Zephyr Endobronchial Valve (EBV)

PMA P070025
Anesthesiology and Respiratory Devices
Advisory Panel Presentation
December 5, 2008
Emphasys Medical

John McCutcheon
President and CEO
Emphasys Medical

- Founded in 2000
- Sole product is Zephyr EBV System
- 48 Employees
- Located in Redwood City, CA
- CE Mark
Proposed Indication:
“To improve FEV$_1$ and six minute walk test distance in patients with severe, heterogeneous emphysema who have received optimal medical management.”
Zephyr EBV FDA Panel Presenters

Clinical Problem, Device, Trial Design
Gerard Criner, MD
Temple University

Baseline Characteristics, Conduct of Study and Safety
Armin Ernst, MD
Beth Israel Deaconess Medical Center

Efficacy Results
Frank Sciurba, MD
University of Pittsburgh

Conclusion and Post Approval Study
Gerard Criner, MD
Temple University
Additional Advisors

**Investigators**
- Geoff McLennan, MD, PhD
  University of Iowa
- Charlie Strange, MD
  Medical Univ. South Carolina

**Imaging Core Lab**
- Jonathan Goldin, MD
  UCLA Medical Center

**Statistician**
- Richard Chiacchierini, PhD
  RPC Consulting

**CEC Chair**
- Christopher Cooper, MD
  UCLA Medical Center

**DSMB Chair**
- Robert Wise, MD
  Johns Hopkins University
Clinical Problem

Gerard Criner, MD, FCCP
Professor of Medicine
Florence P. Bernheimer Distinguished Service Chair
Director, Pulmonary and Critical Care Medicine
and Temple Lung Center
Temple University School of Medicine
Emphysema

• Emphysema is a progressive, debilitating disorder that markedly impairs quality of life

• Pharmacologic intervention in patients with predominately emphysema is poorly described, but believed to be of limited value

• Only smoking cessation alters the decline in lung function

• Only supplemental oxygen can improve survival. Benefits limited to most severe subset
Pathophysiological Effects of Emphysema

• Irreversible destruction of lung tissue; involves alveolus and small airway
  – Airflow obstruction
  – Impaired gas exchange
  – Gas trapping impairs lung, chest and respiratory muscle mechanics

• Significant patient variability in severity and distribution of extent of emphysema (e.g., heterogeneity)
The Inactivity - Dyspnea Spiral

- Hyperinflation
- Increased Dyspnea
- Increased Dyspnea
- Mortality
- Deconditioning
- Decreased Activity
Treatment Options

GOLD* Stage:
- I Mild
  - Typically seek medical attention
- II Moderate
- III Severe
  - ↑ dyspnea
  - ↓ exercise capacity
  - repeated exacerbations
- IV Very Severe
  - Appreciably impaired
  - Exacerbations may be life-threatening

Influenza vaccine
Short acting bronchodilator

+ Long term oxygen
+ Inhaled glucocorticosteroids
+ Long acting bronchodilators
+ Pulmonary rehabilitation

*Global Initiative for Chronic Obstructive Lung Disease
Disease Progresses Despite Maximal Therapy

Mortality: ~40% in 5 years

Exercise (6MWT): ↓ 63.7 m (-17%) in 2 years

Lung Volume Reduction Surgery: A Surgical Treatment of Hyperinflation
National Emphysema Treatment Trial (NETT)

Unblinded, multicenter, randomized clinical trial comparing medical treatment with lung volume reduction surgery (LVRS) to medical treatment alone in patients with severe emphysema.

Primary endpoints: Survival, Maximum exercise

Secondary endpoints: Lung function, QOL, 6MWT, Cost-effectiveness
NETT Summary

Randomized 1218 patients; identified subgroups

- Survival
- Exercise capacity
- Quality of life

Median follow-up of 29 mos (2.4 yrs) as of Dec 02
Only 60% of patients reached 2 yr testing mark
NETT Subgroup Treatment Effects

- Non High Risk Patients: Mortality RR = 0.89; Exercise OR = 6.78; SGRQ OR = 5.06
  - **Upper Lobe/ Low Exercise**: Mortality RR = 0.47; exercise OR = \(\infty\); SGRQ OR = 8.38
  - **Upper Lobe/ High Exercise**: Mortality RR = 0.98; Exercise OR = 5.81; SGRQ OR = 5.67

- Non Upper Lobe/Low Exercise: Mortality RR = 0.81; Exercise OR = 1.77; SGRQ OR = 7.35
- Non Upper Lobe/High Exercise: Mortality RR = 2.06; Exercise OR = 0.90; SGRQ OR = 1.35

Heterogeneity of Emphysema on HRCT Predicts LVRS Response
**NETT: Complications of LVRS**

<table>
<thead>
<tr>
<th>Complication</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>90 day mortality</td>
<td>5.2%</td>
</tr>
<tr>
<td>30 day morbidity</td>
<td></td>
</tr>
<tr>
<td>Air leaks</td>
<td>90% (50% &gt; 7 days)</td>
</tr>
<tr>
<td>Major pulmonary</td>
<td>30%</td>
</tr>
<tr>
<td>(Re-intubation, pneumonia, tracheostomy, ventilator support, failure to wean)</td>
<td></td>
</tr>
<tr>
<td>Major cardiovascular</td>
<td>20%</td>
</tr>
<tr>
<td>(Arrhythmia, MI, pulmonary embolus)</td>
<td></td>
</tr>
</tbody>
</table>

→ In 2007, only 104 Medicare patients underwent LVRS

NETT Efficacy: 6 Months

NIH/CMS Sponsored Study of LVRS (n = 1218)

Weighing the Clinical Balance: Benefits vs. Complications of LVRS

LVRS Benefits
- ↑ lung function,
- ↑ exercise performance
- ↑ QOL
- ? decreased mortality

LVRS Risks
- peri-procedural mortality
- air leaks
- pain
- respiratory tract infection
- prolonged hospitalization

Symptomatic patients despite maximal medical treatment
Treatment Options

Surgical interventions:
- LVRS or transplant

Unmet Clinical Need
- Long term oxygen
- Inhaled glucocorticosteroids

Influenza vaccine
- Short acting bronchodilator
- Pulmonary rehabilitation

Severely Impaired

GOLD* Stage:
- I Mild
- II Moderate
- III Severe
- IV Very Severe

*Global Initiative for Chronic Obstructive Lung Disease
Endobronchial Valve Therapy
Zephyr Endobronchial Valve (EBV)

- Implantable one-way valve
- Modifies airflow in lung
- Bronchoscopic delivery
- Performed under local or general anesthesia
- Removable
Procedure Overview

- Prevents inspiratory inflow
- Allows trapped gas / fluids to escape
- Seals and vents
- Multiple valves placed in segmental bronchi
- Isolates diseased target lobe
EBV Procedure Overview

<table>
<thead>
<tr>
<th>Delivery</th>
<th>Deployment</th>
<th>Inspiration</th>
<th>Expiration</th>
</tr>
</thead>
</table>

24
Before and After EBV
Right Upper Lobe Procedure

Before 1 Month After
Before and After EBV
Right Upper Lobe Procedure

Before 1 Month After
Zephyr EBV Removal
Zephyr Endobronchial Valve (EBV)

IDE Clinical Trial Design – G020230

VENT: Endobronchial Valve for Emphysema Treatment Trial
### 2003 FDA Advisory Panel

<table>
<thead>
<tr>
<th>Trial Design</th>
<th>Panel Recommendation</th>
<th>VENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target patient population</td>
<td>Similar to NETT</td>
<td>✓</td>
</tr>
<tr>
<td>Endpoints</td>
<td>Physiologic, exercise tolerance and clinical endpoints</td>
<td>✓</td>
</tr>
<tr>
<td>Duration</td>
<td>Efficacy: 6 months</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Safety: 12 months</td>
<td>✓</td>
</tr>
<tr>
<td>Control</td>
<td>Optimal medical management (i.e., no sham) w/pulmonary rehabilitation</td>
<td>✓</td>
</tr>
</tbody>
</table>
## Methodology

<table>
<thead>
<tr>
<th>Methodology Area</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterogeneous Emphysema</td>
<td>- Digital HRCT</td>
</tr>
<tr>
<td></td>
<td>- Scored by Core Lab</td>
</tr>
<tr>
<td></td>
<td>- Target lobe — adjacent lobe % emphysema</td>
</tr>
<tr>
<td>Pulmonary Rehabilitation</td>
<td>- 6 - 8 weeks</td>
</tr>
<tr>
<td></td>
<td>- 12 - 18 sessions</td>
</tr>
<tr>
<td></td>
<td>- Upper and lower limb strength and endurance</td>
</tr>
<tr>
<td>Optimal Medical Management</td>
<td>- Smoking cessation</td>
</tr>
<tr>
<td></td>
<td>- Bronchodilator therapy</td>
</tr>
<tr>
<td></td>
<td>- Vaccination</td>
</tr>
<tr>
<td></td>
<td>- Optimized oxygen therapy</td>
</tr>
<tr>
<td>Sample Size Calculation</td>
<td>Based on assumption of $15 \pm 33.7%$ for FEV$_1$</td>
</tr>
<tr>
<td></td>
<td>and $17 \pm 41.5%$ for 6MWT. Both had very large variance assumptions.</td>
</tr>
</tbody>
</table>
Zephyr EBV VENT Pivotal Trial

Prospective RCT at 31 US Centers
321 Patients
Heterogeneous Emphysema

Pulmonary Rehab
and Optimal Medical Management

Baseline Testing

Zephyr EBV +
Optimal Medical Management
n = 220

2:1 Randomization

Optimal Medical Management
n = 101
Key Study Entrance Criteria

**Inclusion**
- 40 to 75 years of age
- BMI ≤ 31.1 (men)
  BMI ≤ 32.3 (women)
- Nonsmoking for 4 months
- Heterogeneous emphysema based on HRCT
- 15% < FEV₁ < 45% predicted
- TLC > 100% predicted
- RV > 150% predicted
- Post rehabilitation 6MWT > 140m

**Exclusion**
- Alpha-1 antitrypsin deficiency
- Evidence of large bullae
- Sputum production > 60 ml / day
- Significant bronchiectasis
- Recurrent respiratory infections requiring hospitalization
- Unable to complete 3 minutes unloaded pedaling on cycle ergometry
- DLCO < 20% predicted value
- Arrhythmia, recent MI
- Pulmonary hypertension

⇒ Mirrors NETT Criteria
Primary Endpoint Considerations

Challenges are well recognized:

NIH\textsuperscript{1}: “No single parameter in patients with COPD is sufficient to be considered the gold standard to assess outcome”

FDA\textsuperscript{2}: “Six Minute Walk test ...may prove difficult in standardizing and garnering consistent results over time. These factors may limit the sensitivity of these measures...since true, but small, clinical benefits may be obscured by measurement noise”

FDA\textsuperscript{2}: “..some [treatments] may have relatively small, but statistically significant, effects on a single measure ... This may be because [of]....the inherent complexity and heterogeneity of COPD. In such a situation, two efficacy endpoints may need to be declared ...to support efficacy.”

\textsuperscript{1} Fishman, AP, 1994
\textsuperscript{2} FDA Draft Guidance for Industry: Chronic Obstructive Pulmonary Disease; Nov 2007
Co-primary Efficacy Endpoints

Percent change in FEV$_1$ from baseline to 6 months

and

Percent change in 6MWT from baseline to 6 months

Analysis Plan Definition of Study Success

“For effectiveness, the differences between arms for the percent change from baseline at 180 days for both FEV$_1$ and 6MWT reach statistical significance (one-sided test at $p < 0.025$) in favor of the treatment group.”
## Secondary Efficacy Endpoints

<table>
<thead>
<tr>
<th>Secondary Efficacy Endpoints</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGRQ - St. George’s Respiratory Questionnaire</td>
<td>Disease-specific QOL</td>
</tr>
<tr>
<td>mMRC - Modified Medical Research Council</td>
<td>Dyspnea</td>
</tr>
<tr>
<td>Cycle Ergometry Maximum Workload</td>
<td>Exercise tolerance</td>
</tr>
<tr>
<td>Supplemental Oxygen Utilization</td>
<td>Daily O₂ consumption</td>
</tr>
</tbody>
</table>

→ To control for multiplicity, these four were prospectively chosen from the original nine.
Composite Index: BODE

• Background
  – Developed in response to limitations inherent in using single endpoint to assess a multidimensional disease

• Calculation
  – 10 point scale based on values to 4 key variables
    B – Body Mass Index (BMI)
    O – Obstructive Airway Disease (FEV$_1$)
    D – Dyspnea (mMRC)
    E – Exercise Tolerance (6MWT)
  – Lower score is better

→ Integrates both FEV$_1$ and 6MWT
BODE vs. FEV\textsubscript{1} Predictive of Survival

Baseline BODE

A

Baseline FEV\textsubscript{1}

B

Primary Safety Endpoint
Major Complications Composite (MCC)

Evaluated at 6 months and 12 months

- Death
- Pneumonia distal to valve
- Respiratory failure with ≥ 24 hours ventilation
- Pneumothorax / air leak > 7 days
- Massive hemoptysis (> 300 ml)
- Empyema

→ Higher rates were assumed given active intervention vs. non-active control
Study Oversight and Management

• Independent Clinical Events Committee
  – Adjudicated severity and relatedness of all adverse events

• Independent Data Safety Monitoring Board
  – Decisions to halt / continue trial

• Independent Statistical Analysis

• HRCT Core lab (UCLA)

• QOL Core Labs (UCSD)
Study Results: Conduct of Study, BL Characteristics, and Safety

Armin Ernst, MD, FCCP
Chief, Interventional Pulmonology
Beth Israel Deaconess Medical Center
Associate Professor of Medicine and Surgery
Harvard Medical School
VENT: Summary Findings

Positive Trial: Primary Endpoints Met

• Efficacy
  – Demonstrated volume reduction / redistribution
  – Superiority in both co-primary endpoints: FEV$_1$ and 6MWT at 6 months
  – Superiority in all four secondary endpoints at 6 months
  – Superiority in composite endpoint: BODE

• Safety
  – Higher MCC rate (ns)
  – Equivalent 1 year mortality rate
RESULTS: Baseline Characteristics
Baseline Characteristics Well Matched

<table>
<thead>
<tr>
<th></th>
<th>Zephyr EBV</th>
<th>Control</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (% male)</td>
<td>60.5%</td>
<td>48.5%</td>
<td>0.052</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65.3</td>
<td>64.9</td>
<td>ns</td>
</tr>
<tr>
<td>History of smoking (yes)</td>
<td>99.6%</td>
<td>98.0%</td>
<td>ns</td>
</tr>
<tr>
<td>Pack Years</td>
<td>63.3</td>
<td>61.7</td>
<td>ns</td>
</tr>
<tr>
<td>Continuous O₂</td>
<td>43.9%</td>
<td>41.7%</td>
<td>ns</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73.1</td>
<td>71.7</td>
<td>ns</td>
</tr>
<tr>
<td>Height (meters)</td>
<td>1.7</td>
<td>1.7</td>
<td>ns</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.1</td>
<td>24.8</td>
<td>ns</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7.7%</td>
<td>5.0%</td>
<td>ns</td>
</tr>
<tr>
<td>Abnormal ECG</td>
<td>45.9%</td>
<td>42.6%</td>
<td>ns</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (mmHg)</td>
<td>129.1</td>
<td>129.9</td>
<td>ns</td>
</tr>
<tr>
<td>Diastolic (mmHg)</td>
<td>73.8</td>
<td>74.6</td>
<td>ns</td>
</tr>
</tbody>
</table>

→ Only gender approaches significance, but not predictive of outcomes in multivariate analysis
Baseline Lung Function Well Matched

<table>
<thead>
<tr>
<th></th>
<th>Zephyr EBV Mean</th>
<th>Control Mean</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁ (liters)</td>
<td>0.87</td>
<td>0.84</td>
<td>ns</td>
</tr>
<tr>
<td>FEV₁ (% Predicted)</td>
<td>30%</td>
<td>30%</td>
<td>ns</td>
</tr>
<tr>
<td>FVC (liters)</td>
<td>2.71</td>
<td>2.62</td>
<td>ns</td>
</tr>
<tr>
<td>FVC (% Predicted)</td>
<td>70%</td>
<td>70%</td>
<td>ns</td>
</tr>
<tr>
<td>FEV₁ / FVC</td>
<td>0.33</td>
<td>0.33</td>
<td>ns</td>
</tr>
<tr>
<td>RV (% Predicted)</td>
<td>216%</td>
<td>212%</td>
<td>ns</td>
</tr>
<tr>
<td>TLC (% Predicted)</td>
<td>124%</td>
<td>125%</td>
<td>ns</td>
</tr>
<tr>
<td>RV / TLC</td>
<td>0.63</td>
<td>0.63</td>
<td>ns</td>
</tr>
<tr>
<td>DLCO (% Predicted)</td>
<td>33%</td>
<td>36%</td>
<td>ns</td>
</tr>
</tbody>
</table>

→ No significant differences
Consistent with severe emphysema population
### Other Baseline Variables Well Matched

<table>
<thead>
<tr>
<th></th>
<th>Zephyr EBV Mean</th>
<th>Control Mean</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO₂ (mmHg)</td>
<td>69.1</td>
<td>68.4</td>
<td>ns</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>40.5</td>
<td>41.6</td>
<td>0.044</td>
</tr>
<tr>
<td>pH</td>
<td>7.4</td>
<td>7.4</td>
<td>ns</td>
</tr>
<tr>
<td>Oxygen Saturation</td>
<td>93%</td>
<td>93%</td>
<td>ns</td>
</tr>
<tr>
<td>Six Minute Walk Test (m)</td>
<td>334</td>
<td>351</td>
<td>ns</td>
</tr>
<tr>
<td>Cycle Ergometry (max. watts)</td>
<td>45</td>
<td>43</td>
<td>ns</td>
</tr>
<tr>
<td>SGRQ</td>
<td>51.5</td>
<td>50.1</td>
<td>ns</td>
</tr>
<tr>
<td>mMRC</td>
<td>1.7</td>
<td>1.7</td>
<td>ns</td>
</tr>
<tr>
<td>BODE</td>
<td>4.4</td>
<td>4.2</td>
<td>ns</td>
</tr>
</tbody>
</table>

→ Only statistically significant difference = PaCO₂, but not predictive of outcomes in multivariate analysis
VENT Enrolled Patients with Severe and Very Severe Emphysema

VENT Mean 
FEV$_1$ % Predicted = 30%

% of VENT Pts: 46% 54%

GOLD Stage*: I Mild II Moderate III Severe IV Very Severe

FEV$_1$ / FVC ratio: < 70% < 70% < 70% < 70%

FEV$_1$ % Predicted: ≤ 80% 50% ≤ FEV$_1$ < 80% 30% ≤ FEV$_1$ < 50% FEV$_1$ ≤ 30%

GOLD Workshop Report, Management of COPD, March 8, 2004
RESULTS: Conduct of Study
Follow-up Windows & Missing Data

- Protocol window narrowly defined: 6 mo +/- 14 days
- Completed Cases (extended window): 6 mo -30 / +45 days
- Benchmark NETT: 6 mo +/- 91 days
- VENT rates (20%) consistent with other landmark trials in this patient population such as TORCH, UPLIFT, OPTIMAL, etc.

→ Sensitivity analysis – primary endpoint results consistent across windows

** Wedzicha et al, INSPIRE AmJRespCCM Vol 177: 19-26, 2008
Eligibility Violations

• Inclusion / Exclusion Violations
  - 23 during initial screening, but eligible at enrollment
  - At baseline: 39 / 321 (12.1% of patients)

• Small, nominal differences between value and eligibility criterion
  – 11 Blood tests (Cotinine, PaCO\textsubscript{2}, PaO\textsubscript{2})
  – 24 Plethysmography
  – 5 Spirometry
  – 9 Other (PR, Vaccination, Hypertension, BMI, DLco)

• Co-primary endpoints met with or without eligibility violations
Protocol Deviations

• Protocol deviations in 2,492 of 79,240 (3.1%) monitored fields over course of study

• Typically minor

• Balanced between arms

• Co-primary endpoints met with and without “clinically important” deviations
RESULTS: Safety
## Analysis Populations

<table>
<thead>
<tr>
<th>Study Population and Definition</th>
<th>EBV n (%)</th>
<th>Control n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent to Treat (ITT)</td>
<td>220 (100%)</td>
<td>101 (100%)</td>
</tr>
<tr>
<td>All randomized subjects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modified Intent to Treat (mITT)</td>
<td>214 (97.3%)</td>
<td>87 (86.1%)</td>
</tr>
<tr>
<td>Treatment: Patients receiving treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control : Patients with ≥ 1 follow-up visit</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

→ ITT population used for primary efficacy  
mITT population used for safety analysis
Safety Data Review Outline

Review four categories of events:

1. Major Complications Composite (MCC) events
2. Non-MCC adverse events
3. Other events unique to treatment arm
4. Rehospitalizations
## Primary Safety Endpoint – MCC

<table>
<thead>
<tr>
<th>Condition</th>
<th>EBV n = 214</th>
<th>Control n = 87</th>
<th>p value</th>
<th>EBV n = 214</th>
<th>Control n = 87</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Complication Composite</td>
<td>6.1%</td>
<td>1.2%</td>
<td>0.08</td>
<td>10.3%</td>
<td>4.6%</td>
<td>0.17</td>
</tr>
<tr>
<td>Death</td>
<td>2.8%</td>
<td>0.0%</td>
<td>0.19</td>
<td>3.7%</td>
<td>3.5%</td>
<td>1.00</td>
</tr>
<tr>
<td>Pneumonia distal to valve</td>
<td>1.4%</td>
<td>NA</td>
<td>----</td>
<td>4.2%</td>
<td>NA</td>
<td>----</td>
</tr>
<tr>
<td>Respiratory failure ≥ 24 hours ventilation</td>
<td>1.9%</td>
<td>1.2%</td>
<td>1.00</td>
<td>2.8%</td>
<td>2.3%</td>
<td>1.00</td>
</tr>
<tr>
<td>Pneumothorax / air leak &gt; 7 days</td>
<td>1.4%</td>
<td>1.2%</td>
<td>1.00</td>
<td>1.9%</td>
<td>1.2%</td>
<td>1.00</td>
</tr>
<tr>
<td>Massive hemoptysis (&gt; 300ml)</td>
<td>0.5%</td>
<td>0.0%</td>
<td>1.00</td>
<td>0.5%</td>
<td>0.0%</td>
<td>1.00</td>
</tr>
<tr>
<td>Empyema</td>
<td>0.0%</td>
<td>0.0%</td>
<td>----</td>
<td>0.0%</td>
<td>0.0%</td>
<td>----</td>
</tr>
</tbody>
</table>

→ MCC nominally higher as anticipated (ns)

Per subject occurrence rates
Distal Pneumonia Details

9 – Patients (4.2 %)

9 - Drug Therapy

3 - Valve Removal

3 - Resolved

5 - Resolved

1 – Ongoing at Exit

- Managed effectively with antibiotics and / or valve removal
- None required ventilator support
- One ongoing at study exit
  - Started day 356, discharged on oral antibiotics
## Treatment Arm Mortality Details

<table>
<thead>
<tr>
<th>Cause of Death (through 1 Year)</th>
<th>Days Post Treatment</th>
<th>Device Related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic colitis, sepsis, colectomy, respiratory failure</td>
<td>21</td>
<td>no</td>
</tr>
<tr>
<td>Massive hemoptysis, respiratory failure (detailed on next slide)</td>
<td>22</td>
<td>yes</td>
</tr>
<tr>
<td>Respiratory failure secondary to COPD</td>
<td>121</td>
<td>no</td>
</tr>
<tr>
<td>Emphysema with subpleural bullae</td>
<td>131</td>
<td>no</td>
</tr>
<tr>
<td>Stage IV adenocarcinoma: liver, adrenal glands, lymph glands</td>
<td>147</td>
<td>no</td>
</tr>
<tr>
<td>Respiratory failure secondary to a COPD exacerbation</td>
<td>161</td>
<td>no</td>
</tr>
<tr>
<td>COPD exacerbation, community acquired pneumonia</td>
<td>230</td>
<td>no</td>
</tr>
<tr>
<td>Metastatic cancer, liver</td>
<td>284</td>
<td>no</td>
</tr>
</tbody>
</table>

→ Only one event rated possibly or probably device related per CEC
**Single Case of Massive Hemoptysis**

<table>
<thead>
<tr>
<th>Timing*</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>- Recurrent hemoptysis, possible vomiting of blood, dyspnea</td>
</tr>
</tbody>
</table>
| Day 8   | - Increased hemoptysis followed by cardio-respiratory arrest  
          - Resuscitated, intubated and ventilated |
| Week 3  | - Clear evidence of irreversible hypoxic brain injury  
          - Withdrawal of support and subsequent death |
| Autopsy Findings | - All valves in position, no evidence of perforation, migration, or intrusion into blood vessels  
                      - No clear source of bleeding |
| CEC Conclusions | - No clear link between hemoptysis and device or procedure  
                            - Adjudicated Possibly Procedure Related and Probably Device Related |
| Actions | - Event reported to the DSMB, FDA, IRBs, investigators  
           - Recommendations for careful monitoring of subjects with hemoptysis |

*Post treatment*
→ Equivalent between arms by Kaplan-Meier analysis (p = 0.876, log rank test)
→ 12 month rates equivalent: EBV 3.7%, Control 3.5% (p = 1.000, Fisher’s exact test)
→ No difference by multivariate analysis (p = 0.482, Cox regression)
Safety Data Review Outline

Review four categories of events:

1. Major Complications Composite events
2. Non-MCC adverse events
3. Other events unique to treatment arm
4. Rehospitalizations
Non-MCC Adverse Events: 1 Year

Seven AEs significant or trending to significance

<table>
<thead>
<tr>
<th>Event</th>
<th>Zephyr n =214</th>
<th>Control n = 87</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD Exac (w or w/o hosp)</td>
<td>63.1%</td>
<td>54.0%</td>
<td>0.154</td>
</tr>
<tr>
<td>Other Hemoptysis</td>
<td>42.1%</td>
<td>2.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non–cardiac Chest Pain</td>
<td>16.4%</td>
<td>3.5%</td>
<td>0.002</td>
</tr>
<tr>
<td>Increased SOB</td>
<td>9.8%</td>
<td>2.3%</td>
<td>0.030</td>
</tr>
<tr>
<td>Nausea or Vomiting</td>
<td>8.4%</td>
<td>1.2%</td>
<td>0.017</td>
</tr>
<tr>
<td>Other Pulmonary Infection</td>
<td>8.4%</td>
<td>1.2%</td>
<td>0.017</td>
</tr>
<tr>
<td>Hypoxemia</td>
<td>7.0%</td>
<td>0.0%</td>
<td>0.007</td>
</tr>
</tbody>
</table>
COPD Exacerbations Timing

• Anticipated response to intervention
• 40% occur in first 90 days
• Treatment and control equivalent after day 90
• Medically manageable
COPD Exacerbations: SAEs

- Greatest difference in first 90 days
- Trends to control rates
- SAE designation due to rehospitalization or bronchoscopic exam
Hemoptysis Timing

- Expected following bronchoscopic intervention
- Typically blood-tinged sputum
- Most resolve without intervention
Hemoptysis Timing: SAEs

- 11.7% (n = 25) cumulative rate for EBV at 12 months
- 1.4% (n = 3) reported by site as severe
- SAE designation due to rehospitalization or bronchoscopic exam
- Decreases over time
Other Elevated AEs

- Other elevated AEs:
  - Non cardiac chest pain
  - Nausea
  - Hypoxemia
  - Shortness of breath
  - Other pulmonary infection

- Typical following bronchoscopic intervention / anesthesia

- Majority occur within first 30 days
Safety Data Review Outline

Review four categories of events:

1. Major Complications Composite events
2. Non-MCC adverse events
3. Other events unique to treatment arm
4. Rehospitalizations
### AEs Unique to Treatment Arm

<table>
<thead>
<tr>
<th></th>
<th>0 - 6 Months</th>
<th>7 – 12 Months</th>
<th>12 Months Cumulative*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>13.1%</td>
<td>7.5%</td>
<td>18.2%</td>
</tr>
<tr>
<td>Distal pneumonia</td>
<td>1.4%</td>
<td>2.8%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Migration / expectoration</td>
<td>6.5%</td>
<td>2.3%</td>
<td>7.9%</td>
</tr>
<tr>
<td>Granulation</td>
<td>5.1%</td>
<td>3.3%</td>
<td>7.9%</td>
</tr>
<tr>
<td>Catheter-induced bronchial trauma</td>
<td>0.5%</td>
<td>0.0%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

→ Majority are SAEs due to re-bronch (per CEC convention)

*Per Patient Rates
Valve Migration / Expectoration

• **Definition**
  - Migration: Movement of valve from original placement location
  - Expectoration: Migrated valve coughed out

• **Cause**
  - Technique dependent
    - (undersized, too proximal)

• **Clinical Manifestation**
  - Prolonged cough, minor hemoptysis, dyspnea or exacerbation
  - No occult migrations detected by CT
Valve Migration / Expectoration

Frequency (1yr):
- 7.9% (17 / 214) of patients
- 2.8% (23 / 820) of valves

Events:

<table>
<thead>
<tr>
<th>Event</th>
<th>n (patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migration</td>
<td>9</td>
</tr>
<tr>
<td>Expectoration</td>
<td>8</td>
</tr>
</tbody>
</table>

Sequelae: No long term implications

Treatment: All migrations removed successfully

Action: Site communication / retraining mid-trial
Product and Technique Modification

Product modification:
- Depth measurement

Training:
- Modified technique
- Updated instructions for use

International commercial experience:
- Confirms effectiveness of training and product modification
Granulation Tissue

Description:
- Typical foreign body reaction
- Possibly due to valve misplacement

Frequency (1yr):
7.9% (17 / 214) of patients

Severity:
94% rated mild / moderate by site

Treatment:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valve removal</td>
<td>71%</td>
</tr>
<tr>
<td>Electrocautery + Mitomycin</td>
<td>6%</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>6%</td>
</tr>
<tr>
<td>Exploratory bronchoscopy</td>
<td>6%</td>
</tr>
<tr>
<td>Drug therapy</td>
<td>6%</td>
</tr>
<tr>
<td>No treatment</td>
<td>6%</td>
</tr>
</tbody>
</table>
Safety Data Review Outline

Review four categories of events:

1. Major Complications Composite events
2. Non-MCC adverse events
3. Other events unique to treatment arm
4. Rehospitalizations
Rehospitalization

• Higher rate at one year in EBV group
  – 39.7% for Treatment vs. 25.3% for Control, (p = 0.024)
  – Expected for active intervention

• Primary causes for rehospitalization (per patient):
  COPD Exacerbation: 17.3%    Pneumonia: 8.4%
  Valve Replacement: 5.6%     Hemoptysis: 5.6%

• 25% of Treatment rehospitalizations were ≤ 1day LOS

• Mean LOS: 5.8 days for EBV vs. 8.6 for Control
Safety Conclusion

• No increased mortality in treatment arm

• Peri-procedural increase in events as expected
  - Typically minor and transient
  - Rates decrease over time

• Only two SAE types statistically significant at 1 year
  - COPD exacerbations, hemoptysis
  - Most peri-procedural
  - Rates equilibrate over time

• Removable
Efficacy Results

Frank Sciurba, MD, FCCP

Associate Professor of Medicine
Division of Pulmonary and Critical Care Medicine
Director, Emphysema Research Center
University of Pittsburgh
Efficacy Data Review Outline

1. Primary and Secondary Endpoints
   - 6 month data for key variables

2. Supporting Evidence
   - Confirmation of mechanism of action
   - Responder analysis

3. Predictors of Outcome

4. Durability of Effect: Longitudinal Analysis
## Analysis Populations

<table>
<thead>
<tr>
<th>Study Population and Definition</th>
<th>EBV n (%)</th>
<th>Control n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent to Treat (ITT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All randomized subjects</td>
<td>220 (100%)</td>
<td>101 (100%)</td>
</tr>
<tr>
<td>Completed Cases (CC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects with evaluable data</td>
<td>179 (81.4%)</td>
<td>75 (74.3%)</td>
</tr>
</tbody>
</table>

→ ITT population used for primary efficacy
→ CC population used for all other analyses
Primary Endpoints

**FEV$_1$**
- Volume exhaled in first second (ml)
- Most accepted measure of severity of respiratory mechanics
- Reproducible physiologic measure

**6MWT**
- Distance walked in 6 minutes
- Global clinical measure of patient exercise capacity
- Performed using ATS standardized instructions and methodology
Study Success Criteria

“For effectiveness, the differences between arms for the percent change from baseline at 180 days for both FEV\textsubscript{1} and 6MWT reach statistical significance (one-sided test at p < 0.025) in favor of the treatment group.”
Co-primary Endpoints:
Change at 6 Months (ITT)

- Multiple imputation of missing values
- Provides point estimate of delta (between group difference of change from baseline to 6 months)

\[
\begin{align*}
\text{FEV}_1 & : \quad \text{Delta} = 6.8\%, \ p = 0.002 \\
6\text{MWT} & : \quad \text{Delta} = 5.8\%, \ p = 0.019
\end{align*}
\]

⇒ VENT met both co-primary efficacy endpoints
Change in $\text{FeV}_1$ and 6MWT at 6 Months (CC)

**FEV$_1$ Change**

$\Delta = 7.2\%$, $p < 0.001$

Abs. $\Delta = 64.2\text{ ml}$, $p < 0.001$

**6MWT Change**

$\Delta = 5.8\%$, $p = 0.008$

Abs. $\Delta = 23.5\text{ m}$, $p = 0.009$

- **Zephyr EBV (n = 179)**
  - FEV$_1$ Change: $5.3\%$
  - 6MWT Change: $4.3\%$
- **Control (n = 75)**
  - FEV$_1$ Change: $-1.9\%$
  - 6MWT Change: $-1.5\%$
- **Zephyr EBV (n = 178)**
  - FEV$_1$ Change: $5.3\%$
  - 6MWT Change: $4.3\%$
- **Control (n = 73)**
  - FEV$_1$ Change: $-1.9\%$
  - 6MWT Change: $-1.5\%$
## Secondary Endpoints at 6 Months

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>ITT (Primary Analysis)</th>
<th>CC</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Delta</td>
<td>p value</td>
<td>Delta</td>
</tr>
<tr>
<td>SGRQ (QOL)</td>
<td>-3.4</td>
<td>0.017</td>
<td>-3.4</td>
</tr>
<tr>
<td>mMRC (dyspnea)</td>
<td>-0.26</td>
<td>0.018</td>
<td>-0.30</td>
</tr>
<tr>
<td>Cycle Ergometry (watts)</td>
<td>3.8</td>
<td>0.020</td>
<td>5.0</td>
</tr>
<tr>
<td>Supplemental Oxygen (liters / day)</td>
<td>-12.0</td>
<td>0.020</td>
<td>-100.1</td>
</tr>
</tbody>
</table>

→ VENT met secondary efficacy endpoints
Change in BODE Index at 6 Months (CC)

Δ = -0.53, p = 0.002

→ Highly significant improvement
## Protocol Violations and Missing Data

### Effect on 6 Month Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Δ % FEV&lt;sub&gt;1&lt;/sub&gt; (n)</th>
<th>p value</th>
<th>Δ % 6MWT (n)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT</td>
<td>6.8 (321)</td>
<td>0.002</td>
<td>5.8 (321)</td>
<td>0.019</td>
</tr>
<tr>
<td>CC</td>
<td>7.2 (254)</td>
<td>&lt; 0.001</td>
<td>5.8 (251)</td>
<td>0.008</td>
</tr>
<tr>
<td>In protocol window (± 14 days)</td>
<td>7.6 (200)</td>
<td>&lt; 0.001</td>
<td>5.5 (195)</td>
<td>0.025</td>
</tr>
<tr>
<td>Without Inc./Exc. violations</td>
<td>7.6 (210)</td>
<td>&lt; 0.001</td>
<td>7.8 (208)</td>
<td>0.018</td>
</tr>
<tr>
<td>Without protocol violations*</td>
<td>8.6 (185)</td>
<td>&lt; 0.001</td>
<td>10.9 (183)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

→ Significant improvements regardless of visit window, eligibility violations, or protocol violations

*Clinically-meaningful violations
Efficacy Data Review Outline

1. Primary and Secondary Endpoints
   - 6 month data for key variables

2. Corroborating Analyses
   - Mechanism of action
   - Responder analysis

3. Predictors of Outcome

4. Durability of Effect: Longitudinal Analysis
Demonstrated Target Lobe Volume Reduction at 6 Months

- Independently assessed by HRCT Core Lab
- Significant reduction in target lobe volume
- Significant expansion of adjacent lobe volume
- Achieved intended effect
- High correlation with change in FEV$_1$, $p < 0.001$
Efficacy Data Review Outline

1. Primary and Secondary Endpoints
   - 6 month data for key variables

2. Corroborating Analyses
   - Mechanism of action
   - Responder analysis

3. Predictors of Outcome

4. Durability of Effect: Longitudinal Analysis
### Responder Analysis Thresholds

<table>
<thead>
<tr>
<th>Variable</th>
<th>Threshold</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁</td>
<td>≥ 15% improvement</td>
<td>- Pre-specified in protocol</td>
</tr>
<tr>
<td>6MWT</td>
<td>≥ 15% improvement</td>
<td>- Pre-specified in protocol</td>
</tr>
<tr>
<td>SGRQ</td>
<td>≥ 8 point score reduction</td>
<td>- NETT</td>
</tr>
<tr>
<td>mMRC</td>
<td>≥ 1 point score reduction</td>
<td>- 1 point on 0-4 pt integer scale</td>
</tr>
<tr>
<td>Cycle</td>
<td>≥ 10 watt increase</td>
<td>- NETT</td>
</tr>
<tr>
<td>O₂</td>
<td>Increase/decrease</td>
<td>- Pre-specified in protocol</td>
</tr>
<tr>
<td>BODE</td>
<td>≥ 1 point score reduction</td>
<td>- NETT</td>
</tr>
</tbody>
</table>
Responder Analysis at 6 Months

- FEV1 (≥15%)
- 6MWT (≥15%)
- SGRQ (≥ 8 Points)
- mMRC (Improve ≥ 1 Point)
- Cycle Ergometry (watts)
- Oxygen Use (Decrease)
- BODE (≥ 1 Point)
## Responder Analysis at 6 Months

<table>
<thead>
<tr>
<th></th>
<th>EBV n / N (%)</th>
<th>Control n / N (%)</th>
<th>RR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FEV₁ ≥ 15%</strong></td>
<td>42 / 179 (23.5)</td>
<td>8 / 75 (10.7)</td>
<td>2.2</td>
<td>(1.1, 4.5)</td>
<td>0.013</td>
</tr>
<tr>
<td><strong>6MWT ≥ 15%</strong></td>
<td>45 / 178 (25.3)</td>
<td>13 / 73 (17.8)</td>
<td>1.4</td>
<td>(0.8, 2.5)</td>
<td>0.133</td>
</tr>
<tr>
<td><strong>SGRQ</strong></td>
<td>49 / 158 (31.0)</td>
<td>7 / 61 (11.3)</td>
<td>2.8</td>
<td>(1.3, 5.7)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>mMRC</strong></td>
<td>47 / 162 (29.0)</td>
<td>11 / 67 (16.4)</td>
<td>1.8</td>
<td>(1.0, 3.2)</td>
<td>0.031</td>
</tr>
<tr>
<td><strong>Cycle Ergometry</strong></td>
<td>41 / 166 (24.7)</td>
<td>9 / 69 (13.0)</td>
<td>1.9</td>
<td>(1.0, 3.7)</td>
<td>0.032</td>
</tr>
<tr>
<td><strong>Oxygen Decrease</strong></td>
<td>56 / 95 (59.0)</td>
<td>15 / 40 (37.5)</td>
<td>1.6</td>
<td>(1.0, 2.4)</td>
<td>0.012</td>
</tr>
<tr>
<td><strong>BODE</strong></td>
<td>64 / 160 (40.0)</td>
<td>11 / 59 (18.6)</td>
<td>2.2</td>
<td>(1.2, 3.8)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

→ Proportion of responders higher in treatment arm for all measures
## Responder Analysis Clinical Significance

<table>
<thead>
<tr>
<th>Threshold</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ 15% $\Delta FEV_1$ = 131 ml</td>
<td>• Equal to 2-3 years of typical decline due to emphysema&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>• Equals 4 years smoking cessation</td>
</tr>
<tr>
<td>1 point BODE</td>
<td>• Data from NETT study (Martinez et al&lt;sup&gt;2&lt;/sup&gt;)</td>
</tr>
<tr>
<td></td>
<td>• Decrease &gt; 1 point at 6 months associated with 43% decrease in mortality risk</td>
</tr>
<tr>
<td>4 point SGRQ</td>
<td>• All of the following relative to baseline&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>- Can wash / dress more quickly</td>
</tr>
<tr>
<td></td>
<td>- Can now walk up stairs without having to stop</td>
</tr>
<tr>
<td></td>
<td>- Can now go out for shopping / entertainment</td>
</tr>
</tbody>
</table>

<sup>1</sup>Am J Respir Crit Care Med Vol 166. pp 675–679, 2002


<sup>3</sup>COPD: Journal of Chronic Obstructive Pulmonary Disease, 2:75–79
Efficacy Data Review Outline

1. Primary and Secondary Endpoints
   - 6 month data for key variables

2. Corroborating Analyses
   - Mechanism of action
   - Responder analysis

3. Predictors of Outcome

4. Durability of Effect: Longitudinal Analysis
Predictors of Outcome

• Multivariate, mixed model analysis to identify predictors, pre-specified in statistical analysis plan

• Further analysis (dichotomization) dictated by statistical analysis plan

• Designed to identify important predictors of clinical outcomes from pre-specified set of variables

• Two key predictors identified based on this analysis
  – Heterogeneity
  – Fissure Integrity
Heterogeneity

- Independently assessed by HRCT Core lab
- Based on continuous measure of quantitative emphysema score (-910HU)
- Heterogeneity: difference between target and adjacent lobe
- Consistent with proposed mechanism of action and surgical literature
Heterogeneity

- Independently assessed by HRCT Core lab
- Based on continuous measure of quantitative emphysema score (-910HU)
- Heterogeneity: difference between target and adjacent lobe
- Consistent with proposed mechanism of action and surgical literature
Co-Primary Endpoints
Heterogeneity Sensitivity

Co-Primary Endpoints
Heterogeneity Sensitivity

$\Delta \% \text{FEV}_1$

$\Delta \% \text{6MWT}$

75% of Subjects

Heterogeneity $\geq 6\%$

All Subjects

$\Delta \% \text{FEV}_1$

$\Delta \% \text{6MWT}$

$p = 0.008$

$p = 0.002$

$p = 0.004$

$p < 0.001$

$p < 0.001$

$p < 0.001$

$p < 0.001$

$\rightarrow \text{FEV}_1$ and 6MWT responses increase with increasing heterogeneity
Percent Change in FEV₁ and 6MWT in High Heterogeneity Subgroup* at 6 Months (CC)

FEV₁ % Change
Δ = 12.3%, p < 0.001
Abs. Δ = 111.2 ml, p < 0.001

6MWT % Change
Δ = 14.4%, p = 0.001
Abs. Δ = 50.4 m, p < 0.001

* Dichotomized at median baseline heterogeneity score (15%)
## High Heterogeneity

### 6 Month Responder Analysis (CC)

<table>
<thead>
<tr>
<th></th>
<th>EBV n / N (%)</th>
<th>Control n / N (%)</th>
<th>Relative Rate</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FEV(_1) ≥ 15%</strong></td>
<td>32 / 91 (35.2)</td>
<td>5 / 40 (12.5)</td>
<td>2.8</td>
<td>(1.2, 6.7)</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>6MWT ≥ 15%</strong></td>
<td>28 / 90 (31.1)</td>
<td>5 / 38 (13.2)</td>
<td>2.4</td>
<td>(1.0, 5.7)</td>
<td>0.025</td>
</tr>
</tbody>
</table>
Fissure Integrity

- Independently assessed by HRCT Core lab
- Categorized as:
  - Complete
  - Incomplete
- Incomplete fissures
  - Proxy for inter-lobar airflow
  - Attenuates volume reduction
Greater Target Lobe Volume Reduction Complete Fissure Subgroup at 6 Months (CC)

- Proxy for collateral ventilation
- Creates closed system
- Rates of Complete Fissure
  - Right Oblique = 54%
  - Right Horizontal = 39%
  - Left Oblique = 62%

**Zephyr EBV Treatment Only**

<table>
<thead>
<tr>
<th>Lobe Type</th>
<th>Change in Volume (ml)</th>
<th>n = 68</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target Lobe</td>
<td>-713</td>
<td></td>
</tr>
<tr>
<td>Adjacent Lobe</td>
<td>401</td>
<td></td>
</tr>
</tbody>
</table>

**Change in Volume (ml)**
Change in FEV$_1$ and 6MWT
Complete Fissure Subgroup at 6 Months (CC)

FEV$_1$ Change
Δ 16.2%, p = 0.001
Δ 136.2 ml, p<0.001

6MWT Change
Δ 11.4%, p = 0.075
Δ 44.5 m, p = 0.085

Zephyr EBV
n=68
Control
n=33

Zephyr EBV
n=68
Control
n=32
Efficacy Data Review Outline

1. Primary and Secondary Endpoints
   - 6 month data for key variables

2. Corroborating Analyses
   - Mechanism of action
   - Responder analysis

3. Predictors of Outcome

4. Durability of Effect: Longitudinal Analysis
FEV$_1$ Longitudinal Results

→ Treatment does not erode over time per multivariate, longitudinal analysis, $p < 0.001$
6MWT Longitudinal Results

→ Treatment does not erode over time per multivariate, longitudinal analysis, \( p = 0.014 \)

**Completed Cases**

**High Heterogeneity**
BODE Longitudinal Analysis

Completed Cases

<table>
<thead>
<tr>
<th>Percent Change from Baseline</th>
<th>Baseline</th>
<th>6 Months</th>
<th>1 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delta</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

High Heterogeneity

<table>
<thead>
<tr>
<th>Percent Change from Baseline</th>
<th>Baseline</th>
<th>6 Months</th>
<th>1 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delta</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Efficacy Conclusions

• Met primary and secondary endpoints
  – Lung function, exercise tolerance, and QOL
• Achieved target lobe volume reduction
• BODE (integrative parameter) corroborates treatment effect
• Favorable responder analysis across numerous measures
• Enhanced efficacy in subjects with High Heterogeneity and Complete Fissures
• Sustained benefit at 12 months
Training, Post Approval Study Proposal, and Conclusion

Gerard Criner, MD, FCCP

Professor of Medicine
Florence P. Bernheimer Distinguished Service Chair
Director, Pulmonary and Critical Care Medicine
and Temple Lung Center
Temple University School of Medicine
Training and Post Approval Studies
Physician Training

• Goal is controlled introduction

• Didactic:
  – Labeling
  – Pivotal trial results
  – Bronchoscopy video of implant procedure
  – HRCT assessment of destruction, heterogeneity

• Hands-on
  – Device preparation and loading
  – Valve implants and removals in simulated lung anatomy
  – Proctoring of initial cases
Zephyr EBV
Proposed Post Approval Studies

• PAS I - VENT Long Term Follow-up
  – Primary Objective: Collect and report long-term safety and efficacy data at three and four years post enrollment in the VENT study

• PAS II – Post Market Assessment
  – Primary Objective: Evaluate the training effectiveness and longer-term safety of the Zephyr EBV during commercial use by various physicians with a range of experience.
Zephyr EBV
PAS I - VENT Long Term Follow-up

• Design: Multi-center, observational
  – Up to 284 patients and 29 institutions
  – Follow-up treatment and control groups

• Follow-Up:
  – 3 and 4 years post VENT enrollment

• Subject Population
  – VENT mITT population

• Study Objective: Assess Long-term Safety
  – Safety: Adverse Events
  – Physiologic: FEV$_1$, FVC
  – Exercise: 6MWT
  – Clinical: BODE, Survival
Zephyr EBV
PAS II - Post Market Assessment

• Design: Prospective, observational, open-label study
  – 200 patients and 30 institutions

• Follow-up:
  – 30 and 180 Days, 1, 2 and 3 years post procedure

• Subject Population
  – In compliance with the indications for use and restrictions of the approved labeling

• Study Objectives:
  – Safety: Serious adverse events
  – Training Effectiveness: Migration and expectoration rates
VENT Study Summary

- VENT is a landmark study
  - After NETT it is the largest interventional trial ever conducted in severe emphysema
  - Largest interventional study in severe emphysema ever conducted by industry
  - First ever prospective randomized controlled trial to evaluate lung volume reduction via endobronchial treatment
  - First to evaluate regional effects of lobar treatment
  - HRCT data provides novel paradigm for subject selection, mechanistic effect and outcome assessment that is impervious to placebo effect
Study Conduct

- Visit windows employed for analysis reasonable for this patient population and narrower than NETT
- Missing data rates are similar to other landmark studies in severe COPD populations
- No impact on study outcomes due to protocol or eligibility deviations
  - Primary endpoints met regardless of whether protocol or eligibility deviations are included in the analysis
Study Summary: Safety

• Equivalent mortality to control

• Complications
  – Peri-procedural increase in events as expected
  – Typically minor and transient
  – Rates decrease over time
  – Medically-manageable, no surgical interventions

• Removable device
Established Clinically Significant Efficacy

• Met primary and secondary efficacy endpoints
• Responder analysis shows clinically meaningful changes in significant % of treated cohort with minimal morbidity and mortality
• Changes in BODE signify disease modifying therapy
**Treatment Options:**

**GOLD* Stage:**

- **I** Mild
  - Typically seek medical attention

- **II** Moderate

- **III** Severe
  - ↑ dyspnea
  - ↓ exercise capacity
  - repeated exacerbations

- **IV** Very Severe
  - Appreciably impaired
  - Exacerbations may be life-threatening

**Severe Impairment**

- + Long acting bronchodilators
- + Pulmonary rehabilitation
- + Inhaled glucocorticosteroids
- + Long term oxygen

**Zephyr EBV, LVRS, Transplant**

---

*Global Initiative for Chronic Obstructive Lung Disease*
## Assessing the Risks and Benefits of Treatments in Severe Emphysema

<table>
<thead>
<tr>
<th>Factors</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Clinical benefit</td>
<td>• Medical Management</td>
</tr>
<tr>
<td>• Morbidity</td>
<td>• EBV</td>
</tr>
<tr>
<td>• Mortality</td>
<td>• LVRS</td>
</tr>
<tr>
<td>• Patient preference</td>
<td>• Transplant</td>
</tr>
</tbody>
</table>
Zephyr EBV Risk / Benefit

- Severe emphysematous patients with limited options
- Reasonable, anticipated, manageable risks
- Clinically important benefits in substantial number of patients
- Benefits outweigh risks
- Study results demonstrated reasonable assurance of safety and effectiveness
Zephyr EBV

Reasonable Assurance of Safety and Effectiveness
AFTERNOON SLIDES
### Primary Safety Endpoint – MCC

<table>
<thead>
<tr>
<th>Event</th>
<th>6 months</th>
<th>12 months</th>
<th>p value</th>
<th>6 months</th>
<th>12 months</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBV n = 214</td>
<td>Control n = 87</td>
<td>Delta (95% CI)</td>
<td>p value</td>
<td>EBV n = 214</td>
<td>Control n = 87</td>
<td>Delta (95% CI)</td>
</tr>
<tr>
<td>Major Complication Composite</td>
<td>6.1%</td>
<td>1.2%</td>
<td>4.93% (1.02, 8.83)</td>
<td>0.08</td>
<td>10.3%</td>
<td>4.6%</td>
</tr>
<tr>
<td>Death</td>
<td>2.8%</td>
<td>0.0%</td>
<td>2.80% (0.59, 5.02)</td>
<td>0.19</td>
<td>3.7%</td>
<td>3.5%</td>
</tr>
<tr>
<td>Pneumonia distal to valve</td>
<td>1.4%</td>
<td>NA</td>
<td>----</td>
<td>----</td>
<td>4.2%</td>
<td>NA</td>
</tr>
<tr>
<td>Respiratory failure ≥ 24 hours ventilation</td>
<td>1.9%</td>
<td>1.2%</td>
<td>0.72% (-2.16, 3.60)</td>
<td>1.00</td>
<td>2.8%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Pneumothorax / air leak &gt; 7 days</td>
<td>1.4%</td>
<td>1.2%</td>
<td>0.25% (-2.5, 3.0)</td>
<td>1.00</td>
<td>1.9%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Massive hemoptysis (&gt; 300ml)</td>
<td>0.5%</td>
<td>0.0%</td>
<td>0.47% (-0.45, 1.38)</td>
<td>1.00</td>
<td>0.5%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Empyema</td>
<td>0.0%</td>
<td>0.0%</td>
<td>----</td>
<td>----</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

→ MCC nominally higher as anticipated (ns)
# Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Remained Mean</th>
<th>Withdrew Mean</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (% male)</td>
<td>42.75%</td>
<td>54.05</td>
<td>ns</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65.09</td>
<td>65.35</td>
<td>ns</td>
</tr>
<tr>
<td>History of smoking (yes)</td>
<td>99.28%</td>
<td>97.30%</td>
<td>ns</td>
</tr>
<tr>
<td>Pack Years</td>
<td>60.0</td>
<td>65.8</td>
<td>ns</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.00</td>
<td>24.83</td>
<td>ns</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6.88%</td>
<td>2.70%</td>
<td>ns</td>
</tr>
<tr>
<td>Abnormal ECG</td>
<td>44.57%</td>
<td>54.05%</td>
<td>ns</td>
</tr>
</tbody>
</table>

→ No significant differences
### Baseline Lung Function

<table>
<thead>
<tr>
<th></th>
<th>Remained Mean</th>
<th>Withdrew Mean</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FEV₁</strong> (liters)</td>
<td>0.87</td>
<td>0.83</td>
<td>ns</td>
</tr>
<tr>
<td><strong>FEV₁</strong> (% Predicted)</td>
<td>30%</td>
<td>30%</td>
<td>ns</td>
</tr>
<tr>
<td><strong>FVC</strong> (liters)</td>
<td>2.68</td>
<td>2.62</td>
<td>ns</td>
</tr>
<tr>
<td><strong>FVC</strong> (% Predicted)</td>
<td>70%</td>
<td>71%</td>
<td>ns</td>
</tr>
<tr>
<td><strong>FEV₁ / FVC</strong></td>
<td>0.33</td>
<td>0.32</td>
<td>ns</td>
</tr>
<tr>
<td><strong>RV</strong> (% Predicted)</td>
<td>214%</td>
<td>214%</td>
<td>ns</td>
</tr>
<tr>
<td><strong>TLC</strong> (% Predicted)</td>
<td>125%</td>
<td>124%</td>
<td>ns</td>
</tr>
<tr>
<td><strong>RV / TLC</strong></td>
<td>0.63</td>
<td>0.64</td>
<td>ns</td>
</tr>
<tr>
<td><strong>DL&lt;sub&gt;CO&lt;/sub&gt;</strong> (% Predicted)</td>
<td>34%</td>
<td>37%</td>
<td>ns</td>
</tr>
</tbody>
</table>

→ No significant differences
### Other Baseline Variables Well Matched

<table>
<thead>
<tr>
<th></th>
<th>Remained Mean</th>
<th>Withdraw Mean</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PaO₂ (mmHg)</strong></td>
<td>68.88</td>
<td>69.06</td>
<td>ns</td>
</tr>
<tr>
<td><strong>PaCO₂ (mmHg)</strong></td>
<td>40.68</td>
<td>41.91</td>
<td>ns</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td>7.43</td>
<td>7.42</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Oxygen Saturation</strong></td>
<td>93%</td>
<td>94%</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Six Minute Walk Test (m)</strong></td>
<td>341.71</td>
<td>325.2</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Cycle Ergometry (max. watts)</strong></td>
<td>45.3</td>
<td>39.2</td>
<td>ns</td>
</tr>
</tbody>
</table>

→ No significant differences