

Non-Voting Question 1

1. The clinical study for the ELEVAIR Coils demonstrated a statistically significant absolute difference in 6MWT between the treatment and control arm at 12 months (median difference of 14.6 meters, adjusted mean difference of 10.2 meters). In addition, this study demonstrated statistically significant improvement in the secondary endpoints of FEV1, 6MWT responder rate and SGRQ. Potential confounders affecting the interpretation of these results include:
 - Post-randomization differences in patient management. For instance, data regarding pulmonary rehabilitation maintenance was not collected;
 - Open-label design affecting patient reported outcomes such as SGRQ;
 - Lack of correlation between US and OUS results and
 - Single arm observational crossover study conflicting with pivotal study results

Please discuss the following questions:

Non-Voting Question 1a

- a. The primary effectiveness endpoint evaluated the absolute difference in 6MWT between the treatment and control arm at 12 months. The results showed a median difference of 14.6 meters (adjusted mean difference of 10.2 meters). Please comment on the clinical significance of the observed treatment effect in 6MWT.

Non-Voting Question 1b

- b. The median percent change in FEV1 at 12 Months was 3.8% in the Coil Treatment group and -2.5% in the Control group, resulting in the median difference between the treatment and control group of 7%. Please comment on the clinical significance of the observed treatment effect in the percent change in FEV1.

Non-Voting Question 1c

- c. The SGRQ improved by -8.9 points at 12 months in the Coil Treatment Group as compared to the Control group. Please comment on the clinical significance of the SGRQ improvement in the context of an open-label trial and the increase in COPD-related adverse events including hospitalization and emergency room visits for the treatment arm.

Non-Voting Question 1d

- d. The observed treatment effect for the US subgroup was consistently smaller than that for the OUS subgroup for all the primary and secondary effectiveness endpoints. Also, the treatment by region interaction effects were statistically significant for 6MWT, FEV1 and SGRQ suggesting that pooled results may not be generalizable to the US population. Please comment on pooling of the US and OUS data for an overall assessment of effectiveness of coil treatment for the US population.

Non-Voting Question 2

2. Multiple subgroup analyses were performed:
- In the treatment arm, the pivotal study enrolled mainly subjects with homogeneous emphysema 77 % (122/158). The median treatment effect for the 6MWT at 12 months for the homogeneous emphysema subjects was 9 meters. In the crossover study the homogeneous emphysema subjects had a median decline of -20 meters in 6MWT at 12 months.
 - In the treatment arm, the pivotal study enrolled 23 % subjects (36/158) with heterogeneous emphysema. The median difference between the treatment and the control in 6MWT was 27.4 meters based on the small number of subjects with heterogeneous emphysema.
 - After study results were available and analyzed, the sponsor focused on the subpopulation with $RV \geq 225\%$ for all effectiveness endpoints and included “severe hyperinflation” in the indications for use. Data of 80 subjects (73 in US) with $175\% < RV < 225\%$ was not included. For the primary effectiveness endpoint of 6MWT, the coil treated subjects with $RV < 225\%$ declined more than the control subjects with $RV < 225\%$. Additionally, in the crossover study, $RV \geq 225\%$ subpopulation did worse than $RV < 225\%$ subpopulation.

Non-Voting Question 2a

a. Based on the proposed mechanism of action of compression of diseased tissue to allow more normal tissue to expand, the prior NETT study results, and pivotal study results, please comment on the observed treatment effect in the homogeneous and heterogeneous emphysema subpopulations.

Emphysema Status	Treatment Group	6MWT Median Change from Baseline (meters)	6MWT Median Difference (Coil Treatment vs. Control) [95% CI] (meters)
Homogeneous	Control (N=121)	-4.6 (-39.0, 27.0)	10.8 [-4.8, 26.2]
	Coil Treatment (N=122)	9.0 (-33.0, 39.3)	
	Crossover (N=62)	-20.10	N/A
Heterogeneous	Control (N=36)	-14.2 (-47.0, 25.2)	27.4 [-7.7, 59.7]
	Coil Treatment (N=36)	21.0 (-27.0, 59.4)	
	Crossover (N=18)	25.0	N/A

Non-Voting Question 2b

b. Please comment on the study results in the pivotal and crossover studies based on RV cut-offs ($RV \geq 225\%$ vs $RV < 225\%$).

Residual Volume	Treatment Group (N)	6MWT Median Change from Baseline (meters)	6MWT Median Difference (Coil Treatment vs. Control) [95% CI] (meters)
RV \geq 225%	Control (N=120)	-8.6 (-43.3, 24.4)	23.8 [7.4, 39.6]
	Coil Treatment (N=115)	15.0 (-31.1, 56.0)	
	Crossover (N=47)	-18.29	N/A
RV < 225%	Control (N=37)	0.0 (-38.0, 50.3)	-12.9 [-42.1, 17.0]
	Coil Treatment (N=43)	-9.8 (-36.0, 25.6)	
	Crossover (N=33)	-9.8	N/A

Non-Voting Question 3

3. A central core laboratory was contracted to review all computed tomography (CT) scans for the pivotal and crossover studies to make recommendations for each site for lobe location of coil placement. Please comment on the method of centralized scoring and patient selection and how this can be generalized to the real-world use.

Non-Voting Question 4a

4. There were more adverse events in the treatment arm at 12 months in comparison to the control arm. The device/procedure-related serious adverse events occurred in 45.8% of subjects in the treatment arm. 7 out of 10 deaths were possibly or probably device-related. Adverse events included COPD exacerbation (69.7% of treatment subjects and 58.0% of control subjects respectively), hemoptysis/hemorrhage (60% vs 0%), lower respiratory tract infections (32.9% vs 8.9%), pneumothorax (11.6 vs 0.6%), cough (18% vs 2%) and dyspnea (21.3% vs 7.6%). In the long-term safety follow up the most common AEs were COPD exacerbation and lower respiratory tract infections. Additionally, there was no reduction in COPD-related complications in coil treated patients.

Please comment on the following:

- a. Please discuss the safety of the coil treatment with regards to device related mortality, increased risk of COPD exacerbations, pneumonia, and pneumothorax in relation to underlying disease.

Non-Voting Question 4b

b. After the completion of the study, pneumonias were retrospectively adjudicated by the CEC to re-define some of these cases as non-infectious localized tissue reactions to the coils (termed Coil Associated Opacity”, or “CAO”). The safety of CAOs has not been established as there were related deaths with autopsy reports with fibrosis at the site of coil implantation.

Please discuss the increased risk of pneumonia, definition and the implication of the CAO with progressive fibrosis in coil treated subjects.

Diagnosis	Suggested Treatment Course
Pneumonia Likely	Antibiotics
Purulent sputum	
Fever >100.5°F	
Positive blood culture	
Pneumonia Suspected	Corticosteroids at discretion of investigator
CXR Opacity is central/lobar, segmental	
Positive sputum culture	
WBC > 12K with >5% bands, shifts	
CAO Likely	Suggest no antibiotics*
CXR Opacity is peripheral, localized to area around Coils, horse-shoe shaped	Corticosteroids 30 mg x 5 days
Fever <100.5°F	
WBC <12K without shifts	Ibuprofen at investigator discretion
Negative blood or sputum culture	Suggest follow-up with CXR in 7d to confirm DX
No change from baseline sputum	

**If high clinical suspicion of infectious process, start antibiotic therapy*

Non-Voting Question 4c

- c. There is limited data on the applicant's recommendation for bronchoscopic coil removal within 2 months of deployment. There were no coil removals during the clinical trial and furthermore, the limited autopsy results have shown fibrosis around the coils. Please comment on the coil removal recommendation provided in the labelling for patients with severe emphysema.

Non- Voting Question-Future Post-Market Study



The presence of a post-market study plan does not alter the requirements for pre-market approval and a recommendation from the Panel on whether the benefits outweigh the risks. **The premarket data must reach the threshold for providing reasonable assurance of safety and effectiveness before the device can be found approvable** and any future post-market study could be considered.

The applicant is proposing a post market study with the primary effectiveness endpoints of change in SGRQ, from baseline to 12 months post first implant. The proposed primary safety endpoint is the composite rate of device- and/or procedure-related serious respiratory adverse events (RAEs) through 12 months. RAEs will be defined as AEs of the following types: Lower Respiratory Tract Infection/Pneumonia, COPD Exacerbation, Severe Hemoptysis, Pneumothorax, Respiratory failure.

Should the device be found approvable, please comment on whether a post-approval study would be recommended, and if so:

- a. Please comment on which safety and effectiveness endpoints should be collected.
- b. Please comment whether a registry would be an appropriate mechanism to collect the desired information.