Elevair Endobronchial Coil System (P170004)

Meeting of The Anesthesiology and Respiratory Therapy Devices Panel

June 14, 2018
FDA Review Team

Derya Coursey, PhD – Lead Review
Lila Bahadori, MD – Clinical/Pulmonary
Yanping Qu, PhD – Statistics
Heather Benz, PhD – Patient Preference Study
Martin Ho – Patient Preference Study
Yuzhi Hu, PhD – Epidemiology
Maria Iacono, PhD – MRI Compatibility
Terry Woods, PhD – MRI Compatibility
Hanniebey Wiyor, PhD – Human Factors
Philip Lafleur – Manufacturing
Marisa White – Bioresearch and Monitoring
Anne Hawthorn, JD – Patient Labeling
Purpose of Panel Meeting

• Obtain feedback regarding aspects of the data provided in support of the Elevair Endobronchial Coil System if:
  – study population supports the proposed indications for use
  – study outcomes are clinically significant

• Obtain the Panel’s recommendation regarding the Benefit-Risk profile of the Elevair Endobronchial Coil System
Outline

- Study Overview – Derya Coursey, PhD
- Clinical Review- Lila Bahadori, MD
- Patient Preference Study – Heather Benz, PhD
- Applicant Proposed Future Post Market Study-Lila Bahadori, MD
- Panel Questions (Afternoon Session)

*FDA’s questions to the Panel will be presented in the afternoon. Key points in FDA’s presentation pertaining to the Panel questions will be highlighted in orange boxes at the bottom of the slides.*
Study Overview

Derya Coursey, PhD
Biomedical Engineer
Lead Reviewer

Respiratory Devices Branch
Office of Device Evaluation
Center for Devices and Radiological Health
Class III Device

• Provide reasonable assurance of safety and effectiveness (Federal Food, Drug, Cosmetic Act, §513(a)(1)(C))

• Relevant factors (21 CFR 860.7(b)):
  – Intended patient population
  – Conditions of use
  – Probable benefit to health vs. probable injury
Proposed Indications For Use

The ELEVAIR Endobronchial Coil System is indicated for bronchoscopic placement of ELEVAIR Coils in patients with severe emphysema (homogeneous and/or heterogeneous) and severe hyperinflation to improve quality of life, lung function, and exercise capacity.

The Panel will be asked to make a recommendation on benefit/risk of the Elevair Endobronchial Coil based on the proposed Indications for Use.
Lung Volume REDuction Coil Treatment in Patients With Emphysema (RENEW) Study (pivotal):

- Multicenter (US and OUS), 1:1 randomized, assessor-blinded, subject and investigator unblinded
- Stratified based on emphysema type
- Treatment and Control:
  - optimal medical management and pulmonary rehabilitation before enrollment
  - no sham control
- Sample Size:
  - based on secondary endpoint of FEV1
Clinical Study: IDE G110066

Crossover Study:

– Control arm of pivotal study enrolled after 12 months
– Single arm, observational
– Similar inclusion/exclusion criteria except for the requirement of pre-treatment pulmonary rehabilitation
Pivotal Study Endpoints

• **Primary Effectiveness at 12 months: (treatment-control)**
  – $\Delta 6\text{MWT}$ - change from baseline

• **Secondary Effectiveness at 12 months: (treatment-control)**
  – 6MWT responder rate: $\Delta 6\text{MWT} \geq 25$ meters.
  – $\Delta \text{SGRQ}$: Change in SGRQ from baseline
  – $\Delta \text{FEV1}\%$ : % Change in FEV1 from baseline

• **Primary Safety Analyses at 12 months:**
  – Major Complications
Major Changes in the Protocol

• Removal of cap on homogeneous emphysema patient enrollment:
  – Initial cap was limited to 150 subjects (75 in coil; 75 in control)

• Change of inclusion criterion: RV ≥225% to RV ≥175 %:
  – 169 of 315 subjects had been already enrolled.
  – The cut off value defining the effectiveness population was changed:
    • The applicant is basing the effectiveness analysis on RV ≥ 225 %.
Pooling of US and OUS

• Pooling US and OUS data:
  – Assumption: comparable treatment effect

• The treatment by region interaction effects are statistically significant for 6MWT, FEV1 and SGRQ at 0.15 level:
  – It may not be appropriate to use the pooled data for treatment effect assessment for US population.

*The Panel will be asked to discuss the pooling US and OUS data for overall assessment for US population.*
The applicant is basing the effectiveness analysis on $RV \geq 225\%$.

- 91% of $RV < 225\%$ are in US.
- There is no pre-specified hypothesis for this sub-population with multiplicity adjustment.

The Panel will be asked to discuss the proposed data cut off for overall effectiveness.
Statistical Analysis Plan Changes

• The original pre-specified primary statistical analysis method:
  – Parametric analysis of covariance (ANCOVA)
  – Results are not statistically significant (p=0.0967)
    • None of the secondary endpoints should be formally tested

• The final pre-specified primary statistical method was changed to non-parametric ANCOVA:
  – Results are statistically significant (p=0.0153)
    • Secondary endpoints would be allowed to be formally tested
Analysis Group for Pivotal

Effectiveness Analysis Group:
• Intention to Treat (ITT)- primary and secondary effectiveness
  – All randomized patients (157 control, 158 treatment)

Safety Analysis Group:
• Modified ITT- primary safety population
  – All randomized patients for control or who entered the procedure room for treatment (157 control, 155 treatment)
Elevair Endobronchial Coil System Clinical Review

Lila Bahadori, MD
Pulmonary Medicine

Respiratory Devices Branch
Office of Device Evaluation
Center for Devices and Radiological Health
Clinical Overview-Outline

• Procedure Overview
• Study Results: Safety and Effectiveness
• Other Publications
• Clinical Uncertainties
Procedure Overview

• Central core laboratory assessed lung parenchyma damage per CT scoring plan and transmitted recommendations for bilateral lobe treatment
• Bilateral lobe treatment: 2 bronchoscopies 1-4 months apart
• Recommended: 10-12 coils for upper lobes; 10-14 for lower lobes

The Panel will be asked to discuss applicability of centralized scoring and treatment recommendation to real-world.
Treatment Planning

• CT based method of patient selection developed by applicant
• Treatment planning:
  – Based on lobar damage visual assessment and scoring
  – Not based on densitometry or other analytic metrics
• Different scoring method than the National Emphysema Treatment Trial (NETT) visual scoring
Pivotal-Key Inclusion Exclusion Criteria

Major Inclusion:
• ≥35 years
• Bilateral emphysema by core lab
• FEV$_1$ ≤45%
• TLC >100%
• RV ≥ 175%
• mMRC ≥2
• Pulmonary rehabilitation

Major Exclusion:
• Severe homogeneous emphysema
• Change in FEV1 >20% or > 200ml post BD
• DLCO <20%
• Giant bullae >1/3 lung volume
• >20 mg daily prednisone use
• Inability to walk >140 meters in 6 minutes
• Co-morbidities that would impact exercise capacity
Highlights of Inclusion Criteria

• Initially enrolled subjects with RV ≥ 225 %.
  – changed from ≥225% to ≥175% predicted when 53.7 % already enrolled.

• Based on the NETT trial results, patients that benefit from LVRS are patients with heterogeneous emphysema:
  – Based on early feasibility study with coils, patients with homogeneous emphysema were also enrolled (77 %).

• One major difference between the pivotal and crossover study:
  – No requirement of a completion of pulmonary rehabilitation program prior to coil treatment.
### Study Population and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Pivotal</th>
<th>Control</th>
<th>Crossover</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean ± SD N=</strong></td>
<td><strong>158</strong></td>
<td><strong>157</strong></td>
<td><strong>102</strong></td>
</tr>
<tr>
<td>6MWT (meters)</td>
<td>312.0 ± 79.9</td>
<td>302.7 ± 79.3</td>
<td>313.6 ± 82.0</td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td>0.71 ± 0.2</td>
<td>0.72 ± 0.2</td>
<td>0.7 ± 0.2</td>
</tr>
<tr>
<td>FEV1 % Predicted</td>
<td>25.7 ± 6.3</td>
<td>26.3 ± 6.7</td>
<td>26.4 ± 6.2</td>
</tr>
<tr>
<td>SGRQ</td>
<td>60.1 ± 12.8</td>
<td>57.4 ± 14.8</td>
<td>57.9 ± 15.6</td>
</tr>
<tr>
<td>Homogeneous</td>
<td>77.2 % (122)</td>
<td>77.1 % (121)</td>
<td>80.4 % (82)</td>
</tr>
<tr>
<td>Heterogeneous</td>
<td>22.8 % (36)</td>
<td>22.9 % (36)</td>
<td>19.6 % (20)</td>
</tr>
<tr>
<td>GOLD 4</td>
<td>75.9 %</td>
<td>71.3 %</td>
<td>73.5 %</td>
</tr>
<tr>
<td>BODE Score</td>
<td>5.97 ± 1.262</td>
<td>6.04 ± 1.322</td>
<td>5.7 ± 1.4</td>
</tr>
<tr>
<td>Number of comorbidities</td>
<td>0-3</td>
<td>71.5% (113)</td>
<td>75.2% (118)</td>
</tr>
<tr>
<td></td>
<td>≥4</td>
<td>28.5% (45)</td>
<td>24.8% (39)</td>
</tr>
</tbody>
</table>

- Mainly GOLD 4\(^1\)
- Mostly homogeneous patients
- Baseline characteristics including 6MWT and pulmonary function tests are similar
- Expected treatment effect between pivotal and crossover most likely not confounded with baseline characteristics.

\(^1\) Global Initiative for Chronic Obstructive Lung Disease
EFFECTIVENESS RESULTS
OVERALL STUDY POPULATION
Effectiveness Results Outline

- Primary Endpoint at 12 months
- Secondary Endpoints at 12 months
- Subgroup Analysis:
  - US vs OUS
  - Homogeneous vs Heterogeneous
  - RV cut off
- Results beyond 12 months
- Conclusion
Effectiveness Results Outline

- Primary Endpoint at 12 months
- Secondary Endpoints at 12 months
- Subgroup Analysis:
  - US vs OUS
  - Homogeneous vs Heterogeneous
  - RV cut off
- Results beyond 12 months
- Conclusion
Primary Endpoint- 6MWT Change

- Used as surrogate for exercise capacity
  - How far you could walk in six minutes
- Clinical significance:
  - Minimal Clinically Important Difference (MCID): Mean change of 25 meters\(^1\)
  - Pulmonary rehabilitation can result in 43.9 meter improvement\(^2\)
- Pooled results of US and OUS ($\Delta6MWT = \text{median 14.6 meters; mean 10.2}$)
  - Statistically significant with non-parametric ANCOVA ($p=0.0153$):


The Panel will be asked to discuss the clinical significance of $\Delta6MWT$ of 14.6 meters.
6MWT Change

- Median Change from Baseline (Meters):
  - **Coil**: 10.3 meters
  - **Control**: -7.6 meters
  - **Crossover**: -14.8 meters

- Change in 6MWT from Baseline (Meters):
  - **Coil**: 14.6 meters
  - **Control**: -25 m
  - **Crossover**: 25 m

- Number of Subjects:
  - **Coil**: N=158
  - **Control**: N=157
  - **Crossover**: N=80

- Median Change: Δ=14.6 meters
- 95% CI: 0.4, 28.7
- p=0.0153
Clinical Significance of 6MWT Change
Effectiveness Results Outline

• Primary Endpoint at 12 months
• **Secondary Endpoints at 12 months**
• Subgroup Analysis:
  – US vs OUS
  – Homogeneous vs Heterogeneous
  – RV cut off
• Results beyond 12 months
• Conclusion
6MWT Responder Rate: $\Delta 6MWT \geq 25$ meters

The Panel will be asked to discuss the clinical significance of 6MWT responder rate difference of 11.7%.
Variability of the 6MWT Results

Change from Baseline at 12 months

<table>
<thead>
<tr>
<th>Category</th>
<th>≥ 25 m improved</th>
<th>≥ 50 m improved</th>
<th>≥ 75 m improved</th>
<th>≥ -25 m declined</th>
<th>≥ -50 m declined</th>
<th>≥ -75 m declined</th>
</tr>
</thead>
</table>
| No data on pulmonary rehabilitation maintenance
The Panel will be asked to discuss the clinical significance of FEV1 % change of 7 %.
The Panel will be asked to discuss the clinical significance of SGRQ change in an unblinded study.
Coil Group: Change in 6MWT vs SGRQ

SGRQ = -4 Points

Δ6MWT= 25 m

SGRQ = -4 Points
Coil Group: Change in FEV1 vs SGRQ

ΔFEV1 = 100 ml
SGRQ = -4 Points

Spearman Correlation Coefficient: -0.2393
Pearson Correlation Coefficient: -0.2394
Effectiveness Results Outline

• Primary Endpoint at 12 months
• Secondary Endpoints at 12 months
• **Subgroup Analysis:**
  – US vs OUS
  – Homogeneous vs Heterogeneous
  – RV cut off
• Results beyond 12 months
• Conclusion

*The Panel will be asked to discuss the pooling of US and OUS data for overall assessment for US population.*
US vs OUS 6MWT Results

- Median Change in 6MWT from Baseline (meters)
  - **US**: 4.9 (-0.7, -18.9, -22)
  - **OUS**: 13 (1, -22)

- **Substantial imbalance for US vs OUS baseline for example**:
  - 6MWT, age, BMI, incidence of several comorbidities, SGRQ and RV% predicted

- **Pooled results may not be appropriate for US population**.

- **OUS control declined more than US control** (-22 m vs -0.7 m)
US vs OUS: Coil-Control

- **6MWT (meters):**
  - US: 5.9 meters
  - OUS: 31.7 meters

- **FEV1 (% change):**
  - US: 4.8
  - OUS: 10.7

- **SGRQ (total score):**
  - US: -7.3
  - OUS: -11.6

- **6MWT Responder (%):**
  - US (Coil): 26%
  - US (Control): 34%
  - OUS (Coil): 27%
  - OUS (Control): 44%
Effectiveness Results-Outline

• Primary Endpoint at 12 months
• Secondary Endpoints at 12 months
• **Subgroup Analysis:**
  – US vs OUS
  – **Homogeneous vs Heterogeneous**
  – RV cut off
• Results beyond 12 months
• Conclusion

_The Panel will be asked to discuss the effectiveness results for homogeneous and heterogeneous emphysema population._
Homogeneous vs Heterogeneous 6MWT Results

- Stratified: 23% (HT) vs 77% (HM)

- Study population is different than population identified to benefit from NETT trial.

**Homogeneous**

- Sample sizes:
  - N_{coil} = 122
  - N_{control} = 121
  - N_{crossover} = 62

**Heterogeneous**

- Sample sizes:
  - N_{coil} = 36
  - N_{control} = 36
  - N_{crossover} = 62
HM vs HT: Coil-Control

6MWT  Homogeneous  (meters)  Heterogeneous

FEV1  Homogeneous  (% Change)  Heterogeneous

SGRQ  Homogeneous  (total score)  Heterogeneous

6MWT  Homogeneous  Responder(%)  Heterogeneous

Coil  Control
Effectiveness Results Outline

• Primary Endpoint at 12 months
• Secondary Endpoints at 12 months
• **Subgroup Analysis:**
  – US vs OUS
  – Homogeneous vs Heterogeneous
  – RV cut off
• Results beyond 12 months
• Conclusion

*The Panel will be asked to discuss the analysis change to subjects with RV ≥ 225% and the impact of excluding 25% of study results.*
The applicant is basing the effectiveness analysis on RV ≥ 225 %.

25 % of data is excluded.

There is no pre-specified hypothesis test for this subpopulation with multiplicity adjustment.

RV ≥ 225 % cut off is not clinically supported.
RV Cut Off 6MWT Results

- **Pivotal**: RV <225 %: treatment declined more than control.

- **Crossover**: RV ≥ 225 % declined more than RV <225 %.

RV ≥225 %
- N_{coil}=115
- N_{control}=120
- N_{crossover}=47

RV < 225 %
- N_{coil}=43
- N_{control}=37
- N_{crossover}=33
RV Cut off: Coil-Control

6MWT
- RV < 225% (meters)
  - RV ≥ 225%

FEV1 (% Change)
- RV < 225%
- RV ≥ 225%

SGRQ (total score)
- RV < 225%
- RV ≥ 225%

6MWT Responder(%) RV < 225%
- Coil: 34%
- Control: 26%

RV ≥ 225%
- Coil: 24%
- Control: 42%

-8%
Effectiveness Results Outline

• Primary Endpoint at 12 months
• Secondary Endpoints at 12 months
• Subgroup Analysis:
  – US vs OUS
  – Homogeneous vs Heterogeneous
  – RV cut off
• Results beyond 12 months
• Conclusion
Long Term Effectiveness Results

- Data cut off July 17, 2017
- At 12 month, control exited the study
- At 24 month, Ncoil = 114; Ncrossover = 26
- At 36 month, Ncoil = 49; Ncrossover = 5
6MWT Change Longitudinal Results

![Graph showing 6MWT change over months post baseline with various data points and trend lines for Coil, Control, and Crossover groups. Notable changes include -17, -47, -39, and -90 meters.]
FEV1 % Change Longitudinal Results
SGRQ Change Longitudinal Results

Mean Change SGRQ Total Score vs. Month Post Baseline

- Coil
- Control
- Crossover

Median

Change Longitudinal Results

- Month Post Baseline

- Baseline
- 1
- 3
- 5
- 6
- 9
- 12
- 24
- 36

- SGRQ Total Score
- 0
- 2
- 4
- 6
- 8
- 10
- 12

- Mean Change SGRQ Total Score
- -12
- -8
- -4
- 0
- 4
- 8
- 12

- Change Longitudinal Results
- 7.3
- -3.6
- -0.4
- -4.4
Effectiveness Conclusion

1. Factors that may impact the estimation of the treatment effect:
   – Lack of blinding: The patients may be susceptible to the placebo effect, and the investigators may exhibit treatment bias.
   – Maintenance pulmonary rehabilitation

2. The applicant is basing the effectiveness analysis on RV ≥ 225 %:
   – 25 % of data is excluded
   – Crossover results are not consistent with the pivotal results for this RV cut off

3. Pooled study results statistically significant with uncertain clinical significance:
   – Pooled results may not be generalizable to US population.
   – Statistical significance was achieved for the primary endpoint in the ITT population with non-parametric ANCOVA.
SAFETY RESULTS
PIVOTAL
Safety Results Outline

• Adverse Events (AEs): Includes all events
  – All subjects are counted at most once for each event
• Serious Adverse Events (SAEs):
  – Subcategory of AEs
• Major Complications (MCs):
  – Primary Safety Analysis
  – Subcategory of SAEs
• Deaths
• Other events: hospitalizations, ER visits, unscheduled physician visits
Overall Safety Results: 12 months

More AEs, SAEs and MCs in treatment than control: % subjects and % events.
Adverse Events Through 12 months

% of subjects with other AEs (treatment vs. control):
- Chest discomfort 12.9% vs 0.6%
- Non-cardiac chest pain 13.5% vs 0%

1Includes bronchopulmonary aspergillosis, lung infection, lung infiltration, lung consolidation, lung infection pseudomonal, pneumonia, pneumonia staphylococcal, Pseudomonas infection, lower respiratory tract infection
2Includes acute respiratory failure, respiratory arrest, respiratory failure
Serious Adverse Events Through 12 months

SAEs through 12 Months-RENEW Study-% Subjects

- COPD Exacerbations: 28% (coil: 20%, control: 20%)
- Lower Respiratory Infections\(^1\): 24% (coil: 6%, control: 18%)
- Pneumothorax: 10% (coil: 1%, control: 9%)
- Respiratory Failure\(^2\): 5% (coil: 2%, control: 3%)
- Hemoptysis/Hemorrhage: 4% (coil: 0%, control: 4%)

\(^1\)Includes bronchopulmonary aspergillosis, lung infection, lung infiltration, lung consolidation, lung infection pseudomonal, pneumonia, pneumonia staphylococcal, Pseudomonas infection, lower respiratory tract infection

\(^2\)Includes acute respiratory failure, respiratory arrest, respiratory failure
Major Complications through 12 months

- COPD exacerbation-hospitalization > 7 days
- Lower respiratory infections-symptoms with infiltrate on CXR and hospitalization
- Hemoptysis-requiring transfusion/embolization/surgery
- Pneumothorax-chest tube >7 days
- Respiratory failure-mechanical ventilator support > 24 hours
- Unanticipated bronchoscopy-removal of coil secondary to device related AE (does not include intraprocedural removal/repositioning) (0%)
Deaths Through 12 Months

• Coil treatment: 10/155 (6.5%)
  • 7 deaths potentially related to device/procedure

• Control: 8/157 (5.1%)
  • 4 related to COPD exacerbation

• Crossover: 9/101 (8.9%)
  • 2 deaths potentially related to procedure
## Pivotal Treatment Arm Mortality Details

<table>
<thead>
<tr>
<th>Cause of death (through 12 months)</th>
<th>Days post last coil placement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraprocedural pulmonary hemorrhage</td>
<td>0</td>
</tr>
<tr>
<td>RUL opacification and respiratory failure 3 days later</td>
<td>6</td>
</tr>
<tr>
<td>Right pneumothorax 14 days later; respiratory failure</td>
<td>39</td>
</tr>
<tr>
<td>Progressive RUL infiltrates started 30 days after procedure</td>
<td>73</td>
</tr>
<tr>
<td>URI at 96 days, followed by RUL pneumonia (MRSA and aspergillus positive cultures)</td>
<td>148</td>
</tr>
<tr>
<td>Pneumonia and COPD exacerbation</td>
<td>163</td>
</tr>
<tr>
<td>Multiple COPD exacerbations; RUL pneumonia and respiratory failure</td>
<td>254</td>
</tr>
<tr>
<td>Subacute endocarditis and multiorgan system failure</td>
<td>86</td>
</tr>
<tr>
<td>Sigmoid perforation and complications</td>
<td>43</td>
</tr>
<tr>
<td>Metastatic bone cancer</td>
<td>202</td>
</tr>
</tbody>
</table>
Crossover Device Related Mortality

<table>
<thead>
<tr>
<th>Cause of death (through 12 months)</th>
<th>Days post last coil treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>RUL infiltrate 28 days later with worsening; massive hemoptysis</td>
<td>58</td>
</tr>
<tr>
<td>Massive hemoptysis</td>
<td>10</td>
</tr>
<tr>
<td>Post procedure PTX with multiple complications; coil at base of left hemithorax; VATS</td>
<td>17</td>
</tr>
</tbody>
</table>

Other causes of deaths through 12 months:
- COPD exacerbation
- Pneumonia:
  - Elevated lactic acid-153 days after 2\textsuperscript{nd} treatment
  - Aspergillus pneumonia-68 days after 2\textsuperscript{nd} treatment
Death Case Studies
Autopsy results in Pivotal and Crossover Study

• Pivotal death (d#73): Progressive RUL infiltrates started 30 days after procedure
  – Autopsy: extensive fibrosis of varying age and architecture at the site of the coils in the RUL
• Crossover Death (d#58): massive hemoptysis
  – Autopsy: right lung completely fused to the apical chest wall, with extensive necrosis and coils still in situ
• Crossover Death (d#10): massive hemorrhage
  – Autopsy: diffuse hemorrhage, coil hematomas, typically characterized as a discrete hematoma around each coil.
  – No gross specimens were available for second opinion

Limited autopsy results indicate that the local reaction may be a serious adverse event
Crossover Death: Coil Removal Attempt

- Crossover Death related to complications of procedure with recurrent pneumothorax
  - No clinical safety data on coil removal

The Panel will be asked to discuss the safety of coil removal
Pneumonia vs Coil Associated Opacity (CAO)
Pneumonia vs CAO

• 14/40 (35%) events in the treatment group were adjudicated as CAO after study completion by CEC.
• Either can be a serious AE
• Concerns with retrospective adjudication:
  – Insufficient clinical details
  – Subjects treated with antibiotics
  – chest x-rays results were not provided
  – Based on adjudications provided—difficult to distinguish
Pneumonia vs CAO

Examples of pneumonias re-adjudicated as CAO:

» Subject with **purulent sputum** and high right lobar infiltrate

» Subject with chills, low grade fever, discolored **sputum positive for aspergillus**

» Subject with fever, chills, RUL dense consolidation, **sputum positive for MRSA** and pseudomonas

» Subject with *right* infiltrate 40 days after *left* coil implant

» Subject with fever and chest pain 240 days post procedure

<table>
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<th>Pneumonia likely</th>
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<tbody>
<tr>
<td><strong>Purulent sputum</strong></td>
</tr>
<tr>
<td>Fever &gt;100.5°F</td>
</tr>
<tr>
<td>Positive blood culture</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pneumonia Suspected</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive sputum culture</strong></td>
</tr>
<tr>
<td>WBC &gt;12K with &gt;5% bands, shifts</td>
</tr>
</tbody>
</table>
Pneumonia vs CAO

Examples of inability to adjudicate:

» Subject with fever, dyspnea, wbc 12.2, CXR with RUL volume loss
» Subject with blood and sputum culture positive for Pseudomonas aeruginosa
» Subject hospitalized with positive blood culture for pseudomonas and Aspergillus
» Subject with fever, increased discolored sputum and RUL infiltrate
» Subject with increased purulent sputum positive for Stenotrophonas maltophilia.

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<table>
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<tr>
<th>Pneumonia Suspected</th>
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</thead>
<tbody>
<tr>
<td>CXR opacity is central/lobar segmental</td>
</tr>
<tr>
<td>Positive sputum culture</td>
</tr>
<tr>
<td>WBC &gt;12K with &gt;5% bands, shifts</td>
</tr>
</tbody>
</table>
Pneumonia vs CAO

Examples of SAE adjudicated as “CAO”:

» Subject died 6 days after 2\textsuperscript{nd} procedure with RUL opacification

» Subject received 5 weeks of IV and oral antibiotics with steroids

\textit{CAO can be a serious complication}
Hospitalization/ER Visits at 12 Months

Hospitalization/ER Visits at 12 Months Compared to 12 Months Prior to Study - % Subjects

- Hospitalization
  - Coil: 23.9%
  - Control: 4.5%
  - Crossover: 16.7%

- ER Visits
  - Coil: 7.1%
  - Control: -0.6%
  - Crossover: 8.8%

Increased unexpected hospitalizations and ER visits
Oxygen Use-Complete Case

Oxygen Use for RENEW and Crossover

No change in oxygen utilization at 12 Months
Safety Conclusion

• Mortality comparable between the treatment and control arm:
  – treatment deaths are potentially related to device complications
• COPD related serious adverse events higher in treatment arm:
  – COPD exacerbation
  – Pneumonia
  – Pneumothorax
• CAO is not well characterized and can be a serious complication
• Increased hospitalization and unexpected ER visits in the treatment arm
• SGRQ results do not correlate with the reported COPD related adverse events
PUBLISHED LITERATURE
CONCLUSIONS AND RELEVANCE Among patients with emphysema and severe hyperinflation treated for 12 months, the use of endobronchial coils compared with usual care resulted in an improvement in median exercise tolerance that was modest and of uncertain clinical importance, with a higher likelihood of major complications. Further follow-up is needed to assess long-term effects on health outcomes.

JAMA. 2016; 315(20):2178-2189
CONCLUSIONS AND RELEVANCE  In this preliminary study of patients with severe emphysema followed up for 6 months, bronchoscopic treatment with nitinol coils compared with usual care resulted in improved exercise capacity.........Further investigation is needed to assess durability of benefit............
REVOLENS Study

• Data for review based on publication only-no CRF and line data
• Lack of blinding: effect on 6MWT and SGRQ
• Crossover results not provided
• Unknown differences in treatment decisions: Scoring and SOC
• Unknown protocol and SAP modifications:
  – Conflicting information about the handling of missing data between the published SAP and the main body of the publication.
  – Secondary endpoints are exploratory: no prespecified multiplicity adjustment.
• Randomization: Ratio of 1:1 in blocks of 4.
  – Potential bias due to fixed block size such as (T,C,C,?)
CONCLUDING REMARKS
Clinical Issues Summary

• Significance of the safety data in a risk/benefit analysis
• Factors that may impact the estimation of the treatment effect:
  – Effect of maintenance pulmonary rehabilitation program on results
  – Pulmonary rehabilitation is required for pivotal, but not for crossover
  – Effect of lack of study blinding on SGRQ: results do not correlate with increased dyspnea, COPD exacerbations, pneumonias, hospitalization
• Target lobe selections not tested outside of central core laboratory assessment
Clinical Issues Summary

• Clinical uncertainties of study results:
  – Endpoints met statistical significance with uncertain clinical significance
  – Based on comparison to controls: OUS control did worse (-21 m decline) than US control (-5 m decline)
  – No improvement in 6MWT in crossover and RV ≥ 225 % did worse

• Pooled results may not be generalizable to US population.

• Effect of emphysema heterogeneity on study outcome:
  – Study population different than population identified by NETT to benefit from lung volume reduction

• Impact of data cut-off

• Observational Crossover study results conflicting with pivotal study
Patient Preference Information (PPI) Study

Heather Benz, PhD
Patient Preference

Division of Biomedical Physics
Office of Science and Engineering Laboratories
Center for Devices and Radiological Health
Recommended Qualities of Patient Preference Information (PPI) Studies

• Well-designed PPI studies can provide valid scientific evidence regarding patients’ risk tolerance and perspective on benefit.

• Recommended qualities of PPI studies\(^1\):
  
  A. All about Patients
  
  B. Good Study Design
    • Established Good Research Practices
    • Effective Benefit-Risk Communication
    • Minimal Cognitive Bias
    • Relevance
  
  C. Good Study Conduct and Analysis

• Early interactions with the Agency are encouraged.\(^1\)

Comparison of Treatments: RENEW Clinical Trial and PPI Study

<table>
<thead>
<tr>
<th>RENEW Clinical Trial</th>
<th>PPI study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2 Arms:</strong></td>
<td><strong>3 Treatments:</strong></td>
</tr>
<tr>
<td>• Optimal medical care ($n = 157$)</td>
<td>• Medicines</td>
</tr>
<tr>
<td>• Optimal medical care plus coil ($n = 158$)</td>
<td>• Implantable lung device</td>
</tr>
<tr>
<td></td>
<td>• Lung Surgery</td>
</tr>
</tbody>
</table>
Comparison of Benefit: RENEW Clinical Trial and PPI Study

**RENEW Clinical Trial**

**Secondary outcome:**
SGRQ (3 domains): Symptom frequency and severity, activities and breathlessness, impact

SGRQ improved by -8.9 points at 1 year (MCID -4).

45% of the Treatment group experienced a 1-step improvement in section 2 part 2.

**SGRQ Section 2 Part 2:**

<table>
<thead>
<tr>
<th>Activity</th>
<th>True</th>
<th>False</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting or lying still</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Getting washed or dressed</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Walking around the home</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Walking outside on the level</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Walking up a flight of stairs</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Walking up hills</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Playing sports or games</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

**PPI Study**

**Treatment benefit:**
Chance of improvement in shortness of breath in the next year (a 1-step improvement in modified SGRQ section 2 part 2)

**Modified SGRQ Section 2 Part 2 representation:**

![Modified SGRQ Section 2 Part 2 representation](image)
# Comparison of Risks: RENEW Clinical Trial and PPI Study

<table>
<thead>
<tr>
<th>RENEW Clinical Trial</th>
<th>PPI Study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subjects reporting pneumonia SAEs:</strong>&lt;br&gt;17.5% additional risk of pneumonia requiring hospitalization through 12 months</td>
<td><strong>Additional risk of pneumonia requiring hospitalization:</strong>&lt;br&gt;Additional risk of pneumonia requiring hospitalization in the next year (0 to 15%)</td>
</tr>
<tr>
<td><strong>Subjects reporting pneumonia AEs:</strong>&lt;br&gt;21% additional risk of lower respiratory tract infections including pneumonia through 12 months</td>
<td><strong>No information presented on other pneumonia AEs.</strong></td>
</tr>
</tbody>
</table>
PPI Study Design Concerns

Misalignment between PPI study benefits and risks and clinical benefits and risks:

• Respondents may have falsely assumed fewer medications were required with the implantable lung device when responding to the PPI survey.

• One question out of 16 total from the SGRQ was used to represent the coil benefit in the PPI survey.

• The risks presented in the PPI study do not map to the clinical risks:
  • Pneumonia requiring hospitalization in RENEW trial was greater than the risk of pneumonia requiring hospitalization presented to the PPI survey respondents.
  • Additional risks, such as overall risk of lower respiratory infection and risk of serious flare-ups, were not presented in PPI survey.
Non-RENEW Site PPI Respondents Significantly Preferred Medication over Device

- Survey respondents were recruited through clinical sites with experience in the treatment of emphysema.

- RENEW site respondents \((n = 165)\) preferred device over medicines, whereas non-RENEW site respondents \((n = 37)\) preferred medicines over device.

- Preference weights for all other attributes were very similar for the two groups.

- The RENEW and non-RENEW estimates cannot be pooled.
Benefit Presented in PPI Study Does Not Correlate with FEV₁

Scatterplot of Change in SGRQ Question 11 Total Score and Change in FEV₁ at 12 Months - ITT Population (RENEW)

Spearman Correlation Coefficient: 0.1893
Pearson Correlation Coefficient: 0.2287
Spearman Correlation Coefficient: 0.1893
Conclusion

• The results of a PPI study are intended to show that a substantial proportion of well-informed representative patients would accept the probable risks in exchange for the probable benefits.

• A PPI study for regulatory applications includes the benefits and risks that will be relevant to the benefit-risk assessment.

• When the PPI study benefits and risks do not map to the clinical trial outcomes, the PPI study has limited application to the specific device.

The applicant’s PPI study results may not be relevant to this benefit-risk assessment.
Applicant Proposed Future Post-Market Study

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Pulmonary

Respiratory Devices Branch
Office of Device Evaluation
Center for Devices and Radiological Health
Reminder

• The discussion of a post-market study prior to FDA determination of device approvability **should not** be interpreted to mean FDA is suggesting that the device is safe and effective.

• The plan to conduct a post-market study does not decrease the threshold of evidence required by FDA for device approval.

• The premarket data submitted to the Agency and discussed today must stand on their own in demonstrating a reasonable assurance of safety and effectiveness and an appropriate benefit/risk balance.
Applicant Proposed Post-Market Study

• New Enrollment, 300 subjects

• Primary effectiveness: Change in SGRQ at 12 months
  – Subjective outcome

• Composite respiratory related adverse events for safety: Lower Respiratory Tract Infection/Pneumonia, COPD Exacerbation, Severe Hemoptysis, Pneumothorax, Respiratory failure

The Panel will be asked to discuss the type of post-market study including registry.