VENT PIVOTAL TRIAL CLINICAL SUMMARY

Title:	**Endobronchial Valve for Emphysema PalliatioN Trial**
Short Title:	**VENT Pivotal Trial**
Protocol Number:	**Emphasys Protocol 630 – 0001 – J**
IDE Number:	**G020230**
Product:	**Emphasys Zephyr Endobronchial Valve**
Short Product Name	**Zephyr EBV**
Sponsor:	**Emphasys Medical, Inc.**

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DEFINITIONS

In this Clinical Study Report, the following terms have the specific meanings as defined below.

1. Acute Technical Success: Complete exclusion of the target lobe determined via bronchoscopy at the conclusion of the procedure.
2. BODE: A composite index of pulmonary disease state which includes the BMI, Airflow Obstruction, Dyspnea and Exercise Capacity index.
   Completed Case (CC): All randomized and eligible subjects who received study-directed treatment and who had 6 months of follow-up.
3. Core Radiology Lab (CRL): Lab at the University of California Los Angeles responsible for implementing standardized HRCT image collection at each site, and performing quantitative image analysis of screening HRCT scans to determine subject eligibility.
4. Density Score (DS): The proportion (in %) of lobar lung parenchyma destroyed by emphysema as established by HRCT. A synonym for Emphysema Score (in %).
5. Destruction score: The sum of the upper lobe and lower lobe integer Emphysema Scores.
6. Emphysema Score (ES): The proportion (in %) of lobar lung parenchyma destroyed by emphysema as established by HRCT. A synonym for Density Score.
7. Forced Expiratory Volume (FEV_1): The forced expiratory volume in one second is the volume of gas that can be forcefully exhaled in one second after a maximal inspiration.
8. Forced Expiratory Volume Percent Predicted (FEV_1 % predicted): A measure of FEV_1 normalized for race, gender, age, and height.
9. Heterogeneity score (HS): The difference (in %) between ipsilateral lobe Density Scores.
10. HRCT Density Score: A computer-automated grading of the percent emphysematous destruction on a lobar level by HRCT.
11. Imputation: Random assignment of values for missing data in the Intent-to-Treat population. Imputation is performed multiple times (Multiple Imputation) in order to ensure that results are not due to chance.
12. Intent-to-Treat (ITT): All randomized subjects analyzed by the groups to which they were randomly assigned, regardless of the actual treatment received. ITT1 is the first of multiple imputation populations, ITT2, is the second, etc.
13. Ipsilateral Lung, Non-target Lobe Volume – The volume of the remaining, non-targeted lobe(s) of the target lung as determined by the Core Radiology Lab computer analysis.

14. Lobar Exclusion (Acute): Bronchoscopic confirmation that all airways feeding the Target Lobe have been blocked with a valve.
15. Major Complications Composite (MCC): The primary safety outcome for VENT. A per-subject assessment of Major Complications from day 0 to 180.
16. Multiple Imputation: Statistical method of replacing missing data with plausible values by multiple simulated versions. Each simulated dataset is analyzed by standard methods and the results are combined to produce estimates and confidence intervals that incorporate missing-data uncertainty.
17. Six Minute Walk Test (6MWT): A test that measures a subject's exercise capacity by the distance in meters that he / she can walk in six minutes.
18. Target Lobe: The lung lobe that was to be treated as determined by the Study Protocol at Section 7.8.2 Treatment Targeting.
19. Target Lobe Atelectasis Score at Total Lung Capacity ($TLAS_{TLC}$): The change in target lobe volume determined by computer analysis of the changes in the HRCT scans performed at total lung capacity and recorded at baseline and 6 months post-procedure. $TLAS_{TLC}$ is calculated with the following formula:

$$TLAS = \frac{\left(Volume_{Day180} - Volume_{Baseline}\right)}{Volume_{Baseline}}$$

    The resulting value—expressed either as a percent or a decimal—indicates progressive volume loss up to a hypothetical complete atelectasis (−100% or −1.00). Therefore, the TLAS is a relative measure of target lobe volume reduction over 6 months of study follow-up.
20. Target Lobe Volume: The volume of the target lobe determined by the Radiology Core Lab computer analysis.

1 INTRODUCTION

1.1 Rationale for Endobronchial Valve Treatment

The placement of endobronchial valves is intended to improve the respiratory mechanics in patients with emphysema by preventing airflow to lung regions with poor elastic recoil. Preventing air from entering the most diseased area is intended to induce local volume reduction of these inelastic regions, thereby increasing the net elasticity of the treated lung. The Zephyr EBV is a minimally-invasive alternative treatment for patients considering LVRS. As with LVRS, endobronchial valves do not treat the underlying pathology and therefore do not slow the progression of the disease or reduce a patient's susceptibility to COPD exacerbations or chest infections that are common in these patients; however, improvements in FEV_1 and BODE have been shown to increase survival and improvements in quality of life indices and exercise tolerance are clinically-meaningful to these patients.

1.2 Pilot Clinical Studies

Pilot clinical studies were performed with several device iterations. At the time the VENT Pivotal Trial began, 71 subjects with advanced emphysema had received Zephyr EBV Treatment at 9 international sites. Thirty-eight of these subjects had been treated unilaterally with complete lobar exclusion. This subgroup was the pilot group, which informed the design of the VENT Pivotal Trial. 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%. These data were subsequently published as part of a larger registry.

Overall, the morbidity and mortality of the Zephyr EBV procedure compared favorably to a meta-analysis of Lung Volume Reduction Surgery (LVRS) data. 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.

2 INVESTIGATIONAL DEVICES

2.1 Emphasys Zephyr Endobronchial Valve (Zephyr EBV)

The Emphasys 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, as shown in Figure 1. The Zephyr EBV comes in two sizes, 4.0 mm to 7.0 mm (the "4.0" or "small" valve) and 5.5 mm to 8.5 mm (the "5.5" or "large" valve), allowing bronchial lumens with diameters from 4.0 mm to 8.5 mm to be treated.

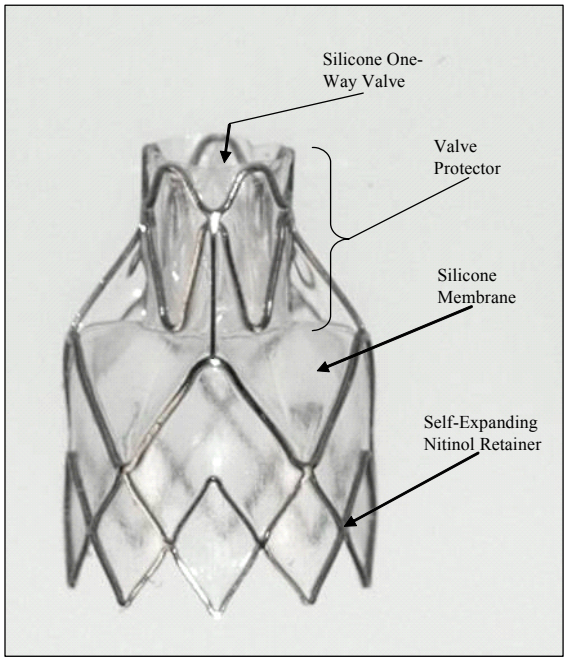


Figure 1 Emphasys Zephyr Endobronchial Valve (EBV)

The Zephyr EBV is designed to be implanted into targeted 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, as shown below in Figure 2. 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.

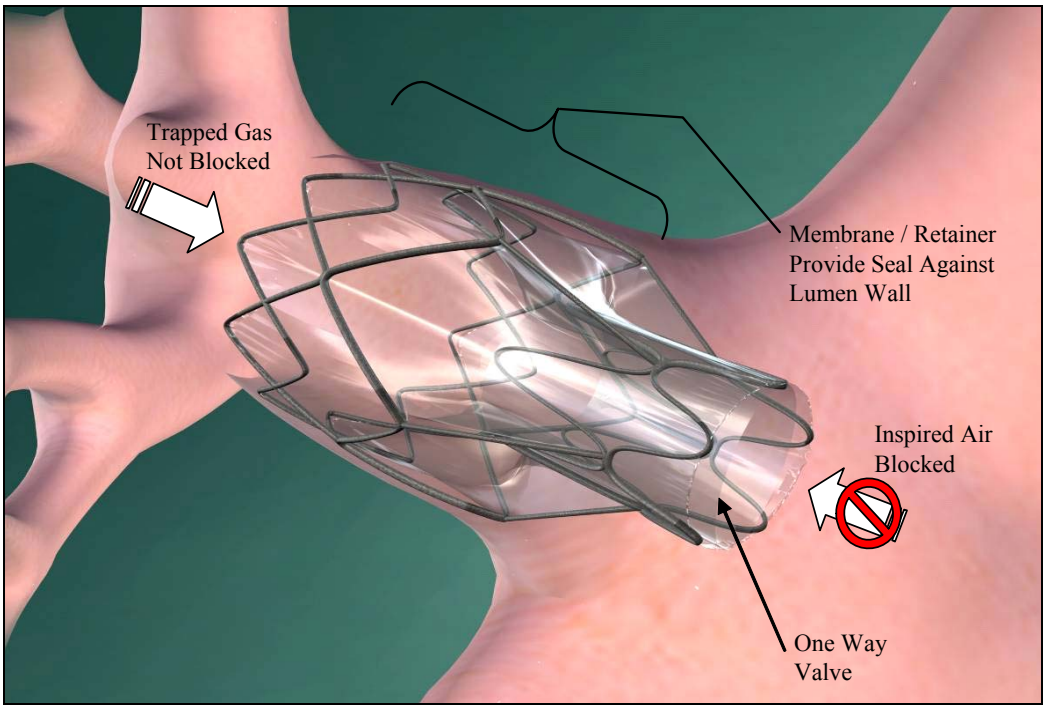


Figure 2 Emphasys Zephyr Endobronchial Valve (EBV)

2.2 Zephyr Delivery Catheter and Zephyr Loader System

The Zephyr EBV is implanted in the target bronchial lumen using the Zephyr Endobronchial Delivery Catheter (Zephyr EDC), shown in Figure 3. Immediately prior to implantation, the Zephyr EBV is compressed and loaded into the distal end of the Zephyr EDC with the Zephyr Loading System (Zephyr ELS) (see Figure 4). 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 as illustrated in Figure 2. The silicone membrane covering the retainer prevents tissue in-growth. The Zephyr EBV can be removed bronchoscopically, if necessary, using standard flexible rats-tooth grasping forceps.

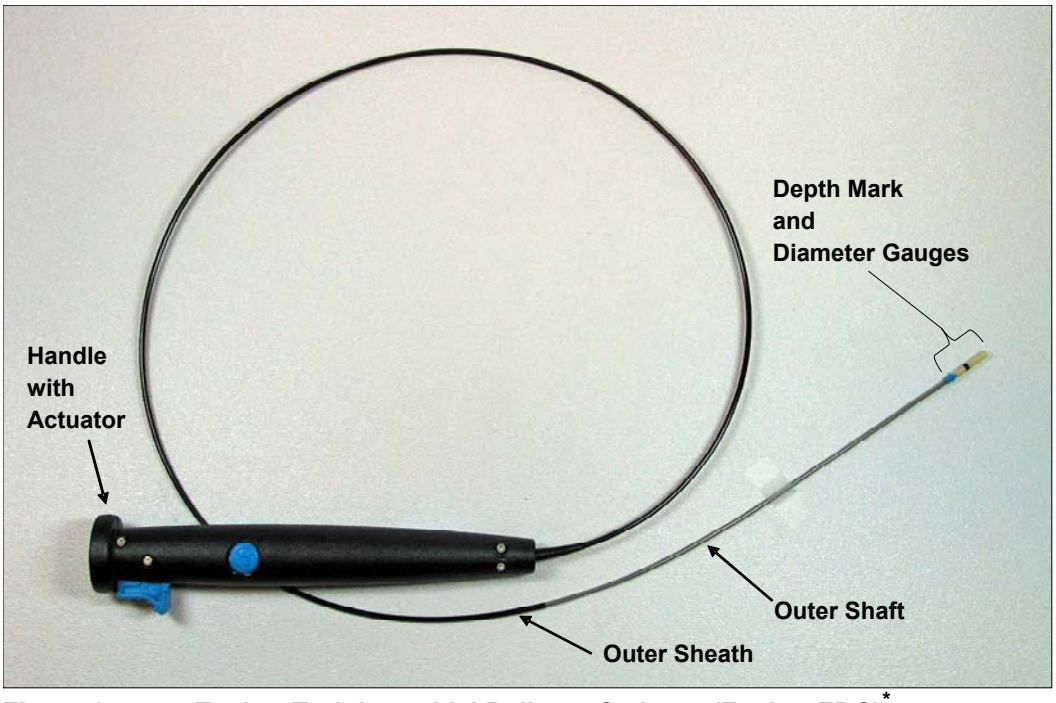


Figure 3 Zephyr Endobronchial Delivery Catheter (Zephyr EDC)*

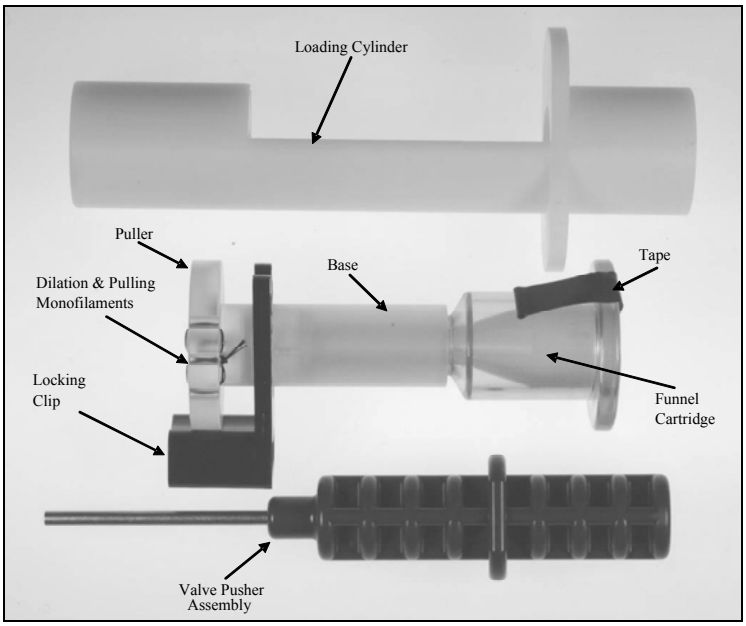


Figure 4 Zephyr Endobronchial Loader System (Zephyr ELS)

* Depth Mark (also called "Marker Band") was implemented after completion of VENT

3 STUDY DESIGN AND ANALYSIS

3.1 VENT Pivotal Trial Overview

The VENT Pivotal Trial was a randomized, controlled, multi-center trial enrolling 321 subjects with severe heterogeneous emphysema. The major study parameters—including the use of a control group, the target patient population, the primary and secondary outcomes and length of subject follow-up were all based on the recommendations of the FDA Advisory Panel Meeting held in February, 2003 (see Table 1). This Panel was convened to provide the FDA with expert opinion on the design of trials for bronchoscopic treatment of emphysema. The study was conducted under IDE G020230 and received full approval from the FDA on August 18, 2003.

Table 1 Recommendations of the February 2003, Special FDA Advisory Panel

FDA Question for Panel	Panel Recommendation	VENT Protocol
Target patient population	LVRS-eligible patients	NETT inclusion/exclusion
Endpoints	Must have physiologic (FEV_1 or RV), exercise tolerance, and quality of life	Co-primary endpoints: 1 physiologic and 1 exercise tolerance. Quality of life in secondary
Length of follow-up	Six months effectiveness, one year safety	Six months effectiveness, one year safety
Control	Optimal medical management	Optimal medical management, including pulmonary rehabilitation

The study was designed to include two co-primary effectiveness endpoints: the percent change from baseline to 6 months in both FEV_1 and 6MWT in Zephyr EBV Subjects compared to Control Subjects. Superiority had to be demonstrated in both measures.

The primary safety outcome was the Major Complication Composite at 6 months. Given that this study was a comparison of an active implantable intervention to medical management, there was no expectation of safety equivalence between the Zephyr EBV Group and the Control Group and there was no *a priori* safety inference test established. The MCC rate for the pilot study lobar-exclusion subgroup was 19.1% at 90 days. Even with some expected MCC rate in the Control arm, it was assumed that the Zephyr EBV Treatment would have a significantly higher MCC rate than the non-active control.

The protocol specified an assessment of safety at one year.

3.2 VENT Sites and Principal Investigators

VENT study sites and principal investigators are listed below in Table 2.

Table 2 VENT Sites and Principal Investigators

VENT Clinical Site	Principal Investigator
Baptist Memorial Hospital	Emmel Golden, MD
Beth Israel Deaconess Medical Center (BIDMC)	Armin Ernst, MD
Botsford Hospital	Gary T. Ferguson, MD
Cedars-Sinai Medical Center	Robert J. McKenna, Jr., MD, F.A.C.S.
Henry Ford Hospital	Mike Simoff, MD
Inova Fairfax Institute of Research	Steven Nathan, MD
Mayo Clinic	Eric Edell, MD
Medical University of South Carolina (MUSC)	Charlie Strange, MD
Morton Plant (Bay Area Chest)	Eli H. Freilich, MD
National Jewish Medical & Research Center	Russell P. Bowler, MD., Ph.D.
New York Presbyterian	Roger Maxfield, MD
Palmetto Richland Memorial Hospital	Don Elton, MD
Peoria Pulmonary Associates	William P. Tillis, MD
Pulmonary Associates	Bernie Levine, MD
Remington-Davis Clinical Research	Edward M. Cordasco, Jr., D.O.
S. Arizona VA Health Care System (SAVAHCS)	Sammy Campbell, MD
Sarasota Memorial Hospital	Kirk Voelker, MD
Shands Hospital - University of Florida	Michael Jantz, MD
Southern Illinois University (SIU)	Stephen Hazelrigg, MD
St. Francis Hospital	Mark Boomer, MD
St. Vincent's Hospital Manhattan	Joe Cicenia, MD
Temple University Hospital	Gerard J. Criner, MD
Topeka Pulmonary (Veritas)	William M. Leeds, D.O., F.C.C.P.
Tulane University Hospital	Kevin Kovitz, MD, MBA
University of California Davis	Andrew Chan, MD
University of Iowa Medical Center	Geoffrey McLennan, MD, PhD
University of Kentucky	Rolando Berger, MD
University of Maryland	Jim Britt, MD
University of Michigan Medical Center	Steven Gay, MD
University of Pittsburgh Medical Center (UPMC)	Frank Sciurba, MD*
Veteran Affairs Medical Center - Houston	Sheila Goodnight-White, MD

*Study Principal Investigator

3.3 Subject Screening, Preparation and Randomization

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 supervised 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).

3.4 Inclusion / Exclusion Criteria

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

1. Subject diagnosed by Core Radiology 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 exclusion criteria 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

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. Eligible lobes were the right upper lobe, right lower lobe, left upper lobe (including lingula), and left lower lobe. The right middle

lobe was not eligible for treatment. 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. Staged procedures and bilateral valve placement were not permitted in the VENT Pivotal Trial. The success of lobar exclusion (Acute Technical Success) was determined via bronchoscopy at the conclusion of the procedure.

3.4.1 All Study Subjects: Follow-up Procedures

Follow-up assessments were scheduled for all study subjects at 2–3 days, 1 week, 1, 3, and 6 months, and at 1year.

Spirometry was performed both pre and post bronchodilator treatment based on American Thoracic Society standards (1994). Body plethysmography post bronchodilator treatment was performed according the American Association of Respiratory Care Clinical Practice Guideline (2001). Diffusing capacity (DL_{CO}) was measured using the single-breath carbon monoxide method according to American Thoracic Society standards (1995). Six-Minute Walk testing (6MWT) was performed according to American Thoracic Society standards (2002) ; dyspnea and overall fatigue was measured in all subjects using the Borg Scale prior to and immediately following performance of the 6MWT. Cycle ergometry to determine maximum workload was performed according to the protocol used in the NETT study and with concurrent Borg scale testing. Supplemental oxygen requirements were self-reported by study subjects including conditions of usage, duration of use and flow rate.

Health related quality of life (QoL) measurement was performed at baseline, 6 months, and 1 year using several instruments, including the St. George's Respiratory Questionnaire (SGRQ), the Modified Medical Research Council survey (mMRC) and the Quality of Well Being Scale (QWB). The QWB and mMRC were also administered at the 1 month follow-up visit.

3.4.2 Analysis Populations

The analysis populations include the multiple-imputation intent-to-treat (ITT), modified intent-to-treat (mITT), and completed cases (CC).

- The ITT population was defined as all randomized subjects analyzed by the groups to which they were randomly assigned, regardless of the actual treatment received. Multiple imputation methods were used to account for missing data and the results combined for analysis.
- The mITT population was defined as all randomized subjects who received study-directed treatment and had any follow-up visits.

- The CC population was defined as all randomized subjects who received study directed treatment and who had 180-day (6-month) observations within a window of 150–225 days.

The primary effectiveness endpoint and secondary effectiveness endpoints were analyzed using the multiple-imputation ITT population. Confirmatory and additional effectiveness analyses were performed using the CC population. Safety analyses were performed using the mITT population.

3.5 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 potential baseline predictors of success – Inter-lobar collateral flow proxy (fissure integrity), disease severity, disease heterogeneity
4. Volume redistribution assessment – Target lobe and adjacent lobe volume change from baseline to 180 day follow-up
    a. Quantify intended anatomical treatment effect
    b. Explore potential correlation of lobar volume changes with outcomes measures

The collection and analysis of high resolution computed tomography (HRCT) images were coordinated by a Core Radiology Lab (MedQia, in association with the David Geffen School of Medicine at UCLA).

3.5.1 Quantitative Image Analysis

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.

3.5.2 Density (Emphysema) and Heterogeneity Scoring

<u>Density (or Emphysema) Score</u>: The percentage of each lung lobe volume below the pre-defined Hounsfield threshold was then reported as the Density Score in % 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.

Heterogeneity Score: The Heterogeneity Score for a subject was the difference between the Density Scores of the target lobe and the ipsilateral non-target lobe (in %).[†] This Heterogeneity Score was a pre-specified covariate and was included as a baseline variable in all of the multivariate analyses.

3.5.3 Fissure Integrity Assessment

A manual reading of fissure integrity was conducted in the target lung of each subject using the baseline HRCT full-inspiration image. Each fissure in the lung was a Fissure Score ("Complete" or "Incomplete") by trained radiologists at the Core Radiology Lab. Radiologists were blinded to treatment arm. The HRCT image below in Figure 5 shows an example of a complete fissure in the right lung and an incomplete fissure in the left lung. A fissure had to be complete in all views in order to be assigned "Complete". Fissure Score was a pre-specified baseline covariate and was thought to be a proxy for inter-lobar collateral flow. If so, one would expect greater volume reduction in the treated lobe when the fissures bordering the target lobe were Complete. Fissure Score was included as a baseline variable in all of the multivariate analyses.

[*] For the purposes of determining inclusion criteria, the Density Score was converted into integer scores as follows: 0% = 0, 1 – 25% = 1, 26 – 50% =2, 51 – 75% = 3 and > 75% = 4.

[†] For the purposes of determining inclusion criteria, the Heterogeneity Score was converted into the difference between the upper lobe Density Score and the lower lobe Density Score; if the difference was ≥ 1, the subject was eligible.

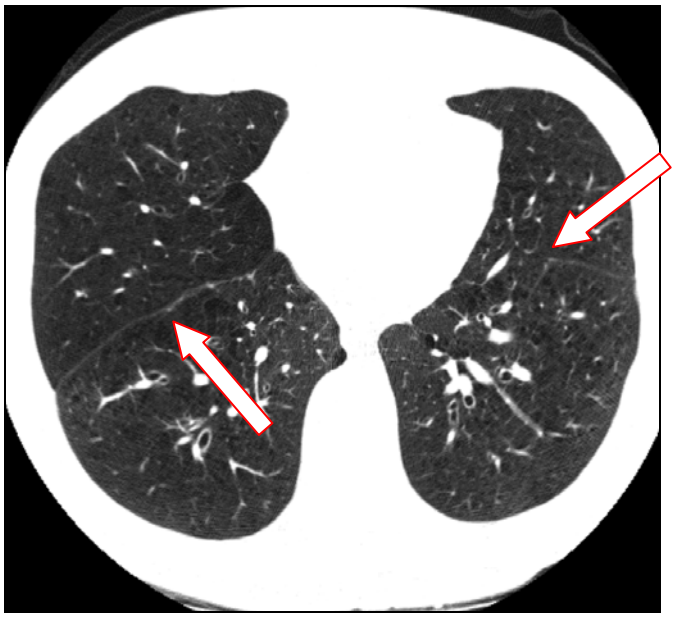


Figure 5 Fissure Integrity Example

3.5.4 Target Lobe Atelectasis Score (TLAS) Methodology

The Core Radiology Lab calculated volumes by lobe. The Target Lobe Atelectasis Score (TLAS) was determined for that lobe by the following formula:

$$TLAS = \frac{\left(Volume_{Day180} - Volume_{Baseline}\right)}{Volume_{Baseline}}$$

The resulting value—expressed either as a percent or a decimal—indicates progressive volume loss up to a hypothetical complete atelectasis (−100% or −1.00). Therefore, the TLAS was a measure of Target Lobe Volume Reduction (TLVR) over 6 months of study follow-up. TLVR was hypothesized to be a morphological response to Zephyr EBV Treatment.

4 STUDY ACCOUNTABILITY AND POPULATION

4.1 Site Enrollment

Thirty one (31) Investigators at 31 Investigational Sites enrolled a total of 321 study subjects (220 Zephyr EBV Treatment and 101 Control) between December 22, 2004 and April 27, 2006.

4.2 Subject Accountability

There were 220 study subjects randomized to receive the Zephyr EBV. Of these, six subjects did not have the procedure: three withdrew consent, two were lost to follow-up due to medical reasons, and one was unwilling to comply with the visit schedule. The 214 Zephyr EBV Subjects who did receive Zephyr EBV Valves comprised the modified Intent-to-Treat (m-ITT) cohort for safety evaluation.

For 220 Zephyr EBV Subjects through 6 months of follow-up, 9 subjects withdrew informed consent and 6 died, leaving 205 subjects alive and evaluable at 6 months, of whom 193 (94.1%) had an evaluable visit for 6 months. By the time of the one year safety assessment, 12 Zephyr EBV Subjects withdrew informed consent and 8 had died, leaving 200 subjects alive and evaluable. By 1 year of follow-up, 16 of the 200 eligible subjects had not completed their final study visit, 14 of whom were considered as being lost to follow-up.

Table 3 Cumulative Subject Accountability Table by Visit – Zephyr EBV Subjects

Zephyr EBV Subjects	1 Month Visit	3 Month Visit	6 Month Visit	1 Year Visit
Enrolled	**220**	**220**	**220**	**220**
Died [1]	0	2	6	8
Withdrawn [1]	5	8	9	12
Eligible at Visit [2]	**215**	**210**	**205**	**200**
Visit at Interval [3]	191 (88.8%)	196 (93.3%)	193 (94.1%)	184 (92.0%)
Visit in Window [3]	120 (55.8%)	111 (52.9%)	135 (65.9%)	148 (74.0%)
Visit in Extended Window [3, 4]	0 (0.0%)	0 (0.0%)	37 (18.0%)	30 (15.0%)
Visit Beyond Window [3]	71 (33.0%)	85 (40.5%)	21 (10.2%)	6 (3.0%)
No Visit [3]	24 (11.2%)	14 (6.7%)	13 (5.9%)	16 (8.0%)
Lost to Follow-up [1]	5 (2.3%)	6 (2.9%)	9 (4.4%)	14 (7.0%)

[1] Deaths, withdrawn subjects and lost to follow-up are cumulative.
[2] The number eligible is the number enrolled minus the number that died and the number that withdrew.
[3] The denominator is the number eligible at that visit.
[4] For the 6 Month visit, the extended window ranged from 150 - 225 days and for the 1 Year visit, the extended window was from 305 - 425 days. No extended window at 1 Month or 3 Months.

There were 101 study subjects randomized to Control. Of these, 14 did not return for their first office visit post-randomization. The remaining 87 comprised the modified Intent-to-Treat (mITT) cohort for safety evaluation.

For 101 Control Subjects through 6 months of follow-up, 8 subjects withdrew informed consent and none had died, leaving 93 subjects alive and potentially evaluable at 6 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 1 year of follow-up, 13 of the 89 eligible subjects had not completed their final study visit, of whom 12 had been lost to follow-up.

Table 4 Cumulative Subject Accountability Table by Visit – Control Subjects

Control Subjects	1 Month Visit	3 Month Visit	6 Month Visit	1 Year Visit
Enrolled	**101**	**101**	**101**	**101**
Died [1]	0	0	0	3
Withdrawn [1]	6	7	8	9
Eligible at Visit [2]	**95**	**94**	**93**	**89**
Visit at Interval [3]	84 (88.4%)	75 (79.8%)	79 (84.9%)	76 (85.4%)
Visit in Window [3]	74 (77.9%)	46 (48.9%)	59 (63.4%)	70 (78.7%)
Visit in Extended Window [3, 4]	0 (0.0%)	0 (0.0%)	16 (17.2%)	5 (5.6%)
Visit Beyond Window [3]	10 (10.5%)	29 (30.9%)	4 (4.3%)	1 (1.1%)
No Visit [3]	11 (11.6%)	19 (20.2%)	14 (15.1%)	13 (14.6%)
Lost to follow-up [1]	8 (8.4%)	9 (9.6%)	10 (10.8%)	12 (13.5%)

[1] Deaths, withdrawn subjects and lost to follow-up are cumulative.
[2] The number eligible is the number enrolled minus the number that died and the number that withdrew.
[3] The denominator is the number eligible at that visit.
[4] For the 6 Month visit, the extended window ranged from 150 - 225 days and for the 1 Year visit, the extended window was from 305 - 425 days. No extended window at 1 Month or 3 Months

5 BASELINE CHARACTERISTICS

5.1 Demographic Data

The mean age of study subjects in both groups was about 65 years. 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). Gender was included as a baseline covariate in all multivariate models and was not an independent predictor for any of the outcomes. Caucasian race was the majority for both groups (see Table 5).

Table 5 Subject Demographics

Characteristic	Zephyr EBV	Control	
Continuous Measures	**Mean N = 220**	**Mean N = 101**	**p value**
Age (years)	65.3	64.9	0.562
BMI (kg/m^2)	25.1	24.8	0.506
Systolic BP (mm Hg)	129.1	129.9	0.674
Diastolic BP (mm Hg)	73.8	74.6	0.494
Categorical Measures			**p value**
Gender (Male)	60.4%	48.5%	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)	

5.2 Medical History

As shown in Table 6 below, key medical factors were similar between Zephyr EBV Subjects and Control Subjects.

Table 6 Baseline Medical History

Characteristic	Zephyr EBV N = 220	Control N = 101	p value
Diabetes	7.7%	5.0%	0.478
Abnormal ECG	45.9%	42.6%	0.629
Smoking	99.6%	98.0%	0.234
Packs-years Mean	63.3	61.7	0.636

5.3 Lung Function Parameters

There were no significant differences in any baseline lung function parameters between the Zephyr EBV Subjects and the Control Subjects (see Table 7).

Table 7 Baseline Lung Functions

Characteristic	Zephyr EBV Mean (N)	Control Mean (N)	p value
FEV_1 (liters)	0.87 (220)	0.84 (101)	0.315
FEV_1 % Predicted	30% (219)	30% (101)	0.998
FVC (liters)	2.71 (220)	2.62 (101)	0.278
FVC % Predicted	70% (219)	70% (101)	0.925
FEV_1 / FVC	0.33 (220)	0.33 (101)	0.605
DL_{CO} (ml CO / min / mm Hg)	9.52 (220)	10.15 (101)	0.681
DL_{CO} % Predicted	33% (220)	36% (101)	0.114
RV (liters)	4.79 (217)	4.63 (100)	0.159
RV % Predicted	216% (217)	212% (100)	0.284
TLC (liters)	7.60 (217)	7.37 (100)	0.118
TLC % Predicted	124% (217)	125% (100)	0.621

Based on the lung function parameters, all subjects were either GOLD Class III (Severe) or Class IV (Very Severe) stage of COPD.

5.4 Arterial Blood Gas Analysis

Baseline arterial blood gas values were largely similar between the Zephyr EBV Subjects and the Control Subjects. The partial pressure of oxygen (69.1 and 68.4 mmHg, p = 0.51) and the oxygen saturation (93% and 93%, p = 0.71) were not different, nor was the pH (7.43 and 7.42, p = 0.48). However, the Zephyr EBV Subjects had a slightly lower mean partial pressure of carbon dioxide (40.5 compared with 41.6 mmHg, p = 0.044) (see Table 8). Baseline $PaCO_2$ was included as a covariate in all multivariate analyses and was not predictive of any outcome variables.

Table 8 Baseline Arterial Blood Gas Analysis

Characteristic	Zephyr EBV Mean (N)	Control Mean (N)	p value
PaO_2 (mm Hg)	69.1 (220)	68.4 (100)	0.514
$PaCO_2$ (mm Hg)	40.5 (220)	41.6 (100)	**0.044**
pH	7.43 (220)	7.42 (101)	0.475
Oxygen saturation (%)	93% (215)	93% (97)	0.713

6 ZEPHYR EBV IMPLANTATION PROCEDURE

6.1 Procedure Details

6.1.1 Procedure Time

The mean Zephyr EBV procedure duration, the time between bronchoscope insertion and bronchoscope removal, was 33.8 minutes (median 28 minutes, range 6 to 100 minutes).

6.1.2 Target Lobes

Target lobes were defined by pre-procedural imaging assessments. Target lobes were largely in the upper lobes (76.6%) and predominantly on the right side (61.6%). The right upper lobe was the target in 52.3% of Zephyr EBV Subjects; the right lower lobe in 9.3%; the left upper lobe including lingula in 24.3%; and the left lower lobe in 14.0%.

Table 9 Zephyr Endobronchial Valve Target Lobes

Zephyr EBV Subjects	N = 214 [1]
Target Lobe	**% (n)**
Right upper lobe (RUL)	52.3% (112)
Right lower lobe (RLL)	9.3% (20)
Left upper lobe (LUL)	24.3% (52)
Left lower lobe (LLL)	14.0% (30)

[1] Denominator is the 214 Zephyr EBV Subjects who underwent procedure; 6 subjects randomized to the Zephyr EBV Subjects Group did not undergo a Zephyr EBV implantation procedure.

Right upper lobes were disproportionately targeted for two reasons: (1) left upper lobe destruction including the lingula typically had less destruction whereas the right upper lobe destruction was not "diluted" by right middle lobe destruction; and (2) if the targeting algorithm resulted in a tie between the RUL and LUL, the RUL was arbitrarily chosen in advance to be the default target.

6.1.3 Anesthesia and Airway Management

Conscious sedation was used during the implantation procedure in 71.5% of subjects, with the remaining 28.5% having general anesthesia. This choice of anesthesia was reflected in the proportion of subjects who were intubated (35.1%) or ventilated (29.9%) during the implantation procedure.

Flexible bronchoscopy alone was utilized in 211 (98.6%) Zephyr EBV implantation procedures, while the remaining 3 (1.4%) used a rigid bronchoscope only.

6.2 Procedural Outcomes

6.2.1 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).

6.2.2 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. Acute technical success was not achieved for 11 Zephyr EBV Subjects 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%).

6.2.3 Valves Removed and Replaced During the Initial Procedure

Eight hundred twenty (820) valves were placed in Zephyr EBV Subjects. To valve these 820 target locations, 963 Zephyr EBV valves were initially deployed during the procedure and 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 143 valves removed during the initial procedure, 70 were placed too proximally, 28 were placed too distally, and 5 were too small for the selected airway. Other reasons (40) 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.

A "Depth Mark" was added to the distal end of the delivery catheter subsequent to the study conclusion in order to mitigate placement errors and reduce the rate of intra-procedural valve removals (See Figure 3, Section 2.2). This modification has been successfully used in commercial European applications.

7 PRIMARY AND SECONDARY EFFECTIVENESS OUTCOMES

7.1 Primary Effectiveness Outcome: Percent Change in FEV_1 and 6MWT by Intent-to-Treat, Multiple Imputation

The co-Primary Effectiveness Endpoints were the percent change from baseline in FEV_1 and 6MWT at 6 months. Inference testing using multiple-imputation, intent-to-treat (ITT) analysis with a one-sided superiority test at a significance level of 0.025 for each of the two co-primary effectiveness measures was employed.

The VENT Pivotal Trial met both of its co-primary effectiveness endpoints. Both FEV_1 and 6MWT percent changes from baseline to 6 months were significantly greater in the Zephyr EBV Subjects compared to the Control Subjects. The mean percent change in FEV_1 was 6.8% greater for Zephyr EBV Subjects compared with Control Subjects (p = 0.002) and the median* percent change in 6MWT was 5.8% greater for Zephyr EBV Subjects compared with Control Subjects (p = 0.019), (see Table 10).

Table 10 Primary Effectiveness Outcome: Multiple-Imputation, Intent-to-Treat Percent Change in FEV_1 and 6MWT at 6 Months[5]

Primary Effectiveness Outcome	Delta (%) (95% CI)	p value
Mean Percent Change in FEV_1	6.8 [1] (2.1, 11.5)	**0.002** [2]
Median Percent Change in 6MWT	5.8 [3] (0.5, 11.2)	**0.019** [4]

[1] Multiple-imputation difference in means and confidence interval.
[2] Multiple-imputation combined parametric p-value.
[3] Multiple-imputation point estimate of difference in medians and confidence interval.
[4] Multiple-imputation combined non-parametric p-value.
[5] N = 220 for Zephyr EBV Treatment and N = 101 for Control

The study met its primary effectiveness endpoint as both co-primary endpoints were highly statistically significant.

7.2 Completed Cases Analysis

Completed Cases subjects were defined as the subset of all randomized and eligible subjects who received study-directed treatment and who had 6 months of follow-up. No imputation was required for this analysis. The Complete Cases cohort consisted of 179 Zephyr EBV Subjects for FEV_1, 178 Zephyr EBV Subjects for 6MWT, 75 Control

* Medians are reported for non-parametric distributions.

Subjects for FEV_1, and 73 Control Subjects for 6MWT. This represents over 80% of the Zephyr EBV Subjects and 72% of the Control Subjects. All subsequent effectiveness analyses utilize the Completed Cases Cohort unless otherwise indicated.

7.2.1 Pre-Specified, Analysis-Plan-Generated Subgroup Analyses

The VENT Pivotal Trial pre-specified subgroup analyses based on independent predictor variables which were retained as interactions in the multivariate model. This *a priori* method prevents introducing bias in the selection of subgroups. Heterogeneity Score had a significant interaction with FEV_1 and with 6MWT. Fissure Score had a significant interaction with FEV_1. All subgroup analyses were performed using the Completed Cases population.

The Heterogeneity Score measured the difference in disease severity between ipsilateral lobes of the lung, calculated as the difference in percentage destruction (Density Score) as determined by HRCT. As Heterogeneity Score was a continuous variable, the median baseline value for Heterogeneity Score (15%) was chosen as the threshold for defining a "high heterogeneity" subgroup. High Heterogeneity as a predictor of Zephyr EBV treatment response is physiologically-plausible. Subjects with High Heterogeneity have less destruction in the non-targeted lobe and thus more potentially expandable lung parenchyma compared with subjects with less heterogeneous emphysema, and would theoretically tend to respond better. Degree of heterogeneity is a parameter that can be assessed at baseline using HRCT.

Fissure Integrity was assessed by HRCT as a radiological proxy for interlobar collateral airflow. Completeness of the interlobar fissure as a predictor of Zephyr EBV Treatment response is physiologically-plausible as a complete fissure would result in greater volume reduction in the treated lobe due to isolation from unwanted collateral air movement. Fissure integrity is a parameter that can be assessed at baseline using HRCT.

7.2.2 Change in FEV_1 and 6MWT at 6 Months

Zephyr EBV Subjects had a significantly greater improvement in both FEV_1 and 6MWT from baseline to 6 months compared with Control Subjects (see Table 11).

Table 11 Mean Change in FEV_1 and 6MWT at 6 Months

Change from Baseline	Zephyr EBV Mean (SD) N Median (Min, Max)	Control Mean (SD) N Median (Min, Max)	Delta (95% CI)	p value
FEV_1 (%)	5.3 (19.6) 179 3.8 (−38.3, 78.9)	–1.9 (12.2) 75 –3.4 (–27.7, 38.6)	7.2 [1] (3.2, 11.2)	**<0.001 [2]**
FEV_1 (mL)	42.0 (160.9) 179 30.0 (−310.0, 640.0)	−22.1 (102.6) 75 −20.0 (−210.0, 440.0)	64.2 [1] (30.9, 97.4)	**<0.001 [2]**
6MWT (%)	4.3 (22.7) 178 3.5 (–83.3, 108.0)	–1.5 (22.5) 73 –2.3 (–54.9, 71.4)	5.8 [3] (1.3, 11.7)	**0.008 [4]**
6MWT (meters)	10.2 (66.3) 178 14.5 (-210.0, 257.0)	–10.8 (76.0) 73 –9.0 (–325.4, 152.4)	23.5 [3] (3.82. 38.0)	**0.009 [4]**

[1] Difference of means and unequal variance t-test confidence interval
[2] One-sided unequal variance t-test
[3] Difference of medians
[4] One-sided Wilcoxon rank-sum test

As expected, FEV_1 and 6MWT deteriorated for the Control Subjects. Even with this progressive, chronic disease, Zephyr EBV Subjects improved in both outcomes. The Zephyr EBV Treatment response is in addition to optimal medical management and rigorous pre-baseline pulmonary rehabilitation.

7.2.3 Subgroup Analysis: High Heterogeneity

Heterogeneity Score remained as an interaction in the pre-specified multivariate, mixed model analysis for both the FEV_1 and 6MWT. Subgroup analysis for study subjects with High Heterogeneity Scores (≥ 15%) revealed an improved response in both FEV_1 and 6MWT for Zephyr EBV treatment compared to the overall population, consistent with the physiologic rationale of this treatment (see Table 12).

Table 12 Subgroup Analysis: Mean Change in FEV_1 and 6MWT in High Heterogeneity Subgroup at 6 Months

	Zephyr EBV Mean (SD) N Median (Min, Max)	Control Mean (SD) N Median (Min, Max)	Delta (95% CI)	p value
FEV_1 (%)	10.1 (22.3) 91 7.5 (–38.3, 78.9)	−2.2 (11.3) 40 –4.2 (–21.0, 25.5)	12.3 [1] (6.5, 18.1)	**<0.001 [2]**
FEV_1 (mL)	83.2 (184.3) 91 60.0 (–280.0, 640.0)	–28.0 (83.9) 40 –40.0 (–210.0, 140.0)	111.2 [1] (64.8, 157.5)	**<0.001 [2]**
6MWT (%)	7.3 (26.6) 90 6.8 (–83.3, 108.0)	–5.9 (21.9) 38 –7.6 (–54.9, 66.7)	14.4 [3] (6.3, 21.0)	**<0.001 [4]**
6MWT(meters)	19.2 (71.8) 90 23.6 (–210.0, 257.0)	–25.2 (78.4) 38 –26.8 (–325.4, 152.4)	50.4 [3] (20.2, 66.0)	**<0.001 [4]**

[1] Difference of means and unequal variance t-test confidence interval
[2] One-sided unequal variance t-test
[3] Difference of medians
[4] One-sided Wilcoxon rank-sum test

7.2.4 Subgroup Analysis: Fissure Integrity

Fissure Integrity remained in the pre-specified, multivariate, mixed-model analysis as a significant interaction with Zephyr EBV treatment for % change in FEV_1 at six months. Fissure Integrity was not a predictor for change in 6MWT. The changes in FEV_1 for the Complete Interlobar Fissure Subgroup (N = 68 for Zephyr EBV and N = 33 for Control) are shown in Table 13 below.

Table 13 Subgroup Analysis: Mean Change in FEV_1 by Fissure Integrity at 6 Months

	Zephyr EBV Mean (SD) N Median (Min, Max)	Control Mean (SD) N Median (Min, Max)	Delta [1] (95% CI)	p value [2]
FEV_1 (%)	13.5 (22.9) 68 9.5 (–28.7, 78.9)	–2.7 (10.2) 33 –3.7 (–21.0, 25.5)	16.2 (9.65, 22.76) [1]	**<0.001**
FEV_1 (mL)	101.6 (183.5)68 80.0 (–290.0, 640.0)	–34.6 (84.5) 33 –30.0 (–210.0, 140.0)	136.2 (83.2, 189.1)	**<0.001**

[1] Difference of means and unequal variance t-test confidence interval
[2] One-sided unequal variance t-test

7.2.5 Responder Analysis: FEV_1 and 6MWT

The proportion of Completed-Cases Zephyr EBV Subjects with ≥ 15% improvement in FEV_1 from baseline to 6 months was 23.5% compared with 10.7% of Control Subjects. That is, Zephyr EBV Subjects were 2.2 times more likely than Control Subjects to improve their FEV_1 by ≥ 15% through 6 months of follow-up.

In the High Heterogeneity Subgroup, the proportion of Completed-Cases Zephyr EBV Subjects with ≥ 15% improvement in FEV_1 from baseline to 6 months was 35.2% compared with 12.5% of Control Subjects. That is, Zephyr EBV Subjects in the High Heterogeneity Subgroup were 2.8 times more likely than Control Subjects in the High Heterogeneity Subgroup to improve their FEV_1 by ≥ 15% through 6 months of follow-up (see Table 14).

Table 14 Responder Analysis: Subjects with FEV_1 Improvement ≥ 15% at 6 Months

Increase ≥ 15% in FEV_1	Zephyr EBV % (n / N)	Control % (n / N)	Relative Rate (95% CI)	p value
Overall	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 Zephyr EBV Subjects with ≥ 15% improvement in 6MWT from baseline to 6 months was 25.3% compared with 17.8% of Control Subjects. That is,

Zephyr EBV Subjects were 1.4 times more likely than Control Subjects to improve their 6MWT by ≥ 15% through 6 months of follow-up.

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

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

Increase ≥ 15% in 6MWT	Zephyr EBV % (n / N)	Control % (n / N)	Relative Rate (95% CI)	p value
Overall	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**

7.3 Secondary Effectiveness Outcomes

7.3.1 Change in St. George's Respiratory Questionnaire Score

The St. George's Respiratory Questionnaire (SGRQ) is a standardized questionnaire for quality of life (QoL) assessment in airways disease, designed to allow comparative measurements of health between groups and to quantify changes in health following interventions. Three scales (Symptoms, Activity and Impacts) are combined into an overall score from 0 (best) to 100 (worst).

When the change from baseline in the SGRQ score was considered using multiple-imputation, Intent-to-Treat analysis, the Zephyr EBV Subjects had a mean 3.4 point improvement (score reduction) relative to Control Subjects (p = 0.017) (see Table 16). These findings of significance were confirmed by Completed-Cases univariate and multivariate mixed-model analyses.

Table 16 Secondary Effectiveness Outcome: Change in SGRQ Score at 6 Months

	Zephyr EBV Mean (SD) N Median (Min, Max)	Control Mean (SD) N Median (Min, Max)	Delta (95% CI) [1]	p value [2]
Multiple-Imputation, Intent-to-Treat*			–3.4 (–6.6, –0.3)	**0.017**
Completed Cases	–2.7 (13.3) 158 –2.2 (–35.9, 55.0)	0.7 (9.7) 62 1.5 (–25.8, 27.9)	–3.4 (–6.6, –0.2)	**0.019**

[1] Difference of means and unequal variance t-test confidence interval
[2] One-sided unequal variance t-test
* Multiple imputation derives a combined difference in outcomes between Zephyr EBV and Control arms, but does not derive changes for each individual arm.

A *post-hoc* responder analysis was performed on the proportion of Completed-Cases Subjects with significant improvement in SGRQ from baseline to 6 months. The analysis was performed using ≥ 8 points improvement (more than –8 point decline) to define a responder. This was based on the MCID value used in the NETT trial for lung volume reduction surgery. In order to improve by only 4 units, a subject would have to report that, compared to their state before starting treatment, he/she can now wash and dress more quickly, walk up stairs without having to stop, and go out for shopping or entertainment. All three of these improvements would have to occur to achieve a 4-unit improvement in SGRQ. The proportion of Zephyr EBV Subjects with ≥ 8 point improvement in SGRQ was 31.0% compared with 11.3% of Control Subjects. That is, Zephyr EBV Subjects were 2.8 times more likely than Control Subjects to improve their SGRQ by ≥ 8 points through 6 months of follow-up (see Table 17).

Table 17 Responder Analysis: Subjects with SGRQ Improvement of ≥ 8 Points at 6 Months

Improvement ≥ 8 Points in SGRQ	Zephyr EBV % (n / N)	Control % (n / N)	Relative Rate (95% CI)
Completed Cases	31.0 (49 / 158)	11.3 (7 / 62)	2.8 (1.3, 5.7)

7.3.2 Change in Modified Medical Research Council Dyspnea Scale

The Modified Medical Research Council Dyspnea Scale (mMRC) is a brief questionnaire designed to quantify the extent of dyspnea while performing activities of daily life, ranging from 0 (not troubled with breathlessness except during strenuous exercise) to 4 (too breathless to leave house, OR breathless when dressing/undressing).

When the change from baseline in the mMRC Dyspnea Scale was considered using the multiple imputation, Intent-to-Treat dataset, the Zephyr EBV Subjects had a mean 0.26 point improvement (score reduction) relative to Control Subjects (p = 0.018) (see Table

18). These findings of significance were confirmed by Completed-Cases univariate and multivariate mixed-model analyses.

Table 18 Secondary Effectiveness Outcome: Change in mMRC Dyspnea Scale at 6 Months

	Zephyr EBV Mean (SD) N Median (Min, Max)	Control Mean (SD) N Median (Min, Max)	Delta [1] (95% CI)	p value [2]
Multiple-Imputation, Intent-to-Treat*			–0.26 (–0.49, –0.02)	**0.018**
Completed Cases	–0.09 (1.04)162 0.00 (−3.00, 3.00)	0.21 (0.83) 67 0.00 (–2.00, 2.00)	–0.30 (–0.56, –0.05)	**0.011**

[1] Difference of means and unequal variance t-test confidence interval
[2] One-sided unequal variance t-test
* Multiple imputation derives a combined difference in outcomes between Zephyr EBV and Control arms, but does not derive changes for each individual arm.

A *post hoc* responder analysis was performed on the proportion of Completed-Cases Subjects with significant improvement in mMRC from baseline to 6 months. There is no clear MCID established in the literature for mMRC based on empirical evidence. An MCID of ≥ 1 point (≤ –1 point decline) was used since the mMRC Dyspnea Scale has only 5 categories, scored 0 – 4, and thus the smallest difference a subject can score is 1 point. Additionally, a similar dyspnea scale, the Transition Dyspnea Index, has a recommended MCID of 1 point.

The proportion of Zephyr EBV Subjects with ≥ 1 point improvement in the mMRC Scale Index was 29.0% compared with 16.4% of Control Subjects. That is, Zephyr EBV Subjects were 1.8 times more likely than Control Subjects to improve their mMRC score by ≥ 1 point through 6 months of follow-up (see Table 19).

Table 19 Responder Analysis: Subjects with mMRC Dyspnea Scale Improvement of ≥ 1 Point at 6 Months

Improved ≥ 1 Point in mMRC	Zephyr EBV % (n / N)	Control % (n / N)	Relative Rate (95% CI)
Completed Cases	29.0 (47 / 162)	16.4 (11 / 67)	1.8 (1.0, 3.2)

7.3.3 Change in Maximum Workload during Cycle Ergometry

Maximum exercise capacity in watts was determined by cycle ergometry in a testing protocol closely modeled on that used in the NETT study.

When the change from baseline in the maximum workload during cycle ergometry was considered using the multiple imputation, Intent-to-Treat dataset, the Zephyr EBV

Subjects had a median 3.8 watt improvement relative to Control Subjects (p = 0.020) (see Table 20). These findings of significance were confirmed by Completed-Cases univariate and multivariate mixed-model analyses.

Table 20 Secondary Effectiveness Outcome: Change in Maximum Workload during Cycle Ergometry (watts) at 6 Months

	Zephyr EBV Mean (SD) N Median (Min, Max)	Control Mean (SD) N Median (Min, Max)	Delta (95% CI)	p value
Multiple-Imputation, Intent-to-Treat*			3.8 [1] (0.2, 7.4)	**0.020** [2]
Completed Cases	0.1 (15.3) 166 0.0 (–110.0, 50.0)	–4.4 (12.8) 69 –5.0 (–40.0, 45.0)	5.0 [3] (0.0, 5.0)	**0.004** [4]

[1] Difference of means and unequal variance t-test confidence interval
[2] One-sided unequal variance t-test
[3] Difference of medians and non-parametric confidence interval
[4] One-sided Wilcoxon rank-sum test
* Multiple imputation derives a combined difference in outcomes between Zephyr EBV and Control arms, but does not derive changes for each individual arm.

A *post-hoc* responder analysis was performed on the proportion of subjects with significant improvement in Maximum Workload during Cycle Ergometry from baseline to 6 months. The MCID level used was 10 watts, based on the published assessments of the NETT cohort. Ten watts was considered a high threshold and was chosen in the NETT trial based on the high morbidity associated with LVRS. The proportion of Completed Cases Zephyr EBV Subjects with ≥ 10 watt improvement in Maximum Workload during Cycle Ergometry was 24.7% compared with 13.0% of Control Subjects. That is, Zephyr EBV Subjects were 1.9 times more likely than Control Subjects to show a ≥ 10 watt improvement in Maximum Workload during Cycle Ergometry through 6 months of follow-up (see Table 21).

Table 21 Responder Analysis: Subjects with Improvement in Maximum Workload during Cycle Ergometry ≥ 10 Watts at 6 Months

Increase ≥ 10 watts in max workload	Zephyr EBV % (n / N)	Control % (n / N)	Relative Rate (95% CI)
Completed Cases	24.7 (41 / 166)	13.0 (9 / 69)	1.9 (1.0, 3.7)

7.3.4 Change in Use of Supplemental Oxygen

The change from baseline to 6 months in subject-reported supplemental oxygen use during various conditions (continuous, during rest, during sleep and during exertion) was compared between the Zephyr EBV Subjects and Control Subjects. When the change from baseline in use of supplemental oxygen was considered using the multiple

imputation, Intent-to-Treat dataset, the Zephyr EBV Subjects had a median 12.0 liter/day reduction in oxygen requirement relative to Control Subjects (p = 0.020) (see Table 22). Reduction in use of supplemental oxygen did not reach statistical significance in the Completed Cases Cohort (p = 0.184).

Table 22 Secondary Effectiveness Outcome: Use of Supplemental Oxygen (liters / day)

	Zephyr EBV Mean (SD) N Median (Min, Max)	Control Mean (SD) N Median (Min, Max)	Delta (95% CI)	p value
Multiple-Imputation, Intent-to-Treat*			–12.0 [1] (–76.7, 52.7)	**0.020** [2]
Completed Cases	-17.1 (912.8) 171 0.0 (-3840.0, 3750.0)	82.9 (744.0) 75 0.0 (-2220.0, 3360.0)	-100.1 [3] (-318.6, 118.4)	0.184 [4]

[1] Difference of medians and non-parametric confidence interval. Confidence interval crosses zero despite statistical significance due to nonparametric, bimodal distribution of baseline data.
[2] One-sided Wilcoxon rank-sum test
[3] Difference of means and unequal variance t-test confidence interval. Although difference means is greater than for the ITT group, does not reach statistical significance due to unequal variances requiring an underpowered t-test of a non-parametric distribution.
[4] One-sided unequal variance t-test
* Multiple imputation derives a combined difference in outcomes between Zephyr EBV and Control arms, but does not derive changes for each individual arm.

The protocol pre-specified the analysis of the proportion of subjects whose oxygen consumption increased and the proportion of subjects whose oxygen decreased. Only those subjects who began the study on supplemental oxygen could have decreased utilization, while all subjects could theoretically increase oxygen consumption. Therefore, the denominator for decreased supplemental oxygen consumption is the number of subjects who entered the study on supplemental oxygen. The denominator for increased supplemental oxygen consumption is the Completed Cases cohort with oxygen utilization recorded. A greater proportion of Zephyr EBV Subjects showed a reduction in supplemental oxygen usage than Control Subjects (59% vs. 38% respectively) (see Table 23). Fewer Zephyr EBV Subjects increased their supplemental oxygen usage than Control Subjects, but this did not reach statistical significance.

Table 23 Proportion of Subjects with Decreased Supplemental O_2 Usage and Proportion of Subjects with Increased Supplemental O_2 Usage

	Zephyr EBV % (n / N)	Control % (n / N)	Relative Rate (95% CI)	p value
Decreased Supplemental O_2	59.0 (56 / 95)	37.5 (15 / 40)	1.6 (1.0, 2.4)	**0.012**
Increased Supplemental O_2	27.0 (48 / 178)	33.8 (26 / 77)	0.8 (0.5, 1.2)	0.065

7.4 Other Pre-Specified Outcomes Analyses

Additional pre-specified analyses on study outcomes included percent change in residual volume and diffusing capacity (DL_{CO}) and change in the BODE Index and the Quality of Well Being Scale using the CC population. There was no significant difference between groups in RV, DL_{CO}, or QWB (see Table 24).

Table 24 Change in Other Pre-Specified Outcomes

	Zephyr EBV Mean (SD) N Median (Min, Max)	Control Mean (SD) N Median (Min, Max)	Delta (95% CI)	p value
RV (%)	−1.29 (19.83) 176 −1.03 (−63.1, 65.8)	0.69 (21.95) 74 −2.27 (−44.2, 124.7)	1.25 [1] (−5.1, 3.64)	0.405
DL_{CO} (%)	1.81 (19.07) 178 1.05 (−46.8, 59.4)	−2.12 (17.45) 75 −1.69 (−85.6, 30.4)	2.74 [2] (−2.31, 6.67)	0.139
QWB	−0.01 (0.11) 173 0.00 (−0.4, 0.2)	−0.02 (0.10) 71 −0.01 (−0.3, 0.3)	0.01 (−0.01, 0.04)	0.170
BODE	−0.21 (1.25) 160 0.00 (−4.0, 3.0)	0.32 (1.07) 59 0.00 (−3.0, 3.0)	0 [2] (−1.00, −0.00)	**0.002**

[1] Difference of the medians -1.03 - (-2.27) = 1.25 due to rounding.
[2] Difference of the medians

There was a statistically significant improvement in the BODE Index.

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). A *post hoc* responder analysis was performed on the proportion of Completed Cases Subjects with significant improvement in the BODE Index from baseline to 6 months. The MCID level used was 1 unit, based on the studies of Celli and Martinez showing a survival benefit associated with a 1 unit improvement in BODE. In the Celli study, for each one-point increment in the BODE score the hazard ratio for death from any cause was 1.34 (95% CI 1.26, 1.42).

The proportion of Zephyr EBV Subjects with ≥ 1 point improvement (≤ –1 point decline) in the BODE Index was 40.0% compared with 18.6% of Control Subjects. That is, Zephyr EBV Subjects were 2.2 times more likely than Control Subjects to show a ≥ 1 point improvement (≤ –1 point decline) in this clinically-important index through 6 months of follow-up (see Table 25).

Table 25 Responder Analysis: Subjects with ≥ 1 Point Improvement in the BODE Index at 6 Months

Improvement ≥ 1 Point in BODE	Zephyr EBV % (n / N)	Control % (n / N)	Relative Rate (95% CI)
Completed Cases	40.0 (64 / 160)	18.6 (11 / 59)	2.2 (1.2, 3.8)

7.5 Impact of Protocol Violations on Primary Outcomes

Protocol violations were categorized based on their potential clinical impact by clinical study personnel blinded to the study arm. Pre-specified criteria for inclusion in this group were protocol violations of baseline or six month FEV_1, baseline or six month 6MWT, or pulmonary rehabilitation.

For change in FEV_1, there were 49 Zephyr EBV Subjects and 20 Control Subjects with potentially, clinically important protocol violations. Zephyr EBV Subjects with protocol violations performed worse than those without by 2.6%. Control Subjects with protocol violations performed better than those without by 2.8%.

Table 26 Protocol Violation Impact on FEV_1 Mean % Change (CC)

FEV_1 Mean % Change	Zephyr EBV Mean (SD) n Median (Min, Max)	Control Mean (SD) n Median (Min, Max)	Delta (95% CI)	p-value
Protocol Violation	3.42 (19.22) 49 1.67 (-21.01, 78.85)	0.16 (14.92) 20 -2.24 (-19.15, 38.60)	3.91 [3] (-5.19, 9.79) [4]	0.275 [5]
No Protocol Violation	6.01 (19.74) 130 4.06 (-38.33, 65.67)	-2.61 (11.11) 55 -3.66 (-27.69, 23.81)	8.62 [1] (4.10, 13.15)	**<0.001** [2]
delta	-2.59	2.77		

[1] Difference in means and unequal variance t-test confidence interval
[2] One-sided unequal variance t-test
[3] Difference in medians
[4] Non-parametric confidence interval
[5] One-sided Wilcoxon rank sum test

For change in 6MWT, there were 48 Zephyr EBV Subjects and 20 Control Subjects with potentially, clinically important protocol violations. Zephyr EBV Subjects with protocol violations performed worse than those without by 7.0%. Control Subjects with protocol violations performed better than those without by 8.4%.

Table 27 Protocol Violation Impact on 6MWT Mean % Change (CC)

6MWT Mean % Change	Zephyr EBV Mean (SD) n Median (Min, Max)	Control Mean (SD) n Median (Min, Max)	Delta (95% CI)	p-value
Protocol Violation	-0.79 (23.71) 48 0.00 (-53.45, 59.26)	4.63 (28.76) 20 -0.19 (-54.92, 71.43)	-5.42 [1] (-18.84, 8.01)	0.788 [2]
No Protocol Violation	6.19 (23.71) 130 5.89 (-83.33, 107.98)	-3.77 (19.44) 53 -4.98 (-50.43, 46.67)	10.87 [3] (3.88, 15.17)[4]	**0.001** [5]
delta	-6.98	8.40		

[1] Difference in means and equal variance t-test confidence interval
[2] One-sided t-test
[3] Difference in medians
[4] Non-parametric confidence interval
[5] One-sided Wilcoxon rank-sum test

Protocol violations did not bias the study in favor of the treatment arm, and seem to have biased the study against Zephyr EBV Treatment.

8 PRIMARY SAFETY OUTCOME

8.1 Primary Safety Outcome: Major Complications Composite at 6 Months (per Subject)

The Primary Safety Outcome for the VENT Pivotal Trial was the proportion of subjects in each group with one or more Major Complications through 6 months of follow-up, using the mITT population. No *a priori* inference test was established and there was no expectation of equivalence between the Zephyr EBV Treatment Group and the non-active Control Group. The MCC rate for the pilot study lobar-exclusion subgroup was 19.1% at 90 days. Even with some expected MCC events in the Control arm, it was assumed that the Zephyr EBV Treatment would have a significantly higher MCC rate than the Control.

There were 6 Zephyr EBV Subjects and 14 Control Subjects that had no treatment and no follow-up at 30-days or later, leaving 214 of 220 Zephyr EBV Subjects and 87 of 101 Control Subjects for safety analysis (Zephyr EBV Treatment : Control mITT ratio = 2.5 : 1). Subjects who had one or more of these events during study follow-up were considered to have experienced an MCC on the date of the first such adverse event to occur. The Major Complications Composite (MCC) consisted of the events listed in the following table.

Table 28 Components of the Major Complications Composite (MCC)

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

Note that one of the components of the MCC (*i.e.* Pneumonia distal to the implanted valves) could not occur in the Control Group.

One or more MCCs occurred in 6.1% of Zephyr EBV Subjects and in 1.2% of Control Subjects (p = 0.075) (see Table 29). The difference in MCC rates was not statistically significant.

At six months, death occurred in 2.8% Zephyr EBV Subjects and in no Control Subjects (p = 0.187). Only one of the deaths in the first six months was determined to be possibly or probably device-related. In the second six months of follow-up, death occurred in 0.9% of Zephyr EBV Subjects and in 3.5% of Control Subjects (p = 0.147). The

cumulative mortality rate over the year of follow-up was 3.7% for Zephyr EBV and 3.5% for Control (p = 1.000). Table 30 provides a listing of deaths.

Table 29 Primary Safety Outcome: Major Complications Composite at 6 Months*

Safety Outcome	Zephyr EBV % (n / N)	Control % (n / N)	Delta (95% CI) [1]	p value [2]
MCCs at 6 months[3]	6.1% (13 / 214)	1.2% (1 / 87)	4.9% (1.0, 8.8)	0.075
Death, all-cause	2.8% (6 / 214)	0.0% (0 / 87)	2.8% (0.6, 5.0)	0.187
Empyema	0.0% (0 / 214)	0.0% (0 / 87)	--	--
Massive hemoptysis	0.5% (1 / 214)	0.0% (0 / 87)	0.5% (−0.5, 1.4)	1.000
Distal pneumonia	1.4% (3 / 214)	--	--	--
Prolonged pneumothorax	1.4% (3 / 214)	1.2% (1 / 87)	0.3% (−2.5, 3.0)	1.000
Respiratory failure > 24 hours	1.9% (4 / 214)	1.2% (1 / 87)	0.7% (−2.2, 3.6)	1.000

[1] Fisher's exact 95% confidence interval
[2] Two-sided Fisher's exact test
[3] A subject may have had more than one MCC event. In this case, the subject would be counted in multiple individual event numerators but only once in MCC numerator.
* Treatment : Control mITT ratio = 2.5:1

No subject in either group had empyema and one (0.5%) Zephyr EBV Subject had massive hemoptysis (see Section 8.4.4 for a discussion of this event). Pneumonia distal to a valve occurred in 1.4% of Zephyr EBV Subjects (see Section 8.4.3 for more detail on these events). Prolonged pneumothorax occurred in 1.4% of Zephyr EBV Subjects and in 1.2% of Control Subjects. Respiratory failure requiring mechanical ventilation for more than 24 hours occurred in 1.9% of Zephyr EBV Subjects and in 1.2% of Control Subjects.

A multivariate Cox regression analysis was done to evaluate the impact of covariates on the occurrence of at least one MCC in the 180 day window. No covariates survived the final model and Zephyr EBV Treatment was not significantly associated with MCC at 6 months (p = 0.144).

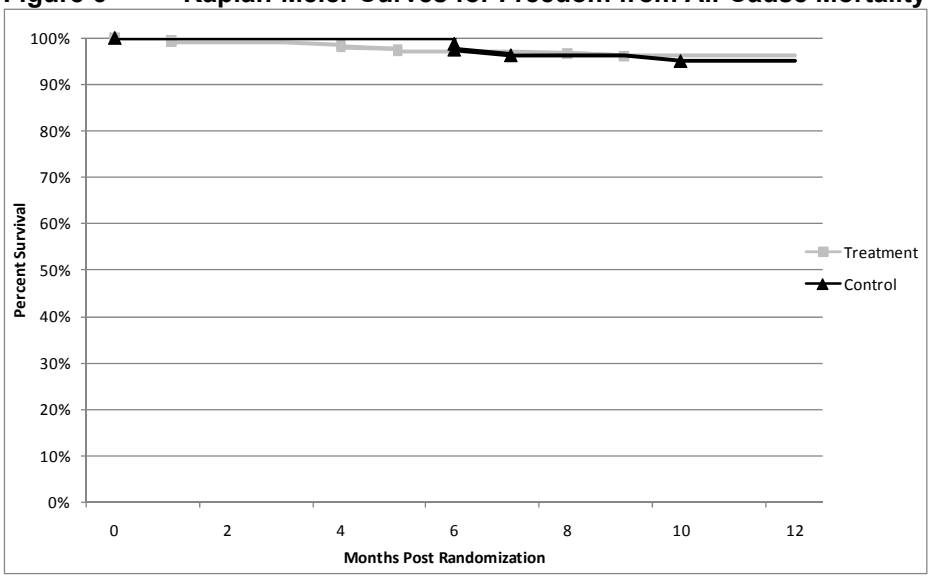
8.2 One Year Safety

8.2.1 All-Cause Mortality

Equivalent outcomes for all-cause mortality through one year were demonstrated by Kaplan-Meier analysis. There were 3.7% deaths in the Zephyr EBV Subjects and 3.5% deaths in the Control Subjects cumulatively through one year (p = 1.000). There was no

difference in the survival curves for the Zephyr EBV Subjects and Control Subjects (96.0% and 96.3% freedom from all-cause mortality respectively, p = 0.876, log rank test) (see Figure 6).

Figure 6 Kaplan-Meier Curves for Freedom from All-Cause Mortality



8.2.2 Per-Subject Listing of Deaths

Over the year of study follow-up, there were 8 Zephyr EBV Subjects who died (3.7%) and 3 Control Subjects (3.5%). Only one of the deaths in Zephyr EBV Subjects was determined to be possibly or probably device-related (see Table 30).

Table 30 Per-Subject Listing of Deaths [1]

Randomization Arm	Cause of Death	CEC Adjudication [2]	
		Device Related	Procedure Related
Zephyr EBV	Ischemic Colitis	No	No
Zephyr EBV	Massive hemoptysis, respiratory failure, hypoxic brain injury	Probably	Possibly
Zephyr EBV	Stage IV adenocarcinoma of the liver, adrenal glands, and lymph glands	No	No
Zephyr EBV	Respiratory failure secondary to COPD exacerbation associated with septic shock	Remotely	No
Zephyr EBV	Severe pulmonary emphysema with sub-pleural bullae	Remotely	No
Zephyr EBV	Respiratory failure secondary to advanced COPD and emphysema	No	No
Zephyr EBV	Metastatic liver cancer	No	No
Zephyr EBV	Community acquired pneumonia	Remotely	No
Control	Respiratory failure secondary to COPD	n/a	n/a
Control	Iatrogenic pneumothorax from lung biopsy – respiratory failure	n/a	n/a
Control	Non-small cell lung cancer	n/a	n/a

Deaths between groups are not disproportionate – Zephyr EBV = 3.7%, Control = 3.5% – based on 2:1 enrollment
[2] CEC Choices for Probability of Relatedness: Not Related, Remotely, Possibly, Probably
[3] Detailed discussion below in Section 8.4.4

8.2.3 MCCs by Time Period of 6 to 12 Months (per Subject)

The rate of occurrence of MCCs during the second 6 months of follow-up demonstrated an equivalent rate of MCCs in Zephyr EBV Subjects (4.7%) compared with Control Subjects (4.6%). Zephyr EBV Subjects had a 0.9% mortality rate during this period compared with Control Subjects (3.5%). No subjects in either group had empyema or massive hemoptysis in the 6 to 12 month follow-up period. Pneumonia distal to a valve occurred in 2.8% of Zephyr EBV Subjects, an event that could not occur in Control Subjects. One Zephyr EBV Subject had a pneumothorax lasting more than 7 days, and there was an equivalent rate of respiratory failure, 0.9% in Zephyr EBV Subjects and 1.2% in Control Subjects (see Table 31).

Table 31 Major Complication Composite for First and Second 6-Month Time Periods

MCCs by Time Period	0 – 194 Days		195 – 386 Days	
	Zephyr EBV	Control	Zephyr EBV	Control
MCCs	6.1% (13 / 214)	1.2% (1 / 87)	4.7% (10 / 214)	4.6% (4 / 87)
Death	2.8% (6 / 214)	0.0% (0 / 87)	0.9% (2 / 214)	3.5% (3 / 87)
Empyema	0.0% (0 / 214)	0.0% (0 / 87)	0.0% (0 / 214)	0.0% (0 / 87)
Massive hemoptysis	0.5% (1 / 214)	0.0% (0 / 87)	0.0% (0 / 214)	0.0% (0 / 87)
Distal pneumonia	1.4% (3 / 214)	--	2.8% (6 / 214)	--
Pneumothorax	1.4% (3 / 214)	1.2% (1 / 87)	0.5% (1 / 214)	0.0% (0 / 87)
Respiratory failure > 24 hours	1.9% (4 / 214)	1.2% (1 / 87)	0.9% (2 / 214)	1.2% (1 / 87)

The MCC rates in the Zephyr EBV Treatment Subjects spike in the first quarter post-procedure and decline over time such that they are equivalent to the Control Subject rate from months 7-12 (see Figure 7 below).

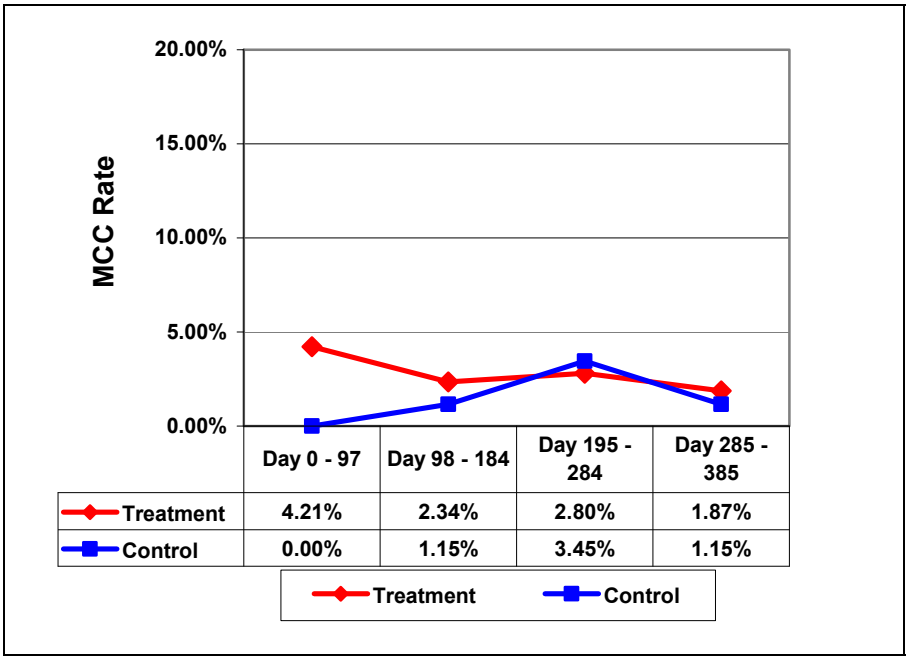


Figure 7 Per Subject MCC Rates by Quarter of Follow-up

8.3 Serious Adverse Events (SAEs)

Serious adverse events (SAEs) through 1 year of follow-up are summarized in the following table.

Table 32 Per-Subject Serious Adverse Events through 1 Year

Serious Adverse Events through 1 year	Zephyr EBV N = 214 % (95% CI)	Control N = 87 % (95% CI)	p value
All-cause mortality	3.7% (1.6 - 7.2%)	3.5% (0.7 - 9.8%)	1.000
Arrhythmia	2.3% (0.8 - 5.4%)	2.3% (0.3 - 8.1%)	1.000
CHF	0.5% (0.0 - 2.6%)	1.2% (0.0 - 6.2%)	0.495
CAD	1.9% (0.5 - 4.7%)	1.2% (0.0 - 6.2%)	1.000
Stroke	0.5% (0.0 - 2.6%)	0.0% (0.0 - 4.2%)	1.000
COPD exacerbation with hospitalization	18.2% (13.3 - 24.1%)	10.3% (4.8 - 18.7%)	0.117
COPD exacerbation w/o hospitalization	2.8% (1.0 - 6.0%)	0.0% (0.0 - 4.2%)	0.187
Other pulmonary infection	3.3% (1.3 - 6.6%)	0.0% (0. 0 - 4.2%)	0.199
Respiratory failure	3.3% (1.3 - 6.6%)	3.5% (0.7 - 9.8%)	1.000
Pneumonia not distal to valve	7.0% (4.0 - 11.3%)	9.2% (4.1 - 17.3%)	0.485
New/worse hypercapnia	1.4% (0.3 - 4.0%)	0.0% (0.0 - 4.2%)	0.559
Hypoxemia	1.9% (0.5 - 4.7%)	0.0% (0.0 - 4.2%)	0.328
Massive hemoptysis	0.5% (0.0 - 2.6%)	0.0% (0.0 - 4.2%)	1.000
Other hemoptysis[1]	11.7% (7.7 - 16.8%)	0.0% (0.0 - 4.2%)	**<0.001**
Air leak > 7 days	1.9% (0.5 - 4.7%)	1.2% (0.0 - 6.2%)	1.000
Expanding pneumothorax	1.9% (0.5 - 4.7%)	2.3% (0.3 - 8.1%)	1.000
Stable pneumothorax	0.9% (0.1 - 3.3%)	0.0% (0.0 - 4.2%)	1.000
Non-cardiac chest pain	0.9% (0.1 - 3.3%)	0.0% (0.0 - 4.2%)	1.000
Lung mass / cancer	0.0% (0.0 - 1.7%)	1.2% (0.0 - 6.2%)	0.289
Other non-pulmonary infections	1.4% (0.3 - 4.0%)	1.2% (0.0 - 6.2%)	1.000
Other pain	0.5% (0.0 - 2.6%)	0.0% (0.0 - 4.2%)	1.000

Serious Adverse Events through 1 year	Zephyr EBV N = 214 % (95% CI)	Control N = 87 % (95% CI)	p value
Gastrointestinal	3.7% (1.6 - 7.2%)	1.2% (0.0 - 6.2%)	0.455
Other general	5.1% (2.6 - 9.0%)	3.5% (0.7 - 9.8%)	0.764
Valve-specific SAEs			
Expectoration / migration	7.5% (4.3 - 11.9%)		
Pneumonia distal to valve	4.2% (1.9 - 7.8%)		
Bronchial granulation tissue	6.5% (3.6 - 10.7%)		
Bronchial trauma	0.5% (0.0 - 2.6%)		

[1]Other hemoptysis (SAE) is defined as any non-massive hemoptysis (less than 300 ml of blood in 24 hours and no resultant respiratory failure) adjudicated as serious by the Clinical Events Committee.

COPD Exacerbations (combined with and without hospitalization) and hemoptysis had greater rates in the Zephyr EBV Group over the course of one year.

The rate of Zephyr EBV Treatment Subjects with COPD exacerbations peaked in the first quarter post randomization and then declined steadily over the 1-year study follow-up period to a rate very similar to Control (see Figure 8 below).

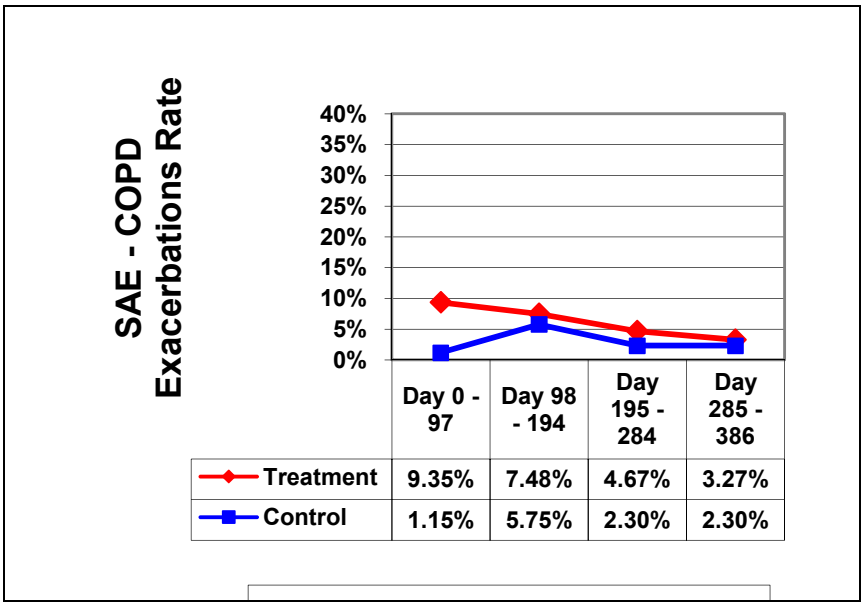
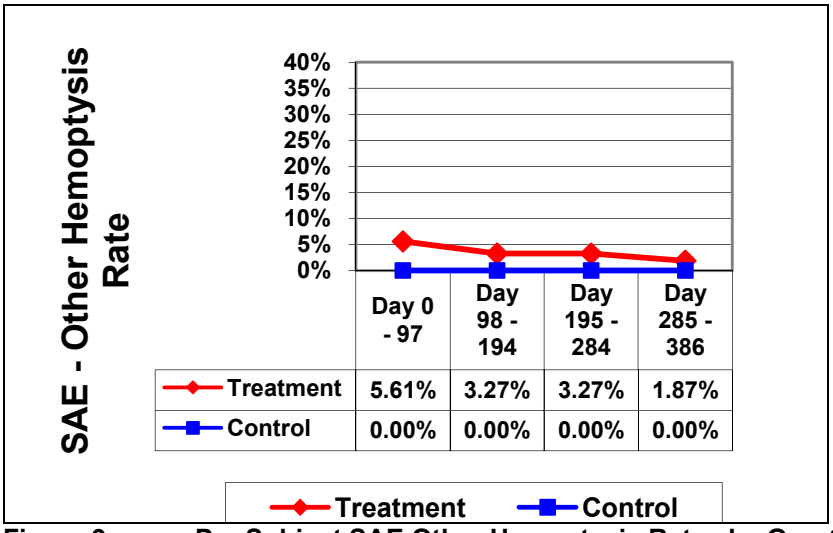


Figure 8 **Per Subject SAE COPD Exacerbation Rates by Quarter of Follow-up (includes Exacerbations with and without Hospitalization)**

Similarly, the rate of Zephyr EBV Treatment Subjects with hemoptysis peaked in the first quarter post randomization but then remained at a low rate (2-3%) over the remainder of the 1-year study follow-up period (see Figure 9 below).



	Day 0 - 97	Day 98 - 194	Day 195 - 284	Day 285 - 386
Treatment	5.61%	3.27%	3.27%	1.87%
Control	0.00%	0.00%	0.00%	0.00%

Figure 9 Per Subject SAE Other Hemoptysis Rates by Quarter of Follow-up

8.4 Zephyr EBV Subjects with Specific Adverse Events

8.4.1 Granulation Tissue

Seventeen (17) Zephyr EBV Subjects (7.9% of 214 subjects) were found to have granulation tissue proximal to valves during the course of study follow-up. The observed granulation tissue was believed by investigators to be typical reactive tissue that can form adjacent to any foreign body present in the airways, such as that which forms at the distal end of an indwelling metal tracheostomy. Twelve (12) of these subjects had valves removed, one subject was treated by electrocautery and topical Mitomycin, one subject was treated by exploratory bronchoscopy and cryotherapy, one subject was treated by exploratory bronchoscopy alone, one subject was treated with drug therapy, and one subject received no treatment for the granulation formation.

Based on bronchoscopic assessment, granulation tissue formation was determined to commonly result from improper valve placement. A “Depth Mark” was added to the distal end of the delivery catheter subsequent to the study conclusion in order to mitigate improper placement (See Figure 3, Section 2.2). This modification has been successfully used in commercial European applications and is expected to reduce the frequency of the occurrence of granulation tissue formation.

8.4.2 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 214 Zephyr EBV Treatment Subjects. Of these 820 valves, 23 valves (2.8%) in 17 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.

Based on HRCT and bronchoscopic assessment, migration and expectoration was determined to commonly result from improper valve placement. A "Depth Mark" was added to the distal end of the delivery catheter subsequent to the study conclusion in order to mitigate placement errors (See Figure 3, Section 2.2). This modification has been successfully used in commercial European applications and is expected to reduce the frequency of the occurrence of migration and expectoration.

8.4.3 Pneumonia Distal to Valves

Nine (9) Zephyr EBV Subjects (4.2%) had pneumonia distal to valves during the 1 year follow-up period. All subjects received drug therapy and valves were removed from 3 of the 9 subjects (33.3%). Pneumonia resolved for eight (8) of the nine (9) subjects during the study follow-up period and one was ongoing at the end of the 1-year study follow-up period. The subject with an unresolved pneumonia distal to valves at study exit had been admitted for treatment (drug therapy and bronchoscopy) during the trial and was discharged on oral antibiotics three days post study exit. The valves in this subject were not removed during bronchoscopy (see Table 33).

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* Effort was made to obtain bronchoscopic video of the placement procedure when valve migration was reported. Of the 23 instances of Zephyr EBV migration, procedural video was obtained for 14. A qualitative assessment was made by Emphasys technical personnel. They identified 3 probable root-causes for the migration (see bullet points below). Based on these findings, additional training was initiated. Additionally, a visual "marker band" was added to the distal end of the delivery catheter in order to aid physicians in calibrating the depth of the bronchial target and the longitudinal position of the valve relative to the carina of the target bronchus. This marker band was not implemented during the conduct of the study.

- Bronchial target too short for Zephyr EBV placement (2/14)
- Zephyr EBV placed too proximal within target bronchus (6/14)
- Bronchial target too large in diameter for Zephyr EBV placement (5/14)
- Zephyr EBV did not migrate – compared follow-up video to procedural video (1/14)

Table 33 Zephyr EBV Subjects with Pneumonia Distal to Valves

Subject ID	Actions Taken	Days Post Procedure	Resolved
	Drug Therapy, Valve Removal	0[1]	Yes
	Drug Therapy, Bronchoscopy	356	Ongoing at study exit
	Drug Therapy, Hospitalization	163	Yes
	Drug Therapy	275	Yes
	Drug Therapy, Bronchoscopy, Hospitalization	230	Yes
	Drug Therapy	208	Yes
	Drug Therapy, Valve Removal	258	Yes
	Drug Therapy, Valve Removal	208	Yes
	Drug Therapy, Hospitalization	15	Yes

Date of onset was reported by site as Unknown. Earliest possible onset date was the date of the Zephyr EBV procedure.

8.4.4 Massive Hemoptysis

There was one case of massive hemoptysis in the Zephyr EBV Group. Subject was treated in the right upper lobe and complained of recurrent hemopt possible vomiting of blood, and dyspnea between the original procedure and Day 8 of follow-up. On Day 8, the subject experienced increased hemoptysis followed by cardiorespiratory arrest. He was intubated and ventilated. Bronchoscopy revealed bleeding from the right upper and middle lobes, more in the right upper. After two weeks clear evidence of irreversible hypoxic brain led to withdrawal of support and subsequent death. Autopsy revealed advanced bullous emphysema with all 4 Zephyr EBVs in position without perforation, migration or intrusion into blood vessels, and without any clear source of bleeding. This event was reviewed by the DSMB and promptly communicated to the FDA, IRBs and participating Investigators with recommendations for close monitoring of subjects with recurrent hemoptysis. No other case of massive hemoptysis occurred during study follow-up.

8.5 Valve Removal during Study Follow-Up

Eighty seven (87) valves were removed in 31 (14.5%) Zephyr EBV Subjects during the one-year follow-up period, with 85 of the 87 valves (97.7%) being successfully removed. The only 2 valves which were not successfully retrieved were in a subject who had 2 of 4 attempted valves removed in a single procedure and no subsequent attempt to remove the remaining 2 valves. Table 34 summarizes reasons for attempted valve removals.

Table 34 Per-Subject Reasons for Attempted Valve Removal during Study Follow-up

Zephyr EBV Group (per subject)	% (n) [1]
Migration	3.7% (8 / 214)
Subject's Request	3.3% (7 / 214)
Placed in Incorrect Airway	1.4% (3 / 214)
Continuing COPD Exacerbation	0.9% (2 / 214)
Post Obstructive Pneumonia	0.5% (1 / 214)
Pneumonia, Hemoptysis	0.5% (1 / 214)
Hemoptysis	0.5% (1 / 214)
Hemoptysis & Granulation Tissue	0.5% (1 / 214)
Granulation	0.5% (1 / 214)
Granulation and Migration	0.5% (1 / 214)
Increased Dyspnea	0.5% (1 / 214)
To Access Distal Airway for Biopsy	0.5% (1 / 214)
Other	1.4% (3 / 214)

[1] Denominator = 214 subjects with valves placed

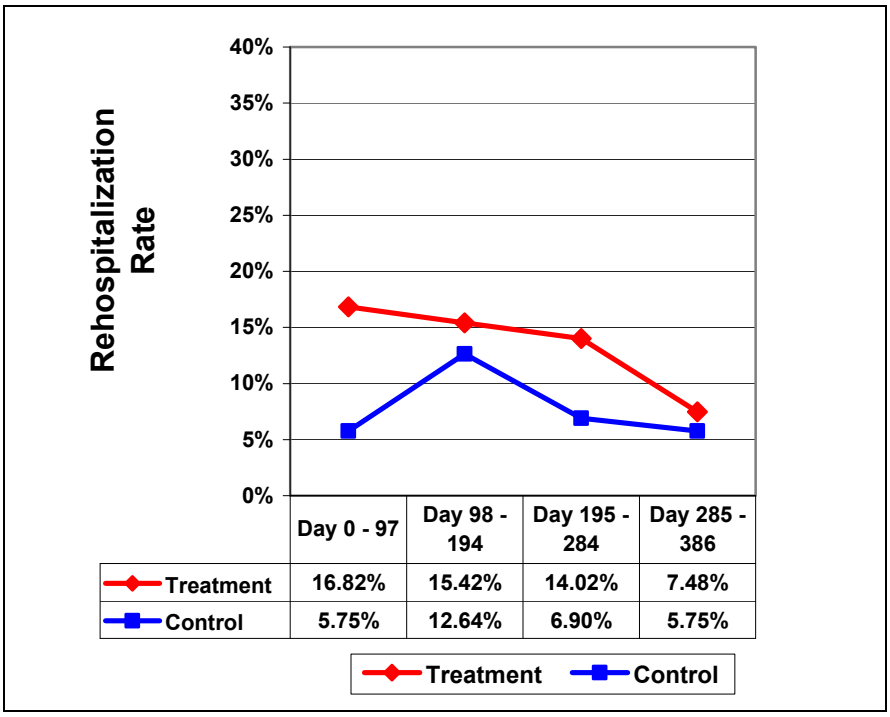
8.5.1 Rehospitalization

Rehospitalization rates through 6 months were 27.1% for Zephyr EBV Subjects and 16.1% for Control Subjects, a difference that bordered on significant (p = 0.052). For the period from 6 to 12 months, this difference began to converge, with 19.6% for Zephyr EBV Subjects and 12.6% for Control Subjects (see Table 35). Most of this difference occurred during the first quarter of follow-up in subjects who required removal of one or more Zephyr valves.

Table 35 Rehospitalization Rates for First and Second 6-Month Time Periods (per Subject)

Rehospitalization	Zephyr EBV Subjects %	Control Subjects %	Risk Ratio (95% CI)	p value
From 0 to 6 Months	27.1%	16.1%	1.7 (1.0, 2.9)	0.052
From 6 to 12 Months	19.6%	12.6%	1.6 (0.8, 2.9)	0.182

Rehospitalization rates were higher for Zephyr EBV Subjects than for Control Subjects during the first three quarters post randomization. The rates were very similar by the fourth quarter post randomization (see Figure 10Figure 10), indicating that the reasons for increased rehospitalization resolved over time. This was likely due to the removal of valves for some Subjects and a "settling in" of the valves for others. All adverse events were plotted over time and all showed the same pattern of reducing over time, nearing or equaling the Control rates after six to nine months. Based on these declining rates, there does not appear to be a chronic risk of rehospitalization after this initial period.



	Day 0 - 97	Day 98 - 194	Day 195 - 284	Day 285 - 386
Treatment	16.82%	15.42%	14.02%	7.48%
Control	5.75%	12.64%	6.90%	5.75%

Figure 10 Per Subject Rehospitalization Rates by Quarter of Follow-up

8.6 Summary: Primary Safety Outcome

At 6 months of follow-up, Control Subjects had a 1.2% (1 / 87) rate of MCCs compared to Zephyr EBV Subjects who had a 6.1% (13 / 214) rate of MCCs, a difference that was not significant (p = 0.075, Fisher's exact test). A Cox regression analysis was done to evaluate the impact of covariates on the occurrence of at least one MCC in the 180 day window. No covariates survived the final model and Zephyr EBV Treatment was not significantly associated with MCC at 6 months (p = 0.144).

In the second six months of follow-up, the MCC rate in Zephyr EBV Subjects (4.7%) and the MCC rate in Control Subjects (4.6%) were almost identical. Over the year of follow-up, the MCC rate for Control Subjects (4.6%) and for Zephyr EBV Subjects (10.3%) were not significantly different (p = 0.172, Fisher's exact test).

All-cause mortality over one year was equivalent for the two groups: 3.5% for the Control Subjects and 3.7% for the Zephyr EBV Subjects (p = 0.876, log rank test).

Rehospitalization rates through 6 months were 27.1% for Zephyr EBV Subjects and 16.1% for Control Subjects, a difference that bordered on significant (p = 0.052). For the period from 6 to 12 months, this difference began to converge, with 19.6% for Zephyr EBV Subjects and 12.6% for Control Subjects. Most of this difference occurred during the first quarter of follow-up in subjects who required removal of one or more Zephyr valves.

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 rates diminish over time and were often resolved by removing the valves. This compares favorably to ineffective medical therapy (which also has associated adverse events), unavailable lung transplantation, and the much higher risk LVRS. These data provide valid scientific evidence of reasonable assurance that the Zephyr EBV is safe for its intended patient population.

9 TARGET LOBE VOLUME REDUCTION

Several analyses of target lobe volume change in Zephyr EBV Subjects were performed to explore the morphological effect of Zephyr EBV treatment. It was hypothesized that Zephyr EBV treatment would lead to target lobe volume reduction (TLVR) as measured by the Target Lobe Atelectasis Score (TLAS).

9.1 Zephyr EBV Treatment Leads to TLVR

Target Lobe Volume Reduction (TLVR) was assessed by Target Lobe Atelectasis Score at total lung capacity ($TLAS_{TLC}$) (see Section 3.5.4). TLAS is a direct measure of target lobar volume change over time, calculated as the percentage difference in HRCT-assessed volume from baseline to 6 months.

Implantation of the Zephyr EBV in study subjects was associated with a large and highly significant difference in the $TLAS_{TLC}$ ($p < 0.001$) at 6 months between Zephyr EBV Subjects (−20.6%) and Control Subjects (−1.7%), (see Table 36). Thus, Zephyr EBV Treatment results in a net reduction of 19% in the target lobe as compared to the Control Group.

Table 36 Effect of Zephyr EBV Treatment on $TLAS_{TLC}$

	Zephyr EBV Mean (SD) N Median (Min, Max)	Control Mean (SD) N Median (Min, Max)	Delta (95% CI)
$TLAS_{TLC}$	−20.6% (27.3%) 172 −12.2% (−97.7%, 19.3%)	−1.7% (7.0%) 73 −1.1% (−27.5%, 9.8%)	−18.9% (−23.3, −14.5)

9.2 TLVR Leads to Volume Redistribution

HRCT assessment of volume redistribution demonstrated a statistically significant reduction in target lobe volume and the attendant increases in adjacent non-target lobe volumes (see Table 37). These results demonstrate the achievement of the hypothesized mechanism of target lobe volume reduction and expansion of the healthier adjacent lobe.

Table 37 Volume Redistribution Results - CC (6 Months)

Change from Baseline	Zephyr EBV Mean (N)	Control Mean (N)	Delta	p value
Target Lobe Volume Change (mL)	-378.4 (189)	-16.3 (79)	-362.1	**< 0.001**
Ipsilateral Non-Target Lobe Volume Change at TLC (mL)	207.7 (189)	-35.4 (79)	243.1	**<0.001**

9.3 Relationship between Target Lobe Volume Reduction and FEV_1

Analysis of the relationship between TLVR measured by $TLAS_{TLC}$ and therapeutic benefit measured by percent change in FEV_1 at 6 months demonstrates a difference between Control Subjects and Zephyr EBV Subjects. Control Subjects have no significant relationship between these two variables, whereas Zephyr EBV Subjects demonstrate much more substantial reductions in $TLAS_{TLC}$ and a significant association between $TLAS_{TLC}$ and Percent Change in FEV_1 in the Zephyr EBV Subjects ($r^2 = 0.279$, $p < 0.001$, $n = 179$). This is demonstrated in the following chart:

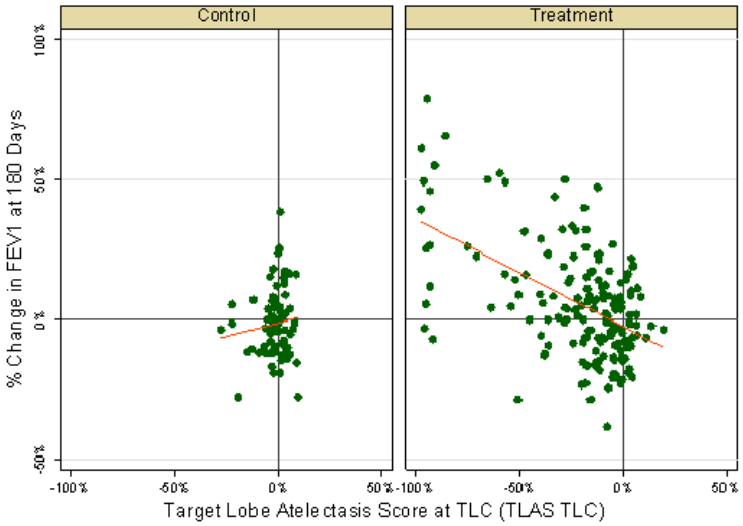


Figure 11 $TLAS_{TLC}$ vs. % Change in FEV_1

9.4 Fissure Integrity and Target Lobe Volume Reduction

Zephyr EBV Treatment Subjects with Complete Fissures in the target lobe as determined by HRCT had significantly larger reductions in $TLAS_{TLC}$ compared to Zephyr EBV Treatment Subjects with Incomplete Fissures.

For the left lung, subjects with a complete left oblique fissure had a greater reduction in $TLAS_{TLC}$ (−40.1%) compared with subjects whose left oblique fissures were incomplete (−20.7%, $p = 0.011$) (see Table 38).

Table 38 Left Target Lung, Fissure Integrity and $TLAS_{TLC}$ (CC)

	Incomplete Left Oblique Fissure Mean (SD) N Median (Min, Max)	Complete Left Oblique Fissure Mean (SD) N Median (Min, Max)	Delta 95% CI
$TLAS_{TLC}$	−20.7% (22.8%) 25 −11.7% (−71.0, 19.3%)	−40.1% (36.9%) 40 −27.9% (−96.1, 4.0%)	−19.4% (−34.2, −4.6)

The right lung, with two fissures, is more complicated, but the same positive effect of HRCT-determined fissure integrity on the magnitude of $TLAS_{TLC}$ response is present. Subjects with both fissures complete have a significantly greater change in $TLAS_{TLC}$ of −33.0% compared to −4.4% if neither fissure is complete (see Table 39).

Table 39 Right Target Lung, Fissure Integrity and $TLAS_{TLC}$

	$TLAS_{TLC}$ Mean (SD) N Median (Min, Max)
Both Fissures Complete	−33.0% (27.9%) 23 −25.4% (−97.7, 3.3%)
Right Horizontal-Only Complete	−13.3% (12.0%) 13 −12.6% (−36.4, 3.7%)
Right Oblique-Only Complete	−10.1% (10.1%) 24 −10.7% (−36.3, 8.6%)
Neither Fissure Complete	−4.4% (10.9%) 39 −2.6% (−37.9, 13.8%)

9.5 Volume Redistribution Discussion

These analyses support the clinical hypothesis that Zephyr EBV-induced target lobe volume reduction along with adjacent lobe volume increases lead to improved breathing mechanics as evidenced by FEV_1 results. Furthermore, the strong correlation between target lobe fissure integrity and target lobe volume reduction supports the hypothesis that fissure integrity is a surrogate for inter-lobar collateral flow. Significant inter-lobar collateral flow would allow air to re-enter the treated lobe distal to the valves and inhibit the volume reduction that would be seen if the lobe was a closed system.

10 ONE YEAR EFFECTIVENESS ANALYSIS

10.1 Introduction

Although the VENT Pivotal Study was not designed to assess effectiveness outcomes past 6 months, *post hoc* assessments of effectiveness outcome measures were made for Completed Cases subjects with one year follow-up data.

10.2 Effectiveness Outcome Measures at 1 Year

10.2.1 Change in FEV_1 at 1 Year

At the end of 1 year of follow-up, Zephyr EBV Subjects demonstrated a 6.7% higher FEV_1 and Control Subjects a 1.4% lower FEV_1, for an 8.1% net difference between the two groups (95% CI 4.0, 12.2%), (see Table 40). This persistent Zephyr EBV treatment benefit was slightly larger than the 7.2% net difference observed at 6 months.

Table 40 Change in FEV_1 at 1 Year

FEV_1 – Change from Baseline	Zephyr EBV Mean (SD) N Median (Min, Max)	Control Mean (SD) N Median (Min, Max)	Delta [1] (95% CI)
Overall (%)	6.7 (22.1) 175 2.0 (–34.2, 88.4)	–1.4 (10.8) 74 –1.7 (–29.1, 31.6)	8.1 (4.0, 12.2)
Overall (mL)	50.4 (185.9) 175 20.0 (–420.0, 730.0)	–13.9 (99.1) 74 –15.0 (–320.0, 360.0)	64.3 (28.5, 100.1)
High Heterogeneity Subgroup (%)	13.6 (24.2) 87 10.2 (-32.5, 88.4)	-1.6 (10.4) 41 0.0 (-29.1, 21.8)	15.2 (9.1, 21.2)
High Heterogeneity Subgroup (mL)	110.8 (204.2) 87 70.0 (–320.0, 730.0)	–21.5 (88.0) 41 0.0 (–320.0, 120.0)	132.3 (81.1, 183.4)

[1] Difference of means and unequal variance t-test confidence interval

In the High Heterogeneity Subgroup at the end of 1 year of follow-up, Zephyr EBV Subjects demonstrated a 13.6% higher FEV_1 and Control Subjects a 1.6% lower FEV_1, for a 15.2% net difference between the two groups (95% CI 9.1, 21.2%). This persistent Zephyr EBV treatment benefit was greater than the 8.1% net difference observed in the entire Completed Cases cohort at 1 year.

10.2.2 Change in 6MWT at 1 Year

At the end of 1 year of follow-up, Zephyr EBV Subjects demonstrated a 0.4% reduction and Control Subjects a 3.9% reduction in 6MWT, for a 3.6% net Zephyr EBV treatment benefit (see Table 41).

Table 41 Change in 6MWT at 1 Year

6MWT – Change from Baseline	Zephyr EBV Mean (SD) N Median (Min, Max)	Control Mean (SD) N Median (Min, Max)	Delta (95% CI)
Overall (%)	–0.4 (26.3) 173 1.1(-98.3, 108.0)	–3.9 (16.9) 75 -3.2 (-63.1, 31.6)	3.6 [1] (–1.8, 9.2)
Overall (meters)	–2.6 (76.3) 174 4.0 (–242.5, 257.0)	–18.1 (67.3) 75 –10.0 (–373.7)	14.0 [2] (–2.7, 30.3)
High Heterogeneity Subgroup (%)	3.1 (29.2) 87 3.2 (-75.6, 108.0)	-5.0 (19.2) 41 -3.5 (-63.1, 29.5)	8.2 [1] (-0.4, 16.7)
High Heterogeneity Subgroup (meters)	5.1 (83.1) 88 11.6 (–242.5, 257.0)	–24.7 (78.8) 41 –15.0 (–373.7, 97.5)	26.6 [2] (4.0, 51.0)

[1] Difference of means and unequal variance t-test confidence interval [difference due to rounding]
[2] Difference of medians and non-parametric confidence interval

In the High Heterogeneity Subgroup at the end of 1 year of follow-up, Zephyr EBV Subjects demonstrated a 3.1% higher 6MWT and Control Subjects a 5.0% reduction, for an 8.2% net Zephyr EBV treatment benefit.

10.2.3 Change in SGRQ, mMRC, Cycle Ergometry, and Supplemental O_2 at 1 Year

At the end of 1 year of follow-up, Zephyr EBV Subjects demonstrated a mean 1.7 point improvement (score reduction) and the Control Subjects had a mean 1.3 point deterioration (score increase) in SGRQ, a net Zephyr EBV treatment benefit of −3.0.

There was no difference in the mMRC Scale at one year.

Zephyr EBV Subjects had a mean 2.0 watt deterioration and the Control Subjects had a mean 5.1 watt deterioration in maximum workload during cycle ergometry, a net Zephyr EBV treatment benefit of 3.2 watts.

Zephyr EBV Subjects showed an increased use of supplemental oxygen of 109.5 liters / day and the Control Subjects showed an increased use of 172.3 liters / day, a net Zephyr EBV treatment benefit of −62.8 liters a day (see Table 42).

Table 42 Change in SGRQ, mMRC, Cycle Ergometry and Supplemental O_2 at 1 Year

SGRQ – Change from Baseline	Zephyr EBV Mean (SD) N Median (Min, Max)	Control Mean (SD) N Median (Min, Max)	Delta (95% CI)
SGRQ	-1.7 (14.4) 149 -2.1 (-39.3, 46.6)	1.3 (9.0) 61 0.9 (-19.7, 28.7)	-3.0 [1] (-6.3, 0.2)
mMRC	0.03 (1.10) 159 0.00 (-4.00, 3.00)	0.14 (1.09) 66 0.00 (-3.00, 4.00)	0.00 [2] (0.00, 0.00)
Cycle Ergometry (watts)	-2.0 (17.3) 154 0.00 (-120.0, 50.0)	-5.1 (12.3) 69 0.0 (-50.0, 20.0)	3.2 [1] (-0.8, 7.2)
Supplemental O_2 (liters / day)	109.5 (1100.61) 171 0.0 (-3840.0, 4965.0)	172.3 (744.05) 72 0.0 (-1680.0, 3150.0)	-62.8 [1] (-302.5, 176.9)

[1] Difference of means and unequal variance t-test confidence interval
[2] Difference of medians and non-parametric confidence interval

10.3 Matched Cohort 3 Month, 6 Month, and 1 Year FEV_1 and 6MWT Analysis

A *post hoc*, matched-cohort data analysis was performed for FEV_1 and 6MWT for subjects with relevant data at baseline, 3 months, 6 months and one year to investigate the timing and durability of treatment response in comparable subjects. There were 133 Zephyr EBV Subjects and 57 Control Subjects with FEV_1 data at baseline, three months, six months, and one year. There were 129 Zephyr EBV Subjects and 56 Control Subjects with 6MWT data at baseline, three months, six months, and one year.

10.3.1 Matched Cohort 3 Month, 6 Month, and 1 Year FEV_1 Outcomes

Matched-cohort Zephyr EBV Subjects had a net increase in FEV_1 of 3.9% compared with the matched-groups Control Subjects at three months. This improvement continued to increase 7.1% at six months, and to 8.8% at one year (see Table 43).

Table 43 Matched Cohort 3 Month, 6 Month , and 1 Year % Change in FEV_1

Percent Change in FEV_1	Zephyr EBV Mean (SD) N Median (Min, Max)	Control Mean (SD) N Median (Min, Max)	Delta [1] (95% CI)
3 Months	4.9 (19.8) 133 1.2 (-33.7, 88.3)	0.9 (11.8) 57 -1.2 (-26.4, 39.2)	3.9 (-0.7, 8.5)
6 Months	5.3 (19.0) 133 3.8 (-38.3, 65.7)	-1.8 (11.3) 57 -2.5 (-27.7, 25.5)	7.1 (2.7, 11.5)
1 Year	6.7 (21.6) 133 2.0 (-33.9, 88.4)	-2.1 (11.0) 57 -2.0 (-29.1, 23.0)	8.8 (4.1, 13.5)

[1] Difference of means and unequal variance t-test confidence interval differences due to rounding

This continued benefit on disease progression throughout 1 year of follow-up as measured by FEV_1 is demonstrated in the following chart.

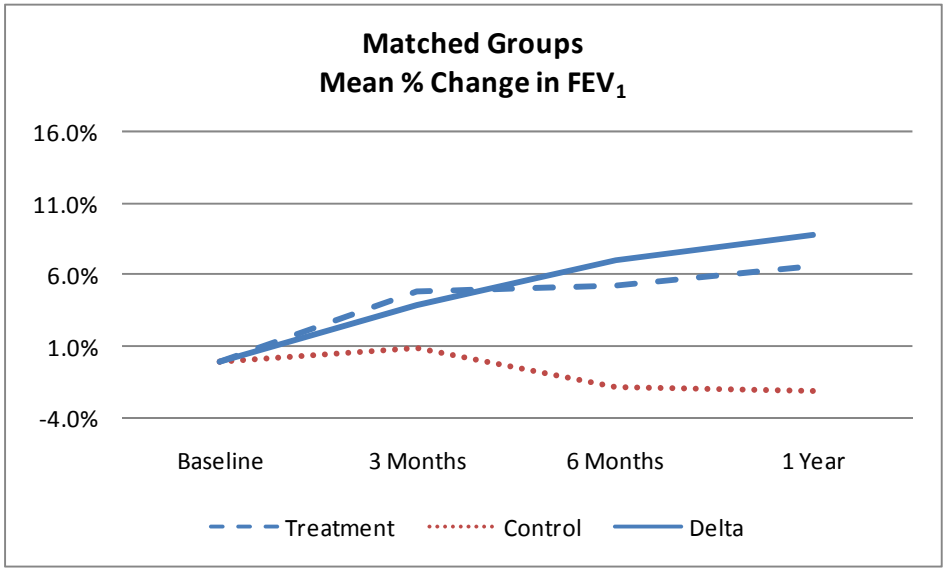


Figure 12 Matched Cohort 3 Month, 6 Month, and 1 Year FEV_1 Outcomes

10.3.2 High Heterogeneity Subgroup Matched Cohort 3 Month, 6 Month, and 1 Year FEV_1 Outcomes

Matched-cohort Zephyr EBV Subjects in the High Heterogeneity Subgroup had a net increase in FEV_1 of 7.6% compared with the matched-groups Control Subjects at three months. This improvement increased to a net increase in FEV_1 of 11.9% compared with the matched-pairs Control Subjects at six months, and to 13.7% at one year (see Table 44).

Table 44 High Heterogeneity Subgroup: Matched Cohort 3 Month, 6 Month, and 1 Year % Change in FEV_1

Percent Change in FEV_1	Zephyr EBV Mean (SD) N Median (Min, Max)	Control Mean (SD) N Median (Min, Max)	Delta [1] (95% CI)
3 Months	8.5 (21.9) 66 3.5 (-26.1, 88.3)	0.9 (11.4) 30 -1.3 (-26.4, 32.7)	7.6 (0.8, 14.3)
6 Months	10.0 (22.0) 66 7.7 (-38.3, 65.7)	-1.8 (11.5) 30 -4.2 (-19.2, 25.5)	11.9 (5.1, 18.6)
1 Year	12.3 (23.6) 66 9.6 (-32.5, 88.4)	-1.4 (11.4) 30 0.7 (-29.1, 21.8)	13.7 (6.6, 20.8)

[1] Difference of the means and unequal variance t-test confidence interval (10.0) - (-1.8) = 11.9 due to rounding)

This continued benefit on disease progression in the High Heterogeneity Subgroup through 1 year of follow-up as measured by FEV_1 is demonstrated in the following chart.

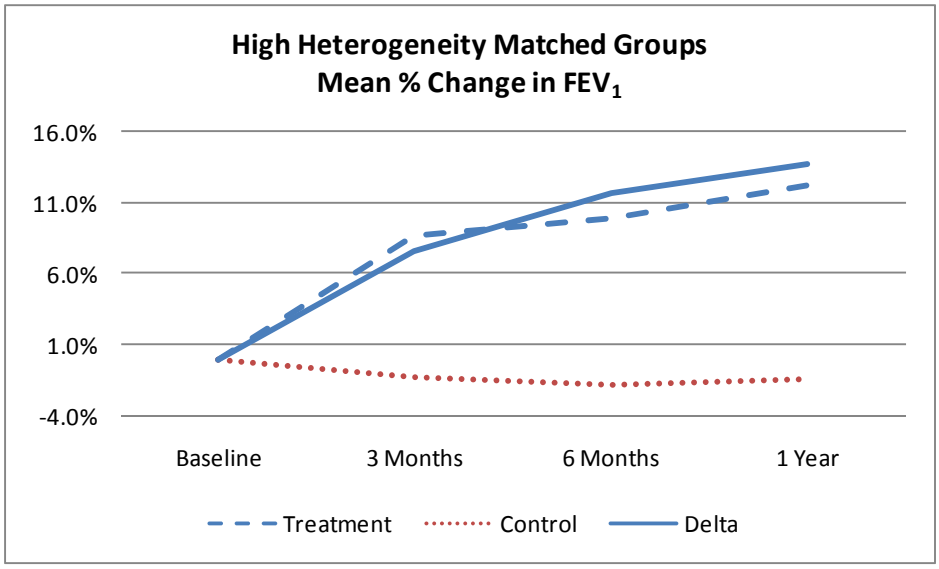


Figure 13 **High Heterogeneity Subgroup Matched Cohort 3 Month, 6 Month, and 1 Year FEV_1 Outcomes**

10.3.3 Matched Cohort 3 Month, 6 Month, and 1 Year 6MWT Outcomes

Matched-cohort Zephyr EBV Subjects had a net increase in 6MWT of 7.4% compared with Control Subjects at three months. At six months, Zephyr EBV Subjects had a net increase in 6MWT of 6.8% compared with Control Subjects, and a net increase of 5.5% at 1 year (see Table 45).

Table 45 **Matched Cohort 3 Month, 6 Month, and 1 Year Data for % Change in 6MWT**

Percent Change in 6MWT	Zephyr EBV Mean (SD) N Median (Min, Max)	Control Mean (SD) N Median (Min, Max)	Delta (95% CI)
3 Months	6.9 (18.3) 129 6.6 (-43.7, 83.2)	0.3 (19.2) 56 -0.8 (-55.4, 50.0)	7.4 [2] (1.2, 11.5)[3]
6 Months	4.9 (22.3) 129 4.7 (-53.9, 108.0)	-1.2 (24.5) 56 -2.1 (-54.9, 71.4)	6.8 [2] (0.5, 13.1)[3]
1 Year	1.9 (24.8) 129 2.5 (-72.3, 108.0)	-3.5 (16.7) 56 -3.3 (-63.1, 31.6)	5.5 [1] (-0.7, 11.7)

[1] Difference of means and unequal variance t-test confidence interval (1.9 – (-3.5) = 5.5 due to rounding)
[2] Difference of medians
[3] Non-parametric confidence interval

Figure 14 below demonstrates that the 6MWT benefit in the Zephyr EBV Treatment Group peaks at three months and then declines at a rate similar to that of the Control Group. Thus, the 6MWT benefit persists at one year.

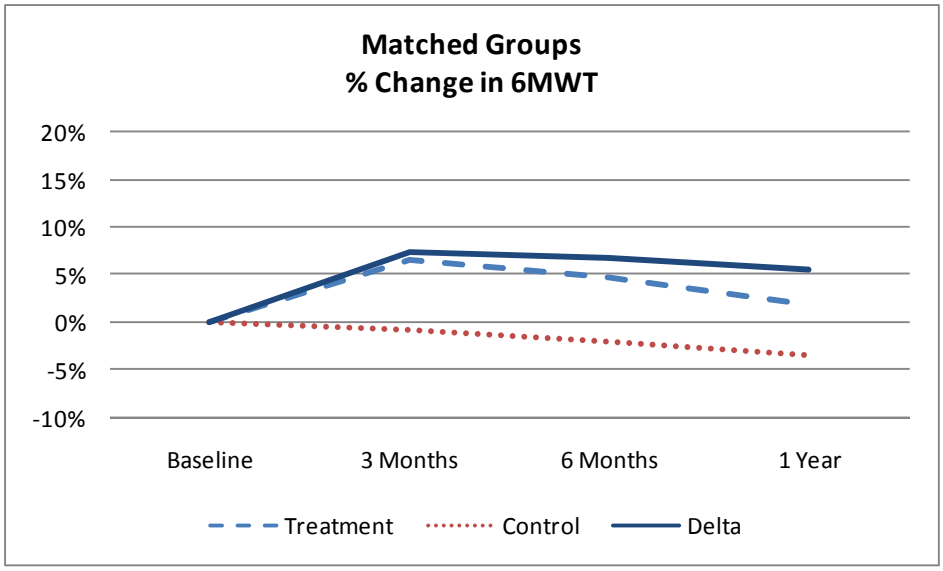


Figure 14 Matched Cohort 3 Month, 6 Month, and 1 Year 6MWT Outcomes

10.3.4 High Heterogeneity Matched Cohort 3 Month, 6 Month, and 1 Year 6MWT Outcomes

Matched-cohort Zephyr EBV Subjects in the High Heterogeneity Subgroup had a net increase in 6MWT of 9.4% compared to Control Subjects at three months. At six months, High Heterogeneity Zephyr EBV Subjects had a net increase in 6MWT of 14.7% compared to Control Subjects, and a net increase of 11.0% at 1 year (see Table 46).

Table 46 High Heterogeneity Subgroup: Matched Cohort 3 Month, 6 Month, and 1 Year Data for % Change in 6MWT

Percent Change in 6MWT	Zephyr EBV Mean (SD) N Median (Min, Max)	Control Mean (SD) N Median (Min, Max)	Delta (95% CI)
3 Months	7.8 (21.5) 65 6.9 (-43.7, 83.2)	-3.1 (20.9) 29 -2.6 (-55.4, 50.0)	9.4 [2] (2.1, 17.7)[3]
6 Months	9.2 (25.4) 65 7.1 (-53.8, 108.0)	-7.4 (23.3) 29 -7.5 (-54.9, 66.7)	14.7 [2] (7.6, 25.2)[3]
1 Year	6.7 (29.2) 65 6.3 (-72.3, 108.0)	-4.3 (18.8) 29 -3.4 (-63.1, 25.0)	11.0 [1] (1.0, 21.0)

[1] Difference of means and unequal variance t-test confidence interval
[2] Difference of medians (6.9) - (-2.6) = 9.4 and (7.1) - (-7.5) =14.7 due to rounding)
[3] Non-parametric confidence interval

Figure 15 below demonstrates that the 6MWT benefit in the High Heterogeneity Zephyr EBV Treatment group peaks at 6 months but still persists at one year.

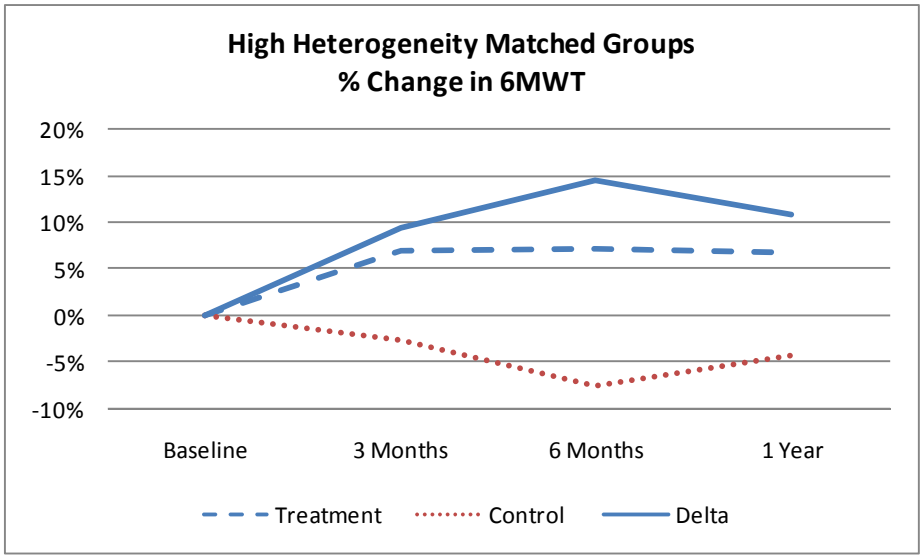


Figure 15 High Heterogeneity Subgroup Matched Cohort 3 Month, 6 Month, and 1 Year 6MWT Outcomes

10.4 Conclusions

These exploratory, one year completed-cases and matched-cohort results further substantiate the results in the co-primary outcomes at 6 months, and show that there is a sustained clinical benefit for the Zephyr EBV Treatment group over the year of follow up. Although effectiveness through one year was not a study endpoint, this analysis provides further reasonable assurance of device effectiveness. As emphysema is a progressive disease, one would expect a continuous decline in lung function, even in the Zephyr EBV Treatment Group. As with other therapies in this patient population, a gradual decline in functional status is expected to occur. However, this decline appears to occur at the same rate as the natural history (control) of the disease, and a responder remains at an advantage relative to their natural history.

11 DISCUSSION AND STUDY CONCLUSIONS

Overview: The VENT Pivotal Trial was a randomized, controlled, multi-center trial that enrolled subjects with severe heterogeneous emphysema to assess the safety and effectiveness of the Emphasys Endobronchial Valve (Zephyr EBV) and procedure compared to optimal medical management. Zephyr EBV Subjects underwent bronchoscopic Zephyr EBV implantation and both Zephyr EBV Subjects and Control Subjects received optimal medical management. Six month follow-up for all subjects included assessment of a variety of relevant pulmonary and general outcome measures as evaluated by specific spirometry, body plethysmography, QoL and exercise tests; a one year follow-up visit was also performed. The co-primary effectiveness outcomes were the percent changes in both FEV_1 and 6MWT in Zephyr EBV Subjects compared to Control Subjects determined at the 6 month follow-up visit; superiority had to be demonstrated in both measures to meet the outcome. The primary safety outcome was the Major Complication Composite at 6 months.

Validity of Results: The VENT Pivotal Trial enrolled 321 subjects and randomization resulted in highly comparable treatment groups with severe, heterogeneous emphysema (220 Zephyr EBV Subjects, 101 Control Subjects). Study subjects were assessed, treated and followed under the provisions of the approved study protocol, with a high degree of subject, device and imaging accountability. Monitoring procedures, data handling and statistical practice ensured that the results reported in this Clinical Study Report are valid scientific evidence.

Procedure: The bronchoscopic initial implantation procedure was quick (33.8 minutes) with 71.5% of subjects treated with conscious sedation only. A mean of 3.8 valves were implanted per Zephyr EBV Subject, with Acute Technical Success in 94.9%. Valves were frequently removed and replaced without difficulty during implantation procedures, allowing the operator to achieve optimal positioning.

Primary Effectiveness Outcome: The VENT Pivotal Trial met its co-primary outcomes, with a significantly better percent change in both FEV_1 and 6MWT in Zephyr EBV Subjects when compared to Control Subjects at 6 months of follow-up (see Table 47). These significant differences existed whether the analysis was performed with imputation for missing values or with completed cases only, and were confirmed by pre-specified multivariate analysis.

Table 47 Primary Effectiveness Endpoint Results - ITT (6 Month)

Multiple Imputation Primary Effectiveness Outcomes	Delta % (95% CI)	p value
Percent Change in FEV_1	6.8 (2.1, 11.5)	**0.002**
Percent Change in 6MWT	5.8 (0.5, 11.2)	**0.019**

[1] Delta is the difference in the percent change of the Zephyr EBV group compared to the Control group at six months after multiple imputation

Secondary Effectiveness Outcomes: The four secondary effectiveness outcomes were met, with the changes in the St. Georges Respiratory Questionnaire, the Modified Medical Research Council Dyspnea Scale, the maximum workload measured by cycle ergometry, and supplemental oxygen utilization all significantly better in the Zephyr EBV Subjects when compared with the Control Subjects (see Table 48).

Table 48 Secondary Effectiveness Endpoint Results - ITT (6 Month)

Secondary Effectiveness Outcomes - ITT	Delta (95% CI)	p value
SGRQ (points)	–3.44 (–6.6, –0.3)	**0.017**
mMRC (points)	–0.26 (–0.49, –0.02)	**0.018**
Maximum workload (watts)	3.8 (0.2, 7.4)	**0.020**
Supplemental O_2 (L / day)	–12.0 (–76.7, 52.7)*	**0.020**

*Confidence interval crosses zero despite statistical significance due to nonparametric, bimodal distribution of baseline data.

Primary Safety Outcome: At 6 months of follow-up, Control Subjects had a 1.2% rate of Major Complication Composite events (MCCs) compared with 6.1% for Zephyr EBV Subjects, a trend that was not significant (p = 0.075) (see Table 49).

Table 49 Per Subject Major Complications Composite

MCCs by Time Period	0 – 194 Days		195 – 386 Days	
	Zephyr EBV	Control	Zephyr EBV	Control
MCCs	6.1% (13 / 214)	1.2% (1 / 87)	4.7% (10 / 214)	4.6% (4 / 87)
Death	2.8% (6 / 214)	0.0% (0 / 87)	0.9% (2 / 214)	3.5% (3 / 87)
Empyema	0.0% (0 / 214)	0.0% (0 / 87)	0.0% (0 / 214)	0.0% (0 / 87)
Massive hemoptysis	0.5% (1 / 214)	0.0% (0 / 87)	0.0% (0 / 214)	0.0% (0 / 87)
Distal pneumonia	1.4% (3 / 214)	--	2.8% (6 / 214)	--
Pneumothorax	1.4% (3 / 214)	1.2% (1 / 87)	0.5% (1 / 214)	0.0% (0 / 87)
Respiratory failure > 24 hours	1.9% (4 / 214)	1.2% (1 / 87)	0.9% (2 / 214)	1.2% (1 / 87)

Only one of the deaths in the first six months was determined to be possibly or probably device-related. All-cause mortality over one year was equivalent for the two groups: 3.5% for the Control Subjects and 3.7% for the Zephyr EBV Subjects ($p = 0.876$, log rank test). The MCC rate in the second 6 months of follow-up was almost identical: 4.6% for Control Subjects and 4.7% for Zephyr EBV Subjects. Zephyr EBV treatment was not significantly associated with the occurrence of MCCs through 6 months.

Additional Pre-Specified Analyses: The change in BODE Index was significantly better in the Zephyr EBV Subjects than Control Subjects ($p = 0.002$) at six months. Percent changes in residual volume and diffusing capacity were slightly but not significantly better in Zephyr EBV Subjects, and the Quality of Wellbeing instrument revealed no difference between the groups at six months.

Zephyr EBV treatment effect was substantially greater in High Heterogeneity subjects for both primary outcome measures: Zephyr EBV Subjects had higher FEV_1 (10.1%) and 6MWT (7.3%) changes compared with Control Subjects FEV_1 (−2.2%, $p < 0.001$) and 6MWT (−5.9%, $p < 0.001$). Complete fissure integrity also was associated with a greater treatment response for FEV_1, with Zephyr EBV Subjects having a 13.5% improvement compared with Control Subjects -2.7% (delta 16.2%, $p < 0.001$).

Clinical Importance (Responder Analyses): Responder analyses performed at generally accepted levels of minimal clinically important differences (MCIDs) on key outcome measures revealed that single lobe Zephyr EBV treatment confers a consistent pattern of clinical benefit for FEV_1, 6MWT, SGRQ, mMRC, maximum workload by cycle ergometry and the BODE Index, all key clinical indicators of disease status.

Treatment, Volume Reduction and FEV_1: Treatment with Zephyr EBV and the presence of complete fissure integrity are associated with significantly greater target lobe volume reduction (TLVR) and with significantly better FEV_1 outcomes at 6 months.

Safety Profile: A review of the adverse event (AE) profile of the Zephyr EBV reveals that implanted subjects had higher rates of emphysema related conditions, including such manifestations as COPD exacerbations, other pulmonary infections, increase shortness of breath and hypoxemia. Use of the Zephyr EBV was associated with higher rates of hemoptysis and atypical chest pain. When considering serious adverse events (SAEs) only COPD exacerbations requiring hospitalization and hemoptysis emerged as significantly more frequent events. For both AEs and SAEs, event rates in the Zephyr EBV Subjects tended to decline during study follow-up and approach the rates of the Control Subjects.

There was a trend towards higher hospitalization rates for Zephyr EBV Subjects (27.1%) compared with Control Subjects (16.1%) through 6 months, which was borderline significant ($p = 0.052$); this difference appeared to be driven largely by study-related valve removal procedures and greater sensitivity to COPD exacerbations given the open-label study design. Rehospitalizations diminished during the course of follow-up.

Key aspects of the Zephyr EBV safety profile that have emerged from the VENT Pivotal Trial include the following characteristics:

- Granulation tissue, valve migration, and pneumonia distal to the valve are adverse events that are specifically related to the use of this device. The frequency of occurrence for granulation tissue and valve migration is expected to be reduced by the implementation of a “depth mark” and training.
- These events diminish with time.
- The device can be safely removed with a high degree of success, and when valve removal is performed as a result of an adverse event, the adverse event generally resolves.
- There was no difference in all-cause mortality between the Zephyr EBV Subjects and Control Subjects over the 1-year study follow-up.

Outcome Measures at One Year: Although the VENT Pivotal Study was not designed or sized to test significance of effectiveness measures at 1 year of follow-up, outcome measurements continued to favor Zephyr EBV Treatment over the Control through this time point. These results were confirmed by responder analysis and matched cohort analysis.

Conclusion: The VENT Pivotal Trial results demonstrate that unilateral treatment of severe heterogeneous emphysema in medically optimized subjects achieved substantial additional improvement in a variety of outcomes including FEV_1 and 6MWT over that

achieved by approved medical treatments alone. This level of additional improvement in maximally treated, severely ill subjects is clinically important. Such findings constitute valid scientific evidence demonstrating the effectiveness of the Zephyr EBV device in improving important subjective and objective measures of health in a population of subjects with severe heterogeneous emphysema. While there are several clear risks of the use of the Zephyr EBV device, these tend to diminish over time and usually resolve after device removal. Use of the Zephyr EBV in patients with severe heterogeneous emphysema provides an important palliative benefit that exceeds the attendant risks.