SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: One-way valve system

Device Trade Name: Zephyr® Endobronchial Valve System

Device Procode: NJK (Valve, Pulmonary)

Applicant's Name and Address: Pulmonx Corporation
700 Chesapeake Drive
Redwood City, CA 94063

Date(s) of Panel Recommendation: N/A

Premarket Approval Application (PMA) Number: P180002

Date of FDA Notice of Approval: June 29, 2018

Breakthrough Device: Granted breakthrough device status (formerly known as the Expedited Access Pathway, or EAP) on May 4, 2017 because the device intends to treat patients with severe emphysema, an irreversible and life threatening progressive disease. This represents a breakthrough technology as the device offers bronchoscopic lung volume reduction without surgery and its associated risks. This device offers significant clinically meaningful advantage over the current standard of care and therefore its availability is also in the best interest of patients.

II. INDICATIONS FOR USE

The Pulmonx Zephyr® Endobronchial Valves are implantable bronchial valves indicated for the bronchoscopic treatment of adult patients with hyperinflation associated with severe emphysema in regions of the lung that have little to no collateral ventilation.

III. CONTRAINDICATIONS

- Patients for whom bronchoscopic procedures are contraindicated
- Patients with evidence of active pulmonary infection
- Patients with known allergies to Nitinol (nickel-titanium) or its constituent metals (nickel or titanium)
- Patients with known allergies to silicone
- Patient who have not quit smoking
- Patients with large bullae encompassing greater than 30% of either lung

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Zephyr® Endobronchial Valve labeling.

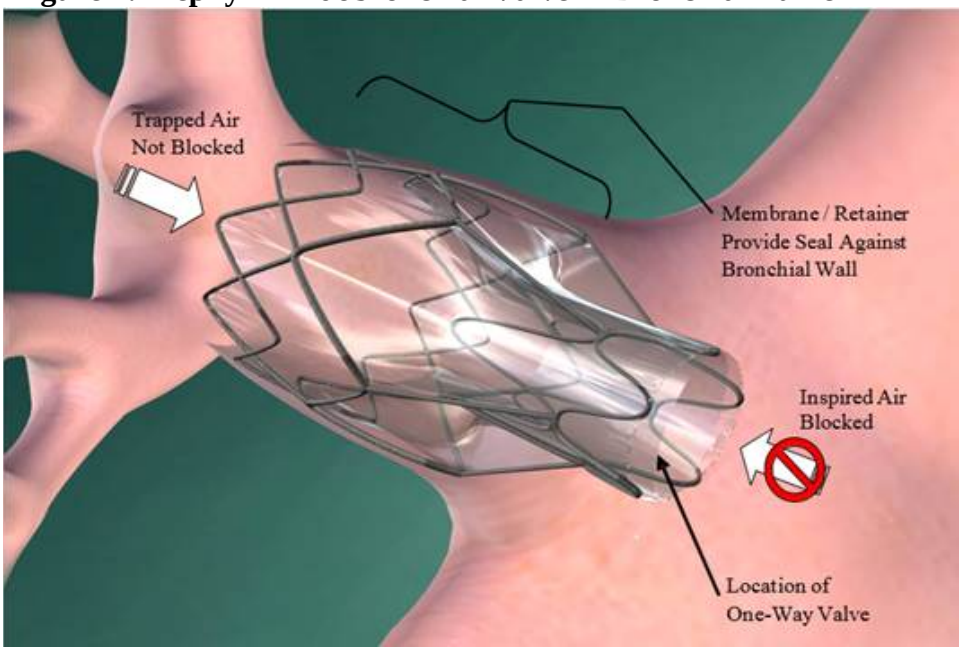
V. DEVICE DESCRIPTION

The Zephyr® Endobronchial Valve (Zephyr Valve) is an endobronchial implant designed to occlude a hyperinflated lobe of the lungs with multiple valves, allowing air to escape while blocking airflow into the treated lobe (***Figure 1***). This is intended to result in a reduction in lung volume and hyperinflation in the targeted area.

The Zephyr® Endobronchial Valve System consists of the following major components:

The **Zephyr Endobronchial Valve (EBV)** is a one-way, removable, silicone, duckbill valve mounted in a nitinol, self-expanding retainer that is covered with a thin silicone membrane. The valve is available in three (3) sizes (4.0 EBV, 4.0-LP EBV, and 5.5 EBV) and implanted during bronchoscopy in bronchial lumens ranging from 4.0 to 8.5 mm in diameter. More than one valve may be needed to achieve the desired clinical outcome. In the pivotal study, the median number of valves used per procedure was four (4). The maximum number of valves used during a procedure was eight (8).

Figure 1: Zephyr® Endobronchial Valve in Bronchial Lumen

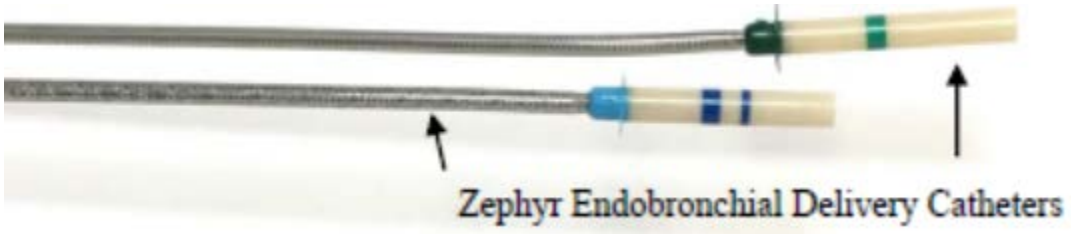


The Endobronchial Loader System (ELS) (***Figure 2***) is designed to compress and load the EBV into the housing of the Endobronchial Delivery Catheter (EDC). The Zephyr Valve is secured in an uncompressed or expanded state inside the ELS during manufacturing and is shipped and stored in its expanded state. Immediately prior to use, the Zephyr Valve is compressed within the ELS and then transferred into the Zephyr EDC. The ELS is a non-patient contacting, single use, disposable device.

Figure 2: Zephyr® Endobronchial Loader System

The flexible **Zephyr® Endobronchial Delivery Catheter (EDC)** (***Figure 3***) facilitates placement of the EBV into the targeted bronchus. The Zephyr EDC is guided to the treatment location through the working channel of a standard adult flexible bronchoscope with constant visual feedback. The Zephyr Valve is then deployed and released to expand inside the target airway. The Zephyr EDC is a single-patient use, disposable device.

Figure 3: Zephyr® Endobronchial Delivery Catheter



The Zephyr® Endobronchial Valve System is designated for professional use only.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several alternatives for the treatment of severe 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.

- Medications for relief of the symptoms of emphysema
- Smoking cessation
- Pulmonary rehabilitation
- Long-term administration of oxygen to patients
- Lung volume reduction surgery (LVRS)
- Lung transplantation

VII. MARKETING HISTORY

The Zephyr Valve received the CE mark in 2003 and is commercially available in Argentina, Australia, Austria, Belgium, Brazil, Chile, China, Colombia, Czech Republic, Denmark, France, Germany, Hong Kong, Ireland, Israel, Italy, Malaysia, Netherlands, Norway, Portugal, South Africa, South Korea, Spain, Sweden, Switzerland, Turkey, United Arab Emirates, United Kingdom, and Vietnam. The Zephyr Valve has not been withdrawn from marketing for any reason related to its safety or effectiveness.

VIII. PROBABLE ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the probable adverse effects (e.g., complications) associated with the use of the device:

- Acute respiratory distress syndrome
- Airway erosion
- Airway stenosis
- Aphonia
- Bowel function impairment
- Bronchitis
- Bronchospasm
- Chest Pain
- Chronic obstructive pulmonary disease (COPD) exacerbation
- Cough
- Death
- Disorientation/anxiety
- Dyspnea
- Empyema
- Epistaxis
- Fever
- Granulation tissue/ulceration formation
- Headache
- Heart arrhythmia
- Heart Failure
- Hematoma
- Hemoptysis
- Hemothorax
- Hypotension
- Hypercapnia
- Hypoxemia
- Iatrogenic injuries
- Impaired lung function
- Increased mucus secretions
- Infection
- Insomnia
- Musculoskeletal event
- Myocardial infarction
- Nausea/vomiting
- Pain
- Pleural effusion
- Pneumonia
- Pneumothorax
- Pulmonary embolism
- Pulmonary shunting
- Residual volume increase
- Respiratory failure
- Sepsis
- Shortness of breath
- Sore throat
- Stroke/CVA/TIA
- Systemic inflammatory response syndrome (SIRS)
- Valve migration/expectoration
- Vocal cord injury
- Wheeze or whistling

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

IX. SUMMARY OF NONCLINICAL STUDIES

Pulmonx conducted the following nonclinical studies to evaluate the Zephyr® Endobronchial Valve System:

A. Laboratory Studies

Biocompatibility

Pulmonx has conducted biocompatibility evaluations of the Zephyr® Endobronchial Valve System in compliance with applicable requirements in the Good Laboratory Practice (GLP) regulations in 21 CFR 58, applicable ISO 10993 standard, *Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process* and the FDA guidance, *Use of International Standard ISO 10993-1*, "*Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process*," published June 16, 2016. For the Zephyr® Endobronchial Valve, as a device with permanent duration contact (> 30 days) with endobronchial tissue, the biocompatibility evaluation addressed the following: cytotoxicity, sensitization, intracutaneous reactivity, acute systemic toxicity, materials mediated pyrogen, genotoxicity, implantation, subacute/subchronic toxicity, chronic toxicity, and carcinogenicity. To address the subacute/subchronic toxicity, chronic toxicity, genotoxicity, and carcinogenicity endpoints for Zephyr Valves, a material characterization through chemical analysis testing and a toxicological risk assessment were performed.

For the Zephyr® Endobronchial Delivery Catheter, as a device with limited exposure contact (≤ 24 hours) with endobronchial tissue, the biocompatibility evaluation addressed the following: cytotoxicity, sensitization, and intracutaneous reactivity.

Table 1 and ***Table 2*** summarize the biocompatibility testing performed for the Zephyr® Endobronchial Valve and Zephyr® Endobronchial Delivery Catheter, including information about the test, purpose, and results. The tests were conducted as per the performance Standards listed in the Table. The results of these evaluations support the conclusion that the Zephyr® Endobronchial Valve System is biocompatible for its intended use.

Table 1: Zephyr® Endobronchial Valve (EBV) Biocompatibility Summary

Test	Purpose	Results
Minimal Essential Media (MEM) Elution test per ISO 10993-5: 2009 for cytotoxicity	To evaluate the potential for cytotoxicity.	Pass. No evidence of causing cell lysis; no evidence of reactivity.
ISO Guinea Pig Maximization Sensitization test per ISO 10993-10: 2010	To evaluate the allergenic potential or sensitizing capacity.	Pass. No sensitization response was observed.
Intracutaneous Reactivity per ISO 10993-10: 2010	To evaluate intracutaneous reactivity or local irritation.	Pass. No significant dermal reactions were observed.

Test	Purpose	Results
Acute Systemic Toxicity per ISO 10993-11: 2006	To evaluate potential toxic effects as a result of a single-dose systemic injection.	Pass. No clinical signs consistent with toxicity were observed.
Materials Mediated Pyrogen per ISO 10993-11: 2006 and USP 38 Section <151>	To determine if the test article extract causes a febrile response.	Pass. The maximum temperature rise met the requirements for absence of pyrogens.
In Vivo Mouse Micronucleus Assay per ISO 10993-3: 2014	To evaluate the potential for genotoxicity.	Pass. The levels of micronucleated cells were within normal negative ranges. No overt signs of toxicity.
ISO Intramuscular Implant test per ISO 10993-6: 2016*	To evaluate the local effects of a test article in direct contact with living skeletal muscle tissue.	Pass. The Irritant Ranking Score was minimal or no reaction. Based on the gross and histopathologic evaluations, the test article was considered a non-irritant.
Chemical analysis and toxicological risk assessment per ISO 10993-17: 2002, ISO 10993-18: 2005, ASTM D4128-06, ASTM D1971-11, USP 39 Section <621>, USP 39 Section <730>, USP 39 Section <736>, and USP 39 Section <643>	To address the subacute/subchronic toxicity, chronic toxicity, and carcinogenicity endpoints.	Low likelihood of adverse effects from subacute/ subchronic toxicity, chronic toxicity, genotoxicity, and carcinogenicity. The compounds detected were below their respective Recommended Daily Intake and below the Threshold of Toxicology Concern.

*Testing was performed on the ISO 10993-6:1995 version; gap assessment concluded changes in the 2007 and 2016 versions had no effect on testing performed.

Table 2: Zephyr® Endobronchial Delivery Catheter (EDC) Biocompatibility Summary

Test	Purpose	Results
Minimal Essential Media (MEM) Elution test per ISO 10993-5: 2009 for cytotoxicity	To evaluate the potential for cytotoxicity.	Pass. No evidence of causing cell lysis; no evidence of reactivity.
ISO Guinea Pig Maximization Sensitization test per ISO 10993-10: 2010	To evaluate the allergenic potential or sensitizing capacity.	Pass. No sensitization response was observed.
Intracutaneous Reactivity per ISO 10993-10: 2010	To evaluate intracutaneous reactivity or local irritation.	Pass. No significant dermal reactions were observed.

In-Vitro Bench Testing

The integrity and performance of the Zephyr® Endobronchial Valve System was evaluated through *in vitro* bench testing. The completed testing demonstrates that applicable material, functional, system compatibility, and durability in the product specifications have been met. These specifications were found to be adequate to ensure the device will perform safely and effectively under expected clinical conditions. The Zephyr® Endobronchial Valve System has completed all *in vitro* bench testing demonstrating that it conforms to user needs and its indication for use. ***Table 3*** summarizes the bench testing performed for the Zephyr® Endobronchial Valve, including information about the test, purpose, acceptance criteria, and results. ***Table 4*** summarizes the bench testing performed for the Zephyr® Endobronchial Delivery Catheter, including information about the test, purpose, acceptance criteria, and results.

Table 3: Summary of Zephyr® Endobronchial Valve Bench Testing

Test	Purpose	Acceptance Criteria	Results
Zephyr® Endobronchial Valve			
Valve Flow vs. Pressure Test	Quantify the pressure across the valve when subjected to a specific flow rate.	The pressure measured across the valve must be within specified limits.	Pass
Leak Test	Determine the inhalation pressure required to generate a leak in the Zephyr Endobronchial Valve in a bronchial model.	The valve device must not leak in the direction of inhalation when deployed at the minimum and maximum labeled diameters.	Pass
Valve Response Test	Evaluate the valve response time of the Zephyr Endobronchial Valve in terms of the time it takes for the valve to close and create a seal in the inhalation direction.	The valve must close within the time specified in the product specification.	Pass
Valve Inversion Test	Evaluate the valve resistance to inversion when subjected to pressure differentials common in bronchoscopic procedures.	The valve must not invert and must return to its original position within the valve protector when subject to pressure differentials common in bronchoscopic procedures (175 in H_20).	Pass
Inspiratory Migration Test	Evaluate the migration resistance of the Zephyr Endobronchial Valve within a bronchial model during a simulated maximal inhalation.	The device must not migrate > 1mm distally.	Pass
Cough Migration Test	Evaluate the migration resistance of the Zephyr Endobronchial Valve within a bronchial model during a simulated cough.	The device must not migrate > 1mm proximally.	Pass

Test	Purpose	Acceptance Criteria	Results
Wet Cracking Pressure Test	Quantify the pressure required for the valve component to open in exhalation during simulated physiological conditions.	The valve must vent at or below pressure differentials developed during early clinical research based on clinical outcomes.	Pass
Deployed Length Verification Test	Confirm that the deployed length of the sealing portion of the Zephyr Endobronchial Valve meets the specification.	The valve device must fit within the targeted bronchial segment.	Pass
Radial Expansion Test	Quantify the radial force exerted by the Zephyr Endobronchial Valve during radial expansion.	At the minimum labeled diameter, the radial force of the valve device retainer (implant frame) must be atraumatic relative to the bronchi. The radial force value correlates to no necrosis as per histopathological assessment.	Pass
		At the maximum labeled diameter, the radial force of the valve device retainer (implant frame) must be sufficient to resist migration. The radial force value correlates to little to no migration as evaluated bronchoscopically.	
Valve Deployment Force Test	Evaluate the force required to deploy a Zephyr Endobronchial Valve out of the Zephyr Endobronchial Delivery Catheter.	The device must be compatible with the delivery catheter. The force required to deploy the valve must be less than the force generated by the catheter.	Pass
Valve Loading Tests	Evaluate the force required to load the valve device. Evaluate the tensile strength of the Loading Tool Assembly used to pull the valve device into the funnel.	The loading force of the valve device must be less than the tensile force of the cord bundle used to pull the device into the funnel.	Pass
	Evaluate the ability of the device to be loaded and deployed.	The valve device must be capable of being successfully loaded and deployed one time without compromising its ability to meet functional requirements.	
Retainer (Implant Frame) Strut Strength Test	Determine the tensile strength of the Zephyr Endobronchial Valve retainer (implant frame) struts.	The tensile strength of the retainer (implant frame) strut shall be at least 25% greater than the maximum force specified to load the valve device.	Pass
Removability Test	Confirm the Zephyr Endobronchial Valve (EBV) can be removed through an endotracheal tube.	Must be removable through a 7.5 mm endotracheal tube.	Pass

Test	Purpose	Acceptance Criteria	Results
Retainer (Implant Frame) Cycle Fatigue Test	Assess the durability of the Valve Device Nitinol frame (retainer) following 6 years of simulated coughing at worst case cough frequency and cough pressure.	No membrane or strut fractures after 6 years of simulated worst case cough cycles.	Pass
Valve Cycle Fatigue Test	Assess the durability of the valve component following cyclic conditioning for the period of time necessary to simulate expected worst case use.	Following the cyclic conditioning, the valve device must pass the following tests: • Valve flow vs. pressure test • Leak test • Valve response test • Valve inversion test • Wet cracking pressure test	Pass
Corrosion Testing	To assess the resistance to corrosion of the device compared to a tracheobronchial stent of similar material that is implanted in the lung. Testing conducted as per ASTM F2129 Standard Test Method for Conducting Cyclic Potentiodynamic Polarization Measurements to Determine the Corrosion Susceptibility of Small Implant Devices.	All materials must perform (performance measured as breakdown potential or corrosion margin of safety) equal to or better than a tracheobronchial stent of similar material that is implanted in the lung.	Pass
Drug Compatibility	To assess the compatibility of the valve device to inhaled COPD medications.	The valve device must not change significantly when exposed to inhaled COPD medications.	Pass

Test	Purpose	Acceptance Criteria	Results
MRI Testing	To assess the conditions of safe use of the valve device during Magnetic Resonance Imaging (MRI) as per ASTM F2052 - Standard test method for measurement of magnetically induced displacement force on medical devices in the magnetic resonance environment, ASTM F2213 - Measurement of magnetically induced torque on medical devices in the MR environment, ASTM F2182 - Radio frequency induced heating on or near passive implants during MRI, ASTM F2119 - Standard test method for evaluation of MR image artifacts from passive implants, ASTM F2503 - Marking Medical Devices for Safety in the Magnetic Resonance Environment.	The valve must not pose any unacceptable hazard (heating, image artifact, displacement and torque) in a specified MR environment with specified conditions of use.	Pass

Table 4: Summary of Zephyr® Endobronchial Delivery Catheter Bench Testing

Test	Purpose	Acceptance Criteria	Results
Zephyr® Endobronchial Delivery Catheter			
Inner Shaft to Hardstop Tensile Test	Evaluate the tensile strength of the inner shaft to hardstop joint in the Zephyr Endobronchial Delivery Catheter.	All attachment joints must remain attached throughout the forces expected during clinical use and valve deployment(s).	Pass
Inner Shaft Tensile Strength Test	Evaluate the tensile strength of the inner shaft to inner shaft retention lock joint within the Zephyr Endobronchial Delivery Catheter handle.		Pass
Housing to Outer Shaft Tensile Strength Test	Evaluate the tensile strength of the housing to outer shaft bond in the Zephyr Endobronchial Delivery Catheter.		Pass
Outer Shaft to Handle Tensile Strength Test	Evaluate the tensile strength of the outer shaft to handle joint in the Zephyr Endobronchial Delivery Catheter.		Pass
Outer Shaft Torque Test	Evaluate the torsional strength of the outer shaft of the Zephyr Endobronchial Delivery Catheter.		Pass

Test	Purpose	Acceptance Criteria	Results
Outer Shaft to Handle Torque Test	Evaluate the torsional strength of the outer shaft to handle joint of the Zephyr Endobronchial Delivery Catheter.		Pass
Outer Sheath Tensile Strength Test	Evaluate the tensile strength of the bond joint between the outer sheath and handle in the Zephyr Endobronchial Delivery Catheter.		Pass
Delivery Catheter Placement Test	Evaluate the Zephyr Endobronchial Delivery Catheter's ability to advance to the simulated target bronchus and place a Zephyr Endobronchial Valve in a simulated target bronchus.	The catheter must be able to deliver an EBV to the simulated bronchus through the 2.8 mm working channel of an adult bronchoscope. The delivery catheter must be capable of performing this at least six (6) times.	Pass
Delivery Catheter Sizing Gauge Endurance Test (Part 1-Performance)	Evaluate the functional endurance of the sizing gauges on the Zephyr Endobronchial Delivery Catheter by measuring the sizing gauges after six insertion/retraction cycles.	Must remain functional after six insertions and retractions through a bronchoscope.	Pass
Delivery Catheter Sizing Gauge Endurance Test (Part 2-Safety)	Evaluate the endurance of the sizing gauges on the Zephyr Endobronchial Delivery Catheter by inspecting the sizing gauges after 15 insertion/retraction cycles.	Sizing gauges must remain intact and attached after 15 insertions and retractions through an adult bronchoscope.	Pass
Depth Mark Verification Test	Verify the depth mark distance(s) on the Zephyr Endobronchial Delivery Catheter meet the dimensional requirements.	The delivery catheter housing must contain mark(s) accurately indicating the length of the retention portion of the valve device being placed.	Pass
Delivery Catheter Force Test	Verify that the distal output load and handle load of the Zephyr Endobronchial Delivery Catheter meet the product specification requirements.	When placed inside the 2.8 mm working channel of an adult bronchoscope at a bend of 180º, the force generated by the catheter must be greater than the force required to deliver the valve device. The force exerted by the user to deploy the valve shall be within the expected capability of the user.	Pass
Catheter Working Length Verification Test	Verify that the working length of the Zephyr Endobronchial Delivery Catheter meets the dimensional requirements.	The working length of the delivery catheter must exceed the length of the bronchoscope working channel of an adult bronchoscope.	Pass

Test	Purpose	Acceptance Criteria	Results
Handle Safety Test	Evaluate the force required to overcome the safety lock feature of the actuator on the Zephyr Endobronchial Delivery Catheter handle.	The actuator lock must withstand a force greater than what is expected during insertion through the 2.8 mm working channel of an adult bronchoscope.	Pass

Sterilization Validation

The Zephyr® Endobronchial Valve System is sterilized with 100% Ethylene Oxide (EO) gas. The sterilization cycle was validated in accordance with ISO 11135-1:2007, *Ethylene oxide - Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices*, and AAMI Technical Information Report 28:2009, *Product adoption and process equivalence for ethylene oxide sterilization*. The purpose of the testing is to demonstrate that the sterilization process is capable of sterilizing the Zephyr® Endobronchial Valve System to a minimum Sterility Assurance Level (SAL) of 10^{-6}. A summary of the sterilization validation testing performed is provided in ***Table 5***. The process validation study demonstrated that the Zephyr Valves and Zephyr EDC can be routinely processed to meet a Sterility Assurance Level (SAL) of 10^{-6}. The results for ethylene oxide (EO) and ethylene chlorohydrin (ECH) met the requirements of ISO 10993-7:2008, "*Biological evaluation of medical devices – Part 7: Ethylene oxide sterilization residuals.*" Product was at releasable levels after 48 hours of heated aeration for a one-time exposure and 48 hours heated aeration for a two-time exposure. These times are in addition to an 18 hour period of ambient aeration.

Table 5: Summary of Sterilization Validation Testing

Acceptance Criteria	Results
Microbiological Performance Qualification Test (per ISO 11135-1:2007)	
All half cycle parameters must be met for the four (4) runs.	Pass. All half cycle parameters were met for each of the four (4) runs.
Positive controls must show growth.	Pass. All positive controls showed growth.
The minimum required lethality (SAL) is achieved.	Pass. The cycles performed in the execution of this study yielded the specified lethality to internal surrogate process challenge device (PCD) in the half cycle. Therefore, with a full cycle, the SAL of 10^{-6} biological indicator spore population placed in the load will be equal to or less than 10^{-6}, providing a spore log reduction (SLR) of the biological indicator equal to or greater than 12.
The half cycles must demonstrate 100% Biological Indicator (BI) lethality of the internal and/or master PCD.	Pass. The half cycles demonstrated 100% BI lethality of the internal and/or master PCD.

Acceptance Criteria	Results
The minimum required amount of internal temperature and relative humidity sensors must be functional at the completion of each half cycle.	Pass. The minimum required amount of internal temperature and relative humidity sensors was functional at the completion of each half cycle.
Physical Performance Qualification Test (per ISO 11135-1:2007, unless otherwise noted)	
All full cycle parameters must be met for the three (3) runs.	Pass. All full cycle parameters were met for each of the three (3) runs.
The full cycle must demonstrate 100% BI lethality of the external process challenge device (EPCD).	Pass. All full cycles demonstrated 100% BI lethality of the EPCD.
Positive controls must show growth.	Pass. All positive controls showed growth.
The results for EO and ECH residuals will meet the requirements of ISO 10993-7:2008, following aeration.	Pass. The results for EO and ECH met the requirements of ISO 10993-7:2008.

Packaging Validation

Packaging validation testing has been completed for the Zephyr® Endobronchial Valve System in accordance with applicable standards. The Zephyr Valves and EDC package systems were subjected to ethylene oxide sterilization, conditioning, and distribution testing outlined in the ASTM D4169, "*Standard Practice for Performance Testing of Shipping Containers and Systems.*" ***Table 6*** summarizes the packaging validation testing conducted, including information about the test, purpose, acceptance criteria, and results. The ability of the package systems to protect the Zephyr Valves and Zephyr EDC from hazards typically associated with the shipping and distribution environment has been validated and maintained through the shelf-life of the product.

To evaluate the physical condition of the device packaging post-distribution conditioning per ASTM D4332, "*Standard Practice for Conditioning containers, Packages, or Packaging Components for Testing*"

Table 6: Summary of Zephyr® Endobronchial System Packaging Validation Testing

Test	Purpose	Acceptance Criteria	Results
Visual Inspection	To evaluate the physical condition of the device packaging post-conditioning per ASTM D4332, *"Standard Practice for Conditioning Containers, Packages, or Packaging Components for Testing."* (packaging carton, overshipper box, pouch, labels)	No visual damage post-distribution as specified in protocol.	EBV: Pass EDC: Pass
Dye Penetration	To detect if there are any leaks in the pouch in accordance with ASTM	Each pouch must meet requirements per ASTM	EBV: Pass

Test	Purpose	Acceptance Criteria	Results
	F1929-98, "*Standard Test Method for Detecting Seal Leaks in Porous Medical Packaging by Dye Penetration.*"	F1929-98 following worst case handling as specified in test protocol.	EDC: Pass
Pouch Peel Tensile Strength	To determine the pouch peel tensile strength of the pouch seal.	Peel strength of the pouch must be > 2.0 lbs.	EBV: Pass EDC: Pass

Shelf Life Testing

A shelf-life of two (2) years has been established for the Zephyr® Endobronchial Valve System based on product and package shelf-life testing. The integrity and performance of the device after aging was evaluated through functional testing and visual inspections. The shelf-life testing performed after aging repeated the tests summarized in ***Table 3***, ***Table 4***, and ***Table 6***, and all testing passed. The completed testing validates the proposed shelf-life duration of two (2) years and demonstrates that applicable requirements in the product specifications have been met. The device has completed the testing demonstrating that it conforms to user needs and its intended uses throughout its proposed shelf-life.

B. Animal Studies

The Zephyr® Endobronchial Valve System has been extensively studied in the sheep model. Performance was demonstrated by the evaluation of implantation, removability, atelectasis, and migration. No long-term safety concerns have been identified based on histological examination of the implant sites. ***Table 7*** summarizes the preclinical study conducted for the Zephyr 4.0-LP Endobronchial Valve, including information about the test, purpose, acceptance criteria, and results.

Table 7: Summary of Zephyr 4.0-LP Endobronchial Valve 30 Day Implantation Study in Sheep Model

Test	Purpose	Acceptance Criteria	Results
Implant Placement	Evaluate the ability of the device to be deployed in the target airway with correct placement and occlude the target airway.	Device must be able to deploy distal to the carina of the target airway per the IFU. Device must also occlude the target airway.	Devices were placed properly to occlude the target airway.
Acute Removability	Verify that the device can be removed after placement.	Device must be able to be removed after proper placement in an airway.	Devices were placed and successfully removed with minimal resistance and without any complications.
Sub-chronic Removability	Verify that the device can be removed after placement and 30±2 day implantation.	Device must be able to be removed after proper placement and 30±2 day implantation in an airway.	Devices were placed and successfully removed after 29 days of implantation.
Migration	Verify that the device maintains its original position in the airway.	Device must be seated distal to the carina and occlude the airway for each of the original placement locations.	10 out of 12 of the devices maintained position. Two (2) devices migrated and were assumed to be expectorated. The root cause for these migrations was the growth of the animal over the 29 day implantation period. The body mass for both sheep increased by at least 8% during the implantation period. This root cause is not expected in the clinical setting and the results were determined to be acceptable.
Pathology	Evaluate the histopathological effects of the device at the implant sites after 30 day implantation.	Histological analysis of the implant site must yield an acceptable result for clinical use as determined by a pathologist.	Pathologist concluded that tissue specimens examined had "mild cellular reactions consistent with a Sub-chronic host response to a bio- compatible foreign body implantation". Additionally, "laceration and/or tissue perforation were not noted." Therefore, the pathology results are considered acceptable.

C. Human Factors/Usability Testing

Human factors and usability validation testing was completed for the Zephyr® Endobronchial Valve System in accordance with the FDA Guidance, *Applying Human Factors and Usability Engineering to Medical Devices*, published February 3, 2016. The results from the human factors and usability validation testing demonstrated that all 20 test participants, currently licensed pulmonologists or thoracic surgeons residing in the

U.S., were able to complete all four (4) critical tasks of the Zephyr® Endobronchial Valve System procedure. There were no occurrences of use errors during the testing, and the testing supports the conclusion that the use error rates with the Zephyr® Endobronchial Valve System have been reduced to the extent possible and are acceptable.

X. SUMMARY OF PRIMARY CLINICAL STUDY

Prior Clinical Study

The VENT trial[1], conducted in 2004, was a randomized, controlled study with U.S. and European cohorts, comparing Zephyr EBV treatment to a Control group of subjects who received optimum medical care. Post-hoc subgroup analyses (***Table 8***) were performed to identify the population that was to be studied in the pivotal trial.

Table 8: Overview of VENT post-hoc sub-group

No. of Sites	No. of Patients	Planned Follow-up	Outcomes
31 (U.S.) 23 (OUS)	122 (61 EBV with complete fissures and lobar occlusion & 61 Controls with complete fissures)	Primary endpoint at 6 months Follow-up out to 12-months	• Co-Primary Endpoints Mets: The mean group difference (EBV-SoC*) for the change in FEV_1 and 6MWD from Baseline to 6-months was 24.8% (mean, $p<0.001$) and 18.0 m (median, $P< 0.0397$), respectively • Significant improvements in residual volume (L), mMRC§, & SGRQ‡ at 6-months. • Increase in respiratory adverse events during 30-Day Treatment Period (Hemoptysis & Non-cardiac chest pain) • Acceptable long-term safety profile, with a higher observed rate of Hemoptysis in the EBV group.

*SoC (Standard of Care) (i.e., Control Group)
**Sponsored by Emphasys Medical (acquired by Pulmonx)
§Modified Medical Research Council (mMRC)
‡St. George's Respiratory Questionnaire (SGRQ)

LIBERATE Pivotal Trial

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of the Zephyr® Endobronchial Valves (Zephyr Valves) for the treatment of patients with severe emphysema in the U.S., UK, Brazil, and the Netherlands under IDE #G120008. 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 15, 2013 and September 30, 2017. The database for this PMA reflected data collected through November 16, 2017 at 24 investigational

sites and included 190 patients (130 patients at 18 U.S. sites and 60 patients at 6 OUS sites).

The study was a prospective, multi-center, randomized, controlled, two-arm, one way crossover, unmasked, pivotal clinical study. Qualifying subjects with heterogeneous emphysema were randomized at a 2:1 ratio into either the Zephyr EBV treatment arm or Control (Standard of Care) arm. All subjects underwent bronchoscopy with Chartis assessment for collateral ventilation. To conduct the Chartis assessment for collateral ventilation, the Pulmonx Chartis System (composed of the Chartis® Catheter (K111522) and Chartis® Console (K111764)), was used and is designed to measure pressure and flow to calculate resistance to airflow and quantify collateral ventilation in isolated lung compartments. This procedure was performed to select the target lobe for EBV placement. The subjects in the EBV arm had Zephyr® Endobronchial Valves placed in the target lobe to achieve lobar occlusion and continued to receive optimal medical management according to current clinical practice guidelines based on GOLD 2013 recommendation. The Control group subjects only received optimal medical management according to current clinical practice guidelines based on GOLD 2013 recommendations for the duration of the study. However, following their 12-month evaluation, the Control group subjects could be crossed over to Zephyr EBV treatment.

Random assignment was performed using a stratified permuted block design, generated separately for each clinical site, with assignment stratified by anatomical site of the planned treatment (e.g., right lung or left lung). An interim analysis was performed when 74 subjects completed their 12-month follow-up, to evaluate effectiveness for continuing crossover of Control arm subjects at the 1-year follow-up to Zephyr EBV treatment.

The primary effectiveness endpoint in the Zephyr EBV treatment and Control arms were compared using the standard normal Z-statistic for both the interim and end of 12-month study analyses. To preserve an overall Type I error rate of 0.05 for the study, the Z-statistic had to exceed 2.571 at the interim analysis and 2.004 at the final analysis for the null hypothesis of no difference to be rejected.

Secondary effectiveness endpoints were analyzed using an Analysis of Covariance (ANCOVA) model with treatment as a fixed effect and the corresponding baseline as a covariate. To control the family-wise Type I error rate at 0.05, the Hochberg step-up procedure was utilized for multiplicity adjustment. The Intent-to-Treat (ITT) population consisting of all randomized subjects was used as the primary analysis population for all the effectiveness endpoints analyses.

A Data and Safety Monitoring Board (DSMB) comprising of three (3) voting members was established to oversee subject safety in the LIBERATE Study. A Clinical Events Committee (CEC) comprising of four (4) voting members was established to adjudicate select respiratory, all serious adverse events and all device-related adverse events in the LIBERATE Study.

1. Clinical Inclusion and Exclusion Criteria

There were three (3) sets of enrollment criteria: screening, baseline, and procedure. Enrollment in the LIBERATE study was limited to patients who met the following inclusion criteria.

Screening Inclusion

- Signed Screening or Study Procedure Informed Consent using a form that was reviewed and approved by the IRB.
- Age 40 to 75 years.
- Body Mass Index (BMI) less than 35 kg/m^2.
- Stable with less than 20mg prednisone (or equivalent) daily.
- Nonsmoking for 4 months prior to screening interview.

Baseline Inclusion

- Completed a supervised pulmonary rehabilitation program less than equal to 6 months prior to the baseline exam or is regularly performing maintenance respiratory rehabilitation if initial supervised therapy occurred greater than 6 months prior.
- Baseline evaluation occurred ≤120 days after screening exam.
- Signed written informed consent to participate in study using a form that was reviewed and approved by the IRB.
- Continued nonsmoking between initial screening and baseline exams.
- Willing and able to complete protocol required study follow-up assessments and procedures.
- FEV_1 between 15% and 45% of predicted value at baseline exam.
- Post-rehabilitation 6-minute walk distance between 100 meters and 500 meters at baseline exam.
- Current Pneumococcus vaccination.
- Current Influenza vaccination.

Procedure Eligibility Inclusion

- Procedure occurs < 60 days following baseline exam.
- Continues to meet all screening and baseline eligibility criteria.
- Little or no collateral ventilation (CV-) as determined using the Chartis System.

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

Screening Exclusion

- Currently enrolled in another clinical trial studying an experimental treatment.
- Previously enrolled in this study for which protocol required follow up is not complete.

- Clinically significant (greater than 4 tablespoons per day) sputum production.
- Two or more COPD exacerbation episodes requiring hospitalization in the last year at screening.
- Two or more instances of pneumonia episodes in the last year at screening.
- Unplanned weight loss >10% usual weight <90 days prior to enrollment.
- History of exercise-related syncope.
- Myocardial Infarction or congestive heart failure within 6 months of screening.
- Prior lung transplant, LVRS, bullectomy or lobectomy.
- Clinically significant bronchiectasis.
- Unable to safely discontinue anti-coagulants or platelet activity inhibitors for 7 days.
- Uncontrolled pulmonary hypertension (systolic pulmonary arterial pressure >45 mm Hg) or evidence or history of CorPulmonale as determined by recent echocardiogram (completed within the last 3 months prior to screening visit).
- Pulmonary nodule requiring surgery as noted by chest X-ray or CT scan.
- High resolution computed tomography (HRCT) collected per CT scanning protocol within the last 3 months of screening date and evaluated by clinical site personnel using Myrian CT software (K071000) shows:
    a. Parenchymal destruction score of greater than 75% in all three right lobes or both left lobes.
    b. Emphysema heterogeneity score less than 15% (Not Applicable for Crossover subjects).
    c. Large bullae encompassing greater than 30% of either lung.
    d. Insufficient landmarks to evaluate the CT study using the software as it is intended.
- Left ventricular ejection fraction (LVEF) less than 45% as determined by recent echocardiogram (completed within the last 3 months prior to screening visit).
- Resting bradycardia (<50 beats/min), frequent multifocal PVCs, complex ventricular arrhythmia, sustained SVT.
- Dysrhythmia that might pose a risk during exercise or training.
- Post-bronchodilator FEV_1 less than 15% or greater than 45% of predicted value at screening.
- Total lung capacity (TLC) less than 100% predicted (determined by body plethysmography) at screening.
- Residual volume (RV) less than 175% predicted (determined by body plethysmography) at screening.
- Diffusion capacity for carbon monoxide (DLCO) less than 20% predicted value at screening.
- 6-minute walk distance less than 100 meters or greater than 450 meters at screening.

- PaCO2 greater than 50mm Hg (Denver greater than 55 mm Hg) on room air at screening.
- PaO2 less than 45 mm Hg (Denver less than 30 mm Hg) on room air at screening.
- Elevated white cell count (>10,000 cells/μL) at screening.
- Presence of alpha-1 anti-trypsin deficiency as determined by local laboratory ranges.
- Plasma cotinine level greater than 13.7 ng/ml (or arterial carboxyhemoglobin >2.5% if using nicotine products) at screening.
- Any disease or condition that interferes with completion of initial or follow-up assessments.

Baseline Exclusion

- Myocardial infarction or diagnosis of congestive heart failure between screening and baseline exams.
- Fever or other clinical evidence of active infection at baseline exam.
- Two (2) or more COPD exacerbation episodes between screening and baseline exams.
- Two (2) or more pneumonia episodes between screening and baseline exams.

Procedure Eligibility Exclusion

- Evidence of collateral ventilation (CV+) as determined using the Chartis System.
- Collateral ventilation could not be determined using the Chartis System.
- Collateral ventilation assessment was not conducted using the Chartis System.

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at 45-days, 3-months, 6 months, 9 months, and 1 year postoperatively. Subjects in the Zephyr EBV treatment arm had additional daily phone call follow-ups for the first 10 days, and office visits at 7 days and 30 days.

The Zephyr EBV treatment arm will have annual follow-up visit out to 5 years. Control group subjects who crossed over to the Zephyr EBV treatment arm after completing their 12 months follow-up will also undergo annual follow-up visits for an additional 5 years.

The key assessments performed at specific timepoints are shown in ***Table 9***.

Table 9: Key assessments performed at each visit

TESTING	Screen Eligibility	Pre-Baseline	Baseline Eligibility	Day 0 - Index Procedure	Day 1	Day 2	Day 3	Day 4	Day 5 (or day of Discharge)	Daily Phone Call *(for 10 days after Discharge)*	Day 7 After Discharge	30 Days	45 Days	3 Months	6 Months	9 Months	1 Year	2 to 5 Year	ET/ EWD
IMAGING																			
Chest X-ray				X[EBV]	X[EBV]	X[EBV]	X[EBV]	X[EBV]	X[EBV]		X[EBV]	X[EBV]	X						
Electrocardiography	X																X		
ECG	X																		
High Resolution CT Scan	X												X[EBV]				X[EBV]		
LUNG FUNCTION TESTING																			
Spirometry	X		X										X		X		X	X	X
Body Plethysmography	X												X				X		
Diffusing Capacity	X												X				X		
EXERCISE TOLERANCE																			
Six-Minute Walk Test	X		X										X		X		X		
BASIC MEDICAL																			
Medical History	X																		
Pulse Oximetry (first 24 hours after procedure)				X[CONT.]	X[EBV]														
Vital Signs / Physical Exam	X		X	X					X[EBV]		X[EBV]	X[EBV]	X	X	X		X		X
Symptom Checklist										X[EBV]	X[EBV]								
Review of Medications	X											X[EBV]	X	X	X	X	X		X
BLOOD WORK																			
Arterial Blood Gases (ABGs)	X			X[CONT.]	X[EBV]												X		

TESTING	Screen Eligibility	Pre-Baseline	Baseline Eligibility	Day 0 - Index Procedure	Day 1	Day 2	Day 3	Day 4	Day 5 (or day of Discharge)	Daily Phone Call *(for 10 days after Discharge)*	Day 7 After Discharge	30 Days	45 Days	3 Months	6 Months	9 Months	1 Year	2 to 5 Year	ET/ EWD
Complete Blood Counts (CBCs)	X																X		
Alpha-1 Antitrypsin	X																		
Plasma Cotinine or Arterial Carboxyhemoglobin	X																X		
Serum Fibrinogen	X			$X^{CONT.}$	X^{EBV}												X		
MEDICAL MANAGEMENT																			
Pulmonary Rehabilitation		X			T						X^{EBV}								
Pneumococcal Vaccine			X																
Influenza Vaccine			X																
HEALTH SURVEYS																			
SGRQ			X											X	X		X		
mMRC			X										X		X		X		
BDI/TDI			X											X	X	X	X		
CAT			X											X	X	X	X		
SF-36			X														X		
EQ-5D			X														X		
Health Care Utilization			X											X	X	X	X		
DAILY DIARY* **																			
PR Compliance			X										X	X	X	X	X		
Exact-PRO			X		X^{EBV}	X^{EBV}	X^{EBV}	X^{EBV}	X^{EBV}	X^{EBV}	X^{EBV}	X^{EBV}	X	X	X	X	X		
Health Status Change			X		X^{EBV}	X^{EBV}	X^{EBV}	X^{EBV}	X^{EBV}	X^{EBV}	X^{EBV}	X^{EBV}	X	X	X	X	X		
SAFETY																			

TESTING	Screen Eligibility	Pre-Baseline	Baseline Eligibility	Day 0 - Index Procedure	Day 1	Day 2	Day 3	Day 4	Day 5 (or day of Discharge)	Daily Phone Call *(for 10 days after Discharge)*	Day 7 After Discharge	30 Days	45 Days	3 Months	6 Months	9 Months	1 Year	2 to 5 Year	ET/ EWD
Adverse Events				X	X^{EBV}	X^{EBV}	X^{EBV}	X^{EBV}	X^{EBV}	X^{EBV}	X^{EBV}	X^{EBV}	X	X	X	X	X	X	X

CONT.: Assessments required for subjects randomized to the Control arm.
EBV: Assessments required for subjects randomized to the EBV arm.

3. Clinical Endpoints

With regards to safety, adverse events up to 45 days (short term) and from day 46 to 1 year (long term) were evaluated.

With regards to effectiveness, the primary effectiveness endpoint was the percentage of study subjects in the Zephyr EBV treatment arm who met the threshold of ≥15% improvement in post-bronchodilator forced expiratory volume in one second (FEV_1) as compared to the Control arm at 1 year.

Secondary effectiveness endpoints included:

1. FEV_1: Difference between study arms in absolute change from baseline for FEV_1 at 1 year.
2. Six-minute Walk Distance (6MWD): Difference between study arms in absolute change from baseline for 6MWD at 1 year.
3. St. George's Respiratory Questionnaire (SGRQ): Difference between study arms in absolute change from baseline for SGRQ score at 1 year.

Other additional endpoints included other measures of lung function, exercise capacity, breathlessness, and quality of life. Additionally, the 6MWD responder rate for the percent of subjects with improvement of ≥25 m and ≥54 meters was also collected.

With regards to success/failure criteria, the study would be considered a success if the difference between the Zephyr EBV treatment and Control arms for the percentage of subjects meeting the threshold of ≥15% improvement in post-bronchodilator FEV_1 was statistically significant (two-sided test at $p \leq 0.05$) in favor of the Zephyr EBV treatment group at 1 year.

B. Accountability of PMA Cohort

At the time of database lock, of 190 patients enrolled in the PMA study, 91.6 % (174) of enrolled patients were available for analysis at the completion of the study (data from four (4) additional patients from treatment arm was not available), the 12 month post-operative visit. Patient accountability is summarized in the ***Figure 4*** and ***Table 10*** below.

Figure 4: Patient Accountability

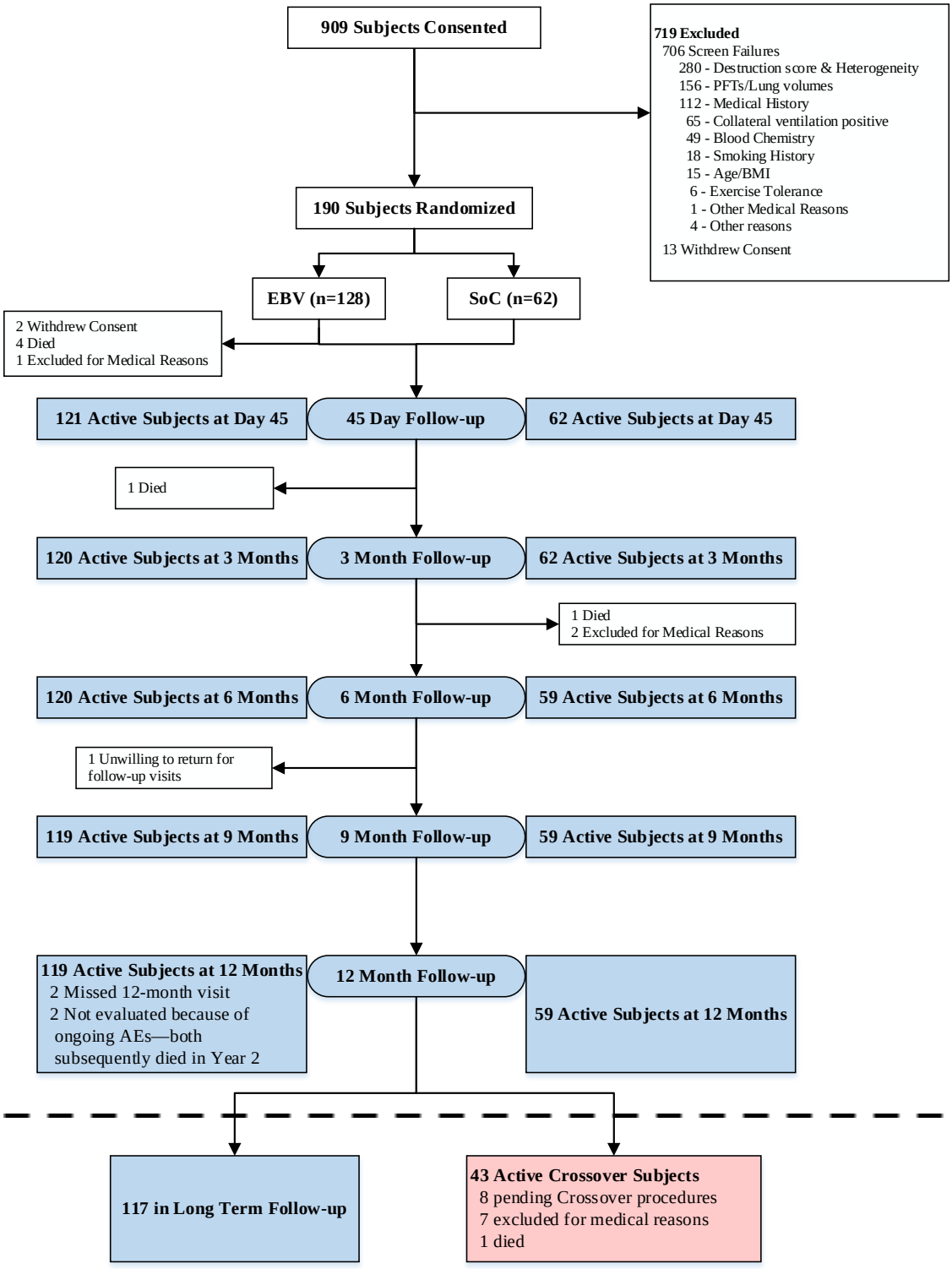


Table 10: Summary of Subject Enrollment and Evaluability (Randomized Subjects)

	EBV	Control
Number of Subjects Randomized	128	62
Number of Subjects Included in the Intent-to-Treat Population	128 (100.0%)	62 (100.0%)
Number of Subjects Excluded from the Intent-to-Treat Population	0 (0.0%)	0 (0.0%)
Number of Subjects Included in the Completed Cases Population	115 (89.8%)	59 (95.2%)
Number of Subjects Excluded from the Completed Cases Population	13 (10.2%)	3 (4.8%)
Reason for Exclusion from Completed Cases Population		
Did Not Receive Treatment as Randomized	0 (0.0%)	0 (0.0%)
Did Not Attend 1 Year Follow-up Visit	13 (10.2%)	3 (4.8%)
Number of Subjects Included in the Per-Protocol Population	108 (84.4%)	55 (88.7%)
Number of Subjects Excluded from the Per-Protocol Population	20 (15.6%)	7 (11.3%)
Reason for Exclusion from Per-Protocol Population		
Did Not Receive Treatment as Randomized	0 (0.0%)	0 (0.0%)
Did Not Meet Study Eligibility	11 (8.6%)	5 (8.1%)
Did Not Have Follow-up within Window for Primary Endpoint	16 (12.5%)	5 (8.1%)
Number of Subjects Included in the Safety Population	128 (100.0%)	62 (100.0%)
Number of Subjects Excluded from the Safety Population	0 (0.0%)	0 (0.0%)

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a pivotal study performed in the U.S. Baseline demographics and clinical characteristics of the study population are presented in ***Table 11***, ***Table 12***, and ***Table 13*** below.

Overall, the Control and treatment arm baseline characteristics were similar, except there were more males (53.2% in Control vs. 43.8 % in treatment) and stage IV GOLD (74.2 % in Control vs. 57.8 % in treatment) subjects in the Control group. The majority of subjects enrolled in the study (91.4%) were caucasians. These differences are not expected to impact the clinical trial.

Table 11: Baseline Demographics

Variable	EBV (N=128)		Control (N=62)		t-test p-value
	Mean	SD (Min, Max)	Mean	SD (Min, Max)	
Age (years)	64.0	6.85 (46 to 75)	62.5	7.12 (45 to 74)	0. 161[a]
Weight (lbs.)	152.41	32.44 (88.0 to 251.33)	153.34	35.09 (85.50 to 230.00)	0.857[a]

Variable	EBV (N=128)		Control (N=62)		t-test p-value
	Mean	SD (Min, Max)	Mean	SD (Min, Max)	
Height (inches)	65.69	4.03 (58.0 to 74.0)	66.33	3.44 (60.0 to 73.0)	0.285[a]
BMI (kg/m^2)	24.67	3.90 (15.3 to 36.6)	24.32	4.38 (15.4 to 34.0)	0.577[a]
Pack Year Smoking History	50.78	26.88 (0.0 to 122.5)	48.59	28.48 (2.0 to 135.0)	0.606[a]
Categorical Measures	n (%)		n (%)		
Gender – Males	56 (43.8)		33 (53.2)		0.278[b]
Gender – Females	72 (56.3)		29 (46.8)		
Race • **American Indian or Alaska Native**	1 (0.8)		0 (0.0)		
• **Asian**	1 (0.8)		0 (0.0)		
• **Black or African American**	8 (6.3)		3 (4.8)		
• **Native Hawaiian or other Pacific Islander**	0 (0.0)		0 (0.0)		
• **White**	117 (91.4)		57 (91.9)		
• **Multiple**	1 (0.8)		1 (1.6)		
• **Chooses not to provide information**	0 (0.0)		1 (1.6)		

[a] P-value from two-sided t-test assuming equal variance.

[b] P-value from two-sided Fisher's exact test.

Table 12: Baseline Clinical Characteristics – Lung Function Measures

Variable	EBV (N=128)		Control (N=62)		t-test p-value
Pulmonary Function Tests and Lung Volumes	**Mean (n)**	**SD (Min, Max)**	**Mean (n)**	**SD (Min, Max)**	
Forced Expiratory Volume in 1 sec. (FEV_1) – Post-bronchodilator (L)	0.763 (128)	0.252 (0.279 to 1.428)	0.752 (62)	0.217 (0.471 to 1.374)	0.767[a]
Forced Expiratory Volume in 1 sec. (FEV_1) – Post-bronchodilator (% predicted)	28.0 (128)	7.45 (15 to 45)	26.2 (62)	6.28 (16 to 44)	0.101[a]

Variable	EBV (N=128)		Control (N=62)		t-test p-value
Forced Vital Capacity (FVC) (L)	2.596 (128)	0.865 (0.940 to 4.493)	2.631 (62)	0.790 (0.978 to 5.041)	0.792[a]
Forced Vital Capacity (FVC) (% predicted)	71.2 (128)	15.99 (38 to 111)	68.5 (62)	13.59 (37 to 108)	0.248[a]
FEV_1/FVC	0.302 (128)	0.063 (0.17 to 0.46)	0.294 (62)	0.063 (0.19 to 0.50)	0.421[a]
Diffusing Capacity (mL CO/min/mm Hg)	8.528 (126)	3.475 (3.53 to 25.72)	8.342 (61)	2.708 (4.23 to 15.49)	0.714[a]
Diffusing Capacity (% predicted)	34.6 (126)	11.34 (20 to 72)	33.1 (61)	9.84 (20 to 59)	0.393[a]
Residual Volume (RV) (L)	4.709 (126)	1.046 (1.70 to 8.00)	4.759 (61)	0.901 (3.10 to 6.48)	0.752[a]
Residual Volume (% predicted)	224.5 (126)	42.45 (175 to 349)	224.6 (61)	38.86 (175 to 359)	0.987[a]
Total Lung Capacity (TLC) (L)	7.537 (126)	1.593 (5.00 to 13.00)	7.634 (61)	1.369 (5.25 to 10.40)	0.683[a]
Total Lung Capacity (% predicted)	133.5 (126)	21.17 (105 to 307)	130.2 (61)	12.44 (106 to 161)	0.256[a]
RV/TLC	0.631 (126)	0.086 (0.13 to 0.81)	0.626 (61)	0.073 (0.45 to 0.79)	0.689[a]
Functional Residual Capacity (FRC) (L)	5.807 (126)	1.301 (3.73 to 12.18)	5.903 (61)	1.106 (3.80 to 8.10)	
GOLD Stage	54 (42.2%) Stage III 74 (57.8%) Stage IV		16 (25.8%) Stage III 46 (74.2%) Stage IV		0.037[b]
HRCT Characteristics					
Emphysema Destruction score of the Target Lobe at -910 HU*	70.9 (128)	8.52 (50 to 88)	70.9 (62)	8.77 (51 to 86)	0.998[a]
Ipsilateral Lobe Destruction Score (%)	45.4 (128)	11.12 (11 to 68)	44.8 (62)	12.36 (11 to 69)	0.739[a]
Heterogeneity Index[†]	25.5 (128)	9.85 (15 to 70)	26.1 (62)	9.81 (15 to 61)	0.694[a]

[a] P-value from two-sided t-test assuming equal variance.

[b] P-value from Fisher's Exact test.

[c] Classification of airflow limitation severity in COPD (based post-bronchodilator FEV_1): GLOBAL STRATEGY FOR THE DIAGNOSIS, MANAGEMENT, AND PREVENTION OF COPD (2017 REPORT)

Note: Baseline results are the latest results prior to EBV or Assessment procedure.
To convert Diffusing Capacity from SI units (mmol / min / kPa) to standard units (mL CO /min /mmHg), values were multiplied by 2.987.

* Emphysema destruction score was assessed as the percentage of voxels of less than -910 Hounsfield units on CT.

† Volume weighted Heterogeneity Index assessed as the difference in the Emphysema destruction score between the target and the ipsilateral lobe. A difference of ≥15% was required between target and ipsilateral lobes

Table 13: Baseline Clinical Characteristics – Exercise Tolerance and Quality of Life Measures

Variable	EBV (N=128)		Control (N=62)		t-test p-value
Exercise Tolerance and Quality of Life Measures	**Mean (n)**	**SD (Min, Max)**	**Mean (n)**	**SD (Min, Max)**	
6 Minute Walk Distance (m)	311.33 (128)	81.33 (142 to 482)	301.91 (62)	78.54 (102 to 474)	0.450[a]
BORG before 6MWD	1.16 (128)	1.391 (0.0 to 7.0)	1.07 (62)	1.201 (0.0 to 4.0)	
BORG after 6MWD	4.45 (128)	2.174 (0.0 to 10.0)	4.94 (62)	2.282 (0.5 to 10.0)	
SGRQ Total score‡	55.15 (127)	14.09 (30.1 to 88.1)	53.10 (61)	14.14 (25.9 to 91.8)	0.352[a]
mMRC Dyspnea Grade score§	2.4 (126)	0.97 (0 to 4)	2.2 (62)	0.83 (0 to 4)	0.091[b]
BODE Index**	5.34 (126)	1.52 (2.0 to 10.0)	5.32 (62)	1.56 (2.0 to 9.0)	0.819[b]
CAT Total score ǁ	19.2 (128)	6.32 (5 to 37)	19.3 (62)	6.35 (6 to 34)	0.890[a]
EQ-5D Index	0.7 (127)	0.16 (0 to 1)	0.7 (61)	0.16 (0 to 1)	0.647[b]
EQ-5D VAS score	58.4 (121)	20.46 (4 to 100)	53.1 (59)	20.76 (5 to 80)	0.159[b]

[a] P-value from two-sided t-test assuming equal variance.

[b] P-value from Wilcoxon Rank Sum Test.

‡ St. George's Respiratory Questionnaire (SGRQ) scores range from 0 to 100, with higher scores indicating worse quality of life.

§ Modified Medical Research Council (mMRC) Dyspnea Scale ranges from 0 to 4, with higher scores indicating more severe dyspnea.

ǁ COPD Assessment Test (CAT) score ranges from 0-40 with higher scores indicating a more severe impact of COPD on a patient's life.

** BODE Index (Body mass index, airflow Obstruction, Dyspnea and Exercise capacity) score ranges from 0 to 10 based on a multidimensional scoring system to include FEV_1, Body-Mass Index, 6 Minute Walk Distance, and the modified MRC Dyspnea score. Higher scores denote a greater risk of mortality.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the 190 patients available for the Treatment Period (Day of procedure/randomization to 45 days) and 184 patients available for the Longer-Term Period (46 days after the study procedure/randomization until the 1-year follow-up visit). The key safety outcomes for this study are presented below in ***Table 14*** and ***Table 15***. Adverse events are reported in ***Table 16***, ***Table 17***, and ***Table 18***.

Table 14: Key Safety Outcomes within 45 Days of EBV/Assessment Procedure (Safety Subjects)

	EBV (N=128)	**Control (N=62)**
Total Number of Adverse Events Reported	352	35
Subjects Reporting Any Adverse Event	106 (82.8%)	25 (40.3%)
Total Number of Serious Adverse Events Reported	63	5
Subjects Reporting Any Serious Adverse Event	48 (37.5%)	5 (8.1%)
Subjects Who Died	4	0
Subjects Reporting Adverse Events by Maximum Severity		
Severe	30 (23.4%)	4 (6.5%)
Moderate	45 (35.2%)	10 (16.1%)
Mild	31 (24.2%)	11 (17.7%)
Subjects Reporting Adverse Events by Strongest Relationship to Study Device (Investigator Reported)		
Definitely	39 (30.5%)	NA
Probably	24 (18.8%)	
Possibly	18 (14.1%)	
Not Related	25 (19.5%)	
Unknown	0 (0.0%)	
Subjects Reporting Adverse Events by Strongest Relationship to Study Procedure (Investigator Reported)		
Definitely	29 (22.7%)	NA
Probably	18 (14.1%)	
Possibly	34 (26.6%)	
Not Related	25 (19.5%)	
Unknown	0 (0.0%)	

Table 15: Key Safety Outcomes between 46 Days Post EBV/Assessment Procedure and One Year Visit (Safety Subjects)

	EBV (N=122)	Control (N=62)
Total Number of Adverse Events Reported	326	144
Subjects Reporting Any Adverse Event	110 (90.2%)	51 (82.3%)
Total Number of Serious Adverse Events Reported	86	47
Subjects Reporting Any Serious Adverse Event	48 (39.3%)	21 (33.9%)
Subjects Who Died	1	1
Subjects Reporting Adverse Events by Maximum Severity		
Severe	28 (23.0%)	15 (24.2%)
Moderate	59 (48.4%)	23 (37.1%)
Mild	23 (18.9%)	13 (21.0%)
Subjects Reporting Adverse Events by Strongest Relationship to Study Device (Investigator Reported)		
Definitely	6 (4.9%)	NA
Probably	14 (11.5%)	
Possibly	30 (24.6%)	
Not Related	59 (48.4%)	
Unknown	1 (0.8%)	
Subjects Reporting Adverse Events by Strongest Relationship to Study Procedure (Investigator Reported)		
Definitely	3 (2.5%)	NA
Probably	7 (5.7%)	
Possibly	17 (13.9%)	
Not Related	83 (68.0%)	
Unknown	0 (0.0%)	

Adverse effects that occurred in the PMA clinical study:

For the short term, periprocedural period up to 45 days, the overall number of subjects reporting any adverse event was higher in the EBV group at 106 (82.8%) vs. 25 (40.3%) in the Control group (***Table 14***). There were a higher number of respiratory adverse events in the Zephyr EBV group compared to the Control group during the Treatment Period (79.7% subjects vs. 30.6% subjects). All adverse events occurring at an incidence rate of ≥3.0% in either the Zephyr EBV or Control groups during the Treatment Period (Day of procedure/ randomization to 45 days) and Longer-Term Period (46 days after the study procedure/ randomization until the 1-year follow-up visit is provided in (***Table 16***).

The most common respiratory adverse events in the Zephyr EBV vs. Control subjects during the Treatment Period were pneumothorax in 29.7% vs. 0.0% subjects, respectively; chest pain in 25.8% vs. 1.6% subjects, respectively; COPD exacerbations in 19.5% vs. 11.3% subjects, respectively; cough in 18.0% vs. 4.8% subjects, respectively; and dyspnea in 16.4% vs. 3.2% subjects, respectively.

There were more respiratory-related serious adverse events (SAEs) (***Table 17***) in the Zephyr EBV group with 35.2% vs. 4.8% in the Control group. The most common serious adverse event during the short term period was pneumothorax, which occurred in 34 (26.6%) of the EBV treated subjects. There were also four (4) early deaths (3.1%) with three (3) related to pneumothoraces (***Table 16***). Other respiratory serious adverse events included increased COPD exacerbations (7.8% of EBV subjects (10 events) vs. 4.8% of Control subjects (3 events)), respiratory failure (1.6% of EBV subjects (2 events)), dyspnea (1.6% of EBV subjects (4 events)), and pneumonia (1 EBV subject). The non-respiratory adverse events were observed in both arms at rates expected for subjects with COPD.

In the Longer-Term Period (46 days after the study procedure/randomization until the 1-year follow-up visit), the frequency of respiratory SAEs (***Table 18***) was comparable between arms, with 33.6% of the Zephyr EBV group subjects and 30.6% of the Control group subjects experiencing one or more respiratory SAE. Some of the higher number of adverse events in the Zephyr EBV group during this period were associated with protocol-allowed bronchoscopy procedures for valve adjustment. There were eight (8) subjects (6.6%) that had a pneumothorax after 45 days in the EBV arm, five (5) of which had undergone a second bronchoscopy for valve adjustment. The Control group had a higher frequency of COPD exacerbations that were SAEs (29 events in 19 (30.6%) subjects compared to 40 events in 28 (23.0%) subjects in the Zephyr EBV group), a higher frequency of pneumonias (6 events in 5 (8.1%) subjects compared to 7 events in 7 (5.7%) subjects in the Zephyr EBV group), and respiratory failure (3 events in 2 (3.2%) subjects compared to 1 event in 1 (0.8%) subject in the Zephyr EBV group). During the Longer-Term Period from 46 days to the 12-month visit date, death occurred in 0.8% of subjects in the Zephyr EBV group (1 subject), and 1.6% of the Control group (1 subject), both due to disease progression.

Table 16: Adverse Events Occurring in at Least 3% of Subjects in Either Group

	Treatment Period (Day of Procedure/ Randomization to 45 Days)		Longer-Term Period (45 Days from the Study Procedure/Randomization until 12-Month Visit Date	
	Zephyr EBV (N=128)	Control (N=62)	Zephyr EBV (N=122)	Control (N=62)
Respiratory				
Pneumothorax	38 (29.7%)	0 (0.0%)	8 (6.6%)	0 (0.0%)
Chest pain	33 (25.8%)	1 (1.6%)	8 (6.6%)	0 (0.0%)
COPD	25 (19.5%)	7 (11.3%)	69 (56.6%)	35 (56.5%)

	Treatment Period (Day of Procedure/ Randomization to 45 Days)		Longer-Term Period (45 Days from the Study Procedure/Randomization until 12-Month Visit Date	
	Zephyr EBV (N=128)	Control (N=62)	Zephyr EBV (N=122)	Control (N=62)
Respiratory				
Cough	23 (18.0%)	3 (4.8%)	6 (4.9%)	2 (3.2%)
Dyspnea	21 (16.4%)	2 (3.2%)	16 (13.1%)	1 (1.6%)
Haemoptysis	11 (8.6%)	1 (1.6%)	12 (9.8%)	0 (0.0%)
Oropharyngeal Pain	10 (7.8%)	3 (4.8%)	0 (0.0%)	0 (0.0%)
Pleural Effusion	9 (7.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Chest discomfort	8 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypoxia	7 (5.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pneumonia	6 (4.7%)	0 (0.0%)	11 (9.0%)	6 (9.7%)
Death	4 (3.1%)	0 (0.0%)	1 (0.8%)	1 (1.6%)
Sputum increased	4 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pulmonary mass	0 (0.0%)	0 (0.0%)	7 (5.7%)	3 (4.8%)
Upper respiratory tract infection	1 (0.8%)	0 (0.0%)	7 (5.7%)	0 (0.0%)
Bronchitis	1 (0.8%)	0 (0.0%)	6 (4.9%)	3 (4.8%)
Lower respiratory tract congestion	3 (2.6%)	0 (0.0%)	5 (4.1%)	0 (0.0%)
Sinusitis	0 (0.0%)	0 (0.0%)	3 (2.5%)	3 (4.8%)
Respiratory failure	2 (1.6%)	0 (0.0%)	1 (0.8%)	2 (3.2%)
Pharyngitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.2%)
Non-Respiratory				
Headache	10 (7.8%)	1 (1.6%)	4 (3.3%)	0 (0.0%)
Nausea	10 (7.8%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Constipation	8 (6.3%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Functional Gastrointestinal disorder	6 (4.7%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Arrhythmia	5 (3.9%)	0 (0.0%)	2 (1.6%)	2 (3.2%)
Dizziness	4 (3.1%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Pyrexia	4 (3.1%)	1 (1.6%)	0 (0.0%)	0 (0.0%)
Infection	1 (0.8%)	1 (1.6%)	10 (8.2%)	4 (6.5%)
Urinary Tract Infection	1 (0.8%)	1 (1.6%)	2 (1.6%)	4 (6.5%)
Diverticulitis	0 (0.0%)	0 (0.0%)	1 (0.8%)	2 (3.2%)
Nephrolithiasis	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.2%)

Table 17: Respiratory Serious Adverse Events Occurring within 45 Days Post EBV/Assessment Procedure and One Year Visit (Safety Subjects)

Class[a] Preferred Term	EBV Subjects[b] (N=128) n (%)	Events: n	Control Subjects[b] (N=62) n (%)	Events: n
Respiratory Adverse Events	45 (35.2%)	55	3 (4.8%)	3
Anesthetic complication pulmonary	1 (0.8%)	1	0	
Chest pain	1 (0.8%)	1	0	
Chronic obstructive pulmonary disease	10 (7.8%)	10	3 (4.8%)	3
Dyspnea	2 (1.6%)	4	0	
Pleural effusion	2 (1.6%)	2	0	
Pneumonia	1 (0.8%)	1	0	
Pneumothorax	34 (26.6%)	34	0	
Respiratory failure	2 (1.6%)	2	0	

[a]Respiratory Serious Adverse Events map to primary, secondary, or tertiary MedDRA System Organ Class of "Respiratory, thoracic and mediastinal disorders."
[b]Subjects are counted once at each level of summarization.

Table 18: Respiratory Serious Adverse Events Occurring between 46 Days Post EBV/Assessment Procedure and One Year Visit (Safety Subjects)

Class[a] Preferred Term	EBV Subjects[b] (N=122) n (%)	Events: n	Control Subjects[b] (N=62) n (%)	Events: n
Respiratory Adverse Events	41 (33.6%)	64	19 (30.6%)	39
Chronic obstructive pulmonary disease	28 (23.0%)	40	19 (30.6%)	29
Dyspnea	3 (2.5%)	3	0	
Haemoptysis	2 (1.6%)	2	0	
Pleural effusion	1 (0.8%)	1	0	
Pneumonia	7 (5.7%)	7	5 (8.1%)	6
Pneumothorax	8 (6.6%)	8	0	
Pulmonary embolism	0		1 (1.6%)	1
Pulmonary mass	1 (0.8%)	1	0	
Respiratory failure	1 (0.8%)	1	2 (3.2%)	3
Respiratory tract infection	1 (0.8%)	1	0	

[a]Respiratory serious adverse events map to primary, secondary, or tertiary MedDRA System Organ Class of "Respiratory, thoracic and mediastinal disorders."
[b]Subjects are counted once at each level of summarization.

2. Effectiveness Results

The analysis of effectiveness was based on the 190 evaluable patients at the 12-month time point. Key effectiveness outcomes are presented in ***Table 19*** and ***Table 20***.

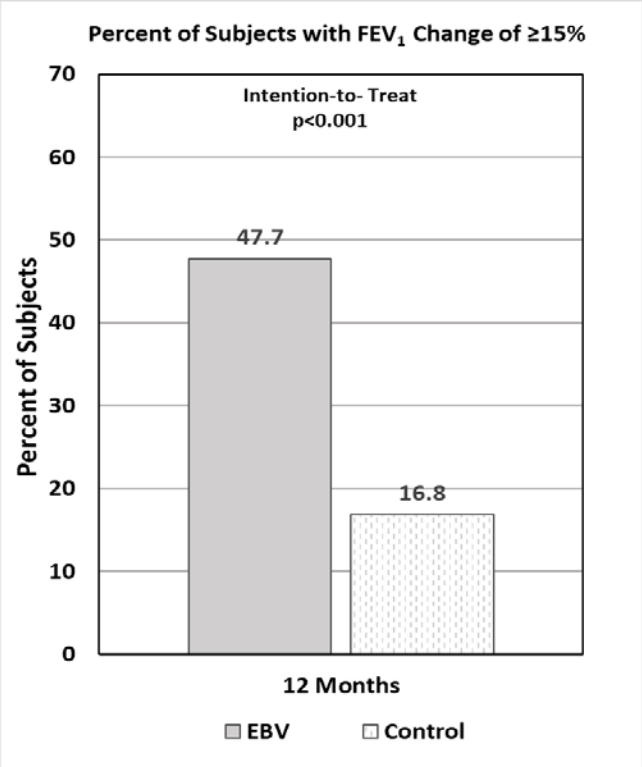
The LIBERATE study met the primary effectiveness endpoint. After 12 months of follow-up, the proportion of subjects with ≥15% improvement in post-bronchodilator FEV_1 was statistically significantly greater in the Zephyr EBV treatment group than in the Control group (47.7% vs. 16.8%, treatment difference = 31.0%, 95% CI = (18.0%, 43.9%), $p < 0.001$, see ***Table 19***, ***Figure 5***.

Table 19: Primary Analysis of the Primary Effectiveness Endpoint (Intent-to-Treat Population)

	Zephyr EBV (N=128)	Control (N=62)	Delta (95% CI)	Z-statistic	P-value
Percent of Subjects with ≥15% Improved Post-Bronchodilator FEV_1 at 1 Year	47.7%	16.8%	31.0% (18.0% to 43.9%)	4.130	<0.001

Note: To account for the interim analysis, Z>2.004 is the threshold for significance. Intermittent missing values imputed with linear interpolation. Truncated missing values imputed with multiple imputation (propensity score method). Death prior to 1-year endpoint imputed as failure. Values have been adjusted for multiple imputation. Averages across imputations are presented for Z and p-value.

Figure 5: Primary Effectiveness Endpoint (Percent of Subjects with FEV_1 Improvement of ≥15% at 12-months)



The three (3) secondary effectiveness endpoints were also met for the study since the mean change from baseline in FEV_1, 6MWD, and SGRQ score after 12 months of follow-up were all clinically meaningful and statistically significantly better in the Zephyr EBV treatment group than in the Control group (all $p < 0.005$ after Hochberg step-up procedure for multiplicity testing adjustment). Specifically, as ***Table 20*** and ***Figure 6*** show:

- the mean change from baseline to 12 months in post-bronchodilator FEV_1 was 0.104L ± 0.200 (mean ± SD) in the Zephyr EBV treatment group and -0.003L ± 0.194 in the Control group, with a treatment difference of 0.106 liters (95% CI = (0.047, 0.165));
- the mean change from baseline to 12 months in 6MWD was 12.98m ± 81.54 in the Zephyr EBV treatment group and -26.33m ± 81.50 in the Control group, with a treatment difference of 39.31 meters (95% CI = (14.64, 63.98)); and
- the mean change from baseline to 12 months in SGRQ score was -7.55 points ± 15.71 in the Zephyr EBV treatment group and -0.50 points ± 15.50 in the Control group, with a treatment difference of -7.05 points (95% CI = (-11.84, -2.27)).

Table 20: Primary Analysis Results for the Secondary Effectiveness Endpoints (ITT Population)

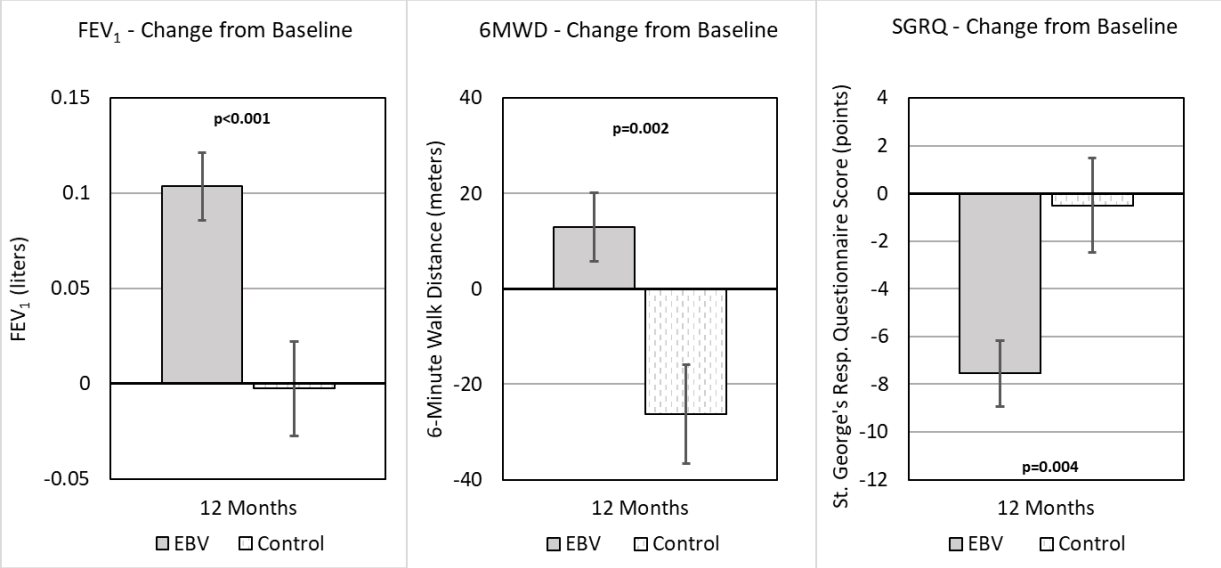
	EBV (N=128)	**Control (N=62)**	**Delta**	**Treatment P-Value[a]**
Post-Bronchodilator FEV_1 (L)				
1 Year – Absolute Change from Baseline				
LS Mean[a]	0.1035	-0.0026	0.1061	<0.001*
LS SD[a]	0.20029	0.19394		
95% Confidence Interval[a]	(0.0688, 0.1382)	(-0.0509, 0.0457)	(0.0471, 0.1651)	
Six Minute Walk Distance (m)				
1 Year – Absolute Change from Baseline				
LS Mean[a]	12.98	-26.33	39.31	0.002*
LS SD[a]	81.537	81.500		
95% Confidence Interval[a]	(-1.15, 27.11)	(-46.62, -6.04)	(14.64, 63.98)	
St. George's Respiratory Questionnaire (points)				
1 Year – Absolute Change from Baseline				
LS Mean[a]	-7.55	-0.50	-7.05	0.004*
LS SD[a]	15.708	15.504		

	EBV (N=128)	Control (N=62)	Delta	Treatment P-Value[a]
95% Confidence Interval[a]	(-10.28, -4.82)	(-4.39, 3.39)	(-11.84, -2.27)	

[a] P-values, least squares means, standard deviations and confidence intervals from an analysis of covariance (ANCOVA) with factor of treatment and the respective baseline value as a covariate. Values have been adjusted for multiple imputation.

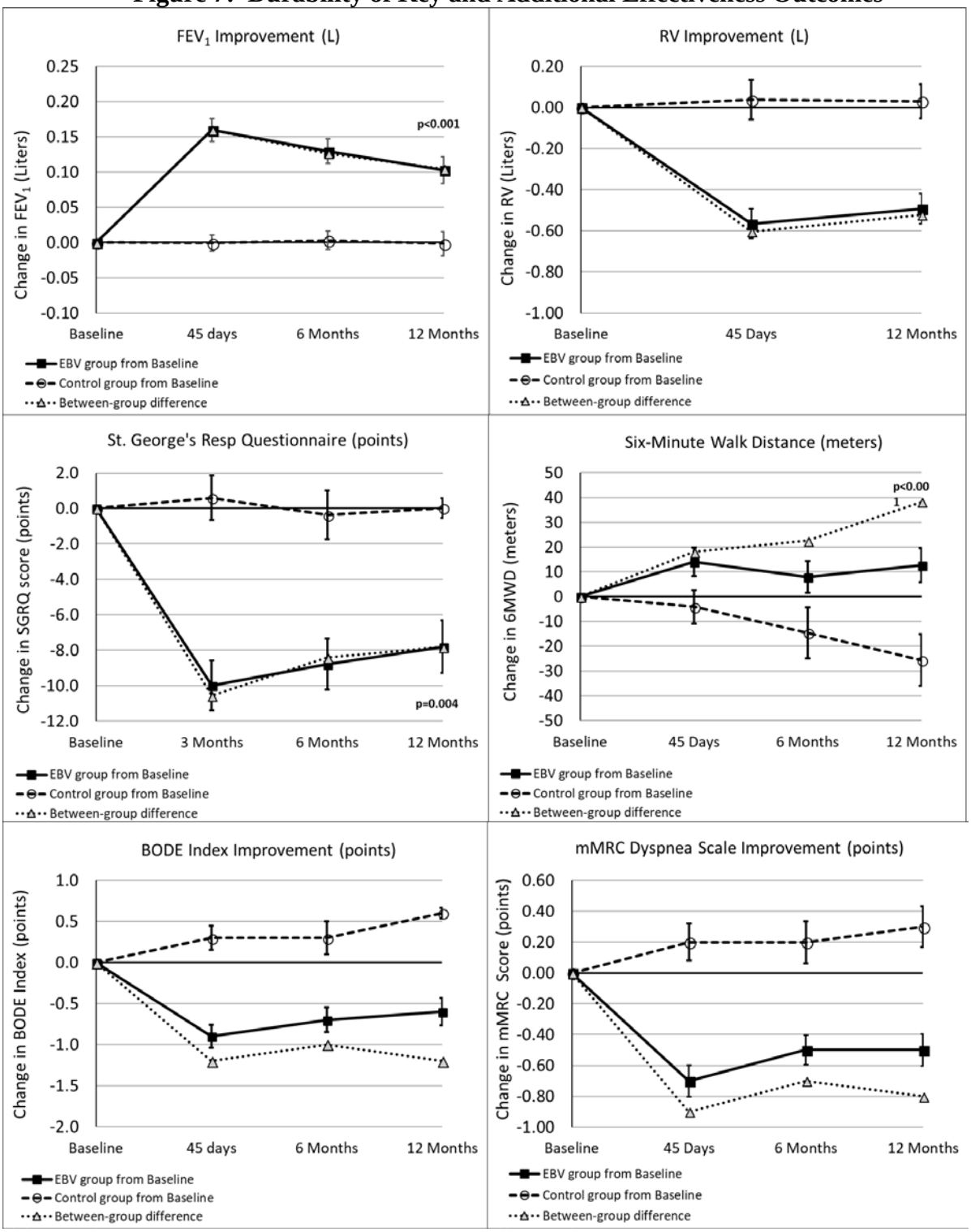
Note: To control the family-wise type I error rate at 5%, the Hochberg step-up procedure was utilized, and each p-value with an (*) is to be considered statistically significant.

Figure 6: Secondary Effectiveness Endpoints



The durability of key and additional effectiveness outcomes is shown graphically in ***Figure 7***.

Figure 7: Durability of Key and Additional Effectiveness Outcomes



RV: Residual Value.

Data from the LIBERATE study demonstrated that Pulmonx Zephyr® Endobronchial Valve System was effective in improving lung function, exercise capacity, and quality of

life at 1 year post-procedure in patients with severe heterogeneous emphysema who had little to no collateral ventilation as determined by Pulmonx Chartis System.

Protocol Deviations

There was a total of 560 protocol deviations during the conduct of the LIBERATE study with 129 Major deviations and 431 Minor deviations. All deviations are summarized in ***Table 21***. These deviations did not have a major impact on the tested endpoint and safety evaluations.

Table 21. Summary of Major and Minor Protocol Deviations

Deviation Type	Number of Deviations
MAJOR	129
Informed Consent not properly obtained	6
Subject did not meet Inclusion/Exclusion criteria	38
Safety calls or follow-up missed	48
Protocol required evaluation test not done	18
Treatment period chest x-ray	15
45 Day CT Scan	2
Screening ECG	1
Secondary Valve Procedure performed outside of protocol specified window	4
Other	15
Existing test results used for subject eligibility	8
Subject discharged 1 day early	1
Late reporting of serious adverse event	2
Protocol required visit performed remotely	4
MINOR	431
Follow-up visit missed	25
Follow-up visit outside protocol required window	92
Protocol required evaluation test not done	155
Test or procedure done outside of protocol required window	45
Other	114
Test or procedure performed by un-trained staff	1
Test or procedure not performed per protocol	11
Daily diary not completed or not downloaded per protocol	57
Past-procedure pulmonary rehab not completed per protocol	37
Pulmonary rehabilitation log missing	8
TOTAL DEVIATIONS	560

3. Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with outcomes: race, ethnicity, regional location, gender, and age. Treatment effects on proportion of subjects with ≥15% improvement in post-bronchodilator FEV_1 at 1 year between the Zephyr EBV treatment and Control groups were consistent across the

subgroups defined by race, ethnicity, study site, and geography (U.S. vs. non-U.S.), as no significant treatment-by-subgroup interactions were observed (all $p > 0.15$). While the treatment-by-age and treatment-by-gender interactions for the primary effectiveness outcome were found to be statistically significant (both $p < 0.15$), the interactions were quantitative, meaning that the treatment differences observed in the subgroups of age and gender were all in the same direction favoring the Zephyr EBV treatment.

4. 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 33 principal investigators of which none were full-time or part-time employees of the sponsor and one 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: 1
- 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

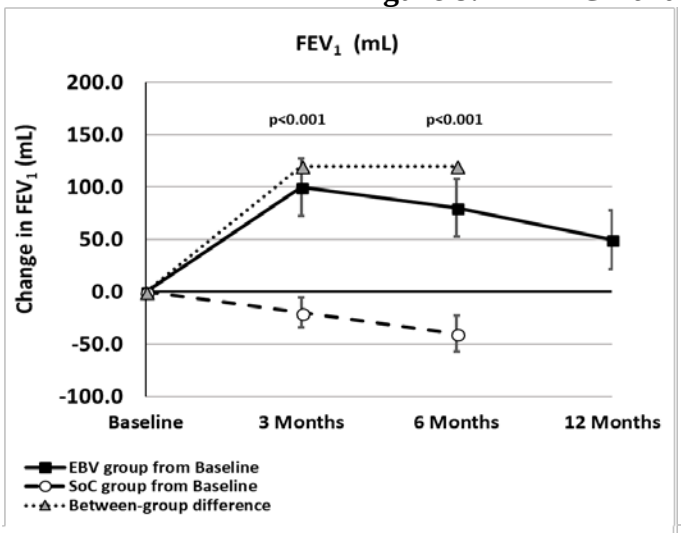
In addition to the results of the pivotal trial, the use of Zephyr Valves for the treatment of severe emphysema was also supported by the results from 12 months of follow-up in the IMPACT and TRANSFORM trials that were conducted solely in Europe.

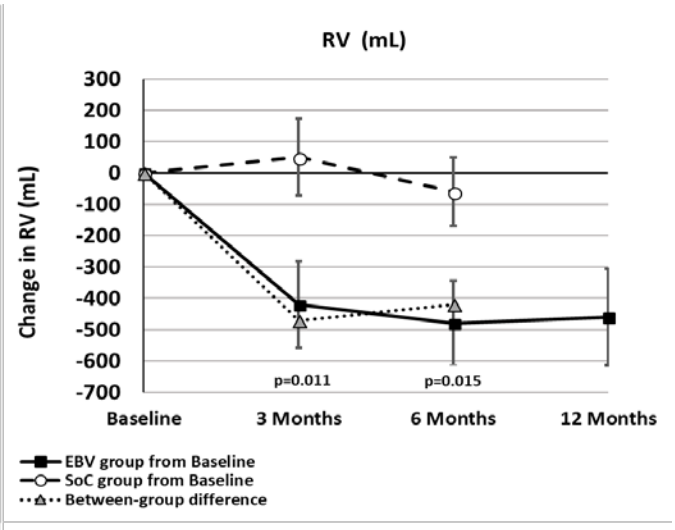
The IMPACT trial[2] used a 1:1 randomization scheme to assign 93 subjects with severe homogeneous emphysema to either a Zephyr EBV or a Control (Standard of Care) arm. The safety analysis showed a higher number of respiratory adverse events in the EBV group compared to the Control group during the short-term treatment period up to 30 days (65.1% subjects versus 8.0% subjects). The most common respiratory adverse events in the EBV vs. Control subjects during the Treatment Period were COPD

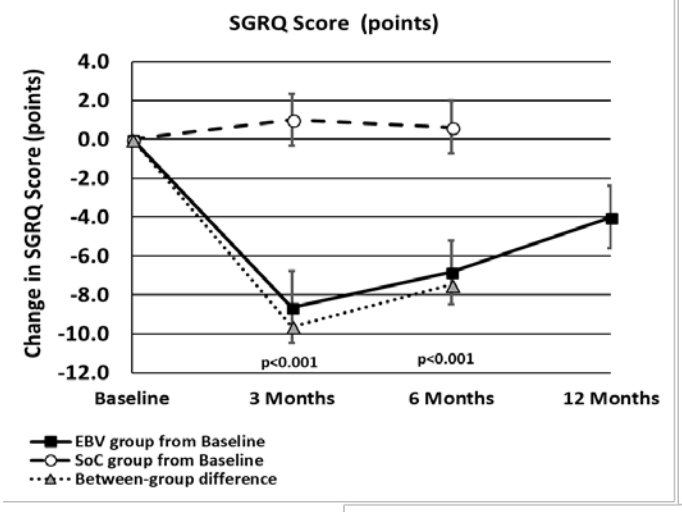
exacerbations in 27.9% vs. 4.0% subjects, respectively; pneumothorax in 23.3% vs. 0.0%, respectively; and cough in 9.3% vs. 0.0%, respectively. The primary effectiveness endpoint was percentage change from baseline in FEV_1 at 3 months. The mean percentage change from baseline in FEV_1 at 3 months was 13.7% in the Zephyr EBV group and -3.2% in the Control group, with a treatment difference of 17.0%. The trial had 12-month data on all EBV-treated subjects (***Figure 8***). Follow-up data at 12 months did not have a comparison to Control.

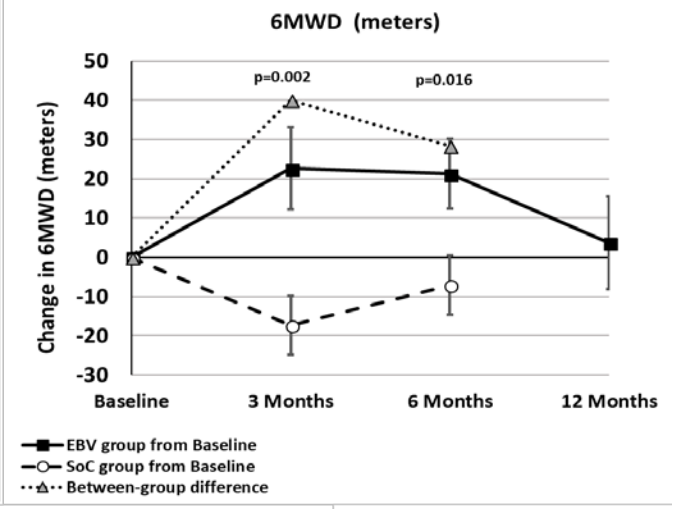
The TRANSFORM trial[3] used a 2:1 randomization scheme to assign 97 subjects with severe heterogeneous emphysema to either a Zephyr EBV or a Control (Standard of Care) arm. The safety analyses showed a higher number of respiratory adverse events in the EBV group compared to the Control group during the short-term treatment period up to 45 days (70.8 % subjects vs. 15.6% subjects). The most common respiratory adverse events in the EBV vs. Control subjects during the Treatment Period were pneumothorax in 27.7% vs. 0.0%, respectively, dyspnea in 20.0% vs. 0.0%, respectively, and COPD exacerbations in 15.4% vs. 9.4% subjects, respectively. The primary effectiveness endpoint was percentage of subjects achieving ≥12% improvement in FEV_1 at 3 months. The percentage of subjects with FEV_1 change ≥12% at 3 months was 55.4% in the Zephyr EBV group and 6.5% in the Control group, with a treatment difference of 48.9%. The trial had 12-month data for 48 out of 65 EBV-treated subjects (***Figure 9***). Follow-up data at 12 months did not have a comparison to Control.

Figure 8: IMPACT trial 12 Month Data









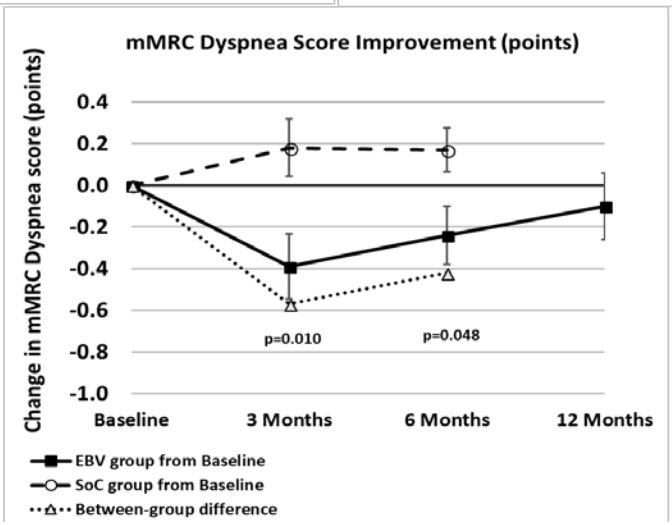
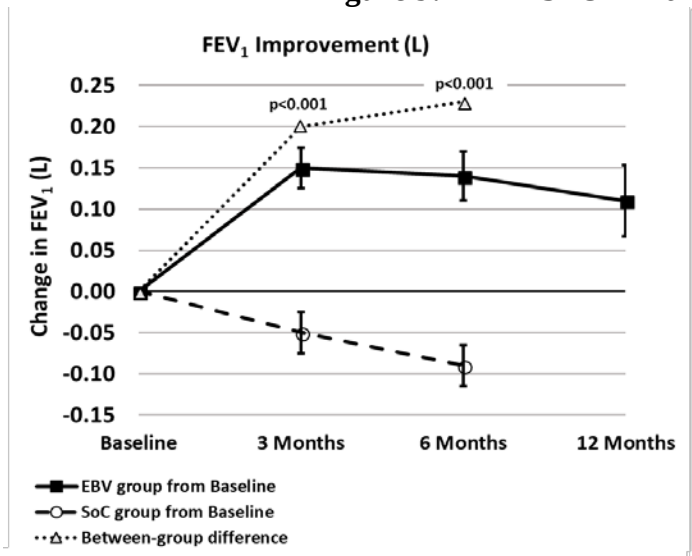
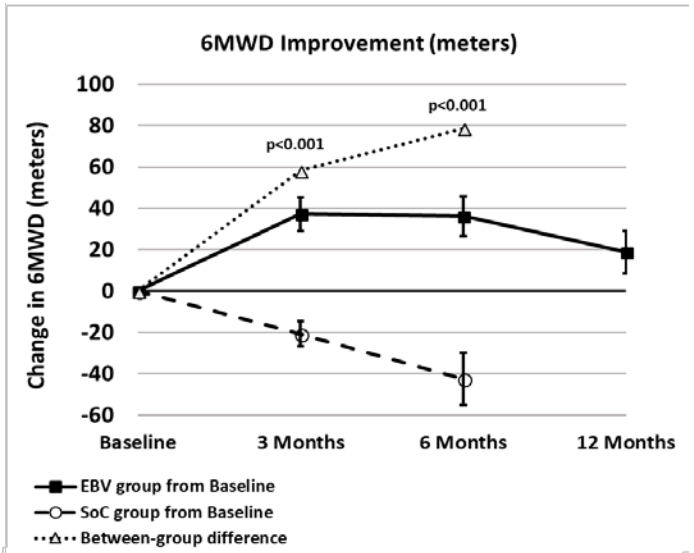
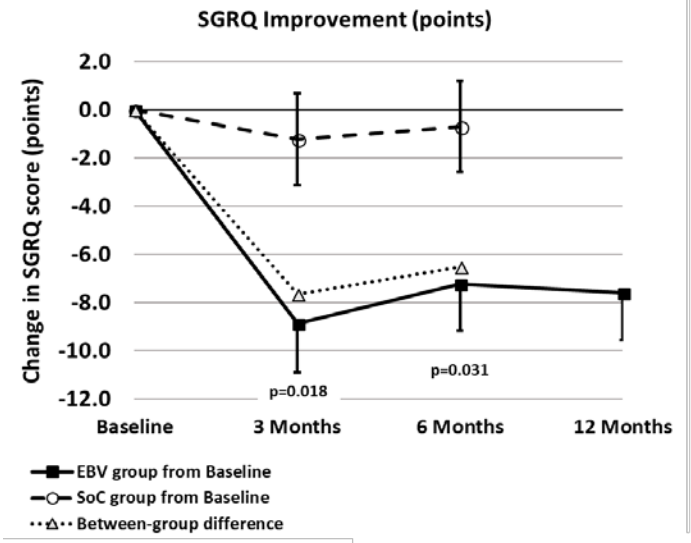
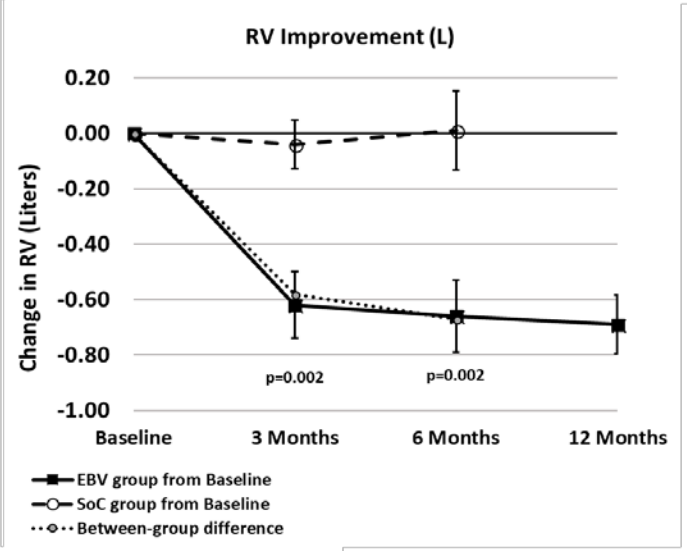


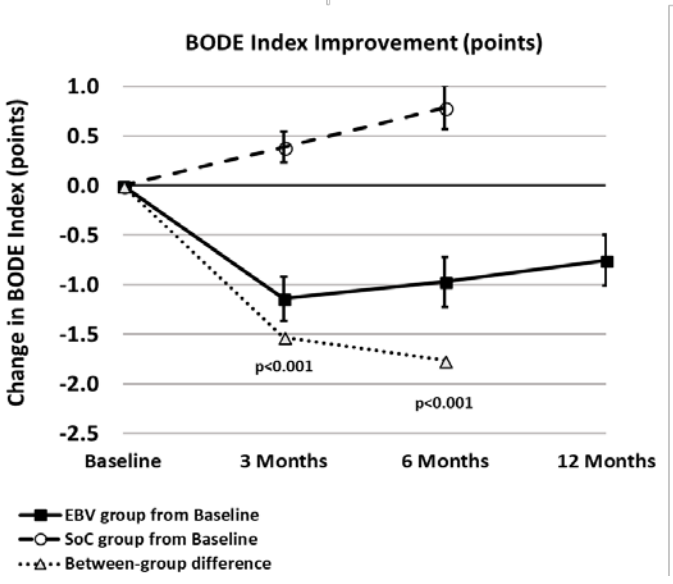
Figure 9: TRANSFORM trial 12 Month Data











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 there were no questions for which Panel input was required.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The LIBERATE trial compared Zephyr EBV with standard of care in subjects with severe heterogeneous emphysema out to 12 months. The study met its primary and secondary endpoints from a clinical and statistical standpoint. The endpoints were chosen based on endpoints that would have a meaningful impact on subjects with severe COPD. FEV_1 was used as a surrogate for lung function, 6MWD for exercise tolerance, and SGRQ for quality of life measures. Other non-hypothesis driven additional effectiveness measures related to a perception of dyspnea, hyperinflation, exercise tolerance, and health care utilization were also collected. Major findings from the clinical trial included:

- The Primary Effectiveness Endpoint evaluated the percentage of study subjects in the Zephyr EBV treatment arm who met the threshold of ≥15% improved forced expiratory volume in one second (FEV_1) as compared to the Control arm at 1 year. The percent of subjects that had a change of ≥15% was 47.7% in the treatment arm vs. 16.8% in the Controls (delta 31.0% with $p<0.001$).

- The Secondary Effectiveness Endpoint results were as follows:
    a. FEV_1: The difference in the FEV_1 absolute change between study arms from baseline and at 1 year was 0.106L, $p<0.001$.
    b. Six-Minute Walk Distance (6MWD): The difference between study arms in absolute change from baseline for 6MWD at 1 year was 39.31 meters, $p=0.002$.
    c. St. George's Respiratory Questionnaire: The difference between study arms in absolute change from baseline for SGRQ score at 1 year showed improvement with a difference of −7.05, $p=0.004$.

- The other effectiveness measures showed that at 12 months, there was improvement in lung functions and quality of life measures in favor of the Zephyr EBV group. The 12 month percent responders for the 6MWD ≥ 25m was 41.8% vs 19.6% in treatment vs. Control, respectively. For 6MWD ≥ 54m, the rates were 30.5% vs 11.5% in treatment vs. Control, respectively.

The pivotal study showed improved measures for lung function in FEV_1, exercise tolerance in the 6MWD, and quality of life parameters in the SGRQ in comparison to the Control group. The change in lung function met the MCID of 10% per Jones, et al,[4]

which has been associated with clinical anchoring to endpoints such as exacerbations, perception of dyspnea, and decline in lung function. The responder rate for the 6MWD ≥ 25m was almost double the Control arm. Additionally, the change in 6MWD at 12 months was similar to changes seen with LVRS and within ranges expected when evaluating response to treatment.[5]

B. Safety Conclusions

The risks of the device are based on data collected in the LIBERATE clinical study that was conducted to support PMA approval, as described above. The safety evaluation was based on a short term evaluation of events up to 45 days and a longer-term evaluation from day 46 - 1 year. For the short term, periprocedural period up to 45 days, the overall number of subjects reporting any adverse event was higher in the EBV group at 106 (82.8%) vs. 25 (40.3%) in the Control group. There were more respiratory related SAEs in the Zephyr EBV group with 35.2% vs. 4.8% in the Control group. The most common serious adverse event during the short term period was pneumothorax, which occurred in 34 (26.6%) of the EBV treated subjects. There were also four (4) early deaths with three (3) related to pneumothoraces. Other respiratory serious adverse events included increased COPD exacerbations 7.8% of EBV subjects (10 events) vs. 4.8% of Control subjects (3 events), respiratory failure 1.6% of EBV subjects (2 events), dyspnea 1.6% (4 events) of EBV subjects, pneumonia in 1 subject compared to control that had none of the other listed respiratory SAEs. The non-respiratory adverse events were observed at rates expected for subjects with COPD. For the longer-term safety evaluation, the frequency of respiratory SAEs were comparable, with 33.6% in the treatment arm and 30.6% in the Control arm. There were eight (8) subjects (6.6%) that had a pneumothorax after 45 days in the EBV arm, five (5) of which had undergone a second bronchoscopy for valve adjustment. The incidence rate of COPD exacerbations was higher in the Control group than in the EBV group. The Control group experienced 29 COPD in 19 subjects (30.6%), whereas the EBV group experienced 40 exacerbations in 28 subjects (23%).

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.[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.[8] 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 select group of patients, surgical options such as surgical lung volume reduction or lung transplantation may be

considered. The Zephyr® Endobronchial Valve System is an alternative technique to achieve bronchoscopic lung volume reduction using a minimally invasive approach. The study met its primary and secondary endpoints, clinically and statistically. There was a 31% difference in the number of subjects that had ≥ 15% improvement in FEV_1 in comparison to Controls at 12 months. The secondary endpoints all had clinically meaningful changes in comparison to Controls at 12 months with an FEV_1 of 0.106 L, p <0.001 (MCID 100 ml), 6MWD 39.31 meters, p=0.002 (MCID 25 meters) and SGRQ difference of - 7.05, p=0.004 (MCID -4). Other non-hypothesis driven additional effectiveness measures related to a perception of dyspnea, hyperinflation and exercise tolerance showed the 6MWD responder rate for ≥ 25 m to be more than double the Control, reduction in treated lobe volume reduction, RV, RV/TLC and DLCO. An OUS trial, IMPACT[1] studied 93 subjects with homogeneous emphysema in a multicenter randomized controlled trial and found that this subset of patients may also benefit from this treatment. The durability of effect beyond 12 months is not known.

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval, as described above. Safety results show that most of the immediate risks of this device are related to anesthesia, the bronchoscopic procedure and deployment. In the perioperative period, up to 45 days, the incidence of respiratory serious adverse events was higher in the treatment arm, with pneumothorax being the most common adverse events with an incidence of 26.6%. This adverse event is expected with this procedure in the COPD population; however, this is a serious event and patients will need close monitoring. There were four (4) in the first 12 months post-treatment as a result of complications of the procedure and device, with four (4) deaths related to pneumothorax. Several publications have suggested that pneumothorax is an indicator of greater clinical response and a predictor of success;[9,10,11] however, this is still a serious complication that can impact morbidity and mortality. Other risks include valve expectoration (1.6%) and risks related to repeat bronchoscopy to remove/replace valves (including risks of anesthetic complications).

Additional factors considered in determining probable risks and benefits for the Zephyr® Endobronchial Valve System included the lack of availability of non-surgical treatment options for patients that have maximized medical therapy and a comparison to surgical options such as lung volume reduction or lung transplant. The expected benefits with this type of device are improved patient outcomes, decreased anesthesia, decreased hospital stay, and decreased morbidity associated with surgical procedures. This is a less invasive procedure compared to surgical options. Lung volume reduction surgery, for instance, 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.

1. Patient Perspectives

   Patient perspectives considered during the review included: A patient preference information (PPI) study was conducted by Pulmonx to assess how willing patients with severe emphysema would be to accept the risks associated with a treatment profile similar to Zephyr Valves in return for the benefits when compared to another reference treatment profile. A discrete-choice experiment (DCE) survey was administered online to 294 patients enrolled in a COPD Foundation Patient-Powered Research Network. The attribute describing the improvement in ability to breathe and do day-to-day activities in the next year did not directly correspond to either one of the two (2) patient-reported outcomes (PROs): the mMRC and SGRQ. Therefore, the results of the patient preference study were not relevant to the benefit-risk assessment for this device.

In conclusion, given the available information above, the data support that for patients with hyperinflation with severe emphysema in regions of the lung that have little or no 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 LIBERATE study demonstrated clinically meaningful improvement in measures for lung function, exercise capacity, and quality of life parameters. Although the perioperative adverse events (up to 45 days) were higher in the treatment group, these risks were less than what would be expected with the surgical procedure of lung volume reduction, and adverse events observed in the treatment group from 45 days to 12 months were comparable in number and type to those observed in the Control group. 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 June 29, 2018. The final conditions of approval cited in the approval order are described below.

1. ODE Lead PMA Post-Approval Study - *LIBERATE Extension Study*: The Office of Device Evaluation (ODE) will have the lead for this clinical study, which was initiated prior to device approval. The LIBERATE Extension Study will be a prospective, single arm cohort study to evaluate long term safety and effectiveness in subjects treated with the Zephyr Valve. The LIBERATE study was a premarket study which was initiated prior to device approval. The study protocol included planned follow up of the initial EBV treated group and the crossover group out to 5 years. All adverse events will be

collected and analyzed in a descriptive manner and will be summarized by seriousness, severity, and relatedness. Forced Expiratory Volume in 1 second (FEV_1) will be collected annually as a measure of effectiveness. Evaluations will be done annually out to 5 years.

2. OSB Lead PMA Post-Approval Study - *ZEVR-Zephyr Valve Registry*: The Office of Surveillance and Biometrics (OSB) will have the lead for studies initiated after device approval. The ZEVR-Zephyr Valve Registry is a multi-center, single-arm, prospective post-approval registry study to provide ongoing safety and effectiveness assessment of the Zephyr Endobronchial Valve (EBV) treatment of patients with hyperinflation associated with severe emphysema, in regions of the lung that have little to no collateral ventilation. A total of 150 patients will be enrolled and followed through three years of follow-up, with interim visits at 45-days, 6, 12, 24 and 36 months post-procedure. This study will include up to 10 centers, a minimum of 5 centers.

   The primary safety endpoints are the 45-day pneumothorax rate and device/procedure related serious adverse events including but not limited to chronic obstructive pulmonary disease exacerbations, pneumonia, hemoptysis, expectoration, respiratory failure. Other effectiveness endpoints include: Treated Lobar Volume Reduction (TLVR) at 45 days, Forced Expiratory Volume in 1 second (FEV_1) at 6, 12, 24 and 36 months, 6-Minute Walk Distance (6MWD), St. George's Respiratory Questionnaire (SGRQ), and Body mass, Airflow Obstruction, Dyspnea and Exercise capacity index (BODE) at 6 and 12 months post-procedure.

   Descriptive statistics such as means, standard deviations, medians, and 95% confidence intervals will be reported for all continuous variables. Dichotomous variables will be reported as percentages and 95% confidence intervals and the numerator and denominator will be reported and defined.

   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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