P170004
Elevair™ Endobronchial Coil System

PANEL PACK
SPONSOR EXECUTIVE SUMMARY

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1. SYNOPSIS

1.1. Introduction and Disease Background

Emphysema, a subtype of chronic obstructive pulmonary disease (COPD), is a chronic, progressive, incurable disease that affects an estimated 3.5 million adults in the US and is a leading cause of morbidity and mortality worldwide. Symptoms of emphysema include shortness of breath, cough, and diminished exercise capacity. Pathologically, emphysema is characterized by the gradual destruction and disappearance of alveolar walls which results in reduced lung elasticity and recoil pressure, causing smaller airways to collapse prematurely during exhalation. These effects lead to persistent airway obstruction, air trapping, and hyperinflation. Moreover, hyperinflation flattens the diaphragm, the major muscle of breathing, which greatly impedes its effective function. Breathlessness and dyspnea caused by air trapping and subsequent hyperinflation lead to significant morbidity and poor quality of life. This shortness of breath results in sustained physical inactivity, which further impairs respiratory function, leading to more breathlessness. In the severe emphysema patient, this downward spiral may eventually lead to respiratory failure requiring ventilator support and mortality.

Global standard of care guidelines for the treatment of emphysema include smoking cessation, pharmacotherapies, pulmonary rehabilitation, vaccinations, and oxygen therapy in some patients. In cases of severe emphysema that cannot be managed adequately by these treatments, current options are limited to lung volume reduction surgery and lung transplantation. These are major surgical procedures with restrictive eligibility criteria, scarce availability, and significant morbidity and mortality risks.

The ELEVAIR Endobronchial Coil System (ELEVAIR System) was developed to provide a minimally invasive approach to lung volume reduction using novel technology, thereby providing a treatment option that is more accessible to severe emphysema patients. This executive summary presents the results of the pivotal clinical trial (RENEW) and supporting trials which together demonstrate the safety and effectiveness of the ELEVAIR System in patients with severe emphysema and severe hyperinflation, a patient population that has exhausted current realistically available therapies.

1.2. ELEVAIR Endobronchial Coil System (ELEVAIR System)

The ELEVAIR System uses a minimally invasive, bronchoscopic technique to place nitinol shape-memory Coils into the lungs as a treatment for severe emphysema. The ELEVAIR System procedure is a bilateral treatment, targeting the most damaged lobe in each lung, and is performed in two separate sessions, approximately 1 to 3 months apart. ELEVAIR Coils decrease hyperinflation and lung volume by compressing the most damaged tissue and restoring lung elastic recoil. Reduction in hyperinflation improves lung function, which leads to improvements in quality of life and exercise capacity in patients with severe emphysema.

The ELEVAIR System consists of two main components, the Coil and the Delivery System. All components are biocompatible and provided sterile. The Delivery System, designed to work

through a standard bronchoscope with a 2.8mm diameter working channel, is disposable. The nitinol Coils are intended as permanent implants.

The ELEVAIR System (branded outside the United States as the RePneu Coil System) was CE mark certified on October 8, 2010 and has been commercially available in select countries inside and outside of Europe since that time.

1.3. Pre-clinical Testing

The ELEVAIR Coil and the ELEVAIR Delivery System successfully completed a full battery of pre-clinical testing that included biocompatibility testing, in vitro bench testing, pre-clinical animal testing, human factors/usability testing, sterilization testing, and packaging and shelf life studies.

1.4. IDE Clinical Program

Overview

The design of the RENEW Pivotal Trial (IDE G110066) was developed considering input received from FDA during IDE review. The final version of the RENEW protocol and the RENEW statistical analysis plan (SAP) are included as Attachments 5 and 6.

The PneumRx IDE Clinical Program includes four key phases:

- a non-randomized "Roll-In" phase used to train newly enrolling study sites,
- a randomized Pivotal Trial phase ("RENEW"),
- a non-randomized Crossover phase, and
- a long-term follow-up phase for up to 5 years post procedure for treated subjects in all earlier phases.

The Crossover study was intended to allow Control subjects from RENEW who completed the 12-month randomized phase and who met Crossover study eligibility criteria to receive treatment with the ELEVAIR System, if they desired. The Crossover design was also intended to encourage continued study participation in the RENEW Control arm.

RENEW Pivotal Trial

The primary evaluations of safety and effectiveness supporting this Premarket Approval Application (PMA) are based on the prospective, multi-center, randomized, assessor-blinded RENEW Pivotal Trial. The RENEW Trial compared outcomes in subjects treated with the ELEVAIR System in combination with optimal medical therapy to outcomes in a control group receiving optimal medical therapy alone. The RENEW Trial evaluated effectiveness of ELEVAIR System treatment through changes in exercise capacity (measured using the six-minute walk test, 6MWT), quality of life (measured using the St. George's Respiratory Questionnaire, SGRQ), and lung function (measured using forced expiratory volume in 1 second, FEV_1, and residual volume, RV). Residual volume measures the volume of air that remains in the lungs after full expiration, and is an assessment of hyperinflation.

315 subjects with severe homogeneous or heterogeneous emphysema were enrolled at 26 clinical sites in the US, Canada, and EU, and were randomized to optimal medical care (N=157) or to optimal medical care plus bilateral treatment with the ELEVAIR System (N=158). An additional 46 subjects were treated with the ELEVAIR System in the Roll-In phase, and 101 subjects were treated with the ELEVAIR System in the Crossover phase. Subjects randomized in the RENEW Trial represented a group of patients with severe (GOLD 3, 26% of subjects) and very severe (GOLD 4, 74% of subjects) emphysema, with both homogeneous (77% of subjects) and heterogeneous (23% of subjects) emphysema distribution. The RENEW population had substantial airflow restriction (FEV_1 approximately 26% of predicted value) and hyperinflation (RV approximately 245% of predicted value), and most subjects had multiple chronic comorbid conditions.

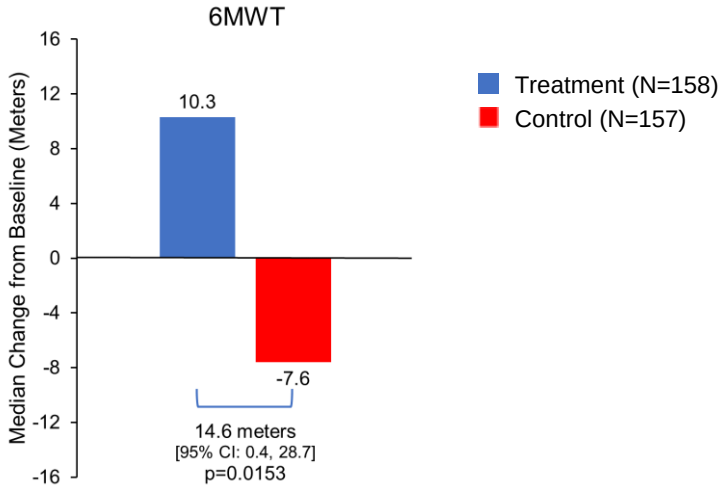
Protocol Amendment

Because the ELEVAIR Coils were designed to treat hyperinflation, the RENEW Trial enrolled patients with severe hyperinflation, initially defined as RV ≥225% predicted. After reaching approximately 53.7 % of its target enrollment, the RENEW protocol was amended to change the residual volume (RV) threshold for inclusion from 225% to 175% predicted. This change was made based on data from several small, ongoing clinical studies and initial post-market data from a European registry that suggested patients with RV values between 175% and 225% predicted could benefit from the procedure. When the protocol was amended, 84% of the final population enrolled outside the US (OUS) and 44% of the US population had been recruited. This temporal difference in enrollment status between the US and OUS sites resulted in the US population containing a higher proportion of RV <225% subjects (36%) compared to the OUS population (6%). Overall, 75% of RENEW subjects had baseline RV ≥225% predicted.

Effectiveness

The primary effectiveness endpoint was absolute change in 6MWT, comparing treatment to control at 12 months, in the intention-to-treat (ITT) population. The primary endpoint analysis was met (Figure 1), with a median 14.6 meter improvement in the Treatment group compared to the Control group (p=0.0153). (Median values are reported for primary and secondary endpoints for which the data are significantly skewed. See Section 6.1.4.1 and the SAP, Attachment 6, for further details.)

Figure 1. Primary Effectiveness Outcome, ITT Population [RENEW][a]

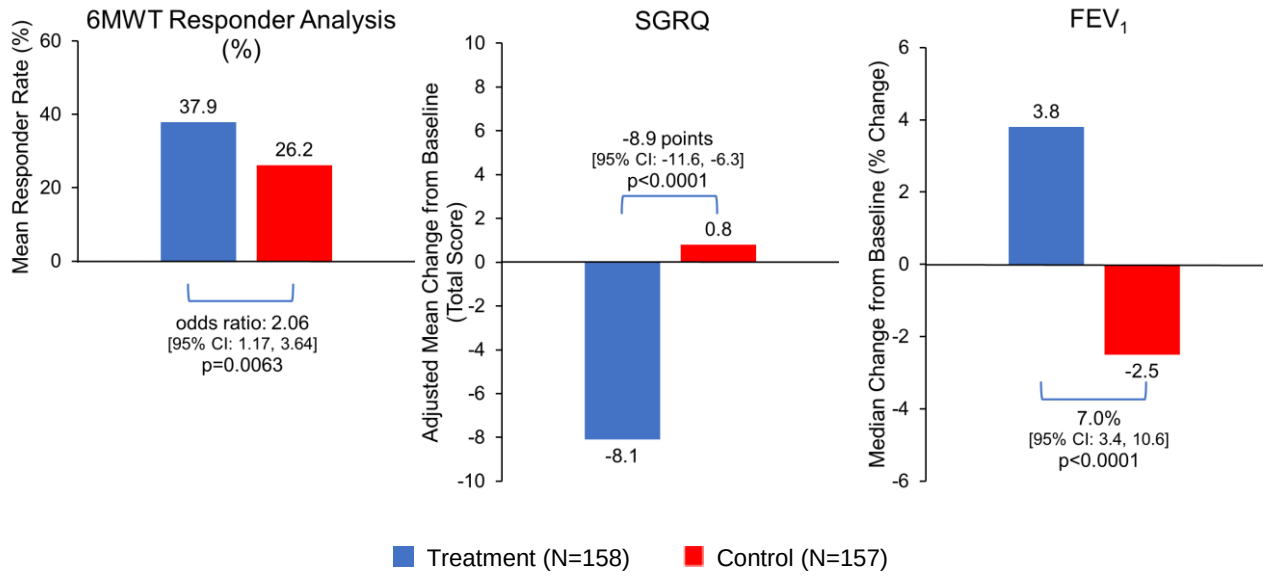


[a]Absolute change from baseline to 12 months in 6MWT after multiple imputation. Note that the nonparametric median between-group difference is not the simple between-group difference in medians.
Note: This plot was not provided within the PMA; however, the underlying information / analysis was provided in the PMA application to FDA.

All secondary effectiveness endpoint analyses in RENEW were also met at 12 months (Figure 2). The secondary effectiveness endpoints and analysis results were:

- 6MWT responder analysis (responder defined as an increase from baseline of at least 25 meters) – Treatment: 37.9%, Control: 26.2%; p=0.0063
- Absolute change in SGRQ total score – adjusted mean between-group improvement of −8.9 points; p<0.0001 (note that a decrease in SGRQ score represents an improvement in quality of life)
- Percent change in FEV_1 – median between-group improvement of 7.0%; p<0.0001

Figure 2. Secondary Effectiveness Outcomes, ITT Population [RENEW][a]



[a]6MWT responder analysis, SGRQ absolute change from baseline, and FEV_1 percent change from baseline at 12 months after multiple imputation. Note that the nonparametric median between-group difference is not the simple between-group difference in medians.
Note: This plot was not provided within the PMA; however, the underlying information / analysis was provided in the PMA application to FDA.

Finally, all other prospectively defined effectiveness endpoint analyses were in favor of Treatment, showing substantially better outcomes in the RENEW Treatment group compared to the Control group. These endpoints and analysis results were:

- SGRQ responder analysis (responder defined as a decrease from baseline of at least 4 points) – Treatment: 61.2%, Control: 27.7%; nominal p<0.0001
- Absolute change in RV – adjusted mean between-group improvement of −0.31 liters; nominal p=0.0010
- Absolute change in RV/TLC (residual volume/total lung capacity) – adjusted mean between-group improvement of −3.50%; nominal p<0.0001

<u>Additional Effectiveness Analyses in RV ≥225% Subpopulation</u>

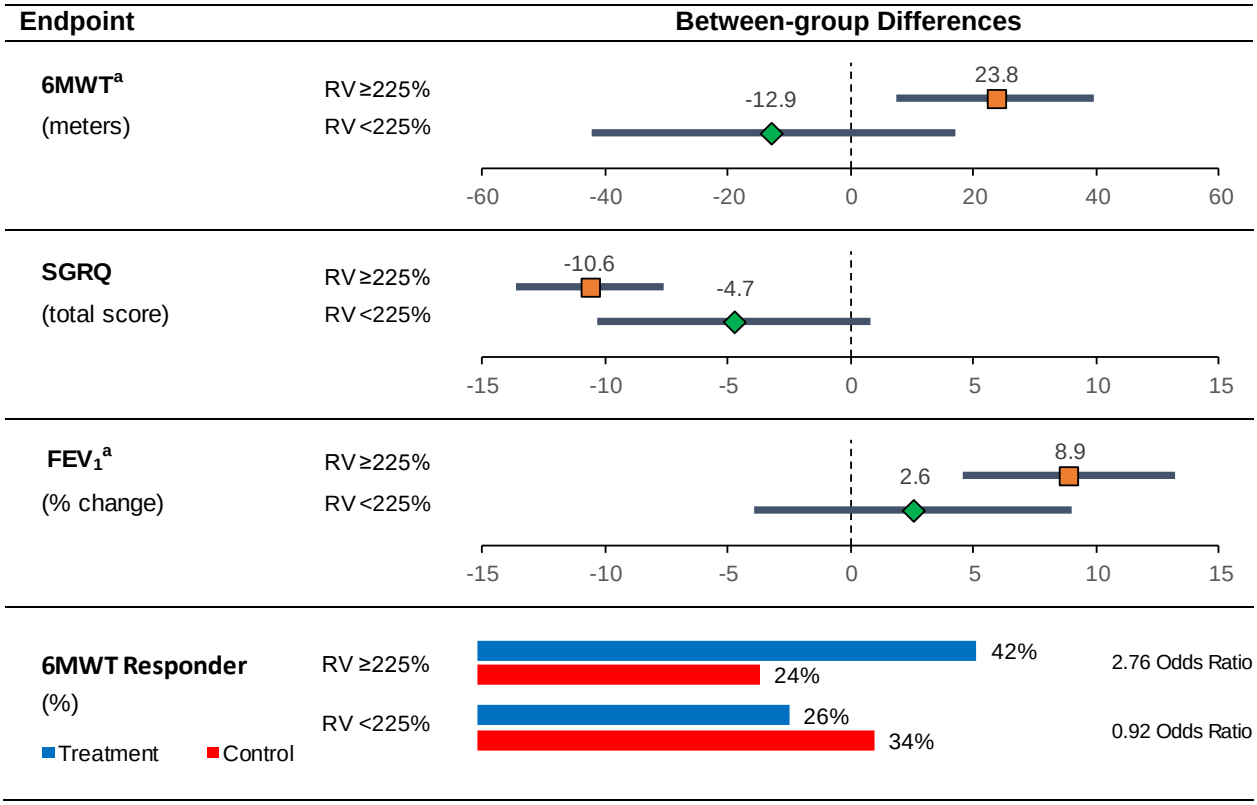
Pre-specified analyses by RV status at baseline (detailed in final SAP, Attachment 6) demonstrated that RENEW subjects with RV ≥225%, corresponding to the originally defined protocol population and representing 75% of all subjects enrolled in RENEW, showed robust improvements in the Treatment group compared to the Control group (Figure 3):

- 6MWT – median between-group improvement of 23.8 meters; nominal p=0.0039
- 6MWT responder analysis – Treatment: 42.3%, Control: 23.9%; nominal p=0.0019
- SGRQ – adjusted mean between-group improvement of −10.6 points; nominal p<0.0001
- FEV_1 – median between-group improvement of 8.9%; nominal p<0.0001

In contrast, Coil-treated subjects with RV <225% deteriorated with respect to the Control group in the 6MWT and the 6MWT responder rate, although they showed improvement or stability with respect to SGRQ and FEV_1 (Figure 3).

Subjects with homogeneous and heterogeneous emphysema both benefitted from treatment with the ELEVAIR System.

Figure 3. Primary and Secondary Effectiveness Outcomes by Severity of Hyperinflation after Multiple Imputation, ITT Population [RENEW][a]



[a]Between-group difference expressed as median. Subject (n) by subgroup and treatment group: RV ≥225% Treatment (115), RV ≥225% Control (120), RV <225% Treatment (43), RV <225% Control (37).
Note: These plots were not provided within the PMA; however, the underlying information / analysis was provided in the PMA application to FDA.

Long-term Effectiveness Analyses

Although the primary evaluation of the controlled phase of the RENEW trial was at 12 months, 24-month follow-up of the RENEW Treated subjects is complete. These long-term data show that improvements in quality of life (SGRQ) and lung function (RV) versus baseline were sustained through at least 24 months post treatment with the ELEVAIR System.

Summary of Effectiveness Analyses

In summary, the effectiveness results from the primary analysis of the ITT population met all primary and secondary effectiveness endpoint analyses. However, outcomes in the originally defined protocol population (RV ≥225% subpopulation) demonstrated the most clinically

significant results. This finding is consistent with the mechanism of action of the Coils, which are designed to reduce hyperinflation by compressing diseased lung parenchyma and improving lung elastic recoil.

Therefore, PneumRx is seeking approval for use of the Elevair System in patients with severe hyperinflation, with the RENEW analysis of subjects with RV ≥225% predicted serving as clinical guidance for targeted severity of hyperinflation.

Safety

The primary safety analysis in RENEW was the difference between Treatment and Control groups in the proportion of subjects reporting Major Complications (MC) through 12 months. MCs included death as well as potential adverse events of special interest known to occur with bronchoscopy in this patient population, including specifically defined instances of pneumothorax, hemoptysis, COPD exacerbation, lower respiratory tract infection (LRTI), respiratory failure, and unanticipated bronchoscopy to perform Coil removal.

The primary safety analysis showed comparable rates of MCs between the Treatment and Control groups in all categories except LRTI, which led to a higher overall MC rate for ELEVAIR System treated subjects compared to Control subjects (34.8% versus 19.1%, nominal p=0.0021). Notably, mortality rates were similar in the two groups at 12 months (6.5% and 5.1% in Treatment and Control groups, respectively).

Serious adverse events such as COPD exacerbation, pneumonia, and pneumothorax are relatively common in the severe emphysema population. Consistent with this fact, a high incidence of SAEs was reported for both Treatment and Control groups in the RENEW Trial through the 12-month follow-up period. SAEs that were reported at a higher incidence in the Treatment group compared to the Control group included pneumonia (22.6% versus 5.1%, respectively) and pneumothorax (9.7% versus 0.6%). The two bronchoscopic procedures used for Coil placement likely contributed to increased adverse event rates seen in the Treatment group compared to the Control group, which did not undergo sham bronchoscopy. Although not statistically different between Treatment and Control groups, serious COPD exacerbation and bleeding (hemoptysis/hemorrhage) events were also identified as significant risks of Coil treatment in the RENEW Trial. COPD exacerbation was the most common SAE in both Treatment and Control groups (27.7% versus 20.4%) and was the most common device and/or procedure-related SAE. Serious hemoptysis/hemorrhage events, although rare after Coil treatment, were associated with death in 1% of Coil-treated subjects throughout the IDE clinical program.

Investigation of the higher rate of pneumonia SAEs in the Treatment group compared to the Control group revealed that some of these reported pneumonia events were a previously unrecognized, non-infectious, local inflammatory response to the Coil, rather than pneumonia. This inflammatory response, which presents similarly to pneumonia on radiographic imaging, is referred to as “Coil-Associated Opacity”, or CAO, by PneumRx. A retrospective review of all pneumonia events reported during RENEW estimated that approximately 35% of these events

were actually CAO. Because serious CAO events present in a manner similar to pneumonia but are inflammatory in nature rather than infectious, it is important that CAO and pneumonia events be diagnosed and managed appropriately. CAO is described in the IFU, and methods of differentially diagnosing and treating CAO versus pneumonia will be incorporated into physician training.

Serious adverse events reported post 12 months are relatively low and are consistent with expectations for the severe emphysema patient population.

No notable differences in safety events were seen between the RV ≥225% subpopulation and the overall RENEW safety population.

Roll-In and Crossover

Forty-six subjects were treated with the ELEVAIR System in the non-randomized, single-arm, assessor-blinded Roll-In phase. The treatment protocol was identical to that of RENEW. Data were analyzed separately from RENEW data using descriptive statistics. Improvements at 12 months compared to baseline were seen in the primary and all secondary endpoints (6MWT: 8.6 meters; 6MWT responder rate: 42%; SGRQ: −13.3 points; FEV_1: 1.7%). Results in subjects with RV ≥225% were similarly improved with Coil treatment (6MWT: 5.2 meters; 6MWT responder rate: 39%; SGRQ: −15.0 points; FEV1: 1.7%). The most common SAEs by subject were COPD exacerbation (23.9%) and pneumonia (23.9%). Four deaths occurred, each of which was unrelated to the device or the procedure. The overall safety and effectiveness results were analogous to those of Coil-treated subjects in the randomized RENEW trial.

The Crossover phase of the PneumRx IDE Clinical Program was a non-randomized, uncontrolled follow-up of RENEW Control subjects electing to undergo device treatment after completion of the 12-month RENEW primary assessment. The effectiveness outcomes from the 101 subjects who elected crossover treatment were disparate from those of the Coil-treated RENEW subjects, from those of the other two randomized controlled clinical trials of the ELEVAIR System (RESET and REVOLENS; see Additional Clinical Studies below), and from the earlier 3 single-arm trials of the device. The RENEW Crossover subjects (RV ≥225% or RV <225%) did not experience clinical improvement at 12 months in 6MWT or FEV_1. Crossover subjects experienced a 14.8 meter decrease in 6MWT compared to baseline, with a 26% 6MWT responder rate, and FEV_1 decreased slightly (−1.3%). However, SGRQ was clinically improved compared to baseline (−4.8 points), with a 54% SGRQ responder rate. Safety outcomes through 12 months were similar to those seen in RENEW and Roll-In, with the most common SAEs being COPD exacerbation and pneumonia; the mortality rate was 8.9%.

Several factors may have confounded the Crossover results, including the shorter interval between Coil placement procedures, a change in recommended antibiotic and corticosteroid prophylaxis, and potential selection bias in those choosing to enroll in Crossover. The non-randomized and uncontrolled nature of the Crossover study design, together with these possible confounding factors, limit the interpretation and generalizability of these results.

Conclusions

The totality of the data collected in the IDE Pivotal Clinical Program support a favorable overall benefit-risk profile for use of the ELEVAIR System in conjunction with standard-of-care medical therapy in the treatment of patients with severe emphysema (homogeneous and/or heterogeneous) and severe hyperinflation (RV ≥225%).

1.5. Additional Clinical Studies

In addition to the RENEW Randomized Pivotal Trial, two additional randomized controlled trials have been completed comparing the safety and effectiveness of the ELEVAIR System versus standard medical therapy alone.

The RESET trial was the earliest prospective randomized controlled study of the ELEVAIR System. It was a multi-center, open label trial conducted in the United Kingdom, with 1:1 randomization to treatment with the ELEVAIR System or standard of care and with a total enrollment of 47 subjects. Important differences in study design between RESET and RENEW were: a different primary endpoint (SGRQ), a 3-month primary endpoint evaluation with follow-up to 12 months, no RV% minimum inclusion requirement, and 1 or 2 treatments with a shorter treatment interval (1 month). The primary effectiveness endpoint was met with an adjusted mean improvement of −10.5 points in SGRQ, more than double the minimal clinically important difference. Secondary endpoints at 3 months showed improvements in lung function, exercise capacity and quality of life. During the randomized phase, adverse event rates were comparable between arms, and no deaths occurred. The study found the ELEVAIR System to be a safe and effective treatment for patients with heterogeneous and homogeneous emphysema that provides clinically meaningful benefits over standard of care medical therapy.

The second randomized controlled trial, REVOLENS, was sponsored by the Reims University Hospital in France and primarily financed by the French Ministry of Health with limited additional support from PneumRx. REVOLENS was a prospective, multi-center, randomized (1:1) post-market trial in 100 patients with severe emphysema. The study was similar to RENEW in design, inclusion criteria, treatment and duration. Enrollment was restricted to subjects with severe hyperinflation (RV >220%), making the safety and effectiveness results directly comparable to those of the originally defined RENEW population (RV ≥225% subpopulation). The REVOLENS primary effectiveness endpoint, 6MWT response rate (≥54 meters) at 6 months, was met with 36% (18/50) of Coil-treated subjects meeting or exceeding the response threshold compared to 18% (9/50) of Control subjects (p=0.03, one-sided superiority test at α=0.05 significance level). Secondary effectiveness analyses performed at 6 and 12 months follow-up further demonstrated improvements from baseline with Coil treatment in quality of life (SGRQ, mMRC Dyspnea Scale) and lung function (FEV_1, RV, RV/TLC). Safety outcomes were comparable to those reported for RENEW with similar mortality rates between study arms and an increased incidence of serious pneumonia events associated with ELEVAIR Coil therapy. Follow-up to 24 months post treatment confirmed that the long-term safety profile is consistent with expectations for the severe emphysema population, and improvements in SGRQ and RV

compared to baseline are sustained for at least 24 months after Coil treatment. Thus, these results effectively mirror those of the RENEW Trial.

Finally, PneumRx has also completed 3 single arm clinical studies evaluating the safety and effectiveness of the ELEVAIR System in the EU, and a large EU registry is ongoing to evaluate outcomes of ELEVAIR System therapy in the post-market setting. These studies confirm the findings from the RENEW, RESET, and REVOLENS randomized trials and support the positive benefit-risk profile established by RENEW for the ELEVAIR System in treatment of patients with severe emphysema (homogeneous and/or heterogeneous) and severe hyperinflation.

1.6. Patient Preference Evaluation

In support of benefit-risk determination, PneumRx conducted a patient preference study that used a discrete choice experiment to quantify patients' benefit-risk preferences in a sample (n=202) of individuals with severe emphysema who were representative of the intended ELEVAIR System treatment population (not the RENEW subjects themselves). These preferences were then used to predict how emphysema patients would evaluate the benefits and risks associated with an endoscopic Coil-like intervention such as the ELEVAIR System. Preferences revealed through this testing indicated that a substantial proportion (32%) of the overall sample population, and 51% of the study sample with severe hyperinflation (RV ≥225%), would likely prefer a treatment such as the ELEVAIR System therapy versus continuing with maximum medical therapy alone.[a] These preference study results suggest that a meaningful population of severe emphysema patients may opt to pursue ELEVAIR Coil therapy as an additional treatment option, if it were available to them.

1.7. Post-Market Plan

PneumRx is committed to obtaining optimal clinical results in the US post-market setting through several mechanisms:

- A comprehensive physician training program on device treatment is being developed based on the RENEW training program and programs currently in use in the EU post-market settings
- A 3-year post-approval study in the US to confirm the safety and effectiveness of the ELEVAIR System for patients with severe emphysema and severe hyperinflation
- 5-year follow-up of all treated US IDE subjects (RENEW Pivotal Trial, Roll-In, and Crossover)
- Post-market surveillance procedures consistent with industry best practices

[a] To evaluate the 17.5% additional risk of pneumonia requiring hospitalization observed in the ITT population (17.3% additional risk of pneumonia requiring hospitalization observed in the RV≥225% population) in the RENEW study of the ELEVAIR System, patient preference for the additional risk of pneumonia requiring hospitalization was extrapolated using the parameters estimated in the preference model because the 17.5% (17.3%) observed risk was above the maximum level of 15% included in the patient preference study.

1.8. Conclusions and Benefit-Risk Determination

Treatment with the ELEVAIR System has repeatedly demonstrated statistically significant and clinically meaningful improvements in quality of life, lung function, and exercise capacity in patients with severe emphysema and severe hyperinflation. The RENEW pivotal clinical trial presented here showed clinically meaningful results in all primary and secondary endpoints, representing clinically relevant improvements in quality of life, lung function, and exercise capacity. These effectiveness results occurred with an acceptable safety profile in the context of the severity of disease and the expected risks of bronchoscopic procedures in this patient population.

While the data from the RENEW Trial primary analysis of the ITT population present compelling evidence of effectiveness, PneumRx concludes that these data support the most effective application of the ELEVAIR System in patients with severe hyperinflation, defined in RENEW as RV ≥225% predicted. This originally defined protocol population represented 75% of the patients enrolled in RENEW, and these patients experienced the greatest overall benefit and the largest responder rates. Therefore, patients with severe hyperinflation will experience the most favorable benefit-risk profile with use of the ELEVAIR System. Based on these data, the proposed indications for use of the device are:

> 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.

In the analysis of the RENEW Trial data, PneumRx has defined severe hyperinflation as the population with RV ≥225% predicted. In clinical practice, the Sponsor believes that clinicians should target this population but should also have the ability to exercise discretion to incorporate overall patient health status as well as patient preference for course of treatment into clinical decision-making.

The ELEVAIR System will provide a much needed, more readily available, and minimally invasive treatment for patients with severe emphysema and severe hyperinflation despite optimal medical management.

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Abbreviations

6MWD	Six-Minute Walk Distance
6MWT	Six-Minute Walk Test
AE	Adverse Event
ATS	American Thoracic Society
CAO	Coil-Associated Opacity
CEC	Clinical Events Committee
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CXR	Chest X-ray
DLCO	Diffusion Capacity of the Lung for Carbon Monoxide
DMC	Data Monitoring Committee
ERS	European Respiratory Society
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
IFU	Instructions for Use
ITT	Intention-To-Treat
LT	Lung Transplant
LVR	Lung Volume Reduction
LVRS	Lung Volume Reduction Surgery
MC	Major Complication
MCID	Minimal Clinically Important Difference
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
mMRC	Modified Medical Research Council dyspnea scale
NETT	National Emphysema Treatment Trial
OUS	Outside the United States
$PaCO_2$	Partial Pressure of Arterial Carbon Dioxide
PaO_2	Partial Pressure of Alveolar Oxygen
PP	Per Protocol
RAE	Respiratory Adverse Event of interest
RV	Residual Volume
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SGRQ	St. George's Respiratory Questionnaire
SSED	Summary of Safety and Effectiveness Data
TLC	Total Lung Capacity
UADE	Unanticipated Adverse Device Effect

2. DISEASE BACKGROUND AND UNMET MEDICAL NEED

2.1. Disease Background

Emphysema is a chronic, incurable, life-threatening and irreversibly debilitating disease affecting an estimated 3.5 million people in the US.[b] Patients with severe emphysema are subject to a progressive decline in lung function, exercise capacity, and quality of life. The crippling effects of end-stage emphysema include severe coughing, chronic and severe dyspnea, severe limitation of activities, frequent illnesses, lung infections and death. Emphysema patients are often too sick to work, to exercise, or to care for others. Often needing support and care themselves, these patients suffer from a severely reduced quality of life because of their disease.

A sub-type of chronic obstructive pulmonary disease (COPD), emphysema is characterized by destruction of alveolar walls and the connective tissues that normally hold airways open, which results in a decrease in tissue elasticity and lung functionality. Loss of tissue elasticity causes smaller airways to collapse prematurely during exhalation, which reduces airway patency and increases airway resistance upon exhalation. This resistance, in turn, results in air trapping in the distal airways, leading to inefficient expiration and a corresponding reduction in the amount of fresh air drawn into the lung upon inspiration. Symptomatically, these phenomena manifest for the patient as chronic breathlessness. Emphysema severity is commonly graded using the GOLD grading system, which is based on the extent of airflow restriction (i.e., FEV_1 percent predicted) in the patient (GOLD 2018).

In severely emphysematous lungs, smaller airways may collapse completely during exhalation (Leaver 1973), trapping air in the lungs and resulting in “hyperinflation”, or permanent pathologic enlargement of the lung. This hyperinflation leads to the characteristic “barrel-chested” appearance that is typical in patients with severe emphysema. In cases of clinically significant hyperinflation, the healthier regions of the lung become compressed by the hyperinflated portion, which significantly compromises gas exchange even in these healthier areas. Hyperinflated lungs also flatten the normally domed configuration of the diaphragm, limiting its contractility and force generation, thereby further impairing breathing mechanics and reducing inspiratory capacity. Lung hyperinflation can occur at rest (static hyperinflation), but is generally more pronounced during exertion (dynamic hyperinflation) due to the increase in ventilatory requirements during exercise and a corresponding decrease in expiratory time (Gagnon 2014).

The physiological effects of hyperinflation are profound in severe emphysema patients. Indeed, although COPD and emphysema are defined and graded by expiratory flow limitation (GOLD 2018), hyperinflation has been shown to correlate better with diminished quality of life (e.g., dyspnea, exercise intolerance, inability to complete activities of daily living) than do spirometry values such as FEV_1 (O’Donnell 1999, Garcia-Rio 2009). Moreover, measures of hyperinflation (residual volume percent predicted, residual volume/total lung capacity) are significantly associated with, and independent predictors of, mortality in the severe emphysema population (Martinez 2006, Burgel 2012, Ozgür 2012, Shin 2015).

[b] CDC FastStats, http://www.cdc.gov/nchs/fastats/default.htm. Accessed March 13, 2018.

2.2. Standard of Care for Emphysema

Medical therapy for the management of COPD and emphysema has been evaluated by consensus review panels, and is published and regularly updated (GOLD 2018, ATS/ERS 2004, Qaseem 2011). All guidelines recommend the following: smoking cessation, pharmacologic treatment including bronchodilators and corticosteroids, pneumococcal and flu vaccinations per local guidelines, and pulmonary rehabilitation, as well as supplemental oxygen therapy in some patients.

Pharmacologic treatment is not customized to the type of COPD (i.e., emphysema-predominant, chronic bronchitis-dominant, or ACOS); rather, medications are typically prescribed, alone or in combination, based on disease severity, patient-specific symptoms, and the patient's response to each treatment. The goal of pharmacotherapy is to reduce symptoms, reduce the frequency and severity of exacerbations, mitigate dyspnea, and improve the health status and exercise capacity of the patient. However, no available medication has been demonstrated to modify the long-term decline in lung function associated with COPD and emphysema. Furthermore, pharmacotherapies are generally insufficient to manage the symptoms and impact to quality of life seen in patients with severe emphysema.

2.3. Surgical Treatments for Emphysema

2.3.1. Lung Volume Reduction Surgery

Lung Volume Reduction Surgery (LVRS) is a surgical option for patients with advanced, bilateral, heterogeneous emphysema that entails removal of approximately 20-35% of poorly functioning, hyperinflated lung tissue from the upper lobe of each lung. After the diseased lung tissue is removed, the remaining ~65% of the lung expands via negative pressure to fill the chest cavity, increasing tissue elastance and improving respiratory mechanics. By eliminating the diseased lung tissue, the remaining lung and surrounding muscles (intercostals and diaphragm) can work more efficiently (Sciurba 1996). This, in turn, makes breathing easier and helps improve patient quality of life.

In ideal patients, LVRS has been demonstrated to provide significant benefits, including improvement in lung function, exercise capacity, quality of life and survival (Fishman 2003). However, patients undergoing LVRS also experience higher morbidity rates due to the surgery than do patients receiving standard medical therapy alone. LVRS patients showed an overall morbidity rate of 59%, with 28% of patients needing in-hospital stay or rehabilitation facilities for 1 month or more after surgery (Pompeo 2014). Age, FEV_1, and DLCO were identified as risk factors for major pulmonary morbidity, whereas non-upper-lobe predominant emphysema distribution increased operative mortality and cardiovascular morbidity.

Because LVRS involves significant morbidity, with significant mortality risks in specific populations, its adoption has been limited, by patient and physician demand, to patients with the most favorable potential benefit-risk balance (Fishman 2003, Naunheim 2006, DeCamp 2008).

Currently, fewer than 200 LVRS procedures for emphysema patients are performed annually in the US. An ideal candidate for LVRS is a patient (1) who has disabling emphysema despite complete compliance with optimal medical therapy, including smoking cessation; (2) who is able and willing to participate in pulmonary rehabilitation both before and after surgery, (3) whose other medical conditions are well controlled and is not otherwise at high risk for complications from the surgery; and, most importantly (4) who has a pattern of emphysema that is amenable to surgical management.[c] Generally, patients with severe, bilateral, upper lobe predominant (heterogeneous) emphysema, who present with low baseline exercise capacity but no significant cardiac or other comorbidity, are good candidates for LVRS (Fishman 2003). Notably, homogeneous emphysema isn't considered amenable to treatment using LVRS, leaving patients with homogeneous emphysema with only lung transplantation as a potential option for treatment options of their disease.

2.3.2. Lung Transplantation

Lung transplantation, performed as either a unilateral (single lung) or bilateral procedure, is a final surgical option for treatment of severe emphysema. In addition to a survival benefit, lung transplantation can provide significant improvements in exercise capacity and quality of life to emphysema patients who are fortunate enough to become eligible for this surgery. However, due to the limited availability of donor organs and the introduction in 2005 of a lung allocation system that uses net transplant benefit criteria, the number of emphysema patients who receive lung transplant is low (approximately 500 procedures conducted per year in the US in patients diagnosed with COPD or emphysema, Valapour 2018). Thus, lung transplantation is simply not an option for the great majority of the COPD and emphysema populations (Shah 2013).

2.4. Unmet Medical Need Addressed by the ELEVAIR System

Of the 3.5 million people in the US with emphysema, approximately 1.2 million have GOLD stage 3 or 4 disease.[d] There is currently no cure for emphysema and no therapy that halts progression of the disease. Once emphysema becomes severe and can no longer be managed adequately by medical therapies, only surgical options (lung volume reduction surgery and lung transplantation) remain, and these are available to only a small subset of patients. Both LVRS and lung transplantation have severely restrictive eligibility criteria that keep these therapies from addressing the needs of the vast majority of severe emphysema patients. Given the limitations of the existing treatments, there remains a significant unmet medical need for additional safe and effective treatments for patients with severe emphysema. The ELEVAIR Endobronchial Coil System is a first-of-its-kind, implantable device designed to improve quality of life, lung function, and exercise capacity, which represents a compelling alternative to the limited treatment options available for patients with severe emphysema and severe hyperinflation.

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[c] Keck School of Medicine of USC. http://www.surgery.usc.edu/cvti/thoracic-lungvolumereductionsurgery.html. Accessed March 30, 2018.
[d] Based on data extrapolated from the National Health and Nutrition Examination Survey. https://www.cdc.gov/nchs/data/databriefs/db180.pdf.

3. DEVICE DESCRIPTION, MECHANISM OF ACTION AND PROCEDURE DESCRIPTION

3.1. Indications for Use

The proposed indications for use are:

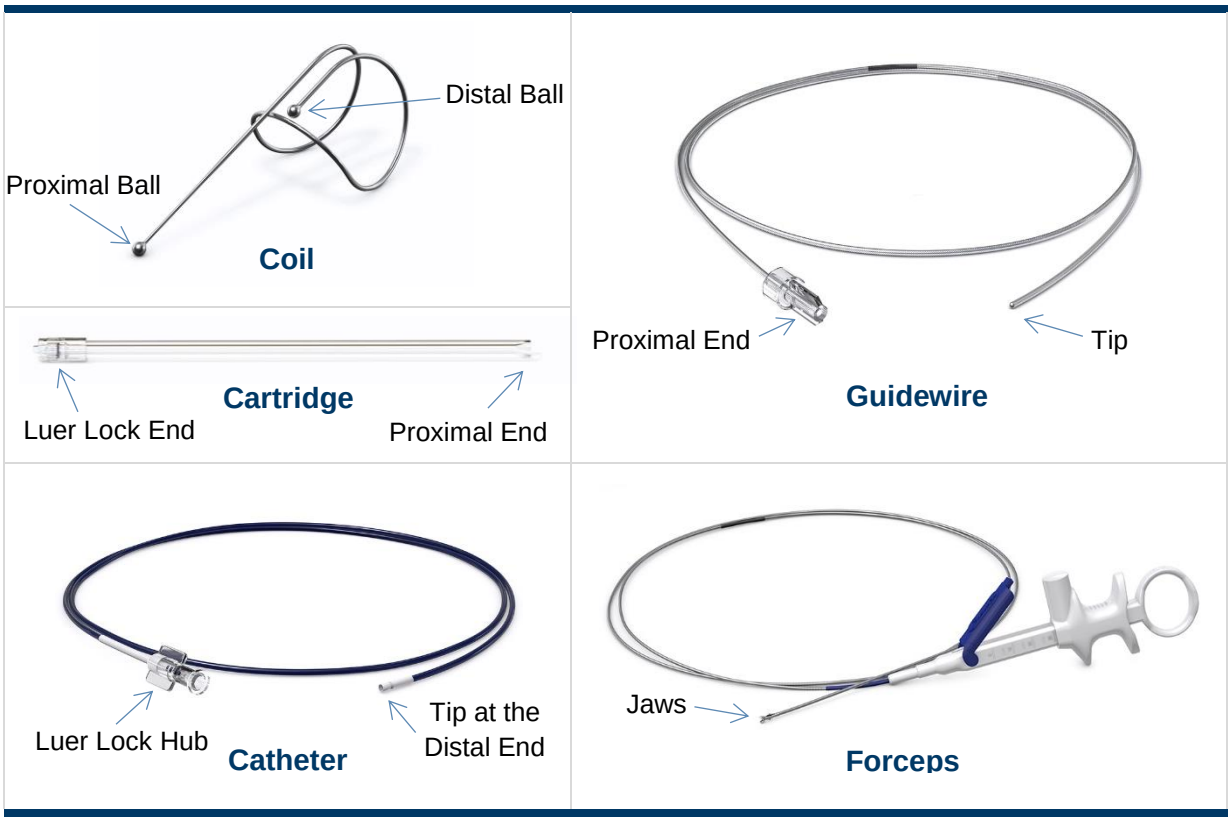
> The ELEVAIR Endobronchial Coil System is indicated for bronchoscopic placement of ELEVAIR Coils in patients with severe emphysema (homogeneous and/or heterogeneous) and severe hyperinflation to improve quality of life, lung function, and exercise capacity.

The above indication statement is similar to those used throughout the PneumRx US IDE clinical program, the indications granted for the device under the CE mark, and is reflective of the safety and effectiveness data obtained to date for the ELEVAIR System. In the data analyses presented from the RENEW Trial, PneumRx has defined the population with severe hyperinflation as those subjects with a residual volume ≥225% predicted.

3.2. Description of ELEVAIR Endobronchial Coil System

The ELEVAIR System consists of two main components: sterile ELEVAIR Endobronchial Coils (referred to as “ELEVAIR Coils” or “Coils”) and a sterile, disposable ELEVAIR Endobronchial Coil Delivery System (referred to as “ELEVAIR Delivery System” or “Delivery System”). The ELEVAIR System components are shown in Figure 4 (illustrated components not to scale).

Figure 4. ELEVAIR System components



3.2.1. ELEVAIR Coil

The ELEVAIR Coil is composed of passivated nitinol, which is a biocompatible, superelastic nickel-titanium alloy used extensively in implantable medical devices (Shabalovskaya 2002, Duerig 1996). Passivation provides a uniform, protective surface finish to the underlying nitinol and mitigates against potential corrosion. The ELEVAIR Coil is available in three lengths (100mm, 125mm, and 150mm) to accommodate anatomical variations in airway length. The most proximal end of the Coil has a smaller diameter than the rest of the Coil to reduce rigidity, lessen pressure of the Coil on the airway wall and to facilitate recapture, if necessary. The distal and proximal ends of the Coil terminate with a smooth, atraumatic ball.

The Coil is terminally sterilized using electron beam irradiation.

3.2.2. ELEVAIR Delivery System

The ELEVAIR Delivery System consists of a Guidewire, Catheter, Cartridge, and Forceps (shown in Figure 4). The Guidewire guides the Catheter to the target airway and facilitates the selection of the appropriate Coil length. The Catheter provides a conduit for Coil delivery to the target airway site. The Cartridge temporarily straightens the Coil to allow loading into the Catheter and couples to the hub of the Catheter. The Forceps grasp the proximal end of the Coil and are used to deliver the Coil to the target airway through the Catheter. The Catheter

and Forceps can also be used to remove and/or re-position the Coil, if necessary, during the implantation procedure. A single Delivery System is used to deliver multiple Coils to the same patient in a single procedure.

The Delivery System is terminally sterilized using ethylene oxide.

3.3. Mechanism of Action of the ELEVAIR Coil

The Coil was designed to treat the specific pathophysiologic challenges of the emphysema disease state. In emphysema patients with hyperinflation, elevated residual volume results in severely reduced inspiratory capacity (total volume of air that can be taken into the lungs after normal expiration). That is, their resting lung volume during normal breathing is elevated such that they can inhale little additional air when taking a deep breath. By reducing hyperinflation, inspiratory capacity is immediately improved, thus allowing more air to be inhaled and exhaled with each breath. In addition, a reduction in hyperinflation means that the lung volume is now better matched to the size of the chest cavity. This allows the diaphragm curvature to be restored, and thus reduces the work of breathing, while also reducing added mechanical stress placed on surrounding organs (e.g., the heart). Thus, reduction of hyperinflation translates into improved lung function and, ultimately, into clinical benefits to the patient, which include improvements in quality of life and exercise capacity.

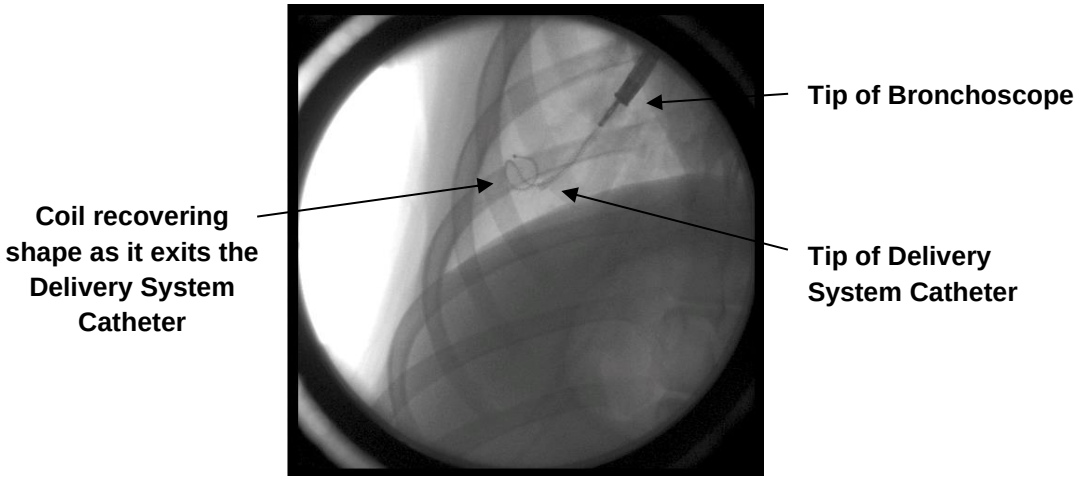
The ELEVAIR Coils reduce hyperinflation and overall lung volume by:

- Compressing diseased tissue, thereby allowing more normal tissue to expand;
- Restoring lung elastic recoil to tether open and maintain airway patency; and
- Adjusting lung compliance to shift preferential filling from diseased tissue to healthier tissue.

Because the Coil acts by a mechanical action to reduce lung volume by compressing emphysematous lung tissue, the desired effects are achieved without the concern of collateral ventilation (passage of air directly between lobes of a lung via openings in the lobar fissures) interfering with treatment outcome.

The Coil is deployed using a minimally invasive approach through a bronchoscope and requires no incision. The Coils are straightened for loading into the Delivery System, and this straightened shape is maintained as the Coil is advanced down the Catheter to the generally straight airways. Shape recovery, which is driven by the super-elastic properties of nitinol, occurs when the Coil is deployed (Figure 5).

Figure 5. Three-dimensional shape recovery of the ELEVAIR Coil



During shape recovery, as the ends of the device draw together, a long segment of treated airway is gathered together and compressed. Since the airways are interconnected to a network of smaller airways, and interstitial collagen fibers stretch between these airways, normally creating elastic recoil, any distortion of the airway path generally increases elastic recoil in the lung tissue and enhances radial suspension of the surrounding airway network. By improving lung elastic recoil and reducing hyperinflation, the ELEVAIR Coil (1) reduces airflow resistance in and out of the lungs, and (2) allows the healthiest tissue to function more efficiently.

3.4. Description of ELEVAIR Coil Placement Procedure

High resolution computed tomography (HRCT) is used during treatment planning to (1) exclude patients based on the presence of imaging contraindications, and (2) identify the (bilateral) lung lobes most appropriate for treatment in those patients who meet the imaging treatment criteria. Treatment should target the most damaged lobe (upper or lower) in each lung.

The patient is prepared for bronchoscopy per standard institutional practice; general anesthesia or conscious sedation is administered to perform Coil placement. All local institutional policies relevant to radiography, general anesthesia, and/or sedation should be observed.

The bronchoscope is inserted into the patient and navigated to the selected airway per the bronchoscope manufacturer's instructions. After performing a visual inspection of all lobes, the physician navigates the bronchoscope to the lobe selected for treatment and then to the airways to be treated, as identified during treatment planning. If the patient's host pathogens have not been documented, collection of a bronchial wash at the first procedure may provide useful information for treatment of any potential subsequent adverse events.

The physician inserts the Catheter and Guidewire into the working channel of the bronchoscope per the ELEVAIR System Instructions for Use, navigates to the distal airways of the selected

treatment lobe, and verifies the Catheter position via fluoroscopy. Each Coil is delivered while monitoring the position via fluoroscopy, in accordance with ELEVAIR System Instructions for Use, ensuring adequate distance from the pleura is maintained. Most patients receive 10-14 Coils per treatment, with a single lobe treated during each bronchoscopy session. The patient is allowed to recover from anesthesia and is monitored as per standard hospital practice. Most patients can be discharged by the day after the procedure.

At discharge, the physician should verify by chest X-ray that the Coils are in the appropriate locations and to confirm absence of pneumothorax; prophylactic medications are prescribed as described in the treatment plan. The patient should be contacted one week post treatment for a status update to evaluate the patient for adverse events and to ensure that medications are taken and patient activity levels are appropriate. The patient should be contacted three weeks post treatment for another status update and to schedule the second treatment. Coil treatments should be scheduled 1-3 months apart, allowing time for any peri-procedural events to resolve. After the second procedure, the patient should receive the same follow-up as after the first procedure, and should be encouraged to schedule regular visits with his/her routine pulmonologist for ongoing management of his/her emphysema.

Additional specifics regarding the Coil placement procedure are available in the ELEVAIR System Instructions for Use (see Attachment 3).

4. PRECLINICAL TESTING PROGRAM

A series of non-clinical laboratory studies were performed to evaluate the PneumRx ELEVAIR Endobronchial Coil System. These studies included biocompatibility; sterilization; packaging and shelf-life; in vitro and *ex vivo* bench testing; animal studies of performance, safety and retrievability; and human factors / usability testing.

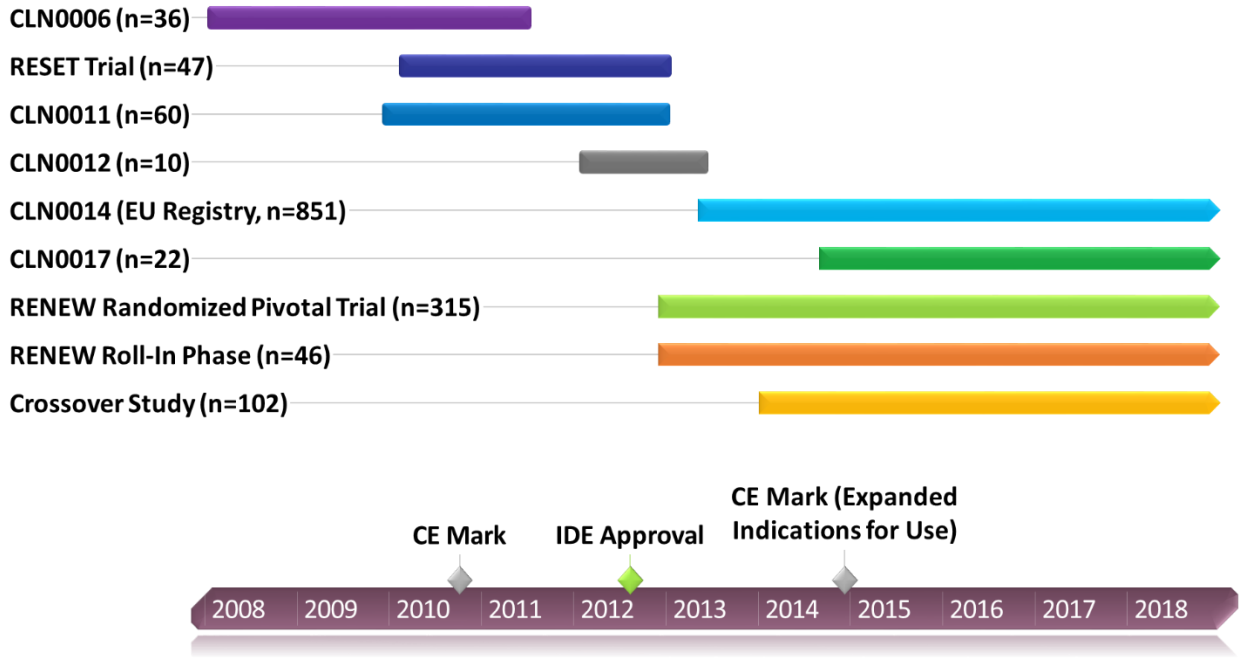
Biocompatibility testing was performed on the ELEVAIR System (ELEVAIR Coil and ELEVAIR Delivery System) in accordance with the requirements of industry standard ISO 10993-1. Testing of the Coils included cytotoxicity, sensitization, irritation / intracutaneous reactivity, acute and subchronic / chronic systemic toxicity, hemocompatibility, genotoxicity, implantation toxicity, and pyrogenicity. In addition, metal degradation testing per current FDA Guidance and auger electron spectroscopy testing per ISO 10993-19 were performed to evaluate corrosion resistance and biocompatibility with respect to metal degradation. Testing of the Delivery System included cytotoxicity, sensitization, irritation / intracutaneous reactivity, acute subchronic / chronic systemic toxicity, and hemocompatibility. Collectively, these studies demonstrated that the ELEVAIR Coil and ELEVAIR Delivery System are biocompatible for their intended use.

5. SUMMARY OF ELEVAIR SYSTEM CLINICAL TESTING PROGRAM

The ELEVAIR System has undergone extensive clinical evaluation over a period of more than 10 years. These studies are briefly summarized in this section and include studies conducted under US IDE (RENEW Randomized Pivotal Trial, Roll-In, and Crossover studies), four studies conducted in the EU that supported the initial CE mark and subsequent expanded indications

for use (CLN0006, CLN0008 [RESET], CLN0011, and CLN0012), and two post-market studies in the EU (EU Registry, which is still enrolling, and CLN0017). The timeline for these studies is presented in Figure 6 below.

Figure 6. PneumRx-Sponsored Clinical Studies of the ELEVAIR System



After first receiving the CE mark in October 2010, PneumRx initiated a prospective, multi-center (US, EU, and Canada) clinical program under IDE G110066 to support market authorization in the United States. The IDE Clinical Program includes two ongoing clinical protocols: the RENEW Pivotal Trial ("Lung Volume Reduction Coil Treatment in Patients with Emphysema (RENEW) Study"), and a Crossover study that enrolled Control subjects from the Pivotal Trial. The RENEW protocol included both a randomized phase, designed to evaluate safety and effectiveness of the ELEVAIR System for PMA approval, and a Roll-In phase designed to provide study sites that had not participated in previous clinical trials of the ELEVAIR System with experience in the use of the device prior to initiation of randomization.

The RENEW Trial and Crossover study included clinical sites in the United States, and outside the United States (European Union and Canada). Treatment of COPD and emphysema is well standardized and aligned with clinical care guidelines and statements released by consensus review panels for multiple medical societies, including the American Thoracic Society (ATS), the European Respiratory Society (ERS), and the Global Initiative for Chronic Obstructive Lung Disease (GOLD). Thus, the standard of care for treatment of severe emphysema is similar in each of these regions, and the OUS data are directly applicable to the demonstration of safety and effectiveness of the ELEVAIR System. Both the RENEW Trial and the Crossover study were executed under an approved IDE (G110066) and in accordance with Good Clinical Practice (GCP) regulations.

A detailed summary of safety and effectiveness data is presented for the RENEW Randomized Pivotal Trial in Section 6 below. Although neither the RENEW Roll-in phase nor the Crossover study were designed with the primary objective of evaluating safety or effectiveness of the ELEVAIR System and neither incorporated a concurrent control arm, each collected similar types of data as the RENEW Randomized Pivotal Trial. Thus, brief summaries of findings from the Roll-In phase and Crossover study are also included (Section 7.2).

6. RENEW RANDOMIZED PIVOTAL TRIAL

This section summarizes safety and effectiveness data from the Randomized Pivotal Trial of the ELEVAIR System (RENEW, "Lung Volume Reduction Coil Treatment in Patients with Emphysema (RENEW) Study"). This study was executed in compliance with the Institutional Review Board regulations (21 CFR 56), the Informed Consent regulation (21 CFR 50), and the Investigational Device Exemptions regulations concerning sponsors of clinical investigations and clinical investigators (21 CFR 812). The ClinicalTrials.gov record for the RENEW Pivotal Trial is NCT01608490.

6.1. Trial Design

The RENEW Pivotal Trial was a prospective, multi-center (international), randomized, assessor-blinded, controlled trial designed to evaluate the safety and effectiveness of the ELEVAIR System in subjects with severe bilateral emphysema (homogeneous and/or heterogeneous). The RENEW Trial compared outcomes in subjects treated with the ELEVAIR System in combination with optimal medical therapy to outcomes in a control group receiving optimal medical therapy alone. The objectives of the RENEW Trial were to determine whether treatment with the ELEVAIR System results in improved exercise capacity, quality of life, and lung function.

The final version of the RENEW Trial protocol is provided as Attachment 5 to this executive summary.

6.1.1. Amendment of Trial Eligibility Criteria (RV Threshold)

The initial version of the RENEW Trial protocol under which subjects were enrolled prospectively defined the study population as those subjects with FEV_1 ≤45% predicted (i.e., severe, GOLD 3 and 4 emphysema) and RV ≥225% predicted. This original RV criterion was based on limited data collected through a European feasibility study. In a protocol amendment submitted to FDA just after the mid-point of RENEW Trial enrollment, the protocol inclusion criterion regarding RV was changed to allow subjects to be eligible with RV ≥175% predicted. This protocol change was intended to broaden the target patient population of the RENEW Trial, and was based on a newer clinical data set combining data from several small, ongoing clinical studies as well as initial post market data from a European registry study. While still limited, this combined data set suggested that subjects with RV between 175% and 225% may benefit from Coil treatment. This change opened RENEW Trial participation to subjects whose hyperinflation

was, on average, less advanced, as evidenced by the amount of residual volume. 169 of the 315 randomized subjects were enrolled in the study prior to FDA approval of the protocol amendment; consequently, these subjects had baseline RV ≥225%. Of the 146 subjects randomized after protocol revision, 80 subjects had baseline RV <225% predicted. Thus, as of completion of enrollment, 74.6% (235/315) of subjects had RV ≥225% predicted, and 25.4% (80/315) of subjects had RV <225% predicted.

Amendment of the protocol resulted in addition to the statistical analysis plan (SAP) of a subgroup analysis by severity of hyperinflation (RV ≥225% predicted versus RV <225% predicted). This addition was made to the RENEW SAP prior to database lock for the primary endpoint analysis. As will be shown in Section 6.5.1.4, the results of this analysis showed that subjects with RV ≥225% predicted at baseline demonstrated improved effectiveness outcomes following Coil therapy as compared to those with RV <225% predicted. Primary, secondary, and other effectiveness endpoints are presented herein for both the ITT population (total enrolled trial population; see Section 6.5.1) and for the RV ≥225% subpopulation (see Section 6.5.2).

While the RENEW Trial met all primary and secondary endpoints based on analysis of the full ITT population, each pre-specified endpoint showed greater clinical improvement in the originally defined protocol population (RV ≥225% subpopulation). That effectiveness of the ELEVAIR System would be increased in patients with relatively higher baseline RV is consistent with the mechanism of action of the Coils, which are designed to reduce hyperinflation through compression of diseased lung parenchyma and concomitant improvement of lung elastic recoil. Analysis of the safety endpoints showed similar safety outcomes in the originally defined protocol population (RV ≥225% subpopulation) and in the full ITT population. Based on the increased benefit observed in the originally defined population and similar levels of risk in the two populations, the proposed indications for use statement for the ELEVAIR System was updated to limit the intended population to those patients with severe emphysema and severe hyperinflation, with the RENEW analysis of subjects with RV ≥225% predicted serving as clinical guidance for targeted severity of hyperinflation.

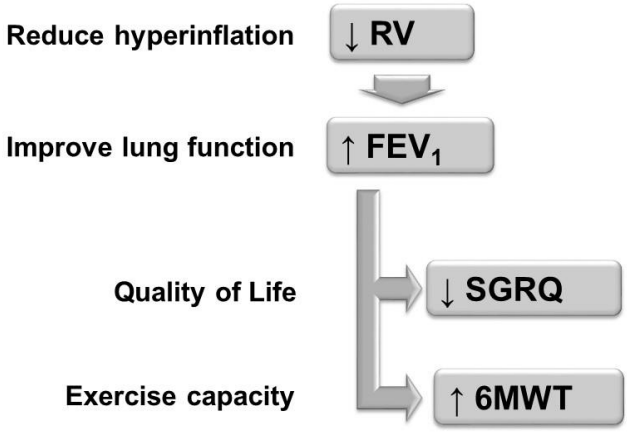
6.1.2. Clinical Endpoints and Analyses

The Intention-to-Treat (ITT) population included all randomized subjects (regardless of whether treatment was attempted) and was used to evaluate all effectiveness endpoints. The Per-Protocol (PP) population included only those subjects who completed the study without noteworthy study protocol deviations (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 included all ITT subjects who were randomized (Control group) or who entered the procedure room (Treatment group), regardless of whether device deployment was attempted.

The effectiveness endpoints in RENEW were selected based on discussions with FDA and were intended to provide a comprehensive assessment of the treatment benefits of the ELEVAIR

System. These benefits, together with the associated RENEW endpoint, are summarized in Figure 7. By reducing hyperinflation, measured in RENEW as a reduction in residual volume (RV), ELEVAIR Coils improve lung function, as measured by forced expiratory volume in 1 second (FEV_1). Improvements in lung function translate into clinical benefits to the patient, including improvements in quality of life, assessed using the St. George's Respiratory Questionnaire (SGRQ), and exercise capacity, measured using the 6-minute walk test (6MWT). These endpoints are discussed in more detail below.

Figure 7. Relationship of Effectiveness Endpoints in RENEW



6.1.2.1. Primary Effectiveness Endpoint

The primary effectiveness endpoint for the RENEW Trial was the absolute change from baseline in the **Six-Minute Walk Test (6MWT)** at 12 months, in the Treatment group versus the Control group.

The 6MWT is a self-paced test of exercise capacity that measures the distance that a person can walk on a hard, flat surface in six minutes. Six-Minute Walk Distance (6MWD) reflects the distance walked during a six-minute walk test, but may be used interchangeably with 6MWT for the purposes of this executive summary. The 6MWT is generally reflective of a patient's ability to perform activities of daily living, and lower 6MWT scores correlate with greater physical impairment. Improvement in 6MWD is a downstream effect of improvement in lung function through reduction in hyperinflation. While 6MWT is a relevant measure of clinical benefit to the emphysema patient, it can also be influenced by cardiovascular status, muscle status, and blood-flow to the legs, as well as motivation of the patient, arthritis, and other factors. A commonly accepted minimal clinically important difference (MCID) for 6MWT in COPD patients is 25 meters (Holland 2010).

6.1.2.2. Secondary Effectiveness Endpoints

Secondary effectiveness endpoints included:

- **6MWT responder analysis**: responders defined as subjects with an improvement of ≥25 meters (Holland 2010), comparing baseline to 12 months, Treatment group versus Control group.
- **St. George's Respiratory Questionnaire (SGRQ)**: absolute difference in SGRQ results, comparing baseline to 12 months, Treatment group versus Control group.
- **Forced Expiratory Volume in 1 second (FEV_1)**: percent change in FEV_1 results measured using spirometry, comparing baseline to 12 months, Treatment group versus Control group.

SGRQ is a disease-specific patient-reported outcome assessment designed to measure quality of life in patients with chronic airflow limitation. SGRQ includes domains that assess physical impairment, symptom severity, and psychosocial impact of the patient's disease. SGRQ has been well validated for use in COPD studies, and improvement (decrease) of 4 points is a commonly accepted MCID in SGRQ total score (Jones 2005, Cazzola 2008, FDA COPD Guidance "Chronic Obstructive Pulmonary Disease: Use of the St. George's Respiratory Questionnaire as a PRO Assessment Tool").

FEV_1 assesses the amount of air that can be forcefully expelled in the first second of exhalation and is a critical parameter for evaluating lung function in patients with chronic lung diseases. Lower FEV_1 scores, especially in comparison with predicted values for a healthy person, are generally associated with more severe stages of emphysema. FEV_1 is a component of the most widely used grading system (GOLD) for classifying the severity of COPD. An accepted MCID for FEV_1 in the severe COPD population is 10% (Donohue 2005, Cazzola 2008, Jones 2014).[e]

6.1.2.3. Additional Effectiveness Endpoints

Additional effectiveness endpoints that were tested for statistical significance included:

- **SGRQ responder analysis**: responders defined as subjects with an improvement of ≥4 points (Jones 2005, Cazzola 2008, FDA COPD Guidance "Chronic Obstructive Pulmonary Disease: Use of the St. George's Respiratory Questionnaire as a PRO Assessment Tool"), comparing baseline to 12 months, Treatment versus Control.
- **Residual Volume (RV)**: absolute difference in RV results measured using plethysmography, comparing baseline to 12 months, Treatment versus Control.
- **Residual Volume/Total Lung Capacity (RV/TLC)**: absolute difference in RV/TLC results measured using plethysmography, comparing baseline to 12 months, Treatment versus Control.

[e] FEV_1 responder analysis, using the MCID of 10% as the responder threshold, is shown in Sections 6.5.1.2 and 6.5.2.2. Note that this was not a pre-specified endpoint in the RENEW Trial.

RV assesses the volume of air that remains in the lungs after full expiration. Due to their inability to expel air efficiently, patients with severe emphysema generally have significantly elevated residual volume and resulting hyperinflation. As with other pulmonary function tests (e.g., FEV_1, TLC, etc.), RV is a measure of the severity of a patient's lung impairment, with higher residual volume being associated with more severe disease symptoms including dyspnea (breathlessness). The MCID for improvement in RV in severe emphysema patients is estimated to be 0.35 liters (Hartman 2012).[f] RV/TLC, which assesses residual volume as a fraction of total lung capacity, is another measure of hyperinflation in patients with chronic lung disease.

6.1.2.4. Primary Safety Analysis

The primary safety analysis for the RENEW Trial was the proportion of subjects experiencing one or more Major Complications (MCs) through the 12-month follow-up visit. MCs are events of particular interest because they are known to occur following bronchoscopic intervention in GOLD 3 and 4 patients. MCs were defined in the RENEW protocol as any of the following:

- **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 one or more Coils due to a device-related AE. (Note: This definition does not include re-positioning, replacement or removal of the Coil(s) during the initial placement procedure.)

6.1.3. Sample Size and Power Considerations

Based on previous studies, a sample size of 315 was selected to provide greater than 95% power to detect a treatment difference in effectiveness, assuming 5% lost to follow-up and treatment difference in change in 6-minute walk distance of 59 meters (SD 80 meters) and in FEV_1 of 0.05 liters (SD 0.10 liters) using a 1-sided *t* test at α=0.025. For adverse event rates

[f] RV responder analysis, using the MCID of 0.35 liters as the responder threshold, is shown in Sections 6.5.1.3 and 6.5.2.3. Note that this was not a pre-specified endpoint in the RENEW Trial.

less than 20%, a sample size of 315 would provide approximately 80% power to detect a 12% difference between treatment groups.

Sample size and power calculations were not performed prospectively for any of the pre-specified subgroup analyses (severity of hyperinflation, region, emphysema distribution, gender).

6.1.4. Pre-Specified Statistical Analysis Plan and Success/Failure Criteria

The IDE application submitted to FDA for review and approval of the RENEW Trial included a preliminary SAP in addition to the clinical protocol and other associated study documentation. Subsequent to FDA approval of IDE G110066, the SAP was updated by PneumRx to provide clarity on analyses already included in the SAP and to specify additional analyses to be performed. The revised SAP was finalized and signed-off prior to database lock and before aggregate study results were unblinded.

Key updates to the SAP included:

- Addition of a non-parametric rank ANCOVA analysis to the primary and secondary analyses, to be considered the primary analysis when marked skewness in the residuals of the parametric ANCOVA is seen both statistically and graphically
- Addition of subgroup analyses to be performed (gender, emphysema distribution, region, and RV %)
- Additional clarification regarding protocol deviations that would or would not merit exclusion from the Per Protocol (PP) population.

A copy of the SAP that was used for all RENEW Trial endpoints and analyses is provided (see Attachment 6).

6.1.4.1. Effectiveness Endpoints

The hypothesis testing for the primary effectiveness endpoint was a one-sided superiority test at α=0.025 significance level. The hypothesis testing for each secondary endpoint was a one-sided superiority test with adjustments on family wise type I error at α=0.025, using the Hochberg step-up procedure (Hochberg 1988). The familywise type I error was controlled for the primary and secondary endpoint hypothesis testing in the ITT population. Effectiveness analyses were performed for both the ITT and PP populations, with the primary analysis based on the ITT population. All missing 12-month values for effectiveness endpoints were estimated by Markov Chain Monte Carlo (MCMC) multiple imputation. Tests of superiority were to be based on either parametric or non-parametric (e.g., using ranked data) methods, consistent with the statistical assumptions required to support the analyses.

The primary effectiveness endpoint, absolute change in 6MWT (meters) from baseline to the 12-month follow-up visit, was compared between the Treatment and Control groups and expressed

as an absolute change in meters. As specified in the statistical analysis plan, due to significant skewness (see Section 6.5.1.1), the primary analysis test of superiority was based on non-parametric methods (i.e., a rank ANCOVA extension of the Wilcoxon rank sum test). For the non-parametric model, median values were reported as the appropriate point estimate of central tendency (or "population average") rather than the adjusted means. The rank ANCOVA model included baseline 6MWT as a covariate and factors of treatment, analysis center, and emphysema distribution. Results from the parametric ANCOVA model and associated means adjusted for covariates were also reported. The treatment effect by analysis center was evaluated to assess the appropriateness of pooling the data across centers. In addition, sensitivity analyses (e.g., worse case, complete case, etc.) were conducted to explore the impact of missing observation estimation on effectiveness assessment using 6MWT (outcomes discussed in Section 6.8).

The proportion of 6MWT responders was compared using logistic regression with baseline 6MWT as a covariate and factors of treatment, analysis center, and emphysema distribution. A subject was classified as a 6MWT responder if the 12-month change from baseline in 6MWT was at least 25 meters (Holland 2010).

For SGRQ and FEV_1 continuous secondary endpoints, the inferential p-values comparing the 2 groups were computed following the same methodology specified for the primary variable, using the appropriate baseline values as covariates. Due to significant skewness (see Section 6.5.1.2), the analysis of the secondary endpoint, percent change in FEV_1, was based on non-parametric methods, with accompanying median values, as described for the primary endpoint. The proportion of SGRQ responders was evaluated as described above for 6MWT responder analysis, using baseline SGRQ as a covariate. A subject was classified as an SGRQ responder if the 12-month change from baseline was at least −4 points (Jones 2005, Cazzola 2008, FDA 2018 COPD Guidance "Chronic Obstructive Pulmonary Disease: Use of the St. George's Respiratory Questionnaire as a PRO Assessment Tool").

P-values for hypothesis tests that were not based on pre-specified statistical adjustments for multiplicity are denoted as 'nominal' p-values to indicate the familywise type I error for these multiple statistical tests was not controlled

Other effectiveness endpoints were tested for their statistical significance on both ITT and PP populations, with one-sided tests at α=0.025, without adjustment for multiplicity, using the same methodology as for the secondary endpoints and using the corresponding covariate variable(s).

6.1.4.2. Safety Endpoints

The safety variables included the incidence and severity of adverse events (AEs), including device and/or procedure-related AEs. All reported AEs were summarized by treatment group. Frequency counts and percentage (%) of subjects within each classification category are provided by treatment group. Statistical comparisons between treatment groups were evaluated

with the Fisher's Exact test for AE categories that have an incidence of more than five percent in either treatment group.

The primary safety endpoint, the proportion of subjects in each treatment group who experienced 1 or more Major Complication(s), was reported along with exact 95% confidence intervals. A statistical comparison between the proportions of subjects in each treatment group was evaluated using Fisher's exact test. Additionally, Major Complication event rates were computed using Poisson regression so that each subject's follow-up time could be considered along with event counts. Summary tabulations are presented by treatment arm.

Pass/fail criteria were not pre-specified for the primary safety analysis. The MC rate at 12 months in the Treatment group compared to the Control group was to be considered during benefit-risk analysis in light of benefits in quality of life, lung function, and/or exercise capacity provided by ELEVAIR System treatment.

6.1.4.3. Subgroup Analyses

The following subgroup analyses were pre-specified in the SAP for the primary and secondary endpoints and analyzed for the ITT population using ANCOVA or logistic regression after MCMC multiple imputation with the corresponding baseline value as a covariate and factors of treatment, analysis center, and emphysema distribution[g]:

- Severity of hyperinflation (RV ≥225% vs. RV <225%)
- Region (US versus Outside the US)
- Emphysema distribution (homogeneous vs. heterogeneous)
- Gender (female vs. male)

6.1.5. External Evaluation Groups

Four external evaluation groups were utilized during the conduct of the RENEW Pivotal trial. The Core Radiology Lab was responsible for instructing study sites in correct acquisition of HRCT scans, performing study eligibility assessment during Screening, and developing the ELEVAIR Coil treatment plan for each enrolled subject based on assessment of lobar damage via HRCT. A Data Monitoring Committee (DMC) was established to act in an independent, expert, and advisory capacity to regularly review all adverse event data and monitor overall subject safety. A Clinical Events Committee (CEC) was responsible for the independent assessment and adjudication of safety data per the definition of Major Complications in the protocol. Finally, Pulmonary Function Experts were contracted by PneumRx to assess the qualifications and competency of individuals performing PF testing at RENEW Trial sites, with the goal of ensuring the accuracy and reproducibility of pulmonary function testing performed during the RENEW Trial.

[g] Although the analysis was pre-specified, the addition of analysis center as a factor was added in response to feedback received from FDA.

6.1.6. Inclusion and Exclusion Criteria

The full list of inclusion and exclusion criteria are provided in the RENEW clinical protocol (Attachment 5). Key inclusion criteria for the RENEW Trial included:

- CT scan indicates bilateral emphysema, as determined by the Core Radiology Lab using the criteria presented in the "CT Scoring Plan for Core Radiology Lab".
- Subject had post-bronchodilator FEV_1 ≤45% predicted
- Subject had RV ≥175% predicted
  (This inclusion criterion was broadened from the original criterion of RV ≥225% during study enrollment, as described in Section 6.1.1).
- Subject had marked dyspnea, scoring ≥2 on mMRC (modified Medical Research Council) scale of 0-4.
- 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.
- 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.

Key exclusion criteria for the RENEW Trial included:

- Subject had Diffusion Capacity of the Lung for Carbon Monoxide (DLCO) <20% of predicted.
- Subject had a history of recurrent clinically significant respiratory infections, defined as 3 hospitalizations for respiratory infection during the year prior to enrollment.
- Subject had severe pulmonary hypertension defined by right ventricular systolic pressure >50 mm Hg via right heart catheterization and/or echocardiogram.
- Subject had clinically significant bronchiectasis.
- 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.

6.1.7. Randomization

Subjects were block randomized to Treatment (ELEVAIR System plus optimal medical therapy) or Control (optimal medical therapy alone) groups at a ratio of 1:1, stratified by heterogeneous or homogeneous emphysema to ensure a balance of subjects with each type of disease in both study arms.

6.1.8. Description of Study Treatment

Subjects in both the Treatment and Control groups received standard of care pharmacologic treatment per the latest GOLD guidelines.

Each subject in the Treatment group was scheduled for bilateral treatment (i.e., Coils implanted in both lungs, one lobe per lung and per the Treatment plan communicated to the Investigators by the Core Radiology Lab), with a 4-month interval between treatments. This extended interval was intended to ensure sufficient time for the majority of peri-procedural adverse events to

resolve prior to second treatment. The lung lobe selected for each treatment was determined through scoring of the subject's pre-treatment CT and selecting the upper or lower lobe with the greatest emphysematous damage in each lung for treatment. In cases where upper and lower lobes were scored as having the same degree of emphysematous damage, the upper lobe was selected for treatment. Each treatment included bronchoscopy under general anesthesia or moderate sedation and Coil placement according to the Instructions for Use. Only a single lung lobe was treated within each individual treatment. The subjects remained in the hospital under observation per standard hospital practice. Since the therapy with the ELEVAIR System targets local diseased regions of the lung, multiple Coils are necessary to achieve adequate effect. The suggested Coil dose for RENEW was 10 to 12 Coils for treatment of an upper lobe and 10 to 14 Coils for a lower lobe, which are larger, with some variation expected based on each individual subject's lung anatomy.

6.1.9. Summary of Follow-up Schedule and Evaluations

After treatment, each Treatment group subject was scheduled to be followed for 5 years, and each Control group subject was scheduled to be followed for 12 months, with a 12-month primary safety and effectiveness evaluation. To support similar levels of attention and care for both study arms, Control group subjects underwent the same schedule of visits and assessments through 12 months as the Treatment group, except they did not undergo any treatments or procedures associated specifically with Coil placement, including bronchoscopies, prophylactic antibiotic and steroid treatment, chest X-rays post Coil placement, or 12-month CT scan. All RENEW subjects, regardless of study arm, received optimal medical therapy, per the treating physician determination, which included maintenance bronchodilator therapy (inhaled long-acting β-agonist bronchodilator, inhaled anticholinergic bronchodilator, or both), which could be combined with theophylline and/or inhaled corticosteroids at the physician's discretion.

To avoid bias in endpoint data collection, a qualified and trained "blinded assessor", who had no knowledge of subject treatment assignment, performed all 6MWT and pulmonary function testing during the RENEW Trial. If possible, the same blinded assessor conducted all evaluations for any individual study subject, especially the assessments performed during the baseline and 12-month follow-up visits. A questionnaire was used to confirm blinding of assessors.

Information on AEs was collected during all study visits.

6.2. Subject Accountability

The RENEW Trial began enrollment on December 3, 2012, and subject enrollment was completed on October 10, 2014. Thirty-four (34) study sites screened 731 subjects for this study. 315 subjects were enrolled, with 158 subjects randomized to the Treatment group and 157 subjects randomized to the Control group. These subjects were treated at 26 investigational sites located in the US, Canada, and EU, as shown in Supplemental Table 1 (Attachment 1). An additional 46 subjects were treated with ELEVAIR Coils as Roll-In subjects

and were not included in the RENEW Trial analysis (see Section 7.2 for further information on Roll-In subject outcomes).

The disposition of subjects screened and randomized into the RENEW Trial is presented in Figure 8. Of 315 subjects enrolled, 283 subjects (90%) completed the 12-month follow-up period, 14 subjects withdrew or were lost to follow-up prior to completing the follow-up period (7 Treatment group, 7 Control group), and 18 subjects died (10 Treatment group, 8 Control group) (Table 1).

Follow-up in the RENEW Trial is complete through 24 months post treatment 1. 114 Treatment group subjects completed the 24-month follow-up visit. As of the cutoff date for this clinical summary (July 17, 2017), 36-month follow-up is ongoing, with 49 Treatment group subjects having completed the 36-month visit.

The disposition of subjects in the RV ≥225% subpopulation is summarized in Supplemental Table 2 (Attachment 1). 235 subjects with RV ≥225% were enrolled, with 115 in the Treatment group and 120 in the Control group. No notable differences were seen between the RV ≥225% and ITT populations with respect to proportions of subjects available for follow-up at 12 months or reasons for study discontinuation.

Figure 8. Subject Disposition Through 12 Months [RENEW]

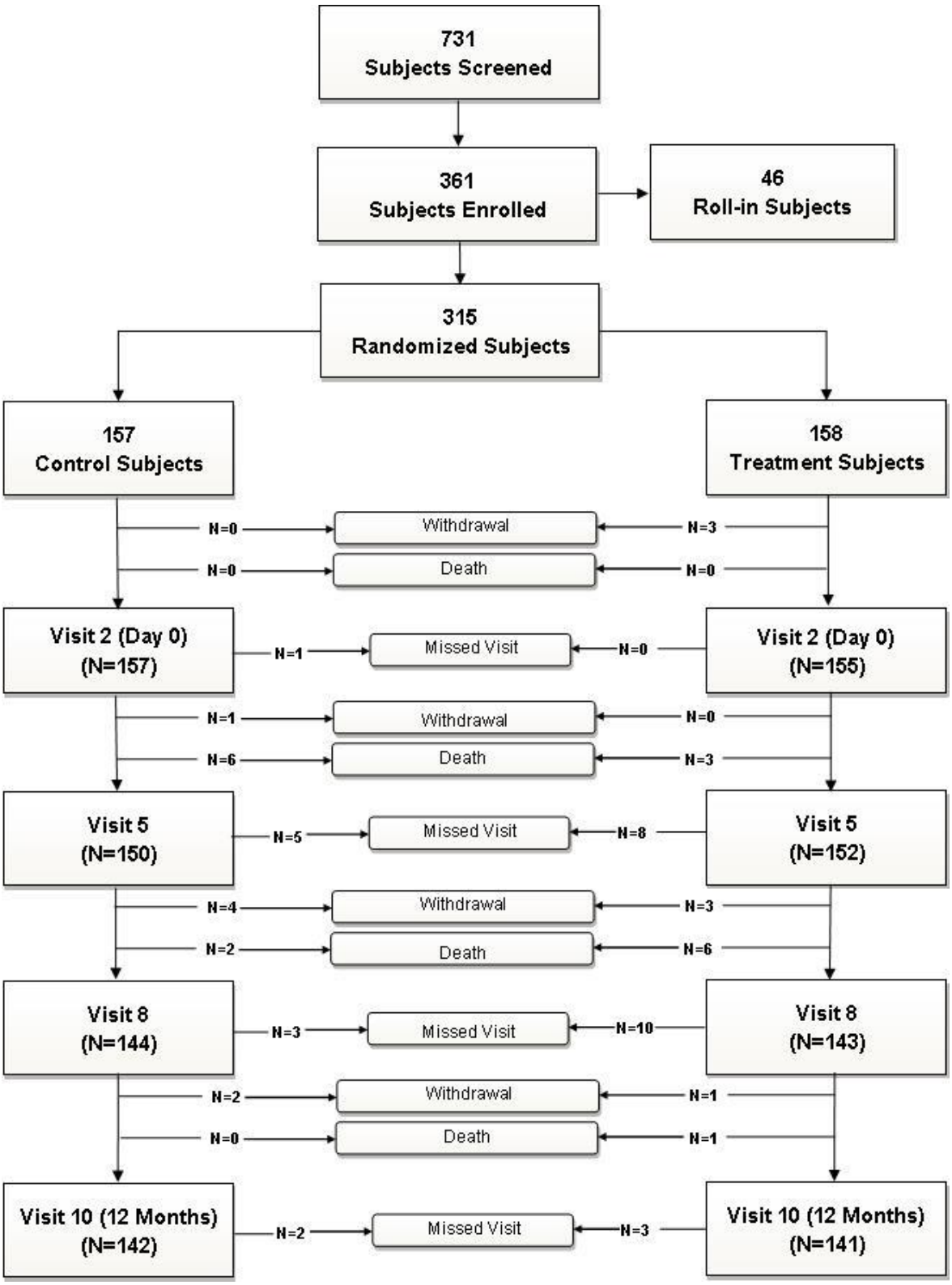


Table 1. Subject Disposition, All Screened Subjects [RENEW]

Subject Status	Treatment	Control	Total
Number of subjects, n			
Screened			731
Screen failed			346
Randomized	158	157	315
Randomized but not treated	3	0	3
Enrolled as Roll-In	46	n/a	46
Populations, n			
ITT	158	157	315
Safety	155	157	312
PP	132	143	275
Subjects who completed study to 12 months, %	89.2% (141/158)	90.4% (142/157)	89.8% (283/315)
Subjects who attended 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, n	10	8	18
Subjects lost to follow-up, n	0	2	2
Subjects who withdrew consent, n	4	1	5
Subjects withdrawn by investigator, n	3	4	7
Subjects who completed study to 24 months, %	89.4% (126/141)	n/a	89.4% (126/141)
Subjects who attended 24-month visit, %	80.9% (114/141)	n/a	80.9% (114/141)
Subjects who completed study to 36 months, %	43.7% (55/126)[1]	n/a	43.7% (55/126)[1]
Subjects who attended 36-month visit, %	38.9% (49/126)[1]	n/a	38.9% (49/126)[1]

1 36-month follow-up ongoing as of date of data cutoff.

6.3. Subject Demographics and Baseline Disease Characteristics

Subject demographics and baseline disease characteristics are presented in this section for the entire RENEW Trial population. At the completion of enrollment, the majority of subjects met the original protocol enrollment criteria for RV: 74.6% of subjects had baseline RV ≥225% predicted (i.e., severe hyperinflation), and 25.4% had baseline RV <225% predicted. As a result, the demographics and baseline characteristics for the RV ≥225% subpopulation are similar to those of the entire population, although as expected average RV% predicted, TLC, and RV/TLC are increased. Demographics and baseline characteristics for the RV ≥225% subpopulation are provided in Supplemental Tables 3 and 4 (Attachment 1).

Baseline demographics for the ITT population are summarized in Table 2. There were no statistically significant differences between study arms in any of the demographic characteristics. Demographics in the PP population were similar to those in the ITT population for both study groups.

Table 2. Baseline Demographics, ITT Population [RENEW]

Demographic Characteristic	Treatment (N=158)	Control (N=157)	p-value
Age (years), mean ± SD	63.4 ± 8.1	64.3 ± 7.8	0.4532
Gender, % (n)			0.2741
Female	54.4% (86)	50.3% (79)	
Male	45.6% (72)	49.7% (78)	
BMI (kg/m^2), mean ± SD	24.9 ± 4.6	24.5 ± 4.9	0.2432
Ethnicity, % (n)			0.3225
Hispanic or Latino	0.6% (1)	1.3% (2)	
Not Hispanic or Latino	99.4% (157)	98.7% (155)	
Race, % (n)			0.2890
American Indian or Alaska Native	0.0% (0)	0.0% (0)	
Black or African American	3.8% (6)	2.5% (4)	
Asian	0.0% (0)	0.6% (1)	
White	95.6% (151)	96.8% (152)	
Native Hawaiian or Other Pacific Islander	0.0% (0)	0.0% (0)	
Other	0.6% (1)	0.0% (0)	

Baseline disease characteristics for the ITT population are summarized in Table 3. Subjects randomized in the RENEW Trial represented a group of patients with severe (GOLD 3, 26% of subjects) and very severe (GOLD 4, 74% of subjects) emphysema, with both homogeneous (77% of subjects) and heterogeneous (23% of subjects) emphysema distribution. The RENEW population had substantial airflow restriction (FEV_1 approximately 26% of predicted value) and hyperinflation (RV approximately 245% of predicted value) and, as is common in the severe emphysema population, most subjects had been diagnosed with multiple chronic comorbid conditions.

There were no significant differences between the Treatment and Control groups in post-bronchodilator spirometry, lung volumes, or diffusion capacity. A statistically significant between-group difference in cardiac comorbidity at baseline was noted, with the Treatment group having the higher rate of comorbidity (25.9% vs. 17.8%). The difference in mean SGRQ scores in the Treatment group compared to the Control group approached statistical significance in the ITT analysis (mean 60.1 vs. 57.4; p=0.0503) and was statistically different in the PP population (p=0.0379), indicating a potentially more symptomatic group in the Treatment arm at baseline. Apart from cardiac comorbidity and SGRQ, there were no notable differences in baseline characteristics between the ITT and PP populations.

Table 3. Baseline Disease Characteristics, ITT Population [RENEW]

Disease Characteristic	Treatment (N=158)	Control (N=157)	P-value
6MWT (meters), mean ± SD	312.0 ± 79.9	302.7 ± 79.3	0.8137
Emphysema Distribution, % (n)			0.7105
Heterogeneous	22.8% (36)	22.9% (36)	
Homogeneous	77.2% (122)	77.1% (121)	
Post-bronchodilator Spirometry, mean ± SD			
FVC % Predicted	67.8 ± 14.3	67.4 ± 15.0	0.6414
FEV_1 % Predicted	25.7 ± 6.3	26.3 ± 6.7	0.4807
FEV_1/FVC (%)	28.8 ± 6.8	29.9 ± 6.8	0.0544
Post-bronchodilator Lung Volumes, mean ± SD			
RV % Predicted	245.9 ± 39.1	244.5 ± 38.7	0.9103
TLC % Predicted	139.2 ± 15.6	138.8 ± 16.1	0.7240
RV/TLC Measured (%)	67.1 ± 6.7	67.3 ± 6.3	0.3988
Diffusion Capacity (DLCO) % Predicted, mean ± SD	34.1 ± 10.5	34.5 ± 10.7	0.7091
Quality of Life			
SGRQ Total Score, mean ± SD	60.1 ± 12.8	57.4 ± 14.8	0.0503
mMRC Dyspnea Scale, % (n)			0.8747
0	0.0% (0)	0.0% (0)	
1	0.0% (0)	0.0% (0)	
2	34.2% (54)	35.7% (56)	
3	43.7% (69)	44.6% (70)	
4	22.2% (35)	19.7% (31)	
Other Subject Characteristics			
GOLD 4, % (n)	75.9% (120)	71.3% (112)	0.4770
BODE Score, mean ± SD	5.97 ± 1.26	6.04 ± 1.32	0.8412
Smoking Pack Year History, mean ± SD	50.7 ± 27.9	50.3 ± 23.5	0.5798
Number of Comorbidities[1], mean ± SD	2.6 ± 2.0	2.3 ± 1.8	0.0720
Number of Comorbidities[1], % (n)			0.2733
0-3	71.5% (113)	75.2% (118)	
≥4	28.5% (45)	24.8% (39)	
Cardiac Comorbidity[2]			0.0226
Yes	25.9% (41)	17.8% (28)	
No	74.1% (117)	82.2% (129)	

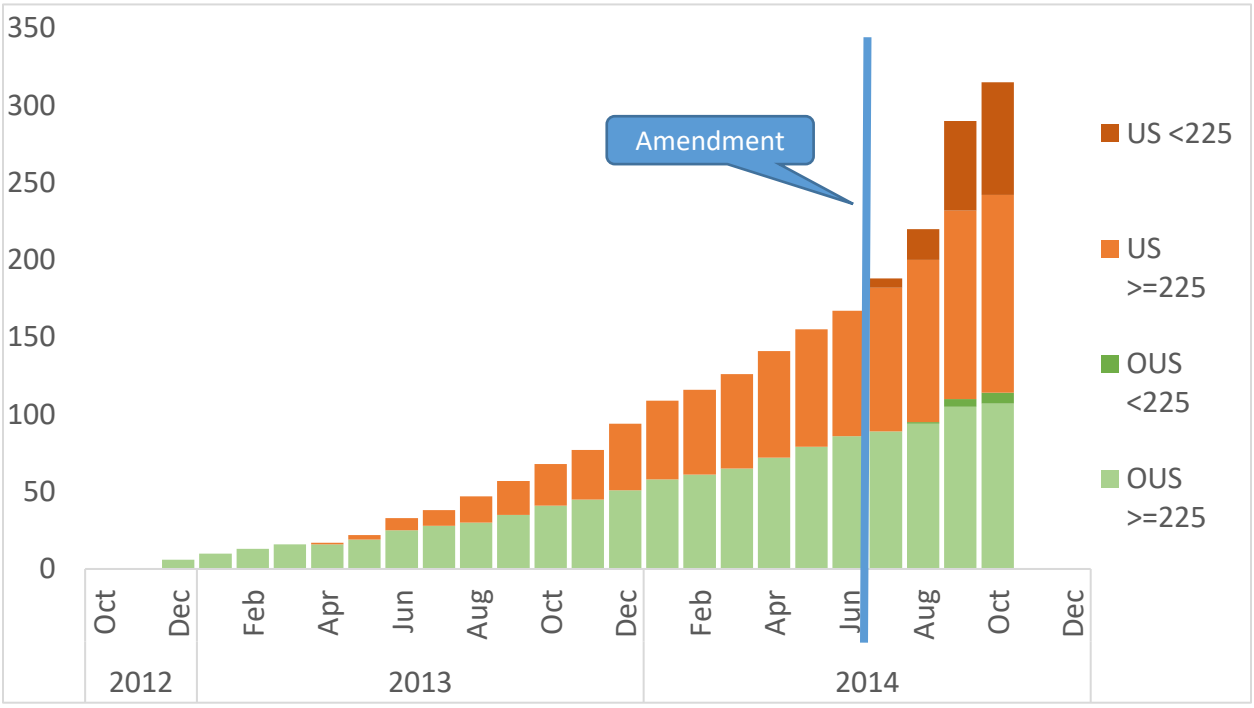
1 Comorbidities include Arthritis, Cachexia (BMI <18.5 kg/m^2), Cardiac Disease (Angina, Atrial Fibrillation, Congestive Heart Failure, or Coronary Artery Disease), Depression, Diabetes, Edema, GERD, Hyperlipidemia, Hypertension, Obesity (BMI >30 kg/m^2), Osteoporosis, Peripheral Vascular Disease, Renal Dysfunction, Sleep Apnea, and Stroke.

2 Cardiac comorbidities include Angina, Atrial Fibrillation, Congestive Heart Failure, and Coronary Artery Disease.

It is important to note, however, that the timing of the RENEW protocol amendment reducing the eligibility criterion from RV ≥225% to RV ≥175% did result in unbalanced enrollment of subjects with RV <225% between US and OUS sites. Because the OUS sites participating in the RENEW Trial had nearly reached their enrollment targets at the time of the protocol amendment, nearly all the subjects with RV <225% (91.3%, 73/80) were enrolled in the US (see Figure 9 below). Indeed, subjects with lower RV constituted over one-third of the total US enrollment in RENEW (36.3%, 73/201). In comparison, subjects with lower RV only represented 6% (7/114) of the enrolled OUS study population. This imbalance in subjects with severe hyperinflation likely affected the results of the subgroup analysis by region in the ITT

population (discussed in Section 6.5.1.4). Reference Supplemental Table 5 (Attachment 1) for a comparison of key demographics and baseline characteristics in US and OUS subjects.

Figure 9. RENEW Pivotal Trial Enrollment (ITT) by Region and Residual Volume



6.4. Procedural Results

Procedural results for the Treatment group in the RENEW Trial are summarized in Table 4. The Control group in the RENEW Trial received optimal medical therapy alone (no bronchoscopy or Coil placement). Therefore, procedural results are reported for the Treatment group only.

299 ELEVAIR System procedures were performed in the 155 subjects in the Treatment group, with 92.9% (144/155) of Treatment group subjects treated bilaterally. Eleven (11) subjects were treated unilaterally; 8 were the result of worsening condition or ongoing AEs that prevented second treatment, and 3 subjects died prior to the second treatment. The mean (SD) procedure time (from bronchoscope insertion to removal) was 42 (16) minutes.

The total number of Coils implanted was 3132, with approximately 10 Coils implanted per procedure. Procedural results for the first and second procedure were very similar (Table 4). 84.3% of procedures were performed in the upper lobes, with approximately equal distribution right/left. The mean number of Coils per lobe was slightly greater in the lower lobe procedures, as anticipated given their larger size. Most of the Coils used were either 100mm (44.1%) or 125mm (49.4%).

In the vast majority of cases (93.3%, 279/299 procedures), subjects were discharged from the hospital by the day following the procedure.

Table 4. Procedural Results and Device Usage, ITT Population [RENEW]

Procedural Characteristic	1st Procedure (N=155) (M=1613)	2nd Procedure (N=144) (M=1519)	Overall (N=299) (M=3132)
Procedure duration (minutes[1]), mean ± SD (n)	43.2 ± 16.4 (155)	40.9 ± 16.2 (144)	42.1 ± 16.3 (299)
Fluoroscopy time (minutes), mean ± SD (n)	13.5 ± 8.6 (152)	12.9 ± 8.3 (144)	13.2 ± 8.4 (296)
Post-procedure hospital stay (days[1]), mean ± SD (n)	2.0 ± 0.5 (154)	2.1 ± 1.4 (144)	2.1 ± 1.0 (298)
Implant locations (n)			
Left Lower Lobe	1.9% (3)	15.3% (22)	8.4% (25)
Left Upper Lobe	12.3% (19)	70.1% (101)	40.1% (120)
Right Lower Lobe	12.3% (19)	2.1% (3)	7.4% (22)
Right Upper Lobe	73.5% (114)	12.5% (18)	44.1% (132)
Number of coils implanted by sizes (m)			
100 mm	46.7% (754)	41.3% (627)	44.1% (1381)
125 mm	46.9% (757)	51.9% (789)	49.4% (1546)
150 mm	6.3% (102)	6.8% (103)	6.5% (205)
Number of coils implanted by location, per procedure, mean ± SD (n)			
Right Upper	10.0 ± 0.9 (114)	10.2 ± 0.5 (18)	10.0 ± 0.9 (132)
Left Upper	10.0 ± 0.3 (19)	10.1 ± 0.9 (101)	10.1 ± 0.8 (120)
Right Lower	12.8 ± 2.2 (19)	10.3 ± 2.9 (3)	12.5 ± 2.4 (22)
Left Lower	13.0 ± 1.0 (3)	13.0 ± 1.3 (22)	13.0 ± 1.2 (25)
Number of coils per procedure, mean ± SD (n)	10.4 ± 1.5 (155)	10.5 ± 1.4 (144)	10.5 ± 1.5 (299)

1 Procedure duration counted as the time between bronchoscope insertion and removal.

2 Day of procedure counted as day 1.

Note: N = total number of procedures; n = number of procedures in a specific category; M = total number of Coils implanted, m = number of Coils in a specific category.

6.5. Effectiveness Results

6.5.1. Effectiveness Endpoints in ITT Population (Total Enrolled Trial Population)

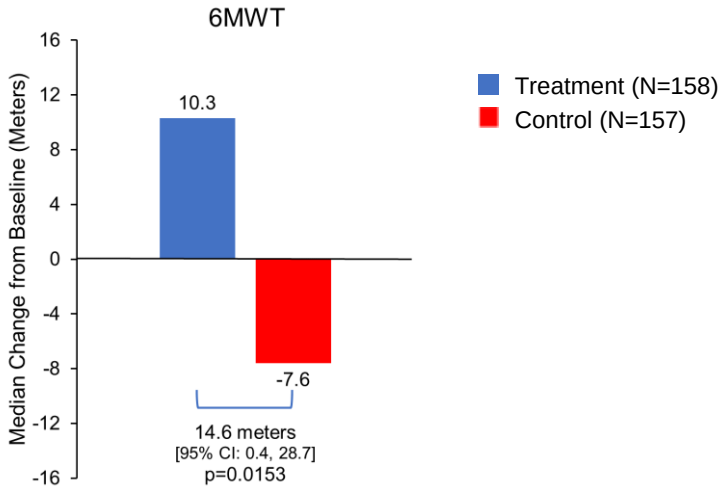
All effectiveness endpoint analyses were met in the ITT population in the RENEW Pivotal Trial.

6.5.1.1. Primary Effectiveness Endpoint in ITT Population (Total Enrolled Trial Population)

The primary effectiveness endpoint for the RENEW Trial was the absolute change from baseline in the Six-Minute Walk Test (6MWT) at 12 months, in the Treatment group versus the Control group. The analysis was performed for both the ITT and PP populations, with the primary analysis based on the ITT population. As defined in the SAP, a non-parametric analysis method and median values were used to evaluate and report the primary effectiveness endpoint due to significant skewness in the 6MWT data (Shapiro-Wilk normality test $p<0.0001$).

The primary effectiveness endpoint analysis of the RENEW Trial was met ($p=0.0153$; Figure 10). ITT subjects in the Treatment group exhibited a median improvement in 6MWT versus the Control group of 14.6 meters (adjusted mean 10.2 meters) at 12 months compared to baseline. The PP analysis also showed statistical significance in the primary endpoint (rank ANCOVA nominal $p=0.0093$).

Figure 10. Primary Effectiveness Outcome, ITT Population [RENEW][a]



[a]Absolute change from baseline to 12 months in 6MWT after multiple imputation. Due to skewness of the data, p-value is based on rank ANCOVA. Note that the nonparametric median between-group difference is not the simple between-group difference in medians. Additional detail, including results from the parametric analysis method (ANCOVA), is provided in Supplemental Table 6 (Attachment 1).
Note: This plot was not provided within the PMA; however, the underlying information / analysis was provided in the PMA application to FDA.

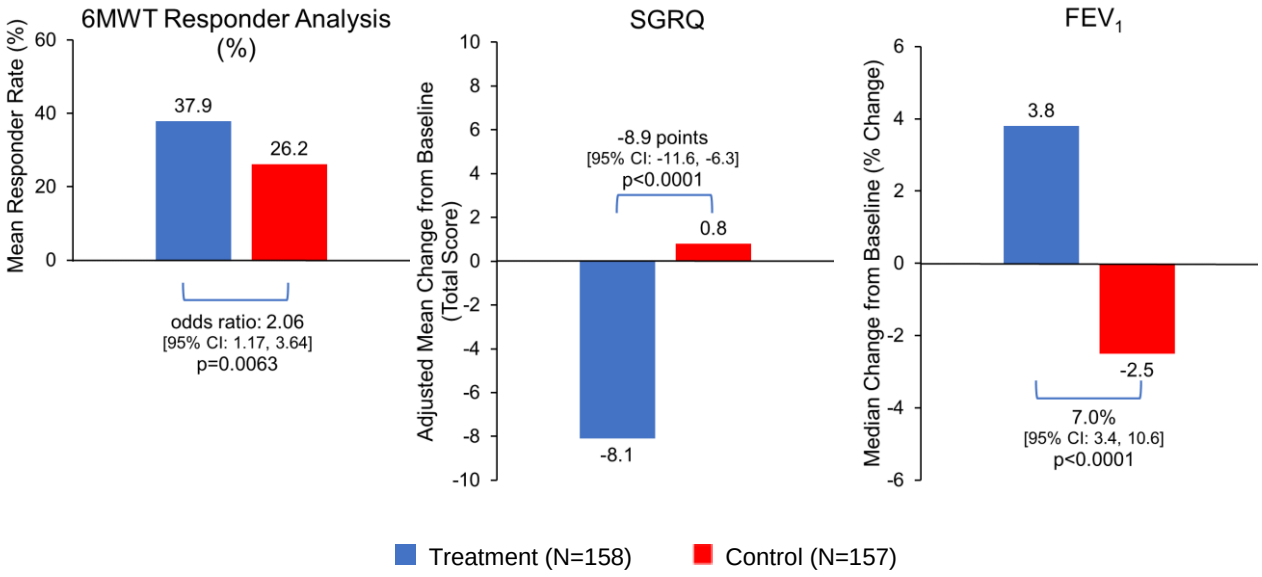
6.5.1.2. Secondary Effectiveness Endpoints in ITT Population (Total Enrolled Trial Population)

The secondary effectiveness endpoints for the RENEW Trial compared Treatment and Control group improvements at 12 months versus baseline in 6MWT responder rate (response defined as improvement of at least 25 meters [Holland 2010]), SGRQ, and FEV_1. For each of the secondary endpoints, the primary analysis was performed on the ITT population.

All secondary effectiveness endpoint analyses for the RENEW Trial were met (Figure 11). A significantly higher proportion of Treatment group subjects were 6MWT responders compared to Control (p=0.0063), with mean responder rates of 37.9% and 26.2% in Treatment and Control groups, respectively. The Treatment group demonstrated an adjusted mean improvement of −8.9 points in SGRQ total score compared to the Control group (p<0.0001). Due to significant skewness (Shapiro-Wilk normality test p<0.0001), the primary analysis for FEV_1 was based on rank ANCOVA, as described for the primary effectiveness endpoint. The median between-group (Treatment versus Control) difference in FEV_1 at 12 Months was 7.0% (p<0.0001), with an adjusted mean between-group difference of 8.8%. Additional analyses of FEV_1 responder rates, using the MCID of 10% (Donohue 2005, Cazzola 2008, Jones 2014) as the response

threshold, showed adjusted mean responder rates of 40.2% and 15.7% in Treatment and Control groups, respectively.[h]

Figure 11. Secondary Effectiveness Outcomes, ITT Population [RENEW][a]



[a]6MWT responder analysis, SGRQ absolute change from baseline, and FEV_1 percent change from baseline at 12 months after multiple imputation. Due to skewness in the FEV_1 data, p-value for FEV_1 is based on rank ANCOVA. Note that the nonparametric median between-group difference is not the simple between-group difference in medians.
Note: These plots were not provided within the PMA; however, the underlying information / analysis was provided in the PMA application to FDA.

6.5.1.3. Other Effectiveness Endpoints in ITT Population (Total Enrolled Trial Population)

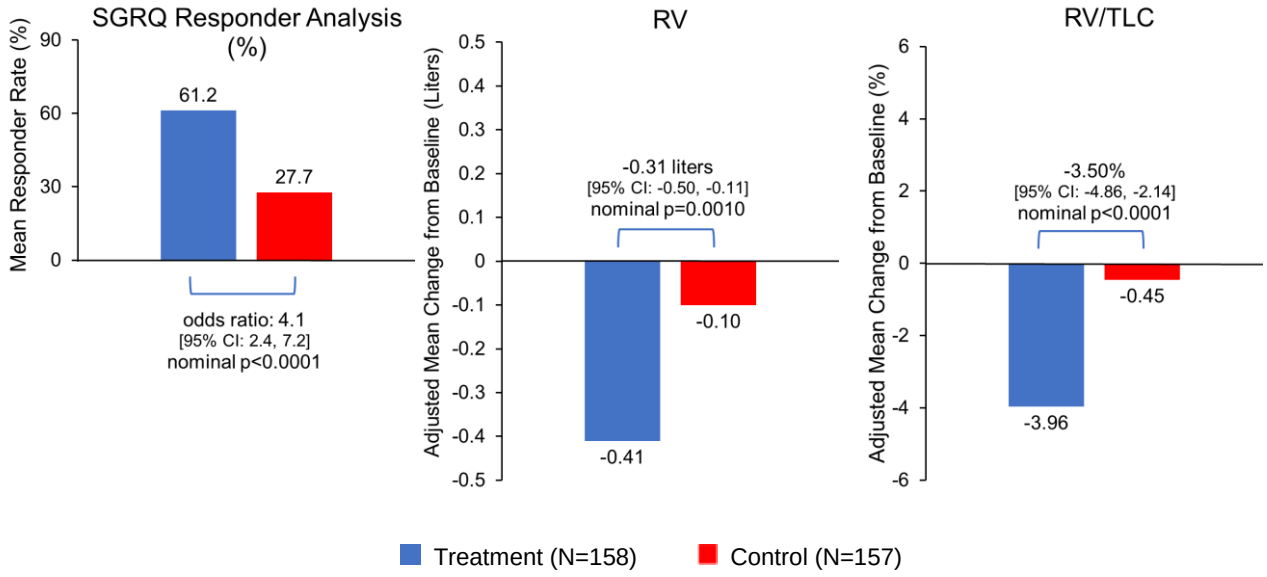
Other effectiveness endpoints for the RENEW Trial compared Treatment and Control group improvements at 12 months versus baseline in SGRQ responder rate (response defined as improvement of at least 4 points in SGRQ total score [Jones 2005, Cazzola 2008, FDA COPD Guidance "Chronic Obstructive Pulmonary Disease: Use of the St. George's Respiratory Questionnaire as a PRO Assessment Tool"]), RV, and RV/TLC without control for multiplicity. As with the other RENEW endpoints, the primary analysis for each of these additional endpoints was performed on the ITT population.

All additional effectiveness endpoint analyses for the RENEW Trial were in favor of Treatment (Figure 12). 61.2% of Treatment group subjects, compared to 27.7% of Control group subjects, experienced an improvement of 4 points or more in SGRQ (nominal p<0.0001). Following treatment with the ELEVAIR System, subjects in the Treatment group showed substantial

[h] FEV_1 responder analysis was not a pre-specified secondary endpoint and was conducted as an exploratory analysis.

improvements in hyperinflation by a reduction in RV of 0.31 liters (nominal p=0.0010) and a reduction in RV/TLC of 3.5% (nominal p<0.0001), compared to the Control group.

Figure 12. Other Effectiveness Outcomes, ITT Population [RENEW][a]



[a]SGRQ responder analysis, RV absolute change from baseline, and RV/TLC absolute change from baseline at 12 months after multiple imputation. Nominal p-values unadjusted for multiplicity are reported.
Note: These plots were not provided within the PMA; however, the underlying information / analysis was provided in the PMA application to FDA.

6.5.1.4. Additional Analyses in ITT Population (Total Enrolled Trial Population)

The following subgroup analyses, pre-specified in the RENEW statistical analysis plan, were conducted for the primary and secondary effectiveness endpoints:

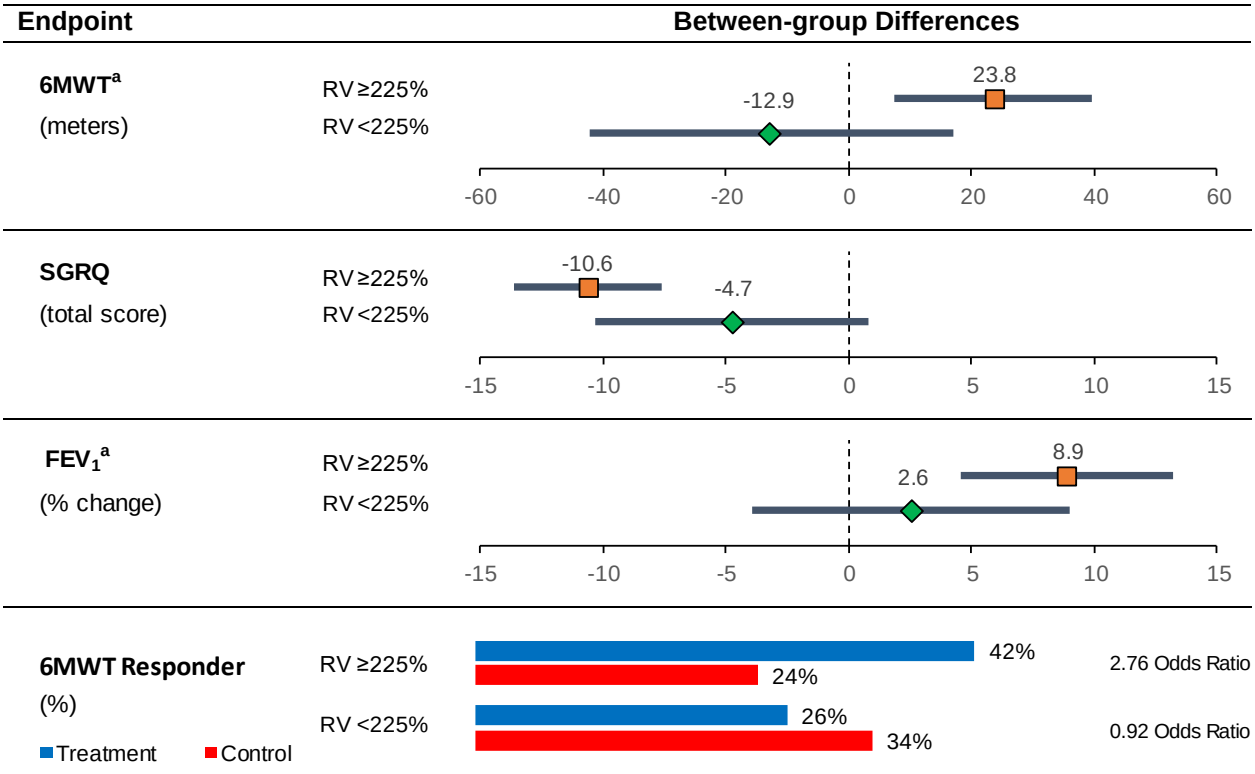
- Severity of hyperinflation (RV ≥225% vs. RV <225%)
- Region (US vs. Outside the US)
- Emphysema distribution (homogeneous vs. heterogeneous)
- Gender (female vs. male)

These pre-specified analyses showed that effectiveness outcomes were more favorable in the RV ≥225% subpopulation compared to the RV <225% subpopulation, and thus were improved when compared to the overall RENEW ITT population (Figure 13 below). The RV ≥225% subpopulation correspond to the originally defined protocol population and represents 75% of all subjects enrolled in RENEW.

Detailed outcomes for the primary, secondary, and other effectiveness endpoints in RV ≥225% subjects, together with post hoc analyses indicating treatment benefit across region (US vs. OUS) and emphysema distribution (homogeneous vs. heterogeneous) in the RV ≥225% subpopulation, are presented in Section 6.5.2. Improved treatment effect in patients with higher

baseline RV is consistent with the mechanism of action of the Coils, which are designed to reduce hyperinflation by compressing diseased lung parenchyma and improving lung elastic recoil. This reduction in hyperinflation leads to improved lung function (i.e., increased FEV_1), which in turn translates into improved clinical benefits to the patient in quality of life (SGRQ) and exercise capacity (6MWT).

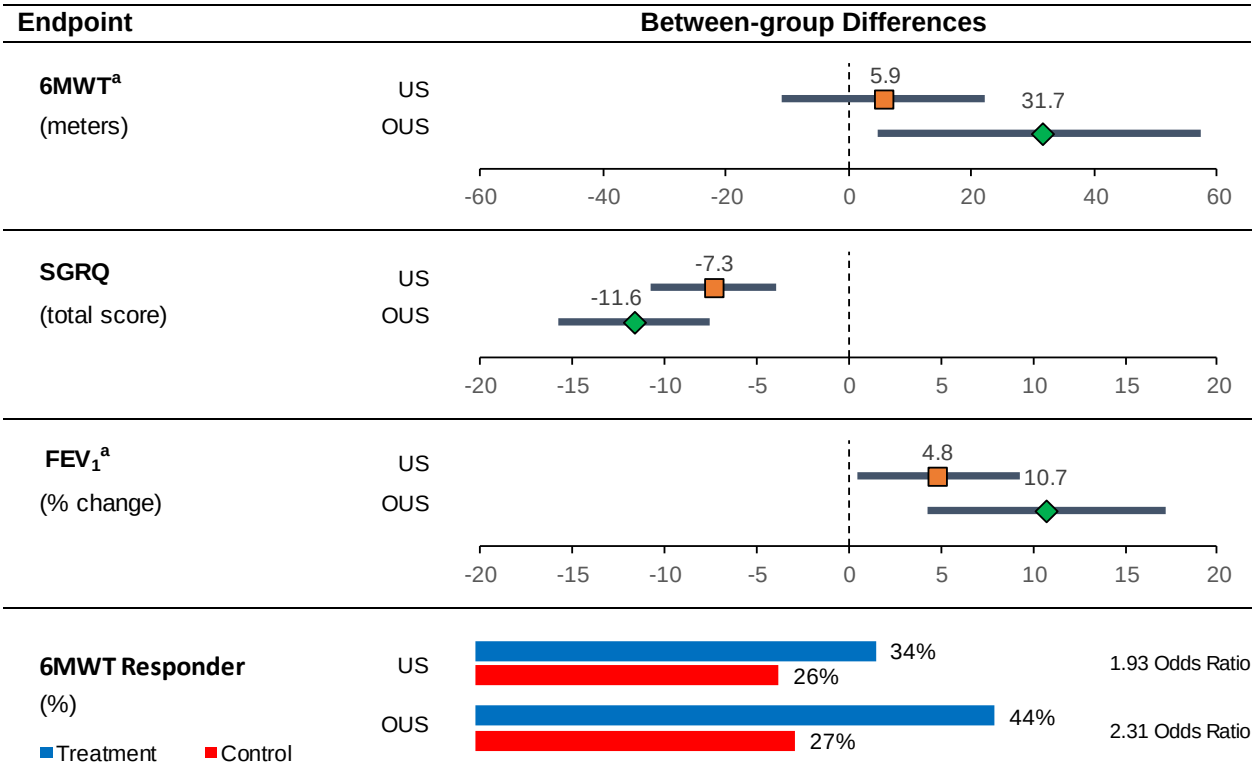
Figure 13. Primary and Secondary Effectiveness Outcomes by Severity of Hyperinflation after Multiple Imputation, ITT Population [RENEW][a]



[a]Between-group difference expressed as median. Subject (n) by subgroup and treatment group: RV ≥225% Treatment (115), RV ≥225% Control (120), RV <225% Treatment (43), RV <225% Control (37).
Note: These plots were not provided within the PMA; however, the underlying information / analysis was provided in the PMA application to FDA.

In addition, greater improvements were observed in OUS subjects in the overall RENEW Trial population (Figure 14). This is driven by the lower proportion of subjects with RV <225% in the OUS population. As described in Section 6.3, the timing of the protocol amendment reducing the eligibility criterion from RV ≥225% to RV ≥175% resulted in a low proportion of subjects with RV <225% in the enrolled OUS study population (6%), and a comparatively high proportion of the RV <225% subpopulation in the US (36.3%).

Figure 14. Primary and Secondary Effectiveness Outcomes by Region after Multiple Imputation, ITT Population [RENEW][a]



[a]Between-group difference expressed as median. Subject (n) by subgroup and treatment group: US Treatment (95), US Control (106), OUS Treatment (63), OUS Control (51).
Note: These plots were not provided within the PMA; however, the underlying information / analysis was provided in the PMA application to FDA.

Post hoc multivariate and subgroup analyses were conducted to further explore the apparent difference in effectiveness based on region (see discussion in Section 6.5.2.5 below). These analyses indicated that the differences were strongly influenced by the differential enrollment by baseline RV. Indeed, the greater number of subjects with relatively low baseline RV (<225% predicted) in the US cohort, with mean RV percent predicted at baseline of 237% in the US compared to 260% in OUS, is now understood to be the driving factor behind the lesser benefits seen with Coil treatment in the US.

Results for the other pre-specified subgroup analyses showed that subjects in the ITT population benefitted from Coil treatment across emphysema distribution (homogeneous vs. heterogeneous) and gender (see Attachment 1, Supplemental Tables 7 and 8).

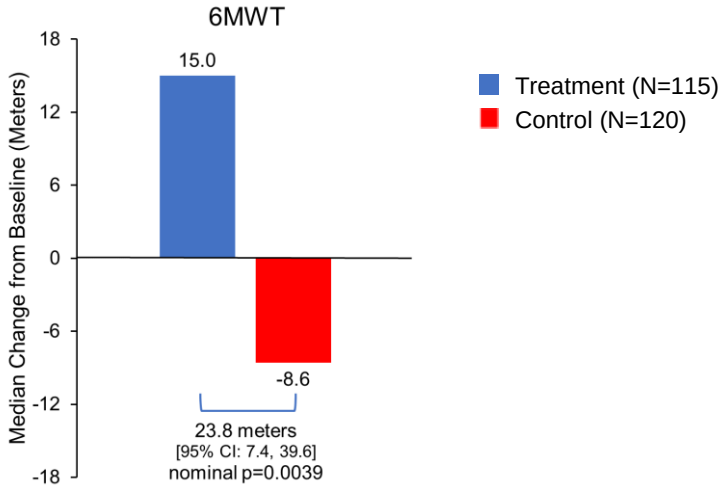
6.5.2. Effectiveness Endpoints in Originally Defined Protocol Population (RV ≥225% Subpopulation)

6.5.2.1. Primary Effectiveness Endpoint in Originally Defined Protocol Population (RV ≥225% Subpopulation)

As in the ITT population, the primary effectiveness endpoint (absolute change in 6MWT at 12 months, Treatment versus Control) was evaluated in the RV ≥225% subpopulation using a non-parametric analysis method (rank ANCOVA), due to significant skewness in the 6MWT data.

The primary effectiveness endpoint analysis of the RENEW Trial in the RV ≥225% subpopulation, showed a greater difference between Treatment and Control groups than was observed in the overall ITT population (nominal p=0.0039) (Figure 15). Subjects in the Treatment group exhibited a median improvement in 6MWT versus the Control group of 23.8 meters (adjusted mean 17.9 meters) at 12 months compared to baseline.

Figure 15. Primary Effectiveness Outcome, RV ≥225% Subpopulation [RENEW][a]



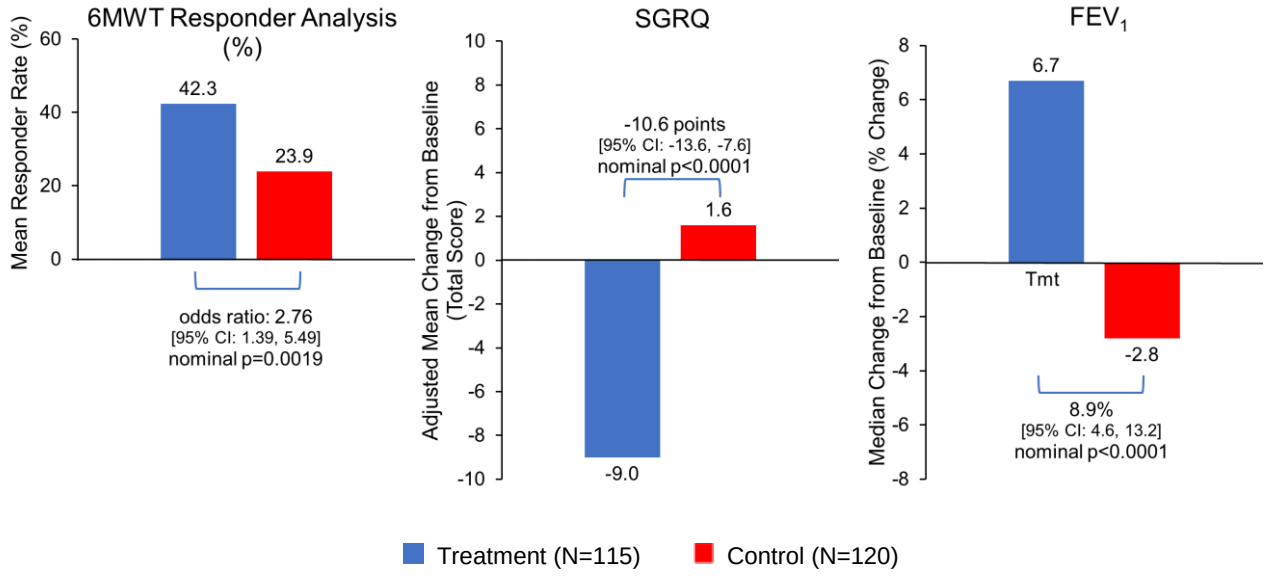
[a]Absolute change from baseline to 12 months in 6MWT after multiple imputation. Due to skewness of the data, nominal p-value is based on rank ANCOVA. Note that the nonparametric median between-group difference is not the simple between-group difference in medians. Additional detail, including results from the parametric analysis method (ANCOVA), is provided in Supplemental Table 9 (Attachment 1).
Note: This plot was not provided within the PMA; however, the underlying information / analysis was provided in the PMA application to FDA.

6.5.2.2. Secondary Effectiveness Endpoints in Originally Defined Protocol Population (RV ≥225% Subpopulation)

The secondary effectiveness endpoints for the RENEW Trial, comparing Treatment and Control group changes at 12 months versus baseline in 6MWT responder rate, SGRQ, and FEV_1, were evaluated for the RV ≥225% subpopulation.

All secondary effectiveness endpoint analyses for the RENEW Trial in the RV ≥225% subpopulation, showed increased differences between Treatment and Control than observed in the overall ITT population (Figure 16). Treatment group subjects experienced substantially higher 6MWT responder rates than Control group subjects (mean responder rates of 42.3% and 23.9%, respectively, nominal p=0.0019). Subjects treated with Coils demonstrated adjusted mean improvement compared to Control subjects of −10.6 points in SGRQ total score (nominal p<0.0001). Due to significant skewness, the primary analysis for FEV_1 was based on rank ANCOVA, as described for the primary endpoint. The median between-group difference in FEV_1 was 8.9% (nominal p<0.0001), with an adjusted mean between-group difference of 11.0%. Analyses of FEV_1 responder rates, using the MCID of 10% (Donohue 2005, Cazzola 2008, Jones 2014) as the response threshold, showed adjusted mean responder rates of 49.4% and 18.7% in Treatment and Control groups, respectively.[i]

Figure 16. Secondary Effectiveness Outcomes, RV ≥225% Subpopulation [RENEW][a]



[a]6MWT responder analysis, SGRQ absolute change from baseline, and FEV_1 percent change from baseline at 12 months after multiple imputation. Nominal p-values are reported without adjustment for multiplicity. Due to skewness in the FEV_1 data, p-value for FEV_1 is based on rank ANCOVA. Note that the nonparametric median between-group difference is not the simple between-group difference in medians.
Note: These plots were not provided within the PMA; however, the underlying information / analysis was provided in the PMA application to FDA.

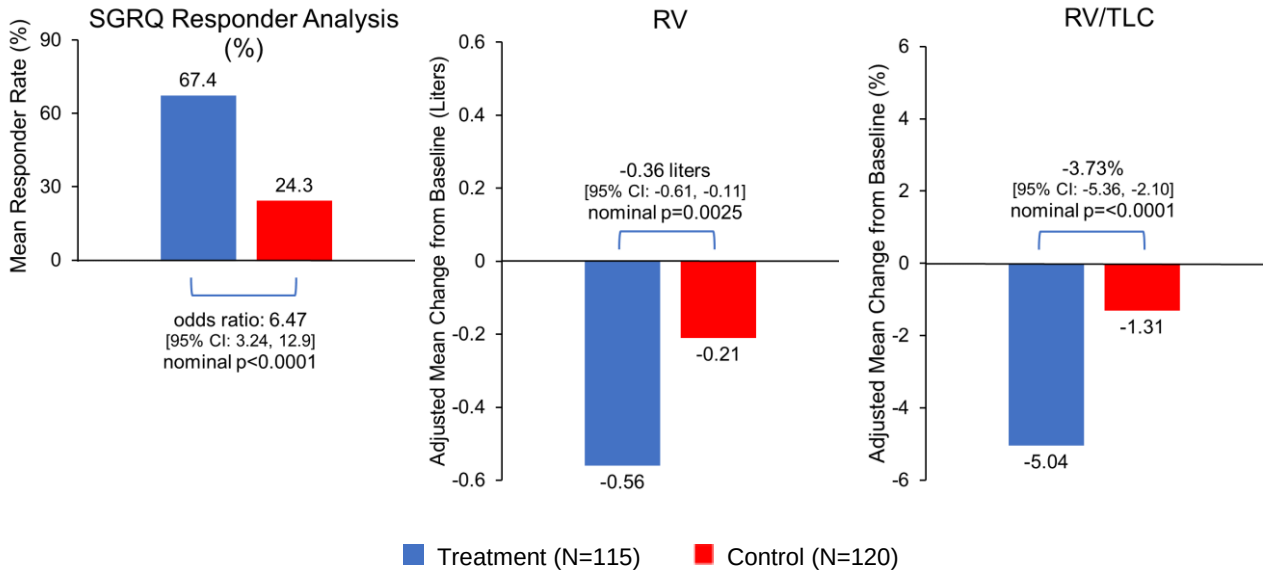
[i] FEV_1 responder analysis was not a pre-specified secondary endpoint and was conducted as an exploratory analysis.

6.5.2.3. Other Effectiveness Endpoints in Originally Defined Protocol Population (RV ≥225% Subpopulation)

All of the other effectiveness endpoints for the RENEW Trial, comparing SGRQ responder rates and improvement in RV and RV/TLC between Treatment and Control group at 12 months versus baseline, were evaluated in the RV ≥225% subpopulation.

Each of these effectiveness endpoint analyses was in favor of Treatment for the RV ≥225% subjects (Figure 17). 67.4% of Treatment group subjects, compared to 24.3% of Control group subjects, experienced an improvement of 4 points or more in SGRQ (nominal p<0.0001). Treatment group subjects also showed substantial improvements in hyperinflation by a reduction in RV of 0.36 liters (nominal p=0.0025) and a reduction in RV/TLC of 3.73% (nominal p<0.0001), compared to the Control group.

Figure 17. Other Effectiveness Outcomes, RV ≥225% Subpopulation [RENEW][a]

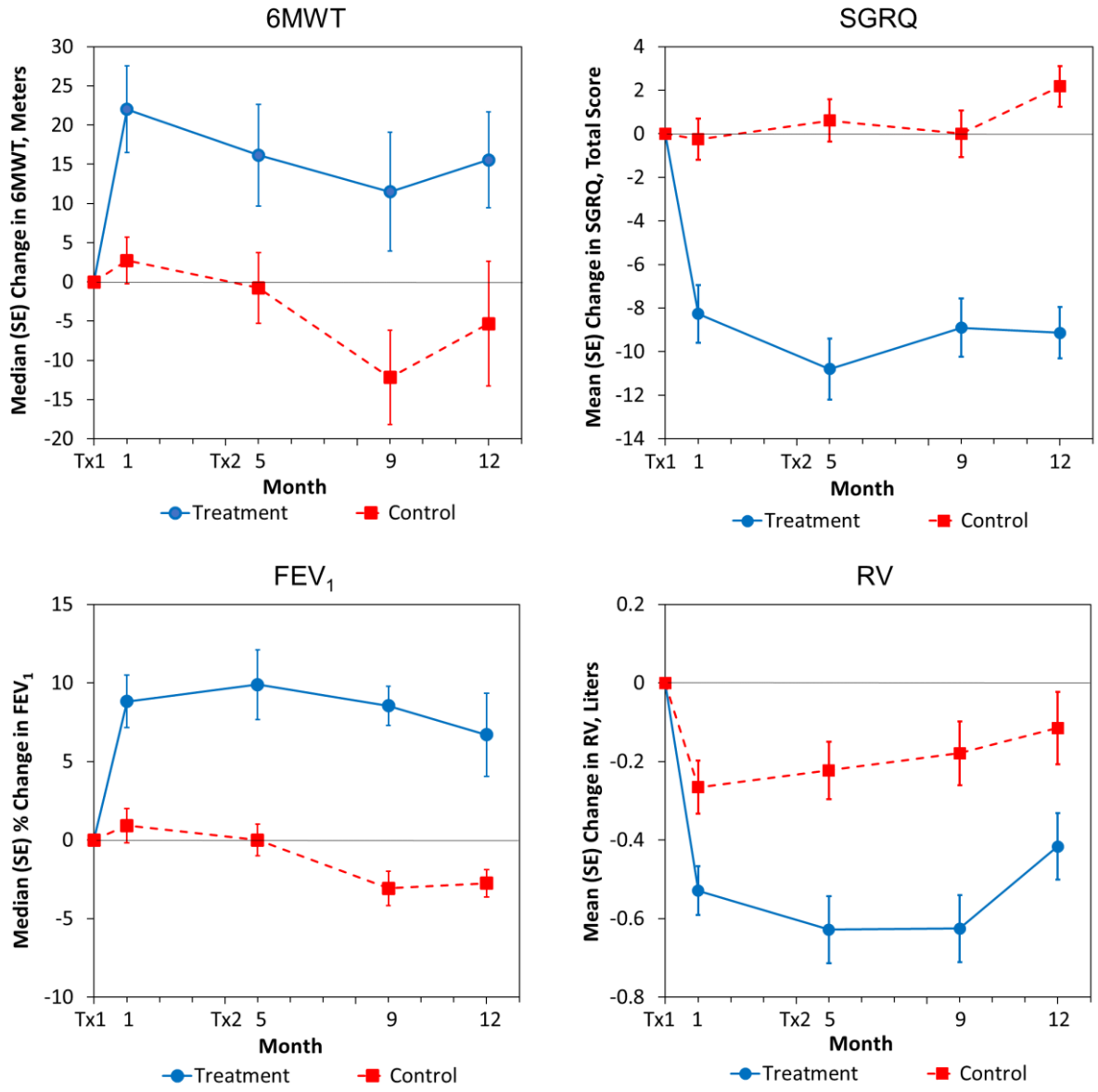


[a]SGRQ responder analysis, RV absolute change from baseline, and RV/TLC absolute change from baseline at 12 months after multiple imputation. Nominal p-values are reported without adjustment for multiplicity.
Note: These plots were not provided within the PMA; however, the underlying information / analysis was provided in the PMA application to FDA.

6.5.2.4. Effectiveness Outcomes by Time in Originally Defined Protocol Population (RV ≥225% Subpopulation)

Key effectiveness outcomes in RV ≥225% subjects are plotted by time in Figure 18. Effectiveness measures including 6MWT, SGRQ, FEV_1, and RV improve shortly after Coil treatment, and these treatment effects were sustained and consistent through 12 months post treatment. Long-term effectiveness outcomes at 24 months post-treatment are provided in Section 6.5.3.

Figure 18. Key Effectiveness Outcomes by Time in RV ≥225% Subpopulation [RENEW][a]



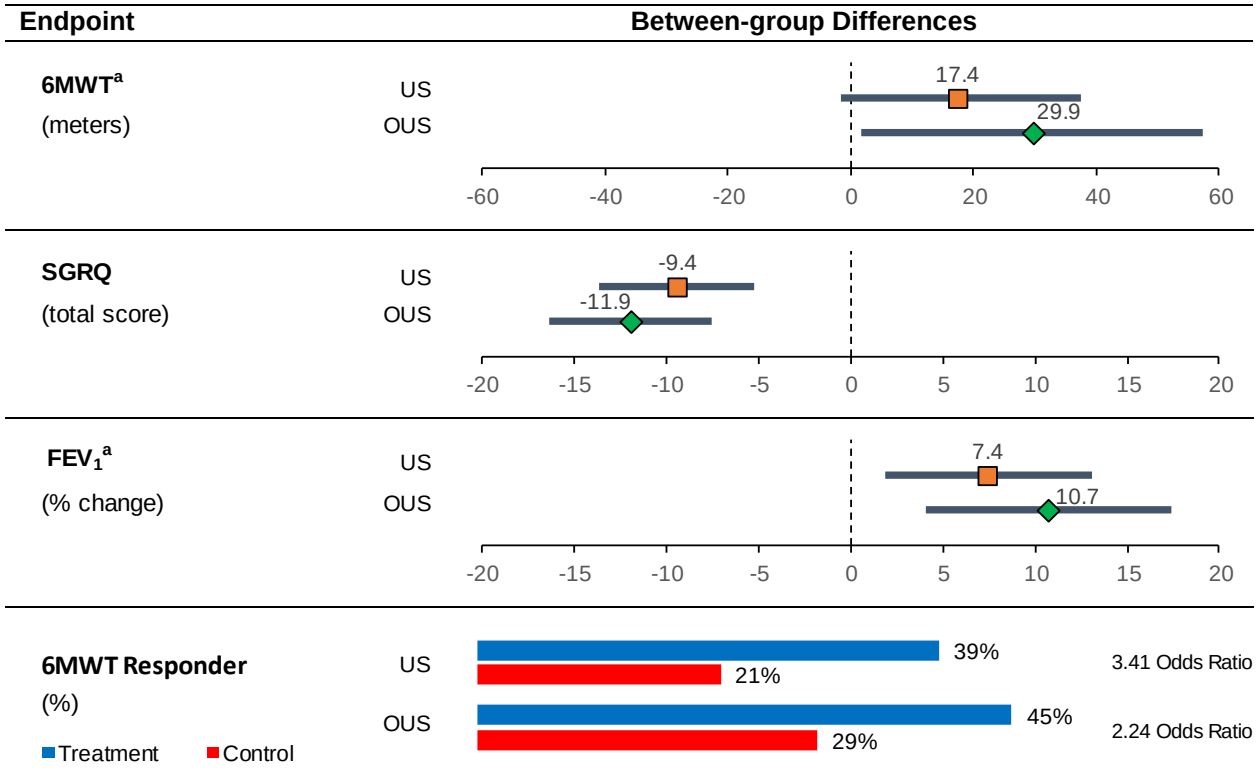
[a]Change from baseline in 6MWT, SGRQ, RV, and % change in FEV_1, by study visit. SE of the median calculated using the non-parametric bootstrap estimate.
Note: These plots, and the calculation of the SE of the median for 6MWT and FEV_1, were not provided within the PMA; however, the other underlying information / analysis was provided in the PMA application to FDA.

6.5.2.5. Post Hoc Analyses in Originally Defined Protocol Population (RV ≥225% Subpopulation)

PneumRx conducted additional analyses to further understand the observed inconsistencies in effectiveness outcomes by region for the ITT population (Figure 14). Post hoc subgroup

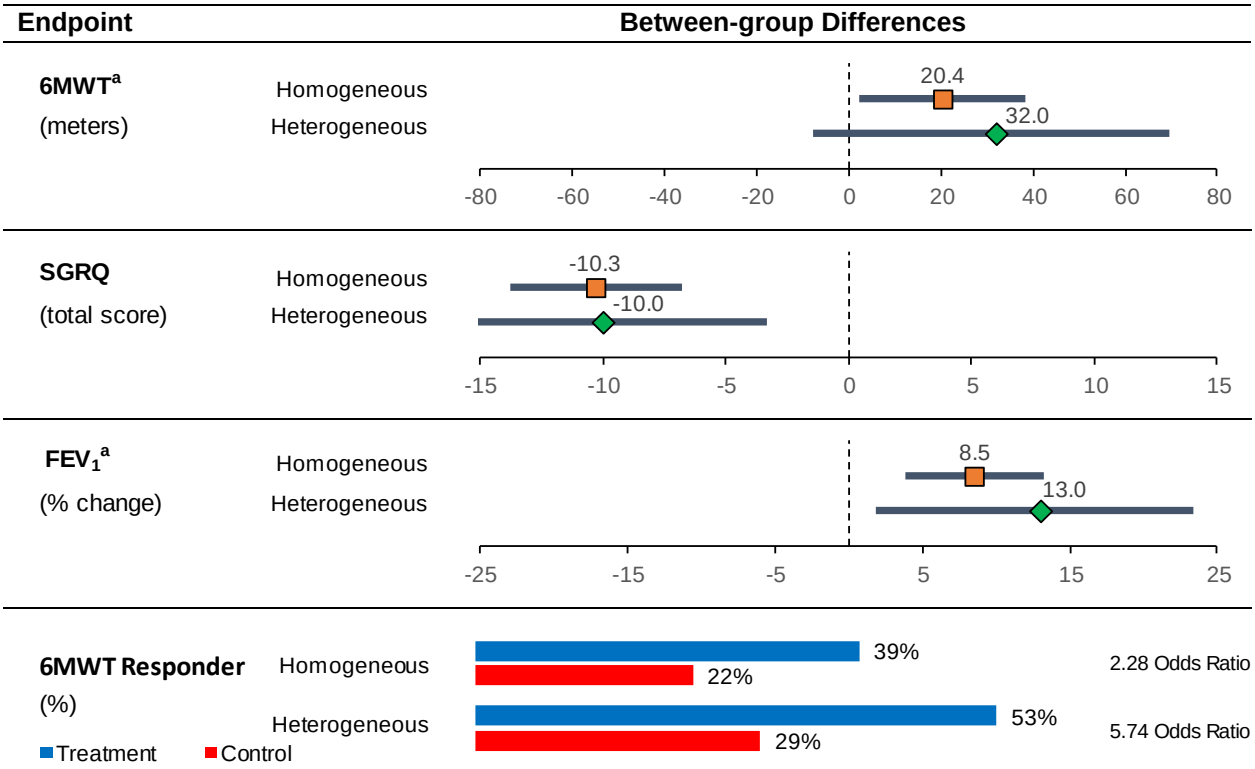
analysis of treatment responses by baseline RV percent predicted and region showed comparable clinical benefit in primary and secondary effectiveness outcomes in the RV ≥225% subpopulation across regions (Figure 19), with somewhat lower benefit seen in US patients in 6MWT. Similar analyses by baseline RV percent predicted and emphysema distribution confirmed that outcomes were similar across emphysema distributions in the RV ≥225% subpopulation (Figure 20), although improved from that seen in the ITT population (Supplemental Table 7, Attachment 1).

Figure 19. Primary and Secondary Effectiveness Outcomes by Region after Multiple Imputation, RV ≥225% Subpopulation [RENEW]



[a]Between-group difference expressed as median. Subject (n) by subgroup and treatment group: US Treatment (56), US Control (72), OUS Treatment (59), OUS Control (48).
Note: These plots were not provided within the PMA; however, the underlying information / analysis was provided in the PMA application to FDA

Figure 20. Primary and Secondary Effectiveness Outcomes by Emphysema Distribution after Multiple Imputation, RV ≥225% Subpopulation [RENEW]



[a]Between-group difference expressed as median. Subject (n) by subgroup and treatment group: Homogeneous Treatment (88), Homogeneous Control (89), Heterogeneous Treatment (27), Heterogeneous Control (31).
Note: These plots were not provided within the PMA; however, the underlying information / analysis was provided in the PMA application to FDA

Further analyses suggested that comorbid disease burden may also be a factor influencing effectiveness outcomes after treatment with ELEVAIR Coils. Post hoc analyses by comorbidity frequency showed that subjects with fewer comorbidities (Supplemental Table 10, Attachment 1), and specifically without cardiac comorbidity (defined as angina, atrial fibrillation, coronary artery disease, or congestive heart failure) (Supplemental Table 11, Attachment 1), experienced the greatest benefit, particularly in 6MWT outcome.

6.5.3. Post 12-Month Effectiveness Analyses

24-month follow-up is complete for the RENEW Randomized Trial, and additional long-term follow-up is ongoing up to 5 years for Treatment group subjects. Note that Control group subjects exited the RENEW Trial per protocol at 12 months and are no longer being followed.

24-month effectiveness outcomes in the ITT population are summarized in Table 5. Compared to baseline, median 6MWT and FEV_1 were slightly declined at 24 months, whereas SGRQ and RV continued to show improvement. Outcomes in the RV ≥225% subpopulation (Table 6) were similar to or improved compared to those in the ITT population. Despite being at or slightly

declined versus baseline, 6MWT and FEV_1 outcomes at 24 months in Coil-treated subjects in the RV ≥225% subpopulation were consistent with or improved versus 12-month Control group outcomes, suggesting that outcomes are still improved at 24 months compared to expectations of outcomes with medical therapy alone. The durability of improvements in quality of life through 24 months is an important benefit of treatment with ELEVAIR Coils, given the progressive nature of emphysema and expectations for worsening health status in patients receiving optimal medical therapy alone.

Table 5. Descriptive Summary of Key Effectiveness Outcomes from Long-term Follow-up, ITT Population [RENEW]

Outcome	Control Group	Treatment Group	
	Change from Baseline at 12 Months	Change from Baseline at 12 Months	Change from Baseline at 24 Months
6MWT (meters)			
Mean ± SD (n)	−7.8 ± 62.4 (140)	0.1 ± 71.6 (137)	−17.2 ± 67.7 (112)
Median	−5.3	10.7	−11.1
Range (min, max)	(−253.0, 144.3)	(−213.0, 133.0)	(−219.4, 136.7)
SGRQ (total score)			
Mean ± SD (n)	1.0 ± 9.9 (139)	−8.4 ± 12.4 (138)	−4.4 ± 13.5 (114)
Median	1.2	−7.2	−5.1
Range (min, max)	(−21.7, 30.0)	(−45.8, 19.9)	(−40.3, 40.4)
FEV_1 (percent change)			
Mean ± SD (n)	−1.7 ± 12.6 (140)	7.1 ± 21.3 (137)	2.3 ± 20.2 (112)
Median	−2.5	3.6	−1.3
Range (min, max)	(−29.4, 43.2)	(−33.9, 73.9)	(−28.4, 93.5)
RV (liters)			
Mean ± SD (n)	−0.05 ± 0.85 (140)	−0.34 ± 0.79 (136)	−0.29 ± 0.83 (110)
Median	−0.03	−0.29	−0.28
Range (min, max)	(−3.7, 4.6)	(−2.8, 1.9)	(−3.0, 3.0)

Table 6. Descriptive Summary of Key Effectiveness Outcomes from Long-term Follow-up, RV ≥225% Subpopulation [RENEW]

Outcome	Control Group	Treatment Group	
	Change from Baseline at 12 Months	Change from Baseline at 12 Months	Change from Baseline at 24 Months
6MWT (meters)			
Mean ± SD (n)	−12.4 ± 64.5 (104)	5.3 ± 73.7 (98)	−14.2 ± 67.5 (86)
Median	−5.3	15.5	−5.4
Range (min, max)	(−253.0, 144.3)	(−213.0, 133.0)	(−219.5, 136.7)
SGRQ (total score)			
Mean ± SD (n)	2.2 ± 9.4 (103)	−9.1 ± 11.7 (99)	−4.5 ± 13.5 (87)
Median	1.5	−7.3	−5.1
Range (min, max)	(−18.8, 30.0)	(−34.1, 16.0)	(−32.6, 40.4)
FEV_1 (percent change)			
Mean ± SD (n)	−1.5 ± 12.1 (104)	9.6 ± 22.0 (98)	4.4 ± 20.9 (86)
Median	−2.8	6.7	0.8
Range (min, max)	(−29.4, 43.2)	(−33.9, 73.9)	(−28.4, 93.5)
RV (liters)			
Mean ± SD (n)	−0.12 ± 0.94 (104)	−0.42 ± 0.83 (97)	−0.33 ± 0.89 (84)
Median	−0.09	−0.38	−0.29
Range (min, max)	(−3.7, 4.6)	(−2.8, 1.9)	(−3.0, 3.0)

6.6. Safety Results

6.6.1. Major Complications

The primary Safety analysis for the RENEW Trial was the percentage of subjects with Major Complications (MCs), as defined in Section 6.1.2.4, through 12 months follow-up. Table 7 presents the analysis of MCs based on subject counts for each event type, as well as the event rate per year. Event rates were computed using Poisson regression to consider each subject's follow-up time along with event counts.

The percent of subjects experiencing one or more MC was greater in the Treatment group compared to the Control group (34.8% versus 19.1%, nominal p=0.0021). The most common MCs were Lower Respiratory Tract Infection, COPD exacerbation, and Death in both groups. In the peri-procedural period (30 days following either Coil procedure), the overall MC rate for the Treatment group was approximately 3 times that seen over the entire 12-month follow-up period for the same group (1.393 versus 0.529 events per patient year of follow-up). Following the 9-month visit, MC rates were similar in both groups.

The difference in the 12-month MC rate was primarily driven by an increased rate of Lower Respiratory Tract Infections (LRTIs) in the Treatment group, with similar event rates observed between the two groups in all other individual MC categories, including death. Of the 40 reported LRTIs in the Treatment group, nearly all were either resolved (31 events) or resolved with sequelae (7 events) as of the data cutoff for this clinical summary. LRTI MCs occurred at a median of 55 days following the closest ELEVAIR Coil procedure (range 2 to 243 days) and

resolved a median of 15 days following onset (range 2 to 160 days). Thirty-four (34) of the 40 events were deemed to be possibly (29) or probably (5) related to the device.

Table 7. Major Complications through 12 Months, Safety Population [RENEW]

Event	Subjects, % (Subject Count)			Event Rate per Year (Event Count)		
	Treatment (N=155)	Control (N=157)	P-value	Treatment	Control	P-value
Total Major Complication Events [95% CI]	34.8% (54) [27.4%, 42.9%]	19.1% (30) [13.3%, 26.1%]	0.0021	0.529 (80)	0.256 (38)	0.0002
Death	6.5% (10)	5.1% (8)	0.6360	0.066 (10)	0.054 (8)	0.6683
Pneumothorax	0.6% (1)	0.6% (1)	>0.9999	0.007 (1)	0.007 (1)	0.9888
Hemoptysis	1.3% (2)	0.0% (0)	0.2460	0.013 (2)	0.000 (0)	N/A
COPD Exacerbation	11.6% (18)	8.3% (13)	0.3496	0.139 (21)	0.094 (14)	0.2638
Lower Respiratory Infections[1]	18.7% (29)	4.5% (7)	<0.0001	0.264 (40)	0.061 (9)	<0.0001
Respiratory Failure	3.9% (6)	3.8% (6)	>0.9999	0.040 (6)	0.040 (6)	0.9725
Unanticipated Bronchoscopy	0.0% (0)	0.0% (0)	N/A	0.000 (0)	0.000 (0)	N/A

1 All reported pneumonia events categorized as lower respiratory tract infection MCs are included. See Section 6.6.7 for discussion of retrospective review of all pneumonia events in RENEW, which determined that a portion of reported pneumonias were cases of non-infectious localized tissue reaction to the Coils (termed “Coil Associated Opacity”, or “CAO” by PneumRx).

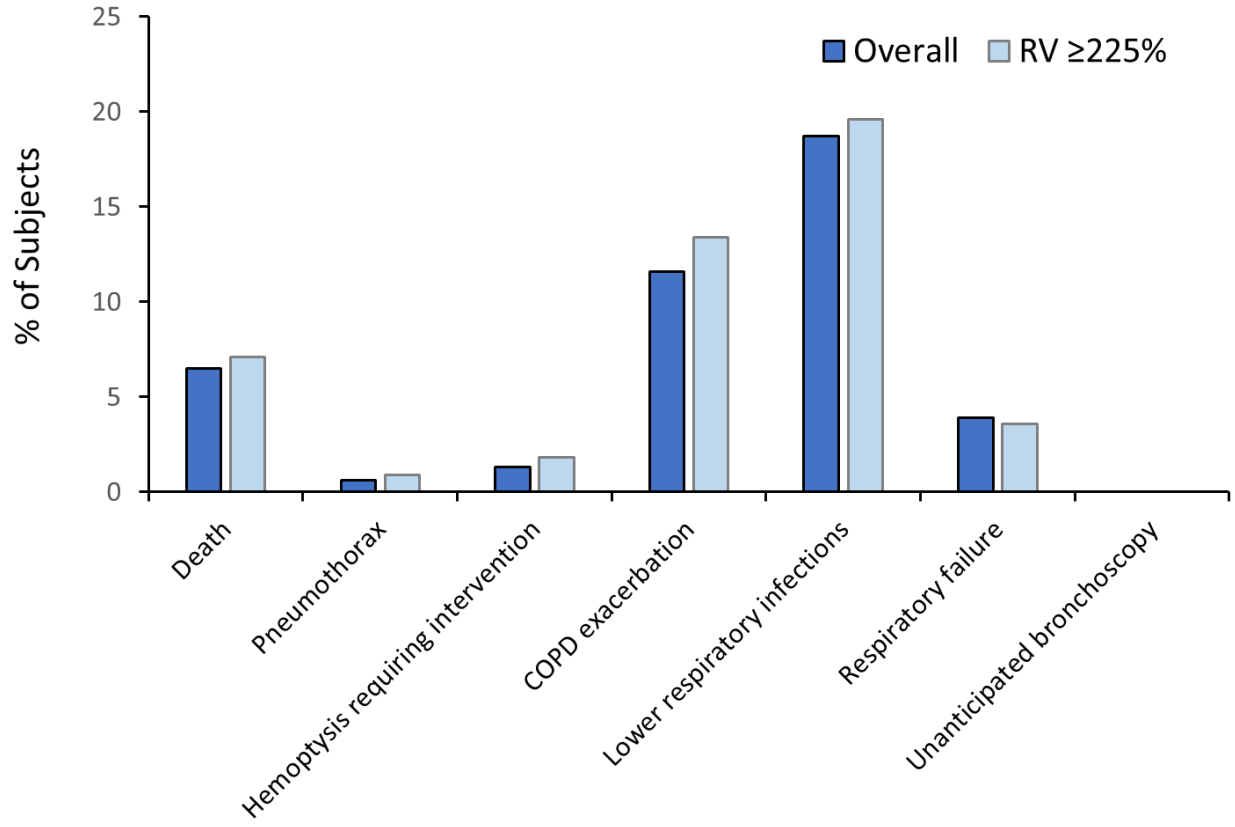
Because increased effectiveness of ELEVAIR System treatment was seen in subjects with higher RV at baseline (see Section 6.5.2), the above safety analysis was also conducted for the RV ≥225% subgroup (Table 8). No clinically significant differences were evident in Coil-treated subjects in any of the MC categories, including mortality, in the RV ≥225% subpopulation compared to the overall safety population (Figure 21), and the total incidence and event rate of MCs were also similar in the two populations.

Additional analyses in the RV ≥225% subpopulation showed no difference in safety outcomes versus the overall safety population, including comparisons of SAE rates (Section 6.6.3). Thus, the presentation of the device safety profile is focused on the entire safety population to improve sensitivity and ensure comprehensiveness in the safety discussion.

Table 8. Major Complications through 12 Months, RV ≥225% Subpopulation [RENEW]

Event	Subjects, % (Subject Count)			Event Rate per Year (Event Count)		
	Treatment (N=112)	Control (N=120)	P-value	Treatment	Control	P-value
Total Major Complication Events [95% CI]	38.4% (43) [29.4%, 48.1%]	20.0% (24) [13.3%, 28.3%]	0.0023	0.532 (58)	0.276 (31)	0.0032
Death	7.1% (8)	5.8% (7)	0.7918	0.073 (8)	0.062 (7)	0.7532
Pneumothorax	0.9% (1)	0.8% (1)	>0.9999	0.009 (1)	0.009 (1)	0.9835
Hemoptysis	1.8% (2)	0.0% (0)	0.2320	0.018 (2)	0.000 (0)	N/A
COPD Exacerbation	13.4% (15)	8.3% (10)	0.2895	0.147 (16)	0.098 (11)	0.3024
Lower Respiratory Infections	19.6% (22)	5.0% (6)	0.0009	0.248 (27)	0.071 (8)	0.0020
Respiratory Failure	3.6% (4)	3.3% (4)	>0.9999	0.037 (4)	0.036 (4)	0.9670
Unanticipated Bronchoscopy	0.0% (0)	0.0% (0)	N/A	0.000 (0)	0.000 (0)	N/A

Figure 21. Comparison of Major Complications through 12 Months in Coil-Treated Subjects, Overall Versus RV ≥225% Subpopulations [RENEW]



Note: This plot was not provided within the PMA; however, the underlying information / analysis was provided in the PMA application to FDA

6.6.2. Deaths

Eighteen (18) subject deaths occurred in the safety population within the 12-month follow-up period in the RENEW Randomized Trial (Table 7). These include 10 of 155 subjects (6.5%) in the Treatment group and 8 of 157 subjects (5.1%) in the Control group. Of the 10 deaths in the Treatment group, 3 were assessed by the investigator to be not related to the device or procedure. Four (4) of the 10 were assessed as being possibly or probably related to the device only, and 3 of the 10 were assessed as being possibly or probably related to both the device and the procedure. Mortality rates in both groups were similar to published mortality rates in GOLD 3 and 4 patients (11% annually [Fishman 2003]; 15-24% over 3-year period [Jenkins 2009]).

Adverse event types associated with deaths through 12 months in the RENEW Trial are summarized in Table 9. Additional details on event relatedness and timing are provided in Supplemental Table 12 (Attachment 1).

Table 9. Adverse Events Associated with Deaths through 12 Months, Safety Population [RENEW]

Adverse Event (MedDRA)	Treatment Group	Control Group
Chronic obstructive pulmonary disease	3***	4
Pulmonary hemorrhage	1*	0
Respiratory arrest	0	1
Respiratory failure	2*	0
Bronchopulmonary aspergillosis	1*	0
Pneumonia	1*	1
Septic shock	0	1
Cardiac-respiratory arrest	0	1
Bone neoplasm malignant	1	0
Renal failure acute	1	0

* One of the deaths considered possibly or probably device or procedure related.

*** Three of the deaths considered possibly or probably device or procedure related

6.6.3. Serious Adverse Events

Serious events, including COPD exacerbations, lower respiratory tract infections and others, are relatively common in the severe emphysema population. Annually, 18% of GOLD 3 patients and 33% of GOLD 4 patients will experience a severe COPD exacerbation that requires hospitalization (Hurst 2010). In addition, the relative risk of lower respiratory tract infection (including pneumonia) in GOLD 3 and 4 patients is 3.3 times that of the population with normal lung function (Benfield 2008). These risks of respiratory-related adverse events are compounded in patients undergoing bronchoscopy. For example, in a clinical study of GOLD 3 and 4 patients in which the control group underwent a single sham bronchoscopy procedure, 11% of control subjects experienced one or more SAEs and 25% of control subjects experienced one or more AEs within a 3-month follow-up period (Ninane 2012). Treatment group subjects underwent two bronchoscopy procedures as part of bilateral Coil placement.

SAEs that were reported at significant frequency through 12 months (2.5% of subjects or more) in either arm of the RENEW Trial are presented in Table 10 below. 61.9% (96/155) of Treatment group subjects experienced one or more SAEs compared to 34.4% (54/157) of Control group subjects. 211 SAEs were reported in the Treatment group, and 92 SAEs were reported in the Control group. The most common SAEs in both groups were COPD exacerbation and pneumonia. Compared to the Control group, the Treatment group experienced higher incidence of serious pneumonia and pneumothorax events. In addition to pneumonia, pneumothorax, and COPD exacerbation SAEs, Treatment group subjects also experienced a small number of bleeding SAEs (reported as hemoptysis or hemorrhage). The majority of serious bleeding events resolved with medical treatment. However, across RENEW, Roll-In, and Crossover, 3 deaths were attributed to bleeding, which represents approximately 1% of Coil-treated subjects. The risk associated with bleeding is described in the labeling for the ELEVAIR System, together with recommendations for careful consideration of risk factors for increased bleeding (e.g., use of antiplatelet or anticoagulant therapy, presence of bronchiectasis) in patients undergoing Coil treatment.

SAEs reported through 12 months in the RV ≥225% subpopulation are summarized in Supplemental Table 13 (Attachment 1). The incidence and types of SAEs reported most frequently in the RV ≥225% subpopulation were similar to those in the overall safety population (Figure 22).

Table 10. Most Frequently Reported Serious Adverse Events through 12 Months, Safety Population[1] [RENEW]

Event (MedDRA)	Subjects, % (Subject Count)			Event Count	
	Treatment (N=155)	Control (N=157)	Nominal P-value	Treatment	Control
Total serious adverse events	61.9% (96)	34.4% (54)	<0.0001	211	92
Chronic obstructive pulmonary disease	27.7% (43)	20.4% (32)	0.1457	70	46
Pneumonia[2, 3]	22.6% (35)	5.1% (8)	<0.0001	38	10
Pneumothorax	9.7% (15)	0.6% (1)	0.0002	15	1
Hemoptysis/Hemorrhage[4]	3.9% (6)	0.0% (0)	N/A	6	0
Bronchitis	3.2% (5)	1.3% (2)	N/A	5	2
Dyspnea	3.2% (5)	0.6% (1)	N/A	6	1
Medical device complication[5]	3.2% (5)	0.0% (0)	N/A	5	0
Respiratory failure	3.2% (5)	0.6% (1)	N/A	5	1

1 Events reported by 2.5% or more of subjects in either study arm are presented, in order of decreasing incidence by subject in the Treatment group. Nominal p-values without adjustment for multiplicity are provided for events with subject counts >5% in either study arm.

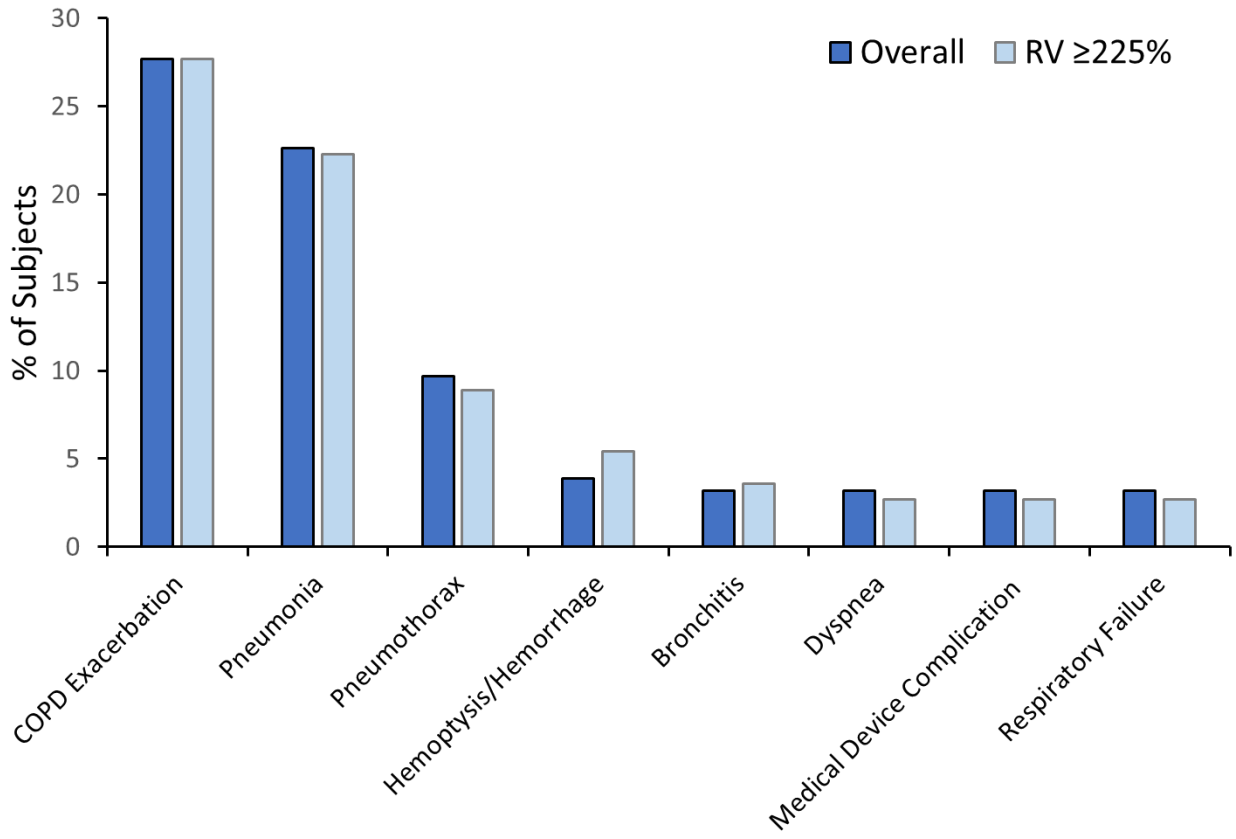
2 Considered to include any of the following MedDRA preferred terms: Pneumonia, Pneumonia bacterial, Pneumonia staphylococcal, Bronchopulmonary aspergillosis, Pneumonia necrotizing, Pneumonia respiratory syncytial viral, Lower respiratory tract infection. Pooling of pneumonia events in this manner was not provided within the PMA.

3 All reported pneumonia SAEs are included. See Section 6.6.7 for discussion of retrospective review of all pneumonia events in RENEW, which determined that a portion of reported pneumonias were cases of non-infectious localized tissue reaction to the Coils (termed “Coil Associated Opacity”, or “CAO” by PneumRx).

4 Considered to include any of the following MedDRA preferred terms: Hemoptysis, Post procedural hemorrhage, Procedural hemorrhage, Pulmonary hemorrhage, Respiratory tract hemorrhage.

5 Events that were recognized as coil-associated opacities (CAOs) at time of diagnosis were categorized under the “Medical device complication” Preferred Term.

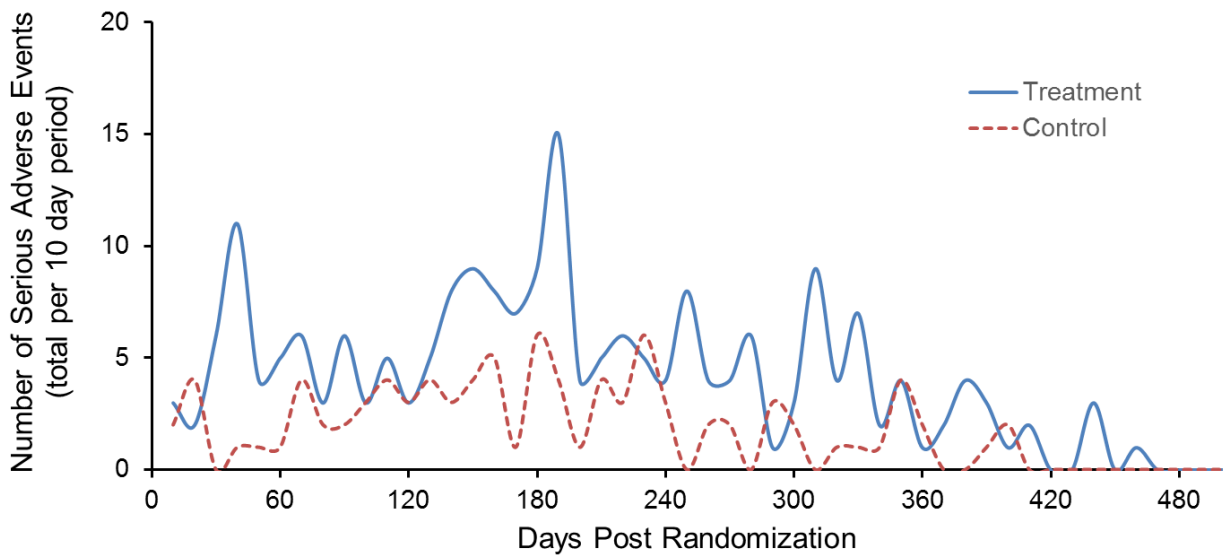
Figure 22. Comparison of SAEs through 12 Months in Coil-Treated Subjects, Overall Versus RV ≥225% Subpopulations [RENEW]



Pneumonia and Hemoptysis/Hemorrhage events are pooled as described in Table 10.
Note: This plot, and the pooling of pneumonia events, was not provided within the PMA; however, the other underlying information / analysis was provided in the PMA application to FDA.

As seen in Figure 23, Treatment group subjects experienced a greater number of SAEs during the first 30 days following the procedure. These peri-procedural SAEs are discussed in greater detail in Section 6.6.5.

Figure 23. Serious Adverse Events by Time [RENEW]



Study treatment #1 typically occurred within the first 60 days post randomization and study treatment #2 typically occurred approximately 4 months later. The peaks in SAEs correspond to these two time periods.

Note: This plot was not provided within the PMA application to FDA.

6.6.4. Device and/or Procedure-Related Serious Adverse Events

During the 12-month RENEW randomized phase, 45.8% (71/155) of subjects reported 128 SAEs that were determined to be device and/or procedure-related. Event relationship was determined by the investigator; related events include those events categorized as “Possibly” or “Probably” related to the device or procedure. Related SAEs that were reported through 12 months in at least 2.5% of subjects are summarized in Table 11. The most common related SAEs reported for Coil-treated subjects were COPD exacerbation, pneumonia, and pneumothorax, with low incidences of related hemoptysis/hemorrhage, CAO (once the CAO response was recognized, it was coded under MedDRA as medical device complication), and bronchitis events also reported. With the exception of bronchitis, which never resulted in a major complication or a subject death, these event categories represent the more significant risks associated with ELEVAIR Coil treatment and are discussed in the labeling for the ELEVAIR System.

Table 11. Most Frequently Reported Device and/or Procedure-Related Serious Adverse Events through 12 Months, Safety Population[1] [RENEW]

Event (MedDRA)	Subjects, % (Subject Count) Treatment (N=155)	Event Count
Total device and/or procedure-related serious adverse events	45.8% (71)	128
Chronic obstructive pulmonary disease	20.0% (31)	49
Pneumonia[2, 3]	18.7% (29)	31
Pneumothorax	9.7% (15)	15
Hemoptysis/Hemorrhage[4]	3.9% (6)	6
Medical device complication[5]	3.2% (5)	5
Bronchitis	2.6% (4)	4

1 Events that were reported by at least 2.5% of subjects in either study arm are presented, in order of decreasing incidence by subject.
2 Considered to include any of the following MedDRA preferred terms: Pneumonia, Pneumonia bacterial, Pneumonia staphylococcal, Bronchopulmonary aspergillosis, Pneumonia necrotizing, Pneumonia respiratory syncytial viral, Lower respiratory tract infection. Pooling of pneumonia events in this manner was not provided within the PMA.
3 All reported pneumonia device and/or procedure-related SAEs are included. See Section 6.6.7 for discussion of retrospective review of all pneumonia events in RENEW, which determined that a portion of reported pneumonias were cases of non-infectious localized tissue reaction to the Coils (termed “Coil Associated Opacity”, or “CAO” by PneumRx).
4 Considered to include any of the following MedDRA preferred terms: Hemoptysis, Post procedural hemorrhage, Procedural hemorrhage, Pulmonary hemorrhage, Respiratory tract hemorrhage.
5 Events recognized as coil-associated opacities (CAOs) at time of diagnosis were categorized under the “Medical device complication” Preferred Term.

6.6.5. Peri-Procedural Serious Adverse Events

Peri-procedural SAEs (those occurring within 30 days of either Coil treatment procedure, or within study visits 2 or 5 for Control group subjects) that were reported at a frequency of 2.5% of subjects or more in either study arm are presented in Table 12 below. The most frequently occurring peri-procedural SAEs by subject were pneumonia, COPD exacerbation, and pneumothorax.

Notably, it is not uncommon for patients with severe emphysema to undergo bronchoscopy as a part of standard of care in managing their disease. Although bronchoscopy is considered relatively safe, the risks of the procedure and of the required anesthesia are more significant in patients whose airways are inflamed or damaged by disease, as in the emphysema population. Due to the destruction of lung tissue, patients with severe emphysema show an increased risk of pneumothorax even in the absence of bronchoscopy (Nakajima 2010, van Berkel 2010), and this risk is further compounded when these patients undergo bronchoscopy (Ouellette 2006). Consistent with these findings, the ATS lists bronchoscopy-associated risks as follows[j]:

- Discomfort and coughing
- Reduced oxygen (usually mild and usually returns to normal without treatment)
- Lung leak or collapse (not common generally, but more common if a biopsy is taken)
- Bleeding (usually minor and stops without treatment)
- Infection

The ATS counsels that serious risks from bronchoscopy, such as an air leak or serious bleeding, occur at a rate of less than 5%.

Table 12. Most Frequently Reported Peri-Procedural Serious Adverse Events through 12 Months, Safety Population[1] [RENEW]

Event (MedDRA)	Subjects, % (Subject Count)			Event Count	
	Treatment (N=155)	Control (N=157)	P-value	Treatment	Control
Pneumonia[2, 3]	11.6% (18)	2.5% (4)	0.0017	18	4
Chronic obstructive pulmonary disease	9.7% (15)	3.8% (6)	0.0438	16	6
Pneumothorax	9.0% (14)	0.0% (0)	<0.0001	14	0
Hemoptysis/Hemorrhage[4]	3.2% (5)	0.0% (0)	N/A	5	0
Medical device complication[5]	2.6% (4)	0.0% (0)	N/A	4	0

1 Events reported by 2.5% or more of subjects in either study arm are presented, in order of decreasing incidence by subject in the Treatment group. P-value is provided only for events with subject counts >5% in either study arm.
2 Considered to include any of the following MedDRA preferred terms: Pneumonia, Pneumonia bacterial, Pneumonia staphylococcal, Bronchopulmonary aspergillosis, Pneumonia necrotizing, Pneumonia respiratory syncytial viral, Lower respiratory tract infection. Pooling of pneumonia events in this manner was not provided within the PMA.
3 All reported pneumonia peri-procedural SAEs are included. See Section 6.6.7 for discussion of retrospective review of all pneumonia events in RENEW, which determined that a portion of reported pneumonias were cases of non-infectious localized tissue reaction to the Coils (termed “Coil Associated Opacity”, or “CAO” by PneumRx).
4 Considered to include any of the following MedDRA preferred terms: Hemoptysis, Post procedural hemorrhage, Procedural hemorrhage, Pulmonary hemorrhage, Respiratory tract hemorrhage.
5 Events that were recognized as coil-associated opacities (CAOs) at time of diagnosis were categorized under the “Medical device complication” Preferred Term.

[j] American Thoracic Society Patient Information Series. https://www.thoracic.org/patients/patient-resources/resources/flexible-bronchoscopy.pdf.

6.6.6. Adverse Events

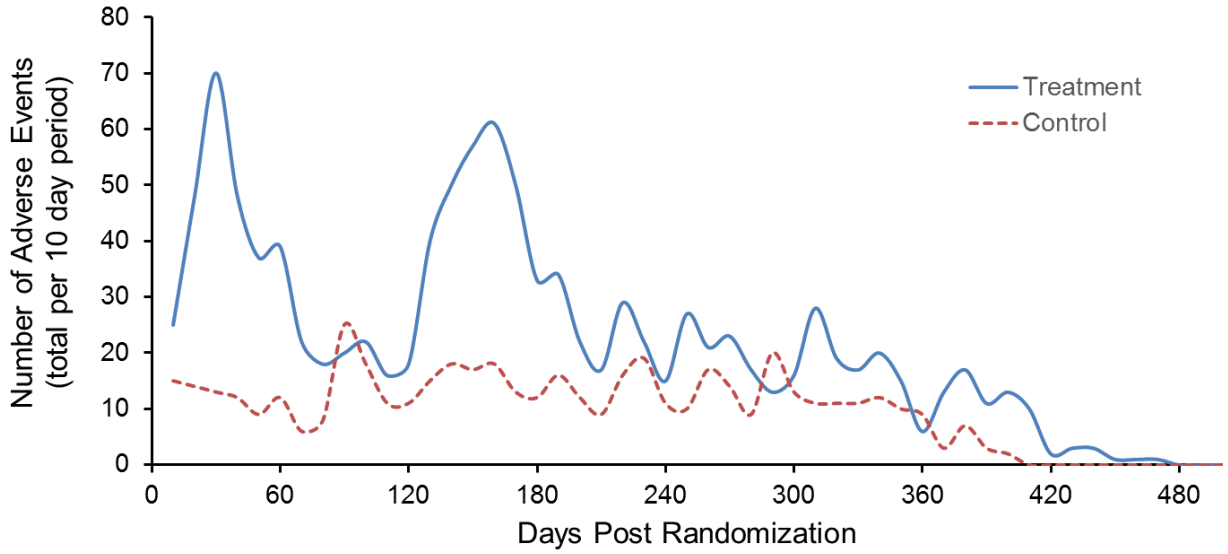
Overall, 100.0% of Treatment group subjects and 88.5% (139/157) of Control group subjects reported at least one AE through 12 months. The high incidence of reported AEs in both study arms is consistent with expectations for a GOLD 3 and 4 patient population with multiple chronic comorbid conditions. The Treatment group reported a greater number of AEs overall (1110 AEs, versus 492 AEs in the Control group), although importantly subjects in the Treatment group underwent two separate bronchoscopies whereas the Control group did not receive a procedural intervention (no active control device or sham control was utilized), which likely contributed to the higher adverse event rate seen in the Treatment group. The majority of the AEs experienced by subjects in the RENEW Trial were anticipated in this patient population with severe emphysema undergoing bronchoscopy and are able to be managed with standard of care treatment (GOLD 2018). 86.2% of AEs in the Treatment group and 85.2% of AEs in the Control group were characterized as “mild” or “moderate” by the investigator.

AEs that were reported at a frequency through 12 months of 5.0% of subjects or more in either arm of the RENEW Trial are shown in Supplemental Table 14 (Attachment 1). The following AEs were reported more frequently in the Treatment group compared to the Control group: hemoptysis, pneumonia, COPD exacerbation, dyspnea, cough, non-cardiac chest pain, chest discomfort, headache, pneumothorax, wheezing, and oropharyngeal pain[k].

Many of the frequently occurring AEs correspond to events that are common in the severe emphysema population (e.g., cough, wheezing, dyspnea, bronchitis), whereas others are likely to be associated, at least in part, with the bronchoscopy and/or accompanying anesthesia/ sedation required for Coil placement (e.g., hemoptysis, chest pain, chest discomfort, oropharyngeal pain, headache). These latter events, and indeed many of the AEs reported for the Treatment group overall, occurred most often during the peri-procedural period (within 30 days of either Coil treatment) (see Figure 24). The most common peri-procedural AEs by subject were hemoptysis (57.4%), COPD exacerbation (37.4%), and cough (14.2%). Peri-procedural hemoptysis AEs were almost entirely mild in severity and resolved without medical intervention. Outside of the peri-procedural window, the rates of adverse events reported by the two study arms were similar.

[k] Lung neoplasms were also reported more frequently in the Treatment group, due to the 12-month CT scan received by the Treatment group subjects that the Control group subjects did not receive.

Figure 24. Adverse Events Occur Primarily within the Peri-Procedural Periods [RENEW]



Study treatment #1 typically occurred within the first 60 days post randomization and study treatment #2 typically occurred approximately 4 months later. The peaks in AEs correspond to these two time periods.

Note: This plot was not provided within the PMA application to FDA.

6.6.7. Device-Specific Adverse Events (Coil-Associated Opacity)

Following DMC review of safety data for the Pivotal Clinical Program, PneumRx initiated an investigation into all reported pneumonia cases. Through this safety review and discussion with study investigators, PneumRx learned of difficulty in distinguishing infectious pneumonia from an inflammatory local tissue reaction to the Coil observed on imaging studies, referred to as "Coil Associated Opacity" or CAO. Some degree of CAO was observed in clinical trials up to two months following the Coil implantation procedure. Most of these events are asymptomatic or symptomatically mild and resolve with limited intervention. However, on occasion, these events do become serious and, in that case, can present in a manner similar to pneumonia; both pneumonia and CAO may show focal opacity or infiltrates on chest X-ray (CXR) or CT scan and may be accompanied by chest or pleuritic pain/discomfort, increased dyspnea or shortness of breath, and fatigue. However, other symptoms that are common in pneumonia (e.g., elevated white cell counts, purulent sputum, positive sputum/blood cultures and/or fever) are not common in cases of CAO and may be useful in differentiating pneumonia from CAO.

The outcome of the investigation by PneumRx was a diagnostic and treatment algorithm, developed by an advisory committee of experienced RENEW Trial investigators and approved by the DMC, which could be applied when patients present with pneumonia-like signs or symptoms (Table 13).

Table 13. Recommended Diagnosis and Treatment of Serious CAO Events

Diagnosis	Suggested Treatment Course
Pneumonia Likely	• Antibiotics • Corticosteroids at discretion of investigator
Purulent sputum	
Fever >100.5°F	
Positive blood cultures	
Pneumonia Suspected	
CXR opacity is central/lobar, segmental	
Positive sputum culture	
WBC >12K with >5% bands, shifts	
CAO Likely	• Suggest no antibiotics* • Corticosteroids • Ibuprofen at investigator discretion • Suggest follow-up with CXR in 7d to confirm diagnosis **If high clinical suspicion of infectious process, start antibiotic therapy*
CXR opacity is peripheral, localized to area around Coils, horse-shoe shaped	
Fever <100.5°F	
WBC <12K without shifts	
Negative blood or sputum culture	
No change from baseline sputum	

Recognition of CAO as an adverse event that is distinct from pneumonia, together with recommendations for its treatment, became available more than 2 months after all Coil procedures had been completed in the RENEW Trial. Because this may have led to misclassification of some CAO events as pneumonia, the study CEC conducted a blinded retrospective analysis of all site-reported pneumonia events, using the above recommendations for discrimination, to determine the most appropriate diagnosis for reported pneumonia events. Of 58 pneumonia events reported in the Treatment group, 40 had sufficient information to be adjudicated by the CEC, and 14 (35%) were determined to have been likely CAO events. In the Control group, 17 pneumonia events were reported, 9 could be adjudicated, and none were determined to be likely CAO events, supporting the specificity of the criteria applied during this blinded review.

6.6.8. Unanticipated Adverse Device Effects

One unanticipated adverse device effect (UADE), an allergy to titanium (one of the constituents of the ELEVAIR Coil), was reported for a subject enrolled in the RENEW Randomized Trial. The subject's allergic reaction was treated appropriately, and the Coils were left implanted.

Two unanticipated adverse device effects were reported during the Crossover study. The first UADE reported in the Crossover study was a fatal pulmonary bleeding event, which occurred 10 days after the first Coil placement procedure. The investigator assessed the event as possibly related to both the device and the procedure. The independent DMC reviewed the autopsy report, pathologist's report, and independent radiologist's interpretation of the patient's CT. The DMC felt that tissue changes in the area of the Coils (metaplastic squamous epithelium) observed on pathology supported their interpretation that the event resulted from locally compromised tissue, and that it was not possible to say whether this event was solely due to the Coil(s).

The second UADE reported in the Crossover study was a recurrent pneumothorax that occurred 5 days after the subject underwent his second Coil placement procedure. A chest x-ray performed shortly after the procedure due to the subject's shortness of breath revealed a pneumothorax; a chest tube was placed with re-expansion of the lung. After the subject's first pneumothorax was resolved, a chest X-ray showed a change in the location of one of the Coils, which was subsequently determined to be in an extra-pulmonary intra-pleural location; this Coil was removed via thoracoscopy. Three days later, the subject was found to have a recurrent pneumothorax, with persistent air leak and substantial subcutaneous emphysema. Subsequent to unsuccessful attempts to address the pneumothorax through surgery, the family determined that only comfort measures should be undertaken; the subject was terminally extubated and expired 16 days after the placement procedure. PneumRx's investigations and the DMC's interpretation of available clinical data indicated that the event may have been complicated by repeated deflations and inflations of the lung that were performed during management of the recurrent pneumothorax. Pressure changes, as well as other manipulations and interventions of the pleural space, may have acted to distort the lung and may have caused or contributed to the Coil displacement.

6.6.9. Device Removals

As of the data cutoff for this clinical summary, no RENEW subjects have undergone Coil removal or repositioning after completion of the placement procedure, either during the initial 12-month randomized phase or during the post 12-month, long-term follow-up phase. As described in section 6.6.8 above, one removal was performed during the Crossover study due to a shift in Coil position subsequent to pneumothorax.

6.6.10. Long-term Safety

As of the data cutoff for this clinical summary, 24-month follow-up for RENEW is complete, and follow-up through 5 years is ongoing. Control group subjects exited the study following the 12-month visit and thus are not discussed in this summary of long-term safety. Long-term safety outcomes are discussed below for the overall safety population in RENEW. No clinically meaningful differences in mortality, SAE, or AE rates were noted in long-term safety outcomes for the RV ≥225% subpopulation compared to the overall safety population.

As noted previously, the peri-procedural period for the Treatment group was the period when AEs and SAEs were most commonly reported. By the end of the 12-month randomized phase, the reports of AEs and SAEs in the Treatment group were similar to that of the Control group (Figure 23 and Figure 24). Between 12 and 24 months, the rates and types of adverse events experienced by Treatment group subjects were similar to that of the Control group during the 12-month randomized phase, and consistent with the underlying disease (e.g., reports of COPD exacerbation and pneumonia).

Twelve (12) deaths occurred between 12 and 24 months. This mortality rate (8.5%) is consistent with expectations for patients with severe (GOLD 3 and 4) emphysema (11% annually [Fishman 2003]; 15-24% over 3-year period [Jenkins 2009]). One of the deaths

(reported term: extensive necrotizing pneumonia) was assessed by investigator as being possibly related to the device. The other deaths were determined to be unrelated to device or procedure and were associated with adverse events common in the severe emphysema population (e.g., COPD exacerbation, respiratory failure, lung cancer).

6.7. Device Malfunctions

During the RENEW Trial, there were 29 device malfunctions reported in 299 procedures (9.7%); none of these malfunctions resulted in harm to a subject. These device malfunctions were received from investigators and regarded components of both the ELEVAIR Coil (Coil: 5 malfunctions, Shell packaging: 6 malfunctions) and the ELEVAIR Delivery System (Catheter: 9 malfunctions, Guidewire: 5 malfunctions, Forceps: 4 malfunctions).

Malfunctions related to the Shell packaging the Coils primarily included reports of the Coil getting stuck or kinked when attempting to load the Coil from the Shell into the Cartridge; these events were subsequently addressed through introduction of a minor dimensional change to the sizing of the Shell. The majority of the malfunctions associated with the Delivery System were due to tortuous patient anatomy that kinked the Catheter, Guidewire or Forceps.

6.8. Deviations and Missing Data

Protocol deviations were monitored on a regular basis throughout the course of the study by the study operations team, as well as the DMC. Major protocol deviations, defined as any deviation from the protocol or other study specific procedures that could impact the scientific soundness of the research plan or the rights, safety, or welfare of human subjects, are summarized in Supplemental Table 15 (Attachment 1). 107 major protocol deviations occurred in 83 subjects (54 Treatment group subjects and 29 Control group subjects).

The most common major deviations overall were visit out of window (28), visit not done (21), PFT blinded assessor unblinded (13), and ICF version issues (11). The majority of deviations for out of window and not done visits were missed due to ongoing AEs that either delayed or prevented the subject from completing the required testing and represent less than 2% of the expected study visits over the initial 12 months of follow-up. Of the 13 occurrences of PFT assessor unblinding, 11 were the result of a systematic unblinding noted at a single center. Upon discovery, a corrective action was put in place at the site. The PFT assessor was removed from the study and a new PFT assessor was certified by the PF expert and trained to the protocol. Additional deviations included use of commercially labeled product rather than investigational use labeled product (1 event; occurred at a European site, commercially labeled product is identical to investigational product, except for product labeling), and the investigator choosing to treat a lobe other than that identified by the Core Lab (4 events).

A portion of the missed visits were Visit 5 (Treatment 2) for Treatment group subjects. Eleven (11) Treatment group subjects were treated unilaterally (1 lung only); 8 of these were due to worsening condition or ongoing AEs that prevented second treatment, and 3 subjects died prior to the second treatment.

Rates of missing data for effectiveness endpoints were consistent with expectations for this severe emphysema patient population. Missing 12-month values, resulting from deaths (18), withdrawals or loss to follow-up (14), or missed visits or tests (7), occurred in 11-14% of subjects, and were similar between treatment arms. Sensitivity analyses, using alternate methods for handling of missing data, were conducted to explore the impact of missing data on effectiveness assessment using 6MWT. Estimated treatment effects for the primary endpoint were consistent across ITT and PP populations and across missing data sensitivity analyses (see Supplemental Tables 16 and 17, Attachment 1), indicating that results were robust to both choice of analysis population and to methods of missing data estimation.

It is concluded that protocol deviations and missing data did not impact the safety of study subjects or limit the scientific validity of the study. The PP population excluded subjects with certain deviations that may have impacted outcomes (e.g., unilateral treatment); however, the results of analysis of the effectiveness endpoints for the PP population were generally comparable to results for the ITT population. Moreover, sensitivity analyses demonstrated that estimations of the treatment effects for the primary effectiveness endpoint were consistent irrespective of the method used for handling of missing data.

6.9. Conclusions from RENEW Trial

The RENEW Randomized Pivotal Trial demonstrated that the ELEVAIR Endobronchial Coil System is a safe and effective minimally invasive bronchoscopic lung volume reduction therapy that improves quality of life (SGRQ), lung function (FEV_1), and exercise capacity (6MWT) in patients with severe emphysema. The RENEW Trial met all effectiveness endpoint analyses in the ITT population and in the RV ≥225% subpopulation, with consistently greater improvement in clinical outcomes compared with the Control group in subjects with RV ≥225% (severe hyperinflation). The RV ≥225% subpopulation represented 75% of all enrolled subjects and corresponded to the originally defined protocol population, prior to a late protocol amendment that lowered the RV threshold for entry to 175% predicted. Improved effectiveness outcomes in patients with relatively higher baseline RV is consistent with the mechanism of action of the Coils, which are designed to reduce hyperinflation through compression of diseased lung parenchyma and improvement of lung elastic recoil. Consistent and clinically meaningful outcomes were shown in subjects with RV ≥225% regardless of emphysema distribution (homogeneous and/or heterogeneous), and benefits were sustained for at least 24 months after Coil treatment, compared to expectations of outcomes with medical therapy alone.

As expected for patients undergoing bronchoscopic intervention, major complications were more frequent in the study arm receiving Coil treatment, largely due to a higher rate of lower respiratory tract infections, including pneumonia. Incidence of other major complication categories, including mortality, were similar between Coil-treated and control subjects. Other than pneumonia, serious adverse events that were associated with Coil treatment included pneumothorax, CAO, COPD exacerbation, and hemoptysis/hemorrhage. The safety profile of

the ELEVAIR System observed in RENEW is acceptable, particularly for the enrolled patient population with severe emphysema who have limited or no available treatment options.

Primary outcomes from the RENEW Randomized Pivotal Trial have been published (Sciurba 2016; article provided in Attachment 4). Additional relevant clinical data and analysis from RENEW are available in a recent systematic review published by the Cochrane Collaboration (van Agteren 2017).

7. ADDITIONAL CLINICAL STUDIES OF THE ELEVAIR SYSTEM

A brief summary of additional clinical studies of the ELEVAIR System is provided in the sections that follow. A more detailed summary of these studies is provided for reference in Attachment 2.

7.1. Additional Randomized Controlled Trials of the ELEVAIR System

7.1.1. REVOLENS Trial

Outcomes from the REVOLENS 12-month primary follow-up, and from long-term (24-month) follow-up, have been published (Deslée 2016, provided in Attachment 4; Deslée 2017), and a summary of trial outcomes taken directly from these publications is provided herein. As noted above, additional detail on the REVOLENS trial is also provided for reference in Attachment 2.

Study Design: The REVOLENS Trial was sponsored by Reims University Hospital, France and was primarily financed by the French Ministry of Health under the STIC program.[l] REVOLENS was a prospective, post-market, multi-center, randomized controlled trial designed to analyze the efficacy, safety, cost, and cost-effectiveness of ELEVAIR Coil treatment in patients with severe emphysema.

The overall design of the REVOLENS trial was similar to the RENEW Pivotal Trial. Subjects were randomized 1:1 to receive Coil treatment or standard of care medical therapy. REVOLENS had a 12-month randomized phase, with long-term follow-up to 5 years for treated subjects. Bilateral Coil treatments were separated by 1-3 months, and CT scoring of emphysema distribution and treatment planning was performed by individual study sites rather than by a core radiology lab. Subjects and Investigators were not blinded to study arm assignment.

REVOLENS used 6MWT responder analysis (≥54 meters, based on Redelmeier 1997) at 6 months as the primary effectiveness endpoint. Similar to the major complication endpoint used in RENEW, REVOLENS incorporated two composite safety scores to assess special safety events of interest: death, pneumothorax, hemoptysis, and invasive ventilation occurring with 24

[l] The STIC program is sponsored by the French government with the purpose of conducting comparative studies that demonstrate the clinical utility and health economics of innovative diagnostic or therapeutic products whose clinical efficacy has been validated/established (e.g., CE marked medical devices).

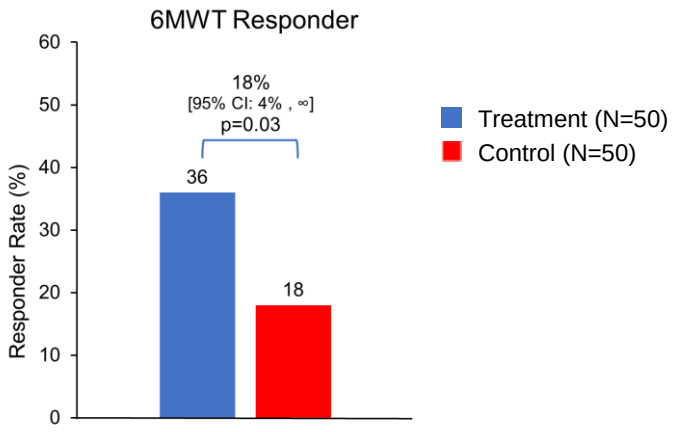
hours of Coil treatment; and death, hemoptysis, pneumonia, pneumothorax, invasive ventilation, and lung transplantation within 12 months of treatment.

Inclusion and exclusion criteria were similar to RENEW, except for inclusion criteria for FEV_1 (<50% predicted) and RV (>220%).

Study Results: REVOLENS enrolled 100 subjects with baseline characteristics similar to those seen in RENEW. Subjects had severe emphysema (FEV_1 approximately 26.5% of predicted) and severe hyperinflation (RV approximately 270% of predicted), and both homogeneous and heterogeneous disease (67% and 33% of subjects, respectively) was represented.

The primary effectiveness endpoint for the REVOLENS trial was met (Figure 25), with a significantly greater proportion of 6MWT responders in the Treatment group compared to the Control group at 6 months (36% [18/50] versus 18% [9/50], p=0.03, one-sided superiority test at α=0.05 significance level). Secondary effectiveness outcomes showed clinically meaningful improvements compared to the Control group in SGRQ, FEV_1, and RV at 12 months post treatment (Table 14). Mean improvement in 6MWT at 12 months (+21 meters) was similar to the treatment effect seen in the RENEW Trial. Long-term follow-up (24 months) of Coil-treated subjects (n=32) showed continued clinically significant within-group improvement in SGRQ (−7.9 points), but 6MWT and FEV_1 had returned to approximately baseline levels (Deslée 2017). These primary and secondary effectiveness outcomes were highly consistent with results from the RENEW Trial.

Figure 25. Primary Effectiveness Outcome, ITT Population [REVOLENS][a]



[a]6MWT responder analysis at 6 months after multiple imputation. Data source (Deslée 2016).

Table 14. Key Secondary Effectiveness Endpoints at 12 Months, ITT Population[1] [REVOLENS]

Endpoint	Treatment Group (N=50)	Control Group (N=50)	Difference (One-sided 95% CI)	p-value
6MWT, meters	−2 [−29, 25]	−23 [−42, −4]	21 [−5, ∞]	0.12
SGRQ, total score	−9.1 [−14.1, −4.2]	1.5 [−1.8, 4.7]	−10.6 [−5.8, −∞]	<0.001
FEV_1, percent change	8 [3, 13]	−3 [−8, 2]	11 [5.2, ∞]	0.002
RV, liters	−0.47 [−0.67, −0.26]	−0.11 [−0.35, 0.12]	−0.36 [−0.10, −∞]	0.004
RV/TLC, percent change	−5 [−7, −2]	0 [−3, 2]	−5 [−1.6, −∞]	0.008
mMRC Dyspnea Scale, score	−0.5 [−0.8, −0.1]	−0.1 [−0.3, −0.1]	−0.4 [−0.05, −∞]	0.02

1 Data source (Deslée 2016)

Assessment of safety at 12 months showed an increase in total incidence of events included in the composite safety score in Coil-treated subjects compared to Control subjects (28% versus 12%, p=0.046). As seen in the RENEW Trial, this difference was predominantly driven by an increase in pneumonia SAEs. Other categories of safety events contributing to the composite safety score, including mortality, were similar between study arms at 12 months.

Table 15. Composite Safety Score through 12 Months[1] [REVOLENS]

Event	Treatment Group		Control Group		Difference, % [95% CI][2]	P-value
	Patients, % (n)	No. of Events at 12 mo	Patients, % (n)	No. of Events at 12 mo		
Death	8% (4)	4	6% (3)	3	2% [−8%, 12%]	0.99
Pneumothorax	2% (1)	1	0% (0)	0	2% [−2%, 6%]	0.99
Hemoptysis	0% (0)	0	0% (0)	0	n/a	n/a
Invasive ventilation	2% (1)	1	6% (3)	3	−4% [−12%, 4%]	0.62
Pneumonia	18% (9)	11	4% (2)	2	14% [2%, 26%]	0.03
Lung transplantation	0% (0)	0	0% (0)	0	n/a	n/a
Total	28% (14)	17	12% (6)	8	16% [1%, 31%]	0.046

1 Data source (Deslée 2016). Data shown as number of events and number of patients with at least one event. Two-sided tests used for safety analyses.

2 Difference between groups in percentage of subjects with events through 12 months.

Conclusions: The REVOLENS study showed improvements in quality of life (SGRQ), lung function (FEV_1, RV, RV/TLC), and exercise capacity (6MWT) at 6 and 12 months post Coil treatment in patients with severe bilateral homogeneous and heterogeneous emphysema and severe hyperinflation (RV >220% predicted). Compared to Control subjects receiving standard of care medical therapy, Coil treatment was associated with an increase in pneumonia SAEs, but mortality rates and incidence of other important safety events were similar between groups. Given the similarity in study design and patient population between REVOLENS and RENEW, the REVOLENS findings provide confirmatory evidence of the safety and effectiveness of the ELEVAIR System in patients with severe emphysema and severe hyperinflation.

7.1.2. RESET Trial

Outcomes from the RESET 3-month randomized phase, together with the Crossover phase and 12-month follow-up on all treated subjects, have been published (Shah 2013, Zoumot 2015). A brief summary of the RESET trial is provided herein, and a detailed summary is provided in Attachment 2.

Study Design: RESET was a prospective, multi-center, randomized controlled trial conducted in the United Kingdom to compare the safety and effectiveness of the ELEVAIR System to standard of care medical therapy in subjects with heterogeneous and homogeneous emphysema.

Subjects were randomized (1:1) to receive Coil treatment or standard of care medical therapy. Treatment group subjects received either one or two (bilateral) treatments that were separated by approximately 1 month. The primary safety and effectiveness analysis was performed at 3 months after treatment, at which time control subjects were eligible for crossover treatment with Coils. All Coil-treated subjects were followed for 12 months.

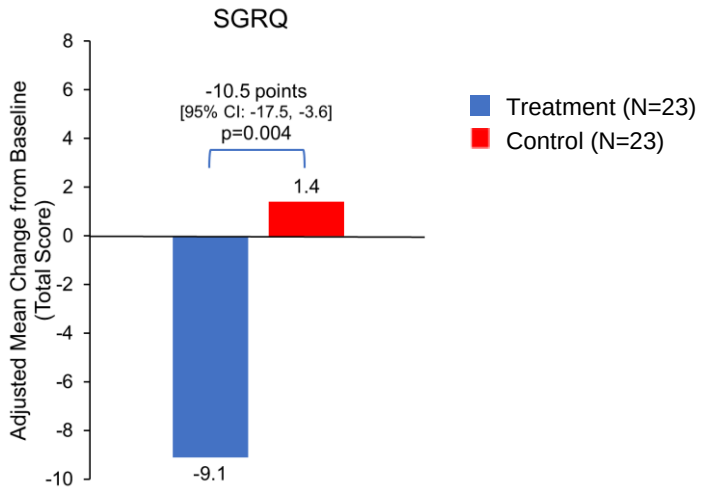
The primary effectiveness endpoint for RESET assessed statistical significance of the adjusted mean absolute change from baseline in SGRQ between Treatment and Control groups. The primary safety analysis identified the number and type of device and/or procedure-related adverse effects associated with ELEVAIR System therapy.

RESET inclusion and exclusion criteria were generally similar to those used in the RENEW Pivotal Trial, with the exception that RESET did not include a minimum RV threshold, and prior completion of pulmonary rehabilitation was not a requirement for enrollment.

Study Results: RESET enrolled 47 subjects at 2 investigational sites in the UK. Analysis of baseline disease characteristics between study arms showed imbalances in emphysema distribution (greater proportion of homogeneous subjects in Control group), SGRQ, 6MWT, and mMRC Dyspnea Scale scores. Each of these imbalances suggested that the Treatment group was comprised of subjects with more severe disease or greater disability.

The primary effectiveness endpoint was met in the RESET trial (Figure 26), with an adjusted mean improvement of −10.5 points in SGRQ in Coil-treated subjects compared to Control subjects at 3 months (p=0.004). RESET also reported improvements in 6MWT, FEV_1, RV, and mMRC Dyspnea Scale score in the Treatment group compared to the Control group (Table 16).

Figure 26. Primary Effectiveness Outcome [RESET][a]



[a]SGRQ absolute change from baseline at 3 months.

Table 16. Secondary Effectiveness Endpoints at 3 Months [RESET]

Endpoint[1]	Change vs. Baseline		Difference (Treatment vs. Control)	p-value
	Treatment Group (N=23)	Control Group (N=23)		
6MWT (meters)	53.0 [29.2, 76.8]	−17.4 [−41.2, 6.4]	70.4 [40.1, 100.7]	<0.001
FEV_1 (percent change)	14.1 [6.7, 21.4]	2.5 [−4.9, 9.9]	11.6 [2.2, 21.0]	0.017
RV (liters)	−0.50 [−0.74, −0.26]	−0.15 [−0.39, 0.08]	−0.35 [−0.65, −0.04]	0.026
mMRC Dyspnea Scale	−0.33 [−0.70, 0.05]	0.15 [−0.22, 0.52]	−0.48 [−0.95, −0.00]	0.049
TLC (liters)	−0.24 [−0.38, −0.09]	−0.13 [−0.28, 0.02]	−0.11 [−0.29, 0.08]	0.264
Supplemental Oxygen (L/min)	−0.04 [−0.25, 0.18]	0.01 [−0.21, 0.22]	0.04 [−0.23, 0.31]	0.750

1 Shown as adjusted mean [95% CI]

No notable differences between study arms in incidence of SAEs or AEs were seen through 3 months in the RESET Trial. The most commonly reported device or procedure-related adverse events were chest infection, chest pain, and pneumothorax. No deaths occurred in either study arm during the 3-month randomized phase. During the 12-month follow-up phase, which monitored Coil-treated subjects from the randomized and crossover phase, 5 subjects died (Zoumot 2015). None of these deaths were determined to be device or procedure-related.

Conclusions: The RESET randomized controlled trial showed that treatment with ELEVAIR Coils can be a safe alternative to standard of care medical therapy, with low SAE rates in a patient population with advanced heterogeneous and homogeneous emphysema. Subjects treated with ELEVAIR Coils showed clinically meaningful benefits over standard of care medical therapy in the trial, with improvements in quality of life (SGRQ, mMRC Dyspnea Scale), lung function (FEV_1), and exercise capacity (6MWT) at 3 months post treatment.

7.2. Other Studies and Analyses under the US IDE Program

In addition to its randomized phase, the RENEW Trial incorporated a Roll-In phase under the same protocol, under which the first two subjects enrolled at study sites that had not participated in previous clinical trials of the ELEVAIR System were designated as Roll-In subjects, who were not part of the randomized study population. These "Roll-In" subjects were intended to provide the investigator and his/her staff with experience in the use of the ELEVAIR System and the treatment procedure prior to initiation of randomization.

A separate protocol for the Crossover study allowed Control subjects who completed the 12-month randomized portion of the RENEW Pivotal Trial and who met Crossover eligibility criteria to receive treatment with the ELEVAIR System. It was anticipated that the availability of the Crossover study would aid in enrollment into RENEW and would also help to minimize loss-to-follow-up in the RENEW Control group during the control period.

Neither the RENEW Roll-In cohort or Crossover study were designed with the primary goal of demonstrating safety or effectiveness of the ELEVAIR System in the target patient population. These studies were not powered for significance and no success/failure criteria were applied. Subject outcomes at 12 months were compared to baseline values and were analyzed using descriptive statistics.

7.2.1. RENEW Roll-In Phase

A brief summary of the RENEW Roll-In phase is provided below. Additional detail is provided for reference in Attachment 2.

Study Design: The RENEW Roll-In phase enrolled a prospective, multi-center, single arm, assessor-blinded study cohort under the same protocol as the RENEW Randomized Trial. The first two subjects enrolled during RENEW at each clinical site without prior experience with the device were enrolled as Roll-In subjects. Data from Roll-In subjects were analyzed separately from that of the RENEW Treatment group.

As it was run under the same protocol as the RENEW Randomized Trial, the Roll-in phase shared the same study design (e.g., inclusion and exclusion criteria, treatment and follow-up schedule, data collection, etc.). However, Roll-in phase results were summarized using descriptive statistics only.

Study Results: A total of 46 subjects were enrolled as Roll-In subjects at 24 North American sites. Roll-In subject demographics and baseline characteristics were consistent with those of the RENEW Randomized Pivotal Trial. The Roll-In cohort included subjects with both heterogeneous (34.8%) and homogeneous (65.2%) severe emphysema, characterized by significant hyperinflation (mean RV of 253% predicted) and flow restriction (mean FEV_1 of 26% predicted).

Twelve-month effectiveness outcomes for the Roll-In subjects are summarized in Table 17. Roll-In subjects demonstrated improvements in exercise capacity (6MWT), quality of life (SGRQ), and lung function (FEV_1) compared to baseline that were similar to those reported for the Treatment group in the RENEW randomized phase (see Section 6.5). As seen in the RENEW Pivotal Trial, outcomes in the RV ≥225% subpopulation were similar to or improved versus those in the ITT population.

Table 17. Effectiveness Outcomes at 12 Months, ITT Population and RV ≥225% Subpopulation [Roll-In]

Endpoint	Measure	ITT Population (N=46)[1]	RV ≥225% Subpopulation (N=40)[1]
6MWT	Absolute change (meters) Mean ± SD (N) Median	 6.4 ± 76.0 (36) 8.6	 5.7 ± 74.7 (31) 5.2
	Responder rate, % (n/N)	41.7% (15/36)	38.7% (12/31)
SGRQ	Absolute change (total score) Mean ± SD (N) Median	 −13.3 ± 18.7 (36) −15.0	 −15.0 ± 18.6 (31) −17.3
	Responder rate, % (n/N)	72.2% (26/36)	77.4% (24/31)
FEV_1	Percent change Mean ± SD (N) Median	 8.1 ± 30.5 (36) 1.7	 8.7 ± 31.5 (31) 1.7
RV	Absolute change (liters) Mean ± SD (N) Median	 −0.7 ± 1.0 (35) −0.7	 −0.9 ± 1.0 (30) −0.7
RV/TLC	Absolute change Mean ± SD (N) Median	 −5.4 ± 8.2 (35) −4.0	 −6.2 ± 7.9 −5.0

1 Missing data were not imputed for the Roll-In cohort.

Through the 12-month follow-up period, 41.3% (19/46) of Roll-In subjects experienced one or more MCs. The most common MCs were lower respiratory tract infections (21.7%), including pneumonias, and COPD exacerbations (17.4%). The 12-month mortality rate in the Roll-In cohort was similar to published mortality rates in GOLD 3 and 4 patients (11% annually [Fishman 2003]; 15-24% over 3-year period [Jenkins 2009]). None of the deaths were deemed related to either device or procedure by the reporting investigator.

Serious adverse events reported in at least 2.5% of Roll-In subjects through 12 months are summarized in Table 18. The most common SAEs by subject were COPD exacerbation and pneumonia. The types and incidence of SAEs reported for Roll-In subjects were consistent with safety outcomes for the Treatment group in the RENEW Trial. No clinically meaningful differences were seen in the safety profiles between the RV ≥225% Roll-In subjects and the overall safety population.

Table 18. Most Frequently Reported Serious Adverse Events through 12 Months, Safety Population[1] [Roll-In]

Event (MedDRA)	Subjects, % (Subject Count) Roll-In (N=46)	Event Count
Chronic obstructive pulmonary disease	23.9% (11)	15
Pneumonia[2]	23.9% (11)	16
Pneumothorax	10.9% (5)	5
Respiratory failure	8.7% (4)	4
Pulmonary embolism	6.5% (3)	3
Acute myocardial infarction	4.3% (2)	2
Acute respiratory failure	4.3% (2)	4
Hemoptysis/Hemorrhage[3]	4.3% (2)	2
Myocardial infarction	4.3% (2)	2

1 SAEs reported by 2.5% or more of subjects are presented, in order of decreasing incidence by subject.
2 Considered to include any of the following MedDRA preferred terms: Pneumonia, Pneumonia bacterial, Pneumonia staphylococcal, Bronchopulmonary aspergillosis, Pneumonia necrotizing, Pneumonia respiratory syncytial viral, Lower respiratory tract infection.
3 Considered to include any of the following MedDRA preferred terms: Hemoptysis, Post procedural hemorrhage, Procedural hemorrhage, Pulmonary hemorrhage, Respiratory tract hemorrhage.

Conclusions: The effectiveness and safety outcomes for RENEW Roll-In subjects are consistent with those of the randomized subjects in the RENEW Trial. Improvements in exercise capacity, quality of life, and lung function were seen following Coil treatment and maintained through 24 months. These data support the conclusions from the randomized RENEW Trial that the ELEVAIR System exhibits a favorable benefit/risk profile in conjunction with standard-of-care pharmacological treatment in subjects with heterogeneous and homogeneous emphysema.

7.2.2. Crossover Study

A brief summary of the Crossover study is provided below. Additional detail is provided for reference in Attachment 2.

Study Design: The Crossover study was a prospective, multicenter, single-arm study that was established to provide an option for RENEW Control subjects to receive ELEVAIR System therapy upon completion of their 12-month control period, if they continued to meet eligibility requirements.

Subjects enrolled in the Crossover study were screened using similar inclusion and exclusion criteria as the RENEW Randomized Trial population, with minor exceptions; the RV threshold for inclusion into the Crossover study was 175% predicted throughout the study. Crossover subjects followed a similar treatment and follow-up schedule as the RENEW Randomized Trial Treatment group and the Roll-In cohort, except for the timing between Coil placement procedures, which was reduced from 4 months to 2 months based on accumulated safety experience in European studies. Additionally, a more specific recommendation for the initiation of prophylactic corticosteroid treatment was added to the protocol as a result of findings from

the RENEW Trial related to CAO. Following completion of the 12-month visit, subjects are to be followed annually for an additional 4 years, for a total of 5 years of follow-up.

Effectiveness in the Crossover subjects was evaluated using the same variables (6MWT, SGRQ, FEV_1, RV) as were used for evaluation of effectiveness for the randomized phase of RENEW. However, the Crossover phase was not powered for significance, no Control group was included for comparison, and no success/failure criteria were applied. Crossover study results were summarized using descriptive statistics only.

Study Results: 102 subjects were enrolled into the Crossover study at 23 study sites, and 101 subjects received at least one treatment with ELEVAIR Coils. Subjects enrolled in the Crossover study had demographic and baseline characteristics that were generally similar to subjects in the RENEW Trial. The study enrolled a group of severe (26.5% GOLD 3 and 73.5% GOLD 4) emphysema patients with significant hyperinflation (mean RV of 242% predicted), airflow restriction (mean FEV_1 of 26% predicted), and multiple chronic comorbid conditions.

Descriptive summaries of Crossover effectiveness outcomes versus baseline are summarized in Table 19. At 12 months following treatment with the ELEVAIR Coils, improvement was seen in quality of life, and lung function was stable. Exercise capacity, however, declined at 12 months post initial treatment. With the exception of 6MWT, outcomes in the RV ≥225% subpopulation were generally similar to or improved versus those in the ITT population.

Table 19. Subject Effectiveness Outcomes at 12 Months, ITT Population and RV ≥225% Subpopulation [Crossover]

Endpoint	Measure	Overall Population (N=84)[1]	RV ≥225% Subpopulation (N=48)[1]
6MWT	Absolute change (meters) Mean ± SD (N) Median	 −22.9 ± 72.6 (80) −14.8	 −32.1 ± 79.0 (47) −18.3
	Responder rate, % (n/N)	26.3% (21/80)	25.5% (12/47)
SGRQ	Absolute change (total score) Mean ± SD (N) Median	 −4.8 ± 14.8 (83) −4.7	 −6.3 ± 13.6 (48) −7.3
	Responder rate, % (n/N)	54.2% (45/83)	60.4% (29/48)
FEV_1	Percent change Mean ± SD (N) Median	 2.2 ± 21.1 (83) −1.3	 3.0 ± 23.3 (48) −1.9
RV	Absolute change (liters) Mean ± SD (N) Median	 −0.30 ± 0.70 (81) −0.26	 −0.43 ± 0.74 (47) −0.35
RV/TLC	Absolute change Mean ± SD (N) Median	 −1.9 ± 6.3 (81) −1.0	 −2.5 ± 6.1 (47) −1.0

1 Missing data in the Crossover study were not imputed.

These 12-month effectiveness outcomes are inconsistent with those seen in the RENEW Randomized Pivotal Trial (see Section 6.5 of the Sponsor Executive Summary), other prior randomized controlled trials of the ELEVAIR System (REVOLENS [Deslée 2016], RESET [Shah

2013]), and a meta-analysis of clinical outcomes across several ELEVAIR System clinical studies (Slebos 2015). Interpretation of Crossover study outcomes is limited due to the absence of randomization, a concurrent Control arm, or pre-specified hypotheses.

Through the 12-month follow-up, 31.7% (32/101) of Crossover subjects experienced 1 or more MCs. The most common major complications by subject were lower respiratory tract infections (16.8%) and COPD exacerbations (9.9%). The proportion of subjects experiencing MCs, as well as the rates of MCs were similar to those reported for the treatment arm of the RENEW Trial. Importantly, the mortality rate in the Crossover study was similar to published mortality rates in GOLD 3 and 4 patients (11% annually [Fishman 2003]; 15-24% over 3-year period [Jenkins 2009]). Six (6) of the 9 deaths were deemed possibly or probably associated with device or procedure.

Serious adverse events reported in at least 2.5% of Crossover subjects through 12 months are summarized in Table 20. The most common SAEs by subject were COPD exacerbation and pneumonia. The types and incidence of SAEs reported during the Crossover study were consistent with safety outcomes for the Treatment group in the RENEW Trial. A post hoc review of safety outcomes was performed for Crossover subjects with RV ≥225%, which corresponded to 62 of the 101 subjects in the Crossover Safety population overall. As seen for the RENEW Pivotal Trial, no clinically meaningful differences were seen in the safety profiles between the RV ≥225% subjects and the overall safety population.

Table 20. Most Frequently Reported Serious Adverse Events through 12 Months, Safety Population[1] [Crossover]

Event (MedDRA)	Subjects, % (Subject Count) Crossover (N=101)	Event Count
Chronic obstructive pulmonary disease	22.8% (23)	29
Pneumonia[2]	17.8% (18)	21
Hemoptysis/Hemorhage[3]	7.9% (8)	8
Pneumothorax	4.0% (4)	5
Medical device complication[4]	3.0% (3)	3

1 SAEs reported by 2.5% or more of subjects are presented, in order of decreasing incidence by subject.
2 Considered to include any of the following MedDRA preferred terms: Pneumonia, Pneumonia bacterial, Pneumonia staphylococcal, Bronchopulmonary aspergillosis, Pneumonia necrotizing, Pneumonia respiratory syncytial viral, Lower respiratory tract infection. Pooling of pneumonia events in this manner was not provided within the PMA.
3 Considered to include any of the following MedDRA preferred terms: Hemoptysis, Post procedural hemorrhage, Procedural hemorrhage, Pulmonary hemorrhage, Respiratory tract hemorrhage.
4 Adverse events that were recognized as coil-associated opacities (CAOs) at time of diagnosis were categorized under the “Medical device complication” Preferred Term.

Conclusions: The safety data collected in the Crossover study to date are consistent with those from the RENEW Trial for use of the ELEVAIR System in conjunction with standard-of-care pharmacological treatment in subjects with bilateral heterogeneous and homogeneous emphysema. Descriptive analyses of effectiveness outcomes in the Crossover study were inconsistent with those seen in RENEW. Study design factors (non-randomized, lack of

concurrent control, change in interval between Coil placement procedures and recommended antibiotic and corticosteroid prophylaxis, potential for selection bias in enrollment) limit the interpretation and generalizability of these results.

7.3. Other Studies Conducted Outside the United States

In addition to RESET, PneumRx conducted three single-arm clinical studies (CLN0006, CLN0011, and CLN0012) in the EU to support the initial CE mark for the ELEVAIR System[m], as well as to support expansion of the CE mark indications for use. The primary and long-term results of these studies have been published (Herth 2010, Slebos 2012, Deslée 2014, Klooster 2014, Slebos 2015). Additional details on these studies are provided in Attachment 2.

These studies incorporated inclusion and exclusion criteria that were similar to the RENEW criteria, and enrolled similar patient populations with severe, bilateral emphysema with significant flow restriction (mean FEV_1 ≤30% predicted) and hyperinflation (mean RV >240% predicted).

The studies demonstrated consistent, statistically significant and clinically meaningful benefits quality of life (SGRQ), lung function (FEV_1), and exercise capacity (6MWT). Adverse events during these studies occurred at rates consistent with expectations for the severe emphysema patient population undergoing multiple bronchoscopy procedures. SAEs reported were generally respiratory in nature (e.g., COPD exacerbation, pneumonia, pneumothorax, hemoptysis, dyspnea, chest pain) and resolved with medical treatment. No deaths occurred during the primary follow-up period in any of the studies.

In addition, PneumRx is currently conducting a post-market observational Registry in the EU (CLN0014). Enrollment, treatment, and follow-up for the Registry is ongoing. Initial outcomes (N=851) support safety and effectiveness of the ELEVAIR System in the post-market setting. Finally, follow-up has recently completed for a small post-market study (n=22) in the EU designed to advance the understanding of the mechanism of action of ELEVAIR Coils (CLN0017 protocol). Analysis of CLN0017 outcomes is ongoing, and results are not available at this time.

8. PATIENT PREFERENCE EVALUATION

To better understand the intended treatment population's perspectives regarding benefits and risks of emphysema treatment options, PneumRx conducted a quantitative patient preference study to assess the benefit and risk preferences of a sample of patients with severe emphysema. These preferences were then used to predict how emphysema patients might evaluate the specific benefits and risks associated with the ELEVAIR System. None of the participants in the patient preference study had participated in the RENEW Trial or otherwise received Coil treatment.

[m] At the time these studies were conducted, the ELEVAIR System was branded as the RePneu® (Lung Volume Reduction) Coil System., although the device itself was the same as the current device.

FDA has long considered that patient perspectives can and should be considered in evaluating the benefit-risk profile of certain devices, when such information is available and when that information is of sufficient quality to meet the standard of valid scientific evidence that FDA requires when making determinations as to the safety and effectiveness of a device.

In its Patient Preference Guidance[n], FDA recommended qualities of patient preference studies that are important to ensuring that the data collected constitute valid scientific evidence as described above, and provided insight into how the Agency plans to incorporate this information into benefit-risk evaluations and regulatory decision-making.

PneumRx consulted these FDA Guidance documents extensively, as well as clinical experts in the fields of pulmonology, interventional pulmonology, and thoracic surgery, during the design of its patient preference study. Finally, the study was conducted in accordance with principles established by FDA for patient preference evaluation (Ho 2015) and good research practice guidelines published by the International Society for Pharmacoeconomics and Outcomes Research (Bridges 2011, Johnson 2013, Hauber 2016).

8.1. Study Design

Objectives: In collaboration with RTI Health Solutions (Research Triangle Park, NC), PneumRx conducted a non-interventional patient preference study to assess, in patients with severe emphysema, the benefit-risk preferences for three possible types of treatments for emphysema: maximum medical therapy, ELEVAIR Coils, and lung volume reduction surgery (without lung transplant).

The objective of the patient preference study was to quantify patients' preferences for various characteristics ('attributes') associated with emphysema treatments, including attributes related to treatment type, chance of benefit, and risks of treatment-related adverse events. These estimates of patients' preferences would then be used to calculate the proportion of patients who would perceive that the benefits associated with ELEVAIR Coil therapy would outweigh the associated risks (i.e., net benefit calculations), relative to continuing to receive optimal medical therapy alone.

Study Design: The preference study used a discrete choice experiment to quantify patients' preferences for several clinically relevant attributes of emphysema treatments among individuals with severe emphysema. A survey was developed, pretested, finalized and administered online to respondents who were recruited through US clinics experienced in the

[n] Patient Preference Information – Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling. Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders. FDA Center for Devices and Radiological Health, Center for Biologics Evaluation and Research. August 24, 2016.

treatment of patients with severe emphysema. Informed consent was obtained and documented for all respondents prior to their participation in the study.

Six different treatment attributes were selected based on clinical relevance and known importance/meaningfulness to both patients and physicians. These included one attribute describing treatment type, one attribute describing treatment benefit (chance of improvement in shortness of breath with activity in the next year, where shortness of breath with activity was characterized using an adaptation of item 11 from SGRQ), and four attributes describing possible treatment-related risks that are commonly associated with therapies for severe emphysema (difference in the number of emphysema flare-ups[o] in the next year, additional risk of pneumothorax in the next year, additional risk of pneumonia requiring hospitalization in the next year, and additional risk of dying in the next year). The selection of improvement in shortness of breath with activity as the treatment benefit was based on recognition that improving breathlessness is, for patients, the primary goal of any emphysema treatment. Three to four 'levels' were selected for each attribute, with the goal of spanning or encompassing the entire range of clinically relevant outcomes for that attribute.

Enrollment Criteria: Enrollment criteria were selected to ensure that study participants were reflective of RENEW Trial subjects and the intended patient population for ELEVAIR System therapy. However, none of the participants in the patient preference study had participated in RENEW or otherwise received treatment with the ELEVAIR Coils, and none had undergone either lung volume reduction surgery or lung transplant.

Key inclusion criteria for the study included the following:

- Aged 35 years or older
- Diagnosis of emphysema
- Forced vital capacity <80% predicted
- Marked dyspnea, scoring ≥2 on the modified Medical Research Council (mMRC) dyspnea scale of 0 to 4
- Post-bronchodilator forced expiratory volume in 1 second (FEV_1) ≤35% predicted

Key exclusion criteria included the following:

- Documented asthma as the primary respiratory diagnosis
- Documented residual volume less than 175% predicted
- Documented severe clinical bronchiectasis with more than one-third cup of mucus production daily
- Documented severe pulmonary hypertension, as defined by right ventricular systolic pressure > 50 mmHg or otherwise clinically indicated
- Diagnosis of alpha-1 antitrypsin deficiency
- Prior lung surgery, lung transplant, or Coil procedures
- Hospitalized three or more times for respiratory infections in the prior year

[o] Defined as a moderately severe COPD exacerbation.

- Self-reported ability to play sports or perform other physical activities, walk uphill, and/or walk upstairs without breathlessness

Study Endpoint: The key endpoint for the preference study was the proportion of patients who would perceive that the preference-weighted benefits of an ELEVAIR Coil-like treatment outweigh the preference-weighted risks, relative to maximum medical therapy alone.

8.2. Study Results

Study Population: The preference study enrolled participants between August 9, 2016 and November 7, 2016 at 8 study sites, 7 of which were also RENEW trial sites. 272 individuals accessed the online survey, of which 227 were determined to be eligible for the study based on screening questions included in the survey, and 205 individuals completed the survey. 202 completed surveys met pre-specified data quality criteria and constitute the full sample for subsequent analyses.

Demographics, baseline disease characteristics, and comorbidity status of participants in the preference study were similar to those of the subjects enrolled in the RENEW Randomized Pivotal Trial, and were consistent with expectations for the severe emphysema population in the US. Mean post-bronchodilator FEV_1 and residual volume for the patient preference study participants was 25% (i.e., GOLD 3 and 4) and 237% of predicted values, respectively.

Nearly all respondents (97.5%, 197/202) reported that they were currently taking medicines to treat their emphysema, and yet all participants reported continuing moderate to severe levels of dyspnea. Thus, the survey respondents are representative of a population of individuals for whom their current medical therapy was insufficient to treat their progressing emphysema symptoms.

Study Outcome: Preference data collected from the patient preference survey were analyzed to calculate the proportion of the sample for whom the preference-weighted treatment attributes for a Coil-like treatment were greater than preference-weighted treatment attributes of a maximum-medical-therapy-like treatment. This can be interpreted to represent the proportion of the sample for whom the incremental benefits of an ELEVAIR Coil-like treatment profile are perceived to outweigh the incremental risks of that profile, relative to maximum medical therapy (Ho 2015). The Coil-like profile and the maximum-medical-therapy-like treatment profile describe an implantable lung device and a medicine, respectively, and the other attributes were based directly on 12-month outcomes from the RENEW Randomized Pivotal Trial. These profiles are summarized in Table 21.

Table 21. Coil-Like Treatment Profile and Maximum-Medical-Therapy-Like Treatment Profile, Full Sample [Patient Preference]

Attribute	Coil-Like Profile	Maximum-Medical-Therapy-Like Profile
Type of treatment	Implantable lung device[1]	Medicines
Chance of improvement in shortness of breath with activity in the next year	44.9% (44.9 out of 100 treated patients)[2]	26.4% (26.4 out of 100 treated patients)[2]
Difference in number of flare-ups in the next year	1-2 more flare-ups	No difference
Additional risk of collapsed lung in the next year	Small chance (10%)	No additional risk
Additional risk of pneumonia requiring hospitalization in the next year	17.5 percentage points (17.5 cases out of 100 treated patients)[3]	No additional risk
Additional risk of dying in the next year	1.4 percentage points (1.4 cases out of 100 treated patients)[4]	No additional risk

1 In the description of the treatment attribute of "Implantable lung device" in the survey, it was stated that even with implantable lung devices, medicines are taken each day.

2 The survey characterized chance of improvement in shortness of breath with activity in the next year using an adaptation of item 11 from SGRQ. The values of 26.4% and 44.9% for the maximum-medical-therapy-like profile and the Coil-like profile, respectively, correspond to the percentages of Control and Treatment group subjects that showed at least a one-step improvement in item 11 at 12 months in the RENEW Trial.

3 To evaluate the 17.5% additional risk of pneumonia requiring hospitalization observed in the ITT population (17.3% additional risk of pneumonia requiring hospitalization observed in the RV≥225% population) in the RENEW study of the ELEVAIR System, patient preference for the additional risk of pneumonia requiring hospitalization was extrapolated using the parameters estimated in the preference model because the 17.5% (17.3%) observed risk was above the maximum level of 15% included in the patient preference study.

4 Calculated using the 12-month mortality rates from the RENEW Trial. This is a conservative profile as the mortality rates in the RENEW Treatment and Control groups were similar (nominal p=0.6360; see Section 6.6.2 for additional discussion).

The results indicate that outcomes of a Coil-like treatment profile would be preferred to the outcomes of a maximum-medical-therapy-like treatment profile by 32% of the sample, suggesting that a substantial proportion of the severe emphysema population would perceive that the benefits of ELEVAIR Coil treatment outweigh its risks.[p]

Preferences in Patients with RV ≥225%: Based on outcomes from the RENEW Pivotal Trial, the proposed ELEVAIR System indications for use target patients with both severe emphysema and severe hyperinflation, with the RENEW analysis of subjects with RV ≥225% predicted serving as clinical guidance for targeted severity of hyperinflation. Consistent with this indication, PneumRx completed a post hoc analysis to evaluate the preferences of patients with baseline RV ≥225% predicted.

[p] To evaluate the 17.5% additional risk of pneumonia requiring hospitalization observed in the ITT population (17.3% additional risk of pneumonia requiring hospitalization observed in the RV≥225% population) in the RENEW study of the ELEVAIR System, patient preference for the additional risk of pneumonia requiring hospitalization was extrapolated using the parameters estimated in the preference model because the 17.5% (17.3%) observed risk was above the maximum level of 15% included in the patient preference study.

Preferences specific to the survey sample population with RV ≥225% were used to perform net benefit calculations (i.e., the proportion of the sample for whom the benefits of a Coil-like treatment would be perceived to outweigh the risks), using updated treatment profiles consistent with RENEW outcomes for RV ≥225% subjects in the Treatment and Control groups. Because of improved SGRQ outcomes for RV ≥225% subjects in RENEW, the updated Coil-like profile incorporated a 47.5% chance of improvement in shortness of breath with activity, versus a 24.0% chance for the maximum-medical-therapy-like profile, together with minor adjustments to the risk of pneumonia and risk of dying to reflect slight decreases in these events in the RENEW RV ≥225% subpopulation compared to the overall RENEW population.

The results indicate that, in the sample with RV ≥225%, outcomes of a Coil-like treatment profile would be preferred to a maximum-medical-therapy-like treatment profile by 51% of the sample.[q] The higher percentage of patients who perceive a net benefit to Coil treatment is consistent with the higher symptom burden in patients with severe hyperinflation, which is anticipated to correlate with increased willingness to accept risk when considering the potential benefits of additional treatment options.

8.3. Study Conclusions

PneumRx's patient preference study used a discrete choice experiment, administered through an online survey, to generate quantitative data on patient benefit-risk preferences in a sample of individuals with severe emphysema that are reflective of patients enrolled in the RENEW Pivotal Trial and the intended commercial treatment population. These preferences were then used to quantify how emphysema patients perceive the benefits and risks associated with an endoscopic coil-like intervention.[p] This assessment showed that 32% of patients with severe emphysema, and 51% of patients with severe emphysema and severe hyperinflation, would likely prefer a treatment such as the ELEVAIR System therapy over maximum medical therapy alone. These preference study results suggest that a meaningful population of emphysema patients may opt to pursue ELEVAIR Coil therapy as an additional treatment option, if it were available to them.

9. COMMERCIAL EXPERIENCE OUTSIDE THE UNITED STATES

The ELEVAIR System (branded outside the United States as the RePneu Coil System) was CE mark certified on October 8, 2010 and has been commercially available in select countries inside and outside of Europe since that time. Under the CE mark, the System is indicated for use in patients with homogeneous and/or heterogeneous severe emphysema to improve quality of life, lung function, and exercise capacity.

[q] To evaluate the 17.5% additional risk of pneumonia requiring hospitalization observed in the ITT population (17.3% additional risk of pneumonia requiring hospitalization observed in the RV≥225% population) in the RENEW study of the ELEVAIR System, patient preference for the additional risk of pneumonia requiring hospitalization was extrapolated using the parameters estimated in the preference model because the 17.5% (17.3%) observed risk was above the maximum level of 15% included in the patient preference study.

The device has never been withdrawn from market in any country for any reason related to safety and/or effectiveness. The device has never been marketed in the United States, by PneumRx or any other commercial entity, under the RePneu, ELEVAIR, or any other brand name.

From receipt of the CE mark in 2010 through February 28, 2018, PneumRx has distributed approximately 5,700 Delivery Systems and 57,000 Coils for commercial use outside of company-sponsored post-market studies. Customer complaints, including those that contain a reported adverse event or procedural difficulty, have been rare in the post-market setting. The most frequently reported events received by the company via the customer complaints procedure as of February 28, 2018, regardless of whether they had been assessed as related to the device or procedure, are summarized in Table 22. The types of reported events are consistent with the known and documented risks that are communicated elsewhere in this executive summary (see Section 6.6), and with the draft US product IFU provided with this Panel briefing package, although there have been a higher number of device removals and potential use errors reported through the complaint program.

Table 22. Summary of Adverse Events / Procedural Difficulties Reported through Post-Market Vigilance Program[1]

Adverse Event / Difficulty	# Complaints	% Patient Treatments[2]
Pneumothorax	55	0.96
COPD exacerbation	47	0.82
Pneumonia	45	0.79
Hemoptysis	42	0.74
Medical device removal	20 (22 Procedures, 44 Coils removed)	0.35
Procedure-use error	17	0.30
Bleeding[3]	14	0.24
Respiratory failure	14	0.24

1 May 13, 2011 (onset of OUS commercialization) through February 28, 2018.
2 Assumes that each Delivery System distributed reflects 1 treatment performed.
3 The “bleeding” events listed were all pulmonary bleeding events, approximately equivalent to the MedDRA Preferred Term “hemorrhage”.

Twenty (20) complaints were received describing 22 removal procedures performed to remove one or more Coils. Note that the potential need for removal of Coils is anticipated, and procedural guidance for bronchoscopic Coil removal is provided in the IFU and through training required of users. Discussion of additional removal methods (e.g., thoracoscopy, surgery) is also planned for inclusion in the physician training program.

The most common reasons for Coil removal were pleural/thoracic pain and pneumothorax. Of the 22 Coil removal procedures, 10 were performed via bronchoscopy, 6 were performed surgically, 3 via thoracoscopy, and in 3 cases the route of removal was not stated.

The majority of the complaints of use error were reports of placement of a Coil too distally, either touching or puncturing the pleura (any resulting pain, pneumothorax, or removals are

counted as separate events). In approximately half of the reports of distal placement, the placement resulted in a subsequent Coil removal. Other reported use errors included users accidentally grasping 2 Coils while attempting to manipulate/reposition 1 Coil, or other types of difficulties manipulating the Coils.

10. POST-MARKET PLAN

10.1. Physician Training Program

The commercial launch of the ELEVAIR System in the US will be based on a "Centers of Excellence" model, in which treatment will only be offered at a select group of medical facilities. A subset of the selected facilities, referred to as "model treatment centers", will work with PneumRx to host the peer-to-peer portion of the PneumRx Physician Training Program.

Each hospital intending to offer ELEVAIR Coil treatment will be qualified and subject to the following Site Requirements:

- ELEVAIR Coil procedures must only be performed by physicians who have successfully completed the PneumRx Training process
- Hospitals must confirm that appropriate infrastructure, equipment, and trained support personnel are available to support advanced interventional pulmonary procedures.

In addition to site qualification, the scope of the PneumRx training program includes 1) training and documentation of peer-to-peer course completion, 2) training effectiveness verification through case proctoring, and 3) ongoing program monitoring through specific training program data collection and through the existing PneumRx post market surveillance program.

Physicians wishing to be trained in use of the ELEVAIR System will typically be pulmonologists, interventional pulmonologists, or thoracic surgeons, and will have performed at least 50 interventional bronchoscopy procedures in the past two years.

PneumRx's course of physician training will include didactic, practical, and proctoring/Clinical Specialist training. Didactic training for participating physicians will be conducted through an online program. Practical training will be delivered through a structured, peer-to-peer program, held at a PneumRx-authorized Model Treatment Center. Focused sessions will offer didactic review of ELEVAIR System technology and procedural steps, as well as hands-on skills training using a bronchial model custom-designed by PneumRx. Physician trainees will have to demonstrate competency in all steps of the procedure on the model without any prompting from the trained PneumRx Representative.

After completion of peer-to-peer training, Proctoring / Clinical Specialist training will be conducted at the physician's site by trained PneumRx Representatives. The PneumRx Proctor must be in attendance for at least the first 5 cases with each physician trainee and their support team.

10.2. Clinical Studies and Post-Market Surveillance

In addition to the comprehensive Physician Training program, PneumRx has developed a wide-ranging post-market plan to support continued study of the long-term safety and effectiveness of the ELEVAIR System. This multi-faceted plan incorporates the following elements:

- Post-approval study in the US, with follow-up to three years
- Continuing five-year follow-up of subjects in the US IDE Clinical Program (RENEW Pivotal Trial, Roll-In cohort, and Crossover study)
- Post-market studies in the EU, with follow-up to three years
- Post-market surveillance procedures

10.2.1. US Post-Approval Study

PneumRx plans to conduct a prospective, observational, multi-center post-approval study (PAS) in the US, following premarket approval of the ELEVAIR System, and has submitted a proposed protocol to FDA for review (see Attachment 7). The primary objective of the proposed PAS is to demonstrate, in the post-approval setting, the safety of the ELEVAIR System for the treatment of severe emphysema by assessing the rate of device or procedure-related respiratory adverse events of interest (RAE). A secondary objective is to demonstrate, in the post-approval setting, the effectiveness of the ELEVAIR System for the treatment of severe emphysema by assessing the impact on subject quality of life using the St. George's Respiratory Questionnaire (SGRQ). The null and alternative hypotheses for the primary safety and effectiveness endpoints are based upon performance seen in the RENEW Trial, with an objective of demonstrating that the results observed in RENEW are representative of those seen in commercial use.

The proposed PAS will be conducted at up to 30 sites and will enroll patients who are appropriate for Coil treatment based on the Instructions for Use, when approved by FDA, who are scheduled for treatment with the ELEVAIR System, and who consent to have their clinical data collected in the study. A minimum of 300 subjects will be enrolled over approximately 2 years. Total study enrollment will be dependent upon product sales and therapy adoption, but it is the company's goal for a significant percentage of all patients treated in the first two years of US commercial launch to be enrolled in the PAS.

Subjects will be scheduled for bilateral treatment, with 1 to 3 months between Coil placement procedures. Post-procedure patient follow-up will be per each participating institution's standard of care; a study-specific follow-up visit will be recommended at 6 and 12 months after the first procedure, and then annually for up to 3 years from the date of the first procedure.

The proposed primary safety endpoint will be a composite rate of device- or procedure-related serious RAEs of interest through 12 months post-first implantation procedure. RAEs will be defined as AEs of the following types: Lower Respiratory Tract Infection/Pneumonia, COPD Exacerbation, Severe Hemoptysis, Pneumothorax, and Respiratory failure. A secondary safety endpoint will be the frequency of individual device- or procedure-related respiratory AEs through 12 months post-first implantation procedure in subjects treated with the ELEVAIR System.

Additional information will be collected regarding the incidence of Coil Associated Opacity, Coil migration, and Coil removal.

The proposed primary effectiveness measure will assess changes in quality of life, as measured by SGRQ, from baseline to 12 months post-first implantation procedure. Secondary effectiveness measures will assess changes in pulmonary function (including FEV_1, RV, and RV/TLC) and exercise capacity (6MWT) from baseline to 12 months post-first implantation procedure, and other clinical parameters similar to those captured during the RENEW Trial.

Progress of the PAS, together with a summary of safety and effectiveness data collected to date, will be regularly communicated to FDA as part of the annual report to the PMA.

10.2.2. US IDE Clinical Program (5-year Follow-Up)

The RENEW Pivotal Trial, Roll-In cohort, and Crossover study include subject follow-up for 5 years from the date of the first Coil treatment; subjects treated with Coils under the US IDE Clinical Program will continue to have follow-up visits scheduled, per protocol, yearly through 60 months. Collected safety and effectiveness data will be summarized in detail and provided to FDA for review as part of annual IDE reporting.

10.2.3. EU Post-Market Studies

PneumRx is currently conducting a post-market Registry in the EU with a primary objective of evaluating patient reported relief of symptoms following treatment with the ELEVAIR System in a real-world setting. Results for the initial 851 of the planned maximum of 2,000 patients have been analyzed; patients will be followed for up to 3 years.

PneumRx is also in the process of initiating an EU post-market study, ELEVATE, that will enroll 210 subjects to be followed for up to 3 years.

10.2.4. Post-Market Surveillance Plan

Data from clinical studies is combined with information from PneumRx's ongoing European commercial experience for periodic review as part of PneumRx's Post Market Surveillance (PMS) plan. PMS activities include weekly review of customer complaints, and quarterly summaries of AE/SAE reports from ongoing clinical studies, customer complaints, published literature, and other sources of information. Data collected through PMS activities are reviewed quarterly by a cross-functional Vigilance Team, with members from Vigilance, Medical, Clinical, Regulatory, and Quality. This team assesses the vigilance data against product risk analyses and the product IFU. Findings and recommendations from the PMS process are reviewed by the Medical Education Department, which will consider if there are particular elements of the training program that may require enhancement.

11. BENEFIT-RISK DISCUSSION

The benefits and risks of the ELEVAIR System are derived from 12-month outcomes for the RENEW RV ≥225% subpopulation, supported by long-term safety and effectiveness data from RENEW and by findings from the REVOLENS randomized control trial. REVOLENS shared a similar design, duration, patient population (RV >220%), and outcomes assessment as RENEW, and provides confirmatory evidence of benefits and risks in the intended treatment population. Outcomes from other randomized controlled trials and single arm studies of the ELEVAIR System are consistent and supportive of the benefit-risk conclusions discussed herein.

Finally, PneumRx has accumulated extensive clinical and procedural experience with the device over approximately 7 years of OUS commercialization, which has enabled development of a robust physician training program, and detailed, accurate labeling so that users are well-informed about the ELEVAIR System use, benefits, and risk management.

Severe Emphysema Patients are Underserved: A Clear, Unmet Medical Need

Emphysema is a chronic and progressively debilitating disease, with no cure and no approved non-surgical treatments that provide restoration of lung function. In its late stages, emphysema can prevent individuals from holding a job, maintaining social interactions, or even participating in basic conversation and performing simple activities of daily living and self-care. Treatment options for the severe emphysema population, estimated at approximately 1.2 million people in the US, are limited to lung volume reduction surgery and lung transplantation. These surgical options have restrictive eligibility criteria and pose significant morbidity and mortality risk, and are not widely used in the United States. In fact, less than 1,000 patients undergo LVRS and lung transplantation each year, contributing to a significant unmet medical need for alternative treatment options for severe emphysema patients who have maximized available standard of care medical therapies.

Benefits of ELEVAIR System Treatment

The ELEVAIR Coil is designed to reduce hyperinflation through compression of diseased lung parenchyma and concomitant improvement of lung elastic recoil. Reduction of hyperinflation in patients with severe emphysema improves lung function, which in turn leads to improvement in quality of life and exercise capacity. The results of RENEW, supported by other randomized clinical trials (REVOLENS) and single arm studies, demonstrate consistent, robust, and clinically meaningful benefits of the ELEVAIR System in treatment of subjects with severe emphysema and severe hyperinflation.

Clinical study data indicate strong and consistent benefit of ELEVAIR System treatment:

- *Clinically meaningful improvements in Exercise Capacity (6MWT)*
  RENEW and REVOLENS have demonstrated improvements after Coil treatment of 23.8 meters and 21 meters, respectively, compared to Control subjects receiving optimal

medical therapy. Moreover, 6MWT responder analyses, using response thresholds of either 25 meters (RENEW) or 54 meters (REVOLENS, 6-month assessment) showed that patients are substantially more likely to experience clinical benefit in exercise capacity with Coil treatment compared to standard of care.

- *Clinically meaningful improvements in Quality of Life (SGRQ)*
  Treatment with the ELEVAIR System provides robust improvement in quality of life for emphysema patients. Both RENEW and REVOLENS showed substantial SGRQ improvements (−10.6 points in both studies), and both trials also demonstrated that an SGRQ benefit versus baseline of more than −4 points is sustained through at least 24 months post treatment. The SGRQ responder rate in RENEW was much higher in Coil-treated subjects compared to the Control subjects (67% versus 24% when using a response threshold of 4 points). These results demonstrate that Coil Treatment greatly improves QOL for these patients.

- *Clinically meaningful improvements in Lung Function (FEV_1)*
  Treated patients experienced substantial improvements in FEV_1 of 8.9% (RENEW) and 11% (REVOLENS), correlated with robust reductions in hyperinflation (RV and RV/TLC) that are consistent with device design and mechanism of action. This cascade of benefits, with decreased hyperinflation enabling improved lung function, which in turn leads to improved clinical outcomes (quality of life, exercise capacity) is well understood and central to all lung volume reduction therapies.

Analyses of RENEW Trial outcomes demonstrated that the benefits described above are consistent in patients with severe hyperinflation irrespective of emphysema disease distribution (homogeneous vs. heterogeneous). This is a critical benefit of Coil therapy, as patients with severe homogeneous emphysema are considered poor candidates for surgical lung volume reduction and thus have no treatment options available to them, except for lung transplantation in a rare number of cases.

Notably, results from the RENEW Randomized Trial supported the addition of Coils to the clinical practice guidelines published by the Global Initiative for Chronic Obstructive Lung Disease (GOLD). The GOLD guidelines now include Coils as an option for minimally invasive, bronchoscopic intervention in patients with advanced emphysema, regardless of emphysema distribution or presence of collateral ventilation, to reduce end-expiratory lung volume and improve exercise tolerance, health status, and lung function. The guidelines state that Coils may be considered “in selected patients with heterogeneous or homogenous emphysema and significant hyperinflation refractory to optimized medical care” (GOLD 2018).

Risks of ELEVAIR System Treatment

The ELEVAIR System has an acceptable and well-characterized safety profile. The ELEVAIR Coil placement procedure is generally well tolerated; however, there is a small number of significant risks associated with the procedure which are important to communicate to patients

considering the Coil treatment. These risks are identified in the proposed labeling for the ELEVAIR System, and physician training materials. Patients treated with the ELEVAIR System have reported serious complications, including pneumonia/CAO, pneumothorax, bleeding, and COPD exacerbation, which in some cases led to Major Complications, including death. However, mortality rates in Coil-treated patients have been similar to those receiving standard of care in controlled clinical studies, and to expectations for this patient population. Pneumonia, pneumothorax, and COPD exacerbation, although sometimes serious, are relatively common in severe emphysema patients. They are generally considered, by physicians who regularly treat this disease, to be expected and treatable complications with a well-understood risk profile. Bleeding, while common after bronchoscopy and Coil placement, is usually mild and readily resolves with little or no medical intervention. In rare cases, bleeding after Coil treatment may be serious, and across the entire IDE Clinical Program, 1% of Coil-treated patients died following a severe bleeding event. A final significant risk, Coil Associated Opacity (CAO), is a local inflammatory response to the Coil that presents similarly to pneumonia on radiographic imaging. CAO is generally asymptomatic or symptomatically mild and resolves with limited intervention. Occasionally, CAO can be serious. A diagnosis and treatment algorithm has been developed to facilitate rapid identification and proper medical management of CAO in Coil-treated patients.

These risks, while serious, are acceptable for patients with severe emphysema who have maximized their benefit from optimal medical therapy and face growing symptom burden and morbidity. Available alternative therapies for such patients are surgical, which present with similar or increased risks when compared to the ELEVAIR System. LVRS, for example, presents similar risk of pneumonia, but much higher risk of pneumothorax, together with significant risk of other major pulmonary and cardiovascular morbidities. Patients considering lung transplant face the possibility of graft failure, infection, bronchiolitis, acute and chronic rejection of the transplanted organ, and must commit to a lifelong course of immunosuppressant therapy to manage this risk. Immunosuppressant medications themselves elevate the risk of developing post-transplant hypertension, diabetes, renal dysfunction, and other comorbidities that also require constant management.

Understanding the Benefit-Risk Tradeoff from the Patient Perspective

PneumRx conducted patient preference testing in Coil naïve patients with severe emphysema to better understand the tradeoffs that this patient population is willing to make with respect to the benefits and risks of interventions like the ELEVAIR System. Estimates of patient preferences for treatment type, treatment benefit, and treatment risks were used to calculate the proportion of patients who would consider the benefits of treatment with Coils to outweigh the risks, compared to optimal medical therapy alone. This study showed that 51% of patients with severe emphysema and severe hyperinflation (RV ≥225%) would see a net benefit to Coil treatment and would likely prefer a treatment such as the ELEVAIR System therapy over

maximum medical therapy alone.[r] These preference study results suggest that a meaningful population of emphysema patients may opt to pursue ELEVAIR Coil therapy as an additional treatment option if it were available to them.

Benefit-Risk Summary

Beyond the impact of optimal medical therapy alone, randomized clinical trials of lung volume reduction using the ELEVAIR System have demonstrated clinically meaningful improvements through at least 12 months in quality of life (SGRQ), lung function (FEV_1), and exercise capacity (6MWT) in patients with homogeneous and/or heterogeneous severe emphysema and severe hyperinflation, with the RENEW analysis of subjects with RV ≥225% predicted serving as clinical guidance for targeted severity of hyperinflation. Treatment with the ELEVAIR System is associated with a small number of significant risks, including pneumonia/CAO, pneumothorax, severe hemoptysis/bleeding, and COPD exacerbation. Mortality rates with Coil treatment are similar to those seen with optimal medical therapy, however, and the risks are acceptable for patients with severe emphysema who have maximized available treatment options. Patient preference testing has confirmed that approximately half of the intended treatment population would likely prefer perceive treatment with the ELEVAIR System over optimal medical therapy alone and would potentially choose to this treatment if it were available to them. The Sponsor concludes that the benefits of treatment with the ELEVAIR System outweigh the associated risks, and a significant proportion of the targeted patient population agrees with this assessment. Thus, the ELEVAIR System presents an important new, minimally invasive option for bronchoscopic lung volume reduction that improves quality of life, lung function, and exercise capacity in patients with severe emphysema and severe hyperinflation.

12. OVERALL CONCLUSIONS

The preclinical and clinical data in this PMA application support the reasonable assurance of safety and effectiveness of the ELEVAIR System. Based on prospective, randomized, controlled clinical trial results, it is reasonable to conclude that a substantial portion of the indicated patient population will achieve clinically meaningful results with access to this technology. The clinical benefits of the ELEVAIR System, which include improvements in quality of life, lung function, and exercise capacity, outweigh the risks associated with the device and placement procedures when used in the indicated population and in accordance with the directions for use.

In conclusion, the ELEVAIR System represents a reasonable therapeutic approach and viable treatment alternative for patients with homogeneous and heterogeneous severe emphysema and severe hyperinflation, with the RENEW analysis of subjects with RV ≥225% predicted

[r] To evaluate the 17.3% additional risk of pneumonia requiring hospitalization observed in the RV≥225% population in the RENEW study of the ELEVAIR System, patient preference for the additional risk of pneumonia requiring hospitalization was extrapolated using the parameters estimated in the preference model because the 17.3% observed risk was above the maximum level of 15% included in the patient preference study.

serving as clinical guidance for targeted severity of hyperinflation.

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14. ATTACHMENTS

Attachment 1: Supplemental Tables
Attachment 2: Detailed Summary of Additional Clinical Studies
Attachment 3: Proposed Instructions for Use
Attachment 4: Background Articles

- RENEW Randomized Pivotal Trial (Sciurba 2016)
- REVOLENS randomized clinical trial (Deslée 2016)

Attachment 5: RENEW Clinical Protocol
Attachment 6: RENEW Statistical Analysis Plan
Attachment 7: Proposed Post Approval Study Protocol