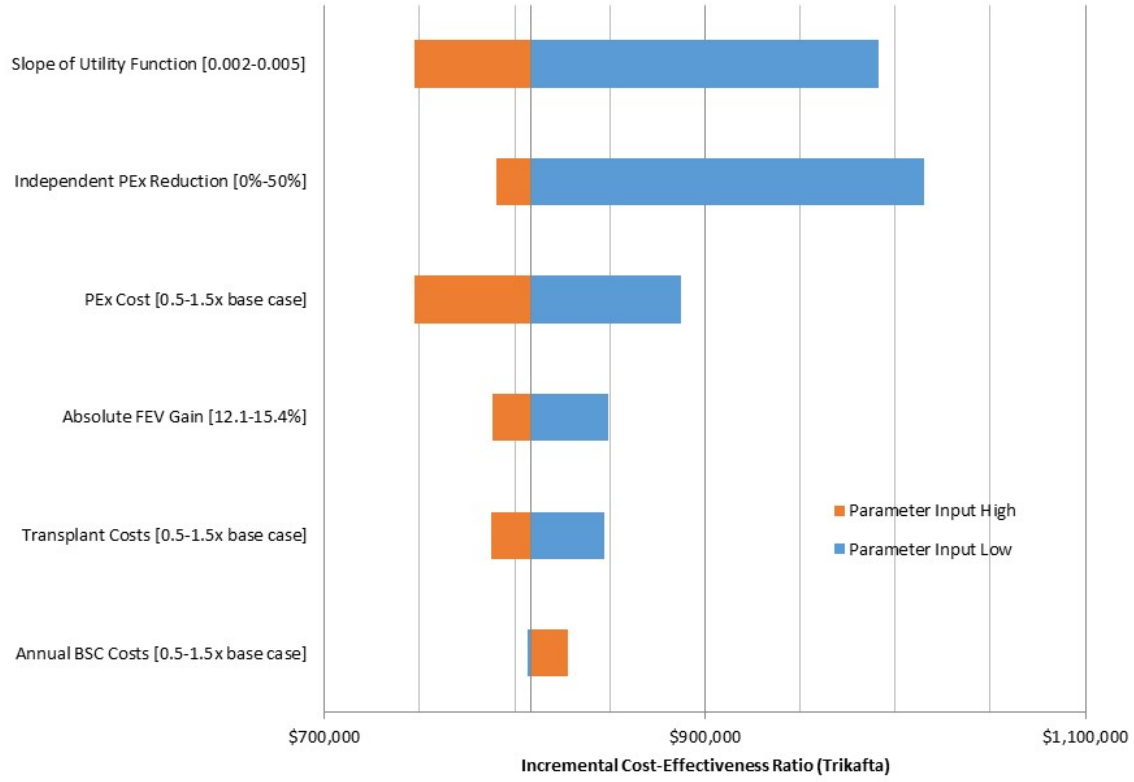
The impacts of variations in input values on cost-per-QALY estimates are shown for Trikafta in CF individuals homozygous for *F508del* mutation in Figure 5.4, and in individuals heterozygous for *F508del* mutation and minimal function mutation in Figure 5.5. The analyses were most sensitive to assumptions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

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



PEx: acute pulmonary exacerbation; BSC: best supportive care

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



PEx: acute pulmonary exacerbation; BSC: best supportive care

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

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

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

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

Table 5.12 shows the 95% credible intervals for each probabilistic sensitivity analysis. This interval included the ICER from 95% of the simulations done in the sensitivity analysis. For example, the 95% credible interval for the incremental cost-effectiveness ratios for Kalydeco compared with best supportive care was $745,800 to $2,028,800 per QALY for CF individuals eligible for Kalydeco monotherapy.

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

CF Population and CFTR Modulator	95% Credible Interval from Probabilistic Sensitivity Analyses
Population 1 - Eligible for Kalydeco Monotherapy	
Kalydeco plus BSC	$745,900 - $2,028,800 per QALY gained
Population 2 - Homozygous for the *F508del* Mutation	
Symdeko plus BSC	$735,100 - $1,827,300 per QALY gained
Trikafta plus BSC	$695,600 - $1,344,200 per QALY gained
Population 3 - Heterozygous *F508del* with Residual Function Mutation	
Symdeko plus BSC	$614,100 - $1,564,000 per QALY gained
Trikafta plus BSC	$546,900 - $1,200,400 per QALY gained
Population 4 - Heterozygous *F508del* with Minimal Function Mutation	
Trikafta plus BSC	$628,900 - $1,191,400 per QALY gained

Scenario Analyses Results

Modified Societal Perspective

We incorporated the costs associated with lost productivity in individuals with CF as a result of not being able to work full time in the absence of CFTR modulator therapies as well as lost productivity due to acute pulmonary exacerbations (Table 5.13). For individuals eligible for Kalydeco we projected that the difference in lifetime (discounted) indirect costs was $73,200. We acknowledge that the indirect costs are likely an underestimate due to the lack of data on the impact of caregiver burden with CFTR modulators. In addition, the indirect costs due to employment are realized in the future and thus the gains are diminished by discounting. Including productivity losses in the analysis resulted in incremental cost-effectiveness ratios for Kalydeco very similar to those seen in the base case ($1,050,000 per QALY societal vs. $1,060,000 per QALY base case). The impact on indirect costs would need to be substantial in order for the cost-effectiveness ratios from a societal perspective to reach commonly-used thresholds. Estimates for the incremental cost-effectiveness ratios for the CFTR modulators for the other two populations also tracked very closely with base case estimates (Table 5.13).

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

Treatment vs. BSC	Incremental Costs (Direct)	Incremental QALYs	Cost Per QALY Gained
Population 1 - Eligible for Kalydeco Monotherapy			
Kalydeco plus BSC	$6,321, 000	5.96	$1,050,000
Population 2 - Homozygous for the *F508del* Mutation			
Symdeko plus BSC	$5,793,000	5.44	$1,050,000
Trikafta plus BSC	$6,272,000	6.94	$892,000
Population 3 - Heterozygous *F508del* with Residual Function Mutation			
Symdeko plus BSC	$5,913,000	5.83	$1,000,000
Trikafta plus BSC	$6,585,000	7.71	$843,000
Population 4 - Heterozygous *F508del* with Minimal Function Mutation			
Trikafta plus BSC	$5,171,000	6.32	$805,000

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

Long-Term Effectiveness Assumptions

In the base case we assumed that CFTR modifiers would result in 50% of the annual declines in $ppFEV_1$ as for best supportive care, after the first two years without any decline. In this scenario analysis we varied that assumption from 0% (i.e., no declines in $ppFEV_1$ over an individual's lifetime)

to 100% (i.e., the same annual declines as those on best supportive care after the first two years on drug) (Table 5.14). For CF individuals eligible for Kalydeco, the incremental cost-effectiveness ratio for Kalydeco was $667,000 per QALY when we assumed that there was no long-term decline in $ppFEV_1$ (i.e., the drug increased $ppFEV_1$ at the start of therapy and individuals' lung function remained constant for the remainder of their lifetime). Similar declines in incremental cost-effectiveness ratios were found with other drugs and populations (Table 5.14).

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

Treatment vs. BSC	0% Decline	25% Decline	75% Decline	100% Decline
Population 1 - Eligible for Kalydeco Monotherapy				
Kalydeco plus BSC	$667,000	$818,000	$1,444,000	$2,150,000
Population 2 - Homozygous for the *F508del* Mutation				
Symdeko plus BSC	$671,000	$824,000	$1,450,000	$2,170,000
Trikafta plus BSC	$644,000	$751,000	$1,120,000	$1,440,000
Population 3 - Heterozygous *F508del* with Residual Function Mutation				
Symdeko plus BSC	$630,000	$763,000	$1,250,000	$1,750,000
Trikafta plus BSC	$587,000	$684,000	$984,000	$1,220,000
Population 4 - Heterozygous *F508del* with Minimal Function Mutation				
Trikafta plus BSC	$602,000	$694,000	$966,000	$1,160,000

BSC: best supportive care

$ppFEV_1$ Recovery After Pulmonary Exacerbation Assumptions

In the base case we assumed that CF individuals' $ppFEV_1$ would fully recover to baseline following pulmonary exacerbations, allowing only for the natural decline in lung function and the impact of the CFTR drugs on that natural decline. In this scenario analysis we varied that assumption from 0% (i.e., no additional decline in $ppFEV_1$ due to pulmonary exacerbation) to 5% (i.e., a 5% absolute decline in $ppFEV_1$ for each pulmonary exacerbation experienced) (Table 5.15). For CF individuals eligible for Kalydeco therapy, the incremental cost-effectiveness ratio for Kalydeco was $794,000 per QALY when we assumed that there was a 5% absolute decline in $ppFEV_1$ for each pulmonary exacerbation experienced. Similar declines in ICERs were found with other drugs and populations (Table 5.15).

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

Treatment vs. BSC	1% Decline	3% Decline	5% Decline
Population 1 - Eligible for Kalydeco Monotherapy			
Kalydeco plus BSC	$909,000	$812,000	$794,000
Population 2 - Homozygous for the *F508del* Mutation			
Symdeko plus BSC	$894,000	$756,000	$712,000
Trikafta plus BSC	$762,000	$637,000	$594,000
Population 3 - Heterozygous *F508del* with Residual Function Mutation			
Symdeko plus BSC	$787,000	$656,000	$611,000
Trikafta plus BSC	$684,000	$577,000	$543,000
Population 4 - Heterozygous *F508del* with Minimal Function Mutation			
Trikafta plus BSC	$685,000	$583,000	$548,000

BSC: best supportive care

Independent Utility Effect

In the base case we assumed that CF individuals' utility was based only on lung function (i.e., $ppFEV_1$, pulmonary exacerbations, lung transplantations). In this scenario analysis we varied an independent utility effect (i.e., using a multiplier to the lung-function-informed utility) due to CFTR therapy from 1 (no independent effect) to 1.05 (a 5% increase in utility with drug), above that due to lung function improvement (Table 5.16). For CF individuals eligible for Kalydeco therapy, the incremental cost-effectiveness ratio for Kalydeco was $918,000 per QALY when we assumed that there was a 5% increase in utility due to drug that in independent of lung function improvement. Similar declines in ICERs were found with other drugs and populations (Table 5.16).

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

Treatment vs. BSC	1% Increase	2% Increase	4% Increase	5% Increase
Population 1 - Eligible for Kalydeco Monotherapy				
Kalydeco plus BSC	$1,030,000	$995,000	$940,000	$918,000
Population 2 - Homozygous for the *F508del* Mutation				
Symdeko plus BSC	$1,030,000	$989,000	$925,000	$900,000
Trikafta plus BSC	$877,000	$852,000	$810,000	$793,000
Population 3 - Heterozygous *F508del* with Residual Function Mutation				
Symdeko plus BSC	$924,000	$893,000	$833,000	$806,000
Trikafta plus BSC	$789,000	$765,000	$721,000	$702,000
Population 4 - Heterozygous *F508del* with Minimal Function Mutation				
Trikafta plus BSC	$796,000	$774,000	$736,000	$718,000

BSC: best supportive care

CFTR Effect on Risk of CFRD

In the base case we assumed that CFTR modulator therapy did not reduce an individual's risk of developing CFRD. In this scenario analysis we allowed CFTR modulator treatment to reduce the annual risk of CFRD between 5% and 23% (Table 5.17). For CF individuals eligible for Kalydeco, the incremental cost-effectiveness ratio for Kalydeco was $1,050,000 per QALY when we assumed that there was a 23% reduction in the annual risk of CFRD due to the drug. Similar declines in ICERs were found with other drugs and populations (Table 5.17).

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

Treatment vs. BSC	5% Decrease	23% Decrease
Population 1 - Eligible for Kalydeco Monotherapy		
Kalydeco plus BSC	$1,060,000	$1,050,000
Population 2 - Homozygous for the *F508del* Mutation		
Symdeko plus BSC	$1,060,000	$1,050,000
Trikafta plus BSC	$901,000	$893,000
Population 3 - Heterozygous *F508del* with Residual Function Mutation		
Symdeko plus BSC	$961,000	$957,000
Trikafta plus BSC	$814,000	$811,000
Population 4 - Heterozygous *F508del* with Minimal Function Mutation		
Trikafta plus BSC	$812,000	$806,000

Eligibility Age of 6 Years Old for Trikafta

Anticipating that the eligibility age for Trikafta will soon be lowered to age 6, we conducted an analysis where we started CFTR modulator therapy at that age (assuming the same treatment effects as ages 12+). Table 5.18 shows the cost-effectiveness results in the three eligible populations.

Table 5.18. Incremental Cost-Effectiveness Ratios Compared to Best Supportive Care (BSC) for the Base Case (Discounted at 3% per Year)

Treatment vs. BSC	Total cost	QALYs	Cost Per QALY Gained
Population 2 - Homozygous for the *F508del* Mutation			
BSC	$2,031,000	17.19	--
Trikafta Plus BSC	$8,300,000	23.73	$959,000
Population 3 - Heterozygous *F508del* with Residual Function Mutation			
BSC	$2,195,000	17.77	--
Trikafta Plus BSC	$8,632,000	24.34	$980,000
Population 4 - Heterozygous *F508del* with Minimal Function Mutation			
BSC	$2,132,000	15.33	--
Trikafta Plus BSC	$8,053,000	21.96	$893,000

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

Reduced Need for Best Supportive Care Therapies with Trikafta

Our results were not sensitive to variations in the best supportive care (e.g., disease management) costs when varied by a factor of 0.5-1.5 of the base case values, though those analyses assume that the best supportive care costs varied for both CFTR treated and untreated patients. The results were slightly more sensitive when we allowed best supportive care costs to decrease only for the Trikafta treated patients (under the assumption that Trikafta will alleviate the need for other supportive treatments). For example, when we reduced the cost of best supportive care by 75%, the ICER for Trikafta in CF individuals homozygous for *F508del* mutation changed from $904,000 per QALY to $829,000 per QALY. The incremental cost-effectiveness ratio for Trikafta in CF individuals heterozygous for *F508del* mutation with a residual function mutation changed from $850,000 per QALY to $783,000 per QALY. The incremental cost-effectiveness ratio for Trikafta in CF individuals heterozygous for *F508del* mutation with a minimal function mutation changed from $818,000 per QALY to $735,000 per QALY.

Curative Scenario

Even though Trikafta is not considered curative, we examined an extreme-case scenario for Trikafta for eligible CF patients who are either homozygous for the *F508del* mutation or who are heterozygous for the *F508del* mutation and a minimal function mutation. Expected lifetime costs and QALYs for these two populations are the same starting at birth so we grouped them together as the comparator. For patients treated with Trikafta we assumed that the only costs were due to Trikafta and derived the benefit using the QALYs of the general population starting from birth (with drug beginning at 6 months and full adherence to therapy). The discounted QALYs gained for Trikafta under this scenario were approximately 10.26 (27.79 minus 17.53). The discounted cost associated with Trikafta – net of costs associated with those not receiving Trikafta – was an estimated $7,145,000 ($9,172,000 minus $2,027,000), yielding an incremental cost-effectiveness ratio of $696,000 per QALY.

Threshold Analysis Results

Annual prices necessary to reach cost-effectiveness thresholds of $50,000, $100,000, $150,000, $200,000, $300,000 and $500,000 per QALY are listed in Table 5.19 for each CF population and CFTR modulator. Threshold prices for Trikafta are calculated only for cost-effectiveness thresholds less than $200,000 per QALY because it does not qualify for the ultra-rare disease framework. We strongly caution readers against assuming that the values provided in this section will approximate the health benefit price benchmarks (HBPBs) that will be presented in the next version of this Report. Based on reviewer and public input as well as manufacturer and internal model review, these results may change substantially.

Threshold prices were higher for the CF population heterozygous for *F508del* mutation and residual function mutation for Symdeko, and higher for CF individuals heterozygous for *F508del* mutation for Trikafta. A discount of approximately 35% to 51% would be necessary to reach a cost-effectiveness threshold of $500,000/QALY for Kalydeco and Symdeko. A discount of approximately 65% to 66% would be necessary to reach a cost-effectiveness threshold of $200,000/QALY for Trikafta.

Table 5.19. Threshold Analysis Results Presented as Annual Prices

	Annual WAC	Price to Achieve $50,000 per QALY	Price to Achieve $100,000 per QALY	Price to Achieve $150,000 per QALY	Price to Achieve $200,000 per QALY	Price to Achieve $300,000 per QALY	Price to Achieve $500,000 per QALY
Population 1 - Eligible for Kalydeco Monotherapy							
Kalydeco	$311,700	$51,100	$62,600	$74,000	$85,400	$108,300	$154,100
Population 2 - Homozygous for the *F508del* Mutation							
Symdeko	$292,200	$57,600	$72,100	$86,600	$101,100	$130,100	$188,100
Trikafta	$311,700	$61,400	$76,900	$92,400	$107,800	N/A	N/A
Population 3 - Heterozygous *F508del* with Residual Function Mutation							
Symdeko	$292,200	$59,300	$73,800	$88,400	$102,900	$132,000	$190,200
Trikafta	$311,700	$63,200	$78,800	$94,300	$109,800	N/A	N/A
Population 4 - Heterozygous *F508del* with Minimal Function Mutation							
Trikafta	$311,700	$64,600	$78,700	$92,900	$107,000	N/A	N/A

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

Note that Symdeko and Trikafta are each used for treatment in multiple populations. Therefore, we also calculated population-weighted threshold prices using estimated numbers of patients in each population. (We assumed approximately 8,870 CF individuals homozygous for *F508del* mutation, 1,926 CF individuals heterozygous for *F508del* mutation with a residual function mutation, and 6,070 CF individuals heterozygous for *F508del* mutation with a minimal function mutation.) The blended annual prices for Symdeko across the two relevant populations at the $50,000, $100,000 and $150,000 per QALY threshold prices were approximately $57,900, $72,400 and $86,900, respectively, and at the $500,000 per QALY threshold price was approximately $188,000. The blended annual prices for Trikafta across the three relevant populations at the $50,000, $100,000 and $150,000 per QALY threshold prices were approximately $62,800, $77,800 and $92,800, respectively, and at the $200,000 per QALY threshold price was approximately $108,000.

Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental Appendix materials).

We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

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

Prior Economic Models

We identified one prior published, US-based cost-effectiveness analyses of Kalydeco conducted by Dilokthornsakul and colleagues, who modeled the long-term costs and outcomes of Kalydeco treatment of CF patients with the *G551D* mutation.[118] 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[118] were undiscounted, results were also presented using a discount rate of 3%. Discounted incremental QALYs were 5.21, incremental lifetime costs approximately $3,658,300, and the base-case incremental cost–effectiveness ratio was approximately $705,300 per QALY (2013 US$ converted to 2019 using the personal consumption expenditure [PCE] price index). Our current model estimated incremental QALYs of 5.96, incremental costs of $6,320,900, and an incremental cost-effectiveness ratio of approximately $1,060,600 per QALY. Starting age for treatment in the earlier Kalydeco model was 25 years old, while we modeled treatment initiation at six months old. Dilokthornsakul et al. also assumed that the drug price would drop to 10% of that amount after patent expiration in 2027. 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.

Prior to these analyses, Whiting and colleagues had modeled the cost-effectiveness of Kalydeco treatment of CF patients aged six years or older (with median age = 20 years) with *G551D* mutation in the United Kingdom.[100] They modified a deterministic simulation model developed by Vertex Pharmaceuticals, adding in lung transplantations. This analysis was conducted from the UK National Health Service perspective, with a lifetime horizon and 3.5% discount rate for costs and outcomes. For long-term effects of Kalydeco treatment on $ppFEV_1$ decline, they modeled three different scenarios: conservative, with same rate of decline as for standard care; intermediate, with 66% rate of decline; and optimistic, with stable $ppFEV_1$ over lifetime. The cost of Kalydeco used in the model was £182,000 (approximately $317,000 in 2019 US$), with the assumption that it would decline to

£20,000 in 14 years, due to loss of patent exclusivity. They used UK-based utility values and costs for usual care, making these results less comparable to our US-based analysis. This model led to estimated QALY gains of 1.27 (in the conservative scenario) to 5.26 (in the optimistic scenario), the latter being closest to our current model estimate of 5.96 incremental QALYs. The incremental cost-effectiveness ratio was estimated to vary between £335,000 and £1,274,000 per QALY (approximately $584,000 to $2,221,000 in 2019 US$).

5.4 Summary and Comment

We developed 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 base case models did not account for non-lung (or weight) aspects of the disease, nor did they decrease the need for CF-related supportive care. However, we did address these limitations by conducting several relevant scenario analyses. Overall, all drugs (plus best supportive care) evaluated were very effective compared with best supportive care alone in all populations studied, with QALY gains ranging from 5.44 to 7.71 (discounted). With (discounted) CFTR drug-related costs ranging from $5.2 million to $6.6 million, the incremental cost-effectiveness ratios of drugs plus best supportive care compared with best supportive care alone were approximately $0.8 to $1.1 million per QALY for all drugs in all populations considered, with the lower ranges associated with Trikafta. Our results were robust to variations to parameter estimates, adopting a societal perspective, or using life years gained as the health outcome, except for unit drug costs.

Limitations

There are several limitations to our analysis that deserve mention. We used $ppFEV_1$ as the primary marker of lung function to characterize the progression of CF over time. Trials generally did not include patients with either very low or very high lung function, which may impact the generalizability of our results. Furthermore, based on available evidence, only the effect of the CFTR modulators on lung function, weight and acute pulmonary exacerbations are included in the model. As any surrogate marker of disease, it is not a perfect marker for progression. We conducted a scenario analysis and found that a 5% increase in non-respiratory-related utility would decrease the incremental cost-effectiveness ratios by approximately 12% to 17% for all drugs and populations. In addition, limited evidence exists about the drugs' impact on individual's ability to work or attend school, or the degree to which caregiver burden is reduced by CFTR modulator drugs. Such information would better inform our analysis from a societal perspective. More importantly, we only had short-term measures of drug effect and had to make assumptions about their effect over the lifetime of the patient. In addition, we used trial-based estimates of discontinuation of these therapies to be consistent with the efficacy estimates; real-world patterns

of discontinuation may differ from these. As an extreme scenario analysis, we evaluated Trikafta as a curative therapy and found that the cost-effectiveness ratio of lifetime therapy with Trikafta continued to far exceed commonly used cost-effectiveness thresholds even under the assumption that it maintained individuals with CF in normal health such that they never experienced any symptoms or complications of CF.

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 for Kalydeco and Symdeko with total eligible populations below 10,000 and still found that drug prices would need to be reduced by about 35% to 51% to be considered cost effective at this threshold.

6. Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. We also recognize that there may be broader contextual issues related to the severity of the condition, whether other treatments are available, and ethical, legal, or other societal priorities that influence the relative value of illnesses and interventions. These general elements are listed in the table below, and the subsequent text provides detail about the elements that are applicable to the comparison of adding versus not adding CFTR modulators to standard care for CF patients. We sought input from stakeholders, including individual patients, patient advocacy organizations, and clinicians to inform the contents of this section.

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

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

Table 6.1. Potential Other Benefits and Contextual Considerations

Potential Other Benefits
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.
This intervention will have a significant impact on improving the patient's ability to return to work or school and/or their overall productivity.
This intervention will have a significant positive impact outside the family, including on schools and/or communities.
This intervention will have a significant impact on the entire "infrastructure" of care, including effects on screening for affected patients, on the sensitization of clinicians, and on the dissemination of understanding about the condition, that may revolutionize how patients are cared for in many ways that extend beyond the treatment itself.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
Potential Other Contextual Considerations
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
Compared to best supportive treatment, there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to best supportive treatment, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

6.1 Potential Other Benefits

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

We heard from many patients and caregivers who reported that individuals who experience large clinical benefits from modulator therapy, Trikafta in particular, are able to spend substantially less time on other aspects of their care regimen and in some cases have reduced/eliminated use of some other therapies (e.g., hypertonic saline, insulin, laxatives), while others need to continue full best supportive care. Spending less time on these other aspects of CF care may help some patients return to work or school. Similarly, reducing the number of non-modulator treatments patients take would translate to less caregiver time spent on treatment regimens, which would reduce the impact of CF on family and caregivers. However, as mentioned in Section 4, there is currently no data to inform individual decision-making around which treatments are essential versus those that may be reduced or stopped. There is a randomized trial, SIMPLIFY, currently recruiting participants to begin to answer this question.[24]

Improved health and symptom control may also translate to caregiver benefits by decreasing anxiety associated with a loved one having a severe condition.

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

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

6.2 Contextual Considerations

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

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

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

7. Health-Benefit Price Benchmarks

ICER does not provide health-benefit price benchmarks (HBPBs) as part of the draft report because results are likely to change based on public comment. We strongly caution readers against assuming that the values provided in the Threshold Analysis Results section will approximate the HBPBs that will be presented in the next version of this Report. Based on reviewer and public input as well as manufacturer and internal model review, these results may change substantially.

8. Potential Budget Impact

8.1 Overview

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

8.2 Methods

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

This potential budget impact analysis includes the estimated number of individuals with CF in the US who would be eligible for treatment with Trikafta (populations 2, 3, and 4 above). To estimate the size of the potential candidate populations for treatment, we used estimates from the CF Foundation Patient Registry (CFFPR) of individuals with CF in the US who were greater than 12 years old and had any *F508del* mutation.[134] We assumed that all eligible patients would add or switch to Trikafta upon reaching 12 years of age. The CFFPR in 2018 reports 8,870 CF patients homozygous for the *F508del* mutation aged 12 and older (population 2), all of whom were assumed to be eligible for Trikafta. We assumed that 20% of these patients (1,774) would initiate Trikafta in each of the five years for population 2.

We also assumed that all patients over the age of 12 and heterozygous for an *F508del* mutation with a residual function mutation (population 3) were eligible for Trikafta. To calculate the number in this population, we used estimates of the number of patients aged 12 and older with heterozygous *F508del* mutation multiplied by the proportions of patients with residual versus minimal function mutations in patients with Class IV-V mutations (79%) or other mutations (29%). Applying these proportions, our potential budget impact model assumes 1,925 cystic fibrosis patients heterozygous for *F508del* mutation with residual function mutations in the United States

will be eligible for Trikafta. We assumed that 20% of these patients would initiate Trikafta in each of the five years, or 385 patients per year.

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

For patients eligible for Trikafta who were also eligible for Symdeko (Populations 2 and 3), we used data from the CF Foundation Patient Registry Annual Data Report for 2018,[5] which reported that 68.5% of eligible patients were prescribed CFTR modulators, to estimate the proportion of patients eligible for Trikafta who would currently be treated with Symdeko. For patients who are homozygous for the *F508del* mutation (populations 2) and patients who are heterozygous for the *F508del* mutation with a residual function mutation (population 3), we assumed that Trikafta plus best supportive care would displace a mix of Symdeko plus best supportive care (for 68.5% of eligible patients) and best supportive care alone (for 31.5% of eligible patients). For patients who are heterozygous for the *F508del* mutation with a minimal function mutation (population 4), we assumed Trikafta treatment would be added to best supportive care alone.

ICER's methods for estimating potential budget impact are described in detail elsewhere[135] and have been recently updated. The intent of our revised approach to potential budgetary impact is to document the percentage of patients who could be treated at selected prices without crossing a potential budget impact threshold that is aligned with overall growth in the U.S. economy. For 2019-2020, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to be approximately $819 million per year for new drugs.

8.3 Results

The tables below illustrate the five-year annualized per-patient potential budget impact of Trikafta in the relevant populations. The results in each table are based on the list price ($311,741 per year) and the blended annual threshold prices for cost-effectiveness thresholds of $150,000, $100,000, and $50,000 per QALY versus best usual care ($92,800, $77,800, and $62,800, respectively). We used the blended threshold prices across the three eligible populations as these seemed more policy relevant than the use of separate threshold prices for each population.

Tables 8.1 illustrates the five-year annualized per-patient potential budget impact of Trikafta compared to best usual care in the population homozygous for the *F508del* mutation (population 2). For population 2, the average annualized potential budgetary impact when using Trikafta's list price was an additional per-patient cost of approximately $82,000 versus the mix of Symdeko and best supportive care. Its average annualized potential budget impacts at the threshold prices for $50,000 to $150,000 per QALY were estimated to be cost-saving relative to a mix of Symdeko and best supportive care alone. Note that we estimate cost-savings for Trikafta at these prices because of the high cost offset from the comparator mix ($236,000 per patient), which includes the cost of Symdeko at its current price for the majority of patients.

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

	Average Annual Per Patient Budget Impact			
	At List Price	**At $150,000/ QALY Price**	**At $100,000/ QALY Price**	**At $50,000/ QALY Price**
Trikafta	$318,000	$118,000	$105,000	$91,000
Symdeko (68.5%) & BSC (31.5%)	$236,000			
Net Impact	$82,000	-$118,000	-$131,000	-$145,000

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

Table 8.2 illustrates the five-year annualized per-patient potential budget impact of Trikafta compared to the mix of Symdeko and best supportive care in the population over the age of 12 and heterozygous for an *F508del* mutation with a residual function mutation (population 3). For population 3, the average annualized potential budgetary impact when using Trikafta's list price was an additional per-patient cost of approximately $76,000 versus the mix of Symdeko and best supportive care. Its average annualized potential budget impacts at the threshold prices for $50,000 to $150,000 per QALY were estimated to be cost-saving relative to a mix of Symdeko and best supportive care alone. As in population 2, note that we estimate cost-savings for Trikafta at these prices because of the high cost offset from the comparator mix ($240,000 per patient), which includes the cost of Symdeko at its current price.

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

	Average Annual Per Patient Budget Impact			
	At List Price	At $150,000/ QALY Price	At $100,000/ QALY Price	At $50,000/ QALY Price
Trikafta	$316,000	$118,000	$104,000	$90,000
Symdeko (68.5%) & BSC (31.5%)	$240,000			
Net Impact	$76,000	-$123,000	-$136,000	-$150,000

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

Table 8.3 illustrates the five-year annualized per-patient potential budget impact of Trikafta compared to best usual care in the population heterozygous for the *F508del* mutation with minimal function mutation (population 4). For Trikafta, the average annualized potential budgetary impact when using its list price was an additional per-patient cost of approximately $253,000 versus best supportive care. Its average annualized potential budget impact versus best supportive care at the threshold prices for $50,000 to $150,000 per QALY ranged from approximately $27,000 to approximately $54,000 per patient. Note that the cost offset for this population is much smaller ($72,000 per patient) because it includes costs for best supportive care alone.

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

	Average Annual Per Patient Budget Impact			
	At List Price	At $150,000/ QALY Price	At $100,000/ QALY Price	At $50,000/ QALY Price
Trikafta	$325,000	$126,000	$112,000	$99,000
BSC	$72,000			
Net Impact	$253,000	$54,000	$40,000	$27,000

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

The annual potential budgetary impacts of treating the combined Trikafta-eligible populations using list price (WAC) compared to the $819 million threshold is shown in Table 8.4. For Populations 2 and 3, the annualized potential budget impact of treating all patients with Trikafta would not exceed the $819 million ICER potential budget impact threshold at list price (again, assuming cost offsets from a mix of Symdeko and best supportive care alone). However, for Population 4, the annualized potential budget impact of treating with Trikafta at list price would exceed the $819 million ICER potential budget impact threshold by 11%. Only approximately 90% of the 6,070 patients in Population 4 could be treated before exceeding the potential budget impact threshold at this price. When combined for all populations, the annualized potential budget impact of treating the entire eligible population with Trikafta at list price would exceed the $819 million ICER potential budget impact threshold by 74%. While the total number of patients eligible for treatment with Trikafta is relatively low (n = 16,866), the increased cost per patient from using Trikafta over current treatment mix leads to a total estimate exceeding the potential budget impact threshold.

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

	Eligible Population	N Treated per Year	Annual BI per Patient	Total Annual BI (millions)	Percent of Threshold
Homozygous *F508del* (Population 2)					
Trikafta	8,870	1,774	$82,000	$429.6	52%
Heterozygous *F508del* with Residual Function Mutation (Population 3)					
Trikafta	1,925	385	$76,000	$86.6	11%
Heterozygous *F508del* with Minimal Function Mutation (Population 4)					
Trikafta	6,070	1,214	$253,000	$909.1	111%
Total Trikafta-Eligible US CF Population*					
Trikafta	16,865	3,373	$143,000	$1,425.3	174%

BI: budget impact

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

****

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

References

1. Comeau AM, Parad RB, Dorkin HL, et al. Population-based newborn screening for genetic disorders when multiple mutation DNA testing is incorporated: a cystic fibrosis newborn screening model demonstrating increased sensitivity but more carrier detections. *Pediatrics.* 2004;113(6):1573.
2. Scotet V, Dugueperoux I, Saliou P, et al. Evidence for decline in the incidence of cystic fibrosis: a 35-year observational study in Brittany, France. *Orphanet journal of rare diseases.* 2012;7:14.
3. Parad RB, Comeau AM. Newborn screening for cystic fibrosis. *Pediatric annals.* 2003;32(8):528-535.
4. Grosse SD, Boyle CA, Botkin JR, et al. Newborn screening for cystic fibrosis: evaluation of benefits and risks and recommendations for state newborn screening programs. *MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports.* 2004;53(Rr-13):1-36.
5. Cystic Fibrosis Foundation. Cystic Fibrosis Foundation Patient Registry 2018 Annual Data Report. 2019; https://www.cff.org/Research/Researcher-Resources/Patient-Registry/2018-Patient-Registry-Annual-Data-Report.pdf.
6. Agrawal A, Mehta D, Sikachi R, Du D, Wang J. Nationwide trends of hospitalizations for cystic fibrosis in the United States from 2003 to 2013. *Intractable Rare Dis Res.* 2017;6(3):191-198.
7. O'Sullivan BP, Freedman SD. Cystic fibrosis. *The Lancet.* 2009;373(9678):1891-1904.
8. 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.
9. 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.
10. US Food and Drug Administration (FDA). FDA approves new breakthrough therapy for cystic fibrosis. 2019; https://www.fda.gov/news-events/press-announcements/fda-approves-new-breakthrough-therapy-cystic-fibrosis.
11. Balk E, Trikalinos T, Kuntz K, et al. *Modulator Treatments for Cystic Fibrosis: Effectiveness and Value; Final Evidence Report and Meeting Summary.* Boston, MA: Institute for Clinical and Economic Review; June 7 2018.
12. 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.
13. Bessonova L, Volkova N, Higgins M, et al. Data from the US and UK cystic fibrosis registries support disease modification by CFTR modulation with ivacaftor. *Thorax.* 2018;73:731-740.
14. Cystic Fibrosis Foundation. What is Cystic Fibrosis. 2017; https://www.cff.org/What-is-CF/About-Cystic-Fibrosis/. Accessed October 24, 2017.
15. Clinical and Functional Translation of CFTR. CFTR2.org. 2018; https://www.cftr2.org/.
16. 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.
17. 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.

18. National Institute for Health and Care Excellence (NICE). *Lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation.* nice.org June 2016 2016.
19. 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.
20. 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.
21. 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.
22. 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.
23. Wainwright CE, Elborn JS, Ramsey BW, et al. Lumacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR. *The New England journal of medicine.* 2015;373(3):220-231.
24. Cystic Fibrosis Foundation. Research We Fund. 2019.
25. Cystic Fibrosis Research Inc. Voice of the Cystic Fibrosis Patient: A Summary Report of the Externally-Led Patient-Focused Drug Development Meeting on Cystic Fibrosis. 2018; http://cfri.org/wp-content/uploads/2019/03/EL-PFDD.CFRI_.VoiceofCFPatientReport.pdf. Accessed February 4, 2020.
26. Center for Evaluation of Value and Risk in Health (CEVR). Tufts Medical Center Specialty Drug Evidence and Coverage (SPEC) Database. 2020; https://cevr.tuftsmedicalcenter.org/databases/spec-database. Accessed January 14, 2020.
27. FDA Approves KALYDECO® (ivacaftor) as First and Only CFTR Modulator to Treat Eligible Infants with CF as Early as Six Months of Age [press release]. April 30 2019.
28. FDA Approves KALYDECO® (ivacaftor) as First and Only Medicine to Treat the Underlying Cause of CF in Children Ages 12 to <24 Months with Certain Mutations in the CFTR Gene [press release]. August 15 2018.
29. FDA Approves ORKAMBI® (lumacaftor/ivacaftor) as First Medicine to Treat the Underlying Cause of Cystic Fibrosis for Children Ages 2-5 Years with Most Common Form of the Disease [press release]. August 7 2018.
30. FDA Approves SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) to Treat the Underlying Cause of CF in Children Ages 6-11 Years with Certain Mutations in the CFTR Gene [press release]. June 21 2019.
31. Ren CL, Morgan RL, Oermann C, et al. Cystic Fibrosis Foundation Pulmonary Guidelines. Use of Cystic Fibrosis Transmembrane Conductance Regulator Modulator Therapy in Patients with Cystic Fibrosis. *Annals of the American Thoracic Society.* 2018;15(3):271-280.
32. Lahiri T, Hempstead SE, Brady C, et al. Clinical Practice Guidelines From the Cystic Fibrosis Foundation for Preschoolers With Cystic Fibrosis. *Pediatrics.* 2016:peds.2015-1784.
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. Cystic Fibrosis Foundation. Clinical Care Guidelines. 2019; https://www.cff.org/Care/Clinical-Care-Guidelines/.
35. National Institute for Health and Care Excellence (NICE). Data Collection Agreement. 2019.

36. National Institute for Health and Care Excellence (NICE). Elexacaftor, tezacaftor and ivacaftor fixed dose combination therapy for treating cystic fibrosis with the F508del mutation [ID1661]. 2019; https://www.nice.org.uk/guidance/proposed/gid-ta10566.
37. National Institute for Health and Care Excellence (NICE). Cystic fibrosis: diagnosis and management. 2017.
38. Canadian Agency for Drugs and Technology in Health (CADTH). Final CDEC Recommendation - Ivacaftor (Kalydeco - Vertex Pharmaceuticals (Canada) Incorporated); Indication: Cystic Fibrosis with G551D Mutation. 2013; https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_Kalydeco_March-25-13_e.pdf.
39. Canadian Agency for Drugs and Technology in Health (CADTH). CDEC Final Recommendation - Ivacaftor (Kalydeco - Vertex Pharmaceuticals Inc.); Indication: Cystic Fibrosis with G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or G970R mutation. 2014; https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_SR0379_Kalydeco_Dec-23-14.pdf.
40. Canadian Agency for Drugs and Technology in Health (CADTH). CADTH Canadian Drug Expert Commmittee Final Recommendation: Ivacaftor (Kalydeco - Vertex Pharmaceuticals Inc.); Indication: Cystic Fibrosis with R117H Mutation. 2015; https://www.cadth.ca/sites/default/files/cdr/complete/SR0430_complete_Kalydeco_R117H_Nov-23-15_e.pdf.
41. Canadian Agency for Drugs and Technology in Health (CADTH). Lumacaftor/ivacaftor (Orkambi - Vertex Pharmaceuticals (Canada) Incorporated). 2018.
42. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Ann Intern Med.* 1997;126(5):376-380.
43. Higgins J, Green S,. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0.* The Cochrane Collaboration; 2011.
44. 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.
45. Agency for Healthcare Research and Quality. U.S. Preventive Services Task Force Procedure Manual. 2008.
46. Agency for Healthcare Research and Quality. *U.S. Preventive Services Task Force Procedure Manual.* 2008.
47. Ollendorf DA, Pearson SD. ICER Evidence Rating Matrix: A User's Guide. 2020; https://icer-review.org/methodology/icers-methods/icer-evidence-rating-matrix/. Accessed January 31, 2020.
48. 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.
49. 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.
50. Rucker G, Petropoulou M, Schwarzer G. Network meta-analysis of multicomponent interventions. *Biometrical journal Biometrische Zeitschrift.* 2019.
51. Guimbellot JS, Baines A, Khan U, et al. Long Term Effects of Ivacaftor in G551D Patients: Five Year Follow-up Data in GOAL-E2. *Pediatric Pulmonology.* 2018;53(2):232-232.
52. Middleton PG, Mall M, Drevinek P, et al. Elexacaftor-Tezacaftor-Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele. *New England Journal of Medicine.* 2019;381(19):1809-1819.

53. Heijerman H, McKone E, Downey D, et al. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blink, randomised, phase 3 trial. *Lancet (London, England).* 2019;394(10212):1940-1948.
54. Keating D, Marigowda G, Burr L, et al. VX-445–Tezacaftor–Ivacaftor in Patients with Cystic Fibrosis and One or Two Phe508del Alleles. *New England Journal of Medicine.* 2018;379(17):1612-1620.
55. Keating D, Wilson L, Williams E, Kotsimbos T, Wilson J. Ivacaftor withdrawal syndrome during a randomised placebo-controlled cross-over study. *Journal of Cystic Fibrosis.* 2019;18(S1):S130-130.
56. Rosenfeld M, Cunningham S, Harris WT, et al. An open-label extension study of ivacaftor in children with CF and a CFTR gating mutation initiating treatment at age 2-5years (KLIMB). *Journal of Cystic Fibrosis.* 2019;18(6):838-843.
57. Wilson J, Allen-Graham J, Talbot A, et al. Treatment with ivacaftor in CF patients with the G551D mutation is associated with improvement in cognition. *Journal of Cystic Fibrosis.* 2018;17:S57-57.
58. Bell S, Mainz J, MacGregor G, et al. Patient-reported outcomes in patients with cystic fibrosis with a G551D mutation on ivacaftor treatment: results from a cross-sectional study. *BMC Pulmonary Medicine.* 2019;19(146):1-9.
59. Feng L, Grosse SD, Green R, Fink A, Sawicki GS. Precision Medicine in Action: The Impact of Ivacaftor on Cystic Fibrosis-Related Hospitalizations. *Health Affairs.* 2018;37(5):773-779.
60. Hubert D, Fajac I, Munck A, et al. An Observational Study of Ivacaftor in Patients with Cystic Fibrosis in France: First Interim Analysis of Health Care Resource Utilization from the BRIO Study. *Value in Health.* 2018;21(3):342-342.
61. Kirwan L, Fletcher G, Harrington M, et al. Temporal trends in key outcome measures in cystic fibrosis patients

treated with ivacaftor: real-world data from the Irish CF registry. *Journal of Cystic Fibrosis.* 2017;16:S48-48.
62. McCormick J, Cho D, Lampkin B, et al. Ivacaftor improves rhinologic, psychologic, and sleep-related quality of life in G551D cystic fibrosis patients. *International Forum of Allergy & Rhinology.* 2019;9(3):292-297.
63. Volkova N, Moy K, Evans J, et al. Disease progression in patients with cystic fibrosis treated iwth ivacaftor: Data from national US and UK registries. *Journal of Cystic Fibrosis.* 2019;19:68-79.
64. Ramsey BW, Davies J, McElvaney NG, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *The New England journal of medicine.* 2011;365(18):1663-1672.
65. 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.
66. 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.
67. 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.
68. 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.

69. 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.
70. 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.
71. Mayer-Hamblett N, Zemanick ET, Odem-Davis K, VanDevanter DR, Rowe S, Konstan M. CFTR Modulator-Induced Sweat Chloride Changes Across the Cystic Fibrosis Population: First Results from the CHEC-SC Study. *Pediatric Pulmonology.* 2019;54(S2):229-229.
72. 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.
73. McKone EF, Emerson SS, Edwards KL, Aitken ML. Effect of genotype on phenotype and mortality in cystic fibrosis: a retrospective cohort study. *Lancet (London, England).* 2003;361(9370):1671-1676.
74. Chilvers M, Davies JC, Ratjen F, et al. Long-term safety and efficacy of lumacaftor/ivacaftor therapy in patients aged 6–11 years with cystic fibrosis homozygous for the F508del-CFTR mutation (F/F). *Journal of Cystic Fibrosis.* 2019;18:S23.
75. Chilvers M, Owen C, G M, et al. Safety and Efficacy of Lumacaftor/Ivacaftor in patients aged ≥6 years with CF homozygous for f508del-CFTR (phase 3 extension study). *Pediatric Pulmonology.* 2017;52(Suppl 47):319-320.
76. McColley SA, Konstan MW, Ramsey BW, et al. Lumacaftor/Ivacaftor reduces pulmonary exacerbations in patients irrespective of initial changes in FEV1. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society.* 2019;18(1):94-101.
77. McNamara JJ, McColley SA, Marigowda G, et al. Safety, pharmacokinetics, and pharmacodynamics of lumacaftor and ivacaftor combination therapy in children aged 2-5 years with cystic fibrosis homozygous for F508del-CFTR: an open-label phase 3 study. *The Lancet Respiratory medicine.* 2019;7(4):325-335.
78. Flume P, Lekstrom-Himes J, Fischer Biner R, et al. A phase 3, open-label study of tezacaftor/ivacaftor (TEZ/IVA) therapy: interim analysis of pooled safety, and efficacy in patients homozygous for F508del-CFTR. *Journal of Cystic Fibrosis.* 2018;17:S64-S65.
79. Yang Y, Rizio A, Chuang C-C, et al. Effects of tezacaftor/ivacaftor (TEZ/IVA) treatment in patients with cystic fibrosis homozygous for F508del-CFTR: patient-reported outcomes in a phase 3 randomized, controlled trial (EVOLVE). *Thorax.* 2018;73(Suppl 4):A42-A42.
80. Burgel P, Munck A, Durieu I, et al. Real-Life Safety and Effectiveness of Lumacaftor–Ivacaftor in Patients with Cystic Fibrosis. *American journal of respiratory and critical care medicine.* 2020;201(2):188-197.
81. Kirwan L, Rice M, Babu S, Zhou S, Fletcher G, Jackson AD. Key outcomes in cystic fibrosis patients treated with Orkambi for 12 months: real-world data from the Irish Cystic Fibrosis Registry. *Journal of Cystic Fibrosis.* 2019;18:S131-131.
82. Wark PA, Tong K, Dorahy D, et al. A multicentre, observational case-control study to determine the effect of lumacaftor/ivacaftor in patients with severe lung disease and cystic fibrosis. *Pediatric Pulmonology.* 2019;54(S2):432-432.
83. 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.
84. Taylor-Cousar JL, Munck A, McKone E, et al. Tezacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del. *The New England journal of medicine.* 2017;377(21):2013-2023.

85. 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.
86. 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.
87. 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.
88. Chilvers M, Davies JC, Ratjen F, et al. Long-term safety and efficacy of lumacaftor/ivacaftor therapy in patients aged 6-11 years with cystic fibrosis homozygous for the F508del-CFTR mutation. *Journal of Cystic Fibrosis.* 2019;18(S1):S23-23.
89. Chuang C, Rizio A, Loop B, et al. Effects of tezacaftor/ivacaftor (TEZ/IVA) treatment in patients heterozygous for F508del-CFTR and a residual function mutation: patient-reported outcomes in a phase 3 randomized, controlled trial (EXPAND). *Thorax.* 2018;73(Suppl 4):A41-A41.
90. Walker S, Flume P, McNamara J, et al. A phase 3 study of tezacaftor in combination with ivacaftor in children aged 6 through 11years with cystic fibrosis. *Journal of Cystic Fibrosis.* 2019;18(5):708-713.
91. Rowe SM, Daines C, Ringshausen FC, et al. Tezacaftor–Ivacaftor in Residual-Function Heterozygotes with Cystic Fibrosis. *New England Journal of Medicine.* 2017;377(21):2024-2035.
92. 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.
93. 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.
94. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: Second panel on cost-effectiveness in health and medicine. *JAMA.* 2016;316(10):1093-1103.
95. McKone E, Goss CH, Aitken ML. Genotype as a Predictor of Prognosis in Cystic Fibrosis. *Chest.* 2006;130(5):1441-1447.
96. 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.
97. Konstan MW, Morgan WJ, Butler SM, et al. Risk factors for rate of decline in forced expiratory volume in one second in children and adolescents with cystic fibrosis. *J Pediatr.* 2007;151(2):134-139, 139.e131.
98. 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.
99. Goss CH, Burns JL. Exacerbations in cystic fibrosis: epidemiology and pathogenesis (part 1). *Thorax.* 2007;62(4):8.
100. 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.
101. 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.

102. 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.
103. 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.
104. 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.
105. 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.
106. 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.
107. The National Institute for Health and Care Excellence. NICE Committee Papers. 2016.
108. The National Institute for Health and Care Excellence. Lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation. 2016.
109. Arias E, Xu J. United States Life Tables, 2017. *National vital statistics reports.* 2019;68(7).
110. 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.
111. Cystic Fibrosis Foundation. *Cystic Fibrosis Foundation Patient Registry 2016 Annual Data Report.* cff.org2017.
112. 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.
113. 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.
114. 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.
115. Pharmaceutical Pricing. U.S. department of Veterans Affairs; 2018. Accessed January 16th, 2018.
116. 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.
117. 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.
118. 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.
119. Moreno SG, Ray JA. The value of innovation under value-based pricing. *Journal of Market Access & Health Policy.* 2016;4:10.3402/jmahp.v3404.30754.
120. Garrison LP, Jr., Mansley EC, Abbott TA, 3rd, Bresnahan BW, Hay JW, Smeeding J. Good research practices for measuring drug costs in cost-effectiveness analyses: a societal perspective: the

ISPOR Drug Cost Task Force report--Part II. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2010;13(1):8-13.
121. National Institute for Health and Care Excellence. Lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation: Technology appraisal guidance [TA398]. 2016; https://www.nice.org.uk/guidance/ta398/chapter/4-Committee-discussion#cost-effectiveness-2. Accessed February 28, 2020.
122. Dagoni R. Outrage as Teva Charges $18,275 for Generic Drug in US. *Jerusalem Post*2018.
123. 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.
124. Ouyang L, Grosse SD, Amendah DD, Schechter M. Healthcare expenditures for privately insured people with cystic fibrosis. *Pediatric Pulmonology.* 2009;44(10):989-996.
125. 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.
126. Grosse SD, Do T, Vu M, Feng L, Berry J, Sawicki GS. Healthcare expenditures for privately insured US patients with cystic fibrosis, 2010-2016. *Pediatric Pulmonology.* 2018;53(12):1611-1618.
127. Bentley TS, Phillips SJ. *2017 U.S. organ and tissue transplant cost estimates and discussion.* Milliman;2017.
128. 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.
129. Neri L, Lucidi V, Catastini P, Colombo C. Caregiver burden and vocational participation among parents of adolescents with CF. *Pediatr Pulmonol.* 2015.
130. 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.
131. Sanders DB, Bittner RC, Rosenfeld M, Hoffman LR, Redding GJ, Goss CH. Failure to recover to baseline pulmonary function after cystic fibrosis pulmonary exacerbation. *American journal of respiratory and critical care medicine.* 2010;182(5):627-632.
132. 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.
133. Hanmer J, Lawrence W, Anderson J, Kaplan R, DG F. Report of Nationally Representative Values for the Noninstitutionalized US Adult Population for 7 Health-Related Quality-of-Life Scores. *Medical Decision Making.* 2006;26(4):391-400.
134. Cystic Fibrosis Foundation. Cystic Fibrosis Foundation Patient Registry (Unpublished Data). In. Bethesda, MD2018.
135. Pearson S. The ICER Value Framework: Integrating Cost Effectiveness and Affordability in the Assessment of Health Care Value. *Value in Health.* 2018;21(3):258-265.
136. 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.
137. Ollendorf DA, Pearson SD. An integrated evidence rating to frame comparative effectiveness assessments for decision makers. *Medical care.* 2010;48(6 Suppl):S145-152.
138. ClinicalTrials.gov. A Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of VX-661/Ivacaftor in Pediatric Subjects With Cystic Fibrosis (CF). 2019; https://clinicaltrials.gov/ct2/show/results/NCT02953314. Accessed 01/22/2020.

139. ClinicalTrials.gov. A Study to Evaluate the Safety and Efficacy of Long Term Treatment With VX-661 in Combination With Ivacaftor in Subjects With Cystic Fibrosis Who Have an F508del-CFTR Mutation. 2019; https://clinicaltrials.gov/ct2/show/NCT02565914.
140. ClinicalTrials.gov. Rollover Study to Evaluate the Safety and Efficacy of Long-term Treatment With Lumacaftor in Combination With Ivacaftor. 2019; https://clinicaltrials.gov/ct2/show/NCT02544451.
141. McColley SA, Konstan MW, Ramsey BW, et al. Association between changes in percent predicted fev1 and incidence of pulmonary exacerbations, including those requiring hospitalization and/or iv antibiotics, in patients with CF treated with lumacaftor in combination with ivacaftor. *Pediatric Pulmonology.* 2015;50:282.
142. Food and Drug Administration. Ivacaftor Prescribing Information. In:2017.
143. Food and Drug Administration. U.S. Prescribing Information - Symdeko. In: HHS, ed. www.fda.gov2018.
144. Pickard AS, Law EH, Jiang R, et al. United States Valuation of EQ-5D-5L Health States Using an International Protocol. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2019;22(8):931-941.
145. 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.
146. 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.
147. 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.
148. 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.
149. 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.
150. Accurso FJ, Rowe SM, Clancy JP, et al. Effect of VX-770 in persons with cystic fibrosis and the G551D-CFTR mutation. *The New England journal of medicine.* 2010;363(21):1991-2003.
151. 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.
152. Konstan MW, Plant BJ, Elborn JS, et al. Efficacy response in CF patients treated with ivacaftor: post-hoc analysis. *Pediatr Pulmonol.* 2015;50(5):447-455.
153. 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.
154. 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.
155. 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.

156. Barry PJ, Plant BJ, Simmonds NJ, et al. Ivacaftor decreases mortality in G551D patients with severe lung disease. *Pediatric Pulmonology.* 2015;50:275-276.
157. 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.
158. 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.
159. 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.
160. 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.
161. 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.
162. 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.
163. 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.
164. 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.
165. 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.
166. 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.
167. 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.
168. 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.
169. 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.
170. 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.
171. 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.
172. Stalvey MS, Pace J, Niknian M, et al. Growth in Prepubertal Children With Cystic Fibrosis Treated With Ivacaftor. *Pediatrics.* 2017;139(2).

173. 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.
174. Heltshe SL, Godfrey EM, Josephy T, Aitken ML, Taylor-Cousar JL. Pregnancy among cystic fibrosis women in the era of CFTR modulators. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society.* 2017.

APPENDICES

Appendix A. Search Strategies and Results

Table A1. PRISMA 2009 Checklist

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

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

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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

Table A2. Elexacaftor/tezacaftor/ivacaftor

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

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

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

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

Search strategy of EMBASE (11/08/2019)

Table A4. Elexacaftor/tezacaftor/ivacaftor

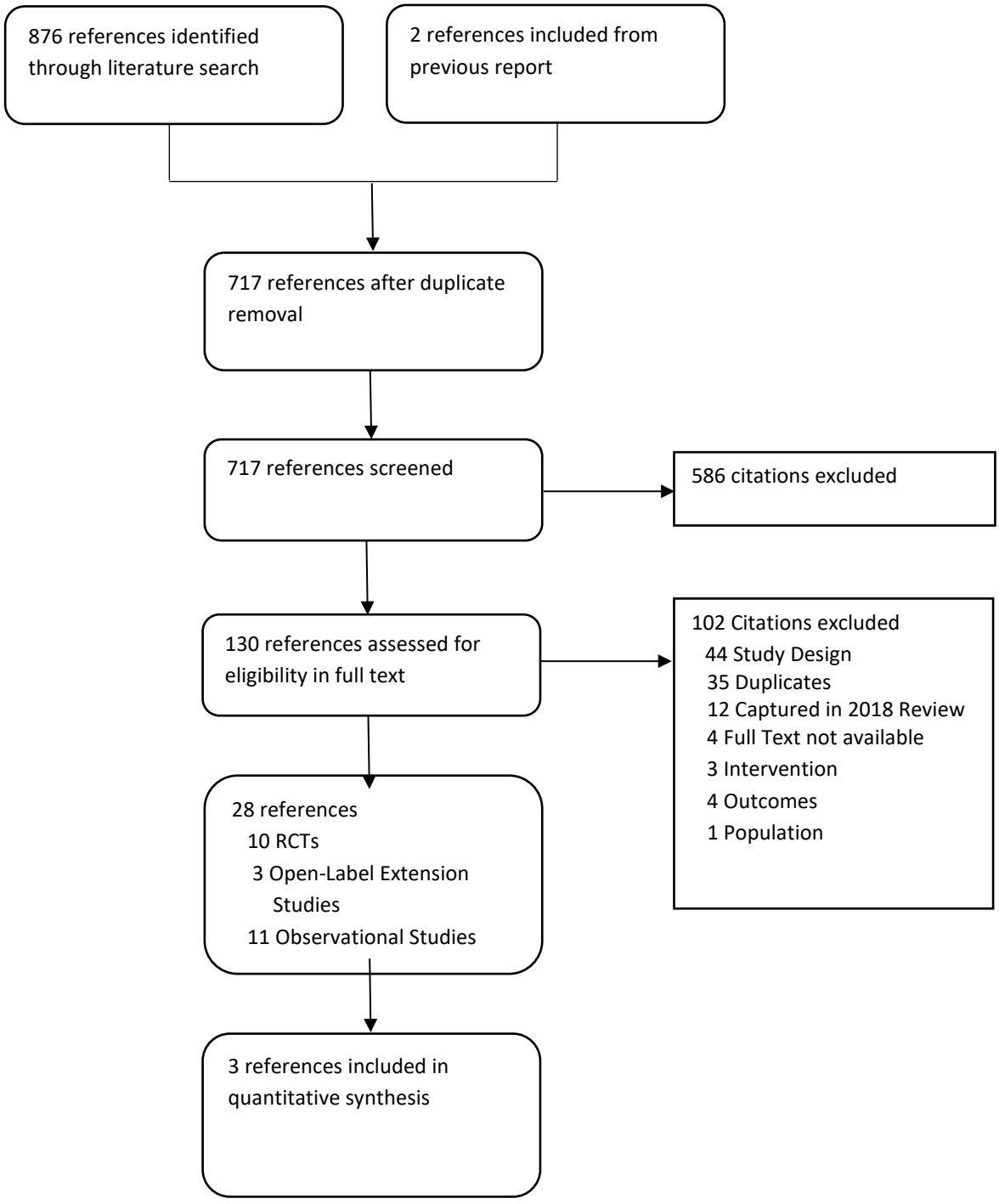
#	Search Terms
#1	'cystic fibrosis'/exp OR 'cystic fibrosis':ti,ab
#2	(deltaF508-CFTR OR deltaF508-CFTR protein OR f508del):ti,ab
#3	'cystic fibrosis transmembrane conductance regulator'/exp OR ('cystic fibrosis transmembrane conductance regulator' OR 'CFTR'):ti,ab
#4	'cystic fibrosis transmembrane conductance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

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

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

#15	#14 AND (2017:py OR 2018:py OR 2019:py)
#16	#15 AND [English]/lim

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



Appendix B. Previous Systematic Reviews and Technology Assessments

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

Technology Assessments

NICE

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

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

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

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

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

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

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

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

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

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

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

CADTH

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

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

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

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

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

CADTH recommends Kalydeco for the treatment of CF in patients ages 18 years and older with the *R117H* CFTR mutation if the following clinical criteria and condition are met 1) Confirmed CF diagnosis that is accompanied by chronic sinopulmonary disease and 2) in consultation with clinical

experts, discontinuation criteria should be developed for non-responders. Furthermore, CADTH stipulated that the price of Kalydeco should be substantially decreased.

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

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

Previous Systematic Reviews

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

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

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

This systematic review and meta-analysis was conducted to examine the efficacy and safety of Orkambi and Symdeko combination therapy in the treatment of CF patients who are homozygous for the *F508del*-CFTR mutation. Five randomized controlled trials (RCTs) were included in the quantitative analysis. Efficacy was evaluated based on lung function, nutritional status, and CFQR respiratory domain scores. Safety was assessed based on the occurrence of adverse events and the

number of AEs that led to treatment discontinuation. The two combination therapies were found to significantly improve $ppFEV_1$, CFQ-R respiratory domain score, as well as BMI when compared to placebo. Orkambi and Symdeko were found to have a safety profile comparable to placebo, although the proportion of discontinuations due to AEs was significantly higher for the combination therapies when compared to placebo.

Patel S, Sinha IP, Dwan K, Echevarria C, Schechter M, Southern KW. Potentiators (specific therapies for class III and IV mutations) for cystic fibrosis. *The Cochrane database of systematic reviews.* 2015(3):Cd009841.

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

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

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

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

Cystic Fibrosis Foundation, Borowitz D, Parad RB, et al. Cystic Fibrosis Foundation practice guidelines for the management of infants with cystic fibrosis transmembrane conductance regulator-related metabolic syndrome during the first two years of life and beyond. Journal of Pediatrics. 2009;155(6):S106-116.

We identified one systematic review and guidline document from the Cystic Fibrosis Foundation for the use of Kalydeco and Orkambi.[136] The guideline was designed to advise clinicians, CF patients, and their families on the use of Kalydeco and Orkambi. A multidisciplinary committee was

assembled to develop clinical questions using the Patient-Intervention-Comparison-Outcome (PICO) format. A systematic review of evidence for Kalydeco and Orkambi was conducted to identify relevant publications that met the PICO criteria.

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

Appendix C. Ongoing Studies

Trial	Study Design	Study Arms	Patient Population	Key Outcomes	Estimated Completion
Elexacaftor (ELX) / Tezacaftor (TEZ) / Ivacaftor (IVA)					
Evaluation of VX-445/ TEZ/ IVA in Cystic Fibrosis Subjects 6 Through 11 Years of Age NCT03691779 Vertex Pharmaceuticals	Phase 3, open-label, non-randomized, sequential assignment Estimated N: 56	**Experimental** Part A: - Morning: VX-445/ IVA - Evening: IVA Part B: - Morning: VX-445/ TEZ/ IVA - Evening: IVA (dose to be based on the outcome of Part A)	**Inclusions** - Ages 6 – 11 years - Homozygous or heterozygous for F508del mutation (F/F or F/MF genotypes) - ppFEV$_1$ value ≥40% for age, sex, and height **Exclusions** - Clinically significant cirrhosis with or without portal hypertension - Glucose-6-phosphate dehydrogenase (G6PD) deficiency - Lung infection with organisms associated with a more rapid decline in pulmonary status - Solid organ or hematological transplantation	**Primary Outcomes** *[Day 1 through 15]* Part A: - Observed pre-dose concentration of VX-445, TEZ, and IVA - Maximum Observed Concentration of VX-445, TEZ, and IVA - Area under the concentration versus time curve during a dosing interval of VX-445, TEZ, and IVA Part B: Safety and tolerability as assessed by number of subjects with AEs and SAEs *[Time Frame: from baseline through safety follow-up (28 Weeks)]* **Secondary Outcomes** Part A *[Day 1 through 15]* - Maximum observed concentration of VX-445, TEZ, and IVA metabolites - Observed pre-dose concentration of VX-445, TEZ, and IVA metabolites - Area under the concentration versus time curve during a dosing interval of VX-445, TEZ, and IVA metabolites - Safety and tolerability as assessed by number of subjects with AEs and [from baseline through safety follow-up (28 Weeks)] Part B *[Baseline through Weeks 12 and 24]* - Absolute change in ppFEV$_1$ - Absolute change in sweat chloride - Absolute change in CFQ-R respiratory domain score - Absolute change in BMI and BMI for age-z-score	January 2020

Trial	Study Design	Study Arms	Patient Population	Key Outcomes	Estimated Completion
				- Absolute change in weight and weight for age-z-score - Absolute change in height and height for age-z-score - Absolute change in the Modified Facial Hedonic Scale - Trough of VX-445/TEZ/IVA, and IVA metabolites - Absolute change in LCI2.5	
Clinical Outcomes of Triple Combination Therapy in Severe Cystic Fibrosis Disease NCT04038710 National Jewish Health	Observational, prospective study, cases only Estimated N: 7	Patients that are eligible to enroll in Vertex's triple combination therapy through the expanded access program	**Inclusions** - Ages ≥12 years - Confirmed CF diagnosis - Ability to reproducibly perform spirometry - Physician decision to treat with TCT through the EAP program **Exclusions** - Any acute lower respiratory symptoms treated with oral, inhaled or intravenous antibiotics or systemic corticosteroids within the 2 weeks prior - Major or traumatic surgery within 12 weeks - Initiation of any new chronic therapy within 4 weeks - Use of an investigational agent within 28 days - History of lung or liver transplantation or listing for organ transplantation	**Primary Outcomes** *[Baseline up to 52 weeks]* - Pulmonary Function (FEV1 values) **Secondary Outcomes** *[Baseline up to 52 weeks]* CFQ-R score	March 2020

Trial	Study Design	Study Arms	Patient Population	Key Outcomes	Estimated Completion
A Study Evaluating the Efficacy and Safety of VX445/ Tezacaftor/ Ivacaftor in Cystic Fibrosis Subjects, Homozygous for F508del NCT04105972 Vertex Pharmaceuticals	Phase 3b, randomized, double-blind, parallel assignment Estimated N: 158	**Experimental** - Morning: ELX/TEZ/IVA - Evening: IVA **Comparator** - Morning: TEZ/IVA or IVA - Evening: IVA	**Inclusions** - Ages ≥12 years - Homozygous for F508del mutation (F/F) - FEV1 value ≥40% and ≤90% of predicted mean for age, sex, and height **Exclusions** - Clinically significant cirrhosis with or without portal hypertension - Lung infection with organisms associated with a more rapid decline in pulmonary status - Solid organ or hematological transplantation	**Primary Outcomes** *[Baseline through Week 24]* - Absolute change in CFQ-R respiratory domain score **Secondary Outcomes** *[Baseline through Week 24]* - Absolute change in $ppFEV_1$ - Absolute change in sweat chloride (SwCl) - Safety and tolerability as assessed by number of subjects with AEs and SAEs *[Baseline through Week 28]*	September 2020
A Phase 3 Study of VX-445 Combination Therapy in Cystic Fibrosis (CF) Subjects Heterozygous for F508del and a Gating or Residual Function Mutation (F/G and F/RF Genotypes) NCT04058353 Vertex Pharmaceuticals	Phase 3, randomized, double-blind, parallel assignment Estimated N: 250	**Experimental** Morning: ELX/TEZ/IVA Evening: IVA **Comparator** Morning: TEZ/IVA or IVA Evening: IVA	**Inclusions** - Ages ≥12 years - Confirmed CF diagnosis - Heterozygous for F508del and either a gating or residual function mutation (F/G and F/RF genotypes) - FEV1 value ≥40% and ≤90% of predicted mean for age, sex, and height **Exclusions** - Clinically significant cirrhosis with or without portal hypertension - Lung infection with organisms associated with a more rapid decline in pulmonary status - Solid organ or hematological transplantation	**Primary Outcomes** *[Baseline through Week 8]* - Absolute change in $ppFEV_1$ for ELX/TEZ/IVA arm **Secondary Outcomes** *[Baseline through Week 8]* - Absolute change in sweat chloride (SwCl) for ELX/TEZ/IVA group (and compared to control group) - Absolute change in $ppFEV_1$ for ELX/TEZ/IVA group compared to the control group - Absolute change from baseline in CFQ-R respiratory domain score for ELX/TEZ/IVA group (and compared to control group) - Safety and tolerability as assessed by number of subjects with AEs and SAEs	October 2020

Trial	Study Design	Study Arms	Patient Population	Key Outcomes	Estimated Completion
Impact of Triple Combination CFTR Therapy on Sinus Disease NCT04056702 Jennifer Taylor-Cousar / CFF	Observational, prospective cohort study Estimated N: 70	**Cohort 1** - ELX/TEZ/IVA **Cohort 2** - No treatment (patients ineligible for treatment)	**Inclusions** - 18 – 89 years - CF and comorbid chronic sinus disease **Exclusions** - Sinus surgery within the last 6 months or planned sinus surgery during the study period - Recent pulmonary exacerbation or viral infection within two weeks of initial visit	**Primary Outcomes** *[From baseline up to 6 months]* - Change in Sinus CT opacification **Secondary Outcomes** *[From baseline up to 6 months]* - Change in 22-item Sino-Nasal Outcome Test (SNOT-22) score - Change in Questionnaire for Olfactory Disorders (QOD) score	April 2021
A Study Evaluating the Long-term Safety and Efficacy of VX-445 Combination Therapy NCT03525574 Vertex Pharmaceuticals	Phase 3, open-label, single group assignment Estimated N: 507	**Experimental** - Morning: VX-445/ TEZ/ IVA - Evening: IVA	**Inclusions** - Completed study drug treatment in a parent study (VX17-445-102, VX17-445-103); or had study drug interruption(s) in a parent study but completed study visits up to the last scheduled visit of the Treatment Period in the parent study. **Exclusions** - History of drug intolerance in a parent study that would pose an additional risk to the subject - Current participation in an investigational drug trial (other than a parent study)	**Primary Outcomes** *[Baseline up to 100 weeks]* - Safety and tolerability as assessed by number of subjects with AEs and SAEs **Secondary Outcomes** *[Baseline up to 96 weeks]* - Absolute change from baseline in ppFEV$_1$ - Absolute change in sweat chloride (SwCl) - Number of pulmonary exacerbations (PEx) - Time to first PEx - Absolute change in BMI and BMI z-score - Absolute change in body weight - Absolute change from baseline in CFQ-R respiratory domain score	June 2021
A Study Evaluating the Long-term Safety of VX-445 Combination Therapy NCT04043806 Vertex Pharmaceuticals	Phase 3, open-label, single group assignment Estimated N: 480	**Experimental** - Morning: ELX/TEZ/IVA - Evening: IVA	**Inclusions** - 12 years and older - Currently participating in NCT03447262 **Exclusions** - History of drug intolerance in study NCT03447262 that would pose an additional risk to the subject - Current participation in an investigational drug trial (other than study NCT03447262)	**Primary Outcome** [*Baseline through Week 100*] - Safety and tolerability as assessed by number of subjects with AEs and SAEs	May 2022

Trial	Study Design	Study Arms	Patient Population	Key Outcomes	Estimated Completion
Study Evaluating the Long-term Safety and Efficacy of VX-445 Combination Therapy NCT04058366 Vertex Pharmaceuticals	Phase 3, open-label, single group assignment Estimated N: 250	**Experimental** - Morning: ELX/ TEZ/ IVA - Evening: IVA	**Inclusions** - 12 years and older - Completed study drug treatment in parent study (VX18-445-104; NCT04058353); or had study drug interruption(s) in parent study but completed study visits up to the last scheduled visit of the Treatment Period in the parent study **Exclusions** - History of study drug intolerance in parent study that would pose an additional risk to the subject	**Primary Outcomes** *[From Baseline up to Week 100]* - Safety and tolerability as assessed by number of subjects with AEs and SAEs **Secondary Outcomes** *[From Baseline up to Week 96]* - Absolute change in ppFEV$_1$ - Absolute change in sweat chloride (SwCl) - Absolute change in BMI - Absolute change in BMI z-score - Absolute change in body weight - Absolute change in CFQ-R respiratory domain score	August 2022
A Prospective Study to Evaluate Biological and Clinical Effects of Significantly Corrected CFTR Function (PROMISE) NCT04038047 David Nichols, MD (Seattle Children's Hospital) / CFF	Observational, prospective, Cohort Study Estimated N: 400	**Cohort** ELX/TEZ/IVA	**Inclusions** - Ages ≥12 years - CF diagnosis with CFTR mutations consistent with the FDA approved indication - Willing to fast for 8 hours prior to study visits - Enrolled in the CFF Patient Registry - Clinically stable with no significant changes in health status within the 14 days prior **Exclusions** - Use of Trikafta within the 180 days prior - Acute use of oral, inhaled or intravenous antibiotics, or systemic corticosteroids for lower respiratory tract symptoms within 2 weeks prior - Initiation of any new chronic therapy within the 4 weeks prior - Use of an investigational agent within the 28 days prior - Use of chronic oral corticosteroids (equivalent to 10 mg. or more per day of prednisone) within the 28 days prior	**Primary Outcomes** *[Baseline through 6 and 24 months]* - Change in sweat chloride - Change in FEV1 **Secondary Outcomes** *[Baseline through 6 and 24 months]* - Change in weight - Change in BMI - Change in CFQ-R	November 2022

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

Trial	Study Design	Study Arms	Patient Population	Key Outcomes	Estimated Completion
			- Presence of a condition or abnormality that would compromise the safety of the patient or the quality of the data - Any acute lower respiratory symptoms treated with oral, inhaled, or IV antibiotics, or systemic corticosteroids within the 2 weeks prior - Major or traumatic surgery within 12 weeks - Unable or unwilling to fast (including no enteric tube feedings) for at least 6 hours prior each visit - Initiation of any new chronic therapy within 4 weeks - Use of an investigational agent and/or oral corticosteroids within 28 days prior to Visit 1 - Treatment for nontuberculous mycobacterial infection, consisting of greater than or equal to two antibiotics (oral, IV, and/or inhaled) within 28 days prior to Visit 1 - History of lung or liver transplantation, or listing for organ transplantation	- Weight in kilograms - BMI - Fecal elastase - Measure of pancreatic function - Transaminase measurements - Bronchodilator requirements in doses/day - Determination of changes in bronchodilator use following transition - Insulin requirements in units/day	
Gut Imaging for Function & Transit in Cystic Fibrosis Study 2 (GIFT-CF2) NCT04006873 Nottingham University Hospitals NHS Trust	Phase 2, randomized, triple-blind, crossover assignment Estimated N: 12	**Experimental** - Morning: TEZ/IVA - Evening: IVA **Comparator** - Placebo	**Inclusions** - Confirmed diagnosis of CF, either by sweat test or genetic testing **Exclusions** - Currently taking CFTR modulator drug - ppFEV$_1$ <40% - Contra-indication to MRI scanning - Unable to stop medications directly prescribed to alter bowel habit, such as laxatives or anti-diarrheas, on the study day - Previous resection of any part of the GI tract apart from appendicectomy or cholecystectomy. Surgical relief of	**Primary Outcomes** *[1 day of scanning]* - Oro-caecal Transit Time **Secondary Outcomes** *[1 day of scanning]* - Gastric volume - Small bowel water content - Colonic volume - Gastrointestinal symptoms **Other Outcomes** *[1 day of scanning]* - Sigmoid colon volume - T1 relaxation of ascending colon chyme - Fat fraction of ascending colon chyme - Faecal elastase - Sputum and faecal microbiome	August 2020

Trial	Study Design	Study Arms	Patient Population	Key Outcomes	Estimated Completion
			meconium ileus or DIOS will be permitted unless clinical records show excision of intestine >20cm in length. - Intestinal stoma - Diagnosis of inflammatory bowel disease or coeliac disease confirmed by biopsy - Gastrointestinal malignancy	- Faecal calprotectin	
Novel Therapeutic Approaches for Treatment of CF Patients With W1282X Premature Termination Codon Mutations NCT03624101 University of Alabama at Birmingham	Phase 4, open-label, single group assignment Estimated N: 5	**Experimental** - Morning: TEZ/IVA - Evening: IVA *(Subjects will receive Symdeko in 3 intermittent four-week intervals, followed by a 4-week follow-up period (for safety and to detect efficacy changes upon washout))*	**Inclusions** - Ages ≥18 years - Body weight ≥16kg - CF diagnosis and documentation of the presence of a nonsense mutation of the CFTR gene, as determined by historical genotyping - FEV1 ≥30% and ≤ 90% of predicted for age, gender, and height **Exclusions** - Any change in a chronic treatment/prophylaxis regimen for CF or for CF-related conditions within 2 weeks prior to screening - Ongoing participation in any other therapeutic clinical trial - Evidence of pulmonary exacerbation or acute upper or lower respiratory tract infection within 2 weeks - History of solid organ or hematological transplantation; positive hepatitis B surface antigen test; hepatitis C antibody test; or HIV - Major complication of lung disease within 4 weeks prior to screening - Current smoker or a smoking history of ≥ 10 pack-years - Prior or ongoing medical condition, medical history, physical findings, electrocardiogram findings, or laboratory abnormality that could	**Primary Outcomes** - Lung function (change in FEV_1) at 24 weeks	November 2020

Trial	Study Design	Study Arms	Patient Population	Key Outcomes	Estimated Completion
			adversely affect the safety of the subject, makes it unlikely that the course of treatment or follow-up would be completed, or could impair the assessment of study results		
A Study to Evaluate the Safety and Efficacy of Long-term Treatment With TEZ/IVA in CF Subjects With an F508del CFTR Mutation NCT03537651 Vertex Pharmaceuticals	Phase 3, open-label, single group assignment Estimated N: 130	**Experimental** - Subjects <40 kg: Morning: TEZ/ IVA - Evening: IVA Subjects ≥40 kg: - Morning: TEZ/ IVA - Evening: IVA	**Inclusions** - Ages ≥6 years - Completed the Week 24 Visit in Study 113 Part B or the Week 8 Visit in Study 115 - Eligible CFTR Mutation **Exclusions** - Ongoing participation in another study with investigational drug	**Primary Outcomes** *[From baseline up to 28 days after Last Dose]* - Safety and tolerability of long-term TEZ/IVA treatment based on AEs and SAEs **Secondary Outcomes** *[Baseline through 96 weeks]* - Absolute change in lung clearance index2.5 - Absolute change in sweat chloride - Absolute change in CFQ-R respiratory domain score - Absolute change in BMI	December 2020
A Study to Evaluate the Safety and Efficacy of Long-Term Treatment With VX-661 in Combination With Ivacaftor in Subjects With Cystic Fibrosis Who Have an F508del-CFTR Mutation NCT02565914 Vertex Pharmaceuticals	Phase 3, open-label, parallel assignment Estimated N: 1116	**Experimental** Part A-C: Morning: VX-661 / IVA Evening: IVA **Comparator** Part A: Observational Control Group (no intervention)	**Inclusion** - Ages ≥12 years - Subjects entering the treatment cohort must have completed study drug Treatment Period in a parent study - Subjects re-enrolling in the Part A treatment cohort must have received ≥4 weeks of treatment - Subjects entering the Part A Observational Cohort must be <18 years old, received at least 4 weeks of treatment and completed visits up to the last scheduled visit of the Treatment Period of a parent study (and the Safety Follow up Visit for subjects from NCT02508207), but do not meet eligibility criteria for enrollment into the Treatment Cohort **Exclusion**	**Primary Outcomes** *[Baseline up to 3 years]* Part A: Safety and tolerability of long-term treatment of VX-661 in combination with ivacaftor based on AEs, ophthalmologic exams, clinical laboratory values, standard digital electrocardiograms, vital signs, and pulse oximetry **Secondary Outcomes** *[Baseline through Week 96]* Part A: - Relative change from baseline in ppFEV$_1$ - Absolute change from baseline in CFQ-R respiratory domain score - Absolute change from baseline in body weight and in body weight z-score for subjects aged <20 years - Absolute change from baseline in height z-score for subjects aged <20 years - Time-to-first pulmonary exacerbation	March 2023

Trial	Study Design	Study Arms	Patient Population	Key Outcomes	Estimated Completion
			- History of any comorbidity that might confound the results of the study or pose an additional risk to the subject - History of drug intolerance in the parent study that would pose an additional risk to the subject - Participation in an investigational drug trial other than the parent studies of NCT02565914 or other eligible Vertex studies investigating VX-661 in combination with ivacaftor, or use of a commercially available CFTR modulator	- Pharmacokinetic (PK) parameters: trough concentrations of VX-661, a VX-661 metabolite (M1-661), ivacaftor, ivacaftor metabolite (M1-ivacaftor) - Observational Cohort: Safety, as determined by related SAEs *[Baseline up to 3 years]* Parts A and B: - Absolute change from baseline in % $ppFEV_1$ - Number of pulmonary exacerbations - Absolute change from baseline in BMI and in BMI z-score for subjects aged <20 years Part B and C: - Safety and tolerability assessments including number of subjects with AEs and SAEs events *[Baseline through safety follow-up visit]*	
iPS Cell Response to CFTR Modulators: Study of Symdeko in CF Patients Carrying Partial Function Mutations NCT03506061 Emory University / NHLBI	Phase 2, open-label, single group assignment Estimated N: 22	**Experimental** - TEZ/IVA	**Inclusion** - Ages ≥12 years - A clinical diagnosis of CF and a partial function mutation not currently covered or likely to be covered for FDA treatment with a CFTR modulator. - Sweat chloride < 70 mmol/L - Pancreatic sufficiency as indicated by no exogenous pancreatic enzyme supplement therapy - FEV1% predicted ≥40 to ≤ 90% post bronchodilator - Clinically stable in the past 4 weeks with no evidence of CF exacerbation - BMI > 18 kg/m2 **Exclusion** - SUD within the last year - Pulmonary exacerbation or changes in therapy for pulmonary disease in the 4 weeks prior to screening	**Primary Outcomes** *[From baseline to Week 4]* - Change in FEV1 **Secondary Outcomes** *[From baseline to Week 4]* - Change in sweat chloride - Change in nasal potential difference (NPD) measurements - Change in CFQ-R Score	May 2023

Trial	Study Design	Study Arms	Patient Population	Key Outcomes	Estimated Completion
			- Cirrhosis or elevated liver transaminases > 3 times the ULN - Inhibitors or inducers of CYP3A4, or other medicines known to negatively influence Symdeko administration - History of solid organ transplant - History of non-TB mycobacterial infection (any positive culture in the past 18 months) or active therapy for these infections. - Treatment in the last 6 months with either Kalydeco or Orkambi - Treatment with another investigational drug or other intervention within one month prior to enrollment, throughout the duration of study participation, and for an additional four weeks following final drug administration		
Functional Respiratory Imaging (FRI) to Assess the Short-term Effect of the Product ORKAMBI (Lumacaftor/ Ivacaftor) on Lung Function in ORKAMBI naive Patients With Cystic Fibrosis Homozygous for Phe508del NCT03956589	Phase 4, open-label, single group assignment Estimated N: 20	**Experimental** - TEZ/IVA	**Inclusions** - Documented diagnosis of CF (homozygous for F508del mutation) - Age ≥ 12 years - ppFEV$_1$ > 50% - Patient must be on a stable regimen of CF medication for 4 weeks prior to Visit **Exclusions** - Anticipated requirement for hospitalization within the next three weeks - History of pneumothorax within the past 6 months - History of hemoptysis requiring embolization within the past 12 months - IV antibiotics within the past 4 weeks - Ongoing exacerbation or Allergic bronchopulmonary aspergillosis - Posttransplant patients - Patients with severe hepatic impairment	**Primary Outcomes** *[Baseline and at 3 months]* - Change in specific image-based airway resistance - Change in specific image-based airway volumes (siVaw) **Secondary Outcomes** *[Baseline and at 3 months]* - Internal Airflow Distribution - Air Trapping - Airway Wall Volume - Aerosol Deposition - Dynamic lung volumes - Static lung volumes - Airway resistances - Lung clearance index - 6-minute walking test - Sweat chloride test - CFQ-R - Digital lung auscultation - Exacerbation frequency	December 2019

Trial	Study Design	Study Arms	Patient Population	Key Outcomes	Estimated Completion
University Hospital, Antwerp					
Lumacaftor (LUM) / Ivacaftor (IVA)					
Validation of Respiratory Epithelial Functional Assessment to Predict Clinical Efficacy of Orkambi®. (PREDICT-CF) NCT03894657 Assistance Publique - Hôpitaux de Paris	Open-label, single group assignment Estimated N: 104	**Experimental** LUM/IVA	**Inclusions** - Ages ≥12 years - Homozygous for F508del Mutation - Patient never received Orkambi® in the past **Exclusions** - Homozygous F508del patients who do not meet the treatment indications according to the marketing authorization application - Active smoker - Severe nasal mucosa disrepair - Contraindications to xylocaine anesthesia, - Participation with another interventional study with drug	**Primary Outcomes** *[Baseline and at 24 week]* - Percentage of FEV_1 **Secondary Outcomes** - Z-score of FEV_1 *[Baseline, week 24 and 48]* - Percentage of FEV_1 *[Week 48]* - % of FVC; RFC *[Baseline, Week 24 and 48]* - Lung clearance index *[Baseline and Week 48]* - Height; Weight *[Baseline, Week 24 and 48]* - Colony forming unit (CFU) *[Baseline, Week 24 and 48]* - Number of exacerbations *[Baseline and Week 48]* - Sweat Chloride *[Baseline and Week 48]* - Level in Forskolin/ IBMXdependant Short Circuit Current *[At Baseline]* - Percentage of cells displaying apical staining *[At baseline]* - Area under the curve of LUM/IVA *[Week 24 and 48]* - Drug concentrations of LUM/IVA *[At Week 24 and 48]*	
Gastrointestinal Study at Orkambi Therapy in CF Patients NCT03859531 Karolinska University Hospital	Observational, Prospective cohort Study Estimated N: 20	**Cohort** LUM/IVA	**Inclusions** - CF Patients who are homozygous for F508del - Ages > 12 years **Exclusions** - Patients who the patency capsule does not pass within 48 hours - FEV1 < 30% - Liver function blood tests >3 xULN - Bilirubin >2 xULN - AST or ALT alone >5 xULN	**Primary Outcomes** *[Change from baseline at 6 months]* - Concentration of fecal calprotectin - Concentration of fecal elastase-1 - Change in small bowel capsule endoscopy (SBCE) **Secondary Outcomes** *[Change from baseline at 6 months]* - Change in CRP - Change in sedimentation rate - Concentration of serum electrophoresis	June 2020

Trial	Study Design	Study Arms	Patient Population	Key Outcomes	Estimated Completion
			- Previous lung transplant	- Change in liver function tests - Change in bilirubin	
Orkambi Treatment in 2 to 5 Year Old Children With CF NCT03795363 Children's Hospital of Philadelphia	Observational, Prospective Cohort Study Estimated N: 32	**Cohort** LUM/IVA	**Inclusions** - CF and homozygous for F508del mutations, approved for treatment - Ages 2 to <6 years **Exclusions** - On parenteral nutrition - Use of any medications that inhibit or induce cytochrome P450 (CYP) 3A - Liver function tests elevated above 3x the reference range for age and sex - Severe lung disease	**Primary Outcomes** *[At 24 weeks]* - Sleeping or Resting Energy Expenditure - Anthropometric Assessment **Secondary Outcomes** *[At 24 weeks]* - Fecal Elastase/Pancreatic Function - Fecal Calprotectin/Gut Inflammation - Plasma Total Fatty Acids **Other Outcome Measures** *[At 24 weeks]* - Dietary Intake - Serum fat soluble vitamin levels - Changes in bile acid concentration levels - Changes in concentration levels of serum calprotectin - Muscle-fat Stores - Growth Status Changes	May 2020
Orkambi Exercise Study (Orkambi) NCT02821130 University of British Columbia	Observational Prospective Cohort Study Estimated N: 11	**Cohort** LUM/IVA	**Inclusions** - Confirmed CF diagnosis and homozygous for F508del mutation - Ages ≥19 years - Stable clinical status - FEV1 < 90% predicted - BMI > 16 or <30 kg/m2 - Non-smoking or past smoking history of less than 20 pack-years **Exclusions** - A disease other than CF that could importantly contribute to dyspnea or exercise limitation - Chronic airway infection - Contraindications to clinical exercise testing - Use of supplemental oxygen or desaturation less than 85% with exercise	**Primary Outcomes** - Change in iso-time dyspnea rating from baseline to visit 3 and 4 during constant load exercise tests **Secondary Outcomes** *[At 1 and 3 months]* - Change from baseline cardio-respiratory responses during constant-load exercise tests - Change from baseline chronic activity-related dyspnea - Change from baseline QoL - Change from baseline physical activity - Change from baseline pulmonary function measures	December 2019

Trial	Study Design	Study Arms	Patient Population	Key Outcomes	Estimated Completion
			- Diagnosis of pneumothorax in past 4 weeks - History of organ transplantation		
Monitoring Response to Orkambi in Cystic Fibrosis Lung Disease by Inhaled Xenon MRI NCT02848560 Children's Hospital Medical Center, Cincinnati	Prospective, observational, Case-Control Estimated N: 38	**Treatment Group** - LUM/IVA **Control Group** - Not eligible for Orkambi Prescription	**Inclusions** Treatment Group: - Ages 6 – 12 - Homozygous F508del mutation - Anticipated to be a candidate for treatment with Orkambi Control Group: - Ages 6 – 12 at enrollment - Two non-functional CFTR mutations with one of them being F508del CFTR mutation - Not eligible for CFTR modulation therapy **Exclusions** - FEV_1% predicted <60% - Standard MRI exclusions (metal implants, claustrophobia)	**Primary Outcomes** - Hyperpolarized 129Xe magnetic resonance imaging (MRI) Image Analysis at year 3	February 2019
Impact of the Introduction of ORKAMBI on Anxiety, Depression, Quality of Life and Adherence of Adolescents and Young Adults (ORK-AJA) NCT03659214 Assistance Publique - Hôpitaux de Paris	Retrospective Cohort Study Estimated N: 60	**Treatment Group** - LUM/IVA **Control Group** - Not treated with Orkambi or treated with Kalydeco	**Inclusions** Treatment Group: - Patients with proven CF Control Group: - Patients not carrying 2 DF508 causing mutations - Patients not treated with Orkambi or treated with Kalydeco - Patients not carrying to G551D, G178R, S549N, S549R, G551S, G1244E, S1251N. S1255P or G1349D mutation **Exclusions** - Transplanted patients - Ages <12 or > 20 years	**Primary Outcome** *[At 24 months]* - Score of Generalized Anxiety Disorder (GAD-7) **Secondary Outcomes** *[At 24 months]* - Score of Patient Health Questionnaire (PHQ-9) - Scores of Cystic Fibrosis Questionnaire (CFQ 14+) - GIRERD Scale	December 2018

Trial	Study Design	Study Arms	Patient Population	Key Outcomes	Estimated Completion
Longitudinal Assessment of Exercise Capacity and Vascular Function in Patients With CF NCT03338595 Augusta University	Longitudinal Cohort Study Estimated N: 30	**Cohort** LUM/IVA	**Inclusions** - Patients diagnosed with CF - Homozygous for F508del mutation - Prescribed Orkambi - Ages ≥7 years - ppFEV$_1$ > 40% - Resting oxygen saturation > 85% - Patients with or without CFRD - Traditional CF-treatment medications **Exclusions** - ppFEV$_1$ < 40% - Resting oxygen saturation <85% - Clinical diagnosis of heart disease - Pulmonary artery hypertension - Use of VX-770 within 6 months prior	**Primary Outcome** - Maximal exercise capacity at year 1 **Secondary Outcome** - Flow mediated dilation at year 1	May 2020
Observational Study of Glucose Tolerance Abnormalities in Patient With Cystic Fibrosis Homozygous for Phe 508 Del CFTR Treated by Lumacaftor-Ivacaftor (GLUCORRECTOR) NCT03512119 University Hospital, Strasbourg, France	Observational Cohort Study Estimated N: 100	**Cohort** LUM/IVA	**Inclusions** - Patients with CF homozygous F508del mutation aged 12 years and older - Combined LUMA/IVA treatment scheduled or already started - Glucose intolerance in oral glucose tolerance test (OGTT) (ADA criteria) or newly diabetes diagnosed at the OGTT (ADA criteria) or diabetic patients with insulin requirement ≤ 0.3 unit/kg/day or without insulin treatment - Signed informed consent of patient and of one parent OR legal representative for minor subject **Exclusions** - Hypersensitivity to the active substances or to any of the excipients of LUM/IVA - Lung and/or liver transplant - Known diabetes with insulin treatment > 0.3 unit/kg/day	**Primary Outcome** - Measure of 2 hours plasma glucose value (mmol/l) of OGTT, change from baseline at 1 year **Secondary Outcomes** *[Time Frame: Day 0 and Year 1]* - Fasting and one hour glucose value of OGTT (mmol/l) - C peptide and insulin values at T0, 1,2 hours of OGTT - Glucose, insulin, and C peptide AUC of OGTT - HOMA-R, HOMA-S - Mean glucose value per day and 2 h after meal (mg/dl)	October 2018
Safety and Pharmacokinetic	Phase 3, 2-part, open-	**Experimental** Part A: LUM/IVA	**Inclusions** - Ages 1 to < 2 years	**Primary Outcome** *[From baseline to safety follow-up; up to 10 days after last dose]*	September 2020

Trial	Study Design	Study Arms	Patient Population	Key Outcomes	Estimated Completion
Study of Lumacaftor/Ivacaftor in Subjects 1 to Less Than 2 Years of Age With Cystic Fibrosis, Homozygous for F508del NCT03601637 Vertex Pharmaceuticals	label, non-randomized, single group assignment Estimated N: 40	- Cohort 1 [18 to <24 months] - Cohort 2 [12 to <18 months] Part B: LUM/IVA	- Homozygous for F508del (F/F) **Exclusions** - Any clinically significant laboratory abnormalities at the Screening Visit that would interfere with the study assessments or pose an undue risk for the subject - Solid organ or hematological transplantation	Part A: Area under the concentration versus time curve during a dosing interval (AUCtau) of LUM/IVA Part B: safety and tolerability as assessed by number of subjects with AEs and SAEs **Secondary Outcome** *[From baseline to safety follow-up; up to 10 days after last dose]* Part A: safety and tolerability as assessed by number of subjects with AEs and SAEs Part A: average observed pre-dose concentrations Part B: absolute change in sweat chloride from baseline at week 24 Part B: average observed pre-dose concentration (Trough) of LUM/IVA and their respective metabolites from baseline to safety follow-up (up to 2 weeks after last dose)	
A Study to Explore the Impact of Lumacaftor/Ivacaftor on Disease Progression in Subjects Aged 2 Through 5 Years With Cystic Fibrosis, Homozygous for F508del NCT03625466 **Vertex Pharmaceuticals**	Phase 2, randomized, placebo-controlled, double-blind to open-label, trial Estimated N: 50	**Experimental** - LUM/IVA	**Inclusions** - Confirmed CF F508del Homozygous diagnosis - Weight ≥ 8kg **Exclusions** - Solid organ or hematological transplantation - Clinically significant lab abnormalities or comorbidities that would pose a risk for study	**Primary Outcome** *[From baseline at week 48]* - Absolute change in MRI global chest score **Secondary Outcomes** *[From baseline at week 48]* - Absolute change in lung clearance index, weight-for-age z-score, stature-for-are z-score, BMI-for-age z-score	November 2020
Effect of Lumacaftor/Ivacaftor in Children With Cystic Fibrosis	Multi-center observational study	**Cohorts** - LUM/IVA - TEZ/IVA	**Inclusions** - Ages 6-18 years - CF F508del homozygous diagnosis **Exclusions**	**Primary Outcome** - Change in lung clearance index (LCI) at 12 months **Secondary Outcome**	February 2021

Trial	Study Design	Study Arms	Patient Population	Key Outcomes	Estimated Completion
Homozygote for F508del on Small Airway Function (ROOTS) NCT04138589 University Medical Center Groningen	Estimated N: 30		- Unable to perform acceptable, repeatable lung function tests	- Change in PRAGMA-CF score at 12 months	
Ivacaftor (IVA)					
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 NCT02725567 Vertex Pharmaceuticals	Phase 3, Open-label extension, single group assignment Estimated N: 35	**Experimental:** IVA (Part A) - 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 IVA (Part B) - Group 5: Participants 12 to < 24 months - Group 6: Participants 6 to < 12 months - Group 7: Participants 0 to < 6 months	**Inclusions** - Ages up to 24 months - Confirmed CF diagnosis with 1 of the following 9 CFTR mutations on at least 1 allele: G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, or G1349D **Exclusions** - History of any illness or condition that might confound the results of the study or pose an additional risk in administering study drug to the subject - Colonization with organisms associated with a more rapid decline in pulmonary status at screening - History of abnormal liver function or abnormal liver function at screening - History of solid organ or hematological transplantation - Use of any moderate or strong inducers or inhibitors of cytochrome P450 (CYP) 3A within 2 weeks prior - Participation in a clinical study involving administration of either an investigational or a marketed drug	**Primary Outcomes** Part A: - Safety, as determined by number of subjects with AEs, clinically relevant abnormal laboratory values, standard 12 lead electrocardiograms, vital signs, and ophthalmologic examinations *[Day 1 up to Day 70]* - Peak concentrations (C3-6h) of IVA, M1 IVA, and M6 IVA *[After 4 days]* - Trough concentrations (Ctrough) of IVA, M1 IVA, and M6 IVA *[After 4 days]* Part B: - Safety, as determined by number of subjects with AEs, clinically relevant abnormal laboratory values, standard 12 lead ECGs, vital signs, and ophthalmologic examinations *[Day 1 up to Week 24]* **Secondary Outcomes** *[Through Week 24]* - Peak concentrations (C3-6h) of IVA, M1 IVA, and M6 IVA - Trough concentrations (Ctrough) of IVA, M1 IVA, and M6 IVA - Absolute change from baseline in sweat chloride using quantitative pilocarpine iontophoresis	June 2020

Trial	Study Design	Study Arms	Patient Population	Key Outcomes	Estimated Completion
			within 30 days or 5 terminal half-lives before screening - Hemoglobin (Hgb) <9.5 g/dL at screening - Chronic kidney disease of ≥Stage 3 - Non-congenital or progressive lens opacity or cataract at Screening		
A Study to Evaluate the Safety of Long-term Ivacaftor Treatment in Subjects With Cystic Fibrosis Who Are Less Than 24 Months of Age at Treatment Initiation and Have an Approved Ivacaftor-Responsive Mutation NCT03277196 Vertex Pharmaceuticals	Phase 3, open-label, parallel assignment Estimated N: 75	**Experimental** - IVA **Comparator** - No intervention (observational arm)	**Inclusions** - Ages ≤24 months - Subjects transitioning from Study 124 Part B must have completed the last study visit of Study 124 Part B - Subjects Not from Study 124 Part B: Confirmed diagnosis of CF, or 2 CF-causing mutations; IVA-responsive CFTR mutation on at least 1 allele **Exclusions** Subjects from Study 124 Part B: - History of any illness or condition that might confound the results of the study or pose an additional risk in administering IVA to the subject. - Subjects receiving commercially available IVA treatment Subjects Not from Study 124 Part B: - History of any illness or condition that might confound the results of the study or pose an additional risk in administering IVA to the subject - An acute upper or lower respiratory infection, or pulmonary exacerbation, or changes in therapy for pulmonary disease within 4 weeks - Abnormal liver function at screening - Hemoglobin <9.5 g/dL at screening - History of solid organ or hematological transplantation	**Primary Outcomes** - Safety assessments based on the number of subjects with AEs and SAEs *[Baseline through safety follow-up; up to 24 weeks after last dose]* **Secondary Outcomes** - Absolute change in sweat chloride *[Baseline through Week 96]*	June 2021

Trial	Study Design	Study Arms	Patient Population	Key Outcomes	Estimated Completion
			- Use of any moderate or strong inducers or inhibitors of CYP3A within 2 weeks		
Observational Study of Outcomes in Cystic Fibrosis Patients With Selected Gating Mutations on a CFTR Allele (The VOCAL Study) NCT02445053 Vertex Pharmaceuticals	Observational, prospective cohort study Estimated N: 90	**Cohort** - IVA	**Inclusions** - Ages ≥6 years - CF diagnosis with 1 of the following CFTR mutations on at least 1 allele: G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, or G1349D **Exclusions** - Previously exposed to Kalydeco, except currently treated patients who started Kalydeco treatment within 6 months of enrollment - Currently enrolled in a Kalydeco interventional study or other interventional therapeutic clinical study directed at CFTR modulation - History of organ transplantation	**Primary Outcomes** *[48 Months]* - Number of pulmonary exacerbations and duration of treatment for pulmonary exacerbations during compared to the period before IVA treatment - Percentage of patients with cultures positive for Pseudomonas aeruginosa during compared to the period before IVA treatment - Percentage of patients with cultures positive for bacteria other than Pseudomonas aeruginosa and for fungi during compared to the period before IVA treatment - Absolute change in $ppFEV_1$ - Absolute change in weight, weight-for-age Z score, BMI, and BMI-for-age Z-score - Incidence and prevalence of comorbidities during compared to the period before IVA treatment - Incidence and cause of deaths - Incidence and reason for organ transplantations **Other Outcomes** *[48 Months]* - Effect of IVA treatment on HRQoL in patients with CF and in caregivers of pediatric patients enrolled	December 2020
A Study to Confirm the Long-term Safety and Effectiveness of Kalydeco in Patients With Cystic Fibrosis Who Have an R117H-CFTR Mutation, Including	Observational Cohort Study Estimated N: 150	**Cohort 1** Intervention (Cohort will not be utilized) **Cohort 2** Non-interventional (IVA) **Cohort 3** Historical participants who have never been exposed to IVA	**Inclusions** - Ages ≥6 years Cohort 2: - Confirmed CF diagnosis with at least 1 allele of the R117H-CFTR mutation - Enrolled in the US CFF Patient Registry - With a record of Kalydeco treatment initiation from 01 January 2015 through 31 December 2016 Cohort 3:	**Primary Outcomes** *[36 Months]* - Lung function measurements ($ppFEV_1$ and FVC) - Pulmonary exacerbations, use of IV antibiotics - Nutritional parameters (BMI, BMI-for-age z-score, weight, and weight-for-age z-score) - Death or transplantation - Hospitalizations - Selected Complications (Symptomatic sinus disease, Pulmonary complications, CF-related diabetes (CFRD) and distal intestinal obstruction syndrome (DIOS), Hepatobiliary complications, Pancreatitis)	December 2019

Trial	Study Design	Study Arms	Patient Population	Key Outcomes	Estimated Completion
Pediatric Patients NCT02722057 Vertex Pharmaceuticals		(matched on age, gender, and lung function to patients in cohort 2)	- Patients with CF in CFF Patient Registry as of January 1, 2009 - At least one R117H-CFTR mutation - No prior exposure to IVA		
Nutritional Impact of Ivacaftor Treatment in 6 Month to 2 Year Old Children With CF Gating Mutations NCT03783286 Children's Hospital of Philadelphia	Observational, prospective cohort study Estimated N: 18	**Cohort** - IVA	**Inclusions** - Ages 1 – 2 years - CF with at least one CFTR gating mutation of these ten (G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1439D, or R117H) - Usual state of good health **Exclusions** - On parenteral nutrition - Use of any medications which are as inhibitors or inducers of cytochrome P450 (CYP) 3A - Liver function tests elevated above 3x the reference range for age and sex - Other illness affecting growth or nutritional status	**Primary Outcomes** *[12 Weeks]* - Change from baseline of Sleeping Energy Expenditure - Change from baseline in BMI, BMI z scores **Secondary Outcomes** *[12 Weeks]* - Fecal Elastase I/Pancreatic Function - Fecal Calprotectin/Gut Inflammation - Plasma Total Fatty Acids *[4 to 6 months]* **Other Outcomes** - Dietary measure - Serum fat soluble vitamins A, D, E and K, bile acids, and serum calprotectin - Muscle/fat stores - Growth Status/Growth Velocity	June 2020

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

Appendix D. Comparative Clinical Effectiveness Supplemental Information

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

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor" (see Appendix Table F2)[46] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

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

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

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

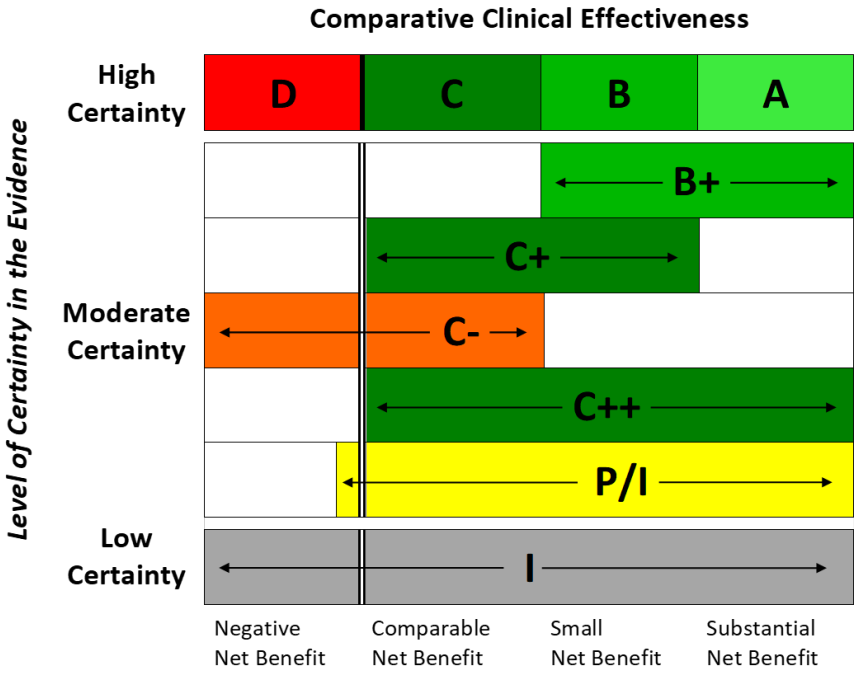
Note that case series are not considered under this rating system–because of the lack of comparator, these are generally considered to be of poor quality.

ICER Evidence Rating

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

- The magnitude of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND
- The level of certainty in the best point estimate of net health benefit.[47,137]

Figure D1. ICER Evidence Rating Matrix



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

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

Table D1. Study Design

Trial & Author	Design & duration of follow-up	Population, Total N	Interventions and dosing procedures	Inclusion Criteria	Exclusion Criteria
Elexacaftor (ELX) / Tezacaftor (TEZ) / Ivacaftor (IVA)					
Trial 1 **Middleton 2019[52]**	Phase 3, multicenter, randomized, double-blind, placebo-controlled trial Follow-Up: - 4-week screening period - 24-week intervention period - 4-week safety follow-up (OLE)	**Heterozygous** (F508del/minimal function mutation) N=403	Intervention: ELX 200 mg / TEZ 100 mg / IVA150 mg (AM) + IVA 150mg (PM) Comparator: Placebo (AM) + Placebo (PM)	- 12 years or older with confirmed CF diagnosis - F508del/minimal function genotype (heterozygous) - ppFEV$_1$ between 40-90% - Stable CF disease	- History of any illness or clinical condition that might confound the study results or pose an additional risk in administering study drug(s) to the patient - Abnormal laboratory values - Acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy for sinopulmonary disease within 28 days - Lung infection with organisms associated with a more rapid decline in pulmonary status - Participation in a study of an investigational treatment within 28 days or 5 terminal half-lives (whichever is longer) before screening

Trial & Author	Design & duration of follow-up	Population, Total N	Interventions and dosing procedures	Inclusion Criteria	Exclusion Criteria
Trial 2 **Heijerman 2019**[53]	Phase 3, multicenter, randomized, double-blind, active-controlled trial Follow-Up: - 4-week run-in period (TEZ/IVA treatment) - 4-week treatment period - 4-week safety follow-up	**Homozygous** (F508del/ F508del) N=107	**Run-in Period** Intervention: TEZ 100mg / IVA 150mg (AM) + IVA 150mg (PM) **Treatment Period** Intervention: ELX 200 mg / TEZ 100 mg / IVA150 mg (AM) + IVA 150mg (PM) Comparator: Placebo / TEZ 100mg / IVA 150mg (AM) + IVA 150mg (PM)	- 12 years or older with confirmed CF diagnosis - Homozygous for the F508del mutation (F/F) - $ppFEV_1$ between 40-90% - Stable CF disease	- History of any illness or clinical condition that might confound the study results or pose an additional risk in administering study drug(s) to the patient - Abnormal laboratory values - Acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy for sinopulmonary disease within 28 days - Lung infection with organisms associated with a more rapid decline in pulmonary status - Participation in a study of an investigational treatment within 28 days or 5 terminal half-lives (whichever is longer) before screening
Keating 2018[54]	Phase 2, randomized, double-blind, placebo- or active-controlled, parallel group assignment, dose-ranging study	**Homozygous** (F508del/ F508del) N=33	Intervention: ELX 200 mg / TEZ 100 mg / IVA 150 mg (AM) + IVA 150mg (PM) Comparator: Triple placebo	- 18 years or older with CFTR genotypes of F508del/minimal function (heterozygous) or homozygous F508del - $ppFEV_1$ between 40-90% - Stable disease	- Respiratory infection or change in therapy for sinopulmonary disease within 28 days before first dose of study drug - Lung infection with organisms associated with more rapid decline in pulmonary status - History of clinically significant cirrhosis, hemolysis, solid organ

Trial & Author	Design & duration of follow-up	Population, Total N	Interventions and dosing procedures	Inclusion Criteria	Exclusion Criteria
	Follow-Up: - 4-week run-in period (TEZ/IVA treatment) - 4-week treatment period	**Heterozygous** (F508del/minimal function mutation) N=28	Intervention: ELX 200 mg / TEZ 100 mg / IVA 150 mg (AM) + IVA 150mg (PM) Comparator: Placebo / TEZ 100 mg / IVA 150 mg (AM) + IVA 150mg (PM)		or hematological transplantation - Participation in an investigational treatment study other than a CFTR modulator within 28 days
Tezacaftor (TEZ) / Ivacaftor (IVA)					
EVOLVE **Taylor-Cousar 2017[84]** **Yang 2018[79]**	Phase 3, placebo-controlled, double-blind, parallel group assignment Follow-Up: 24 weeks	**Homozygous** (F508del/ F508del) N=504	Intervention: TEZ 100 mg / IVA 150 mg (AM) + IVA 150mg (PM) Comparator: Placebo (AM) + Placebo (PM)	- 12 years or older with confirmed F508del homozygous diagnosis of CF - $ppFEV_1$ at time of screening = 40- 90% - Stable disease	- History of any comorbidity that might pose an additional risk or confound the study results - Clinically significant abnormalities at screening - Acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy for pulmonary disease within 28 days prior to study - History of transplantation - Participation in previous phase 3 trials of LUM/IVA; or had received LUM/IVA through an early- or extended-access program

Trial & Author	Design & duration of follow-up	Population, Total N	Interventions and dosing procedures	Inclusion Criteria	Exclusion Criteria
Walker 2019[90] **ClinicalTrials.gov 2019**[138]	Phase 3, open-label, multicenter study Part A Follow-Up: - 14 days treatment - 14 days wash-out and safety follow-up Part B Follow-Up: - 24 weeks treatment period - Either 4 weeks of safety follow-up or enrolment in 96-week OLE study	Part A: **Homozygous** (F508del/F508del) **or heterozygous** (F508del + residual function, or F508del + gating mutation) N=13 Part B: **Homozygous** (F/F genotype) **or heterozygous** (F508del + residual function mutation) N=70	**Part A** Intervention: - **Cohort 1** (<25 kg): TEZ 50 mg / IVA 75 mg (AM) + IVA 75mg (PM) - **Cohort 2** (≥25 kg): TEZ 50 mg / IVA 150 mg (AM) + IVA 150mg (PM) **Part B** Intervention: - **Cohort 1** (<40 kg): TEZ 50 mg / IVA 75 mg (AM) + IVA 75mg (PM) - **Cohort 2** (≥40 kg): TEZ 100 mg / IVA 150 mg (AM) + IVA 150mg (PM)	- Children ages 6 - 11 years with confirmed CF diagnosis - Weight ≥ 15 kg at screening - Stable CF disease - ppFEV$_1$ ≥ 40% at screening - 28 days wash-out period for investigational LUM/IVA or physician prescribed Orkambi before start of study required - Physician prescribed Kalydeco could be taken up until day 1 of study Eligible mutations – Part A: Homozygous (F508del/F508del), F508del + residual function mutation, or F508del + gating mutation Eligible mutations – Part B: F/F genotype, or F508del + residual function mutation	- History of comorbidities that might confound results or pose additional risks to the participant; - Clinically significant laboratory abnormalities at screening - Acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy for pulmonary disease within 28 days of study - Colonization with organisms associated with a more rapid decline in pulmonary status at screening - History of solid-organ or hematologic transplant

Trial & Author	Design & duration of follow-up	Population, Total N	Interventions and dosing procedures	Inclusion Criteria	Exclusion Criteria
EXTEND **Flume J CF 2018**[78] **ClinicalTrials.gov**[139]	Phase 3, open-label extension study (interim analysis) Follow-Up: - Safety: 86 weeks - Efficacy: 48 weeks *(Results of interim analysis present efficacy data at 24 weeks)*	**Heterozygous** (F508del-CFTR + residual function mutation) **or homozygous** (F508del/ F508del) N=613	Intervention: TEZ 100 mg / IVA 150 mg (AM) + TEZ 100 mg / IVA 150 mg (PM)	**Part A:** Completed study drug treatment period in a parent study (NCT02070744, NCT02347657, NCT02516410, NCT02392234, NCT02412111) or study drug treatment and the Safety Follow up Visit for subjects from NCT02508207 **Part B**: Completed study drug treatment during the Treatment Period in Part A **Part C**: Did not withdraw consent from Part B and completed drug treatment	- History of any comorbidity that might confound the results of the study or pose an additional risk to the subject - History of drug intolerance in the parent study - Participation in an investigational drug trial (including studies investigating VX-661/ivacaftor or lumacaftor/ivacaftor) other than the parent studies of NCT02565914 or other eligible Vertex studies investigating VX-661 in combination with ivacaftor, or use of a commercially available CFTR modulator
Lumacaftor (LUM) / Ivacaftor (IVA)					

Trial & Author	Design & duration of follow-up	Population, Total N	Interventions and dosing procedures	Inclusion Criteria	Exclusion Criteria
TRAFFIC and TRANSPORT **Wainwright 2015[23]**	TRAFFIC: Phase 3, multinational, randomized, double-blind, placebo-controlled, parallel-group study TRANSPORT: Phase 3, multinational, randomized, double-blind, placebo-controlled, parallel-group study Follow-Up: - TRAFFIC: 24 weeks - TRANSPORT: 24 weeks - Rollover Safety Study (PROGRESS)	**Homozygous** (F508del/ F508del) N=1108	Intervention: - **Arm I**: LUM 600 mg / IVA 250 mg (AM) + IVA 250mg (PM) - **Arm II**: LUM 400 mg / IVA 250 mg (AM) + LUM 400 mg / IVA 250 mg (PM) Comparator: Placebo (AM) + Placebo (PM)	- 12 years or older with confirmed f508del homozygous diagnosis of CF - $ppFEV_1$ = 40- 90% of the predicted normal values at time of screening - Stable disease	- Any comorbidity that increases risk in the study - Abnormal lab values - Respiratory event within 4 weeks of first day on drug - Colonization with certain bacteria - Prolonged QT interval - History of transplant - Use of strong inhibitors, moderate inducers, or strong inducers of CYP3A within 14 days

Trial & Author	Design & duration of follow-up	Population, Total N	Interventions and dosing procedures	Inclusion Criteria	Exclusion Criteria
TRAFFIC and TRANSPORT – subgroup analysis **McColley 2019[76]**	Post hoc analysis of pooled data from TRAFFIC and TRANSPORT studies **Subgroups of LUM 400 mg /IVA 250 mg (AM) + LUM 400 mg/IVA 250 mg (PM):** - Absolute change of $ppFEV_1 \leq 0$ - Absolute change of $ppFEV_1 > 0$ - Relative change of $ppFEV_1 < 5\%$ - Relative change of $ppFEV_1 \geq 5\%$	**Homozygous** (F508del/ F508del) N=1108	Intervention: LUM 400 mg / IVA 250 mg (AM) + LUM 400 mg / IVA 250 mg (PM) Comparator: Placebo (AM) + Placebo (PM)	See TRAFFIC and TRANSPORT (Wainwright 2015)	See TRAFFIC and TRANSPORT (Wainwright 2015)

Trial & Author	Design & duration of follow-up	Population, Total N	Interventions and dosing procedures	Inclusion Criteria	Exclusion Criteria
McNamara 2019[77]	Phase 3, open-label, multicentre, two-part study <u>Follow-Up (Part A - Safety)</u>: - 15 days treatment period - 10 days follow-up after last dose <u>Follow-Up (Part B - Efficacy and Safety):</u> - 24 weeks treatment period - 2 weeks wash-out period - Option to roll over into long-term OLE	**Homozygous** (F508del/ F508del) Part A: N=12 Part B: N=60	<u>Intervention</u> - **Cohort 1** (<14kg): LUM 100mg / IVA 125mg (AM) + LUM 100mg / IVA 125mg (PM) - **Cohort 2** (≥14kg): LUM 150 mg / IVA 188 mg (AM) + LUM 150 mg / IVA 188 mg (PM)	- Children ages 2-5 years - Weight ≥ 8kg - Confirmed F508del homozygous diagnosis of CF	- History of any comorbidity that would confound the results of the study or posed an additional risk to the patient - Clinically significant laboratory abnormalities - Acute upper or lower respiratory infection, pulmonary exacerbation, or change in therapy for pulmonary disease within 28 days - History of solid organ or hematological transplantation

Trial & Author	Design & duration of follow-up	Population, Total N	Interventions and dosing procedures	Inclusion Criteria	Exclusion Criteria
Chilvers 2017[75] **Chilvers 2019**[74] **ClinicalTrials.gov**[140]	Open-label extension, non-randomized, parallel assignment, two-part study (only results for treatment period 1 are reported) Follow-Up: - 96 weeks	**Homozygous** (F508del/ F508del) N=239	Intervention - LUM/IVA (Part A) → LUM/IVA (Part B) - Placebo (Part A) → LUM/IVA (Part B) Comparator Observational Cohort (Patients who completed parent study but were not eligible/ elected OLE)	Participants from Parent Studies 109 (NCT02514473) and 011B (NCT01897233)	For treatment cohort only - History of a comorbidity or laboratory abnormality that might confound results of the study or add risk for the patient - History of drug intolerance in prior study - History of poor compliance with study drug and/or procedure in prior study - Participation in an investigational drug trial
Ivacaftor (IVA)					
KLIMB **Rosenfeld 2019**[56]	Open-label extension study in children who completed Part B of the KIWI study (a 24-week Phase 3, open-label, single arm study) Follow-up: - 84 weeks	**Heterozygous** (F508del + gating mutation) N=33	Weight-based granules of IVA twice daily - **Weight < 14kg**: IVA 50 mg (AM) + IVA 50 mg (PM) - **Weight ≥ 14 kg**: IVA 75 mg (AM) + IVA 75 mg (PM) - Children (n=1) who turned 6 years of age during KLIMB received IVA	Children who completed Part B of the KIWI study	- Participants who prematurely discontinued from previous study - Participants who received commercially available ivacaftor treatment - History of study treatment intolerance or history of illness that may confound results.

Trial & Author	Design & duration of follow-up	Population, Total N	Interventions and dosing procedures	Inclusion Criteria	Exclusion Criteria
			150 mg (AM) + IVA 150 mg (PM) as tablets		

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

Table D2. Baseline Characteristics I

Trial & Author	Arms	N	Female, n (%)	Age			$ppFEV_1$					Sweat Chloride Concentration, mean mmol/L (SD)
				Mean years (SD)	12 to <18 years, n (%)	≥18 years, n (%)	Mean % (SD)	<40%, n (%)	40 to <70%, n (%)	70 to 90%, n (%)	>90%, n (%)	
Elexacaftor (ELX) / Tezacaftor (TEZ) / Ivacaftor (IVA)												
Trial 1 Middleton 2019[52]	ELX/TEZ/IVA	200	96 (48.0)	25.6 (9.7)	56 (28.0)	144 (72.0)	61.6 (15.0)	18 (9.0)	114 (57.0)	66 (33.0)	2 (1.0)	102.3 (11.9)
	Placebo	203	98 (48.3)	26.8 (11.3)	60 (29.6)	143 (70.4)	61.3 (15.5)	16 (7.9)	120 (59.1)	62 (30.5)	5 (2.5)	102.9 (9.8)
Trial 2 Heijerman 2019[53]	ELX/TEZ/IVA	55	31 (56.4)	28.8 (11.5)	16 (29.1)	39 (70.9)	61.6 (15.4)†	6 (10.9)	31 (56.4)	18 (32.7)	0 (0)	91.4 (11.0)
	Placebo/TEZ/IVA	52	28 (53.8)	27.9 (10.8)	14 (26.9)	38 (73.1)	60.2 (14.4)†	4 (7.7)	34 (65.4)	14 (26.9)	0 (0)	90.0 (12.3)
Keating 2018[54]	ELX/TEZ/IVA	21	11 (52.4)	33.3 (10.3)	0 (0)	21 (100)*	59.4 (18.0)	4 (19.0)	11 (52.4)	5 (23.8)	1 (4.8)	103.9 (9.7)
heterozygous population	Placebo	12	2 (16.7)	29.7 (7.5)	0 (0)	12 (100)*	59.0 (14.9)	2 (16.7)	7 (58.3)	3 (25.0)	0 (0)	103.1 (8.2)

Trial & Author	Arms	N	Female, n (%)	Age			ppFEV$_1$					Sweat Chloride Concentration, mean mmol/L (SD)
				Mean years (SD)	12 to <18 years, n (%)	≥18 years, n (%)	Mean % (SD)	<40%, n (%)	40 to <70%, n (%)	70 to 90%, n (%)	>90%, n (%)	
Keating 2018[54]	ELX/TEZ/IVA	21	9 (42.9)	29.9 (7.6)	0 (0)	21 (100)*	60.0 (15.1)	1 (4.8)	15 (71.4)	4 (19.0)	1 (4.8)	92.7 (11.1)
homozygous population	Placebo/TEZ/IVA	7	1 (14.3)	27.9 (8.0)	0 (0)	7 (100)*	62.8 (13.2)	0 (0)	4 (57.1)	3 (42.9)	0 (0)	99.5 (9.0)
Tezacaftor (TEZ) / Ivacaftor (IVA)												
EVOLVE Taylor-Cousar 2017[84] Yang, 2018[79]	TEZ/IVA	248	121 (48.8)	26.9 (11.2)	58 (23.4)	190 (76.6)	59.6 (14.7)	23 (9.3)	157 (63.3)	65 (26.2)	2 (0.8)	101.3 (10.9)
	Placebo	256	125 (48.8)	25.7 (9.5)	58 (22.7)	198 (77.3)	60.4 (15.7)	24 (9.4)	152 (59.4)	73 (28.5)	7 (2.7)	100.5 (10.2)
Walker 2019[90]	TEZ/IVA (Part A)	13	7 (53.8)	8.1 (1.8)	N/A		89.1 (14.8)	NR				NR
	TEZ/IVA (Part B)	70	34 (48.6)	8.1 (1.8)	N/A		91.1 (12.3)	NR				99.1 (19.2), n=64
EXTEND Flume 2018[78]	TEZ/IVA	613	NR									
Lumacaftor (LUM) / Ivacaftor (IVA)												
TRAFFIC and TRANSPORT Wainwright 2015[23]	LUM600/IVA	368	182 (49.5)	24.5 (Range: 12-54)	96 (26.1)	272 (73.9)	60.8 (Range: 31.1–92.3)	24 (6.5)	241 (65.5)	98 (26.6)	3 (0.8)	NR
	LUM400/IVA	369	182 (49.3)	25.3 (Range: 12-57)	98 (26.6)	271 (73.4)	60.5 (Range: 31.3–96.5)	29 (7.9)	233 (63.1)	100 (27.1)	3 (0.8)	NR
	Placebo	371	181 (48.8)	25.4 (Range: 12-64)	96 (25.9)	275 (74.1)	60.4 (Range: 33.9–99.8)	28 (7.5)	238 (64.2)	97 (26.1)	3 (0.8)	NR
TRAFFIC and TRANSPORT - sub-group analysis McColley 2019[141]	LUM/IVA Absolute ppFEV$_1$ change ≤ 0	146	73 (50.0)	NR	34 (23.3)	112 (76.7)	NR	8 (5.5)	≥ 40: 134 (91.8)			NR
	LUM/IVA Absolute ppFEV$_1$ change > 0	223	109 (48.9)	NR	64 (28.2)	159 (71.3)	NR	21 (9.4)	≥ 40: 202 (90.6)			NR

Trial & Author	Arms	N	Female, n (%)	Age			ppFEV$_1$					Sweat Chloride Concentration, mean mmol/L (SD)
				Mean years (SD)	12 to <18 years, n (%)	≥18 years, n (%)	Mean % (SD)	<40%, n (%)	40 to <70%, n (%)	70 to 90%, n (%)	>90%, n (%)	
	LUM/IVA Relative ppFEV$_1$ change < 5%	228	110 (48.2)	NR	59 (25.9)	169 (74.1)	NR	13 (5.7)	≥ 40: 211 (92.5)			NR
	LUM/IVA Relative ppFEV$_1$ change ≥ 5%	141	72 (51.1)	NR	39 (27.7)	102 (72.3)	NR	16 (11.3)	≥ 40: 125 (88.7)			NR
	Placebo	371	181 (48.8)	NR	96 (25.9)	275 (74.1)	NR	28 (7.5)	≥ 40: 338 (91.1)			NR
McNamara 2018[77] (Part A)	LUM200/IVA250	4	2 (50.0)	2.3 (0.5)	N/A		NR					NR
	LUM300/IVA376	8	2 (25.0)	4.0 (0.9)	N/A		NR					NR
McNamara 2018[77] (Part B)	LUM200/IVA250	19	9 (47.4)	2.6 (0.4)	N/A		83.8 (10.9)	NR				105.5 (8.0)
	LUM300/IVA376	41	20 (48.8)	4.2 (0.9)	N/A			NR				106.0 (7.2), n=37
Chilvers 2017[75] Chilvers 2019[74] *BL reported are pooled BL at the beginning of the parent studies*	LUM/IVA → LUM/IVA	143	83 (58.0)	8.9 (1.6) §	NR		89.7 (13.8)	NR				103.8 (10.4), n=160
	Placebo → LUM/IVA‡	96	56 (58.3)		NR		88.9 (11.7)	NR				103.4 (9.8), n=98
Ivacaftor (IVA)												
KLIMB Rosenfeld 2019[56]	Weight-based IVA	33	6 (18.2)	3.7 (1.0)	0 (0)*	0 (0)*	NR	NR				51.6 (22.9)

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

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

Table D3. Baseline Characteristics II

Trial	Arms	N	BMI, mean (SD)	Weight, mean kg (SD)	Height, mean cm (SD)	CFQ-R Respiratory Domain Score, mean (SD)	Lung Clearance Index 2.5, mean (SD)	*Pseudomonas aeruginosa* – positive, n (%)
Elexacaftor (ELX) / Tezacaftor (TEZ) / Ivacaftor (IVA)								
Trial 1 **Middleton 2019[52]**	ELX/TEZ/IVA	200	21.5 (3.1)	NR	NR	68.3 (16.9)	NR	150 (75.0)*
	Placebo	203	21.3 (3.1)	NR	NR	70.0 (17.8)	NR	142 (70.0)*
Trial 2 **Heijerman 2019[53]**	ELX/TEZ/IVA	55	21.8 (3.2)	NR	NR	70.6 (16.2)	NR	39 (71.0)*
	Placebo/TEZ/IVA	52	21.9 (4.1)	NR	NR	72.6 (17.9)	NR	31 (59.6)*
Keating 2018[54] *heterozygous population*	ELX/TEZ/IVA	21	22.1 (1.7)	60.5 (8.8)	165.1 (10.0)	61.1 (17.5)	NR	19 (90.5)
	Placebo	12	22.9 (2.9)	69.6 (8.2)	174.7 (12.4)	57.4 (14.1)	NR	10 (83.3)
Keating 2018[54] *homozygous population*	ELX/TEZ/IVA	21	22.3 (2.8)	65.2 (12.0)	170.5 (10.4)	71.2 (17.3)	NR	15 (71.4)
	Placebo/TEZ/IVA	7	24.0 (4.1)	74.7 (16.0)	175.9 (13.1)	73.0 (22.3)	NR	5 (71.4)
Tezacaftor (TEZ) / Ivacaftor (IVA)								
EVOLVE **Taylor-Cousar 2017[84]** **Yang 2018[79]**	TEZ/IVA	248	21.0 (3.0)	NR	NR	70.1 (16.8)	NR	185 (74.6)
	Placebo	256	21.1 (2.9)	NR	NR	69.9 (16.6)	NR	182 (71.1)
Walker 2019[90]	TEZ/IVA (Part A)	13	17.1 (2.4)	30.5 (8.5)	NR	NR	NR	NR
	TEZ/IVA (Part B)	70	17.4 (2.7)	30.7 (10.0)	131.0 (13.0)	81.8 (13.8)	NR	NR
EXTEND **Flume 2018[78]**	TEZ/IVA	613	NR					
Lumacaftor (LUM) / Ivacaftor (IVA)								
TRAFFIC and TRANSPORT **Wainwright 2015[23]**	LUM600/IVA	368	21.0 (Range: 14.2, 35.1)	NR	NR	NR	NR	NR
	LUM400/IVA	369	21.5 (Range: 14.6, 31.4)	NR	NR	NR	NR	NR

Trial	Arms	N	BMI, mean (SD)	Weight, mean kg (SD)	Height, mean cm (SD)	CFQ-R Respiratory Domain Score, mean (SD)	Lung Clearance Index 2.5, mean (SD)	*Pseudomonas aeruginosa* – positive, n (%)
	Placebo	371	21 .0 (Range: 14.1,32.2)	NR	NR	NR	NR	NR
TRAFFIC and TRANSPORT – subgroup analysis **McColley 2019[76]**	LUM/IVA Absolute ppFEV$_1$ change ≤ 0	146	NR	NR	NR	NR	NR	120 (82.2)
	LUM/IVA Absolute ppFEV$_1$ change > 0	223	NR	NR	NR	NR	NR	166 (74.4)
	LUM/IVA Relative ppFEV$_1$ change < 5%	228	NR	NR	NR	NR	NR	179 (78.5)
	LUM/IVA Relative ppFEV$_1$ change ≥ 5%	141	NR	NR	NR	NR	NR	107 (75.9)
	Placebo	371	NR	NR	NR	NR	NR	276 (74.4)
McNamara 2019[77] (Part A)	LUM200/IVA250	4	16.9 (0.6)	12.5 (0.9)	86.0 (4.6)	NR	NR	NR
	LUM300/IVA376	8	15.9 (1.0)	16.4 (1.5)	101.7 (6.0)	NR	NR	NR
McNamara 2019[77] (Part B)	LUM200/IVA250	19	16.0 (1.1)	12.7 (1.0)	89.1 (3.4)	NR	7.6 (0.9), n=5	NR
	LUM300/IVA376	41	16.0 (1.0)	17.1 (2.3)	103.4 (6.1)	NR	9.3 (2.0), n=32	NR
Chilvers 2017[75] **Chilvers 2019[74]** *BL reported are pooled BL at the beginning of the parent studies*	LUM/IVA → LUM/IVA	143	16.6 (1.8), n=101	NR	NR	78.5 (14.3), n=135	10.2 (2.4), n=128	NR
	Placebo → LUM/IVA	96	16.6 (2.0), n=101	NR	NR	77.1 (15.5), n=78	10.3 (2.2), n=101	NR
Ivacaftor (IVA)								
KLIMB **Rosenfeld 2019[56]**	Weight-based IVA	33	NR	Weight z-score, mean (SD): 0.07 (0.83)	Height z-score, mean (SD): -0.31 (0.95)	NR	NR	NR

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

* within previous two years

Table D4. Efficacy at 4 weeks I

Trial	Arms	N	ppFEV$_1$		Sweat Chloride		CFQ-R Respiratory Domain Score	
			Absolute Change, Points (95%CI)	Treatment Δ (95%CI), p-value	Absolute Change, mmol/L (95%CI)	Treatment Δ (95%CI), p-value	Absolute Change, points (95%CI)	Treatment Δ (95%CI), p-value
Elexacaftor (ELX) / Tezacaftor (TEZ) / Ivacaftor (IVA)								
Trial 1 **Middleton 2019[52]**	ELX/TEZ/IVA	200	13.6 (12.4, 14.8)	13.8 (12.1, 15.4), p<0.001	-41.2 (-43.1, -39.2)	-41.2 (-44.0, -38.5), p<0.001	18.1 (15.9, 20.4)	20.1 (16.9, 23.2), p<0.001
	Placebo	203	-0.2 (-1.3, 1.0)		0.1 (-1.9, 2.0)		-1.9 (-4.2, 0.3)	
Trial 2 **Heijerman 2019[53]**	ELX/TEZ/IVA	55	10.4 (8.6, 12.2)	10.0 (7.4, 12.6), p<0.0001	-43.4 (-46.9, -40.0)	-45.1 (-50.1, -40.1), p<0.0001	16.0 (12.1, 19.9)	17.4 (11.8, 23.0), p<0.0001
	Placebo/TEZ/IVA	52	0.4 (-1.4, 2.3)		1.7 (-1.9, 5.3)		-1.4 (-5.4, 2.6)	
Keating 2018[54] *heterozygous population*	ELX/TEZ/IVA	21	13.8 (10.9, 16.6)	13.8 (NR), NR	-39.1 (-44.9, -33.3)	36.9 (NR), NR	25.7 (18.3, 33.1)	21.5 (NR), NR
	Placebo	12	0.0 (-3.9, 4.0)		-2.2 (-9.9, 5.6)		4.2 (-5.6, 14.0)	
Keating 2018[54] *homozygous population*	ELX/TEZ/IVA	21	11.0 (7.9, 14.0)	10.6 (NR), NR	-39.6 (-45.3, -33.8)	40.4 (NR), NR	20.7 (12.5, 29.0)	15.5 (NR), NR
	Placebo/TEZ/IVA	7	-0.4 (-5.4, 6.2)		0.8 (-9.3, 11.0)		5.2 (-9.5, 19.9)	
Tezacaftor (TEZ) / Ivacaftor (IVA								
EVOLVE **Taylor-Cousar 2017[84]** **Yang, 2018[79]**	TEZ/IVA	248	3.4 (2.6, 4.1)*	3.5 (NR), NR	-9.6 (-10.8, -8.4)*	-9.2 (NR), NR	5.6 (3.7, 7.5)*	4.6 (NR), NR
	Placebo	256	-0.1 (-0.8, 0.5)*		-0.4 (-1.8, 0.7)*		1.1 (-0.9, 2.9)*	
Walker 2019[90]	TEZ/IVA (Part B)	70	NR		-13.0 (-16.2, -9.9)	N/A	NR	
Lumacaftor (LUM) / Ivacaftor (IVA)								
TRAFFIC and TRANSPORT	LUM600/IVA	368	2.5 (1.7, 3.1)*	2.4 (NR), NR	NR		5.4 (3.8, 6.9)*	3.4 (NR), p<0.025
	LUM400/IVA	369	2.6 (1.7, 3.2)*	2.5 (NR), NR	NR		6.2 (4.6, 7.9)*	4.2 (NR), p<0.025

Trial	Arms	N	ppFEV$_1$		Sweat Chloride		CFQ-R Respiratory Domain Score	
			Absolute Change, Points (95%CI)	Treatment Δ (95%CI), p-value	Absolute Change, mmol/L (95%CI)	Treatment Δ (95%CI), p-value	Absolute Change, points (95%CI)	Treatment Δ (95%CI), p-value
Wainwright 2015[23]	Placebo	371	0.1 (-0.7, 0.8)*	---	NR		2.0 (0.4, 3.5)*	---
TRAFFIC and TRANSPORT – subgroup analysis **McColley 2019[76]**	LUM/IVA	1108	4 Weeks data NR					
McNamara 2019[77] (Part B)	LUM/IVA (pooled)	60	NR		-24.7 (-20.7, -28.4)*	N/A	NR	

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

*numbers are digitized and should be interpreted with caution

Table D5. Efficacy at 4 weeks II

Trial	Arms	N	BMI		Weight		Height		LCI2.5	
			Absolute Change, kg/m2 (95%CI)	Treatment Δ (95%CI), p-value	Absolute Change, kg (95%CI)	Treatment Δ (95%CI), p-value	Absolute Change, cm (95%CI)	Treatment Δ (95%CI), p-value	Absolute Change, points (95% CI)	Treatment Δ (95%CI), p-value
Elexacaftor (ELX) / Tezacaftor (TEZ) / Ivacaftor (IVA)										
Trial 1 **Middleton 2019[52]**	ELX/TEZ/IVA	200	0.54 (0.50, 0.58)*	0.44 (NR), NR	NR		NR		NR	
	Placebo	203	0.10 (0.05, 0.15)*		NR		NR		NR	
Trial 2 Heijerman 2019[53]	ELX/TEZ/IVA	55	NR	0.60 (0.41, 0.79), p<0.0001	NR	1.6 (1.0, 2.1), p<0.0001	NR		NR	
	Placebo/TEZ/IVA	52	NR		NR		NR		NR	
Keating 2018 heterozygous population	ELX/TEZ/IVA	21	NR		NR		NR		NR	
	Placebo	12	NR		NR		NR		NR	
Keating 2018	ELX/TEZ/IVA	21	NR		NR		NR		NR	

Trial	Arms	N	BMI		Weight		Height		LCI2.5	
			Absolute Change, kg/m2 (95%CI)	Treatment Δ (95%CI), p-value	Absolute Change, kg (95%CI)	Treatment Δ (95%CI), p-value	Absolute Change, cm (95%CI)	Treatment Δ (95%CI), p-value	Absolute Change, points (95% CI)	Treatment Δ (95%CI), p-value
homozygous population	Placebo/TEZ/IVA	7	NR		NR		NR			
Tezacaftor (TEZ) / Ivacaftor (IVA)										
EVOLVE **Taylor-Cousar 2017** **Yang 2018**	TEZ/IVA	248	0.11 (0.04, 0.17)*	-0.03 (NR), NR	NR		NR		NR	
	Placebo	256	0.14 (0.07, 0.20)*		NR		NR		NR	
Walker 2019	TEZ/IVA (Part B)	70	NR		NR		NR		NR	
Lumacaftor (LUM) / Ivacaftor (IVA)										
TRAFFIC and TRANSPORT (Wainwright 2015)	LUM600/IVA	368	0.12 (0.06, 0.17)*	(NR), n.s.	NR		NR		NR	
	LUM400/IVA	369	0.10 (0.06, 0.17)*	(NR), n.s.	NR		NR		NR	
	Placebo	371	0.11 (0.06, 0.17)*	---	NR		NR		NR	
McColley 2019	LUM/IVA	1108	4-week data not reported							
McNamara 2018 (Part B)	LUM/IVA (pooled)	60	NR		NR		NR		-0.6 (-1.1, -0.1)*	N/A

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

* numbers are digitized and should be interpreted with caution

Table D6. Efficacy at 24 weeks I

Trial	Arms	N	$ppFEV_1$		Sweat Chloride		Pulmonary Excacerbations (PE)			
			Absolute Change, % (95%CI)	Treatment Δ (95%CI), p-value	Absolute Change, mmol/L (95%CI)	Treatment Δ (95%CI), p-value	Events, n (AER)	Δ RR (95%CI), p-value	Number of PE leading to hosp., ER/PY	Δ hosp., RR (95%CI), p-value
Trial 1	ELX/TEZ/IVA	200	13.9 (12.8, 15.0)	14.3	-42.2 (-44.0, -40.4)	-41.8	41 (0.4)	0.4 (0.3, 0.6), p<0.001	0.1	0.3 (0.1, 0.6), NR

Trial	Arms	N	ppFEV$_1$		Sweat Chloride		Pulmonary Excacerbations (PE)			
			Absolute Change, % (95%CI)	Treatment Δ (95%CI), p-value	Absolute Change, mmol/L (95%CI)	Treatment Δ (95%CI), p-value	Events, n (AER)	Δ RR (95%CI), p-value	Number of PE leading to hosp., ER/PY	Δ hosp., RR (95%CI), p-value
Middleton 2019[52]	Placebo	203	-0.4 (-1.5, 0.7)	(12.7, 15.8), p<0.001	-0.4 (-2.2, 1.4)	(-44.4, -39.3), p<0.001	113 (1.0)		0.2	
Tezacaftor (TEZ) / Ivacaftor (IVA)										
EVOLVE 2017 Taylor-Cousar 2017[84] Yang, 2018[79]	TEZ/IVA	248	3.4 (2.7, 4.0)	4.0 (3.1, 4.8), p<0.001	-9.9 (-10.9, -8.9)	-10.1 (-11.4, -8.8), NR	78 (0.6)	0.7 (0.5, 0.9) p=0.005	0.3	0.5 (0.3, 0.8), NR
	Placebo	256	-0.6 (-1.3, 0.0)		0.2 (-0.8, 1.2)		122 (1.0)		0.5	
Walker 2019[90]	TEZ/IVA (Part B)	70	0.9 (- 0.6, 2.3)	N/A	-14.5 (-17.4, -11.6)	N/A	NR			
EXTEND (interim analysis at 24 weeks - homozygous population) Flume 2018[78]	Placebo → TEZ/IVA	231	4.3 (3.3, 5.4)	0.9 (NR), NR	NR		NR (0.65)†	NR		
	TEZ/IVA → TEZ/IVA*	228	3.4 (2.3, 4.5)		NR		NR (0.72)†	NR		
Lumacaftor (LUM) / Ivacaftor (IVA)										
TRAFFIC and TRANSPORT Wainwright 2015[23]	LUM600/IVA	368	2.6 (1.8, 3.4)‡	3.3 (2.3, 4.3) p<0.001	NR		173 (0.8)	0.7 (0.6, 0.9) p=0.001	0.3‡	0.2 (NR), p<0.001
	LUM400/IVA	369	2.3 (1.4, 3.1)‡	2.8 (1.8, 3.8) p<0.001			152 (0.7)	0.6 (0.5, 0.8) p<0.001	0.2‡	0.3 (NR), p=0.003
	Placebo	371	-0.3 (-1.1, 0.5)‡	---			251 (1.1)	---	0.5‡	---
TRAFFIC and TRANSPORT - sub-group analysis	LUM/IVA Absolute ppFEV$_1$ change ≤ 0	146	NR		NR		NR (0.9) ‡	0.7 (0.6, 1.0), p=0.0441	0.2	0.4 (0.2, 0.7), p=0.0009

Trial	Arms	N	ppFEV$_1$		Sweat Chloride		Pulmonary Excacerbations (PE)			
			Absolute Change, % (95%CI)	Treatment Δ (95%CI), p-value	Absolute Change, mmol/L (95%CI)	Treatment Δ (95%CI), p-value	Events, n (AER)	Δ RR (95%CI), p-value	Number of PE leading to hosp., ER/PY	Δ hosp., RR (95%CI), p-value
McColley 2019[76]	LUM/IVA Absolute ppFEV$_1$ change > 0	223	NR		NR		NR (0.6) ‡	0.5 (0.4, 0.7), p<0.0001	0.2	0.4 (0.2, 0.6), p<0.0001
	LUM/IVA Relative ppFEV$_1$ change < 5%	228	NR		NR		NR (0.7) ‡	0.6 (0.5, 0.8), p=0.0003	0.1	0.3 (0.2, 0.5), p<0.0001
	LUM/IVA Relative ppFEV$_1$ change ≥ 5%	141	NR		NR		NR (0.7) ‡	0.6 (0.4, 0.8), p=0.0013	0.2	0,5 (0.3, 0.8), p=0.0053
	Placebo	371	NR		NR		NR (1.1) ‡	---	0.5	---
McNamara 2019[77] (Part B)	LUM/IVA (pooled)	60	0.5 (-6.9, 7.9)	N/A	-31.7 (-35·7, -27.6), n=52	N/A	NR			
Chilvers 2017[75]	LUM/IVA → LUM/IVA	143	2.8 (0.7, 4.9), n=134	NR	-24.2 (-27.0, -21.4), n=127	NR	NR			
	Placebo → LUM/IVA	96	2.0 (-0.8, 4.9), n=86		-29.0 (-32.8, 25.2), n=85	NR	NR			
Ivacaftor (IVA)										
KLIMB **Rosenfeld 2019[56]**	IVA	33	NR		-4.5 (NR)	N/A	NR			

95%CI: 95% Confidence Interval, AER: annualized event rate, ER/PY: event rate per patient year, hosp.: hospitalization, kg: kilograms, LCI: lung clearance index, mmol/L: millimoles per liter, n: number, N: total number, N/A: not applicable, NR: not reported, ppFEV$_1$: percent predicted forced expiratory volume in 1 second, RR: risk ratio, SD: standard deviation, Δ: difference

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

Table D7. Efficacy at 24 Weeks II

Trial	Arms	N	BMI		Weight		Height		CFQ-R Respiratory Domain Score		$LCI_{2.5}$	
			Absolute Change, kg/m^2 (95%CI)	Treatment Δ (95%CI), p-value	Absolute Change, kg (95% CI)	Treatment Δ (95%CI), p-value	Absolute Change, cm (95%CI)	Treatment Δ (95%CI), p-value	Absolute Change, points (95% CI)	Treatment Δ (95%CI), p-value	Absolute Change, mean (95%CI)	Treatment Δ (95%CI), p-value
Elexacaftor (ELX) / Tezacaftor (TEZ) / Ivacaftor (IVA)												
Trial 1 **Middleton 2019[52]**	ELX/TEZ/IVA	200	1.13 (0.99, 1.26)	1.04 (0.85, 1.23), p<0.001	3.4 (3.0, 3.8)	2.9 (2.3, 3.4)	NR		17.5 (15.6, 19.5)	20.2 (17.5, 23.0), p<0.001	NR	
	Placebo	203	0.09 (−0.05, 0.22)		0.5 (0.2, 0.9)		NR		-2.7 (-4.6, -0.8)		NR	
Tezacaftor (TEZ) / Ivacaftor (IVA)												
EVOLVE 2017 **Taylor-Cousar 2017[84]** **Yang 2018[79]**	TEZ/IVA	248	0.2 (0.1, 0.3)	0.1 (-0.1, 0.2), p=0.41	NR		NR		5.0 (3.5, 6.5)	5.1 (3.2, 7.0), NR	NR	
	Placebo	256	0.1 (0.03, 0.2)		NR		NR		-0.1 (-1.6, -1.4)		NR	
Walker 2019[90]	TEZ/IVA (Part B)	70	0.2 (0.1, 0.4)	N/A	1.7 (1.3, 2.0), n=67	N/A	2.7 (2.4, 2.9), n=67	N/A	3.4 (1.4, 5.5)	N/A	NR	N/A
EXTEND (interim analysis at 24 weeks - homozygous population) **Flume 2018[78]**	Placebo → TEZ/IVA	231	0.25 (0.13, 0.38)	0.02 (NR), NR	NR	NR	NR	NR	3.7 (1.5, 6.0)	0.6 (NR), NR	NR	
	TEZ/IVA → TEZ/IVA	228	0.23 (0.11, 0.36)		NR	NR	NR	NR	3.1 (0.8, 5.3)			

Trial	Arms	N	BMI		Weight		Height		CFQ-R Respiratory Domain Score		$LCI_{2.5}$	
			Absolute Change, kg/m^2 (95%CI)	Treatment Δ (95%CI), p-value	Absolute Change, kg (95% CI)	Treatment Δ (95%CI), p-value	Absolute Change, cm (95%CI)	Treatment Δ (95%CI), p-value	Absolute Change, points (95% CI)	Treatment Δ (95%CI), p-value	Absolute Change, mean (95%CI)	Treatment Δ (95%CI), p-value
Lumacaftor (LUM) / Ivacaftor (IVA)												
TRAFFIC and TRANSPORT **Wainwright 2015[23]**	LUM600/IVA	368	0.4 (0.31, 0.50)*	0.3 (0.2, 0.4) p<0.001	NR		NR		4.9 (3.5, 6.5)*	3.1 (0.8, 5.3) p=0.007	NR	
	LUM400/IVA	369	0.3 (0.26, 0.46)*	0.2 (0.1, 0.4) p<0.001	NR		NR		4.1 (2.5, 5.7)*	2.2 (0.0, 4.5) p=0.05	NR	
	Placebo	371	0.1 (0.05, 0.23)*	---	NR		NR		1.9 (0.3, 3.5)*	---	NR	
TRAFFIC and TRANSPORT - sub-group analysis **MColley 2019[76]**	LUM/IVA Absolute $ppFEV_1$ change ≤ 0	146	NR		NR		NR		NR		NR	
	LUM/IVA Absolute $ppFEV_1$ change > 0	223	NR		NR		NR		NR		NR	
	LUM/IVA Relative $ppFEV_1$ change < 5%	228	NR		NR		NR		NR		NR	
	LUM/IVA Relative $ppFEV_1$ change ≥ 5%	141	NR		NR		NR		NR		NR	
	Placebo	371	NR		NR		NR		NR		NR	
McNamara 2019[77] (Part B)	LUM/IVA (pooled)	60	0.3 (0.1, 0.5), n=57	N/A	1.4 (1.2, 1.7)	N/A	3.6 (3.3, 3.9)	N/A	NR		-0.6	N/A

Trial	Arms	N	BMI		Weight		Height		CFQ-R Respiratory Domain Score		$LCI_{2.5}$	
			Absolute Change, kg/m^2 (95%CI)	Treatment Δ (95%CI), p-value	Absolute Change, kg (95% CI)	Treatment Δ (95%CI), p-value	Absolute Change, cm (95%CI)	Treatment Δ (95%CI), p-value	Absolute Change, points (95% CI)	Treatment Δ (95%CI), p-value	Absolute Change, mean (95%CI)	Treatment Δ (95%CI), p-value
											(-1.2, 0.0), n=21	
Chilvers 2017[75]	LUM/IVA → LUM/IVA	143	0.8 (0.6, 1.0), n=139	NR	NR		NR		7.7 (5.2, 10.3), n=112	NR	-1.1 (-1.5, -0.7), n=78	NR
	Placebo → LUM/IVA	96	0.4 (0.2, 0.6), n=93	NR	NR		NR		3.0 (-0.2, 6.2), n=88	NR	-1.0 (-1.5, -0.5), n=68	NR
Ivacaftor (IVA)												
KLIMB **Rosenfeld 2019[56]**	IVA	33	-0.2 (NR)*†	N/A	NR		NR		NR		NR	

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

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

Table D8. Long-term Efficacy Outcomes I

Trial	Arms	N	Follow-Up Duration	Absolute Change in $ppFEV_1$, % (SE)	Absolute Change in Sweat Chloride, mmol/L (SE)	Pulmonary Excacerbations (PE)		Absolute Change in CFQ-R Respiratory Domain Score, points (95% CI)
						Number of events (AER)	Number of PE leading to hospitalization, ER/PY	
Chilvers 2019[74]	LUM/IVA → LUM/IVA	143	96 weeks	3.1 (1.0, 5.1)	-22.9 (-25.5, -20.3), n=122	0.5 (0.3, 0.6)	NR	7.4 (4.8, 10.0), n=108
	Placebo → LUM/IVA	96		0.0 (-2.7, 2.7)	-22.8 (-26.3, -19.3), n=78	0.3 (0.2, 0.4)	NR	6.6 (3.1, 10.0), n=65
KLIMB Rosenfeld 2019[56]	IVA	33	84 weeks	NR	-8.5 (-18.9, 1.8), n=20	n (%): 10 (30.3)	n (%): 6 (18.2)	NR

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

Table D9. Long-term Efficacy Outcomes II

Trial	Arms	N	Follow-Up Duration	BMI		Weight		Height		Absolute Change in LCI2.5, points (95% CI)
				Absolute Change in BMI, kg/m2 (SE)	Absolute Change in BMI z score (SE)	Absolute Change in Weight, kg (SE)	Absolute Change in Weight z score (SE)	Absolute Change in Height, cm (SE)	Absolute Change in Height z score (SE)	
Chilvers 2019[74]	LUM/IVA → LUM/IVA	143	96 weeks	1.8 (1.6, 2.0), n=130	0.2 (0.1, 0.3)	10.3 (9.6, 11.0)*	0.1 (0.04, 0.2)	13.4 (12.9, 14.0)*	-0.01 (-0.1, 0.1)	-0.9 (-1.3, -0.5), n=88
	Placebo → LUM/IVA	96		2.0 (1.8, 2.3), n=83	0.3 (0.2, 0.4)	11.0 (10.1, 11.8)*	0.2 (0.1, 0.3)	13.5 (12.8, 14.1)*	0.02 (-0.1, 0.1)	-0.9 (-1.3, -0.4), n=69
KLIMB Rosenfeld 2019[56]	IVA	33	84 weeks	NR	-0.1 (-0.3, 0.2)	NR	0.0 (-0.2, 0.2)	NR	0.1 (0.0, 0.3)	NR

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

* measured from baseline in parent study

Table D10. Patient Reported Outcomes

Trial	Arms	N	Follow-Up (weeks)	Treatment Burden, treatment effect vs placebo (95%CI), p-value	Health Perception, treatment effect vs placebo (95%CI), p-value	Physical Functioning, treatment effect vs placebo (95%CI), p-value	Social Functioning, treatment effect vs placebo (95%CI), p-value	Emotional Functioning, treatment effect vs placebo (95%CI), p-value	Role Functioning, treatment effect vs placebo (95%CI), p-value	Vitality, treatment effect vs placebo (95%CI), p-value
Tezacaftor (TEZ) / Ivacaftor (IVA)										
EVOLVE **Taylor-Cousar 2017[84]** **Yang 2018[79]**	TEZ/IVA	481	24 weeks	3.4 (1.6, 5.1), p<0.05	3.2 (1.2, 5.2), n.s.*	3.8 (1.9, 5.8), p<0.05	1.5 (0.0, 3.0), n.s.	0.6 (-1.0, 2.2), n.s.*	1.5 (-0.3, 3.4), n.s.	2.3 (0.1, 4.5), n.s.

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

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

Table D11. Harms I

Trial	Arms	N	Any AE, n (%)	SAEs		TEAE, n (%)	AE leading to D/C, n (%)	Death, n (%)	Infective Pulmonary Exacerbations of CF, n (%)
				Any SAE, n (%)	Rash Events, n (%)				
Elexacaftor (ELX) / Tezacaftor (TEZ) / Ivacaftor (IVA)									
Trial 1 **Middleton 2019[52]**	ELX/TEZ/IVA	202	188 (93.1)	28 (13.9)	3 (1.5)	NR	2 (1.0)	0 (0)	44 (21.8)
	Placebo	201	193 (96.0)	42 (20.9)	1 (0.5)	NR	0 (0)	0 (0)	95 (47.3)
Trial 2 **Heijerman 2019[53]**	ELX/TEZ/IVA	55	32 (58.1)	2 (3.6)	1 (1.8)	12 (21.8)	0 (0)	0 (0)	1 (1.8)
	Placebo/TEZ/IVA	52	33 (63.5)	1 (1.9)	0 (0)	9 (17.3)	0 (0)	0 (0)	6 (11.5)
Keating 2018[54] ***heterozygous population***	ELX/TEZ/IVA	21	18 (85.7)	0 (0)	NR	NR	0 (0)	0 (0)	2 (9.5)
	Placebo	12	12 (100)	2 (16.7)	NR	NR	0 (0)	0 (0)	4 (33.3)
Keating 2018[54] ***homozygous population***	ELX/TEZ/IVA	21	19 (90.5)	0 (0)	NR	NR	1 (4.8)	0 (0)	5 (23.8)
	Placebo/TEZ/IVA	7	5 (71.4)	1 (14.3)	NR	NR	1 (14.3)	0 (0)	1 (14.3)

Trial	Arms	N	Any AE, n (%)	SAEs		TEAE, n (%)	AE leading to D/C, n (%)	Death, n (%)	Infective Pulmonary Exacerbations of CF, n (%)
				Any SAE, n (%)	Rash Events, n (%)				
Tezacaftor (TEZ) / Ivacaftor (IVA)									
EVOLVE **Taylor-Cousar 2017[84]** **Yang, 2018[79]**	TEZ/IVA	251	227 (90.4)	31 (12.4)	NR	64 (25.5)	7 (2.8)	0 (0)	75 (29.9)
	Placebo	258	245 (95.0)	47 (18.2)	NR	66 (25.6)	8 (3.1)	0 (0)	96 (37.2)
Walker 2019[90]	TEZ/IVA (Part A)	13	12 (92.3)	0 (0)	0 (0)*	NR	0 (0)	0 (0)	0 (0)
	TEZ/IVA (Part B)	70	65 (92.9)	6 (8.6)	NR	1 (1.4)	1 (1.4)	0 (0)	16 (22.9)
EXTEND † **Flume 2018[78]**	TEZ/IVA	613	601 (98.0)	194 (31.6)	NR	NR	3 (0.5)	0 (0)	331 (54.0)
Lumacaftor (LUM) / Ivacaftor (IVA)									
TRAFFIC and TRANSPORT **Wainwright 2015[23]**	LUM600/IVA	369	356 (96.5)	84 (22.8)	NR	NR	14 (3.8)	0 (0)	145 (39.3)
	LUM400/IVA	369	351 (95.1)	64 (17.3)	NR	NR	17 (4.6)	0 (0)	132 (35.8)
	Placebo	370	355 (95.9)	106 (28.6)	NR	NR	6 (1.6)	0 (0)	182 (49.2)
TRAFFIC and TRANSPORT – sub-group analysis **McColley 2019[76]**	LUM/IVA	1108	Safety Data NR						
McNamara 2019[77]	LUM/IVA Part A (pooled)	12	10 (83)	0 (0)	NR	NR	1 (8.3)	NR	NR
	LUM/IVA Part B (pooled)	60	59 (98.3)	4 (6.7)	NR	NR	NR	NR	2 (3.3)
Chilvers 2019[74]‡	LUM/IVA → LUM/IVA	143	141 (98.6)	43 (30.1)	NR	NR	9 (3.8)	0 (0)	59 (41.3)
	Placebo → LUM/IVA	96	93 (96.9)	29 (30.2)	NR	NR		0 (0)	34 (35.4)
Ivacaftor (IVA)									
KLIMB **Rosenfeld 2019[56]**	Weight-based IVA	33	33 (100)	11 (33.3)	NR	NR	1 (3.0)	NR	NR

AE: adverse event, CF: cystic fibrosis, D/C: discontinuation, n: number, N: total number, NR: not reported, SAE: serious adverse event, TEAE: treatment-emergent adverse
* assumption made based on SAEs: 0 (0), † at 86 weeks, ‡time frame: from day 1 up to 100 weeks

Table D12. Harms II

Trial	Arms	N	Sputum increased, n (%)	Headache, n (%)	Cough, n (%)	Rash, n (%)	Diarrhea, n (%)	Upper Resp. Tract Infection, n (%)	Nasopharyngitis, n (%)	Oropharyngeal pain, n (%)	Hemoptysis, n (%)	Fatigue, n (%)	Pyrexia, n (%)	Nausea, n (%)	Vomiting, n (%)
Elexacaftor (ELX) / Tezacaftor (TEZ) / Ivacaftor (IVA)															
Trial 1 **Middleton 2019[52]**	ELX/TEZ/IVA	202	40 (19.8)	35 (17.3)	34 (16.8)	22 (10.9)	26 (12.9)	24 (11.9)	22 (10.9)	20 (9.9)	11 (5.4)	9 (4.5)	NR	NR	NR
	Placebo	201	39 (19.4)	30 (14.9)	77 (38.3)	13 (6.5)	14 (7.0)	22 (10.9)	26 (12.9)	25 (12.4)	28 (13.9)	20 (10.0)	NR	NR	NR
Trial 2 **Heijerman 2019[53]**	ELX/TEZ/IVA	55	NR	3 (5.5)	8 (14.5)	2 (3.6)	NR	4 (7.3)	4 (7.3)	4 (7.3)	2 (3.6)	NR	NR	NR	NR
	Placebo/TEZ/IVA	52	NR	4 (7.7)	4 (7.7)	2 (3.8)	NR	2 (3.8)	2 (3.8)	0 (0)	5 (9.6)	NR	NR	NR	NR
Keating 2018[54] *heterozygous population*	ELX/TEZ/IVA	21	5 (23.8)	2 (9.5)	7 (33.3)	NR	0 (0)	NR	4 (19.0)	NR	2 (9.5)	NR	1 (4.8)	1 (4.8)	NR
	Placebo	12	3 (25.0)	2 (16.7)	1 (8.3)	NR	1 (8.3)	NR	0 (0)	NR	2 (16.7)	NR	1 (8.3)	2 (16.7)	NR
Keating 2018[54] *homozygous*	ELX/TEZ/IVA	21	8 (38.1)	0 (0)	7 (33.3)	NR	0 (0)	NR	1 (4.8)	NR	3 (14.3)	NR	3 (14.3)	1 (4.8)	NR
	Placebo/TEZ/IVA	7	0 (0)	1 (14.3)	1 (14.3)	NR	0 (0)	NR	1 (14.3)	NR	0 (0)	NR	1 (14.3)	1 (14.3)	NR

Trial	Arms	N	Sputum increased, n (%)	Headache, n (%)	Cough, n (%)	Rash, n (%)	Diarrhea, n (%)	Upper Resp. Tract Infection, n (%)	Nasopharyngitis, n (%)	Oropharyngeal pain, n (%)	Hemoptysis, n (%)	Fatigue, n (%)	Pyrexia, n (%)	Nausea, n (%)	Vomiting, n (%)
population															
Tezacaftor (TEZ) / Ivacaftor (IVA)															
EVOLVE **Taylor-Cousar 2017[84] Yang, 2018[79]**	TEZ/IVA	251	36 (14.3)	44 (17.5)	66 (26.3)	4 (1.6)	17 (6.8)	NR	42 (16.7)	22 (8.8)	26 (10.4)	16 (6.4)	28 (11.2)	23 (9.2)	NR
	Placebo	258	42 (16.3)	37 (14.3)	84 (32.6)	13 (5.0)	23 (8.9)	NR	39 (15.1)	29 (11.2)	35 (13.6)	31 (12.0)	32 (12.4)	18 (7.0)	NR
Walker 2019[90]	TEZ/IVA (Part A)	13	1 (7.7)	3 (23.1)	3 (23.1)	1 (7.7)	NR	0 (0)	1 (7.7)	1 (7.7)	NR	NR	1 (7.7)	NR	0 (0)
	TEZ/IVA (Part B)	70	3 (4.3)	6 (8.6)	25 (35.7)	0 (0)	NR	6 (8.6)	6 (8.6)	6 (8.6)	NR	NR	13 (18.6)	NR	7 (10.0)
EXTEND † **Flume 2018[78]**	TEZ/IVA	613	NR	NR	240 (39.2)	NR	NR	NR	156 (25.4)	NR	NR	NR	NR	NR	NR
Lumacaftor (LUM) / Ivacaftor (IVA)															
TRAFFIC and TRANSPORT **Wainwright 2015[23]**	LUM600/IVA	369	55 (14.9)	58 (15.7)	121 (32.8)	NR	36 (9.8)	24 (6.5)	23 (6.2)	44 (11.9)	52 (14.1)	NR	NR	29 (7.9)	NR
	LUM400/IVA	369	54 (14.6)	58 (15.7)	104 (28.2)	NR	45 (12.2)	37 (10.0)	48 (13.0)	24 (6.5)	50 (13.6)	NR	NR	46 (12.5)	NR
	Placebo	370	70 (18.9)	58 (15.7)	148 (40.0)	NR	31 (8.4)	20 (5.4)	40 (10.8)	30 (8.1)	50 (13.5)	NR	NR	28 (7.6)	NR

Trial	Arms	N	Sputum increased, n (%)	Headache, n (%)	Cough, n (%)	Rash, n (%)	Diarrhea, n (%)	Upper Resp. Tract Infection, n (%)	Nasopharyngitis, n (%)	Oropharyngeal pain, n (%)	Hemoptysis, n (%)	Fatigue, n (%)	Pyrexia, n (%)	Nausea, n (%)	Vomiting, n (%)
TRAFFIC and TRANSPORT – sub-group analysis McColley 2019[76]	LUM/IVA	1108	Safety Data NR												
McNamara 2019[77]	LUM/IVA Part A (pooled)	12	NR	NR	5 (41.7)	NR	NR	NR	NR	NR	NR	NR	NR	NR	2 (16.7)
	LUM/IVA Part B (pooled)	60	NR	NR	38 (63.3)	NR	NR	10 (16.7)	NR	NR	NR	NR	17 (28.3)	NR	17 (28.3)
Chilvers 2019[74]‡	LUM/IVA → LUM/IVA	143	18 (12.6)	29 (20.3)	91 (63.6)	10 (7.0)	16 (11.2)	36 (25.2)	21 (14.7)	32 (22.4)	8 (5.6)	10 (7.0)	45 (31.5)	13 (9.1)	30 (21.0)
	Placebo → LUM/IVA	96	7 (7.3)	26 (27.1)	64 (66.7)	10 (10.4)	8 (8.3)	13 (13.5)	16 (16.7)	18 (18.8)	1 (1.0)	11 (11.5)	27 (28.1)	11 (11.5)	15 (15.6)
Ivacaftor (IVA)															
KLIMB Rosenfeld 2019[56]	Weight-based IVA	33	NR	NR	24 (72.7)	4 (12.1)	NR	5 (15.2)	NR	NR	NR	NR	13 (39.4)	NR	13 (39.4)

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

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

Table D13. Study Quality

Trial	Comparable Groups	Non-differential Follow-up	Patient/ Investigator Blinding (Double-Blind)	Clear Definition of Outcomes	Selective outcome reporting	Measurements Valid	Intention to treat analysis	Approach to Missing Data	USPSTF Rating
Middleton 2019[52]	yes	yes	yes	yes	no	yes	ITT	MMRM	good
Heijerman 2019[53]	yes	yes	yes	yes	no	yes	mITT	MMRM	good
Keating 2018[54]	yes	yes	yes	yes	no	yes	ITT	MMRM	good
Taylor-Cousar 2017[84]	yes	yes	yes	yes	no	yes	ITT	MMRM	good
Walker 2019[90]	N/A	N/A	N/A	yes	no	yes	ITT	MMRM	poor
Wainwright 2015[23]	yes	yes	yes	yes	no	yes	mITT	MMRM	good
McNamara 2019[77]	N/A	yes	N/A	yes	no	yes	ITT	?	poor

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

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

Trial & Author	Intervention & N	Follow-Up Duration	Baseline Characteristics	Efficacy Outcomes	Safety Data
EXPAND Chuang 2018[89]	- Tezacaftor/ Ivacaftor - Placebo N=240	Average of 4 and 8 weeks	See EXPAND abstraction table in 2018 cystic fibrosis review	Patient Reported Outcomes *(Treatment effect vs placebo (95%CI), p-value)* <u>Treatment Burden:</u> 2.8 (0.8, 4.8), p<0.05 <u>Health Perception:</u> 9.2 (6.7, 11.7), p<0.05 <u>Physical Functioning:</u> 7.1 (4.5, 9.7), p<0.05 <u>Social Functioning:</u> 3.1 (1.3, 4.9), p<0.05 <u>Emotional Functioning:</u> 2.6 (0.8, 4.3), n.s.	NR

Trial & Author	Intervention & N	Follow-Up Duration	Baseline Characteristics	Efficacy Outcomes	Safety Data
				Role Functioning: 3.3 (1.0, 5.6), p<0.05 Vitality: 8.3 (5.6, 10.9), p<0.05	
NCT01937325 Post-hoc analysis **Wilson 2018[57]**	- Ivacaftor - Placebo N=20	4 weeks followed by a 3-month open-label extension	Age, mean years (Range): 32.5 (18-65) Female, n (%): 8 (40.0) MOCA score, mean (SD): 27.2 (5.4) TMT, mean time (SD): 34.0 sec (8.7)	**At 4 Weeks** MOCA score, mean change (Range): - IVA: 3.95 (−3.70, 18.18), p=0.042 - Placebo: 0.41 (-10.0, 11.54), p=0.675 TMT, mean time change (SD): No statistically significant improvement **At 3 Months** MOCA score, mean change (Range): - IVA: 5.69 (-10.00, 21.74) p=0.006 TMT, mean time change (SD): No statistically significant improvement	NR
NCT01937325 Post-hoc analysis **Keating 2019[55]**	No treatment (Ivacaftor withdrawal) N=20	4 weeks	*After 4 weeks of treatment (before withdrawal)* $ppFEV_1$, mean % (SD): 73.0 (24.0) Sweat Chloride, mean mmol/L (SD): 103.8 mmol/L (14.0)	$ppFEV_1$, mean % change (SD): 10.1 (NR), p<0.05 Sweat Chloride, mean mmol/L change (SD): 41.1 (NR), p<0.001 VO2Max: -2.7 (NR), n.s.	NR

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

Table D15. Observational Studies

Study	Study Design, Data Source (Year) & Duration of Follow-Up	Intervention(s) & Dosing Schedule	Inclusions & Exclusion Criteria	Baseline Characteristics	Outcomes	Harms / Complications
Ivacaftor						
Bessonova 2018[13]	Ongoing, observational, post-approval safety study U.S. Cystic Fibrosis Foundation Registry (CFFR) 2014 Follow-Up: 3 years following commercial availability (2011-2014)	- IVA (n=1256) - Matched comparator group (patients who had never received IVA treatment; n=6200) N=7456	**Inclusions** All patients included in US CFFR in 2014	**Female, n (%)** - IVA: 630 (50.2) - Comparator Group: 3092 (49.9) **ppFEV$_1$ Categories (%)** IVA: - <40%: 90 (7.2) - 40 to <70%: 290 (23.1) - ≥70%: 639 (50.9) - Missing: 237 (18.9) Comparator: - <40%: 435 (7.0) - 40 to <70%: 1330 (21.5) - ≥70%: 3191 (51.5) - Missing: 1244 (20.1) **PEx, n (%)** - IVA: 444 (28.5) - Comparator: 2187 (37.4) **Hospitalizations, n (%)** - IVA: 443 (38.4) - Comparator: 2294 (39.3)	**Organ Transplantation, n (AR%)** - IVA: 2 (0.2) - Comparator: 68 (1.1) - RR (95%CI), p-value: 0.15 (0.04, 0.59), p=0.0017 **PEx, n (AR%)** - IVA: 349 (27.8) - Comparator: 2684 (43.3) - RR (95%CI), p-value: 0.64 (0.58, 0.70), p<0,0001 **Hospitalization (for any reason), n (AR%)** - IVA: 346 (27.5) - Comparator: 2671 (43.1) - RR (95%CI), p-value: 0.64 (0.58, 0.70), p<0.0001 **ppFEV$_1$, mean %-change (SE)** - IVA (n=636): 1.4 (1.3) - Comparator (n=2854): -5.3 (0.4) - p-value: p<0.0001 **CFRD, n (%)** - IVA: 382 (30.4) - Comparator: 2449 (39.5)	**Death, n (AR%)** - IVA: 8 (0.6) - Comparator: 97 (1.6) - RR (95%CI), p-value: 0.41 (0.20, 0.84), p=0.0110 **Gastrointestinal Complications, n (%)** - IVA: 467 (37.2) - Comparator: 2474 (39.9) - RR (95%CI): 0.93 (0.86, 1.01) **Pulmonary Complications, n (%)** - IVA: 431 (34.3) - Comparator: 2207 (35.6) - RR (95%CI): 0.96 (0.89, 1.05) **Hepatobiliary, n (%)** - IVA: 58 (4.6) - Comparator: 484 (7.8) - RR (95% CI): 0.59 (0.45, 0.77) **Bone/Joint, n (%)** - IVA: 222 (17.7) - Comparator: 1389 (22.4) - RR (95%CI): 0.79 (0.69, 0.90)

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

Study	Study Design, Data Source (Year) & Duration of Follow-Up	Intervention(s) & Dosing Schedule	Inclusions & Exclusion Criteria	Baseline Characteristics	Outcomes	Harms / Complications
				Hospitalizations, n (%) - IVA: 173 (45.3) - Comparator: 862 (43.3)	- p-value: p<0.001 **CFRD, n (%)** - IVA: 85 (20.7) - Comparator: 602 (29.1) - RR (95%CI), p-value: 0.71 (0.58, 0.87), p<0.0007 **Depression, n (%)** - IVA: 18 (4.4) - Comparator: 122 (5.9) - RR (95%CI), p-value: 0.74 (0.46, 1.20), p=0.26	**Bone/Joint, n (%)** - IVA: 75 (18.2) - Comparator: 573 (27.7) - RR (95%CI): 0.66 (0.53, 0.82)
Volkova 2019[63]	Observational, post-approval safety study US Cystic Fibrosis Foundation Registry (CFFR) 2016 Follow-Up: 5 years (2012-2016)	- IVA (n=635) - Comparator (patients without IVA use during first year of market availability; n=1874) N=2,509	**Inclusions** All patients with a record of IVA use during first calendar year of market availability who were still on treatment in 2016, and who had not received a lung transplant *No inclusion/ exclusion criteria based on patient age*	**Female, n (%)** - IVA: 328 (51.7) - Comparator: 915 (48.8) **BMI, mean kg/m^2 (95%CI)** - IVA: 20.3 (20.0, 20.6) - Comparator: 20.0 (19.8, 20.2) **ppFEV$_1$, mean % (SD)** - IVA: 79.0 (25.3) - Comparator: 81.7 (23.7) **ppFEV$_1$ Categories, n (%)** IVA: - <40%: 38 (6.0) - 40 to <70%: 146 (23.0)	**ppFEV$_1$, mean %-change (95%CI)** - IVA: -0.7 (-1.6, 0.2) - Comparator: -8.3 (-9.0, -7.7) - RR (95%CI): NR **Hospitalizations, n (%)** - IVA: 167 (26.3) - Comparator: 830 (44.3) - RR (95%CI): 0.59 (0.52, 0.68) **BMI, mean kg/m^2 change (95%CI)** - IVA: 2.4 (2.1, 2.6) - Comparator: 1.6 (1.5, 1.7) - RR (95%CI): NR **PEx, n (%)** - IVA: 163 (25.7)	See Bessonova 2018

Study	Study Design, Data Source (Year) & Duration of Follow-Up	Intervention(s) & Dosing Schedule	Inclusions & Exclusion Criteria	Baseline Characteristics	Outcomes	Harms / Complications
			or genotype were applied	- ≥70%: 393 (61.9) - Missing: 58 (9.1) <u>Comparator:</u> - <40%: 66 (3.5) - 40 to <70%: 351 (18.7) - ≥70%: 1184 (63.2) - Missing: 273 (14.6) **PEx, n (%)** - IVA: 230 (37.5) - Comparator: 592 (33.1) **Hospitalizations, n (%)** - IVA: 232 (37.8) - Comparator: 644 (36.0) **P. Aeruginosa, n (%)** - IVA: 359 (56.5) - Comparator: 937 (50.0)	- Comparator: 825 (44.0) - RR (95%CI): 0.58 (0.51, 0.67) **CFRD, n (%)** - IVA: 227 (35.7) - Comparator: 766 (40.9) - RR (95%CI): 0.87 (0.77, 0.98) **P. Aeruginosa, n (%)** - IVA: 286 (45.1) - Comparator: 1044 (55.7) - RR (95%CI): 0.81 (0.73, 0.89)	
	Observational, post-approval safety study UK CFR 2016 <u>Follow-Up</u>: 4 years (2013-2016)	- IVA (n=247) - Comparator (n=1230) N=1,477		**Female, n (%)** - IVA: 113 (45.7) - Comparator: 588 (47.8) **BMI, mean (95%CI)** - IVA: 20.6 (20.1, 21.1) - Comparator: 20.5 (20.3, 20.7) **ppFEV$_1$, mean (SD)** - IVA: 73.0 (23.6)	**ppFEV$_1$, mean %-change (95%CI)** - IVA: 4.9 (3.3,6.6) - Comparator: -4.3 (-5.1, -3.4) - RR (95%CI): NR **Hospitalizations, n (%)** - IVA: 65 (26.3) - Comparator: 549 (44.6) - RR (95%CI): 0.59 (0.47, 0.73)	See Bessonova 2018

Study	Study Design, Data Source (Year) & Duration of Follow-Up	Intervention(s) & Dosing Schedule	Inclusions & Exclusion Criteria	Baseline Characteristics	Outcomes	Harms / Complications
				- Comparator: 73.4 (22.4) **ppFEV$_1$ Categories, n (%)** <u>IVA:</u> - <40%: 26 (10.5) - 40 to <70%: 69 (27.9) - ≥70%: 132 (53.4) - Missing: 20 (8.1) <u>Comparator:</u> - <40%: 93 (7.6) - 40 to <70%: 388 (31.5) - ≥70%: 646 (52.5) - Missing: 103 (8.4) **PEx, n (%)** - IVA: 133 (53.8) - Comparator: 556 (45.2) **Hospitalizations, n (%)** - IVA: 116 (47.0) - Comparator: 505 (41.1) **P. Aeruginosa, n (%)** - IVA: 156 (63.2) - Comparator: 704 (57.2)	**BMI, mean kg/m^2 change (95%CI)** - IVA: 1.9 (1.6, 2.1) - Comparator: 0.9 (0.8, 1.0) - RR (95%CI): NR **PEx, n (%)** - IVA: 81 (32.8) - Comparator: 707 (57.5) - RR (95%CI): 0.57 (0.47, 0.67) **CFRD, n (%)** - IVA: 46 (18.6) - Comparator: 358 (29.1) - RR (95%CI): 0.65 (0.49, 0.84) **P. Aeruginosa, n (%)** - IVA: 96 (38.9) - Comparator: 688 (55.9) - RR (95%CI): 0.70 (0.59, 0.82)	
Feng 2018[59]	Retrospective cohort, single center study	IVA (N=143)	**Inclusions** - ICD-9-CM or ICD-10-CM diagnosis for CF on ≥ one	**Age, n (%)** - Children (6-17 years): 53 (37.0) - Adults (18-65 years): 90 (63.0)	**All-cause Hospitalizations, n (rate/PY)** - Overall: 37 (0.26) - Children: 13 (0.25) - Adults: 24 (0.27)	NR

Study	Study Design, Data Source (Year) & Duration of Follow-Up	Intervention(s) & Dosing Schedule	Inclusions & Exclusion Criteria	Baseline Characteristics	Outcomes	Harms / Complications
	MarketScan Research Database (Treatment Pathways 4.0 including Commercial and Medicare Supplemental databases) <u>Follow-Up</u>: 12 months prior to IVA treatment (baseline) compared to 12 months post-IVA treatment (within group comparison		inpatient claims or on ≥two outpatient claims at least 30 days apart - At least 1 prescription claim for monotherapy, between ages 6-65 - 12 months of continuous enrollment before and after first filled prescription **Exclusions** NR	**All-cause Hospitalizations, n (rate/PY)** - Overall: 82 (0.57) - Children: 32 (0.60) - Adults: 50 (0.56) **CF-related Hospitalizations, rate/PY** - Overall: 42 (0.29) - Children: 17 (0.32) - Adults: 25 (0.28) **Effect of Medication Adherence on All-cause Hospitalizations, n (rate/PY)** - 3 to 9 fills: 20 (0.38) - 10 to 12 fills: 28 (0.31)	**CF-related Hospitalizations, n (rate/PY)** - Overall: 8 (0.006) - Children: 3 (0.006) - Adults: 5 (0.006) **All-cause Hospitalizations based on Medication Adherence, n (rate/PY)** - 3 to 9 fills: 11 (0.21) - 10 to 12 fills: 9 (0.10)	
BRIO Study **Hubert 2018[60]**	Prospective, ongoing, multi-centre observational study 33 French Cystic Fibrosis Centers	IVA (N=107)	**Inclusions** - Patients with CF - ≥ 6 years old - ivacaftor-responsive mutations **Exclusions**	**Age, mean years (SD)** 21.1 (14.3) **Female, n (%)** 47 (44.0) **Hospitalization days/PY** 5.3	**Change in All-Cause Hospitalizations/PY, RR (95%CI)** 0.40 (0.26, 0.61) **Hospitalization days/PY (RR; 95%CI)** 2.5 (0.46; 0.22, 0.95)	NR

Study	Study Design, Data Source (Year) & Duration of Follow-Up	Intervention(s) & Dosing Schedule	Inclusions & Exclusion Criteria	Baseline Characteristics	Outcomes	Harms / Complications
	Follow-Up: Interim analysis of health care resource utilization for 12 months pre- and 12 months post-ivacaftor initiation		NR	**Days of Antibiotic use/PY** 20.9	**Number of antibiotics/PY for PEx Treatment, RR (95%CI)** 0.47 (0.32, 0.68) **Days of Antibiotic use/PY (RR; 95%CI)** 11.4 (0.54; 0.40, 0.72)	
GOAL Study **McColley 2019[62]** **Extension of GOAL Study** **Guimbellot 2018[51]**	Multicenter, prospective, longitudinal cohort-study Long-term, Observational Extension to the GOAL Study Cystic Fibrosis Foundation Registry Follow-Up: - GOAL: 6 months - Extension: 5 years	IVA - GOAL: N= 153 - Extension: N=96	**Inclusions** - ≥ 6 years of age - ≥ 1 copy of G551D mutation	**GOAL Study** **SNOT-20, subset mean score (SD)** - Rhinology: 1.04 (0.99) - Ear/Face: 0.31 (0.56) - Sleep: 1.13 (1.34) - Psychological: 0.80 (0.92) **Extension** **Age, mean years (SD)** - Overall: 19.8 (NR) - < 18 years (n=52): 11.6 (NR) - ≥ 18 years (n=44): 29.5 (NR) **Female, n (%)** 43 (44.8) **ppFEV$_1$, mean % (SD)** - Mean ppFEV$_1$: 82.0 - < 18 years: 94.7	**GOAL Study (at 6 months)** **SNOT-20, subset mean score change, p-value** - Rhinology: -0.25, p<0.01 - Ear/Face: 0.03, p=0.608 - Sleep: -0.18, p=0.074 - Psychological: -0.26, p<0.01 **ppFEV$_1$, mean % change (95%CI)** 7.9 (5.8, 10.1), p<0.0001 **BMI, mean kg/m^2 change (95%CI)** NR **CFQR-R score, mean change (95%CI):** 8.8 (4.8, 12.8), p<0.0001 **Sweat Chloride, mean mEq/L change (95%CI)** NR	NR

Study	Study Design, Data Source (Year) & Duration of Follow-Up	Intervention(s) & Dosing Schedule	Inclusions & Exclusion Criteria	Baseline Characteristics	Outcomes	Harms / Complications
				- ≥ 18 years: 67.0 **BMI, mean kg/m²** - < 18 years: 17.9 - ≥ 18 years: 23.4	**Extension (at 5.5 years)** **ppFEV$_1$, mean % change (95%CI)** - Overall: 0.8 (-2.0, 3.6), n.s. - < 18 years: -2.0 (-5.9, 2.0), p=0.3228 - ≥ 18 years: 4.3 (0.6, 8.1), p=0.0237 **BMI, mean kg/m² change (95%CI)** - Overall: 2.5 (2.0, 3.1), p<0.0001 - < 18 years: 3.6 (2.9, 4.3), p<0.0001 - ≥ 18 years: 1.2 (0.4, 2.0), p=0.003 **CFQR-R score, mean change (95%CI):** 6.7 (2.5, 10.9), p=0.002 **Sweat Chloride, mean mEq/L change (95%CI)** - Overall: -49.5 (-55.0, -44.1), p<0.0001 - < 18 years: -47.3 (-54.9, -39.8), p<0.0001 - ≥ 18 years: -52.4 (-60.6, -44.3), p<0.0001	
Bell 2019[58]	Cross-sectional observational study	- IVA (n=72) - Standard of care (n=137)	**Inclusions** IVA	**Age, mean years (SD)** - IVA: 23.9 (13.9) - SOC: 24.6 (11.1)	**CFQ-R Domains** Body Image, LSM (SE) - IVA: 74.9 (2.9) - SOC: 67.8 (2.2)	

Study	Study Design, Data Source (Year) & Duration of Follow-Up	Intervention(s) & Dosing Schedule	Inclusions & Exclusion Criteria	Baseline Characteristics	Outcomes	Harms / Complications
	5 countries (France, UK< Germany, Australia, and Ireland) Follow-up: mean duration of IVA exposure was 21.8 months		- Patients with a CF diagnosis with CF with ≥ 1 G551D mutation - Received IVA for >3 month SOC - homozygous for F508del mutation **Exclusions** - Participation in a clinical trial - Experiencing pulmonary exacerbation at clinic visit	**Female, n (%)** - IVA: 41 (60.3) - SOC: 44 (35.2) **ppFEV$_1$, mean % (SD)** - IVA: 79.8 (25.6) - SOC: 70.7 (28.8) **BMI, mean kg/m^2 (SD)** - ≥ 19 years old: 22.2 (3.2) - < 19 years old, z-score: 0.001 (0.87) Weight (6-11 and ≥14-year versions only) G551D/IVA: 80.7 F508del/SOC: 64.2 P < 0.01	- n.s. Digestive Symptoms, LSM (SE) - IVA: 85.5 (2.2) - SOC: 78.0 (1.7) - p < 0.05 Eating Problems, LSM (SE) - IVA: 91.1 (2.1) - SOC: 84.2 (1.6) - p < 0.05 Emotional Functioning, LSM (SE) - IVA: 78.8 (2.8) - SOC: 75.0 (1.9) - n.s. Health perceptions, LSM (SE)* - IVA: 67.6 (2.6) - SOC: 58.6 (1.8) - p < 0.01 Physical Functioning, LSM (SE) - IVA: 74.6 (2.6) - SOC: 66.6 2.0) - p < 0.05 Respiratory Symptoms, LSM (SE) - IVA: 75.4 (2.4) - SOC: 62.5 (1.8) - p < 0.001 Role Functioning, LSM (SE)† - IVA: 77.0 (2.9) - SOC: 73.5 (2.3) - n.s.	

Study	Study Design, Data Source (Year) & Duration of Follow-Up	Intervention(s) & Dosing Schedule	Inclusions & Exclusion Criteria	Baseline Characteristics	Outcomes	Harms / Complications
					School Functioning, LSM (SE)¥ - IVA: 83.1 (8.7) - SOC: 82.7 (9.7) - n.s. Social Functioning, LSM (SE)‡ - IVA: 70.2 (2.1) - SOC: 68.6 (1.5) - n.s. Treatment Burden, LSM (SE) - IVA: 65.3 (2.7) - SOC: 54.8 (1.6) - p < 0.01 Vitality, LSM (SE)* - G551D/IVA: 63.5 (3.1) - F508del/SOC: 55.9 (1.9) - p < 0.05 **EQ-5D-5L** Index Score (0-1), LSM (SE) - IVA (n=72): 0.90 (0.02) - SOC (n=137): 0.81 (0.02) - p < 0.01 VAS Score (0-100), n; LSM (SE) - IVA (n=72): 75.7 (1.8) - SOC (n=135): 70.0 (1.4) - p = 0.0136 **WPAI** Productivity loss, LSM (SE) - IVA (n=27) 24.62 (6.69) - SOC (n=32): 34.57 (6.73)	

Study	Study Design, Data Source (Year) & Duration of Follow-Up	Intervention(s) & Dosing Schedule	Inclusions & Exclusion Criteria	Baseline Characteristics	Outcomes	Harms / Complications
					- p = 0.3242 <u>Activity Impairment, LSM (SE)</u> - IVA (n=70): 21.63 (2.95) - SOC (n=135): 28.30 (2.19) - p = 0.08	
Kirwan 2017[61]	Observational Cohort Study Irish Cystic Fibrosis Registry <u>Follow-up:</u> 30 months pre and post ivacaftor treatment	IVA (N=114)	**Inclusions** CF patients treated with IVA **Exclusions** NR	**Age groups, n (%)** - <18 years: 54 (47) - ≥18 years: 60 (53) **Female, n (%)** 51 (45)	**ppFEV$_1$%** 7.7% increase (p < 0.001) **PEx, n** - Pre-IVA: 820 - Post-IVA: 523 **Duration of PEx, days** 43 fewer days per patient post commencement of treatment (p < 0.001) **Hospitalization (for PEx), n** Pre-IVA: 158 Post-IVA: 109 **Total days of Hospitalization, days** - Pre-IVA: 16.8 - Post-IVA: 13.0 - p=0.0301 **Mean BMI and BMI z score** Increased over treatment period (p < 0.001)	NR

Study	Study Design, Data Source (Year) & Duration of Follow-Up	Intervention(s) & Dosing Schedule	Inclusions & Exclusion Criteria	Baseline Characteristics	Outcomes	Harms / Complications
Lumacaftor/Ivacaftor						
Burgel 2020[80]	Multicenter Observational Study French Cystic Fibrosis Reference Network <u>Follow-Up:</u> 52 weeks	LUM/IVA (N=845) - Adults ≥18 years (n=553) - Adolescents 12-17 years (n=292) <u>Dosing</u>: - Twice daily LUM 400mg/ IVA 250mg (n=744) - reduced doses (not specified; n=101)	**Inclusions** - CF patients ≥ 12 years - homozygous for the F508del CFTR mutation - started LUM/IVA in 2016 **Exclusions** - Patients who received a lung transplant - Patients ineligible for LUM/IVA	**Age, median years [IQR]** 22.0 [16, 30] **Female, n (%)** 377 (44.6) **ppFEV$_1$, median % [IQR]** 65 [47, 80] **ppFEV1 < 40%, n (%)** 124 (14.8) **BMI, median kg/m^2 [IQR]** 19 [17, 21]	*LUM/IVA (N=821)* - *Contin. Treatment, n=631* - *Intermit. Treatment, n=45* - *Discount. Treatment, n=145* **ppFEV$_1$, absolute % change (SD)** - Overall: 2.7 (8.9) - Contin. treatment: 3.7 (8.6) - Intermit. treatment: 2.4 (8.5) - Discont. treatment: -1.4 (9.0) - Adolescents with cont. treatment (n=258): 4.76 (8.17) - Adults with cont. treatment (n=373): 2.91 (8.85) **Weight gain, mean kg** - Overall: 2.1 **BMI increase, mean kg/m^2** - Overall: 0.5	**TEAEs, n (%)** 494 (59.4) **AEs leading to Discont., n (%)** 154 (18.2) **Death, n (%)** 2 (1.3) **Respiratory AEs, n (%)** 316 (38.0) **Digestive AEs, n (%)** 181 (21.8) **Menstrual Abnormality, n (%)** 53 (6.4) **Fatigue, n (%)** 37 (4.4) **Headache, n (%)** 19 (3.3) *AEs were more prevalent in patients with diabetes (65.4% v. 56.8%; p=0.024)*
Wark 2019[82]	Retrospective cohort study	- LUM/IVA (n=72)	**Inclusions** - CF patients > 12 years	NR	**Mean rate of change in ppFEV$_1$, slope (95% CI)** - LUM/ IVA: 0.34 (-0.29, 1.03)	Harms not reported but mention of high rate of side effects

Study	Study Design, Data Source (Year) & Duration of Follow-Up	Intervention(s) & Dosing Schedule	Inclusions & Exclusion Criteria	Baseline Characteristics	Outcomes	Harms / Complications
	7 Australian CF centers Follow-Up: 52 weeks	- Untreated Control Group (ineligible for LUM/IVA treatment; n=30)	- homozygous for f508del CFTR mutation - ppFEV$_1$ < 40% **Exclusions** NR		- Control: -0.34 (-0.72, -0.04) **Reduction in PEx (95% CI)** LUM/IVA vs. Control: 0.49 (0.3, 0.7), p=0.001 No differences in ppFEV$_1$ at weeks 4, 12, 24, and 52 when 2 groups were compared	**Treatment Discont., n/N (%)** 44/102 (43%)
Multiple Treatment Regimens						

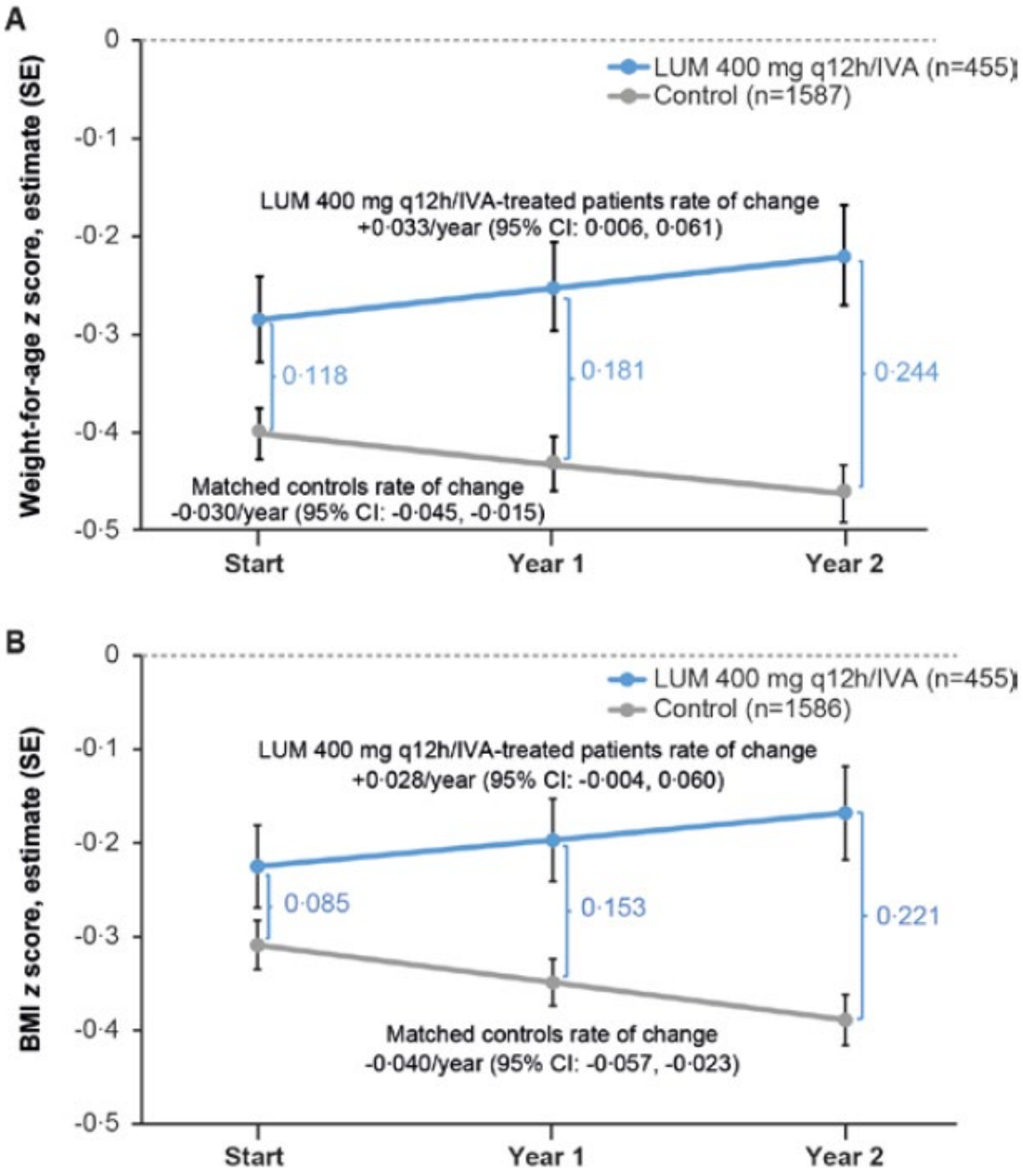
Study	Study Design, Data Source (Year) & Duration of Follow-Up	Intervention(s) & Dosing Schedule	Inclusions & Exclusion Criteria	Baseline Characteristics	Outcomes	Harms / Complications
Mayer-Hamblett 2019[71]	Population-based Epidemiologic Study (CHEC-SC) CF Foundation Patient Registry (CFFPR) Follow-up: - 12 months	- IVA (n=319) - LUM/IVA (n=661) - TEZ/IVA (n=285)	**Inclusions** CF patients who have been prescribed commercially approved CFTR modulator for over 3 months **Exclusions** NR	**Age, n (%)** IVA - 2-5 years: 32 (10) - 6-11 years: 62 (19) - 12-17 years: 61 (19) - 18-25 years: 57 (18) - ≥26 years: 106 (33) LUM/IVA - 2-5 years: 0 (0) - 6-11 years: 171 (26) - 12-17 years: 208 (32) - 18-25 years: 156 (24) - ≥26 years: 125 (19) TEZ/IVA - 2-5 years: 0 (0) - 6-11 years: 0 (0) - 12-17 years: 103 (36) - 18-25 years: 80 (28) - ≥26 years: 102 (36) **Genotype, n(%)** IVA - Gating: 167 (52) - R117H: 54 (17) - Splice: 52 (16) - Missense: (42 (13) - F508del Homozygous: 0 (0) - Other: 4 (1)	**Sweat Chloride, mean change (SD)** IVA - G511D: -51.4 (26.1) - R117H: -24.1 (19.9) F508del Homozygous - LUM/IVA: -20.5 (19.3) - TEZ/IVA: -12.6 (18.9)	NR

Study	Study Design, Data Source (Year) & Duration of Follow-Up	Intervention(s) & Dosing Schedule	Inclusions & Exclusion Criteria	Baseline Characteristics	Outcomes	Harms / Complications
				LUM/IVA - Gating: 1 (0.2) - R117H: 0 (0) - Splice: 0 (0) - Missense: 0 (0) - F508del Homozygous: 660 (99) - Other: 1 (0.2) TEZ/IVA - Gating: 0 (0) - R117H: 0 (0) - Splice: 20 (7) - Missense: 9 (3) - F508del Homozygous: 253 (88) - Other: 3 (1)		

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

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

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

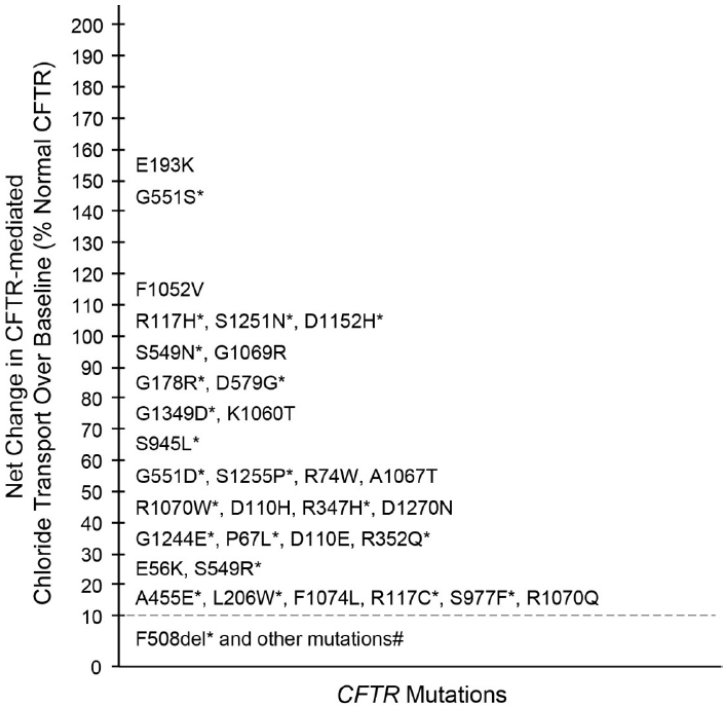


Genetic Specific Data on CFTR Modulators

Ivacaftor

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

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



*Clinical data exist for these mutations

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

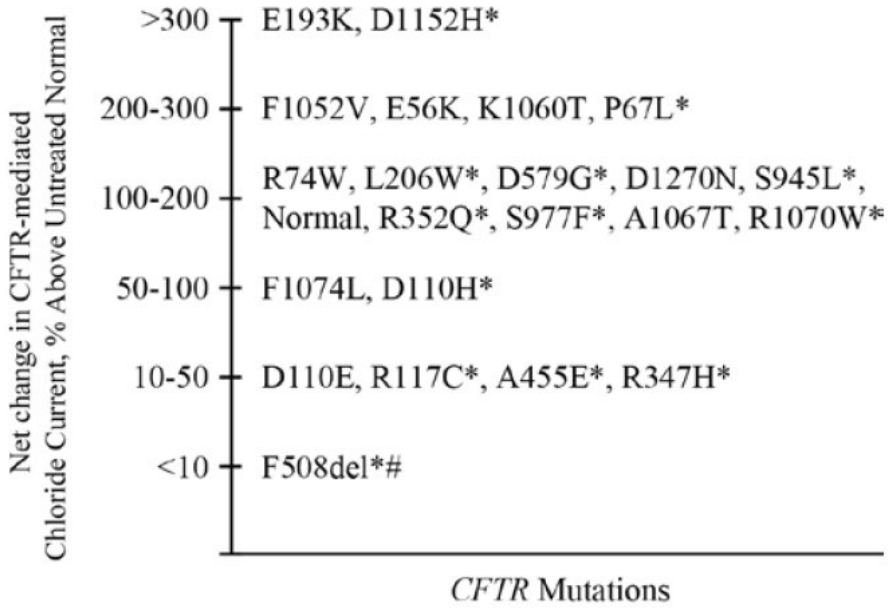
Mutation (n)	Absolute Change in percent predicted FEV_1*†	Absolute Change in CFQ-R Respiratory Domain Score (Points)*§	Absolute Change in Sweat Chloride (mmol/L)*§
3272-26A→G (23)	3.5 (-9.1, 16.0)	8.0 (-11.1, 27.8)	-2.3 (-25.0, 11.8)
3849+10kBc→T (40)	5.1 (-6.8, 16.2)	7.5 (-30.6, 55.6)	-4.6 (-80.5, 23.0)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

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

Symdeko[143]

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

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



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

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

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

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

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

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

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

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

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

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

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

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

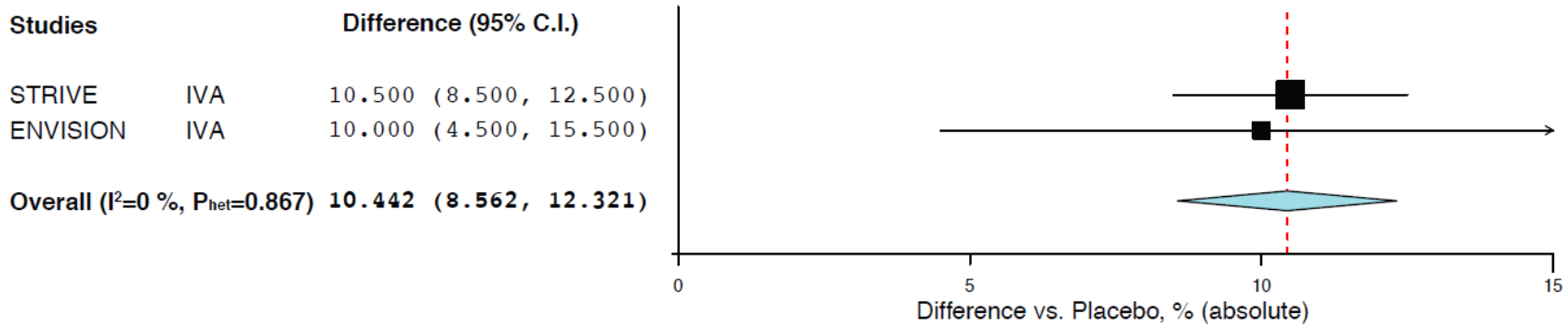
Table D18. NMA Results for Absolute Change from Baseline in Sweat Chloride, Mean (95% Confidence Interval)

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

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

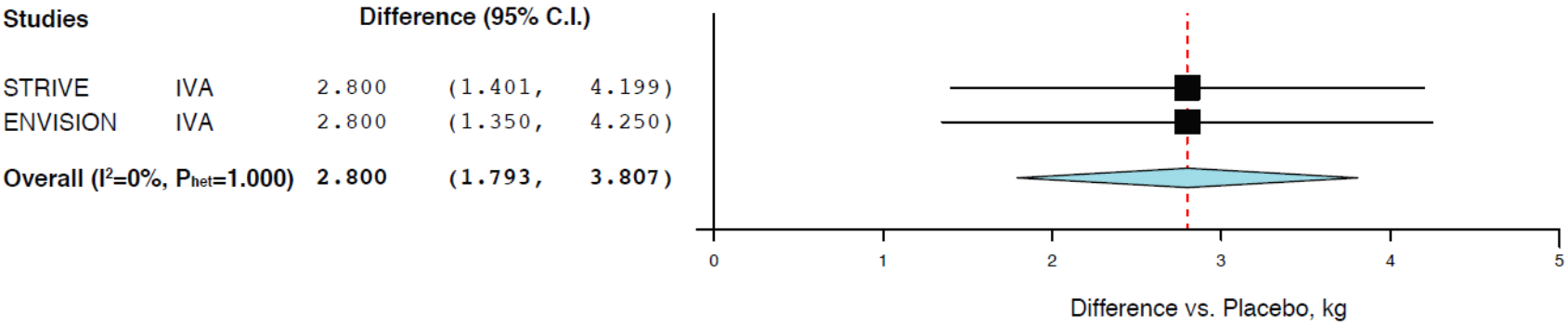
Forest Plots from Meta-Analysis

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



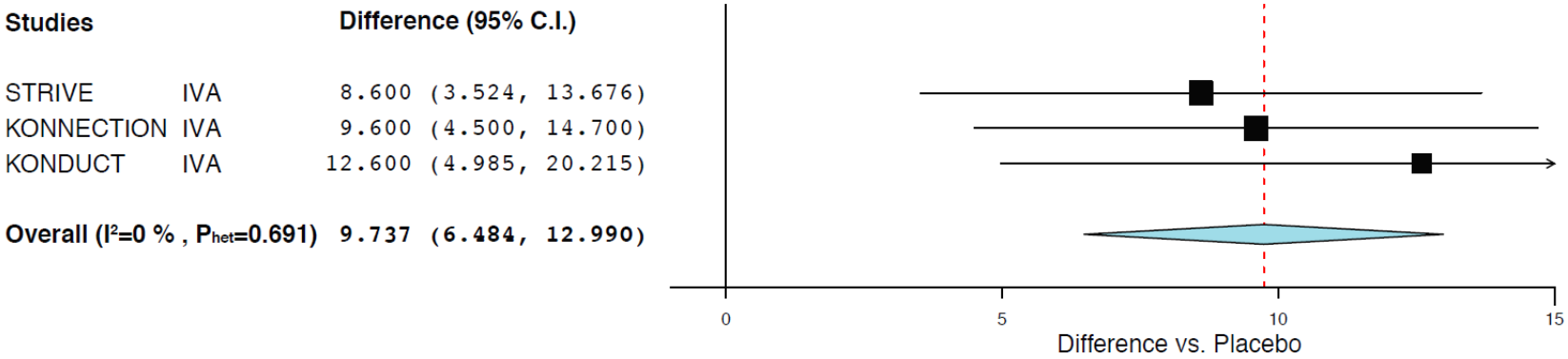
C.I: confidence interval, IVA: ivacaftor, Phet: chi-square P value for heterogeneity

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



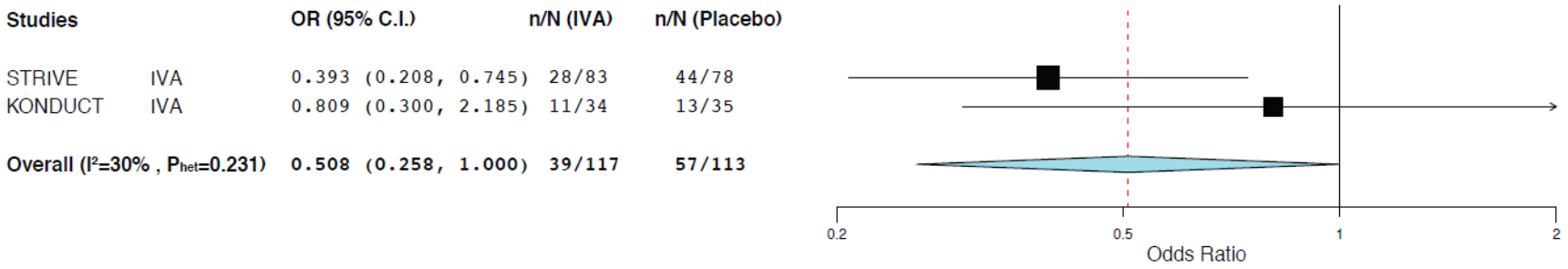
C.I.: confidence interval, IVA: ivacaftor, Phet: chi-square P value for heterogeneity

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



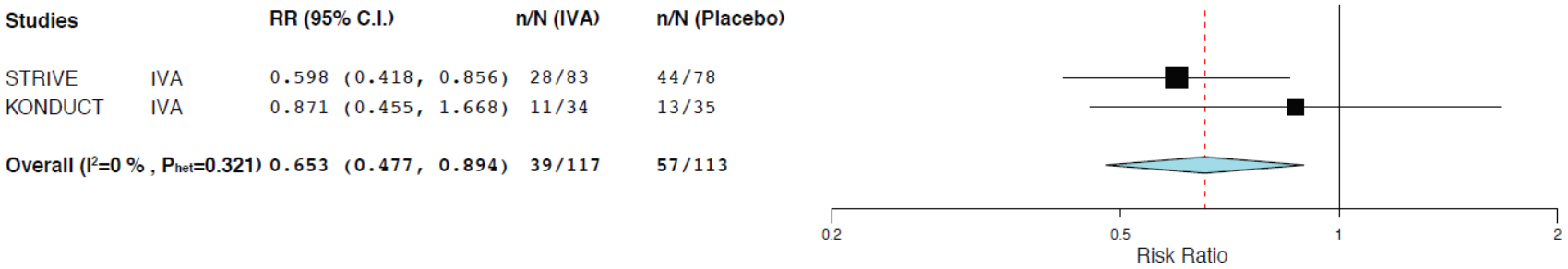
C.I.: confidence interval, CFQ-R: Cystic Fibrosis Questionnaire-Revised, IVA: ivacaftor, Phet: chi-square P value for heterogeneity.

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



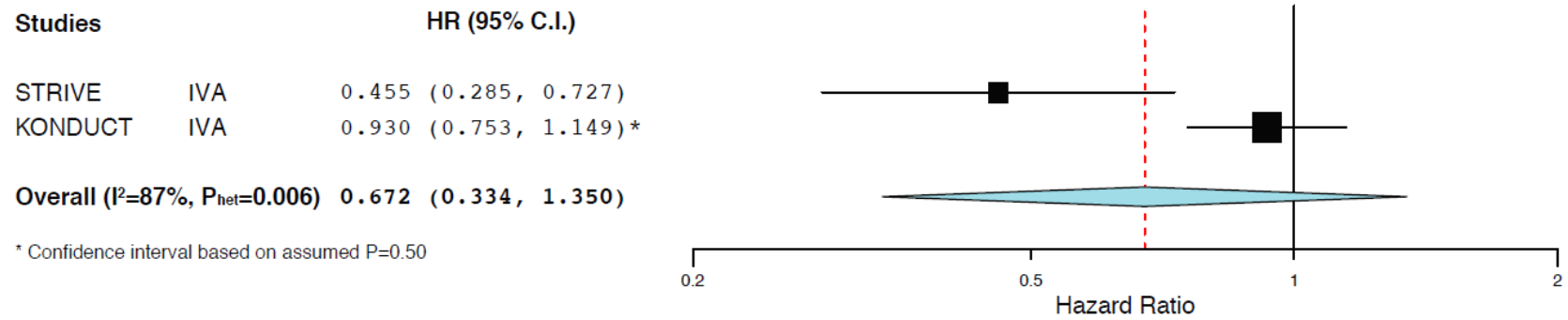
Abbreviations: C.I.: confidence interval, IVA: ivacaftor, OR: odds ratio, P_{het} = chi-square P value for heterogeneity.

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



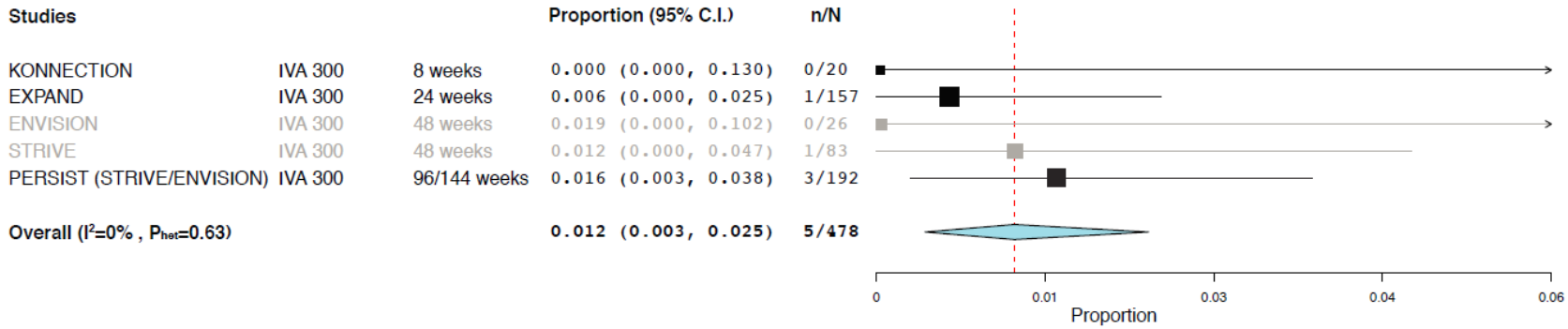
C.I.: confidence interval, IVA: ivacaftor, Phet = chi-square P value for heterogeneity, RR: risk ratio.

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



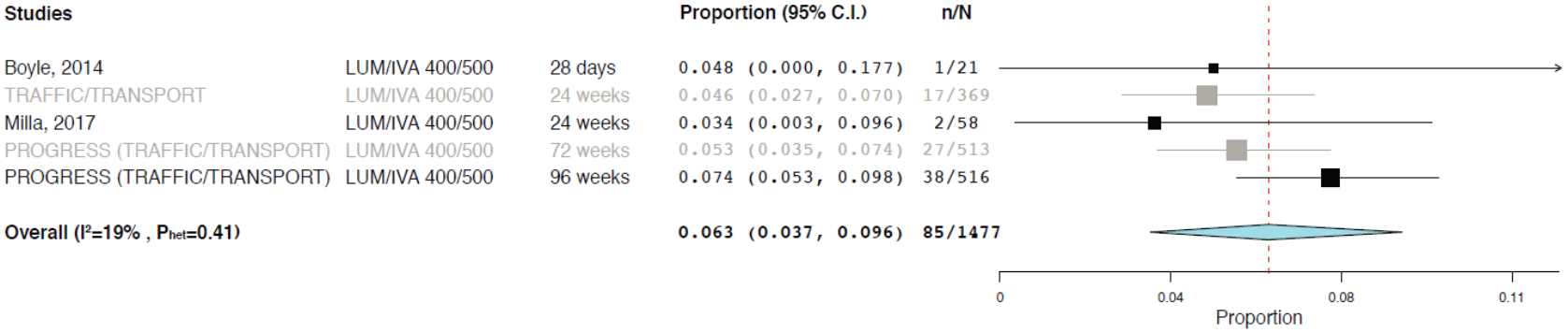
C.I.: confidence interval, HR: hazard ratio, IVA: ivacaftor, Phet = chi-square P value for heterogeneity.

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



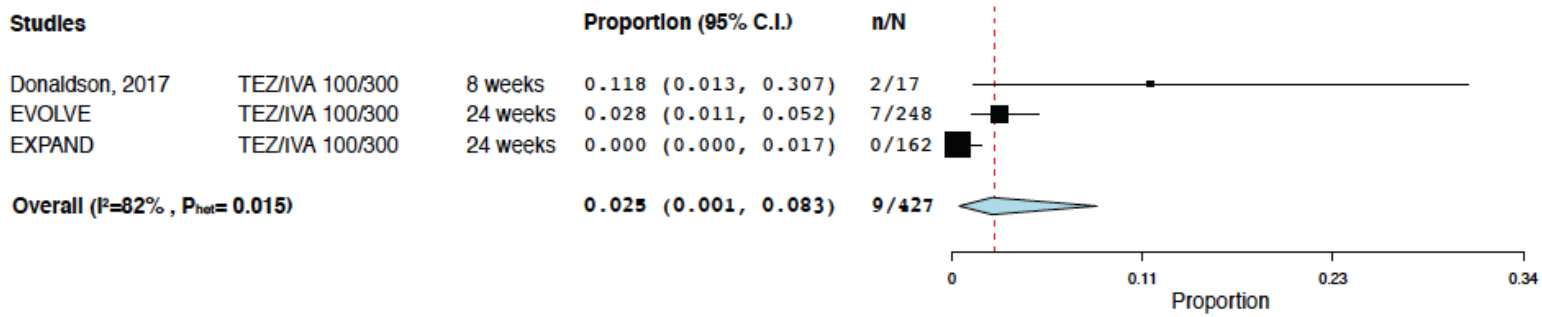
Studies in grey provide shorter-term results than subsequent studies and are not included in the meta-analysis
C.I.: confidence interval, IVA: ivacaftor, P_{het}: chi-square P value for heterogeneity.

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



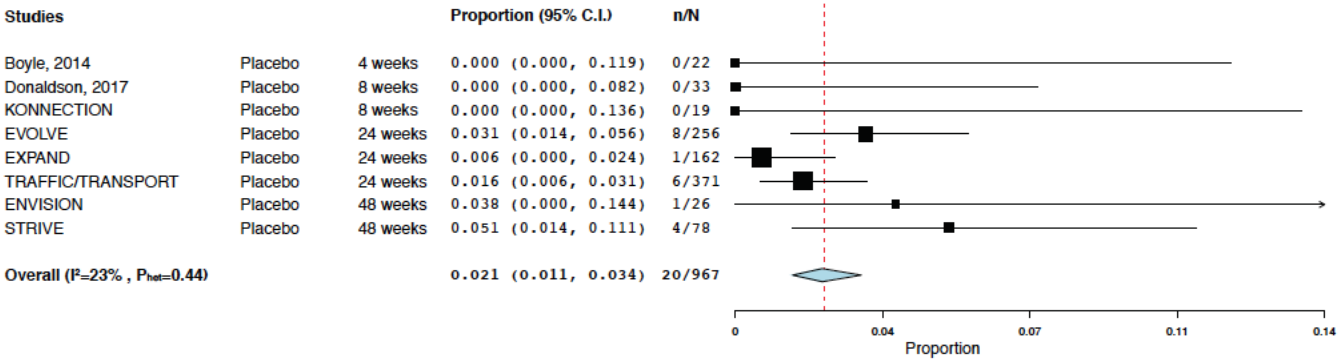
Studies in grey provide shorter-term results than subsequent studies and are not included in the meta-analysis
C.I.: confidence interval, LUM/IVA: lumacaftor/ivacaftor (with daily dosage in mg per drug), P_{het} : chi-square P value for heterogeneity

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



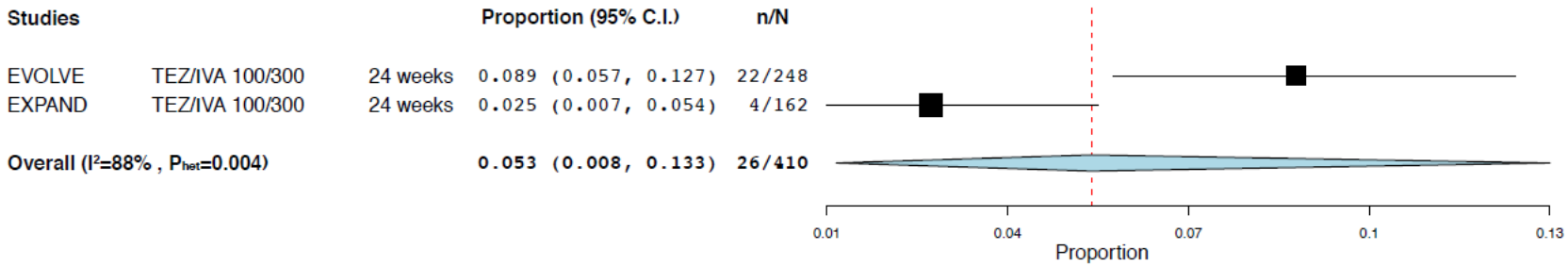
C.I.: confidence interval, Phet: chi-square P value for heterogeneity, TEZ/IVA: tezacaftor/ivacaftor (with daily dosage in mg per drug)

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



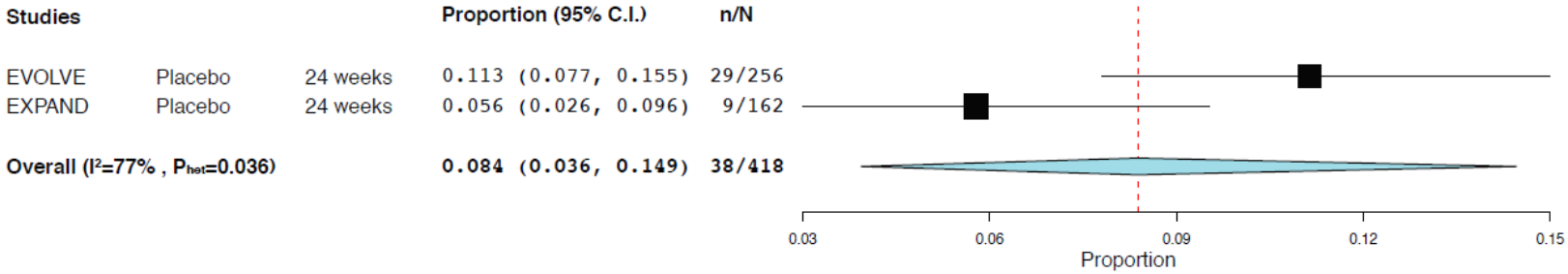
C.I.: confidence interval, P_{het}: chi-square P value for heterogeneity

Figure D16. Meta-Analysis of Proportion of Patients with Grade 3 or 4 Adverse Events on Tezacaftor/Ivacaftor



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

Figure D17. Meta-Analysis of Proportion of Patients with Grade 3 or 4 Adverse Events on Placebo



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

Appendix E. Comparative Value Supplemental Information

Description of evLYG Calculations

The cost per evLYG considers any extension of life at the same "weight" no matter what treatment is being evaluated. Below are the stepwise calculations used to derive the evLYG.

1. First, we attribute a utility representing the age- and gender-adjusted utility of the general population in the US that are considered healthy. We generally use a value of 0.851 for the age- and gender-adjusted utility of the general population in the US that are considered healthy.[144] However, the younger CF population included in these analyses had a higher average utility; we therefore used a utility value of 0.92 to represent the general population utility for this analysis.

2. For each cycle (Cycle I) in the model where using the intervention results in additional years of life gained, we multiply this general population utility with the additional life years gained (ΔLYG).

3. We sum the product of the life years and average utility (cumulative LYs/cumulative QALYs) for Cycle I in the comparator arm with the value derived in Step 2 to derive the equal value of life years (evLY) for that cycle.

4. If no life years were gained using the intervention versus the comparator, we use the conventional utility estimate for that Cycle I.

5. The total evLY is then calculated as the cumulative sum of QALYs gained using the above calculations for each arm.

6. We use the same calculations in the comparator arm to derive its evLY.

Finally, the evLYG is the incremental difference in evLY between the intervention and the comparator arms.

Table E1. Impact Inventory

Sector	Type of Impact	Included in This Analysis from… Perspective?		Notes on Sources
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	☒	☒	
	Health-related quality of life effects	☒	☒	
	Adverse events	☒	☒	Modeled through discontinuation rate.
Medical Costs	Paid by third-party payers	☒	☒	
	Paid by patients out-of-pocket	☒	☒	
	Future related medical costs	☒	☒	
	Future unrelated medical costs	☐	☐	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	☐	
Non-Health Care Sectors				
Productivity	Labor market earnings lost	NA	☒	
	Cost of unpaid lost productivity due to illness	NA	☒	
	Cost of uncompensated household production	NA	☒	
Consumption	Future consumption unrelated to health	NA	☐	
Social services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

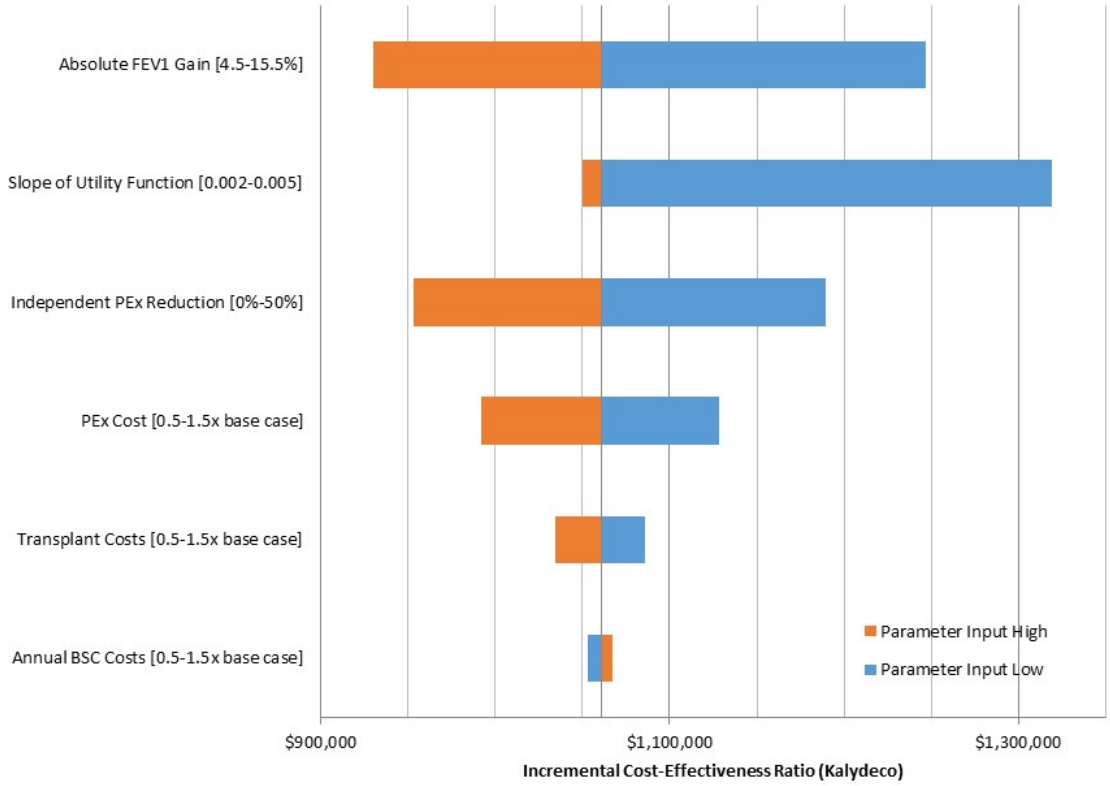
Table E.2. Undiscounted Results for the Base-Case Effectiveness Measures for CFTR Modulators Plus Best Supportive Care (BSC) Compared to BSC Alone, By Study Population

Population and Treatment	Total Life Years	Total QALYs	Total Cost
Population 1 - Eligible for Kalydeco Monotherapy			
BSC	37.77	31.33	$4,747,125
Kalydeco Plus BSC	54.10	48.43	$17,946,955
Population 2 - Homozygous for the *F508del* Mutation			
BSC	37.09	29.04	$3,935,114
Symdeko Plus BSC	52.24	45.33	$16,068,596
Trikafta Plus BSC	57.15	51.33	$18,110,967
Population 3 - Heterozygous *F508del* with Residual Function Mutation			
BSC	39.77	31.03	$4,463,842
Symdeko Plus BSC	57.95	51.21	$17,576,380
Trikafta Plus BSC	64.37	59.43	$20,194,907
Population 4 - Heterozygous *F508del* with Minimal Function Mutation			
BSC	26.17	19.27	$3,546,718
Trikafta Plus BSC	40.10	33.72	$13,232,316

PEx: pulmonary exacerbations; QALY: quality adjusted life year; BSC: best supportive care

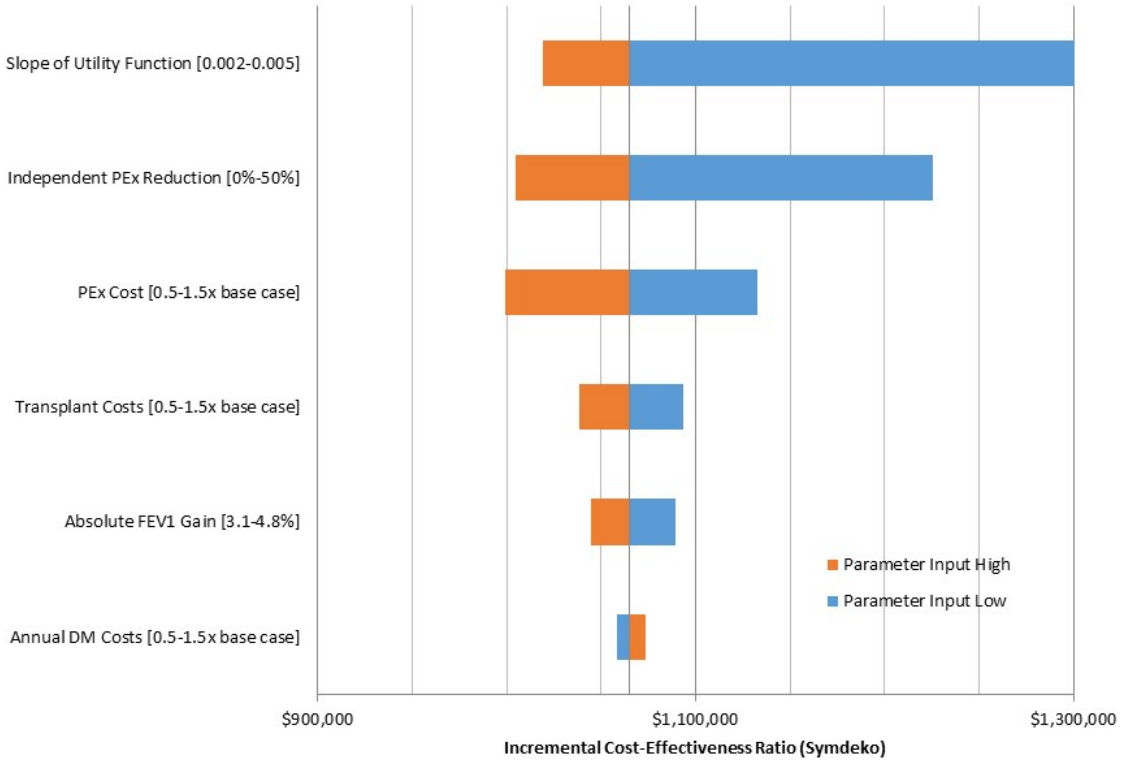
One-Way Sensitivity Analyses

Figure E1. Tornado Diagram for One-Way Sensitivity Analyses of Cost per QALY Gained for Ivacaftor Plus Best Supportive Care Versus Best Supportive Care Alone in CF Individuals Eligible for Kalydeco Monotherapy



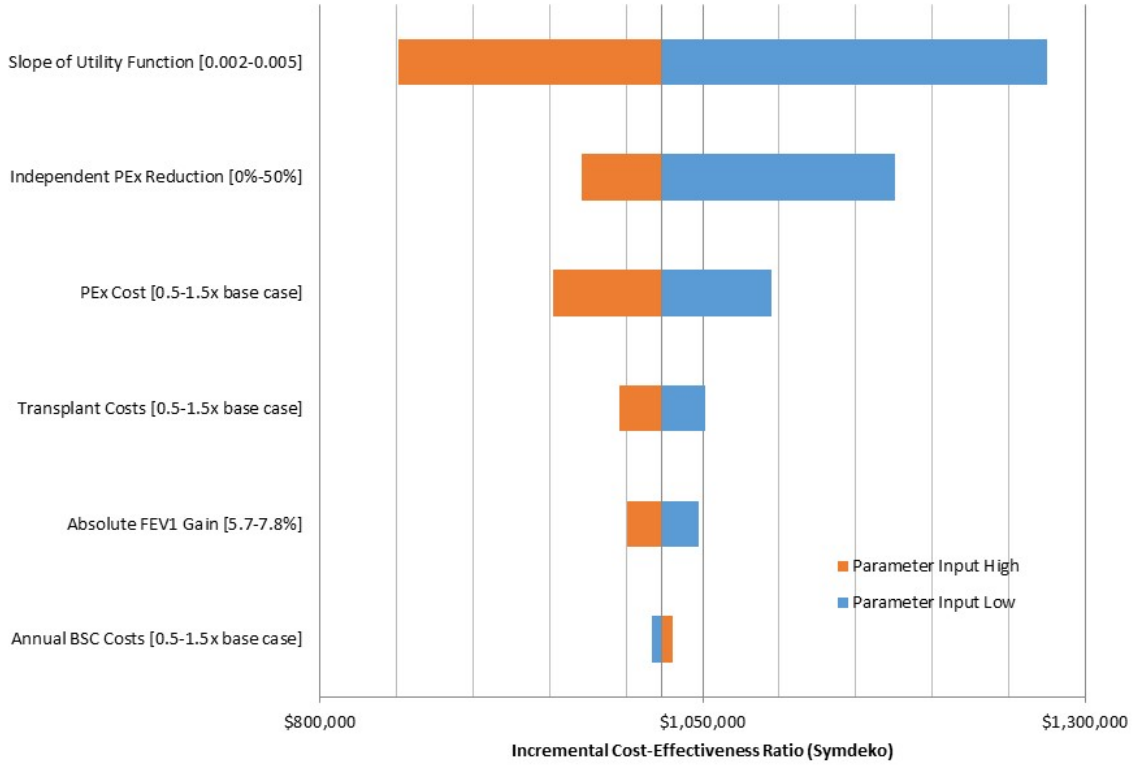
PEx: acute pulmonary exacerbation; BSC: best supportive care

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



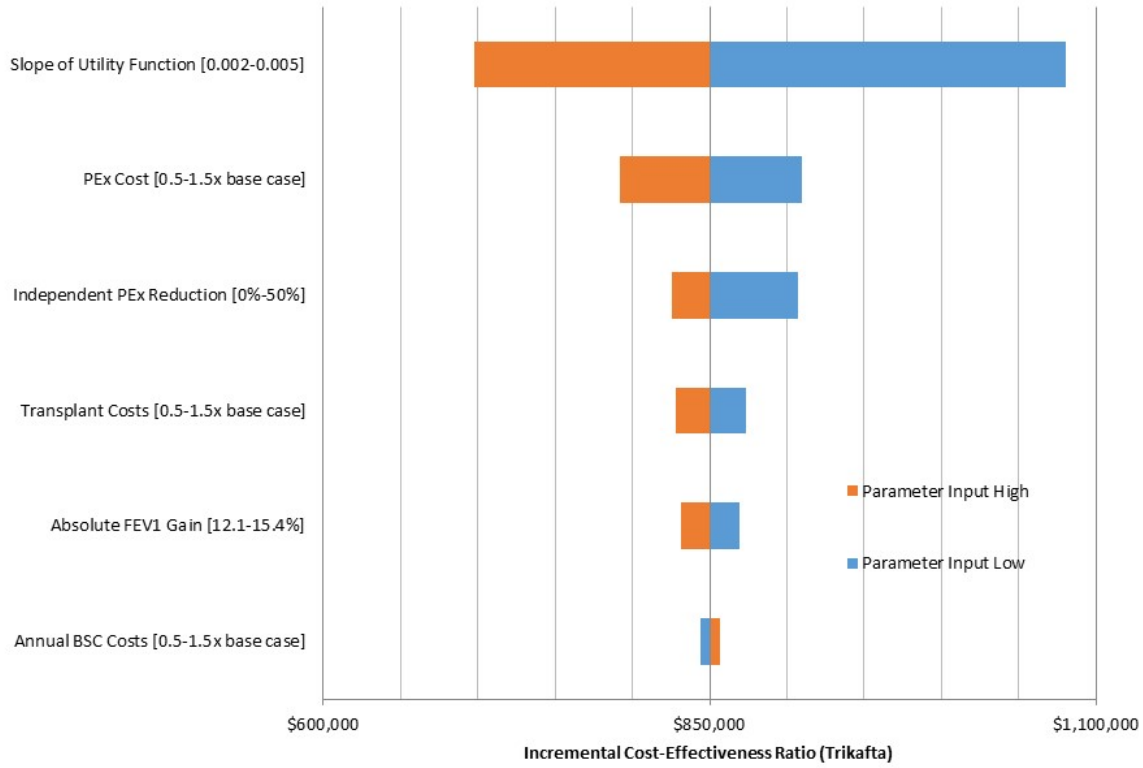
PEx: acute pulmonary exacerbation; BSC: best supportive care

Figure E3. Tornado Diagram for One-Way Sensitivity Analyses of Cost per QALY Gained for Symdeko Plus Best Supportive Care Versus Best Supportive Care Alone in CF Individuals Heterozygous for *F508del* Mutation and Residual Function Mutation



PEx: acute pulmonary exacerbation; BSC: best supportive care

Figure E4. Tornado Diagram for One-Way Sensitivity Analyses of Cost per QALY Gained for Trikafta Plus Best Supportive Care Versus Best Supportive Care Alone in CF Individuals Heterozygous for *F508del* Mutation and Residual Function Mutation



PEx: acute pulmonary exacerbation; BSC: best supportive care

Probabilistic Sensitivity Analyses

Figure E5. Incremental Costs and Incremental Effectiveness for Kalydeco Plus Best Supportive Care Versus Best Supportive Care Alone in CF Individuals Eligible for Kalydeco Monotherapy (1,000 Iterations)

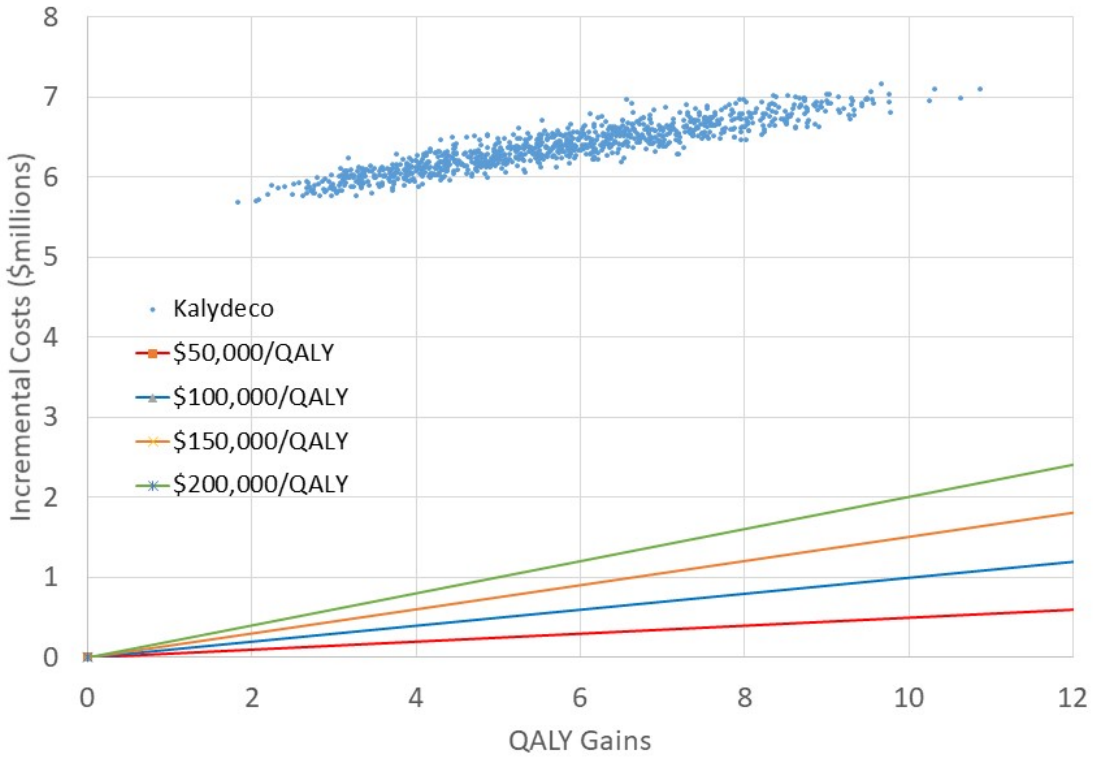


Figure E6. Incremental Costs and Incremental Effectiveness for Symdeko Plus Best Supportive Care Versus Best Supportive Care Alone and Trikafta plus Best Supportive Care Versus Best Supportive Care Alone in CF Individuals Homozygous for *F508del* Mutation (1,000 Iterations)

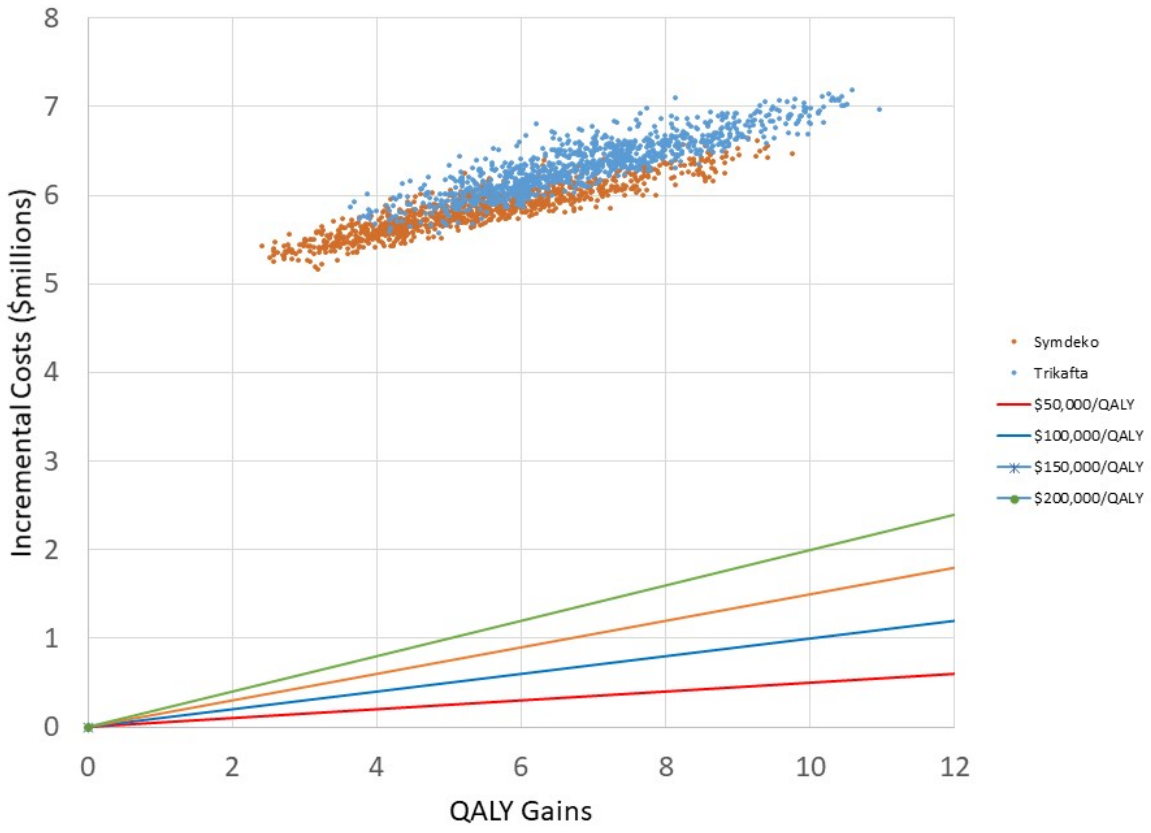

Incremental Costs ($millions)
QALY Gains
0
1
2
3
4
5
6
7
8
0
2
4
6
8
10
12
Symdeko
Trikafta
$50,000/QALY
$100,000/QALY
$150,000/QALY
$200,000/QALY

Figure E7. Incremental Costs and Incremental Effectiveness for Symdeko Plus Best Supportive Care Versus Best Supportive Care Alone and Trikafta plus Best Supportive Care Versus Best Supportive Care Alone in CF Individuals Heterozygous for *F508del* Mutation and Residual Function Mutation (1,000 Iterations)

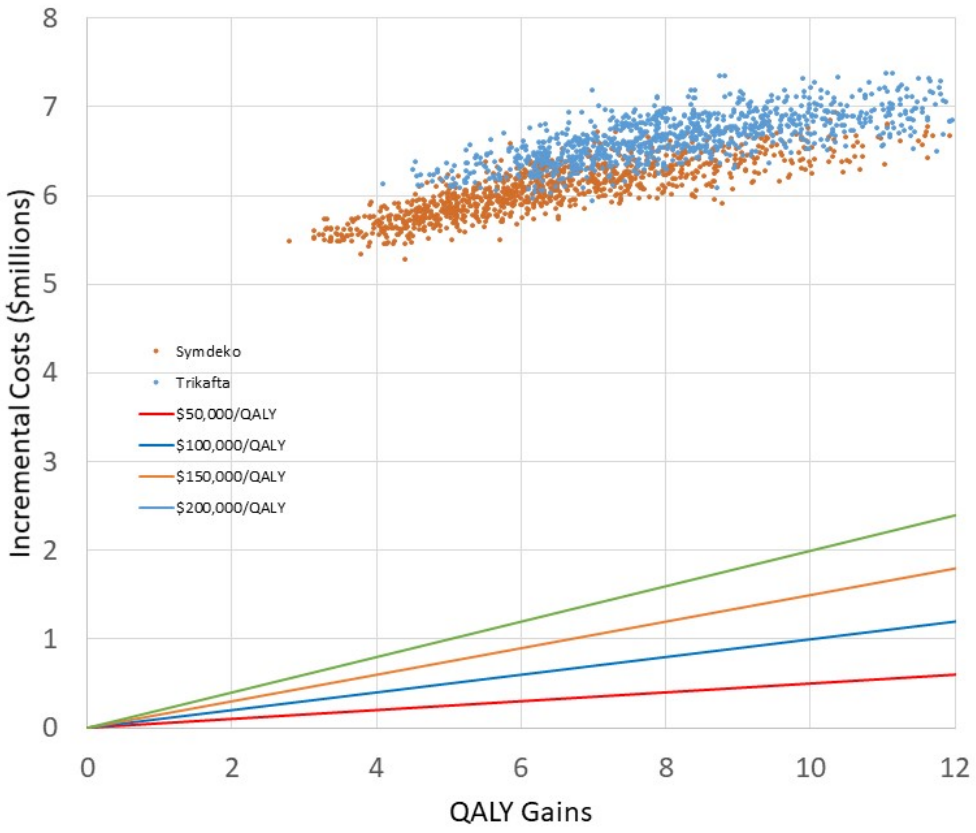
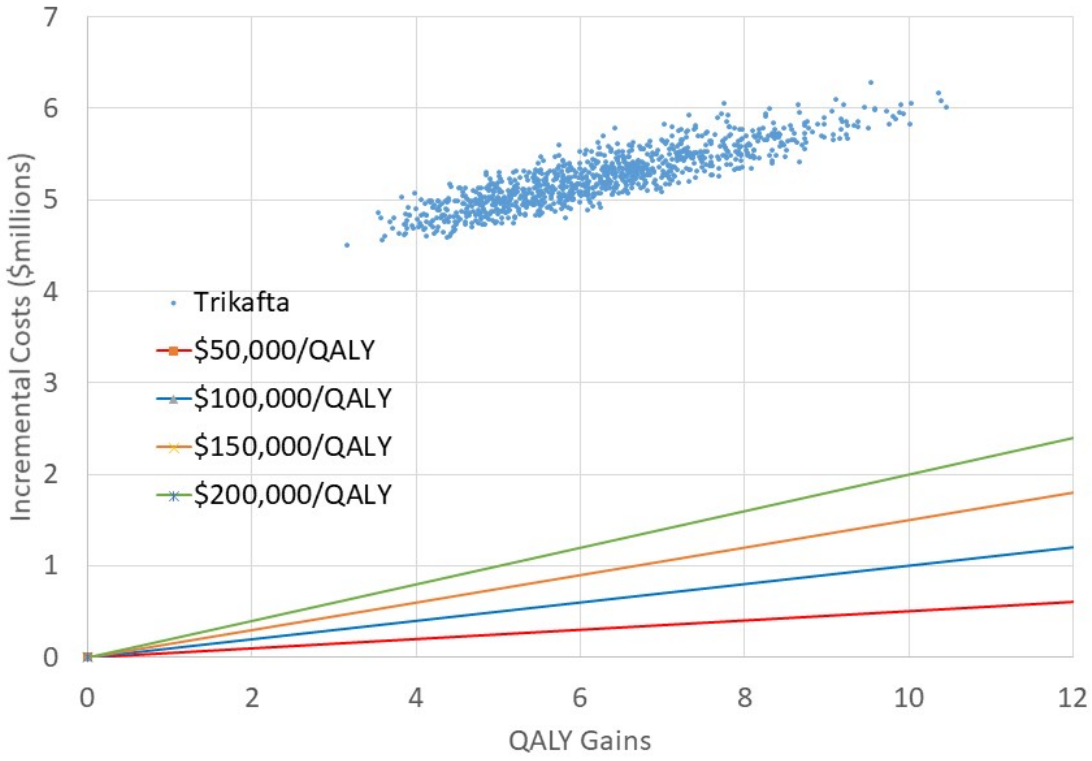


Figure E8. Incremental Costs and Incremental Effectiveness for Trikafta plus Best Supportive Care Versus Best Supportive Care Alone in CF Individuals Heterozygous for *F508del* Mutation and Minimal Function Mutation (1,000 Iterations)



Appendix F. Evidence Tables from 2018 Review

Author & Year of Publication, (Trial), Quality Rating	Study Design and Duration of Follow-up, (Sites & geographical location)	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Symdeko						
Taylor-Cousar [84] ***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)

				* 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 [91] ***NEJM*** **2017** **EXPAND - Heterozygous F508d** **Good**	Phase 3, randomized, double-blind, multicenter, placebo-controlled, two-period, three-intervention crossover trial Trial conducted at 86 sites from March 27, 2015, to Feb 16, 2017. Duration of follow-up: 24 weeks	**N=248** (1) Placebo (n=162) (2) IVA: Kalydeco, 150 mg every 12 hours (n=157) (3) TEZ/IVA; tezacaftor 100 mg once daily with ivacaftor 150 mg every 12 hours (n=162) Incomplete block design Randomized 1:1:1:1:1:1 to 6 blocks each containing two interventions of 8 weeks with an 8-week washout period between. Participants were randomized to receive two of three interventions studied for 8 weeks each with an 8-week washout period between.	**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 • Solid organ transplant • Used inhibitors or inducers of CYP3A4	**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) (3) 33 (40) **$ppFEV_1$** **Mean, percentage points (SD)**	**$ppFEV_1$** **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) 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**	**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) (3) 21 (13) **Cough, n (%)** (1) 30 (19) (2) 17 (11)

			• 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	(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) (2) 61 (75) (3) 60 (72) Missing (1) 13 (16) (2) 9 (11) (3) 12 (14)	**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) 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)
Donaldson [145] ***Am J Resp Crit Care Med***	Phase 2, randomized, placebo-controlled, multicenter, dose-escalation study	**N=41**	**Inclusion** • Confirmed diagnosis of CF	**Pooled Homozygous *F508del*** (1) N=17 (2) N=24	**$ppFEV_1$** **Mean (least-squares) absolute change from baseline, percentage points (95% CI)**	**AE in all homozygous *F508del*** **Any AE, n (%)**

2017 **Phase 2** **Good**	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***	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)	• 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 • 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 •	**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)	(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)	(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)

Orkambi						
Wainwright [23] ***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 All data reported are pooled groups of two studies – TRAFFIC and TRANSPORT	**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) (3) Placebo: Lumacaftor-matched placebo every 12 hours in combination with ivacaftor-matched placebo every 12 hours (n=371)	**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 **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	**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** (1) 60.8 (2) 60.5 (3) 60.4 **BMI** **Mean, kg/m^2** (1) 21.0 (2) 21.5 (3) 21.0	**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 **$ppFEV_1$** **Mean relative change from baseline** Within-group, % (p-value) (1) 5.4 ($p < 0.001$) (2) 4.6 ($p < 0.001$) (3) -0.17 ($p = 0.80$) Between-group difference, % (95% CI) (1) 5.6 (3.8 to 7.3) (2) 4.8 (3.0 to 6.6) (3) NA **BMI** **Mean absolute change from baseline, kg/m^2 (p-value)** Within group (1) 0.41 ($p<0.001$) (2) 0.37 ($p<0.001$)	**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) **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)

			• History of cataract or lens opacity or evidence of cataract or lens opacity determined to be clinically significant		(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) (2) 152; 0.61 (0.49 to 0.76) (3) 251; NA	
Elborn [92] ***Lancet Resp Med*** **2016** **TRAFFIC and TRANSPORT Subgroup analysis**	**See Wainwright** Prespecified subgroup analyses of pooled efficacy and safety data by lung function. **For Demographics data:** (1) Placebo n=371 (<40%ppFEV$_1$=28) LUM 400 mg q12 Iva 250 mg q12, n=731 (2) Baseline ppFEV$_1$ <40% n=53 (3) Baseline ppFEV$_1$ ≥40% n=687	**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%) •	**Pooled Analysis** **< 40% vs. ≥40% ppFEV$_1$** **Lumacaftor 400mg q 12 hrs/ Ivacaftor 250 mg q 12hrs** **ppFEV$_1$** **Mean absolute change from baseline vs. placebo, percentage points (95% CI)** (1) reference (2) 3.3. (0.2 to 6.4) (3) 2.8 (1.7 to 3.8) **ppFEV$_1$** **Mean (least-squares) relative change from baseline vs placebo, % (95% CI)** (1) reference (2) 9.1 (0.7 to 17.4)	**Pooled Analysis** **< 40% vs. ≥40% ppFEV$_1$** **Both doses (600mg & 400mg)** **Any AE, n (%)** (1) 350 (96) (2) 52 (98) (3) 649 (96) **Infective PEx of CF, n (%)** (1) 182 (50) (2) 27 (51) (3) 248 (37) **Cough, n (%)** (1) 147 (40) (2) 21 (40) (3) 203 (30)

	(4) Screening $ppFEV_1$ <70% n=527 (5) Screening $ppFEV_1$ • ≥70% n=204 • For Results at 24 weeks: (1) Placebo (2) LUM 400 mg q12 Iva 250 mg q12, • FEV1<40% (3) LUM 400 mg q 12 Iva 250 mg q 12, FEV1≥40%			**$ppFEV_1$** **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) (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) 4.5 (2.7 to 6.3) **BMI** **Least-squares mean vs. placebo, kg/m² (95% CI)** (1) reference (2) 0.3 (-0.2 to 0.8) (3) 0.2 (0.1 to 0.4) **CFQ-R Respiratory domain** **Least-squares mean vs. placebo, points (95% CI)** (1) reference (2) −4.2 (−12.0 to 3.7) (3) 2.9 (0.5 to 5.3) **PEx** **Event rate ratio (95%CI)** (1) reference (2) 0.59 (0.33 to 1.05) (3) 0.61 (0.48 to 0.77) **PEx** **No. events requiring IV antibiotics, rate ratio (95%CI)** (1) Reference (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)	**Headache, n (%)** (1) 57 (16) (2) 10 (19) (3) 103 (15)
Konstan [85] ***Lancet Resp Med***	Phase 3, multicenter, parallel group, open-label trial.	**N=1030** (1) LUM/IVA: continued 400 mg of lumacaftor	**Inclusion** • Confirmed diagnosis of CF	**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)

2017 **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	every 12 hours in combination with 250 mg of ivacaftor every 12 hours (n=340) (2) LUM/IVA: Placebo transitioned to 400 mg lumacaftor every 12 hours in combination with ivacaftor 250 mg every 12 hours (n=176) At 72 weeks (primary efficacy), those on LUM/IVA in Traffic/Transport had received 96 weeks of active drug.	• Homozygosity for the *F508del*-CFTR mutation • Age of 12 years or older **Exclusion** • Any comorbidity or lab abnormality that may confound study results or increase potential harm to participant • History of drug intolerance in the prior study • Pregnancy or breast-feeding • History of poor compliance with 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) **BMI** **Mean absolute change from baseline, kg/m^2** At 72 weeks (1) 0.69 (0.56 to 0.81)	**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

					(2) 0.62 (0.45 to 0.79) <u>At 96 weeks</u> (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)** <u>At 72 weeks</u> (1) 5.7 (3.7 to 7.5) (2) 3.3 (0.7 to 5.9) <u>At 96 weeks</u> (1) 3.5 (1.3 to 5.8) (2) 0.5 (−2.7 to 3.6) **PEx, No. of events per patient-year (95%CI)** (1) 0.65 (0.56 to 0.75) (2) 0.69 (0.56 to 0.85) **PEx, No. of events requiring hospital admission per patient-year (95%CI)** (1) 0.24 (0.19 to 0.29) (2) 0.30 (0.22 to 0.40) **PEx, No. of events requiring intravenous antibiotics per patient-year (95%CI)** (1) 0.32 (0.26 to 0.38) (2) 0.37 (0.29 to 0.49)	
Konstan [146] ***Pediatric Pulmonology***	**See Konstan 2017**	**N=176** (1) LUM/IVA: 400 mg of lumacaftor every 12	**See Konstan 2017**	**See Konstan 2017**	**ppFEV$_1$ Mean (least-squares) relative change from**	**Most commonly reported AEs:** Infective PEx of CF (48%)

2015 **Abstract**	Interim analysis of PROGRESS at 24 weeks	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)			**baseline, percent (SE); p-value** 24 weeks of PROGRESS* (1) 2.6 (0.47); p<0.0001 (2) 3.5 (0.64); p<0.0001 **BMI** **Mean (least-squares) absolute change from baseline, kg/m² (SE); p-value** 24 weeks of PROGRESS* (1) 0.56 (0.06); p<0.0001 (2) 0.37 (0.08); p<0.0001 **CFQ-R Respiratory domain** **Mean absolute change from baseline, points (SE); p-value** 24 weeks of PROGRESS* (1) 6.3 (0.85); p<0.0001 (2) 5.1 (1.17); p<0.0001 **PEx** **Event rate per year (95%CI)** (1) 0.6 (0.5 to 0.8) (2) 0.6 (0.5 to 0.8) *Interim analysis	Cough (39%) Headache (17%) Dyspnea (17%) Abnormal respiration (14%)
McColley [141] ***Pediatric Pulmonology*** **2015** **Abstract**	**See Wainwright 2015** Post hoc analysis TRAFFIC and TRANSPORT evaluating the association between changes in percent	Stratified analysis by: • ≤0% or • >0% absolute improvement in $ppFEV_1$ AND • ≥5 or	**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:	**NA**

	predicted FEV1 and PE rates	• <5% relative improvement in $ppFEV_1$ from baseline to Day 15 •			0.62 (0.47 to 0.80) <u>≥5% relative improvement:</u> 0.60 (0.44 to 0.82) **PEx requiring hospitalization** <u>≤0% absolute improvement:</u> 0.40 (0.23 to 0.69) <u>>0% absolute improvement:</u> 0.38 (0.24 to 0.59) <u><5% relative improvement:</u> 0.31 (0.19 to 0.51) <u>≥5% relative improvement:</u> 0.50 (0.31 to 0.82) **PEx requiring antibiotics** <u>≤0% absolute improvement:</u> 0.49 (0.33 to 0.74) >0% absolute improvement: 0.40 (0.28 to 0.58) <5% relative improvement: 0.37 (0.25 to 0.54) ≥5% relative improvement: 0.54 (0.37 to 0.80)	
Taylor-Cousar[147] ***Journal of Cystic Fibrosis*** **2017**	Open-label prospective study of LUM/IVA in patients homozygous for *F508del* with $ppFEV_1$<40% Six centers in United States	**N=46** LUM/IVA 400 mg q 12 hours with IVA 250 mg q 12 hours (n=28) ½ dose necessary for 39% of patients at start of study (n=18)	**Inclusion** • Confirmed diagnosis of CF • Homozygosity for the *F508del*-CFTR mutation • Age of 12 years or older • $ppFEV_1$<40%, adjusted for age, gender and height	**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)**	**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)	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)

	Duration of follow-up: 24 weeks		**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	**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	**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 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	**Respiration abnormal: 26 (57)** Cough 21 (46) Dyspnea 20 (43)
Jennings [93] ***Annals ATS*** **2017**	Retrospective observational study, pre/post treatment with LUM/IVA	**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**	**$ppFEV_1$** **Mean change from baseline, percentage points (range)** 0.11 (−39 to 20)	**Reported Side Effects, n (%)** 46 (39.7) **Discontinuation** 20 (17.2)

	One center: Johns Hopkins Duration of follow-up: 11 months Subgroup by age and FEV_1			**Mean, years (range)** 24.7 (12-59) **$ppFEV_1$** **Mean, percentage points (range)** 67.4 (20-115) **CF-related diabetes (CFRD), No. (%)** 26 (22.4) ***Pseudomonas* positive No. (%)** 71 (61.2) **MRSA positive No. (%)** 35 (30.2) ***B. cepacia* complex positive, No. (%)** 8 (6.9) **Proton-pump inhibitor use, No. (%)** 51 (44) **Anti-depressant use, No. (%)** 21 (18.1) **Azole use, No. (%)** 6 (5.2)		**Chest tightness/discomfort** 23 (19.8) **Dyspnea** 12 (10.3) **Increased cough/congestion** 10 (8.6) **Diarrhea** 5 (4.3) **Nausea** 3 (2.6) **Decreased appetite** 2 (1.7) **Rash** 2 (1.7) **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 [83] ***Lancet Resp Med*** **2017**	Phase III, randomized, double-blind, placebo-controlled, multinational trial Nine countries: USA,	**N=206** (1) LUM/IVA: Lumacaftor 200 mg and ivacaftor 250 mg q 12 (n=104)	**Inclusion:** • Age 6-11 • Confirmed diagnosis of cystic fibrosis • Weight at least 15 kg	**Mean age, years (SD)** (1) 8.7 (1.6) (2) 8.9 (1.6) **Sex** **Female, n (%)** (1) 63 (61) (2) 58 (57)	**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)	**Any AE, n (%)** (1) 98 (95) (2) 98 (97) **Any SAE, n (%)** (1) 13 (13) (2) 11 (11)

Homozygous *F508del*	Australia, Belgium, Canada, Denmark, France, Germany, Sweden, and the UK Duration of follow-up: 24 weeks Enrollment: July 23, 2015 to Sept 20, 2016	(2) Placebo (n=102)	• ppFEV1≥70% and lung clearance index (LCI) ≥ 7.5 • homozygous *F508del* **Exclusion:** • Any comorbidity or lab abnormality that may confound study results or increase potential harm to participant • Acute respiratory tract infection, PE, or changes in therapy for pulmonary disease within 28 days of treatment initiation • History of solid organ transplant	**$ppFEV_1$** **Mean, percentage points (SD)** (1) 88.8 (13.7) (2) 90.7 (10.8) **Weight** **Mean, kg (SD)** (1) 29.4 (6.5) (2) 30.2 (6.8) **LCI** **Mean (SD)** (1) 10.3 (2.4) (2) 10.3 (2.2)	Difference: −1·1 (−1.4 to −0.8) p<0·0001 **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 decline	**Study discontinuation, n (%)** (1) 1 (1)* respiration abnormal (2) 0 (0) **Elevated liver enzymes of clinical significance, n (%):** (1) 13 (13) (2) 8 (8) **Cough, n (%)** (1) 46 (45) (2) 47 (47) **Infective PEx of CF, n (%)** (1) 20 (19) (2) 18 (18) **Oropharyngeal pain, n (%)** (1) 15 (15) (2) 10 (10) • **Pyrexia, n (%)** (1) 15 (15) (2) 20 (20) **Acute change in $ppFEV_1$ immediately after study drug administration @ day 1, mean absolute change (SD)** **< 2 hours post-dose** (1) -5.5 (8.2) (2) -0.1 (5.1) **4-6 hours post-dose** (1) -7.7 (7.3) (2) -1.4 (7.1) **24 hours post-dose**

						(1) -4.1 (10.1) (2) -1.7 (6.8)
Milla [86] ***Am J Respir Crit Care Med*** **2017** **Homozygous *F508del***	Open-label, phase III Duration of follow-up: 24 weeks active med with 2 week washout	**N=58** (54 completed 24 weeks) Lumacaftor 200 mg q 12 hours with 250 mg of ivacaftor q 12 hours	**Inclusion**: • Age 6-11 at screening • Confirmed diagnosis of cystic fibrosis • ppFEV1≥40% • Homozygous *F508del* • Stable disease **Exclusion**: • Any comorbidity or lab abnormality that may confound study results or increase potential harm to participant	**Mean age, years (SD)** 9.1 (1.53) **Sex Female, n (%)** 31 (53.4) **ppFEV$_1$** **Mean, percentage points (SD)** 91.4 (13.7) **Weight** **Mean, kg (SD)** 31.5 (6.1) **Weight-for-age z-score** **Mean (SD)** -0.03 (1.03) **BMI-for-age z-score** **Mean (SD)** 0.01 (0.90)	**ppFEV$_1$** **Mean (least-squares) absolute change from baseline, percentage points (95% CI)** 24 weeks 2.5 (-0.2 to 5.2) **BMI** **Mean (least-squares) absolute change from baseline, kg/m^2 (95% CI)** 24 weeks 0.64 (0.46 to 0.83) **BMI-for-age z-score** **Mean (least-squares) absolute change from baseline (95% CI)** 24 weeks 0.15 (0.08 to 0.22) **Weight-for-age Z score** **Mean (least-squares) absolute change from baseline (95% CI)** 24 weeks 0.13 (0.07 to 0.19) **CFQ-R** **Mean (least-squares) absolute change from baseline, points (95% CI)** 24 weeks 5.4 (1.4 to 9.4) **LCI (exploratory endpoint; n=30)**	**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) 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)

					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	**Cataract, n (%):** 1 (1.7)
Boyle [148] ***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 Duration of follow-up: 28 days	**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) (2) Placebo (n=24; pooled across cohort 2 and 3)	**Inclusion**: • Age 18+ • Confirmed diagnosis of cystic fibrosis • $ppFEV_1 \geq 40\%$ • At least one *F508del* (we only report on two copies) **Exclusion**: • Any comorbidity or lab abnormality that may confound study results or increase potential harm to participant • PE or change in treatment within 14 days first dose • Prolonged QT/QTc interval • Solid organ transplant • Used inhibitors or inducers of CYP3A4 • In another trial in last 3 months	**Only LUM/IVA group baseline provided - placebo pooled (mixed hetero and homozygous)** **Age** **Mean, years (SD)** (1) 25.5 (6.7) (2) 30.8 (12.4) **Sex** **Female, n (%)** (1) 5 (45) (2) 9 (33) **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)	**$ppFEV_1$** **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)** (1) 8.2 (1.8 to 14.7) (2) −2.1 (−6.3 to 2.2)	**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** 1/15 **Cough, n (%)** (1) 3 (27) (2) 6 (22) **Headache, n (%)** (1) 2 (18) (2) 5 (19)

Ivacaftor						
Ramsey [64] ***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 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	**Age** **Mean, years (range)** (1) 26.2 (12-53) (2) 24.7 (12-53) **Sex** **Female, n (%)** (1) 44 (53) (2) 40 (51) **$ppFEV_1$** **Mean, percentage points** (1) 63.5 (2) 63.7 **Weight** **Mean, kg** (1) 61.7 (2) 61.2 **BMI** **Mean, kg/m^2** (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.	**$ppFEV_1$** **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) **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	**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) **Hemoptysis, n (%)** (1) 1 (1) (2) 4 (5)

Davies [65] ***Am J Respir Care Med*** **2013** **ENVISION – *G551D*** **Good**	Phase 3, randomized, double-blind, placebo-controlled trial Duration of follow-up: 48 weeks	**N=52** (1) IVA: 150 mg of ivacaftor twice daily (n=26) (2) Matched Placebo (n=26)	**Inclusion** • 6-11 years of age • Confirmed CF diagnosis • *G551D* mutation on at least one *CFTR* allele • FEV_1 of 40-105% of the predicted value for persons of their age, sex, and height • Body weight ≥15kg **Exclusion** • History of illness or condition that may confound results or pose safety risk • Acute respiratory infection, PE, or changes in therapy 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	**Age** **Mean, years (range)** (1) 8.9 (6-12) (2) 8.9 (6-12) **Sex** **Female, n (%)** (1) 17 (65) (2) 10 (38) **$ppFEV_1$** **Mean, percentage points (range)** (1) 84.7 (52.4-133.8) (2) 83.7 (44.0-116.3) **Weight** **Mean, kg (range)** (1) 31.8 (18.8-62.6) (2) 30.0 (17.8-46.3) **BMI** **Mean, kg/m² (range)** (1) 17.1 (14.2-26.0) (2) 16.8 (13.8-22.1) **CFQ-R Respiratory domain** **Mean, points** (1) 78 (2) 80	**$ppFEV_1$** **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** **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.	**Any AE, n (%)** (1) 26 (100) (2)25 (96.2) **SAE, n (%)** (1) 5 (19) (2) 6 (23) **Interruption d/t AE, n (%)** (1) 1 (4) (2) 3 (12) **Discontinuation d/t AE, n (%)** (1) 0 (2) 1 (4) **PEx of CF, n (%)** (1) 8 (31) (2) 8 (31) **Cough, n (%)** (1) 13 (50) (2) 19 (73) **Headache, n (%)** (1) 7 (27) (2) 4 (15)
McKone [70]	Phase 3, open-label extension	**N=192**	**Inclusion** • *G551D* mutation on at least one *CFTR* allele	**Age** **Mean, years (SD)**	**$ppFEV_1$**	**Any AE, n (%)** STRIVE and ENVISION placebo groups:

Lancet Respir Med **2014** **PERSIST – *G551D*** **Good**	Duration of follow-up: 96 weeks	(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 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	• 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 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	(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) d.) 9 (41) **$ppFEV_1$** **Mean, percentage points (SD)** (1) a.) 71.9 (18.5) b.) 62.2 (18.7) c.) 94.9 (14.5) d.) 83.6 (17.4) **BMI** **Mean, kg/m² (SD)** (1) a.) 23.0 (4.0) b.) 21.9 (3.5) c.) 18.6 (2.9) d.) 16.8 (2.2) **Weigh** **Mean, kg (SD)** (1) a.) 66.0 (14.9) b.) 61.4 (13.1) c.) 37.9 (11.7) d.) 32.4 (8.9)	**Mean absolute change from baseline, percentage points (SD)** (1) a.) 9.4 (10.8) b.) 9.5 (11.2) c.) 10.3 (12.4) d.) 10.5 (11.5) **BMI** **Mean absolute change from baseline, kg/m² (SD)** (1) 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 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%) Week 48-96: 44 (23%) STRIVE and ENVISION placebo groups: Week 1-48: 15 (17%) Week 48-96: 19 (21%) STRIVE and ENVISION ivacaftor groups: Week 48-96: 23 (22%) Week 96-144: 25 (24%) **Deaths, n (%)** (1) 2 **Discontinuation d/t AE, n (%)** (1) 3 (2) **PEx, no. of events (%)** (1) STRIVE and ENVISION placebo groups: Week 1-48: 30 (34%) Week 48-96: 35 (39%) STRIVE and ENVISION ivacaftor groups: Week 48-96: 46 (45%) Week 96-144: 46 (45%)

						Cough, n (%) (1) STRIVE and ENVISION placebo groups: Week 1-48: 27 (30%) Week 48-96: 16 (18%) STRIVE and ENVISION ivacaftor groups: Week 48-96: 32 (31%) Week 96-144: 27 (26%) **Headache, n (%)** (1) STRIVE and ENVISION placebo groups: Week 1-48: 11 (12%) Week 48-96: 7 (8%) STRIVE and ENVISION ivacaftor groups: Week 48-96: 14 (14%) Week 96-144: 17 (17%)
De Boeck [66] ***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** (1) 0.50	**ppFEV$_1$** **Mean absolute change* from baseline, percentage points (95% CI)** (1) 7.5 (2) −3.2 Difference=10.7 (7.3 to 14.1) **BMI** **Mean absolute change from baseline, kg/m^2 (95% CI)** (1) 0.7 (2) 0.02 Difference=0.7 (0.34 to 0.99) **CFQ-R respiratory domain** **Mean absolute change from baseline, points (95% CI)** (1) 8.9	**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) (2) 7 (39)

		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	(2) 0.23	(2) −0.7 Difference= 9.62 (4.5 to 14.7) *Mixed-effects model for repeated measures.	**Discontinuation d/t AE, n (%)** (1) 0 (2) 0
Moss [67] ***NEJM*** **2015** **KONDUCT – R117H** **Good**	Phase 3, multicenter, placebo controlled, double blind, parallel group trial Duration of follow-up: 24 weeks	**N=69** (1) IVA: 150 mg of ivacaftor every 12 hours for 24 weeks (n=34) (2) Placebo (n=35)	**Inclusion** • 6 years of age or older • Confirmed diagnosis of CF • Arg117His-CFTR mutation • $ppFEV_1$ of at least 40 **Exclusion** • Gating mutation (1 or more) • History of illness or condition that may confound results or pose safety risk • Acute respiratory infection, PE, or changes in therapy for pulmonary disease within 4 weeks of enrollment	**Age** **Mean, years (SD)** (1) 29.2 (16.6) (2) 32.7 (17.4) **Sex** **Female, n (%)** (1) 19 (56.0) (2) 20 (57.0) **$ppFEV_1$** **Mean, percentage points (SD)** (1) 75.7 (19.3) (2) 70.2 (18.9) **BMI** **Mean, kg (SD)** (1) 24.5 (6.3) (2) 23.1 (6.0)	**$ppFEV_1$** **Mean absolute change from baseline, percentage points (SD)** (1) 2.6 (1.2) (2) 0.5 (1.1) Difference=2.1 (95% CI:-1.13 to 5.35) **$ppFEV_1$** **Mean relative change from baseline % (SD)** (1) 4.8 (1.9) (2) -0.2 (1.8) Difference= 5.0 (95% CI:-0.24 to 10.31) **BMI** **Mean absolute change from baseline, kg/m^2 (SD)** (1) 0.49 (0.67) (2) 0.23 (0.65)	**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) **Needing admission to hospital, n patients (events)** (1) 2 (2) (2) 6 (7)

			• Abnormal liver function at screening • History of solid organ or hematological transplant • History or alcohol, medication, or illicit drug abuse within 1 year of study initiation • On-going participation in another clinical trial within 30 days of screening • Any "non-CF-related" illness within 2 weeks of study initiation • Concomitant use of CPY3A4 inhibitors or inducers	**CFQ-R Respiratory domain** **Mean, points (SD)** (1) 75.3 (20.1) (2) 66.4 (24.4)	Difference=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 intravenous antibiotic therapy, n patients (events)** (1) 2 (2) (2) 6 (8)
Davies [68] ***Lancet Respiratory*** **2016** **KIWI – gating mutations**	Two-part, open-label, single-arm, phase 3 study 15 hospitals in the USA, UK, and Canada Part B enrolled June 28, 2013 to Sept 26, 2013	**N=34 (Part B, only)** Part A: 4-day ivacaftor q 12 hours for pharmacokinetic and safety (two doses) - 50 mg if they weighed <14 kg (n=4), and 75 mg if they weighed ≥14 kg (n=5) Part B: 24-week safety (1) 50 mg (n=10) (2) 75 mg (n=24)	**Inclusion** • Children aged 2–5 years • Weight 8 kg or more • Confirmed diagnosis of CF • *CFTR* gating mutation on at least one allele (Gly551Asp, Gly178Arg, Ser549Asn, Ser549Arg, Gly551Ser, Gly970Arg, Gly1244Glu, Ser1251Asn, Ser1255Pro, or Gly1349Asp) **Exclusion** • History of illness or condition that may confound results or pose safety risk	**Part B reported (only)** **Age** **N (%)** Age 2: 9 (26%) Age 3: 11 (32%) Ages 4 and 5: 14 (41%) **Sex** **Female, n (%)** 6 (18) **Weight-for-age z-score** **Mean, score (SD)** -0.2 (0.8) **Height-for-age z-score,** **Mean, score (SD)** -0.3 (0.8)	**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 **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**	**Harms Part A not reported** **Harms Part B:** **Patients with any AE, n (%)** (1) 10 (100) (2) 23 (96) **SAE, no. events (no. pts, %)** (1) 4 (3, 30) (2) 3 (3, 13) **SAE: Infective PEx of CF, n (%)** (1) 1 (10) (2) 1 (4)

			• 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	**Mutations, n (%)** G551D homozygous: 1(3) G551D heterozygous with *F508del*: 26 (76) G551D heterozygous not *F508del*: 5 (15) Ser549Asn heterozygous: 2 (6)	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	**AE: Infective PEx of CF, n (%)** (1) 1 (10) (2) 4 (17) **Cough, n (%)** (1) 4 (40) (2) 15 (63) **Vomiting, n (%)** (1) 3 (30) (2) 7 (29) **Hepatic enzyme elevation, n (%)** (1) 3 (30) (2) 2 (8)
Rowe [69] ***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	**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)	**$ppFEV_1$** **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)	**Not reported**

			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	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) Ages 18+: 66.5 (13.7) **BMI** **Mean, kg/m² (SD)** 21.3 (4.5) By age Ages 6-11: 17.2 (2.4) Ages 12-17: 21.0 (4.1) Ages 18+: 23.3 (4.1) **CFQ-R Respiratory domain** **Mean, points (SD)** Pooled not reported By age Ages 6-11: 83.6 (12.2) Ages 12-17: (76.2) (15.6) Ages 18+: 62.4 (20.5)	Ages 12-17: 3.3 (3.3) Ages 18+: 1.5 (3.5) **BMI** **Mean absolute change from baseline, kg/m² (95% CI)** 1 mo: 0.4 (0.3 to 0.5) 3 mo: 0.6 (0.4 to 0.7) 6 mo: 0.8 (0.6 to 1.0) 6 mo, by age group (SD) Ages 6-11: 1.1 (1.2) Ages 12-17: 0.9 (1.0) Ages 18+: 0.5 (1.3) **CFQ-R Respiratory domain** **Mean absolute change from baseline, (95% CI)** 1 mo: 9.7 (7.1 to 12.4) 3 mo: 10.9 (8.1 to 13.7) 6 mo: 7.4 (4.1 to 10.7) 6 mo, by age group (SD) Ages 6-11: -0.7 (16.7) Ages 12-17: 7.6 (14.6) Ages 18+: 11.7 (20.7)	
Flume [149] ***J Cyst Fibros***	Post-hoc analysis of participants who experienced PExs from STRIVE	**N=See STRIVE**	**See STRIVE**	**See STRIVE**	**PEx** **No. subjects (%)** (1) 28 (33.7) (2) 44 (56.4)	**See STRIVE**

2017 **STRIVE** **Good**	randomized clinical trial (Ramsey, 2011) This study analyzed only those who reported a PEx during STRIVE Duration of follow-up: 48 weeks (STRIVE)	(1) IVA: 150 mg of ivacaftor twice daily (n=83) (2) Matched placebo (n=78)		**Characteristics of participants who had ≥1 protocol-defined PEx during study (baseline data prior to PEx)** (1) n=2 (2) n=44 **Age** **Mean, years (SD)** (1) 26.9 (7.81) (2) 24.4 (9.29) **Age, n (%)** (1) • <18: 4 (14.3) • ≥18: 24 (85.7) (2) • <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)**	**No. of PExs (event rate)** (1) 47 (0.589) (2) 99 (1.382) **No. of days per pt with event, mean (SD)** (1) 13.54 (27.27) (2) 36.67 (49.54) **No. of pts treated with IV antibiotics for PEx, n (%)** (1) 15 (18.1) (2) 27 (34.6) **No. of events treated with IV antibiotics, n (event rate)** (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)	

				(1) −0.95 (0.94) (2) −0.54 (0.95) **ppFEV$_1$ prior to first PEx** **Mean, percentage points (SD)** (1) 68.36 (20.67) (2) 61.64 (16.75)	* Full long-term recovery=return to ≥100% of ppFEV$_1$ measurement most closely preceding PEx.	
Accurso [150] ***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: 28 days	**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 • Ongoing participation in another therapeutic clinical trial, or prior participation in an investigational study	**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 250mg vs. placebo: p=0.78 **CFQ-R Respiratory domain**	**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

			without appropriate washout		**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 [151] ***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/m² (SD)** Year 3 (1) 22.3 (3) (2) 21 (3) **CFQ-R** **Mean, points (SD)** Year 3 (1) 95 (5) (2) 50 (4) **No. of PEs per year (SD)** Year 3 (1) 2 (2) (2) 5.5 (3)	**NR**
Sawicki [106] ***Am J Respir Crit Care Med***	Non-randomized comparative study; G551D individuals 6+ years of age who received ivacaftor	**N=1,075** (1) Ivacaftor (n=189), G551D only	**Inclusion:** **G551D** • Participation in STRIVE, ENVISION, and/or PERSIST	**$ppFEV_1$** **Mean, percentage points (SD)** (1) 65.7 (19.5)	**$ppFEV_1$** **Annualized rate of decline, percent (SE)** Year 3 (1) -0.91 (0.34)	**NR**

2015	during a phase 3 study (STRIVE, ENVISION, and/or PERSIST) were matched to up to 5 *F508del* homozygous individuals using the Cystic Fibrosis Foundation Patient Registry (CFFPR). Individuals were matched by propensity score which included sex, baseline age, year of CF diagnosis, sweat chloride value, CF-related diabetes, weight-for-age z score, BMI, use of inhaled medications and ppFEV$_1$ (among others) Duration of follow-up: up to 3 years	(2) Regular care (n=886), *F508del* homozygous only	• 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	(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)	(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) (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 [104]	Pooled and stratified data from STRIVE and ENVISION	**See STRIVE and ENVISION**	**See STRIVE and ENVISION**	**Age** **Mean, years (SD)** Ages ≤20	**Weight** **Mean (least-squares) change from baseline, kg***	**Not reported**

Dig Dis Sci **2016**	randomized clinical trials			(1) 12 (4.2) (2) 12 (4.3) <u>Ages >20</u> (1) 31 (8.4) (2) 29 (8.0) **ppFEV$_1$** **Mean, percentage points (SD)** <u>Ages ≤20</u> (1) 77.5 (17.64) (2) 77.9 (19.01) <u>Ages >20</u> (1) 60.3 (15.03) (2) 59.1 (15.57) **BMI** **Mean, kg (SD)** <u>Ages ≤20</u> (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)	<u>Ages ≤20</u> (1) 4.9 (2) 2.2 Difference=2.7 (95% CI:1.14 to 4.29) <u>Ages >20</u> (1) NR (2) NR **Weight** **Mean weight-for-age z-score, change from baseline*** <u>Ages ≤20</u> (1) 0.29 (2) -0.06 Difference=0.35 (95%CI: 0.202 to 0.508) <u>Ages >20</u> (1) NR (2) NR **BMI** **Mean change from baseline, kg/m^2*** <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) 41.8 (15.12) <u>Ages >20</u> (1) 64.9 (13.87) (2) 65.4 (13.26)	(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 [152] ***Pediatr Pulmonol*** **2015**	Post-hoc analysis of STRIVE and ENVISION looking at ivacaftor 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.	**See STRIVE and ENVISION**	**See STRIVE and ENVISION**	**Tertiles, by absolute change in $ppFEV_1$, percentage points:** <u>Ivacaftor (n=109)</u> Lower tertile: FEV ≤5.56 (n=37) Middle tertile: FEV >5.56 and ≤13.5 (n=36) Upper tertile: FEV>13.59 (n=36) <u>Placebo (n=100)</u> 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)** <u>Ivacaftor</u> Lower: 23.1 (13.7) Middle: 24.9 (10.6) Upper: 18.3 (8.3) <u>Placebo</u>	**$ppFEV_1$** **Mean absolute change from baseline, percentage points (95% CI)*** <u>Lower Tertile</u> 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) <u>Middle Tertile</u> 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=	**PEx, mean no. of days experienced (SD)** Lower ivacaftor: 15.61 (30.57) Lower placebo: 29.79 (50.63) Difference=14.18 Middle ivacaftor: 14.59 (26.45) Middle placebo: 33.64 (49.67) Difference=19.05 Upper ivacaftor: 5.83 (15.94) Upper placebo: 28.02 (40.24) Difference=22.19 (p=0.0019)

				Lower: 22.1 (11.2) Middle: 23.4 (11.4) Upper: 18.0 (8.7) **ppFEV$_1$** **Mean, percentage points (SD)** Ivacaftor Lower: 72.1 (23.0) Middle: 64.5 (18.2) Upper: 68.9 (11.7) Placebo Lower: 73.1 (19.7) Middle: 66.7 (18.7) Upper: 64.6 (18.8) **Weight** **Mean, kg (SD)** Ivacaftor Lower: 56.5 (22.5) Middle: 58.3 (15.1) Upper: 48.8 (15.8) Placebo Lower: 53.1 (21.4) Middle: 57.0 (15.9) Upper: 50.7 (17.8)	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** **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 [132] ***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	**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*	**Not reported**

	Functioning, Treatment Burden, Vitality, and Weight. 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.				4.4 (p=0.006) Respiratory Symptoms* 8.6 (p<0.001) Role Functioning -0.6 (p=0.651) Social Functioning* 4.3 (p=0.003) Treatment Burden 3.3 (p=0.042) Vitality 5.5 (p=0.002)* Weight 5.3 (p=0.053) *Placebo reported decrease in CFQ-R score between baseline and 48 weeks.	
Heltshe [153] ***Clin Infect Dis*** **2015**	Combination data from GOAL and Cystic Fibrosis Foundation Patient Registry analyzing *Pseudomonas aeruginosa* (PA) incidence, prevalence, and association with clinical outcomes during treatment with ivacaftor. GOAL data (6 mos. of ivacaftor) supplemented with CFFPR data from year before and year after ivacaftor treatment initiation for comparison.	**See GOAL**	**See GOAL**	**PA infection duration in year prior to treatment with ivacaftor, n/N (%)** Persistent* 59/145 (40%) Intermittent 30/148 (20%) Infection-free 59/148 (40%) *Note: participants with persistent infection tended to be older, had lower FEV_1, and higher hospitalization rates at baseline.	**PA culture positivity, odds ratio*** 0.65 (35% reduction) **PA prevalence after ivacaftor initiation by baseline category, n/N infection free (%)*** Persistent 5/48 (10%) Intermittent 21/30 (70%) **Frequency of PA isolation after ivacaftor initiation, n/N (%)*** More frequent 7/143 (5%) Less frequent 36/134 (27%) No change	**Not reported**

	Duration of follow-up: 2 years (Median follow-up in the CFFPR=12.5 mos.)				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 [154] ***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) **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 (%)**	**See Outcomes**

					(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 [155] ***J Cyst Fibros*** **2016** **Abstract**	Non-randomized comparative long-term post-approval observational safety study using data from UK and US CF patient registries. Only US data is reported Comparators not receiving ivacaftor were matched to ivacaftor recipients based on age, sex, and genotype severity. Duration of follow-up: 1 year (2014)	**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 (%)** (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)	**See Outcomes**
Barry [156] ***J Cyst Fibros***	Non-randomized comparative prospective cohort study measuring	**N=56** (1) Ivacaftor (n=21)	**NR**	**NR** Ivacaftor group received drug in prior	**Deaths, n/N** (1) 5/21 (2) 12/21	**See Outcomes**

2015 **Abstract**	effects of ivacaftor on death and transplantation among CF patients with FEV_1 <40. Duration of follow-up: Median = 1126 days	(2) Standard of care (n=35)		multi-center cohort study and had baseline FEV_1 <40 and continued treatment during prospective cohort study.	**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)	
Volkova [157] ***J Cyst Fibros*** **2016** **Abstract**	Non-randomized comparative long-term post-approval observational safety study using a United Kingdom CF registry. 2012 registry data served as baseline. Patients with a 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.	**N=1,642** (1) Ivacaftor (n=277) (2) Standard of care (n=1365)	**NR**	**$ppFEV_1$** **Mean, percentage points (SD)** (1) 70.6 (24.8) (2) 71.4 (23.6) **PEx** **Annual risk, %** (1) 51.6 (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	**$ppFEV_1$** **Mean, percentage points (SD)** 2013 (1) 75.8 (25.7) (2) 70.6 (24.3) 2014 (1) 77.8 (25.6) (2) 70.8 (24.2)	**PEx** **Annual risk, %** 2013 (1) 49.5 (2) 56.8 2014 (1) 34.3 (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 [158] ***Am J Resp Crit Care Med*** **2012** **Abstract**	Subgroup analysis of STRIVE and ENVISION ivacaftor treatment effect on mean absolute change from baseline ppFEV$_1$ at 24 weeks by baseline age and FEV$_1$. Duration of follow-up: 24 weeks	**N=213** (1) Ivacaftor (See STRIVE and ENVISION) (2) Placebo (See STRIVE and ENVISION)	**See STRIVE and ENVISION**	**Age** **N ivacaftor/n placebo** 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%)	**ppFEV$_1$** **Mean absolute change from 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)	**See STRIVE and ENVISION**

				(1) 12 (2) 6 **High FEV_1** **N ivacaftor/n placebo** STRIVE (Not defined) (1) 4 (2) 5 ENVISION (ppFEV_1>90%) (1) 10 (2) 11		
Flume [159] ***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 [160] ***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)	**See Outcomes**

	Average duration of ivacaftor exposure was 1.4 years Duration of follow-up: 5 years				**No. of organ transplantation, annual risk (%)** (1) 2 (0.2) (2) 53 (1.1) Unadjusted relative risks (95% CI) = 0.19 (0.05 to 0.76) **No. of hospitalization, annual risk (%)** (1) 247 (24.7) (2) 2055 (41.7) 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 [161] ***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 **CFQ-R Eating domain**	

	Clinical data was collected from patient medical records. Duration of follow-up: survey administered once				**Mean (least-squares) score*** (1) 91.1 (2) 84.2 **CFQ-R Health Perceptions domain** **Mean (least-squares) score*** (1) 67.6 (2) 58.6 **CFQ-R Physical Functioning domain** **Mean (least-squares) score*** (1) 74.6 (2) 66.6 **CFQ-R Treatment Burden domain** **Mean (least-squares) score** (1) 65.3 (2) 54.8 **CFQ-R Vitality domain** **Mean (least-squares) score*** (1) 63.5 (2) 55.9 **CFQ-R Weight domain** **Mean (least-squares) score*** (1) 80.7 (2) 64.2 **EQ-5D-5L index score*** (1) 0.90 (2) 0.81 **VAS score (p-value)*** (1) 75.7 (2) 70.0 **School productivity loss (%)**	

					(1) 24.6 (2) 33.6 **Activity impairment (%)** (1) 21.6 (2) 28.3 *Statistically significant difference between ivacaftor and standard of care	
Accurso [162] ***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**
Davies [163] ***J of Cyst Fibros***	Phase 2, randomized, double-blind, placebo-controlled, crossover, multicenter study.	**N=7** (interim analysis)	**Inclusion** • 6 years of age or older • Confirmed diagnosis of CF, with GG551D-CFTR mutation	**Age** **Mean, years (SD)** 14.0 (8.6)	**$ppFEV_1$** **Treatment difference for the mean change from baseline, percentage points (p-value)**	**Any AE, n/N** During placebo: 5/7 During ivacaftor: 6/7

2012 **Abstract**	Duration of follow-up: 12 weeks (2 four-week treatment periods with four-week washout between)	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	• FEV_1 of at least 90% LCI of at least 7.4	**LCI** **Mean (SD)** 9.2 (1.9) **$ppFEV_1$** **Mean, percentage points (SD)** 98.5 (6.4)	7.2 (p=0.1264) **LCI** **Mean change from baseline treatment difference (p-value)** −2.22 (p=0.0097)	**SAE, n/N** 1/7
Elborn [164] ***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)	Not reported

					(4) 3.0 (2.3)	
Plant [165] ***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** **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)	**Not reported**
Suthoff [166] ***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**	**Not reported**

					Percent of subjects reporting* Improvement (p-value) (1) 49 (2) 29 Decline (1) 30 (2) 50 **CFQ-R Vitality domain** **Percent of subjects reporting*** Improvement (p-value) (1) 49 (2) 23 Decline (1) 36 (2) 50 **CFQ-R Treatment Burden domain** **Percent of subjects reporting*** Improvement (p-value) (1) 44 (2) 22 Decline (1) 26 (2) 41 **CFQ-R Health Perceptions domain** **Percent of subjects reporting*** Improvement (p-value) (1) 44 (2) 17	

					Decline (1) 28 (2) 45 **CFQ-R Physical Functioning domain** **Percent of subjects reporting*** Improvement (p-value) (1) 35 (2) 12 Decline (1) 13 (2) 40 **CFQ-R Eating Problems domain** **Percent of subjects reporting*** Improvement (p-value) (1) 25 (2) 10 Decline (1) 12 (2) 27 **CFQ-R Weight Problems** **Percent of subjects reporting*** Improvement (p-value) (1) 19 (2) 13 Decline (1) 9 (2) 28 *p<0.05 for difference between treatment groups	

					in the percent improved and declined	
Hathorne [167] ***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**
Wainwright [168] ***Pediatr Pulmonol*** **2014**	12 months data from the Australian CF Data Registry (ACFDR). Duration of follow-up:	**N=331** (1) IVA: n=17 (2) Matched placebo: n=314	**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)**	**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)**	Not Reported

Abstract	24 weeks	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.		(1) 38.3 (12.4) (2) 45.4 (14.5) **BMI** **Mean, kg (SD)** (1) 20.4 (2.6) (2) 20.5 (2.8)	(1) 2.9 (0.0 to 27.5) (2) 23.5 (8.2 to 45.2) Difference: p=0.015	
Barry [169] ***Chest*** **2014**	Retrospective case-control study of patients receiving ivacaftor on the compassionate use program in the UK and Ireland. Duration of follow-up: 1-1.75 years (1 year before ivacaftor treatment and 90-270 days on ivacaftor) Median time on ivacaftor: 237 days	**N=56** (1) IVA: cases had at least 3 months treatment with ivacaftor by the time of data collection (n=21) (2) Matched control subjects: each case was matched up to 2 control subjects (n=35)	**Inclusion** • Confirmed diagnosis of CF • At least one G551D allele • $ppFEV_1$ < 40% • Minimum of 3 months treatment with ivacaftor **Exclusion** • Patients with FEV1 <40% were excluded from phase 3 clinical trials	**Age** **Mean, years (range)** (1) 22 (20-31) (2) 23 (21-27) **$ppFEV_1$** **Mean, percentage points (SD)** (1) 26.5 (7.2) (2) 30.3 (7.5) **Weight** **Median, kg (IQR)** (1) 49.8 (44.4-60.7) (2) 54 (49.0-62.4) **BMI** **Mean, kg/m²** (1) 19.1 (2.9) (2) 20.2 (5.2) **Sex** **Female, %** (1) 52 (2) 49	**$ppFEV_1$** **Mean, percentage points (SD)** (1) 30.7 (9.9) (2) NR **$ppFEV_1$** **Median absolute change from baseline, percentage points (IQR)** (1) 3.8 (0.2 to 7.7) (2) 0.6 (-2.1 to 2.8) **Weight** **Median, kg (IQR)** (1) 51.6 (48.6 to 66.8) (2) NR **Weight** **Median change from baseline, kg (IQR)** (1) 2.3 (-0.4 to 4.2) (2) 0.6 (-0.5 to 3.2) **BMI** **NR, kg/m²** (1) 20.2 (2) NR	No adverse events reported in the treatment group. 2 previously listed control subjects underwent lung transplantation.

					BMI **Median change from baseline, kg/m² (IQR)** (1) 0.84 (NR) (2) 0.2 (NR)	
Davies [170] ***Lancet Respir Med*** **2013**	Phase 2, multicenter, placebo-controlled, double-blind 2x2 crossover study. Duration of follow-up: 28 days	**N=20** **Demographics:** (1) Placebo → IVA: 28 days of placebo twice daily, 28-day washout period, and 28 days of 150 mg ivacaftor twice daily (n=10) (2) IVA → Placebo: 28 days of 150 mg ivacaftor twice daily, 28-day washout period, 28 days of placebo twice daily (n=10) **Results, at 28 days** (1) IVA (n=18) (2) Placebo (n=17)	**Inclusion** • Confirmed diagnosis of CF • At least one G551D-CFTR allele • $ppFEV_1$ > 90% • Age of 6 years or older • Weight ≥ 15 kg • LCI > 7.4	**By arm (treatment order 1 or 2)** **Age** **Mean, years (SD)** (1) 19.8 (13.35) (2) 13.4 (7.12) **$ppFEV_1$** **Mean, percentage points (SD)** (1) 92.6 (7.43) (2) 101.8 (11.59) **BMI** **Mean, kg (SD)** (1) 22.7 (6.96) (2) 19.4 (3.71) **Sex** **Female, n (%)** (1) 4 (40) (2) 6 (60) **CFQ-R Respiratory domain** **Mean, score (SD)** (1) 71.7 (13.4) (2) 75.6 (18.2) **LCI** **Mean (SD)** (1) 8.88 (1.46) (2) 9.17 (1.66)	**Results are pooled for all subjects during ivacaftor and placebo weeks.** **$ppFEV_1$** **Mean, percentage points (95% CI)** Ivacaftor: 104.97 Placebo: 94.85 Difference= 8.67 (2.36 to 14.97) **CFQ-R Respiratory domain** **Mean, points (95% CI)** Ivacaftor: 83.33 Placebo: 79.97 Difference= 3.99 (−5.32 to 1.33) **LCI (95% CI)** Ivacaftor: 8.13 Placebo: 9.40 Difference= −2.16 (−2.88 to 1.44)	**Any AE, n (%)** Ivacaftor: 13 (72%) Placebo: 15 (79%) **SAE, n** Ivacaftor: 3 Placebo: 1

Edgeworth [171] ***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 • $ppFEV_1 \geq 25\%$ **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 (%)** 8 (40)	**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) 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)	**All participants** **No. hospitalizations for PEs** 5 **Abdominal discomfort, n** 3 **Elevated creatinine kinase, n** 1
Stalvey [172] ***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	**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)	**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

		(3) Placebo: n=23		**$ppFEV_1$** **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) (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 [173] ***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	**Not reported**

					Percent with change in only weight 37 **Percent with change in only lung function** 8 **Percent with FEV_1 response and baseline FEV_1 of:** ≥80: 43 40-79: 60 <40: 48 **Percent with weight response and baseline FEV_1 of:** ≥80: 84 <80: 72	
Multiple Regimens						
Heltshe [174] ***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

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