# SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

## I. GENERAL INFORMATION

Device Generic Name: Endobronchial Valve

Device Trade Name: Spiration® Valve System

Device Procode: NJK

Applicant's Name and Address: Spiration, Inc.
6675 185th Avenue NE
Redmond, WA 98052

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P180007

Date of FDA Notice of Approval: December 3, 2018

Priority Review: Granted priority review status on June 18, 2015 because the Spiration Valve® System (SVS) is intended to treat a life-threatening or irreversibly debilitating disease or condition and the SVS offers significant, clinically meaningful advantages over existing legally marketed alternatives.

Breakthrough Device: Granted breakthrough device status (formerly known as the Expedited Access Pathway, or EAP) on June 18, 2015 because the SVS may offer a meaningful clinical benefit for patients with end stage lung disease who have already exhausted all other options available to treat their disease.

## II. INDICATIONS FOR USE

The 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.

## III. 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
- Patients with known allergies to silicone
- Patient who have not quit smoking
- Patients with large bullae encompassing greater than 30% of either lung
- Patients with diffuse homogeneous emphysema

## IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Spiration Valve System labeling.

## V. DEVICE DESCRIPTION

The Spiration Valve is designed for placement in selected regions of bronchial airways using a flexible bronchoscope. The Spiration Valve is designed to limit airflow to the distal portions of the lungs that may be affected by disease (i.e., emphysema), or damage (i.e., air leaks), while still allowing fluid and air movement in the proximal direction. The valve is removable when necessary, using a flexible bronchoscope and forceps.

The appropriate SVS valve size is selected after the airways have been evaluated using the Airway Sizing Kit. The Valve is deployed into the bronchial tree using the deployment catheter passed through the working channel of a flexible bronchoscope with working channel 2.6 mm or greater. While the Valve limits airflow into the targeted diseased lung tissue, it also permits normal mucus drainage from the distal portion of the lung.

The valves are provided in sizes 5 mm, 6 mm, 7 mm, and 9 mm to accommodate airway diameters ranging from 4.75 to 8.75 mm that are anticipated in segmental and sub-segmental bronchi. The key components of the valve are shown below.

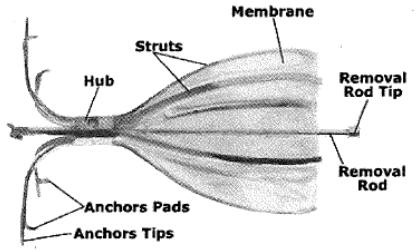



***Figure 1. Key Components of Spiration Valve***

The valve is comprised of a frame made from a super-elastic, biocompatible alloy (Nitinol) and a polyurethane membrane. The frame consists of six (6) struts that support the membrane and five (5) anchors that secure the valve in position in the airway. The membrane is held against the airway mucosa by the flexible struts and will expand and contract with airway movement during breathing. It permits fluid to pass proximally between the membrane and the airway wall while controlling airflow distally. The anchors have tips that gently penetrate the airway wall to a controlled depth, preventing the valve from migrating.

Each valve is supplied sterile inside one sterile cartridge (See Figure 2 below). The cartridge is marked with a size indicator to distinguish one valve size from the other. The cartridge is designed to fit inside a loading tool used to insert the valve into the tip of the deployment catheter.

***Figure 2. Valve in Cartridge (7 mm size shown)***

*Catheter Delivery System and Loader - Model C26N*
The Spiration Valve is delivered to the target airway through the instrument channel of a bronchoscope with the use of a deployment catheter and loader. The reloadable delivery system is provided sterile and designed for multiple valve loadings and deployments during a single patient procedure. The deployment catheter is constructed with a stabilization wire inside the catheter, which the SVS Valve in position while the valve is unsheathed from the catheter. The delivery system is provided sterile, and is intended for single patient use. Up to 10 Valves can be placed with one reloadable catheter.

The loader is a tool used to insert the valve into the tip of the catheter. After the cartridge is placed in the loader, the catheter tip is inserted into the loader and the loader plunger is depressed to load the valve into the tip of the catheter.

The catheter is used to deliver the valve to its target location. The catheter is passed through the channel of a flexible bronchoscope with a working channel inner diameter of 2.6 mm or greater. The Model C26N catheter is designed to be compatible with the 5 mm, 6 mm, 7 mm, and 9 mm valve cartridges. Materials incorporated into the C26N proximal shaft and handle are designed to enhance catheter navigation, user grip, catheter visualization, and navigation through the catheter.

*Airway Sizing Kit*
The Airway Sizing Kit is intended for use with the Spiration Valve System to determine the appropriate size valve needed to treat a target airway. It requires the use of a balloon catheter. The kit consists of a glass syringe and medical grade polymer calibration gauge. The kit is provided sterile and is intended for single patient use. It is used in conjunction with a balloon catheter, which measures the size of the targeted airway.

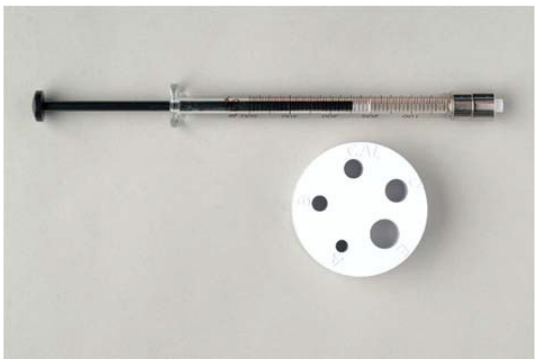


***Figure 3. Airway Sizing Kit***

*Valve Deployment*
The Spiration Valve System requires the use of a bronchoscope for minimally invasive procedures to treat patients with the Spiration Valve. In addition to providing visualization of the bronchial airways, the bronchoscope has an instrument channel that allows the valve to be delivered and deployed for treatment.

The 5 mm, 6 mm, 7 mm, and 9 mm valve cartridges are compatible with the C26N reloadable delivery system. To load a valve, the valve cartridge is snapped into the loader. The catheter is then connected to the loader and the loader plunger is depressed to introduce the valve into the catheter tip. With the valve loaded, the catheter is passed through the bronchoscope instrument channel and navigated to the target airway location. When the catheter retractor is actuated, the catheter shaft unsheathes and the valve is deployed. The valve's target position is maintained by the catheter's inner stabilization wire and tip.

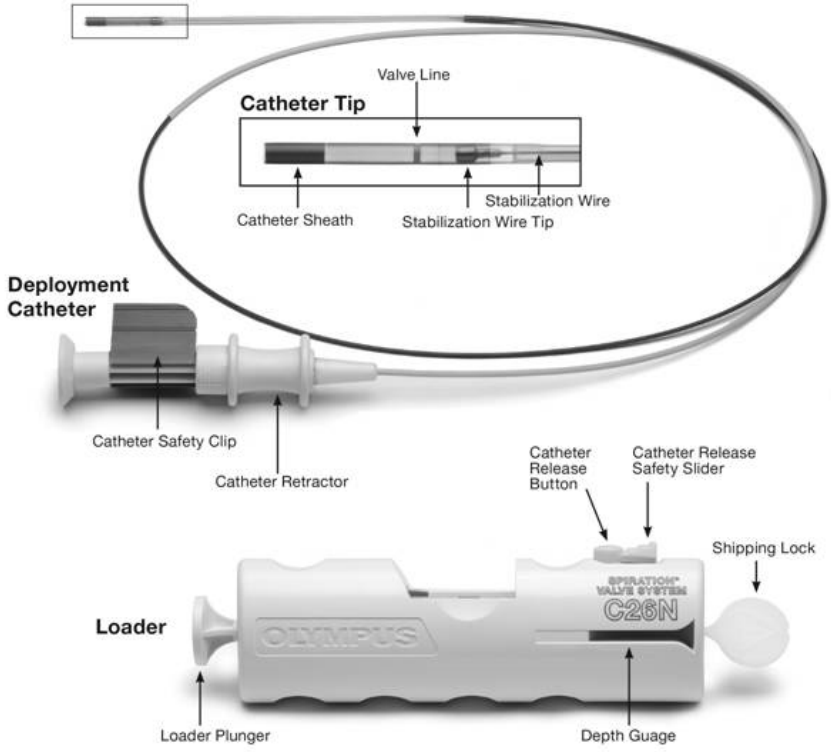



***Figure 4. C26N, 2.6mm Reloadable Catheter Delivery System***

*Valve Removal*
The valve is designed to be removable. Using appropriate bronchoscopy forceps delivered through the flexible bronchoscope working channel, the user can grip the central removal rod and withdraw the valve and the bronchoscope through the airway.

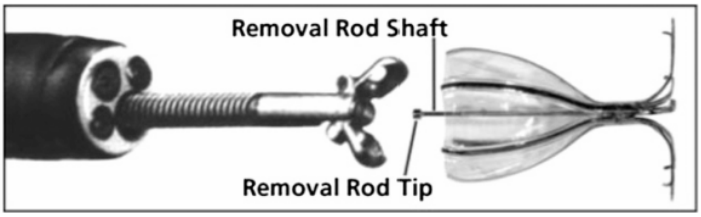



***Figure 5. Removal Rod Shaft and Removal Rod Tip***

*Packaging*

The valve in cartridge, deployment catheter, and loader are packaged with protective nylon and Tyvek® pouches compatible with ethylene oxide (EO) sterilization. The valve in cartridge is sterilized in a validated EO sterilization cycle to a Sterility Assurance Level (SAL) of $10^{-6}$. The Spiration Valve System is labeled for three (3) years of shelf life. Testing to establish package integrity and functional testing of the Spiration Valve System was conducted on real time aged product for the Valve and the Airway Sizing accessory and on accelerated-aged product for the Catheter/Loader. Appropriate bench tests were repeated on the aged product and compared to baseline to ensure that the Spiration Valve System performs as intended throughout its 3-year shelf life.

## VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of emphysema. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

- Pharmacological interventions for the relief of symptoms of emphysema
- Smoking cessation
- Long-term administration of oxygen to patients
- Pulmonary rehabilitation
- Bronchoscopic lung volume reduction with Pulmonx Zephyr Valves
- Lung Volume Reduction Surgery (LVRS)
- Lung transplantation

## VII. MARKETING HISTORY

The SVS received the CE mark in 2008 and is commercially available for treatment of emphysema throughout the European Union, Australia, and New Zealand. The SVS has not been marketed in the United States.

## VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device. Potential complications that may be associated with bronchoscopy and/or valve placement (including removal, if needed) include, but are not limited to, the following:

- Anesthesia complications
- Altered arterial blood gas
- 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
- Pneumothorax
- Pneumonia
- Pleural effusion
- 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

For the specific adverse events that occurred in the clinical studies, please see Section X below.

## IX. SUMMARY OF NONCLINICAL STUDIES

### A. Laboratory Studies

**1. Biocompatibility Testing**

Biocompatibility testing was performed on the patient contacting, implantable and skin contacting components of this device, including the SVS valves and SVS Catheter. This testing was performed in accordance with ISO 10993-1:2003, entitled "Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing."

The patient contacting device components, including the SVS valve and SVS catheter in their final finished form, were used as test articles. The components of the loader, including the plunger pin and the shipping lock, are nonpatient contacting. The loader materials have no potential to make contact with bodily tissues or fluids, therefore, according to IS0-10993-1, Biological Evaluation of Medical Devices - Part 1, biocompatibility testing and toxicological assessment were not required and were therefore not performed.

**Table 1a: Biocompatibility Testing 0f the SVS Catheter**

| Biocompatibility Tests | Purpose | Results |
|---|---|---|
| Cytotoxicity (MEM Elution) per ISO 10993-5: 1999 for C26 model and ISO 10993-5: 2009 for C26N model | To evaluate the potential for a test article extract to inhibit cell growth or produce cell lysis or degeneration *in vitro.* | Pass<br>No evidence of cytotoxicity |
| Sensitization (Guinea Pig Maximization) per ISO 10993-10:1995 for C26 model, and ISO 10993-10: 2013 for C26N model | To evaluate the allergenic potential or sensitizing capacity *in vivo.* | Pass<br>No sensitization response was observed |
| Irritation (Intracutaneous Reactivity) per ISO 10993-10:1995 for C26 model, and ISO 10993-10: 2013 for C26N model | To evaluate potential toxic effects *in vivo* as a result of a single-dose systemic injection of test article extract | Pass<br>Test article did not produce adverse intradermal reactions consistent with reactivity |
| Materials Mediated Pyrogen per ISO 10993-11:1993 | To determine if the test article extract causes a febrile response. | Pass<br>Test article extract did not elicit a pyrogenic response |
| Establishment of allowable limits for leachable substances per ISO 10993-18:2011<br><br>Chemical characterization of materials per ISO 10993-17:2008 | To assess the toxicological risk of materials that may leach from the catheter. Samples are extracted in saline and analyzed for the identification and quantification of materials released from the test articles. | Pass<br>The data and analysis show and conclude that the C26N catheter poses no unacceptable toxicological risk to the patient |

**Table 1b: Biocompatibility Testing of the SVS Valves**

| Biocompatibility Test | Purpose | Results |
|---|---|---|
| Minimal Essential Media (MEM) Elution test per ISO 10993-5:1999 for Cytotoxicity | To evaluate the potential for a test article extract to inhibit cell growth or produce cell lysis or degeneration *in vitro.* | Pass<br>No evidence of cytotoxicity |
| Guinea Pig Maximization Sensitization test per ISO | To evaluate the allergenic potential or sensitizing capacity *in vivo.* | Pass<br>No sensitization response |
| Intracutaneous Reactivity per ISO 10993:1995 | To evaluate potential intracutaneous reactivity produced *in vivo* from intradermal injection of test article extract. | Pass<br>Test article extract did not produce evidence of erythema (redness) or swelling |
| Materials Mediated Pyrogen per United States Pharmacopeia (USP) Rabbit Pyrogen Test Procedure, Section 151 | To determine if the test article extract causes a febrile response *in vivo*. | Pass<br>Test article extract did not elicit a pyrogenic response |
| Acute and chronic systemic toxicity per ISO 10993:2006 | To determine if the test article extract produces adverse *in vivo* systemic effects as expressed by death, convulsions, prostration, weight loss, or other abnormal, unexpected activity. | Pass<br>The test article extract did not produce adverse systemic effects |
| ISO Intramuscular Implant test per ISO 10993-6:1995 | To evaluate the local *in vivo* effects of a test article in direct contact with skeletal muscle tissue. | Pass<br>Test article implantation did not elicit an adverse tissue response when compared to control |
| *In Vitro* Mouse Lymphoma Assay for Genotoxicity per ISO 10993-3:1993 | To evaluate the *in vitro* effects of a test article to induce genetic alterations affecting expression of the thymidine kinase (Tk) gene when tested on mouse lymphoma cells in the presence and absence of exogenous metabolic enzymes. | Pass<br>Test article was considered nonmutagenic (nongenotoxic and nonclastogenic). The mutant frequencies and cloning efficiencies of preparations treated with the test article were within the established limits of acceptance defined for a negative response. |

| Biocompatibility Test | Purpose | Results |
|---|---|---|
| *In Vivo* Mouse Micronucleus Assay for Genotoxicity per ISO 10993-3:1993 | To evaluate the *in vivo* effects of a test article to induce micronuclei formation in immature erythrocytes obtained from the bone marrow of adult mice. | Pass<br>Test article was Considered nonmutagenic. No apparent gross manifestations of toxicity or biologically significant erythropoietic disturbances resulting in delayed mutagenesis. No significant increases in micronucleated cell production as compared to the negative controls. |
| Bacterial Mutagenicity Test - Ames Assay for Genotoxicity per ISO 10993-3:1993 | To evaluate the *in vivo* effects of a test article to induce reversion mutations in the DNA of the bacteria when tested in the presence and absence of exogenous metabolic enzymes. | Pass<br>The test article did not induce substantial increases in mutation reversion rates that are associated with mutagenesis. |
| Establishment of allowable limits for leachable substances per ISO 10993-18:2009<br><br>Chemical characterization of materials per ISO 10993-17:2009 | To assess the toxicological risk of materials that may leach from the catheter. Samples are extracted in polar and non-polar solvents and analyzed for the identification and quantification of materials released from the test articles.<br><br>A toxicological risk assessment was performed using an estimated worst case exposure, with the assumption that no more than 10 valves will be placed in a clinical procedure for the treatment of severe emphysema. | Pass<br>The data and analysis show and conclude that the valve poses no toxicological risk to the patient. |

**2. <u>Physical and Mechanical Testing</u>**

The integrity and performance of the Spiration Valve System was evaluated through bench testing. The completed testing verified that applicable material, functional, system compatibility, and durability product specifications have been met. The following tables summarize the bench testing that was performed on the Nitinol frame of the valve mechanical properties, the SVS Catheter, and SVS Loader.

Attribute data was analyzed using the formulas defined in Standard Operating Procedures (SOPs) or with a non-parametric distribution analysis. Per SOP-00130, a sample of 30 with no failures (one tailed data) was sufficient to show 90% conformance at 95% confidence. Attribute data that includes failures can be analyzed by non-parametric distribution analysis, but the sample size will be larger than 30 to show 90% conformance at 95% confidence. These formulas determined if sufficient samples were tested to conclude that the acceptance criteria defined in the protocol was met with 95% confidence/90% conformance. The following data was analyzed by attribute analysis:

- Loading Success - Anchor Tips
- Grip retention
- Valve Placement

Variable data was analyzed using Minitab statistical software to determine if it meets the 95% confidence/95% conformance acceptance criteria defined in the protocol. The analysis was done using the Parametric Distribution Analysis - Right Censoring analysis tool.

**Table 2a. Bench Testing - Nitinol Mechanical Properties**

| Test | Purpose | Acceptance Criteria | Results |
|---|---|---|---|
| Nitinol Frame | To demonstrate that the valve can withstand loading conditions using Goodman fatigue analysis. | The nitinol frame shall not have any fractures due to fatigue (observed with at least 30x optical microscopy) after the frames are compressed to 6.5% of their mean diameter and subjected to alternating strain amplitudes. These conditions were imposed for 100 million ($100 \times 10^{-6}$) cycles. | Pass |
| Accelerated Radial Fatigue | To demonstrate that the nitinol frame can withstand in situ compressive/ expansive forces approximating 8 years of use without failure of Nitinol frame or delamination of the membrane-strut interface | Device must withstand prespecified tensile strength, loading stress and elongation pressures. | Pass |
| Corrosion Testing - Nitinol Frame | To determine the susceptibility of the metallic components of the valve to corrosion when implanted through *in vitro* and *in vivo* corrosion resistance testing | The nitinol frame was evaluated for corrosion resistance per ASTM F2129. None of the valve samples experienced any breakdown, pitting or other corrosion after being exposed to a potential of at least 1.3 volts. | Pass |

**Table 2b. Bench Testing – Valve Mechanical Properties**

| Test | Test Purpose | Acceptance Criteria | Results |
|---|---|---|---|
| Radial Force - Anchor Strut | To demonstrate struts withstand a radial resistive and an outward radial forces that can be applied to the bronchial wall during breathing and coughing. | The radial resistive force a single anchor applies to the bronchial wall during breathing or coughing shall be a maximum of 0.259 Lbf. The radial chronic outward force a single anchor applies to the bronchial wall during breathing shall be a minimum of 0.049 Lbf. | Pass |
| Radial Force – Membrane Strut | To demonstrate struts withstand a radial resistive and an outward radial forces that can be applied to the bronchial wall during breathing and coughing. | The radial resistive force a single membrane strut applies to the bronchial wall during breathing or coughing shall be a maximum of 0. 184 Lbf. | Pass |
| Elastic Recoil of Anchor Struts and Membrane Struts | To confirm that a compressed valve will fully open after deployment. | When the valve is fully compressed for one hour, the valve shall recoil to its original diameter ±10%. | Pass |
| Slip Resistance | To demonstrate that a properly seated valve withstands distal and proximal pressures without excessive movement in either direction under conditions simulating constant inhalation pressures and acute exhalation pressures simulating cough. | When properly seated, in a simulated airway, the valve shall withstand a pressure of 0.13 psi applied to the proximal end of the device in the distal direction, without moving more than 3.0 mm in the distal or proximal direction. | Pass |
| Slip Resistance (continued) | To demonstrate that a properly seated valve withstands distal and proximal pressures without excessive movement in either direction under conditions simulating constant inhalation pressures and acute exhalation pressures simulating cough. | When properly seated, in a simulated airway, the valve shall withstand a pressure of 4.3 psi applied to the distal end of the device in the proximal direction, without moving more than 3.0 mm in the distal or proximal direction. | Pass |

| Test | Test Purpose | Acceptance Criteria | Results |
|---|---|---|---|
| Valve Resistance – Distal Flow | To demonstrate the valves will limit distal airflow at normal respiration pressure. | The valve (with membrane) shall reduce airflow at least 60% at a pressure gradient of 0. 13 psi. The pressure gradient is applied at the proximal end of the valve in the distal direction. | Pass |
| Valve Resistance – Proximal Flow | To demonstrate the valves will permit proximal airflow normal respiration pressure. | The valve (with membrane) shall allow some airflow in the proximal direction at a pressure gradient of 0.13 psi. The pressure gradient is applied at the distal end of the valve in the proximal direction. | Pass |
| Removal Rod-to-Frame Tensile Strength | To ensure that during application of force on the removal rod, the rod will remain attached to the frame. | The attachment strength between the removal rod and hub shall be a minimum of 5 lbs. in tension. | Pass |
| Drug Compatibility | To verify that the valves meet required specifications after exposure to common pulmonary medications. | After exposing the valves to individual and drugs alone or in combination with albuterol, tiotropium bromide, flucatasone propionate, and/or salmeterol: The attachment strength between the membrane and membrane strut shall be sufficient to prevent delaminating of the membrane-strut interface. | Pass |
| Drug Compatibility (continued) | To verify that the valves meet required specifications after exposure to common pulmonary medications. | The valve shall reduce at least 60% at a pressure gradient of 0.13 psi. The pressure gradient is applied at the proximal end of the valve in the distal direction. | Pass |

| Test | Test Purpose | Acceptance Criteria | Results |
|---|---|---|---|
| Magnetic Resonance Imaging (MRI) Compatibility | To demonstrate that the valve is MRI compatible, MRI testing up to 3.0 Tesla, and will not produce adverse effects of an MRI environment on valve position, valve temperature or image artifact. | The valve will be compatible with MRI up to 3.0 Tesla, and demonstrate conformance to ASTM F2503, "Standard Practice for Marking Medical Devices and Other Items for Safety in the Magnetic Resonance Environment." | Pass |

**Table 2c. Bench Testing – Catheter/Loader**

| Test | Test Purpose | Acceptance Criteria | Pass |
|---|---|---|---|
| Dimensional Verification | To ensure catheter/loader meets dimensional specifications | | Pass |
| Valve Sizes Loading Force | To demonstrate that load and deployment cycles can withstand the loading forces. | Catheters must undergo 10 loading cycles without any failures. | Pass |
| Plunger Pin/Valve Friction | After loading the valve into the distal end of the deployment catheter, testing was done to confirm the peak force required to remove the plunger pin from the compressed valve. | At 22°±2°C the valve shall load into the catheter and deploy from the catheter at least 80% of the time when operated by the user using the instructions for use. | Pass |
| Valve/Catheter Deployment Friction | To confirm that the force required to dislodge the valve from the catheter is within specification | The valve shall deploy from the distal end of the catheter into the bronchus with between 0.25 and 5.0 lbs., as measured at the handle and tested with the distal 40 portion of a catheter placed in a bronchoscope with a bend angle of 180°. | Pass |
| Catheter to Bronchoscope Insertion Force | To confirm that the force needed to insert the catheter into the working channel of a bronchoscope is acceptable. | The amount of force required to pass the catheter through the working channel of the bronchoscope, when the bronchoscope is straight shall not exceed 2.0 Lbf. | Pass |

| Test | Test Purpose | Acceptance Criteria | Results |
|---|---|---|---|
| Valve/Catheter Loading | To confirm the peak force required to dislodge the valve from the catheter is acceptable. | The force that the Loader Tool transfers to the IBV Device shall be less than 5.0 lbs. | Pass |
| Loader Tool Transfer Force | To confirm the transferred from the loading tool to the valve is acceptable. | The force that the Loader Tool transfers to the Valve shall be less than 5.0 lbs. | Pass |
| Loader Tool User Force | To confirm the force that the user experiences when loading a valve into the tip of the catheter is acceptable. | The force that the user experiences when loading a valve into the tip of the catheter shall be less than 8.0 lbs. | Pass |
| Stabilization Wire to Stabilization Wire Tip Joint Strength | To confirm the peak force transmitted to the distal tip of the stabilization wire during handle actuation meets specifications. | The stabilization wire withstand at least 1.60 Lbf. | Pass |
| Kink Resistance | To confirm the distal catheter tip meets specification required to mitigate kinking during placement | | Pass |
| Peak Transmission Force | To confirm the force transmitted from the catheter's distal handle to the stabilization wire tip during valve deployment meets specification | The peak force transmitted to the distal tip of the stabilization wire during handle actuation shall be a minimum of 1.60 lbs. This shall be measured at the distal tip and tested with the distal 40 cm of the Deployment Catheter in a bronchoscope with a bend angle of 180° and a minimum inside radius of 0.3 inches. | Pass |
| Maximum Deployment Force | To confirm the valve can be successfully deployed from distal end of the catheter with acceptable user force | The valve shall deploy from the distal end of the catheter into the bronchus within the specified lbs. criteria. This shall be measured at the handle and tested with the distal part of the catheter when placed in a bronchoscope with a bend angle of 180° and a minimum inside radius of 0.3 inches. | Pass |

| Test | Test Purpose | Acceptance Criteria | Results |
|---|---|---|---|
| Tensile Strength of Catheter Joints<br>• Catheter Sheath to Slider Sleeve<br>• Stabilization Wire to Stabilization Wire Tip<br>• Strain Relief to Slide Housing<br>• Stabilization Wire Cap Joint<br>• Stabilization Rod Wire to Guidewire<br>• Crimp Hub<br>• Distal Catheter Sheath<br>• Catheter Sheath Composite Lap Joint Elongation | To confirm the strength of each joint is within specifications | The joints shall withstand the pre-specified minimum force requirements (range 2.5 - 5.5 Lbf). | Pass |
| Catheter Sheath Transparency | To confirm that the catheter system allows for visual confirmation of whether or not a valve is loaded into the catheter. | The catheter sheath will allow visibility of the stabilization rod and removal rod in the region distal to the stabilization cup, and proximal to the ski tip bend when the valve is loaded into the catheter sheath. | Pass |
| Catheter Flexibility | To confirm the catheter is flexible enough to allow bronchoscope to flex as intended. | All catheter surfaces that make contact with the bronchoscope working channel must be free of features that could interfere with the free passage of the catheter through the working channel of the·bronchoscope. This was be evaluated by using clinical or equivalent bronchoscopes. | Pass |

| Test | Test Purpose | Acceptance Criteria | Results |
|---|---|---|---|
| Catheter Flexibility (continued) | To confirm the catheter is flexible enough to allow bronchoscope to flex as intended. | The valve shall deploy from the distal end of the catheter into the bronchus within the specified lbs. range. This shall be measured at the handle and tested with the distal portion of the catheter when placed in a bronchoscope with a bend angle of 180°. | Pass |
| Sizing System | To Confirm that the sizing system can be reliably used to assist in determining the size of the airways targeted for treatment. | The sizing balloon shall meet the dimensional specifications, and be capable of inflating to a diameter of at least 11.0 mm. The balloon shall not rupture when inflated, at body temperature.<br><br>The custom calibration gauge shall have five (5) holes provided in increments of 1.0 mm (excluding the 7.75 hole) which provide a correlation between balloon diameter and syringe volume. | Pass |

**3. Sterilization, Package Integrity, Shelf Life, and Transport Stability**

The ethylene oxide (EO) sterilization process was successfully validated in accordance with EN ISO 11135:2014, EN ISO 10993-7:2008, and SOP "EO Sterilization Validation" (sterilization validation/requalification SOP"). Test results demonstrated that the sterilization process produces product with a 10-6 sterility assurance level (SAL). This is the probability of one unit in a million being non-sterile and is the requirement for terminally sterilized products. This validation was performed by completing four (4) half cycles and two (2) full cycles of the sterilization process using dummy products

representative of the Spiration Valve System, Airway Sizing Kit and ViziShot FLEX. Two (2) full cycles were run to establish process repeatability and expose the EO residual samples to be tested. The two (2) full cycles used the maximum load configuration. Sterility of the biological indicators (BIs) contained in the external PCDs was verified.

The EO, Ethylene Chlorohydrin (ECH) and, Ethylene Glycol (EG) residual testing was conducted at three (3) time points Day 1, 3, and 5. Day 1 and Day 3 samples were exposed to 1X sterilization; Day 5 samples were 2X sterilized. The worst case conditions, specifically at Day 5 after 2X sterilization, were evaluated against the allowable EO and ECH limits for the various products' intended uses as outlined in ANSI/AAMI/ISO 10993-7:2008. The results confirm that the Spiration Valve System can be adequately sterilized using the new larger eight (8) pallet chamber to a Sterility Assurance Level (SAL) of $10^{-6}$.

**Table 3. Sterilization, Product Stability, and Packaging**

| Test | Purpose | Acceptance Criteria | Results |
|---|---|---|---|
| Sterility validation | To evaluate sterility | Sterility assurance level of $10^{-6}$. No growth in biological indicators (BIs) contained in internal and external process challenge devices (PCDs) as verified for each half cycle. | Pass |
| EO Residuals Analysis - Valves, Assuming 10 Valves per Procedure (Permanent Patient Contact) | To ensure that residuals do not exceed the levels recommended by ISO 10993-7:2008. | The average daily dose of EO is $\leq$ 4 mg in the first 24 hours, $\leq$ 60 mg in the first 30 days, and 2.5 g in lifetime. The average daily dose of ECH is $\leq$ 9 mg. | Pass |
| Ethylene Oxide Sterilization - Catheter (Acute Patient Contact) | Sterilant gas residue analysis was completed per ISO 10993-7:2008. | The average dose of EO within the first 24 hours is $\leq$ 4 mg. The average dose of ECH within the first 24 hours is $\leq$ 9 mg. | Pass |
| Bacterial Endotoxin Residuals | To evaluate endotoxin levels on implant. | The detected endotoxin is < 0.5 EU/ml or 20.0 EU/device. | Pass |
| Product Stability | To evaluate product stability for the shelf life period. | Valves, cartridge, loader and catheter meet all visual, dimensional, and performance requirements. | Pass |

| Test | Test Purpose | Acceptance Criteria | Result |
|---|---|---|---|
| Package Integrity | To evaluate seal integrity for the shelf life period. | Each lot must be packed appropriately to prevent damage during shipping and handling. Packaging and shipping boxes shall withstand transport and extreme environmental Conditions without compromising the integrity of the product, packaging materials, or sterile barrier.<br><br>A certification of analysis (CofA) must accompany each lot of material. The CofA must include the following: Tensile Strength @ Break (psi)<br>Tensile Strength @ Yield (psi)<br>Tensile Elongation @ Break (%)<br>Tensile Elongation @ Yield (%)<br>Tear Strength (Lbf/in) | Pass |

B. **Animal Studies**

Following exploratory studies to evaluate proof of principle, a series of animal studies were submitted to support device safety for clinical use. Initial development studies were conducted on the Spiration Intra-Bronchial Valve (IBV) under IDE G030208, to support clinical use of the IBV as a palliative therapy for emphysema. These initial implant studies were conducted in three (3) different animal models (swine, canine, and ovine) to aid in the selection of the appropriate polymer materials and nitinol frame design, and to evaluate airway sizing requirements. The clinical version of the SVS valves was deployed in the lungs of healthy subjects for chronic testing, to evaluate device-related complications associated with valve placement. The device was deployed using a flexible endoscope. Table 4 summarizes the general design scheme of the chronic animal implantation studies.

**Table 4. Animal Testing Summary**

| Study | Device Design | Animal Model | Total Number of Valves Implanted | Follow-Up (Months) |
|---|---|---|---|---|
| 3a | Nitinol frame, Bionate polymer membrane | Dog (6) | 71 | 1, 3, 6 |
| 3b | Nitinol frame, Bionate polymer membrane | Dog (2) | 22 | 6 |
| 4a | Nitinol frame, Bionate polymer membrane | Sheep (6) | 73 | 1, 3, 6 |

| Study | Device Design | Animal Model | Total Number of Valves Implanted | Follow-Up (Months) |
|---|---|---|---|---|
| 4b | Nitinol frame, Bionate polymer membrane | Sheep (2) | 24 | 6 |
| Pivotal | Spiration Valve - Nitinol frame, Chronoflex membrane | Pig (8) | 48 | 3, 6 |

Adverse events noted for the preclinical studies included (a) migration and/or malposition of the valves, and (b) development of inflammation-type responses in the implanted tissue. The histological evaluation provided evidence of foreign body reactions at 1, 3, and 6 months of valve implantation. In general, the airways distal to the device are described as patent, with healthy appearance. Regardless of the tissue response to valve placement, a subset of the implanted valves were successfully removed at the 1, 3, and 6 month time points. Removal of the valves was associated with mild to moderate ulceration and red blood cell extravasation. Other valves were left in place for necropsy assessment *in situ*.

*General Histological Observations:*
There was evidence of mild to moderate inflammation, with only a few tissue sections showing evidence of "marked" (i.e., severe) inflammation or injury. Other tissue responses included hyperplasia, squamous metaplasia, focal granulomas, mild to moderate vascular edema, and chronic inflammation, whichwas noted where there was direct tissue contact with the valves. In areas more distal tohe implant, the respiratory epithelium was found to be ciliated, with evidence of variable erosion and ulceration of the epithelum, lymphoid aggregates, and edematous submucosalgransulation tissue. There is also evidence of variable erosion and ulceration of the epithelium, lymphoid aggregates, edematous submucosal granulation tissue, and hyperplastic submucosal glands. The regions of lung showing evidence of histopathology were found to be small relative to the total volume of lung. The extent of hyperplasia was noted to be greater in the canine subjects as compared to the ovine or porcine subjects.

*Limitations of the Animal Model:*
Limitations included natural growth in the airways of the juvenile subjects, which was postulated to lead to changes in the sizes and dimensions of the targeted tissue that were implanted with the valves of immature pigs. Valves that were undersized may have contributed to loosening of the valves, and findings of valve movement, valve associated irritation, and development of granulation tissue and hyperplasia. There was one (1) incidence of valve migration in an animal subject, which occurred without apparent veterinary clinical complications. Upon device explant, one (1) device had a broken strut, which was postulated to have occurred during necropsy and dissection.

*Pivotal Animal Study:*
A pivotal study was conducted in accordance with Good Laboratory Practices (GLPs) per 21 CFR Part 58. This study evaluated valves of 5 mm, 6 mm, and 7 mm diameters in healthy Hanford mini-swine. The valves were bronchoscopically placed in segmental airways using

the Deployment Catheter and Loader. A total of 48 valves were placed in eight (8) swine, with each swine receiving six (6) valves (1 of each size in each lung). In each animal, two (2) airways were identified as control areas and left untreated.

At each of the two (2) time points, 3 and 6 months, follow-up evaluations were performed on half (4) of the eight (8) animal subjects. At necropsy, direct observation of the areas distal to the placed devices revealed segmental volume reduction with associated lobular atelectasis and no lesions related to valve placement. Histopathology, necropsy and clinical observations revealed:

- Settling in of the valves, defined as the foreshortening of the valve produced by the expansion of the anchoring points.
- All valves remained in place throughout the defined study period (3 or 6 months) with no migration or expectoration.
- In every placement site the response varied over the length of the valve, being more pronounced in the areas of direct contact with the airway wall (proximal and distal ends), less in the valve hub region, and decreasing to control levels distal to the valve.

Histopathology of the device tissue contact zone revealed localized airway remodeling, with inflammation and fibrosis in the vicinity of the valve placement site. These histological responses are consistent with the mechanical irritation produced by the device. Inflammation was limited to the airway placement sites with no extension into the adjoining parenchyma.

Histomorphometric analysis of the tissue response was done using measurements taken from the cross sections of the airways to demonstrate the amount of remodeling, fibrosis, and inflammatory infiltrates associated with the chronic inflammation.

In the measured sections, remodeling changes were noted to vary as follows:

- minimal proximal to the valve
- moderate at the proximal edge of the valve
- minimal at the hub of the device
- moderate to severe corresponding to the site of the anchor points
- minimal in the sections of airway wall distal to the valve.
- Results indicated that adverse tissue reactions were comparable to control levels in the airways distal to the valves.

*Analysis.* Airway to valve size mismatches observed through animal testing could have exacerbated the adverse histological effects (e.g., settling, granulation tissue, inflammation) observed at or near the valve placement sites. The clinical safety data from Outside the US (OUS) and US clinical trials provide evidence of a relatively low rate of valve migration, suggesting that the human experience with the valves, and by extension SVS Valves, was more favorable than the animal data predicted.

## X. SUMMARY OF PRIMARY CLINICAL STUDIES

### EMPROVE PIVOTAL TRIAL

Spiration, Inc. performed a pivotal clinical study to establish a reasonable assurance of safety and effectiveness of the Spiration Valve for the treatment of patients with severe emphysema in the U.S. and Canada under IDE #G 120192. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

### A. Study Design

Patients were treated between October, 2013 and May, 2017. The database for this PMA reflected data collected through July 18, 2018 at 31 investigational sites and included 172 randomized patients (153 patients at 29 US sites and 19 patients at two (2) OUS sites).

The study was a prospective, multi-center, randomized, controlled, two-arm, pivotal clinical trial. Qualifying subjects with severe heterogeneous emphysema were randomized in a 2:1 ratio to either the Spiration Valve Treatment Arm or the Control (medical management) Arm. In addition, 20 subjects with α1 antitrypsin deficiency were included in a 3rd, Non-Randomized Treatment Arm. The primary endpoint was the difference between the Treatment and Control Arms in the mean change in $FEV_1$ from baseline to 6- months; however, 12 month data was provided.

Randomization was stratified by site, using a blocked randomization scheme with blocks of randomly varying sizes. The study was planned to enroll up to 220 randomized subjects with two interim looks on 100 and 160 subjects to assess sample size adequacy. After the 2nd interim analysis, enrollment was stopped upon recommendation of the Data and Safety Monitoring Board (DSMB).

Data from the study were analyzed using a Bayesian approach. Superiority of the Spiration Valve System over Control was considered established if the posterior probability for the primary effectiveness endpoint was > 0.982, a pre-specified threshold that was chosen to achieve a Type I error rate (under simulation) of at most 0.025. If the primary effectiveness endpoint was met, then the secondary effectiveness endpoints were tested, in the order described below. Secondary endpoints included Target Lobe Volume (TLV) reduction as measured by quantitative CT, health status as measured by St. George's Respiratory Questionnaire (SGRQ), dyspnea as measured by Medical Research Council, Modified Field Questionnaire (mMRC), Exercise capacity as measured by the Six Minute Walk Test (6MWT), and FEV1 Responder, defined as those achieving at least 15% improvement from baseline to 6 months.The posterior probability for claiming a success in a secondary effectiveness endpoint had to be > 0.975. Once a specific test failed to meet its respective "pass" criterion, all subsequent testing would stop.

The Intent to Treat population consisting of all randomized subjects was used as the primary analysis population for the primary and secondary effectiveness endpoints and safety assessment. Data from the Non-Randomized Treatment Arm subjects with α1

antitrypsin deficiency were summarized descriptively and not compared with either the Treatment Arm or the Control Arm.

The study included core laboratory use and independent evaluators. High resolution CT scans were collected for all study participants as part of the study screening process. Images were reviewed by the CT core laboratory for image quality and to determine patient eligibility based on the extent of emphysema destruction, heterogeneity and fissure integrity. Additionally, an independent Clinical Events Committee (CEC) of three (3) physicians was established to review and adjudicate the serious adverse events (SAEs). A DSMB was also established to review the CEC's findings, review the interim data and advise the applicant regarding continuing safety.

1. Clinical Inclusion and Exclusion Criteria
   Enrollment in the EMPROVE study was limited to patients who met the following inclusion criteria:
   - Subject is 40 years of age or older,
   - Subject has severe emphysema and high heterogeneity defined as: a target lobe with ≥ 40% emphysema involvement and ≥ 10 percentage points 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 ≥ 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 ≥ 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 ≥ 2,
   - Subject's obstructive disease is severe as defined by:
     - $FEV_1 \leq 45\%$ of predicted,
   - Subject's hyperinflation is defined by:
     - TLC ≥ 100% of predicted, and
     - RV ≥ 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,
   - Subject provides informed consent and is willing and able to return for all study examinations, and
   - Subjects with α1 antitrypsin deficiency must have confirmatory blood test.

Patients were not permitted to enroll in the EMPROVE study if they met any of the following exclusion criteria:

- Subject has a severe gas exchange abnormality in either $PCO_2$ or $PO_2$ 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/m2,
- 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, or
- Subject participated in a study of an investigational drug or device within the 30 days prior to participation in this study, or is currently participating in another clinical study.

2. Follow-up Schedule

All study subjects were followed at the 1, 3, and 6 month (primary end time point) visits, and then annually through 5 years for the Treatment Arm and through 2 years for the Control Arm.

Preoperatively, subjects that met the inclusion/exclusion criteria underwent office evaluation, pulse oximetry, pulmonary function testing, arterial blood gas, 6MWT, CT scanning, questionnaire completion completion (SGRQ, COPD AssessmentTest - CAT, Short Form Health Assessment - SF-36, Quality of Well-Being Scale - QWB).

Postoperatively, the objective parameters measured during the study included all the above at the timepoints listed below. Adverse events and complications were recorded at all visits.

The key timepoints for the follow-up schedule and required testing are shown below.

**Table 5. Summary of Tests and Procedures**

| | Screening | Baseline | Control Arm Only for Pre-Proc | Treatment Arm Only for Pre-Proc, Rx | 2 Wk | 1 Mo | 3 Mo | 6 Mo | Annual |
|---|---|---|---|---|---|---|---|---|---|
| **Tests** | | | | | | | | | |
| Subject Visit/ Office Evaluation | √ | √ | √ | √ | √ (via phone) | √ | √ | √ | |
| $SpO_2$ and $O_2$ *(if $O_2$ prescribed)* | √ | √ | | | | √ | √ | √ | |
| mMRC Questionnaire | √ | √ | | | | √ | √ | √ | √◊◊◊ |
| 6MWT *(with $O_2$ if prescribed)* | √ | √ | | | | | √ | √ | |
| Spirometry | √ | √ | | | | √ | √ | √ | √◊◊◊ |
| Plethysmography/ Lung Volume | √ | √ | | | | | √ | √ | |
| ABG without O2 | √ | | | | | | √ | √ | |
| CT Scan | √* | √** | | | | | | √◊ | |
| SGRQ Questionnaire | | √ | | | | √ | √ | √ | √◊◊◊ |
| COPD Assessment Test (CAT) | | √ | | | | √ | √ | √ | √◊◊◊ |
| SF-36 Questionnaire | | √ | | | | √ | √ | √ | √◊◊◊ |
| QWB Questionnaire | | √ | | | | | | √ | √◊◊◊ |
| Lung Scan (perfusion only with quantitation; no ventilation) if Needed | | √*** | | | | | | | |
| CXR (PA/LAT) | | | | √**** | | | | √◊ | |
| Bronchoscopy Procedure | | | | √ | | | | | |
| Place SVS Valves | | | | √ | | √***** | √***** | | |

* CT scan for screening was used for degree of emphysema involvement, heterogeneity, and fissure integrity

** CT scan for screening was used for baseline assessment of target lobe volume

*** Lung Scan, if needed, for target lobe selection. Could be performed during 6-week run-in period

**** Portable CXR after procedure and CXR (PA/LAT) before discharge

*****Patients could undergo an additional bronchoscopic procedure at the 1 or 3-month follow-up period to optimize valve placement

◊ Only Treatment Arm had CT scan and CXR at 6 months

◊◊ Treatment Arm includes the α1 antitrypsin patients

◊◊◊ Treatment Arm followed annually through 5 years. Control Arm followed annually through 2 years.

3. Clinical Endpoints

With regards to the safety, assessment was to compare the incidence between the Treatment and Control Arms of a composite (primary) as well as each component (secondary) of thoracic SAEs during the 6-month follow-up period. The components of the thoracic SAE composite are listed in Table 6 below.

**Table 6. Thoracic Serious Adverse Events**

| |
|---|
| Acute asthma or bronchospasm requiring admission to an intensive or critical care unit |
| Acute exacerbation of COPD that is acute onset, life threatening, and requires hospitalization |
| Airway injury from valve placement, valve migration, or airway stenosis from a valve, requiring surgical intervention |
| Death from the procedure or device |
| Massive hemoptysis (estimated over 300 ml in 24 hours and requiring transfusion, surgery, or arterial embolization) attributed to the procedure or device |
| Pneumonia in the valve-treated lobe that requires hospitalization, IV antibiotics, and valve removal |
| Pneumonia NOT in the valve-treated lobe that is life-threatening, acute onset, and requires hospitalization and IV antibiotics |
| Pneumothorax requiring surgical intervention, or prolonged air leak > 7 days defined as the time from chest tube insertion to the time the air leak is not present |
| Respiratory failure that requires mechanical ventilatory support for > 24 hours |
| Tension pneumothorax |

With regards to effectiveness, the primary effectiveness endpoint was the difference between the Treatment and Control Arms in the mean change in $FEV_1$ from baseline to 6 months.

Secondary effectiveness endpoints included:

- Target lobe volume reduction, as measured by quantitative CT (computed by difference in the Treatment Arm at 6 months versus baseline).
- Hyperinflation as measured by the ratio of Residual Volume to Total Lung Capacity (RV/TLC) (computed by the difference between the Treatment and Control Arms in mean change from baseline to 6 months).
- Health Status as measured by St. George's Respiratory Questionnaire (SGRQ) (computed by the difference between the Treatment and Control Arms in mean change from baseline to 6 months).

- Dyspnea as measured by Medical Research Council, Modified Questionnaire (mMRC) (computed by the difference between the Treatment and Control Arms in mean change from baseline to 6 months).
- Exercise capacity as measured by 6MWT)(computed by the difference between the Treatment and ControlArms in mean change from baseline to 6 months).
- The difference between responder rates in the Treatment and Control Arms with a responder defined as ≥ 12%, ≥ 15%, and ≥ 20% improvement in $FEV_1$.

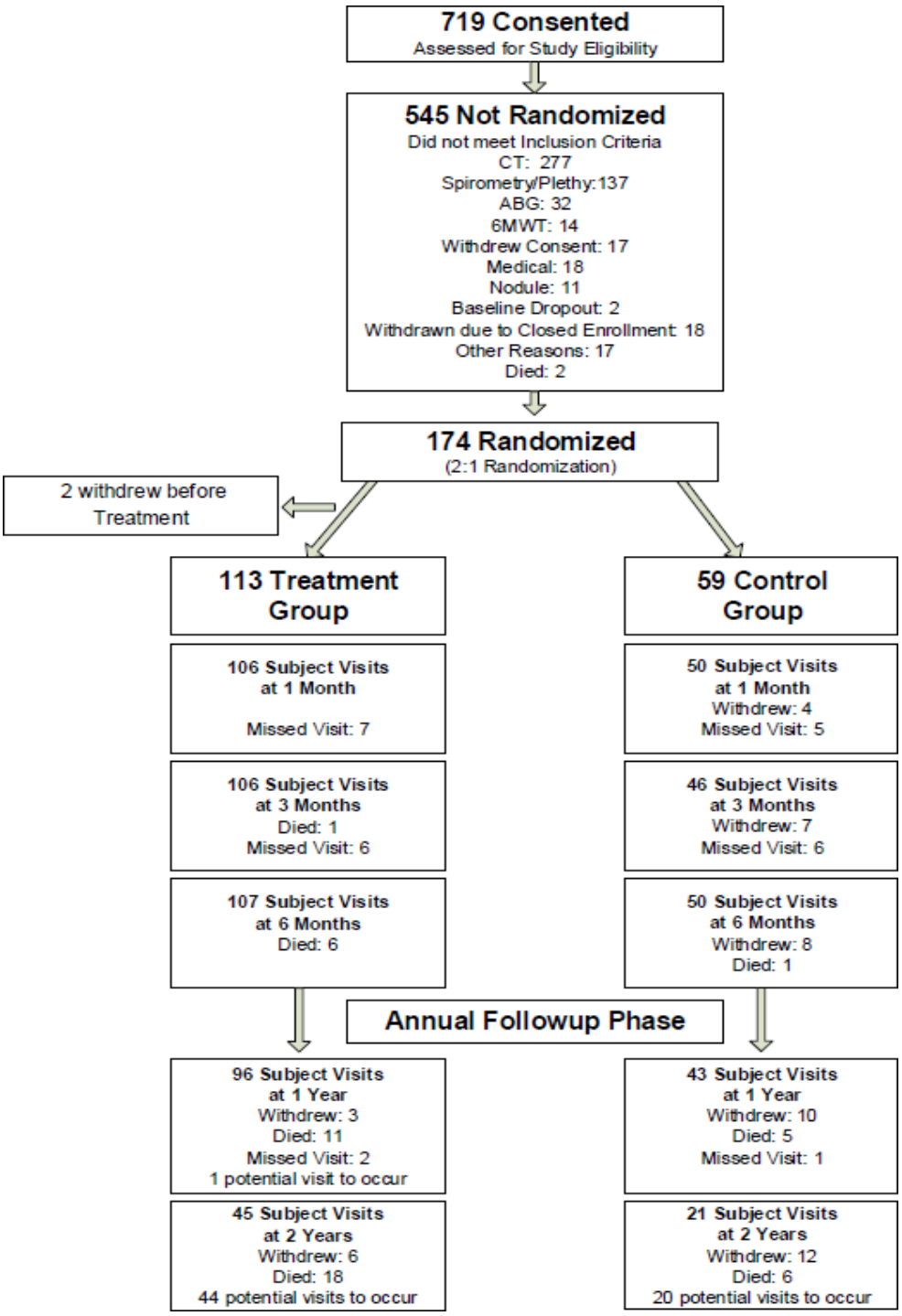
Although, the primary endpoint was evaluated at 6 months, 12 month data was provided for the primary endpoint of the difference between the Treatment and Control Arms in the mean change in $FEV_1$ from baseline and secondary endpoints of SGRQ, mMRC and difference in $FEV_1$ responder rate defined as ≥ 12%, ≥ 15%, and ≥ 20% improvement in $FEV_1$, as a comparison between the Treatment and Control Arms.

With regard to success/failure criteria, study success was defined as: superiority had to be demonstrated to meet the outcome of the primary effectiveness.

B. **Accountability of PMA Cohort**

Although the DSMB recommended stopping enrollment after the second interim analysis with 160 subjects, a total of 172 subjects were in the database by the time of database freeze on November 27, 2017, with 113 (65.7%) in the Treatment Arm and 59 (34.3%) in the Control Arm. Overall subject accountability for the EMPROVE study is included in Figure 6 below.

***Figure 6. Subject accountability***




## C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a pivotal study performed in the US. Baseline demographics and clinical characteristics of the study population are presented below in Table 7.

Overall, the Treatment Arm and the Control Arm baseline characteristics were comparable, except there was a difference in sex with more males (64.4%) enrolled in the Control Arm in comparison to the Treatment Arm (47.8%). The majority of subjects enrolled in the study (91.8%) were Caucasians. These differences did not likely impact the clinical trial.

**Table 7. Demographic and Baseline Characteristics**

| | Treatment Arm (N = 113) | | Control Arm (N = 59) | | Difference (T – C) |
|---|---|---|---|---|---|
| | N | Mean ± S.D. or N (%) | N | Mean ± S.D. or N (%) | 95% BCI |
| **Sex (Male)** | 113 | 54 (47.8%) | 59 | 38 (64.4%) | (-30.9%, -0.8%) |
| **Age (Years)** | 113 | 66.7 ± 6.6 | 59 | 68.1 ± 6.4 | (-3.4, 0.7) |
| **BMI ($kg/m^2$)** | 113 | 25.3 ± 4.3 | 59 | 24.6 ± 5.2 | (-0.8, 2.3) |
| **$FEV_1$ (L)** | 113 | 0.825 ± 0.264 | 59 | 0.792 ± 0.260 | (-0.051, 0.116) |
| **$FEV_1$ (% Pred, L)** | 113 | 30.8 ± 8.1 | 59 | 28.5 ± 8.5 | (-0.4, 5.0) |
| **FVC (L)** | 113 | 2.492 ± 0.754 | 59 | 2.633 ± 0.757 | (-0.384, 0.101) |
| **FVC (% Pred, L)** | 113 | 70.2 ± 16.5 | 59 | 70.5 ± 16.7 | (-5.6, 5.0) |
| **TLC (L)** | 113 | 7.215 ± 1.530 | 59 | 7.649 ± 1.431 | (-0.904, 0.035) |
| **TLC (% Pred, L)** | 113 | 126.5 ± 14.5 | 59 | 128.2 ± 17.0 | (-6.9, 3.5) |
| **RV (L)** | 113 | 4.573 ± 1.253 | 59 | 4.848 ± 1.199 | (-0.665, 0.115) |
| **RV (% Pred, L)** | 113 | 207.5 ± 45.0 | 59 | 213.4 ± 49.3 | (-21.3, 9.4) |
| **RV/TLC Ratio** | 113 | 0.632 ± 0.080 | 59 | 0.632 ± 0.086 | (-0.028, 0.026) |
| **Prescribed $O_2$ (L/min)** | 113 | 1.18 ± 1.43 | 59 | 1.16 ± 1.47 | (-0.45, 0.49) |
| **$PO_2$ (mmHg)** | 112 | 67.9 ± 10.2 | 59 | 68.0 ± 11.6 | (-3.6, 3.5) |
| **$PCO_2$ (mmHg)** | 112 | 40.2 ± 5.7 | 59 | 40.9 ± 6.0 | (-2.7, 1.1) |
| **6MWT (meters)** | 113 | 303.5 ± 84.6 | 59 | 306.9 ± 104.2 | (-34.8, 28.0) |
| **Dyspnea (mMRC)** | 113 | 2.7 ± 0.7 | 59 | 2.7 ± 0.6 | (-0.2, 0.2) |
| **SF-36 PF** | 113 | 26.3 ± 17.8 | 59 | 29.8 ± 17.9 | (-9.3, 2.2) |
| **SF-36 PCS** | 113 | 32.0 ± 8.2 | 59 | 32.8 ± 6.9 | (-3.1, 1.6) |
| **COPD Assessment Test** | 113 | 21.8 ± 6.8 | 59 | 20.0 ± 6.3 | (-0.3, 3.9) |
| **SGRQ Total** | 113 | 57.2 ± 14.8 | 59 | 54.6 ± 13.6 | (-1.9, 7.1) |
| **Target Lobe Volume (L)** | 113 | 1.843 ± 0.602 | 59 | 1.820 ± 0.456 | (-0.140, 0.187) |
| **Target Lobe†** | 113 | | 59 | | |
| **Left Lower** | | 27 (23.9%) | | 9 (15.3%) | (-4.2%, 19.5%) |
| **Left Upper** | | 66 (58.4%) | | 37 (62.7%) | (-17.8%, 12.0%) |
| **Right Lower** | | 7 (6.2%) | | 7 (11.9%) | (-15.9%, 2.8%) |
| **Right Upper** | | 13 (11.5%) | | 6 (10.2%) | (-9.4%, 10.1%) |
| **Emphysema Severity (%)** | 113 | 63.6 ± 10.1 | 59 | 61.6 ± 11.6 | (-1.6, 5.5) |
| **Emphysema Heterogeneity (%)** | 113 | 25.3 ± 12.0 | 59 | 23.3 ± 11.6 | (-1.8, 5.8) |

| | Treatment Arm (N = 113) | | Control Arm (N = 59) | | Difference (T – C) |
|---|---|---|---|---|---|
| | N | Mean ± S.D. or N (%) | N | Mean ± S.D. or N (%) | 95% BCI |
| **Season of Enrollment‡** | 113 | | 59 | | |
| **Jan – Mar** | | 34 (30.1%) | | 18 (30.5%) | (-14.4%, 13.4%) |
| **Apr – Jun** | | 29 (25.7%) | | 16 (27.1%) | (-15.1%, 11.7%) |
| **Jul – Sep** | | 29 (25.7%) | | 12 (20.3%) | (-8.0%, 17.3%) |
| **Oct – Dec** | | 21 (18.6%) | | 13 (22.0%) | (-16.1%, 8.6%) |
| **Race** | 113 | | 59 | | |
| **African-American** | | 6 (5.3%) | | 4 (6.8%) | (-10.8%, 5.4%) |
| **Caucasian** | | 105 (92.9%) | | 53 (89.8%) | (-4.8%, 14.7%) |
| **Other** | | 2 (1.8%) | | 2 (3.4%) | (-9.2%, 3.1%) |

†p = 0.388 for difference in Target Lobe as a 4-way category (Fisher's exact test)

‡p = 0.867 for difference in Season of Enrollment as a 4-way category ($\chi 2$ test)

# p = 0.721 for difference in Race as a 3-way category (Fisher's exact test)

D. **Safety and Effectiveness Results**

1. Safety Results

The analysis of safety was based on the 172 patients available for the 6 month evaluation. No patient contributed more than one event to the analysis. Additional safety data were also provided at 12 months. The key safety outcomes for this study are presented below in Tables 8 through 11.

**Adverse effects that occurred in the PMA clinical study:**

Safety data on all subjects through the 6 month primary safety analysis with additional long term safety data on subjects followed up through 24 months months was available. In the analysis, 31% of the Treatment Arm had a thoracic SAE in comparison to 11.9% of the Control Arm. The most common SAEs were related to pneumothorax (18 events in 14% of Treatment patients vs. 0% in Controls), pneumonia (12 events in 8.8% of Treatment patients vs. 1.7% in Controls) and COPD exacerbations (22 events in 16.8% of Treatment subjects vs. 6 events in 10.2% of Controls). Forty (40) of the 86 events that occurred in the Treatment Arm were adjudicated by the CEC as device related. Non-thoracic SAEs within the first 6 months occurred in 11.5% of Treatment patients in comparison to 3.4% of Control patients. Between 6-12 months, there were thoracic SAEs in 21.4% of Treatment subjects in comparison to 10.6% of Controls. Pneumonia and COPD exacerbation were the most common thoracic SAEs. Between 12 and 24 months, thenumber of patients experiencing thoracic adverse events were comparable between the Treatment and Control Arms (21.5% and 24.2%, respectively. There were also 6 (5.3%) deaths in the Treatment Arm and 1 (1.7%) in the Control Arm in the first 6 months. One (1) death was related to a complication of bilateral pneumothoraces and pneumonia following the procedure and was adjudicated by the CEC as possibly related to the

device. Between 6 and 12 months, there were four (4) (3.5%) deaths in the Treatment Arm and three (3) (5.1%) deaths in the Control Arm. Among the deaths after 6 months, one (1) subject developed an abscess in the treated lobe.

There were also a total of 239 adverse events (non-serious) in the Treatment Arm occurring in 86 (76.1%) subjects, while there were 62 adverse events (AE) occurring in 31 (52.5%) of the Control Arm subjects. Hemoptysis, cough, pneumothorax, and thoracic pain events were statistically significantly different between the two (2) study Arms. There were 14 non-serious AEs of pneumothorax defined as an air leak duration of < 7days in 13 Treatment subjects in the first 6 months.

Analyses of multiple variables such as lung function, exercise capacity, hyperinflation, age, BMI, quality of life measures, number of valves deployed, procedure time, sex, season enrollment, anesthesia type, and sedation level did not reveal any predictors for thoracic adverse events.

Of the 113 Treatment Arm subjects who received one or more valves during the initial study procedure, 26 subjects (23%) underwent 30 repeat bronchoscopy procedures to remove and/or replace valves after the initial procedure, as allowed by the protocol.

**Table 8. Composite of Thoracic SAEs (through 6 months)**

| | Treatment Arm (N = 113) | | Control Arm (N = 59) | | Difference (T–C) | | Ratio T/C | |
|---|---|---|---|---|---|---|---|---|
| | **Pts** | **%** | **Pts** | **%** | **Est** | **(95% BCI)** | **Est** | **(95% BCI)** |
| **Thoracic SAE composite** | 35 | 31.0 | 7 | 11.9 | 19.1 | (5.9, 29.7) | 2.61 | (1.28, 5.46) |

**Table 9. Occurrence of Individual Thoracic SAEs (Through 6 Months)**

| | Treatment Arm (N = 113) | | | Control Arm (N = 59) | | | Difference (T–C) | | Ratio (T/C) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Events** | **Pts** | **%*** | **Events** | **Pts** | **%*** | **Est** | **(95% BCI)** | **Est** | **(95% BCI)** |
| **Acute asthma or bronchospasm requiring admission to an intensive or critical care unit** | 0 | 0 | 0.0 | 0 | 0 | 0.0 | 0.0 | (-5.3, 2.3) | | |
| **Acute exacerbation of COPD that is acute onset, life threatening, and requires hospitalization** | 22 | 19 | 16.8 | 6 | 6 | 10.2 | 5.8 | (-5.1, 16.0) | 1.65 | (0.73, 3.84) |
| **Airway injury from valve placement, valve migration, or airway stenosis from a valve requiring surgical intervention** | 0 | 0 | 0.0 | 0 | 0 | 0.0 | 0.0 | (-5.3, 2.3) | | |
| **Death from the procedure or device**** | 0 | 0 | 0.0 | 0 | 0 | 0.0 | 0.0 | (-5.3, 2.3) | | |

| | Treatment Arm (n=113) | | | Control Arm (n=59) | | | Difference (T-C) | | Ratio (T-C) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Events** | **Pts** | **%*** | **Events** | **Pts** | **%*** | **Est** | **(95% BCI)** | **Est** | **95% (BCI)** |
| **Massive hemoptysis (estimated over 300 ml in 24 hours and requiring transfusion, surgery, or arterial embolization) attributed to the procedure or device** | 0 | 0 | 0.0 | 0 | 0 | 0.0 | 0.0 | (-5.3, 2.3) | | |
| **Pneumonia in the valve-treated lobe that requires hospitalization, IV antibiotics, and valve removal** | 2 | 2 | 1.8 | 0 | 0 | 0.0 | 1.8 | (-3.9, 5.2) | | |
| **Pneumonia NOT in the valve-treated lobe that is life-threatening, acute onset, and requires hospitalization and IV antibiotics** | 10 | 8 | 7.1 | 1 | 1 | 1.7 | 5.4 | (-2.4, 11.1) | 4.18 | (0.68, 19.89) |
| **Pneumothorax requiring surgical intervention or prolonged air leak > 7 days defined as the time from chest tube insertion to the time the air leak is not present** | 16 | 14 | 12.4 | 0 | 0 | 0.0 | 12.4 | (4.6, 18.6) | | |
| **Respiratory failure that requires mechanical ventilatory support for > 24 hours** | 5 | 3 | 2.7 | 0 | 0 | 0.0 | 2.7 | (-3.2, 6.4) | | |
| **Tension pneumothorax that is life- threatening, acute onset, and requires hospitalization and treatment** | 2 | 2 | 1.8 | 0 | 0 | 0.0 | 1.8 | (-3.9, 5.2) | | |
| **Total** | **57** | **35** | **31.0** | **7** | **7** | **11.9** | **19.1** | **(5.9, 29.7)** | **2.61** | **(1.28, 5.46)** |

* Percentage is # patients experiencing event / # patients in Treatment Arm (× 100).

** Procedure/Device relatedness as determined by investigative site.

**Table 10. Occurrence of Individual Thoracic SAEs (6 - 12 Months)**

| | Treatment Arm (N = 103) | | | Control Arm (N = 47) | | | Difference (T–C) | | Ratio (T/C) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Events | Pts | %* | Events | Pts | %* | Est | (95% BCI) | Est | (95% BCI) |
| **Acute asthma or bronchospasm requiring admission to an intensive or critical care unit** | 0 | 0 | 0.0 | 0 | 0 | 0.0 | 0.0 | (-6.6, 2.4) | | |
| **Acute exacerbation of COPD that is acute onset, life threatening, and requires hospitalization** | 20 | 14 | 13.6 | 4 | 4 | 8.5 | 5.1 | (-7.4, 14.2) | 1.60 | (0.59, 4.37) |
| **Airway injury from valve placement, valve migration, or airway stenosis from a valve, requiring surgical intervention** | 0 | 0 | 0.0 | 0 | 0 | 0.0 | 0.0 | (-6.6, 2.4) | | |
| **Death from the procedure or device**** | 1 | 1 | 1.0 | 0 | 0 | 0.0 | 1.0 | (-5.9, 4.1) | | |
| **Massive hemoptysis (estimated over 300 ml in 24 hours and requiring transfusion, surgery, or arterial embolization) attributed to the procedure or device** | 0 | 0 | 0.0 | 0 | 0 | 0.0 | 0.0 | (-6.6, 2.4) | | |
| **Pneumonia in the valve-treated lobe that requires hospitalization, IV antibiotics, and valve removal** | 1 | 1 | 1.0 | 0 | 0 | 0.0 | 1.0 | (-5.9, 4.1) | | |
| **Pneumonia NOT in the valve-treated lobe that is life-threatening, acute onset, and requires hospitalization and IV antibiotics** | 11 | 8 | 7.8 | 1 | 1 | 2.1 | 5.6 | (-3.8, 11.9) | 3.65 | (0.61, 17.38) |
| **Pneumothorax requiring surgical intervention or prolonged air leak > 7 days defined as the time from chest tube insertion to the time the air leak is not present** | 0 | 0 | 0.0 | 0 | 0 | 0.0 | 0.0 | (-6.6, 2.4) | | |
| **Respiratory failure that requires mechanical ventilatory support for > 24 hours** | 1 | 1 | 1.0 | 0 | 0 | 0.0 | 1.0 | (-5.9, 4.1) | | |
| **Tension pneumothorax that is life-threatening, acute onset, and requires hospitalization and treatment** | 0 | 0 | 0.0 | 0 | 0 | 0.0 | 0.0 | (-6.6, 2.4) | | |
| **Total** | **34** | **22** | **21.4** | **5** | **5** | **10.6** | **10.7** | **(-3.0, 21.2)** | **2.01** | **(0.85, 4.84)** |

* Percentage is # patients experiencing event / # patients in treatment group (× 100).

** Procedure/Device relatedness as determined by investigative site.

**Table 11. CEC adjudicated SAE Categories (through 6 months)**

| SAE Category (0-6M Only) | Total CEC Reviewed Events | # Events / #Treatment subjects | # Events / #Control subjects | # Device Related per CEC* | # Procedure Related per CEC* |
|---|---|---|---|---|---|
| **Arrhythmia/CV/ BP** | 3 | 3/3 | 0/0 | 1 | 1 |
| **AECOPD 1** | 31 | 25/21 | 6/6 | 11 | 6 |
| **Bronchitis** | 0 | 0/0 | 0/0 | 0 | 0 |
| **Death 2** | 7 | 6/6 | 1/1 | 1 | 0 |
| **Hemoptysis 3** | 2 | 2/2 | 0/0 | 1 | 1 |
| **Infection** | 6 | 6/5 | 0/0 | 2 | 0 |
| **Miscellaneous 4** | 9 | 6/5 | 3/2 | 1 | 0 |
| **Pneumonia** | 13 | 12/9 | 1/1 | 2 | 4 |
| **Pneumothorax 4** | 19 | 19/17 | 0/0 | 16 | 12 |
| **Respiratory Failure** | 5 | 5/3 | 0/0 | 3 | 0 |
| **Thoracic Pain 4** | 2 | 2/2 | 0/0 | 2 | 0 |
| **Total** | **97** | **86/79** | **11/10** | **40** | **24** |

2. Effectiveness Results

Per the EMPROVE trial statistical analysis plan, the analysis for determination of effectiveness of the Spiration Valve System was based on the 172 evaluable patients at the 6-month time point. In addition, results from the complete 12-month data, where applicable, were used to support the durability of the treatment effect. Key effectiveness outcomes are presented in Tables 12 and 13.

Based on the observed data at 6 months, the Treatment Arm showed a mean increase in $FEV_1$ from baseline (+0.099 liters), while the Control Arm showed a mean decrease (-0.002 liters). The pre-specified primary analysis using Bayesian multiple imputation for missing values showed that the estimated difference between the two (2) study groups in mean change from baseline in $FEV_1$ at 6 months was 0.097 liters, with 95% Bayesian Credible Interval (BCI) = (0.057, 0.138). The posterior probability of claiming superiority of the Spiration Valve System over Control with respect to this endpoint was ≈ 1.000, greater than the pre-specified threshold of 0.982. Thus, the primary effectiveness endpoint for this study was met.

The results at 12 months were consistent, indicating a mean difference between the two (2) study groups of 0.088 liters with 95% BCI = (0.037, 0.137) when utilizing Bayesian multiple imputation for missing values. The posterior probability of superiority in this case was > 0.999.

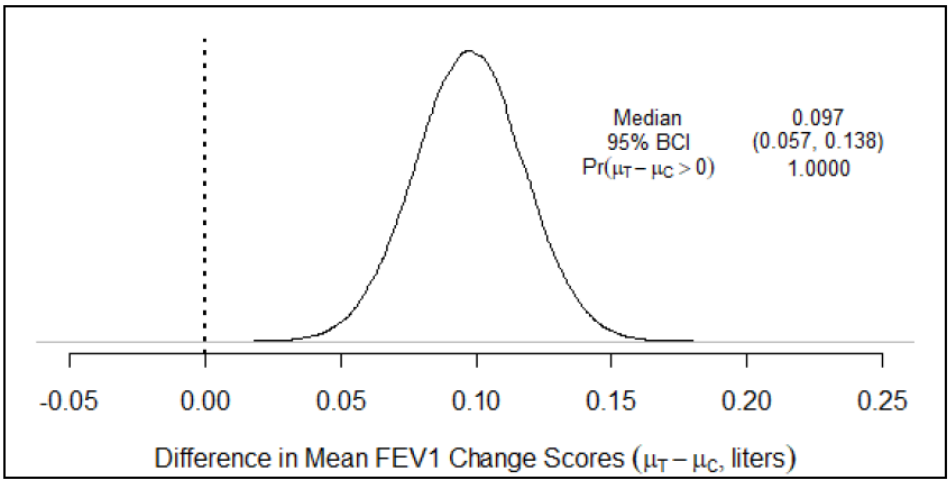
**Table 12. $FEV_1$ – Mean and Change from Baseline (through 12 Months)**

| $FEV_1$ (L) | Treatment Arm | Control Arm | Difference (T–C) | |
|---|---|---|---|---|
| | Mean ± SD (N) [min, median, max] | Mean ± SD (N) [min, median, max] | Estimate*, (95% BCI) | Posterior Probability of ($\mu T > \mu C$) |
| **Baseline** | 0.825 ± 0.264 (113)<br>[0.410, 0.790, 1.460] | 0.792 ± 0.260 (59)<br>[0.370, 0.760, 1.530] | | |
| **1 Mo** | 0.974 ± 0.324 (102)<br>[0.350, 0.920, 1.990] | 0.808 ± 0.221 (50)<br>[0.440, 0.790, 1.460] | | |
| **3 Mo** | 0.940 ± 0.315 (105)<br>[0.350, 0.900, 2.020] | 0.820 ± 0.239 (45)<br>[0.400, 0.820, 1.320] | | |
| **6 Mo** | 0.937 ± 0.296 (106)<br>[0.340, 0.905, 1.820] | 0.811 ± 0.274 (50)<br>[0.440, 0.750, 1.700] | | |
| **12 Mo** | 0.920 ± 0.301 (86)<br>[0.330, 0.860, 1.760] | 0.790 ± 0.257 (39)<br>[0.410, 0.770, 1.460] | | |
| **1 Mo - Baseline** | 0.145 ± 0.173 (102)<br>[-0.190, 0.105, 0.750] | -0.000 ± 0.101 (50)<br>[-0.260, -0.005, 0.240] | | |
| **3 Mo - Baseline** | 0.121 ± 0.172 (105)<br>[-0.330, 0.110, 0.680] | -0.003 ± 0.102 (45)<br>[-0.340, 0.000, 0.180] | | |
| **6 Mo - Baseline** | 0.099 ± 0.154 (106)<br>[-0.260, 0.080, 0.530]<br>95% BCI: (0.069, 0.128) | -0.002 ± 0.098 (50)<br>[-0.240, -0.010, 0.210]<br>95% BCI: (-0.030, 0.026) | | |
| | Completers Only – Without Predictions | | 0.101<br>(0.060, 0.141) | 1.0000 |
| | With Predictions for Missing Values | | 0.097<br>(0.057, 0.138) | 1.0000 |
| **12 Mo - Baseline** | 0.067 ± 0.167 (86)<br>[-0.280, 0.060, 0.600]<br>95% BCI: (0.031, 0.103) | -0.032 ± 0.114 (39)<br>[-0.300, -0.030, 0.390]<br>95% BCI: (-0.069, 0.005) | | |
| | Completers Only – Without Predictions | | 0.099<br>(0.048, 0.151) | 0.9999 |
| | With Predictions for Missing Values | | 0.088<br>(0.037, 0.137) | 0.9997 |

The proportions of subjects with ≥ 15% improvement in $FEV_1$ from baseline based on the observed data were 36.8% and 10.0% in the Treatment and Control Arms, respectively, at 6 months and 37.2% and 5.1% in the Treatment and Control Arms, respectively, at 12 months.

Figure 7 below displays the posterior distribution for the treatment difference in mean $FEV_1$ change from baseline to 6 months ($\mu_t - \mu_c$). Since all the area under the curve is to the right of the dashed vertical line of no treatment difference ($\mu_t - \mu_c = 0$), the posterior probability of ($\mu_t - \mu_c > 0$) is 1.0000. The curve is centered at 0.097, with 95% BCI extending from 0.057 (the 2.5$^{th}$ percentile) to 0.138 (the 97.5$^{th}$ percentile).

***Figure 7. Posterior Distribution of Difference in Mean $FEV_1$ Change from Baseline to 6Months***




In addition, the following four (4) secondary effectiveness endpoints were also met in the EMPROVE trial.

- Target Lobe Volume showed a significant mean reduction (-0.974 liters) in the Spiration Valve System Treated subjects at 6 months, with 95% BCI = (-1.119, -0.829). The posterior probability of superiority was ≈ 1.000.
- Hyperinflation, defined as the ratio of RV/TLC, showed a significantly greater mean improvement (reduction in hyperinflation) in the Spiration Valve System Treated subjects when compared to the Control subjects. The mean difference between the two (2) study groups was -0.040 with 95% BCI = (-0.059, -0.021). The posterior probability of superiority was ≈ 1.000.
- The St. George's Respiratory Questionnaire (SGRQ) showed a significantly greater mean improvement (point reduction) in the Spiration Valve System Treated subjects when compared to the Control subjects. The mean difference between the two (2) study groups was -13.0 points with 95% BCI = (-17.4, -8.7). The posterior probability of superiority was ≈ 1.000. The treatment effect observed at 12 months was consistent with that at 6 months, but with a slight reduction (mean difference = -8.7 points, 95% BCI = (-13.4, -4.0), posterior probability > 0.999).
- The Modified Medical Research Council Dyspnea Scale (mMRC) showed a significantly greater mean improvement (score reduction) in the Spiration Valve System Treated subjects when compared to the Control Subjects. The mean difference between the two (2) study groups was -0.6 with 95% BCI = (-0.9, -0.3). The posterior probability of superiority was ≈ 1.000. The treatment effect observed at 12 months was consistent with that at 6 months, though with a slight improvement (mean difference = -0.9 points for completers, 95% BCI = (-1.2, -0.6), posterior probability ≈ 1.000).

In summary, secondary effectiveness endpoint data up to 6 months in the EMPROVE trial have demonstrated that treatment with the Spiration Valve System was superior over standard of care in improving post-bronchodilator $FEV_1$, target lobe volume, hyperinflation, SGRQ total score, and mMRC dyspnea score.in patients with severe heterogeneous emphysema and low collateral ventilation. The treatment effects observed at 12 months for the $FEV_1$, SGRQ total score, and mMRC dyspnea score were also consistent with those observed at 6 months. The 6MWT did not show a clinically meaningful improvement at 6 months. The difference between groups was 6.9 meters (95% BCI: -14.2, 28.2). No 12-month data were collected for target lobe volume, hyperinflation, and 6-minute walk test in this study.

Valve Removal

A total of 26 Treatment Arm subjects (23%) underwent 30 repeat bronchoscopy procedures to remove and/or replace valves after the initial procedure. Table 13 provides a breakdown of valves permanently removed and those that were removed and replaced through the 12-month timeframe.

**Table 13. Chronic Device Removals (0-12M)**

| Devices Placed per Subject | Devices Removed per Subject | Duration of Placement (days) | Reason | Device(s) replaced? |
|---|---|---|---|---|
| 6 | 6 | 1641 | AE, Suspected infection | No |
| 7 | 1 | 146 | Valve Adjustment | Yes |
| 6 | 2 | 40 | Valve Adjustment | Yes |
| 5 | 5 | 506 | AE, Suspected infection | No |
| 3 | 2 | 39 | Valve Adjustment | Yes |
| 1 | 1 | 98 | Valve Adjustment | Yes |
| 3 | 3 | 53 | Suspected infection | No |
| 2 | 2 | 63 | AE | No |
| 5 | 3 | 456 | Pneumothorax | Yes |
| | 3 | 1 | Pneumothorax | No |
| 9 | 1 | 15 | Pneumothorax | Yes |
| 4 | 2* | 131 | Valve Adjustment, AE suspected infection | Yes |
| 3 | 1 | 91 | Valve Adjustment | Yes |
| 3 | 1 | 604 | AE | No |
| 3 | 1 | 12 | Pneumothorax | No |
| | 2 | 49 | AE, Suspected infection | No |
| 4 | 4 | 488 | Lack of benefit | No |

| Devices Placed per Subject | Devices Removed per Subject | Duration of Placement (days) | Reason | Device(s) replaced? |
|---|---|---|---|---|
| 3 | 1 | 23 | Pneumothorax | No |
| | 1 | 30 | Pneumothorax | No |
| 3 | 1 | 24 | Pneumothorax | No |
| 6 | 1 | 118 | Valve Adjustment | Yes |
| 8 | 3 | 6 | Pneumothorax | Yes |
| 2 | 1 | 63 | Valve Adjustment | Yes |
| | 2** | 35, 98 | AE, Hypoxemia | No |
| 4 | 4 | 3 | Subject Request, Pneumothorax | No |
| 3 | 1 | 9 | Pneumothorax | Yes |
| 4 | 1 | 105 | Valve Adjustment | Yes |
| 3 | 1 | 96 | Valve Adjustment | Yes |
| 3 | 3 | 414 | AE | No |
| 4 | 4 | 303 | AE, Suspected infection | No |
| 3 | 1 | 7 | Pneumothorax | Yes |
| | 1 | 119 | Valve Adjustment | Yes |
| 4 | 1 | 8 | Pneumothorax | Yes |
| 4 | 4 | 8 | Pneumothorax | No |
| 5 | 2 | 11 | Pneumothorax | No |
| 8 | 3 | 7 | Pneumothorax | No |
| 4 | 1 | 8 | Pneumothorax, AE | No |

* One (1) valve removed for suspected infection

** Removal of one (1) original placement and one (1) valve adjustment replacement valve

3. Observational study with Results for Alpha-1 Antitrypsin Deficiency Group

Twenty (20) patients with alpha-1-antitrypsin deficiency were enrolled in the study in a separate treatment arm. Follow up on 17 patients was available at 12 months. In comparison to the main study cohort, patients were younger and could walk two (2) meters more on average at baseline. Effectiveness and safety data are provided in Tables 14 through 16 below. At 12 months, there was a 73 ± 176 ml improvement in the $FEV_1$ in comparison to baseline. For the SAEs, there were five (5) pneumothoraces and one death related to the device as a complication of a pneuomothorax.

**Table 14. $FEV_1$ Measure in α1AT Subjects**

| Outcome | | Treatment Arm | |
|---|---|---|---|
| | | Mean ± SD (N) [min, median, max] | 95% BCI for Mean Change |
| $FEV_1$ (liters) | Baseline | 0.867 ± 0.211 (20) [0.470, 0.860, 1.380] | |
| | 6 Mo | 0.981 ± 0.292 (17) [0.580, 0.950, 1.670] | |
| | 12 Mo | 0.946 ± 0.295 (17) [0.470, 0.900, 1.710] | |
| | 6 Mo–BL | 0.108 ± 0.168 (17) [-0.140, 0.090, 0.450] | (0.022, 0.195) |
| | 12 Mo–BL | 0.073 ± 0.176 (17) [-0.180, 0.040, 0.450] | (-0.017, 0.163) |

**Table 15. α1AT Secondary Effectiveness Outcomes**

| Outcome | | Treatment Arm | |
|---|---|---|---|
| | | Mean ± SD (N) [min, median, max] | 95% BCI for Mean Change |
| Target Lobe Volume (L) | Baseline | 1.830 ± 0.445 (20) [1.092, 1.867, 2.780] | |
| | 6 Mo | 0.687 ± 0.661 (17) [0.000, 0.371, 1.786] | |
| | 6 Mo–BL | -1.128 ± 0.821 (17) [-2.614, -0.863, 0.041] | (-1.551, -0.706) |
| RV (liters) | Baseline | 4.546 ± 1.273 (20) [2.480, 4.300, 7.160] | |
| | 6 Mo | 4.149 ± 1.228 (17) [2.530, 3.830, 7.390] | |
| | 6 Mo–BL | -0.282 ± 0.711 (17) [-1.190, -0.420, 1.440] | (-0.648, 0.083) |
| Hyperinflation (RV/TLC %) | Baseline | 0.613 ± 0.109 (20) [0.323, 0.605, 0.760] | |
| | 6 Mo | 0.586 ± 0.096 (17) [0.394, 0.597, 0.768] | |
| | 6 Mo–BL | -0.031 ± 0.074 (17) [-0.150, -0.031, 0.119] | (-0.070, 0.007) |

| Outcome | | Treatment Arm | |
|---|---|---|---|
| | | **Mean ± SD (N) [min, median, max]** | **95% BCI for Mean Change** |
| **SGRQ** | **Baseline** | 55.2 ± 16.0 (20)<br>[25.8, 56.5, 81.2] | |
| | **6 Mo** | 39.0 ± 12.5 (17)<br>[16.9, 38.2, 65.1] | |
| | **12 Mo** | 45.0 ± 15.6 (17)<br>[19.2, 41.3, 70.0] | |
| **SGRQ** | **Outcome** | **Treatment Group** | |
| | | **Mean ± SD (N) [min, median, max]** | **Mean ± SD (N) [min, median, max]** |
| | **6 Mo–BL** | -14.3 ± 12.9 (17)<br>[-46.8, -14.2, 11.9] | (-20.9, -7.6) |
| | **12 Mo–BL** | -8.2 ± 14.7 (17)<br>[-43.0, -5.8, 18.4] | (-15.8, -0.6) |
| **Dyspnea (mMRC)** | **Baseline** | 2.5 ± 0.7 (20)<br>[2.0, 2.0, 4.0] | |
| | **6 Mo** | 1.7 ± 1.2 (17)<br>[0.0, 1.0, 4.0] | |
| | **12 Mo** | 1.8 ± 1.1 (17)<br>[0.0, 2.0, 4.0] | |
| | **6 Mo–BL** | -0.8 ± 1.1 (17)<br>[-3.0, -1.0, 1.0] | (-1.3, -0.2) |
| | **12 Mo–BL** | -0.7 ± 1.0 (17)<br>[-3.0, -1.0, 1.0] | (-1.2, -0.2) |
| **COPD Assessment Test** | **Baseline** | 20.9 ± 6.6 (19)<br>[10.0, 19.0, 32.0] | |
| | **6 Mo** | 15.0 ± 7.0 (17)<br>[5.0, 14.0, 32.0] | |
| | **12 Mo** | 17.4 ± 7.1 (17) | |

**Table 16. CEC Adjudicated SAE Categories - α1AT Arm (0-12M)**

| SAE Category (0-12M Only) | Total CEC Reviewed Events | # α1AT Subjects | # Device Related per CEC* | # Procedure Related per CEC* |
|---|---|---|---|---|
| **Arrhythmia/CV/BP** | 0 | 0 | | |
| **AECOPD** | 3 | 3 | 2 | 1 |
| **Bronchitis** | 0 | 0 | | |
| **Death** | 1 | 1 | 1 | 1 |
| **Hemoptysis** | 0 | 0 | | |
| **Pneumonia** | 3 | 3 | 1 | 1 |
| **Infection** | 1 | 1 | 0 | 0 |
| **Miscellaneous** | 2** | 2 | 2 | 0 |
| **Pneumothorax** | 5*** | 4 | 5 | 3 |
| **Respiratory Failure** | 3 | 2 | 1 | 0 |
| **Thoracic Pain** | 0 | 0 | | |
| **Total** | 18 | 16 | 12 | 6 |

*Includes " Definitely, Probably or Possibly" related.

** This includes two events which were non-serious AEs, but which was adjudicated by the CEC.

*** This includes one event which was a non-serious AE, but which was adjudicated by the CEC.

4. Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with outcomes:

Treatment effects on mean change from baseline in $FEV_1$ at 6 months between the Treatment and Control Arms were consistent across the subgroups defined by age (< 65 years, 65 - 75 years, > 75 years), sex, race (Caucasian, African American, Others), geography (US, OUS), study site, and target lobe location (left upper, left lower, right upper, right lower), as no significant treatment-by-subgroup interactions were observed (all $p > 0.15$). Therefore, poolability of the subgroups defined by these variables for the result of the primary effectiveness endpoint was confirmed.

5. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. **Financial Disclosure**

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 187 investigators of which none were full-time or part-time employees of the sponsor and three (3) had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payment of other sorts: 3
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 0

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

## XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Clinical investigations that were completed prior to the completion of the EMPROVE pivotal study are briefly described in this section.

European Post-Market Study

Spriation, Inc. conducted a multicenter, single-blind, sham-controlled study designed to assess safety and effectiveness of bronchial valve therapy using a bilateral-partial upper lobe treatment approach without the goal of lobar atelectasis. The study included 37subjects in the Treatment Arm and 36 in the Control Arm and was evaluated at 3 months. The endpoint was a positive responder defined as having both at least a $\geq 4$ point improvement in SGRQ and a lobar volume shift as measured by computed tomography (CT). At 3 months, positive responders were: eight (8) (24%) in the Treatment Arm compared to 0 (0%) in the Control Arm ($p = 0.002$). Mean SGRQ total score improved in both groups (Treatment $-4.3 \pm 16.3$; Control: $-3.6 \pm 10.7$).

Spiration Valve Trial - Original Pivotal Study, US

Spiration, Inc. conducted a a randomized, multicenter, controlled, double-blind study in the US that enrolled 142 Treatment subjects and 135 Control subjects. The primary effectiveness endpoint was disease-related health status as measured by, the St. George's Respiratory Questionnaire (SGRQ) combined with lung volume changes measured by quantitative CT scan. Control subjects were treated with sham bronchoscopy. Results did not show a statistically significant difference in responder rates between Treatment and Control Arms in disease-related health status as measured by the SGRQ. A statistically

significant difference was demonstrated by a decrase in lung volumes of the Treatment Arm vs. Control Arm as measured by computed tomography (CT). Twenty (20) Treatment subjects had an SAE and five (5) Control subjects experienced an SAE. In the Treatment Arm, four (4) SAEs were determined to be device-related, including respiratory failure (1), and pneumothorax (3). Seven (7) SAEs in six (6) subjects that were procedure-related (bronchospasm (2), COPD exacerbation (2), death (1), anesthesia-related (1), and respiratory failure (1)).

The results of this study did not show clinically meaningful improvement in the Treatment Arm. Based on this study, Spiration concluded that the lack of effect was related to longer procedure times. Spiration conducted a post-hoc analysis and used that analysis, in part, to support and design their pivotal study with single lobe treatment for the EMPROVE pivotal study. It is unclear how the increase in procedure time contributed to the lack of effectiveness in the study.

Spiration Randomized Comparative Clinical Study in Heidelberg, Germany

Spiration, Inc. conducted a study of the safety and effectiveness of single lobe complete occlusion vs bilateral partial occlusion treatment. Safety and effectiveness were evaluated at 3 months in 22 subjects with 11 in each arm. Spiration reported effectiveness with single lobe treatment that resulted in measurable improvement in PFT , dyspnea, health status, and exercise (6MWT). There was one pneumothorax in the single lobe group.

Results were provided out to 3 months only, which is not sufficient to evaluate the durability of this treatment. Additionally, it should be noted that Spiration also referred to Pulmonx's VENT trial[18] to support their patient selection, choice of lobe for treatment based on heterogeneity and the presence of complete inter-lobar fissures between the target lobe and ipsilateral lobe on high-resolution computed tomography (HRCT).

China REACH Trial

Spiration, Inc. conducted a prospective, multi-center, non-blinded, randomized, parallel assignment study comparing subjects treated with medical management and the SVS (Treatment Arm) against those that received medical management alone (Control Arm) with an allocation ratio of 2:1, respectively, that was conducted at 12 sites in China. One hundred seven (107) subjects were randomized from 295 screened. After withdrawals, there were 66 subjects in the Treatment Arm and 33 in the Control Arm. The primary effectiveness endpoint was the difference between Treatment and Control Arms in the mean change in forced expiratory volume in 1 second (FEV1 ) from baseline to 3 months. There was an improvement of the FEV1 of 15.2% at 6- months and the responder rate for FEV1 improvement $\geq$ 15% was 41% for Treatment subjects compared to 21% for Control subjects at 6 months. Target lobe volume reduction at 6 months was 757 ml. The 6MWT and SGRQ also showed improvement.

## XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Anesthesiology and Respiratory Therapy Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

## XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

### A. Effectiveness Conclusions

The EMPROVE trial compared the Spiration Valve System with standard of care in subjects with severe emphysema with low collateral ventilation at 6 months. Descriptive 12 month data were also made available for the primary endpoint. The study met its primary endpoint from a clinical and statistical standpoint. Additionally, 20 subjects with alpha 1 antitrypsin deficiency were enrolled in a separate Non-Randomized Arm. $FEV_1$ was used as a surrogate for lung function, 6MWT for exercise tolerance, and SGRQ for quality of life measures. Major findings from the clinical trial included:

- The primary effectiveness endpoint evaluated the difference between the Treatment and Control Arms in the mean change in $FEV_1$ from baseline at 6 months. Results were available for 156 of the 172 subjects for the $FEV_1$ at 6 months with a mean change of 0.101 liters (95% BCI: 0.060 - 0.141) for completers and 0.097 liters (95% BCI: 0.057 - 0.138) with missing data imputed. Additional 12 month data was provided for 125 subjects (86 Treatment and 39 Control) and the difference between the Treatment and Control Arms was 0.088 liters (95% BCI: 0.037 - 0.137) with missing data imputed and 0.099 liters (95% BCI: 0.048 – 0.151) for completers. At 12 months, both the Treatment and Control Arms of the study had a reduction in $FEV_1$ in comparison to baseline; however, the Control Arm had a larger reduction between 6 months and 12 months which accounted for the difference reported at 12 months.

- The secondary effectiveness endpoint evaluated the difference between the Treatment and Control Arms in mean changes from baseline at 6 months for the parameters below. Twelve (12) month data was not available for all the parameters.

  i. Target Lobe Volume (TLV) reduction as measured by quantitative CT scan (baseline to 6 months). The TLV reduction was -0.974 (95% BCI: -1.119, -0.829). Twelve (12) month data was not collected.
  ii. Residual volume reduction at 6 months in completers was -0.361 (-95% BCI: 0.594, -0.127). Twelve (12) month data was not collected.
  iii. Hyperinflation as measured by the ratio of Residual Volume to Total Lung Capacity (RV/TLC) (baseline to 6 months). The difference was -0.039 (95% BCI: -0.058, -0.020).

iv. Health Status as measured by St. George's Respiratory Questionnaire (SGRQ) (baseline to 6 months). SGRQ in completers was reduced by -13.3 (95% BCI: 95% BCI: -17.4, -8.5). At 12 months, the reduction was -9.5 (95% BCI: -14.4, -4.7).

v. Dyspnea as measured by Medical Research Council, Modi 14.7. Field Questionnaire (mMRC) (baseline to 6 months). mMRC was reduced by -0.6 (95% BCI: -0.9, -0.3) in completers. At 12 months, the reduction was -0.9 (95% BCI: -1.2, -0.6).

vi. Exercise capacity as measured by 6MWT (baseline to 6 months). The 6MWT difference was 6.9 m (95% BCI: -14.2, 28.2). Twelve (12) month data was not collected.

vii. $FEV_1$ Responders, defined as those achieving at least 15% improvement from baseline to 6 months. The difference was 25.7% (95% BCI: 12.5, 37.5) in completers and at 12 months was 30.4% (95% BCI: 16.8, 42.5).

- In the single Non-Randomized alpha-1-antitrysin Arm, the comparisons were reported between baseline and 6 months and then 12 months for 17 patients. The $FEV_1$ change at 6 months was 0.108 ± 0.168; however, the improvement at 12 months in comparison to baseline was 0.073 ± 0.176. The 6MWT change at 6 months was 34.6 ± 79.3 meters and the SGRQ improved by -8.2 ± 14.2 at 12 months.

The pivotal study showed improved measures in lung function in $FEV_1$ and quality of life parameters in the SGRQ in comparison to the Control Arm at 1 year in patients with severe emphysema with low collateral ventilation; however, the 6MWT was not improved at 6 months. Based on the study results, there also is a slower decline in lung function in comparison to baseline in the Treatment Arm. The change in lung function met the minimal clinically important difference (MCID) of 10% per Jones, et al,[8] which has been associated with clinical anchoring to endpoints such as exacerbations, perception of dyspnea, and decline in lung function.

B. **Safety Conclusions**

The risks of the device are based on data collected in the EMPROVE clinical study that was conducted to support PMA approval as described above. The primary safety endpoint was the incidence of thoracic SAEs through 6 months. There were more thoracic SAEs in the Spiration Valve group with 31% of the Treatment Arm experiencing thoracic SAEs in comparison to 11.9% of the Control. The most common SAEs were related to pneumothorax (18 events in 14% of Treatment patients vs. 0% in Controls), pneumonia (12 events in 8.8% of Treatment patients vs. 1.7% in Controls), and COPD exacerbations (22 events in 16.8% of Treatment subjects vs. six (5.3%) deaths in the Treatment Arm and 1 (1.7%) in the Control Arm in the first 6 months. Among the deaths after 6 months, one (1) subject developed an abscess in the treated lobe. The percent of patients with SAEs after 12 months was comparable between the the Treatment and Control Arms of the study.

Although the risk of pneumothorax related to the procedure, valve placement, and repeat procedure is increased for the treated subjects, the incidence rate still does not approach the morbidity and mortality seen with lung volume reduction surgery in the first 90 days.[6,7]

## C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. COPD is a progressive disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities.[1] Patients with advanced disease are treated with medications, oxygen, and life style changes, including pulmonary rehabilitation and smoking cessation; however, many patients remain significantly disabled despite optimal medical therapy. For a some patients, surgical options such as surgical lung volume reduction or lung transplantation may be considered. The Spiration Valve System is an alternative technique to achieve bronchoscopic lung volume reduction using a minimally invasive approach. The study met its primary endpoint clinically and statistically. The mean difference in the $FEV_1$ between the Treatment and Control Arms was 0.101 liters (95% BCI: 0.060 - 0.141) at 6 months for completers and 0.099 liters (95% BCI: 0.048 – 0.151) for completers at 12 months. For the secondary endpoints, the difference between the Treatment and Control Arms was a 36 ml reduction in residual volume at 6 months, SGRQ as a surrogate for quality of life showed a 9.5 point improvement at 12 months and the $FEV_1$ responders defined as $\geq$ 15% improvement was a difference of 30.4% at 12 months. However the 6MWT as a surrogate for exercise capacity did not show a clinically significant improvement. The durability of effect beyond 12 months is not known; however, based on published data it is known that the durability decreases after 6 months.[4]

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The main risks of the device are related to thoracic adverse events. Safety results showed an increased incidence of serious thoracic adverse events that occurred in 31% of the Treatment Arm in comparison to 11.9% of Controls at 6 months. Additional safety data showed that 21.4% of the Treatment Arm had serious thoracic adverse events in comparison to 10.6% of the Controls between 6 to 12 months. The most common thoracic serious adverse events were pneumothorax (14% Treatment patients vs. 0% Controls), pneumonia (8.8% Treatment patients vs. 1.7% Controls) and COPD exacerbations (16.8% Treatment subjects vs. 10.2% Controls). Several publications have suggested that pneumothorax is an indicator of greater clinical response and a predictor of success, however, this is still a serious complication that can impact morbidity and mortality. [10,11,12] After 6 months, pneumonia and COPD exacerbations continued to be the most common adverse events. There were six (6) (5.3%) deaths in the Treatment Arm vs. one (1) (1.7%) in the Control Arm, with one (1) of the treatment deaths that was a complication of the device. In the study, there was also one (1) death in the Treatment Arm after 6 months that had a complication of an abscess in the treated

lobe. Most of the immediate risks of this device are related to anesthesia, bronchoscopy, and valve deployment and then repeat procedures for removal or replacement of valves. The ability to remove valves if SAEs persist may help mitigate some risks. During the study, there were also increased hospitalizations with 40.7% of Treated patients in comparison to 15.3% of Controls in the first 6 months.

Additional factors to be considered in determining probable risks and benefits for the Spiration Valve System included the need for non-surgical treatment options for patients that have maximized medical therapy and who may not be surgical candidate for lung volume reduction or lung transplantation or may opt against an invasive procedure. The expected benefits with this type of device are improved patient outcomes, decreased anesthesia, decreased hospital stay, and decreased morbidity in comparison to surgical procedures. Lung volume reduction surgery is associated with mortality rates of 0-17% and overall morbidity of 59% in the first 90 days.[7] Mean inpatient hospital stay for LVRS is 13.5 days and complications included persistent air leaks, pneumonias, and prolonged respiratory failure.[6] Treatment options for patients with advanced COPD are limited. Most of these patients also have significant associated co-morbidities, and not all are candidates for surgical lung volume reduction or lung transplant; therefore, this device offers a less invasive treatment option. There was sufficient data from the pivotal study to evaluate the benefit-risk for this device; however, confirmatory studies will need to be conducted with post approval studies to further evaluate the safety and effectiveness of the Spiration Valve System.

1. Patient Perspectives
   This submission did not include specific information on patient perspectives for this device.

In conclusion, given the available information above, the data support that for patients with severe emphysema that have evidence of low collateral ventilation the probable benefits outweigh the probable risks.

## D. **Overall Conclusions**

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The primary and secondary endpoints of the EMPROVE study demonstrated clinically meaningful improvement in measures for lung function and quality of life parameters. Although the SAEs were higher in the Treatment Arm in the first 6 months after the procedure, these risks were less than what would be expected with the surgical procedure of lung volume reduction. Treatment options for patients with advance COPD are limited because of significant associated co-morbidities. This device offers a less invasive alternative for subjects with severe emphysema, especially those that may not be candidates for surgical lung volume reduction or lung transplant.

## XIV. **CDRH DECISION**

CDRH issued an approval order on December 3, 2018. The final conditions of approval cited in the approval order are described below.

1. Extended Follow-up of the Premarket Cohort (The EMPROVE Extension Study): This study will be conducted as per protocol outline dated November 14, 2018 (email). This is a continued, prospective, long-term follow up of the EMPROVE pre-market cohorts to evaluate the long-term safety and effectiveness of the Spiration Valve® System (SVS) in all active (enrolled and not withdrawn) subjects continuing long-term (beyond 1-year) follow-up in protocol CPR-03434. Control group subjects will be followed annually through 2-years, treatment group subjects and, and α1 antitrypsin deficiency subjects (a separate non- randomized treatment cohort) will be followed annually through 5-years. All serious adverse events and related non-serious adverse events will be assessed at annual follow-up visits by seriousness, severity, and relatedness. The effectiveness assessments, such as, Spirometry, SGRQ, SF-36, COPD Assessment Test (CAT), Modified Medical Research Council dyspnea scale (mMRC), and Quality of Well Being (QWB) questionnaire will be undertaken at annual follow-up visits. Safety and effectiveness assessment will be analyzed with descriptive statistics.

2. The SVS Post-Market Registry Study: You have agreed to conduct a study per protocol outline dated November 20, 2018 (email), as follows:

   You will conduct a multi-center, single-arm, prospective post-approval registry study to provide ongoing safety and effectiveness assessment of the Spiration® Valve System treatment of patients with severe emphysema and evidence of low collateral ventilation, such as fissure integrity, by limiting airflow to selected areas of the lung. A total of 150 patients will be enrolled and followed through 3-years of follow-up, with interim visits at 45-days, 6, 12, 24, and 36 months post-procedure. The SVS Post-Market Registry Study will include a minimum of 10 centers and up to 40 centers.

   The primary safety endpoints are the incidence of thoracic SAEs through 12-months following the first implantation procedure, and the rate (per patient–year) of thoracic serious adverse events. secondary safety endpoints are 45-day pneumothorax rate and the survival rate over 24-months compared to the EMPROVE study control cohort. Other effectiveness endpoints include: Treated Lobar Volume Reduction (TLVR), Residual Volume (RV) and Total Lung Capacity (TLC) determined from High-Resolution Computed Tomography (HRCT) at 6-months, Forced Expiratory Volume in 1 second (FEV1), Modified Medical Research Council dyspnea scale (mMRC), and SGRQ at 6-months, 12-months, 24-months and 36-months. The 6-Minute Walk Distance (6MWD), Body mass, Airflow Obstruction, Dyspnea and Exercise capacity index (BODE) at 6-months and 12-months, and the responder rates based on Minimum Clinically Important Difference (MCID) for Effectiveness Observations.

Descriptive statistics and 95% confidence intervals will be used to summarize safety and effectiveness measures including responder rates and change from baseline at each follow-up visit. No performance goal or hypothesis testing are included.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

## XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

## XVI. REFERENCES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