VENT PIVOTAL TRIAL
CLINICAL STUDY REPORT

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.**
Initial Enrollment:	**December 22, 2004**
Final Enrollment:	**April 27, 2006**
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Good Clinical Practices:	**This study was conducted in compliance with applicable FDA requirements for Investigational Device Exemptions**
Date of Report:	**August 28, 2008**

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CLINICAL STUDY REPORT SYNOPSIS

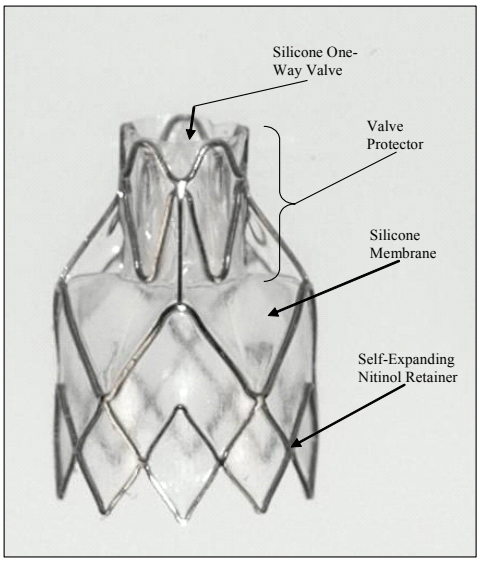
INTRODUCTION:

The Endobronchial Valve for Emphysema PalliatioN Trial ("VENT Pivotal Trial") was a randomized controlled clinical trial to assess the safety and effectiveness of using the Zephyr EBV device in the palliation of subjects with severe heterogeneous emphysema. Three hundred and twenty one (321) subjects were enrolled, assessed, optimized via medication and pulmonary rehabilitation, and then randomized to either a medical Control Group or Zephyr EBV Treatment. Follow-up included assessment of pulmonary parameters such as FEV_1 and the 6 minute walk test ("6MWT"), other secondary outcome measures, the occurrence of Major Complications and other adverse events.

INVESTIGATIONAL DEVICES (FROM SECTION 3.0):

The investigational devices comprised a system to implant one-way valves in the airways, which included the following components:

- Emphasys Zephyr Endobronchial Valve (Zephyr EBV)
- Zephyr Endobronchial Delivery Catheter (Zephyr EDC)
- Zephyr Endobronchial Loader System (Zephyr ELS).



STUDY DESIGN (FROM SECTION 4.0):

The primary objective of the VENT Pivotal Trial was to assess the safety and effectiveness of the Emphasys Endobronchial Valve (Zephyr EBV) and procedure compared to optimal medical management in subjects with heterogeneous emphysema.

The VENT Pivotal Trial was a randomized, controlled, multi-center trial enrolling 321 subjects with severe heterogeneous emphysema. The study design—including the use of a control group, the target patient population, the primary and secondary outcome measures and length of subject follow-up—was substantially based on the recommendations of the FDA Advisory Panel Meeting held in February, 2003.

After granting informed consent and meeting enrollment criteria, study subjects all underwent history and physical examination, evaluation of pulmonary function and morphology including high resolution CT scanning (HRCT), followed by a program of optimal medical management and aggressive pulmonary rehabilitation. Upon successful completion of this program subjects were randomized to either the Control or Zephyr EBV Treatment.

Zephyr EBV Subjects underwent bronchoscopic Zephyr EBV implantation under the provisions of the protocol which limited treatment to only one lobe (upper or lower lobe on one side). Complete exclusion of the target lobe was attempted by placing one or more Zephyr EBVs in lobar, segmental and / or subsegmental airways. Post-procedure, Zephyr EBV Subjects remained in the hospital and were observed for complications for at least 1 day.

Subsequent follow-up for all subjects consisted of assessment of a variety of relevant pulmonary and general outcome measures as evaluated by specific spirometry, body plethysmography, diffusing capacity, QoL instruments and exercise tests. Follow-up and outcome assessments were scheduled for 2 – 3 days, 1 week, 1, 3, and 6 months, and 1 year.

The 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 for the VENT Pivotal Trial was the proportion of subjects in each group with one or more events specified as components of the Major Complications Composite (MCC) through 6 months of follow-up. The components of the MCC were death (all-cause), empyema, massive hemoptysis resulting in respiratory failure or blood loss > 300 cc in ≤ 24 hours, pneumonia distal to the implanted valves, pneumothorax or prolonged air leak > 7 days, and respiratory failure on mechanical ventilation > 24 hours.

STUDY ACCOUNTABILITY (FROM SECTION 5.0):

Thirty one (31) Investigators at 31 Investigative Sites enrolled a total of 321 study subjects between December 22, 2004 and April 27, 2006.

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. 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.

There were no unaccounted devices/components at the end of the clinical study.

All 321 subjects (100.0%) had a baseline HRCT evaluable for inclusion criteria. Of these 321 subjects originally enrolled, 280 were still in study follow-up as of the 6 month follow-up visit (Imaging Evaluable Subjects). Of these 280 Imaging Evaluable Subjects, 273 (97.5%) had a 6-month HRCT accepted by the Core Radiology Laboratory for protocol-specified imaging. HRCTs evaluable for fissure integrity at baseline were obtained in 93.8% of subjects, and paired baseline and 6-month images evaluable for lobar volume reduction at 6 months were obtained in 95.7% of subjects. HRCTs evaluable for valve position and lobar exclusion at 6 months were obtained in 98.5% of the Zephyr EBV Subjects.

BASELINE SUBJECT CHARACTERISTICS (FROM SECTION 6.0):

The mean age of the 101 Control Subjects was 64.9 years and of the 220 Zephyr EBV Subjects the mean age was 65.3 years ($p = 0.56$). Weight and height were comparable; the mean BMI for Control Subjects was 24.8 kg/m^2 and for Zephyr EBV Subjects was 25.1 kg/m^2 ($p = 0.51$). Mean blood pressures for the two groups were nearly identical ($p = 0.67$ systolic and $p = 0.49$ for diastolic). Males predominated in the Zephyr EBV Subject group (60.4%) compared to the Control Subject group (48.5%), the difference was nearly significant ($p = 0.052$). Both groups were almost entirely Caucasian.

All subjects (100%) in both the Control Subject and Zephyr EBV Subject groups were taking bronchodilators, steroids and mucolytics upon study entry.

Key medical factors were similar between the Control Subjects and Zephyr EBV Subjects. Diabetes was present in 5.0% of Control Subjects and 7.7% of Zephyr EBV Subjects ($p = 0.48$). An abnormal ECG upon study enrollment was found in 42.6% of Control Subjects and 45.9% of Zephyr EBV Subjects ($p = 0.63$). All but three study subjects had a history of smoking (98.0% Control Subjects, 99.6% Zephyr EBV Subjects, $p = 0.23$), with similar years of smoking (36.1 and 37.7 years respectively, $p = 0.17$) and pack-years (61.7 and 63.3 pack-years respectively, $p = 0.64$).

Supplemental oxygen use was also not different between the two study groups, with 41.7% of Control Subjects and 43.9% of Zephyr EBV Subjects using oxygen ($p = 0.77$). Hours of oxygen use daily were similar at rest (7.1 and 7.7 hours respectively, $p = 0.49$), during exertion (2.7 and 2.2 hours respectively, $p = 0.28$) and while sleeping (6.8 and 6.7 hours respectively, $p = 0.79$). Oxygen flow rates were also equivalent at rest (1.5 and 1.4 liters / min, $p = 0.58$), during exertion (2.6 and 2.4 liters / min, $p = 0.22$) and while sleeping (2.0 and 1.9 liters / min, $p = 0.21$).

There were no significant differences in any baseline lung function parameters between the Control Subjects and the Zephyr EBV Subjects. FEV_1 and FEV_1 % Predicted were respectively 0.84 liters and 30% in Control Subjects and 0.87 liters and 30% in Zephyr EBV Subjects. FVC and FVC % Predicted were respectively 2.62 liters and 70% in Control Subjects and 2.71 liters and 70% in Zephyr EBV Subjects. DL_{CO} and DL_{CO} % Predicted were respectively 10.15 mL CO / min / mmHg and 36% in Control Subjects and 9.52 mL CO / min / mmHg and 33% in Zephyr EBV Subjects. RV and RV % Predicted were respectively 4.63 liters and 212% in Control Subjects and 4.79 liters and 216% in Zephyr EBV Subjects.

Baseline arterial blood gas values were largely similar between the Control Subjects and the Zephyr EBV Subjects. The partial pressure of oxygen (68.4 and 69.1 mmHg, $p = 0.51$) and the oxygen saturation (93% and 93%, $p = 0.71$) were not different, nor was the pH (7.42 and 7.43, $p = 0.48$). However, the Control Subjects had a slightly higher mean partial pressure of carbon dioxide (41.6 compared with 40.5 mmHg, $p = 0.044$) and a borderline higher bicarbonate (26.9 compared with 26.3 mEq / liter, $p = 0.09$).

Baseline BODE Index scores were quite similar between Control Subjects and Zephyr EBV Subjects, 4.2 and 4.4 respectively ($p = 0.2551$). Baseline SGRQ scores were quite similar between Control Subjects and Zephyr EBV Subjects, 50.1 and 51.5 respectively ($p = 0.3236$). Baseline mMRC dyspnea scores were identical for Control Subjects and Zephyr EBV Subjects, 1.7 and 1.7 respectively ($p = 0.7748$).

Baseline exercise tolerance was the same between the two study groups. The Control Subjects had a slightly lower peak workload on cycle ergometry (43.2 versus 45.0 watts, $p = 0.71$). However, the Control Subjects showed a slightly longer 6MWT (350.9 versus 333.9 meters, $p = 0.15$). Dyspnea and fatigue were rated on a scale from 0 to 10 during exercise testing (Borg Test) at baseline, and there were no significant differences in dyspnea or fatigue scores before or after performing the 6MWT.

High Resolution Computed Tomography (HRCT) baseline characteristics were the same between the two study groups. These characteristics included disease distribution, volume distribution, target lobe disease, target lobe volume, and fissure integrity.

ZEPHYR EBV IMPLANTATION PROCEDURE (FROM SECTION 7.0):

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

Target lobes were defined by pre-procedural imaging assessments. Target lobes were largely in the upper lobes (76.6%) and predominantly in 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 in 24.3%, and the left lower lobe in 14.0%.

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. Three (3) Zephyr EBV Subjects had a rigid bronchoscope used during the Zephyr EBV implantation procedure, the remaining 211 procedures involved only flexible bronchoscopy.

The mean number of valves placed per Zephyr EBV Subject was 3.8 (median 4, range 1 to 9). Acute Technical Success—determined by the implanting site at the time of the procedure, based on the Investigator's assessment of complete exclusion of the target lobe—was found in 94.9% of subjects.

Of the 214 Zephyr EBV Subjects who received one or more valves during the initial study procedure, 96 subjects had a total of 143 valves removed during the procedure. In 89 of these 96 subjects (92.7%), the valves removed during the procedure were successfully replaced with one or more valves, which led to Acute Technical Success (lobar exclusion) as reported by the site.

Of the 143 valves removed during the initial procedure, 92.3% were for valve positioning: 48.9% were placed too proximally, 19.6% too distally and 3.5% were too small for the selected airway. Other removals for sizing or positioning reasons accounted for 20.3% of valves removed during the initial procedure and 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, and incomplete exclusion. Valve or deployment reasons for removal accounted for 7.7% of valves removed during the initial procedure and included: valve appeared non-functional, valve did not deploy properly, valve loaded and deployed backwards, and duckbill appeared inverted.

There were device malfunctions in 21 (9.8%) of Zephyr EBV procedures, and 1 device malfunction in a follow-up procedure to replace an expectorated valve. For the total of 22 subjects with any device malfunction, 35 devices were reported as malfunctioning (18 EBVs, 15 EDCs and 2 ELSs). The majority of the malfunctions were associated with Loading Failures and Delivery Failure due to Anatomical Constraints.

Overall the Zephyr EBV system was easy to use, reliable and successful in achieving lobar exclusion at the time of the initial procedure.

PRIMARY AND SECONDARY EFFECTIVENESS OUTCOMES (FROM SECTION 8.0):

A primary objective of the VENT Pivotal Trial was to assess the effectiveness of the Zephyr EBV in treating patients with severe heterogeneous emphysema. This was to be assessed by determining the FEV_1 and 6MWT values at baseline and at 6 months, and to compare the percentage change from baseline in these tests between the Control Subjects and the Zephyr EBV Subjects. Both measures were to be tested using a one-sided superiority test at a significance level of 0.025, and then be confirmed by multivariate testing.

The VENT Pivotal Trial met its primary effectiveness outcome, 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. These significant differences existed whether the analysis was performed with multiple imputation for missing values or with completed cases only. Treatment with Zephyr EBV remained as a significant factor in both the FEV_1 and 6MWT multivariate models, confirming the univariate finding.

Primary Effectiveness Outcome		**Delta (95% CI)**	**p value**
ITT	**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**
CC	**Percent Change in FEV_1**	7.2 (3.2, 11.2)	**< 0.001**
	Percent Change in 6MWT	5.8 (1.3, 11.7)	**0.008**

The VENT Pivotal Trial met its 4 secondary effectiveness outcomes, with significantly better outcomes at 6 months in the St. George's Respiratory Questionnaire (SGRQ) Score, the modified Medical Research Council Dyspnea Scale (mMRC), the maximum workload during cycle ergometry, and the use of supplemental oxygen in Zephyr EBV Subjects when compared to Control Subjects.

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2° Outcome Measures		Delta (95% CI)	p value
ITT	**Change in SGRQ (points)**	-3.4 (-6.6, -0.3)	**0.0167**
	Change in mMRC (points)	-0.26 (-0.49, -0.02)	**0.0183**
	Change in Max. Workload (watts)	3.8 (0.2, 7.4)	**0.0203**
	Change in Supplemental O_2 (L / day)	-12.0 (–76.7, 52.7)	**0.0198**
CC	**Change in SGRQ (points)**	–3.40 (–6.61, –0.18)	**0.0192**
	Change in mMRC (points)	–0.30 (–0.56, –0.05)	**0.0108**
	Change in Max. Workload (watts)	5.0 (0.0, 5.0)	**0.0044**
	Change in Supplemental O_2 (L / Day)	-100.1 (-318.6, 118.4)	0.1837

PRIMARY SAFETY OUTCOME (FROM SECTION 9.0):

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 = 0.0748, Fisher's exact test). This difference was primarily driven by a trend to greater 6 month mortality in the Zephyr EBV Subjects with 6 deaths: 3 from respiratory failure, one from cancer, one from ischemic colitis and 1 from massive hemoptysis, of which only the death from hemoptysis was related to the device.

All-cause mortality over 12 months was equivalent for the two groups: 3.5% for the Control Subjects and 3.7% for the Zephyr EBV Subjects (p = 0.8763, log rank test).

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 all, with 12 months of follow-up, the MCC rate for Control Subjects (4.6%) and for Zephyr EBV Subjects (10.3%) were not significantly different (p = 0.1724, Fisher's exact test).

ADDITIONAL PRE-SPECIFIED ANALYSES (FROM SECTION 10.0):

Additional effectiveness analyses were performed for residual volume, diffusing capacity, Quality of Wellbeing and the BODE Index. Although Zephyr EBV Subjects trended higher in all these measures, only the BODE Index showed an improvement that was significant (p = 0.0024).

Technical Success (complete lobar exclusion by HRCT at 6 months) was achieved in 56.2% of Zephyr EBV Subjects, with the majority of Technical Failures (78.8%) occurring when one or more valves were found to be in place but not fully occlusive.

Rehospitalization rates through 6 months were 16.1% for Control Subjects and 27.1% for Zephyr EBV Subjects, a difference that bordered on significant ($p = 0.0522$). For the period from 6 to 12 months, this difference began to converge, with 12.6% for Control Subjects and 19.6% for Zephyr EBV Subjects. Most of this difference occurred during the first quarter of follow-up in subjects who required removal of one or more Zephyr valves.

Technical Success subjects had an FEV_1 improvement that was 9.4 percentage points higher in subjects with Technical Success compared with subjects with Technical Failure.

High Heterogeneity subjects demonstrated a substantially larger therapeutic benefit compared with the study population as a whole: FEV_1 improvement at 6 months was 12.3 percentage points higher, and 6MWT at 6 months was 14.4 percentage points higher, in High Heterogeneity Zephyr EBV Subjects compared with High Heterogeneity Control Subjects.

Subjects with Complete Fissure Integrity had an FEV_1 improvement that was 16.2 percentage points higher than subjects with Incomplete Fissure Integrity.

RESPONDER ANALYSES (FROM SECTION 11.0):

Responder analyses for the VENT Pivotal Study effectiveness measures of FEV_1 and 6MWT demonstrated that a substantially larger proportion of Zephyr EBV Subjects achieved clinically important levels of improvement than did Control Subjects.

Outcome Measure	Relative Rate (95% CI)
FEV_1 ≥ 0%	1.4 (1.1 – 1.9)
FEV_1 High Heterogeneity≥ 0%	2.0 (1.3 – 3.2)
FEV_1 ≥ 15%	2.2 (1.1 – 4.5)
FEV_1 High Heterogeneity≥ 15%	2.8 (1.2 – 6.7)
6MWT≥ 0%	1.3 (1.0 – 1.7)
6MWT High Heterogeneity≥ 0%	1.8 (1.1 – 2.8)
6MWT≥ 15%	1.4 (0.8 – 2.5)
6MWT High Heterogeneity≥ 15%	2.4 (1.0 – 5.7)

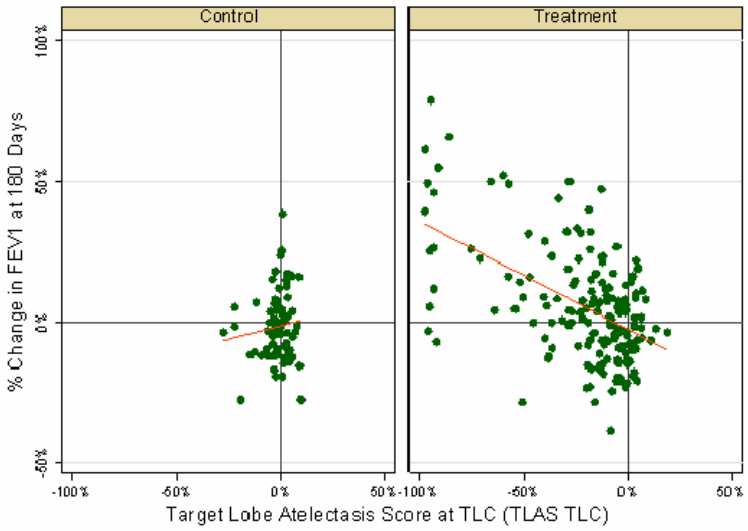
Responder analyses for the VENT Pivotal Study effectiveness measures of SGRQ, mMRC, maximum workload and the BODE Index all demonstrated that a substantially larger proportion of Zephyr EBV Subjects achieved clinically important levels of improvement than did Control Subjects.

Outcome Measure	MCID	Relative Rate (95% CI)
SGRQ	**8 points**	2.8 (1.3 – 5.7)
mMRC	**1 point**	1.8 (1.0 – 3.2)
Ergometry	**10 watts**	1.9 (1.0 – 3.7)
BODE Index	**1 point**	2.2 (1.2 – 3.8)

TREATMENT, VOLUME REDUCTION AND FEV1 (FROM SECTION 12.0):

Analyses of relevant study variables supported the primary rationale of Zephyr EBV treatment, which was that Zephyr EBV treatment led to reduction in target lobe volume reduction (TLVR), which in turn led to improvement in changes in pulmonary function at 6 months.

Zephyr EBV Subjects had a mean change in $TLAS_{TLC}$ at 6 months of −20.6% compared with Control Subjects (−1.7%, $p < 0.0001$). Reduction in TLVR at 6 months as measured by $TLAS_{TLC}$ was significantly associated with improved FEV_1 at 6 months ($r^2 = 0.2785$, $p = 0.000$):



The factors that were significantly associated with TLVR were Technical Success, complete fissure integrity and their combination, demonstrating the importance of exclusion of the target lobe. The factors associated with significantly improved FEV_1 at 6 months were Zephyr EBV treatment, Technical Success, complete fissure integrity, and the combination of Technical Success and complete fissure integrity.

SAFETY PROFILE AT ONE YEAR (FROM SECTION 13.0):

Mortality: all-cause mortality was similar in the two groups through one year of follow-up, with 3.5% (95% CI 0.7 – 9.8%) of Control Subjects and 3.7% (95% CI 1.6 – 7.2%) of Zephyr EBV Subjects dying of any cause during the year. This difference was not significant.

COPD / Emphysema Adverse Events: The VENT Pivotal Study revealed the high degree of pulmonary morbidity present in subjects with severe heterogeneous emphysema, with 77.6% of Zephyr EBV Subjects and 62.1% of Control Subjects having one or more COPD / emphysema category adverse events; this difference was significant (p = 0.0095). This difference was driven by the following subcategories of adverse events: COPD exacerbation (72.4% Zephyr EBV Subjects and 57.5% Control Subjects, p = 0.0141, Other Pulmonary Infection (8.4% compared with 1.2% respectively, p = 0.0174), Increased SOB (9.8% compared with 2.3% respectively, p = 0.0295) and Altered ABGs (8.4% compared with 1.2% respectively, p = 0.0174).

When serious adverse events are examined only COPD with exacerbation is significantly different, with an 23.4% rate for Zephyr EBV Subjects and a 10.3% rate for Control Subjects (p = 0.0101).

Pulmonary / Thoracic Adverse Events: The rate of these adverse events was higher in Zephyr EBV Subjects, 52.8%, compared with Control Subjects, 9.2% ($p < 0.0001$). This difference was driven by the following subcategories of adverse events: hemoptysis (42.1% Zephyr EBV Subjects compared with 2.3% in Control Subjects, $p < 0.0001$), and Noncardiac Chest Pain (16.4% compared with 3.5%, $p = 0.0018$). When serious adverse events are examined, only hemoptysis remains significantly more frequent in Zephyr EBV Subjects, 11.7%, compared with 0.0% in Control Subjects ($p = 0.0003$).

General / Other Adverse Events: The remaining categories of adverse events occurred somewhat more frequently in Zephyr EBV Subjects, 49.1%, compared with Control Subjects, 33.3% ($p = 0.015$). Rates that were higher in Zephyr EBV Subjects included: nausea and vomiting (often related to procedure sedation), headaches, sore throat, and similar minor complaints.

There are no significant differences in the rate of serious adverse events for General / Other adverse events.

Resolution of Adverse Events: Most of these adverse event and serious adverse event rates decline after the first three months of follow-up, suggesting that the passage of time and, when indicated, removal of one or more valves are effective responses to these events.

Valve Expectoration or Migration: Of 820 implanted valves at the completion of the initial procedure, 23 (2.8%) migrated or were expectorated in 17 subjects between Days 0 and 274 without significant sequelae, and 14 subjects had at least one of these valves replaced during study follow-up.

Pneumonia Distal to Valves: 9 Zephyr EBV Subjects (4.2%) had pneumonia distal to valves and received drug therapy (9) and valve removal (3). Eight (8) of the 9 resolved during the study follow-up period and one subject, with onset on Day 356, was still under treatment at the end of the 1-year study follow-up period.

Massive Hemoptysis: One Zephyr EBV Subject experienced dyspnea and hemoptysis between Days 0 and 8, and then presented in cardiorespiratory arrest on Day 8 and died thereafter of hypoxic brain damage. Autopsy revealed bullous emphysema, 4 intact and well-positioned valves, and no obvious source of bleeding.

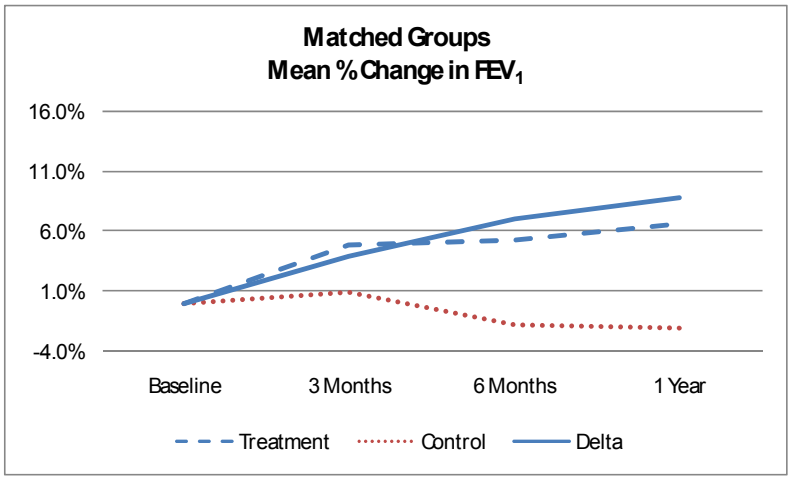
Valve Treatment for Persistent Air Leak: One Zephyr EBV Subject developed complete left pneumothorax on Day 1, with only partial resolution after chest tube placement. Compassionate Use treatment with 2 additional valves in the superior segment of the left lower lobe significantly reduced but did not eliminate the air leak until 8 days later.

Valve Removal During Study Follow-Up: Thirty one (31, 14.5%) Zephyr EBV Subjects had one or more valves removed after the initial procedure. Eighty five (85) of 87 valves attempted were successfully removed (97.7%). Of these 31 subjects, 25 (80.6%) had resolution of the reason for the intervention following valve removal.

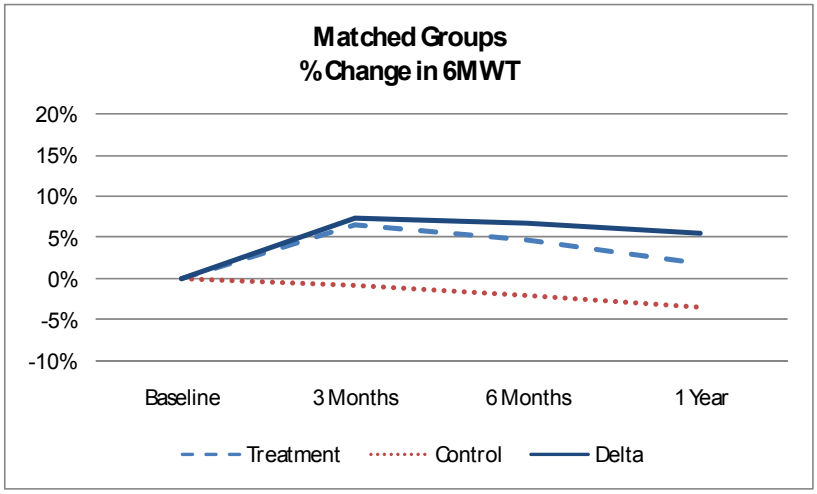
OUTCOME MEASURES AT ONE YEAR (FROM SECTION 14.0):

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.

From matched grouped comparisons of results at 3 months, 6 months, and 1 year FEV1 appears to continue to improve in the Zephyr EBV Treatment Group through the entire 1 year follow-up. The treatment effect remained statistically-significant at 1 year.



Zephyr EBV Treatment Group benefit in 6MWT appears to peak at 3 months while retaining most of the net benefit through 1 year for those Subjects with matched data. However, the treatment effect was not statistically-significant at 1 year.



DISCUSSION AND CONCLUSION (SECTION 15.0):

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, diffusing capacity, QoL and exercise tests; a 12 month 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 (101 Control Subjects, 220 Zephyr EBV 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. These significant differences existed whether the analysis was performed with multiple imputation for missing values or with completed cases only, and were confirmed by pre-specified multivariate analysis.

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**

Secondary Effectiveness Outcomes: All 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 the use of supplemental oxygen, all significantly better in the Zephyr EBV Subjects when compared with the Control Subjects.

Secondary Effectiveness Outcomes - ITT	Delta (95% CI)	p value
Change in SGRQ (points)	–3.4 (–6.6, –0.3)	**0.0167**
Change in mMRC (points)	–0.26 (–0.49, –0.02)	**0.0183**
Maximum workload (watts)	3.8 (0.2, 7.4)	**0.0203**
Change in Supplemental O_2 (L / day)	–12.0 (–76.7, 52.7)	**0.0198**

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 ($p = 0.0748$). This difference was primarily driven by a trend to greater 6 month mortality in the Zephyr EBV Subjects with 6 deaths: 3 from respiratory failure, one from cancer, one from ischemic colitis and 1 from massive hemoptysis, of which only the death from hemoptysis was related to the device.

All-cause mortality over 12 months was equivalent for the two groups: 3.5% for the Control Subjects and 3.7% for the Zephyr EBV Subjects (p = 0.8763, 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.

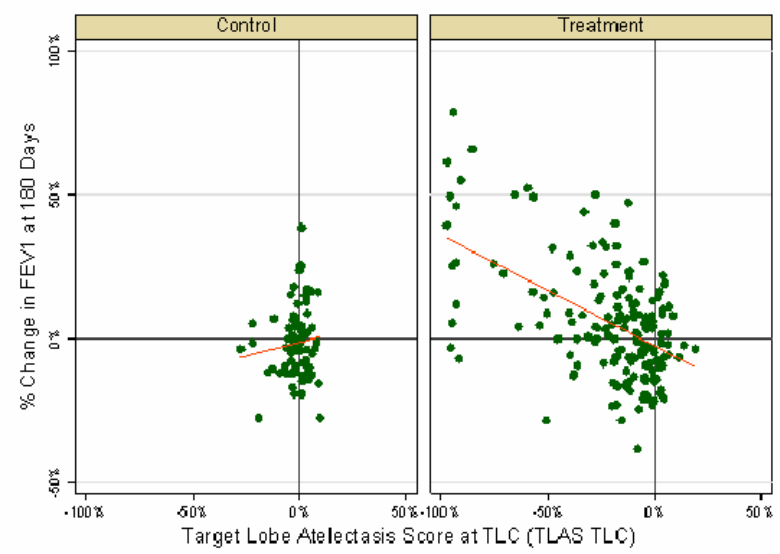
Additional Pre-Specified Analyses: The change in BODE Index was significantly better in the Zephyr EBV Subjects than Control Subjects (p = 0.0024). Percent changes in residual volume and diffusing capacity were slightly but not significantly better in Zephyr EBV Subjects, and the Quality of Wellbeing instrument revealed no difference between the groups.

Technical success (complete lobar exclusion) was found in 56.2% of Zephyr EBV Subjects on HRCT at 6 months. 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 = 0.0522); this difference appeared to be driven largely by study-related valve removal procedures and diminished during the last 6 months of follow-up.

Pre-specified subgroup analyses showed that Zephyr EBV Subjects with Technical Success (HRCT-confirmed target lobe exclusion at 6 months) had a greater mean percent change in FEV_1 (9.4%) compared with Zephyr EBV Subjects without Technical Success (0.0%) , p = 0.0009. 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 < 0.0001) and 6MWT (−5.9%, p = 0.0003). 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 < 0.0001).

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, achieving Technical Success (complete lobar exclusion) and the presence of complete fissure integrity are all 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. These declines in adverse event rates appeared to be independent of valve removals.

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

- Use of the Zephyr EBV was associated with increased rates of COPD related adverse events, hemoptysis, atypical chest pain and perhaps rehospitalization through 1 year of follow-up.
- Granulation tissue, valve migration, and pneumonia distal to the valve are adverse events that are specifically related to the use of this device.
- These phenomena 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 Control Subjects and Zephyr EBV 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 pairs 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 are generally minor, 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.

TABLE OF CONTENTS

1.0 INTRODUCTION....1
1.1 Disease Information....1
1.2 Emphasys Device Information....2
1.3 Rationale for Endobronchial Valve Treatment....2
1.4 Preclinical and Clinical Studies....3

2.0 ETHICAL AND REGULATORY CONSIDERATIONS....5
2.1 Study Responsibility....5
2.2 Subject Confidentiality....5
2.3 Informed Consent and Institutional Review Boards (IRBs)....6
2.4 Operations Committee....6
2.5 Data and Safety Monitoring Board (DSMB)....6
2.6 Clinical Events Committee (CEC)....6

3.0 INVESTIGATIONAL DEVICES....8
3.1 Emphasys Zephyr Endobronchial Valve (Zephyr EBV)....8
3.2 Zephyr Delivery Catheter and Zephyr Loader System....9
3.3 Handling and Storage....11
3.4 Accountability....11

4.0 STUDY DESIGN, MANAGEMENT AND ANALYSIS....12
4.1 VENT Pivotal Trial Overview....12
4.2 Summary of Study Procedures....13
4.2.1 Subject Screening, Preparation and Randomization....13
4.2.2 Inclusion / Exclusion Criteria....13
4.2.3 Zephyr EBV Subjects: Valve Implantation Procedure....15
4.2.4 Zephyr EBV Subjects: Post Implantation Procedure....15
4.2.5 Zephyr EBV Subjects: Valve Removal Procedure....15
4.2.6 All Study Subjects: Follow-up Procedures....16
4.2.7 Adverse Events....16
4.3 Study Management....17
4.3.1 Investigator Selection, Responsibility, Training and Performance....17
4.3.2 Monitoring and Source Documentation....17
4.3.3 Data Transmittal and Record Retention....18
4.3.4 Managing Study Deviations....18
4.3.5 CEC Adverse Event Adjudication....18
4.4 Data Management....18
4.4.1 Data Screening and Acceptance....18
4.4.2 Data Processing and Quality Control....18
4.4.3 Confidentiality and Protection of Study Files....19

4.5 Statistical Analysis Plan 19
4.5.1 Sample Size 19
4.5.2 Error and Bias Control....19
4.5.3 Analytic Methods 20
4.5.4 Baseline, Demographic and Procedural Data....20
4.5.5 Safety Measures and Outcomes....21
4.5.6 Effectiveness Measures and Outcomes 21
4.6 Imaging Procedures....23
4.6.1 Image Acquisition 23
4.6.2 Quality Control....24
4.6.3 Quantitative Image Analysis 24
4.6.4 Density (Emphysema) and Heterogeneity Scoring 24
4.6.5 Fissure Integrity Assessment....25
4.6.6 Lobar Exclusion Assessment....25
4.6.7 Target Lobe Atelectasis Score (TLAS) Methodology....26
4.7 Changes in the Conduct of the Study....26
4.7.1 Protocol Amendments 26
4.7.2 Changes in the Statistical Analysis Plan 26
4.7.3 Additional Analyses Resulting from FDA Communications....27
4.7.4 Changes in the Experimental Devices....27
4.8 Protocol Deviations....28
4.9 Study Definitions....29

5.0 STUDY ACCOUNTABILITY AND POPULATION 37
5.1 Investigators and Site Enrollment....37
5.2 Subject Accountability....38
5.3 Device Accountability....42
5.4 Imaging Accountability 42

6.0 BASELINE SUBJECT CHARACTERISTICS 44
6.1 Demographic Data 44
6.2 Pulmonary Medications....45
6.3 Medical History....45
6.4 Use of Supplemental Oxygen 45
6.5 Lung Function Parameters 46
6.6 Arterial Blood Gas Analysis....47
6.7 BODE Indices....48
6.8 SGRQ Scores....48
6.9 mMRC Dyspnea Scale Scores....49
6.10 Exercise Tolerance....49
6.11 Borg Test Results 50
6.12 HRCT Characteristics....50
6.13 Summary: Study Population....52

7.0 ZEPHYR EBV IMPLANTATION PROCEDURE 53
7.1 Introduction.....53
7.2 Procedure Details.....53
7.2.1 Procedure Time 53
7.2.2 Target Lobes.....53
7.2.3 Anesthesia and Airway Management.....54
7.2.4 Proportion of Procedures Involving a Rigid Bronchoscope.....54
7.3 Procedure Outcomes.....55
7.3.1 Number of Zephyr EBVs Placed Per Subject.....55
7.3.2 Acute Technical Success (Site Determined) 55
7.3.3 Valves Removed and Replaced During the Initial Procedure.....57
7.3.4 Device Malfunctions 58
7.4 Summary: Zephyr EBV Implantation Procedure 59

8.0 Primary and Secondary Effectiveness Outcomes 61
8.1 Introduction.....61
8.2 Primary Effectiveness Outcomes.....61
8.2.1 Percent Change in FEV_1 and 6MWT – Multiple Imputation.....61
8.2.2 Completed Cases: Percent Change in FEV_1 and 6MWT 62
8.3 Secondary Effectiveness Outcomes 63
8.3.1 Change in St. George's Respiratory Questionnaire Score.....63
8.3.2 Change in Modified Medical Research Council Dyspnea Scale 63
8.3.3 Change in Maximum Workload during Cycle Ergometry 64
8.3.4 Change in Use of Supplemental Oxygen.....65
8.4 Summary: 1° and 2° Effectiveness Outcomes 65

9.0 Primary Safety Outcome.....67
9.1 Introduction.....67
9.2 Primary Safety Outcome: Major Complications Composite.....67
9.3 Major Complications Composite: Related Analyses 69
9.3.1 All-Cause Mortality.....69
9.3.2 Cox Regression Analysis of MCCs through Six Months.....70
9.3.3 MCCs by Time Period through 1 Year.....71
9.3.4 MCCs by Valve Removal Status through One Year 71
9.4 Summary: Primary Safety Outcome.....72

10.0 Additional Pre-Specified Analyses 73
10.1 Introduction.....73
10.2 Pre-Specified Outcome Analyses.....73
10.2.1 Percent Change in Residual Volume.....73
10.2.2 Percent Change in Diffusing Capacity 74
10.2.3 Change in Quality of Wellbeing.....74
10.2.4 Change in BODE Index.....74

10.2.5 Technical Success 75
10.2.6 Rehospitalization 76
10.3 Pre-Specified, Analysis-Plan-Generated Subgroup Analyses 77
10.3.1 Technical Success, FEV_1 and 6MWT Outcomes 77
10.3.2 Heterogeneity Score ≥ 15%, FEV_1 and 6MWT Outcomes 78
10.3.3 Complete Fissure Integrity and FEV_1 79
10.4 Summary: Additional Pre-Specified Analyses 80

11.0 Responder Analyses 81
11.1 Introduction 81
11.2 Responder Analyses: FEV_1 82
11.2.1 Subjects with Maintained FEV_1 82
11.2.2 High Heterogeneity Subjects with Maintained FEV_1 82
11.2.3 Subjects with ≥ 15% Improvement in FEV_1 83
11.2.4 High Heterogeneity Subjects with ≥ 15% Improvement in FEV_1 83
11.3 Responder Analyses: 6MWT 83
11.3.1 Subjects with Maintained 6MWT 84
11.3.2 High Heterogeneity Subjects with Maintained 6MWT 84
11.3.3 Subjects with ≥ 15% Improvement in 6MWT 84
11.3.4 High Heterogeneity Subjects with ≥ 15% Improvement in 6MWT 85
11.4 Responder Analyses: Other Effectiveness Outcome Measures 85
11.4.1 Subjects with ≥ 8 Point Improvement in SGRQ Score 85
11.4.2 Subjects with ≥ 1 Point Improvement in mMRC Dyspnea Scale 86
11.4.3 Subjects with ≥ 10 Watt Improvement in Maximum Workload during Cycle Ergometry 87
11.4.4 Subjects with ≥ 1 Point Improvement in the BODE Index 87
11.5 Summary: Responder Analyses 88

12.0 Treatment, Volume Reduction and FEV_1 90
12.1 Introduction 90
12.2 Treatment, Volume Reduction and Improved FEV_1 91
12.2.1 Zephyr EBV Treatment Leads to TLVR 91
12.2.2 TLVR is Significantly Associated with Improved FEV_1 at 6 Months 91
12.3 Factors Associated with Target Lobe Volume Reduction 92
12.3.1 Technical Success and Target Lobe Volume Reduction 92
12.3.2 Fissure Integrity and Target Lobe Volume Reduction 93
12.3.3 Technical Success, Fissure Integrity and Target Lobe Volume Reduction 93
12.4 Factors Associated with Improved FEV_1 94
12.4.1 Technical Success, Fissure Integrity and FEV_1 95
12.5 Summary: Treatment, Volume Reduction and FEV_1 97

13.0 Safety Profile at One Year 98
13.1 Introduction....98
13.2 Review of Adverse Events 98
13.2.1 Adverse Events....98
13.2.2 Adverse Events by Quarter....101
13.2.3 Serious Adverse Events....105
13.2.4 Serious Adverse Events by Quarter....107
13.2.5 Device-Related Adverse Events....109
13.2.6 Procedure-Related Adverse Events....109
13.3 Zephyr EBV Subjects with Specific Adverse Events....110
13.3.1 Granulation Tissue....110
13.3.2 Valve Expectoration or Migration....111
13.3.3 Pneumonia Distal to Valves 113
13.3.4 Massive Hemoptysis....114
13.3.5 Valve Treatment for Persistent Air Leak....114
13.4 Valve Removal during Study Follow-Up 115
13.5 Summary: Adverse Event Profile through One Year 117

14.0 Outcome Measures at One Year....120
14.1 Introduction....120
14.2 Effectiveness Outcome Measures at 1 Year....120
14.2.1 Percent Change in FEV_1 at 1 Year 120
14.2.2 High Heterogeneity Subgroup: Percent Change in FEV_1 at 1 Year 121
14.2.3 Percent Change in 6MWT at 1 Year 121
14.2.4 High Heterogeneity Subgroup: Percent Change in 6MWT at 1 Year 121
14.2.5 Change in SGRQ at 1 Year 122
14.2.6 Change in mMRC Dyspnea Scale at 1 Year 122
14.2.7 Change in Maximum Workload during Cycle Ergometry at 1 Year 123
14.2.8 Change in Use of Supplemental Oxygen at 1 Year....123
14.3 Matched 3, 6, and 12 Month FEV_1 and 6MWT Data....123
14.3.1 Matched 3, 6, and 12 Month FEV_1 Outcomes....124
14.3.2 High Heterogeneity Subgroup Matched 3, 6, and 12 Month FEV_1 Outcomes 125
14.3.3 Matched 3, 6, and 12 Month 6MWT Outcomes....126
14.3.4 High Heterogeneity Matched 3, 6, and 12 Month 6MWT Outcomes....127
14.4 Summary: Effectiveness Outcome Measures at 1 Year 128

15.0 CONCLUSIONS 130

16.0 REFERENCES.....135

17.0 Change Tracker 138

LIST OF TEXT TABLES

Table 1 Major Complications Composite 21
Table 2 Summary of Protocol Deviations 29
Table 3 Subject Enrollment by Site 37
Table 4 Cumulative Subject Accountability Table by Visit – Control Subjects 38
Table 5 Cumulative Subject Accountability Table by Visit – Zephyr EBV Subjects 39
Table 6 Listing: Discontinued Control Subjects (Death, Withdrawal, LTFU) 40
Table 7 Listing: Discontinued Zephyr EBV Subjects (Death, Withdrawal, LTFU) 41
Table 8 Device Accountability: VENT Pivotal Trial Investigational Devices 42
Table 9 Imaging Accountability Table – Control Subjects 43
Table 10 Imaging Accountability Table – Zephyr EBV Subjects 43
Table 11 Subject Demographics 44
Table 12 Baseline Pulmonary Medications 45
Table 13 Baseline Medical History 45
Table 14 Use of Supplemental Oxygen 46
Table 15 Baseline Lung Functions 47
Table 16 Baseline Arterial Blood Gas Analysis 48
Table 17 Baseline BODE Indices 48
Table 18 Baseline SGRQ Scores 49
Table 19 Baseline mMRC Dyspnea Scale Scores 49
Table 20 Baseline Exercise Tolerance 49
Table 21 Baseline Borg Testing Results 50
Table 22 Baseline Disease Distribution (Density Score by Lobe) 50
Table 23 Baseline Volume by Lobe (liters) at TLC 51
Table 24 Target-specific Baseline HRCT Characteristics 51
Table 25 Proportion of Complete Fissures (vs. Partial or Absent) 52
Table 26 Zephyr Endobronchial Valve Procedure Time 53
Table 27 Zephyr Endobronchial Valve Target Lobes 54
Table 28 Anesthesia and Airway Management 54
Table 29 Proportion of Procedures Involving a Rigid Bronchoscope 55
Table 30 Number of Zephyr EBVs Placed Per Subject 55
Table 31 Acute Technical Success (Site Determined) 55
Table 32 Reasons for Acute Technical Failure (Site Determined) 56
Table 33 Listing of Acute Technical Failures 56
Table 34 Subjects with Valves Removed During the Initial Procedure and Not Replaced (Technical Failures) 57
Table 35 Valves Removed During the Initial Procedure 58
Table 36 Categories of Device Malfunctions 58
Table 37 Listing of Device Malfunctions 59
Table 38 Primary Effectiveness Outcome: Multiple-Imputation, Intent-to-Treat Percent Change in FEV_1 and 6MWT at 6 Months 62

Table 39 Completed Cases: Percent Change in FEV_1 and 6MWT at 6 Months 62
Table 40 2° Effectiveness Outcome: Change in SGRQ Score at 6 Months 63
Table 41 2° Effectiveness Outcome: Change in mMRC Dyspnea Scale at 6 Months 64
Table 42 2° Effectiveness Outcome: Change in Maximum Workload during Cycle Ergometry (watts) at 6 Months 64
Table 43 2° Effectiveness Outcome: Use of Supplemental Oxygen (liters / day) 65
Table 44 Components of the Major Complications Composite (MCC) 67
Table 45 Primary Safety Outcome: Major Complications Composite at 6 Months 68
Table 46 Summary: Subjects with One or More MCCs 68
Table 47 Survival Estimates and 95% Confidence Limits through 1 Year for Zephyr EBV and Control Subjects (M-ITT) 70
Table 48 Major Complication Composite for First and Second 6-Month Time Periods 71
Table 49 Percent Change in Residual Volume 73
Table 50 Percent Change in Diffusing Capacity (DL_{CO}) 74
Table 51 Quality of Well Being Scale 74
Table 52 Change in BODE Index 74
Table 53 Reasons for Incomplete Lobar Exclusion on 180 Day HRCT 75
Table 54 Rehospitalization Rates through 6 and 12 Months 76
Table 55 FEV_1 and 6MWT: Treatment Group Only—Effect of Lobar Exclusion on % Change in Primary Outcomes 6 Months (CC) 78
Table 56 Subgroup Analysis: Percent Change in FEV_1 and 6MWT in High Heterogeneity Subgroup at 6 Months (CC) 79
Table 57 Subgroup Analysis: Percent Change in FEV_1 by Fissure Integrity at 6 Months 79
Table 58 Responder Analysis: Subjects with Maintained FEV_1 (Increase ≥ 0%) at 6 Months (CC) 82
Table 59 Responder Analysis: High Heterogeneity Subjects with Maintained FEV_1 at 6 Months (CC) 82
Table 60 Responder Analysis: Subjects with FEV_1 Improvement ≥ 15% at 6 Months (CC) 83
Table 61 Responder Analysis: High Heterogeneity Subjects with FEV_1 Improvement ≥ 15% at 6 Months (CC) 83
Table 62 Responder Analysis: Subjects with Maintained 6MWT (Increase ≥ 0%) at 6 Months (CC) 84
Table 63 Responder Analysis: High Heterogeneity Subjects with Maintained 6MWTat 6 Months (CC) 84
Table 64 Responder Analysis: Subjects with Major Improvement (≥ 15%) in 6MWT at 6 Months (CC) 85
Table 65 Responder Analysis: High Heterogeneity Subjects with 6MWT Improvement ≥ 15% at 6 Months (CC) 85
Table 66 Responder Analysis: Subjects with SGRQ Improvement of ≥ 8 Points at 6 Months (CC) 86

Table 67 Responder Analysis: Subjects with mMRC Dyspnea Scale Improvement of ≥ 1 Point at 6 Months (CC) 86
Table 68 Responder Analysis: Subjects with Improvement in Maximum Workload during Cycle Ergometry ≥ 10 Watts at 6 Months (CC) 87
Table 69 Responder Analysis: Subjects with ≥ 1 Point Improvement in the BODE Index at 6 Months (CC) 88
Table 70 Responder Analysis Summary for Maintenance and ≥ 15% Improvement in FEV_1 and 6MWT at 6 Months 88
Table 71 Responder Analysis Summary for Secondary Effectiveness Outcomes and BODE at 6 Months 89
Table 72 Effect of EBV Treatment on $TLAS_{TLC}$ 91
Table 73 Technical Success (Complete Lobar Exclusion) and $TLAS_{TLC}$ 92
Table 74 Left Target Lung, Fissure Integrity and $TLAS_{TLC}$ (CC) 93
Table 75 Right Target Lung, Fissure Integrity and $TLAS_{TLC}$ 93
Table 76 $TLAS_{TLC}$ in Zephyr EBV Subjects by Lobar Exclusion and Fissure Integrity 94
Table 77 Percent Change in FEV_1 at 6 Months in Zephyr EBV Subjects by Lobar Exclusion and Fissure Integrity 95
Table 78 Adverse Events through 1 year 99
Table 79 Per-Subject Serious Adverse Events through 1 Year 105
Table 80 Zephyr EBV Subjects with Granulation Tissue 110
Table 81 Zephyr EBV Subjects with Valve Migrations or Expectorations 112
Table 82 Summary: Zephyr EBV Subjects with Valve Expectoration or Migration 112
Table 83 Zephyr EBV Subjects with Pneumonia Distal to Valves 114
Table 84 Per-Subject Reasons for Attempted Valve Removal during Study Follow-up 115
Table 85 Summary: Valve Removal during Study Follow-Up 116
Table 86 Percent Change in FEV_1 at 1 Year (CC) 120
Table 87 High Heterogeneity Subgroup: Percent Change in FEV_1 at 1 Year (CC) 121
Table 88 Percent Change in 6MWT at 1 Year (CC) 121
Table 89 High Heterogeneity Subgroup: Percent Change in 6MWT at 1 Year (CC) 122
Table 90 Change in SGRQ at 1 Year (CC) 122
Table 91 Change in mMRC Dyspnea Scale at 1 Year 122
Table 92 Change in Maximum Workload during Cycle Ergometry at 1 Year (CC) 123
Table 93 Change in Use of Supplemental Oxygen at 1 Year (CC) 123
Table 94 Matched 3, 6, and 12 Month % Change in FEV_1 124
Table 95 High Heterogeneity Subgroup: Matched 3, 6, and 12 Month % Change in FEV_1 125
Table 96 Matched 3, 6, and 12 Month Data for Percent Change in 6MWT 126
Table 97 High Heterogeneity Subgroup: Matched 3, 6, and 12 Month Data for Percent Change in 6MWT 127

LIST OF FIGURES

Figure 1 Photograph: Emphasys Zephyr Endobronchial Valve (EBV) 8
Figure 2 Diagram: Emphasys Zephyr Endobronchial Valve (EBV).....9
Figure 3 Photograph: Zephyr Endobronchial Delivery Catheter (Zephyr EDC) 10
Figure 4 Photograph: Zephyr Endobronchial Loader System (Zephyr ELS).....10
Figure 5 Fissure Integrity Example 25
Figure 6 Subject Accountability Flow Chart.....39
Figure 7 Chart: Kaplan-Meier Curves for Freedom from All-Cause Mortality.....70
Figure 8 Chart: MCC Rates by Valve Removal by Quarter.....72
Figure 9 Picture: HRCT Image Example of Non-Lobar Exclusion (Technical Failure).....76
Figure 10 Chart: Per-Subject Rehospitalization Rates by Quarter.....77
Figure 11 Chart: Zephyr EBV Treatment, TLVR and FEV_1.....90
Figure 12 Chart: $TLAS_{TLC}$ vs. % Change in FEV_1 (CC).....92
Figure 13 Chart: $TLAS_{TLC}$ in Zephyr EBV Subjects by Lobar Exclusion and Fissure Integrity 94
Figure 14 Chart: FEV_1 in Zephyr EBV Subjects by Lobar Exclusion and Fissure Integrity.....96
Figure 15 Chart: All COPD/Emphysema Rates by Valve Removal by Quarter.....102
Figure 16 Chart: Other Pulmonary Infection Rates by Valve Removal by Quarter.....102
Figure 17 Chart: Increased Shortness of Breath Rates by Valve Removal by Quarter 103
Figure 18 Chart: Hypoxemia Rates by Valve Removal by Quarter.....103
Figure 19 Chart: Hemoptysis Rates by Valve Removal by Quarter.....104
Figure 20 Chart: Non-cardiac Chest Pain Rates by Quarter.....104
Figure 21 Chart: General Adverse Event Rates by Quarter.....105
Figure 22 Chart: SAEs – COPD Exacerbations Rates by Valve Removal by Quarter 108
Figure 23 Chart: SAEs – All Hemoptysis Rates by Quarter 108
Figure 24 Chart: Matched 3, 6, and 12 FEV_1 Outcomes.....124
Figure 25 Chart: High Heterogeneity Subgroup Matched 3, 6, and 12 Month FEV_1 Outcomes.....125
Figure 26 Chart: Matched 3, 6, and 12 Month 6MWT Outcomes 127
Figure 27 Chart: High Heterogeneity Subgroup Matched 3, 6, and 12 Month 6MWT Outcomes.....128

LIST OF APPENDICES

Related Appendices for all Zephyr EBV Clinical Study Reports:

7-1 HRCT Core Laboratory Methodology
Location: Vol 010:Page 55 (September 21, 2007 original PMA)

7-2 DSMB Charter and Minutes
Location: Vol 010 :Page 128 ((September 21, 2007 original PMA)

7-3 CEC Charter and Minutes
Location: Vol 010:Page 153 (September 21, 2007 original PMA)

7-4 Financial Disclosures and Investigator Certifications
Location: Vol 010 Page 206 (September 21, 2007 original PMA)

Appendices for the VENT Pivotal Trial Clinical Study Report:

7-5-1 Investigators, Study Sites and IRBs
Location: Vol 011:Page 175 (September 21, 2007 original PMA)

7-5-2 Protocol – Location: Vol 011:Page 191 (September 21, 2007 original PMA)

7-5-3 Protocol Amendments
Location: Vol 011:Page 243 (September 21, 2007 original PMA)

7-5-4 Blank Case Report Forms (CRFs)
Location: Vol 012:Page 1 (September 21, 2007 original PMA)

7-5-5 Sample Informed Consent
Location: Vol 012:Page 76 (September 21, 2007 original PMA)

7-5-6 Listing of Protocol Deviations
Location: Vol 012:Page 85 (September 21, 2007 original PMA)

7-5-7 Statistical Analysis Plan
Location: Vol 012:Page 230 (September 21, 2007 original PMA)

7-5-8 Statistical Report with Tables
Location: Vol 01 & 02 : (August 8, 2008 PMA amendment)

7-5-9 Adverse Event Narratives for Selected Subjects
Location: Vol 013:Page 177 (September 21, 2007 original PMA)

7-5-10 Literature References
Location: Vol 014:Page 1 (September 21, 2007 original PMA)

7-5-11 List of CEC Consolidations/Deletions
Location: Vol 014:Page 209 (September 21, 2007 original PMA)

11 Completed CRFs for Deaths and Discontinuations
Location: Vol 019:Page 1 (September 21, 2007 original PMA)

LIST OF ABBREVIATIONS AND ACRONYMS

6MWT	Six minute walk test
95% CI	95 percent confidence interval
AE	Adverse event
BODE Index	BMI / Airway Obstruction / Dyspnea / Exercise Capacity Index
CC	Completed Case
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CQ	Corrections/Query form
CRF	Case Report Form
CRL	Core Radiology Laboratory
CSR	Clinical Study Report
CT	Computed tomography (scan)
CXR	Chest X-ray
DL_{CO}	Diffusing capacity (lung) for carbon monoxide
DS	Density Score
DSMB	Data Safety and Monitoring Board
ECG	Electrocardiogram
ERV	Expiratory reserve volume
ES	Emphysema Score
FDA	Food and Drug Administration
$FEF_{25\text{-}75\%}$	Forced expiratory flow rate (middle 50% of exhaled volume)
FEV_1	Forced expiratory volume (one second)
FEV_1 % predicted	Forced expiratory volume (one second) as a percent of predicted
FiO_2	Fraction of inspired oxygen
FRC	Functional reserve capacity
FVC	Forced vital capacity
GCP	Good Clinical Practice
HRCT	High Resolution Computed Tomography (scan)
HS	Heterogeneity Score
IC	Inspiratory capacity
IDE	Investigational Device Exemption
IRB	Institutional Review Board

ITT	Intent-to-treat
LTFU	Lost to follow-up
LVEF	Left ventricular ejection fraction
LVRS	Lung volume reduction surgery
MCC	Major Complication Composite
MI	Myocardial infarction
mm Hg	Millimeters of mercury (pressure)
mMRC	Modified Medical Research Council Dyspnea Scale
MVV	Maximal voluntary ventilation
NETT	National Emphysema Treatment Trial
$PaCO_2$	Partial pressure of carbon dioxide in arterial blood
PaO_2	Partial pressure of oxygen in arterial blood
P_{EFR}	Peak expiratory flow rate
P_{IFR}	Peak inspiratory flow rate
PFT	Pulmonary function testing
PVC	Premature ventricular contraction
QoL	Quality of Life
QWB	Quality of Well Being (Scale)
RV	Residual volume
SAE	Serious adverse event
SAT	Arterial blood saturation with oxygen
SD	Standard deviation
SGRQ	St. George's Respiratory Questionnaire
SIRS	Systemic inflammatory response syndrome
SVT	Supraventricular tachycardia
Target Lobe	The lobe of the lung targeted for treatment by HRCT algorithm prior to randomization. After randomization to the Zephyr EBV group, the lobe which is treated with Zephyr EBV device(s).
$TLAS_{RV}$	Target lobe atelectasis score at residual volume
$TLAS_{TLC}$	Target lobe atelectasis score at total lung capacity
TLC	Total lung capacity
TLVR	Target Lobe Volume Reduction
UADE	Unanticipated adverse device effect
VQ	Ventilation perfusion (scan)
VTG	Volume of thoracic gas
Zephyr EBV	Zephyr Endobronchial Valve

1.0 INTRODUCTION

1.1 Disease Information

The estimated prevalence of emphysema in the US population in 2004 was 3.5 million people. Half of emphysema patients in the U.S. are 65 years of age or older and 39% are between the ages of 45 and 65. Emphysema is therefore a clinically disabling disease which can adversely affect economic well-being.[1]

Emphysema is a chronic lung disease characterized by the permanent, abnormal distention of air spaces distal to the terminal bronchiole with destruction of the alveolar septa. It is often coexistent with chronic bronchitis, and is most commonly caused by long term cigarette smoking, although air pollution, occupational exposure, infection and familial and genetic factors have also been implicated.

As emphysematous destruction progresses, the loss of alveolar and capillary structures result in reduced lung function. Breathlessness leads to reduced activity and a secondary reduction in cardiovascular conditioning. This in turn exacerbates breathlessness and the negative cycle continues to complete debilitation. Intervening complications include infection, including COPD exacerbation and recurrent pneumonia.

There is no known intervention which can halt or reverse the underlying disease of emphysema, and all treatments to date are palliative. These treatments include continuous supplemental oxygen therapy and medications such as bronchodilators, steroids and mucolytics.

Recent trials of more aggressive interventions attempting to alter lung mechanics have been tried. The National Emphysema Treatment Trial (NETT) showed that surgical removal of the most disease parts of the lungs—known as lung volume reduction surgery (LVRS)—can improve lung function and possibly even survival in carefully selected subsets of patients.[2 - 5] Use of this procedure has been quite limited, given the strict selection criteria and the significant peri-operative morbidity and mortality.

Emphysema remains a significant clinical challenge. Pharmacotherapy and occasionally surgery have clear palliative benefit, but more effective and safer interventions are needed to better serve these patients. The VENT Pivotal Trial of the Emphasys Zephyr Endobronchial Valve (Zephyr EBV) was undertaken to test the safety and effectiveness of a bronchoscopically inserted one-way valve in the treatment of patients with emphysema.

1.2 Emphasys Device Information

Emphasys Medical has developed a bronchoscopic approach to block the inspiratory airflow into targeted, hyperinflated regions of the lung, while permitting exhaled gas to escape. This approach may provide some of the clinical benefits of lung volume reduction surgery (LVRS) without the high risks and costs associated with such an invasive surgical procedure. It may also provide benefits that are not realized through LVRS by preserving lung tissue.

The Emphasys Zephyr Endobronchial Valve (Zephyr EBV) incorporates a one-way valve that is implanted in a bronchial lumen. The one-way valve is supported by a self-expanding retainer that secures the implanted Zephyr EBV in place during all physiological conditions, including coughing. The implanted Zephyr EBV allows air to be vented from the isolated lung segment under normal exhalation pressure, and prevents air from refilling the isolated lung area during inhalation. The Zephyr EBV is provided in two sizes, each intended for a different range of target bronchial lumen diameters.

1.3 Rationale for Endobronchial Valve Treatment

The rationale for using a one-way valve to treat patients with emphysema stems from results of lung volume reduction surgery (LVRS). With LVRS, the objective is to surgically eliminate dysfunctional, over-inflated regions of lung.[6] The National Emphysema Treatment Trial (NETT), along with other studies, has shown that LVRS can offer relief to some patients suffering from emphysema when other treatments have failed.[2 – 5, 7 - 11]

This paradoxical affect of improving lung function by removing (or isolating) lung tissue demonstrates that breathlessness due to emphysema is a function of mechanical compromise in addition to loss of gas-transfer surface area. In some patients, the mechanical compromise is the primary cause of their pulmonary incapacitation and these patients may benefit by addressing the impact of severely emphysematous lung upon the ability to ventilate more normal pulmonary tissue.

Results similar to surgical removal of diseased lung sections during LVRS have also been obtained by plication (folding) and stapling without tissue removal.[12 - 15] These results suggest it is modification of the dysfunctional lung region which is key, and that similar results may be possible without actual resection of tissue.

Because both approaches reduce trapped gas, Emphasys Medical hypothesized that similar results could be achieved bronchoscopically. This approach may provide the clinical benefits of lung volume reduction surgery in a minimally invasive and potentially

reversible manner, thus reducing the morbidity and mortality associated with an open surgical procedure such as LVRS. [16 - 18]

The intended physiological and clinical cascade resulting from placing a valve in the airways leading to diseased lung tissue includes reduced hyperinflation and improved breathing mechanics, improved airflow and gas exchange in viable lung segments, and improved lung function and clinical status.

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. In addition, the valves help to improve gas transfer in the lung by preferentially directing inspiratory flow to the healthier lung sections and by allowing these regions to expand more fully. The resulting lung function improvements should enable patients to increase their daily activity leading to a more active lifestyle and improved QoL.

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.

1.4 Preclinical and Clinical Studies

The Emphasys Endobronchial Valve underwent extensive testing prior to its use in the VENT Pivotal Trial. Biocompatibility testing under FDA guidelines demonstrated that the device was biocompatible for its intended use in the human tracheobronchial tree. *In vivo* assessments were used to optimize device design and to demonstrate its performance before use in human subjects. In particular, long term studies in sheep demonstrated that the device could be reliably placed in the tracheobronchial tree, that it caused volume reduction in the experimentally created obstructed lung segments, that it did not migrate and that it could be removed safely. Most animals had no signs of distal infection; a small proportion had signs of mild subclinical pneumonia.

Pilot clinical studies were performed with several device iterations. At the time the VENT Pivotal Trial began, 71 subjects with advanced emphysema at 9 international sites had been followed post EBV placement. Thirty-eight of these subjects had been treated with complete lobar exclusion. For this 38 subject subset, baseline mean FEV_1 was 31% of predicted, the 6MWT averaged 300 ± 128 meters, DL_{CO} averaged 42% of predicted and RV average 280% of predicted. After 90 days of follow-up, mean FEV_1 had improved from the baseline value by 15%, mean 6MWT by 20%, mean DL_{CO} by 14% and mean RV had decreased by 2%.

Adverse events in these subjects were consistent with the severity of their illness. There were two deaths during study follow-up. One subject died during the first month post

procedure, when valve-related post-obstructive pneumonia did not resolve after EBV removal. One subject died at 161 days post-procedure due to pneumonia in an untreated lobe. In the first 90 days post-procedure, two (2) pneumothoraces required surgical intervention, two (2) pneumothoraces lasted longer than 7 days, and six (6) other pneumothoraces were reported, some requiring chest tubes. There were 12 reports of COPD exacerbation, four reports of valve removal and one pleural effusion.

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

These data suggested a favorable risk-benefit ratio for this novel minimally invasive palliation for severely emphysematous patients, and the VENT Pivotal Trial was designed and approved by the FDA. The remainder of this document details the study's design and results.

2.0 ETHICAL AND REGULATORY CONSIDERATIONS

2.1 Study Responsibility

Emphasys Medical, Inc., the Study Sponsor, was responsible for the overall conduct of the trial. The Sponsor conducted the clinical trial in compliance with Good Clinical Practice (GCP) and all applicable regulatory requirements. The Sponsor designed and implemented study materials to support the trial including Case Report Forms (CRFs). Full-time Sponsor personnel followed approved Standard Operating Procedures in all study activities, including site selection, start-up and regulatory document maintenance activities as well as training of clinical site personnel. Data monitoring and site management were performed by full time Clinical Research staff and contractors. Data management activities were performed directly by a full-time data management team who created a dedicated study database and managed the data, processing, review, query, validation and data lock activities.

The Core Radiology Laboratory (CRL), provided by MedQIA in association with the UCLA David Geffen School of Medicine (Los Angeles, CA), was responsible for implementing standardized HRCT image collection at each investigational site. At enrollment, the CRL performed quantitative image analysis of screening HRCT scans to determine subject eligibility status. For each eligible subject the CRL determined the target lobe based on the VENT Pivotal Trial protocol requirements. Throughout the study, the CRL worked with investigational sites to ensure appropriate quality control measures including collecting and analyzing “phantom” HRCT scans.

Richard P. Chiacchierini Associates provided statistical support for the VENT Pivotal Trial. These activities included helping to write and revise the Statistical Analysis Plan as well as carrying out the actual analyses. This group was also responsible for the preparation of the final statistical reports associated with the trial.

2.2 Subject Confidentiality

Subject confidentiality was maintained throughout the clinical study. Once informed consent was obtained, subjects enrolled in the study were assigned a unique identifier indicating the site number, the subject number and the subjects’ initials. All identifiers were listed on the patient screening log kept at each site. Any documents received by Sponsor to support and/or provide source document verification were redacted and assigned the appropriate subject identifier. All other unique identifiers, for example, Social Security numbers, addresses, etc. were also redacted as appropriate.

All information and data sent to Emphasys Medical concerning subjects or their participation in this study was considered confidential. All data used in the analysis and reporting of this evaluation was used in a manner without identifiable reference to any subject enrolled in the study. Hard copies of all study documentation including CRFs were kept in a locked, secure location. Computer access was password protected and permitted in variable levels according to responsibility.

2.3 Informed Consent and Institutional Review Boards (IRBs)

All informed consent documents required prior IRB approval. Signed written informed consent was mandatory for all study subjects and was obtained prior to initiation of any study specific procedures in the VENT Pivotal Trial. Informed consent was obtained in accordance with FDA regulation 21 CFR Part 50 except for protocol deviations as noted. Each site provided Emphasys Medical with a copy of their original IRB approval letter and the IRB approved consent form. Documentation of continuing IRB annual renewals were provided as appropriate. A sample of the most current informed consent document is included in Appendix 7-5-5.

2.4 Operations Committee

The Operations Committee approved the final trial design and protocol issued to the Data and Safety Monitoring Board (DSMB) and the clinical sites. This committee was responsible for the day-to-day administrative management of the trial, and met as needed to monitor subject enrollment, clinical site progress, and protocol compliance. The Operations Committee was also responsible for reviewing this Clinical Study Report.

2.5 Data and Safety Monitoring Board (DSMB)

The DSMB functioned in accordance with applicable regulatory guidelines, and consisted of a statistician and specialty physicians with relevant knowledge and skills. The DSMB was responsible for making recommendations to the Operations Committee regarding outcome analysis and any potential situations in which patient safety, patient welfare, or the scientific adequacy of the study were at risk. The DSMB also had responsibility for making confidential recommendations to the Operating Committee regarding study continuation or termination based on established safety stopping rules, but this was not necessary during this investigation. The DSMB charter and meeting minutes can be found in Appendix 7-2.

2.6 Clinical Events Committee (CEC)

The Clinical Events Committee (CEC) consisted of Pulmonologists and Thoracic Surgeons who were not otherwise participating in the study and was a distinct and separate group from the DSMB. The CEC met regularly throughout the trial to review

and adjudicate all Adverse Events. The CEC was blinded to Investigator and institution. The CEC charter and meeting minutes can be found in Appendix 7-3.

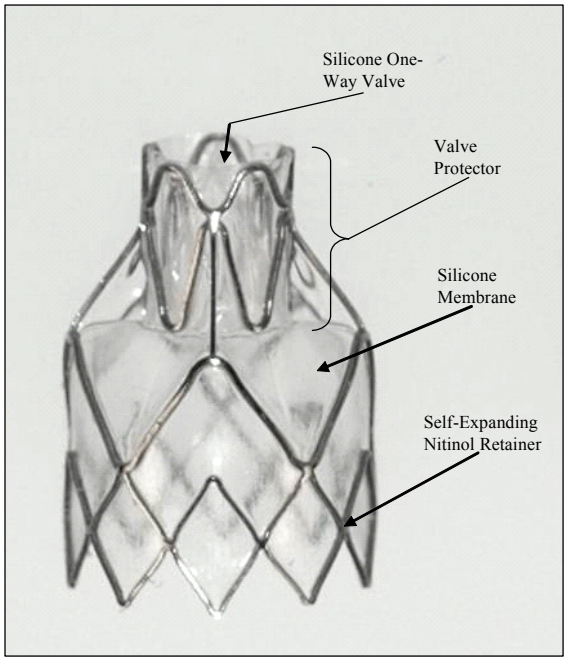
3.0 INVESTIGATIONAL DEVICES

The investigational devices included the Emphasys Zephyr Endobronchial Valve (Zephyr EBV), and the Zephyr Endobronchial Delivery System which consisted of the Zephyr Endobronchial Delivery Catheter (Zephyr EDC) and the Zephyr Endobronchial Loader System (Zephyr ELS).

3.1 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 and 5.5 mm to 8.5 mm, allowing bronchial lumens with diameters from 4.0 mm to 8.5 mm to be treated.

Figure 1 Photograph: 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.

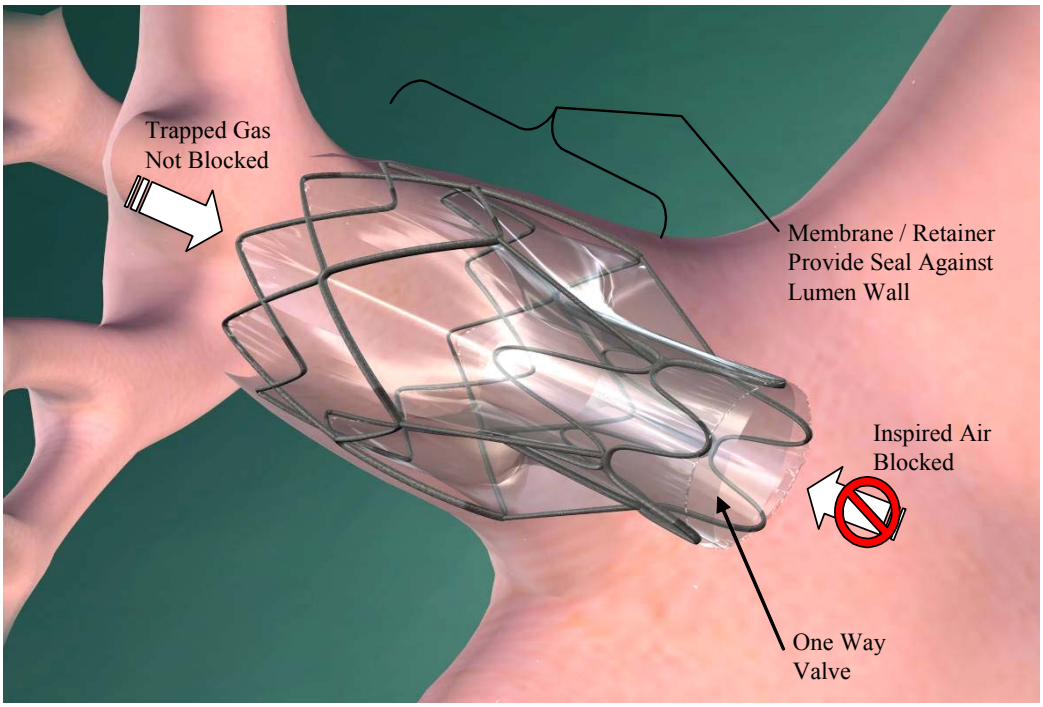


Figure 2 Diagram: Emphasys Zephyr Endobronchial Valve (EBV)

3.2 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 Zephyr EBV can be removed bronchoscopically, if necessary, using standard flexible rats tooth grasping forceps.

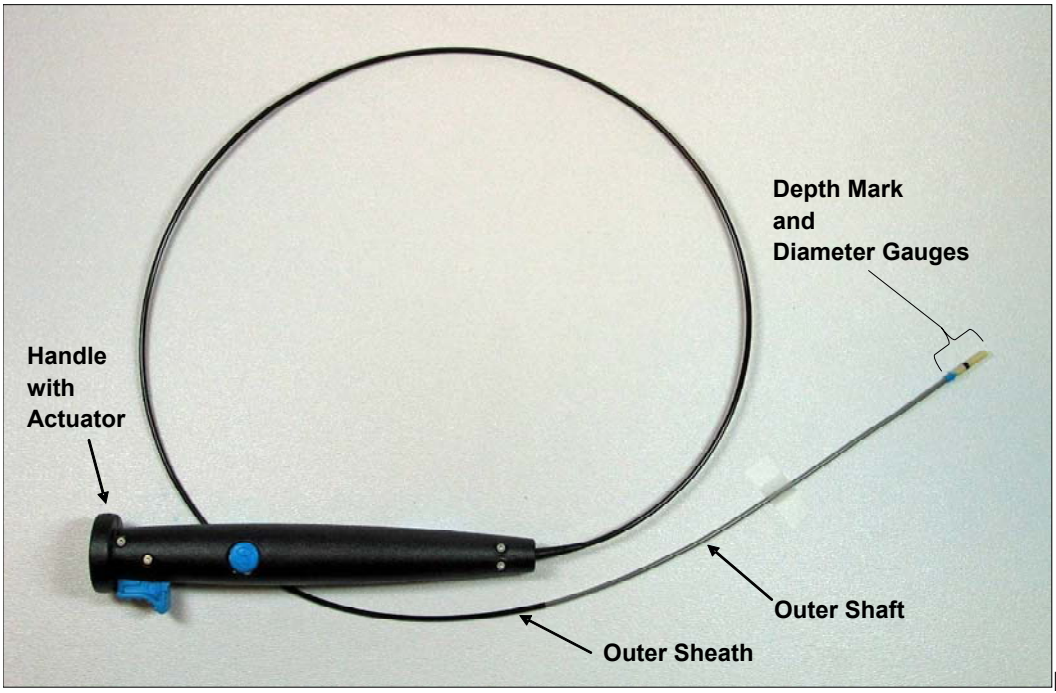


Figure 3 Photograph: Zephyr Endobronchial Delivery Catheter (Zephyr EDC)*

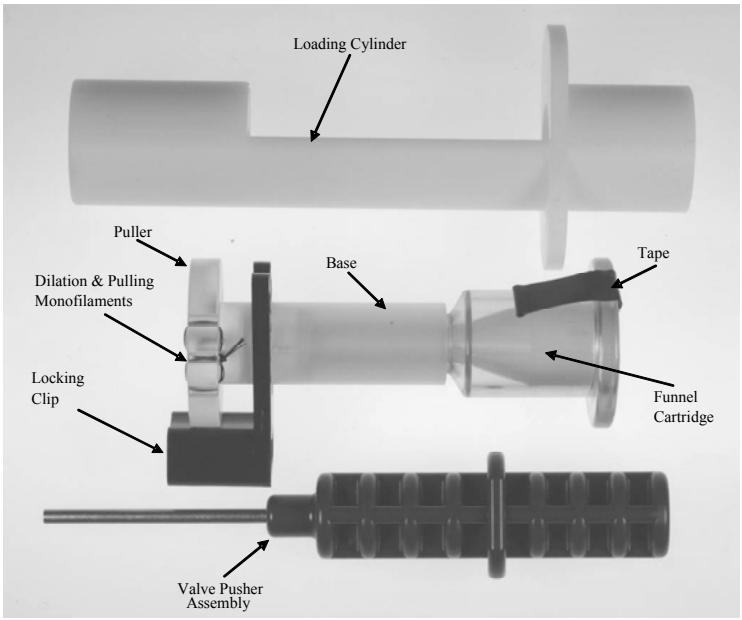


Figure 4 Photograph: Zephyr Endobronchial Loader System (Zephyr ELS)

* Depth Mark (also called "Marker Band") was implemented after completion of VENT (see original PMA Vol. 001, Page 80.

3.3 Handling and Storage

Emphasys Medical personnel oversaw the handling and storage of all investigational devices used in this study. Investigational devices were kept in segregated storage and shipped to approved investigational sites upon the completion of specified documentation. Device shipment receipt was documented by investigational sites and devices were placed in secure storage until used in the clinical study. When necessary, device returns and replacements were effected under a controlled and documented process, which included provisions for handling contaminated devices. Study monitors reviewed device handling and accountability at monitoring visits.

3.4 Accountability

Emphasys Medical supplied each Investigator with an adequate number of investigational devices for completion of the study. Emphasys Medical maintained records for each site of the number of devices shipped, used and returned. Throughout the study, device accountability records were regularly reviewed by the Emphasys Medical-appointed monitor. The Investigator was responsible for ensuring that the device accountability records were complete and up to date at all times.

4.0 STUDY DESIGN, MANAGEMENT AND ANALYSIS

4.1 VENT Pivotal Trial Overview

The primary objective of the VENT Pivotal Trial was to assess the safety and effectiveness of the Emphasys Endobronchial Valve (Zephyr EBV) and procedure compared to optimal medical management in subjects with heterogeneous emphysema.

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.

After granting informed consent and meeting enrollment criteria, study subjects all underwent history and physical examination, evaluation of pulmonary function and morphology including high resolution CT scanning (HRCT), a program of optimal medical management and aggressive pulmonary rehabilitation. Upon successful completion of this program subjects were randomized to either the Control or Zephyr EBV Treatment.

Zephyr EBV Subjects underwent bronchoscopic Zephyr EBV implantation under the provisions of the protocol which limited treatment to only one lobe (upper or lower lobe on one side). Complete exclusion of the target lobe was attempted by placing one or more Zephyr EBVs in lobar, segmental and / or subsegmental airways. Post-procedure, Zephyr EBV Subjects remained in the hospital and were observed for complications for at least 1 day.

Subsequent follow-up for all subjects consisted of assessment of a variety of relevant pulmonary and general outcome measures as evaluated by specific spirometry, body plethysmography, diffusing capacity, QoL and exercise tests. Follow-up and outcome assessments were scheduled for 2 – 3 days, 1 week, 1, 3, and 6 months, and 1 year.

The co-primary effectiveness outcomes were the percent change 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.

4.2 Summary of Study Procedures

For a complete description of study procedures, please refer to the Study Protocol in Appendix 7-5-2 .

4.2.1 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. Disease categorization was performed by the CRL for each pulmonary lobe, resulting in quantitative assessments including a Density (or Emphysema) Score for each lobe and the volume of each lobe at maximal inhalation and maximal exhalation.

Screen subjects then underwent the Optimal Medical Management Program, consisting of smoking cessation support, treatment with bronchodilators and influenza and pneumococcal vaccination. Screen 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 pulmonary rehabilitation program, 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.

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

4.2.2 Inclusion / Exclusion Criteria

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

1. Subject diagnosed by HRCT Core Lab with eligible heterogeneous disease distribution (Section 6.7.5 of the protocol)
2. Age from 40 to 75 years
3. BMI < 31.1 kg / m^2 (men) or < 32.3 kg / m^2 (women)
4. FEV_1 < 45% of predicted value
5. Subject has provided written informed consent using a form that has been reviewed and approved by the IRB / EC

6. Stable with < 20 mg prednisone (or equivalent) daily
7. TLC > 100% predicted
8. RV > 150% predicted
9. $PaCO_2$ < 50 mm Hg (Denver < 55 mm Hg)
10. PaO_2 > 45 mm Hg (Denver > 30 mm Hg) on room air
11. Post rehabilitation 6MWT of > 140 meters
12. Plasma cotinine level < 13.7 ng / ml (or arterial carboxyhemoglobin < 2.5% if using nicotine products)
13. Nonsmoking for 4 months prior to initial interview and throughout screening
14. The subject agrees to all protocol required follow-up intervals
15. The subject has no child bearing potential OR a negative pregnancy test in a woman of childbearing potential
16. The subject is willing and able to complete protocol required baseline assessments and procedures

Candidates who met any of the following 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

4.2.3 Zephyr EBV Subjects: Valve Implantation Procedure

The implantation of the Zephyr EBV valve was performed in eligible Zephyr EBV Subjects, either under general anesthesia on ventilators, or using conscious sedation with unassisted breathing. Antibiotic coverage was given before and after the procedure. The targeted lobe for Zephyr EBV Treatment was ascertained based on the HRCT Scoring Form prepared by the CRL; only one lobe was treated in each study subject. Zephyr EBV implantation was permitted at either the lobar, segmental or subsegmental level, with preference for the earliest generation airway, with an intent to achieve complete lobar exclusion. 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.

4.2.4 Zephyr EBV Subjects: Post Implantation Procedure

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

Any subject with radiographic evidence of atelectasis was kept in-hospital under observation for at least 2 days post procedure. A stable pneumothorax was an expected response to lobar atelectasis and was not treated unless it persisted. When a chest tube became necessary, it was continued until signs of air leak ceased, at which time it was removed.

4.2.5 Zephyr EBV Subjects: Valve Removal Procedure

When removal was necessary, Zephyr EBV valves were removed according to the Instructions for Use. This could occur at any time during the procedure or later during the follow-up interval as deemed necessary by the Investigator. Any subject with either

an increase in RV > 15% or an FEV_1 decrease of > 15% and an RV decrease of < 5% during the first 30 days of follow-up was recommended to be considered for a valve removal procedure. All subjects treated with the Zephyr EBV device, including those that underwent valve removal, were followed for the entire protocol-specified follow-up period.

4.2.6 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).[20] Body plethysmography post bronchodilator treatment was performed according the American Association of Respiratory Care Clinical Practice Guideline (2001).[21] Diffusing capacity (DL_{CO}) was measured using the single-breath carbon monoxide method according to American Thoracic Society standards (1995).[22] Six-Minute Walk testing was performed according to American Thoracic Society standards (2002)[23]; 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[24] 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.

4.2.7 Adverse Events

Adverse events, Serious Adverse Events and Unanticipated Adverse Device Effects were assessed and reported using standard FDA definitions. Abnormal laboratory values were not reported as adverse events; however, any clinical consequence of the abnormality, or the cause of the abnormal values, was reported as an adverse event.

All adverse events (serious and non-serious) were recorded on the Adverse Event CRF. Serious Adverse Events and/or Unanticipated Adverse Device Effects were reported on the Serious and/or Unexpected Adverse Event CRF and the event was required to be reported by telephone or fax to the Adverse Events Coordinator within 24 hours after

learning of the event. Information regarding deaths was documented on the Serious and/or Unexpected Adverse Event and Report of Patient Death CRFs.

4.3 Study Management

4.3.1 Investigator Selection, Responsibility, Training and Performance

Emphasys Medical selected qualified Investigators based upon training and experience, and shipped devices only to participating Investigators. Each Investigator had fully executed clinical contracts; IRB approvals; signed /dated CVs on file and a signed statement attesting to the Investigators' agreement to conduct the study in accordance to the investigational plan, applicable Federal regulations and other specific conditions of approval as may have been imposed by the local governing IRB. Investigator financial disclosures and investigator certificates can be found in Appendix 7-4.

Study sites selected for this clinical study were determined to have a sufficient number of cases available to allow timely enrollment of subjects into this study. The Sponsor monitored the Investigators for evidence of noncompliance with the signed agreements, investigational plan, or conditions included in approvals imposed by an IRB and took necessary steps to ensure such compliance.

4.3.2 Monitoring and Source Documentation

Monitors qualified by training and experience were selected by the Sponsor to monitor the investigational study in accordance with applicable regulations. Emphasys Medical and/or its designee conducted Investigational Site monitoring to ensure that all Investigators were in compliance with the Investigational Plan, the Investigator Agreement, all applicable regulations, and any conditions of approval imposed by the reviewing IRB. Emphasys Medical and/or its designee monitored the sites to ensure the relevant data on completed Case Report Forms (CRFs) was substantiated by source documentation. While Emphasys Medical conducted a significant portion of this monitoring through its own full-time clinical research staff, these efforts were augmented as needed by utilizing two external contract research organizations (Bailer Research, Inc., Lake Hopatcong, NJ and ICRC Inc., Reno, NV).

Values entered on case report forms were compared against subject medical records and other associated source documents to ensure accuracy. For each such visit, monitors were required to sign a monitoring log kept at the site and also prepare a written report documenting their activities. Following each visit, monitors prepared a short summary letter or email to the site summarizing the visit and any action items identified.

Please refer to Appendix 7-5-4 for copies of blank Case Report Forms.

4.3.3 Data Transmittal and Record Retention

Data for the study was collected on 3-part case report forms (CRFs). Once monitored, the original copy of the 3-part form was sent to Sponsor's data management group for processing. Upon receipt, the CRF was logged into a tracking database which was used to determine overall CRF collection status for the study. All received CRFs were filed in locked, fireproof filing cabinets.

4.3.4 Managing Study Deviations

Any noted deviations from the protocol that occurred during the course of the study site were fully documented using a Protocol Deviation Form. Blank copies of these forms were included with each set of subject CRFs. Once completed, these forms were collected and processed in the same manner as all other CRFs.

4.3.5 CEC Adverse Event Adjudication

Over the course of the clinical investigation, the CEC reviewed and adjudicated 1,437 reported events. Some site-reported events were combined into a single coded event to more accurately reflect the clinical course of the event and to eliminate potential double counting of events. Some site-reported events that appeared to be unrelated to the subject's pulmonary status and/or participation in the clinical trial were also removed from data analysis sets presented in Section 9 - Safety Outcomes. The CEC pursued a uniform approach to these designations independent of subject assignment. A listing of site reported events that were either combined and/or removed can be found in Appendix 7-5-11.

4.4 Data Management

4.4.1 Data Screening and Acceptance

Upon receipt by the Sponsor, all CRFs were visually reviewed for completeness and legibility. Any issues noted were queried by Sponsor. This involved completing a 3 part Correction/Query form (CQ form) which would describe the CRF page impacted and briefly describe the finding. A separate column on the form provided room for the site to respond to the query. Working copies of these forms were kept by Sponsor while the original and a site copy were forwarded to the study site. The site would then complete and sign the form and send the original back to Sponsor. Each query was filed on top of the CRF to which it pertains.

4.4.2 Data Processing and Quality Control

CRF data were manually entered into a central, controlled study database. Edit checks were performed to identify possible discrepancies, including for blank fields, statistical

outliers and date and unit inconsistencies. Each suspect data field identified by this process was corrected by reference to the original CRF. For issues that could not be resolved by reviewing in-house documentation, a Correction/Query form was completed and sent to the site. These processes continued repeatedly until all queries were resolved.

A random sample of 10% of subjects entered into the database had their CRFs audited. Every data field on every CRF for each of these subjects was reviewed against the data in the database. An acceptance criteria error rate of 0.5% (i.e. 1 in 200) was established. The observed error rate was well below this threshold.

4.4.3 Confidentiality and Protection of Study Files

All CRFs and associated documents identified subjects only by an alphanumeric code. Any subject name information received from study sites was immediately removed or blacked out and substituted with the subject identifier code. All CRFs and study related documents were organized by site and subject and stored in locked, fireproof filing cabinets.

4.5 Statistical Analysis Plan

The complete Statistical Analysis Plan is included in Appendix 7-5-7 and is summarized in this section.

4.5.1 Sample Size

The null hypothesis and alternative hypothesis are presented below where ΔFEV_1 equals the mean percent improvement response in FEV_1 from baseline for each group at 6 months.

$$H_0: \Delta\ FEV_1(EBV) - \Delta\ FEV_1\ (Control) = 0\%$$

$$H_A: \Delta\ FEV_1(EBV) - \Delta\ FEV_1\ (Control) \neq 0\%$$

The sample size was estimated to detect a 15% difference between the study arms for the mean change of FEV_1 and a 17% change of 6MWT from baseline to 6 months.

A 2:1 treatment allocation favoring Zephyr EBV versus Control was utilized. Based on an estimated 0.41 correlation between the 6MWT and FEV_1, and expected loss rate of 10%, 270 subjects were required to achieve a minimum of 246 subjects (164 EBV, 82 Controls). A two-tailed 5% Type I error was used with 80% overall power.

4.5.2 Error and Bias Control

A variety of proven means of minimizing error and bias in clinical studies were utilized in the VENT Pivotal Trial. Study subjects were qualified for study participation under

explicit inclusion and exclusion criteria. Study subjects were randomized to study arms. All study subjects were treated in accordance with well-defined study procedures, administered and recorded consistently across all study sites by appropriately trained and skilled study staff. Study progress and protocol compliance were overseen by an Operations Committee. Concurrent assessment of safety outcomes, subject welfare and scientific adequacy of the study was maintained by a DSMB. Outcome events were adjudicated by an independent CEC. Regular site monitoring and data quality standards were maintained throughout the study.

4.5.3 Analytic Methods

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. Consented subjects who withdrew consent prior to randomization, or who were found not to meet the inclusion/exclusion criteria prior to randomization, were recorded on a screening log at each clinical site and were not included in the intent-to-treat group. Missing data was multiply-imputed 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 observations within a window of 150 – 225 days.

The primary effectiveness outcome measures and secondary effectiveness outcome measures 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. For the safety analysis, the time was determined by subtracting the randomization date from the event date except for a limited number of subjects whose follow-up schedule had been re-set by the site due to illness or lack of available product. For those subjects, the procedure date was subtracted from the event date.

4.5.4 Baseline, Demographic and Procedural Data

Study subjects were comprehensively evaluated for baseline characteristics, including demographic information, pulmonary medications, medical history, supplemental oxygen

use, lung function, arterial blood gases, exercise tolerance and Borg test results. Zephyr EBV Subjects had data gathered regarding the length of procedure time, target lobes, anesthesia and airway management, use of rigid bronchoscopes, number of valves implanted, Acute Technical Success, valve removal and device malfunctions.

4.5.5 Safety Measures and Outcomes

The primary safety outcome measure for the VENT Pivotal Trial was the Major Complications Composite (MCC). An MCC outcome event occurred when a study subject had one or more of the component events listed in the following table.

Table 1 Major Complications Composite

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

Source: Appendix 7-5-2, Protocol.

The Primary Safety Outcome for the VENT Pivotal Trial was the proportion of subjects in each group with one or more MCCs through 6 months of follow-up, reported with exact 95% confidence intervals. MCCs were further evaluated by Cox regression, by time period through one year, and by valve removal status through one year.

Additional prospectively determined safety outcome measures were:

1. Complications (adverse events and serious adverse events through one year)
2. Device-related and procedure-related AEs during procedure hospitalization
3. Device-related and procedure-related AEs following procedure hospitalization
4. All-cause mortality
5. Rehospitalization

4.5.6 Effectiveness Measures and Outcomes

The two primary effectiveness outcome measures for this study were:

1. Mean percent change in FEV_1 at 6 months
2. Mean percent change in 6MWT at 6 months

The Primary Effectiveness Outcome for the VENT Pivotal Trial was the multiple-imputation, intent-to-treat comparison of the percent change in each of the two outcome measures (FEV_1 and 6MWT) as measured at 180 days compared between Control Subjects and Zephyr EBV Subjects. Both FEV_1 and 6MWT results need to be statistically-significantly different for the Primary Effectiveness Outcome to be met.

The secondary effectiveness outcome measures for this study were:

1. Change in St. George's Respiratory Questionnaire (SGRQ) score from baseline
2. Change in Modified Medical Research Council (mMRC) Dyspnea Scale from baseline
3. Change in maximum workload (watts) as measured by cycle ergometry from baseline
4. Change in supplemental oxygen requirement (liters / day) from baseline

The four Secondary Effectiveness Outcomes for the VENT Pivotal Trial were these four outcome measures as measured at 180 days compared between Control Subjects and Zephyr EBV Subjects in the same multiple-imputation, intent-to-treat manner as the Primary Effectiveness Outcome.

Additional pre-specified effectiveness outcome measures for this study were:

1. Percent change in RV from baseline
2. Percent change in DL_{CO} from baseline
3. Change in Quality of Well Being Scale from baseline
4. Change in BODE Index from baseline
5. Technical Success (Zephyr EBV only)

Pre-specified responder analyses regarding the clinical importance of the observed treatment responses were the following:

1. Subjects with Major Improvement (≥ 15%) in FEV_1
2. Subjects with Major Improvement (≥ 15%) in 6MWT
3. Subjects with Any Improvement (≥ 0%) in FEV_1
4. Subjects with Any Improvement (≥ 0%) in 6MWT

Pre-specified, analysis-plan-generated subgroup analyses were the following:

1. High Heterogeneity
2. Technical Success (Complete Lobar Exclusion)
3. Complete Fissure Integrity

Additional *post hoc* responder analyses were performed in response to FDA inquiries regarding the clinical importance of the treatment responses:

1. Subjects with ≥ 8 point improvement in SGRQ
2. Subjects with ≥ 1 point improvement in mMRC
3. Subjects with ≥ 10 watt improvement in maximum workload during cycle ergometry
4. Subjects with ≥ 1 point improvement in the BODE Index

An investigation of Zephyr EBV treatment, target lobe volume reduction (TLVR) as measured by HRCT and treatment effect as measured by FEV_1 was performed to see if

significant and relevant predictors could be determined for the hypothesized mechanism of action.

Additional *post hoc* assessments of primary and secondary outcome measures using available one year data were performed in response to an FDA request regarding durability of the treatment response.

4.6 Imaging Procedures

Study imaging procedures are fully described in Appendix 7-1, VENT – General CT Manual of Procedures (MOP). High resolution computed tomography (HRCT) images were utilized for the following purposes in the conduct of the trial and subsequent assessment of the results:

1. Subject eligibility screening – Disease severity and distribution at baseline
2. Treatment targeting – Disease distribution at baseline
3. Assessment of baseline predictors of success – Inter-lobar collateral flow proxy (fissure integrity), disease severity, disease heterogeneity, target lobe ventilation (volume change from TLC to RV)
4. Volume reduction assessment – Target lobe volume change from baseline to 180 day follow-up
    a. Quantify effect of treatment
    b. Correlation with outcomes measures to assess volume-reduction mechanism of action
5. Assessment of technical success – Determination of complete lobar exclusion (technical success) at follow-up and the effect of complete lobar exclusion on outcomes

The collection and analysis of high resolution computed tomography (HRCT) images were coordinated by an HRCT Core Lab (MedQia, in association with the David Geffen School of Medicine at UCLA). The process consisted of five general steps:

4.6.1 Image Acquisition

Each investigational site was provided with an imaging Manual of Procedures (MOP) tailored specifically for the type of scanner in use at that site. This manual specified certain scanner and image reconstruction settings necessary to ensure the image would be analyzable by the automated quantitative image analysis software used to assess disease distribution and severity as well as volume distribution by lobe. These specifications also ensured that the baseline and follow-up CTs were captured under identical conditions

In addition, the manual included a section on how to educate and instruct subjects about their breathing during the image acquisition to minimize motion artifacts and also ensure maximal consistency between baseline and follow-up scans.

Full thoracic HRCT images of each subject were captured at two points in the breathing cycle. The first was at maximal inspiration (Total Lung Capacity – TLC), the other was at maximal expiration (Residual Volume – RV).

4.6.2 Quality Control

The imaging Manual of Operations also outlined specific requirements for scan quality control. Sites were required to submit images of phantoms (water-containing test fixtures) which were then assessed by the HRCT Core Lab for appropriate quality and image capture settings.

4.6.3 Quantitative Image Analysis

All study subjects were scheduled for four HRCT scans during the course of the study:

- Baseline at TLC (full inspiration)
- Baseline at RV (full exhalation)
- Day 180 at TLC (full inspiration)
- Day 180 at RV (full exhalation)

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. Follow-up scans were analyzed in an identical manner. Both the full-inspiration and full-expiration scans were analyzed for volume and Density Score by lobe.

4.6.4 Density (Emphysema) and Heterogeneity Scoring

Density (or Emphysema) Score: 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, using both the full-inspiration and full-expiration scans. The Density Scores from the full-inspiration scan were used by the HRCT Core

[*] 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.

Lab to determine subject eligibility and target lobe per the algorithm defined in the protocol.

Heterogeneity Score: The difference between the Density Scores of the target lobe and the ipsilateral non-target lobe (in %) was the Heterogeneity Score for that subject.*

4.6.5 Fissure Integrity Assessment

In addition to quantitative assessment of each HRCT, a manual reading of fissure integrity was also conducted in the target lung of each subject using the baseline HRCT full-inspiration image. Each fissure in the lung was graded by trained radiologists using a three point scale: complete, incomplete or absent.† The HRCT image below shows an example of a complete fissure in the right lung and an incomplete fissure in the left lung. A fissure must be complete in all views in order to be assigned "Complete".

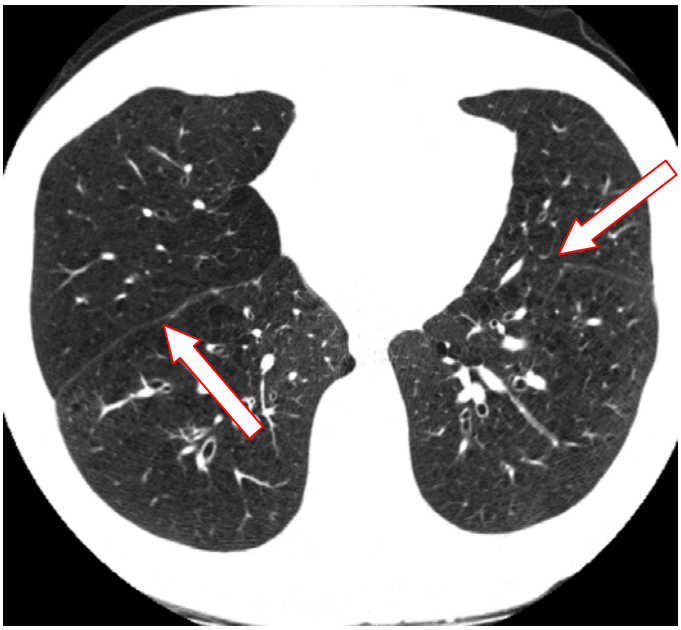


Figure 5 Fissure Integrity Example

4.6.6 Lobar Exclusion Assessment

The 180 day follow-up HRCT for each Zephyr EBV Subject was also read manually to determine whether all airways leading to the target lobe were effectively blocked with valves. If the radiologist determined that the lobe was not fully blocked, the reason for technical failure was noted (e.g. open side branch).

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* 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 patient was eligible.

† The actual results were binary: either complete or incomplete.

4.6.7 Target Lobe Atelectasis Score (TLAS) Methodology

The HRCT Core Lab calculated volumes by lobe at each of the four scans. The Target Lobe Atelectasis Score (TLAS), calculated both at RV ("$TLAS_{RV}$") and at TLC ("$TLAS_{TLC}$"), 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 is a measure of Target Lobe Volume Reduction (TLVR) over 6 months of study follow-up. TLAS was calculated at Residual Volume ($TLAS_{RV}$) and at Total Lung Capacity ($TLAS_{TLC}$). Study analyses were performed using $TLAS_{TLC}$.

4.7 Changes in the Conduct of the Study

4.7.1 Protocol Amendments

The first study subjects were enrolled under Emphasys Medical IDE Protocol version 630-0001-J dated October 22, 2004. There were no changes to the protocol during enrollment and follow-up phases of the study.

4.7.2 Changes in the Statistical Analysis Plan

The original statistical analysis plan (SAP) was found in Appendix H of IDE Protocol version 630-0001-J dated October 22, 2004. Subsequent to this, three revisions of the SAP were submitted to and ultimately approved by the Agency as IDE supplements. These revisions were dated July 11, 2005, November 7, 2006, and April 12, 2007.

The July 11, 2005 revision was originally proposed in an IDE supplement April 12, 2005. This revision clarified that the primary analyses between Zephyr EBV Subjects and Control Subjects would be one-sided tests of superiority, replaced GEE modeling with GLM modeling for multivariate analysis, and added a per-subject analysis of the proportion of subjects with any increase from baseline at 6 months for FEV_1 and 6MWT.

The November 7, 2006 revision was originally proposed in an IDE supplement dated June 16, 2006. This revision clarified and defined potential covariates and better defined analysis plans for the covariates, changed the method of determining successful lobar exclusion based on improved HRCT Core Lab capability, divided adverse event time courses into three categories, and added reduction of oxygen consumption to a secondary analysis of clinical success.

The April 12, 2007 revision was originally proposed in an IDE supplement dated April 12, 2007. This revision clarified the abbreviated analyses to be completed for study subjects that were enrolled under IDE Protocol version 630-0001-I. These subjects are not part of this clinical study report.

These changes did not affect the validity of the data or information resulting from the completion of the approved Protocol, the relationship of likely subject risk to benefit relied upon to approve the Protocol, the scientific soundness of the investigational plan, or the rights, safety, or welfare of the human subjects involved in the investigation.

Please refer to Appendix 7-5-3 for the full text of prior Statistical Analysis Plans.

4.7.3 Additional Analyses Resulting from FDA Communications

Communications with the FDA during the review of the premarket application resulted in additional *post hoc* analyses being included in the Clinical Study Report. These further analyses included justification of the clinical significance of treatment effect (additional responder analyses of outcome measures), and extended data on performance (available primary and secondary effectiveness outcome measures through 12 months).

4.7.4 Changes in the Experimental Devices

At the beginning of the enrollment period, only the Zephyr 4.0 EBV was available for clinical use to treat bronchial lumens ranging in diameter from 4.0 mm to 7.0 mm. In an IDE supplement dated February 10, 2005, the Zephyr 5.5 EBV was submitted for approval to treat lumens from 5.5 mm to 8.5 mm. This was approved by the Agency on March 31, 2005 (G020230/S30 & S31). The molding process for the one-way valve component of the Zephyr 4.0 EBV was modified during the course of trial and discussed in a Notice of IDE Change dated August 15, 2005. Based on Agency input, the Statistical Analysis Plan was updated to analyze the potential impact of valve size and/or valve version on clinical results. All subsequent multivariate models included valve size and valve version.

During the clinical evaluation, 32 Zephyr 5.5 EBV devices were withdrawn because of the potential to create a loose monofilament fragment during device loading using an earlier version of the loading system. The withdrawal was documented in an IDE supplement dated September 12, 2005. Loading system improvements to prevent the recurrence of fragments was documented in a Notice of IDE Change dated March 30, 2006.

4.8 Protocol Deviations

A total of 2,492 protocol deviations of any kind were observed during the conduct of this clinical investigation. These occurred in several categories, including visits or tests occurring outside of scheduled windows, missed subject visits, the performance of telephone follow-up instead of a clinic visit, failure to perform protocol required testing, enrollment of subjects who did not meet eligibility criteria, pulmonary rehabilitation procedures that did not meet protocol requirements, medication use that was noncompliant with the protocol, failure to obtain written informed consent prior to study procedures, and irregularities in performing specified pulmonary function testing.

The majority of these resulted from a Sponsor-initiated remonitoring effort undertaken to ensure lung function tests were being gathered and reported in the standardized manner prescribed by the study protocol. Although this effort generated a large number of minor deviations, the primary outcomes were impacted infrequently, were not significantly different between the two treatment groups and resulted in no significant impact on the scientific integrity of the outcome data.

A total of 99 eligibility criteria deviations occurred. A total of 62 subjects did not meet the inclusion / exclusion criteria at either a screening visit and/or at baseline, excluding subjects whose eligibility was not known at time of Screen 2 or Baseline but were late confirmed to meet the eligibility criteria. In 23 of these (37.1%), criteria that were not met at the screen 2 visit were subsequently met at the baseline visit.. In those cases where eligibility criteria were violated, the magnitude of difference in the observed metric compared to the protocol defined threshold was generally small. The study population enrolled is therefore expected to be consistent with that defined by the study protocol.

A line listing of all protocol deviations is presented in Appendix 7-5-6 and deviations are summarized by categories in the following table. A detailed listing of the 62 subjects that that did not meet inclusion / exclusion criteria at either a screening visit and/or at baseline is presented in Amended Statistical Analysis Report: Section 21.3.

Table 2 Summary of Protocol Deviations

Category (per CRF)				Total #	% of Total
1	Subject contact outside of protocol required window			222	9%
2	Test / procedure done outside of protocol required window			133	5%
3	Missed subject contact			96	4%
4	Subject contact by telephone (office visit required)			24	1%
5	Protocol required test not done			384	15%
6	Subject did not meet eligibility criteria			99	4%
7	PR Program does not meet protocol requirements			35	1%
8	Medication not in compliance with protocol			11	< 1%
9	Written informed consent not obtained prior to procedure			1	< 1%
10	PFT related deviations	Plethysmography	Reproducibility of measurements	256	10%
			# Maneuvers measured	88	4%
		Spirometry	Reproducibility of measurements	140	6%
			# Maneuvers measured	150	6%
		Exercise Tolerance	Cycle Ergometry Ramp Rate	97	4%
			Cycle Ergometry Supplemental O2	38	2%
			6MWT Supplemental O2 variation	69	3%
		Diffusing Capacity	# Maneuvers measured	35	1%
			Reproducibility of measurements	8	< 1%
		Multiple PFT Deviations	Cycle Ergometry and 6MWT	1	< 1%
			PFT Maneuvers	181	7%
			PFT Reproducibility	169	7%
			PFT Reproducibility & Maneuvers	199	8%
			PFTs & Exercise Tolerance & 6MWT	4	< 1%
			PFTs & Exercise Tolerance and Cycle Ergometry	8	< 1%
			Other combinations	6	< 1%
			Unknown	5	< 1%
		Other	EBV Procedure-related	10	< 1%
			Other Protocol Deviation	12	< 1%
			VQ Scan Percentages	8	< 1%
			ABGs O2 Supplementation	3	< 1%
Total				**2,492**	**100%**

Source: P070025, September 21, 2007, Volume 011, Page 57

4.9 Study Definitions

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

1. 95 Percent Confidence Interval (95% CI): An estimated range of values which is likely to include 95% of all randomly selected values from the population. The estimated range is based on the assumption that that population is normally distributed.

2. Acute Technical Success: Complete exclusion of the target lobe determined via bronchoscopy at the conclusion of the procedure. (See Technical Success)
3. Adverse Event (AE): An Adverse Event is any complication whether considered major or minor and whether or not associated directly with the Emphasys Endobronchial Valve procedure.
4. BODE: A composite index of pulmonary disease state which includes the BMI, Airflow Obstruction, Dyspnea and Exercise Capacity index.
5. Body Mass Index (BMI): An index of body weight normalized by height, calculated as (weight [kg] / height $[m]^2$).
6. Borg test: A questionnaire rating perceived exertion.
7. Carina – The ridge at the origin of an airway bifurcation. Denotes the most-proximal point of an airway branch.
8. Case Report Form (CRF): Form completed by sites to record all study related subject data.
9. Chest X-Ray (CXR): A diagnostic test that uses electromagnetic energy beams to produce images of the internal tissues, bones, and organs of the thorax onto film.
10. Chronic Obstructive Pulmonary Disease (COPD): A lung disease characterized by chronic obstruction of lung airflow that interferes with normal breathing and is not fully reversible– encompasses emphysema and chronic bronchitis.
11. Clinical Events Committee (CEC): Committee of Pulmonologists and Thoracic Surgeons not participating in the study who met regularly to review and adjudicate all Adverse Events.
12. Clinical Study Report (CSR): A report summarizing the results of the VENT clinical study.
13. Code of Federal Regulations (CFR): A compilation of the general and permanent rules published in the Federal Register by the Executive departments and agencies of the Federal Government of the United States of America.
14. Completed Case (CC): All randomized and eligible subjects who received study-directed treatment and who had 6 months of follow-up.
15. Computer Tomography (CT): Medical imaging technique using tomography to generate three dimensional images of the scanned body part.
16. Confidence Interval (CI): Gives an estimated range of values which is likely to include an unknown population parameter, the estimated range being calculated from a given set of sample data.
17. 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.

18. Corrections/Query Form (CQ): Form sent to sites to document and resolve completeness, legibility and other issues with case report forms.
19. Cycle ergometry: Stationary cycling used to measure the amount of work a subject can perform.
20. Data Safety Monitoring Board (DSMB): Committee consisting of a statistician and specialty physicians responsible for making recommendations to the Operations Committee regarding outcome analysis and any potential situations in which patient safety, patient welfare, or the scientific adequacy of the study were at risk.
21. Density Score (DS): The proportion (in %) of lobar lung parenchyma destroyed by emphysema as established by HRCT. A synonym for Emphysema Score (in %).
22. Destruction score: The sum of the upper lobe and lower lobe integer Emphysema Scores. See Protocol at Appendix 7-5-2, Section 6.7.5.
23. Diffusing Capacity (Lung) (DL_{CO}): A measure of the rate of carbon monoxide gas transfer across the alveolar-capillary blood-gas membrane.
24. Diffusing Capacity (Lung) % Predicted (DL_{CO} % predicted): A measure of DL_{CO} normalized for gender, age, and height.
25. Electrocardiogram (ECG): A diagnostic test which records the electrical activity of the heart over time.
26. Emphysema Score (ES): The proportion (in %) of lobar lung parenchyma destroyed by emphysema as established by HRCT. A synonym for Density Score.
27. Expiratory Reserve Volume (ERV): The volume of gas that can be voluntarily exhaled beyond the FRC and the RV.
28. FEV_1 / FVC: The calculated ratio of the FEV_1 and FVC.
29. Forced Expiratory Flow ($FEF_{25-75\%}$): The Forced Expiratory Flow is the average flow rate measured over the middle 50% of the exhaled volume.
30. 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.
31. Forced Expiratory Volume Percent Predicted (FEV_1 % predicted): A measure of FEV_1 normalized for race, gender, age, and height.
32. Forced Vital Capacity (FVC): The total volume of gas exhaled during a forced exhalation after a maximal inspiration.
33. Forced Vital Capacity Percent Predicted (FVC % Predicted): FVC normalized for race, gender, age, and height.
34. Fraction of Inspired Oxygen (FiO_2): Percentage of oxygen contained in inspired air.

35. Functional Residual Capacity (FRC): The volume of air present in the lungs at the end of passive expiration.
36. Good Clinical Practice (GCP): An international quality standard that is provided by the International Conference on Harmonisation (ICH). GCP guidelines include protection of human rights as a subject in clinical trial as well as providing standards on how clinical trials should be conducted, and defines the roles and responsibilities of clinical trial sponsors, clinical research investigators, and monitors.
37. Heart failure: A new diagnosis of heart failure or an increase in NYHA functional classification score status of 1 or more.
38. Heterogeneity score (HS): The difference (in %) between ipsilateral lobe Density Scores.
39. Heterogeneity: Degree of non-uniform distribution of diseased, emphysematous areas in the lung.
40. High-Resolution Computed Tomography (HRCT): Computed tomography with narrow collimation to reduce volume-averaging and an edge-enhancing reconstruction algorithm to sharpen the image.
41. Homogeneity: Degree of uniformity in the distribution of diseased.
42. HRCT Density Score: A computer-automated grading of the percent emphysematous destruction on a lobar level by HRCT.
43. Hypoxemia: Increased oxygen requirement (> 24 hour hours post-procedure) to maintain oxygen saturation >90% where increased oxygen requirement is defined as either:
    a. > 1.5 liter/min increase over baseline if by nasal cannula.
    b. > 10% increase in FiO_2 over baseline if by mask.
44. 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.
45. Inspiratory Capacity (IC): The maximum volume of air that can be inspired after reaching the end of a normal, quiet expiration.
46. Institutional Review Board (IRB): A committee of physicians, statisticians, researchers, community advocates, and others that ensures that the design and conduct of a clinical trial is ethical and that the rights of study participants are protected.
47. 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.

48. Ipsilateral Lung, Non-target Lobe Volume – The volume of the remaining, non-targeted lobe(s) of the target lung as determined by the Radiology Core Lab computer analysis.
49. Left Ventricular Ejection Fraction (LVEF): A measure of how much blood the left ventricle of the heart pumps out with each contraction.
50. Lobar Exclusion (6 Months): Core Radiology Lab confirmation that all airways feeding the Target Lobe have been completely blocked by a valve(s), with no detectable leaks around the periphery of the valve.
51. Lobar Exclusion (Acute): Bronchoscopic confirmation that all airways feeding the Target Lobe have been blocked with a valve.
52. Lost To Follow Up (LTFU): Study subject who does not return for protocol required follow-up visits.
53. Lung Volume Reduction Surgery (LVRS): Surgical treatment for advanced emphysema where the most diseased portions of the lungs are removed with the goal of improving lung function.
54. Major Complications Composite (MCCs):

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

55. Major Complications Composite (MCC): The primary safety outcome for VENT. A per-subject assessment of Major Complications from day 0 to 180.
56. Maximum Voluntary Ventilation (MVV): The greatest volume of gas that can be breathed per minute by voluntary effort.
57. Modified Medical Research Council Dyspnea Scale (mMRC): A scale from 0 to 4, which a subject utilizes to grade their breathlessness.
58. 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.
59. Myocardial Infarction (MI): Destruction of heart tissue resulting from obstruction of the blood supply to the heart muscle.
60. National Emphysema Treatment Trial (NETT): A multi-center clinical trial supported by the National Heart, Lung, and Blood Institute (NHLBI) and the Center for Medicare and Medicaid Services (CMS) to study bilateral lung volume reduction surgery.

61. Operations Committee: Committee responsible for the day-to-day administrative management of the trial.
62. Outcome: a specifically defined outcome measure recorded for a study subject at a specified time. Often defined as primary or secondary outcomes, and used in assessing statistical hypotheses.
63. Outcome Measure: a specifically defined observation variable recorded for a subject at various time points after enrollment for the purpose of the ongoing assessment of the effect of a study treatment
64. Oxygen Saturation (SAT): The percentage that arterial blood is saturated with oxygen.
65. Peak Expiratory Flow Rate (P_{EFR}): The maximum flow rate achieved during a forced exhalation.
66. Peak Inspiratory Flow Rate (P_{IFR}): The maximum flow rate achieved during a forced inhalation.
67. Plethysmography: A method of calculating lung volumes by placing the subject in a closed system and measuring pressure and volume changes within the system.
68. Premature Ventricular Contraction (PVC): Premature heartbeats originating from the ventricles of the heart.
69. Pulmonary embolism: Occlusion of one or more pulmonary arteries by emboli as evidenced by a high probability VQ scan evidence of segmental or larger perfusion defects or direct anatomic evidence of pulmonary embolism by other means (e.g. CT, echo or other).
70. Pulmonary Function Testing (PFT): Various tests designed to measure the function of the lungs including FEV_1 and FVC.
71. Quality of Life (QoL): Subjective well-being assessed by either disease-specific or general QoL questionnaires.
72. Quality of Well Being Scale (QWB): A standardized, general quality of life assessment tool.
73. Residual Volume (RV): The volume of undissolved gas contained in the lungs at the end of maximal exhalation.
74. Sepsis: Systemic inflammatory response syndrome (SIRS) with proven microbial etiology established by positive blood culture, where SIRS is defined as subject having two or more of the following conditions:
    a. fever (oral temperature > 38° C) or hypothermia (< 36° C);
    b. tachypnea (> 24 breaths / min);
    c. tachycardia (heart rate > 90 beats / min);
    d. leukocytosis (> 12,000 / μL), leukopenia (< 4,000 / μL), or > 10% bands
75. Serious Adverse Event (SAE): A category of adverse events that are deemed to be serious by the clinical events committee (CEC).

76. Six Minute Walk Test (6MWT): A cardiopulmonary function test that measures a subject's exercise capacity by the distance in meters that he / she can walk in six minutes.
77. Spirometry: Lung function testing involving the assessment of inhaled and exhaled gas volumes.
78. Standard Deviation (SD): A statistical analysis that is the measure of the spread of values in a group.
79. St. George's Respiratory Questionnaire (SGRQ): A standardized quality of life measurement used to assess subjects with obstructive pulmonary diseases.
80. Supraventricular Tachycardia (SVT): A regular, abnormally fast heart beat (tachycardia) caused by rapid firing of electrical impulses from a focus above the atrioventricular node (A-V node) in the heart.
81. Target Lobe: The lung lobe that was to be treated as determined by the Study Protocol at Section 7.8.2 Treatment Targeting.
82. Target Lobe Atelectasis Score at Residual Volume ($TLAS_{RV}$): The change in target lobe volume determined by computer analysis of the changes in the HRCT scans performed at residual volume and recorded at baseline and 6 months post-procedure. $TLAS_{RV}$ 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.
83. Target Lobe Atelectasis Score at Total Lung Capacity ($TLAS_{TLC}$): Calculated in the same way as $TLAS_{RV}$ except it is calculated at total lung capacity instead of residual volume.
84. Target Lobe Volume: The volume of the target lobe determined by the Radiology Core Lab computer analysis.
85. Technical Success: Complete target lobe exclusion in Treatment subjects as confirmed by HRCT scan at 6 months. (See Acute Technical Success)
86. Total Lung Capacity (TLC): The volume of undissolved gas contained in the lungs at the end of maximal inhalation.
87. Total Lung Capacity % Predicted (TLC % predicted): Total Lung Capacity normalized for gender, age, and height.
88. Unanticipated Adverse Device Effect (UADE): Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in

nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

89. Vital Capacity (VC): The difference in volume from maximum inhalation (TLC) to maximum exhalation (RV).
90. Volume of Thoracic Gas (VTG): The volume of gas in the thorax whether in communication with patent airways or trapped in any compartment of the thorax. Usually measured at the end-expiratory level and is then equal to Functional Residual Capacity (FRC).
91. VQ scan: A diagnostic test of the lungs that compares inhaled gas distribution with infused blood perfusion.
92. Zephyr Endobronchial Valve (Zephyr EBV): Implanted device that is the subject of this PMA application.

5.0 STUDY ACCOUNTABILITY AND POPULATION

5.1 Investigators and Site Enrollment

Thirty one (31) Investigators at 31 Investigative Sites enrolled a total of 321 study subjects between December 22, 2004 and April 27, 2006. A list of all participating Investigators and Sites is presented in Appendix 7-5-1. Enrollment into the Control and Zephyr EBV Groups is summarized by site in the table below.

Table 3 Subject Enrollment by Site

Site	Control	EBV	Total
001	4	9	13
002	5	11	16
003	2	6	8
004	4	7	11
005	7	15	22
007	8	16	24
008	0	2	2
009	1	6	7
010	5	10	15
011	0	3	3
012	1	6	7
013	1	1	2
014	8	15	23
015	3	6	9
016	0	1	1
017	1	4	5
018	8	18	26
019	2	5	7
020	1	2	3
021	9	14	23
022	3	8	11
023	4	9	13
024	3	6	9
025	2	2	4
026	4	6	10
027	3	7	10
028	3	8	11
029	5	9	14
030	2	5	7
032	1	0	1
034	1	3	4
Total	**101**	**220**	**321**

Source: Attachment 3, Amended Statistical Analysis Report, Table 5:1

Stratification by site and exercise capacity was successful in achieving a ration of 1:2 Control Subjects to Zephyr EBV Subjects in each of the 4 defined strata. (See Attachment 3, Amended Statistical Analysis Report, Table 5:1)

5.2 Subject Accountability

All 321 study subjects were enrolled according to protocol-defined procedures. Primary outcomes were to be assessed at 6 months of follow-up, with an extended safety assessment at 1 year.

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

[1] Protocol defined windows.
[2] Deaths, withdrawn subjects and lost to follow-up are cumulative.
[3] The number eligible is the number enrolled minus the number that died and the number that withdrew.
[4] The denominator is the number eligible at that visit.
[5] For the 180-day visit, the extended windows ranged from 150 - 225 days and for 365 days the extended window was from 305 - 425 days.
Source: Attachment 3, Amended Statistical Analysis Report, Table 3:1

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 12 month safety assessment, 12 Zephyr EBV Subjects withdrew informed consent and 8 had died,

leaving 184 (92.0%) subjects alive and evaluable. By 1 year of follow-up, 16 eligible subjects had not completed their final study visit, of whom 14 had been lost to follow-up.

Table 5 Cumulative Subject Accountability Table by Visit – Zephyr EBV Subjects

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

[1] Protocol defined windows
[2] Deaths, withdrawn subjects and lost to follow-up are cumulative.
[3] The number eligible is the number enrolled minus the number that died and the number that withdrew.
[4] The denominator is the number eligible at that visit.
[5] For the 180-day visit, the extended windows ranged from 150 - 225 days and for 365 days the extended window was from 305 - 425 days.
Source: Attachment 3, Amended Statistical Analysis Report, Table 3:2

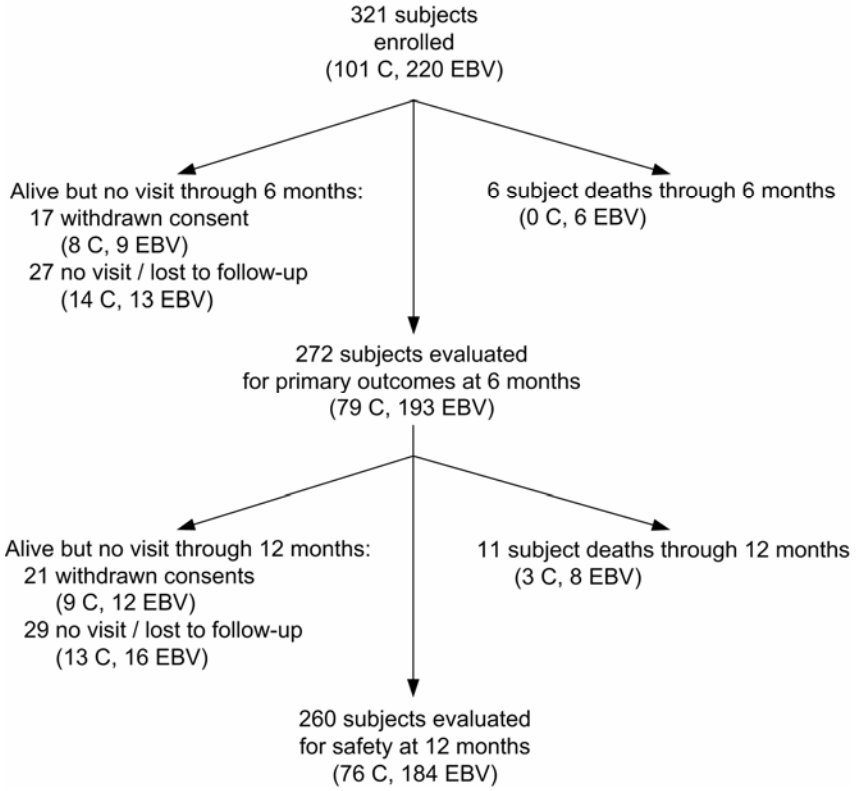

Figure 6 Subject Accountability Flow Chart

C = Control Subjects; EBV = Zephyr EBV Subjects
Source: Attachment 3, Amended Statistical Analysis Report Table 3:6

The following listing contains those Control Subjects who were discontinued due to death or withdrawn consent or who were lost to follow-up through study termination.

Table 6 Listing: Discontinued Control Subjects (Death, Withdrawal, LTFU)

Subject Code[3]	Randomization Date	Discontinuation Date	Days in Study[1]	Reason for Termination
	3/21/2006	3/10/2006	0[2]	Lost to follow-up
	11/7/2005	11/7/2005	0	Lost to follow-up
	9/12/2005	9/12/2005	0	Withdrew Consent
	8/18/2005	8/26/2005	8	Lost to follow-up
	9/14/2005	9/26/2005	12	Lost to follow-up
	4/7/2006	4/20/2006	13	Lost to follow-up
	9/14/2005	9/28/2005	14	Lost to follow-up
	7/20/2005	8/8/2005	19	Withdrew Consent
	3/25/2005	4/14/2005	20	Lost to follow-up
	8/25/2005	9/19/2005	25	Lost to follow-up
	9/16/2005	10/13/2005	27	Withdrew Consent
	3/31/2006	4/28/2006	28	Withdrew Consent
	8/11/2005	9/12/2005	32	Withdrew Consent
	7/11/2005	8/29/2005	49	Withdrew Consent
	7/21/2005	9/15/2005	56	Withdrew Consent
	5/31/2005	7/28/2005	58	Lost to follow-up
	8/8/2005	2/8/2006	184	Withdrew Consent
	4/11/2005	10/13/2005	185	Lost to follow-up
	6/29/2005	1/6/2006	191	Lost to follow-up
	3/9/2006	9/22/2006	197	Lost to follow-up
	6/27/2005	9/26/2005	207	Death
	4/7/2006	7/18/2006	212	Death
	5/2/2005	10/28/2005	230	Death
	4/8/2005	4/5/2006	362	Withdrew Consent

From randomization to last office visit
[2] Subject withdrew post-randomization, but prior to first office visit. Value of 0 was assigned.
[3] Subject ID has three components in the following order: site number, sequence number, and subject code. In Appendix 11, Completed CRFs for Deaths and Discontinuations, subjects are sorted based on site number and sequence number.
Source: Attachment 3, Amended Statistical Analysis Report, Table 3:4

The following listing contains those Zephyr EBV Subjects who were discontinued due to death or withdrawn consent or who were lost to follow-up through study termination.

Table 7 Listing: Discontinued Zephyr EBV Subjects (Death, Withdrawal, LTFU)

[3]	Randomization Date	Discontinuation Date	Days in Study[1]	Reason for Termination
	8/4/2005	8/1/2005	0[2]	Withdrew Consent
	3/27/2006	3/27/2006	0	Withdrew Consent
	6/9/2005	6/9/2005	0	Lost to follow-up
	8/17/2005	8/17/2005	0	Lost to follow-up
	9/16/2005	9/16/2005	0	Lost to follow-up
	11/13/2005	11/18/2005	5	Withdrew Consent
	7/20/2005	8/8/2005	19	Withdrew Consent
	1/24/2005	2/22/2005	29	Withdrew Consent
	7/15/2005	8/15/2005	31	Lost to follow-up
	9/16/2005	3/7/2006	38	Lost to follow-up
	3/31/2006	5/12/2005	38	Lost to follow-up
	1/19/2005	3/16/2005	56	Lost to follow-up
	8/18/2005	10/17/2005	60	Death
	4/15/2005	5/16/2005	66	Death
	3/29/2006	6/8/2006	71	Withdrew Consent
	8/12/2005	11/2/2005	82	Withdrew Consent
	4/19/2005	7/18/2005	90	Lost to follow-up
	6/17/2005	9/15/2005	90	Withdrew Consent
	3/4/2005	6/17/2005	105	Withdrew Consent
	3/2/2006	6/29/2006	119	Lost to follow-up
	2/16/2006	4/20/2006	133	Death
	1/28/2005	5/5/2005	148	Death
	4/13/2005	7/13/2005	154	Death
	4/4/2006	9/19/2006	168	Lost to follow-up
	4/25/2005	10/19/2005	177	Withdrew Consent
	6/13/2005	12/13/2005	183	Lost to follow-up
	10/7/2005	4/14/2006	189	Lost to follow-up
	3/2/2006	9/7/2006	189	Lost to follow-up
	6/23/2005	1/6/2006	197	Withdrew Consent
	12/1/2005	2/20/2006	210	Death
	4/8/2006	10/3/2006	238	Death
	4/12/2005	12/8/2005	240	Withdrew Consent
	11/29/2005	6/23/2006	293	Death
	9/26/2005	12/18/2006	448	Lost to follow-up

o last office visit

[2] Subject withdrew post-randomization, but prior to first office visit. Value of 0 was assigned.

[3] Subject ID has three components: site number, sequence number, and subject code. In Appendix 11, Completed CRFs for Deaths and Discontinuations, subjects are sorted based on site number and sequence number.

Source: Attachment 3, Amended Statistical Analysis Report, Table 3:5

Please refer to Appendix 11, Completed CRFs for Deaths and Discontinuations for completed case report forms for all discontinued subjects.

5.3 Device Accountability

A total of 2,618 Zephyr EBV devices, Zephyr EDC delivery catheters and Zephyr ELS loader systems were shipped to U.S. Investigational Sites as part of the VENT Pivotal Trial under the Investigational Device Exemption. Of the 2,618 individual components shipped, 1,539 were used or implanted in subjects, 995 were returned to Emphasys Medical, and 84 were used as training samples at the site or were opened and discarded. There were no unaccounted devices/components at the end of the clinical study.

Table 8 Device Accountability: VENT Pivotal Trial Investigational Devices

Device	Shipped	Implanted / Used	Returned	Sample / Destroyed	Unaccounted For Devices
Zephyr EBV	1,610	913	634	63	0
Zephyr EDC	689	423	253	13	0
Zephyr ELS	319	203	108	8	0
Total Devices	**2,618**	**1,539**	**995**	**84**	**0**

Source: P070025, September 21, 2007, Volume 011, Page 71

5.4 Imaging Accountability

All 321 subjects (100.0%) had a baseline HRCT evaluable for inclusion criteria. Of these 321 subjects originally enrolled, 280 were still in study follow-up as of the 6 month follow-up visit (Imaging Evaluable Subjects). Of these 280 Imaging Evaluable Subjects, 273 (97.5%) had a 6-month HRCT accepted by the Core Radiology Laboratory for protocol-specified imaging. HRCTs evaluable for fissure integrity at baseline were obtained in 93.8% of subjects, and paired baseline and 6-month images evaluable for lobar volume reduction at 6 months were obtained in 95.7% of subjects. HRCTs evaluable for valve position and lobar exclusion at 6 months were obtained in 98.5% of the Zephyr EBV Subjects.

Table 9 Imaging Accountability Table – Control Subjects

Imaging Accountability	Baseline	6 months
Subjects originally enrolled	101	101
Inadequate baseline HRCT	0	0
Death		0
Withdrawal		8
Lost to follow-up		10
Imaging evaluable subjects at interval	101	83
Core Radiology Lab HRCT imaging:		
Any HRCT	100.0% (101 / 101)	95.2% (79 / 83)
Evaluable for volume reduction % (n / N)		95.2% (79 / 83)
Evaluable for fissure completeness % (n / N)	92.1% (93 / 101)	

Source: Attachment 3, Amended Statistical Analysis Report, Table 4:1

Table 10 Imaging Accountability Table – Zephyr EBV Subjects

Imaging Accountability	Baseline	6 months
Subjects originally enrolled	220	220
Inadequate baseline HRCT	0	0
Death		5
Withdrawal		9
Lost to follow-up		9
Imaging evaluable subjects at interval	220	197
Core Radiology Lab HRCT imaging:		
Any HRCT	100.0% (220 / 220)	98.5% (194 / 197)
Evaluable for volume reduction % (n / N)		95.9% (189 / 197)
Evaluable for fissure completeness % (n / N)	94.5% (208 / 220)	
Evaluable for lobar exclusion % (n / N)		98.5% (194 / 197)

Source: Attachment 3, Amended Statistical Analysis Report, Table 4:2

6.0 BASELINE SUBJECT CHARACTERISTICS

6.1 Demographic Data

The mean age of the 101 Control Subjects was 64.9 years and of the 220 Zephyr EBV Subjects the mean age was 65.3 years (p = 0.56). Weight and height were comparable; the mean BMI for Control Subjects was 24.8 kg/m^2 and for Zephyr EBV Subjects was 25.1 kg/m^2 (p = 0.51). Mean blood pressures for the two groups were nearly identical (p = 0.67 systolic and p = 0.49 for diastolic). 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). Both groups were almost entirely Caucasian.

Table 11 Subject Demographics

Characteristic	Control	Zephyr EBV	
Continuous Measures	**Mean (SD) N Median (Min, Max)**	**Mean (SD) N Median (Min, Max)**	**p value [1]**
Age (years)	64.91 (5.84) 101 65.0 (48.0, 76.0)	65.34 (6.83) 220 66.0 (47.0, 77.0)	0.5623
Weight (kg) [2]	71.71 (13.41) 101 69.5 (44.0, 102.1)	73.11 (14.51) 219 73.3 (33.6, 106.1)	0.1602
Height (meters)	1.68 (0.10) 101 1.68 (1.52, 1.91)	1.70 (0.09) 220 1.71 (1.50, 1.88)	0.1245
BMI (kg/m^2) [3]	24.82 (3.39) 101 24.8 (17.2, 32.1)	25.09 (3.96) 220 25.4 (14.9, 33.0)	0.5056
Systolic BP (mm Hg) [4]	129.92 (16.36) 98 130.0 (96.0, 171.0)	129.07 (16.71) 218 129.0 (91.0, 188.0)	0.6742
Diastolic BP (mm Hg) [4]	74.64 (9.98) 98 75.0 (50.0, 99.0)	73.84 (9.40) 218 73.0 (40.0, 100.0)	0.4935
Categorical Measures	**% (n / N)**	**% (n / N)**	**p value [5]**
Gender (Male)	48.5% (49 / 101)	60.4% (133 / 220)	0.0524
Race			1.0000
Caucasian	98.0% (99 / 101)	96.8% (213 / 220)	
African American	2.0% (2 / 101)	2.3% (5 / 220)	
Hispanic	0.0% (0 / 101)	0.5% (1 / 220)	
Asian	0.0% (0 / 101)	0.5% (1 / 220)	
Other	0.0% (0 / 101)	0.0% (0 / 220)	

[1] Two-sided t-test with equal variance
[2] One test subject did not have a weight recorded.
[3] BMI was computed in the case report form so it was available for all 220 test subjects even though weight was not recorded for 1 test subject.
[4] Blood pressure was not available for 3 control and 2 test subjects.
[5] Two-sided Fisher's exact test
Source: Attachment 3, Amended Statistical Analysis Report, Table 6:1

6.2 Pulmonary Medications

All subjects (100%) in both the Control Subject and Zephyr EBV Subject groups were taking bronchodilators, steroids and mucolytics upon study entry.

Table 12 Baseline Pulmonary Medications

Characteristic	Control % (n/N)	Zephyr EBV % (n/N)
Bronchodilators	100.0% (101 / 101)	100.0% (220 / 220)
Steroids	100.0% (101 / 101)	100.0% (220 / 220)
Mucolytics	100.0% (101 / 101)	100.0% (220 / 220)

Source: Attachment 3, Amended Statistical Analysis Report, Table 6:2

6.3 Medical History

Key medical factors were similar between the Control Subjects and Zephyr EBV Subjects. Diabetes was present in 5.0% of Control Subjects and 7.7% of Zephyr EBV Subjects (p = 0.48). An abnormal ECG upon study enrollment was found in 42.6% of Control Subjects and 45.9% of Zephyr EBV Subjects (p = 0.63). All but three study subjects had a history of smoking (98.0% Control Subjects, 99.6% Zephyr EBV Subjects, p = 0.23), with similar years of smoking (36.1 and 37.7 years respectively, p = 0.17) and pack-years (61.7 and 63.3 pack-years respectively, p = 0.64).

Table 13 Baseline Medical History

Characteristic	Control	Zephyr EBV	p value [1]
Diabetes % (n/N)	5.0% (5 / 101)	7.7% (17 / 220)	0.4777
Abnormal ECG % (n/N)	42.6% (43 / 101)	45.9% (101 / 220)	0.6294
Smoking % (n/N)	98.0% (99 / 101)	99.6% (219 / 220)	0.2339
Years of smoking [2]			
Mean (SD) N	36.12 (8.62) 100	37.74 (8.95) 217	0.1714
Median (Min, Max)	36.5 (10.0, 50.0)	39.0 (15.0, 60.0)	
Packs-years [3]			
Mean (SD) N	61.67 (30.33) 98	63.29 (29.58) 216	0.6355
Median (Min, Max)	60.0 (10.0, 168.0)	60.0 (12.5, 184.0)	

[1] For continuous variables, the two-sided t-test with equal variance was used and for categorical variables, two-sided Fisher's exact test.
[2] Years smoked was not reported for 2 test subjects who stated they were smokers.
[3] Packs smoked was not reported for 2 control and 3 test subjects who stated they were smokers.
Source: Attachment 3, Amended Statistical Analysis Report, Table 6:2

6.4 Use of Supplemental Oxygen

Supplemental oxygen use was also not different between the two study groups, with 41.7% of Control Subjects and 43.9% of Zephyr EBV Subjects using oxygen (p = 0.77).

Hours of oxygen use daily were similar at rest (7.1 and 7.7 hours respectively, p = 0.49), during exertion (2.7 and 2.2 hours respectively, p = 0.28) and while sleeping (6.8 and 6.7 hours respectively, p = 0.79). Oxygen flow rates were also equivalent at rest (1.5 and 1.4 liters / min, p = 0.58), during exertion (2.6 and 2.4 liters / min, p = 0.22) and while sleeping (2.0 and 1.9 liters / min, p = 0.21).

Table 14 Use of Supplemental Oxygen

Characteristic		Control	Zephyr EBV	p value [1]
		% (n / N)	% (n / N)	
Subjects on continuous O_2 [2]		41.7% (30 / 72)	43.9% (65 / 148)	0.7736
		Mean (SD) N Median (Min, Max)	Mean (SD) N Median (Min, Max)	
Hours / Day [3]	Rest	7.13 (6.45) 65 8.0 (0.0, 19.0)	7.66 (6.74) 131 8.0 (0.0, 19.0)	0.4921
	Exertion	2.72 (2.74) 65 2.0 (0.0, 12.0)	2.22 (2.28) 140 1.5 (0.0, 14.0)	0.2803
	Sleep	6.81 (2.64) 64 8.0 (0.0, 10.0)	6.66 (3.00) 138 8.0 (0.0, 12.0)	0.7924
Flow (l / min) [4]	Rest	1.48 (1.20) 69 2.0 (0.0, 3.5)	1.43 (1.24) 134 2.0 (0.0, 5.0)	0.5805
	Exertion	2.59 (1.25) 69 2.5 (0.0, 6.0)	2.43 (1.36) 148 2.0 (0.0, 8.0)	0.2228
	Sleep	1.96 (0.85) 69 2.0 (0.0, 3.5)	1.85 (0.96) 144 2.0 (0.0, 5.0)	0.2142

[1] For continuous variables, the two-sided t-test with equal variance was used and for categorical variables, two-sided Fisher's exact test.
[2] Continuous O_2 use was not reported for 29 control and 72 test subjects.
[3] Continuous O_2 rest hours/day was not reported for 6 control and 17 test subjects, exertion hours/day was not reported for 6 control and 8 test subjects, and sleep hours/day was not reported for 7 control and 10 test subjects who reported on continuous O_2 use.
[4] Continuous O_2 flow was not reported for 2 control and 14 test subjects, exertion flow was not reported for 2 control and 0 test subjects, and sleep flow was not reported for 2 control and 4 test subjects who reported on continuous O_2 use.
Source: Attachment 3, Amended Statistical Analysis Report, Table 6:2

6.5 Lung Function Parameters

There were no significant differences in any baseline lung function parameters between the Control Subjects and the Zephyr EBV Subjects. FEV_1 and FEV_1 % Predicted were respectively 0.84 liters and 30% in Control Subjects and 0.87 liters and 30% in Zephyr EBV Subjects. FVC and FVC % Predicted were respectively 2.62 liters and 70% in Control Subjects and 2.71 liters and 70% in Zephyr EBV Subjects. DL_{CO} and DL_{CO} % Predicted were respectively 10.15 mL CO / min / mmHg and 36% in Control Subjects and 9.52 mL CO / min / mmHg and 33% in Zephyr EBV Subjects. RV and RV %

Predicted were respectively 4.63 liters and 212% in Control Subjects and 4.79 liters and 216% in Zephyr EBV Subjects.

Table 15 Baseline Lung Functions

Characteristic	Control		Zephyr EBV		p value [2]
	Mean (SD) N Median (Min, Max)	Number Missing[1]	Mean (SD) N Median (Min, Max)	Number Missing[1]	
FEV_1 (liters)	0.84 (0.25) 101 0.78 (0.42, 1.56)	0	0.87 (0.26) 220 0.81(0.38, 1.62)	0	0.3150
FEV_1 % Predicted	30% (8%) 101 29% (15, 50%)	0	30% (8%) 219 29% (16, 51%)	1	0.9979
FVC (liters)	2.62 (0.82) 101 2.40 (1.11, 5.02)	0	2.71 (0.78) 220 2.59 (1.17, 5.53)	0	0.2783
FVC % Predicted	70% (16%) 101 69% (34, 111%)	0	70% (15%) 219 68% (38, 124%)	1	0.9245
FEV_1 / FVC	0.33 (0.07) 101 0.33 (0.20, 0.51)	0	0.33 (0.06) 220 0.32 (0.20, 0.52)	0	0.6048
DL_{CO} (ml CO / min / mm Hg)	10.15 (5.69) 101 9.15 (4.46, 56.31)	0	9.52 (3.11) 220 9.00 (3.30,21.92)	0	0.6807
DL_{CO} % Predicted	36% (16%) 101 34% (18, 166%)	0	33% (9%) 220 32% (14, 64%)	0	0.1138
VTG (liters)	5.65 (1.32) 100 5.32 (3.24, 8.99)	1	5.84 (2.25) 217 5.75 (2.75, 9.73)	3	0.1274
RV (liters)	4.63 (1.20) 100 4.38 (2.63, 8.52)	1	4.79 (1.15) 217 4.63 (2.34, 9.41)	3	0.1590
RV % Predicted	212% (47%) 100 202% (120, 362%)	1	216% (44%) 217 210% (117, 377%)	3	0.2839
TLC (liters)	7.37 (1.55) 100 6.97 (4.96, 11.77)	1	7.60 (1.44) 217 7.65 (4.80, 11.85)	3	0.1177
TLC % Predicted	125% (16%) 100 125% (92, 171%)	1	124% (15%) 217 123% (95, 165%)	3	0.6208
RV / TLC	0.63 (0.08) 100 0.63 (0.43, 0.82)	1	0.63 (0.09) 217 0.63 (0.35, 0.88)	3	0.8160
IC (liters)	1.72 (0.60) 100 1.62 (0.67, 3.55)	1	1.75 (0.57) 217 1.66 (0.47, 3.64)	3	0.4753
VC (liters)	2.75 (0.87) 100 2.57 (1.28, 5.23)	1	2.79 (0.86) 217 2.70 (0.96, 6.32)	3	0.4950

[1] The number missing is the number of subjects not reporting a value for the variable being measured.
[2] Two-sided t-test with equal variance
Source: Attachment 3, Amended Statistical Analysis Report, Table 6:3

6.6 Arterial Blood Gas Analysis

Baseline arterial blood gas values were largely similar between the Control Subjects and the Zephyr EBV Subjects. The partial pressure of oxygen (68.4 and 69.1 mmHg, p = 0.51) and the oxygen saturation (93% and 93%, p = 0.71) were not different, nor was the

pH (7.42 and 7.43, p = 0.48). However, the Control Subjects had a slightly higher mean partial pressure of carbon dioxide (41.6 compared with 40.5 mmHg, p = 0.044) and a borderline higher bicarbonate (26.9 compared with 26.3 mEq / liter, p = 0.09).

Table 16 Baseline Arterial Blood Gas Analysis

Characteristic	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	p value [1]
PaO_2 (mm Hg)	68.44 (8.09) 100 69.0 (54.0, 90.0)	69.14 (10.26) 220 68.0 (47.7, 111.0)	0.5138
$PaCO_2$ (mm Hg)	41.61 (4.82) 100 42.0 (26.8, 51.0)	40.53 (4.25) 220 40.25 (30.0, 51.0)	0.0440
pH	7.42 (0.03) 101 7.42 (7.36, 7.50)	7.43 (0.03) 220 7.42 (7.35, 7.51)	0.4752
Bicarbonate (mEq / liter)	26.85 (2.71) 101 26.5 (19.6, 34.1)	26.30 (2.66) 217 26.0 (19.1, 35.5)	0.0894
Oxygen saturation (%)	93% (3%) 97 94% (78, 98%)	93% (3%) 215 94% (85%, 100%)	0.7130

[1] t-test with equal variance Source: Attachment 3, Amended Statistical Analysis Report, Table 6:4

6.7 BODE Indices

Baseline BODE Index scores were quite similar between Control Subjects and Zephyr EBV Subjects, 4.2 and 4.4 respectively (p = 0.2551).

Table 17 Baseline BODE Indices

Characteristic	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	p value [1]
BODE Index	4.2 (1.3) 92 4.0 (2.0, 8.0)	4.4 (1.6) 198 4.0 (1.0, 9.0)	0.2551

[1] Two-sided Wilcoxon rank-sum test
Source: Attachment 3, Amended Statistical Analysis Report, Table 6.13

6.8 SGRQ Scores

Baseline SGRQ scores were quite similar between Control Subjects and Zephyr EBV Subjects, 50.1 and 51.5 respectively (p = 0.3236).

Table 18 Baseline SGRQ Scores

Characteristic	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	p value [1]
SGRQ Scores	50.1 (12.3) 89 50.6 (23.3, 80.7)	51.5 (13.9) 203 51.6 (5.8, 78.6)	0.3236

[1] Two-sided Wilcoxon rank-sum test
Source: Attachment 3, Amended Statistical Analysis Report, Table 6.14

6.9 mMRC Dyspnea Scale Scores

Baseline mMRC dyspnea scores were identical for Control Subjects and Zephyr EBV Subjects, 1.7 and 1.7 respectively (p = 0.7748).

Table 19 Baseline mMRC Dyspnea Scale Scores

Characteristic	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	p value [1]
mMRC Scores	1.7 (0.8) 92 2.0 (0.0, 4.0)	1.7 (0.9) 199 2.0 (0.0, 4.0)	0.7748

[1] Two-sided Wilcoxon rank-sum test
Source: Attachment 3, Amended Statistical Analysis Report, Table 6.15

6.10 Exercise Tolerance

Baseline exercise tolerance was the same between the two study groups. The Control Subjects had a slightly lower peak workload on cycle ergometry (43.2 versus 45.0 watts, p = 0.71). However, the Control Subjects showed a slightly longer 6MWT (350.9 versus 333.9 meters, p = 0.15).

Table 20 Baseline Exercise Tolerance

Characteristic	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	p value [1]
Peak Workload on Cycle Ergometry (watts)	43.2 (21.3) 101 40.0 (5.0, 120.0)	45.0 (23.9) 220 40.0 (5.0, 135.0)	0.7149
6MWT Distance (m)	350.9 (83.2) 101 344.0 (192.0, 598.6)	333.9 (87.4) 220 335.1 (140.0, 563.9)	0.1479

[1] Two-sided t-test with equal variance
Source: Attachment 3, Amended Statistical Analysis Report, Table 6:5

6.11 Borg Test Results

Dyspnea and fatigue were rated on a scale from 0 to 10 during exercise testing (Borg Test) at baseline, and there were no significant differences in dyspnea or fatigue scores before or after performing the 6MWT, as noted in the Table below.

Table 21 Baseline Borg Testing Results

Characteristic	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	p value [1]
Dyspnea before 6MWT	1.0 (1.1) 96 0.5 (0.0, 5.0)	1.0 (1.3) 207 0.5 (0.0, 8.0)	0.6291
Dyspnea after 6MWT	4.0 (2.1) 97 3.0 (1.0, 10.0)	4.2 (2.1) 209 4.0 (0.0, 10.0)	0.2675
Fatigue before 6MWT	1.1 (1.5) 96 0.5 (0.0, 8.0)	1.1 (1.5) 203 0.5 (0.0, 8.0)	0.6130
Fatigue after 6MWT	3.0 (2.1) 96 3.0 (0.0, 8.0)	3.1 (2.2) 205 3.0 (0.0, 10.0)	0.8264

[1] The two-sided Wilcoxon rank sum test
Source: Attachment 3, Amended Statistical Analysis Report, Table 6:6

6.12 HRCT Characteristics

The degree of emphysematous destruction was rated by the Core Radiology on a scale from 0% to 100% — 0% indicating no emphysematous destruction in that lobe, 100% indicating complete destruction. There were no differences in Density Score by lobe between the two study groups (see Table 22).

Table 22 Baseline Disease Distribution (Density Score by Lobe)

Characteristic	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	p value
Right Upper Lobe DS (%)	63.2 (14.9) 101 64.0 (23.0, 90.0)	64.8 (14.2) 220 67.0 (9.0, 89.0)	0.3563 [1]
Right Middle Lobe DS (%)	54.6 (17.3) 101 57.0 (16.0, 85.0)	53.1 (17.9) 220 56.0 (0.0, 86.0)	0.5164 [1]
Right Lower Lobe DS (%)	49.2 (17.2) 101 50.0 (10.0, 83.0)	47.1 (17.6) 220 45.0 (3.0, 91.0)	0.3220 [2]
Left Upper Lobe DS (%)	60.0 (13.4) 101 61.0 (18.0, 85.0)	60.1 (13.2) 220 62.0 (16.0, 87.0)	0.8430 [1]
Left Lower Lobe DS (%)	47.5 (17.2) 101 49.0 (4.0, 80.0)	45.7 (18.7) 220 47.0 (5.0, 85.0)	0.4181 [1]

[1] Two-sided Wilcoxon rank-sum test
[2] Two-sided t-test with equal variance

Source: Attachment 3, Amended Statistical Analysis Report, Table 6.16

Similarly, the volume of each lobe was evaluated by the Core Radiology Lab. The distribution of volume by lobe was quite similar between the two study groups (see Table 23).

Table 23 Baseline Volume by Lobe (liters) at TLC

Characteristic	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	p value
Right Upper Lobe Volume	1.56 (0.43) 101 1.48 (0.79, 2.94)	1.63 (0.48) 220 1.54 (0.53, 3.65)	0.2366 [1]
Right Middle Lobe Volume	0.45 (0.18) 101 0.43 (0.01, 1.03)	0.49 (0.21) 220 0.46 (0.00, 1.23)	0.1199 [2]
Right Lower Lobe Volume	1.53 (0.43) 101 1.45 (0.56, 3.12)	1.56 (0.45) 220 1.51 (0.71, 3.83)	0.6544 [1]
Left Upper Lobe Volume	1.69 (0.45) 101 1.62 (0.94, 3.11)	1.78 (0.48) 220 1.72 (0.81, 3.17)	0.0883 [1]
Left Lower Lobe Volume	1.50 (0.45) 101 1.46 (0.62, 2.74)	1.52 (0.42) 220 1.49 (0.76, 2.86)	0.5829 [1]

[1] Two-sided Wilcoxon rank-sum test
[2] Two-sided t-test with unequal variance
Source: Attachment 3, Amended Statistical Analysis Report, Table 6.17

There were no differences in Target Lobe Density Score (DS) (p = 0.2087), Heterogeneity Score (p = 0.3534), Target Lobe Volume (p = 0.3055), and Ipsilateral Lung, Non-target Lobe Volume (0.3334).

Table 24 Target-specific Baseline HRCT Characteristics

Characteristic	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	p value [1]
Target Lobe Density Score (%)	66.9 (10.9) 101 66.0 (51.0, 89.0)	68.5 (10.2) 220 68.0 (51.0, 91.0)	0.2087
Heterogeneity Score (%)	15.0 (16.7) 101 15.0 (-20.0, 58.0)	17.1 (15.2) 220 15.0 (-19.0, 74.0)	0.3534
Target Lobe Volume (L)	1.73 (0.45) 101 1.67 (0.79, 2.94)	1.81 (0.51) 220 1.76 (0.81, 3.83)	0.3055
Ipsilateral Lung, Non-target Lobe Volume (L)	1.69 (0.50) 101 1.60 (0.66, 2.91)	1.73 (0.46) 220 1.70 (0.72, 3.25)	0.3334

[1] Two-sided Wilcoxon rank-sum test
Source: Attachment 3, Amended Statistical Analysis Report, Table 6.18

The proportion of subjects in the Control Group with Complete Fissures was nominally higher than the Zephyr EBV Group, but this difference did not reach significance (p = 0.2542).

Table 25 Proportion of Complete Fissures (vs. Partial or Absent)

Characteristic	Control % (n / N)	Zephyr EBV % (n / N)	p value [1]
Complete Fissure Score [2]	45.2 (42 / 93)	38.0 (79 / 208)	0.2542

[1] Two-sided Fisher's exact test
[2] For Complete Fissure on right lung, both Right Horizontal and Right Oblique Fissures must be Complete.
Source: Attachment 3, Amended Statistical Analysis Report, Table 6.19

6.13 Summary: Study Population

The VENT Pivotal Trial population achieved its intended target population of subjects with severe emphysema:

- FEV_1 % predicted = 30% both groups
- FEV_1 / FVC = 0.33 both groups
- RV % predicted 212% (Control) and 216% (Zephyr EBV)

Randomization was successful overall: 31.5% Control Subjects and 68.5% Zephyr EBV Subjects, close to the intended rate of 1:2. Randomization was well balanced across study sites and strata of exercise capacity and target lobe location.

Review of demographic data, use of pulmonary medications, medical history, use of supplemental oxygen, lung functions, arterial blood gas results, exercise tolerance, Borg test results, BODE indices, SGRQ scores, mMRC Dyspnea Scale scores, and HRCT characteristics were all comparable between Control Subjects and Zephyr EBV Subjects.

These results confirm that the screening and randomization procedures utilized by the VENT Pivotal Trial resulted in the enrollment of adult subjects with severe emphysema into two highly comparable study groups. Those few parameters showing significant or near significant differences were included in multivariate analyses of study outcomes as discussed in subsequent sections.

7.0 ZEPHYR EBV IMPLANTATION PROCEDURE

7.1 Introduction

The Zephyr EBV Implantation Procedure was characterized for the Zephyr EBV Subjects by a number of acute assessments. These included:

7.2. Procedure Details
- 7.2.1. Procedure Time
- 7.2.2. Target Lobes
- 7.2.3. Anesthesia and Airway Management
- 7.2.4. Proportion of Procedures Involving a Rigid Bronchoscope

7.3. Procedure Outcomes
- 7.3.1. Number of Zephyr EBVs Placed Per Subject
- 7.3.2. Acute Technical Success (Site Determined)
- 7.3.3. Valves Removed and Replaced During the Initial Procedure
- 7.3.4. Device Malfunctions

7.4. Summary: Zephyr EBV Implantation Procedure

A detailed presentation for each of these procedural parameters and outcomes follows in this section of the Clinical Study Report.

7.2 Procedure Details

7.2.1 Procedure Time

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

Table 26 Zephyr Endobronchial Valve Procedure Time

Zephyr EBV Subjects	Mean (SD) N [1] Median (Min, Max)
Procedure time (min)	33.8 (20.5) 212 28.0 (6, 100)

[1] Denominator is the 212 Zephyr EBV Subjects with procedure time data.
Source: Attachment 3, Amended Statistical Analysis Report, Table 7:1

7.2.2 Target Lobes

Target lobes were defined by pre-procedural imaging assessments. Target lobes were largely in the upper lobes (76.6%) and predominantly in 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 in 24.3%, and the left lower lobe in 14.0%.

Table 27 Zephyr Endobronchial Valve Target Lobes

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

[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.
Source: Attachment 3, Amended Statistical Analysis Report, Table 7:1

7.2.3 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.

Table 28 Anesthesia and Airway Management

Zephyr EBV Subjects	% (n / N) [1]
Anesthesia	
General	28.5% (61 / 214)
Conscious sedation	71.5% (153 / 214)
Intubated during procedure	
Yes	35.1% (75 / 214)
No	64.9% (139 / 214)
Ventilated during procedure	
Yes	29.9% (64 / 214)
No	70.1% (150 / 214)

[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.
Source: Attachment 3, Amended Statistical Analysis Report, Table 7:1

7.2.4 Proportion of Procedures Involving a Rigid Bronchoscope

Three (3) Zephyr EBV Subjects had a rigid bronchoscope used during the Zephyr EBV implantation procedure, the remaining 211 procedures involved only flexible bronchoscopy.

Table 29 Proportion of Procedures Involving a Rigid Bronchoscope

Zephyr EBV Subjects	% (n / N) [1]
Rigid bronchoscope used	
Yes	1.4% (3 / 214)
No	98.6% (211 / 214)

[1] Denominator is the214 Zephyr EBV Subjects who underwent procedure; 6 subjects randomized to the Zephyr EBV Subjects Group did not undergo a Zephyr EBV implantation procedure.
Source: Attachment 3, Amended Statistical Analysis Report, Table 7:1

7.3 Procedure Outcomes

7.3.1 Number of Zephyr EBVs Placed Per Subject

A total of 820 valves was 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).

Table 30 Number of Zephyr EBVs Placed Per Subject

Zephyr EBV Subjects	Mean (SD) N [1 2] Median (Min, Max)
Number of valves placed	3.83 (1.39) 214 4.0 (1.0, 9.0)

[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.
[2] Average valves implanted are net of valves removed intra-procedure
Source: Attachment 3, Amended Statistical Analysis Report, Table 7:1

7.3.2 Acute Technical Success (Site Determined)

Acute Technical Success—determined by the implanting site at the time of the procedure, based on the Investigator's bronchoscopic assessment of complete exclusion of the target lobe—was found in 94.9% of subjects.

Table 31 Acute Technical Success (Site Determined)

Zephyr EBV Subjects	% (n / N) [1]
Acute Technical Success	94.9% (203 / 214)

[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.
Source: Attachment 3, Amended Statistical Analysis Report, Table 7:1

Eleven (11) Zephyr EBV Subjects had acute technical failure, based on an inability to obtain complete lobar exclusion of the target lobe. The reasons for technical failure were: segment too small for valve (27.3%), unable to place valve (36.4%), side branch airway too small (9.1%), unable to valve apical segment, (18.2%), and other (9.1%). The Acute Technical Failures are listed in the table below.

Table 32 Reasons for Acute Technical Failure (Site Determined)

EBV Group	% (n / N) [1]
Procedural Failures	100.0% (11 / 11)
Segment too small for valve	27.3 % (3 / 11)
Unable to place valve	36.4% (4 / 11)
Other	9.1% (1 / 11)
Side branch airway too small	9.1% (1 / 11)
Unable to valve apical segment	18.2% (2 / 11)

[1] Denominator is the site reported failures to achieve complete lobar exclusion.
Source: Attachment 3, Amended Statistical Analysis Report, Table 7:1

Table 33 Listing of Acute Technical Failures

Subject ID	Reason for Failure to Achieve Lobar Exclusion
	Small side branch airway could not be occluded
	B6a segment was too small to place a valve
	Valve could not be placed in one of the subsegments of the superior bronchus due to the severe angle of the airway
	B7 segment was too small for valve placement.
	Unable to cannulate B1 and this segment was not treated.
	Unable to place a valve in segment LB6c, but segment was partially occluded by other valves
	Unable to place a valve in RB1b due to severe angle of segment
	Following valve deployment in RB1b2, a hole was revealed in the airway
	Initially placed valves in B1a and B1b nested together and had to be removed; Investigator unable to valve the more proximal B1 segment
	B6c segment was too small for valve
	One lumen was too large

Source: P070025, September 21, 2007, Volume 011, Page 85

7.3.3 Valves Removed and Replaced During the Initial Procedure

Ninety-six (96) Zephyr EBV subjects had a total of 143 valves removed during the 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 Acute Technical Success as reported by the site. Seven (7) of the 96 subjects (7.3%) did not go on to Acute Technical Success for the following reasons: lumen too large (1 / 7), lumen too small (2 / 7), small side branch could not be occluded (2 / 7), and unable to place valve in segment due to severe angle of airway (2 / 7).

Table 34 Subjects with Valves Removed During the Initial Procedure and Not Replaced (Technical Failures)

	% (n / N) [1]
Zephyr EBV Subjects	100.0% (7 / 7)
Lumen too large	14.3% (1 / 7)
Lumen too small	28.6% (2 / 7)
Small side branch could not be occluded	28.6% (2 / 7)
Severe angulation	28.6% (2 / 7)

[1] Denominator is 7 Zephyr EBV Subjects from Table 27 above with valves removed during the initi

Source: P070025, September 21, 2007, Volume 011, Page 86

Of the 143 valves removed during the initial procedure, 92.3% were for valve positioning: 48.9% were placed too proximally, 19.6% too distally and 3.5% were too small for the selected airway. Other removals for sizing or positioning reasons accounted for 20.3% of valves removed during the initial procedure and 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, and incomplete exclusion. Valve or deployment reasons for removal accounted for 7.7% of valves removed during the initial procedure and included: valve appeared non-functional, valve did not deploy properly, valve loaded and deployed backwards, and duckbill appeared inverted.

Table 35 Valves Removed During the Initial Procedure

Zephyr EBV Treatment	% (n / N) [1]
Total Valves Removed	100.0% (143 / 143)
Size / Positioning	92.3% (132 / 143)
Placed too proximally	48.9% (70 / 143)
Placed too distally	19.6% (28 / 143)
Valve too small	3.5% (5 / 143)
Other – Size / Positioning	20.3% (29 / 143)
Valve / Deployment	7.7% (11 / 143)

[1] Denominator is 143 valves removed during the initial Zephyr EBV implantation procedure.
Source: P070025, September 21, 2007, Volume 011, Page 86

7.3.4 Device Malfunctions

There were device malfunctions in 21 (9.8%) of Zephyr EBV procedures, and 1 device malfunction in a follow-up procedure to replace an expectorated valve. For the total of 22 subjects with any device malfunction, 35 devices were reported as malfunctioning (18 EBVs, 15 EDCs and 2 ELSs). The majority of the malfunctions were associated with Loading Failures and Delivery Failure due to Anatomical Constraints; the primary reasons for these device malfunctions are summarized in the following Table.

Table 36 Categories of Device Malfunctions

Zephyr EBV Group	% (n / N) [1]
Procedures with Device Malfunctions	100.0% (22 / 22)
Loading Failure	45.5% (10 / 22)
Delivery Failure / Anatomical	31.8% (7 / 22)
Deployment Failure	9.1% (2 / 22)
Iatrogenic Injury	4.5% (1 / 22)
Other / Unknown	9.1% (2 / 22)

[1] Denominator is with device malfunctions: 21 during the initial Zephyr EBV implantation procedure and 1 during follow-up bronchoscopy to replace an expectorated valve.
Source: P07002 21, 2007, Volume 011, Page 87

The following Table lists those subjects whose procedure was associated with a device malfunction. Of the 22 malfunctions reported, 21 did not have adverse events associated with the malfunction. In one procedure an airway perforation was reported.

Table 37 Listing of Device Malfunctions

Subject ID	EBV	EDC	ELS	Failure Category	Sequelae
	1			Delivery Failure / Anatomical	None
	1			Other	None
	1			Delivery Failure / Anatomical	None
		2		Loading Failure	None
	2	1		Loading Failure	None
	2	1		Loading Failure	None
	1			Delivery Failure / Anatomical	None
	1			Delivery Failure / Anatomical	None
	1			Deployment Failure	None
		1		Deployment Failure	None
	1	1	1	Loading Failure	None
	1			Other	None
	1			Delivery Failure / Anatomical	None
	2	2		Loading Failure	None
	1	1	1	Loading Failure	None
		1		Loading Failure	None
		1		Delivery Failure / Anatomical	None
		1		Delivery Failure / Anatomical	None
		1		Iatrogenic Injury (Airway Perforation)	SAE
	1	1		Loading Failure	None
		1		Loading Failure	None
	1			Loading Failure	None
Totals	**18**	**15**	**2**		

Source: P070025, September 21, 2007, Volume 011, Page 88

7.4 Summary: Zephyr EBV Implantation Procedure

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

Target lobes were defined by pre-procedural imaging assessments. Target lobes were largely in the upper lobes (76.6%) and predominantly in 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 in 24.3%, and the left lower lobe in 14.0%.

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.

Three (3) Zephyr EBV Subjects had a rigid bronchoscope used during the Zephyr EBV implantation procedure, the remaining 211 procedures involved only flexible bronchoscopy.

The mean number of valves placed per Zephyr EBV Subject was 3.8 (median 4, range 1 to 9).

Acute Technical Success—determined by the implanting site at the time of the procedure, based on the Investigator's assessment of complete exclusion of the target lobe—was found in 94.9% of subjects.

Of the 214 Zephyr EBV Subjects who received one or more valves during the initial study procedure, 96 subjects had a total of 143 valves removed during the procedure. In 89 of these 96 subjects (92.7%), the valves removed during the procedure were successfully replaced with one or more valves, which led to Acute Technical Success (lobar exclusion) as reported by the site.

Of the 143 valves removed during the initial procedure, 92.3% were for valve positioning: 48.9% were placed too proximally, 19.6% too distally and 3.5% were too small for the selected airway. Other removals for sizing or positioning reasons accounted for 20.3% of valves removed during the initial procedure and 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, and incomplete exclusion. Valve or deployment reasons for removal accounted for 7.7% of valves removed during the initial procedure and included: valve appeared non-functional, valve did not deploy properly, valve loaded and deployed backwards, and duckbill appeared inverted.

There were device malfunctions in 21 (9.8%) of Zephyr EBV procedures, and 1 device malfunction in a follow-up procedure to replace an expectorated valve. For the total of 22 subjects with any device malfunction, 35 devices were reported as malfunctioning (18 EBVs, 15 EDCs and 2 ELSs). The majority of the malfunctions were associated with Loading Failures and Delivery Failure due to Anatomical Constraints.

Overall the Zephyr EBV system was easy to use, reliable and successful in achieving lobar exclusion at the time of the initial procedure.

8.0 PRIMARY AND SECONDARY EFFECTIVENESS OUTCOMES

8.1 Introduction

The VENT Pivotal Study protocol and Statistical Analysis Plan specified a Primary Effectiveness Outcome and four Secondary Effectiveness Outcomes. The effectiveness of the Zephyr Endobronchial Valve in the treatment of subjects with severe heterogeneous emphysema was assessed by a number of analyses, as detailed in the following Section 8 outline:

8.2. Primary Effectiveness Outcomes
- 8.2.1. Percent Change in FEV_1 and 6MWT – Multiple-Imputation Intent-to-Treat
- 8.2.2. Completed Cases: Percent Change in FEV_1 and 6MWT

8.3. Secondary Effectiveness Outcomes
- 8.3.1. Change in St. George's Respiratory Questionnaire Score
- 8.3.2. Change in mMRC Dyspnea Scale
- 8.3.3. Change in Maximum Workload during Cycle Ergometry
- 8.3.4. Change in Use of Supplemental Oxygen

8.4. Summary: Primary and Secondary Effectiveness Outcomes

8.2 Primary Effectiveness Outcomes

A primary objective of the VENT Pivotal Trial was to assess the effectiveness of the Zephyr EBV in treating subjects with severe heterogeneous emphysema.

This was to be measured by determining the FEV_1 and 6MWT values at baseline and at 6 months, and to compare the percentage change from baseline in these tests between the Control Subjects and the Zephyr EBV Subjects. 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.

8.2.1 Percent Change in FEV_1 and 6MWT – Multiple Imputation

The VENT Pivotal Trial met its Primary Effectiveness Outcome in favor of Zephyr EBV treatment by multiple-imputation, intent-to-treat analysis. For this analysis, 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).

Table 38 Primary Effectiveness Outcome: Multiple-Imputation, Intent-to-Treat Percent Change in FEV_1 and 6MWT at 6 Months

Primary Effectiveness Outcome	Delta (%) (95% CI)	p value
Percent Change in FEV_1	6.8 [1] (2.1, 11.5)	**0.002** [2]
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.
Source: Attachment 3, Amended Statistical Analysis Report, Table 9:1.

8.2.2 Completed Cases: Percent Change in FEV_1 and 6MWT

The intent-to-treat imputations were confirmed by a 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.

Zephyr EBV Subjects had a significantly greater percent improvement in both FEV_1 and 6MWT from baseline to 6 months compared with Control Subjects.

Completed Cases at 6 months:
FEV_1: Control: −1.9%; Zephyr EBV: +5.3% (Δ = +7.2%, p = 0.0003)
6MWT: Control: −1.5%; Zephyr EBV: +4.3% (Δ = +5.8%, p = 0.0079)

Table 39 Completed Cases: Percent Change in FEV_1 and 6MWT at 6 Months

Percent Change from Baseline		Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta (95% CI)	p value
Completed Cases	**FEV_1**	–1.9 (12.2) 75 –3.4 (–27.7, 38.6)	5.3 (19.6) 179 3.8 (−38.3, 78.9)	7.2 [1] (3.2, 11.2)	**0.0003** [2]
	6MWT	–1.5 (22.5) 73 –2.3 (–54.9, 71.4)	4.3 (22.7) 178 3.5 (–83.3, 108.0)	5.8 [3] (1.3, 11.7)[4]	**0.0079** [5]

[1] Difference of means and unequal variance t-test confidence interval
[2] One-sided unequal variance t-test
[3] Difference of medians
[4] Non-parametric confidence interval
[5] One-sided Wilcoxon rank-sum test
Source: Attachment 3, Amended Statistical Analysis Report, Tables 10:1 and 10:2

8.3 Secondary Effectiveness Outcomes

The VENT Pivotal Trial specified four secondary effectiveness outcomes:

- Change in St. George's Respiratory Questionnaire score from baseline
- Change in Modified Medical Research Council Dyspnea Scale score from baseline
- Change in maximum workload during cycle ergometry from baseline
- Change in the use of supplemental oxygen from baseline

These outcomes, and related analyses, are summarized below.

8.3.1 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 = 0.0167). These findings of significance were confirmed by Completed-Cases univariate and multivariate mixed-model analyses.

Table 40 2° Effectiveness Outcome: Change in SGRQ Score at 6 Months

2° Outcome: SGRQ Change from Baseline	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta (95% CI) [1]	p value [2]
Multiple-Imputation, Intent-to-Treat			–3.4 (-6.6, -0.3)	**0.0167**
CC Subjects	0.7 (9.7) 62 1.5 (–25.8, 27.9)	–2.7 (13.3) 158 –2.2 (–35.9, 55.0)	–3.4 (–6.6, –0.2)	**0.0192**

[1] Difference of means and unequal variance t-test confidence interval
[2] One-sided unequal variance t-test
Source: Attachment 3, Amended Statistical Analysis Report, Table 25:1.& 11.1a

8.3.2 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 = 0.0183). These findings of significance were confirmed by Completed-Cases univariate and multivariate mixed-model analyses.

Table 41 2° Effectiveness Outcome: Change in mMRC Dyspnea Scale at 6 Months

2° Outcome: mMRC Change from Baseline	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta [1] (95% CI)	p value [2]
Multiple-Imputation, Intent-to-Treat			–0.26 (–0.49, –0.02)	**0.0183**
CC Subjects	0.21 (0.83) 67 0.00 (–2.00, 2.00)	–0.09 (1.04)162 0.00 (−3.00, 3.00)	–0.30 (–0.56, –0.05)	**0.0108**

[1] Difference of means and unequal variance t-test confidence interval
[2] One-sided unequal variance t-test
Source: Attachment 3, Amended Statistical Analysis Report, Table 25.1 & 11.1a

8.3.3 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 = 0.0203). These findings of significance were confirmed by Completed-Cases univariate and multivariate mixed-model analyses.

Table 42 2° Effectiveness Outcome: Change in Maximum Workload during Cycle Ergometry (watts) at 6 Months

2° Outcome: Cycle Ergometry – Change from Baseline	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta (95% CI)	p value
Multiple-Imputation, Intent-to-Treat			3.8 [1] (0.2, 7.4)	**0.0203** [2]
CC Subjects	–4.4 (12.8) 69 –5.0 (–40.0, 45.0)	0.1 (15.3) 166 0.0 (–110.0, 50.0)	5.0 [3] (0.0, 5.0)	**0.0044** [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
Source: Attachment 3, Amended Statistical Analysis Report, Table 25:1.&11.1a

8.3.4 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 = 0.0198).

Mixed model, multivariate analysis of the Completed Cases dataset did not result in a significant main effect or interaction for Use of Supplemental Oxygen.

Table 43 2° Effectiveness Outcome: Use of Supplemental Oxygen (liters / day)

2° Outcome: Supplemental O_2 – Change from Baseline	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta (95% CI)	p value
Multiple-Imputation, Intent-to-Treat Subjects			–12.0 [1] (–76.7, 52.7)	**0.0198** [2]
CC Subjects	82.9 (744.0) 75 0.0 (-2220.0, 3360.0)	-17.1 (912.8) 171 0.0 (-3840.0, 3750.0)	-100.1 [3] (-318.6, 118.4)	0.1837 [4]

[1] Difference of medians and non-parametric confidence interval
[2] One-sided Wilcoxon rank-sum test
[3] Difference of means and unequal variance t-test confidence interval
[4] One-sided unequal variance t-test
Source: Attachment 3, Amended Statistical Analysis Report Table 25.1&.11.1a

8.4 Summary: 1° and 2° Effectiveness Outcomes

The VENT Pivotal Trial met its Primary Effectiveness Outcomes in favor of Zephyr EBV treatment by univariate testing, with a significantly better improvement in both FEV_1 and 6MWT in Zephyr EBV Subjects when compared to Control Subjects at 6 months of follow-up. These significant differences existed whether the analysis was performed with multiple imputation for missing values or with Completed Cases only.

<u>ITT at 6 months:</u>
FEV_1: $\Delta = +6.8\%$, $p = 0.002$
6MWT: $\Delta = +5.8\%$, $p = 0.019$

<u>Completed Cases at 6 months:</u>
FEV_1: $\Delta = +7.2\%$, $p < 0.001$
6MWT: $\Delta = +5.8\%$, $p = 0.008$

The Vent Pivotal Trial met its 4 secondary effectiveness outcomes: SGRQ, mMRC, cycle ergometry, and supplemental oxygen use.

- **The St. George's Respiratory Questionnaire (SGRQ)** showed significantly greater mean improvement (score reduction) for Zephyr EBV Subjects compared to the Control Subjects ($\Delta = -3.4$, $p = 0.0167$) at 6 months.
- **The Modified Medical Research Council Dyspnea Scale (mMRC)** showed significantly greater mean improvement (score reduction) for Zephyr EBV Subjects compared to the Control Subjects ($\Delta = -0.26$, $p = 0.0183$) at 6 months.
- **Maximum workload during cycle ergometry** showed significantly greater mean improvement for Zephyr EBV Subjects compared to the Control Subjects ($\Delta = 3.8$ watts, $p = 0.0203$).
- **Use of supplemental oxygen** showed a statistically-significant improvement in the self-reported use of supplemental oxygen in the Zephyr EBV Subjects compared to Control Subjects ($\Delta = -12.0$ L / day, $p = 0.0198$).

The VENT Pivotal Trial of unilateral treatment of severe heterogeneous emphysema in medically optimized subjects met its Primary Effectiveness Outcome and its 4 Secondary Effectiveness Outcomes, showing significantly better treatment group outcome measures in Zephyr EBV Subjects when compared to Control Subjects.

9.0 PRIMARY SAFETY OUTCOME

9.1 Introduction

The Primary Safety Outcome for the Zephyr EBV Pivotal Trial was the Major Complications Composite. This outcome measure was also subjected to several related analyses to clarify MCC experience over time and in relation to covariates.

9.2. Primary Safety Outcome: Major Complications Composite
9.3. Major Complications Composite: Related Analyses
  9.3.1. All-Cause Mortality
  9.3.2. Cox Regression Analysis of MCCs through Six Months
  9.3.3. MCCs by Time Period through One Year
  9.3.4. MCCs by Valve Removal Status through One Year
9.4. Summary: Primary Safety Outcome

9.2 Primary Safety Outcome: Major Complications Composite

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 determined. There were 14 Control Subjects and 6 Zephyr EBV Subjects that had no treatment and no follow-up at 30-days or later, leaving 87 of 101 Control Subjects and 214 of 220 Zephyr EBV Subjects for safety analysis. 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 44 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

Source: P070025, September 21, 2007, Volume 011, Page 199

Eighteen (18) MCC events occurred in a total of 14 VENT Pivotal Trial subjects. One or more MCCs occurred in 1.2% of Control Subjects and in 6.1% of Zephyr EBV Subjects (p = 0.0748).

Death occurred in no Control Subjects and in 6 (2.8%) Zephyr EBV Subjects (p = 0.1867). Further information on all-cause mortality is presented in Section 9.3.1, All-Cause Mortality.

No subject in either group had empyema, and 1 Zephyr EBV Subjects had massive hemoptysis. Pneumonia distal to a valve occurred in 1.4% of Zephyr EBV Subjects; an event that could not occur in Control Subjects. Prolonged pneumothorax occurred in 1.2% of Control Subjects and in 1.4% of Zephyr EBV Subjects. Respiratory failure requiring mechanical ventilation for more than 24 hours occurred in 1.2% of Control Subjects and in 1.9% of Zephyr EBV Subjects.

Table 45 Primary Safety Outcome: Major Complications Composite at 6 Months

Safety Outcome	Control % (n / N)	Zephyr EBV % (n / N)	Delta (95% CI) [1]	p value [2]
MCCs at 6 months	1.2% (1 / 87)	6.1% (13 / 214)	4.9% (1.0, 8.8)	0.0748
Death, all-cause	0.0% (0 / 87)	2.8% (6 / 214)	2.8% (0.6, 5.0)	0.1867
Empyema	0.0% (0 / 87)	0.0% (0 / 214)	--	--
Massive hemoptysis	0.0% (0 / 87)	0.5% (1 / 214)	0.5% (−0.5, 1.4)	1.0000
Distal pneumonia	--	1.4% (3 / 214)	--	--
Prolonged pneumothorax	1.2% (1 / 87)	1.4% (3 / 214)	0.3% (−2.5, 3.0)	1.0000
Respiratory failure > 24 hours	1.2% (1 / 87)	1.9% (4 / 214)	0.7% (−2.2, 3.6)	1.0000

[1] Fisher's exact 95% confidence interval
[2] Two-sided Fisher's exact test
Source: Attachment 3, Amended Statistical Analysis Report, Table 16:4

Clinical narratives for each of the subjects experiencing one or more MCCs during the VENT Pivotal Trial follow-up are contained in Appendix 7-5-9, Adverse Event Narratives for Selected Subjects.

Table 46 Summary: Subjects with One or More MCCs

Group	MCC Event(s)	Onset (days) [1]
Zephyr EBV	Pneumothorax > 7 days	44
Zephyr EBV	Pneumonia distal to valve	270

Group	MCC Event(s)	Onset (days) [1]
Zephyr EBV	Respiratory failure > 24 hours Death (ischemic colitis)	54 60
Control	Death (respiratory failure)	230
Zephyr EBV	Pneumonia distal to valve	212
Zephyr EBV	Pneumothorax > 7 days	12
Zephyr EBV	Massive hemoptysis Death (massive hemoptysis)	31 48
Zephyr EBV	Death (hepatic cancer)	154
Zephyr EBV	Pneumonia distal to valve	15
Zephyr EBV	Pneumothorax > 7 days Respiratory failure > 24 hours	217 222
Zephyr EBV	Death (respiratory failure)	161
Zephyr EBV	Pneumothorax > 7 days	47
Zephyr EBV	Respiratory failure > 24 hours Death ("severe emphysema")	122 148
Zephyr EBV	Respiratory failure > 24 hours Death (metastatic cancer)	85 293
Zephyr EBV	Pneumonia distal to valve	222
Zephyr EBV	Pneumonia distal to valve	363
Control	Pneumothorax > 7 days Respiratory failure > 24 hours Death (post biopsy pneumothorax)	165 180 207
Zephyr EBV	Respiratory failure > 24 hours Death (respiratory failure)	84 133
Zephyr EBV	Respiratory failure > 24 hours	334
Zephyr EBV	Pneumonia distal to valve	179
Control	Respiratory failure > 24 hours	317
Zephyr EBV	Pneumonia distal to valve	243
Zephyr EBV	Pneumonia distal to valve	296
Zephyr EBV	Pneumonia distal to valve	20 [2]
Control	Death (lung cancer)	212
Zephyr EBV	Death (pneumonia)	248

er randomization

[2] Date of onset was reported by site as Unknown. Earliest possible onset date was the date of the EBV procedure, which was 20 days post-randomization

Source: Attachment 3, Amended Statistical Analysis Report, Table 16:1

9.3 Major Complications Composite: Related Analyses

9.3.1 All-Cause Mortality

Equivalent outcomes for all-cause mortality through 1 year were demonstrated by Kaplan-Meier analysis. There were 8 (3.7% of 214) deaths in the Zephyr EBV Subjects