2.0 SUMMARY OF SAFETY AND EFFECTIVENESS DATA

2.1 General Information

Device Generic Name:	Endobronchial Valve
Device Trade Name:	Emphasys® Zephyr® Endobronchial Valve System (Zephyr® EBV® System)
Applicant's Name and Address:	Emphasys Medical Inc. 700 Chesapeake Drive Redwood City, CA 94063
PMA Number:	P070025
Date of Panel Recommendation:	TBD
Date of Notice of Approval to the Applicant:	TBD

2.2 Indications for Use

The Emphasys® Zephyr® Endobronchial Valve System (Zephyr® EBV® System), which consists of the implantable Zephyr Endobronchial Valve (Zephyr EBV), the Zephyr Delivery Catheter (Zephyr EDC) and the Zephyr Loader System (Zephyr ELS), is intended to improve FEV_1 and 6 minute walk test distance in patients with severe, heterogeneous emphysema who have received optimal medical management.

2.3 Contraindications

The Zephyr EBV is contraindicated in the following patient types:

- Patients for whom bronchoscopic procedures are contraindicated.
- Patients with evidence of active infection in the lung lobe targeted for valve therapy.
- Patients with known allergies to Nitinol (nickel-titanium) or silicone.

2.4 Warnings and Precautions

The warnings and precautions can be found in the Zephyr Endobronchial Valve System labeling (Instructions for Use).

2.5 Device Description

The Emphasys Zephyr Endobronchial Valve System (Zephyr EBV System) consists of the Zephyr Endobronchial Valve (Zephyr EBV), the Zephyr Delivery Catheter (Zephyr EDC) and the Zephyr Loader System (Zephyr ELS). The key design characteristics of these elements are described in Table 1.

Table 1 The Zephyr Endobronchial Valve System Product Description

System Component	Detail
Zephyr Endobronchial Valve	
- Available Valve Diameters (size range)	4.0 (4.0 – 7.0mm); 5.5 (5.5-8.0mm)
- Valve material	Self-expanding nickel-titanium retainer covered in silicone
Zephyr Delivery Catheter	
- Length	76 cm
- Required bronchoscope working channel diameter	2.8 mm
Zephyr Loader System	
- How provided	Packaged together with valve as single use disposable

The Zephyr Endobronchial Valve (Zephyr EBV) is a one-way, silicone, duckbill valve mounted in a nickel-titanium (Nitinol), self-expanding retainer that is covered with a silicone membrane. It is intended to be implanted into bronchial lumens within the lungs of patients with advanced emphysema. Once implanted, the retainer anchors the Zephyr EBV in place in the bronchial lumen. The silicone membrane covering the retainer provides a peripheral seal between the device and the bronchial wall. The one-way valve blocks inhaled air flow into hyperinflated regions of the lung distal to the device while allowing trapped gas to vent from the hyperinflated regions.

The Zephyr EBV is implanted into a bronchial lumen using the Zephyr Delivery Catheter (Zephyr EDC). Immediately prior to implantation, the Zephyr EBV is compressed and loaded into the distal end of the Zephyr EDC with the Zephyr Loader System (Zephyr ELS). The Zephyr EDC containing the loaded Zephyr EBV is advanced to the targeted bronchus through the working channel of a bronchoscope. Once the physician visually determines that the Zephyr EDC is at the target location, the Zephyr EBV is deployed. This deployment releases the compressed Zephyr EBV which expands and grips the bronchial lumen wall. The Zephyr EBV can be removed bronchoscopically, if necessary, using standard flexible rats tooth grasping forceps.

2.6 Alternative Practices and Procedures

Emphysema, caused primarily by smoking, is characterized by the gradual, irreversible breakdown of tissue and loss of elastic recoil within the lungs, causing them to lose the ability to expel air and efficiently absorb oxygen. As this chronic condition inexorably progresses, the diseased, hyperinflated areas of the lung eventually fill the chest cavity, leaving less and less volume available for remaining viable lung tissue.

Lung volume reduction surgery (LVRS) has been shown to offer relief to patients suffering from emphysema. The objective of lung volume reduction surgery is to eliminate dysfunctional, over-inflated regions of lung by tissue removal. The National Emphysema Treatment Trial (NETT), which was jointly sponsored by the NIH and NHLBI, randomized 1,218 patients with advanced emphysema comparing LVRS to medical therapy. In NETT, patients with bilateral, predominantly upper-lobe disease and low exercise capacity showed improved 2-year survival after LVRS when compared to medical therapy. Results similar to surgical tissue removal have been obtained by plication (folding) and stapling without removal.

If LVRS is not a viable option, standard medical therapy includes continuous supplemental oxygen therapy and increasing regimens of medications including bronchodilators, steroids and mucolytics. Intensive pulmonary rehabilitation may also improve symptoms.

2.7 Marketing History

The Zephyr Endobronchial Valve System is commercially available in the following countries:

- Argentina
- Australia
- Austria
- Belgium
- Brazil
- Denmark
- France
- Germany
- Hong Kong
- Ireland
- Italy
- Malaysia
- Netherlands
- New Zealand
- Singapore
- Sweden
- United Kingdom

As of July 2008, approximately 1,500 Zephyr EBV Systems have been distributed commercially outside of the United States (OUS). No commercial products have been withdrawn from the market in any country for any reason.

2.8 Potential Adverse Effects of the Device on Health

Potential adverse events that may be associated with the Zephyr EBV System are listed in Table 2 below.

Table 2 Potential Adverse Events Associated with the Zephyr EBV System

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

2.9 Summary of Non-Clinical Laboratory Studies

A series of nonclinical laboratory studies was performed related to the Zephyr EBV and the Zephyr EDC.

2.9.1 Biocompatibility Testing

A series of GLP biocompatibility tests was conducted to demonstrate that the components of the Zephyr EBV System are non-toxic. Testing of the Zephyr EBV and Zephyr EDC was performed in accordance with the FDA-modified matrix described in, "Biological Evaluation of Medical Devices: Use of ISO-10993 (Memorandum G95-1)" and the "Guidance for the Content of Premarket Notifications for Esophageal and Tracheal Prostheses - April 28, 1998." Finished devices were used as samples for testing wherever possible. When coupons of nitinol and silicone were used, the test article was processed in the same manner as the finished device. Test samples were exposed to ethylene oxide sterilization prior to biocompatibility testing. The studies are summarized in Table 3 and Table 4.

Table 3 Zephyr EBV and Zephyr EDC Biocompatibility Testing Results

Description of Test	Test Article & Results
Cytotoxicity – ISO MEM Elution Method	Zephyr EBV and Zephyr EDC: Pass; Non-cytotoxic
ISO Intracutaneous Reactivity (rabbit)	Zephyr EBV and Zephyr EDC: Pass; Negligible irritation
Sensitization – ISO Guinea Pig Maximization Method	Zephyr EBV and Zephyr EDC: Pass; Non-sensitizing

Table 4 Zephyr EBV Biocompatibility Testing Results

Title	Test Article & Results
Twelve week Muscle Implantation with Histopathology (rabbit)	Nitinol/silicone coupon: Pass
Systemic (Subchronic) Toxicity in the Rat following Subcutaneous Implant	Zephyr EBV: Pass; Non-toxic
In-vitro Mouse Lymphoma Assay	Zephyr EBV: Pass; Non-mutagenic
Salmonella Typhimurium Reverse Mutation Assay: Ames Test	Zephyr EBV: Pass; Non-mutagenic
In-vitro Mammalian Chromosome Aberration Assay (Hamster ovary)	Zephyr EBV: Pass; Non-genotoxic

2.9.2 In-Vitro (Bench) Testing

A series of *in vitro* (bench) studies was conducted in accordance with the "Guidance for the Content of Premarket Notifications for Esophageal and Tracheal Prostheses - April 28, 1998" on the Zephyr EBV System.

A summary of the bench testing performed on the Zephyr EBV and Zephyr EDC is provided in Table 5, Table 6 and Table 7 below. The testing for the Zephyr EBV is divided into dimensional and functional testing and materials assessment. Bench studies were completed on both the 4.0 and 5.5 sizes of the Zephyr EBV, Zephyr ELS and Zephyr EDC.

Table 5 Zephyr EBV – Dimensional and Functional Testing

Test	Description of Test & Test Articles	Conclusion
Valve Flow vs. Pressure Test	Testing was conducted on both sizes of Zephyr EBV devices to determine the pressure necessary for a valve to vent at specific flow rates. All tested devices met specification.	Pass
Leak Test	Testing was conducted on both sizes of Zephyr EBV devices to determine the pressure required to generate a leak. All tested devices met specification.	Pass
Valve Response Time Test	Testing was conducted on both sizes of Zephyr EBV devices to determine the time elapsed for a valve to close and seal. All tested devices met specification.	Pass
Valve Inversion Test	Testing was conducted on both sizes of Zephyr EBV devices to determine the pressure required to invert the valve. All tested devices met specification.	Pass
Cough Migration Test	Testing was conducted on both sizes of Zephyr EBV devices to determine the distance a device migrates in the proximal direction under simulated conditions. No devices had measurable proximal migration.	Pass
Inspiratory Migration Test	Testing was conducted on both sizes of Zephyr EBV devices to determine the distance a device migrates in the distal direction under simulated conditions. No devices had measurable distal migration.	Pass
Valve Cracking Pressure Test	Testing was conducted on both sizes of Zephyr EBV devices to determine the pressure required to crack open the valve. All tested devices met specification.	Pass
Dimensional Verification	Testing was conducted on both sizes of Zephyr EBV device to verify that they meet dimensional specifications. All devices measured within specification.	Pass
Dimensional Verification After Compression	Testing was conducted on both sizes of Zephyr EBV devices to determine the diameter change after loading and deployment. All tested devices met specification.	Pass

Table 5 Zephyr EBV – Dimensional and Functional Testing

Test	Description of Test & Test Articles	Conclusion
Radial Expansion Test	Testing was conducted on both sizes of Zephyr EBV devices to determine the radial force exerted by the device during expansion. All tested devices met specification.	Pass
Retainer Cyclic Fatigue Test	An accelerated cyclic fatigue study was conducted on both sizes of Zephyr EBV devices at the diameter corresponding to maximum alternating strain. No strut fractures were observed and no significant silicone membrane deterioration was observed.	Pass
Finite Element Analysis	An analysis of the nitinol retainer for both sizes of the Zephyr EBV was conducted. Locations of maximum crimp strain were determined. Simulated fatigue conditions determined maximum alternating and mean strains in the retainer.	N/A
Valve Cyclic Fatigue Test	An accelerated cyclic fatigue study was conducted on the valve component for both sizes of the Zephyr EBV device. All tested devices met specification after cyclic fatigue.	Pass
Deployment Test	Testing was conducted on both sizes of Zephyr EBV devices to determine the force required to deploy the device from the housing of the Zephyr EDC. All tested devices met specification.	Pass
Removability Test	Testing was conducted on both sizes of the Zephyr EBV device to determine the ease of removal through an endotracheal tube. All tested devices were removed.	Pass
Retainer Strut Strength Test	Testing was conducted on both sizes of Zephyr EBV device to determine the tensile strength of the retainer struts. All tested devices met specification.	Pass
Loader Test	Testing was conducted on both sizes of the Zephyr Loader System to confirm functionality and determine the tensile strength of the monofilament bundle to puller bond. All tested devices successfully loaded EBV devices. All bond strengths met specification.	Pass

Table 6 Zephyr EBV - Material Assessment

Test	Description of Test & Test Articles	Conclusion
Corrosion Test	Testing was conducted on both sizes of Zephyr EBV devices to determine the breakdown potential of the retainer when subjected to ASTM F2129 cyclic polarization. All tested devices met specification.	Pass
Drug Compatibility Assessment	Testing was conducted on test plaques of silicone to evaluate the compatibility of the silicone of the valve with commonly used inhaled medications.	Potential drug interactions were determined to be negligible or none.
MRI Safety Report	Testing was conducted on the Zephyr 5.5 EBV to determine the presence of magnetic field interactions, heating and image artifact of the Zephyr EBV in association with the use of an MRI scanner.	The following statement has been added to the Instructions for Use: Non-clinical testing has demonstrated that the Zephyr EBV is MR Conditional immediately following implantation. The Zephyr EBV can be scanned safely under: • Static magnetic field of 3 Tesla or less • Spatial gradient field of 720 Gauss/cm or less • Specific Absorption Rate (SAR) for 15 minutes of scanning: - Whole body average of 3.0 W/kg - Spatial peak of 5.8 W/kg In non-clinical testing, the Zephyr EBV produced a temperature rise of less than or equal to 0.5°C at maximum MR system reported SAR of 3.0 W/kg for 15 minutes of MR scanning in a 3 Tesla MR scanner (Excite, Software G3.0-052B, General Electric Healthcare, Milwaukee, WI). This amount of heating is considered to be physiologically inconsequential and will not impose an additional risk or hazard to the patient undergoing an MRI procedure under these conditions. MR image quality may be compromised if the area of interest is in the exact same area or relatively close to the position of the device. Therefore, it may be necessary to optimize MR imaging parameters to compensate for the presence of this implant.

Table 7 Zephyr EDC – Dimensional and Functional Testing

Test	Description of Test & Test Articles	Conclusion
Tensile Strength Tests	Testing was conducted on both sizes of the delivery catheter to determine tensile strengths of catheter components (inner shaft, housing, outer shaft to handle and sheath). All tested devices met specification.	Pass
Torque Strength Tests	Testing was conducted on both sizes of the delivery catheter to determine torque strengths of catheter components (outer shaft and outer shaft to handle). All tested devices met specification.	Pass
Placement Test	Testing was conducted on both sizes of the delivery catheter to confirm the ability to accurately deploy a Zephyr EBV device. All tested devices met specification.	Pass
Heated Deployment Test	Testing was conducted on both sizes of the delivery catheter to confirm the ability to successfully deploy a Zephyr EBV device in worst-case simulated anatomy after repeated use. All tested devices met specification.	Pass
Diameter Gauge Endurance Test	Testing was conducted on both sizes of delivery catheter to confirm that the diameter gauge can maintain its accuracy and integrity after repeated insertion through a bronchoscope. All tested devices met specification.	Pass
Depth Gauge Dimensional Verification	Testing was conducted on both sizes of delivery catheter to verify that the depth gauge meets dimensional specifications. All devices measured within specification.	Pass
Deployment Force Test	Testing was conducted on both sizes of delivery catheter to determine the handle load and distal output load during deployment. All tested devices met specification.	Pass
Handle Safety Test	Testing was conducted on both sizes of the delivery catheter to determine the force required to defeat the safety lock on the handle. All tested devices met specification.	Pass

2.9.3 Animal Testing

A series of non-GLP animal studies was performed. These studies were performed in the bronchial anatomy of sheep. The studies were conducted to evaluate delivery, removability (both acute and chronic), migration resistance, valve inversion, atelectasis and pathology associated with Zephyr EBV device implantation. These studies support the safety, proof of concept, and overall product performance.

Different Zephyr EBV device iterations were used over the course of the animal studies. Iterations to retainer geometry, silicone membrane process parameters and valve molding parameters were assessed to arrive at the final design. An earlier "over-the-wire" system device design (EBV-OTW) was used as a control in many of the animal studies. A summary of the animal studies is provided in Table 8.

Table 8 Summary of Supportive Animal Studies

Study #	EBV Design	Animal Model	Follow-up Duration	Purpose
1	Zephyr EBV device iterations and EBV-OTW controls	Sheep	7 days	Evaluation of delivery and migration
2	Zephyr EBV device iterations and EBV-OTW controls	Sheep	7 days	Evaluation of delivery, migration and atelectasis
3	Zephyr EBV device iterations and EBV-OTW controls	Sheep	42 days	Evaluation of delivery, removability, migration, atelectasis and pathology
4	Zephyr EBV device iterations and EBV-OTW controls	Sheep	30 days	Evaluation of delivery, removability, migration, atelectasis and pathology
5	Zephyr EBV device iterations and EBV-OTW controls	Sheep	181-202 days	Evaluation of delivery, migration, atelectasis, pathology and bronchoscopic follow-up
6	Zephyr EBV device iterations and EBV-OTW controls	Sheep	7 days	Evaluation of delivery, migration and atelectasis.
7	Zephyr EBV device iterations and EBV-OTW controls	Sheep	36 days	Evaluation of delivery, removability, migration, atelectasis, pathology and bronchoscopic follow-up
8	Zephyr EBV device iterations and EBV-OTW controls	Sheep	8 days	Evaluation of delivery, removability, migration, atelectasis and bronchoscopic follow-up
9	Zephyr EBV device iterations	Sheep	28 days	Evaluation of delivery, migration, atelectasis and pathology.
10	Zephyr EBV device iterations and EBV-OTW controls	Sheep	30 days	Evaluation of delivery, removability, migration, atelectasis and pathology
11	Zephyr EBV device iterations and EBV-OTW controls	Sheep	10 days	Evaluation of delivery, migration, inversion and atelectasis.
12	Zephyr EBV device iterations	Sheep	29 days	Evaluation of removability, migration, atelectasis, pathology and bronchoscopic follow-up

Table 8 Summary of Supportive Animal Studies

Study #	EBV Design	Animal Model	Follow-up Duration	Purpose
13	Zephyr EBV device iterations	Sheep	7 days	Evaluation of removability, migration and atelectasis.
14	Zephyr EBV device iterations	Sheep	31 days	Evaluation of migration, atelectasis, pathology and bronchoscopic follow-up

2.9.4 Shelf Life

Testing to establish package integrity and functional testing of the Zephyr EBV System was conducted on accelerated-aged product. Appropriate bench tests were repeated on the aged product and compared to baseline to ensure that the Zephyr EBV System performed acceptably. The data generated support a shelf life of one year.

2.9.5 Sterilization

The Zephyr EBV system is sterilized using Ethylene Oxide (EtO) sterilization and has been validated per AAMI/ISO 11135:1994 "Medical Devices – Validation and Routine Control of Ethylene Oxide Sterilization." Results obtained from the sterilization studies show that the product satisfies a minimum sterility assurance level (SAL) of $10^{-6.}$ The amount of bacterial endotoxins was verified to be within specification limits.

2.10 Summary of Clinical Studies

Pilot clinical studies were performed with several device iterations. At the time the VENT Pivotal Trial began, 71 subjects with advanced emphysema at nine international sites had been followed post EBV placement. Thirty-eight (38) of these subjects had been treated with complete lobar exclusion. For this 38 subject subset, baseline mean FEV_1 was 31% of predicted, the 6MWT averaged 300 ± 128 meters, DL_{CO} averaged 42% of predicted and RV average 280% of predicted. After 90 days of follow-up, mean FEV_1 had improved from the baseline value by 15%, mean 6MWT by 20%, mean DL_{CO} by 14% and mean RV had decreased by 2%.

Adverse events in these subjects were consistent with the severity of their illness. There were two deaths during study follow-up. One subject died during the first month post procedure, when valve-related post-obstructive pneumonia did not resolve after EBV removal. One subject died at 161 days post-procedure due to pneumonia in an untreated lobe. In the first 90 days post-procedure, two (2) pneumothoraces required surgical intervention, two (2) pneumothoraces lasted longer than 7 days, and six (6) other pneumothoraces were reported, some requiring chest tubes. There were twelve reports of COPD exacerbation, four reports of valve removal and one pleural effusion.

Overall, the morbidity and mortality of the Zephyr EBV procedure compared favorably to a meta-analysis of LVRS data.[19] Early mortality (from 0 to 30 days) was 2.6% compared to LVRS (2.5 to 7.0%), prolonged air leak was 2.6% compared to LVRS (30 to 48%), surgical exploration was required in 5.3% compared to LVRS (2.5 to 10%), respiratory failure occurred in 0% compared to LVRS (2 to 13%) and pneumonia occurred in 2.6% compared to LVRS (9 to 22%). Overall, the per-patient rate of these serious complications was 13.2% compared to the mean estimate for LVRS of 73%.

These data suggested a favorable risk-benefit ratio for this novel minimally invasive palliation for severely emphysematous patients, and the VENT Pivotal Trial was designed and approved by the FDA.

The principal clinical evidence in support of safety and effectiveness of the Zephyr EBV System comes from the VENT (Endobronchial Valve for Emphysema PalliatioN Trial) Pivotal Trial. The VENT Pivotal Trial was a randomized, controlled, multicenter clinical trial designed to assess the safety and effectiveness of using the Zephyr EBV device in the palliation of patients with severe heterogeneous emphysema. Three hundred and twenty-one (321) patients were enrolled across 31 clinical sites in the United States. Prior to randomization, all patients received optimized medical management including pulmonary rehabilitation. Patients were then randomized to either ongoing medical management (Control group) or Zephyr EBV therapy (Treatment group). Patients were randomized in a 2:1 ratio (2 Treatment : 1 Control). Follow-up contacts were scheduled at 2-3, 7-10, 30, 90

180 and 365 days. The study's co-primary efficacy endpoints were mean percent change from baseline in FEV_1 and 6 minute walk test (6MWT) at six months. The primary safety endpoint was the proportion of patients in each group experiencing one or more events specified as components of the Major Complications Composite (MCC) through six months of follow-up. The MCC components consisted of:

- Death, all-cause
- Empyema
- Massive hemoptysis resulting in respiratory failure or blood loss > 300cc in ≤ 24hr
- Pneumonia distal to the implanted valves
- Pneumothorax or prolonged air leak > 7 days
- Respiratory failure on mechanical ventilation for > 24 hours

Following informed consent, the first phase of screening consisted of historical and physical examination. Subjects meeting these initial screens underwent spirometry, plethysmography, diffusing capacity, exercise tolerance, and a high resolution computed tomography (HRCT) scan of the chest following the Core Radiology Lab (CRL) protocol.

Screened subjects then underwent the Optimal Medical Management Program, consisting of smoking cessation support, treatment with bronchodilators, and influenza and pneumococcal vaccination. Screened subjects also had aggressive pulmonary rehabilitation, involving upper and lower limb endurance and strength training in clinic and at home, and when necessary, oxygen therapy to maintain saturation at rest and exercise of > 90%. After the completion of six to eight weeks of pulmonary rehabilitation, subjects were re-tested by spirometry, plethysmography, 6MWT, cycle ergometry, blood gases, and QoL instruments in order to screen for eligibility post pulmonary rehabilitation and to establish study baseline parameters.

Screened subjects who satisfactorily completed all these procedures and remained eligible for study participation were then randomized into two groups at a ratio of 2 to 1, with two subjects randomized to Zephyr EBV Treatment (Zephyr EBV Subjects) for each subject randomized to Control (Control Subjects), stratified by target lobe (upper versus lower) and exercise capacity (high versus low).

2.11 Inclusion / Exclusion Criteria

Candidates had to meet all of the following <u>inclusion criteria</u> to be eligible for enrollment in the study:

1. Subject diagnosed by HRCT Core Lab with eligible heterogeneous disease distribution (Section 6.7.5 of the protocol)

2. Age from 40 to 75 years
3. BMI < 31.1 kg / m^2 (men) or < 32.3 kg / m^2 (women)
4. FEV_1 < 45% of predicted value
5. Subject has provided written informed consent using a form that has been reviewed and approved by the IRB / EC
6. Stable with < 20 mg prednisone (or equivalent) daily
7. TLC > 100% predicted
8. RV > 150% predicted
9. $PaCO_2$ < 50 mm Hg (Denver < 55 mm Hg)
10. PaO_2 > 45 mm Hg (Denver > 30 mm Hg) on room air
11. Post rehabilitation 6MWT of > 140 meters
12. Plasma cotinine level < 13.7 ng / ml (or arterial carboxyhemoglobin < 2.5% if using nicotine products)
13. Nonsmoking for 4 months prior to initial interview and throughout screening
14. The subject agrees to all protocol required follow-up intervals
15. The subject has no child bearing potential OR a negative pregnancy test in a woman of childbearing potential
16. The subject is willing and able to complete protocol required baseline assessments and procedures

Candidates who met any of the following <u>exclusion criteria</u> were not eligible for enrollment in the study:

1. FEV_1 < 15% predicted value
2. DL_{CO} < 20% predicted value
3. Evidence of large bullae (encompassing > 30% of either lung) in a non-target lobe
4. An HRCT Density (Emphysema) Score of 4-4-4 in the right lung or 4-4 in the left lung
5. Unplanned weight loss of > 10% usual weight in 90 days prior to enrollment or total body weight < 70% of ideal body weight
6. Prior lung transplant, LVRS, median sternotomy, bullectomy or lobectomy
7. Alpha-1 antitrypsin deficiency
8. Pleural or interstitial disease that precludes surgery
9. Clinically significant bronchiectasis
10. Pulmonary nodule requiring surgery
11. History of recurrent respiratory infections (> 1 hospitalization in the last year)
12. Clinically significant (> 4 tablespoons per day) sputum production
13. Fever, elevated white cell count, or other evidence of active infection
14. Dysrhythmia that might pose a risk during exercise or training
15. Congestive heart failure within 6 months and LVEF < 45%
16. Clinical suspicion or proven history of pulmonary hypertension

17. Evidence or history of cor pulmonale
18. Resting bradycardia (< 50 beats / min), frequent multifocal PVCs, complex ventricular arrhythmia, sustained SVT
19. History of exercise-related syncope
20. MI within 6 mo and LVEF < 45%
21. Evidence of systemic disease or neoplasia expected to compromise survival during 5-yr period
22. Any disease or condition that interferes with completion of initial or follow-up assessments
23. Subject is currently enrolled in another clinical trial or has been previously enrolled in the VENT Pivotal Trial for which protocol required follow up is not complete
24. Subject is unable to complete 3 minutes of unloaded pedaling on cycle ergometer

2.12 Zephyr EBV Subjects: Valve Implantation Procedure

The implantation of the Zephyr EBV valve was performed in eligible Zephyr EBV Subjects, either under general anesthesia or using mild sedation with unassisted breathing. Antibiotic coverage was given before and after the procedure. The targeted lobe for Zephyr EBV Treatment was ascertained based on an HRCT targeting algorithm. Only one lobe was treated in each study subject. Zephyr EBV implantation was permitted at either the lobar, segmental or subsegmental level, with preference for the earliest generation airway, with an intent to achieve complete lobar exclusion. The success of lobar exclusion (deemed to be an "Acute Technical Success" in this study) was determined via bronchoscopy at the conclusion of the procedure.

Subjects were recovered from the anesthesia per hospital protocol and monitored by pulse oximetry during the first 24 hours post-procedure. Supplemental oxygen therapy was titrated to achieve 90% oxygen saturation prior to hospital discharge. Chest physiotherapy was used to clear mucus or air remaining behind the valve, as was coughing unless there was evidence of atelectasis. All subjects were given a standard course of prophylactic antibiotics and post-operative inhaled bronchodilators.

2.13 Imaging Procedures

High resolution computed tomography (HRCT) images were utilized for the following purposes in the conduct of the trial and subsequent assessment of the results:

1. Subject eligibility screening – Disease severity and distribution at baseline
2. Treatment targeting – Disease distribution at baseline
3. Assessment of baseline predictors of success – Inter-lobar collateral flow proxy (fissure integrity), disease severity, disease heterogeneity

4. Volume reduction assessment – Target lobe volume change from baseline to 180 day follow-up

The collection and analysis of high resolution computed tomography (HRCT) images were coordinated by an HRCT Core Lab.

2.14 Subject Accountability

All 321 study subjects were enrolled according to protocol-defined procedures. Primary outcomes were to be assessed at 6 months of follow-up, with an extended safety assessment at one year.

For 220 Zephyr EBV Subjects through six months of follow-up, 9 subjects withdrew informed consent and 6 died, leaving 205 subjects alive and evaluable at six months, of whom 193 (94.1%) had an evaluable visit for six months. By the time of the one year safety assessment, 12 Zephyr EBV Subjects withdrew informed consent and 8 had died, leaving 200 (92.0%) subjects alive and evaluable. By one year of follow-up, 16 of the eligible 200 subjects had not completed their final study visit, 14 of whom were considered as being lost to follow-up.

For 101 Control Subjects through six months of follow-up, 8 subjects withdrew informed consent and none had died, leaving 93 subjects alive and potentially evaluable at six months, of whom 79 (84.9%) had an evaluable visit. By the time of the one year safety assessment, 9 subjects withdrew informed consent and 3 had died, leaving 89 subjects alive and evaluable of whom 76 (85.4%) had an evaluable visit. By one year of follow-up, 13 of the 89 eligible subjects had not completed their final study visit, 12 of whom were considered as being lost to follow-up.

2.15 Demographic Data

The baseline demographic data for the two groups are shown below in Table 9. The mean age of the 220 Zephyr EBV Subjects was 65.3 years and the mean age was 64.9 years for the 101 Control Subjects ($p = 0.56$). Weight and height were comparable. Males predominated in the Zephyr EBV Subject group (60.4%) compared to the Control Subject group (48.5%), the difference was nearly significant ($p = 0.052$).

Table 9 Subject Demographics

Characteristic	Zephyr EBV	Control	p value
Continuous Measures	**Mean (SD) N Median (Min, Max)**	**Mean (SD) N Median (Min, Max)**	
Age (years)	65.3 (6.8) 220 66.0 (47.0, 77.0)	64.9 (5.8) 101 65.0 (48.0, 76.0)	0.562
Weight (kg)	73.1 (14.5) 219 73.3 (33.6, 106.1)	71.7 (13.4) 101 69.5 (44.0, 102.1)	0.160
Height (meters)	1.70 (0.09) 220 1.71 (1.50, 1.88)	1.68 (0.10) 101 1.68 (1.52, 1.91)	0.125
BMI (kg/m^2)	25.1 (4.0) 220 25.4 (14.9, 33.0)	24.8 (3.4) 101 24.8 (17.2, 32.1)	0.506
Systolic BP (mm Hg)	129.1 (16.7) 218 129.0 (91.0, 188.0)	129.9 (16.4) 98 130.0 (96.0, 171.0)	0.674
Diastolic BP (mm Hg)	73.8 (9.4) 218 73.0 (40.0, 100.0)	74.6 (10.0) 98 75.0 (50.0, 99.0)	0.494
Categorical Measures	**% (n / N)**	**% (n / N)**	**p value**
Gender (Male)	60.4% (133 / 220)	48.5% (49 / 101)	0.052
Race			1.000
Caucasian	96.8% (213 / 220)	98.0% (99 / 101)	
African American	2.3% (5 / 220)	2.0% (2 / 101)	
Hispanic	0.5% (1 / 220)	0.0% (0 / 101)	
Asian	0.5% (1 / 220)	0.0% (0 / 101)	
Other	0.0% (0 / 220)	0.0% (0 / 101)	

There were no significant differences in any baseline lung function parameters between the Control Subjects and the Zephyr EBV Subjects. Based on the lung function parameters, all subjects were either GOLD Class III (Severe) or Class IV (Very Severe) stage of COPD.

2.16 Procedural Outcomes

2.16.1 Number of Zephyr EBVs Placed Per Subject

Eight hundred twenty (820) valves were placed in Zephyr EBV Subjects. The mean number of valves placed per Zephyr EBV subject was 3.8 (median 4.0, range 1 to 9).

2.16.2 Acute Technical Success

Acute Technical Success was defined as complete exclusion of the target lobe as determined by the investigator's assessment at the end of the bronchoscopic procedure. Acute Technical Success was observed in 94.9% of Zephyr EBV subjects. Eleven (11) Zephyr EBV Subjects did not experience Acute Technical Success based on an inability to obtain complete lobar exclusion of the target lobe. The reasons for the lack of technical success were: unable to place valve (1.9%), segment too small

for valve (1.4%), side branch airway too small (0.5%), unable to valve apical segment, (0.9%), and other (0.5%).

2.16.3 Valves Removed and Replaced During the Initial Procedure

Of the 963 Zephyr EBV valves deployed during the initial procedure, 143 (14.8%) were removed (in 96 Zephyr EBV Subjects) during the initial implantation procedure. In 89 of these 96 subjects (92.7%), the valves removed during the procedure were successfully replaced during that same procedure with one or more new valves, which led to their categorization as an Acute Technical Success.

Of the 963 valves deployed during the initial procedure, 70 (7.3%) were placed too proximally, 28 (2.9%) were placed too distally, and 5 (0.5%) were too small for the selected airway. Other reasons, 40 (4.2%), for valves removed during the initial procedure included: valve was dislodged while removing other valves, valves placed in wrong airway, first valve placed interfering with placement of other valves, valve was too large for the selected airway, incomplete exclusion, valve appeared non-functional, valve did not deploy properly, valve loaded and deployed backwards, and duckbill appeared inverted.

2.17 Effectiveness Results of the VENT Trial

The co-primary efficacy endpoints of the VENT study were FEV_1 and 6MWT using intent-to-treat analysis with multiple imputation. To meet these endpoints, the study had to show that at six months follow-up, the mean percent change from baseline was statistically higher in the treatment group for both variables.

Results for patients with imputed data showed the difference between treatment and control group to be 6.8% for FEV_1 and 5.8% for 6MWT. Both findings were highly statistically significant. Differences in the four secondary endpoints also reached statistical significance (Table 10).

Table 10 Primary and Secondary Efficacy Endpoint Results by Intent-to-Treat Analysis

	Mean Change from Baseline at 6 Months	
Primary Endpoints	**Delta (95% CI)**	**p value**
FEV_1 (% change)	6.8 (2.1, 11.5)	**0.002**
6MWT (% change)	5.8 (0.5, 11.2)	**0.019**
Secondary Endpoints		
SGRQ	-3.4 (-6.6, -0.3)	**0.017**
mMRC	-0.26 (-0.49, -0.02)	**0.018**
Cycle Ergometry Peak Workload (watts)	3.8 (0.2, 7.4)	**0.020**
Supplemental Oxygen Use (liters / day)	-12.0 (-76.7, 52.7)	**0.020**

Results for patients with available data showed the difference between treatment and control group means to be 7.2% for FEV_1 and 5.8% for 6MWT (see Table 11). Both findings were highly statistically significant. Differences in three of the four secondary endpoints reached statistical significance. There was also a significant improvement in the BODE Index. The BODE is a composite index that incorporates changes in both of the VENT trial's co-primary endpoints (6MWT and FEV_1) as well as one of the VENT trial's secondary endpoints (mMRC). The remaining element of the BODE index is the change in body mass index (BMI).

Table 11 Efficacy Endpoint Results (Completed Cases)

	Mean Change from Baseline at 6 Months				
Primary Endpoints	**Zephyr EBV Mean ± SD (n)**	**Control Mean ± SD (n)**	**Delta**	**(95% CI)**	**p value**
FEV_1 (% change)	5.3 ± 19.6 (179)	-1.9 ± 12.2 (75)	7.2	(3.2, 11.2)	**<0.001**
6MWT (% change)	4.3 ± 22.7 (178)	-1.5 ± 22.5 (73)	5.8	(1.3, 11.7)	**0.008**
Secondary Endpoints					
SGRQ	-2.7 ± 13.3 (158)	0.7 ± 9.7 (62)	-3.4	(-6.6, -0.2)	**0.019**
mMRC	-0.1 ± 1.0 (162)	0.2 ± 0.8 (67)	-0.3	(-0.6, -0.1)	**0.011**
Cycle Ergometry Peak Workload (watts)	0.1 ± 15.3 (166)	-4.4 ± 12.8 (69)	5.0*	(0.0, 5.0)*	**0.004**
Supplemental Oxygen Use (liters/day)	-17.1 ± 912.8 (171)	82.9 ± 744.0 (75)	-100.1	(-318.6, 118.4)	0.184

*Delta and 95% CI calculated using the median due to non-parametric distribution

2.17.1 Target Lobe Volume Changes at 6 Months

Lung lobe volumes were measured at follow-up and compared to baseline values. Treatment with Zephyr Endobronchial Valves resulted in a statistically significant reduction in target lobe volume at six months (see Table 12). Zephyr EBV treatment also resulted in a statistically significant increase in the volume of non-targeted lobes indicating a redistribution of airflow within the lung at six months.

Table 12 Lung Volume Redistribution at 6 Months Following EBV Therapy

Target Lobe Volume Change (ml)			Non-Target Lobe Volume Change* (ml)		
Zephyr EBV Mean ± SD (n)	**Control Mean ± SD (n)**	**p value**	**Zephyr EBV Mean ± SD (n)**	**Control Mean ± SD (n)**	**p value**
-378.4 ± 530.1 (189)	-16.3 ± 134.7 (79)	**<0.001**	207.7 ± 340.2 (189)	-35.4 ± 169.8 (79)	**<0.001**

* Total volume change for all non-treated lobes in the treated lung

2.17.2 High Heterogeneity Patient Cohort

Baseline HRCT images were analyzed quantitatively using automated software which used edge detection algorithms and other processing techniques to automatically define that portion of the HRCT corresponding to lung tissue. The software calculated the proportion of image voxels that fell below a pre-defined Hounsfield unit threshold

(i.e. a certain grey-scale level) which correlates to the degree of emphysematous lung destruction. This was done on a lobar basis. Lobar Density Score was the average density of the lobe. The right middle lobe was considered a separate lobe, while the lingula was considered to be part of the left upper lobe. Follow-up scans were analyzed in an identical manner.

The percentage of each lung lobe volume below the pre-defined Hounsfield threshold was then reported as the Density Score in per cent for that lobe. For example, a Density Score of 75% meant that 75% of the volume in that lobe met the Hounsfield threshold and was considered destroyed by emphysema. These metrics were calculated for each lobe separately.

The difference between the Density Scores of the target lobe and the ipsilateral non-target lobe (in per cent) was the Heterogeneity Score for that subject. It was hypothesized that degree of heterogeneity could be an important predictor of improvement. Heterogeneity Score was included as a baseline variable in all of the multivariate analyses.

Multivariate, mixed-model analyses were used to test the relation between pre-specified covariates and changes in the co-primary endpoints. Heterogeneity remained in the mixed model analyses as a predictor of outcome for both co-primary endpoints. Based on these findings, the median heterogeneity score (15%) was used to divide the study population into a high heterogeneity (≥15%) and a low heterogeneity (<15%) group for further analysis.

2.17.2.1 Efficacy Outcome Measures at 6 and 12 Months

Efficacy results for the high heterogeneity group are given in Table 13. In this completed cases cohort, Zephyr Endobronchial Valve therapy resulted in statistically significant improvements in FEV_1 and 6MWT at 6 and 12 months when compared to optimized medical management alone.

Table 13 Efficacy Measures - High Heterogeneity Group

METRIC	MEAN CHANGE FROM BASELINE					
	Zephyr EBV Mean ± SD	(n)	Control Mean ± SD	(n)	Delta (95% CI)	p value
6 MONTH						
FEV_1 (ml)	83.2 ± 184.3	(91)	-28.0 ± 83.9	(40)	111.2 (64.9, 157.5)	**<0.001**
6MWT (meters)	19.2 ± 71.8	(90)	-25.2 ± 78.4	(38)	50.4* (20.2, 66.0)*	**<0.001**
FEV_1 %	10.1 ± 22.3	(91)	-2.2 ± 11.3	(40)	12.3 (6.5, 18.1)	**<0.001**
6MWT %	7.3 ± 26.6	(90)	-5.9 ± 21.9	(38)	14.4* (6.3, 21.0)*	**<0.001**
12 MONTH						
FEV_1 (ml)	110.8 ± 204.2	(87)	-21.5 ± 88.0	(41)	132.3 (81.1, 183.4)	**<0.001**
6MWT (meters)	5.1 ± 83.1	(88)	-24.7 ± 78.8	(41)	26.6* (4.0, 51.0)*	**0.013**
FEV_1 %	13.6 ± 24.2	(87)	-1.6 ± 10.4	(41)	15.2 (9.1, 21.2)	**<0.001**
6MWT %	3.1 ± 29.2	(88)	-5.0 ± 19.2	(41)	8.2 (-0.4, 16.7)	**0.031**

*Delta and CI calculated using the median due to non-parametric distribution

2.17.2.2 Responder Analysis

Responder analyses were performed on several effectiveness outcome measures to further explore the clinical importance of the observed changes. These further analyses were only performed on those outcome measures that had been found to be statistically significant on pre-specified hypothesis testing of the continuous variable. Responder analyses of secondary effectiveness endpoints, SGRQ, mMRC and cycle ergometry, were not pre-specified but were based on published minimal clinically important differences

The proportion of Completed-Cases Zephyr EBV Subjects with ≥ 15% improvement in FEV_1 from baseline to six months was 23.5% compared with 10.7% of Control Subjects. Zephyr EBV Subjects were 2.2 times more likely than Control Subjects to improve their FEV_1 by ≥ 15% through six months of follow-up (see Table 14).

In the High Heterogeneity Subgroup, the proportion of Completed-Cases Zephyr EBV Subjects with ≥ 15% improvement in FEV_1 from baseline to six months was 35.2% compared with 12.5% of Control Subjects. Zephyr EBV Subjects in the High Heterogeneity Subgroup were 2.8 times more likely than Control Subjects to improve their FEV_1 by ≥ 15% through six months of follow-up (see Table 14).

Table 14 Responder Analysis - Subjects with FEV1 Improvement ≥ 15% at 6 Months (CC)

Increase ≥ 15% in FEV_1	Zephyr EBV % (n / N)	Control % (n / N)	Relative Rate (95% CI)	p value
CC Subjects	23.5 (42 / 179)	10.7 (8 / 75)	2.2 (1.1, 4.5)	**0.013**
High Heterogeneity Subjects	35.2 (32 / 91)	12.5 (5 / 40)	2.8 (1.2, 6.7)	**0.006**

The proportion of Completed-Cases Zephyr EBV Subjects with ≥ 15% improvement in 6MWT from baseline to six months was 25.3% compared with 17.8% of Control Subjects. Zephyr EBV Subjects were 1.4 times more likely than Control Subjects to improve their 6MWT by ≥ 15% through six months of follow-up (see Table 15).

In the High Heterogeneity Subgroup, the proportion of Completed-Cases Zephyr EBV Subjects with ≥ 15% improvement in 6MWT from baseline to six months was 31.1% compared with 13.2% of Control Subjects. Zephyr EBV Subjects in the High Heterogeneity Subgroup were 2.4 times more likely than Control Subjects to improve their 6MWT by ≥ 15% through six months of follow-up (see Table 15).

Table 15 Responder Analysis - Subjects with Major Improvement (≥ 15%) in 6MWT at 6 Months (CC)

Increase ≥ 15% in 6MWT	Zephyr EBV % (n / N)	Control % (n / N)	Relative Rate (95% CI)	p value
CC Subjects	25.3 (45 / 178)	17.8 (13 / 73)	1.4 (0.8, 2.5)	0.133
High Heterogeneity Subjects	31.1 (28 / 90)	13.2 (5 / 38)	2.4 (1.0, 5.7)	0.025

2.17.3 Intact Fissure Patient Cohort

During the VENT trial, an imaging core lab assessed the integrity of each fissure at baseline. Each fissure was given a binary score of complete or incomplete. For data analysis, patients were considered to have complete fissures if all fissures bordering the target lobe were graded complete. Multivariate analysis identified fissure integrity as an additional predictor of FEV_1 improvement at follow-up.

2.17.3.1 Target Lobe Volume Changes at 6 Months

Target lobe volume reduction following valve implantation was greatest in the intact fissure patient cohort. Volume changes in non-target lobes were also highest in this group. See Table 16.

Table 16 Lung Volume Redistribution at 6 Months – Intact Fissure Group

Target Lobe Volume Change (ml)			Non- Target Lobe Volume Change* (ml)		
Zephyr EBV Mean ± SD (n)	**Control Mean ± SD (n)**	**p value**	**Zephyr EBV Mean ± SD (n)**	**Control Mean ± SD (n)**	**p value**
-712.5 ± 668.0 (68)	2.2 ± 111.5 (34)	**<0.001**	400.5 ± 427.3 (68)	-14.7 ± 123.7 (34)	**<0.001**

* Total volume change for all non-treated lobes in the treated lung

2.17.3.2 Impact of Fissure Integrity on FEV_1

The impact of fissure integrity on FEV_1 is given in Table 17 and Table 18. Endobronchial valve treatment in this group resulted in even greater improvements in FEV_1 at 6 and 12 months that were highly statistically significant.

Table 17 Efficacy Measures – Intact Fissure Group

METRIC	MEAN CHANGE FROM BASELINE					
	Zephyr EBV Mean ± SD	**(n)**	**Control Mean ± SD**	**(n)**	**Delta (CI)**	**p value**
6 MONTH						
FEV_1 (ml)	101.6 ± 183.5	(68)	-34.6 ± 84.5	(33)	136.2 (83.2, 189.1)	**<0.001**
FEV_1 %	13.5 ± 22.9	(68)	-2.7 ± 10.2	(33)	16.2 (9.7, 22.8)	**<0.001**
12 MONTH						
FEV_1 (ml)	132.8 ± 191.8	(68)	-16.6 ± 87.5	(32)	149.4 (93.9, 204.8)	**<0.001**
FEV_1 %	17.2 ± 23.8	(68)	-1.7 ± 9.6	(32)	18.9 (12.3, 25.6)	**<0.001**

Table 18 Responder Analysis - Intact Fissure Group

METRIC	PROPORTION OF PATIENTS MEETING THRESHOLD			
	Zephyr EBV % (n)	Control % (n)	Relative Rate (95% CI)	p value
6 MONTH				
$FEV_1 \Delta \geq 0\%$	72.1 (68)	42.4 (33)	1.7 (1.1, 2.6)	**0.004**
$FEV_1 \Delta \geq 15\%$	42.7 (68)	6.1 (33)	7.0 (1.8, 27.7)	**<0.001**
12 MONTH				
$FEV_1 \Delta \geq 0\%$	76.5 (68)	40.6 (32)	1.9 (1.2, 2.9)	**0.001**
$FEV_1 \Delta \geq 15\%$	45.6 (68)	6.3 (32)	7.3 (1.9, 28.6)	**<0.001**

2.18 Safety Results for the VENT Trial

The Zephyr EBV System was evaluated in a multi-center, randomized controlled trial of three hundred and twenty-one (321) patients enrolled across 31 clinical sites in the United States. This trial, called the VENT (Endobronchial Valve for Emphysema PalliatioN Trial) Pivotal Trial randomized patients to either ongoing medical management (Control group) or Zephyr EBV therapy (Treatment group). Patients were randomized in a 2:1 ratio (2 Treatment : 1 Control). Safety data analysis in the VENT study was based on the modified intention to treat patient cohort (i.e. randomized patients who received study-directed treatment and had any follow-up). The per-patient rates of study defined Major Complications and other adverse events observed in the VENT study are summarized in the following tables. The proportion of patients experiencing a Major Complication Composite event at six months or one year following Zephyr EBV therapy was not statistically significantly different than the rates observed in control patients (see Table 19).

Table 19 Per-Patient Major Complications Composite

	Primary Safety Endpoint 6 months			Additional Safety Analysis 12 months (cumulative)		
	EBV N = 214	Control N = 87	p value	EBV N = 214	Control N = 87	p value
Major Complication Composite (MCC)	6.1%	1.2%	0.075	10.3%	4.6%	0.172
Death	2.8%	0.0%	0.187	3.7%	3.5%	1.000
Respiratory Failure with ≥ 24 hours ventilation	1.9%	1.2%	1.000	2.8%	2.3%	1.000
Massive Hemoptysis	0.5%	0.0%	1.000	0.5%	0.0%	1.000
Pneumothorax / air leak lasting > 7 days	1.4%	1.2%	1.000	1.9%	1.2%	1.000
Empyema	0.0%	0.0%	----	0.0%	0.0%	----
Pneumonia distal to implanted valve	1.4%	NA	----	4.2%	NA	----

The primary safety endpoint was evaluated at six months. Follow-up for the subjects continued through one year. Adverse Events observed through one year are shown in Table 20.

Table 20 Per-Patient Adverse Events through 1 Year – All Patients

Event	Zephyr EBV N = 214	Control N = 87	p value
All Cause Mortality [1]	3.7%	3.5%	1.000
All Cardiovascular	7.9%	6.9%	1.000
COPD/Emphysema Related			
Exacerbation w/o hospitalization	57.5%	50.6%	0.307
Exacerbation with hospitalization	18.2%	10.3%	0.117
Pneumonia not distal to valve	11.2%	10.3%	1.000
Other pulmonary infection	8.4%	1.2%	**0.017**
Any respiratory failure	3.3%	3.5%	1.000
w/ ≥ 24 hours ventilation [1]	2.8%	2.3%	1.000
Increased shortness of breath	9.8%	2.3%	**0.030**
Hypoxemia	7.0%	0.0%	**0.007**
New/worse hypercapnea	2.3%	1.2%	0.677
Cough	6.1%	1.2%	0.075
Bronchospasm	1.9%	0.0%	0.328
Other Pulmonary/Thoracic Related			
Massive hemoptysis [1]	0.5%	0.0%	1.000
Other hemoptysis	42.1%	2.3%	**<0.001**
Pneumothorax	5.1%	2.3%	0.360
Air leak > 7 days [1]	1.9%	1.2%	1.000

Event	Zephyr EBV N = 214	Control N = 87	p value
Expanding pneumothorax	1.9%	2.3%	1.000
Stable pneumothorax	1.4%	1.2%	1.000
Empyema [1]	0.0%	0.0%	--
Pleural effusion	0.5%	0.0%	1.000
Non-cardiac chest pain	16.4%	3.5%	**0.002**
All Valve/Implant Related			
Expectoration/aspiration/migration	7.9%		--
Pneumonia distal to valve [1]	4.2%		--
Bronchial granulation tissue	7.9%		--
Bronchial trauma	0.5%		--
Other/General			
Nausea or vomiting	8.4%	1.2%	**0.017**

[1] A component of the Major Complications Composite

2.18.1 Valve Expectoration or Migration

Valve migration occurred when the valve was not retained in the original position within the target bronchus. Valve migration outside the target bronchus occurred when the valve migrated to a non-target bronchus, and valve expectoration occurred when the valve migrated out of the target bronchus and was subsequently coughed out by the subject. There were 820 valves implanted in the two hundred fourteen (214) Zephyr EBV Treatment Subjects. Of these 820 valves, 23 valves (2.8%) in seventeen subjects migrated or were expectorated. Of these, 23 expectorated or migrated valves, 5 migrated within the target bronchus, 9 migrated outside the target bronchus, and 9 were expectorated. Fourteen (14) of the 17 Zephyr EBV Subjects that experienced migration or expectoration had at least one of the migrated or expectorated valves replaced.

2.18.2 Valve Removal

Zephyr Endobronchial Valves were shown to be removable in the VENT study. During the follow-up period, a total of 87 valve removal attempts were made in thirty-one patients. Individual valve removal was successful in 98% of attempts. In 32% of patients, valve removal was precipitated by migration. In 19% of patients removal was undertaken to reposition valves or to allow alternative treatments. In the remaining patients, removal was performed for a range of reasons such as hemoptysis, pneumonia, granulation tissue formation, dyspnea, continuing COPD exacerbations, or patient request.

2.19 Zephyr EBV Europe Trial

Concurrent with enrollment in the VENT Pivotal Trial in the United States, subjects were enrolled in a parallel study with the Zephyr EBV System in Europe. This clinical study was termed Zephyr EBV Europe Trial. The Zephyr EBV Europe Trial was a randomized, controlled, multi-center trial which enrolled 171 subjects with severe heterogeneous emphysema. Study subjects underwent clinical assessment, evaluation of pulmonary function and morphology including high resolution CT scanning (HRCT), and a program of optimal medical management and aggressive pulmonary rehabilitation. Upon successful completion of this program subjects were randomized into two groups at a ratio of 2 to 1, with two subjects randomized to the Experimental Group (Zephyr EBV treatment) for each subject randomized to the control group.

The mean percent change from baseline for FEV1 was numerically higher in the Zephyr EBV Group (6.6%) than in the Control Group (0.8%) at 6 months. The 6MWT results indicate that the mean percent change is also numerically higher for the Zephyr EBV Group (9.7%) than the Control Group (7.7%) at 6 months. These data are summarized in Table 21 below.

Table 21 Zephyr EBV Europe Trial - Principal Effectiveness Data at 6 Months

	Zephyr EB Mean % change ± SD (N)	Control Mean % change ± SD (N)
FEV_1	6.6 ± 20.1% (91)	0.8 ± 19.1% (55)
6MWT	9.7 ± 35.7% (88)	7.7 ± 34.8% (55)

At one year, the major complication composite rate (MCC) was 18.9% for Zephyr EBV Subjects versus 8.3% for Control Subjects (p = 0.076). Mortality rates were similar (5.4% Zephyr EBV Treatment and 6.7% for Control, p = 0.742). These data are summarized in Table 22 below.

Table 22 Zephyr EBV Europe Trial - Principal Safety Data at 1 Year

	Zephyr EBV N = 111 % (n)	Control N = 60 % (n)	p value
Major Complication Composite (MCC)	18.9% (21)	8.3% (5)	0.076
Death	5.4% (6)	6.7% (4)	0.742
Empyema	0.0% (0)	0.0% (0)	—
Massive hemoptysis	0.9% (1)	0.0% (0)	1.000
Pneumonia distal to valve	5.4% (6)	n/a	n/a
Pneumothorax > 7 days	4.5% (5)	0.0% (0)	0.164
RF > 24 hours Mechanical Ventilation	6.3% (7)	3.3% (2)	0.497

2.20 EBV-OTW Clinical Study

Prior to initiation of the VENT Pivotal Trial, a clinical study of the earlier device iteration, the EBV-OTW System, was conducted in the United States and Europe under a nearly identical protocol. Clinical data for subjects treated with the EBV-OTW device in the United States and Europe were pooled for the purposes of analysis of the EBV-OTW Clinical Study. The EBV-OTW Clinical Study was a two-arm, randomized, controlled, multi-center trial enrolling 62 subjects with heterogeneous emphysema. Study subjects underwent history and physical examination, evaluation of pulmonary function and morphology including high resolution CT scanning (HRCT), and a program of optimal medical management and aggressive pulmonary rehabilitation. Upon successful completion of this program subjects were randomized into two groups at a ratio of 2 to 1, with two subjects randomized to the Experimental Group (EBV-OTW) for each subject randomized to the Control Group.

The mean percent change from baseline for the FEV1 was numerically greater for the EBV-OTW Subjects (11.5%) than for the Control Subjects (4.3%) at 6 months. The mean percent change from baseline for the 6MWT was numerically greater for the Control Subjects (7.2%) than for the EBV-OTW Subjects (5.7%) at 6 months. These data are summarized below in Table 23.

Table 23 EBV-OTW Clinical Study - Principal Effectiveness Data at 6 Months

	EBV-OTW Mean % change ± SD (N)	Control Mean % change ± SD (N)
FEV_1	11.5 ± 22.3% (37)	4.3 ± 27.3% (17)
6MWT	5.7 ± 27.8% (38)	7.2 ±18.7% (16)

There was no difference in the Major Complications Composite (MCC) rate between groups through one year as shown below in Table 24.

Table 24: EBV-OTW Clinical Study - Principal Safety Data at 1 Year

	Zephyr EBV N = 43 % (n)	Control N = 19 % (n)	p value
Major Complication Composite (MCC)	2.3% (1)	0.0% (0)	1.000
Death	0.0% (0)	0.0% (0)	—
Empyema	0.0% (0)	0.0% (0)	—
Massive hemoptysis	0.0% (0)	0.0% (0)	—
Pneumonia distal to valve	2.3% (1)	n/a	n/a
Pneumothorax > 7 days	0.0% (0)	0.0% (0)	—
RF > 24 hours Mechanical Ventilation	0.0% (0)	0.0% (0)	—

2.21 Conclusions Drawn from the Studies

The safety and effectiveness of the Zephyr EBV System has been demonstrated by the results of biocompatibility, bench, animal, sterilization and shelf life, and clinical testing.

The biocompatibility testing demonstrated the biological safety of the device materials for the intended use of the device. The bench studies demonstrated that the product met performance characteristics and is suitably designed for its intended use. Animal studies support the safety, proof of concept, and overall performance of the product. Results obtained from the sterilization studies show that the product satisfies a minimum sterility assurance level (SAL) of 10^{-6}, and the results of package integrity and product functionality testing support a one-year shelf life for the product.

The results of the VENT study demonstrate that the adverse events with Zephyr EBV treatment are, as expected, higher at six months as compared to standard medical management. However, the adverse event rate diminishes over time, and many of the adverse events were resolved by removing the valves and reversing the procedure. The Primary Safety Endpoint, MCC, did not show a statistically significant difference at any time point.

Equivalent outcomes for all-cause mortality through one year were demonstrated by Kaplan-Meier analysis. There was no difference in the survival curves for Zephyr EBV subjects and Control Subjects (96.0% and 96.3% freedom from all-cause mortality respectively at one year, p=0.876, log rank test).

These data provide valid scientific evidence of reasonable assurance that the Zephyr EBV is safe for its intended patient population. The Primary Safety Endpoint, MCC did not reach statistical significance.

- No difference in one year survival
- Adverse event rates reduced over time

VENT met its co-primary endpoints and four secondary endpoints. These endpoints provide valid scientific evidence that the Zephyr EBV improves lung function, exercise tolerance, and quality of life in a significant portion of the target patient population.

- Primary endpoints met
- Secondary endpoints met
- Composite outcome (BODE) shows significant improvement
- Responder analyses confirm clinically-important improvements

2.22 Panel Recommendation

TBD

2.23 FDA Decision

TBD

2.24 Approval Specifications

Directions for Use: TBD

Hazards to Health from Use of the Device: TBD

Post-approval Requirements and Restrictions: TBD