Modulator Treatments for Cystic Fibrosis: Effectiveness and Value

Public Meeting – May 17, 2018

WIFI network: TritonNet
Login ID: gst-cianciolola
Password: +3$nTaK=
Welcome and Introduction

• Why are we here today?
  – Cystic fibrosis has a profound effect on patients and families, and innovative treatments have made a significant difference in their lives, with additional innovation on the horizon

“…for those who battle CF, every day is filled with hours of respiratory therapy, countless pills, and often multiple injections, IVs, and hospitalizations. Every hospitalization is painful, isolating, frightening, and expensive.”

  -Siri Vaeth and Sue Landgraf, Cystic Fibrosis Research, Inc

“When I was diagnosed with cystic fibrosis in 1984 at the age of three years old, my parents were told that they should not expect me to live to see my twelfth birthday….We still have a long way to go and while CFTR modulators are not a perfect answer and do not work for all those suffering from CF, they are an important and valuable piece to allow us to live and thrive.”

  -Chad Riedy
Welcome and Introduction

• Why are we here today?

“Vertex is exploiting its monopoly to gouge patients and payers.”

-- Juliana Keeping, Mother of CF patient aged 5

Vertex is generating profits from its current drugs, but its newer drugs should be even more profitable. CEO Jeffrey Leiden noted that Vertex now “has a nice problem of accumulating cash very rapidly.” At the end of 2017 that nice problem translated to over $2 billion in cash, cash equivalents, and marketable securities.

-- Motley Fool

Negotiations came to a head this month when Vertex… pulled the trials because CEPS wanted an 80% discount to the biotech’s latest offer on Orkambi. “If countries can’t recognize the innovation that we can bring – and an 80% discount isn’t recognizing innovation – then it is not a viable business option for our other medicines.”

-- BioCentury
Welcome and Introduction

• Why are we here today?
  – New treatments raise important questions about appropriate use, and cost
  – Need for objective evaluation and public discussion of the evidence on effectiveness and value
  – **Goal**: Accelerate the transition to a sustainable health care system in which all patients are guaranteed access to innovative, high-value care
Welcome and Introduction

• Midwest Comparative Effectiveness Public Advisory Council (CEPAC)

• The Institute for Clinical and Economic Review (ICER)
Sources of Funding, 2018

- **Non-profit foundations**: 78%
- **Manufacturer grants, contracts and contributions**: 9%
- **Contributions from health plans and provider groups**: 3%
- **ICER Policy Summit only**: 10%

*ICER*
Welcome and Introduction

How was the ICER report on CFTR modulators for cystic fibrosis developed?

- Scoping with guidance from patient groups, clinical experts, manufacturers, and other stakeholders
- Evidence analysis by Brown University external consultants and ICER staff
- University of Minnesota cost-effectiveness modeling
- Public comment and revision
- Expert report reviewers
  - Manu Jain, MD, MS
  - Brian O’Sullivan, MD
  - Cystic Fibrosis Foundation
- How is the evidence report structured to support CEPAC voting and policy discussion?
Goal: Sustainable Access to Innovative High-Value Care for All Patients

Long-Term Value for Money
- Comparative Clinical Effectiveness
- Incremental cost-effectiveness
- Other Benefits or Disadvantages
- Contextual Considerations

Short-Term Affordability
- Potential Budget Impact
Agenda

9:30 am: Welcome and Opening Remarks

9:45 am: Presentation of the Evidence

Evidence Review: Ethan Balk, MD, MPH, Brown University
Thomas Trikalinos, MD, PhD, Brown University

Cost Effectiveness: Karen Kuntz, ScD, University of Minnesota

11:00 am: Public Comments and Discussion

11:45 am: Lunch

12:45 pm: Midwest CEPAC Deliberation and Votes

2:15 pm: Policy Roundtable

3:30 pm: Reflections and Wrap Up

4:00 pm: Meeting Adjourned
Evidence Review

Thomas Trikalinos, MD, PhD
Ethan Balk, MD, MPH

Center for Evidence Synthesis in Health
Brown University School of Public Health
Key Review Team Members

Geri Cramer, MBA, RN, ICER
Kristin Mickle, MPH, ICER
Leslie Xiong, BA, ICER
Aqsa Mugal, BA, ICER

Disclosures:
We have no conflicts of interest relevant to this report.
Cystic Fibrosis (CF)

• The most common life-shortening genetic disorder in white people
• Autosomal recessive trait (~1:3000 births, varies by race)
• Progressive disease that adversely affects respiratory function, nutrition, and growth
Pathogenesis

- Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene
- CFTR protein regulates salt transport across cell membranes
- >1800 CFTR mutations associated with CF; ~300 fully characterized
- Result in absent, non-functioning, or abnormally functioning CFTR protein on cell membrane
Clinical Presentation, Respiratory

• Thickened secretions in organ lumens result in progressive organ damage

• Lungs
  – Infections early in life
  – Chronic and exacerbated infection damages bronchial wall and diminishes lung function
  – End stage disease results in lung failure and death
Clinical Presentation, Other

• Gastrointestinal system
  – Pancreatic insufficiency
  – Malnutrition; low weight /growth

• Endocrine system
  – Diabetes

• Reproductive system
  – Low fertility (women), infertility (men)
Management, Disease

• Early diagnosis and treatment may result in better nutritional and pulmonary outcomes later in life

• Symptom and complication control
  – Airway hygiene
  – Nutritional support, diet
  – Insulin
  – Treatment of exacerbations

• Disease modulation
  – CFTR modulators
Management, Other

- Comprehensive monitoring and treatment approach
- Burdensome for patients and caregivers
- Costly
- Adherence can be an issue
CFTR Modulator Drugs

• ↑ Cl⁻ transport through ion channel (gating)
  • Ivacaftor

• ↑ Transport of CFTR protein to cell membrane
  • Lumacaftor
  • Tezacaftor

• Kalydeco® (ivacaftor)  FDA approved 2012
• Orkambi® (lumacaftor/ivacaftor)  approved 2015
• Symdeko™ (tezacaftor/ivacaftor)  approved 2018
Indications

• **Kalydeco** (ivacaftor)
  • “Gating” and residual function mutations
    • To increase ion transport across the cell membrane

• **Orkambi** (lumacaftor/ivacaftor)
  • \(F508\text{del}\) mutation, homozygous (2 copies)
    • To increase protein transfer to and ion transport across the cell membrane

• **Symdeko** (tezacaftor/ivacaftor)
  • \(F508\text{del}\) mutation, homozygous (2 copies)
  • \(F508\text{del}\) mutation, heterozygous (1 copy with a 2\(^{\text{nd}}\) residual function mutation)
  • Other, rarer responsive mutations
    • To increase protein transfer to and ion transport across the cell membrane
Scope of the Review: PICO, 1

- **Population**: Adults and children with CF
  1. Gating and residual function mutations
  2. \textit{F508del} homozygous
  3. \textit{F508del} heterozygous with 2\textsuperscript{nd} residual function mutation

- **Interventions**: Indicated CFTR modulators
  - With best/standard supportive care

- **Comparators**: No or other CFTR modulators
  - With best/standard supportive care
Scope of the Review: PICO, 2

Patient-centered clinical outcomes and harms
- \( \text{ppFEV}_1 \) (% predicted forced expiratory volume 1 sec)
- Pulmonary exacerbations
- Quality of life
  - CFQ-R Respiratory Domain (CF questionnaire, revised)
- Weight and growth
- Death, hospitalizations, lung transplantation
- Harms/adverse events
  - Fertility, pancreatitis, functional status, mental health, work/school, social function, finances, caregiver/family burden
Evidence Base

1. Kalydeco for gating and residual fxn mutations
   - 4 RCTs in 3 specific populations (by mutation)
   - 1 matched cohort in all indicated patients
   - 1 pre-post cohort in all indicated patients (not in report)
     - All ≥ 6 years old

2a. Orkambi for homozygous F508del
   - 3 RCTs (6-11 y/o and ≥12 y/o)

2b. Symdeko for homozygous F508del
   - 1 RCT (mean age 26 y/o)

3. Symdeko for heterozygous F508del
   - 1 cross-over RCT, with Kalydeco (≥12 y/o)
<table>
<thead>
<tr>
<th>Studies</th>
<th>ppFEV&lt;sub&gt;1&lt;/sub&gt; (Abs Difference), % Points</th>
<th>Pulmonary Exacerbations</th>
<th>CFQ-R RD (Difference)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>G551D Mutation (Randomized Controlled Trials)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STRIVE ENVISION</td>
<td>10.4 (8.6, 12.3)</td>
<td>HR 0.46 (0.29, 0.73)</td>
<td>9.7 (6.5 to 13.0)</td>
</tr>
<tr>
<td><strong>Non-G551D Mutation (Randomized Controlled Trial)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KONNECTION</td>
<td>10.7 (7.3, 14.1)</td>
<td>nd</td>
<td>9.6 (4.5, 14.7)</td>
</tr>
<tr>
<td><strong>R117H Mutation (Randomized Controlled Trial)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KONDUCT</td>
<td></td>
<td>HR 0.93 (nd)</td>
<td></td>
</tr>
<tr>
<td>6-11 y/o (N=17)</td>
<td>−6.3 (−12.0, −0.7)</td>
<td>−6.1 (−15.7, 3.4)</td>
<td></td>
</tr>
<tr>
<td>≥18 y/o (N=50)</td>
<td>5.0 (1.2, 8.8)</td>
<td>12.6 (5.0, 20.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Any Indicated Mutation, implied (Matched Cohort Study)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US Cohort</td>
<td></td>
<td>RR 0.64 (0.58, 0.70)</td>
<td></td>
</tr>
</tbody>
</table>

**Abs:** absolute, **HR:** hazard ratio, **nd:** no data (not reported), **ppFEV<sub>1</sub>**: predicted forced expiratory volume in 1 second, **CFQ-R RD:** Cystic Fibrosis Questionnaire-Revised Respiratory Domain (quality of life measure), **RR:** risk ratio, **y/o:** years old.
Kalydeco for Gating and Residual Function Mutations, Other Outcomes

- US Cohort N=1256 vs. 6000 matched controls
  - Any indicated mutation (implied)
  - 1 year follow-up
    - Death: RR 0.41 (0.20, 0.84)
    - Organ Transplant: RR 0.15 (0.04, 0.59)
    - Hospitalization: RR 0.64 (0.58, 0.70)

- US Cohort pre-post Rx N=143 (not in report)
  - Any indicated mutation
  - 1 year periods
    - Hospitalization, all: 55% reduction (MC 38%)
    - Hospitalization, CF: 81% reduction (MC 46%)
      ▪ And associated lower costs
      ▪ Smaller reductions in Medicaid sample (N=100)
## Orkambi & Symdeko for Homozygous F508del

<table>
<thead>
<tr>
<th>Studies</th>
<th>ppFEV₁ (Abs Difference), % Points</th>
<th>Pulmonary Exacerbations (Rate Ratio)</th>
<th>CFQ-R RD (Difference)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Orkambi vs. Placebo</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ratjen et al.</td>
<td>2.4 (0.4, 4.4)</td>
<td>nd</td>
<td>2.5 (−0.4, 5.4)</td>
</tr>
<tr>
<td>TRAFFIC TRANSPORT</td>
<td>2.8 (1.8, 3.8) 42% slower rate of decline</td>
<td>0.61 (0.49, 0.76)</td>
<td>2.2 (0.0, 4.5)</td>
</tr>
<tr>
<td><strong>Symdeko vs. Placebo</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EVOLVE</td>
<td>4.0 (3.1, 4.8)</td>
<td>0.53 (0.34, 0.82)</td>
<td>5.1 (3.2, 7.0)</td>
</tr>
<tr>
<td><strong>Symdeko vs. Orkambi</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evolve vs. Tr/Tr</td>
<td>1.2 (−0.1, 2.5)</td>
<td>0.87 (0.53, 1.42)</td>
<td>2.9 (0.0, 5.8)</td>
</tr>
</tbody>
</table>

**Abs:** absolute, **nd:** no data (not reported), **ppFEV₁:** predicted forced expiratory volume in 1 second, **CFQ-R RD:** Cystic Fibrosis Questionnaire-Revised Respiratory Domain (quality of life measure), **Tr/Tr:** TRAFFIC and TRANSPORT (combined).
### Symdeko for Heterozygous F508del

<table>
<thead>
<tr>
<th>Study</th>
<th>ppFEV$_1$ (Absolute Diff), % Points</th>
<th>Pulmonary Exacerbation, Rate Ratio</th>
<th>CFQ-R Respiratory Domain (Difference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXPAND</td>
<td>6.8 (5.7, 7.8)</td>
<td>0.54 (0.26, 1.13)</td>
<td>11.1 (8.7, 13.6)</td>
</tr>
</tbody>
</table>

**Diff:** difference, **ppFEV$_1$:** predicted forced expiratory volume in 1 second, **CFQ-R RD:** Cystic Fibrosis Questionnaire-Revised Respiratory Domain (quality of life measure).
Harms with CFTR Modulators

• Adverse events generally mild or self-limited
  – No reported deaths ascribed to drugs
• Adverse events common with placebo
  – Often higher than with drugs

• Orkambi
  – Chest tightness: ~10-20%
  – Drug discontinuation due to adverse event: 6%
Controversies and Uncertainties

• Unknown comparative value for several clinical outcomes of interest, particularly non-pulmonary effects

• Long-term effects on health, quality of life, treatment burden, management costs unknown

• Standard of care variable, even in studies and may impact incremental benefit
  – May be a particular issue in US, which lags other comparable countries in health status and survival
Evidence Ratings

• Kalydeco for gating mutation ($G551D, R117H, \text{other}$)
  • "A" (superior, high certainty substantial benefit)
• Orkambi for homozygous $F508del$
  • "B" (incremental, high certainty of small benefit)
• Symdeko for homozygous $F508del$
  • "B+" (incremental or better, moderate certainty of small or substantial benefit, high certainty of at least a small benefit)
• Symdeko for heterozygous $F508del$
  • "B+" (incremental or better, moderate certainty of small or substantial benefit, high certainty of at least a small benefit)
Other Potential Benefits and Contextual Considerations

• If effective, **may reduce burden** of therapy, caregiver/family burden, school/work, social stressors and functional status
  - No evidence for this
  - Caregivers concerned that increased pill burden

• **Health disparities** may be exacerbated among commercially insured

• **Novel treatments**. First to directly target dysfunctional proteins.
Public Comments Received

• Review does not adequately account for disease severity and the multi-system nature of CF
  – Nutrition versus respiratory
  – Other outcomes not in literature (e.g., diabetes)

• Not adequately capturing benefits and risks
  – Orkambi has more side effects than Symdeko
  – ppFEV1 and pulmonary exacerbation definitions
  – Minimally clinical important differences (MCID)
Summary

• Among those ≥6 years old, CFTR modulators generally
  – Improve ppFEV1
  – Reduce rates of pulmonary exacerbations
  – May improve respiratory-related quality of life.
  – May reduce death, transplantation, hospitalizations
    ▪ Most evidence 6-12 months follow-up
    ▪ Some evidence of maintenance of effects for up to 3 years

• Harms appear to be non-serious and self-limited
  – Orkambi has risk of chest tightness, likely resulting in higher rate of discontinuation for adverse events
Cost-Effectiveness

Karen Kuntz, ScD
Kael Wherry, MS
Ian Williamson, MBA

University of Minnesota, School of Public Health
Division of Health Policy and Management
Key Team Members

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 cystic fibrosis patients
Methods in Brief
Methods Overview

- **Comparators**: CFTR drugs + best supportive care (BSC), BSC alone
- **Populations**: Described on next slide
- **Model**: Discrete-time microsimulation model
- **Setting**: United States
- **Perspective**: Payer
- **Time Horizon**: Lifetime
- **Discount Rate**: 3% per year (costs and outcomes)
- **Cycle Length**: Annual

- **Primary Outcomes**:
  - Lifetime cost (2017 US dollars)
  - Quality-adjusted life years (QALYs) gained
  - Life years gained
  - Acute pulmonary exacerbations
  - Incremental cost-effectiveness ratios
Populations and CFTR Modulators

1. **CF individuals with gating mutation**
   - Kalydeco (ivacaftor) at age 2

2. **CF individuals homozygous for \(F508del\) mutation**
   - Orkambi (lumacaftor/ivacaftor) at age 6
   - Symdeko (tezacaftor/ivacaftor) at age 6

3. **CF individuals heterozygous for \(F508del\) mutation with residual function mutation**
   - Symdeko (tezacaftor/ivacaftor) at age 12
   - Kalydeco (ivacaftor) at age 12
Model Schematic

Assign initial patient characteristics
- Start age
- Sex
- ppFEV₁
- Weight-for-age z-score
- Pancreatic sufficiency

Update ppFEV₁
  - Annual decline

Drug Effect
  - Increase in ppFEV₁ and weight-for-age z-score

Drug discontinuation

Quality of Life

Lung transplantation

Pulmonary exacerbations (#)

Cystic fibrosis-related diabetes

B. cepacia infection

Advance 1 year in age

Alive

Dead
CFTR Modulator Effectiveness

• Impact on ppFEV₁
  – Immediate increase in ppFEV₁
  – No change for first two years
  – Annual declines in ppFEV₁, 50% of that without drug

• Impact on weight-for-age z-score
  – Immediate increase in z-score; constant for lifetime

• Independent effect on pulmonary exacerbations
  – Changes in ppFEV₁ reduce PEx
  – We modeled an independent reduction and calibrated to the RR reported in trials
### Direct Costs by Disease Severity

<table>
<thead>
<tr>
<th></th>
<th>ppFEV₁ ≥70%</th>
<th>ppFEV₁ 40%-69%</th>
<th>ppFEV₁ &lt;40%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease Management</strong></td>
<td>$25,367</td>
<td>$33,462</td>
<td>$57,210</td>
</tr>
<tr>
<td><em><em>PEx</em> (age &lt;18)</em>*</td>
<td>$52,988</td>
<td>$83,956</td>
<td>$124,386</td>
</tr>
<tr>
<td><em><em>PEx</em> (age 18+)</em>*</td>
<td>$48,015</td>
<td>$76,322</td>
<td>$109,372</td>
</tr>
<tr>
<td><strong>Lung Transplant</strong></td>
<td></td>
<td>$905,191</td>
<td></td>
</tr>
<tr>
<td><strong>Post-Transplant (Year 1)</strong></td>
<td></td>
<td>$273,665</td>
<td></td>
</tr>
<tr>
<td><strong>Post-Transplant (Year 2+)</strong></td>
<td></td>
<td>$103,913</td>
<td></td>
</tr>
</tbody>
</table>

* PEx = pulmonary exacerbation requiring IV antibiotics
### Economic Inputs: Annual Drug Costs

<table>
<thead>
<tr>
<th>CFTR Modulator Drug</th>
<th>Annual Drug Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kalydeco</td>
<td>$309,842</td>
</tr>
<tr>
<td>Orkambi</td>
<td>$264,086</td>
</tr>
<tr>
<td>Symdeko</td>
<td>$282,656</td>
</tr>
</tbody>
</table>

WAC from REDBOOK; net price from Federal Supply Schedule
Modified Societal Perspective

• Loss of productivity
  – Inability to work (lower unemployment rates)
  – Due to illness (associated with pulmonary exacerbation)

• Caregiver burden
  – No direct evidence on reduction in caregiver burden with CFTRm drugs
  – Evidence that there is no relationship between caregiver burden and ppFEV$_1$
# Clinical Inputs: Quality of Life Values

<table>
<thead>
<tr>
<th>Condition</th>
<th>EQ-5D Utility</th>
<th>Comparable to:</th>
</tr>
</thead>
<tbody>
<tr>
<td>ppFEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>(Schechter 2015)</td>
<td></td>
</tr>
<tr>
<td>&gt;90</td>
<td>0.920</td>
<td></td>
</tr>
<tr>
<td>80-89</td>
<td>0.873</td>
<td></td>
</tr>
<tr>
<td>70-79</td>
<td>0.838</td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>0.801</td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>0.765</td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>0.729</td>
<td></td>
</tr>
<tr>
<td>30-39</td>
<td>0.692</td>
<td></td>
</tr>
<tr>
<td>20-29</td>
<td>0.653</td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>0.625</td>
<td></td>
</tr>
<tr>
<td>Acute Pulmonary Exacerbation</td>
<td>-0.174</td>
<td></td>
</tr>
<tr>
<td>Lung Transplantation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>0.320</td>
<td></td>
</tr>
<tr>
<td>Year 2+</td>
<td>0.838</td>
<td></td>
</tr>
</tbody>
</table>
Results
## Lifetime Health Outcomes

<table>
<thead>
<tr>
<th>Population and Treatment</th>
<th>Average Number of PEx</th>
<th>Total Life Years</th>
<th>Total QALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CF Individuals with a Gating Mutation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSC</td>
<td>32.75</td>
<td>22.16</td>
<td>15.92</td>
</tr>
<tr>
<td>Kalydeco + BSC</td>
<td>18.86</td>
<td>26.52</td>
<td>22.65</td>
</tr>
<tr>
<td><strong>CF Individuals Homozygous for F508del Mutation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSC</td>
<td>26.02</td>
<td>20.77</td>
<td>14.74</td>
</tr>
<tr>
<td>Orkambi + BSC</td>
<td>11.45</td>
<td>24.57</td>
<td>20.21</td>
</tr>
<tr>
<td>Symdeko + BSC</td>
<td>13.36</td>
<td>24.70</td>
<td>20.25</td>
</tr>
<tr>
<td><strong>CF Individuals Heterozygous for F508del with Residual Function Mutation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSC</td>
<td>25.51</td>
<td>18.98</td>
<td>12.92</td>
</tr>
<tr>
<td>Symdeko + BSC</td>
<td>12.68</td>
<td>23.25</td>
<td>18.88</td>
</tr>
<tr>
<td>Kalydeco + BSC</td>
<td>10.85</td>
<td>23.07</td>
<td>18.74</td>
</tr>
</tbody>
</table>
## Lifetime Costs (2017 US dollars)

<table>
<thead>
<tr>
<th>Population and Treatment</th>
<th>CFTR Modulator Drug Cost</th>
<th>Total Direct Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CF Individuals with a Gating Mutation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSC</td>
<td>$0</td>
<td>$2,227,765</td>
</tr>
<tr>
<td>Kalydeco + BSC</td>
<td>$7,443,121</td>
<td>$8,666,308</td>
</tr>
<tr>
<td><strong>CF Individuals Homozygous for F508del Mutation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSC</td>
<td>$0</td>
<td>$2,108,199</td>
</tr>
<tr>
<td>Orkambi + BSC</td>
<td>$5,847,893</td>
<td>$6,983,336</td>
</tr>
<tr>
<td>Symdeko + BSC</td>
<td>$6,290,005</td>
<td>$7,478,684</td>
</tr>
<tr>
<td><strong>CF Individuals Heterozygous for F508del with Residual Function Mutation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSC</td>
<td>$0</td>
<td>$2,081,180</td>
</tr>
<tr>
<td>Symdeko + BSC</td>
<td>$5,934,935</td>
<td>$7,091,919</td>
</tr>
<tr>
<td>Kalydeco + BSC</td>
<td>$6,447,156</td>
<td>$7,557,596</td>
</tr>
</tbody>
</table>
## Overall Incremental Results

<table>
<thead>
<tr>
<th>Treatment vs. BSC</th>
<th>Cost Per LY Gained</th>
<th>Cost Per QALY Gained</th>
<th>Cost Per PEx Averted</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CF Individuals with a Gating Mutation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kalydeco + BSC</td>
<td>$1,476,543</td>
<td>$956,762</td>
<td>$463,571</td>
</tr>
<tr>
<td><strong>CF Individuals Homozygous for F508del Mutation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orkambi + BSC</td>
<td>$1,280,892</td>
<td>$890,739</td>
<td>$334,495</td>
</tr>
<tr>
<td>Symdeko + BSC</td>
<td>$1,367,400</td>
<td>$974,348</td>
<td>$424,212</td>
</tr>
<tr>
<td><strong>CF Individuals Heterozygous for F508del and Residual Function Mutation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symdeko + BSC</td>
<td>$1,174,508</td>
<td>$840,568</td>
<td>$390,600</td>
</tr>
<tr>
<td>Kalydeco + BSC</td>
<td>$1,340,171</td>
<td>$941,110</td>
<td>$373,541</td>
</tr>
</tbody>
</table>
Sensitivity Analyses (Symdeko, homozygous)

- Independent PEx Reduction [0.5-1.0]
- Discount Rate [1%-5%]
- Slope of Utility Function [0.002-0.005]
- Avg. Annual BSC Costs [$49,979-$149,937]
- Avg. PEx Cost [$41,253-$123,759]
- Absolute ppFEV1 Gain [3.1%-4.8%]
- Avg. Transplant Costs [$589,428-$1,768,284]
- Avg. Annual DMCosts [$19,340-$58,020]

PEx: acute pulmonary exacerbation; BSC: best supportive care; DM: disease management; Probability of transplant among individuals with ppFEV$_1$<30%
Probabilistic Sensitivity Analysis (PSA) (Kalydeco for gating mutations)

Incremental Costs ($millions) vs QALY Gains

$150,000/QALY
Scenario Analyses – Modified Societal Perspective

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

• Long-Term Effectiveness Assumption
  – **Best case**: No long-term decline in ppFEV$_1$ with CFTR modulator drug

• ppFEV$_1$ Recovery After Pulmonary Exacerbation
  – **Best case**: There is a 5% absolute decline in ppFEV$_1$ for each pulmonary exacerbation experienced

• Independent Utility Effect
  – **Best case**: CFTR modulator drugs result in a 5% increase in utility, above that due to lung function improvements
Scenario Analyses Results (Best Case)

ICER ($/QALY, in thousands)

- Kalydeco (1)
- Orkambi
- Symdeko (2)
- Kalydeco (3)
- Symdeko (3)

LT Eff  ppFEV1 Recovery  NR Utility
Limitations

• Modeled lifetime outcomes derived from short-term trial outcomes

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

• We did not have a direct measure of CFTR modulator benefit on utilities
Public Comments Received

- QALY collapses multifactorial benefits of CFTR modulator into single outcome measure that does not capture overall impact to multiple organ systems
- Did not include societal perspective in base case
- Did not include potential changes in cost of CFTRm over time
Summary

• CFTR modulator therapies plus best supportive care improves health outcomes compared with best supportive care alone.

• However, in proportion to the clinical benefits, the added costs of CFTR modulator therapies exceeds commonly used thresholds for cost-effectiveness.

• The modified societal perspective scenario analysis did not notably improve the cost-effectiveness of CFTR modulator therapies.
A classification of CFTR mutations

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>CFTR is created, reaches cell surface and functions properly, allowing transfer of chloride and water.</td>
<td>G542X, W1282X, R553X</td>
</tr>
<tr>
<td>Class I</td>
<td>No functional CFTR created.</td>
<td>F508del, N1303K, I507del</td>
</tr>
<tr>
<td>Class II</td>
<td>CFTR protein is created, but misfolded, keeping it from reaching the cell surface.</td>
<td>G551D, S549N, V520F, R117H</td>
</tr>
<tr>
<td>Class III</td>
<td>CFTR protein is created and reaches cell surface, but the gate does not function properly.</td>
<td>R117H, D1152H, R347P</td>
</tr>
<tr>
<td>Class IV</td>
<td>The opening in the CFTR protein ion channel is faulty.</td>
<td>3849+10kbC-&gt;T, 2789+5G-&gt;A, A455E</td>
</tr>
<tr>
<td>Class V</td>
<td>CFTR is created in insufficient quantities.</td>
<td></td>
</tr>
</tbody>
</table>
Key Model Assumptions and Inputs

- \( \text{ppFEV}_1 \) does not increase over time

- Best supportive care is the same in all treatment arms (conditional on \( \text{ppFEV}_1 \) category; as \( \text{ppFEV}_1 \) worsens, supportive care costs increase)

- Treatment discontinuation rates are same as reported in trials, with no further discontinuation after end of trials’ time horizon
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Increase in ppFEV1</th>
<th>Change in weight-for-age z-score</th>
<th>Pulmonary exacerbation RR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CF Patients with Gating Mutation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kalydeco</td>
<td>10.0 (4.5-15.5)</td>
<td>0.35 (0.20-0.51)</td>
<td>0.56</td>
</tr>
<tr>
<td><strong>CF Patients Homozygous for <em>F508del</em> Mutation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orkambi</td>
<td>2.8 (1.8-3.8)</td>
<td>Same as above</td>
<td>0.44</td>
</tr>
<tr>
<td>Symdeko</td>
<td>4.0 (3.1-4.8)</td>
<td>Same as above</td>
<td>0.54</td>
</tr>
<tr>
<td><strong>CF Patients Heterozygous for <em>F508del</em> with Residual Mutation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symdeko</td>
<td>6.8 (5.7-7.8)</td>
<td>Same as above</td>
<td>0.54</td>
</tr>
<tr>
<td>Kalydeco</td>
<td>4.7 (3.7-5.8)</td>
<td>Same as above</td>
<td>0.46</td>
</tr>
</tbody>
</table>

*evidence report*
## Threshold Price Analysis

<table>
<thead>
<tr>
<th></th>
<th>Annual WAC</th>
<th>Annual Net Price</th>
<th>$50K/ QALY</th>
<th>$100K/ QALY</th>
<th>$150K/ QALY</th>
<th>$500K/ QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CF Individuals with a Gating Mutation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kalydeco</td>
<td>$311,719</td>
<td>$309,842</td>
<td>$55,145</td>
<td>$69,142</td>
<td>$83,146</td>
<td>$181,149</td>
</tr>
<tr>
<td>Orkambi</td>
<td>$272,886</td>
<td>$264,090</td>
<td>$55,562</td>
<td>$67,820</td>
<td>$80,063</td>
<td>$165,824</td>
</tr>
<tr>
<td>Symdeko</td>
<td>$292,258</td>
<td>$282,850</td>
<td>$53,210</td>
<td>$65,467</td>
<td>$77,718</td>
<td>$163,501</td>
</tr>
<tr>
<td><strong>CF Individuals Homozygous for F508del Mutation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orkambi</td>
<td>$272,886</td>
<td>$264,090</td>
<td>$55,562</td>
<td>$67,820</td>
<td>$80,063</td>
<td>$165,824</td>
</tr>
<tr>
<td>Symdeko</td>
<td>$292,258</td>
<td>$282,850</td>
<td>$53,210</td>
<td>$65,467</td>
<td>$77,718</td>
<td>$163,501</td>
</tr>
<tr>
<td><strong>CF Individuals Heterozygous for F508del and Residual Function Mutation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kalydeco</td>
<td>$311,719</td>
<td>$309,842</td>
<td>$60,295</td>
<td>$74,175</td>
<td>$88,054</td>
<td>$185,211</td>
</tr>
<tr>
<td>Symdeko</td>
<td>$292,258</td>
<td>$282,850</td>
<td>$57,921</td>
<td>$71,969</td>
<td>$86,016</td>
<td>$184,356</td>
</tr>
</tbody>
</table>

Discount to achieve $500,000/QALY

Discount: 42% for Kalydeco
Discount: 39% for Orkambi
Discount: 43% for Symdeko
Discount: 41% for Kalydeco
Discount: 37% for Symdeko
Manufacturer Public Comment and Discussion
Vertex Pharmaceuticals
Public Comment and Discussion
Conflicts of interest:

• Employee of Cystic Fibrosis Foundation (CFF), which provides research and clinical trial support to health care companies, including Vertex Pharmaceuticals, that results in the Foundation’s receipt of payments, equity interests, and/or fees for service >$5,000 from Vertex Pharmaceuticals and other healthcare companies.

• Dr. Boyle is also an uncompensated Adjunct Professor of Medicine at Johns Hopkins University.
Siri Vaeth, MSW  
Associate Director  
Cystic Fibrosis Research Inc.

Conflicts of interest:
• CFRI provides a broad range of educational, psychosocial, and advocacy programs that receive grant funding from several pharmaceutical companies, including Vertex.
  − These grants are in support of specific CFRI programmatic goals and objectives to serve the nationwide cystic fibrosis community and have no relationship to specific drug therapies.
Chad Riedy
Person with Cystic Fibrosis
National Advocacy Co-Chair, Cystic Fibrosis Foundation

Conflicts of interest:
• National Advocacy Co-Chair at CFF, volunteer position.
• CFF paid for travel expenses to this meeting.
Conflicts of interest:
• No relevant conflicts of interest to report
Juliana Keeping
Parent of a Child with Cystic Fibrosis
Communications Director, Patients for Affordable Drugs

Conflicts of interest:
• Owns shares of stock in Vertex Pharmaceuticals
• Patients for Affordable Drugs is funded in part by the Laura and John Arnold Foundation, which also provides funding to ICER.
Lunch Meeting will resume at 12:30 pm
Voting Questions

WIFI network: TritonNet
Login ID: gst-cianciolola
Password: +3$nTaK=
What is Missouri’s official state insect?

A. 7-spotted ladybug
B. European honey bee
C. Tarantula hawk wasp
D. Monarch butterfly
1. For individuals with approved gating, non-gating, and residual function mutations (including but not limited to G551D and R117H), is the evidence adequate to demonstrate that the net health benefit of treatment with Kalydeco (ivacaftor) with best supportive care is greater than that of best supportive care alone?

A. Yes
B. No
2. For individuals who are homozygous for the F508del mutation, is the evidence adequate to demonstrate that the net health benefit of treatment with Orkambi (lumacaftor/ivacaftor) with best supportive care is greater than that of best supportive care alone?

A. Yes
B. No
3. For individuals who are homozygous for the F508del mutation, is the evidence adequate to demonstrate that the net health benefit of treatment with Symdeko (tezacaftor/ivacaftor) with best supportive care is greater than that of best supportive care alone?

A. Yes
B. No
4. For individuals who are homozygous for the F508del mutation, is the evidence adequate to distinguish the net health benefit between treatment with Symdeko with best supportive care and Orkambi with best supportive care?

A. Yes  
B. No
5. For individuals who are candidates for Symdeko combination therapy because they carry one F508del mutation and residual function mutation that is potentially responsive to Symdeko, is the evidence adequate to demonstrate that the net health benefit of treatment with Symdeko with best supportive care is greater than that of best supportive care alone?
A. Yes
B. No
When compared to best supportive care, does Kalydeco, Orkambi, or Symdeko offer one or more of the following “other benefits”? (select all that apply)

A. Reduced complexity that will significantly improve patient outcomes.
B. Reduce important health disparities
C. Significantly reduce caregiver/family burden
D. Novel mechanism of action or approach...
E. Significant impact on improving return to work/overall productivity
F. Significant positive impact outside the family, including on schools and/or communities.
G. Significant impact on the entire “infrastructure” of care...
H. Other...
Are any of the following contextual considerations important in assessing Kalydeco, Orkambi, or Symdeko’s long-term value for money in patients? (select all that apply)

A. Care of individuals with a condition of particularly high severity
B. Care of individuals with condition with high lifetime burden of illness.
C. First to offer any improvement
D. Compared to best supportive care, there is significant uncertainty about the long-term risk of serious side effects
E. Compared to best supportive care, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
F. Additional considerations…
6. For individuals with approved gating, non-gating, and residual function mutations (including but not limited to G551D and R117H), given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits and contextual considerations, what is the long-term value for money of Kalydeco with best supportive care compared with best supportive care alone?

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

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

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

A. High
B. Intermediate
C. Low
Policy Roundtable
## Policy Roundtable Participants

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

- Meeting recording posted to ICER website next week
- Final Report published on/about June 7
  - Includes description of Midwest CEPAC votes, deliberation, policy roundtable discussion
- Materials available at:
  https://icer-review.org/topic/cystic-fibrosis/
Adjourn