DRAFT PANEL QUESTIONS

ANESTHESIOLOGY AND RESPIRATORY THERAPY DEVICES PANEL
OF THE MEDICAL DEVICES ADVISORY COMMITTEE

PneumRx® Elevair ™ Endobronchial Coil System

June 14, 2018

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:

    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.

    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.

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.

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 data may not be applicable 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.

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 ≥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 ≥225 % subpopulation did worse than RV< 225 % subpopulation.

   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[2] (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[2] (N=18)	25.0	N/A

b. Please comment on the study results in the pivotal and crossover studies based on RV cut-offs (RV≥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 >= 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

3. A central core lab 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.

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 device subjects and 58.0% of control subjects respectively), hemoptysis (58.7% vs 0 %), lower respiratory tract infections (32.9 % vs 8.9 %), pneumothorax (11.6 vs 0.6 %) 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.

    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 autopsy reports with fibrosis at the site of coil implantation. Please discuss the increased risk of pneumonia and the implication of the CAO in coil treated subjects.

    c. There is limited data on the applicant's recommendation for bronchoscopic coil removal within 2 months of deployment. Please comment on the coil removal recommendation for patients with severe emphysema.

5. The applicant has presented data from OUS (France), the REVOLENS study which was sponsored by Reims University Hospital in France. Since this study was not conducted by the applicant, there were limitations on the available data and how the study was conducted. The primary endpoint was improvement of at least 54 meters in 6MWT at 6 months In the JAMA publication, the study reported a 54 meters improvement in the 6MWT in 18/50 subjects in the coil treated group versus 9/50 in the control at 6 months which was reported as statistically significant. However, the 12 month 6MWT difference between the treatment and the control was 21 meters which was not statistically

significant. Please comment if there is sufficient data to draw a benefit conclusion based on this published study.

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 effectives 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.

1. 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.