

**Anesthesiology and Respiratory Therapy Devices Panel**

**Gaithersburg, Maryland**

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**Emphasys Medical, Inc.**

**Zephyr Endobronchial Valve System**

**P070025**

**Sponsor's Executive Summary**

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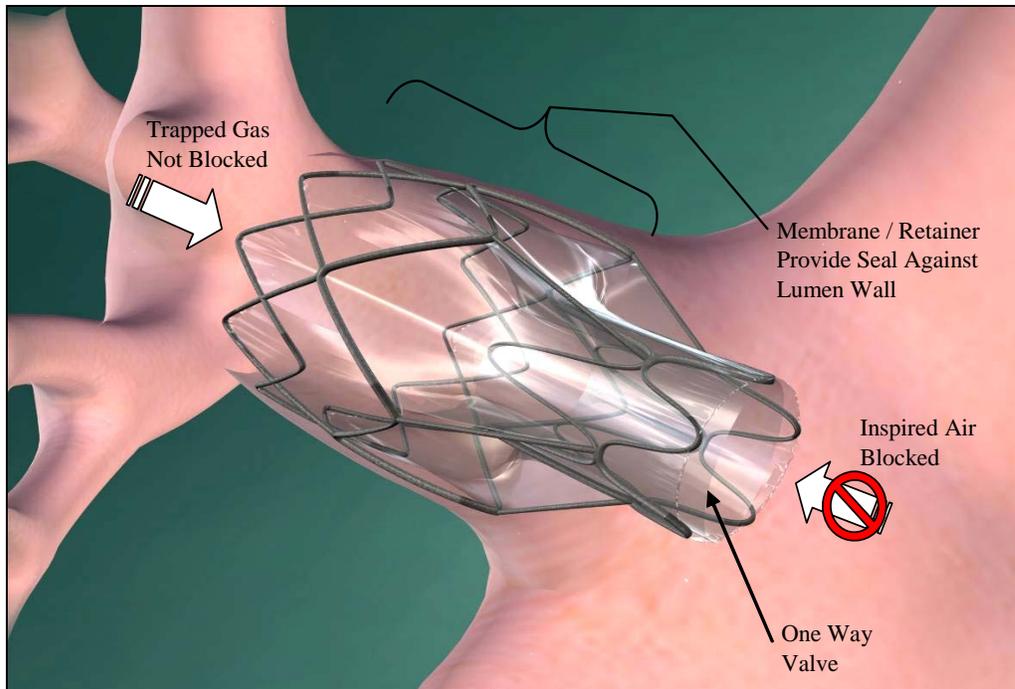
### **Background**

Emphysema is a severely disabling disease most commonly caused by tobacco abuse and characterized by progressive and permanent lung destruction leading to death. The prevalence of emphysema in the US population in 2006 was 4.1 million with Medicare patients (age > 65) representing 50% and an additional 39% of patients between the ages of 45 and 65.<sup>1</sup> As the emphysematous destructive process progresses, alveolar and microvascular structures are destroyed resulting in worsening lung function leading to breathlessness. As symptoms of breathlessness worsen, patients compensate by reducing their activity which has the secondary effect of cardiovascular deconditioning. Patients experience an uninterrupted and progressive deterioration in their quality of life and are very limited in their ability to perform basic daily living activities. This negative spiral leads to progressive debilitation and oxygen dependence resulting in repeated hospitalizations, infections and ultimately death.

Since no current interventions can halt or reverse the disease process, palliative medical therapy includes supplemental oxygen, pulmonary rehabilitation, bronchodilators, steroids and mucolytics all with the goal of improving quality of life. Lung transplantation remains a definitive treatment option; however, scarcity of donors and a recipient population in which half the emphysema patients are older than 65 marginalizes this therapy to all but a few patients. As emphysema's pathophysiology and clinical sequelae of 'breathlessness' result from hyperinflation of diseased lung and impaired respiratory mechanics, the paradoxical affect of improving lung function by removing diseased lung popularized the concept of lung volume reduction surgery (LVRS). Through the resection of the most diseased lung tissue and the resultant expansion of the healthier adjacent lung, or volume redistribution, breathing mechanics are improved. The National Emphysema Treatment Trial (NETT) demonstrated that in selected patients, the mechanical improvement provided by LVRS could significantly improve lung function and survival. Unfortunately, LVRS, even when performed with minimally invasive thoroscopic techniques at high-volume centers, is associated with acute mortality rates of 5-10% and morbidity rates greater than 50%. The morbidity and mortality have resulted in limited adoption of LVRS, with only 122 Medicare patients undergoing the procedure in 2006.<sup>2</sup>

### **Zephyr Endobronchial Valve**

Emphasys Medical hypothesized that effective lung volume reduction could be achieved without surgically resecting lung tissue through the use of bronchoscopically placed endobronchial one-way valves.



**Figure 1 Emphasys Zephyr Endobronchial Valve (EBV)**

The endobronchial valve (Zephyr<sup>®</sup> EBV) was designed to achieve target lobe volume reduction and associated volume redistribution with lower morbidity and mortality. Zephyr EBV treatment involves the bronchoscopic placement of valves to block the airflow into targeted, hyperinflated regions of the lung, leading to the reduction of volume in the targeted lobe and expansion of the healthier adjacent lobe. Unlike LVRS, the ability to remove or add valves in response to changing clinical conditions would allow clinicians to optimize patient outcomes.

### **Preclinical Studies**

Biocompatibility was evaluated through multiple tests: cytotoxicity, intracutaneous reactivity, sensitization, implantation, systemic (subchronic) toxicity, genotoxicity and mutagenicity. The results of this testing showed that the materials of construction of the Zephyr EBV System were biologically safe based on the intended use of the device.

A series of tests were completed to characterize dimensional, functional and material characteristics important to the performance of the device. The Zephyr EBV System performed satisfactorily for all performance aspects.

A number of animal tests were performed to assess the safety and efficacy of the product. The Zephyr EBV system performed satisfactorily in terms of delivery, removability, migration resistance, valve inversion, atelectasis achievement and pathology.

## Clinical Trial and PMA Timeline

The Emphasys Endobronchial Valve was initially evaluated in non-randomized, prospective feasibility studies. Results at 90 days showed significant (15-20%) improvement in FEV<sub>1</sub>, six minute walk test (6MWT), and quality of life scores. More importantly, the morbidity and mortality of the EBV procedure compared favorably to a meta-analysis of LVRS data<sup>3</sup>. 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%.

The IDE for the pivotal clinical study (VENT Pivotal Trial) was approved by the FDA in August 2003. 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. This Panel was convened to provide the FDA with expert opinion on the design of trials for bronchoscopic treatment of emphysema. Following supplements to the IDE, enrollment for the pivotal cohort commenced in December 2004 and concluded in April 2006. The original PMA was submitted in September 2007. FDA granted expedited review status based on the unavailability of other legally marketed therapeutic devices and on the potential that Zephyr EBV Treatment “may offer a viable alternative to surgery in some patients with emphysema, which may be life-threatening or irreversibly debilitating.”

## VENT Pivotal Trial

Based on positive pre-clinical and non-randomized clinical data, the Endobronchial Valve for Emphysema Palliation Trial (VENT Pivotal Trial) was initiated to assess the safety and efficacy of using the Zephyr EBV device in subjects with severe heterogeneous emphysema.

### Design

Study design, including endpoints and statistical methods, were determined with FDA guidance. The VENT trial was a multi-center (31), randomized, controlled trial which enrolled 321 subjects (220 Zephyr EBV Treatment, 101 Control) with severe heterogeneous emphysema. After participating in a rigorous six to eight week standardized pulmonary rehabilitation program, subjects who still met the inclusion/exclusion criteria were randomized (2:1) to either bronchoscopic Zephyr EBV implantation (limited by protocol to treatment of one lobe) or continued best medical therapy.

Co-primary efficacy endpoints were the percent changes in both FEV<sub>1</sub> and 6MWT at six months follow-up. In order to corroborate the primary endpoints with other clinically relevant endpoints, multiple secondary efficacy endpoints including St. Georges Respiratory

Questionnaire (SGRQ), the Modified Medical Research Council Dyspnea Scale (mMRC), maximum exercise capacity by cycle ergometry, and the use of supplemental oxygen were pre-specified.

Change in the BODE index was pre-specified as an additional analysis. BODE is a composite index that incorporates changes in both of the VENT trial’s co-primary endpoints (6MWT and FEV<sub>1</sub>) as well as one of the VENT trial’s secondary endpoints (mMRC). The remaining element of the BODE index is the change in body mass index (BMI). BODE has been shown to be an important outcome predictive of mortality in COPD patients.

In order to demonstrate the achievement of the hypothesized mechanism of target lobe volume reduction and redistribution, High Resolution Computed Tomography (HRCT) assessment of lobar volumes was performed at baseline and six months follow-up. This assessment allowed the calculation and analysis of volume changes from baseline.

Table 1 below lists the primary and secondary effectiveness endpoints and lobar volume measurements that were assessed.

**Table 1 Effectiveness Endpoints**

<b>Primary Endpoints</b>	
FEV <sub>1</sub>	% Change at 6 months
6MWT	% Change at 6 months
<b>Secondary Endpoints</b>	
SGRQ	Change (points) at 6 months
mMRC	Change (points) at 6 months
Cycle Ergometry	Change (watts) at 6 months
Supplemental Oxygen Use	Change (liters/day) at 6 months
<b>Mechanism</b>	
Volume Redistribution	Change (ml) in Target Lobe volume at 6 months Change (ml) in ipsilateral non-target lobe volume at 6 months

The primary safety endpoint was the proportion of subjects at six months experiencing one or more major complications consisting of all cause death, empyema, massive hemoptysis, pneumonia distal to the Zephyr EBV, pneumothorax or prolonged air leak > 7 days, and respiratory failure requiring mechanical ventilation > 24 hours (referred to as Major Complications Composite or MCC). An assessment of adverse events at one year was also pre-specified.

**Subject Demographics:**

Except for gender (males 60% vs. 49% in favor of the Zephyr EBV group,  $p=0.052$ ), and a slightly lower PaCO<sub>2</sub> (40.5 mmHg vs. 41.6 mmHg,  $p=0.044$ ) in the Zephyr EBV group, baseline demographics and comorbidities were similar between groups. Neither PaCO<sub>2</sub> nor gender impacted outcomes in the multivariate assessment. Subjects were taking bronchodilators and/or steroids upon study entry thus demonstrating the severity of their disease state. Supplemental oxygen use, pulmonary function studies, and exercise tolerance were similar between groups. The FEV<sub>1</sub> and FEV<sub>1</sub> % predicted were respectively 0.87 liters and 30% in the Zephyr EBV group and 0.84 liters and 30% in the Control group. These baseline characteristics reflect severe emphysema and are consistent with GOLD Stage III (Severe) and GOLD Stage IV (Very Severe) stages of COPD.<sup>4</sup>

**Procedural Results**

The target lobe for Zephyr EBV insertion was determined by pre-procedural imaging and was predominantly upper lobe (77%) and on the right (62%). Mean procedure duration was an average of 34 minutes (median 28 minutes) with an average of 3.8 valves (median 4, range 1-9) inserted per Zephyr EBV subject. Acute procedural success based on the investigator's assessment of complete exclusion of the target lobe at the end of the procedure was 95%. Successful intra-procedural removal and replacement of deployed valves was common and seen in 45% of Zephyr EBV subjects indicating the ease with which the valves could be repositioned immediately after deployment.

**Efficacy**

As expected, FEV<sub>1</sub> and 6MWT deteriorated for the Control Subjects. Even with this progressive, chronic disease, Zephyr EBV Subjects improved in both outcomes. The Zephyr EBV Treatment response is in addition to optimal medical management and rigorous pre-baseline pulmonary rehabilitation.

The co-primary efficacy endpoints were analyzed using the intent-to-treat (ITT) population with multiple imputation for missing data. The VENT Pivotal Trial met its co-primary efficacy endpoints. The difference in percent changes in FEV<sub>1</sub> and 6MWT from baseline to 6 months in the ITT analyses were both significantly greater in the Zephyr EBV group compared to the Control group (+6.8%,  $p=0.002$  and +5.8%,  $p=0.019$  respectively), see Table 2.

The four secondary effectiveness endpoints were also analyzed using the ITT population. These included St. Georges Respiratory Questionnaire, Modified Medical Research Council Dyspnea Scale, maximum exercise capacity by cycle ergometry and supplemental oxygen use. These endpoints are important to both the patient and physician because they represent clinical parameters reflective of the patient's overall well-being. Additionally, these measures serve as potential confirmatory signals to the findings of the primary endpoints. In

the VENT Pivotal Trial, the Zephyr EBV group demonstrated significantly better outcomes compared to the Control group at 6 months for all four secondary endpoints in the ITT population. The difference between the Zephyr EBV group and the Control group was -3.4 points for SGRQ (p=0.017), -0.26 points for mMRC (p=0.018), +3.8 watts for cycle ergometry (p=0.020) and -12.0 liters per day for supplemental oxygen use (p=0.020) (see Table 2).

**Table 2 Primary and Secondary Effectiveness Endpoint Results - ITT (6 months)**

	Delta	p value
<b>Primary Endpoints</b>		
FEV <sub>1</sub>	6.8%	<b>0.002</b>
6MWT	5.8%	<b>0.019</b>
<b>Secondary Endpoints</b>		
SGRQ (points)	-3.4	<b>0.017</b>
mMRC (points)	-0.26	<b>0.018</b>
Cycle Ergometry (watts)	3.8	<b>0.020</b>
Supplemental Oxygen (liters / day)	-12.0	<b>0.020</b>

The ITT co-primary efficacy results were confirmed in the Completed Cases analysis without imputation for missing data. The difference in percent change in FEV<sub>1</sub> and 6MWT from baseline to 6 months in the Completed Cases analysis were both significantly greater in the Zephyr EBV group compared to the Control group (+7.2%, p<0.001 and +5.8%, p=0.008 respectively), (see Table 3)

**Table 3 Primary Effectiveness Endpoint Results – Completed Cases (6 months)**

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

<sup>1</sup> Difference of means and unequal variance t-test confidence interval

<sup>2</sup> One-sided unequal variance t-test

<sup>3</sup> Difference of medians and non-parametric confidence interval

<sup>4</sup> One-sided Wilcoxon rank-sum test

Secondary effectiveness endpoints were also analyzed by Completed Cases without imputation for missing data. The Zephyr EBV group demonstrated significantly better outcomes compared to the Control group at 6 months in three of the four secondary measures (see Table 4).

**Table 4 Secondary Effectiveness Endpoint Results – Completed Cases (6 months)**

	<b>Zephyr EBV Mean (SD) N Median (Min, Max)</b>	<b>Control Mean (SD) N Median (Min, Max)</b>	<b>Delta (95% CI)</b>	<b>p value</b>
<b>SGRQ (points)</b>	-2.7 (13.3) 158 -2.2 (-35.9, 55.0)	0.7 (9.7) 62 1.5 (-25.8, 27.9)	-3.4 <sup>1</sup> (-6.6, -0.2)	<b>0.019<sup>2</sup></b>
<b>mMRC (points)</b>	-0.09 (1.04) 162 0.00 (-3.00, 3.00)	0.21 (0.83) 67 0.00 (-2.00, 2.00)	-0.30 <sup>1</sup> (-0.56, -0.05)	<b>0.011<sup>2</sup></b>
<b>Cycle Ergometry (watts)</b>	0.1 (15.3) 166 0.0 (-110.0, 50.0)	-4.4 (12.8) 69 -5.0 (-40.0, 45.0)	5.0 <sup>3</sup> (0.0, 5.0)	<b>0.004<sup>4</sup></b>
<b>Supplemental Oxygen (liters/day)</b>	-17.1 (912.8) 171 0.0 (-3840.0, 3750.0)	82.9 (744.0) 75 0.0 (-2220.0, 3360.0)	-100.1 <sup>1</sup> (-318.6, 118.4)	0.184 <sup>2</sup>

<sup>1</sup> Difference of means and unequal variance t-test confidence interval

<sup>2</sup> One-sided unequal variance t-test

<sup>3</sup> Difference of medians and non-parametric interval

<sup>4</sup> One-sided Wilcoxon rank-sum test

Additionally, there was a statistically significant improvement in the multidimensional BODE index with a -0.53 mean point difference between the Zephyr EBV group and the Control group at 6 months (p=0.002)

The HRCT assessment of volume redistribution demonstrated a statistically significant reduction in target lobe volume and the attendant increases in adjacent non-target lobe volumes (see Table 5). These results demonstrate the achievement of the hypothesized mechanism of target lobe volume reduction and expansion of the healthier adjacent lobe.

**Table 5 Volume Redistribution Results – Completed Cases (6 Months)**

<b>Change from Baseline</b>	<b>Zephyr EBV Mean (N)</b>	<b>Control Mean (N)</b>	<b>Delta<sup>1</sup></b>	<b>p value<sup>2</sup></b>
Target Lobe Volume Change (mL)	-378.4 (189)	-16.3 (79)	-362.1	<b>&lt; 0.001</b>
Ipsilateral Non-Target Lobe Volume Change at TLC (mL)	207.7 (189)	-35.4 (79)	243.1	<b>&lt;0.001</b>

<sup>1</sup> Difference of means

<sup>2</sup> One-sided unequal variance t-test

A pre-specified analytic plan was also used to identify and further define clinically plausible subgroups that had a greater response to Zephyr EBV treatment. Zephyr EBV subjects (Completed Cases) with greater disease distribution heterogeneity (high heterogeneity) were found to experience even greater improvements in FEV<sub>1</sub> and 6MWT at 6 months (+12.3%, p<0.001 and +14.4%, p<0.001 respectively). Zephyr EBV subjects (Completed Cases) with complete fissures separating the target lobe from adjacent pulmonary parenchyma were also

found to experience greater target lobe volume reduction and redistribution and greater percent improvements in FEV<sub>1</sub> at 6 months (+16.2%, p<0.001). Both disease distribution heterogeneity and fissure integrity were assessed by an independent Core Radiology Lab based on high resolution computed tomography (HRCT). Both HRCT characteristics can be utilized during patient screening to facilitate proper patient selection and treatment targeting.

## **Safety**

The primary safety endpoint of the VENT Pivotal Trial was the proportion of subjects at six months experiencing one or more events included in a pre-defined Major Complications Composite (MCC). This composite consisted of all cause death, empyema, massive hemoptysis, pneumonia distal to the Zephyr EBV, pneumothorax or prolonged air leak > 7 days, and respiratory failure requiring mechanical ventilation > 24 hours. As was expected, at six months the Zephyr EBV group showed a trend toward more MCCs compared to the Control group (6.1% vs. 1.2%; p=0.075) (see Table 6). The difference was not statistically significant. Such a difference was expected given that the Control group received medical management and did not receive bronchoscopic intervention with its attendant procedural complications. However, during the six to twelve months follow-up period, MCC rates were equivalent between the Zephyr EBV (4.7%) and Control (4.6%) group (p=1.000). Cumulatively at one year, the overall MCC rates were not statistically different between the Zephyr EBV (10.4%) and Control (4.6%) group (p=0.172), and in a Cox regression model Zephyr EBV treatment was not significantly associated with MCC at six months (p=0.144).

At six months, death occurred in 2.8% of Zephyr EBV Subjects and in no Control Subjects (p = 0.187). Only one of the deaths was determined to be possibly or probably device-related. In the second six months of follow-up, death occurred in 0.9% of Zephyr EBV Subjects and in 3.5% of Control Subjects (p = 0.147). The cumulative mortality rate over the one year of follow-up was 3.7% for Zephyr EBV and 3.5% for Control (p = 1.000).

**Table 6 Per-Subject Major Complications Composite**

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

Additional safety analyses were performed to fully characterize the safety profile of the Zephyr EBV system. Use of the Zephyr EBV was associated with an increased rate of emphysema-related adverse events, hemoptysis, non-cardiac chest pain and rehospitalization through one year follow-up compared to the Control group. As with MCC, these complications diminished with time.

Adverse events specific to the Zephyr EBV included valve migration, pneumonia distal to the valve, and granulation tissue. Based on bronchoscopic and HRCT review, both migration and granulation tissue formation most commonly resulted from improper placement of Zephyr EBVs in the target bronchi. Based on these assessments, a depth marker band was developed and implemented to complement the diameter gauge on the Zephyr Delivery Catheter. The depth marker, accompanied by a training program, is intended to mitigate the risk and reduce the occurrence of these adverse events. Despite these device-specific complications, the primary safety endpoint of the VENT Pivotal Trial (MCC) was not statistically different between groups at both its pre-specified six and 12 month time frames.

Zephyr EBV devices (85/820, 10.4%) were removed from thirty-one subjects with a 98% success rate during the follow-up period either due to persistent adverse events or from subjects that did not receive a clinical benefit. After removal, subjects were able to undergo additional procedures, including LVRS or lung biopsy. This provides evidence that the Zephyr EBV is removable and maintains therapeutic and diagnostic options.

## Conclusions

By meeting its primary endpoints, the VENT Pivotal Trial has demonstrated the safety and effectiveness of the Zephyr EBV device compared to randomized controls in treating subjects with severe heterogeneous emphysema. Additionally, positive results for the secondary efficacy endpoints involving multiple quality of life and health indices confirm the clinical significance of the primary efficacy endpoint results. The Zephyr EBV was demonstrated to effectively achieve target lobe volume reduction and redistribution, which were strongly correlated to improvements in lung function.

Clinically plausible subgroups that had a greater response to Zephyr EBV treatment were identified. The HRCT characteristics that define these groups can be utilized to screen and select appropriate patients and to guide proper treatment targeting.

The equivalent one year survival rates coupled with the tendency of observed adverse events to diminish over time to levels commensurate with the Control group suggest an acceptable safety profile. This safety profile is further enhanced by the potential removability of the device.

Taken together, the risk-to-benefit profile for the Zephyr EBV device compares favorably to medical management and more invasive and rarely used treatments such as lung transplantation and LVRS. In a patient population faced with a progressive terminal disease with few existing treatment options, Zephyr EBV therapy has been shown to improve lung function, exercise tolerance and quality of life for patients suffering from this devastating disease, thus providing physicians with a new option in the continuum of care for patients with advanced emphysema.

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<sup>1</sup> Trends in COPD (Chronic Bronchitis and Emphysema) Morbidity and Mortality: American Lung Association; 2007: December 2007

<sup>2</sup> Ingenix Report, 2006 Medicare MEDPAR database, ICD-9-CM Procedure Code 32.22

<sup>3</sup> Scirba FC. Early and Long-Term Functional Outcomes Following Lung Volume Reduction Surgery. Clin Chest Med 1997;18:259-76

<sup>4</sup> Global Initiative for Chronic Obstructive Lung Disease (GOLD): NHLBI/WHO Workshop Report; 2006.