FDA Executive Summary

P170004
PneumRx, Inc.
Elevair Endobronchial Coil System

Prepared for the
June 14, 2018 Meeting of the
The Anesthesiology and Respiratory Therapy Devices Panel

Division of Anesthesiology, General Hospital, Respiratory, Infection Control and Dental Devices
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration

1 Table of Contents

List of Figures

List of Tables

List of Abbreviations

Abbreviation	Definition
6MWT	Six Minute Walk Test
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATS	American Thoracic Society
CAO	Coil Associated Opacity
CEC	Clinical Events Committee
COPD	Chronic Obstructive Pulmonary Disease
FEV1	Forced Expiratory Volume in 1 second
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ITT	Intent To Treat
LVR	Lung Volume Reduction
LVRS	Lung Volume Reduction Surgery
MC	Major Complication
MCID	Minimal Clinically Important Difference
mMRC	Modified Research Council Dyspnea Scale
OUS	Outside of United States
RV	Residual Volume
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SGRQ	St. George's Respiratory Questionnaire
TLC	Total Lung Capacity

1 Synopsis

This is Food and Drug Administration's (FDA) Executive Summary of the pre-market approval (PMA) application, P170004, for the first-of-a-kind device Elevair Endobronchial Coil System from PneumRx Inc. (applicant). The applicant provided non-clinical and clinical data and FDA does not have any non-clinical concerns. The purpose of this advisory panel meeting is to obtain the Panel's feedback regarding the clinical data provided in this PMA application.

The Elevair endobronchial coil is a nitinol coil that is deployed bronchoscopically to achieve non-surgical lung volume reduction in patients with severe emphysema. The clinical evidence submitted to support this application is a prospective,12-month assessor blinded, randomized, multi-center trial (RENEW study) performed in the U.S., Canada and Europe with four-years of additional follow-up. Subjects and investigators were not blinded. There was a subsequent single arm crossover study of eligible control group subjects to receive coil treatment at 12 months. In this trial, both the treatment and control arms were treated with standard of care based on the GOLD recommendations[1]. Accordingly, all subjects received pharmacological treatment and were required to complete a pulmonary rehabilitation program prior to enrollment.

The RENEW pivotal study randomized 315 subjects in a 1:1 ratio at 20 United States (US) sites and 6 Out of United States (OUS) sites. The control subjects in the RENEW study were followed for 12 months, and then had the option to enroll in a crossover study. The crossover study was conducted as a prospective, multi-center, single arm study that included 102 subjects.

The RENEW clinical trial was designed to evaluate the difference in 6MWT, FEV1 and SGRQ outcomes between the treatments at 12 months as surrogates for exercise tolerance, lung function and quality of life. For the primary effectiveness endpoint of change in 6MWT, there was a median difference in the 6MWT of 14.6 meters (adjusted mean difference of 10.2 meters) between the treatment and control groups for the intent to treat (ITT) population at 12 months. This median difference was statistically meaningful (p=0.0153). Regarding the secondary endpoints at 12 months, the 6MWT responder rate, as defined by a minimum improvement of 25 meters, was 37.9% versus 26.2% in treatment and control for the ITT population, respectively (p=0.0063). The percent median change in FEV1 improved by 7% (p <0.0001) and SGRQ improved by -8.9 units (p< 0.0001) compared to the control group.

The long-term data analyses showed a loss of treatment effect beyond 12 month; however, without a control arm it is not possible to determine how these subjects would have performed without treatment. In the pivotal study, 114 subjects (81%) completed the 24-month follow-up visit and 49 subjects (39%) completed the 36-month follow-up visit as of the cut-off date. The 6MWT declined by mean -17.2 meters at 24 months and mean -39.3 meters at 36 months compared to baseline. FEV1 was similar to baseline at the 24 and 36

month follow up. SGRQ mean was -4.4 points at 24 months and was similar to baseline at 36 months.

The single arm crossover effectiveness results were not consistent with the pivotal study results although the inclusion criteria were similar for the two studies. At 12 months, the 6MWT was reduced by a mean of - 22.9 meters compared to baseline before coil treatment. The 6MWT responder rate at 12 months was 26.3%, which was similar to the responder rate observed in the control group of the pivotal study and mean percent change in FEV1 showed a minimal change of 2.2%. The mean change in SGRQ score was -4.8 at 12 months.

As part of the benefit-risk evaluation for the coil treatment, the adverse events were analyzed. The most frequently reported adverse event (AE) in both the treatment and control groups was COPD exacerbation (69.7% of subjects and 58.0% of subjects, respectively). The treatment arm had an increased percent of subjects with AEs of 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 comparison to controls in the first 12 months post treatment. Device/procedure related serious adverse events (SAEs) occurred in 45.8% of subjects in the treatment arm. The mortality rate in the two arms were comparable; however, most of the deaths in the treatment group were device possibly or probably and/or procedure-related adverse events. The expectation of treatment in COPD patients would be a decrease in disease related AEs and health care resource utilization such as hospitalization after coil treatment. However, there was no reduction in COPD related AEs such as COPD exacerbation, lower respiratory tract infection or dyspnea. In addition, there was increased health care resource utilization in the 12 months after the treatment.

The single, prospective, multicenter randomized trial supporting this application demonstrated a statistically significant improvement in 6MWT, FEV1 and SGRQ at 12 months; however, the clinical meaningfulness of the observed changes in these endpoints is uncertain. Data regarding maintenance pulmonary rehabilitation were not collected as part of the study. Therefore, the effect of this confounding factor on the study results is unknown. The SGRQ results need to be interpreted with caution since there was no sham blinded arm. In addition, there were more COPD-related AEs in the treatment group compared controls, which did not correlate with the improvement observed in the SGRQ results. Moreover, there are significant risks associated with the coil treatment and the subsequent single-arm crossover study of the control patients did not replicate the results of the treatment arm during the randomized portion of the pivotal study. Given the uncertain clinically meaningful benefit, the panel will be asked to consider the totality of the evidence while weighing the benefit-risk profile of the Elevair Endobronchial Coil System for patients with severe emphysema.

2 Introduction

This is Food and Drug Administration’s Executive Summary of the pre-market approval (PMA) application, P170004, for the Elevair Endobronchial Coil System

from PneumRx Inc. (applicant). The Elevair Endobronchial Coil System consists of a sterile single-use coil implant and a sterile, single-procedure (disposable) Delivery System comprised of a cartridge, catheter, guidewire and forceps. The Delivery System is intended to be used to deliver multiple coils into a patient during an implantation procedure for the treatment of severe emphysema. The coil is made of passivated nitinol and includes 100 mm, 125 mm, and 150 mm coil sizes.

This summary contains an overview of current treatment options, a device description, a summary of non-clinical (Appendix 14.8) and clinical studies conducted by the applicant, and additional analyses performed by Food and Drug Administration (FDA, also referred to as the Agency). The purpose of this advisory panel meeting is to obtain the Panel's feedback regarding the clinical data provided in this PMA application. The Advisory Committee (Panel) will be asked to comment on several topics of interest to the FDA. In addition, Panel members will be asked to provide recommendations and vote on whether the data provided demonstrate a reasonable assurance of safety and effectiveness, as well as a favorable benefit-risk profile, for the Elevair Endobronchial Coil System in patients with severe emphysema.

3 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.

4 Clinical Background

COPD is a progressive disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases[1]. It is the leading cause of disability worldwide and currently it is the fourth leading cause of death in the world and the third leading cause of death in the US. The parenchymal lung tissue destruction results in loss of lung elasticity with reduced lung recoil, increased airway resistance and air trapping. These anatomical changes lead to increased symptoms of breathlessness, reduced exercise capacity, impaired quality of life, increased morbidity with COPD exacerbations, respiratory infections, respiratory failure and increased mortality[2].

Patients with advanced disease are treated with medications, oxygen and life style changes including pulmonary rehabilitation. Medical management includes smoking cessation and pharmacological intervention with bronchodilators, anti-inflammatories and antibiotics. For a select group of patients surgical lung volume reduction or lung transplantation is recommended. Treatment options for patients with advance disease are limited because of significant associated co-morbidities, strict patient selection criteria and donor shortages. Surgical lung volume reduction was developed over 20 years ago and has emerged as an effective treatment modality for select patients with emphysema. It has shown long-lasting

improvements in lung function, exercise capacity, quality of life and survival[3]. The large randomized multicenter trial, National Emphysema Treatment Trial (NETT) found that patients with upper-lobe emphysema and low base-line exercise capacity had a survival advantage over patients treated with medical management[4]. Although, there are functional benefits to lung-volume reduction surgery, there is increased short-term morbidity and mortality. To avoid the perioperative morbidity and mortality of lung volume reduction surgery (LVRS) and with the improvements in interventional pulmonary strenuous efforts have been directed toward developing various nonsurgical, endoscopic approaches to lung volume reduction in patients with advanced emphysema.

5 Rationale for Presentation to Panel

In addition to the fact that the Elevair Endobronchial Coil System is a first-of-a-kind device, the Agency is presenting this PMA application to the Panel based on the reasons listed below. The Agency has questions regarding the study results and interpretation of the clinical findings. Specifically, the Agency has identified the following issues related to this clinical study:

- The primary effectiveness endpoint of change in 6MWT from baseline between the treatment and control at 12 months has uncertain clinical importance.
- The secondary effectiveness endpoint of SGRQ showed improvement. However, there was no sham control or effective blinding.
- The difference between the treatment and the control 6MWT responder rate was 11.7 % at 12 months. As part of the inclusion criteria, the subjects were required to complete a pulmonary rehabilitation program within 6 months prior to treatment. Although, per protocol, all subjects were encouraged at each visit to continue maintenance, data regarding which subjects continued with a maintenance program was not collected. It is unknown if the differences observed in the responder rates between the treatment and control were confounded by ongoing maintenance therapy.
- 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.
- The study enrolled mainly homogeneous emphysema subpopulation (77%). However, the treatment effect did not show clinically meaningful change in this group. Based on the proposed mechanism of action, inconsistent clinical results and the prior NETT study[4] , it is uncertain if there is coil treatment effect in patients with homogeneous emphysema.
- The crossover population was 65% of the control group of the pivotal study and had similar inclusion/exclusion criteria. The study results showed worsening parameters after 12 months of treatment compared to their own baseline. Like the

pivotal study subjects, the cross-over subjects would be the patient type that would be treated with this type of device in routine clinical practice.

- There were increased serious adverse events in the treatment group that was associated with an increased risk of thoracic major complications that included pneumonia, COPD exacerbations, hemoptysis, and pneumothorax. The majority of the deaths in the treatment arm were possibly or probably device and/or procedure related.
- There was increased hospitalization and unexpected emergency room (ER) visits in the treatment arm compared to the control arm.

6 Device Description

The Elevair Endobronchial Coil System (ELEVAIR System) (*Figure 1*) consists of a sterile single-use coil implant and a sterile single-procedure (disposable) delivery system. The Delivery System is intended to be used to deliver multiple coils into one patient during an implantation procedure.

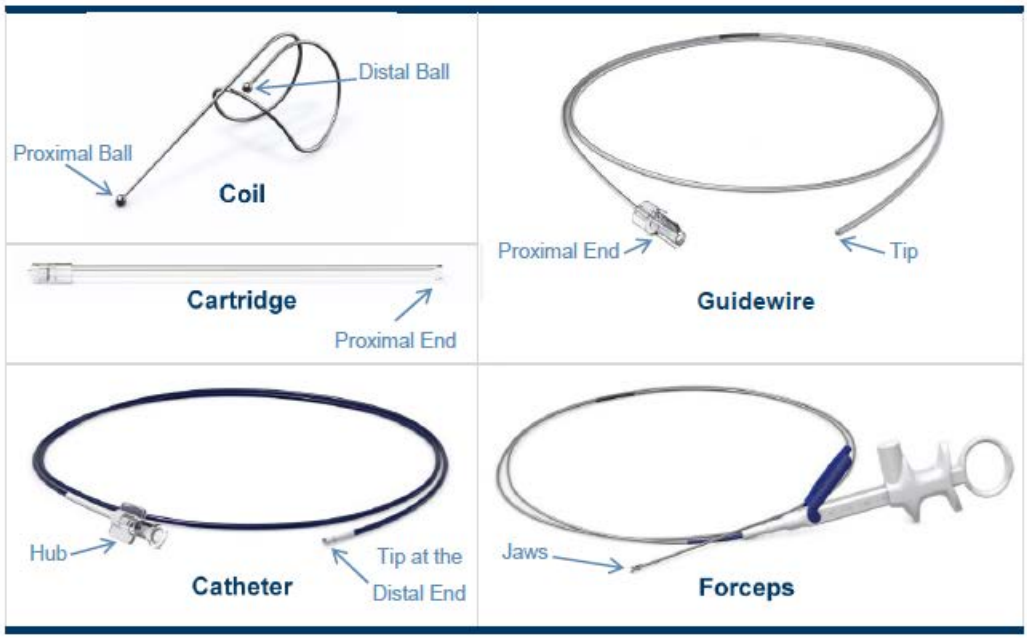


Figure 1: Elevair Endobronchial Coil System

Coil:

The coil (*Figure 2)* is made entirely of passivated nitinol which is composed of nickel and titanium. Passivation is a process that is used to mitigate against corrosion. Coils are provided in three lengths: 100 mm, 125 mm and 150 mm. The most proximal end of the coil (6.9 mm – 12.7 mm, depending on coil size) has a smaller diameter than the rest of the coil. The distal and proximal ends of the coil terminate with a ball.

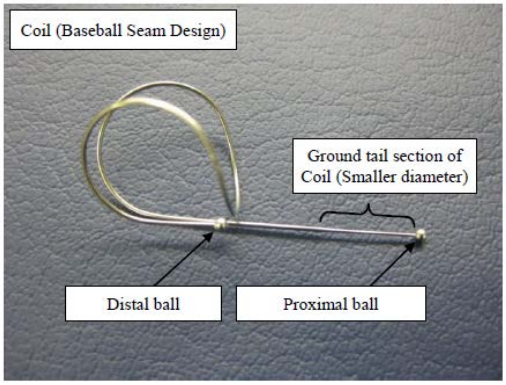


Figure 2: Coil components

Delivery System:

The delivery system consists of guidewire, catheter, cartridge and forceps (*Figure 3*). The delivery system is used in conjunction with a minimum 2.8 mm diameter working channel therapeutic bronchoscope and fluoroscopy for visualization beyond the bronchoscope:

- The guidewire guides the catheter to the airway and facilitates the selection of appropriate coil length;
- The catheter provides a conduit to the target airway site for coil delivery;
- The cartridge temporarily straightens the coil to allow loading into the catheter; couples to the hub of the catheter; and,
- The forceps grasps the proximal end of the coil and is used to deliver the coil to the target airway through the catheter or to retrieve the coil if appropriate.

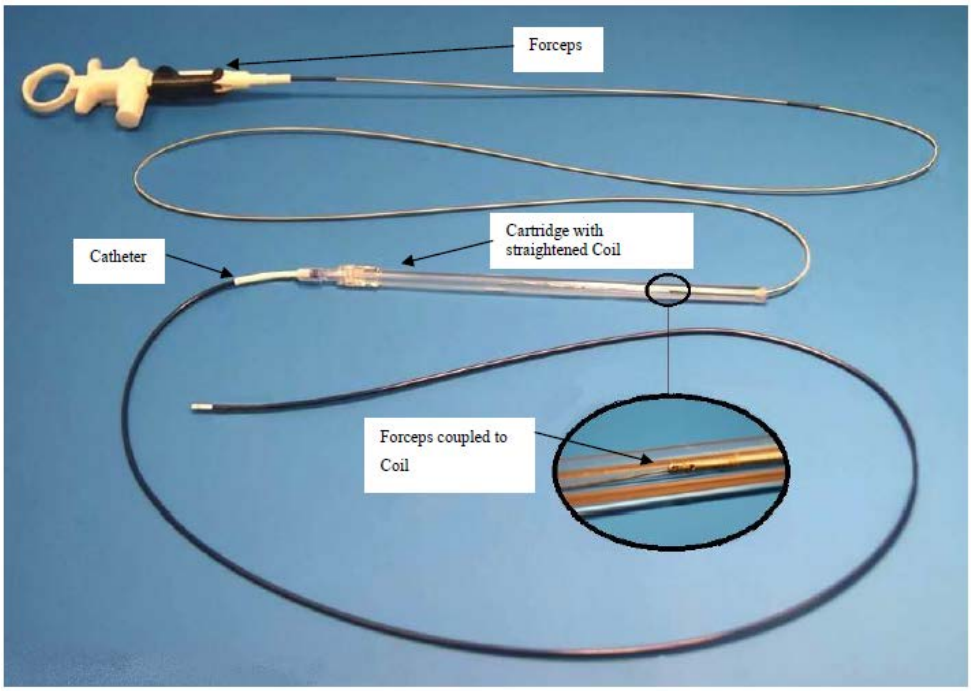


Figure 3: Delivery System

Mechanism of Action:
The mechanism of action of the ELEVAIR System is hypothesized to cause a reduction of hyperinflation and lobar volume through:

- compression of diseased tissue to allow more normal tissue to expand;
- restoration of lung tension to tether open and maintain airway patency;
- adjustment of lung compliance to shift preferential filling from diseased tissue to healthy tissue.

The coil is deployed using a bronchoscope and is designed to recover to "baseball seam" shape (*Figure 2*) after being straightened for insertion into the subsegmental airways. The straightened shape (of the coil) is maintained during advancement of the coil down the catheter to the airways; shape recovery occurs when the coil is deployed (*Figure 4*).

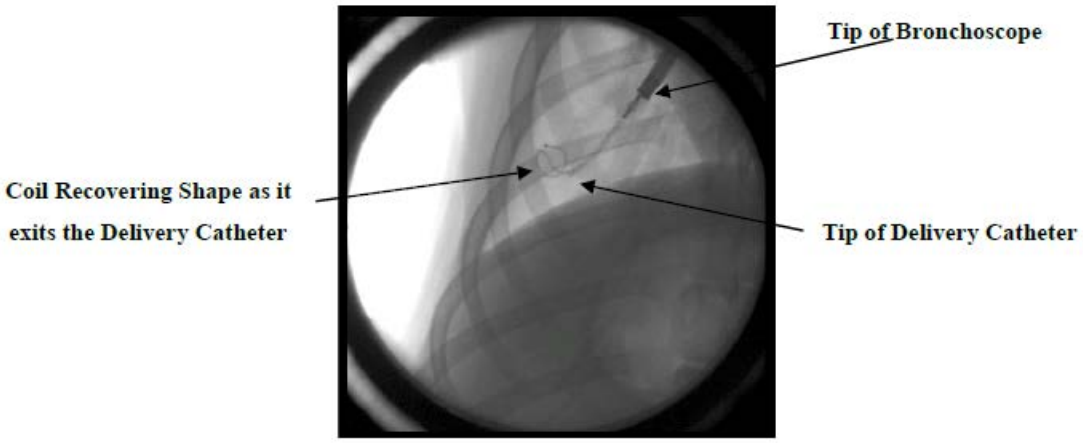


Figure 4: Shape Recovery of the ELEVAIR Coil

During shape recovery, as the ends of the device draw together, a long segment of the treated airway is transitioned into the baseball seam shape and the airways adjacent to the distal and proximal ends of the coil are drawn more closely together (*Figure 5*). The coil is theorized to reduce the effective length of the treated airway, thereby increasing tension in the lung tissue.

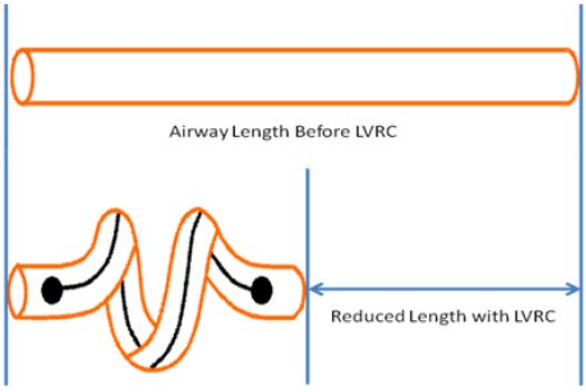


Figure 5: Coil Effect on the Airway Length

Coil Removal:
The coil should be considered a permanent implant. However, according to the applicant, if removal is medically indicated, the preferred route of removal is bronchoscopic. Bronchoscopic removal (outside of coil removal or repositioning performed during the initial implantation procedure) is accomplished with a 2.0 mm working channel bronchoscope under fluoroscopy by 1) re-capturing the proximal end of the coil with the forceps and 2) advancing the scope distally, as far as possible, while proximally retracting the forceps to remove the coil from the airway and into the bronchoscope working channel. Removing coils bronchoscopically can become difficult after 2 or more months of implantation, depending on the amount of tissue regrowth present. If bronchoscopic removal is not possible, surgical removal may be required.

FDA Comment: The recommendations for coil removal were based on animal studies.

7 Pivotal and Crossover Clinical Study and Design

The applicant conducted a clinical study in subjects with homogeneous and/or heterogeneous severe emphysema: Lung Volume Reduction Coil Treatment in Patients with Emphysema (RENEW) Randomized trial. This study also included a RENEW Roll-In cohort (single arm), and a Crossover study (single arm). Section 14.1 of the appendix includes studies conducted by the applicant prior to the pivotal study presented in the executive summary.

A total of 315 subjects were enrolled in the randomized phase of the study at 26 sites (6 OUS sites, 20 US sites), which included 158 subjects randomized to the coil treatment group and 157 subjects randomized to the control group. All treatment and control subjects in the study were treated with standard of care medical therapy based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations and were also required to complete pulmonary rehabilitation prior to study enrollment. Standard-of-care pharmacologic therapy may have included an inhaled long-acting β-agonist, inhaled anticholinergic, or both. These drugs could also be combined with theophylline and/or inhaled corticosteroids at the discretion of the subject's treating physician.

Subjects in the coil Treatment group received treatments with the Elevair System approximately 4 months apart in the pivotal study. Treatment group subjects were scheduled to be followed for 5 years following the initial coil procedure, whereas control group subjects exited the study following the 12-month visit. Upon completion of the control period of the RENEW study (12-month visit), control subjects were eligible to undergo screening and enroll in the Crossover Study, which offered treatment with the coils. These control subjects who crossed over also had to meet a similar inclusion/exclusion criteria to the RENEW study to be eligible. In the crossover study. 124 subjects were screened and 102 (82%) were enrolled.

7.1 Objective

The primary objective of the RENEW study was to determine whether treatment with the Elevair Endobronchial Coil System (ELEVAIR) resulted in improved exercise capacity, as measured by improvements in the 6 Minute Walk Test (6MWT). Secondary objectives of the RENEW study were to determine whether treatment with the Elevair System resulted in improved lung function and quality of life as measured by improvements in pulmonary function testing (PFT) and the St. George's Respiratory Questionnaire (SGRQ).

7.2 Study design

The RENEW Randomized Trial was a prospective, multi-center, randomized, assessor blinded, controlled study designed to demonstrate the safety and effectiveness of the Elevair Endobronchial Coil System in a population of patients with severe emphysema. At study entry, after provision of written informed consent, screening procedures were performed. The screening procedures included lung computed tomography (CT) scans, which were evaluated by the CT core laboratory.

The applicant developed a CT based method to select patients and plan the coil treatment using lobar damage visual assessment and scoring. This method was used to score the most severe damage in each lobe. The core laboratory assessed lung parenchyma damage per a CT Scoring Plan (*Appendix 14.2*), and transmitted subject eligibility assessment and recommendations on bilateral lobes to be treated to the study site and the study sponsor. Subjects who qualified for study participation based on CT scan findings and the inclusion and exclusion criteria were then block randomized in a 1:1 ratio to the treatment group or the control group. The randomization was stratified by homogeneous versus heterogeneous emphysema. All subjects in the pivotal trial, including the control group, received standard-of-care medical therapy for emphysema, including pharmacological treatment and the completion of a pulmonary rehabilitation program prior to enrollment.

Each subject randomized to the treatment group was scheduled to undergo 2 bronchoscopy procedures, approximately 4 months apart, for placement of coils. Only one lobe was to be treated per lung, and only one lung was to be treated per procedure. The treatment plan recommended treatment in the upper or lower lobe with the highest character score in each lung, as indicated by the treatment planning chart (*Appendix14.2, Table 20*). The suggested treatment was 10 to 12 coils for upper lobes and 10 to 14 coils for lower lobes. Differing lung anatomy created variation in number and size of coils implanted per lobe. The 4-month separation was designed to give subjects time to recover from the initial coil procedure and allow for resolution of any ongoing adverse events prior to undergoing the second coil procedure. *Figure 6* is a chest X-ray image showing the lungs of a patient treated bilaterally with coils.

Treatment planning was based on the CT core laboratory readers assignment character score for each lung lobe. The single axial slice with the greatest severity of damage (largest total area of tissue defects). Readers then compared the average damage observed in that slice (not the single largest defect in the slice) with the provided visual standards of lung damage to

assign a score for the lobe. This was not an average of the entire lobe. This method characterized the slice with the greatest combination of tissue defects that could possibly interrupt the transmission of tension by the Coils across the lobe of interest. Based on the final character score a treatment plan was recommended or the subject was excluded.

At each study site without prior experience with coils, the first 2 subjects who met all study eligibility criteria were not randomized, but were enrolled into the RENEW study as roll-in subjects and assigned to treatment with the coils, as part of investigator and staff training.

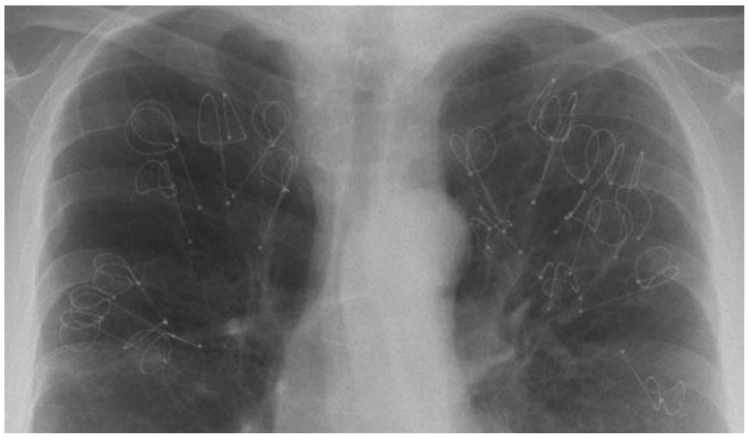


Figure 6: Bilaterally treated lungs

All subjects underwent pulmonary function tests (PFT) and 6MWT during study participation at predefined time points. Prior to testing, the subject's current medications were reviewed and adjusted. During the 6MWT, the subject was allowed to use supplemental Oxygen (O_2), if needed. Oxygen titration was done prior to the baseline 6MWT and was not to exceed 6 L/min flow via nasal cannula. If, while at rest prior to test initiation, the subject was unable to maintain a SpO2 of 90% on 6 L/min via nasal cannula, the study coordinator was to ask the investigator for guidance before initiating the 6MWT. A trained individual who had no knowledge of the treatment assignment was assigned to perform the 6MWT and PFT. These assessors were trained to perform the 6MWT and PFT tests per protocol-specific training materials and the ATS Guidelines. In order to reduce testing variability, site personnel were asked to:

- have the same assessor perform testing for the same subject throughout his/her participation on the study. If this was not possible, at a minimum, have the same assessor perform testing at Visit 1 (Baseline Evaluation) and Visit 10 (12-month Follow-up Evaluation) for each subject, if possible.
- use the applicant-provided standard instructions/phrases of encouragement for each subject.

FDA Comment: A central core laboratory reviewed all CT scans and assigned a score with treatment recommendations. It is unknown, whether this method of scoring and patient selection can be generalized to real world use.

7.3 Inclusion/Exclusion Criteria

The inclusion/exclusion criteria for the study was based on definitions of severe emphysema with hyperinflation (*Appendix 14.3, Table 21*). The study inclusion criteria initially enrolled subjects with RV ≥ 225 %. In July 2014, the inclusion criterion was revised and the cutoff for the RV was changed from ≥225% to ≥175% predicted. At the time of the change 169 of the 315 subjects had been enrolled. Of the 146 subjects randomized after the protocol revision, 80 (54.8%) subjects had baseline RV < 225% predicted. The exclusion criterion also excluded subjects with significant co-morbidities that would impact their ability to improve their exercise tolerance.

The control group was allowed treatment with the coil after they met the inclusion/exclusion criteria for the cross-over study. The 12-month visit of the RENEW study was used for the baseline data of the subjects being evaluated for the crossover study unless the RENEW data was taken more than 6 weeks prior to crossover screening. The inclusion/exclusion criteria were similar between the pivotal study and crossover study. Dyspnea scoring ≥2 on mMRC (Modified Research Council Dyspnea Scale), TLC>100% predicted and the requirement for performing pulmonary rehabilitation were removed from the cross-over inclusion criteria. The dyspnea score and TLC values were not expected to impact the study, as they were part of the initial inclusion criteria and not expected to improve prior to crossover enrollment.

FDA Comment: The following are the major highlights of the inclusion criteria:

- ***Prior experience based on the NETT trial results[4] showed that the group of patients that benefit from LVRS are patients with heterogeneous emphysema; however, an early feasibility study with this device showed that patients with homogeneous emphysema may also benefit from coil treatment and therefore, the RENEW pivotal study enrolled subjects with mostly homogeneous emphysema.***
- ***The inclusion criterion cutoff for the RV ≥ 225% was pre-specified; however, this cutoff was not clinically supported.***
- ***One major difference between the pivotal and crossover study was the requirement of a completed pulmonary rehabilitation program prior to enrollment into the pivotal study.***

7.4 Endpoints

7.4.1 Effectiveness

The **primary effectiveness endpoint**

- The primary effectiveness endpoint was the mean absolute change from baseline in the 6MWT at 12 months. Superiority of coil treatment vs. control was to be tested (overall type I error one-sided, $\alpha = 0.025$).

If superiority was established for the primary effectiveness endpoint, the following **secondary effectiveness endpoints** would be tested using Hochberg's step-up procedure for superiority of coil treatment vs. control (overall type I error one-sided, $\alpha = 0.025$):

- Six Minute Walk Test (6MWT): responder analysis, comparing baseline to 12 months, responders defined as subjects with an improvement of ≥25 meters.
- St. George's Respiratory Questionnaire (SGRQ): absolute difference in SGRQ results comparing baseline to 12 months.
- Forced Expiratory Volume in 1 second (FEV1): percent change in FEV1 results measured using spirometry, comparing baseline to 12 months.

Other effectiveness endpoints defined in the study protocol included:

- SGRQ response at 12 months, responder analysis. In this analysis, response was defined as an improvement of ≥4 points from baseline.
- Residual Volume (RV): Mean absolute difference from baseline in RV at 12 months measured using plethysmography.
- Residual Volume/Total Lung Capacity (RV/TLC): Mean absolute difference from baseline in Residual Volume/Total Lung Capacity (RV/ TLC) at 12 months measured using plethysmography.

In addition to those noted above, the study protocol also defined a number of additional measures of interest that would be analyzed using descriptive statistics. These included mean change in Inspiratory Capacity (IC), mean change in FEV1, percentage change in 6MWT, percentage change in RV, oxygen usage, drug usage for treatment of emphysema, unanticipated doctor visits, number of days missed from school/work, and Emergency Room visits.

7.5 Safety

The primary safety analysis in this study was defined as the proportion of subjects experiencing 1 or more major complications (MCs) through the 12-month follow-up visit.

MCs in the RENEW protocol were defined as:

- *Death*;
- *Pneumothorax* that required a chest drainage tube for more than 7 days (from time of chest drainage tube insertion to the time of chest drainage tube removal);
- *Hemoptysis* requiring blood transfusion(s), arterial embolization, or surgical/endoscopic procedure;
- *COPD exacerbation* that became life-threatening or disabling as a result of an increase in respiratory symptoms requiring in-patient hospitalization of >7 days with or without mechanical ventilation;
- *Lower respiratory infections* (including pneumonia) defined by new or increased clinical symptoms such as fever, chills, productive cough, chest pain, dyspnea, and an infiltrate on plain chest x-ray and hospitalization for administration of intravenous antibiotics and/or steroids;
- *Respiratory failure* defined as a requirement for mechanical ventilator support (whether via endotracheal tube or mask) for >24 hours;

- *Unanticipated bronchoscopy* in order to remove 1 or more coils due to device related AE. (Note: This definition does not include repositioning, replacement, or removal of the Coil(s) during the initial placement procedure.)

A Clinical Events Committee (CEC) evaluated all Adverse Events (AEs) and Serious Adverse Events (SAEs) that were potential MCs and determined whether the reported events met the MC criteria. Subjects were counted at most once for each major complication event type. All safety endpoints were analyzed using descriptive statistics.

7.6 Study Analysis Plan Summary

RENEW Pivotal Study:
Both the primary and secondary effectiveness analyses were based on the ITT population. Tests of superiority were based on either parametric or non-parametric (e.g., using rank transformed data) ANCOVA methods. Where distributions were markedly skewed, non-parametric ANCOVA of rank transformed data was considered the primary analysis. Each ANCOVA or rank transformed ANCOVA model included factors of treatment, emphysema heterogeneity status, analysis center and the corresponding baseline covariate.

The primary and secondary effectiveness analyses were tested for superiority using 1-sided tests with an overall significance level of 0.025. To control the familywise Type 1 error rate, secondary effectiveness analyses were performed with adjustment for multiple comparisons using Hochberg's step-up procedure, and only when the primary effectiveness analysis was statistically significant.

Missing 12-month values for effectiveness endpoints were estimated by MCMC multiple imputations for continuous variables assuming data were missing at random. The full statistical analysis plan is included in *Appendix 14.6*.

The following three prespecified subgroup analyses were presented for the primary and secondary endpoints:

- US versus OUS (out of the US)
- Heterogeneity of emphysema
- Severity of air trapping (RV $\geq$ 225% vs. RV < 225%)

Gender was also a prespecified subgroup analysis. The median 6MWT change between control and treatment was 11.8 meters for female subjects and 18.0 meters for male subjects. All secondary endpoint results were similar in males and females.

Crossover Study:
Crossover study was an observational study and only descriptive summaries of the results are provided.

7.7 Changes in the Conduct of the Study and Planned Analyses

7.7.1 Changes in the Conduct of the Study

The RENEW protocol was conditionally approved by FDA on 11 May 2012. A subsequent version of the protocol was approved on 20 Sep 2012 which allowed the enrollment of a total of 315 randomized subjects at up to 30 study sites, and up to 2 Roll-In subjects per North American study site without prior coil experience.

A summary of the important protocol changes is provided below:

- The cap on the number of homogeneous emphysema subjects was removed from the randomization scheme. The study was initially limited up to 150 subjects (75 in the coil arm and 75 in the control arm). This change was approved by FDA on 15 Jan 2014.

- The inclusion criterion for RV was changed from ≥225% to ≥175% predicted when one hundred sixty-nine (169) of 315 randomized subjects had been enrolled. The applicant stated that the rationale for this change was to broaden the target population of the RENEW study candidates. This revision also clarified the exclusion criterion by allowing the rare candidate for whom asthma could clearly be ruled out despite showing a change in FEV1 >20% to be enrolled into the study. This change was approved by FDA on 02 Jul 2014.

FDA Comments: The changes have an impact on the generalization of the study results. After the study completion and unclear clinical significance of the overall results, the applicant focused only the subpopulation of RV ≥ 225%.

7.7.2 Changes in the Planned Statistical Analyses

The original Statistical Analysis Plan (SAP) for the RENEW study was finalized on 16 Dec 2013(version 0.5). The planned primary statistical analysis method in SAP (version 0.5) was to compare the adjusted mean change in 6MWT from Baseline to the 12-month between coil group and control group. The comparison of the adjusted mean change in 6MWT was based on a parametric analysis of covariance (ANCOVA) with factors of treatment and investigational site and covariates of baseline 6MWT and emphysema.

After the protocol was finalized, the applicant made the following changes to their SAP(v0.5) on 17 Sep 2015 when the RENEW pivotal study was almost completed:

"*Tests of superiority will be based on either parametric or non-parametric methods consistent with the statistical assumptions required to support the analyses. Specifically, the tests of superiority will be based on an ANCOVA with factors of treatment, analysis center, baseline 6MWT and emphysema heterogeneity or on rank transformed data submitted to an ANCOVA*

with the same factors. An evaluation of the residuals from ANCOVA based on 6MWT for complete cases will be performed both graphically and quantitatively to assess the normality assumption. If distributions are markedly skewed, a rank transformed ANCOVA analysis will be conducted. Results of the rank-transformed analyses then will be considered the primary analysis; however, results of the non-ranked-transformed analyses will also be presented."

Throughout this summary document, the footnotes below each table of the effectiveness results indicate which and where analysis method was used.

The changes on the primary statistical method were made after the protocol was finalized, but before the study database through Visit 10 (i.e., the 12-month, primary endpoint visit) was locked on 02 Dec 2015 and before the aggregate study results were unblinded. FDA received the notice of this change in an IDE Annual Report filed on 11 May 2016, five months after the database lock date.

FDA Comment: The change in statistical analysis plan can impact the interpretation of study results. The difference on adjusted means in 6MWT between the coil group and control group was not statistically significant using the originally proposed parametric ANCOVA model that compares the means. The difference on unadjusted means in 6MWT between the coil group and control group was also not statistically significant using the two sample t-test from an exploratory analysis conducted by FDA. However, the results are statistically significant with the later proposed non-parametric ANCOVA model for the median comparison. Therefore, statistical significance on the primary effectiveness endpoint was not consistent across different statistical analysis methods.

7.8 Study Population

Subjects randomized in the RENEW study were comprised of 26.35% GOLD 3 and 73.65% GOLD 4 emphysema patients (*Table* 1). One hundred forty-four (144) of the 155 subjects treated in the coil treatment group (92.9%) had a second (bilateral) treatment performed. 11 subjects were treated unilaterally (1 side only) due to death (n=3) or clinical worsening (n=8).

Subjects enrolled in the Crossover study had demographics and baseline characteristics similar to subjects in the randomized RENEW study (Table 2). The study also enrolled severe GOLD 3 and 4 (26.5% GOLD 3 and 73.5% GOLD 4) emphysema patients.

Table 1: Study Population for RENEW Pivotal

RENEW Pivotal ($Total_n$=315; US_n=201, OUS_n=114)			RV ≥225% (n=235)	RV <225% (n=80)	Total
Treatment (n=158) GOLD 3= 38 GOLD 4= 120 Homogeneous=122 Heterogenous=36	US (n=95)	Homogeneous	45	30	75
		Heterogeneous	11	9	20
	OUS (n=63)	Homogeneous	43	4	47
		Heterogeneous	16	0	16
Control (n=157) GOLD 3= 45 GOLD 4= 112 Homogeneous=121 Heterogenous= 36	US (n=106)	Homogeneous	55	30	85
		Heterogeneous	17	4	21
	OUS (n=51)	Homogeneous	34	2	36
		Heterogeneous	14	1	15

Table 2: Study Population for Crossover

Crossover			RV≥225% (n=62)	RV<225% (n=40)	Total
Treatment (n=102) GOLD 3= 27 GOLD 4= 75 Homogeneous=82 Heterogenous= 20	US (n=68)	Homogeneous	30	27	57
		Heterogeneous	7	4	11
	OUS (n=34)	Homogeneous	17	8	25
		Heterogeneous	8	1	9

FDA Comment: The study population was mainly GOLD 4 subjects with homogeneous emphysema. The distribution was similar between the treatment and control groups and the subsequent crossover group.

7.8.1 Disposition of Subjects

In the pivotal study, 315 subjects were randomized with 158 subjects in the coil treatment group and 157 in the control group (*Table* 3*).* The percent of subjects who completed the study to 12 months was 89.2 % (141/158) in the treatment arm and 90.4 % (142/157) in the control arm.

Table 3: RENEW Pivotal *Study Subject Disposition through 12 Months*

Subject Status	**Treatment**	**Control**	**Total**
Number of Subjects Randomized Randomized But Not Treated	 158 3	 157 0	 315 3
Populations: ITT Safety PP	 158 155 132	 157 157 143	 315 312 275
Subjects Who Completed Study to 12 Months	89.2% (141/158)	90.4% (142/157)	89.8% (283/315)
Subjects Who Completed 12 Month Visit	87.3% (138/158)	89.2% (140/157)	88.3% (278/315)
Subjects Who Discontinued Prior to 12 Months	10.8% (17/158)	9.6% (15/157)	10.2% (32/315)
Subjects Who Died	10	8	18
Subjects Who Were Lost to Follow-Up	0	2	2
Subjects Who Withdrew	4	1	5
Subjects Who Were Withdrawn By Investigator	3	4	7

A total of 102 subjects were enrolled in the crossover study, of these, 101 subjects were treated (*Table 4)* and 85.3% (87/102) of the subjects completed the study to 12 months. Subject disposition post 12 months is provided in *Appendix 14.3 in Table 22 and Table 23* .

Table 4: Crossover Study Subject Disposition through 12 Months

Subject Status	Crossover (N=102)
Number Of Subjects	
Screened	124
Screen Failed	21
Enrolled	102
Enrolled But Not Treated	1
Subjects Who Completed Study To 12 Months	85.3% (87/102)
Subjects Who Completed 12-Month Visit	82.4% (84/102)
Subjects Who Discontinued Prior To 12-Month Post Crossover Treatment 1 Visit	14.7% (15/102)
Subjects Who Died	9
Subjects Who Withdrew Consent	5
Subjects Who Were Withdrawn By Investigator	1

7.8.2 Baseline Characteristics

In the RENEW pivotal study, the baseline demographic characteristics were similar between the coil treatment and control groups (*Appendix 14.3 Table 24)*. The median age of subjects in the ITT population was 63.4 and 64.3 in the coil treatment and control groups, respectively. Both male and female subjects were represented equally in both groups. Greater than 95% of the subjects that were enrolled were Caucasian. There were no clinically meaningful or statistically significant differences (two-sided alpha=0.05) in demographic characteristics between the coil treatment and control groups in the ITT population.

Overall, analyses of the ITT populations revealed no statistically significant differences in baseline disease characteristics between the coil treatment group, control group in RENEW pivotal study (*Table 5*). The baseline disease characteristics for the crossover study were also similar to the pivotal study. The complete baseline disease characteristics are listed in *Appendix 14.3 Table 25*.

Subjects with homogeneous and heterogeneous emphysema were enrolled in the pivotal and crossover study. The distribution of the subjects enrolled with homogeneous emphysema was 77.2% (122/158) in the coil treatment group in the pivotal study, 77.1% (121/157) in the control group and 80.4% in the crossover group. Approximately three-quarters (73.65%) of subjects in the RENEW study were classified as GOLD 4 (75.9% in coil treatment group and 71.3% in control group). Similarly, 73.5 % of subjects in the crossover were classified as GOLD 4. The percentage of subjects with 4 or more comorbidities was similar at baseline

between the coil treatment (28.5 %) and control group (24.8 %) in the pivotal study (*Appendix 14.3 Figure 9*) ; however, the number of subjects with 4 or more comorbidities was less in the crossover group (19.6%). In the RENEW pivotal study, long term oxygen use at baseline was 73 % in the coil group and was 71 % in the control group. In the crossover study, 75 % of the subjects were on long term oxygen at baseline.

In the RENEW study, the average baseline 6MWT and pulmonary function tests were also similar between the treatment and control arms, as well as with the crossover.. The average 6MWT distance at baseline in the pivotal study treatment population was 312.03 meters, 302.70 meters in the control group and 313.6 meters in the crossover group. There were also no significant differences in pulmonary lung function and BODE score between the coil Treatment and control groups (*Table 5 and Appendix 14.3 Table 25*). The baseline pulmonary lung function and BODE score for the crossover study were also similar to the pivotal study. The mean RV for subjects enrolled in the study was 246% and 245% of predicted in the Coil Treatment and Control groups, respectively in RENEW pivotal study and 242% in the crossover. FEV1 averaged approximately 26% of predicted in both groups in RENEW pivotal study and 26.4 % of predicted in the crossover group.

Table 5: Baseline Disease Characteristics-ITT Population in Pivotal and Crossover

	Coil Treatment (N=158)	**Control (N=157)**	**P-value[1]**	**Crossover N=102**
6MWT Total Distance (meters)			0.8137	
Mean ± SD (n) Median Range (min, max)	312.03 ± 79.906 (158) 318.25 (149.4, 540.0)	302.70 ± 79.277 (157) 300.00 (141.1, 670.6)		313.6 ± 82.0 (102) 318.5 (155.0, 548.6)
Lung damage classification			0.7105	
Heterogeneous	22.8% (36/158)	22.9% (36/157)		19.6% (20/102)
Homogeneous	77.2% (122/158)	77.1% (121/157)		80.4% (82/102)
FEV1 (L)			0.5171	
Mean ± SD (n) Median Range (min, max)	0.71 ± 0.202 (158) 0.66 (0.4, 1.2)	0.72 ± 0.210 (157) 0.68 (0.4, 1.7)		0.7 ± 0.2 (102) 0.7 (0.4, 1.5)
FEV1 % Predicted			0.4807	
Mean ± SD (n) Median Range (min, max)	25.71 ± 6.283 (158) 24.94 (12.9, 43.6)	26.27 ± 6.671 (157) 25.63 (11.2, 44.9)		26.4 ± 6.2 (102) 25.6 (16.0, 44.3)
SGRQ Total Score			0.0503	
Mean ± SD (n) Median Range (min, max)	60.05 ± 12.757 (158) 60.04 (26.7, 94.9)	57.44 ± 14.759 (157) 58.83 (8.2, 96.7)		57.9 ± 15.6 (102) 59.3 (22.2, 92.2)
GOLD Stage 4, % (N)	75.9% (120/158)	71.3% (112/157)	0.4770	73.5% (75/102)

	Coil Treatment (N=158)	Control (N=157)	P-value[1]	Crossover N=102
BODE Score			0.8412	
Mean ± SD (n) Median Range (min, max)	5.97 ± 1.262 (158) 6.00 (3.0, 9.0)	6.04± 1.322 (157) 6.00 (3.0, 10.0)		5.7 ± 1.4 (102) 6.0 (3.0, 9.0)
Number of Comorbidities[2]			0.2733	
0-3	71.5% (113/158)	75.2% (118/157)		80.4 % (82/102)
≥4	28.5% (45/158)	24.8% (39/157)		19.6 % (20/102)

[1] For continuous variables, p-value is based on two-way ANOVA with factors of treatment group and investigational sites, for categorical variables, p-value is based on Cochran-Mantel-Haenszel (CMH) test stratified by investigational sites; for situations in which Cochran's rule is not satisfied, Fisher's exact test was used (two-sided alpha=0.05).
[2] The total number of comorbidities of interest were calculated for each subject from the following list: Arthritis, Cachexia (BMI < 18.5 kg/m2), Cardiac Disease (Angina, Atrial Fibrillation, Congestive Heart Failure and Coronary Artery Disease), Depression, Diabetes, Edema, GERD, Hyperlipidemia, Hypertension, Obesity (BMI > 30 kg/m2), Osteoporosis, Peripheral Vascular Disease, Renal Dysfunction, Sleep Apnea and Stroke. In this calculation, the presence of any of the 4 cardiac comorbidities (Angina, Atrial Fibrillation, Congestive Heart Failure or Coronary Artery Disease was only counted once) as Cardiac Disease.

FDA Comment: The baseline characteristics can impact the study results. The characteristics including 6MWT and pulmonary function tests were similar in the treatment, control and crossover groups and therefore, the expected treatment difference between treatment, control, and crossover groups is not likely confounded with baseline characteristics.

8 Study Results

The ITT population for the RENEW pivotal study is comprised of 315 subjects and is defined as all subjects randomized to coil treatment or control, whether or not treatment was attempted. The analyses based on the ITT population were the primary analyses of effectiveness for all protocol-specified tests of significance. The primary endpoint, absolute change in 6MWT from baseline to 12 months was used as a surrogate for functional cardiopulmonary exercise testing and exercise tolerance. The secondary endpoints of FEV1 and SGRQ were chosen as surrogates to evaluate lung function and quality of life measures, respectively. Table 6 provides descriptive summary results of the 6MWT, FEV1, SGRQ and RV % predicted for all available data at baseline and 12 months without imputation of missing data.

Table 6: Descriptive Summary of Results at 12 Months for RENEW and Crossover Study

	Baseline			12 Months post Treatment[1]		
	Coil Treatment	**Control**	**Crossover**	**Coil Treatment**	**Control**	**Crossover**
6MWT Mean ± SD (n) Median Range (min, max)	312.0 ± 79.91 (158) 318.3 (149.4, 540.0)	302.7 ± 79.28 (157) 300.0 (141.1, 670.6)	313.6 ± 82.0 (102) 318.5 (155.0, 548.6)	318.5 ± 100.65 (137) 327.0 (61.0, 584.0)	299.5 ± 87.84 (140) 304.8 (80.0, 548.6)	303.6 ± 92.4 (80) 312.6 (105.2, 495.0)
FEV1(L) Mean ± SD (n) Median Range (min, max)	0.71 ± 0.20 (158) 0.66 (0.38, 1.23)	0.72 ± 0.21 (157) 0.68 (0.35, 1.66)	0.7 ± 0.20 (102) 0.7 (0.4, 1.5)	0.76 ± 0.25 (137) 0.72 (0.36, 2.00)	0.70 ± 0.19 (140) 0.68 (0.31, 1.29)	0.7 ± 0.20 (83) 0.7 (0.4, 1.7)
SGRQ Score Mean ± SD (n) Median Range (min, max)	60.0 ± 12.76 (158) 60.0 (26.7, 94.9)	57.4 ± 14.76 (157) 58.8 (8.2, 96.7)	57.9 ± 15.6 (102) 59.3 (22.2, 92.2)	51.2 ± 15.04 (138) 50.9 (13.9, 89.5)	58.1 ± 15.50 (139) 59.3 (22.2, 92.2)	52.6 ± 18.5 (83) 52.8 (18.9, 97.0)
RV % predicted Mean ± SD (n) Median Range (min, max)	245.9 ± 39.06 (158) 240.0 (175.8, 369.1)	244.5 38.69 (157) 240.6 (175.7, 404.8)	242.1 ± 50.0 (102) 233.7 (167.6, 480.9)	228.0 ±45.52 (136) 219.2 (128.7, 340.8)	240.9 ± 46.94 (140) 236.3 (109.4, 420.9)	219.8 ± 40.8 (81) 217.9 (111.8, 298.5)

[1] Results are based on all available data at 12 months for each study group without imputation of missing data.

There were additional effectiveness endpoints collected at 12 months. These included SGRQ responder analysis of an improvement of ≥4 points from baseline; mean absolute difference from baseline in RV and mean absolute difference from baseline in RV/ TLC. The results are provided in *Appendix14.4* (*Table 27, Table 28, and Table 29*).

The effectiveness results are provided for the ITT population in the following sections for the pivotal study (*Table 7, Table 8, Table 9, Table 10*) based on prespecified multiple imputation of missing data. *Table 7 and Table 9* include the adjusted mean results with the originally proposed parametric ANCOVA with factors of treatment, analysis center, baseline 6MWT (or FEV1) and emphysema heterogeneity as covariates. The two tables also include median comparison with the later proposed non-parametric ANCOVA model with same covariates. For the crossover study results, only descriptive statistics are reported for the complete case without imputation.

The safety population was comprised of 312 subjects and included all subjects in the ITT population who were randomized (for the control group) or who entered the procedure room (for the treatment group), regardless of whether or not device deployment was attempted. Three patients were excluded from the safety population because they were withdrawn from the study prior to treatment.

The post-procedure hospital stay for the study was an overall mean of 2.1days, with the day of the procedure counted as day 1.

8.1 Effectiveness

8.1.1 Primary Effectiveness Analysis-6MWT

The primary effectiveness analysis compared the absolute change in distance (meters) from baseline to 12 months in the 6 Minute Walk Tests (6MWT), between the coil treatment and control groups.

In the RENEW pivotal study the coil treatment group exhibited a median change of 14.6 meters (adjusted mean change of 10.2 meters) in 6MWT over the control group at 12 months compared to baseline (*Table 7,Figure 7*). Median change in 6MWT for coil treatment subjects was 10.3 meters (mean change 0.8 meters) compared to the median change of -7.6 meters in the control group (mean change -8.6 meters).

It was noted that the difference on adjusted means between the coil group and control group was not statistically significant using the originally proposed parametric ANCOVA model (p=0.0967) that compares the means. The results are statistically significant with the later proposed non-parametric ANCOVA model (p=0.0153) for the median comparison. Therefore, statistical significance on the primary effectiveness endpoint was not consistent across different statistical analysis methods. Even though with the non-parametric ANCOVA, the primary effectiveness endpoint was statistically significant (the median difference of 14.6 meters), the lower bound of the 95% confidence interval for the difference of median changes in 6MWT between coil group and control group was only 0.4 meters.

In crossover subjects, the median change in 6MWT at 12 months for the treatment group was a decline of -14.8 meters (mean change of -22.9 meters).

In the pivotal study, 114 subjects completed the 24-month follow-up visit and 49 subjects completed the 36-month follow-up visit as of the cut-off date. In these subjects, the 6MWT declined by a median of -11.1 meters (mean -17.2 meters) at 24 months and a median of -18 meters (mean -39.3 meters) at 36 months compared to baseline in the pivotal study (*Appendix 14.4 Figure 10*). In the crossover study, the 6MWT declined a median of -33 meters (mean -46.5 meters) in 25 subjects at 24 months. Only, 5 subjects have completed the three year follow up as of the cut-off date.

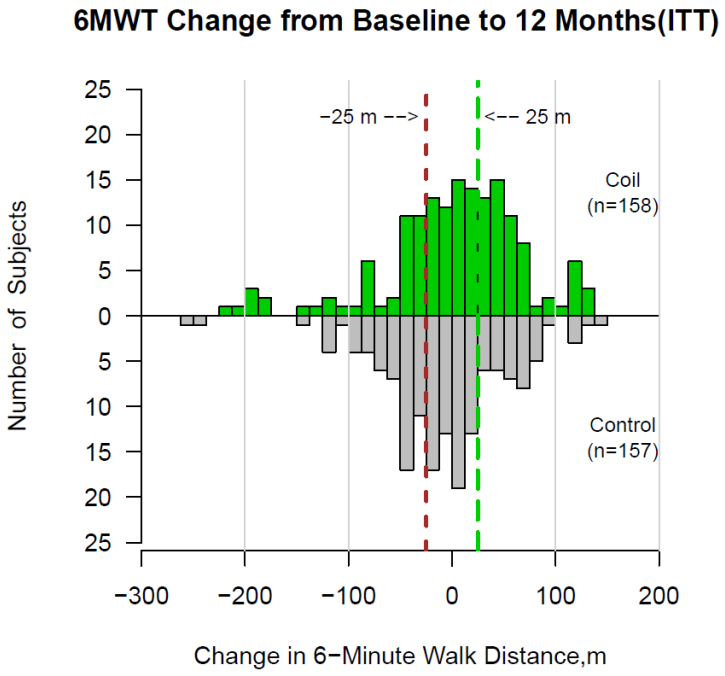


Figure 7: 6MWT Change from Baseline at 12 months for the control and pivotal coil

Table 7: Change from Baseline at 12 Months in 6-Minute Walk Test Distance (Meters) - for RENEW Pivotal and Crossover

	Treatment Group (N)	Baseline 6MWT (meters) Mean ± SE	Mean Change in 6MWT at 12 Months from Baseline (meters) Mean ± SE	Adjusted Mean Change from Baseline (meters) Mean ± SE	Adjusted Mean Difference (Coil Treatment vs. Control) [95% CI][1]	Median Change from Baseline (IQR)[4]	Median Difference (Coil Treatment vs. Control) [95% CI][2]	P-value (One-sided)[3]
RENEW Pivotal Study	**Control (N=157)**	302.7±6.33	-8.6±5.17	-10.7±6.22	10.2 [-5.2, 25.5]	-7.6 (-40.0, 26.0)	14.6 (0.4, 28.7)	0.0153
	Coil Treatment (N=158)	312.0±6.36	0.8 ±5.89	-0.6±6.30		10.3 (-33.0, 45.0)		
Cross-over Study	**Coil Group**	313.6±8.12 (N=102)	-22.9±8.12 (N=80)[5]	NA	NA	-14.8	NA	NA

[1] Difference in least squares means from MCMC multiple imputation results of parametric ANCOVA with factors of treatment, analysis center, baseline 6MWT and emphysema heterogeneity as covariates.

[2] Median difference adjusted for baseline from MCMC multiple imputation results using Hodges Lehmann estimator. The nonparametric median between treatment difference is not the simple between-treatment difference in medians.

[3] Due to significant skewness, p-value was from MCMC multiple imputation results of rank-transformed non-parametric ANCOVA with factors of Treatment, analysis center, baseline 6MWT and emphysema heterogeneity as covariates. P-value is from one-sided

[4] Median (IQR) are median of percentiles from MCMC multiple imputation.

[5] Crossover descriptive statistics are provided. Only 80 of 102 subjects had completed the 6MWT at 12 months.

FDA Comment: Based on ATS guidelines for 6MWT and related publications[6,7,8], the observed median difference between the treatment and the control of 14.6 meters in the 6MWT has uncertain clinical significance.

The pivotal study results on 6MWT were not consistent with cross-over study results. The crossover subjects had a median decline of -14.8 meters (mean decline of -22.9 meters) in the 6MWT in comparison to their baseline at 12 months. It is important to note that the baseline characteristics were similar between the pivotal treatment and crossover groups (Table 5). The main difference between the pivotal and the crossover study was that the requirement for performing pulmonary rehabilitation before treatment was removed and therefore the impact of pulmonary rehabilitation on the results is unknown.

The applicant conducted post hoc analyses to evaluate the difference in results seen between the pivotal treatment group and crossover group. The applicant stated their analyses showed that *"Subjects enrolled in the Crossover study were older on average (median 63 years in RENEW Treatment group compared to a median of 65 years in Crossover…... There was an uncharacteristic increase in both 6MWT and FEV1 between the 9-month and 12-month RENEW Control Visit (which was in most cases also the Crossover Baseline visit) despite progressive decline in the study period prior to this visit."* ***Review of the analyses did not fully support the differences seen between the two populations. The reported older age of the crossover group by 2 years is an unlikely reason for the worsening observed in the 6MWT as subjects had similar baseline characteristics.. Pulmonary rehabilitation can influence 6MWT outcomes.[7] Therefore, based on the inconsistent study results in the pivotal and crossover group, it is unknown if the improvement observed in 6MWT during the pivotal study was due to the coil treatment versus pulmonary rehabilitation. Of note, the applicant's reported "uncharacteristic increase" in 6MWT and FEV1 for the control group between 9 and 12 months, was only a median of 3.82 meters (mean change of 3.58 meters) for the 6MWT and a median of 0.88 % change (mean of 0.85 %) for the FEV1 (Appendix 14.4 Figure 11).***

8.1.2 Secondary Effectiveness Analyses

The following secondary endpoints were compared between Coil Treatment and Control groups:

- 6MWT: responder analysis, from baseline to 12 months, with responders defined as those with an improvement of ≥25 meters in the 6MWT;
- FEV1: mean percent change in FEV1 results from baseline to 12 months, measured using spirometry; and
- SGRQ: mean absolute difference in SGRQ results from baseline to 12 months.

All secondary effectiveness analyses were performed on the ITT population.

The unadjusted mean responder rates from MCMC multiple imputation were 37.9% and 26.2% in the coil treatment and control groups, respectively (*Table 8*). It was also noted that 29.8 % patients in coil group and 39.1 % of patients in the control group showed 6MWT decline greater than 25 meters at 12 months (*Figure 8 and Appendix 14.4 Table 26*).

Crossover 6MWT responder rate was 26.3 % (21/80) which was the same responder rate observed in the control group of the pivotal study and much lower than the responder rate seen in the pivotal treatment arm.

The median percent change in FEV1 at 12 Months was 3.8% (mean 6.9%) in the Coil Treatment group and -2.5% (mean -2%) in the control group (rank ANCOVA $p<0.0001$) for the RENEW pivotal cohort (*Table 9*). The median difference between the treatment and control group was 7% for the RENEW pivotal study. The median percent change in FEV1 at 12 months for the crossover group was -1.3 % (mean 2.2 %). There was not an overall change in the subject GOLD classification based on the FEV1 changes in the study.

In the RENEW pivotal study, the adjusted mean absolute change in SGRQ at 12 months in the coil treatment group showed an improvement of -8.1 points compared to 0.8 points change in the control group ($p<0.0001$) (*Table 10)*. The crossover group showed a mean change of -4.8 points in SGRQ at 12 months. However, there was no sham arm or blinding in the study.

Of the 141 treatment group subjects who completed the randomized phase of the pivotal study (12 months), 114 subjects completed the 24-month follow-up visit and 49 subjects completed the 36-month follow-up visit as of the cut-off date. FEV1 was similar to baseline at the 24 month follow-up visit (median change of -1.3 %, mean change of 2.3%), and declined by a median of -5.2 % (mean of -3.1%) by the 36 month follow-up visit (*Appendix 14.4 Figure 11)*. SGRQ mean was -4.4 points at 24 months and was similar to baseline (-0.4 points) at 36 months (*Appendix 14.4 Figure 12*). In the crossover study, 26 subjects completed the 2-year follow up and 5 subjects have completed the three year follow up as of the cut-off date for this application. At 24 months, FEV1 declined from baseline by a median of -7.5% (mean -0.6%). The SGRQ showed a change with a mean of -3.62 units at 24 months.

Table 8: 6MWT Responder Rate for Pivotal and Crossover Population

		Mean Responder Rate at 12 Months	Difference of Log Odds (Coil Treatment vs. Control) [95% CI][1]	Odds Ratio [95% CI][1]	P-value[1] (One-sided)
RENEW Study	**Control (N=157)**	26.2%	0.72 [0.16, 1.29]	2.06 [1.17, 3.64]	0.0063
	Coil Treatment (N=158)	37.9%			
Crossover Study[2]	**Coil (N=102)**	26.3 % (21/80)	N/A	N/A	N/A

[1] Based on MCMC multiple imputation results of logistic regression with factors of treatment, baseline 6MWT, analysis center and emphysema heterogeneity as covariates.
[2] Crossover descriptive statistics are provided. Only 80 of 102 subjects had completed the 6MWT at 12 months.

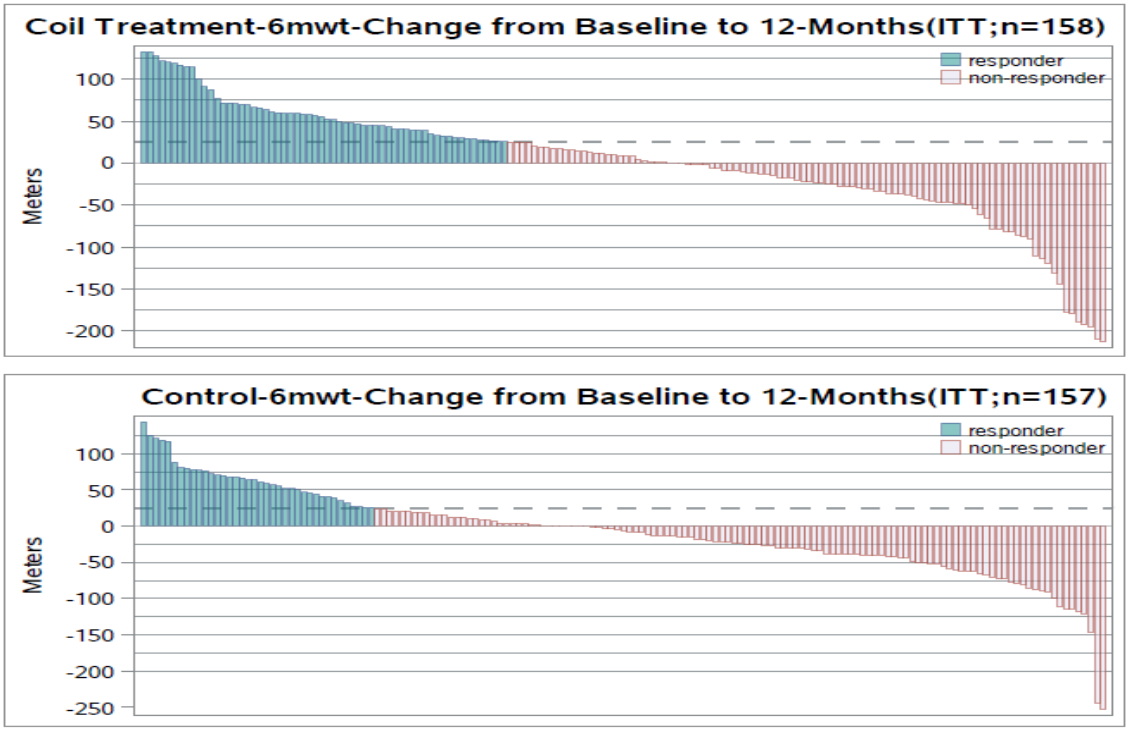


Figure 8: 6MWT change from baseline at 12 months for control for pivotal study

Table 9: Secondary Endpoint Analysis: Percent Change from Baseline to 12 Months in FEV1- RENEW and Crossover Population

	Treatment Group (N)	Baseline FEV1 (Liters) Mean ± SE	Mean Percent Change in FEV1 from Baseline (%) Mean ± SE	Adjusted Mean Percent Change from Baseline (%) Mean ± SE[1]	Adjusted Mean Percent Difference (Coil Treatment vs. Control) (%) [95% CI][1]	Median (IQR) Percent Change from Baseline (%)	Median Difference (Coil Treatment vs. Control) (%) [95% CI][2]	P-value (One-sided)[3]
RENEW Pivotal Study	Control (N=157)	0.7 ± 0.02	-2.0±1.14	-0.8 ± 1.66	8.8 [4.7, 13.0]	-2.5 (-8.9, 4.4)	7.0 [3.4, 10.6]	<0.0001
	Coil Treatment (N=158)	0.7 ± 0.02	6.9±1.78	8.0 ± 1.74		3.8 (-6.3, 16.1)		
Cross-over Study[4]	Coil Group	0.7 ± 0.02 (N=102)	2.2 ±2.31 (N=83)[4]	NA	NA	-1.3	NA	NA

[1]Difference in least squares means and from MCMC multiple imputation results of ANCOVA with factors of treatment, analysis center, baseline FEV1 and emphysema heterogeneity as covariates.
[2]Median difference adjusted for baseline from MCMC multiple imputation results using Hodges Lehmann estimator. The nonparametric median between treatment difference is not the simple between-treatment difference in medians.
[3]Due to significant skewness, p-value from MCMC multiple imputation results of rank ANCOVA with factors of treatment, analysis center, baseline FEV1 and emphysema heterogeneity as covariates. P-value is from one-sided test. Testing results after adjustment made on family-wise type I error using Hochberg method.
[4]Crossover descriptive statistics are provided. Only 83 of 102 subjects had completed the FEV1 test at 12 months.

Table 10: Secondary Endpoint Analysis: Mean Absolute Change from Baseline in SGRQ Score at 12 Months for RENEW and Crossover Cohorts.

	Treatment Group (N)	Baseline SGRQ Mean ± SE	Mean Change in SGRQ from Baseline Mean ± SE	Adjusted Mean Change in SGRQ from Baseline Mean ± SE	Adjusted Mean Difference (Coil Treatment vs. Control)	P-value[2] (One- sided)
RENEW Pivotal Study	Control (N=157)	57.4 ± 1.18	1.0 ± 0.85	0.8 ± 1.05	-8.9 [-11.6, -6.3]	<0.0001
	Coil Treatment (N=158)	60.0 ± 1.01	-8.1 ± 1.03	-8.1 ± 1.08		
Crossover Study[3]	Coil	57.9 ± 1.54 (N=102)	-4.8 ± 1.62 (N=83)[3]	NA	NA	NA

[1]Based on difference in least squares mean from MCMC multiple imputation results of ANCOVA with factors of treatment, analysis center, baseline SGRQ and emphysema heterogeneity as covariates. P-value is based on one-sided test.
[2]Testing results after adjustment made on family-wise type I error using Hochberg method.
[3]Crossover descriptive statistics are provided. Only 83 of 102 subjects had completed the SGRQ at 12 months.

FDA Comment: The secondary endpoints appeared to meet an overall statistical significance but have uncertain clinical significance:

- ***For the 6MWT responder rate, there was a 11.7 % difference between the treatment and the control in the pivotal study at 12 months. Data regarding maintenance pulmonary rehabilitation was not collected as part of the study and therefore it is unknown whether this confounding factor may have contributed to the difference in the responder rate. The responder rate for crossover study was similar to the control arm responder rate in the pivotal study.***
- ***The percent change in FEV1 in the pivotal trial was below reported MCID for COPD treatments.[6] There was almost no change in the FEV1 in the crossover trial at 12 months.***
- ***The quality of life questionnaire, SGRQ showed a reduction that has clinical significance; however, these results must be interpreted with caution. The subjects and clinicians were not blinded in this study and a sham arm was not feasible. The lack of blinding/sham arm may have influenced a subjective outcome such as SGRQ.***

8.1.3 Sub-Group Analyses

The effectiveness results for the following pre-specified subgroups are provided in the following sections:

- US vs. OUS (outside of the US)
- Heterogeneity of emphysema
- Severity of air trapping (RV ≥225% vs. RV <225%).

8.1.3.1 United States (US) and Outside of United States (OUS)

Six (6) of the 26 investigational sites that randomized subjects in the RENEW pivotal study were located outside of the US (OUS). The 6 OUS sites enrolled a total of 114 of the 315 randomized subjects (36.2%) while the 20 US sites enrolled a total of 201 of the 315 randomized subjects (63.8%) (*Table 1*).

The baseline characteristics of the US and OUS subjects were compared. The baseline 6MWT distance was significantly lower in the US and averaged 293 meters in comparison to 332 meters in OUS subjects (*Table 11*), the FEV1 % predicted was comparable (27% versus 25% in US and OUS subjects, respectively), and RV % predicted was lower in US subjects (237% versus 260% in US and OUS subjects, respectively). RV/TLC was similar in both groups. SGRQ was statistically lower in US subjects compared to OUS subjects (56.9 points versus 62.0 points). There was a statistically significant imbalance between the US and OUS subgroups on baseline parameters such as 6MWT, age, BMI, incidence of several comorbidities and SGRQ.

For the primary endpoint, change in 6MWT at 12 months, the OUS Coil Treatment group subjects exhibited a median improvement over Control of 31.7 meters (adjusted mean change

25.8 meters) compared to the median change of 5.9 meters (mean change 2 meters) in US subjects (*Appendix 14.5.1 Table 30*). In the crossover study, the median change in 6MWT in the US population (N=53) was -18.9 meters (mean change -28 meters) and 1 meter (mean -12 meters) in the OUS population (N=27) at 12 months.

For the secondary endpoints, the FEV1 changed in the coil treatment group subjects by a median of 10.7% over control in the OUS subgroup and 4.8% in the US subgroup in the pivotal study (*Appendix 14.5.1 Table 31*). In the crossover study, for US population, the FEV1 showed a median decline of -3.2 % (mean 0.72 %) and OUS population showed median change of 1.74% (mean of 5.2 %) at 12 months. In the pivotal study, SGRQ showed adjusted mean difference of -11.6 and -7.3 points between the treatment and the control in the OUS and US subgroups, respectively (*Appendix 14.5.1,Table 32*). In the crossover group, SGRQ score change was median of -3.15 points (mean -3.6 points) in US population versus median change of -8.41 points (mean -7.2 points) in OUS subgroup at 12 months. The mean 6MWT responder rate in the US coil treatment subgroup was 34 % versus 26% in the control group (*Appendix 14.5.1 Table 33*). The mean responder rate in the OUS subjects was 44 % and 27% in the coil treatment and control subgroups respectively. In the crossover study, the US subgroup had 25% responders (13 out of 53 subjects) versus 29.6% in the OUS study population (8 out of 27 subjects).

Table 11: Primary Effectiveness Results by Region for RENEW and Crossover

Region	Treatment Group (N)	Baseline 6MWT Mean	Median (Mean) Change in 6MWT at 12 Months from Baseline
US	Control (N=106)	293.6	– 0.7 (–3.1)
	Coil Treatment (N=95)	292.9	4.9 (–2.3)
	Crossover[1]	306.9 (N=68)	–18.9 (–28.2) (N=53)
OUS	Control (N=51)	321.5	–22.0 (–19.9)
	Coil Treatment (N=63)	340.8	13.0 (5.3)
	Crossover[1]	327.1 (N=34)	1.0 (–12.41) (N=27)

[1] Crossover descriptive statistics are provided. 80 of 102 subjects completed 6MWT at 12 months.

Poolibility:

The observed treatment effects for the US subgroup were consistently smaller than those for the OUS subgroup for all the primary and secondary effectiveness endpoints. *Table 12* summarizes the results from the poolablitity analyses. These results showed that the Treatment by Region interaction effects are statistically significant for all the effectiveness endpoints at the alpha=0.15 level (with the exception of 6MWT responder rate).

Table 12: Heterogeneity of Treatment Effect Across Regions (US vs OUS)

Endpoint	USA (n=201)	OUS (n=114)	P -Value for Treatment by Region Interaction
Change in 6-MWT: Median difference (Coil vs Control) [95% CI]	5.9 [-10.8, 22.2]	31.7 [4.8, 57.4]	0.087[1]
Mean Responder Rate in 6MWT: Odds Ratio (Coil vs Control) [95% CI]	1.65 [0.84, 3.27]	2.29 [0.94,5.56]	0.301[2]
Percent Change in FEV_1: Median difference (Coil vs Control) [95% CI]	4.8 [0.5, 9.3]	10.7 [4.3, 17.2]	0.074[3]
Change in SGRQ Score: Mean difference (Coil vs Control) [95% CI]	-7.3 [-10.7, -3.9]	-11.6 [-15.7, -7.5]	0.067[4]

[1] P-values based on the complete cases and rank-transformed ANCOVA model with factors of treatment, region, and the interaction term of treatment and region and covariates of baseline 6MWT and emphysema heterogeneity. P-value (for interaction term) is based on two-sided test.
[2] P-values based on the complete cases and logistic regression model with factors of treatment, region, and the interaction term of treatment and region and covariates of baseline 6MWT and emphysema heterogeneity. P-value (for interaction term) is based on two-sided test.
[3] P-values based on the complete cases and rank-transformed ANCOVA model with factors of treatment, region, and the interaction term of treatment and region and covariates of baseline FEV1 and emphysema heterogeneity. P-value (for interaction term) is based on two-sided test.
[4] P-values based on the complete cases and ANCOVA model with factors of treatment, region, and the interaction term of treatment and region and covariates of baseline SGRQ and emphysema heterogeneity. P-value (for interaction term) is based on two-sided test.

FDA Comment: When the clinical data is not suitable for pooling due to the heterogeneity of treatment effects, pooled data may not be applicable to the US population. Therefore, caution should be made when US and OUS data are pooled for an overall effectiveness assessment.

The applicant conducted post-hoc analyses, for the OUS and US subpopulation including baseline 6MWT, SGRQ, comorbidities, age, and BMI to explain the differences in effectiveness results. The US subpopulation was reported as being older (5.7 years years), having a higher BMI (25.3 kg/m2 versus 23.7), and having more subjects with at least 4 comorbidities (36.8 % vs 8.8 %). Although based on these differences, the applicant reported that the US subpopulation was sicker, the baseline SGRQ was lower in the US subpopulation versus OUS subpopulation (56.9 points versus 62 points, respectively).

The post-hoc analyses could not fully explain the differences in the effectiveness results between the US and OUS subjects. The following were noted for the pivotal study for this subgroup:

- ***The 6MWT difference between the treatment and the control for the overall population is driven by the OUS control subjects compared to US control subjects (median change of -22 meters, -0.7 meters, respectively).***
- ***The clinical relevance of how many comorbidities are affecting the effectiveness outcome was chosen post-hoc. The study exclusion criteria excluded subjects that were not expected to improve based on comorbidities. The applicant has stated that the "US subjects were older, with a greater number of chronic comorbid conditions, lower exercise capacity and less air trapping than OUS subjects, which likely influenced the differences observed in effectiveness results." The US population had more subjects with RV <225% and/or >4 comorbidities. The following were noted:***
  - ***There was no clinically meaningful significance in the difference in the 6MWT compared to baseline at 12 months in the treatment group (4.9 meters in the US versus 13 meters in the OUS)***
  - ***Based on applicant's post-hoc analyses regarding the US subpopulation, it is unexpected why the decline in 6MWT in the US control subjects was less than the OUS control subjects at 12 months (-0.7 meters versus -22 meters).***

Additionally, in the crossover group, the US subjects, also had a worsening of 6MWT (median change of -18.9 meters) in comparison to OUS subjects (median change of 1 meters).

8.1.3.2 Homogeneous versus Heterogeneous Emphysema

Randomization was stratified by homogeneous versus heterogeneous emphysema. The original pivotal protocol had an upper limit for homogeneous emphysema subject's enrollment as 150 (75 in treatment and 75 in control). During the clinical trial, the applicant updated the protocol and removed this upper limit.

Of the ITT population in the pivotal study, 22.9% of subjects were classified as having heterogeneous emphysema (72 subjects), and 77.1% of subjects were classified as having homogeneous emphysema (243 subjects) (*Table 1*). No significant differences were seen in baseline demographics or comorbidities between the homogeneous and heterogeneous emphysema subgroups. SGRQ was the only baseline disease characteristic that was significantly different between subgroups, with homogeneous subjects reporting a mean SGRQ of 57.86 compared to 61.75 for heterogeneous subjects.

In the pivotal study, the difference in median change from baseline in 6MWT between the Coil Treatment and Control groups was 10.8 meters in homogeneous subjects versus 27.4 meters in heterogeneous subjects (*Table 13; Appendix 14.5.2 Table 34*). Similarly, the difference in median percent change from baseline in FEV1 between the treatment and control was 9.1% in heterogeneous emphysema and 6.9% in homogeneous emphysema (*Appendix 14.5.2 Table 35*). SGRQ changed over control by a mean of -9.2 and -8.4 points, in the heterogeneous and homogeneous subgroups, respectively (*Appendix 14.5.2 Table 36*).

In the crossover group, the subjects with homogeneous emphysema (N=62) had worsening of both primary and secondary endpoints in comparison to the subjects with heterogeneous emphysema (N=18), (*Table 13*). The 6MWT was reduced by median of -20 meters (mean of -33.4) in the homogenous subgroup in comparison to median change of 25.0 meters (mean of 13.5) in the heterogeneous subgroup. The FEV1 was reduced by median of -3.8% (mean of -1.9%) in the homogeneous subgroup versus median change of 5.05 % (mean of 17.1%) in the heterogeneous. There was reduction in the SGRQ score in both subgroups.

Table 13: Primary Effectiveness Results by Emphysema Status for RENEW and Crossover

Emphysema Status	Treatment Group (N)	Baseline 6MWT Mean	Median (Mean) Change in 6MWT at 12 Months from Baseline
Homogeneous	**Control (N=121)**	302.7	– 4.6 (–7.1)
	Coil Treatment (N=122)	313.4	9.0 (0.7)
	Crossover[1]	314.6 (N=82)	– 20.1 (–33.4) (N=62)
Heterogeneous	**Control (N=36)**	302.7	–14.2 (–13.6)
	Coil Treatment (N=36)	307.4	21.0 (0.8)
	Crossover[1]	309.6 (N=20)	25.0 (13.5) (N=18)

[1] Crossover descriptive statistics are provided. 80 of 102 subjects completed 6MWT at 12 months.

FDA Comment: The clinical benefit of the treatment based on type of emphysema is unclear. The study enrolled mainly homogeneous emphysema subjects (77 %) based on prior early feasibility studies. In the pivotal study, there was a difference in the magnitude of change in 6MWT between the heterogenous and homogeneous emphysema subjects in the treatment group (median 21 meters versus 9 meters, respectively). However, there were insufficient number of subjects (n=36) enrolled in the heterogeneous group to evaluate the effectiveness of the coil treatment in this subpopulation. Additionally, the crossover results contradict the pivotal study results such that the homogeneous emphysema subjects had a median decline of -20 meters (mean -33 meters) in 6MWT at 12 months.

8.1.3.3 Residual Volume (RV)

The RENEW study protocol originally defined the study population emphysema subjects with residual volumes greater than or equal to 225% predicted. In July 2014, the applicant updated the protocol to broaden the target population of the study and include subjects with RV between 175% and 225% predicted. At the time of the protocol change, 53.7 % (169/315) of the subjects had already been enrolled in US and OUS sites. At enrollment completion, 74.6% (235/315) subjects with RV ≥225% predicted and 25.4% (80/315) of subjects with RV < 225% predicted were in the study. The majority of the subjects with RV < 225% (91.3%, 73/80 subjects) were enrolled in the US (*Table 1*).

In the pivotal study, the primary endpoint for subjects with baseline RV ≥225% predicted showed a median difference of 23.8 meters in the coil treatment group compared to control (*Table 14; 14.5.3* Table 38). In the subgroup of coil treated subjects with baseline RV < 225%, the 6MWT showed a median worsening of -12.9 meters compared to controls. In the crossover group, RV ≥225% subjects declined -32 meters and RV <225 % subjects declined -9.7 meters.

In the pivotal study, the mean 6MWT responder rate, a secondary endpoint defined as a change from baseline of ≥25 meters, was 42.3 % for subjects with RV ≥225% and 26.4 % for RV < 225% (*Appendix 14.5.3, Table 41*). In the crossover group, 6MWT responder rate was 25.5 % (12/47) for RV ≥225% subjects and 27.3 % (9/33) for RV <225%. FEV1 percent median difference between treatment and control was 8.9% and 2.6% in the RV ≥225% and RV <225% groups, respectively in the pivotal study (*Appendix 14.5.3, Table 39*). In the crossover study, FEV1 mean percent change for the treatment was 3 % and 1% in the RV ≥225% and RV <225% groups, respectively. In the pivotal study, SGRQ showed -10.6 points change over control in RV ≥225% and -4.7 points mean difference in RV<225% subgroups (*Appendix 14.5.3, Table 40*).In the crossover study, the mean change in SGRQ was -6.3 points and -2.7 points for RV ≥225% and RV <225% groups, respectively (*Appendix 14.5.3, Table 40).*

Table 14: Primary Effectiveness Results for RV ≥225% vs RV<225% for RENEW and Crossover

Residual Volume	Treatment Group (N)	Baseline 6MWT Mean	Median (Mean) Change in 6MWT at 12 Months from Baseline
RV≥225%	Control (N=120)	308.0	–8.6 (–13.1)
	Coil Treatment (N=115)	314.6	15.0 (5.6)
	Crossover[1]	324.3 (N=62)	–18.3 (–32.1) (N=47)
RV<225%	Control (N=37)	285.5	0.0 (–1.9)
	Coil Treatment (N=43)	305.2	–9.8 (–12.1)
	Crossover[1]	297.1 (N=40)	–9.76 (–9.68) (N=33)

[1] Crossover descriptive statistics are provided. 80 of 102 subjects completed 6MWT at 12 months

FDA Comment: After study results were made available, the applicant focused on the population with RV ≥225 %. The RV cut-off value of 225% was not clinically supported (Appendix 14.5.3, Figure 13). It should also be noted that excluding the subjects with RV<225% from the ITT population analysis would result in a post-hoc bias on the effectiveness results since 73 out of 80 subjects with RV <225 % were from the US subgroup.

There were inconsistencies based on the RV cut off. In the pivotal study, for the primary effectiveness endpoint of 6MWT, the coil treated subjects with RV <225 % declined more than the control subjects with RV <225%. The crossover results contradicted the pivotal study results for subjects with RV ≥225% since this population did worse than subjects with RV < 225%.

The applicant also conducted additional post-hoc analysis in this subgroup which included age, BMI and comorbidities. Based on this post-hoc analyses, the subjects with RV<225% were found to have more comorbidities than the subjects with RV ≥225% (44% versus 21%). However, it appears that only the coil treatment subjects with RV<225% were impacted by the larger number of comorbidities as the control subjects with RV <225% did not show worsening of the primary effectiveness endpoint. Additionally, the control subjects with RV <225 % had a higher 6MWT responder rate compared to RV ≥225% control subjects (33.6 % vs 23.9 %).

The post-hoc analyses did not adequately explain the differences in the effectiveness results between the RV ≥225% and RV < 225% subgroups.

8.2 Safety

For safety, all adverse events were reported for the study and based on the CEC adjudication, these were categorized into serious and non-serious adverse events. The serious adverse events are further subcategorized as major complications based on the predefined event definitions (section 7.5).

The primary safety analysis compared the incidence of a major complication in the treatment arm versus the control arm at 12 months. The participating subjects who completed the study through the 24-month follow-up visit are continuing in the long-term follow-up period (treatment group only). The control group subjects exited from the RENEW study at 12-months, as per the protocol. In the cross-over study, 84/102 (82.4%) of the subjects also had completed the 12-month visit.

In the RENEW study, there were a total of 1110 adverse events in 100% of the treatment subjects and 492 adverse events in 88.5% of the control subjects through 12 months. Most frequent AEs were COPD exacerbation in the treatment and control groups and hemoptysis and lower respiratory tract infections in the treatment group. Of the reported adverse events, 61.9% of the treatment subjects had an SAE in comparison to 34.4% of the control subjects. 45.8% of treatment subjects had possibly or probably device/procedure related SAEs.

In the pivotal study, two year follow up data was available on 114 subjects. A total of 315 additional AEs occurred in 112/141 (79.4%) of the Coil Treatment group subjects who continued in the study following the 12-month visit. Of the 315 AEs, 96 (30.5%) met the criteria of a SAE and 18 (18.8%) of those SAEs were possibly or probably related to the device or procedure. The most common SAEs and AEs occurring in the treatment population between 12 and 24 months were COPD exacerbation and pneumonia.

There were 29 malfunctions reported in 299 procedures (9.7%). The majority of the malfunctions were reported to be due to unusually tortuous airway anatomy. There were no coil removals reported in the pivotal study and therefore the safety of removal could not be assessed.

8.2.1 Adverse Events

In the protocol, an AE was defined as any untoward medical occurrence in a study subject. This included symptoms, illness, clinically significant abnormal laboratory value or change in value, or worsening in a subject during a clinical study. When the same AE was reported more than once for the same subject, that event was counted once in the adverse event summaries at the most severe intensity recorded, and at the strongest degree of relationship to study treatment recorded. Adverse events that worsened in severity over time were captured as multiple unique events, with the onset date of the new event corresponding to the date of worsening severity.

In the pivotal study through 12 months, the most frequently reported AE in both the treatment and control groups was COPD exacerbation (69.7% of subjects and 58.0% of subjects respectively), and hemoptysis (58.7% in treatment, 0 % in control) (*Table 15*). The lower respiratory tract infections, including pneumonias, occurred in 29.7% of the treatment subjects compared to 8.9% in the control subjects. The most common device and/or procedure related AEs through 12 months were hemoptysis in 58.1% of the subjects, COPD exacerbation in 47.1%, the lower respiratory tract infections including pneumonias in 24.5%, and pneumothorax in 11.6% of the subjects.

In the crossover group through 12 months, the most frequently occurring AEs were COPD exacerbation in 61.4% of the subjects, hemoptysis in 57.4%, and lower respiratory tract infections including pneumonias in 23.8 % of the subjects.

In the long term safety follow up between 12 and 24 months, in the RENEW pivotal study, a total of 315 AEs occurred in 112 (79.4%) of the 141 coil treatment group subjects. The most common AE was COPD exacerbation (142 events in 56% of subjects) and lower respiratory tract infections (16 events).

In the crossover study between 12 and 24 months, there were 96 AEs in 42(48.3 %) of subjects. The most common AE was COPD exacerbation AE in 25.3% of the subjects.

Table 15: Adverse Events(AEs) in RENEW study through 12 months

Adverse Events through 12M		**% of patients (N)[3]**	**% of events (N)[4]**
AEs	Control	88.5% (139)	30.7% (492)
	Treatment	100% (155)	69.3% (1110)
Lower Respiratory Infections including pneumonia[1]	Control	8.9 %% (14)	20.8 % (16)
	Treatment	29.7 % (46)	79.2% (61)
COPD Exacerbations	Control	58% (91)	44.8% (185)
	Treatment	69.7% (108)	55.2% (228)
Respiratory Failure[2]	Control	9.6% (15)	27.5% (19)
	Treatment	25.8% (40)	72.5% (50)
Pneumothorax	Control	0.6% (1)	5.3% (1)
	Treatment	11.6% (18)	94.7% (18)

Adverse Events through 12M		% of patients (N)[3]	% of events (N)[4]
Hemoptysis	Control	0% (0)	0% (0)
	Treatment	58.7% (91)	100% (140)

[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, dyspnea, respiratory arrest, respiratory failure, respiratory disorder
[3] Subjects were counted at most once for each event type.
[4] Includes all adverse event counts.

8.2.2 Serious AEs

Safety was evaluated by collection of AEs and SAEs from entry into the RENEW study (Visit 1) until the subject had completed or was terminated from the study. Adverse events that worsened in severity over time were captured as multiple unique events. AEs and SAEs were summarized by number of events and percentage of subjects experiencing 1 or more of each event by treatment arm.

This definition of "serious" was applied to any untoward medical event that:
1. Resulted in death
2. Was life-threatening
3. Required inpatient hospitalization or prolongation of existing hospitalization
4. Resulted in persistent or significant disability/incapacity
5. Was a congenital anomaly/birth defect, or
6. Required intervention to prevent permanent impairment or damage.

In the RENEW pivotal study, 62% of coil treatment subjects experienced 1 or more SAEs compared to 34% of control group subjects through 12 months. Of the SAEs ,128 events occurred in 71(45.8%) subjects were possibly or probably device or procedure related. The most common SAEs occurring in subjects in the coil treatment and control groups were COPD exacerbation (27.7% vs 20.4%, respectively) and lower respiratory tract infections including pneumonias (23.9% vs 5.7%, respectively). The coil treatment group also had a higher occurrence rate of pneumothorax (9.7 % vs. 0.6 %) as compared to control (*Table 16*).

In the crossover, a total of 56 subjects (55.4%) experienced one or more SAE(s) through the 12-month follow-up period. The SAEs seen were comparable to the pivotal study. The most commonly occurring SAE was COPD exacerbation in 23 subjects (22.8%) and lower respiratory tract infections including pneumonias in 19 subjects (17.8%). There were 20 pneumonia events in 17 subjects and 13 out of 20 events were related to device or procedure. There were 5 pneumothoraces in 4 subjects that were device and/or procedure related and 1 out of 5 was fatal.

In the long term safety follow up after 12 months, in the RENEW pivotal study, 41% of coil treatment subjects experienced 1 or more SAEs between 12 and 24 months and 27% between

24 and 36 months. The most common SAEs occurring in subjects in the coil treatment post 12 months were COPD exacerbation and pneumonia. In the crossover study, 29.9% of coil treatment subjects experienced 1 or more SAEs between 12 and 24 months and the most common SAE was COPD exacerbation (10.3%).

Table 16: Serious adverse events (SAEs) through 12 months-RENEW Study

SAEs through 12 Month		% of patients (N)[3]	% of events (N)[4]
SAEs	Control	34.3% (54)	30.3% (92)
	Treatment	61.9% (96)	69.6% (211)
Lower Respiratory Infections including pneumonia[1]	Control	5.7% (9)	20.4 % (11)
	Treatment	23.9% (39)	79.6 % (43)
COPD Exacerbations	Control	20.4% (32)	39.7% (46)
	Treatment	27.7% (43)	60.3% (70)
Respiratory Failure[2]	Control	2.5 % (4)	26.3% (5)
	Treatment	8.4 % (13)	73.7% (14)
Pneumothorax	Control	0.6% (1)	6.3 % (1)
	Treatment	9.7% (15)	93.7 % (15)

[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, dyspnea, respiratory arrest, respiratory failure
[3] Subjects were counted at most once for each event type.
[4] Includes all serious adverse events counts.

8.2.3 Major Complications (MC)

The primary safety analysis was based on the percentage of subjects experiencing a pre-defined major complication that included deaths and serious thoracic adverse events. The percentage of subjects experiencing 1 or more major complication (MC) was greater in the Coil Treatment group compared to Control subjects (34.8% versus 19.1%,) (*Table 17*). Of all MC events, 67.8 % (80) occurred in the treatment group versus 32.2 % (38) in the control group.

The most common major complications experienced through 12 months in both groups were Lower Respiratory Tract Infection (LRTI), COPD exacerbations, and death. The difference

seen between groups in the 12-month MC rate was primarily driven by an increased rate of Lower Respiratory Tract Infections (LRTI) in the coil treatment group (18.7% in coil treatment group compared to 4.5% in control). Of the LRTIs, 81.6% (40) of the events occurred in the treatment group and 18.4% (9) in the control arm. Mortality rates were similar in the 2 groups; however, 7 of the 10 deaths in the treatment group were assessed to be possibly or probably related to the device and/or procedure.

Table 17: Major Complications(MCs) through 12 months in RENEW study

	Subject Counts of Each Event	
	Coil Treatment (N = 155)	**Control (N = 157)**
Total Major Complication Events [95% Confidence Interval]	34.8% (54/155) [27.4%, 42.9%]	19.1% (30/ 157) [13.3%, 26.1%]
Death	6.5% (10/155)	5.1% (8/157)
Pneumothorax requiring extended chest tube drainage >7 d	0.6% (1/155)	0.6% (1/157)
Hemoptysis Requiring intervention	1.3% (2/155)	0.0% (0/157)
COPD Exacerbation[1] requiring hospitalization >7 days	11.6% (18/155)	8.3% (13/157)
Lower Respiratory Infections (including pneumonia) requiring administration of intravenous antibiotics and/or steroids[2]	18.7% (29/155)	4.5% (7/157)
Respiratory Failure Requiring mechanical ventilation for >24 hours	3.9% (6/155)	3.8% (6/157)
Unanticipated Bronchoscopy	0.0% (0/155)	0.0% (0/157)

[1]Defined as hospitalization of >7 days with or without mechanical ventilation
[2]New or increased clinical symptoms such as fever, chills, productive cough, chest pain, dyspnea and an infiltrate on plain chest X-ray and hospitalization for administration of intravenous antibiotics and/or steroids

The percentage of subjects experiencing ≥1 MC was 19.1% (27/141) between 12 and 24 months. After 12-months, the most common major complications seen were death in 8.5% (12/141) of subjects, COPD exacerbations in 6.4 % (9/141) and lower respiratory tract infections in 7.8% (11/141) of subjects.

The incidence of lower respiratory tract infections was increased in the treatment arm in comparison to the control group. Based on this difference, the DMC made a recommendation to re-evaluate the subjects adjudicated as having pneumonias. After the completion of the study, the reported 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"). CEC determined that 35%, 14/40 events of the adjudicable pneumonia events in the Treatment group were CAOs.

In the crossover study arm, during the 12-month safety follow up period, 31.7% (32/101) of subjects had a major complication. The most common MC was related to lower respiratory tract infections (16.8%) followed by COPD exacerbations (9.9%). There was also 9/101 (8.9%) deaths in the crossover with six that were possibly or probably related to device/procedure.

FDA Comment: The major complications of COPD exacerbation and lower respiratory tract infections were increased in the treatment arm of the study in the first 12 months post-procedure. This was similarly seen in the crossover population. Retrospectively, after study completion, a clinical definition for pneumonia and CAO was provided and then some of the pneumonias (LRTI) were re-adjudicated as coil associated opacities(CAO). There were inconsistencies in the adjudications, where subjects that met the definition of pneumonia were re-adjudicated as CAO. This entity also cannot be considered a benign process as one of the deaths were related to worsening infiltrates and the subsequent autopsy report showed extensive fibrosis at the site of the coil. The safety of CAO has not been adequately established based on the available case reports and review of the re-adjudications.

8.3 Death

A total of 18 subject deaths occurred in the safety population within the 12-month follow-up period in the RENEW study. These include 10 of 155 subjects (6.5%) in the coil treatment group and 8 of 157 subjects (5.1%) in the control group. Although, the mortality rate between the two arms was comparable, 7/10 deaths in the treatment group were assessed by the investigators to be possibly or probably related to the device and/or procedure.

The 7 device/procedure related deaths were as follows:

- Subject had intraprocedural pulmonary hemorrhage with the second coil implantation.
- Subject had coil placement in the RUL and was hospitalized 1 month later for pneumonia. Follow up CT showed consolidated lung tissue in the RUL with embedded coils. Subjects was discharged and re-admitted 60 days later with progressive RUL infiltrates with subsequent cardiopulmonary arrest on day 73. Autopsy showed extensive fibrosis at the site of the coils in the RUL.

- Subject had second procedure with coil implantation in the RUL and developed drowsiness with respiratory failure and RUL opacification 3 days later And died six days post the second treatment.
- Subject died 254 days post treatment 1 in the RUL with respiratory failure. Coil placement was never performed in the second lung secondary to multiple COPD exacerbations. During the last hospitalization, about 2 weeks prior to death, the subject had a RUL pneumonia with respiratory failure.
- Subject developed increased dyspnea and brownish secretions one week after the second coil treatment in the LUL. Levofloxacin was given with worsening 12 days later. Subject was subsequently admitted to the hospital and 14 days later was reported to have a RUL pneumothorax. The subject died 39 days after the procedure of progressive respiratory failure.
- Subject developed upper respiratory infection (URI) symptoms 96 days post first treatment in the RUL. The subject was admitted one month after the URI and was found to have a RUL pneumonia with cultures positive for aspergillus and methicillin-resistant staphylococcus aureus and died 148 days after coil treatment
- Subject died 163 days post second treatment of COPD exacerbation and pneumonia.

Of the 3 deaths reported as unrelated to the device, the agency could not determine whether 2 of the deaths may have been possibly or probably related tothe device and/or procedure. One subject died 86 days after the second implantation with subacute bacterial endocarditis and multiorgan system failure. Another subject was admitted 26 days after the second implantation secondary to a sigmoid perforation with complications and died 43 days after the procedure.

In the control arm, the majority of deaths were related to COPD exacerbations. Other deaths included 2 with cardio-pulmonary arrests and one with pneumonia and another with surgical complications and pneumonia.

The mortality rate in the crossover was 8.9% (9/101). Two of the deaths were complications related to the device occurring within 30 days of the treatment and included one subject with pulmonary hemorrhage and a second with recurrent pneumothorax and complications related to the coil removal.

In the RENEW study, in the long term follow up, the mortality rate between 12 and 24 months was 8.5% (12/141). Three of the deaths post 12 months were determined as being possibly or probably related to the device by the investigator.

FDA Comment: Although, mortality in the treatment and control arms of the study were comparable; 7 of the 10 deaths in the treatment arm were possibly or probably related to the device/procedure. Additionally, there were 2 device related deaths in the crossover study occurring within 30 days of the treatment.

In the crossover study, there was one death related to recurrent pneumothorax and complications of attempting coil removal. Instructions on coil removal were provided based on animal studies. However, no subjects in the clinical study underwent a successful coil removal or late coil repositioning. Therefore, the safety of coil removal has not been adequately assessed for subjects with severe emphysema.

8.3.1 Other Outcomes

In the RENEW pivotal study, hospitalization rates and emergency room visits were higher in the treatment group in comparison to the control arm and in comparison, to the 12 months prior to the study (*Table 18*). The hospitalization rates decreased from 54.8% to 32.4% at 24 months for the treatment arm.

The crossover also showed increased hospitalization of 43.1% in the 12-months post treatment in comparison to 26.5% in the 12 months prior to the baseline (*Table 18*).

In the RENEW pivotal study, the majority of subjects in both the treatment (76.1%) and control groups (75%) were on supplemental oxygen throughout the study without overall change.

Table 18: Health Care Utilization for RENEW and Crossover Study

	12 M prior to Baseline % of Subjects			12 Months % of Subjects			Difference % of Subjects		
	Coil N=155	Control N=157	Crossover N=102	Coil N=155	Control N=157	Crossover N=102	Coil N=155	Control N=157	Crossover N=102
Hospitalization	31.0%	27.4%	26.5%	54.8%	31.8%	43.1%	23.9%	4.5%	16.7%
Physician Office (Unscheduled)	22.6%	17.2%	38.2%	44.5%	37.6%	49.0%	21.9%	20.4%	10.8%
Emergency Room Visits	10.3%	8.9%	7.8%	17.4%	8.3%	16.7%	7.1%	-0.6%	8.8%

FDA Comment: Overall there was an increase in healthcare utilization post procedure in both pivotal and crossover subjects. The oxygen utilization remained unchanged with coil treatment.

None of the RENEW pivotal study or Crossover treatment subjects received surgical lung volume reduction post Coil treatment. The safety of lung volume reduction surgery after coil implantation is unknown since these are considered permanent implants.

9 Patient Preference Study

The applicant conducted a patient preference study to inform the benefit-risk assessment. A survey with discrete-choice experiment (DCE) format questions was used to elicit preferences from patients with severe emphysema who had not experienced a coil-like therapy. The primary objective of the survey was to quantify patients' preferences for emphysema treatment attributes selected from three treatment types: maximum medical therapy, coil-like therapy, and lung volume reduction surgery without lung transplant. Based on the survey response, this study can estimate the percentage of patients who would accept the risks associated with a coil-like therapy in exchange for the potential benefits instead of receiving maximum medical therapy.

In the DCE format survey, a series of choice questions asked patients to choose between pairs of treatment alternatives. The responses to the questions would reveal patients' preferences for levels of attributes related to:

- The type of treatment
- Treatment effectiveness (chance of improvement in shortness of breath in the next year)
- Treatment risks (in the next year, difference in the number of flare-ups not requiring hospitalization, risk of collapsed lung, risk of pneumonia requiring hospitalization, and risk of dying)

Three limitations of the preference study design prevented it from providing sufficient evidence to reflect preferences of patient population of interest and inform the benefit-risk assessment of a coil-like therapy. Specifically:

1) The description of breathlessness in the patient preference study did not match the RENEW clinical trial secondary endpoint (change in SGRQ score. Treatment benefit in the patient preference survey (chance of improvement in shortness of breath) was defined as the chance of improvement of one level in SGRQ question 11, which asks the respondent to indicate activities that make him/her feel breathless. However, RENEW trial participants' change in responses to this question was not well correlated to their change in SGRQ total score (correlation coefficient of -0.68). Moreover, RENEW trial participants' change in SGRQ question 11 was also poorly correlated with their change in physiological endpoint of FEV_1 (correlation coefficient of 0.19). The applicant failed to demonstrate how patient preferences for a change in one SGRQ question could be used to

estimate patient preferences for the coil as measured with the full SGRQ questionnaire in the RENEW clinical trial.

2) The maximum additional risk of pneumonia requiring hospitalization presented to respondents of the patient preference study was 15%, which was less than the 17.5 % additional risk of pneumonia requiring hospitalization experienced by participants in the RENEW clinical trial. Extrapolating patient preferences above the maximum risk presented to the survey respondents is invalid, because there may not be a predictable relationship between preferences and increased risk.

3) The description of treatment options in the patient preference study may have inadvertently biased respondents by mischaracterizing the coil-like therapy as "an implantable lung device" (instead of "an implantable lung device + medicines") and comparing it to "medicines." Although a description of the two attributes early in the survey stated that even with implantable lung devices, medicines are taken each day, patients may or may not have retained this information when answering preference questions. Good study practices recommend that comprehension questions be used to ensure respondents fully understand that medicines would be required with an implantable lung device. Because the labels of the attributes in the survey were not "an implantable lung device + medicines" and "medicines," patient preference study respondents may have incorrectly assumed that a potential benefit of the implantable lung device would be a reduction in medication.

FDA Comment: The benefit as presented to survey respondents in the patient preference study did not match the endpoint used in the RENEW clinical trial (change in SGRQ total score). The risk of pneumonia presented was below the risk of pneumonia experienced by RENEW clinical trial participants. Therefore, the patient preference study did not elicit preferences relevant to the clinical trial outcomes and cannot inform the benefit-risk assessment of the coil treatment.

10 Applicant's Proposed Future Post Market Study Recommendations

The inclusion of a Post-Market Study section in this summary should <u>not</u> be interpreted to mean that FDA has made a decision on the approvability of this device. The presence of a post-market study plan or commitment 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 post-market study could be considered.

The applicant is proposing a post market study with the primary effectives endpoints of Change in Quality of Life (QOL), as measured by 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. With the assumed 12-month composite serious RAE rate of 44% based on the RENEW study, 300 subjects will provide a precision of ±5.8% in the 95% confidence interval and 95% power to demonstrate non-inferiority to a performance goal of 55%.

FDA Comment: The applicant is proposing the change in SGRQ as the primary effectiveness endpoint. Since SGRQ is a subjective outcome, FDA does not believe that this is adequate as a primary effectiveness endpoint. The panel will be asked to discuss:
-the type of a post market study including possible registry
-relevant endpoints for safety and effectiveness

11 Other Postmarket Data

The applicant provided results for a post-market observational, prospective, multi-center registry study conducted OUS. This registry participants included subjects who were scheduled to have Coil procedure (commercially available under CE mark). Subjects were scheduled to receive two treatments separated by 1 to 3 months. Subjects are followed for up to 3 years. The 100 mm, 125 mm, and 150 mm coils were used in this registry, which are the same coils used in the pivotal and crossover study presented in this executive summary.

As of cut-off date of August 30 2016, a total of 851 subjects were enrolled at 54 investigational sites. The average age was approximately 65 years. 39.95 % (340/851) of subjects had homogeneous and 51.7% (440/851) of the subjects had heterogeneous emphysema. 6.58 % (56/851) had mixed emphysema and 1.76 % (15/851) had missing emphysema data. At baseline the mean FEV1 was 31% predicted, SGRQ was 63.5 points, 6MWT was 276 meters, and RV was 256% of the predicted value.

654 subjects (78.70%) had a second treatment performed. The second treatment was performed at a median of 57 days following initial treatment. In 5 (0.60%) subjects, a third procedure was performed based on investigator discretion. The median post procedure length of hospital stay for subjects in the Registry study was 4 days. At 12 months, the mean change in 6MWT was 5.2 meters, the mean percent change in FEV1 was 1.8 % and the mean change in SGRQ was -5.5 points.

The safety evaluation included 831 subjects. The major respiratory adverse events at 12 months were COPD exacerbations in 427 subjects (617 events), pneumonia in 83 subjects

(88 events), pneumothorax in 76 subjects (80 events), and hemoptysis in 130 subjects (146 events).

Table 19: Effectiveness Summary of OUS Registry Study[1]

	Baseline	Change from Baseline to 6 Months (N=572)	Change from Baseline to 1 Year (N=391)	Change from Baseline to 2 Year (N=118)
6MWT Distance Walked [m]				
n	**613**	**329**	**215**	**75**
Mean (SD)	267.16 (103.19)	19.16 (82.47)	5.16 (86.82)	8.95 (77.06)
Median (Min, Max)	280.0 (15.0, 600.0)	20.0 (-480.0, 254.0)	3.0 (-275.0, 210.0)	9.0 (-255.0, 225.0)
P value	-	<0.0001	0.3845	0.3179
FEV1 [L]-%change				
n	**NA**	**404**	**268**	**89**
Mean (SD)	**NA**	7.50 (23.08)	1.8 (18.31)	0.89 (20.47)
Median (Min, Max)	**NA**	5.09 (-74.5, 157.14)	0.0 (-45.71, 74.36)	0.0 (-38.0, 82.61)
P value	**NA**	<.0001	0.1093	0.6840
SGRQ [points]				
n	**637**	**367**	**256**	**91**
Mean (SD)	63.66 (13.84)	-5.13 (17.47)	-5.46 (15.96)	-2.14 (12.13)
Median (Min, Max)	63.42 (18.08, 99.56)	-5.00 (-62.67, 43.31)	-5.80 (-62.02, 56.54)	-2.07 (-46.58, 20.58)
P value	-	<0.0001	<0.0001	0.0961
RV [L]				
n	**687**	**398**	**262**	**87**
Mean (SD)	5.78 (1.28)	-0.23 (3.40)	-0.23 (1.05)	-0.16 (1.10)
Median (Min, Max)	5.58 (2.99, 9.65)	-0.29 (-4.02, 64.4)	-0.13 (-5.03, 2.26)	-0.03 (-3.66, 2.01)
P value	-	0.1785	0.0005	0.1675
RV % Predicted				
n	**687**	**398**	**262**	**87**
Mean (SD)	258.97 (56.02)	-19.57 (47.68)	-12.70 (47.65)	-11.96 (46.53)
Median (Min, Max)	249.05 (176.2, 521.6)	-14.85 (-219.3, 155.6)	-7.65 (-275.4, 110.3)	-7.6 (-137.4, 96.0)
P value	-	<0.0001	<0.0001	0.0186

	Baseline	Change from Baseline to 6 Months (N=572)	Change from Baseline to 1 Year (N=391)	Change from Baseline to 2 Year (N=118)
RV/ TLC [%]				
n	**686**	**394**	**260**	**87**
Mean (SD)	72.05 (8.35)	-0.49 (46.51)	-1.62 (6.47)	-1.64 (11.21)
Median (Min, Max)	71.89 (46.33, 113.96)	-2.49 (-56.31, 897.97)	-0.81 (-20.92, 117.28)	-0.39 (-67.14, 18.64)
P value	-	0.8347	<.0001	0.1762
FEV1 [L]				
N	**687**	**404**	**268**	**89**
Mean (SD)	0.81 (0.26)	0.05 (0.19)	0.01 (0.16)	0.01 (0.19)
Median (Min, Max)	0.77 (0.27, 3.45)	0.04 (-1.49, 1.1)	0.0 (-0.61, 0.58)	0.01 (-0.38, 0.84)
P value	-	<.0001	0.6027	0.7992

[1]Descriptive results are provided. Paired t-test for continuous variables and a paired Wilcoxon signed rank test for categorical variables are used at two sided alpha of 0.05. No adjustments were made for multiple comparisons.

12 FDA Considerations and Conclusions

The ELEVAIR coil provides bronchoscopic lung volume reduction. It is hypothesized to improve lung elasticity by achieving parenchymal compression when the coils return to the original shape. The RENEW clinical trial was designed to evaluate 6MWT, FEV1 and SGRQ outcomes as surrogates for exercise tolerance, lung function and quality of life.

The primary effectiveness result of median change of 14.6 meters for the 6MWT at 12 months was statistically significant with a later proposed statistical plan, but had uncertain clinically meaningful significance as this is below the MCID of 25 meters. The ATS statement[7] on 6MWT reported a multicenter study of 470 severe COPD patients who performed two 6MWTs 1 day apart, and on average the 6MWT was 20.1 meters (5.8%) higher on the second day.

The 6MWT responder rate was increased by 11.7% in the treatment arm in comparison to the control arms at 12 months. The clinically meaningful MCID for the responder rate for this study population is unknown. There were confounding factors that may have affected the responder rate. As part of the study protocol, data regarding which subjects continued with a maintenance program was not collected. It is unknown if the differences observed in the responder rates between the treatment and control were confounded by differences in ongoing maintenance therapy. In addition, it is unclear what the expected treatment effect would be in this patient population since in the treatment arm, 29.8 % subjects had more than 25 meters decline and 13.7 % subjects more than 75 meters decline (*Appendix 14.4 Table*

26). The FEV1 change of 7% did not meet the 10% MCID for COPD treatments which is based on clinical anchoring to endpoints such as exacerbations, perception of dyspnea, and decline in lung function (but not survival).[6] The SGRQ showed an improvement of -8.9 units at 12 months which met the MCID. This will need to be reviewed with caution as the subjects and clinicians were not blinded in this study and a sham arm was not performed which may have influenced a subjective outcome such as SGRQ. Additionally, there was an increased incidence of COPD exacerbations, lower respiratory tract infections and dyspnea in the treatment arm which does not correlate with improved SGRQ scores.

The applicant conducted multiple subgroup analyses that included comparing the results for US versus OUS subjects, homogeneous versus heterogeneous emphysema and RV ≥225% versus RV < 225%. The US subgroup, the homogeneous emphysema subjects, and the subjects with RV <225 % did not achieve the same degree of treatment effect following Coil treatment. It was noted that there was a statistically significant heterogeneity of treatment effects between US and OUS groups for 6MWT, FEV1 and SGRQ which would affect the pooliblity of the results. Pooled data may not be applicable to the US population. Therefore, caution should be made when US and OUS data are pooled for an overall effectiveness assessment.

Since the review of the overall effectiveness results had uncertain clinical significance, the applicant focused on the subjects with RV ≥225% and performed additional post hoc analyses to explain the results of the pivotal study. Post-hoc analyses included age, BMI and co-morbidities. There were inconsistencies in the conclusion drawn based on these post-hoc analyses. The applicant hypothesized that since subjects with 4 or more comorbidities were more prevalent in the US and RV < 225% subgroups, this may also have contributed to the differing effectiveness results seen by region and RV. However, this was not fully supported as the US control group with RV <225 did not worsen in comparison to the treated subjects.

The effectiveness benefit for the cross-over study population is very limited and contradicted the pivotal study results. It was noted that the baseline characteristics of the subjects treated in the pivotal study and the Crossover subjects (65% of controls) were similar, except the pivotal study had more baseline oxygen use and required pulmonary rehabilitation before coil treatment. It is known that oxygen use and pulmonary rehabilitation can influence 6MWT outcomes[7,8] and therefore the oxygen use and/or pulmonary rehabilitation may have contributed to the modest improvement in the pivotal study results that was not seen with the crossover group. The crossover results also contradicted the pivotal study results for subjects that had RV ≥225%, as those subjects did worse than subjects with RV < 225%. It should be noted that the crossover population represents a similar population as the pivotal treatment group and also represents the intended real world use population, therefore, it is unclear what the device effect would be in real world practice.

There is a higher likelihood of major complications, serious adverse events and device related adverse events in the treatment arm in the first 12 months. The mortality rate was similar between the treatment and control group, however, the mortality in the treatment

group was mainly related to possible or probable complications of the device and/or procedure. The major adverse events included COPD exacerbation, pneumonias, hemoptysis, pneumothorax, respiratory failure. Specifically, the incidence of COPD exacerbations and pneumonias were much higher in the coil treatment group. Based on longitudinal studies for COPD, it is known that these adverse events can contribute to worsening progression of the underlying disease.[12] There was also increased health care utilization costs with increased hospitalizations and unscheduled emergency room (ER) in both the treatment arm and the crossover in comparison to the 12 months prior to treatment. Additionally, the oxygen use did not change after coil treatment.

There have been publications that have evaluated the safety and effectiveness of coil treatment.[11,13,14] There were limitations on the effectiveness data such that some full cohorts were not followed beyond 6 months. Additionally, since a sham procedure was not performed, the placebo effect is unknown. COPD exacerbation, pneumonia and pneumothorax were adverse events that were reported in all these studies. One retrospective study[11] reported abscesses surrounding the coils in 2 patients within 90 days and late complications (>1year) that included severe hemoptysis and pneumothorax with coil perforation into the pleural space. These studies have highlighted that this group of patients are a high risk population for complications and increased mortality secondary to any interventional procedure and therefore the magnitude and duration of effect would need to be adequately demonstrated to justify the safety profile. Additionally, the investigators of the RENEW trial also published the 12 month pivotal study results presented in this executive summary in JAMA[5] and stated that "*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*."

13 References

1. Global Initiative for Chronic Obstructive Lung Disease. Pocket Guide To COPD Diagnosis, Management, And Prevention. A Guide for Health Care Professionals. 2017 Edition.
2. Barnes PJ. Chronic Obstructive Pulmonary Disease. N Engl J Med 2000; 343:269-280.
3. Pompeo, E. Lung Volume Reduction Surgery for Emphysema Treatment: State-of-the-Art and Perspectives. ISRN Pulmonology; 2014. Volume 2014: 1-17.
4. National Emphysema Treatment Trial Research Group. A Randomized Trial Comparing Lung-Volume–Reduction Surgery with Medical Therapy for Severe Emphysema. N Engl J Med 2003; 348:2059-2073
5. Sciurba et al. Effect of Endobronchial Coils vs Usual Care on Exercise Tolerance in Patients With Severe Emphysema The RENEW Randomized Clinical Trial. JAMA; 2016. doi:10.1001/jama.2016.6261
6. Jones et al. Minimal Clinically Important Differences in Pharmacological Trials. Am J Respir Crit Care Med; 2014. 189 (3): 250–255
7. ATS Statement: Guidelines for the Six-Minute Walk Test. Am J Respir Crit Care; 2002. 166: 111–117.

8. Shah et al. Current status of bronchoscopic lung volume reduction with endobronchial valves. Thorax. 2014; 69:280–286.
9. Herth et al. Endoscopic Lung Volume Reduction: An Expert Panel Recommendation. Respiration. 2016; DOI: 10.1159/000444090
10. Kontogianni et al. Coil therapy for patients with severe emphysema and bilateral incomplete fissures – effectiveness and complications after 1-year follow-up: a single-center experience. International Journal of COPD; 2017:12 383–394
11. Vestbo et al. Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE). European Respiratory Journal. 2008: 31:869-873
12. Deslee et al. Lung Volume Reduction Coil Treatment vs Usual Care in Patients With Severe Emphysema The REVOLENS Randomized Clinical Trial. JAMA. 2016; 315(2):175-184.
13. Deslee et al. Lung volume reduction coil treatment for patients with severe emphysema: a European multicentre trial. Thorax 2014; 69:980–986.

14 Appendices

14.1 Previous Studies

Below are the summary of the clinical investigations prior to the pivotal study:

1. **Pilot study (CLN0006):** Multicenter, single-arm, open-label study in Germany and the Netherlands evaluated coil safety in subjects with emphysema. Thirty-six (36) subjects with heterogeneous or homogeneous emphysema were treated either bilaterally (69.4%) or unilaterally with coils, with a mean of 8 coils per procedure. Adverse events occurred in all subjects, with 22% being serious AE. The most common device or procedure related AEs were COPD exacerbation, hemoptysis, dyspnea and chest pain. The primary endpoint, improvement in SGRQ between baseline and 1 and 3 months post final treatment, was 11.1 and 10.1 points in SGRQ score at 1 and 3 months, respectively.

2. **Early Feasibility study (CLN0011):** This was a prospective, multi-center, single-arm, open-label study in Germany, the Netherlands and France to evaluate the safety of coil treatment in subjects with emphysema. Sixty (60) subjects with heterogeneous or homogeneous emphysema were treated either bilaterally (91.6%) or unilaterally with coils, with a mean of 9.8 coils per procedure. Adverse events occurred in 96.7% of subjects, with 18.7% being serious AEs. The most common device or procedure related AEs were hemoptysis, COPD exacerbation, chest pain and pneumonia. The primary effectiveness endpoint, improvement in SGRQ between baseline and 6 months post final treatment, was a mean improvement of 9.9 points.

3. **Randomized control study (CLN0008):** This was the prospective, multi-center, first randomized, controlled open label study with 1:1 randomization to treatment or control (standard of care) to evaluate the safety and effectiveness of coil treatment. After the 3-month follow-up visit, control subjects were crossed over to receive Coil treatment, after which all subjects were followed up for 12 months post final treatment. Of the 47 subjects enrolled in the study, 45 were treated either bilaterally (86.7%) or unilaterally

with Coils (23 during randomized phase, 22 during crossover), with a mean of 9.3 and 9.6 Coils per procedure for the treatment and crossover groups respectively. Adverse events occurred in 95.7% of subjects, with 22.6% being serious AEs. In the randomized phase of the study, the most common device or procedure related AEs were pneumothorax, chest infection, chest pain and COPD exacerbation.,. In the crossover phase, the most common device or procedure related AEs were hemoptysis, dyspnea, pneumothorax and COPD exacerbation. Subjects treated with the coil reported a mean improvement of 9.11 points in SGRQ.

4. **Single arm study (CLN0012):** A study evaluating the safety and performance of the ELEVAIR System in subjects with homogeneous emphysema was conducted as a prospective, single-center, single-arm open-label study. Ten (10) subjects with homogeneous emphysema were treated bilaterally with Coils, with a mean of 11.4 Coils per procedure. Adverse events occurred in 9 of 10 subjects (90%), with 11.5% being serious AEs. The most common device or procedure related AEs were COPD exacerbation, chest pain and hemoptysis. The primary endpoint, mean absolute change in 6-minute walk test (6MWT) between baseline and 6 months post final treatment, showed change of 52.9 meters.

14.2 Treatment Planning Chart for the RENEW Pivotal and Crossover Study

A CT based method was developed to select subjects and plan treatment using lobar damage visual assessment and scoring. A character score was assigned for each of the 4 main lobes (UL, UR, LL, LR) that best matched the damage seen in the provided images. Scores of 0 – 3 were defined as patterns of low to medium damage severity that would be scored using the average (> 50% of the area of the lobe) of the axial CT slice. If a single defect or group of defects fit the 4 or 5 score criteria, then the largest defects would be used to define the character score as a 4 or 5. The scores were defined as listed below:

a. #0 score: Lobe presents with normal tissue or having damage limited to scattered small centrilobular emphysematous holes.

b. #1 score: Lobe presents with more obvious centrilobular disease. Many small (approximately 1-3mm diameter) lung parenchyma tissue defects are present but the parenchyma is still extensively connected and preserved.

c. #2 score: Lobe presents with more advanced centrilobular emphysema. Numerous defects (approximately 3-10mm diameter) can be seen making up the majority of the damage: however the periphery of secondary pulmonary lobule and the interstitium remain intact.

d. #3 score: Lobe presents with mostly non-coalescent bullous centriobular emphysema with between larger 20-30 mm parenchymal defects. The lung tissue is still globally connected (the interstitium and boundary of the second pulmonary lobule can still be seen.) This will look similar to the #2 score but with larger defects.

e. #4 score: Lobe presents with panlobular emphysema or coalescent emphysema with parenchyma defects 30-50mm in size and complete loss of secondary pulmonary lobular structure. In addition, paraseptal damage with a length along the perimeter of 30 to 75mm fall in this category.

f. #5 score: Lobe presents with a single confluent defect that is larger than 50mm or a single paraseptal defect that is longer than 75mm along the perimeter of the length. Lobes that present with little visible continuous structure fall in this category.

The character score was interpreted to recommend a treatment plan or to exclude the subject using the following guidelines:

a. If any of the 4 major lobes received a score of 5, the subject was excluded from the study.

b. If either lung presented with a score of 4 and 4 or a combination of 3 and 4, the lung was considered to be in a severely damaged homogeneous condition and the subject was excluded.

c. Treatments were required to be upper or lower lobe but *not both lobes in a single lung*. The treatment plan recommended treatment in the lobe with the highest character score in each lung as indicated by the treatment planning chart (Table *20*).

Table 20: Treatment planning chart

		Upper Lobe Character Score					
Lower Lobe Character Score		**0**	**1**	**2**	**3**	**4**	**5**
	0	U	U	U	U	U	NT
	1	L	U	U	U	U	NT
	2	L	L	U	U	U	NT
	3	L	L	L	U	NT	NT
	4	L	L	L	NT	NT	NT
	5	NT	NT	NT	NT	NT	NT

U = Upper Lobe Treatment
L = Lower Lobe Treatment
NT = No Treatment (exclude subject)

14.3 Renew Pivotal and Crossover Study Design Additional Tables

Table 21: Inclusion/Exclusion Criteria of RENEW Pivotal *and Crossover Study*

Inclusion Criteria Subjects must have met **all** of the following inclusion criteria to be entered into the study:	
RENEW Pivotal	**Crossover**
1. Subject ≥ 35 years of age. 2. CT scan indicated bilateral emphysema, as determined by the Core Radiology Lab using the criteria presented in the "CT Scoring Plan for Core Radiology Lab". 3. Subject had post-bronchodilator Forced Expiratory Volume in one second (FEV1) ≤ 45% predicted. 4. Subject had Total Lung Capacity (TLC) > 100% predicted. 5. Subject had residual volume (RV) ≥ 175% predicted. (Inclusion Criterion initially required RV ≥225% predicted but was changed to ≥175% predicted during the study enrollment phase). 6. Subject had marked dyspnea scoring ≥ 2 on mMRC scale of 0-4. 7. Subject had stopped smoking for at least 8 weeks prior to entering the study, as confirmed by a Cotinine test or other appropriate diagnostic test. 8. Subject had read, understood and signed the Informed Consent form. 9. Subject had completed a pulmonary rehabilitation program within 6 months prior to treatment and/or was regularly performing maintenance respiratory rehabilitation if initial supervised therapy occurred more than 6 months prior to baseline testing. 10. Subject had received pneumococcal and influenza vaccinations consistent with local recommendations and/or policy.	1. Subject was enrolled as a Control Subject in and completed all required study assessment through the 12-month visit for the RENEW Study. 2. Subject had post-bronchodilator Forced Expiratory Volume (in one second) (FEV1) ≤45% predicted. 3. Subject had residual volume (RV) ≥175% predicted. 4. Subject had stopped smoking for at least 8 weeks prior to entering the study, as confirmed by a cotinine test or other appropriate diagnostic test. 5. Subject had read, understood and signed the Informed Consent Form (ICF). 6. Subject had received pneumococcal and influenza vaccinations consistent with local recommendations and/or policy
Exclusion Criteria Subjects were excluded from the study if **any** of the following conditions applied:	
1. Subject had severe homogeneous emphysema as determined by the Core Radiology Lab. 2. Subject had comorbidities that could have significantly reduce subject's ability to improve exercise capacity (e.g., severe arthritis, planned knee surgery) or baseline limitation on 6MWT not due to dyspnea. 3. Subject had a change in FEV1 > 20% (or, for subjects with pre-bronchodilator FEV1 below 1 L, a change of > 200 mL) post-bronchodilator unless investigator could confirm by other means that subject did not have asthma. 4. Subject had Diffusion Capacity of the Lung for Carbon Monoxide (DLCO) <20% of predicted. 5. Subject had severe gas exchange abnormalities as defined by: a. PaCO2 > 55 mm Hg b. PaO2 < 45 mm Hg on room air (High altitude criterion: PaO2 < 30 mm Hg)	1. Subject had severe homogeneous emphysema as determined by the Core Radiology Lab. 2. Subject had comorbidities that may have significantly reduced subject's ability to improve exercise capacity (e.g. severe arthritis, planned knee surgery) or baseline limitation on 6MWT was not due to dyspnea 3. Subject had a change in FEV1 >20% (or, for subjects with pre-bronchodilator FEV1 below 1L, a change of > 200 mL) post-bronchodilator, unless investigator can confirm by other means that subject does not have asthma. 4. Subject had DLCO <20% of predicted. 5. Subject had severe gas exchange abnormalities as defined by: a. PaCO2 > 55 mm Hg b. PaO2 < 45 mm Hg on room air (High altitude criterion: PaO2 < 30 mm Hg)

6. Subject had a history of recurrent clinically significant respiratory infections, defined as 3 hospitalizations for respiratory infection during the year prior to enrollment.	6. Subject had a history of recurrent clinically significant respiratory infections, defined as 3 hospitalizations for respiratory infection during the year prior to enrollment.
7. Subject had severe pulmonary hypertension defined by right ventricular systolic pressure > 50 mm Hg via right heart catheterization and/or echocardiogram.	7. Subject had severe pulmonary hypertension. If pulmonary hypertension is present, "severe" is defined by right ventricular systolic pressure >50 mm Hg via right heart catheterization and/or echocardiogram.
8. Subject had an inability to walk > 140 meters (150 yards) in 6 minutes.	8. Subject had an inability to walk >140 meters (150 yards) in 6 minutes.
9. Subject had evidence of other severe disease (such as, but not limited to, lung cancer or renal failure) which, in the judgment of the investigator, may compromise survival of the subject for the duration of the study.	9. Subject had evidence of other severe disease (such as, but not limited to, lung cancer or renal failure), which in the judgment of the investigator may compromise survival of the subject for the duration of the study.
10. Subject was pregnant or lactating, or planned to become pregnant within the study time frame.	10. Subject was pregnant or lactating, or planned to become pregnant within the study timeframe.
11. Subject was unable to tolerate bronchoscopy under moderate sedation or general anesthesia.	11. Subject had an inability to tolerate bronchoscopy under moderate sedation or general anesthesia.
12. Subject had clinically significant bronchiectasis.	12. Subject had clinically significant bronchiectasis.
13. Subject had giant bullae > 1/3 lung volume.	13. Subject had giant bullae >1/3 lung volume.
14. Subject had previous LVRS, lung transplantation, lobectomy, LVR devices or other device to treat COPD in either lung.	14. Subject had previous LVRS, lung transplantation, lobectomy, LVR devices or other device to treat COPD in either lung.
15. Subject had been inviolved in pulmonary drug or device stiduies within 30 days prior to this study.	15. Subject had been involved in pulmonary drug or device studies within 30 days prior to this study, with the exception of the RENEW Study.
16. Subject was taking > 20 mg prednisone (or equivalent dose of a similar steroid) daily.	16. Subject was taking >20 mg prednisone (or equivalent dose of a similar steroid) daily.
17. Subject required high level chronic immunomodulatory therapy to treat a moderate to severe chronic inflammatory autoimmune disorder.	17. Subject required high level chronic immunomodulatory therapy to treat a moderate to severe chronic inflammatory autoimmune disorder.
18. Subject was on an antiplatelet (such as Plavix) or anticoagulant therapy (such as heparin or Coumadin) which could not be stopped for 7 days prior to procedure.	18. Subject was on an antiplatelet (such as Plavix) or anticoagulant therapy (such as heparin or Coumadin) which cannot be stopped for seven (7) days prior to procedure.
19. Subject had a sensitivity or allergy to nitinol (nickel-titanium) or its constituent metals.	19. Subject had a sensitivity or allergy to nitinol (nickel-titanium) or its constituent metals.
20. Subject had a known sensitivity to drugs required to perform bronchoscopy.	20. Subject had a known sensitivity to drugs required to perform bronchoscopy.
21. Subject had been diagnosed with alpha-1 antitrypsin deficiency (AATD).	21. Subject had been diagnosed with alpha-1 antitrypsin deficiency (AATD).
22. Subject had any other disease, condition(s) or hab//it(s) that would interfere with completion of study and follow-up assessments, increased risks of bronchoscopy or assessments, or in the judgment of the investigator, would potentially interfere with compliance to this study or would adversely affect study outcomes.	22. Subject had any other disease, condition(s) or habit(s) that would interfere with completion of study and follow-up assessments, would increase risks of bronchoscopy or assessments, or in the judgment of the investigator would potentially interfere with compliance to this study or would adversely affect study outcomes.

Table 22: RENEW Subject Disposition post 12 months.

Subject Status	Coil Treatment
Subjects Who Completed Study to 24 Months[1]	89.4% (126/141)
Subjects Who Completed 24-Month Visit	80.9% (114/141)
Subjects Who Discontinued 12 to 24 Months	10.6% (15/141)
Subjects Who Died	12
Subjects Who Lost To Follow-Up	1
Subjects Who Withdrew Consent	1
Subjects Who Were Withdrawn By Investigator	1
Subjects Who Completed Study to 36 Months[1]	43.7% (55/126)
Subjects Who Completed 36-Month Visit	38.9% (49/126)
Subjects Pending 36 Month Visit [2]	42.1% (53/126)
Subjects Who Discontinued 24 to 36 Months	14.3% (18/126)
Subjects Who Died	11
Subjects Who Lost To Follow-Up	0
Subjects Who Withdrew Consent	3
Subjects Who Were Withdrawn By Investigator	4

[1]Includes subjects that had not discontinued at time of visit [2]Includes subjects that had not reached the 36-month Visit window at time of data cut
Note: Three subjects discontinued (death) after 36 months.

Table 23: Crossover Subject Disposition post 12 months.

Subject Status	Crossover Subjects
Subjects Who Completed Study To 24 Months[1]	37.9%% (33/87)
Subjects Who Completed 24-Month Visit	29.9%% (26/87)
Subjects Pending Completion Of 24 Month Visit[2]	43.7% (38/87)
Subjects Who Discontinued 12 To 24 Months	18.4% (16/87)
Subjects Who Died	9
Subjects Who Withdrew Consents	3
Subjects Who Were Withdrawn By Investigator	4
Subjects Who Completed Study To 36 Months[1]	15.2% (5/33)
Subjects Who Completed 36-Month Visit	15.2% (5/33)
Subjects Pending Completion Of 36 Month Visit[2]	69.7% (23/33)
Subjects Who Discontinued 24 To 36 Months	15.2% (5/33)
Subjects Who Died	2

Subject Status	Crossover Subjects
Subjects Who Withdrew Consents	0
Subjects Who Were Withdrawn By Investigator	3

[1]Includes subjects that had not discontinued at time of visit [2]Includes subjects that had not reached the visit window at time of data cut

Table 24: Baseline Demographic Characteristics - ITT Population in Pivotal and *Crossover*

	Coil Treatment (N=158)	Control (N=157)	P-Value[1]	Crossover (N=102)
Age (year)			0.4532	
Mean ± SD (n) Median Range (min, max)	63.4 ± 8.05 (158) 63.0 (41, 81)	64.3 ± 7.76 (157) 64.0 (45, 82)		64.9 ± 7.7 (102) 65.0 (46.0, 84.0)
Gender			0.2741	
Male	45.6% (72/158)	49.7% (78/157)		43.1% (44/102)
Female	54.4% (86/158)	50.3% (79/157)		56.9% (58/102)
Body Mass Index (BMI) (kg/m²)			0.2432	
Mean ± SD (n) Median Range (min, max)	24.90 ± 4.603 (158) 24.25 (16.7, 40.1)	24.53 ± 4.872 (157) 23.70 (14.4, 39.6)		24.7 ± 4.9 (102) 23.7 (13.8, 41.2)

[1] For continuous variables, p-value is based on two-way ANOVA with factors of treatment group and investigational site. For categorical variables, p-value is based on Cochran-Mantel-Haenszel (CMH) test stratified by investigational site; for situations in which Cochran's rule is not satisfied, Fisher's exact test was used.

Table 25: Baseline Disease Characteristics-ITT Population in Pivotal and Crossover

	Coil Treatment (N=158)	Control (N=157)	P-value[1]	Crossover N=102
6MWT Total Distance (meters)			0.8137	
Mean ± SD (n) Median Range (min, max)	312.03 ± 79.906 (158) 318.25 (149.4, 540.0)	302.70 ± 79.277 (157) 300.00 (141.1, 670.6)		313.6 ± 82.0 (102) 318.5 (155.0, 548.6)
Lung damage classification			0.7105	
Heterogeneous	22.8% (36/158)	22.9% (36/157)		19.6% (20/102)
Homogeneous	77.2% (122/158)	77.1% (121/157)		80.4% (82/102)
Post-bronchodilator Spirometry				
FVC (L)			0.9063	
Mean ± SD (n) Median Range (min, max)	2.47 ± 0.687 (158) 2.49 (1.3, 4.5)	2.46 ± 0.748 (157) 2.35 (1.1, 5.3)		2.4 ± 0.7 (102) 2.3 (1.2, 4.9)

	Coil Treatment (N=158)	Control (N=157)	P-value[1]	Crossover N=102
FVC % Predicted			0.6414	
Mean ± SD (n) Median Range (min, max)	67.75 ± 14.319 (158) 67.97 (39.3, 109.4)	67.40 ± 15.011 (157) 66.32 (30.5, 110.0)		68.6 ± 13.8 (102) 66.5 (43.8, 118.2)
FEV1 (L)			0.5171	
Mean ± SD (n) Median Range (min, max)	0.71 ± 0.202 (158) 0.66 (0.4, 1.2)	0.72 ± 0.210 (157) 0.68 (0.4, 1.7)		0.7 ± 0.2 (102) 0.7 (0.4, 1.5)
FEV1 % Predicted			0.4807	
Mean ± SD (n) Median Range (min, max)	25.71 ± 6.283 (158) 24.94 (12.9, 43.6)	26.27 ± 6.671 (157) 25.63 (11.2, 44.9)		26.4 ± 6.2 (102) 25.6 (16.0, 44.3)
FEV1/FVC (%)			0.0544	
Mean ± SD (n) Median Range (min, max)	28.80 ± 6.806 (158) 30.00 (20.0, 50.0)	29.87 ± 6.792 (157) 30.00 (20.0, 50.0)		29.2 ± 5.9 (102) 30.0 (20.0, 40.0)
Post-bronchodilator Lung Volumes				
Residual Volume (RV) (L)			0.4460	
Mean ± SD (n) Median Range (min, max)	5.28 ± 1.058 (158) 5.20 (2.9, 9.3)	5.33 ± 1.145 (157) 5.18 (3.1, 8.6)		5.2 ± 1.3 (102) 5.1 (3.0, 10.6)
Residual Volume % Predicted			0.9103	
Mean ± SD (n) Median Range (min, max)	245.94 ± 39.062 (158) 240.00 (175.8, 369.1)	244.53 ± 38.693 (157) 240.56 (175.7, 404.8)		242.1 ± 50.0 (102) 233.7 (167.6, 480.9)
Total Lung Capacity (TLC) (L)			0.6238	
Mean ± SD (n) Median Range (min, max)	7.87 ± 1.345 (158) 7.73 (5.4, 11.3)	7.92 ± 1.559 (157) 7.80 (4.9, 11.5)		7.8 ± 1.7 (102) 7.3 (4.9, 13.8)
Total Lung Capacity % Predicted			0.7240	
Mean ± SD (n) Median Range (min, max)	139.21 ± 15.620 (158) 137.71 (111.3, 180.9)	138.78 ± 16.064 (157) 138.85 (104.5, 202.2)		140.1 ± 22.4 (102) 138.2 (104.4, 284.6)
RV/TLC Measured (%)			0.3988	
Mean ± SD (n) Median Range (min, max)	67.05 ± 6.731 (158) 66.56 (45.0, 84.0)	67.32 ± 6.263 (157) 67.30 (50.0, 82.0)		67.0 ± 6.4 (102) 67.6 (51.6, 78.9)
Diffusion Capacity (mmol/min/kPa)			0.7367	
Mean ± SD (n) Median	2.72 ± 0.959 (158) 2.50	2.73 ± 0.938 (157) 2.48		2.7 ± 0.9 (102) 2.4

	Coil Treatment (N=158)	Control (N=157)	P-value[1]	Crossover N=102
Range (min, max)	(1.1, 5.7)	(1.3, 6.1)		(1.3, 6.1)
Diffusion Capacity % Predicted			0.7091	
Mean ± SD (n) Median Range (min, max)	34.12 ± 10.477 (158) 32.86 (16.2, 69.5)	34.47 ± 10.686 (157) 32.42 (19.5, 78.3)		34.1 ± 9.9 (102) 32.1 (20.6, 71.2)
SGRQ Total Score			0.0503	
Mean ± SD (n) Median Range (min, max)	60.05 ± 12.757 (158) 60.04 (26.7, 94.9)	57.44 ± 14.759 (157) 58.83 (8.2, 96.7)		57.9 ± 15.6 (102) 59.3 (22.2, 92.2)
mMRC Dyspnea Scale			0.8747	
0	0.0% (0/158)	0.0% (0/157)		0.0% (0/102)
1	0.0% (0/158)	0.0% (0/157)		8.8% (9/102)
2	34.2% (54/158)	35.7% (56/157)		38.2% (39/102)
3	43.7% (69/158)	44.6% (70/157)		33.3% (34/102)
4	22.2% (35/158)	19.7% (31/157)		19.6% (20/102)
GOLD Stage 4, % (N)	75.9% (120/158)	71.3% (112/157)	0.4770	73.5% (75/102)
BODE Score			0.8412	
Mean ± SD (n) Median Range (min, max) % BODE 7-10	5.97 ± 1.262 (158) 6.00 (3.0, 9.0) 32.3% (51/158)	6.04± 1.322 (157) 6.00 (3.0, 10.0) 33.1% (52/157)		5.7 ± 1.4 (102) 6.0 (3.0), (9.0) 26.5% (27/102)
Smoking Pack Year History			0.5798	
Mean ± SD (n) Median Range (min, max)	50.66 ± 27.945 (157) 45.00 (8.0, 180.0)	50.28 ± 23.483 (157) 45.00 (0.0, 137.0)		48.8 ± 21.8 (102) 44.5 (0.0, 105.0)
Number of Comorbidities[2]			0.2733	
0-3	71.5% (113/158)	75.2% (118/157)		80.4 % (82/102)
≥4	28.5% (45/158)	24.8% (39/157)		19.6 % (20/102)

[1] For continuous variables, p-value is based on two-way ANOVA with factors of treatment group and investigational sites, for categorical variables, p-value is based on Cochran-Mantel-Haenszel (CMH) test stratified by investigational sites; for situations in which Cochran's rule is not satisfied, Fisher's exact test was used.

[2] The total number of comorbidities of interest were calculated for each subject from the following list: Arthritis, Cachexia (BMI < 18.5 kg/m2), Cardiac Disease (Angina, Atrial Fibrillation, Congestive Heart Failure and Coronary Artery Disease), Depression, Diabetes, Edema, GERD, Hyperlipidemia, Hypertension, Obesity (BMI > 30 kg/m2), Osteoporosis, Peripheral Vascular Disease, Renal Dysfunction, Sleep Apnea and Stroke. In this calculation, the presence of any of the 4 cardiac comorbidities (Angina, Atrial Fibrillation, Congestive Heart Failure or Coronary Artery Disease was only counted once) as Cardiac Disease.

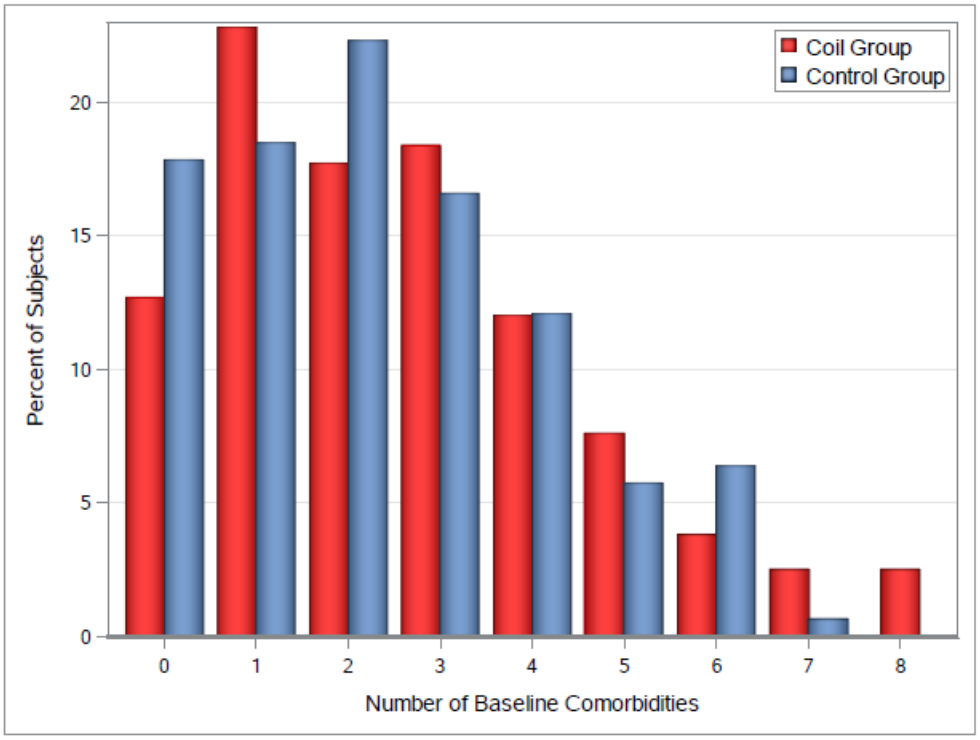


Figure 9: Distribution of Comorbidity Frequency in the control and coil group. *NOTE: The total number of comorbidities of interest were calculated for each subject from the following list: Arthritis, Cachexia (BMI < 18.5 kg/m2), Cardiac Disease (Angina, Atrial Fibrillation, Congestive Heart Failure and Coronary Artery Disease), Depression, Diabetes, Edema, GERD, Hyperlipidemia, Hypertension, Obesity (BMI > 30 kg/m2), Osteoporosis, Peripheral Vascular Disease, Renal Dysfunction, Sleep Apnea and Stroke. In this calculation, the presence of any of the 4 cardiac comorbidities (Angina, Atrial Fibrillation, Congestive Heart Failure or Coronary Artery Disease was only counted once) as Cardiac Disease*

14.4 Additional Effectiveness Results for RENEW Pivotal and Crossover

Table 26: Exploratory Analysis of 6MWT Change from Baseline to 12 Months[4]

	RENEW Pivotal Study				Crossover Study
Change from baseline in 6 MWT at 12 months	**Mean Rate for Coil (%) (N=158)[1]**	**Mean Rate for Control (%) (N=157)[1]**	**Difference of Log Odds (Coil Treatment vs. Control) [95% CI][2]**	**Odds Ratio [95% CI][2]**	**Mean Rate for Coil (%) (N=80)[3]**
≥ 25 m improved	37.9%	26.2%	0.72 [0.16, 1.29]	2.06 [1.17, 3.64]	26.3%
≥ 50 m improved	21.8%	18.2%	0.36 [-0.28, 1.00]	1.43 [0.75, 2.71]	11.3%
≥ 75 m improved	9.7%	7.8%	0.07 [-0.88, 1.02]	1.07 [0.41, 2.77]	6.25%

	RENEW Pivotal Study				Crossover Study
Change from baseline in 6 MWT at 12 months	**Mean Rate for Coil (%) (N=158)[1]**	**Mean Rate for Control (%) (N=157)[1]**	**Difference of Log Odds (Coil Treatment vs. Control) [95% CI][2]**	**Odds Ratio [95% CI][2]**	**Mean Rate for Coil (%) (N=80)[3]**
≥ 100 m improved	7.5%	3.6%	0.52 [-0.69, 1.73]	1.68 [0.50, 5.64]	3.75%
More than -25 m declined	29.8%	39.1%	-0.51 [-1.03, 0.02]	0.60 [0.36, 1.02]	42.5%
More than -50 m declined	17.5%	21.4%	-0.28 [-0.90, 0.34]	0.76 [0.41, 1.41]	30.0%
More than -75 m declined	13.7%	11.4%	0.22 [-0.54, 0.98]	1.24 [0.58, 2.66]	18.8%
More than -100 m declined	8.3%	6.0%	0.51 [-0.50, 1.53]	1.67 [0.60, 4.59]	11.3%

[1] Mean rate is the mean of rates from MCMC multiple imputation.
[2] Based on MCMC multiple imputation results of logistic regression with factors of treatment, analysis center, baseline 6MWTand emphysemaheterogeneity as covariates.
[3] 80 of 102 subjects completed 6MWT at 12 months in the Crossover study.
[4] This table was based on the agency's analyses

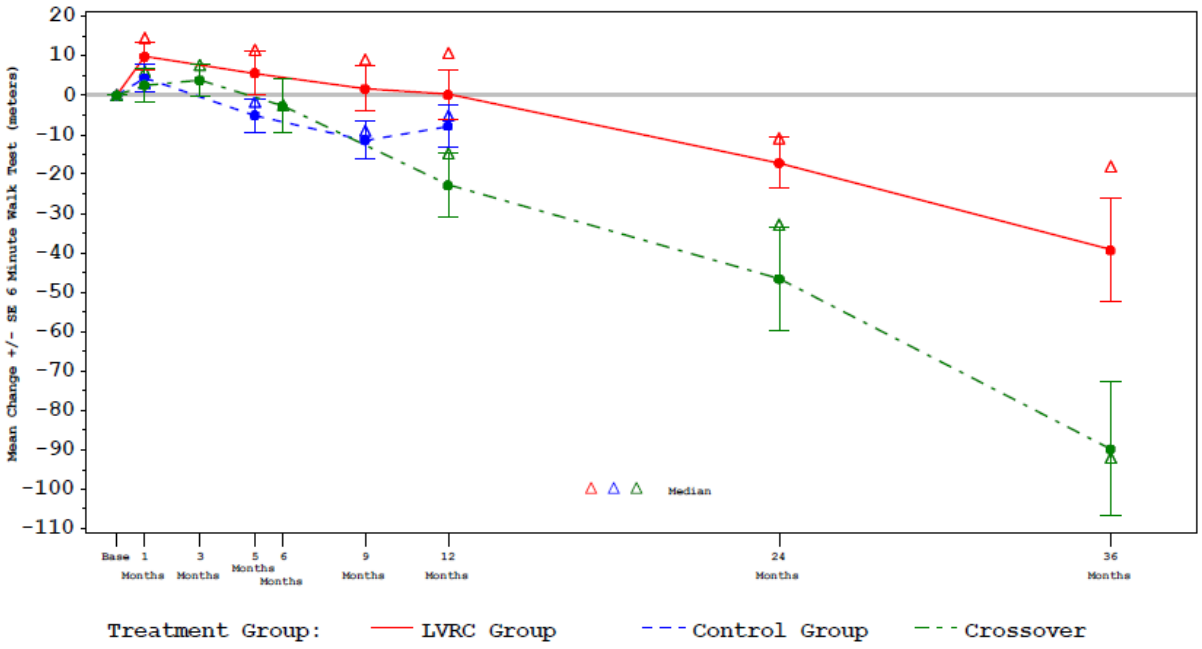


Figure 10: Mean Change in 6MWT by Visit and Treatment for RENEW and Crossover

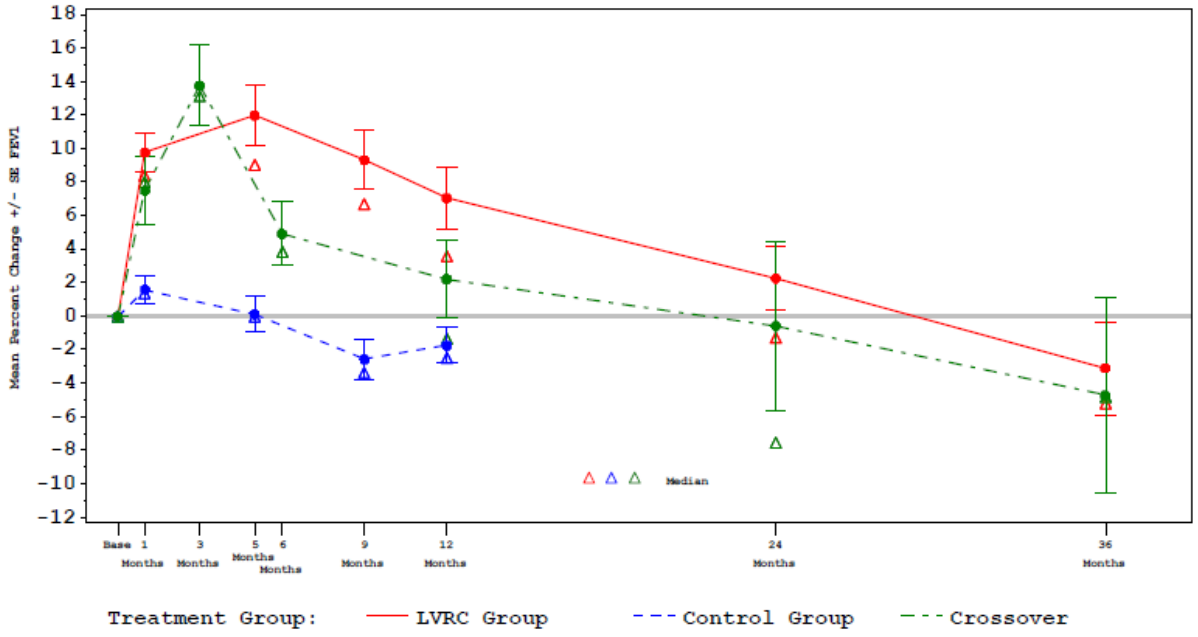


Figure 11: Mean Percent Change in FEV1 by Visit and Treatment for RENEW and Crossover

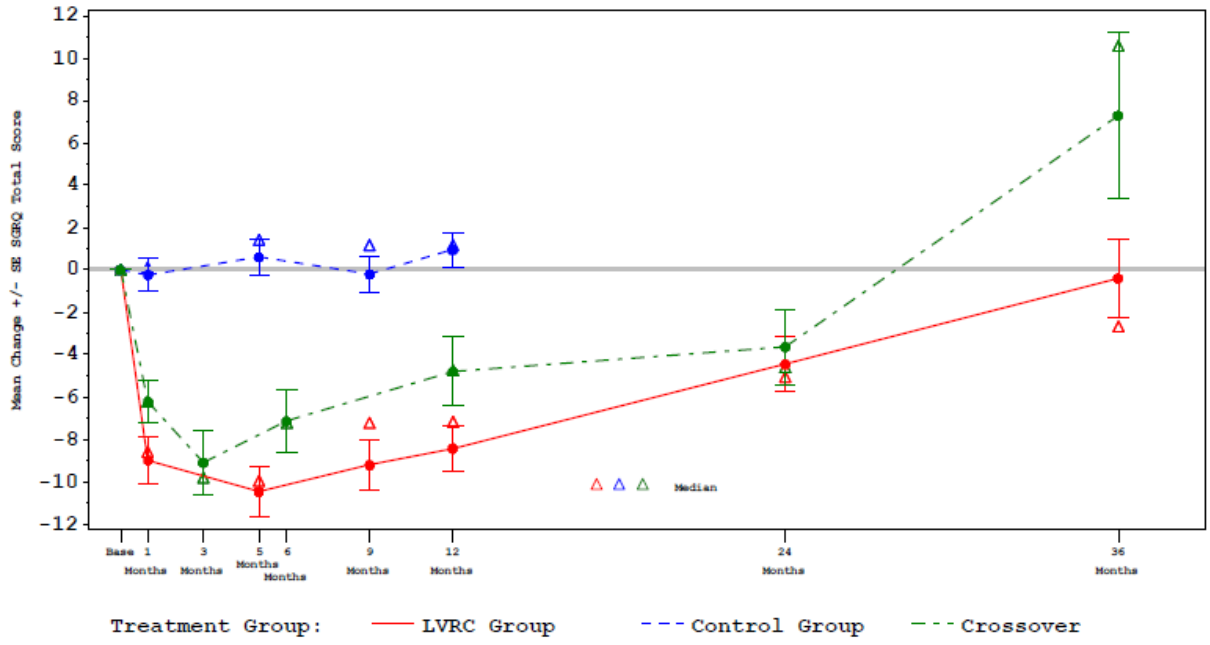


Figure 12: Mean Change in SGRQ by Visit and Treatment for RENEW and Crossover

Table 27: SGRQ Responder Analysis for RENEW Pivotal and Crossover

Treatment Group (N)	Mean Responder Rate at 12 Months	Adjusted Mean Responder Rate At 12 Months	Difference of Log Odds (Coil Treatment vs. Control) [95% CI][1]	Treatment vs. Control Odds Ratio [95% CI][1]
Control (N=157)	30.5%	27.7%	1.4 [0.9, 2.0]	4.1 [2.4, 7.2]
Coil Treatment (N=158)	62.1%	61.2%		
Crossover (N=102)	54.2 % (45/83)[2]	NA	NA	NA

[1]Based on MCMC multiple imputation results of logistic regression with factors of treatment and analysis center and baseline SGRO and emphysema heterogeneity as covariates.
Note: Responder is defined as those with an improvement (decrease) of >= 4 points.
[2] Only 83 of 102 subjects completed 12 months SGRQ in the Crossover study.

Table 28: Mean Absolute Difference from Baseline to 12 Months in Residual Volume (RV)

Treatment Group (N)	Baseline RV (Liters) Mean ± SE	Mean Absolute Change from Baseline (Liters) Mean ± SE	Adjusted Change from Baseline (Liters) Mean ± SE	Difference (Coil Treatment vs. Control) [95% CI][1]
Control (N=157)	5.33 ± 0.09	-0.04 ± 0.07	-0.10 ± 0.08	-0.31 [-0.50, -0.11]
Coil Treatment (N=158)	5.28 ± 0.08	-0.34 ± 0.07	-0.41 ± 0.08	
Crossover	5.2 ± 0.13 (N=102)	-0.3± 0.08 (N=81)	NA	NA

[1]Based on least squares mean difference from MCMC multiple imputation results of ANCOVA with factors of treatment and analysis center and baseline RV and emphysema heterogeneity as covariates.

Table 29: Mean Absolute Difference in Residual Lung Volume/Total Lung Capacity

Treatment Group (N)	Baseline RV/TLC Mean ± SE	Mean Absolute Change from Baseline Mean ± SE	Adjusted Change from Baseline Mean ± SE	Difference (Coil Treatment vs. Control) [95% CI][1]
Control (N=157)	67.32 ± 0.50	-0.03 ± 0.49	-0.45 ± 0.55	-3.50 [-4.86, -2.14]
Coil Treatment (N=158)	67.05 ± 0.54	-3.46 ± 0.53	-3.96 ± 0.56	
Crossover	67.0 ± 0.63 (N=102)	-1.9± 0.70 (N=81)	NA	NA

[1]Based on least squares mean difference from MCMC multiple imputation results of ANCOVA with factors of treatment and analysis center and baseline RV/TLC and emphysema heterogeneity as covariates.

14.5 Subgroup Analysis Results

14.5.1 US versus OUS

Table 30: 6MWT Change at 12 Months by Region for RENEW and Crossover Study

Region	Treatment Group (N)	Baseline Mean ± SE	Mean Change at 12Months from Baseline Mean ± SE	Adjusted Mean Change Mean ±SE[1]	Adjusted Mean Difference (Coil Treatment vs. Control) [95% CI][1]	Median (IQR) Change from Baseline	Median Difference (Coil Treatment vs. Control) [95% CI]
US	**Control (N=106)**	293.6 ± 7.45	-3.1 ± 5.68	-6.3 ± 7.10	2.0 [-15.4,19.4]	-0.7 (-39.0, 34.7)	5.9 [-10.8, 22.2]
	Coil Treatment (N=95)	292.9 ± 7.12	-2.3 ± 6.99	-4.3 ± 7.45		4.9 (-31.1, 39.3)	
	Crossover[4]	306.9 ± 9.65 (N=68)	-28.2 ± 10.9 (N=53)	N/A	N/A	-18.9	N/A
OUS	**Control (N=51)**	321.5 ±11.46	-19.9 ±10.53	-20.6 ±11.97	25.8 [-3.8, 55.4]	-22.0 (-52.0, 26.0)	31.7 [4.8, 57.4]
	Coil Treatment (N=63)	340.8± 10.89	5.3 ± 10.46	5.2 ± 11.14		13.0 (-37.0, 56.5)	
	Crossover[2]	327.1 ±14.79 (N=34)	-12.4 ±10.83 (N=27)	N/A	N/A	1.0	N/A

[1] Based on difference in least squares means from MCMC multiple imputation results of ANCOVA with factors of treatment, analysis center, baseline 6MWT, and emphysema heterogeneity as covariates.
[2] Crossover descriptive statistics are provided. 80 of 102 subjects completed 6MWT at 12 months.

Table 31: FEV1 Percent Change at 12 Months by Region for RENEW and Crossover Study

Region	Treatment Group (N)	Baseline Mean ± SE	Mean Percent Change from Baseline Mean ± SE	Adjusted Mean Percent Change from Baseline Mean ± SE[1]	Adjusted Mean Percent Difference (Coil Treatment vs. Control) [95% CI][1]	Median (IQR) Change from Baseline	Median Difference (Coil Treatment vs. Control) [95% CI]
US	**Control (N=106)**	0.7 ± 0.02	-0.8 ± 1.42	0.2 ± 1.96	6.9 [2.0, 11.8]	-1.2 (-7.9, 6.7)	4.8 [0.5, 9.3]
	Coil Treatment (N=95)	0.7 ± 0.02	5.6 ± 2.12	7.1 ± 2.09		3.5 (-7.4, 14.6)	
	Crossover[2]	0.7 ± 0.02 (N=68)	0.7 ± 2.78 (N=55)	N/A	N/A	-3.19	N/A
OUS	**Control (N=51)**	0.7 ± 0.03	-4.3 ± 1.94	-3.5 ± 3.17	12.5 [4.7, 20.3]	-5.0 (-13.3, 0.0)	10.7 [4.3, 17.2]
	Coil Treatment (N=63)	0.7 ± 0.03	8.9 ± 3.06	9.0 ± 2.92		6.7 (-5.3, 19.5)	
	Crossover[2]	0.7 ± 0.03 (N=34)	5.2 ± 4.17 (N=28)	N/A	N/A	1.7	N/A

[1] Based on difference in least squares means from MCMC multiple imputation results of ANCOVA with factors of treatment, analysis center, baseline FEV1, and emphysema heterogeneity as covariates.
[2] Crossover descriptive statistics are provided. 83 of 102 subjects completed FEV1 at 12 months.
.

Table 32: SGRQ Change at 12 Months by Region for RENEW and Crossover Study

Region	Treatment Group (N)	Baseline Mean ± SE (N)	Mean Change from Baseline Mean ± SE (N)	Adjusted Mean Change from Baseline Mean ± SE (N)[1]	Adjusted Mean Difference (Coil Treatment vs. Control) [95% CI][1]	Median (IQR) Change from Baseline	Median Difference (Coil Treatment vs. Control) [95% CI]
US	Control (N=106)	55.4 ± 1.46	-0.5 ± 1.06	-0.8 ± 1.34	-7.3 [-10.7, -3.9]	N/A	N/A
	Coil Treatment (N=95)	58.6 ± 1.30	-8.6 ± 1.37	-8.1 ± 1.44			
	Crossover[2]	54.8 ± 1.9 (N=68)	-3.6 ± 2.1 (N=55)	NA	N/A	-3.2	N/A
OUS	Control (N=51)	61.7 ± 1.86	4.1 ± 1.33	4.6 ± 1.69	-11.6 [-15.7, -7.5]	N/A	N/A
	Coil Treatment (N=63)	62.3 ± 1.59	-7.4 ± 1.55	-7.0 ± 1.54			
	Crossover[2]	64.2 ± 2.30 (N=34)	-7.2 ± 2.43 (N=28)	NA	N/A	-8.4	N/A

[1] Based on difference in least squares means from MCMC multiple imputation results of ANCOVA with factors of treatment, analysis center, baseline SGRQ, and emphysema heterogeneity as covariates.
[2] Crossover descriptive statistics are provided. 83 of 102 subjects completed SGRQ at 12 months.

Table 33: 6-Minute Walk Test (6MWT) Responder Rate by Region for the RENEW and Crossover Study

Region	Treatment Group (N)	Mean Responder Rate in 6MWT at 12 Months	Adjusted Mean Responder Rate in 6MWT at 12 Months[1]	Difference of Log Odds (Coil Treatment vs. Control) [95% CI][1]	Odds Ratio [95% CI][1]
US	Control (N=106)	25.7%	24.6%	0.50 [-0.18, 1.18]	1.65 [0.84, 3.27]
	Coil Treatment (N=95)	33.9%	35.0%		
	Crossover[2] (N=53)	24.5 % (13/53)	NA	NA	NA
OUS	Control (N=51)	27.1%	25.9%	0.83 [-0.06, 1.72]	2.29 [0.94, 5.56]
	Coil Treatment (N=63)	44.0%	44.5%		
	Crossover[2] (N=27)	29.6 % (8/27)	NA	NA	NA

[1]Based on MCMC multiple imputation results of logistic regression with factors of treatment, baseline 6MWT, and emphysema heterogeneity as covariates, with a random factor of analysis center.
[2] Crossover descriptive statistics are provided. 80 subjects completed 6MWT at 12 months.

14.5.2 Homogeneous vs. Heterogeneous

Table 34: 6MWT Change at 12 Months by Emphysema Status for RENEW and Crossover Study

Emphysema Status	Treatment Group (N)	Baseline Mean ± SE	Mean Change at 12 Months from Baseline Mean ± SE	Adjusted Mean Change at 12 Months from Baseline Mean ± SE[1]	Adjusted Mean Difference (Coil Treatment vs. Control) [95% CI][1]	Median (IQR) Change from Baseline	Median Difference (Coil Treatment vs. Control) [95% CI]
Homogeneous	Control (N=121)	302.7 ± 7.14	-7.1 ± 5.67	-4.2 ±6.28	5.6 [-11.4, 22.6]	-4.6 (-39.0, 27.0)	10.8 [-4.8, 26.2]
	Coil Treatment (N=122)	313.4 ±6.71	0.7 ± 6.31	1.5 ± 6.24		9.0 (-33.0, 39.3)	
	Crossover[2]	314.6 ± 8.97 (N=82)	-33.4 ± 8.87 (N=62)	N/A	N/A	-20.10	N/A
Heterogeneous	Control (N=36)	302.7 ± 13.79	-13.6 ± 12.37	-29.1 ± 12.93	18.6 [-17.1, 54.4]	-14.2 (-47.0, 25.2)	27.4 [-7.7, 59.7]
	Coil Treatment (N=36)	307.4±16.35	0.8 ± 14.58	-10.4 ± 13.00		21.0 (-27.0, 59.4)	
	Crossover[2]	309.6 ± 19.51 (N=20)	13.5 ± 16.98 (N=18)	N/A	N/A	25.0	N/A

[1] Based on difference in least squares means from MCMC multiple imputation results of ANCOVA with factors of treatment, analysis center, baseline 6MWT, and emphysema heterogeneity as covariates.
[2] Crossover descriptive statistics are provided. 80 of 102 subjects completed 6MWT at 12 months.

Table 35: FEV1 Percent Change at 12 Months by Emphysema Status for RENEW and Crossover Study

Emphysema Status	Treatment Group (N)	Baseline Mean ± SE	Mean Percent Change at 12 Months from Baseline Mean ± SE	Adjusted Mean Percent Change at 12 Months from Baseline Mean ± SE[1]	Adjusted Mean Percent Difference (Coil Treatment vs. Control) [95% CI][1]	Median (IQR) Change from Baseline	Median Difference (Coil Treatment vs. Control) [95% CI]
Homogeneous	Control (N=121)	0.7 ± 0.02	-2.6 ± 1.25	-2.1 ± 1.70	8.3 [3.7, 13.0]	-2.4 (-8.9, 3.6)	6.9 [2.9, 10.7]
	Coil Treatment (N=122)	0.7 ± 0.02	6.0 ± 1.90	6.2 ± 1.73		3.3 (-7.8, 15.6)	
	Crossover[2]	0.7 ± 0.02 (N=82)	-1.9 ± 1.96 (N=65)	N/A	N/A	-3.77	N/A
Heterogeneous	Control (N=36)	0.7 ± 0.03	0.2 ± 2.62	-0.2 ± 3.95	11.2 [0.3, 22.2]	-3.3 (-8.6, 7.3)	9.1 [0.3, 16.9]
	Coil Treatment (N=36)	0.7 ± 0.03	10.0 ± 4.30	11.1 ± 4.03		7.3 (-4.2, 17.1)	
	Crossover[2]	0.7 ± 0.04 (N=20)	17.1 ± 7.0 (N=18)	N/A	N/A	5.05	N/A

[1] Based on difference in least squares means from MCMC multiple imputation results of ANCOVA with factors of treatment, analysis center, baseline FEV1, and emphysema heterogeneity as covariates.
[2] Crossover descriptive statistics are provided. 83 of 102 subjects completed FEV1 at 12 months.

Table 36: SGRQ Change at 12 Months by Emphysema Status for RENEW and Crossover Study

Emphysema Status	Treatment Group (N)	Baseline Mean ± SE	Mean Change at 12 Months from Baseline Mean ± SE	Adjusted Mean Change at 12 Months from Baseline (meters) Mean ± SE[1]	Adjusted Mean Difference (Coil Treatment vs. Control) [95% CI][1]	Median (IQR) Change from Baseline	Median Difference (Coil Treatment vs. Control) [95% CI]
Homogeneous	Control (N=121)	56.4 ± 1.35	1.0 ± 0.96	0.5 ± 1.09	-8.4 [-11.4, -5.4]	N/A	N/A
	Coil Treatment (N=122)	59.3 ± 1.15	-7.9 ± 1.13	-7.9 ± 1.07		N/A	
	Crossover[2]	57.2 ± 1.69 (N=82)	-4.4 ± 1.92 (N=65)	N/A	N/A	-4.57	N/A
Heterogeneous	Control (N=36)	61.0 ± 2.36	1.1 ± 1.87	0.7 ± 2.21	-9.2 [-15.4, -3.0]	N/A	N/A
	Coil Treatment (N=36)	62.5 ± 2.13	-9.0 ± 2.35	-8.5 ± 2.27		N/A	
	Crossover[2]	60.9 ± 3.76 (N=20)	-6.2 ± 2.83 (N=18)	N/A	N/A	-7.06	N/A

[1] Based on difference in least squares means from MCMC multiple imputation results of ANCOVA with factors of treatment, analysis center, baseline SGRQ, and emphysema heterogeneity as covariates.
[2] Crossover descriptive statistics are provided. 83 of 102 subjects completed SGRQ at 12 months.

Table 37: 6-Minute Walk Test (6MWT) Responder Rate by Emphysema Status for RENEW and Crossover Study

Emphysema Status	Treatment Group (N)	Mean Responder Rate in 6MWT at 12 Months	Adjusted Mean Responder Rate in 6MWT at 12 Months	Difference in Log Odds (Coil Treatment vs. Control) [95%	Odds Ratio [95% CI][1]
Homogeneous	Control (N=121)	26.2%	25.0%	0.44 [-0.17, 1.05]	1.55 [0.85, 2.85]
	Coil Treatment (N=122)	34.8%	34.0%		
	Crossover[2] (N=62)	19.4% (12/62)	N/A	N/A	N/A
Heterogeneous	Control (N=36)	26.2%	21.0%	1.09 [-0.15, 2.32]	2.96 [0.86, 10.21]
	Coil Treatment (N=36)	48.5%	43.8%		
	Crossover[2] (N=18)	50.0% (9/18)	N/A	N/A	N/A

[1] Based on MCMC multiple imputation results of logistic regression with factors of treatment, baseline 6MWT, and emphysema heterogeneity as covariates, with a random factor of analysis center.
[2] Crossover descriptive statistics are provided. 80 of 102 subjects completed 6MWT test at 12 months.

14.5.3 Residual Volume (RV)

Table 38: 6MWT Change at 12 Months by Residual Volume for RENEW and Crossover Study

Residual Volume	Treatment Group (N)	Baseline Mean ± SE	Mean Change from Baseline Mean ± SE[1]	Adjusted Mean Change from Baseline Mean ± SE[1]	Adjusted Mean Difference (Coil Treatment vs. Control) [95% CI][1]	Median (IQR) Change from Baseline	Median Difference (Coil Treatment vs. Control) [95% CI]
RV >= 225%	Control (N=120)	308.0 ± 7.64	-13.1 ± 6.08	-14.7 ± 7.45	17.9 [-0.7, 36.4]	-8.6 (-43.3, 24.4)	23.8 [7.4, 39.6]
	Coil Treatment (N=115)	314.6 ± 7.65	5.6 ±7.06	3.1±7.98		15.0 (-31.1, 56.0)	
	Crossover[2]	324.3 ± 10.48 (N=62)	-32.1 ± 11.52 (N=47)	N/A	N/A	-18.29	N/A
RV < 225%	Control (N=37)	285.5 ± 10.02	6.1 ± 9.22	-1.9±14.00	-9.9 [-38.6, 18.7]	0.0 (-38.0, 50.3)	-12.9 [-42.1, 17.0]
	Coil Treatment (N=43)	305.2 ± 11.36	-12.1 ± 10.38	-11.8±12.15		-9.8 (-36.0, 25.6)	
	Crossover[2]	297.1 ± 12.57 (N=40)	-9.7 ± 10.63 (N=33)	N/A	N/A	-9.8	N/A

[1] Based on difference in least squares means from MCMC multiple imputation results of ANCOVA with factors of treatment, analysis center, baseline 6MWT, and emphysema heterogeneity as covariates.
[2] Crossover descriptive statistics are provided. 80 of 102 subjects completed 6MWT at 12 months.

Table 39: FEV1 Percent Change at 12 Months by Residual Volume for RENEW and Crossover Study

Residual Volume	Treatment Group (N)	Baseline Mean ± SE	Mean Percent Change from Baseline Mean ± SE	Adjusted Mean Percent Change from Baseline Mean ± SE [1]	Adjusted Mean Percent Difference (Coil Treatment vs. Control) [95% CI][1]	Median (IQR) Change from Baseline	Median Difference (Coil Treatment vs. Control) [95% CI]
RV >= 225%	Control (N=120)	0.7 ± 0.02	-1.8 ± 1.30	-0.3 ± 2.01	11.0 [6.0, 16.1]	-2.8 (-8.8, 4.2)	8.9 [4.6, 13.2]
	Coil Treatment (N=115)	0.7 ± 0.02	9.1 ± 2.14	10.7 ± 2.20		6.7 (-5.2, 19.3)	
	Crossover[2]	0.7 ± 0.02 (N=62)	3.0 ± 3.37 (N=48)	N/A	N/A	-1.94	N/A
RV < 225%	Control (N=37)	0.7 ± 0.04	-2.3 ± 2.34	-4.4 ± 3.60	4.4 [-3.2, 11.9]	-1.4 (-9.8, 4.8)	2.6 [-3.9, 9.0]
	Coil Treatment (N=43)	0.8 ± 0.03	1.1 ± 2.89	-0.0 ±3.15		-1.4 (-9.6, 8.0)	
	Crossover[2]	0.7 ± 0.03 (N=40)	1.1 ± 3.02 (N=35)	N/A	N/A	0.00	N/A

[1] Based on difference in least squares means from MCMC multiple imputation results of ANCOVA with factors of treatment, analysis center, baseline FEV1, and emphysema heterogeneity as covariates.
[2] Crossover descriptive statistics are provided. 83 of 102 subjects completed FEV1 at 12 months.

Table 40: SGRQ Change at 12 Months by Residual Volume for RENEW and Crossover Study

Residual Volume	Treatment Group (N)	Baseline Mean ± SE	Mean Change from Baseline Mean ± SE	Adjusted Mean Change from Baseline Mean ± SE[1]	Adjusted Mean Difference (Coil Treatment vs. Control) [95% CI][1]	Median (IQR) Change from Baseline	Median Difference (Coil Treatment vs. Control) [95% CI]
RV >= 225%	Control (N=120)	57.7 ± 1.35	2.0 ± 0.95	1.6 ± 1.20	-10.6 [-13.6, -7.6]	N/A	N/A
	Coil Treatment (N=115)	60.4 ± 1.21	-8.5 ± 1.18	-9.0 ± 1.30			
	Crossover[2]	58.3 ± 2.07 (N=62)	-6.3 ± 1.97 (N=48)	NA	N/A	-7.34	N/A
RV < 225%	Control (N=37)	56.6 ± 2.44	-2.3 ± 1.80	0.4 ± 2.67	-4.7 [-10.3, 0.8]	N/A	N/A
	Coil Treatment (N=43)	59.2 ± 1.87	-7.2 ± 2.12	-4.3 ± 2.36			
	Crossover[2]	57.3 ± 2.31 (N=40)	-2.7 ± 2.72 (N=35)	N/A	N/A	-3.15	N/A

[1] Based on difference in least squares means from MCMC multiple imputation results of ANCOVA with factors of treatment, analysis center, baseline SGRQ, and emphysema heterogeneity as covariates.
[2] Crossover descriptive statistics are provided. 83 of 102 subjects completed SGRQ at 12 months.

Table 41: 6-Minute Walk Test (6MWT) Responder Rate by Residual Volume for RENEW and Crossover Study.

Residual Volume	Treatment Group (N)	Mean Responder Rate in 6MWT at 12 Months	Adjusted Mean Responder Rate in 6MWT at 12 Months	Difference of Log Odds (Coil Treatment vs. Control) [95% CI][1]	Odds Ratio [95% CI][1]
RV >= 225%	**Control (N=120)**	23.9%	22.9%	0.93 [0.30, 1.56]	2.53 [1.35, 4.74]
	Coil Treatment (N=115)	42.3%	42.9%		
	Crossover[2] (N=47)	25.5 % (12/47)	N/A	N/A	N/A
RV < 225%	**Control (N=37)**	33.6%	28.5%	-0.20 [-1.23, 0.83]	0.82 [0.29, 2.30]
	Coil Treatment (N=43)	26.4%	24.7%		
	Crossover[2] (N=33)	27.3 %	N/A	N/A	N/A

[1] Based on MCMC multiple imputation results of logistic regression with factors of treatment, baseline 6MWT, and emphysema heterogeneity as covariates, with a random factor of analysis center.
[2] Crossover descriptive statistics are provided. 80 subjects completed 6MWT test at 12 months.

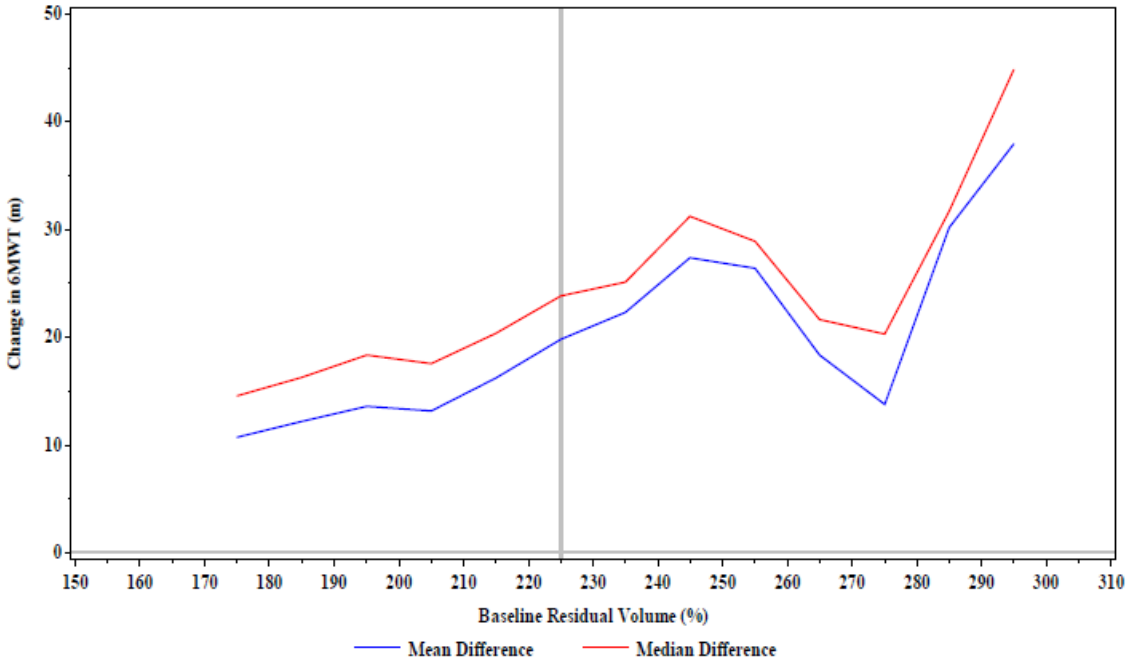


Figure 13: Cumulative Between-Group Difference (treatment-control) of change in 6MWT at 12 months versus Baseline RV Percent Predicated for Pivotal Study

Plotted lines represent y = between-group difference (Treatment – Control) for subjects with baseline RV percent predicted ≥ x.

Mean difference based on least squares means from MCMC multiple imputation results of ANCOVA with factors of treatment and baseline 6MWT and emphysema heterogeneityas covariates.

Median difference based on MCMC multiple imputation results using Hodges Lehmann estimator, adjusted for baseline.

14.6 Statistical Analysis Plan

14.6.1 Analysis Population

The Intent-to-Treat (ITT) population was defined as all subjects randomized to Treatment or the Control group, regardless of whether or not the treatment procedure was attempted. The primary effectiveness analysis was based on the ITT population.

The Per-Protocol (PP) population included subjects who completed the study without noteworthy study protocol deviations (PD) (i.e. any subject or Investigator activity that could have possibly interfered with the therapeutic administration of the treatment or the precise evaluation of treatment effectiveness).

The Safety population was comprised of all ITT subjects who were randomized (for the Control group) or who entered the procedure room (for the Coil Treatment group), regardless of whether or not device deployment was attempted. This population was used in all safety summaries and analyses.

14.6.2 Effectiveness Endpoint Analyses

The primary statistical hypotheses notation follows. Let μ_T and μ_C equal the expected 12 month difference in 6MWT values from baseline for Coil Treatment and Control, respectively. The null and alternative one-sided hypotheses are:

$$H_0: \mu_T - \mu_C \leq 0$$
$$H_1: \mu_T - \mu_C > 0$$

The hypothesis testing for primary effectiveness endpoint was one-sided at alpha = 0.025 significance level. The hypothesis testing for the secondary endpoints was one-sided with adjustments on family wise type I error at alpha = 0.025, using the Hochberg step-up procedure. Efficacy analyses were performed for both the ITT and PP populations, with the primary analysis based on the ITT population.

The primary effectiveness analysis compared change from baseline to 12 months in 6MWT between Elevair Coil Treatment and Control groups using analysis of covariance with factors of treatment and analysis center and covariates of baseline 6MWT and emphysema heterogeneity.

Comparisons between Coil Treatment and Control groups for secondary endpoints and other effectiveness endpoints were conducted using the same methods as for the primary effectiveness endpoint, with ANCOVA for continuous endpoints and logistic regression for responder endpoints. Where distributions were markedly skewed, a non-parametric analysis was conducted using ANCOVA of rank transformed endpoints as the primary analysis, although parametric non-rank transformed results were also presented.

14.6.3 Safety Endpoint Analyses

The proportion of subjects experiencing major complications and treatment emergent AEs/SAEs through the 12-month visit were summarized and compared between treatment groups using Fisher's exact test. Additionally, major complication, AE, and SAE event rates were calculated using Poisson regression. AEs and SAEs were also analyzed by time period post Visit 2 and separately for relationship to device or procedure.

14.6.4 Missing Data Handling

All missing 12 month values for primary and secondary efficacy endpoints were estimated by MCMC multiple imputations for continuous variables assuming data were missing at random.

14.6.5 Subgroup Analyses

The following subgroup analyses for the primary and secondary endpoints were conducted in a similar manner as the corresponding primary and secondary analyses for the ITT population:
• US vs. OUS (outside of the US)
• Heterogeneity of emphysema
• Severity of air trapping (RV ≥225% vs. RV < 225%)
• Gender

14.6.6 Site Poolablity Analyses

This clinical study was conducted under a common protocol at each investigational site, with the intention of pooling the data for analysis. In the event there were too few subjects (i.e. less than 5) in a study group at an investigational site, the site's data was combined with other sites to achieve the desired minimum sample size for each study group. These combined groups were referred to as "analysis centers" in the statistical analyses.

To account for variability across sites, analysis center was included as a class variable in the ANCOVA and logistic regression models for the primary and secondary analysis of effectiveness endpoints. Additionally, the statistical significance of the treatment by analysis center interaction was evaluated to assess the appropriateness of pooling the data across centers for the primary and secondary effectiveness endpoints, change in 6MWT, percent change in FEV1, and change in SGRQ.

14.6.7 Sensitivity Analyses:

The following sensitivity analyses were conducted to explore the impact of missing observation estimation on effectiveness assessment using 6MWT:

- Multiple imputation under the assumption of multivariate normality and a monotone missing data pattern.
- Generalized Estimating Equations (GEE) model using a first-order auto-regressive correlation structure.
- "Complete case" analysis.
- Worst case analysis classifying all missing 12-month 6MWT data as a Failure" (using baseline 6MWT or their last observation of 6MWT, whichever is worse, for the 12-month 6MWT).

14.6.8 Sample Size

The power estimates and sample size calculations for RENEW study were based on data from feasibility studies conducted in Europe. An estimated difference between Elevair Coil Treatment and Control groups of 59 meters and an estimate of 80 meters for the standard

deviation showed that a sample size of 100 subjects per treatment arm had power greater than 95% to detect a between-group difference of 59m in the 6MWT.

An additional power calculation was conducted for the FEV1 secondary effectiveness variable using the feasibility study data. The estimates of change from baseline at the endpoint visit were 0.06L and 0.01L for the VENT and control groups, respectively. A standard deviation of 0.10L showed that a sample size of 151 subjects per treatment arm had a 95% power to detect a between group difference of 0.05L.

For AE rates less than 20%, 151 subjects per treatment group provided approximately 80% power to detect a 12% difference in AE rates between treatment groups. Considerations of power for the primary, secondary, and safety variables suggests that approximately 151 subjects per treatment arm be enrolled in the study. With additional considerations of power needed for per protocol (PP) analyses, approximately 158 subjects per treatment arm (315 subjects total) were planned for enrollment.

14.6.9 Randomization and Blinding

Subjects were block randomized in a 1:1 ratio to Coil Treatment or Control group. The randomization was stratified by homogeneous versus heterogeneous emphysema, to support a balance of patients with differing heterogeneity in both the Coil and Control Groups per FDA's request.

The subject as well as the investigator performing the procedure were not blinded to the study treatment. The investigator would however not assess the subjects for the effectiveness endpoints (pulmonary function tests (PFT) and 6MWT). The PFT and 6MWT assessor (i.e. those working with the subject to collect data on the 6MWT, SGRQ, plethysmography measures, and spirometry measures) were blinded to the treatment received by the subject and the subjects were instructed not to share any information that may identify the treatment received with the assessors.

14.7 Protocol deviation

Major protocol deviations, defined as any deviation from the protocol or other study specific procedures which could impact the scientific soundness of the research plan or the rights, safety, or welfare of human subjects, are summarized in Table 42.A total of 107 major protocol deviations occurred in 83 subjects (54 Coil Treatment and 29 Control).

Table 42: RENEW Major Protocol Deviations (PD) through 12 months

Protocol Deviations	Coil Treatment (N = 158)		Control (N = 157)		Total (N = 315)	
	Subjects[1]	PD Events	Subjects[1]	PD Events	Subjects[1]	PD Events
Major Protocol Deviations	34.2% (54/158)	71	18.5% (29/157)	36	26.3% (83/315)	107
Blinded Assessor	3.8% (6/158)	7	5.7% (9/157)	9	4.8% (15/315)	16
6MWT Blinded Assessor Unblinded	1.3% (2/158)	2	0.6% (1/157)	1	1.0% (3/315)	3
PFT Blinded Assessor Unblinded	3.2% (5/158)	5	5.1% (8/157)	8	4.1% (13/315)	13
Commercial Product Used	0.6% (1/158)	1	0.0% (0/157)	0	0.3% (1/315)	1
Commercial Product Used	0.6% (1/158)	1	0.0% (0/157)	0	0.3% (1/315)	1
Inclusion/Exclusion Criteria Not Met	3.8% (6/158)	6	0.6% (1/157)	1	2.2% (7/315)	7
Exclusion	3.2% (5/158)	5	0.0% (0/157)	0	1.6% (5/315)	5
Inclusion	0.6% (1/158)	1	0.6% (1/157)	1	0.6% (2/315)	2
Informed Consent	7.6% (12/158)	12	2.5% (4/157)	4	5.1% (16/315)	16
Subject Not Re-Consented On Time	1.9% (3/158)	3	1.3% (2/157)	2	1.6% (5/315)	5
Wrong ICF Version Signed	5.7% (9/158)	9	1.3% (2/157)	2	3.5% (11/315)	11
Test Not Done	1.3% (2/158)	2	0.6% (1/157)	3	1.0% (3/315)	5
6-Minute Walk Test (6MWT)	0.6% (1/158)	1	0.6% (1/157)	1	0.6% (2/315)	2
Post-Bronchodilator Spirometry	0.6% (1/158)	1	0.6% (1/157)	1	0.6% (2/315)	2
SGRQ	0.0% (0/158)	0	0.6% (1/157)	1	0.3% (1/315)	1
Test Value Not Done	1.3% (2/158)	2	0.6% (1/157)	1	1.0% (3/315)	3
Post-bronchodilator Lung Volumes- residual Volume/Total Lung Capacity Measured	1.3% (2/158)	2	0.6% (1/157)	1	1.0% (3/315)	3
Not Done to Protocol Test	0.6% (1/158)	1	0.0% (0/157)	0	0.3% (1/315)	1
CT Scan	0.6% (1/158)	1	0.0% (0/157)	0	0.3% (1/315)	1
Visit Not Done	6.3% (10/158)	11	5.7% (9/157)	10	6.0% (19/315)	21
Visit Not Done	6.3% (10/158)	11	5.7% (9/157)	10	6.0% (19/315)	21
Out of Window Visit	12.7% (20/158)	21	4.5% (7/157)	7	8.6% (27/315)	28
Late	12.7% (20/158)	21	4.5% (7/157)	7	8.6% (27/315)	28
Post-Procedure Prophylactic Treatment Not Given	0.6% (1/158)	1	0.0% (0/157)	0	0.3% (1/315)	1
Post-Procedure Prophylactic Treatment Not Given	0.6% (1/158)	1	0.0% (0/157)	0	0.3% (1/315)	1
Procedure Related	2.5% (4/158)	4	0.0% (0/157)	0	1.3% (4/315)	4
Core Lab Suggested Lobes Not Treated	2.5% (4/158)	4	0.0% (0/157)	0	1.3% (4/315)	4
Randomization	1.3% (2/158)	2	0.6% (1/157)	1	1.0% (3/315)	3

Protocol Deviations	Coil Treatment (N = 158)		Control (N = 157)		Total (N = 315)	
	Subjects[1]	PD Events	Subjects[1]	PD Events	Subjects[1]	PD Events
All Criteria Not Confirmed At Randomization	1.3% (2/158)	2	0.6% (1/157)	1	1.0% (3/315)	3
SAE Reporting	0.6% (1/158)	1	0.0% (0/157)	0	0.3% (1/315)	1
Late	0.6% (1/158)	1	0.0% (0/157)	0	0.3% (1/315)	1

[1] A subject is only counted once for each protocol deviation category.
Note: Only Protocol deviations that occurred through 12 months are shown

14.8 Non-Clinical Studies

14.8.1 Bench performance Testing

Table below presents bench testing conducted on the coil, with acceptance criteria and results for each test.

Test	Acceptance Criteria	Results
Dimensional Verification	Coil Overall Length, Proximal Leg Length, Ball Diameter and Coil Wire Diameter must meet established specifications for 100mm, 125mm and 150mm Coils	Ongoing Inspection
Coil Functional Verification	Coil Af Temperature, shape recovery, and functional strength must meet established specifications	Ongoing Inspection
Corrosion Resistance and Nickel Ion Leaching	Cyclic Potentiodynamic Polarization testing followed by Nickel Ion Leaching (60-day duration) must meet established specifications	PASS
MRI Compatibility	Coil to be at least MRI conditional to 1.5-Tesla and 3-Tesla	PASS
Fatigue Resistance and Finite Element Analysis (FEA) Modeling	• Fatigue resistance testing must meet specifications • Fatigue safety factor from Finite Element Analysis must be ≥ 1.0	PASS

Table below presents bench testing conducted on the ELEVAIR delivery system, with acceptance criteria and results for each test.

Test	Acceptance Criteria	Results
Catheter		
Dimensional Verification	Inner Diameter, Outer Diameter, Working Length and Overall Length must meet established specifications	PASS
Overall Tensile Strength	Tensile Strength at the Distal Tip and Proximal End must meet established minimum specifications	PASS
Bending Stiffness	• Must be able to pass through 2.8mm scope in a tortuous path; • Must be able to recover Coil	PASS
Column Strength	• Must be able to pass through 2.8mm scope in a tortuous path; • Must be able to recover Coil	PASS
Marker radio-opacity	Markers must be visible under fluoroscopy	PASS

Friction / Passability	Must be able to pass through 2.8mm scope in a tortuous path	PASS
Cartridge Interface	Must interface with Cartridge	PASS
Cartridge		
Test	**Acceptance Criteria**	**Results**
Dimensional Verification	Inner Diameter and Length must meet established specifications	PASS
Torque Strength	Torque Strength must meet established minimum specification	PASS
Catheter Interface	Must interface with Catheter	PASS
Forceps		
Dimensional Verification	Outer Diameter, Working Length, and Marker Band Location must meet established specifications	PASS
Torque Transmission	Jaws must be able to rotate in accordance with specifications	PASS
Bending Stiffness	Must be able to pass through Catheter in a tortuous path	PASS
Column Strength	Must be able to pass through Catheter with Coil in a tortuous path	PASS
Forceps Functional Verification	Jaw Actuation, Locked Jaw Strength, Manual Actuation Grip Strength must meet established specifications	PASS
Kink Resistance	Must be able to pass through Catheter in a tortuous path with a Coil. If kinking occurs, then must remain functional	PASS
Friction / Passability	Must be able to pass through Catheter in a tortuous path with a Coil and retract Coil into Catheter	PASS
Spool – Pull Wire Joint Strength	Spool – Pull Wire Joint Strength must meet established minimum specification	PASS
Guidewire		
Dimensional Verification	Outer Diameter, Working Length, Radio-opaque Marker Location and PTFE Location must meet established specifications	PASS
Marker Radio-opacity	Must be radio-opaque	PASS
Bending Stiffness	Must be able to pass through Catheter in a tortuous path	PASS
Column Strength	Must be able to pass through Catheter in a tortuous path	PASS
Tensile Strength	Tensile Strength must meet established minimum specifications	PASS
Friction /Passability	Must be able to pass through Catheter in a tortuous path	PASS

14.8.2 Sterility/Shelf Life

The coil is sterilized using electron beam irradiation. The ELEVAIR Delivery System is sterilized using ethylene oxide (EtO). Sterilization validation testing for the coil was performed in accordance with ISO 11137-1:2006 Sterilization of health care products – Radiation – Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices. Results from the sterilization validation demonstrated that an electron beam dose of 25-57 kGy (VDmax 25) provides a sterility assurance level (SAL) of 10-6.

Sterilization validation testing for the ELEVAIR Delivery System was performed in accordance with ISO 11135:2014 Sterilization of health-care products – Ethylene oxide – Requirements for the development, validation and routine control of a sterilization process for medical devices. Results from the sterilization validation demonstrated an SAL of 10-6,

and residuals were within acceptable ranges in accordance with ISO 10993- 7:2008 Biological evaluation of medical devices – Part 7: Ethylene oxide sterilization residuals. Packaging and shelf life validations were performed on the coil and the ELEVAIR Delivery System following 37 months accelerated and real time aging to support a 3-year shelf life of the device. Devices and device packaging were subjected to accelerated aging (per ASTM F 1980-07) and simulated transit testing (per ASTM D 4169-08). Pouch integrity testing was performed (per ASTM F 2096-04) for bubble leaks to ensure maintenance of sterile barrier properties and thus sterility of the devices. The device packaging was determined to be free of gross physical damage, and devices were subjected to functional testing to ensure they meet applicable performance attributes following aging. Results of testing confirm that the coil and the ELEVAIR Delivery System meet specifications throughout the stated shelf life (3 years).

14.8.3 Biocompatibility

Biocompatibility testing was performed on the ELEVAIR System (coil and ELEVAIR Delivery System) in accordance with the requirements of ISO 10993-1. The coil was evaluated as an implant device in permanent (>30 days) contact with tissue/bone. Based on this classification, the following tests were conducted: cytotoxicity, sensitization, irritation/intracutaneous reactivity, systemic toxicity, subchronic toxicity, genotoxicity, and implantation. The coil was also subjected to simulated use, and then cyclic potentiodynamic polarization testing to assess for corrosion resistance in accordance with applicable ASTM standards and nickel ion release testing (60 days duration), per ISO 10993-15, to assess biocompatibility with respect to metal degradation. In addition to these biocompatibility tests, the coil was also subjected to Auger electron spectroscopy, per ISO 10993-19, to assess the surface composition as an indicator of corrosion resistance and biocompatibility.

The ELEVAIR Delivery System was evaluated as an external communicating device in limited contact (<24h) with tissue/bone/dentin. Based on this classification, the following tests were conducted: cytotoxicity, sensitization, irritation/intracutaneous reactivity, and systemic toxicity. Hemocompatibility testing was also conducted to evaluate any adverse effects of blood contacting materials on hemolysis, thrombosis, coagulation, platelets, and complement activation

A summary of the biocompatibility testing conducted is presented in the table below:

Test Performed	Test Description	Coil	Delivery System	Results
Cytotoxicity	ISO MEM Elution Assay with L-929 Mouse Fibroblast Cells	X	X	Non-toxic
Sensitization	ISO Guinea Pig Maximization Sensitization Test	X	X	No evidence of sensitization
Irritation / Intra-cutaneous Reactivity	ISO Intra-cutaneous Reactivity Test	X	X	Non-irritant
Systemic Toxicity (acute)	ISO Acute Systemic Injection Test	X	X	Non-toxic
Hemo-compatibility	Hemolysis – Rabbit Blood – ASTM Indirect Contact		X	Non-hemolytic

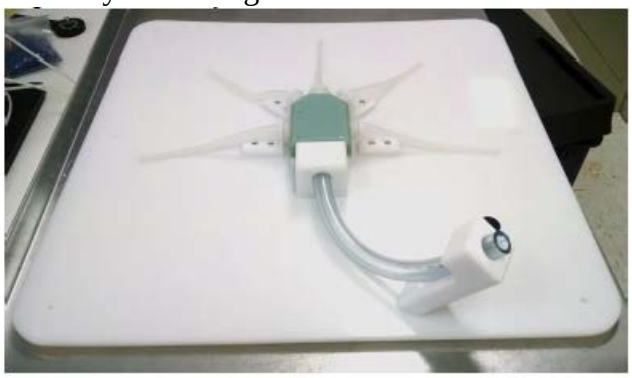
Genotoxicity	Salmonella Typhimurium Reverse Mutation Assay (Ames Test)	X		Non-mutagenic
	Chromosome Aberration Assay for a Medical Device	X		Non-genotoxic
	In vitro Mouse Lymphoma Assay	X		Non-mutagenic
Implantation	A 3 Month, 6 Month, and 12 Month In-Vivo Subchronic and Chronic Evaluation Following Implantation of the PneumRx Lung Volume Reduction Device in the Porcine Lung	X		No evidence of systemic tissue reaction
Subchronic / Chronic Toxicity	A 3 Month, 6 Month, and 12 Month In-Vivo Subchronic and Chronic Evaluation Following Implantation of the PneumRx Lung Volume Reduction Device in the Porcine Lung	X		Non-toxic
Pyrogen	Materials Medicated Rabbit Pyrogen Test	X		Non-pyrogenic
Auger Electron Spectroscopy	Spectroscopic scan of Coil surface layer	X		Non-toxic
Metal Degradation	Corrosion Resistance Cyclic Potentiodynamic Polarization and Nickel Ion Release	X		Non-toxic

14.8.4 Human Factors/Usability

Human factors / usability validation testing was conducted. The simulated-use study environment included:

- Bronchoscope monitor and "fluoroscopy" monitor placed at eye level between1.5-6 feet from the physician,
- Assistant back table with supplies for the study,
- IFU and IFU Reference Card placed near the ELEVAIR System,
- Dimmable lights to allow for variable lighting conditions, and
- Low level distractions.

The study model is given below:



Eighteen (18) representative teams (18 physicians and 18 assistants) participated in the Usability Validation Study. Participants received representative formal training on the ELEVAIR System followed by a minimum one (1) hour training decay period. The formal team training lasted approximately two hours and included a combination of didactics using a standardized slide set and hands on use of the system via a training kit. The standardized kit included a mock bronchoscope, delivery system, coils within their shells, forceps, a rigid,

plastic tube for practicing the deployment of coils at a specific target, and a flexible silicone tube that permits the coil to deploy into its pre-formed shape.

14.8.5 Animal Studies

Four in vivo animal studies (PRE0015, PRE0020, PRE0022, and PRE0023) were completed using a porcine model. Table below is the summary of animal testing:

Study Objectives	Number of Animals	Duration	Results
PRE0015			
Evaluation of in vivo safety of Coil in a porcine model	10 Yucatan Mini Swine (8 test / 2 control)	18 months	Safety to 18 months confirmed by absence of post-operative adverse events, lack of systemic tissue response and minimal to mild localized reaction, with no device migration or clinically significant movement.
PRE0020			
Evaluation of moderate term safety and retrievability of Coil after 2 months in vivo	2 Yucatan Mini Swine	2 months	100% success rate in Coil retrieval at 2 months when proximal balls were bronchoscopically accessible.
PRE0022			
Evaluation of safety and retrievability of Coil after 2 and 4 months in vivo	4 Yucatan Mini Swine	4 months	100% success rate in Coil retrieval at 2 months when proximal balls were bronchoscopically accessible; site of removal at 2 months had healed completely by 4 months.
PRE0023			
Histological evaluation of Coil after chronic implantation for 60 and 90-120 days	3 Yucatan Mini Swine	4 months	Coil showed minimal histopathological tissue reaction and no significant difference between Coil designs evaluated.