

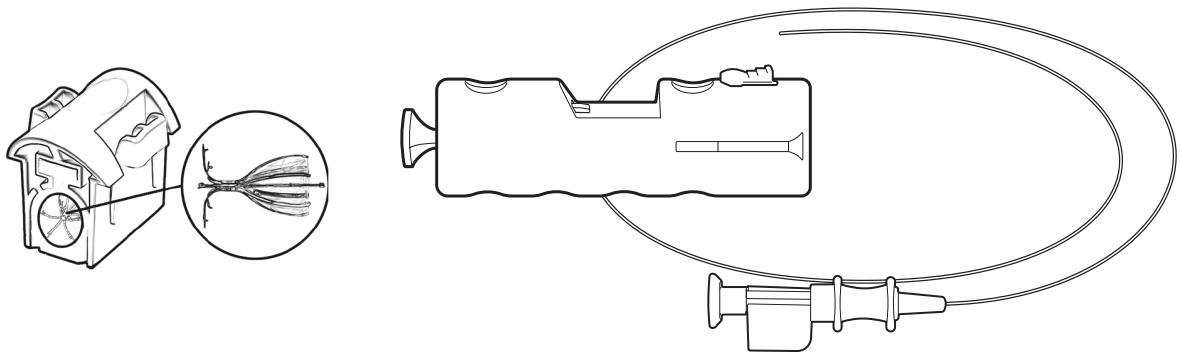


# INSTRUCTIONS FOR USE

## VALVE IN CARTRIDGE & DEPLOYMENT CATHETER AND LOADER

### SPIRATION® VALVE SYSTEM

For the Treatment of Severe Emphysema



REF PI-05356 Rev C2

**Caution:** Federal (USA) law restricts this device to sale by or on the order of a physician.



# Contents















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## 1.0 Symbols and Signal Words

### 1.1 Symbols

The meanings of the symbols shown on the package and/or on the package insert are as follows:

	Consult instructions for use		Keep away from sunlight
	Do not reuse		Magnetic resonance imaging conditional
	Do not resterilize		Lot number
	Use by (expiration date)		Catalog number
	Sterilized using ethylene oxide		Manufacturer
	Keep dry		Temperature limits
	Do not use if package is damaged		For use by prescription only

### 1.2 Signal Words

The following signal words are used throughout this instruction manual:

**WARNING** Indicates a potentially hazardous situation which, if not avoided, could result in death or serious injury.

**CAUTION** Indicates a potentially hazardous situation which, if not avoided, may result in minor or moderate injury. It may also be used to alert against unsafe practice or potential equipment damage.

**NOTE** Indicates additional helpful information.

## 2.0 Indication for Use

Spiration valves are one-way endobronchial valves indicated for adult patients with shortness of breath and hyperinflation associated with severe emphysema in regions of the lung that have evidence of low collateral ventilation.

## 3.0 Contraindications

- Patient is not an appropriate candidate for, or unable to tolerate, flexible bronchoscopy procedures.
- Patients with known or suspected sensitivity or allergy to nickel.
- Patients with evidence of active pulmonary infection.

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- Patients who have not quit smoking.
  - Patients with large bullae encompassing greater than 30% of either lung.
  - Patients with diffuse homogenous emphysema.

## 4.0 Instruction Manual

This instruction manual contains essential information on using the Spiration Valve System in a safe and effective manner.

- CAUTION**
- Before use, thoroughly review this instruction manual and the instruction manuals of all equipment which will be used during the procedure and use the Spiration Valve System as instructed.
  - A thorough understanding of the technical principles, clinical applications, and risks associated with this procedure is necessary before using the device.

If you have any questions or comments about these instructions, please contact your local Olympus representative.

## 5.0 Warranty

Spiration, Inc. warrants that, at the time of shipment, this product has been manufactured and tested according to its specifications in accordance with Good Manufacturing Practices. Spiration makes no warranty and assumes no liability with respect to the reuse, reprocessing or re-sterilization of the device.

This sole and exclusive warranty is in lieu of and excludes all other warranties not expressly set forth herein, whether express or implied by operation of law or otherwise, including, but not limited to, any implied warranties of merchantability or fitness for a particular purpose.

Spiration is not responsible for any harm arising from or caused by handling, storage, cleaning and/or sterilization of the device which may affect its placement or performance; nor is Spiration responsible for the improper or negligent use of the product or the practice of medicine or other matters beyond Spiration's control. Spiration neither assumes, nor authorizes any other person, including a sales representative, to assume for it or agree to any other or additional liability or responsibility in connection with this device.

Customer's sole remedy under this warranty is limited to the replacement of this device. Spiration shall not be liable for any incidental or consequential loss, damage, or expense directly or indirectly arising from the use of this device.

## 6.0 User Qualifications

This procedure cannot be performed without bronchoscopy technical skills and adequate training. The operator must be a physician trained in clinical bronchoscopy techniques and the use of the Spiration Valve System. The following instructions will give technical guidelines but do not obviate formal training in bronchoscopic procedures.

## 7.0 Spiration Valve System Description

The Spiration Valve System consists of a Spiration Valve in Cartridge (“Spiration Valve” or “valve”) and a Deployment Catheter (“catheter”) and Loader (“loader”). The Airway Sizing Kit is an accessory intended to determine the appropriate valve size for each target airway (see Instructions for Use, Airway Sizing Kit, PI-05365).

### 7.1 Spiration Valve in Cartridge

The valve is designed to limit airflow to the portions of the lungs distal to the valve, while still allowing mucus and air movement in the proximal direction. The valve is comprised of a Nitinol frame and a polymer membrane. The membrane is held against the airway mucosa by 6 flexible struts and will expand and contract with airway movement during breathing. The 5 anchors have tips that gently secure the valve to the airway wall at a controlled depth, preventing the valve from migrating. The valve is designed to be removed by grasping the removal rod with flexible bronchoscopy forceps.

The valve is available in 5, 6, 7, and 9 mm diameters and is contained inside a cartridge (Figure 1). The cartridges are uniquely marked to distinguish one valve size from the other. To load a valve, the empty catheter is inserted into the front of the loader and the valve cartridge is snapped into the top of the loader. Then the plunger is depressed to compress the valve and insert it into the catheter tip. The catheter now loaded with a valve is released from the loader tool, and the valve is ready for delivery and deployment to the target airway.

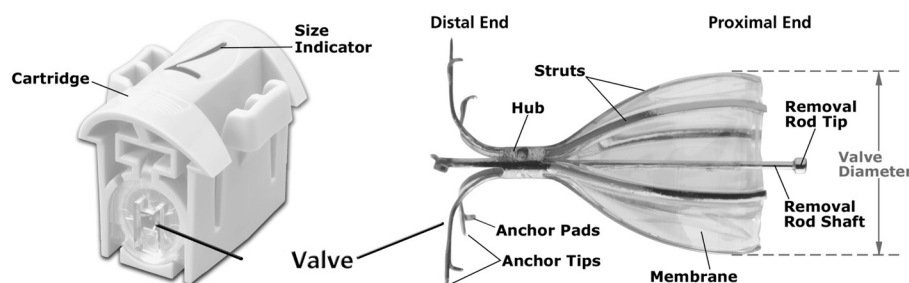


Figure 1: Spiration Valve in Cartridge

### 7.2 Deployment Catheter and Loader

The loader is a tool used to insert the valve into the tip of the catheter. The catheter tip is inserted into the loader, then the cartridge is placed in the loader, and the loader plunger is depressed to load the valve into the tip of the catheter (see Figure 2). The catheter is used to deliver the valve to its target location. The loader and catheter are designed to load and deploy up to a maximum of 10 valves during a single patient procedure. If there are more than 10 valve deployments, a new catheter must be opened and used.

The catheter can be passed through a flexible bronchoscope with an instrument channel inner diameter of 2.6mm or larger. After loading, the catheter is advanced through the bronchoscope instrument channel to the target location. The distal end of the catheter includes a valve line which marks the target position of the proximal end of the valve when deployed. The valve is deployed when the operator actuates the deployment handle of the catheter, retracting the catheter sheath to release the valve.

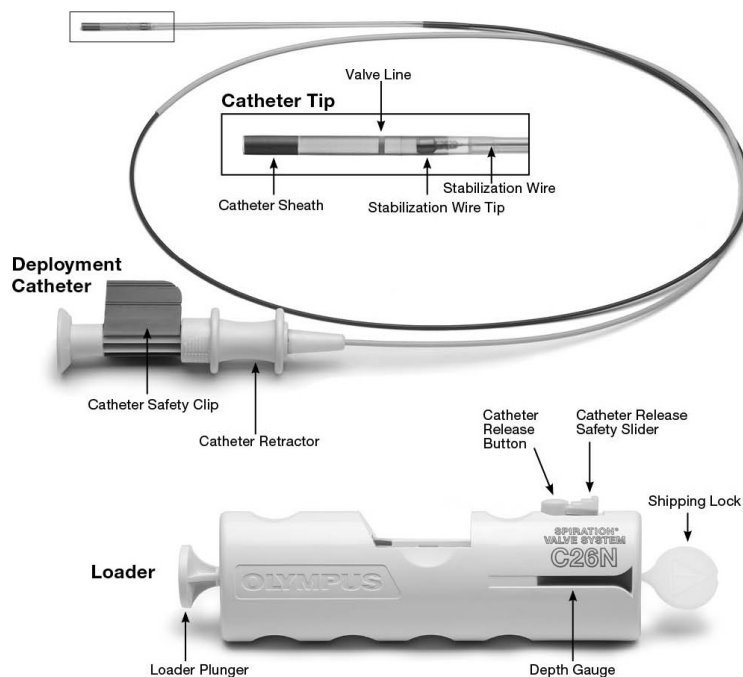


Figure 2: The Deployment Catheter and Loader

## 8.0 Specifications

### 8.1 Valve in Cartridge

The valve in cartridge is supplied in the sizes below. One valve is provided in each cartridge (see Table 1). All cartridges are marked with a size indicator of the valve in the cartridge. Each valve size has a color code as indicated in the table below.

Model	Item Number	Valve Size	Color Code	Valves Required per procedure
SVS-V5-00	N5535500	5mm	Blue	Determined by number of Target Locations
SVS-V6-00	N5535600	6mm	Yellow	
SVS-V7-00	N5535700	7mm	Green	
SVS-V9-00	N5535900	9mm	Black	

Table 1

### 8.2. Deployment Catheter and Loader

The deployment catheter and loader are packaged together (see Table 2).

Model	Item Number	Catheter Working Length	Bronchoscope Channel Inner Diameter	Number Required per Procedure
SVS-C26N-06	N5538900	1020mm	2.6mm or greater	1

Table 2

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## 8.3 Operating Environment

Ambient Temperature	10°C to 40°C (50°F to 104°F)
Relative Humidity	30 to 85%
Air Pressure	700 to 1060hPa (0.71 to 1.08 kgf/cm <sup>2</sup> ) (10.1 to 15.4 psia)

## 9.0 General Warnings and Precautions

The following are general warnings:

The safety and effectiveness of the Spiration Valve System have not been studied in patients with:

- Prior major lung or chest surgery
  - Lung Volume Reduction Surgery (LVRS)
  - Transplant
  - Median sternotomy or thoracotomy
- Known cardiac history of myocardial infarction or congestive heart failure
- Implanted endobronchial valve currently treating a prolonged air leak

The following are general precautions:

- Do not use the Spiration Valve System for other than its intended use.
- The Spiration Valve System should not be used for patients who have active asthma, bronchitis or clinically significant bronchiectasis.
- Only use a bronchoscope with an instrument channel inner diameter of 2.6mm or larger.
- Valve placement should be done only after airway evaluation and sizing with the balloon catheter and Airway Sizing Kit (see Instructions for Use, Airway Sizing Kit).
- Valve placement and removal must be done under bronchoscopic observation with visualization of the target airway.
- Do not allow lubricants to contact the catheter, loader, or valve.
- Once a valve has been loaded and/or deployed, do not attempt to reuse or re-deploy the valve.
- The valve is not designed to be repositioned after it is deployed from the catheter. If the position of the deployed valve is not optimal or appropriate; the valve should be removed and discarded.
- Do not remove the valve from the cartridge.
- Do not reuse the catheter and loader for more than one patient procedure. The catheter and loader are not designed to be re-cleaned, reprocessed, or re-sterilized.
- Do not deploy more than 10 valves using the catheter and loader. If more than 10 valve deployments are needed, a new catheter and loader must be opened and used.

## 10.0 Magnetic Resonance Imaging (MRI) Information

The Spiration Valve was determined to be MR-Conditional according to the terminology specified in the American Society for Testing and Materials (ASTM) International, Designation: F2503. Standard Practice for Marking Medical Devices and Other Items for Safety in the Magnetic Resonance Environment.

Non-clinical testing has demonstrated that the Spiration Valve is MR Conditional. A patient with this device can be scanned safely immediately after placement under the following conditions:

- Static magnetic field of 3-Tesla or less
- Spatial magnetic gradient field of 720-Gauss/cm or less
- Maximum MR system reported whole-body-averaged specific absorption rate (SAR) of 3-W/kg for 15 minutes of scanning.



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In non-clinical testing, the Spiration Valve produced a temperature rise of less than or equal to 0.5° C at a maximum MR system reported whole-body-average specific absorption rate (SAR) of 3-W/kg for 15 minutes of MR scanning in a 3-Tesla MR system (Excite, Software G3.0-052B, General Electric Healthcare, Milwaukee, WI).

MR image quality may be compromised if the area of interest is in the same area or relatively close to the position of the Spiration Valve. Optimization of MR imaging parameters is recommended.

## **11.0 Potential Adverse Events**

### **11.1 Patient Population – EMPROVE Study**

The Spiration Valve System was evaluated in a prospective, randomized, multicenter study. The total randomized cohort was 172 subjects with severe emphysema – 113 subjects in the treatment group and 59 subjects in the control group. The control group received medical management.

### **11.2 Potential Complications**

Potential complications that may be associated with bronchoscopy and/or valve placement include, but are not limited to, the following:

- Altered arterial blood gas
- Anesthesia complications
- Arrhythmia
- Atelectasis
- Bronchial injury
- Bronchitis
- Bronchospasm
- Chest pain
- Chronic Obstructive Pulmonary Disease (COPD) exacerbation
- Death
- Dyspnea
- Empyema/lung abscess
- Hemoptysis (or bleeding)
- Hemothorax
- Hypoxemia
- Iatrogenic injuries
- Infection
- Migration of a valve out of the lung or within the lung
- Myocardial infarction
- Persistent cough
- Pleural effusion
- Pneumothorax
- Pneumonia
- Respiratory failure
- Sore throat
- Thoracic pain
- Tissue hyperplasia or other reaction at valve site
- Valve fracture
- Vocal cord injury
- Wheezing
- Other procedure-related adverse events may occur

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## 12.0 System Compatibility

Only valves and their respective deployment catheters and loaders can be used to perform this procedure. The deployment catheter is compatible with a bronchoscope that has an instrument channel inner diameter of 2.6mm or greater. Individual bronchoscope characteristics may compromise compatibility.

**CAUTION** Using an incompatible bronchoscope may result in equipment or device damage.

## 13.0 Package Inspection, Storage and Handling

### 13.1 Checking the Package

The deployment catheter and loader are supplied sterile and packaged in a sealed pouch. The valve in cartridge is also supplied sterile and is packaged in a sealed pouch separate from the deployment catheter and loader. Prior to use, inspect the Use By date on the package to ensure the product is still usable. Also inspect the pouches and verify that the seals are intact and that there are no holes or tears.

If sterility or performance of the device is suspected to be compromised, do not use the device. Contact your local Olympus representative.

### 13.2 Storage Conditions

Store the product at room temperature in a clean and dry environment. Do not use the valve in the cartridge or the catheter and loader if it has been exposed to temperatures above 50° C or below -15° C.

### 13.3 Handling

The Spiration Valve System should be handled by qualified personnel that have received appropriate training. All materials and components should be opened and used just before a procedure. Product should be handled following guidelines for bronchoscopy and universal health precautions.

- The Spiration Valve System is supplied sterile. Do not attempt to re-sterilize the Spiration Valve System components.
- Do not use the deployment catheter and loader for more than one patient procedure. Do not reuse a valve once it has been deployed.
- Do not remove the valve from the cartridge.

## 14.0 Preparation for the Procedure

### 14.1 Items required and recommended for the Spiration Valve Procedure

Items required for the Procedure (included in or provided with the Spiration Valve System):

- Spiration Valve in Cartridge (multiple sizes)
- Deployment Catheter and Loader (one per patient)

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- Airway Sizing Kit
  - Olympus Balloon Catheter B5-2C

Additional equipment required (not provided with the Spiration Valve System):

- Flexible bronchoscope with an instrument channel inner diameter of 2.6mm or larger

Additional ancillary equipment recommended (not provided):

- An endotracheal (ET) tube or other intubation system

## 14.2 Recommended Use of Endotracheal (ET) Tube or other Intubation System

Sizing, placing and removal of all valves should be conducted under bronchoscopic observation. Valves should be removed through an endotracheal (ET) tube or other intubation system that facilitates access to the airways for the following reasons:

- Allows better control of the upper airways and facilitates ventilation and anesthesia.
- Facilitates the manipulation of the flexible bronchoscope into the areas where valves need to be removed.
- Facilitates removal of the valves by protecting the vocal cords and other structures of the upper airways.

The procedure can be performed without intubation, but this decision should be made by the physician after they have acquired sufficient experience with the Spiration Valve System.

## 15.0 The Procedure

### 15.1 Selecting the Spiration Valve Size

Use the Olympus balloon catheter (B5-2C) together with the Spiration Airway Sizing Kit to determine the appropriate valve size to use for each target airway (See Instructions for Use, Airway Sizing Kit).

**CAUTION** Incorrect valve size will reduce device effectiveness.

### 15.2 Loading the Valve into the Catheter

1. Remove the loader and catheter from the packaging.
2. Inspect the catheter and loader for damage. The shipping lock should be in the loader when it is removed from the packaging. If this is not the case, discard the loader.
3. To remove the shipping lock, slide the catheter release safety slider forward, then fully press the catheter release button down until a click is heard and then release the button (slide, press, release). Now remove the shipping lock.

**CAUTION** If a “click” is not heard, fully re-insert the shipping lock into the loader. Repeat step 3.

4. Verify the catheter retractor is fully forward and the green safety clip is installed over the yellow portion of the handle (Figure 3).



Figure 3. Green safety clip installed over yellow portion of catheter handle.

5. Inspect the catheter's distal tip for damage prior to inserting it into the loader. Damage may include kinks, or deformation. If the catheter is damaged, use a new catheter.
6. Grasp the deployment catheter using the depth gauge on the side of the loader as a guide (see Figure 4).



Figure 4. Depth gauge on loader used to determine where to grasp deployment catheter.

7. Gently insert the catheter into the loader until an audible "click" is heard.

If a "click" is not heard, release the catheter by pushing the catheter release safety slider forward, then pressing the catheter release button down until an audible "click" is heard. Remove the catheter from the loader. Repeat step 7 by inserting the catheter into the loader until an audible "click" is heard. Not hearing a "click" when inserting the catheter into the loader means the catheter has not been properly locked into place inside the loader and the valve may not load properly.

8. Next select a cartridge of the determined valve size. Remove the cartridge from the packaging. Verify a valve is visible through the clear window of the cartridge (Figure 5a).



Figure 5a: Spiration Valve and Cartridge



Figure 5b: Spiration Valve inside Deployment Catheter tip

9. Pull the loader plunger back until the cartridge lockout (red) is not visible and then insert the cartridge into the loader until it locks into place. A click should be heard.
10. Slowly push the loader plunger all the way in to load the valve into the deployment catheter until a click is heard. If a click is not heard, confirm that the plunger is pushed all the way in.
11. Release the catheter by pushing the catheter release safety slider forward, then pressing the catheter release button until an audible “click” is heard. Gently remove the catheter from the loader.
12. Visually inspect the catheter tip to ensure that the valve is loaded correctly, (Figure 5b).

**CAUTION** If any anchor tips protrude from the catheter tip, do not insert the catheter into the bronchoscope. In this case, the valve must be replaced. Pull the catheter retractor to eject the valve for disposal. Direct the catheter tip into a container to avoid losing the ejected valve. Obtain a new cartridge.

13. Pull the loader plunger all the way back and remove the cartridge.
14. Repeat steps 4–13 for loading subsequent valves into the catheter.

### 15.3 Deployment of the Spiration Valve

1. While holding the catheter at the proximal end of the catheter tip, carefully insert the catheter into the instrument channel of the bronchoscope using slow, short strokes (Figure 6).
2. Do not bend or force the distal end of the catheter while inserting into the bronchoscope. This may cause a kink in the catheter which may prevent the valve from deploying.

**NOTE** Only use a bronchoscope with an instrument channel inner diameter of 2.6 mm or larger.



Figure 6: Carefully insert catheter into working channel of bronchoscope.

#### 15.4 Preparing to Advance the Catheter to the Target Location

3. While the bronchoscope is not flexed, advance the catheter until the end of the catheter tip is just visible at the end of the bronchoscope and does not interfere with its operation.

**CAUTION** Applying excessive force to advance the catheter through a bend in the bronchoscope could result in damage to the catheter and/or the instrument channel of the bronchoscope.

#### 15.5 Positioning the Bronchoscope for Spiration Valve Deployment

4. Under bronchoscopic observation, advance and position the bronchoscope so that the target airway location is visible and the tip of the catheter can be directed into the target airway site without bending or kinking the catheter.
5. Advance the catheter so that the yellow valve line on the catheter passes beyond the target location, see Figure 7a.



Figure 7a: Advance catheter yellow valve line beyond target location.

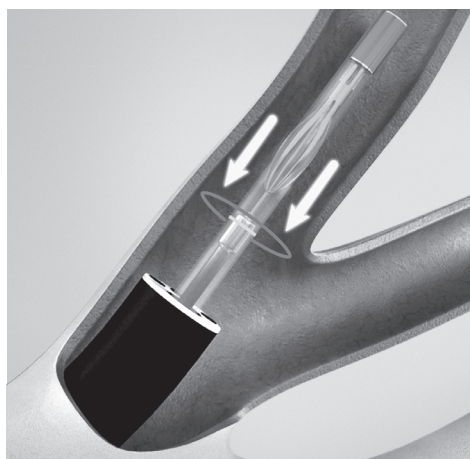


Figure 7b: Pull catheter yellow line to target location.

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- CAUTION**
- While directing the catheter to the target location, do not apply excessive force to advance the catheter.
  - If it is necessary to remove the loaded catheter from the bronchoscope, relax the bronchoscope's distal tip first.
6. Pull the catheter back slowly so that the yellow valve line is at the target location, (Figure 7b). The yellow valve line marks the position where the proximal end of the valve will contact the airway wall once deployed. After deployment, the valve may settle distally over time, so the operator needs to account for this effect.

**CAUTION** If the catheter is pushed to position prior to deployment, the valve may deploy distal to the target location.

7. If the yellow valve line is not at the desired target location, repeat steps 5 and 6. Performing steps 5 and 6 in sequence reduces movement of the catheter inside the bronchoscope channel during deployment.

## 15.6 Deploying the Spiration Valve

**NOTE** The valve line and target location must be visible prior to deploying the valve.

8. Hold the catheter sheath at the bronchoscope instrument channel entry port to maintain the valve line at the target location, so the valve is stabilized during deployment.
9. Remove the green safety clip and set aside for re-use.
10. Under bronchoscopic observation, using a smooth continuous motion, pull on the catheter retractor to deploy the valve. Forces on the catheter can be decreased by limiting bends in the bronchoscope and the catheter and/or by reducing the speed that the catheter retractor is pulled during deployment.
11. Once the valve is completely deployed, under bronchoscopic observation remove the catheter from the bronchoscope.

## 15.7 Checking Spiration Valve Placement

12. Visually examine the valve for position and fit. The valve should be opened and opposing against all borders of the airway.

**CAUTION** If the position of the deployed valve is not optimal or appropriate, remove and properly dispose of the valve.

13. While holding the catheter uncoiled, advance the catheter retractor and re-install the green safety clip over the yellow portion of the handle, see Figure 8.

**NOTE** Ensure the green safety clip is installed over the yellow portion of the handle before loading the next valve.

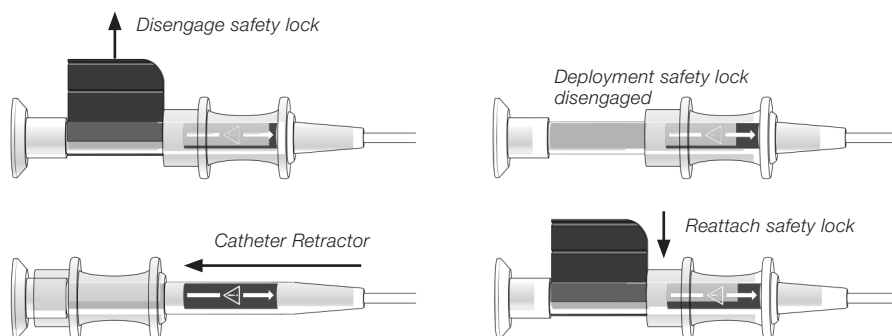


Figure 8

14. Repeat the loading and deployment steps for each additional valve required.

**CAUTION** The catheter and loader are designed to load and deploy up to 10 valves. After 10 valves are loaded and deployed from a loader and catheter, use a new catheter and loader. Using a catheter and loader more than 10 times may lead to system failure.

## 16.0 Conditions Requiring Device Removal

Valves can be temporarily or permanently placed. They may be removed if there are events associated with the valves, such as:

- Persistent bronchospasm occurring after the procedure,
- Valve placement is not optimal for the intended treatment
- Pneumonia occurring in an area beyond the valves,
- Persistent air leak following pneumothorax

## 17.0 Spiration Valve Removal

### 17.1 Items Recommended for Spiration Valve Removal Procedure

- Bronchoscopy forceps
- Flexible bronchoscope compatible with forceps
- An endotracheal (ET) tube or other intubation system, see section 14.2

### 17.2 Removing the Spiration Valve

1. Insert the appropriate forceps (see Table 4) through the instrument channel of the bronchoscope, directing the forceps to the target location (see Instructions for Use provided by the forceps manufacturer).



Forceps	Recommended use Situation
Cupped Biopsy	When the removal rod tip can be visualized and accessed by the biopsy forceps.
Rat-Tooth Jaw Grasping	When the removal rod shaft is being grasped
Pediatric Biopsy	When the maneuverability of the bronchoscope is limited by standard sized forceps but the removal rod tip can be visualized and grasped.

Table 3: Forceps Selection

2. Grasp the removal rod shaft or removal rod tip with the appropriate forceps and gently pull the valve until it is dislodged from the airway wall (see Figure 9).

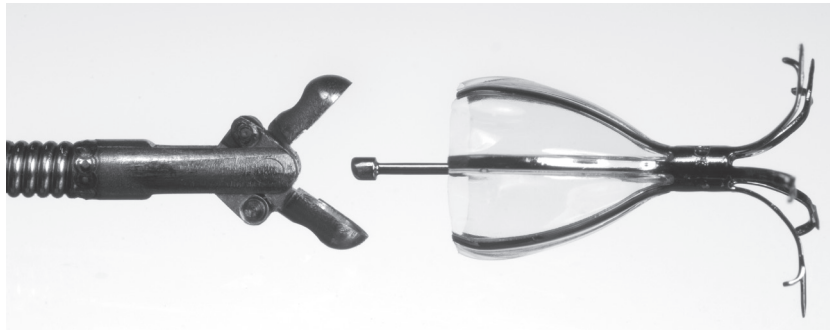


Figure 9: Spiration Valve Removal with Forceps

**NOTE** Before removing the valve from the trachea, pull the valve close up to the end of the bronchoscope (see Figure 10).

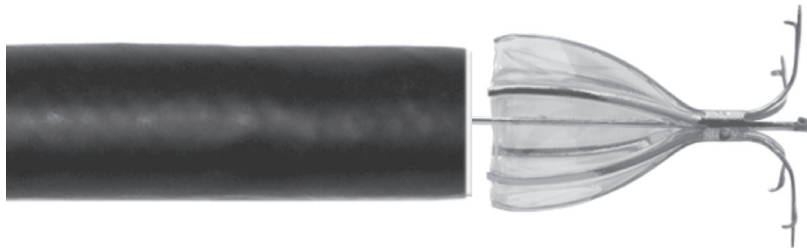


Figure 10: Spiration Valve close to the end of the bronchoscope prior to removal

3. While still firmly holding onto the valve with the forceps, simultaneously remove the bronchoscope and the forceps from the patient. During removal, the valve struts may invert.

**CAUTION** Do not attempt to bring the whole valve through the instrument channel of the bronchoscope. This may cause damage to the bronchoscope.

**NOTE**

- Do not release the valve from the forceps until the valve is completely removed from the patient.
- All valves are single use only.

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## 18.0 Patient Information

A Patient Guide to Valve Therapy for Treatment of Emphysema booklet is available for potential patients.

Patients who receive treatment with the Spiration Valve System should be given a wallet card that indicates that the patient has valve(s) in their lungs and lists the procedure physician's contact information.

## 19.0 Clinical Studies

### 19.1 Objectives

The objective of the EMPROVE study was to evaluate the safety and effectiveness of the Spiration Valve System for the treatment of severe emphysema in a randomized controlled study.

### 19.2 Methods

The EMPROVE study was a multicenter, prospective, randomized, controlled study designed to evaluate treatment with the Spiration Valve System as compared to medical management in the control group. The control group was evaluated in the same fashion as the treatment group.

Interim analyses to calculate the predictive probability of eventual success were conducted to assess sample size adequacy and based on these calculated probabilities the study stopped enrollment when a total of 172 subjects were randomized (2:1) to either treatment (SVS valves and medical management, N=113) or control (medical management alone, N=59). These subjects were enrolled at a total of 31 centers; 29 in the United States and 2 in Canada.

To identify COPD exacerbations prior to baseline testing, a 6-week run-in period allowed participants to achieve treatment stability and be assessed for any change in respiratory symptoms. Subjects were required to complete a pulmonary rehabilitation program within two years of the 6-week run-in period. However, while pulmonary rehabilitation was not mandated in the follow-up period, subjects could continue with their prescribed exercise regimen after treatment.

Randomization occurred at a pre-procedure visit with both investigators and patients being aware of their randomization group.

Statistical analysis included Bayesian statistical modeling incorporating predictive probabilities.

The superiority of the Spiration valve treatment was assessed by determining the posterior probability with a pre-specified threshold value chosen to achieve a type I error rate (under simulation) of  $\leq 0.025$ . Analysis to determine effectiveness and durability was conducted at 6 and 12 months, respectively, after enrollment was stopped.

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## 19.3 Key Inclusion and Exclusion Criteria

Clinical criteria should be considered in determining whether a patient has severe emphysema similar to that evaluated in the EMPROVE study which included the following inclusion and exclusion criteria:

### Key Inclusion Criteria:

- Patient is 40 years or older
- Subject has severe emphysema and high heterogeneity defined as: a target lobe with  $\geq 40\%$  emphysema involvement and  $\geq 10$  percentage point disease severity difference with the ipsilateral lobe
- The target lobe and ipsilateral lobe will be separated with an intact fissure. An intact fissure will be estimated visually to be  $\geq 90\%$  complete with no segmental vessels crossing from one lobe to the adjacent lobe after viewing the HRCT in 3 dimensions
- Subject meets the criteria of the ATS/ERS Guidelines for Management of Stable COPD
- Subject must be able to demonstrate physical ability to participate in the study by performing a 6-minute walk distance of  $\geq 140$  m
- Subject has abstained from cigarette smoking for 4 months and is willing to abstain throughout the study
- Subject must have severe dyspnea which is defined as a mMRC  $\geq 2$
- Subject's obstructive disease is severe as defined by:
  - $FEV_1 \leq 45\%$  of predicted (after bronchodilators)
- Subject's hyperinflation is defined by:
  - $TLC \geq 100\%$  of predicted, and
  - $RV \geq 150\%$  of predicted
- Subject is willing to participate in a controlled study, complete the required follow-up visits, and maintain consistent nutrition and exercise habits during the study period
- Investigator has confirmed that medical management is within standard of care and has been stable and without a COPD exacerbation for 6 weeks or more.

### Key Exclusion Criteria:

- Subject has a severe gas exchange abnormality in either PCO<sub>2</sub> or PO<sub>2</sub> as defined by:
  - $PCO_2 > 55$  mm Hg, or
  - $PO_2 < 45$  mm Hg on room air,
- Subject has co-existing major medical disease, alcoholism, or drug abuse potential that will limit evaluation, participation, or follow-up during the 6-month study period. This includes neurological or musculoskeletal conditions that may interfere with testing,
- Patient has a BMI  $< 15$  kg/m<sup>2</sup>,
- Subject had a hospitalization for COPD exacerbation or respiratory infections in the past 3 months prior to baseline testing,
- Subject has bronchitis with sputum production  $> 4$  Tablespoons or 60 ml per day,
- Subject has an active asthma component to their disease or requires more than 15 mg of prednisone daily,
- Subject has giant bulla ( $> 1/3$  volume in either lung),
- Patient has severe pulmonary hypertension based upon clinical evaluation,
- Subject has had prior lung volume reduction surgery or major lung procedures (lobectomy or greater),
- Subject has a lung nodule anticipated to require evaluation or intervention during the 6-month study period,
- Subject has demonstrated unwillingness or inability to complete screening or baseline data collection procedures,
- Subject has a diffuse emphysema pattern,
- Subject is classified as ASA Class greater than P4 including presence of co-morbidity that could significantly increase the risk of a bronchoscopy procedure.

## 19.4 Patient Demographics

	Treatment Group (N = 113)	Control Group (N = 59)
	Mean $\pm$ S.D. or N (%)	Mean $\pm$ S.D. or N (%)
<b>Sex (Male)</b>	54 (47.8%)	38 (64.4%)
<b>Age (Years)</b>	66.7 $\pm$ 6.6	68.1 $\pm$ 6.4
<b>FEV<sub>1</sub> (L)</b>	0.825 $\pm$ 0.264	0.792 $\pm$ 0.260
<b>FEV<sub>1</sub> (% Pred, L)</b>	30.8 $\pm$ 8.1	28.5 $\pm$ 8.5
<b>TLC (L)</b>	7.215 $\pm$ 1.530	7.649 $\pm$ 1.431
<b>TLC (% Pred, L)</b>	126.5 $\pm$ 14.5	128.2 $\pm$ 17.0
<b>RV (L)</b>	4.573 $\pm$ 1.253	4.848 $\pm$ 1.199
<b>RV (% Pred, L)</b>	207.5 $\pm$ 45.0	213.4 $\pm$ 49.3
<b>RV/TLC Ratio</b>	0.632 $\pm$ 0.080	0.632 $\pm$ 0.086
<b>Prescribed O2 (L/min)</b>	1.18 $\pm$ 1.43	1.16 $\pm$ 1.47
<b>6MWT (meters)</b>	303.5 $\pm$ 84.6	306.9 $\pm$ 104.2
<b>Dyspnea (mMRC)</b>	2.7 $\pm$ 0.7	2.7 $\pm$ 0.6
<b>SGRQ Total</b>	57.2 $\pm$ 14.8	54.6 $\pm$ 13.6
<b>Target Lobe Volume (L)</b>	1.843 $\pm$ 0.602	1.820 $\pm$ 0.456
<b>Target Lobe Treated</b>		
Left Lower	27 (23.9%)	9 (15.3%)
Left Upper	66 (58.4%)	37 (62.7%)
Right Lower	7 (6.2%)	7 (11.9%)
Right Upper	13 (11.5%)	6 (10.2%)
<b>Emphysema Severity (%)</b>	63.6 $\pm$ 10.1	61.6 $\pm$ 11.6
<b>Emphysema Heterogeneity (%)</b>	25.3 $\pm$ 12	23.3 $\pm$ 11.6
<b>Race</b>		
African-American	6 (5.3%)	4 (6.8%)
Caucasian	105 (92.9%)	53 (89.8%)
Other	2 (1.8%)	2 (3.4%)

Table 4: Patient Demographics

## 19.5 Targeted Valve Treatment

The treatment group was intended to receive complete occlusion of one lobe of the lung by using valves to occlude all segments of the lobe. The target lobe was selected based on imaging with computed tomography and, if necessary, lung perfusion. The right middle lobe was not considered an appropriate target. A CT core laboratory determined patient eligibility by assessing extent of emphysema destruction ( $\geq 40\%$  destruction target lobe), heterogeneity ( $\geq 10$  percentage point difference in emphysema destruction between target lobe and ipsilateral other lobe) using quantitative software, and fissure integrity (defined as  $\geq 90\%$  with no segmental vessels crossing from one lobe to the adjacent lobe) based on visual read. If two lobes were similar for emphysema severity and fissure completeness, then the lobe with the lowest perfusion was selected. If both measures are found to be similar, then the lobe on the left side was selected for treatment.

## 19.6 Study Follow-up Regimen

Follow-up and outcome assessments were scheduled for 1, 3, and 6 months, and annually through 2 and 5 years for the control and treatment groups, respectively.

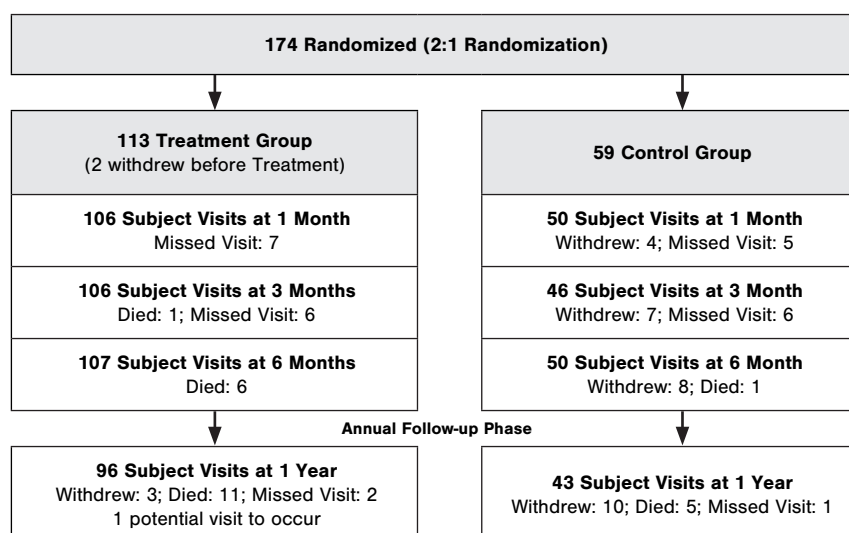


Table 5: Subject Accountability

The following assessments were undertaken at the follow up timeframes:

- Spirometry – to measure  $FEV_1$
- Plethysmography – to assess hyperinflation as measured by residual volume (RV and total lung capacity (TLC))
- High Resolution CT (HRCT) to measure target lobe volume (TLV)
- Health status and QoL, measured by St. George's Respiratory Questionnaire (SGRQ)
- Dyspnea, measured by the modified Medical Research Council (mMRC) score
- Exercise capacity – measured by six-minute walk test (6MWT)

TLV, hyperinflation and 6MWT were not collected at 12-month follow up.

## 19.7 Primary Effectiveness Objective

The primary effectiveness objective of the EMPROVE trial was to establish whether treatment with the SVS is superior to control, as assessed by change from baseline in  $FEV_1$ . The table below displays descriptive statistics for  $FEV_1$  and  $FEV_1$  change-from-baseline (in liters) at baseline, 6 months and 12 months.

FEV <sub>1</sub> (L)	Treatment Group	Control Group	Difference (T-C)	
	Mean ± SD (N) [min, median, max]	Mean ± SD (N) [min, median, max]	Estimate*, (95% BCI)	Posterior Probability of (μ <sup>T</sup> > μ <sup>C</sup> )
Baseline	0.825 ± 0.264 (113) [0.410, 0.790, 1.460]	0.792 ± 0.260 (59) [0.370, 0.760, 1.530]		
6 Mo	0.937 ± 0.296 (106) [0.340, 0.905, 1.820]	0.811 ± 0.274 (50) [0.440, 0.750, 1.700]		
12 Mo	0.920 ± 0.301 (86) [0.330, 0.860, 1.760]	0.790 ± 0.257 (39) [0.410, 0.770, 1.460]		
6 Mo – Baseline	0.099 ± 0.154 (106) [-0.260, 0.080, 0.530] 95% BCI: (0.069, 0.128)	-0.002 ± 0.098 (50) [-0.240, -0.010, 0.210] 95% BCI: (-0.030, 0.026)		
	Completers Only – Without Predictions		0.101 (0.060, 0.141)	1.0000
	With Predictions for Missing Values		0.097 (0.057, 0.138)	1.0000
12 Mo – Baseline	0.067 ± 0.167 (86) [-0.280, 0.060, 0.600] 95% BCI: (0.031, 0.103)	-0.032 ± 0.114 (39) [-0.300, -0.030, 0.390] 95% BCI: (-0.069, 0.005)		
	Completers Only – Without Predictions		0.099 (0.048, 0.151)	0.9999
	With Predictions for Missing Values		0.088 (0.037, 0.137)	0.9997

\* Posterior median

BCI – Bayesian Confidence Interval

Table 6: FEV<sub>1</sub> – Means and Change from Baseline (through 12 Months).

## 19.8 Primary Effectiveness Conclusions

The EMPROVE study treatment of severe heterogeneous emphysema in medically optimized subjects met its Primary Effectiveness Outcome and four Secondary Effectiveness Outcomes, showing significantly better Treatment Group outcome measures in SVS treated subjects when compared to Control subjects.

The EMPROVE study met its Primary Effectiveness Outcomes in favor of SVS treatment, with a significantly better improvement in FEV<sub>1</sub> in SVS Treatment subjects when compared to Control subjects at 6 months of follow-up.

- FEV<sub>1</sub>: Improvement between Treatment and Control groups = 0.097 liters on average (95%BCI: 0.057 – 0.138), with a posterior probability of superiority > 0.99995.

The 12-month results confirm the durability of effect on FEV<sub>1</sub> changes between the study groups

- FEV<sub>1</sub>: Improvement between Treatment and Control groups = 0.099 liters on average (95%BCI: 0.048 – 0.151), with a posterior probability of superiority = 0.9999.

## 19.9 Secondary Effectiveness Conclusions

In addition, the EMPROVE Trial met four secondary effectiveness outcomes: Target Lobe Volume, hyperinflation (RV/TLC), SGRQ and mMRC.

- Target Lobe Volume showed a significant reduction in the SVS Treatment subjects at 6 months. TLV reduction of -0.974 liters (95% BCI: -1.119, -0.829), with a posterior probability that the mean change is less than 0 of >0.99995.
- Hyperinflation, defined as the ratio of RV/TLC, showed significantly greater mean improvement (reduction in hyperinflation) in the SVS Treatment subjects compared to Control subjects at 6 months. The delta between Treatment and Control groups = -0.040 (95% BCI: -0.059 – -0.021), with a posterior probability of superiority > 0.99995.
- The St. George's Respiratory Questionnaire (SGRQ) showed significantly greater mean improvement (point reduction) for SVS Treatment subjects compared to the Control subjects. The delta between Treatment and Control groups was -13.0 points (95% BCI: -17.4 – -8.5), with a posterior probability of superiority > 0.99995. The 12-month results remained statistically significantly different between the study groups and confirm the durability of effect.
- The Modified Medical Research Council Dyspnea Scale (mMRC) showed significantly greater mean improvement (score reduction) for SVS Treatment subjects compared to the Control Subjects. Delta between Treatment and Control groups = -0.6 (95% BCI: -0.9 – -0.3), with a posterior probability of superiority > 0.99995. The results at 12 months show a further improvement in dyspnea score, with a mean difference between study groups of -0.9 points (95% BCI -1.2 – -0.6) and confirm the durability of effect between the study groups.
- The mean change in 6MWT at 6 months in the Treatment Group was -4.4 meters (95% BCI: (-19.4, 10.7)), while the mean change in the Control group was -11.3 meters (95% BCI: -26.2, 3.6). The difference between groups is 6.9 meters (95% BCI: -14.2, 28.2), with a posterior probability of 0.7438 which is not statistically significant.

## 19.10 Primary Safety Objective

	Treatment Group (N = 113)	Control Group (N = 59)	Difference (T-C)		Treatment Group (N = 103)	Control Group (N = 47)	Difference (T-C)	
	%	%	%	(95% BCI)	%	%	%	(95% BCI)
	Short-Term (0-6 Months)				Long-Term (6-12 Months)			
Acute exacerbation of COPD	16.8	10.2	5.8	(-5.1, 16.0)	13.6	8.5	5.1	(-7.4, 14.2)
Death from procedure or device	0.0	—	0.0	(-5.3, 2.3)	1.0	—	1.0	(-5.9, 4.1)
Pneumonia in the valve-treated lobe	1.8	—	1.8	(-3.9, 5.2)	1.0	—	1.0	(-5.9, 4.1)
Pneumonia not in the valve-treated lobe	7.1	1.7	5.4	(-2.4, 11.1)	7.8	2.1	5.6	(-3.8, 11.9)
Pneumothorax requiring surgical intervention or prolonged air leak > 7 days	12.4	0.0	12.4	(4.6, 18.6)	0.0	0.0	0.0	(-6.6, 2.4)
Tension pneumothorax	1.8	0.0	1.8	(-3.9, 5.2)	0.0	0.0	0.0	(-6.6, 2.4)
Respiratory failure	2.7	0.0	2.7	(-3.2, 6.4)	1.0	0.0	1.0	(-5.9, 4.1)
Total	31.0	11.9	18.2	(5.9, 29.7)	21.4	10.6	10.7	(-3.0, 21.2)

BCI – Bayesian Confidence Interval

Table 7: Incidence of Thoracic SAEs at 0-6 months and 6-12 months

## 19.11 Additional Safety Objectives

	Treatment Group (N = 113)	Control Group (N = 59)	Difference (T-C)		Treatment Group (N = 103)	Control Group (N = 47)	Difference (T-C)	
	%	%	%	(95% BCI)	%	%	%	(95% BCI)
	Short-Term (0-6 Months)				Long-Term (6-12 Months)			
Acute onset abdominal pain requiring urgent hospitalization or extended hospitalization	0.0	0.0	0.0	(-6.6, 2.4)	2.9	0.0	2.9	(-4.3, 6.9)
Cardiac rhythm disturbance requiring acute medical intervention	0.9	0.0	0.9	(-4.6, 3.8)	2.9	0.0	2.9	(-4.3, 6.9)
Death from any cause not from the investigational procedure or device	5.3	1.7	3.6	(-3.9, 8.9)	2.9	6.4	-3.5	(-13.9, 3.0)
Emergent surgery that is not due to trauma	0.0	1.7	-1.7	(-8.2, 1.3)	1.0	0.0	1.0	(-5.9, 4.1)
Infection at any site that is life threatening and requires hospitalization and IV antibiotics	3.5	0.0	3.5	(-2.5, 7.7)	1.0	0.0	1.0	(-5.9, 4.1)
Thrombosis or thromboembolism requiring medical management and acute hospitalization	0.0	0.0	0.0	(-6.6, 2.4)	1.0	0.0	1.0	(-5.9, 4.1)
Other	7.1	3.4	3.7	(-4.9, 9.9)	5.8	6.4	-0.6	(-11.4, 6.7)
<b>Total</b>	<b>11.5</b>	<b>3.4</b>	<b>8.1</b>	<b>(-1.1, 15.2)</b>	<b>12.6</b>	<b>12.8</b>	<b>-0.1</b>	<b>(-13.4, 10.0)</b>

BCI – Bayesian Confidence Interval

Table 8: Incidence of Non-Thoracic SAEs at 0-6 months and 6-12 months



## 19.12 Short and Long-Term Mortality

		Treatment Group % (n/N)	Control Group % (n/N)	Difference (T-C) (95% BCI)
Short-Term (0 – 6 Months)	Procedure or Device Related	0% (0/113)	-	0% (-5.3, 2.3)
	All Cause	5.3% (6/113)	1.7% (1/59)	3.7% (-3.9, 8.9)
Long-Term (6 – 12 Months)	Procedure or Device Related	1% (1/103)	-	1.0% (-5.9, 4.0)
	All Cause	2.9% (3/103)	6.4% (3/47)	-3.5% (-13.9, 3.0)

BCI – Bayesian Confidence Interval

Table 9: Short (0–6 months) and Long-Term Mortality (6–12 months) in the EMPROVE study

## 19.13 Safety Conclusions

The primary safety outcome showed that the incidence of the composite thoracic SAE was 31.0% in the Treatment Group vs 11.9% in the Control Group, through the 6-month follow up period. The total incidence of the component thoracic SAEs was higher in the Treatment Group than in the Control Group. This is predominantly due to a statistically significant incidence of pneumothorax events in the Treatment Group. Early onset pneumothorax in the Treatment Group is probably the result of changes in the conformation of the lung as a result of acute reduction in lung volume caused by the valve therapy and is recognized as an expected indicator of target lobe occlusion.

The long-term safety data shows fewer safety events through the 6–12-month follow up periods. The incidence of pneumothorax drops dramatically during the longer-term follow-up.

There were no unanticipated serious device-related adverse events (UADEs) and no migration, erosion, or expectoration events reported during 12-month follow-up period.

There were no statistically significant differences between the study groups for the incidence of non-thoracic SAEs.



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