Modulator Treatments for Cystic Fibrosis: Effectiveness and Value

Public Meeting — August 27, 2020

Meeting materials available at: https://icer-review.org/topic/cystic-fibrosis/
Why are we here today?

- What happens the day these treatments are approved by the FDA?
- Patients can have difficulty accessing drugs
  - Coverage eligibility
  - Costs (out of pocket and insurance premiums)
- What happens to patients and others in the health care “system”
The personal trade-offs when a dollar spent on health insurance can’t be spent on something else

“I live in a constant state of fear”
Whitney Whitman, Alaska

“We don’t have enough money to go out to eat, or take my grandchildren to the movies, much less pay for health insurance”
Tara Sullivan, West Virginia

“We’re not poor people but we can’t afford health insurance,”
Mimi Owens, Louisiana

“If we can control our health-care costs for a couple of years, the difference that makes on our household income is phenomenal”
Keith Buchanan, North Carolina

“If we can control our health-care costs for a couple of years, the difference that makes on our household income is phenomenal”
Keith Buchanan, North Carolina

“Every single decision that you make has to be very carefully calculated so that your finances don’t fall apart”
Corinne Bobbie, Arizona

“This isn’t just philosophical or moral support, it is a financial issue for my business. Turnover costs are so high, and we need to be able to retain employees. We do whatever we can to create a stress-free and healthy work environment, but we often lose people to larger companies that have the scale to provide health care”
Luke Breen, Minnesota

“My wife is a little more antsy than I am about not having insurance, it worries her”
Gustavo Bendeck, Texas

“I’m almost 60 years old and I can’t go see a doctor”
Tara Sullivan, West Virginia

“Why some Americans are risking it and skipping health insurance”

“Employer-centered health insurance is hurting small businesses”
https://www.minnpost.com/community-voices/2019/12/employer-centered-health-insurance-is-hurting-small-businesses/
The personal trade-offs when a dollar spent on health insurance can’t be spent on something else

Gustavo Bendeck, Lubbock, Texas

Gustavo is a 62-year-old physician assistant from Lubbock, Texas. He and his wife, Shirley, received a letter from their health insurance provider telling them that their $1,000-a-month premium was more than doubling to $2,200. Shirley asked Bendeck what would happen next.

“I’m not going to pay this amount of money,” he told her. He looked for other comparable plans, but most wanted about the same. He makes about $117,000 a year after taxes, he said. He and his wife are healthy, so they decided to chance it.

Life hasn’t changed too much since, though they have a little more free cash even though the prescriptions they both take cost more without insurance. Shirley takes a cholesterol drug and a blood-pressure treatment that together cost about $350 a month, more than double when they had insurance coverage. Gustavo takes a blood-pressure drug that costs $70 to $80 for a 90-day supply, compared to $20 when he was insured.

“My wife is a little more antsy than I am about not having insurance, it worries her,” Bendeck said. “What keeps me calmer is that there’s a lot of us out there that do not have insurance.”

The Whitmans, Bird City, Alaska

The Whitman family last had health insurance in 2016. When they last looked, the cheapest plan Whitman could find was $1,734 per month, with a deductible of $10,500 for the family of four. She splits her time between mental health counseling and mediating legal disputes, such as divorces. She made about $110,000 before taxes in 2016.

This lack of coverage means they delay medical care, such as waiting until the 7-year-old daughter had been sick for almost two weeks before taking her to the pediatrician or taping up husband Jason’s finger when he had broken it. Jason’s knee injury and concussion also went untreated.

“It’s a tradeoff they are not entirely comfortable,” Whitman Whitman said.

Luke Breen, Minneapolis, Minnesota

Luke has been a small business owner for 25 years and has seven year-round employees with an additional nine summer seasonal employees. One of his biggest challenges, and one of the biggest challenges for small business owners across America, is the inability of his business to afford health care for his employees.

For small businesses, the ability to compete in their own markets is dictated by outside industries: health insurance markets. Luke’s best employee recently left to take another job, because she turned 27 and was no longer eligible to be on her parents’ health insurance. She didn’t want to leave, but she needed employer-funded health care, so she truly had no choice.

https://www.minnpost.com/community-voices/2019/12/employer-centered-health-insurance-is-hurting-small-businesses/
Organizational Overview

• The California Technology Assessment Forum (CTAF)
• The Institute for Clinical and Economic Review (ICER)
Sources of Funding, 2020
https://icer-review.org/about/support/

- Nonprofit Foundations: 70%
- Health Plans and Provider Group Contributions: 12%
- Manufacturer Contributions: 17%
- Other*: 1%

*Individual and matching contributions, government contracts, and speech stipends
How was the ICER report developed?

• Scoping with guidance from patient groups, clinical experts, manufacturers, and other stakeholders

• UCSF and internal ICER staff: evidence analysis

• University of Minnesota: cost-effectiveness modeling

• Public comment and revision

• Expert reviewers
  • Manu Jain, MD, MSc Professor, Department of Medicine (Pulmonary and Critical Care); Department of Pediatrics, Northwestern University
  • Carlos Milla, MD, Professor of Pediatrics, Pulmonology, Stanford University School of Medicine
  • Brian P. O'Sullivan, MD, Professor of Pediatric Pulmonology, Geisel School of Medicine, Dartmouth College
  • Cystic Fibrosis Foundation

• How is the evidence report structured to support CTAF voting and policy discussion?
## Agenda

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>9:00 am—9:10 am PT</td>
<td><strong>Meeting Convened and Opening Remarks</strong>&lt;br&gt;Steven D. Pearson, MD, MSc</td>
</tr>
<tr>
<td>9:10 am—10:00 am PT</td>
<td><strong>Presentation of the Evidence</strong>&lt;br&gt;Jeffrey A. Tice, MD, University of California, San Francisco&lt;br&gt;Karen Kuntz, ScD, University of Minnesota</td>
</tr>
<tr>
<td>10:05 am – 10:45 am PT</td>
<td><strong>Public Comments and Discussion</strong></td>
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<tr>
<td>10:45 am—11:00 am PT</td>
<td><strong>Break</strong></td>
</tr>
<tr>
<td>11:00 am—11:45 am PT</td>
<td><strong>CTAF Deliberation and Vote</strong></td>
</tr>
<tr>
<td>11:45 am—12:30 pm PT</td>
<td><strong>Lunch</strong></td>
</tr>
<tr>
<td>12:30 pm—1:30 pm PT</td>
<td><strong>Policy Roundtable</strong></td>
</tr>
<tr>
<td>1:30 pm—2:00 pm PT</td>
<td><strong>Reflections from CTAF and Closing Remarks</strong></td>
</tr>
<tr>
<td>2:00 pm PT</td>
<td><strong>Meeting Adjourned</strong></td>
</tr>
</tbody>
</table>
Clinical Experts

**Manu Jain, MD, MSc** Professor, Department of Medicine (Pulmonary and Critical Care); Department of Pediatrics, Northwestern University

- *Dr. Jain has received in excess of $5,000 in advisory fees and research funding from Vertex Pharmaceuticals. He is also on the Speaker’s Bureau of Vertex Pharmaceuticals and Gilead Sciences*

**Carlos Milla, MD** Professor of Pediatrics, Pulmonology, Stanford University School of Medicine

- *Dr. Milla has received in excess of $5,000 in advisory fees and research funding from Vertex Pharmaceuticals, Proteostasis Inc., and Eloxx Pharma. He also receives advisory board honorarium from Vertex Pharmaceuticals*
Patient Experts

Mary Dwight, Senior Vice President of Policy and Advocacy, Cystic Fibrosis Foundation

- CFF has received charitable contributions and/or fees for service in excess of $5,000 from health care companies including Vertex Pharmaceuticals.

- CFF has the option to acquire equity interests >$10,000 from a pharmaceutical company unrelated to this report.

- CFF has entered into therapeutic development award agreements that may result in intellectual property and royalty rights from various pharmaceutical companies.

Mariah Hanley, JD, Individual with CF

- No financial conflicts of interest to disclose

Don Maurice Kreis, JD, MS, Parent of Individual with CF

- No financial conflicts of interest to disclose
Presentation of the Clinical Evidence

Jeffrey A. Tice, MD
Division of General Internal Medicine
University of California San Francisco
Key Review Team Members

Patty Synnott, MALD, MS, ICER (former)

Noemi Fluetsch, MPH, ICER

Avery McKenna, BS, ICER

Special thanks to Judith Walsh, MD, MPH, UCSF

Disclosures:

We have no conflicts of interest relevant to this report.
CF Pathogenesis

• Mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene

• CFTR protein is important for chloride and other anion transportation across cell membranes

• >1,800 CFTR mutations associated with CF

• Mutations in each of the 2 copies of the CFTR gene to have disease
Clinical Presentation: Multi-system

• Lungs
  - Chronic cough
  - Infections throughout life
  - Progressive decline in lung function
  - End stage disease: lung transplant or death

• Pancreas
  - Pancreatic insufficiency / poor growth
  - CF-related Diabetes
  - Skin, liver, intestines, fertility
  - Quality of life, anxiety, depression
Disease Management

• Early diagnosis and treatment has greatly improved quality and length of life

• Best supportive care
  – Chest PT, inhaled therapies
  – Pancreatic enzymes and nutritional support
  – Insulin
  – Antibiotics

• CFTR modulators
CFTR Modulators

• Interventions (all with best supportive care)
  • Trikafta® (elexacaftor/tezacaftor/ivacaftor, Vertex Pharmaceuticals, Inc.) – focus of this update
  • Symdeko® (tezacaftor/ivacaftor, Vertex)
  • Orkambi® (lumacaftor/ivacaftor, Vertex)
  • Kalydeco® (ivacaftor, Vertex)

• Comparators
  • Best supportive care
  • The CFTR modulators when indicated for the same population
Population

• 4 populations
  
  • **Population 1**: Individuals with CF mutations with FDA indications for Kalydeco
  
  • **Population 2**: Individuals with CF homozygous for the *F508del* mutation
  
  • **Population 3**: Individuals with CF heterozygous for the *F508del* mutation and a residual function mutation
  
  • **Population 4**: Individuals with CF heterozygous for the *F508del* mutation and a minimal function mutation
  
• 90% of individuals with CF have mutations eligible for Trikafta
Outcomes

- Pulmonary
  - Percent predicted forced expiratory volume 1 sec (ppFEV$_1$)
  - Pulmonary exacerbations
- Quality of life
  - CF Questionnaire, Revised (CFQ-R) Respiratory Domain
- Other
  - Weight and growth
  - Death, hospitalizations, lung transplantation
  - Adverse events
    - Additional outcomes: Fertility, pancreatitis, functional status, mental health, work/school attendance, social function, finances, caregiver/family burden
Population 2: Homozygous *F508del* Trikafta

- Pivotal Trial: Head to Head with Symdeko
  - 107 participants, age ≥ 12 years
  - 4-week run-in with Symdeko, 4-week trial
  - Good quality
  - Primary outcome: absolute change in ppFEV$_1$
    - + 10.0% (95% CI 7.4-12.6) versus Symdeko
  - Respiratory domain CFQ-R (MCID 4 points)
    - + 17.4 points (11.8-23) versus Symdeko
Population 2: Homozygous *F508del*
Network Meta-Analysis ppFEV$_1$
Population 2: Homozygous *F508del*
Network Meta-Analysis Respiratory QOL

**Absolute Change in CFQ-R Respiratory Domain Score 95%-CI**

- **Orkambi**: 2.2 [0.0; 4.4]
- **Symdeko**: 5.1 [3.2; 7.0]
- **Trikafta**: 22.5 [16.6; 28.4]
- **Placebo**: 0.0

**LS Mean Change**
Population 3: Heterozygous $F508\text{del}$ / Residual Function

- No data for Trikafta except recent press release without details of the results in this population

- Trikafta = Symdeko + elexacaftor

- No additional AEs seen with Trikafta

- Expect benefits to be at least as good as those of Symdeko and likely greater
Population 4: Heterozygous $F508del$ / Minimal Function

• Pivotal Trial: Trikafta versus placebo for 24 weeks
  • N = 403, ages ≥ 12 years
  • Good Quality
  • Primary outcome: absolute change in ppFEV$_1$
    • + 14.3% (95% CI 12.7-15.8)
  • Respiratory domain CFQ-R
    • +20.2 points (95% CI 17.5-23.0)
  • Pulmonary exacerbations
    • RR 0.37 (95% CI 0.25-0.55)
Harms with CFTR Modulators

• Adverse events generally mild or self-limited
  – No reported deaths ascribed to drugs

• Trikafta
  – SAE: rash – did not discontinue therapy
  – Drug discontinuation due to adverse event: 1%
Uncertainties and Controversies

• CF: lifelong illness, Trikafta trials 4 and 24 weeks
  • Uncertain long-term benefits and harms

• ppFEV₁ is a surrogate measure of CF severity and change in ppFEV₁ does not fully capture the benefits of therapy

• Heterogeneity of disease by gene mutation combination and age at initiation of therapy likely impact the magnitude of benefit

• Reduction in disease management therapies may be possible

• Patients ≤12 years of age
Potential Other Benefits and Contextual Considerations

- Trikafta may reduce the burden of therapy, caregiver/family burden, school/work, social stressors

- Trikafta is the first effective modulator therapy for patients with F508del / minimal function

- CF is severe with large impacts on both length and QOL

- CF has a high lifetime burden of illness

- Uncertainty remains about the lifetime impact of Trikafta
Public Comments Received

• Evidence ratings for Trikafta were downgraded for limited evidence
  • Most ratings were “A”
  • No penalties were given for limited evidence in a rare disease where large trials are difficult
Summary

• Among those ≥12 years old, Trikafta
  – Substantially increases ppFEV\(_1\)
  – Markedly improves respiratory-related QOL
  – Markedly reduces the rate of pulmonary exacerbations

• Harms appear to be non-serious and self-limited

• Uncertainties
  • Long term benefits and harms
  • Safety and efficacy in patients younger than 12 years of age
Evidence Ratings

• Trikafta for homozygous *F508del*
  • “A” (*superior*, high certainty of substantial benefit)

• Trikafta for heterozygous *F508del* / residual function
  • ”C++” (*comparable, small, or substantial net health benefit* compared with Symdeko)
  • "B+" (*incremental or better*, moderate certainty of small or substantial benefit, high certainty of at least a small benefit compared with BSC). No data yet, but Symdeko B+

• Symdeko for heterozygous *F508del* / minimal function
  • “A” (*superior*, high certainty of substantial benefit)
Questions?
Presentation of the Evidence and Economic Modeling

Karen M. Kuntz, ScD

Division of Health Policy and Management

University of Minnesota, School of Public Health

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Key Review Team Members

- **Kael Wherry, PhD**, University of Minnesota, School of Public Health
- **Rick Chapman, PhD**, ICER

**Disclosures:**

We have no conflicts of interest relevant to this report.
Objective

To compare lifetime health effects, costs, and cost-effectiveness of CFTR modulator treatment plus best supportive care versus best supportive care alone for CF patients
Methods Overview

- **Model**: Updated previously developed *de novo* discrete-time microsimulation models
- **Setting**: United States
- **Perspective**: Health Care Sector
- **Time Horizon**: Lifetime
- **Discount Rate**: 3% per year (costs and outcomes)
- **Cycle Length**: Annual
- **Outcomes**: Cost per quality-adjusted life year (QALY) gained; cost per life year gained (LYG); cost per equal value LYG (evLYG); cost per acute pulmonary exacerbation averted
Model Schematic

Assign initial patient characteristics
- Start age
- Sex
- ppFEV₁
- Weight-for-age z-score
- Pancreatic sufficiency
- Age at CF-related diabetes
- Age at B. cepacia infection

BSC
Annual decline in ppFEV₁

CFTR Modulator + BSC
Initial ppFEV₁ increase
Initial increase weight-for-age z-score
Annual decline in ppFEV₁*

Acute pulmonary exacerbation(s)

Lung transplantation

Quality of life

Advance 1 year in age

Alive

Dead

*Annual decline in ppFEV₁ begins two years after treatment and is half that of BSC
Key Model Assumptions

• The intensity of best supportive care varies by lung function category (ppFEV\textsubscript{1} ≥70%, 40%-69%, <40%).

• CFTR modulator drugs decrease the annual number of acute pulmonary exacerbations both through the increase in ppFEV\textsubscript{1} as well as an independent effect.
Populations and CFTR Modulators

<table>
<thead>
<tr>
<th>CF Population</th>
<th>6 mo</th>
<th>2 yr</th>
<th>6 yr</th>
<th>12 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Eligible for Kalydeco monotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Homozygous F508del</td>
<td>Orkambi</td>
<td>Symdeko</td>
<td>Trikafta</td>
<td></td>
</tr>
<tr>
<td>3 Heterozygous F508del with residual function mutation</td>
<td>Kalydeco</td>
<td>Symdeko</td>
<td>Trikafta</td>
<td></td>
</tr>
<tr>
<td>4 Heterozygous F508del with minimal function mutation</td>
<td>Kalydeco</td>
<td>Symdeko</td>
<td>Trikafta</td>
<td></td>
</tr>
</tbody>
</table>

All treatments are in addition to best supportive care
## Key Model Inputs: Direct Costs by Disease Severity

<table>
<thead>
<tr>
<th>Costs (2019 US$)</th>
<th>ppFEV$_1$ ≥70%</th>
<th>ppFEV$_1$ 40%-69%</th>
<th>ppFEV$_1$ &lt;40%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease Management</td>
<td>$30,258</td>
<td>$39,914</td>
<td>$68,240</td>
</tr>
<tr>
<td>PEx (age &lt;18)</td>
<td>$63,204</td>
<td>$100,143</td>
<td>$148,368</td>
</tr>
<tr>
<td>PEx (age 18+)</td>
<td>$57,273</td>
<td>$91,037</td>
<td>$130,460</td>
</tr>
<tr>
<td>Lung Transplant</td>
<td></td>
<td>$948,437</td>
<td></td>
</tr>
<tr>
<td>Post-Transplant (Year 1)</td>
<td></td>
<td>$365,773</td>
<td></td>
</tr>
<tr>
<td>Post-Transplant (Year 2+)</td>
<td></td>
<td>$131,738</td>
<td></td>
</tr>
</tbody>
</table>
### Key Model Inputs: Annual CFTR Modulator Costs

<table>
<thead>
<tr>
<th>CFTR Modulator Drug</th>
<th>Annual Drug Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kalydeco</td>
<td>$311,704</td>
</tr>
<tr>
<td>Orkambi</td>
<td>$272,623</td>
</tr>
<tr>
<td>Symdeko</td>
<td>$292,200</td>
</tr>
<tr>
<td>Trikafta</td>
<td>$311,741</td>
</tr>
</tbody>
</table>
### Key Model Inputs: Utilities

<table>
<thead>
<tr>
<th>ppFEV₁</th>
<th>EQ-5D Utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;90</td>
<td>0.920</td>
</tr>
<tr>
<td>80-89</td>
<td>0.873</td>
</tr>
<tr>
<td>70-79</td>
<td>0.801</td>
</tr>
<tr>
<td>60-69</td>
<td>0.765</td>
</tr>
<tr>
<td>50-59</td>
<td>0.765</td>
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<tr>
<td>40-49</td>
<td>0.729</td>
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<tr>
<td>30-39</td>
<td>0.692</td>
</tr>
<tr>
<td>20-29</td>
<td>0.653</td>
</tr>
<tr>
<td>&lt;20</td>
<td>0.625</td>
</tr>
</tbody>
</table>
## Base-Case Results: Lifetime Health Outcomes (undiscounted)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Average Number of PEx</th>
<th>% With Lung Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population 2 – Homozygous for the F508del Mutation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSC</td>
<td>21.13</td>
<td>32.9%</td>
</tr>
<tr>
<td>Trikafta plus BSC</td>
<td>10.51</td>
<td>3.2%</td>
</tr>
<tr>
<td><strong>Population 3 – Heterozygous F508del with Residual Function Mutation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSC</td>
<td>23.99</td>
<td>36.8%</td>
</tr>
<tr>
<td>Trikafta plus BSC</td>
<td>11.20</td>
<td>3.1%</td>
</tr>
<tr>
<td><strong>Population 4 – Heterozygous F508del with Minimal Function Mutation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSC</td>
<td>18.31</td>
<td>32.5%</td>
</tr>
<tr>
<td>Trikafta plus BSC</td>
<td>8.90</td>
<td>5.9%</td>
</tr>
</tbody>
</table>

PEx: acute pulmonary exacerbation
## Base-Case Results: Incremental Effectiveness Measures (discounted)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>QALYs Gained</th>
<th>evLYG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population 2 – Homozygous for the <em>F508del</em> Mutation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trikafta plus BSC vs. BSC</td>
<td>5.49</td>
<td>6.15</td>
</tr>
<tr>
<td>Population 3 – Heterozygous <em>F508del</em> with Residual Function Mutation</td>
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</tr>
<tr>
<td>Trikafta plus BSC vs. BSC</td>
<td>6.08</td>
<td>7.03</td>
</tr>
<tr>
<td>Population 4 – Heterozygous <em>F508del</em> with Minimal Function Mutation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trikafta plus BSC vs. BSC</td>
<td>5.04</td>
<td>6.06</td>
</tr>
</tbody>
</table>

QALYs: quality-adjusted life years; evLYG: equal value life years gained; BSC: best supportive care
## Base-Case Results: Incremental Costs (2019 US$)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Trikafta</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population 2 – Homozygous for the <em>F508del</em> Mutation</td>
<td>Trikafta plus BSC $7,339,000</td>
<td>$6,385,000</td>
</tr>
<tr>
<td>Population 3 – Heterozygous <em>F508del</em> with Residual Function Mutation</td>
<td>Trikafta plus BSC $7,743,000</td>
<td>$6,687,000</td>
</tr>
<tr>
<td>Population 4 – Heterozygous <em>F508del</em> with Minimal Function Mutation</td>
<td>Trikafta plus BSC $6,310,000</td>
<td>$5,317,000</td>
</tr>
</tbody>
</table>
### Base-Case Incremental Cost-Effectiveness Results

<table>
<thead>
<tr>
<th>Drug vs BSC (Population)</th>
<th>Cost Per QALY Gained</th>
<th>Cost Per evLYG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kalydeco (Eligible for Kalydeco only)</td>
<td>$1,370,000</td>
<td>$1,180,000</td>
</tr>
<tr>
<td>Orkambi (Homozygous for <em>F508del</em> mutation)</td>
<td>$1,480,000</td>
<td>$1,360,000</td>
</tr>
<tr>
<td>Symdeko (Homozygous for <em>F508del</em> mutation)</td>
<td>$1,380,000</td>
<td>$1,200,000</td>
</tr>
<tr>
<td>Trikafta (Homozygous for <em>F508del</em> mutation)</td>
<td>$1,160,000</td>
<td>$1,040,000</td>
</tr>
<tr>
<td>Symdeko (Heterozygous <em>F508del</em> / residual function)</td>
<td>$1,340,000</td>
<td>$1,100,000</td>
</tr>
<tr>
<td>Trikafta (Heterozygous <em>F508del</em> / residual function)</td>
<td>$1,100,000</td>
<td>$951,000</td>
</tr>
<tr>
<td>Trikafta (Heterozygous <em>F508del</em> / minimal function)</td>
<td>$1,050,000</td>
<td>$877,000</td>
</tr>
</tbody>
</table>

QALY: quality-adjusted life year; evLYG: equal value life year gained
One Way Sensitivity Analyses (Trikafta, Population 2)

- Slope of Utility Function [0.002-0.005]
- Independent PEx Reduction [0%-50%]
- PEx Cost [0.5-1.5x base case]
- Absolute FEV1 Gain [7.4-12.6%]
- Transplant Costs [0.5-1.5x base case]
- Annual BSC Costs [0.5-1.5x base case]

Incremental Cost-Effectiveness Ratio (Trikafta)
Scenario Analyses: Modified Societal Perspective

• Incorporated lost productivity for patients unable to work full time as well as lost productivity for patients and caregivers due to acute pulmonary exacerbations.
  • Population 2: $1.15 million per QALY
  • Population 3: $1.09 million per QALY
  • Population 4: $1.04 million per QALY
Scenario Analyses: Curative Scenario

• Provided an extreme favorable cost-effectiveness ratio for Trikafta

• Assumed patients live a life span and experience quality of life similar to US population

• Assumed 100% adherence with medication starting at 6 months of age and the only CF costs were Trikafta costs

• Incremental cost-effectiveness ratio was $612,000 per QALY at current prices
Limitations

• Modeled lifetime outcomes derived from short-term trial outcomes

• As with any surrogate marker of disease, ppFEV$_1$ is not a perfect marker

• We did not have trial-based measures of CFTR modulator benefit on utilities
Comments Received

• Lack of long-term real-world data on these therapies, seriously limiting the utility and reliability of the report.
  • Models are most useful in this situation where assumptions can be explored with sensitivity analysis.

• The disease-management costs derived are not valid estimates for current standard of care.
  • We did need to incorporate several assumptions in our cost derivations but received confidential confirmation from two private payers that our annual costs are in line with their observed costs.
Conclusions

• Trikafta plus best supportive care substantially improves health outcomes compared with best supportive care alone

• However, in proportion to the clinical benefits, the added cost of Trikafta well exceeds commonly used thresholds for cost-effectiveness.

• If we assumed a scenario where Trikafta was curative we found that the cost-effectiveness ratio would reduce to $612,000 per QALY at current prices, which is still far from commonly cited thresholds.
Questions?
Public Comment and Discussion
Conflicts of Interest:

• Contributions: CFF has received charitable contributions and/or fees for service >$5,000 from health care companies, including Vertex Pharmaceuticals.

• Equity Interests and Intellectual Property: CFF has entered into therapeutic development award agreements that have and may continue to provide CFF with intellectual property, equity interests, and royalty and milestone payment rights from various pharmaceutical companies.

• Research Support: CFF provides financial support to the Therapeutics Development Network (TDN) which delivers high-quality clinical trials to CF patients in the search for better therapies and a cure. CFF provides financial support to the Data Safety Monitoring Board whose primary responsibility is to protect the safety and welfare of people with CF who participate in TDN approved studies.

• Other Relationships: CFF facilitated, but did not participate in, the development of the CFF Pulmonary Guidelines: Use of CFTR Modulator Therapy in Patients with CF.
Conflicts of Interest:

- CFRI receives educational grants to support our services to the CF community from Vertex Pharmaceuticals, Genentech, Gilead Sciences, AbbVie, Chiesi USA, and Ionis Pharmaceuticals. These grants represent > 25% CFRI’s total budget.
Conflicts of Interest:

- No conflicts of interest to disclose.
Laura Rogers
Parent of an Individual with CF

Conflicts of Interest:

- Laura’s daughter has been enrolled with the Vertex Trikafta trial(s) since July of 2018. There has been appointment, travel and meal reimbursement throughout the trial, and she is currently still enrolled.
Conflicts of Interest:

- Chad is the National Advocacy Co-Chair for the Cystic Fibrosis Foundation.
Break

Meeting will resume at 11:00 am PT
Voting Questions
0. Test Question: In what year did Labor Day become a federal holiday?

A. 1890
B. 1894
C. 1905
D. 1913
Patient Population 2 (Questions 1-2): *Individuals with CF who are homozygous for the F508del mutation*

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

A. Yes

B. No
2. If the answer to Q1 is Yes: Is the evidence adequate to demonstrate that the net health benefit of treatment with Trikafta and best supportive care is greater than that of treatment with Symdeko and best supportive care?

A. Yes
B. No
3. Is the evidence adequate to demonstrate that the net health benefit of treatment with Trikafta with best supportive care is greater than that of best supportive care alone?

A. Yes

B. No
Patient Population 3 (Questions 3-4):
Individuals with CF who are heterozygous for the F508del mutation with a residual function mutation.

4. If the answer to Q3 is Yes: Is the evidence adequate to demonstrate that the net health benefit of treatment with Trikafta and best supportive care is greater than that of treatment with Symdeko and best supportive care?

A. Yes

B. No
Patient Population 4: Individuals with CF who are heterozygous for the F508del mutation with a minimal function mutation.

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

A. Yes
B. No
6. When compared to best supportive care, does treating patients with Trikafta offer one or more of the following potential “other benefits?” (select all that apply)

A. This intervention will significantly reduce caregiver or broader family burden.
B. 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.
C. This intervention will have a significant impact on improving patients’ ability to return to work and/or their overall productivity.
D. This intervention will have a significant positive impact outside the family, including on schools and/or communities.
E. There are other important benefits or disadvantages that should have an important role in judgments of the value of this intervention: ________________
7. Are any of the following contextual considerations important in assessing Trikafta’s long-term value for money? (select all that apply)

A. 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.

B. This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.

C. This intervention is the first to offer any improvement for patients with this condition.

D. Compared to best supportive care, there is significant uncertainty about the long-term risk of serious side effects of this intervention.

E. Compared to best supportive care, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.

F. There are additional contextual considerations that should have an important role in judgments of the value of this intervention: __________________________.
8. Given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits and contextual considerations, what is the long-term value for money of Trikafta with best supportive care compared with best supportive care alone?

A. Low long-term value for money at current pricing
B. Intermediate long-term value for money at current pricing
C. High long-term value for money at current pricing

Patient Population 2: Individuals with CF who are homozygous for the F508del mutation
Patient Population 3:
Individuals with CF who are heterozygous for the F508del mutation with a residual function mutation.

9. Given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits and contextual considerations, what is the long-term value for money of Trikafta with best supportive care compared with best supportive care alone?

A. Low long-term value for money at current pricing
B. Intermediate long-term value for money at current pricing
C. High long-term value for money at current pricing
10. Given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits and contextual considerations, what is the long-term value for money of Trikafta with best supportive care compared with best supportive care alone?

A. Low long-term value for money at current pricing
B. Intermediate long-term value for money at current pricing
C. High long-term value for money at current pricing

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

Meeting will resume at 12:30 pm PT
Policy Roundtable
<table>
<thead>
<tr>
<th>Policy Roundtable Participant</th>
<th>Conflict of Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carlos Milla, MD</strong>, Professor of Pediatrics, Pulmonology, Stanford University School of Medicine</td>
<td>Dr. Milla has received in excess of $5,000 in advisory fees and research funding from Vertex Pharmaceuticals, Proteostasis Inc., and Eloxx Pharma. He also receives advisory board honorarium from Vertex Pharmaceuticals.</td>
</tr>
<tr>
<td><strong>Don Maurice Kreis, JD, MS</strong>, Parent of Individual with CF</td>
<td>No financial conflicts of interest to disclose.</td>
</tr>
<tr>
<td><strong>Janet Zachary-Elkind, Deputy Director, NY State Department of Health, Office of Health Insurance Programs</strong></td>
<td>Janet Zachary-Elkind is an employee of the NY State Department of Health (Medicaid).</td>
</tr>
<tr>
<td><strong>Jeff White, PharmD, MS</strong>, Staff Vice President, Clinical Pharmacy Services, IngenioRX (Anthem)</td>
<td>Dr. White is an employee of IngenioRx (Anthem) and owns stock in Anthem.</td>
</tr>
<tr>
<td><strong>Manu Jain, MD, MSc</strong>, Professor, Department of Medicine (Pulmonary and Critical Care); Department of Pediatrics, Northwestern University</td>
<td>Dr. Jain has received in excess of $5,000 in advisory fees and research funding from Vertex Pharmaceuticals. He is also on the Speaker’s Bureau of Vertex Pharmaceuticals and Gilead Sciences</td>
</tr>
<tr>
<td><strong>Mariah Hanley, JD</strong> Patient Expert, Cystic Fibrosis Foundation</td>
<td>No financial conflicts of interest to disclose.</td>
</tr>
<tr>
<td><strong>Mary Dwight, Senior Vice President of Policy and Advocacy, Cystic Fibrosis Foundation</strong></td>
<td>CFF has received charitable contributions and/or fees for service in excess of $5,000 from health care companies including Vertex Pharmaceuticals. CFF has the option to acquire equity interests &gt;$10,000 from a pharmaceutical company unrelated to this report. CFF has entered into therapeutic development award agreements that may result in intellectual property and royalty rights from various pharmaceutical companies</td>
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CTAF Council Reflections
Next Steps

• Meeting recording posted to ICER website next week

• Final Report published on or around September 23, 2020
  • Includes description of CTAF votes, deliberation, policy roundtable discussion

• Materials available at: https://icer-review.org/topic/cystic-fibrosis/
Adjourn