Elevair™ Endobronchial Coil System
Sponsor Executive Summary
June 14, 2018

Attachment 3: Proposed Instructions for Use

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Elevair™ Endobronchial Coil System
Instructions for Use

CAUTION: Federal law restricts this device to sale by or on the order of a physician.

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1.0 Device Description

The PneumRx® Elevair™ Endobronchial Coil System (also referred to as the “ELEVAIR System”) consists of two main components: sterile ELEVAIR Endobronchial Coils (also referred to as “ELEVAIR Coils” or “Coils”) and a sterile, disposable, single-procedure ELEVAIR Endobronchial Coil Delivery System (also referred to as “ELEVAIR Delivery System” or “Delivery System”). The implantable shape-memory nitinol Coils are designed to improve lung function in patients with severe emphysema (homogeneous and/or heterogeneous) and severe hyperinflation by restoring airway patency and reducing airway collapse during exhalation and exercise.

The ELEVAIR System is used in conjunction with a 2.8mm working channel therapeutic bronchoscope and fluoroscopic imaging to introduce multiple Coils into the lungs using a minimally invasive approach that requires no incision. When implanted in sub-segmental airways of the lung, each nitinol Coil is designed to gather and compress damaged lung tissue, re-tensioning the airway network to mechanically increase elastic recoil in the emphysematous lung. This action may reduce airway collapse and air trapping, while redirecting air to healthier portions of the lung. The Coils are available in several sizes to accommodate various airway lengths.

The ELEVAIR Delivery System consists of a Guidewire, Cartridge, Catheter, and Forceps. The Guidewire guides the Catheter to the target airway and facilitates the selection of the appropriate Coil length. The Cartridge couples to the Catheter and temporarily straightens the Coil, which facilitates Coil advancement into the Catheter. The Catheter delivers the straightened Coil through the bronchoscope and into the target airway. The Forceps grasp the proximal end of the Coil to deliver the Coil to the target airway through the Catheter, where the Coil recovers to its pre-determined shape upon deployment at the target tissue site. The Catheter and Forceps can also be used to remove and/or re-position the Coil, if necessary. A single Delivery System is used to deliver multiple Coils to the same patient in a single procedure.

The ELEVAIR Coils are provided in three sizes: #1 (100mm length), #2 (125mm length), and #3 (150mm length). Each Coil is individually packaged in a protective packaging shell, which is placed inside of a pouch and carton, and sterilized by Electron Beam (E-Beam) radiation. The Delivery System components are pouched together, placed inside of a carton, and sterilized by Ethylene Oxide (EtO) gas.

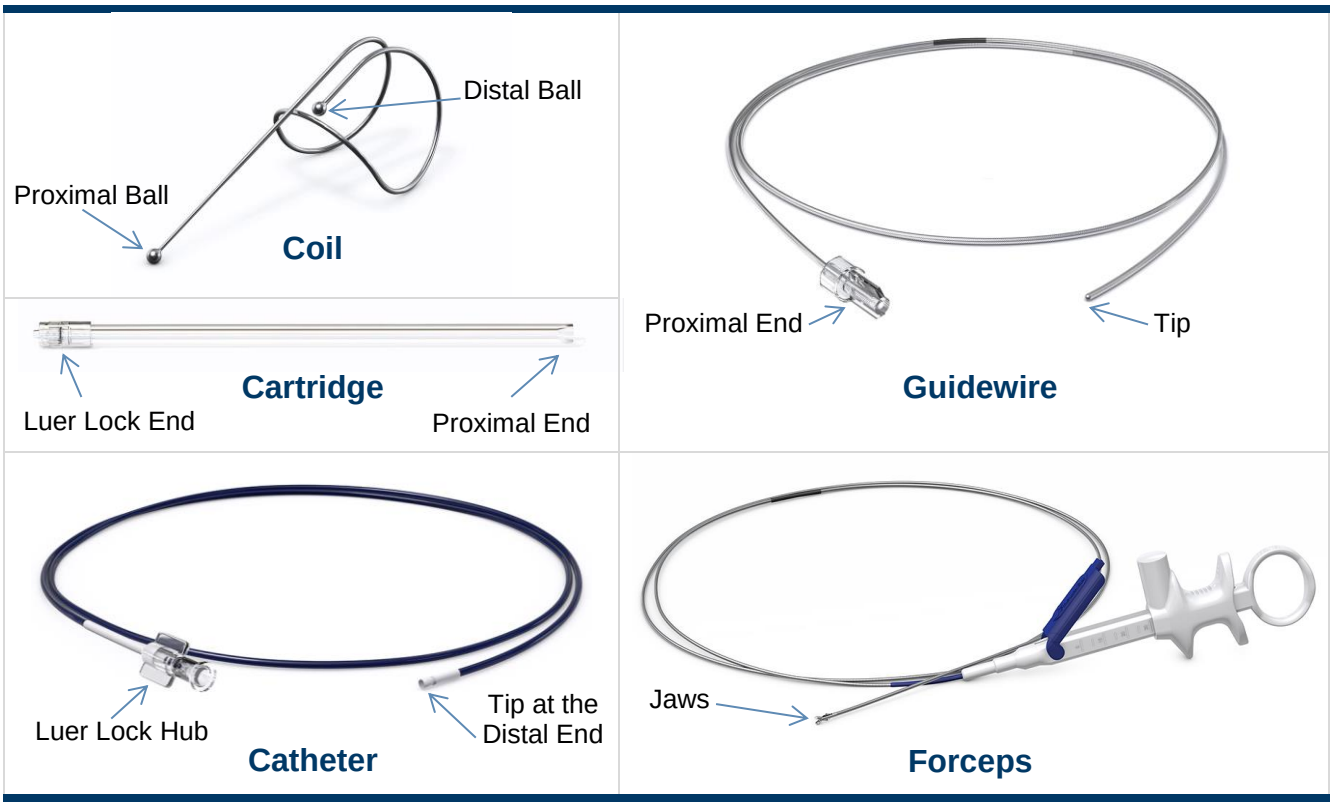

Figure 1: Components of the ELEVAIR System

2.0 Indications for Use

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

3.0 Contraindications

The ELEVAIR Endobronchial Coil System is contraindicated for use in:

- Patients with a known sensitivity to drugs required for performing bronchoscopy or in whom bronchoscopic procedures are contraindicated
- Patients with evidence of active infection in the lungs
- Patients with hypersensitivity or allergy to nitinol (nickel-titanium) or its constituent metals
- Patients with clinically significant bleeding disorders
- Patients with clinically significant pulmonary fibrosis
- Patients with severe bullous disease (defined by bulla >1/3 of lung volume, or single bullous defect >8 cm), or significant paraseptal emphysema
- Patients with clinically significant, generalized bronchiectasis

- Patients with severe pulmonary hypertension defined by right ventricular systolic pressure >50mmHg (preferably measured by right heart catheterization)

Note: For further guidance, see **Section 4.3.5 – Pulmonary Hypertension**.

- Patients taking immunosuppressive drugs other than steroids (e.g., for the treatment of cancer, rheumatoid arthritis, autoimmune disease, or prevention of tissue or organ rejection)
- Patients taking >20mg prednisone (or equivalent dose of a similar steroid) daily

4.0 Warnings

4.1 Clinician Use Warnings

- The ELEVAIR System should only be used by those physicians skilled in the use of therapeutic bronchoscopes and who have appropriate training by a PneumRx representative. Users should be familiar with the principles, clinical applications, complications, side effects, and hazards commonly associated with interventional pulmonology procedures and the ELEVAIR Endobronchial Coil Procedure.

4.2 Coil Removal Warnings

- Bronchoscopic Coil removal **must be medically indicated** (e.g., persistent pleuritic pain). The potential benefit of Coil removal must be weighed against the potential harm including the known risks of bronchoscopy.
- Removing Coils bronchoscopically may become increasingly difficult **after 2 or more months** following implantation, depending on the amount of tissue regrowth present. If bronchoscopic removal is not possible, thoracoscopic retrieval can be considered. See **Section 13.0 – Bronchoscopic Coil Removal Following Implantation** for procedural details.
- If Coil removal is required, do not attempt to cut through, bend or break the Coil in any manner. Mishandling of the Coil in this manner can result in corrosion of the device and creation of sharp surfaces that can lead to injury, illness or death of the patient.

Note: Bronchoscopic Coil removal subsequent to the implantation procedure must be performed using a therapeutic bronchoscope with a minimum 2.0mm inner diameter working channel and a 65cm maximum working length.

4.3 Warnings Regarding Patient Pre-Existing Conditions

4.3.1 Hemoptysis and Anticoagulation

- Hemoptysis is a known complication of Coil treatment and of diagnostic and interventional bronchoscopic procedures in general. In infrequent cases, fatal hemoptysis has occurred in patients who have undergone Coil treatment. As such, the use of anticoagulant drugs in patients undergoing Coil treatment should be carefully considered, as it may be associated with an increased bleeding risk.
    - To decrease the risk of serious pulmonary bleeding events, use of antiplatelet (e.g., aspirin, clopidogrel) or anticoagulant therapy (e.g., warfarin, NOAC's) should be stopped for seven (7) days prior to and seven (7) days following the Coil implantation procedure, or as recommended by the pharmaceutical manufacturer.
    - The benefits and risks of initiation or continuing use of antiplatelet or anticoagulant medications in patients who have undergone Coil treatment should be carefully assessed.

4.3.2 Bronchiectasis and Atelectasis

- Do not implant ELEVAIR Coils in any area of the lung exhibiting bronchiectasis or significant atelectasis. To decrease the risk of serious pulmonary bleeding events, Coil implantation should be performed in patients with bronchiectasis only after careful consideration, avoiding any suspect areas of the lung.

4.3.3 Cancerous Lung Nodules/Other Lung Conditions

- Exercise additional caution when considering treatment of patients with suspicious or confirmed cancerous lung nodules or evidence of other severe disease or lung conditions that may compromise survival of the patient post procedure, in consideration of the patient's likelihood of benefiting from ELEVAIR Coil therapy.

4.3.4 Asthma-predominance

- In patients with asthma COPD overlap, asthma predominant disease should be ruled out by the treating physician.

4.3.5 Pulmonary Hypertension

- Patients with imaging findings indicative of severe pulmonary hypertension (e.g., a segmental artery-to-bronchus ratio greater than 1:1 in three of four pulmonary lobes) should undergo further testing to rule out severe pulmonary hypertension, which is a contraindicated condition.

***Note*:** For additional patient selection considerations, see **Section 6.0 – Individualization of Treatment**.

4.4 ELEVAIR Coil and Delivery System Warnings

- To avoid puncturing the pleura or causing airway trauma, never advance the Guidewire, Catheter, or any other ELEVAIR System component against resistance. If resistance is met, determine the cause and take remedial action before again attempting to advance the ELEVAIR System component.
- Do not attempt to reuse, reprocess, clean or re-sterilize the ELEVAIR System components by any method. Reuse, reprocessing, or re-sterilization using irradiation, steam, ethylene oxide or other chemical sterilants may compromise the structural integrity of the device and/or lead to device failure, and may create the risk of contamination of the device and/or cause patient infection or cross-infection, including but not limited to the transmission of infectious disease(s) from one patient to another. Contamination of the device may lead to injury, illness or death of the patient.
- Do not use the ELEVAIR System components if the carton is compromised upon receipt. Always inspect the pouch seals prior to opening the pouch. Do not use the ELEVAIR System components if the pouch is open or damaged, as device functionality and/or sterility may be compromised. Use of non-sterile or damaged devices may result in patient harm.
- Do not use the ELEVAIR System components if the tamper-evident seal is broken, the "Use By" (expiration) date specified on the package has lapsed, or the device has been dropped or damaged. Never attempt to repair a damaged device. If damage is found, discard the device and call your PneumRx representative for a replacement.
- Do not use the ELEVAIR System if labeling is incomplete or illegible.
- Refer to the Instructions for Use supplied with any ancillary devices to be used in conjunction with the ELEVAIR System for applicable intended use, contraindications, warnings, precautions, and potential complications.
- After use, dispose of the product and packaging in accordance with hospital, administrative and/ or local government policy.

5.0 Precautions

5.1 General Precautions

- Carefully read all labels and instructions prior to using the ELEVAIR System. Observe all contraindications, warnings, and precautions noted throughout these instructions. Failure to follow the Instructions for Use may result in increased risk of patient harm, procedural difficulties, complications, or device damage.

- The ELEVAIR Endobronchial Coil procedure is a bilateral treatment that should be performed in two separate sessions.
- Do not expose the Delivery System to organic solvents (alcohol), as structural integrity and/ or function of the device may be impaired.

5.2 Procedural Precautions

- Always use a bronchoscope for the procedure. The ELEVAIR System is intended to be used with a therapeutic bronchoscope with a 2.8mm inner diameter working channel and a 65cm maximum working length. Use of the ELEVAIR System with bronchoscopes not meeting these criteria may result in equipment or device damage.
- Do not use a kinked Delivery System or Coil.
- Coils should be placed so that they are not in contact with adjacent Coils in order to avoid metal-on-metal friction.
- Avoid placing two Coils in the same airway.
- Do not advance the Catheter without Guidewire support. When advancing the Catheter, always lead with the Guidewire.
- Use fluoroscopy to visualize the Guidewire when it is beyond the visual range of the bronchoscope. Turn on fluoroscopy when the Guidewire fluoroscopy marker band enters the Catheter hub.
- Do not advance the Guidewire against resistance.
- Forcing the Guidewire past a sudden curve in a distal airway could cause tissue to become pinched within the curved portion of the Guidewire.
- Fluoroscopy should remain on to make sure the Guidewire does not move during Catheter advancement.
- Do not force the Catheter around a sharp bend on the Guidewire.
- If unable to advance the Catheter to the distal end of the Guidewire, pull the Guidewire back to be aligned with the tip of the Catheter. Do not force the Catheter.
- Do not pull the Forceps jaws or the Coil out of the proximal end of the Cartridge while loading a Coil. Pushing the Coil back into the Cartridge may cause damage to the Coil. If this happens, do not use the Coil.
- Do not use the Coil if the Coil is dropped or outside of the packaging shell for any reason.
- Grip the Forceps no more than 5cm from the proximal end of the Cartridge to prevent kinking while advancing.

- Do not advance the ELEVAIR System components beyond the visual range of the bronchoscope unless under fluoroscopic visualization. Turn fluoroscopy on when the black proximal marker band on the Forceps enters the Cartridge.
- Do not move the bronchoscope position during the deployment procedure.
- Do not attempt to deliver Coils without using fluoroscopy.
- The Forceps jaws cannot open if they are within the Catheter. The Forceps jaws must extend at least 1cm beyond the distal tip of the Catheter and the bronchoscope to release the Coil.
- Do not reuse the Coil if Coil removal is performed in a procedure separate from the Coil placement procedure. Coil may be reused if removed and redeployed during original bronchoscopy for Coil placement.

6.0 Individualization of Treatment

The risks and benefits should be considered for each patient before use of the ELEVAIR System.

The ELEVAIR System is indicated for treatment of patients with severe emphysema and severe hyperinflation. Clinical data have demonstrated improved clinical benefit (quality of life, lung function, and exercise capacity) in subjects with higher residual volume (RV), including a subgroup analysis demonstrating increased device effectiveness in subjects with RV ≥ 225% predicted. Additional patient selection factors should also be assessed, such as comorbidities that may influence clinical benefit, and important risk factors, including antiplatelet and anticoagulant therapy. See **Section 14.0 – Clinical Studies** and **Sections 3.0 and 4.0 - Contraindications and Warnings.**

The ELEVAIR System should be used with caution and only after careful consideration, especially in patients with:

- History of frequent recurrent clinically significant respiratory infections
- Hypercapnia
- Uncontrolled or severe congestive heart failure or recent myocardial infarction

6.1 Use in Special Populations

The safety and effectiveness of ELEVAIR System therapy has not been evaluated in the following patient populations:

- Pregnant or lactating women
- Patients who have not quit smoking

- Patients with FEV_1 >45% of predicted value
- Patients who have had Lung Volume Reduction Surgery or lobectomy
- Patients with alpha-1 antitrypsin deficiency
- Patients with Residual Volume (RV) <175% predicted
- Patients with low levels of visible parenchymal structure on CT
- Patients with severe gas exchange abnormalities as defined as PaCO2 >55mm Hg, or PaO2 <45mm Hg on room air (high altitude criterion: PaO2 <30mm Hg)
- Patients with DLCO <20% of predicted value

7.0 Potential Adverse Events

Adverse events that may be observed with endobronchial devices, systems for placement of these devices, and related procedures (including diagnostics and bronchoscopy procedures) and use of the ELEVAIR System include, but are not limited to, the events shown below. These events may vary in frequency and severity.

- Allergic Reaction
- Aspiration
- Bleeding or Hemorrhage
- Bronchial Blood Clot
- Bronchial Ulceration
- Bronchospasm
- Cardiac Arrhythmias
- COPD Exacerbation
- Cough
- Death
- Device Dislocation
- Dyspnea
- Emphysema, Subcutaneous
- Hemoptysis, including severe hemoptysis
- Hoarseness
- Hypertension
- Hypotension
- Infection
- Inflammation
- Lung Abscess
- Pain
- Painful Respiration
- Pleural Effusion
- Pleural Fistula
- Pneumonia*
- Pneumonitis
- Pneumothorax
- Procedure-Related Complications (e.g., fever, spasm)
- Pulmonary Embolism
- Respiratory Distress
- Respiratory Failure
- Respiratory Tract Infection
- Sedation-Related Complications (e.g., nausea, vomiting, headache)
- Sepsis
- Tissue Reaction, Localized (a.k.a. Coil Associated Opacity*)
- Tissue Trauma, Procedural (e.g., tissue perforation, dissection)

***Note*:** Additional interventional procedures may be necessary if patients experience some of these potential adverse event(s) following ELEVAIR Coil treatment.

* A recognized, non-infectious localized tissue reaction, also termed Coil Associated Opacity (CAO), may occur in the area of implanted ELEVAIR Coils and is typically diagnosed on imaging (chest X-ray or CT scan). This is believed to be an inflammatory response that may present with pneumonia-like symptoms, including chest or pleuritic pain/discomfort, increased dyspnea, fatigue, and/or haze or infiltrates on chest X-ray, and may be difficult to distinguish from pneumonia. While the clinical symptoms associated with CAO have been observed in clinical trials up to 2 months following the Coil procedure, many of these events are asymptomatic or symptomatically mild, resolve with limited intervention, and do not develop into serious adverse events (SAEs). However, CAO can become severe and require prompt and specific intervention. Thus, patients are advised to contact their treating physician immediately for follow-up if they experience pneumonia-like symptoms.

See **Section 14.1.6 - Safety Results** for a list of adverse events that were reported during the RENEW Pivotal Trial.

8.0 Clinician Use Information

These Instructions for Use are provided as a general informational guide for the safe, effective use of the ELEVAIR System. Medical practitioners should always rely on their clinical experience and judgment, including current sterile techniques and interventional practices when using the ELEVAIR System.

8.1 Materials Required

The following additional materials are required to perform the ELEVAIR Endobronchial Coil procedure:

- Therapeutic bronchoscope with a 2.8mm inner diameter working channel and a 65cm maximum working length

Note: Bronchoscopic Coil removal subsequent to the implantation procedure must be performed using a therapeutic bronchoscope with a minimum 2.0mm inner diameter working channel and a 65cm maximum working length.

- Fluoroscopic imaging equipment
- Sterile saline
- High-walled tray or large table with rim to maintain coiled Guidewire and Forceps when not in use

- Sufficient space to work with ELEVAIR System components, including space for product and to load Coils into Cartridge

8.2 Peri-procedural Care

After careful evaluation to ensure the patient is an appropriate candidate for use of the ELEVAIR System, schedule the procedure. High Resolution Computed tomography (HRCT) or other appropriate method(s) for assessment of emphysematous lung tissue may be used during treatment planning to identify the lung lobes most appropriate for treatment.

A prophylactic regimen of antibiotics should be taken on the day of the procedure and for at least seven (7) days after the procedure. It is recommended that steroids be taken two (2) days before and at least seven (7) days after the procedure.

Perform radiographic procedures and prepare subject for bronchoscopy per standard hospital practice. After the procedure, allow the patient to recover from anesthesia and monitor as per standard hospital practice.

A chest X-ray should be done post-procedure to verify Coil placement and to ensure no pneumothorax is present. A second chest X-ray should be done before discharge, a minimum of 4 hours following the first chest X-ray.

Provide detailed instructions to the patient on expected side-effects of the Coil procedure, including the potential adverse events listed in **Section 7.0 - Potential Adverse Events**, and instruct the patient to contact their treating physician immediately should any of the potential adverse events be experienced.

It is particularly important that patients be instructed at discharge to contact their implanting physician if they experience symptoms that may be indicative of pneumonia or CAO, to ensure that appropriate treatment is delivered.

After the patient recovers, the Coil procedure to treat the contralateral lung should be scheduled, typically 1 to 3 months after the first procedure.

9.0 Patient Information

9.1 Patient Implant Card and Patient Brochure

A Patient Implant Card containing specific information about the ELEVAIR Coils is included in each Delivery System package. After implantation, please note the number and location of ELEVAIR Coils implanted in the section titled “Location & Number of Coils.” Provide the treating facility and physician information in the section titled “Treating Facility Contact Information.” Provide the card to the patient prior to discharge. All patients should keep

this card in their possession at all times and be instructed to present the card any time chest imaging is performed.

PneumRx has developed a Patient Brochure that includes information specifically designed for patients regarding how the ELEVAIR Coils work and procedural information including potential risks and benefits. Copies of the brochure can be obtained from PneumRx online at **www.pneumrx.com/us** or by calling **(855) 570-5151**. Instruct all patients to obtain and read the Patient Brochure prior to treatment.

9.2 Magnetic Resonance Imaging (MRI) Safety Information

MR Conditional

Non-clinical testing and in-vivo electromagnetic simulations have demonstrated that the ELEVAIR Coil is **MR Conditional**. A patient with this device can be scanned safely in an MR system meeting the following conditions:

- Static magnetic field of 1.5T and 3.0T
- Maximum spatial field gradient of 3,000 gauss/cm (30.0 T/m)
- Maximum MR system reported, whole body averaged specific absorption rate (SAR) of <2W/kg (Normal Operating Mode)

Under the scan conditions defined above, the ELEVAIR Coil is expected to produce a maximum temperature rise of 6.5°C after 15 minutes of continuous scanning.

In non-clinical testing, the image artifact caused by the ELEVAIR Coil extended approximately 10mm from this device when imaged with a gradient echo pulse sequence and a 3.0T MRI System.

10.0 How Supplied and Storage

10.1 Delivery System

The Delivery System (Guidewire, Catheter, Cartridge, and Forceps) is assembled onto a backer card, which is pouched and packaged in a carton. The Delivery System is provided STERILE for use in a single patient.

10.2 Coil

Each individual Coil is contained in a protective packaging shell, which is pouched and packaged in a carton containing either one (1) Coil or five (5) Coils. Each Coil is provided STERILE for single use only.

10.3 Storage

Always store the ELEVAIR System components in a dry place.

11.0 Directions for Use

⚠ ***Caution:*** **Always use a bronchoscope for the procedure. The ELEVAIR System is intended to be used with a therapeutic bronchoscope with a 2.8mm inner diameter working channel and a 65cm maximum working length. Use of the ELEVAIR System with bronchoscopes not meeting these criteria may result in equipment or device damage.**

PREPARE DEVICES FOR USE

1. Remove the Guidewire and Catheter together from the packaging hoop.
2. Remove the Forceps and the Cartridge from the packaging.

   ⚠ ***Caution*****: Do not use a kinked Delivery System or Coil.**
3. Flush the Cartridge with sterile saline (prior to first Coil deployment only).

POSITION DELIVERY SYSTEM

4. Identify the airways leading to the diseased parenchyma.
   a. Treatment should target the most damaged lobe (upper or lower) in each lung identified through pre-procedure assessment method.
   b. Deployment of Coils should start in the segment which presents the most difficult access first, and then progress to less difficult segments.
   c. The recommended treatment strategy is to deploy **10-12 Coils in upper lobes** or **10-14 Coils in lower lobes**. When approaching the upper limit, discontinue deploying additional

Coils if increased resistance is felt while advancing the proximal end of the Coil into the lung.

d. To achieve optimal Coil placement, position Coils in the area between the hilum and the pleura, leaving a "Coil-free zone" approximately 4cm adjacent to the pleura. This placement will result in a "fan-like" distribution of Coils in the sub-segmental airways throughout the treated lobe, as shown in **Figure 2**.

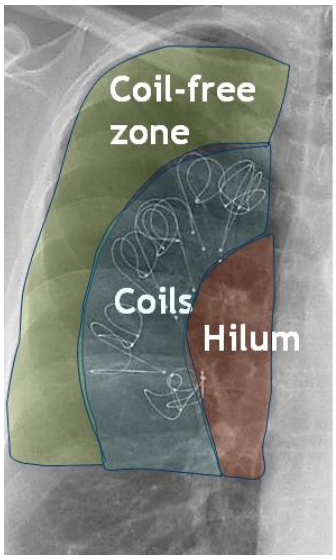

Figure 2: Optimal Coil Placement

⚠ ***Caution*: Coils should be placed so that they are not in contact with adjacent Coils in order to avoid metal on metal friction.**

⚠ ***Caution*: Avoid placing two Coils in the same airway.**

5. Navigate and wedge the bronchoscope into the selected airway (at the ostium leading to sub-segmental airways).
6. Align the tip of the Guidewire and the Catheter (see **Figure 3).**

⚠ ***Caution*: Do not advance the Catheter without Guidewire support. When advancing the Catheter, always lead with the Guidewire.**

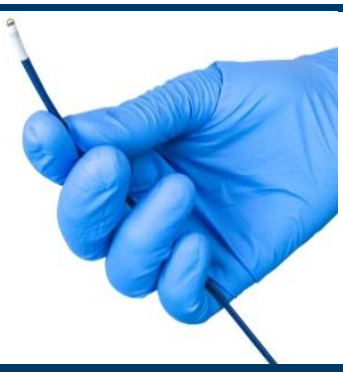

Figure 3: Align Guidewire and Catheter Tips

7. Insert the Catheter and Guidewire into the working channel of the bronchoscope (see **Figure 4**).

Figure 4: Insert Catheter and Guidewire Together

8. Advance the Catheter and Guidewire to the tip of the bronchoscope.
9. Advance the Guidewire to the end of the targeted airway (see **Figure 5**).

   ⚠***Caution*: Use fluoroscopy to visualize the Guidewire when it is beyond the visual range of the bronchoscope. Turn on fluoroscopy when the Guidewire fluoroscopy marker band enters the Catheter hub.**

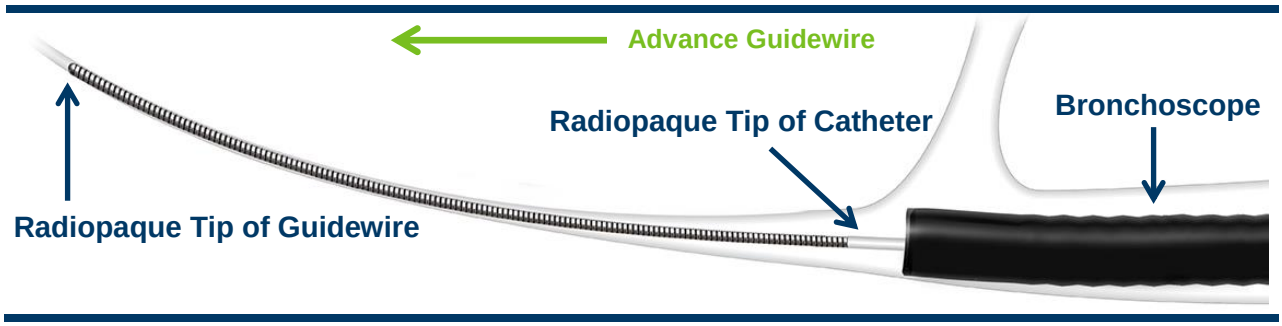

Figure 5: Advancing Guidewire into Targeted Airways

a. Gently navigate the Guidewire into the distal airways under fluoroscopic guidance until the tip reaches the pleura or suddenly curves from a straight path.

⚠ ***Caution*: Do not advance the Guidewire against resistance.**

⚠ ***Caution*: Forcing the Guidewire past a sudden curve in a distal airway could cause tissue to become pinched within the curved portion of the Guidewire.**

10. Retract the Guidewire tip by grasping the proximal end of the Guidewire, adjacent to the Catheter hub, and withdrawing **4-5 cm** (using predetermined measurement reference) from the hub.

11. While holding the Guidewire position fixed relative to the bronchoscope, advance the Catheter distally until it is even with the tip of the Guidewire (see **Figure 6)**.

⚠ ***Caution*: Fluoroscopy should remain on to make sure the Guidewire does not move during Catheter advancement.**

⚠ ***Caution*: Do not force the Catheter around a sharp bend on the Guidewire.**

⚠ ***Caution*: If unable to advance the Catheter to the distal end of the Guidewire, pull the Guidewire back to be aligned with the tip of the Catheter. Do not force the Catheter.**

Figure 6: Catheter Tip Aligned with Guidewire Tip

SELECT COIL

12. Select the appropriate Coil size by counting the number of radiopaque markers on the Guidewire visible outside the bronchoscope (see **Figure 7** and **Table 1**).
    a. The markers indicate the minimum recommended Coil size to be used.
    b. Do not count the Guidewire tip as a marker for Coil selection.
13. Remove the Guidewire from the Catheter while maintaining the Catheter position. Turn fluoroscopy off after the Guidewire is removed from the Catheter.

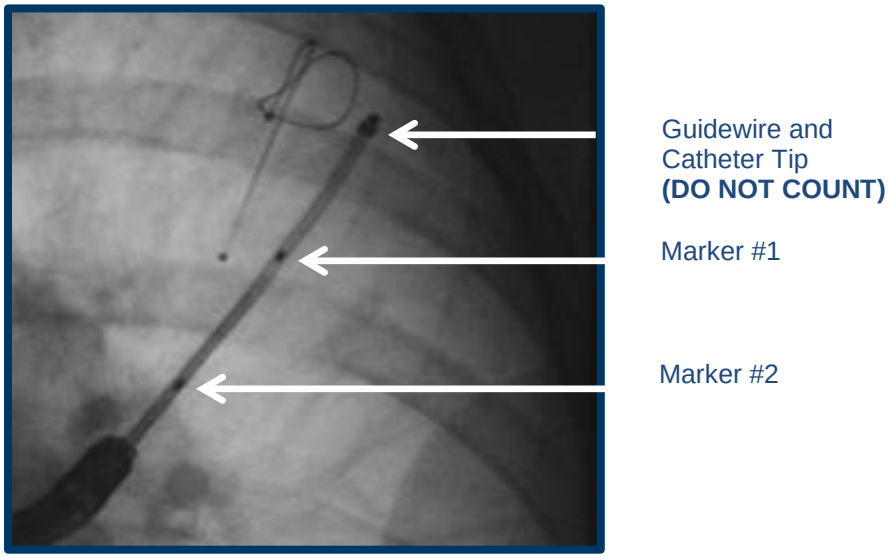

Figure 7: Guidewire Radiopaque Marker Band under Fluoroscopy

Table 1: Coil Size Selection

Number of Radiopaque Markers Visible Outside Bronchoscope	Appropriate Coil Size
0	Determine possibility for Coil #1. While maintaining Catheter position, advance the Guidewire to the end of the airway. If a marker is seen outside of bronchoscope: ➢ Select Coil #1 If **NO** marker is seen outside of bronchoscope: ➢ **DO NOT** deploy a Coil
1	Coil #1 or Coil #2
2	Coil #2 or Coil #3
3	Coil #3

Note: Coil #1 = 100mm length; Coil #2 = 125mm length; Coil #3 = 150mm length

LOAD COIL

14. Remove the plastic shell containing the selected Coil from the carton and pouch.
15. Insert the Forceps into and through the Cartridge, making certain that the Forceps exit the Luer lock end of the Cartridge as shown in **Figure 8**.

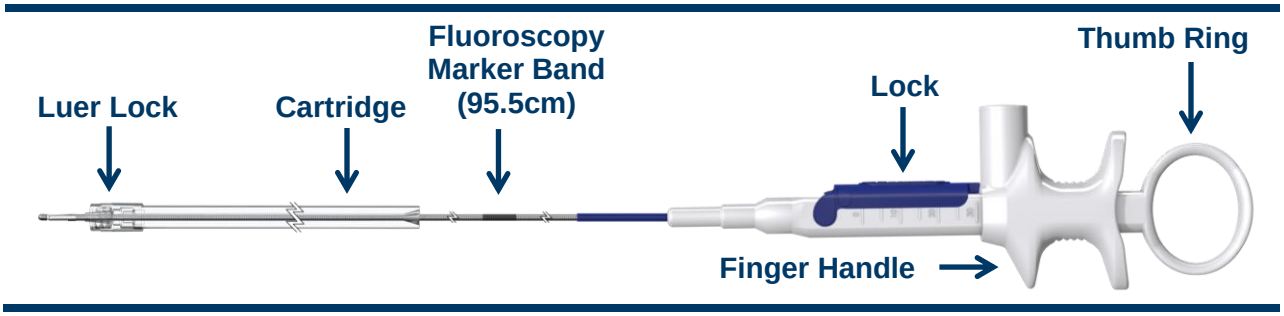

Figure 8: Advancing Forceps through Cartridge

16. Unlock the Forceps by closing the jaws with force and lifting the Lock up (close by squeezing the Finger Handle and Thumb Ring closer together).
17. Open the Forceps jaws by increasing the distance between the Finger Handle and Thumb Ring (see **Figure 9**).

Figure 9: Opening Forceps

18. Grasp the Coil by closing the Forceps jaws around the proximal ball (see **Figure 10**).

Figure 10: Grasp Coil by Closing Forceps Jaws

19. Close and lock the Forceps jaws closed (see **Figure 11** and **Figure 12**). Press the blue locking tab to the handle until an audible clicking sound is heard to prevent releasing the Coil.

Figure 11: Closing Forceps

Figure 12: Locking Forceps

20. Seat the Cartridge into the opening of the plastic protective shell (see **Figure 13**).

Figure 13: Seat Cartridge into Shell

21. Slowly pull the Forceps until the Coil is removed from the plastic protective shell and completely inside the Cartridge (see **Figure 14)**.

⚠***Caution*: Do not pull the Forceps jaws or the Coil out of the proximal end of the Cartridge while loading a Coil. Pushing the Coil back into the Cartridge may cause damage to the Coil. If this happens, do not use the Coil.**

⚠***Caution*: Do not use the Coil if the Coil is dropped or outside of the packaging shell for any reason.**

Figure 14: Pull Coil into Cartridge

22. Connect and lock the Cartridge to the Luer lock hub of the Catheter.
23. Deliver the Coil into the Catheter by advancing the Forceps and Coil (see **Figure 15**).

⚠***Caution*: Grip the Forceps no more than 5cm from the proximal end of the Cartridge to prevent kinking while advancing.**

Figure 15: Advance Coil Until Fluoro Marker Enters Cartridge

24. Turn on fluoroscopy when the fluoroscopy marker band (on Forceps shaft) enters the Cartridge.

⚠***Caution*: Do not advance the ELEVAIR System components beyond the visual range of the bronchoscope unless under fluoroscopic visualization. Turn fluoroscopy on when the black proximal marker band on the Forceps enters the Cartridge.**

25. Advance the Coil distal ball to the distal end of the Catheter and verify the position of the Coil via fluoroscopy.
26. Have the assistant hold the bronchoscope fixed relative to the patient.

⚠***Caution*: Do not move the bronchoscope position during the deployment procedure.**

DEPLOY COIL

⚠ ***Caution*: Do not attempt to deliver Coils without using fluoroscopy.**

WARNING: To avoid puncturing the pleura or causing airway trauma, never advance the Guidewire, Catheter, or any other ELEVAIR System component against resistance. If resistance is met, determine the cause and take remedial action before again attempting to advance the ELEVAIR System component.

27. Deploy the Coil by distally advancing the Forceps. Advance the Coil out of the distal end of the Catheter until the first half-loop is positioned in the target airway (see **Figure 16**).

Note: If the view of the Coil is obstructed, adjust the fluoroscope to allow adequate visualization.

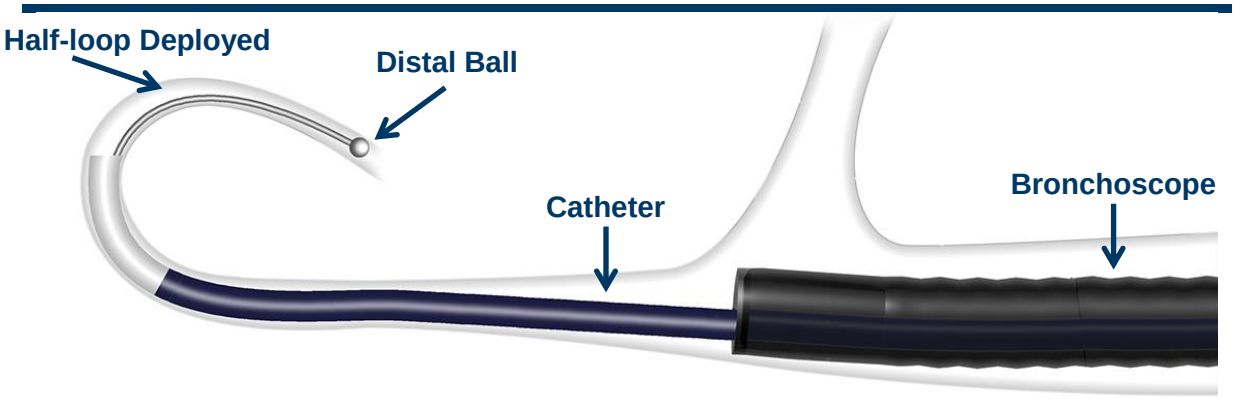

Figure 16: Observing the Partially Deployed Coil

28. Retract the Catheter while maintaining a slight constant pressure to advance the Forceps forward until the Forceps jaws are visible approximately 2cm distal to the end of the bronchoscope. Maintain Forceps position and continue to retract the Catheter into the bronchoscope (see **Figure 17**).

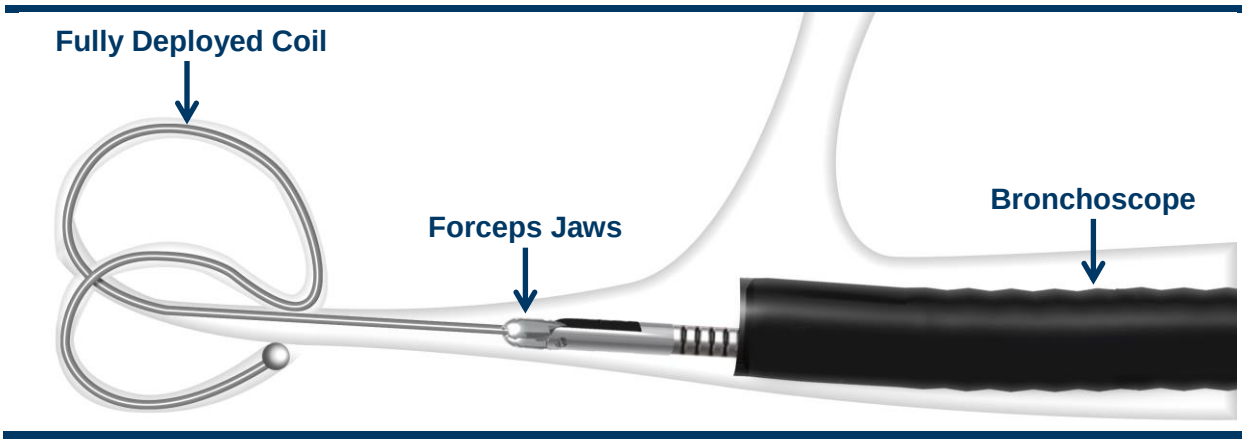

Figure 17: Observing the Completely Deployed Coil

29. Verify the position of the Coil prior to unlocking the Forceps and releasing the Coil.

a. Ideally the proximal end of the Coil is in the segmental airway or more distal.

b. If the Coil has been placed proximal to the airway, continue to place Coils and reassess placement after placement of the last Coil. If the proximal end of the Coil is pressing into the tissue as shown in **Figure 18**, reposition or redeploy the Coil.

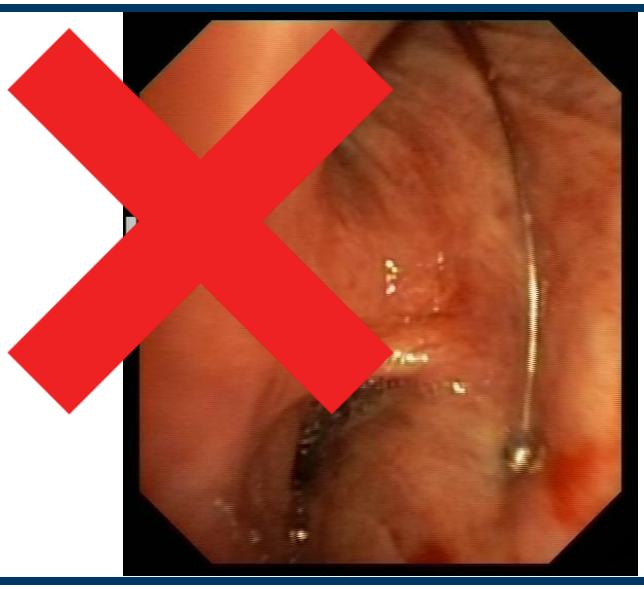

Figure 18: Example of Proximal Placement

c. If Coil position is not ideal (optimal placement shown in **Figure 19)**, see **Section 12.0 – Coil Repositioning Following Deployment**.

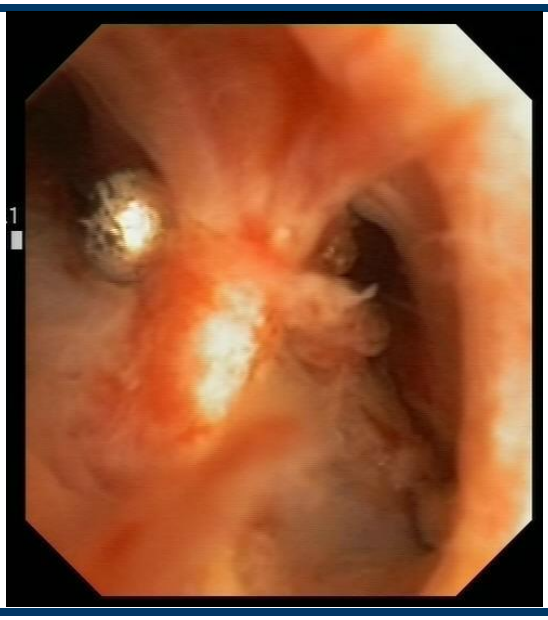

Figure 19: Example of Optimal Coil Placement

DETACH AND REMOVE DELIVERY SYSTEM

30. Gently retract the Forceps approximately 1cm to create slight tension between the Forceps and the Coil. Maintain the tension.
31. Unlock and open the Forceps jaws.

⚠***Caution*: The Forceps jaws cannot open if they are within the Catheter. The Forceps jaws must extend at least 1cm beyond the distal end of the Catheter and the bronchoscope to release the Coil.**

32. Close and lock the Forceps jaws.
33. Confirm that the proximal ball has been released before turning the fluoroscopy off.
34. Unlock the Cartridge from the Catheter (Luer lock), and remove the Cartridge and Forceps from the Catheter together as a unit.
35. Withdraw the distal tip of the Catheter into the bronchoscope.

    Note: The Catheter may remain in the bronchoscope during positioning to the next treatment airway. Repeat Steps 7-35 to deploy additional Coils.

12.0 Coil Repositioning Following Deployment

<table>
<tr>
<td rowspan="3">Note: If the Coil is already released from the Forceps but the proximal ball is not in the segmental airway or more distal, it is recommended to deploy all remaining Coils before attempting to reposition. If a Coil placement is still not ideal as shown in Figure 19 at the end of the treatment, recapture the proximal ball with the Forceps and reposition as described. If you cannot capture the proximal ball with the Forceps, capture the wire and reposition the Coil proximal end until you can capture the proximal ball.</td>
<td>If proximal ball needs to be advanced 0-1 cm
1. Advance the Catheter 2cm past the Forceps jaws, then gently advance the Catheter and Forceps together.
2. Repeat Steps 28 and 29 (See Section 11.0 – Directions for Use).</td>
</tr>
<tr>
<td>If proximal ball needs to be advanced 1-2cm
1. Hold the Forceps and Coil position fixed relative to the bronchoscope and advance the Catheter distally to resheathe up to half of the Coil.
2. Retract the Catheter while advancing the Forceps more distal than during the previous deployment.</td>
</tr>
<tr>
<td>If proximal ball needs to be advanced more than 2cm
Recapture and redeploy the Coil:
1. Resheathe the Coil until it is fully captured in the Catheter.
2. Withdraw the Coil by proximally retracting the Forceps until the Coil is within the Cartridge.
3. Unlock the Luer lock and remove the Cartridge, Coil, and Forceps as a single unit, while leaving the Catheter in place.
4. Introduce the Guidewire into the Catheter and reposition the Catheter so the Coil can be redeployed.</td>
</tr>
</table>

13.0 Bronchoscopic Coil Removal Following Implantation

WARNING: Bronchoscopic Coil removal **must be medically indicated** (e.g., persistent pleuritic pain). The potential benefit of Coil removal must be weighed against the potential harm including the known risks of bronchoscopy.

Note: Coil removal should always be performed using fluoroscopy.

WARNING: Removing Coils bronchoscopically may become increasingly difficult **after 2 or more months** following implantation, depending on the amount of tissue regrowth present. If bronchoscopic removal is not possible, thoracoscopic retrieval can be considered.

WARNING: If Coil removal is required, do not attempt to cut through, bend or break the Coil in any manner. Mishandling of the Coil in this manner can result in corrosion of the device and creation of sharp surfaces that can lead to injury, illness or death of the patient.

⚠***Caution*: Do not reuse the Coil if Coil removal is performed in a procedure separate from the Coil placement procedure. Coil may be reused if removed and redeployed during original bronchoscopy for Coil placement.**

1. To perform bronchoscopic Coil removal subsequent to the implantation procedure, you must have a therapeutic bronchoscope with a minimum 2.0mm inner diameter working channel and a 65cm maximum working length.
2. Use fluoroscopy to determine location of the Coil that needs to be removed.
3. Navigate bronchoscope to the Coil.
4. Insert the Forceps through the bronchoscope channel.
5. Capture the proximal ball with the Forceps. If you cannot capture the proximal ball, capture the wire and reposition the Coil proximal end until you can capture the proximal ball.
6. Lock the Forceps.
7. Advance the bronchoscope (wedge) and retract the Coil into the bronchoscope working channel.

14.0 Clinical Studies

14.1 Summary of Primary Clinical Study (RENEW Pivotal Trial)

14.1.1 Study Design

The RENEW Pivotal Trial was a prospective, multi-center, randomized, assessor-blinded, controlled study designed to evaluate the safety and effectiveness of the ELEVAIR Endobronchial Coil System in a population of patients with severe emphysema.

The objectives of the study were to determine whether treatment with the ELEVAIR System improves exercise capacity, lung function, and quality of life, as measured by improvements in the 6 Minute Walk Test (6MWT), Forced Expiratory Volume in 1 Second (FEV_1), and St. George's Respiratory Questionnaire (SGRQ). Subjects were block randomized 1:1 to the Treatment group (ELEVAIR System plus optimal medical care) or the Control group (optimal medical care alone) stratified by emphysema heterogeneity.

The RENEW Pivotal Trial allowed for investigational sites without prior experience with the ELEVAIR System to enroll and treat up to two (2) Roll-In subjects in order to gain experience in the use of the ELEVAIR System and the treatment procedure prior to initiating the randomized phase of the study. These Roll-In subjects were evaluated separately from the RENEW Pivotal Trial subjects.

Subjects randomized to the Treatment (ELEVAIR) group underwent two (bilateral) bronchoscopy procedures under general anesthesia or moderate sedation, separated by approximately 4 months. During each procedure, subjects were treated with ELEVAIR Coils according to the Instructions for Use. Subjects received prophylactic antibiotics and steroids before and after the procedure. Only a single lobe in a single lung was treated during each bronchoscopy.

Subjects randomized to the Control group received Standard Medical Care pharmacologic treatment per GOLD guidelines [1], and they did not undergo any bronchoscopies or any additional treatments, therapies, or specific exams associated with Coil placement, such as prophylactic antibiotics and steroids, chest X-rays, or 12-month CT scan. Control group subjects were exited from the study after their 12-month follow-up visit. Control group subjects were seen and/or contacted by the site Investigator or designee at the same frequency and

intervals as the Treatment group through 12 months of follow-up to support similar levels of attention and care for both groups.

The primary effectiveness endpoint for the RENEW Pivotal Trial was the absolute change from baseline in the 6MWT at 12 months post Treatment 1, comparing the Treatment and Control groups.

The Intent-to-Treat (ITT) population included all randomized subjects (regardless of whether or not treatment was attempted) and was used to evaluate the clinical endpoints for effectiveness. Missing 12-month values were estimated using the Markov Chain Monte Carlo (MCMC) method of multiple imputation.

The following secondary effectiveness endpoints were tested for their statistical significance comparing baseline to 12 months, Treatment vs. Control:

- 6MWT: responder analysis, responders defined as subjects with an improvement of ≥25 meters [2],
- SGRQ: absolute difference in SGRQ total score,
- FEV_1: percent change in FEV_1 results, measured using spirometry.

The following additional effectiveness endpoints were tested for their statistical significance comparing baseline to 12 months, Treatment vs. Control:

- SGRQ: responder analysis, responders defined as subjects with an improvement of ≥4 points [3],
- Residual Volume (RV): absolute difference in RV results, measured using plethysmography,
- RV/Total Lung Capacity (RV/TLC): absolute difference in RV/TLC results, measured using plethysmography.

The Safety Population included all ITT subjects who were randomized (Control group) or who entered the procedure room (Treatment group), regardless of whether or not device deployment was attempted. The primary safety analysis compared the proportion of subjects in the Treatment and Control groups experiencing one or more Major Complications (MCs) through the 12-month visit. MCs are events of particular interest because they are known to occur following intervention in severe emphysema patients. The subjects will be followed annually for safety and effectiveness at 2, 3, 4, and 5 years post Treatment 1.

An independent Data Monitoring Committee reviewed and evaluated safety events and monitored study safety data.

The clinical database that supported evaluation of safety and effectiveness of the ELEVAIR System included data collected through July 17, 2017.

14.1.2 Subject Accountability

Three hundred fifteen (315) subjects were enrolled in the RENEW Pivotal Trial between December 3, 2012 and October 10, 2014 at 26 investigational sites located in the United States, Canada and the European Union. Two hundred eighty-three (283) subjects (89.8%) completed the 12-month follow-up period. Fourteen (14) subjects (7 Treatment group and 7 Control group) withdrew or were lost to follow-up, and 18 subjects (10 Treatment group, 8 Control group) died prior to completing the follow-up period. The ITT population included 158 Treatment group and 157 Control group subjects. The Safety Population included 155 Treatment group subjects and 157 Control group subjects.

14.1.3 Subject Demographics

The baseline demographic characteristics of subjects randomized in the study are presented in **Table 2**. No significant differences between Treatment and Control groups were seen.

Table 2: Baseline Demographic Characteristics, ITT Population

	Treatment (N = 158)	Control (N = 157)	P-Value[1]
Age (year)			0.4532
Mean ± SD (n)	63.4 ± 8.05 (158)	64.3 ± 7.76 (157)	
Gender			0.2741
Male	45.6% (72/158)	49.7% (78/157)	
Female	54.4% (86/158)	50.3% (79/157)	
Body Mass Index (BMI) (kg/m²)			0.2432
Mean ± SD (n)	24.90 ± 4.603 (158)	24.53 ± 4.872 (157)	
Ethnicity			0.3225
Hispanic or Latino	0.6% (1/158)	1.3% (2/157)	
Not Hispanic or Latino	99.4% (157/158)	98.7% (155/157)	
Race			0.2890
American Indian or Alaska Native	0.0% (0/158)	0.0% (0/157)	
Black or African American	3.8% (6/158)	2.5% (4/157)	
Asian	0.0% (0/158)	0.6% (1/157)	
White	95.6% (151/158)	96.8% (152/157)	
Native Hawaiian or Other Pacific Islander	0.0% (0/158)	0.0% (0/157)	
Other	0.6% (1/158)	0.0% (0/157)	

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

14.1.4 Subject Baseline Disease Characteristics

Baseline disease characteristics are summarized in **Table 3**. No significant differences were seen at baseline, although differences in mean FEV_1/FVC and SGRQ approached significance, with the Treatment group trending toward greater airflow limitation and greater symptom burden at baseline. Patients with homogeneous and heterogeneous emphysema were enrolled in the study, with approximately 77% of subjects in each group having homogeneous emphysema. Pulmonary function test results at baseline were indicative of a group of subjects with advanced emphysema (GOLD 3 and 4) characterized by significant air trapping and flow restriction. Approximately three-quarters (73.7%) of subjects in the RENEW Pivotal Trial were classified as GOLD 4 (76% in the Treatment group and 71% in the Control group).

Table 3: Baseline Disease Characteristics, ITT Population

Baseline (Pre-Treatment Screening)	Treatment (N=158)	Control (N=157)	P-value[1]
6MWT Total Distance (meters) Mean ± SD (n)	312.03 ± 79.906 (158)	302.70 ± 79.277 (157)	0.8137
Lung Damage Classification Heterogeneous Homogeneous	22.8% (36/158) 77.2% (122/158)	22.9% (36/157) 77.1% (121/157)	0.7105
Post-bronchodilator Spirometry			
FVC (L) Mean ± SD (n)	2.47 ± 0.687 (158)	2.46 ± 0.748 (157)	0.9063
FVC % Predicted Mean ± SD (n)	67.75 ± 14.319 (158)	67.40 ± 15.011 (157)	0.6414
FEV_1 (L) Mean ± SD (n)	0.71 ± 0.202 (158)	0.72 ± 0.210 (157)	0.5171
FEV_1 % Predicted Mean ± SD (n)	25.71 ± 6.283 (158)	26.27 ± 6.671 (157)	0.4807
FEV_1/FVC (%) Mean ± SD (n)	28.80 ± 6.806 (158)	29.87 ± 6.792 (157)	0.0544
Post-bronchodilator Lung Volumes			
Residual Volume (RV) (L) Mean ± SD (n)	5.28 ± 1.058 (158)	5.33 ± 1.145 (157)	0.4460
Residual Volume % Predicted Mean ± SD (n)	245.94 ± 39.062 (158)	244.53 ± 38.693 (157)	0.9103
Total Lung Capacity (TLC) (L) Mean ± SD (n)	7.87 ± 1.345 (158)	7.92 ± 1.559 (157)	0.6238
Total Lung Capacity % Predicted Mean ± SD (n)	139.21 ± 15.620 (158)	138.78 ± 16.064 (157)	0.7240
RV/TLC Measured (%) Mean ± SD (n)	67.05 ± 6.731 (158)	67.32 ± 6.263 (157)	0.3988
Diffusion Capacity (mmol/min/kPa) Mean ± SD (n)	2.72 ± 0.959 (158)	2.73 ± 0.938 (157)	0.7367
Diffusion Capacity % Predicted Mean ± SD (n)	34.12 ± 10.477 (158)	34.47 ± 10.686 (157)	0.7091
Health-related Quality of Life			
SGRQ Total Score Mean ± SD (n)	60.05 ± 12.757 (158)	57.44 ± 14.759 (157)	0.0503
mMRC Dyspnea Scale 0 1 2 3 4	0.0% (0/158) 0.0% (0/158) 34.2% (54/158) 43.7% (69/158) 22.2% (35/158)	0.0% (0/157) 0.0% (0/157) 35.7% (56/157) 44.6% (70/157) 19.7% (31/157)	0.8747
GOLD Stage 4, %(n)	75.9% (120/158)	71.3% (112/157)	0.4770
BODE Score Mean ± SD (n)	5.97 ± 1.262 (158)	6.04 ± 1.322 (157)	0.8412
Smoking Pack Year History Mean ± SD (n)	50.66 ± 27.945 (157)	50.28 ± 23.483 (157)	0.5798

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

14.1.5 Procedural Data

Two hundred ninety-nine (299) ELEVAIR Coil procedures were performed in 155 subjects in the Treatment group. A total of 3,132 Coils were implanted in these 299 procedures (median of 10 Coils per procedure), in both upper and lower lobes. One hundred forty-four (144) Treatment group subjects (92.9%) had a second (contralateral) treatment performed. Eleven (11) subjects were treated unilaterally (1 side only). Of these, 8 were due to worsening condition and/or ongoing AEs that prevented second treatment, and 3 subjects died prior to completion of the second treatment. The second ELEVAIR treatment procedure was performed a median of 127 days following the initial treatment (range 107 to 251 days). The mean procedure time for Coil placement was 41 minutes. The majority of subjects (93.3%; 279/299 procedures) were discharged from the hospital the day following the procedure.

14.1.6 Safety Results

Safety was evaluated by collection of site-reported AEs and SAEs from the time of informed consent through study completion or termination. Treatment group subjects were scheduled to be followed for 5 years following the initial Coil procedure, whereas Control group subjects exited the study following the 12-month follow-up visit.

14.1.6.1 Primary Safety Analysis

The RENEW Pivotal Trial protocol defined a group of adverse events of interest (designated as Major Complications; MCs) that are known to occur following bronchoscopic intervention in GOLD 3 and 4 patients [1]. The primary safety analysis was the percentage of subjects experiencing one or more MC through the 12-month follow-up visit, comparing Treatment to Control. Major Complications were defined as:

- **Death**;
- **Pneumothorax** that required a chest drainage tube for more than 7 days (from time of chest drainage tube insertion to the time of chest drainage tube removal);
- **Hemoptysis** requiring blood transfusion(s), arterial embolization, or surgical/endoscopic procedure;
- **COPD exacerbation** that became life-threatening or disabling as a result of an increase in respiratory symptoms requiring in-patient hospitalization of >7 days with or without mechanical ventilation;

- **Lower Respiratory Infections** (including pneumonia) defined by new or increased clinical symptoms such as fever, chills, productive cough, chest pain, dyspnea and an infiltrate on plain chest x-ray and hospitalization for administration of intravenous antibiotics and/or steroids;
- **Respiratory failure** defined as a requirement for mechanical ventilator support (whether via endotracheal tube or mask) for >24 hours; and
- **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.)

A summary of the Major Complications reported through 12 months for the RENEW Treatment and Control groups is presented in **Table 4**. The most common Major Complications in both groups were Lower Respiratory Tract Infection (LRTI), COPD exacerbation, and death. With the exception of LRTIs, there were no statistical differences between the 2 groups in any of the individual Major Complication categories. Because some of the reported pneumonia events within the Treatment group were not responsive to antibiotics but did respond to steroid treatment, it is hypothesized that these events may have actually been a localized inflammatory tissue reaction to the Coils (Coil Associated Opacity, CAO), rather than infectious pneumonia, as described in **Section 7.0 - Potential Adverse Events**.

Table 4: Major Complications through 12 Months

	Subject Counts of Each Event			Event Rate per Unit Time[1] (Year) (Count[2])		
	Treatment (N = 155)	Control (N = 157)	p-value[3]	Treatment (N = 155)	Control (N = 157)	p-value[1]
Total Major Complication Events [95% Confidence Interval][4]	34.8% (54/155) [27.4%, 42.9%]	19.1% (30/157) [13.3%, 26.1%]	0.0021	0.529 (80)	0.256 (38)	0.0002
Death	6.5% (10/155)	5.1% (8/157)	0.6360	0.066 (10)	0.054 (8)	0.6683
Pneumothorax	0.6% (1/155)	0.6% (1/157)	>0.9999	0.007 (1)	0.007 (1)	0.9888
Hemoptysis	1.3% (2/155)	0.0% (0/157)	0.2460	0.013 (2)	0.000 (0)	N/A
COPD Exacerbation	11.6% (18/155)	8.3% (13/157)	0.3496	0.139 (21)	0.094 (14)	0.2638
Lower Respiratory Infections	18.7% (29/155)	4.5% (7/157)	<0.0001	0.264 (40)	0.061 (9)	<0.0001
Respiratory Failure	3.9% (6/155)	3.8% (6/157)	>0.9999	0.040 (6)	0.040 (6)	0.9725
Unanticipated Bronchoscopy	0.0% (0/155)	0.0% (0/157)	N/A	0.000 (0)	0.000 (0)	N/A

[1] Event rate per year and p-value is estimated using Poisson regression.
[2] Total number of events.
[3] By Fisher's exact test.
[4] By Clopper-Pearson method.
Note: Subjects are counted at most once for each major complication event type.

14.1.6.2 Deaths

Eighteen (18) subject deaths occurred in the Safety population within the 12-month follow-up period in the RENEW Pivotal Trial. 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 determined by the investigator to be not related to the device or procedure. Four (4) of the 10 were assessed to be related to the device only, and 3 of the 10 were assessed to be related to both the device and the procedure. There was no statistical difference in mortality between the Treatment and Control groups (p=0.6360).

14.1.6.3 Serious Device and/or Procedure Related Adverse Events

Serious Adverse Events (SAEs) assessed by the investigator to be possibly or probably related to the device, procedure, or both, and that were reported by 2.5% or more of RENEW Treatment group subjects through 12 months are presented in **Table 5**. The most common device and/or procedure related SAEs were COPD exacerbation, pneumonia, and pneumothorax. 48.1% (50/104) of these common SAEs occurred within the first 30 days after treatment, and the majority were reported as resolved (78.8%, 82/104) or resolved with sequelae

(12.5%, 13/104) as of the July 17, 2017 database cut. Overall incidence of pneumonia and pneumothorax SAEs were statistically higher in the RENEW Treatment group than in the Control group. A portion of the reported pneumonia events were retrospectively adjudicated by the study Clinical Events Committee (CEC), which determined that approximately one-third (35%, 14/40) of the adjudicable pneumonia events in the Treatment group were likely a non-infectious Coil Associated Opacity (CAO) as described under **Section 7.0 – Potential Adverse Events**. In addition, there were 5 events specifically reported by an investigator as CAO.

Table 5: Serious Device and/or Procedure Related Adverse Events in the RENEW Study through 12 Months

Serious Adverse Event	Events	Subjects, % (n/N)
Chronic obstructive pulmonary disease[1]	49	20.0% (31/155)
Pneumonia	27	16.1% (25/155)
Pneumothorax	15	9.7% (15/155)
Medical device complication[2]	5	3.2% (5/155)
Bronchitis	4	2.6% (4/155)
Hemoptysis	4	2.6% (4/155)

[1] "Chronic Obstructive Pulmonary Disease" is the term used within the MedDRA coding system to report COPD exacerbation events.
[2] "Medical device complication" refers to Coil Associated Opacity (CAO), in the area of implanted ELEVAIR Coils. CAO is discussed in **Section 7.0 – Potential Adverse Events**.

14.1.6.4 Non-serious Device and Procedure Related Adverse Events

Non-serious Adverse Events (AEs) that were determined by the investigator to be possibly or probably related to the device, procedure or both, that were reported by 5% or more of RENEW Treatment group subjects through 12 months are presented in **Table 6**. The most common device and/or procedure related non-serious AEs were hemoptysis, COPD exacerbation, and cough. The majority (82.2%, 315/383) of these non-serious AEs summarized in **Table 6** occurred within the first 30 days after treatment. 94.8% (363/383) were resolved and 2.3% (9/383) were resolved with sequelae at the time of database cut-off for the PMA application. These events are consistent with those commonly reported by the severe emphysema study population and with those subjects undergoing bronchoscopic interventions [4].

Table 6: Non-Serious Device and/or Procedure Related Adverse Events in the RENEW Study within 12 months

Non-serious Adverse Event	Events	Subjects, % (n/N)
Hemoptysis[1]	134	56.1% (87/155)
Chronic obstructive pulmonary disease[2]	86	38.1% (59/155)
Cough	33	14.8% (23/155)
Non-cardiac chest pain	25	12.3% (19/155)
Chest discomfort	28	11.6% (18/155)
Dyspnea	22	11.0% (17/155)
Wheezing	18	7.7% (12/155)
Headache	12	6.5% (10/155)
Oropharyngeal pain	14	6.5% (10/155)
Bronchitis	13	5.8% (9/155)

[1] 97% (130/134) of hemoptysis events were mild in severity and resolved without medical intervention..
[2] "Chronic Obstructive Pulmonary Disease" is the term used within the MedDRA coding system to report COPD exacerbation events.

14.1.7 Effectiveness Results

14.1.7.1 Primary and Secondary Effectiveness Endpoints

All primary and secondary effectiveness endpoints were met in the RENEW Pivotal Trial. Additionally, subgroup analyses that provide important information on RENEW subgroups that experienced clinical benefits with Coil treatment that were significantly different than those seen in the overall RENEW population are presented in **Section 14.1.7.3**.

The primary effectiveness endpoint was compared between Treatment and Control on the ITT population for the RENEW Pivotal Trial:

6MWT: absolute difference in 6MWT from baseline to 12 months

The primary effectiveness endpoint of the study was met (one-sided p=0.0153, **Table 7**). ITT subjects in the Treatment group exhibited a median improvement in 6MWT compared to the Control group of 14.6 meters (mean 10.2 meters) at 12 months compared to baseline. Treatment group subjects improved in 6MWT distance (median change from baseline of 10.3 meters; mean -0.6 meters), as compared to a worsening in the Control group (median change from baseline of -7.6 meters, mean -10.7 meters).

Additionally, the following secondary effectiveness endpoints were compared between Treatment and Control groups on the ITT population for the RENEW Pivotal Trial:

6MWT: responder analysis, responders defined as subjects with an improvement of ≥25 meters [2], **comparing baseline to 12 months**

The secondary effectiveness endpoint of 6MWT responder was met (**Table 7**). In the ITT population, a higher proportion of Treatment group subjects were 6MWT responders at 12 months, compared to Control (odds ratio 2.06; one-sided p=0.0063 with mean response rates of 37.9% in the Treatment group versus 26.2% in Control group).

SGRQ: responder analysis, absolute difference in SGRQ from baseline to 12 months

The Treatment group reported a mean improvement of 8.1 points in SGRQ, compared to a worsening of 0.8 points in the Control group (one-sided p<0.0001), meeting the secondary effectiveness endpoint (**Table 7**). The magnitude of improvement in the Treatment group was approximately double the minimal clinically important difference of 4 points [3].

FEV_1: percent change in FEV_1 results, measured using spirometry, from baseline to 12 months

The Treatment group reported a median improvement of 3.8% (mean 8.0%) in FEV_1, compared to a median worsening of 2.5% (mean 0.8%) in the Control group (one-sided p<0.0001), meeting the secondary effectiveness endpoint (**Table 7**).

Table 7: Primary and Secondary Effectiveness Endpoints at 12 Months after Multiple Imputation, ITT Population

Primary Effectiveness Endpoints						
Absolute Change in 6MWT (Meters)						
Treatment Group (N)	**Baseline 6MWT Mean ± SE**	**Adjusted Mean Change from Baseline Mean ± SE**	**Mean Difference (Treatment vs. Control) [95% CI][1]**	**Median (IQR) Change from Baseline**	**Median Difference (Treatment vs. Control) [95% CI][2]**	**P-value[3] (One-sided)**
Control (N=157)	302.7 ± 6.33	-10.7 ± 6.22	10.2 [-5.2, 25.5]	-7.6 (-40.0, 26.0)	14.6 [0.4, 28.7]	0.0153
Treatment (N=158)	312.0 ± 6.36	-0.6 ± 6.30		10.3 (-33.0, 45.0)		
Secondary Effectiveness Endpoints						
6MWT Responder Rate						
Treatment Group (N)	**Mean Responder Rate**	**Difference of Log Odds (Treatment vs. Control) [95% CI][4]**		**Odds Ratio [95% CI][4]**		**P-value[4] (One-sided)**
Control (N=157)	26.2%	0.72 [0.16, 1.29]		2.06 [1.17, 3.64]		0.0063
Treatment (N=158)	37.9%					
Absolute Change in SGRQ (Total Score)						
Treatment Group (N)	**Baseline SGRQ Mean ± SE**	**Adjusted Change from Baseline Mean ± SE**		**Difference (Treatment vs. Control) [95% CI][5]**		**P-value[5] (One-sided)**
Control (N=157)	57.4 ± 1.18	0.8 ± 1.05		-8.9 [-11.6, - 6.3]		<.0001
Treatment (N=158)	60.0 ± 1.01	-8.1 ± 1.08				
Percent Change in FEV_1						
Treatment Group (N)	**Baseline FEV_1 (Liters) Mean ± SE**	**Adjusted Mean Percent Change from Baseline Mean ± SE**	**Mean Difference (Treatment vs. Control) [95% CI][6]**	**Median (IQR) Percent Change from Baseline**	**Median Difference (Treatment vs. Control) [95% CI][2]**	**P-value[7] (One-sided)**
Control (N=157)	0.7 ± 0.02	-0.8 ± 1.66	8.8 [4.7, 13.0]	-2.5 (-8.9, 4.4)	7.0 [3.4, 10.6]	<.0001
Treatment (N=158)	0.7 ± 0.02	8.0 ± 1.74		3.8 (-6.3, 16.1)		

[1] Difference in least squares means from MCMC multiple imputation results of ANCOVA with factors of treatment and analysis center and baseline 6MWT and emphysema heterogeneity as covariates.
[2] Median difference adjusted for baseline from MCMC multiple imputation results using Hodges Lehmann estimator. The nonparametric median between treatment difference is not the simple between-treatment difference in medians.
[3] Due to significant skewness, p-value from MCMC multiple imputation results of rank ANCOVA with factors of treatment and analysis center and baseline 6MWT and emphysema heterogeneity as covariates.
[4] Based on MCMC imputation results of logistic regression with factors of treatment and analysis center and baseline 6MWT and emphysema heterogeneity as covariates.
[5] Based on difference in least squares mean from MCMC multiple imputation results of ANCOVA with factors of treatment and analysis center and baseline SGRQ and emphysema heterogeneity as covariates.
[6] Difference in least squares means from MCMC multiple imputation results of ANCOVA with factors of treatment and analysis center and baseline FEV_1, and emphysema heterogeneity as covariates.
[7] Due to significant skewness, p-value from MCMC multiple imputation results of rank ANCOVA with factors of treatment and analysis center and baseline FEV_1 and emphysema heterogeneity as covariates.
Notes: Median (IQR) are median of percentiles from MCMC multiple imputation. 6MWT responder is defined as those with an improvement of greater than or equal to 25 meters.

14.1.7.2 Other Effectiveness Endpoints

All other effectiveness endpoints were met in the RENEW Pivotal Trial. The following additional effectiveness endpoints were compared between Treatment and Control groups on the ITT population:

SGRQ: responder analysis, responders defined as subjects with an improvement of ≥4 points [3], comparing baseline to 12 months

This additional effectiveness endpoint was met. **Table 8** provides a summary of SGRQ response data for the ITT population. The percent of subjects with an SGRQ response was 61.2% in the Treatment group and 27.7% in the Control group (one sided $p<0.0001$).

RV: absolute difference in RV results, measured using plethysmography, comparing baseline to 12 months

This additional effectiveness endpoint was met. **Table 8** provides a summary of changes in RV by treatment group (ITT population). Subjects in the Treatment group showed significant improvements in air trapping compared to the Control group (-0.31 liters, one-sided $p=0.0010$).

RV/TLC: absolute difference in RV/TLC results, measured using plethysmography, comparing baseline to 12 months

This additional effectiveness endpoint was met. **Table 8** provides a summary of changes in RV/TLC by treatment group (ITT population). Subjects in the Treatment group showed significant improvements in hyperinflation compared to the Control group (3.5%, one-sided $p<0.0001$).

Table 8: Other Effectiveness Endpoints at 12 Months after Multiple Imputation, ITT Population

Other Effectiveness Endpoints				
SGRQ Responder Rate				
Treatment Group (N)	**Adjusted Mean Responder Rate**	**Difference of Log Odds (Treatment vs. Control) [95% CI][1]**	**Odds Ratio [95% CI][1]**	**P-value[1] (One-sided)**
Control (N=157)	27.7%	1.4 [0.9, 2.0]	4.1 [2.4, 7.2]	<0.0001
Treatment (N=158)	61.2%			
Absolute Change in RV (Liters)				
Treatment Group (N)	**Baseline RV Mean ± SE**	**Adjusted Change from Baseline Mean ± SE**	**Difference (Treatment vs. Control) [95% CI][2]**	**P-value[2] (One-sided)**
Control (N=157)	5.33 ± 0.09	-0.10 ± 0.080	-0.31 [-0.50, -0.11]	0.0010
Treatment (N=158)	5.28 ± 0.08	-0.41 ± 0.081		
Absolute Change in RV/TLC (Percent)				
Treatment Group (N)	**Baseline RV/TLC Mean ± SE**	**Adjusted Change from Baseline Mean ± SE**	**Difference (Treatment vs. Control) [95% CI][3]**	**P-value[3] (One-sided)**
Control (N=157)	67.3 ± 0.50	-0.45 ± 0.554	-3.50 [-4.86, -2.14]	<0.0001
Treatment (N=158)	67.1 ± 0.54	-3.96 ± 0.564		

[1] Based on MCMC multiple imputation results of logistic regression with factors of treatment and analysis center and baseline SGRQ and emphysema heterogeneity as covariates, using one-sided test for odds ratio of treatment effect.
[2] Based on least squares mean difference from MCMC multiple imputation results of ANCOVA with factors of treatment and analysis center and baseline RV and emphysema heterogeneity as covariates.
[3] Based on least squares mean difference from MCMC multiple imputation results of ANCOVA with factors of treatment and analysis center and baseline RV/TLC and emphysema heterogeneity as covariates.
Note: SGRQ responder is defined as those with an improvement (decrease) of ≥4 points.

14.1.7.3 Subgroup Analyses

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

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

In addition, post-hoc subgroup analyses and additional analyses of the pre-specified subgroups were conducted to further characterize and understand the results of the pre-specified analyses.

Treatment effects were improved in the RV≥225% subgroup (**Table 9**) compared to the overall population (**Table 7**). In addition, although the clinical benefits of ELEVAIR Coil Treatment compared to Control were improved for all effectiveness endpoints in both US and OUS regions, greater improvements were observed in OUS subjects. To better understand these subgroup differences, treatment responses by baseline RV% and region were investigated by post hoc multivariate and subgroup analysis, which revealed that effectiveness outcomes were consistent in the RV≥225% subgroup regardless of region. Further subgroup analyses by comorbidity frequency showed that subjects with 3 or fewer comorbidities, and specifically without cardiac comorbidity (defined as angina, atrial fibrillation, coronary artery disease or congestive heart failure), experienced the greatest benefit, particularly in 6MWT response. This dependency on comorbid burden accounts in part for the difference in clinical benefit seen between RV ≥225% and RV <225% subgroups in RENEW, as the RV ≥225% RENEW subgroup had a lower rate of major comorbidities (mean 2.3 major comorbidities and 22% with cardiac condition) compared to the RV <225% population (mean 3.5 major comorbidities and 37% with cardiac condition). After accounting for comorbidity status, however, increasing severity of air trapping was associated with superior treatment effectiveness in RENEW. This finding is consistent with the mechanism of action of Coils, which are designed to reduce air trapping and airway collapse, and create tissue tension, by compression of diseased lung parenchyma.

Results for the other pre-specified subgroup analyses showed that subjects benefitted from Coil treatment regardless of disease distribution (heterogeneous vs. homogeneous) or gender.

Table 9: Primary and Secondary Effectiveness Endpoints in High RV (RV≥225% predicted) Subgroup at 12 Months after Multiple Imputation, ITT Population

Primary Effectiveness Endpoints					
Absolute Change in 6MWT (Meters)					
Treatment Group (N)	**Baseline 6MWT Mean ± SE**	**Adjusted Mean Change from Baseline Mean ± SE[1]**	**Mean Difference (Treatment vs. Control) [95% CI][1]**	**Median (IQR) Change from Baseline**	**Median Difference (Treatment vs. Control) [95% CI] [2]**
Control (N=120)	308.0 ± 7.64	-13.4 ± 6.84	19.8 [1.8, 37.8]	-8.6 (-43.3, 24.4)	23.8 [7.4, 39.6]
Treatment (N=115)	314.6 ± 7.65	6.4 ± 7.30		15.0 (-31.1, 56.0)	
Secondary Effectiveness Endpoints					
6MWT Responder Rate					
Treatment Group (N)	**Adjusted Mean Responder Rate**		**Difference of Log Odds (Treatment vs. Control) [95% CI][3]**		**Odds Ratio [95% CI][3]**
Control (N=120)	23.9%		0.92 [0.31, 1.52]		2.50 [1.36, 4.58]
Treatment (N=115)	42.3%				
Absolute Change in SGRQ (Total Score)					
Treatment Group (N)	**Baseline SGRQ Mean ± SE**		**Adjusted Change from Baseline Mean ± SE**		**Difference (Treatment vs. Control) [95% CI][4]**
Control (N=120)	57.7 ± 1.35		1.7 ± 1.10		-10.0 [-12.9, -7.0]
Treatment (N=115)	60.4 ± 1.21		-8.3 ± 1.20		
Percent Change in FEV_1					
Treatment Group (N)	**Baseline FEV_1 (Liters) Mean ± SE**	**Adjusted Mean Percent Change from Baseline Mean ± SE**	**Mean Difference (Treatment vs. Control) [95% CI][5]**	**Median (IQR) Percent Change from Baseline**	**Median Difference (Treatment vs. Control) [95% CI][2]**
Control (N=120)	0.7 ± 0.02	-0.4 ± 1.82	10.7 [5.8, 15.5]	-2.8 (-8.8, 4.2)	8.9 [4.6, 13.2]
Treatment (N=115)	0.7 ± 0.02	10.2 ± 1.98		6.7 (-5.2, 19.3)	

[1] Based on difference in least squares means from MCMC multiple imputation results of ANCOVA with factors of treatment and baseline 6MWT and emphysema heterogeneity as covariates.
[2] Median difference adjusted for baseline from MCMC multiple imputation results using Hodges Lehmann estimator. The nonparametric median between treatment difference is not the simple between-treatment difference in medians.
[3] Based on MCMC imputation results of logistic regression with factors of treatment and baseline 6MWT and emphysema heterogeneity as covariates.
[4] Based on difference in least squares mean from MCMC multiple imputation results of ANCOVA with factors of treatment and baseline SGRQ and emphysema heterogeneity as covariates.
[5] Based on difference in least squares means and from MCMC multiple imputation results of ANCOVA with factors of treatment and baseline FEV_1 and emphysema heterogeneity as covariates.
Notes: Median (IQR) are median of percentiles from MCMC multiple imputation. 6MWT responder is defined as those with an improvement of greater than or equal to 25 meters.

14.2 Summary of Supplemental Clinical Information

Four (4) European clinical studies were conducted in the EU to support the CE mark and Investigational Device Exemption (IDE) application for the ELEVAIR System. Three were single arm studies which evaluated the effectiveness and/or safety of the ELEVAIR System in patients with emphysema (CLN0006 [5], [6], CLN0011 [7] and CLN0012 [8]). An additional randomized, control trial was conducted comparing treatment using the ELEVAIR System to Standard Medical Care (CLN0008 [9], [10]). A total of 152 subjects (151 treated) were enrolled across these studies, and follow-up was up to 12 months. Each study collected and assessed adverse events throughout the follow-up period, and effectiveness was evaluated using SGRQ, FEV_1, 6MWT and RV measures. The results and conclusions from these studies further support the safety and effectiveness of the ELEVAIR System:

- Treatment with the ELEVAIR System provides a safe alternative treatment option for subjects with emphysema that can provide clinically meaningful benefits in exercise capacity, lung function and quality of life.
- Subjects with heterogeneous and homogeneous emphysema were both successfully treated with similar safety and effectiveness outcomes.
- The ELEVAIR Coil procedure can be performed safely with low SAE rates, even in a patient population with severe emphysema.

A meta-analysis of the results of these studies has been published [11].

A comprehensive review of supplemental clinical data is provided in the Summary of Safety and Effectiveness data, available on the FDA website at: http://www.fda.gov/medicaldevices/productsandmedicalprocedures/deviceapprovalsandclearances/pmaapprovals/default.htm.

14.3 References

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15.0 Disclaimer of Warranties

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17.0 Symbol Key for Product Labels

LOT	Batch code
REF	Catalog number
	Use-by date (expiration date)
STERILE EO	Sterilized using ethylene oxide
STERILE R	Sterilized using irradiation
	MR Conditional
	Do not re-use
	Do not resterilize
	Do not use if package is damaged
	Keep dry
	Manufacturer
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