FDA Executive Summary

P070025

Emphasys Medical, Incorporated

Emphasys Zephyr Endobronchial Valve System

Anesthesiology and Respiratory Therapy Devices Panel

December 5, 2008

INTRODUCTION

The subject of this Executive Summary is a first-of-a-kind device, Emphasys Zephyr Endobronchial Valve System premarket approval (PMA, P070025) application. The sterile, single use system consists of the valve, valve loader, and a delivery device. The valve consists of an implantable one-way, silicone, duckbill valve mounted in a self-expanding nitinol stent structure that is covered with a silicone membrane. It is implanted in the bronchial lumen via a working channel of a standard bronchoscope using a proprietary delivery system. Once implanted, the one-way valve is intended to prevent air flow into the hyperinflated regions of the lung distal to the valve, while allowing air flow out of the hyperinflated regions, to result in improved FEV_1 and 6 minute walk test distance in patients with severe heterogeneous emphysema.

This PMA has been reviewed by the Anesthesiology and Respiratory Devices Branch of the Division of Anesthesiology, General Hospital, Infection Control, and Dental Devices at the Center for Devices and Radiological Health of the Food and Drug Administration. Your time and effort in review of this application are greatly appreciated.

This summary includes five sections:

1. The first section describes our rationale for presenting this PMA to the advisory panel. It also presents the issues facing the FDA with respect to the interpretation of the clinical data and its statistical analysis.

2. The second section describes the device, Indications for Use proposed by the applicant, and the regulatory history of the device.

3. The third section briefly describes the preclinical studies.

4. The fourth section provides a summary of the clinical study protocol, patient outcomes, and statistical analyses presented in the PMA in support of the safety and effectiveness of the device.

5. The fifth section presents the proposed post-approval study plan.

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1. Rationale for Presentation to Panel

This PMA application for Emphasys Zephyr Endobronchial Valve System is the first-of-a-kind device for the treatment of severe heterogeneous emphysema to undergo FDA review.

FDA is seeking input from the panel regarding the following:

1. The interpretability and validity of the statistical results in light of the protocol violations and missing data;

2. Whether the data presented provide reasonable assurance that the device is safe and effective for its intended use;

3. Discussion regarding risk versus benefit for the indication sought;

4. Whether the labeling sufficiently identifies the appropriate patient population and warnings/precautions/contraindications, and adequately describes a validated method of target lobe identification; and

5. Whether the proposed Post-Approval Study protocols are adequate for extended follow-up of premarket and post-market cohorts.

2. Background Information

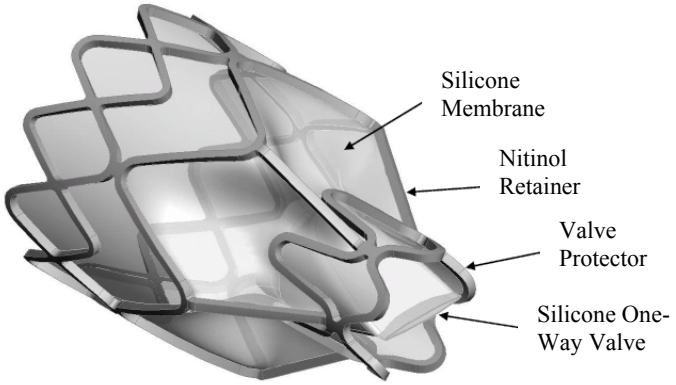
2.1 Indications for Use

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

2.2 Device Description

The Zephyr EBV System is a sterile, single use system consisting of the Zephyr EBV (valve), Zephyr ELS (loader system), and Zephyr EDC (delivery catheter). The valve is an implantable one-way, silicone, duckbill valve mounted in a self-expanding nitinol stent structure that is covered with a silicone membrane as shown in the figure below. Once implanted in the bronchial lumen, the one-way valve is intended to prevent air flow into the hyperinflated regions of the lung distal to the valve, while allowing air flow out of the hyperinflated regions.

Figure 1. Schematic of the Zephyr EBV



The valve is packaged within a loader system for loading the compressed valve into the housing located at the distal end of the delivery catheter just prior to use. The valve is placed in the bronchial lumen using the delivery catheter passed through a bronchoscope with a working channel diameter of 2.8 mm or greater. The delivery catheter housing features a diameter gauge that allows the operator to visually assess the caliber of the target bronchus and a minimum depth gauge marker that allows the operator to insure adequate bronchial wall contact length with the valve.

The Zephyr EBV System is available in two sizes as follows:

Table 1. Available Sizes of the Zephyr EBV System

Valve with Loader	Target Bronchial Diameters	Length
Zephyr 4.0 EBV	4.0 – 7.0 mm	13.0 mm
Zephyr 5.5 EBV	5.5 – 8.5 mm	14.5 mm
Delivery Catheter	Housing Diameter	Usable Length
Zephyr 4.0 and 5.0 EDC	2.5 mm	76 mm

2.3 Regulatory History

The complete Premarket Approval (PMA) application was received by FDA on September 21, 2007, and was assigned to the Anesthesiology and Respiratory Devices Branch of the Division of Anesthesiology, General Hospital, Infection Control, and Dental Devices for review. Four amendments were received to the PMA in response to FDA questions.

2.4 Previous Advisory Panel Recommendations

On February 28, 2003, a General and Plastic Surgery Devices Panel committee meeting was held. One of the general issues discussed was clinical trial design

for devices intended to treat emphysema. At this meeting, the panel made the following four recommendations:

(i) The trials should include only patients who are candidates for no other procedures or those who have refused other treatments. All patients should have received optimized medical treatment for 3 to 6 months before enrollment. Lung volume reduction surgical patients are not the appropriate control group, and comparisons should be made to patients receiving optimized medical treatment in multi-centered studies.
(ii) Safety analyses should include an assessment of deaths, bleeding, mechanical ventilation, pneumonia, air leaks, hospital days, re-operations, respiratory failure, decreases in FEV_1, 3, 6, 9, and 12 month assessments of device positioning, ease of device removal, COPD exacerbations, intubations, bleeding, and a tabulation of patients who were discontinued due to a lack of benefit.
(iii) Effectiveness determinations should include exercise capacity (increase of 10 Watts), 6 minute walk test, St George's Quality of Life Assessment, spirometry (FEV1 increase of 12 to 15%), decrease in oxygen consumption, and increase in length of life.
(iv) The duration of follow-up should continue for at least 6 months for effectiveness and at least 1 year for safety.

3. Preclinical Study Information

The sponsor conducted *in vitro and in vivo* performance and characterization studies of the Zephyr EBV System. Test results demonstrated that the device is compliant with FDA recognized international standards for biocompatibility. Packaging and sterilization processes were validated according to FDA recognized international standards as well. Engineering questions remain regarding the Zephyr EBV fatigue tests. However, FDA is working interactively with the sponsor to resolve these questions. FDA does not believe that these open issues require consideration by the Anesthesiology and Respiratory Therapy Devices Panel at this time.

4. Clinical Studies

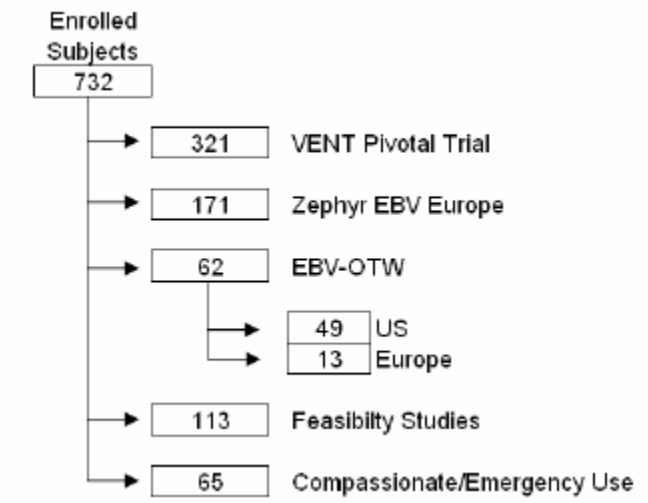
4.1 Study Description

Study Design
The VENT (Endobronchial Valve for Emphysema PalliatioN Trial) Pivotal Trial is an open-label, prospective, randomized, multi-center trial of the Zephyr EBV compared to optimal medical management controls.

Sample Size

The IDE for the VENT pivotal trial was approved for an enrollment of up to 370 subjects (control and treatment). In total, the sponsor enrolled 321 subjects into the VENT pivotal trial at 31 investigational sites in the U.S. between December 2004 and April 2006 using the Zephyr EBV System. This represents the main dataset in support of this PMA application. A total of 732 subjects were enrolled in all of the various studies of the EBV system, as seen in Figure 2.

Figure 2. Subject Enrollment in EBV Studies



"EBV-OTW" refers to studies of the original EBV-OTW or "Over-the-Wire" device which was subsequently modified to the current Zephyr EBV design. Sixty two (62) patients were enrolled in the EBV-OTW study. The enrollment for both the US (VENT Pivotal Trial) and European (Zephyr EBV Europe) studies was reset with the introduction of the Zephyr EBV System such that these studies include the Zephyr EBV device design only.

After the collection of the data and before the original PMA submission, the sponsor and the FDA agreed not to pool the US and European data, as was originally planned, due to potential differences in patient selection, diagnosis, patient demographic characteristics, and covariates. Instead, the sponsor agreed to submit descriptive data from the smaller European study, separate from the US data.

Study Entry Criteria

In the VENT pivotal trial, subjects were evaluated prior to randomization to determine whether they met inclusion criteria and to assess parameters to be used in the randomization scheme. All subjects received optimal medical management including pulmonary rehabilitation and then were randomized to either Zephyr EBV Treatment or a medical Control Group. The Zephyr EBV Treatment group received valve treatment of one targeted lobe (lobar, segmental, or subsegmental

bronchi) to achieve complete lobar exclusion followed by optimal medical management. The Control group received optimal medical management alone.

The study population consisted of subjects with severe heterogeneous emphysema as defined by the major inclusion and exclusion criteria as follows:

Table 2. Major Inclusion and Exclusion Criteria

Inclusion Criteria	**Exclusion Criteria**
40-75 years of age	Homogeneous emphysema
FEV_1 <45% predicted	Large bullae in a non-target lobe
TLC > 100% predicted	FEV_1 < 15% predicted
RV > 150% predicted	DLCO < 20% predicted
Eligible heterogeneous emphysema by HRCT Core Laboratory assessment*	

*Proprietary, non- commercially available method.

The determination of heterogeneous versus homogeneous emphysema was based on a "HRCT Core Laboratory Assessment", a high resolution computed tomography (HRCT) assessment that uses proprietary, non-commercially available software.

Randomization

Patients were randomized in a 2:1 ratio (treatment to control). Randomization was further stratified into the following four groups based on target lobe identification by HRCT Core Laboratory Assessment (see above) and exercise capacity judged by cycle ergometry:

- Upper lobe, low exercise tolerance
- Upper lobe, non-low exercise tolerance
- Lower lobe, low exercise tolerance
- Lower lobe, non-low exercise tolerance.

The intent of the stratification scheme was to assess variables similar to those found to be significant in lung volume reduction surgery (LVRS).

Patient Follow-Up

Patients who received the investigational treatment had hospital visits within 24 hours, in 2-3 days, and 7-10 days. Control patients and treatment patients that had already been discharged from the hospital received phone calls at 2-3 days and 7-10 days. All patients returned for follow-up at 1 month, 3 months, 6 months and 1 year. The visit at which the primary endpoint was measured, 6 months, had a window of +/- 14 days. The extended window of -30/+45 days at 6-months that the sponsor proposed in their PMA submission was not pre-specified in the VENT Pivotal Trial.

Masking

There was no blinding of either subjects or investigators.

The panel will be asked to consider the lack of blinding in the study and its potential effect on the interpretation of the pivotal study results.

4.2 Study Endpoints

Primary Effectiveness Endpoints

The primary effectiveness endpoints were at 6 months. FDA also requested that the sponsor collect all effectiveness data through 12 months.

The two co-primary effectiveness endpoints were:

- Mean percentage change from baseline in Forced Expiratory Volume in one second (FEV_1) at 6 months, and
- Mean percentage change from baseline in 6 minute walk test (6MWT) at 6 months.

Primary and secondary effectiveness endpoints (see below for description of secondary endpoints) were tested with a one-sided superiority test with a significance level of 0.025 on an Intent to Treat (ITT) population, defined as all patients randomized to either the control or treatment arms with imputation of missing values (n=321). Any missing values were imputed using the method described in the Primary Endpoint Populations under section 4.3 VENT Pivotal Trials below. The study was designed to show a statistically-significant difference between treatment arms and powered to show a difference between the treatment and control based on a clinically meaningful difference of 15% for each of the co-primary endpoints, FEV_1 and 6MWT.

The sponsor also pre-specified two additional effectiveness populations, the Completed Cases (CC) population (approx. n=254, depending on the endpoint) and the Per Protocol (PP) population (approx. n=198, depending on the endpoint). The Completed Cases (CC) population included all patients that had a visit at the planned time point (6 months or 12 months). Although the "extended window" visits were out of the pre-specified endpoint window and not agreed upon by FDA, the sponsor included these patients in the CC analysis. The CC population did not include patients that died or missed a visit for any reason. The CC population did include patients that violated the protocol, including patients that failed to meet the inclusion/exclusion criteria.

The Per Protocol (PP) population included all patients that had a visit at the planned time point (6 or 12 months) that did not have any major protocol violations. The only protocol violations that were deemed to be major were violations of the inclusion/exclusion criteria and use of certain medicines that were not part of the protocol. The PP analysis included patients who did not have a visit in the pre-specified window, but who had one visit in the *post hoc* defined "extended window".

Secondary Effectiveness Endpoints

- Mean absolute change from baseline in St George's Respiratory Questionnaire (SGRQ) score.
- Mean absolute change from baseline in the modified Medical Research Council score (mMRC).
- Mean absolute change from baseline in the maximum exercise capacity (watts) by cycle ergometry.
- Mean absolute change from baseline in supplemental oxygen use (liters/day).

Additional Effectiveness Measures

The protocol stated that the following analyses "will be considered exploratory and will not be used for labeling claims":

- Proportion of patients achieving ≥ 15% improvement in FEV_1 at 6 months
- Proportion of patients achieving ≥ 15% improvement in 6MWT at 6 months
- Proportion of patients achieving ≥ 0% improvement in FEV_1 at 6 months
- Proportion of patients achieving ≥ 0% improvement in 6MWT at 6 months
- Technical, procedural, and clinical success rates as assessed by HRCT at 6 months (termed image success)
- Mean absolute change in the Quality of Well Being Scale (QWB)
- Mean percentage change in residual volume (RV)
- Mean percentage change in diffusing capacity (DLCO)
- Mean absolute change in BODE index (i.e., a composite of **b**ody mass index, **o**bstructive airflow as measured by percent predicted FEV_1, **d**yspnea as measured by the mMRC Dyspnea Scale and **e**xercise capacity as measured by the 6MWT)
- Airflow Obstruction, Dyspnea and Exercise Capacity index.
- Mean absolute per patient change in supplemental oxygen use
- Borg dyspnea score

Additional Effectiveness Analyses of the Primary Endpoints

The Statistical Analysis Plan proposed the testing of multiple potential covariates "to determine if specific subsets of the independent variables can be useful in predicting dependent variable." No correction was proposed for multiplicity and no specific independent variables were defined.

Primary Safety Analysis

The primary safety endpoint at 6 months was the Major Complications Composite (MCC), which included death, empyema, massive hemoptysis, pneumonia distal to a valve, and pneumothorax or prolonged air leak. The sponsor proposed, as a success criterion for the MCC, a 30% delta compared to the control group in a modified Intent to Treat (mITT) analysis. The mITT was defined as all randomized patients who received study-directed treatment (Zephyr EBV or control) and had any follow-up.

FDA did not agree with the success criterion for MCC, as it was based on the lung volume reduction surgery study and 30% was believed to be too large. FDA informed the sponsor that an *a priori* decision could not be made regarding the MCC delta, and that FDA intended to evaluate complications in the Zephyr EBV and Control groups when assessing the safety and effectiveness of the device. Therefore, no success criterion for the primary safety endpoint was agreed upon with FDA.

Secondary Safety Analysis

- Survival through one year follow-up
- A composite of death, LVRS, or lung transplantation through one year
- The proportion of subjects hospitalized
- Hospitalization rate.

4.3 VENT Pivotal Trial Results

Patient Accountability, Protocol Violations, and Missing Data

- A total of 2,492 protocol violations were observed during the conduct of this clinical investigation. The majority of these violations were minor and occurred in a variety of different areas, such as visits and tests performed outside of the protocol window.

- The major protocol violations included not meeting inclusion/exclusion criteria and medication noncompliance. In the primary ITT analysis population, 62 out of 321 subjects (19.3%) did not meet the inclusion/exclusion criteria, mainly because of failure to meet plethysmography criteria. An additional 9/321 (2.8%) used medications that were not in compliance with the protocol.

- The Per Protocol (PP) population was a pre-specified effectiveness analysis population. The only difference between the PP population and the Completed Cases (CC) population was that the latter included the major protocol violators. In all of the primary and secondary endpoints, except for SGRQ, the point estimate for the difference between the Zephyr EBV and control groups was larger in the CC population than in the PP. It should also be noted that the 6MWT endpoint and the four secondary endpoints were not statistically significant in the PP population.

- Withdrawals were proportionally higher in the control than the Zephyr EBV group.

Table 3. Withdrawals at 6 and 12 Months

Time	**Control**	**Zephyr EBV**	***p*-value**
6 month	8 (7.9%)	9 (4.1%)	Not provided
12 month	9 (8.9%)	12 (5.5%)	Not provided

- Missing Data: Table 4 shows the number of Zephyr EBV and control subjects that came in for 6 month and 12 month visits. The 6 month visit had a pre-specified window of +/- 14 days, and the 1 year visit had a pre-specified window of +/- 30 days. Due to a large number of patients who were not seen in the pre-specified window, the sponsor extended the 6- and 12-month windows at the time of analysis to -30/+45 days and +/-60 days, respectively. Thus the *post-hoc* 6-month and 12-month extended windows ranged from 150-225 days and 305-425 days, respectively. Data using the pre-specified, agreed-upon windows were not provided. Data were missing in over 19% of patients based on the *post-hoc* extended windows. Data were missing in over 35% of patients in the pre-specified windows.

Table 4. Subject Accountability

	Control Subjects		**Zephyr EBV Subjects**	
	6 Month Visit	1 Year Visit	6 Month Visit	1 Year Visit
Enrolled	101	101	220	220
Died	0 (0%)	3 (3.0%)	6 (2.7%)	8 (3.6%)
Visit in Window	59 (58.4%)	70 (69.3%)	135 (61.4%)	148 (67.3%)
Visit in Extended Window	16 (15.8%)	5 (5.0%)	37 (16.8%)	30 (13.6%)
Visit Beyond Window	4 (4.0%)	1 (1.0%)	21 (9.5%)	6 (2.7%)
Withdrawn	8 (7.9%)	9 (8.9%)	9 (4.1%)	12 (5.5%)
No Visit	14 (13.9%)	13 (13.9%)	12 (5.5%)	16 (7.3%)

The panel will be asked to comment and/or take into account the number of missing values and the effect of the relevant protocol violations in the analysis populations in the review of the pivotal study results.

Patient Demographics

There were no significant differences in demographics between the Zephyr EBV treated and Control groups. Major parameters were:

- Mean age 65 years
- Slight male predominance in Zephyr EBV group (60.5% male in treatment group versus 48.5% in the control group)
- Mean FEV_1 30% predicted
- Mean 6MWT 333.9 m Zephyr EBV, 350.9 m Control
- Mean cycle ergometry 45 watts Zephyr EBV, 43.2 watts Control
- Mean O_2 saturation 93%

The randomization for the study was stratified based on exercise tolerance (high/low) and lobe (upper/lower) because a prior study for lung resection found that treatment was most effective in the upper lobe in patients with low exercise tolerance. Of the patients in the VENT pivotal trial with upper lobe/low exercise tolerance, 74.7% were randomized to the treatment and 25.3% were randomized to the control.

Targeted Lobes

The right upper lobe (RUL) was targeted in the majority of cases. Upper lobes (left or right) were treated in 76.6%. The middle lobe was not targeted. The targeted lobe distribution was as follows:

Table 5. Lobar Distribution of Implanted Valves

RUL 52.3%	**LUL*** 24.3%
RLL 9.3%	**LLL** 14.0%

*Including Lingula

A mean of 3.8 valves were implanted per patient with a median of 4 and a range of 1 to 9 valves. Valves were inserted in the targeted lobes based on the HRCT Core Laboratory algorithm. There was no protocol specification for the number of valves implanted per patient.

Acute Technical Success

Valves were placed in 214 patients. Acute Technical Success, defined as complete exclusion of the target lobe as assessed by the bronchoscopist at the end of the procedure, was 95%. Intraprocedural valve removal information was as follows:

- 45% of subjects had one or more valves removed or replaced.
- 8% (11/143) of valve removals were related to problems with valve deployments.
- The majority of removals were related to valve size and position.

Device Malfunctions

- There were device malfunctions in 10% (21/214) of procedures.
- Almost half (10) were device loading failures
- One was reported as a device malfunction, but was a perforation of the bronchial wall by the delivery catheter with no known device defect
- Nine others were deployment or delivery failures

Primary Endpoint Populations

According to the statistical analysis protocol, the primary analysis was to be on the Intent to Treat (ITT) population. This consisted of 220 subjects randomized to Zephyr EBV treatment group and 101 to the Control group.

The sponsor's imputation method was as follows:

- If a patient had a visit anywhere within the *post-hoc* defined extended window (150-225 days), use the FEV_1 or 6MWT value.
- If a subject died before the end of the extended 6 month window (<225 days), assign that subject the lowest observed FEV_1 or 6MWT value in that treatment group.
- If a patient had visits before and after the extended window, interpolate the FEV_1 value by averaging the before and after visits. Interpolation was not done for the 6MWT, because the trend in 6MWT was not linear.

- If a patient was too sick to attend the 6 month visit, the patient was assigned a 0% improvement.
- For all remaining patients, imputation was done by regression. From the Completed Case (CC) analysis of the 6- month data for each endpoint, the interactions were used to form subgroups and the main effects were used as covariates in the analysis with the baseline value of FEV_1 or 6MWT always included in the model. The linear regressions were done within each subgroup, and the coefficients that remained statistically significant were used to derive an equation for the linear function. For example, for180-day FEV_1, the subgroups were Treatment Group (TRT), Heterogeneity Score (blipsidshettlc[1] - 2 classes), and Fissure Score (fisscore). The main effect covariates were baseline FEV_1, and baseline $PaCO_2$. Using this method, a total of 1002 random imputations were performed. For FEV_1 a parametric test statistic was calculated, and for 6MWT a non-parametric test statistic was calculated. Then these 1002 test statistics were averaged to calculate the *p*-values and confidence intervals.

The modified Intent to Treat (m-ITT) population used in the evaluation of the Primary Safety Endpoint was defined as all randomized patients who received study-directed treatment (Zephyr EBV or Control) and had any follow-up.

The panel will be asked to comment on the interpretation of the statistical results, in light of the missing values imputed for the ITT population.

Additional Endpoint Populations

The statistical analysis plan stated that secondary analyses were to be performed on a Completed Cases (CC) and Per Protocol (PP) basis. The CC population was defined as all randomized and eligible patients who received study-directed treatment (Zephyr EBV or control) and had 6 months of follow-up. The PP population was defined as all randomized patients entirely consistent with the protocol (except for minor protocol violations) and who received study-directed treatment and had 6 months of follow-up.

Table 6. Number of Patients in Analysis Populations.

Population	**ITT** n (%)	**CC** n (%)*	**PP** n (%)*	**m-ITT**
Control				87 (86%)
FEV_1	101 (100%)	75 (74%)	57 (56%)	
6MWT	101 (100%)	73 (72%)	57 (56%)	
Zephyr EBV				214 (97%)
FEV_1	220 (100%)	179 (81%)	141 (64%)	
6MWT	220 (100%)	178 (81%)	140 (64%)	

*Note: CC and PP analyses include *post-hoc* defined "extended window" patients

[1] Baseline Ipsilateral Destruction (or Density) Score Heterogeneity Total Lung Capacity

Data Pooling and Analyses by Site

Data were collected on 321 patients at 31 sites. Due to the large number of sites relative to the number of patients, especially given the 2:1 randomization ratio, the sample sizes in each of the sites were not large enough to draw any conclusions as to whether the effectiveness of the treatment varies from site to site.

Primary Effectiveness Endpoints

The study was designed to show a pre-specified clinical difference between the ITT treatment and control arms of 15% for co-primary endpoints, FEV_1 and 6MWT, (G020230/S004) and as recommended by the General and Plastic Surgery Devices Panel on February 28, 2003. The 15% clinically significant response for an individual was used along with pilot study results to power the trial.[2] In general, it is important to note the confidence intervals to recognize the size of the difference between the treatment and control groups (see below).

Differences achieved between the Zephyr EBV treatment and control groups at 6 months in the ITT population were as follows:

- Delta percent change in FEV_1 of 6.8% (CI 2.1, 11.5; $p = 0.002$)
- Delta percent change in 6MWT of 5.8% (CI 0.5, 11.2; $p = 0.019$)

Below are the results for both co-primary endpoints in all 3 populations at 6 months and additional results from 12 months. Table 7 presents the point estimate and the 95% confidence interval (CI) for the difference between the two groups and marks with an asterisk those results deemed statistically significant.

Table 7. Difference in the Effectiveness Endpoints between Control and Zephyr EBV groups with 95% CI at 6 and 12 months.

Primary Endpoints	**ITT 6 Months**	**CC 6 Months**	**PP 6 Months**	**ITT 12 Months**	**CC 12 Months**	**PP 12 Months**
FEV_1	6.8%* (2.1,11.5)	7.2%* (3.2,11.2)	7.0%* (2.7,11.3)	7.7%* (2.6,12.7)	8.1%* (4.0,12.2)	7.0%* (2.6,11.4)
6MWT	5.8%* (0.5,11.2)	5.8%* (1.3, 11.7)	4.1% (-1.0,10.9)	3.8% (-1.4, 9.0)	3.6% (-1.9, 9.1)	2.8% (-2.8, 8.3)

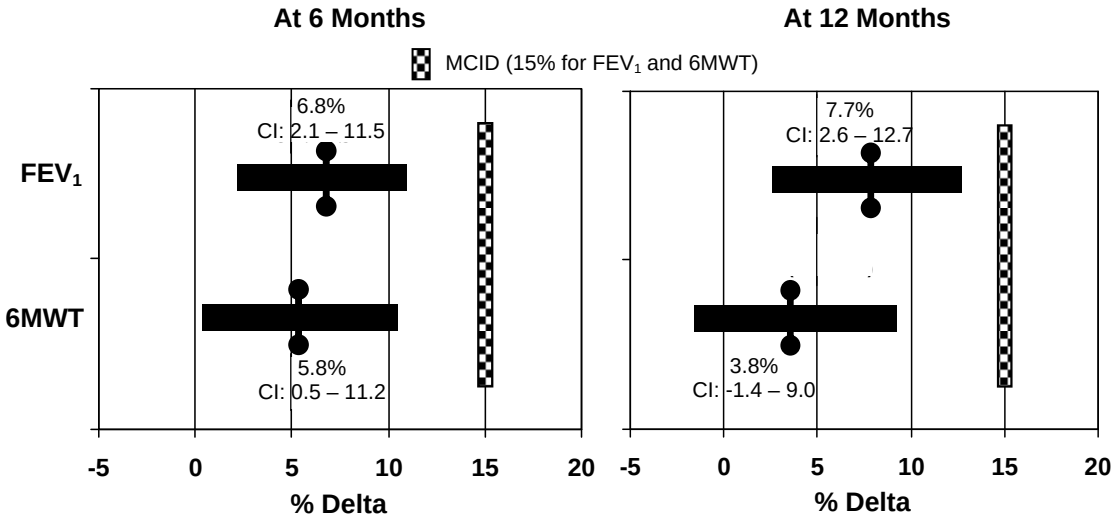
The pre-specified co-primary endpoint was in the ITT population at 6 months. There was a finding of statistically significant differences between the Zephyr EBV and control populations for both co-primary endpoints at 6 months in this population. However, the Zephyr EBV devices are not removed at 6 months

[2] Per protocol 630-0001-J (October 22, 2004) page 3 – "The sample size has been 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 180 days. The 15% improvement in FEV_1 is a clinically significant difference based on the ATS upper threshold bronchodilator response for FEV_1 of 12% - 15%. For the 6MWT, Redelmeier et al considers a 15% improvement (54 meters in an average 371 meters baseline cohort from baseline to be clinically meaningful. A 17% change in 6MWT was selected for detection because it is between the clinically meaningful threshold (15%) and the 6MWT historical results (20.4%)."

and can be permanently left in the patients. Therefore, the duration of the primary endpoint effects was also important to examine. Additional analyses showed that at 3 and 12 months, the Zephyr EBV group was not statistically better than the control group (data not shown) with regards to the 6MWT in any of the three patient populations, but statistically significant for FEV_1.

Due to the expected variation in testing over time, the minimum clinically important difference (MCID) per patient for FEV_1 recognized by the American Thoracic Society/European Respiratory Society Taskforce on Standardisation of Pulmonary Function Testing is > **15%** for yearly testing (*Eur Resp Journal* 2005; 26: 948-968). For 6MWT, a mean improvement in individual subjects with chronic obstructive pulmonary disease (COPD) is reported to be 53 m from a mean baseline of 371 meters (Redelmeir et al. *Am J Respir Crit Care Med* 1997; 155: 1278-1282.). The results summarized in Table 7 show that the average changes in the co-primary endpoints do not meet recognized MCID values for COPD at 6 months or 12 months.

Figure 3. Co-Primary Effectiveness Endpoint Results in the ITT Population



In summary, an analysis of the co-primary effectiveness endpoints showed statistically significant differences at 6 months. However, at no time point did either of the endpoints reach clinical significance.

<u>Secondary Effectiveness Endpoints</u>

In the original IDE Statistical Analysis Plan (SAP) dated Oct 2004 a list of nine secondary endpoints was presented. In the November 2006 IDE supplement, the sponsor specified only four secondary endpoints, including one that was not on the original list (mMRC), and classified everything else as "additional analyses". The four secondary effectiveness endpoints were, per the November 2006 supplement:

1. Absolute change in St. George's Respiratory Questionnaire

2. Absolute change in modified Medical Research Council (mMRC)
3. Absolute change in room oxygen requirement (average liters per day)
4. Absolute change in maximum workload as measured by cycle ergometry.

The sponsor pre-specified that the secondary endpoints would be analyzed using Hochberg's adjustment for multiplicity. To use Hochberg's method, all of the secondary endpoints were ordered from the largest to the smallest *p*-value. If the first or largest *p*-value was not statistically significant at the one-sided 0.025 level, then the second *p*-value would be tested at the one-sided 0.0125 (0.025/2) level and the third at the 0.00833 (0.025/3) level, etc. If the first or largest *p*-value was significant, then all of the *p*-values were considered significant. If secondary endpoints that were not statistically significant were eliminated from the list of secondary endpoints, then it could change the statistical significance of the remaining secondary endpoints. The sponsor analyzed only four of the nine originally identified secondary endpoints.

The estimates of the differences between the treatment and control and their 95% Confidence Intervals (CIs) for all 4 secondary endpoints, in all 3 patient populations, at 6 and 12 months are presented. The Zephyr EBV treatment group met the secondary endpoints for SGRQ, mMRC, and Cycle Ergometry as pre-specified in the Statistical Analysis Plan (ITT population at 6 months). The Zephyr EBV treatment group was also significantly better in the same 3 secondary endpoints in the CC population at six months, but not the PP population. The Zephyr EBV treatment group did not perform statistically better with regards to any of the secondary endpoints at 12 months in any of the three analysis populations. We have bolded the instances in which the confidence interval included zero.

Table 8. Secondary Endpoints in the ITT, CC, and PP Populations at 6 and 12 Months

Secondary Endpoints	**ITT 6 Months**	**CC 6 Months**	**PP 6 Months**	**ITT 12 Months**	**CC 12 Months**	**PP 12 Months**
SGRQ (0 - 100 points)	-3.4* (-6.6,-0.3)	-3.4* (-6.6,-0.2)	**-3.4 (-7.1, 0.3)**	**-1.9 (–5.2, 1.4)**	**-3.0 (-6.3, 0.2)**	**-1.6 (-5.1, 1.9)**
mMRC (0 - 4 points)	-0.3* (-0.5,-0.02)	-0.3* (-0.6,-0.05)	**-0.2 (-0.5,0.06)**	**-0.1 (–0.4, 0.2)**	**0.0 (0.0, 0.0)**	**0.0 (0.0, 0.0)**
Cycle Ergometry (watts)	3.8* (0.2, 7.4)	**5.0* (0.0, 5.0)**	**5.0 (0.0, 5.0)**	**2.2 (–1.8, 6.2)**	**3.2 (-0.8, 7.2)**	**5.0 (-5.0, 5.0)**
Supplemental O_2 (liters/day)	**-12* (–77, 53)**	**-100 (-319,118)**	**0.0 (-120, 0)**	**–12 (–89, 65)**	**-63 (-303,177)**	**40 (-214,295)**

The secondary endpoint for supplemental oxygen use will not be discussed, as methods to regulate oxygen use were not specified in the protocol, and as there are no recognized MCID for this metric.

Additional Effectiveness Measures

The sponsor performed an exploratory responder analysis. It was pre-specified as an 'additional analysis', and it is another way of examining the clinical

significance of the primary endpoints. A clinically meaningful improvement in FEV_1 or 6MWT for a patient was defined as a 15% improvement from baseline. The percent of patients who experienced a 15% improvement from baseline for ITT, CC and PP populations was analyzed. Table 9 shows the results of this responder analysis.

Only FEV_1 for the ITT and CC populations was found to be statistically significant in the Zephyr EBV treatment group in comparison to control. Due to the large number of secondary endpoints, additional analyses, and covariates analyzed, multiplicity issues make it difficult to interpret these *p*-values.

Table 9. Responder Analysis: Percent of Patients Experiencing more than 15% Improvement from Baseline at 6 Months

Population	Variable	Control n/N (%)	EBV n/N (%)	2-sided p-value For the difference
ITT	**FEV_1**	8/101 (7.9)	42/220 (19.1)	**0.012**
	6MWT	13/101 (12.8)	45/220 (20.5)	0.12
CC	**FEV_1**	8/75 (10.7)	42/179 (23.5)	**0.024**
	6MWT	13/73 (17.8)	45/178 (25.3)	0.25
PP	**FEV_1**	6/57 (10.5)	32/141 (22.7)	0.071
	6MWT	9/60 (15.0)	38/155 (24.5)	0.14

7.3% of the Zephyr EBV group and 1.4% of the control group had a ≥ 15% improvement in both FEV_1 and the 6MWT.

Of the remaining additional analyses related to quality of life or pulmonary function tests (i.e., changes in RV, DLCO, QWB, BODE, and Borg), a statistically significant change was only observed for the BODE index. The mean change in the BODE index, which is a composite of metrics that overlaps with metrics separately assessed, was -0.21 for the CC population and -0.06 for the PP population with EBV treatment. The change in the Control CC population was 0.32, and in the PP population 0.34.

Imaged Technical Success at 6 months, based on target lobe exclusion judged by HRCT, was 56.2% of the 194 "evaluable" studies that formed the basis for this assessment. Of the 85 failures (43.8%), most had at least one valve that was not fully occlusive. Other reasons for failure included valve removal, expectorated valves and "site-reported technical failures".

Imaged Procedural Success at 6 months was defined as Technical Success without MCC events. By this definition, Procedural Success at 6 months occurred in 53.1% of the 194 evaluable cases.

Imaged Clinical Success was defined as Procedural Success and improvement in 6MWT ≥ 15% or a decrease in supplemental oxygen use. By this definition, Clinical Success occurred in 27.8% of 176 evaluable cases.

The effect of imaged lobar exclusion was also analyzed in relation to FEV_1 and 6MWT. The delta percentage change for Technical Success versus no Technical Success in FEV_1 was 9.4% ($p = 0.0009$). For the 6MWT the delta was 1.9%, which was not statistically significant ($p = 0.6746$).

Thus, Imaged Technical Success was achieved in slightly over half the patients in whom it could be evaluated.

Effectiveness Subset Analysis

High Heterogeneity Subgroup

The sponsor also examined a subgroup of the data, called the "High Heterogeneity Subgroup", which they described as a physiologically probable subgroup that benefited more from the device. In this subgroup, the responder analysis was statistically and clinically significant for both co-primary endpoints. The following points are relevant for discussion:

i. The sponsor used a pre-specified method to find the High Heterogeneity Subgroup. A complete multiplicity adjustment was not made.

ii. The High Heterogeneity cut-off point of 15% was not pre-specified.

iii. The heterogeneity score was based on software that is not commercially available. Also, it is not clear whether this software has been validated for this use.

iv. The sponsor used two different cutoffs between high and low heterogeneity scores. The High Heterogeneity Subgroup was not defined in the IDE or original PMA submission. However, in Amendment 2, the subgroup was defined as > 10%, and in Amendment 3, the subgroup was defined as > 15%, which was the median of "blipsidshettlc"[3].

v. The High Heterogeneity Subgroup analysis using a 15% cut-off for high and low heterogeneity was reported to be associated with statistically and clinically significant responses in FEV_1 and 6MWT. However, heterogeneity was found to be associated with an increased risk of progression to death or LVRS, based on Cox regression analysis. The *p*-value for the heterogeneity by treatment interaction was $p = 0.0074$. A univariate analysis was provided by the sponsor using a 10% cut-off point for high and low heterogeneity. Analysis was not provided for the 15% heterogeneity cut-off in the subset analysis.

[3] Baseline Ipsilateral Destruction (or Density) Score Heterogeneity Total Lung Capacity

Table 10. Heterogeneity and Progression to Death or LVRS (Amendment 2, Addendum to the Statistical Analysis Report Figure 2.2.2)

HETEROGENEITY	Control	Zephyr EBV
High (>10%)	3.1%	5.5%
Low (<10%)	5.5%	2.0%

Target Lung Volume Reduction

The sponsor claimed that Target Lung Volume Reduction, as measured by Target Lobe Atelectasis Score (TLAS), was a good indicator of success. While the sponsor reported a significant association between TLAS and FEV_1, no association was reported between TLAS and 6MWT.

Matched Groups

The sponsor presented a number of graphs, tables, and other analyses based on a "Matched Groups" population. However, these were not pre-specified by the sponsor and are considered sponsor *post-hoc* analyses. The sponsor pre-specified three different effectiveness analysis populations (ITT, CC, and PP) and one safety analysis population (mITT). The "Matched Groups" population was not pre-specified.

Primary Safety Analysis

The primary safety endpoint was the proportion of patients who experienced the occurrence of a major composite complication (MCC) consisting of death, empyema, massive hemoptysis, pneumonia distal to the implanted valves, pneumothorax or prolonged air leak > 7 days, or respiratory failure with > 24 hours of mechanical ventilation. The safety endpoint was planned to be analyzed on the modified ITT (mITT) population, which was defined as all randomized patients who received study-directed treatment and had any follow-up. The primary safety endpoint summary is listed in Table 11 at the 6 and 12 months time points.

Table 11. Major Complications Composite at 6 and 12 Months
(m-ITT analysis; Zephyr EBV n = 214; Control n = 87)

MCC Component	Control 6 Months	Zephyr EBV 6 Months	Control 12 Months	Zephyr EBV 12 Months
Death	0%	2.80%	3.45%	3.74%
Resp Failure >24 hrs ventilation	1.15%	1.87%	2.30%	2.80%
Massive Hemoptysis	0.0%	0.47%	0.0%	0.47%
Pneumo/prolonged air leak >7 days	1.15%	1.40%	1.15%	1.87%
Empyema	0%	0%	0%	0%
Pneumonia distal to implanted valve	NA	1.40%	NA	4.21%
Subjects with 1 or more MCC	1.15%	6.07%	4.60%	10.28%
Hazard Ratio (EBV: Control)		**5.28**		**2.23**

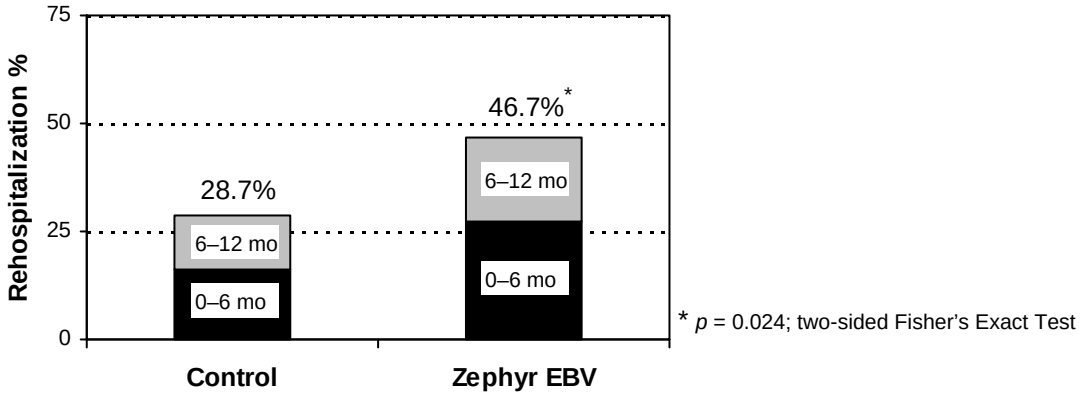
Subjects with 1 or more MCC at 6 months was more than 5 times higher in the Zephyr EBV group than the control and more than 2 times higher at 12 months. The differences in MCC at both time points were not statistically significant. However, it is important to note that the study was not powered to detect a

difference in these low MCC rates, but there was still a trend towards higher adverse event rates and severe adverse event rates in the mITT population of the Zephyr EBV group. The primary safety data from the European study reported in Table 18 also supports this trend.

Secondary Safety Analysis

The sponsor was requested to collect safety data up to 1 year. Survival through 1 year was high (96%) and not significantly different in the Zephyr EBV and Control groups. The composite of death/LVRS/lung transplantation at one year was also not statistically significant (approximately 95% of both groups free of the composite). However, the proportion of patients rehospitalized at 6 and 12 months was greater in the Zephyr EBV group than the Control group and significantly greater at 12 months as depicted in the graph below ($p = 0.024$). At 12 months, the Zephyr EBV group had a hospitalization risk ratio of 1.6 times that of the Control group.

Figure 4. Rehospitalization Rates at 12 Months



Serious Adverse Event (SAE)

Pulmonary related serious adverse events (including MCC events) were significantly more common in the Zephyr EBV treatment group at 6 months and remained statistically significant at 12 months (Table 12).

Table 12. COPD Related Serious Adverse Event

SAE	Control	Zephyr EBV	*p* - value
All COPD Related			
6 months	10.3%	21.5%	0.0315*
12 months	18.4%	28.5%	0.0805
COPD Exacerbations			
6 months	6.9%	16.4%	0.0400*
12 months	10.3%	23.4%	0.0101*

* $p < 0.05$; two-sided Fisher's exact test

Valve related SAEs are shown below in Table 13.

Table 13. Valve Related Serious Adverse Events

VALVE SAE	6 MONTHS	12 MONTHS*
Valve/implant related	10.8%	15.9%
Expectoration/migration	6.1%	7.5%
Distal pneumonia	1.4%	4.2%
Adverse bronchial pathology	4.7%	7.0%

*Cumulative

Adverse Event (AE)

Pulmonary related adverse events were also significantly more common in the Zephyr EBV treated group than the control group at 6 months. As shown in the tables and figure below, the Zephyr EBV treatment group had significantly higher incidences of the following adverse events in days 0-386 (e.g., COPD exacerbation, other pulmonary infection, shortness of breath, non-cardiac pain, nausea/vomiting, hypoxemia, altered ABGs, and hemoptysis). The Zephyr EBV treatment group also had statistically significant higher rates of rehospitalization and suffered valve related adverse events (e.g., valve expectoration, bronchial granulation tissue, dysphonia, and etc). For example, 42% of EBV treatment patients suffered hemoptysis as compared to 2% of control patients.

Table 14. COPD Related Adverse Events at 6 Months

AE	Control	Zephyr EBV	*p*-value
All COPD Related	51.7%	68.7%	0.0079*
COPD Exacerbations	49.4%	63.6%	0.0278*
Increased Shortness of Breath	1.2%	7.9%	0.0289*

*$p < 0.05$; two-sided Fisher's exact test

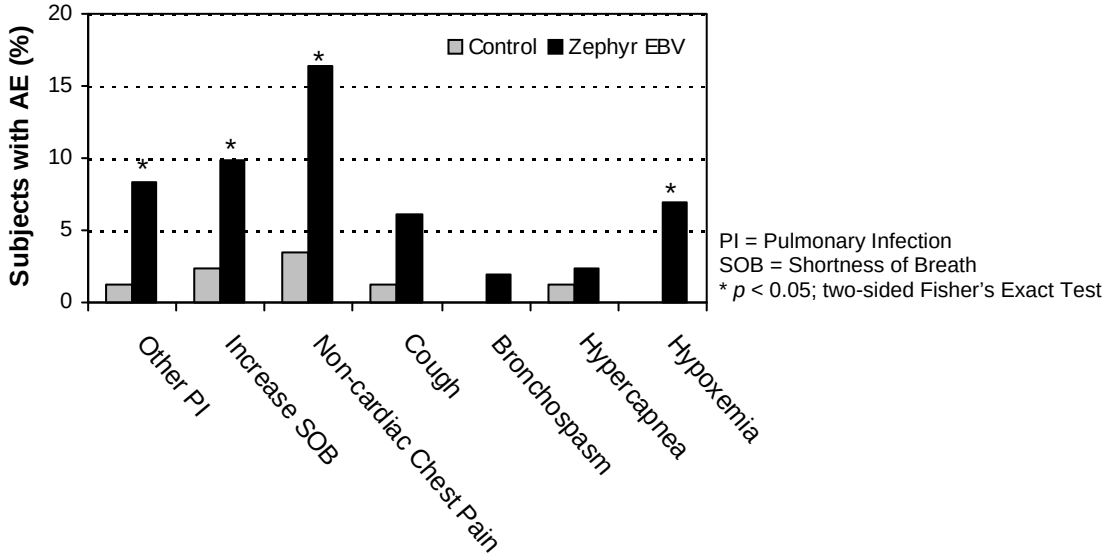
Pulmonary related AEs also remained significant at 12 months.

Table 15. Cumulative COPD Related Adverse Events at 12 Months

AE	Control	Zephyr EBV	*p*-value
All COPD related	62.1%	77.6%	0.0095*
Other Pulmonary Infections	1.2%	8.4%	0.0174*
Increased SOB	2.3%	9.8%	0.0295*

*$p < 0.05$; two-sided Fisher's exact test

Figure 5. COPD and Pulmonary Related Adverse Events at 12 Months



Valve related AEs are shown below in Table 16.

Table 16. Valve Related Adverse Events at 6 and 12 Months

VALVE AE	6 MONTHS	12 MONTHS*
Valve/implant related	13.1%	18.2%
Expectoration/migration	6.5%	7.9%
Distal pneumonia	1.4%	4.2%
Adverse bronchial pathology	5.6%	8.4%

*Cumulative

The panel will be asked to assess whether the data presented demonstrate a reasonable assurance of safety and effectiveness for the intended use of the device.

4.4 Additional Clinical Trials

Additional clinical trials of the device were as follows:

- Zephyr EBV in Europe (n = 171)
- Compassionate and Emergency Use Study mostly for air leaks (n = 65)
- Study with the first generation version of the device EBV-OTW or "Over-the-Wire" (n = 62)
- Zephyr EBV and EBV-OTW studied in feasibility trials (n = 113).

Of note, the Zephyr EBV Europe Trial protocol was nearly identical to the VENT pivotal trial with the same primary and secondary safety and effectiveness endpoints at 6 months. Therefore, this study will be discussed here.

In the original IDE, the sponsor planned the pivotal study to be conducted in both Europe and the U.S., and the plan was to pool the data. However, FDA and sponsor agreed at a later time not to pool the European data with the U.S. data due to potential differences in patient selection, diagnosis, patient demographic characteristics, and covariates. Descriptive data from the European study was submitted. As can be seen in the tables below, the data from the European trial are similar to the U.S. data. Below are the results for the co-primary endpoints at 6 months. No *p*-values or confidence intervals were provided by the sponsor.

171 subjects were enrolled in a 2:1 randomization scheme (111 EBV treated subjects, 60 control subjects) between June 2004 and January 2006. The demographic profile was similar to the VENT trial. The only procedural difference was a greater use of general anesthesia.

The European data showed similar results to the VENT trial. The means were derived from the completed cases population. The secondary effectiveness endpoints were not presented.

Table 17. Zephyr EBV Europe Primary Effectiveness Data at 6 Month

Characteristic	**Control**	**Zephyr EBV**	**Delta**
	Mean (SD) N	**Mean (SD) N**	
Completed Cases (CC)			
FEV_1	0.78% (19.12) 55	6.58% (20.56) 91	5.80%
6MWT	7.74% (34.82) 55	9.72% (35.73) 88	1.98%
Per Protocol (PP)			
FEV_1	-2.61% (17.07) 37	9.27% (18.74) 53	11.88%
6MWT	7.29% (40.01) 36	9.04% (37.18) 51	1.75%

The primary safety endpoint was a Major Complications Composite (MCC), which included death, empyema, massive hemoptysis, pneumonia distal to a valve, and pneumothorax or prolonged air leak. The MCC at 6 months was significantly worse in the EBV group compared to the Control group.

Table 18. EBV Europe Primary Safety Endpoint at 6 Month

Endpoint	**Control n/N (%)**	**Zephyr EBV n/N (%)**	***p*-Value**
Patients Experiencing at least One MCC	2/60 (3.33)	15/111 (13.51)	0.0348*

*$p < 0.05$; two-sided Fisher's exact test

While no real conclusions can be drawn from the European data, the results seem to be consistent with those observed in the VENT Pivotal Trial. There was less than a 2% difference in the 6MWT between the Zephyr EBV treatment and control groups, and a trend of more adverse events in the treatment group.

4.5 Instructions for Use

The Instructions for Use (IFU) contains adequate instructions for Zephyr EBV placement. However, the instructions for selection of the target lobe are not supported by the VENT trial.

The IFU states that at least one lobe (upper or lower) should have "destruction sufficient to warrant treatment" and that the degree of destruction "should be readily apparent." This method for target lobe selection is to be assessed "radiographically", which is different from the method used in the VENT trial, in which a non-commercially available, non-FDA approved software program for HRCT was used. To date, the sponsor has not provided data to demonstrate that the safety and effectiveness profile of the device will be the same, when using a different target lobe selection method.

In addition, the IFU does not limit device use to severe heterogeneous emphysema, the only population tested in the pivotal trial. The IFU also does not specifically limit device use to one lobe, the only method used in the pivotal trial. The IFU states that if both lungs appear suitable for treatment, "consider" treating the lung with greater heterogeneity.

The panel will be asked to comment on the adequacy of the Instructions for Use with respect to the target lobe selection method and the use of the device in a single lobe.

5. Post-Approval Study Plan

Note: The inclusion of a Post-Approval Study section in this summary should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA device. The presence of a post-approval study plan or commitment does not in any way alter the requirements for pre-market approval. A recommendation for approval from the Panel must be based on the pre-market data. The issues noted below are FDA's comments regarding a potential post-approval study should the panel find the device approvable following its discussions and deliberations of the pre-market data, and should the panel recommend a post-approval study.

As of October 10, 2008, the sponsor has submitted one post-approval study (PAS) protocol for the extended follow-up of the pre-market cohort and one PAS outline for the enrollment of a new cohort. FDA continues to work with the sponsor to develop detailed PAS protocols to address device long-term safety and effectiveness.

5.1 Long-Term Follow-up of Premarket Cohort Endobronchial Valve for Emphysema Palliation Trial (VENT) Long-Term Follow-up Protocol (#630-0008- A)

Study Objective:
The sponsor proposes to collect and report long-term safety and effectiveness data on the Emphasys Zephyr® Endobronchial Valve (EBV) in subjects with heterogeneous emphysema who were enrolled in the pre-market study (VENT study).

Study Design:
The VENT Long-Term Follow-up study is a multi-center, observational, follow-up study of the previously enrolled VENT subjects. The VENT study was a multi-center, randomized, prospective clinical trial enrolling 321 subjects (220 EBV subjects and 101 control subjects) at 31 study sites between December 2004 and April 2006. The VENT study included follow-up visits and assessment of safety and effectiveness up to 1 year after randomization.

Study population and Sample Size:
The study population will be surviving subjects previously enrolled in the VENT study. Up to 284 subjects will be available for the Year 4 follow-up visits and only up to 129 subjects will be available for the Year 3 follow-up visits. All subjects in the VENT study have been outside the Year 2 visit windows. Therefore, no data on Year 2 post randomization will be collected.

Duration of Follow-up
The duration of follow-up is 4 years.

Effectiveness Endpoints:
Proposed effectiveness endpoints include the following and will be evaluated with descriptive statistics at 3 and 4 years post randomization with 95% Confidence Intervals by treatment group.

i. FEV_1, FVC and 6MWT:
   - Mean Percent Change from pre-randomization baseline values in FEV_1, FVC, and 6MWT
   - Mean Absolute Change from pre-randomization baseline values in FEV_1, FVC, and 6MWT
   - Mean Percent Change from 6 month visit values in FEV_1, FVC, and 6MWT
   - Mean Absolute Change from 6 month visit values in FEV_1, FVC, and 6MWT

ii. FEV_1 and FVC Percent Predicted Values:
   - Mean Percent Change from pre-randomization baseline values in FEV_1 and FVC percent predicted values
   - Mean Percent Change from 6 month visit values in FEV_1 and FVC percent predicted values

iii. SGRQ, mMRC and BODE:

- Mean Absolute Change from pre-randomization baseline values in SGRQ, mMRC, and BODE
- Mean Absolute Change from 6 month visit values in SGRQ, mMRC, and BODE

In addition to the mean changes, the sponsor will also report original values at baseline (including pre -randomization baseline and 6 month visit values) and follow-up for the effectiveness endpoints.

Safety Outcomes:
Adverse event (AE) rates with 95% Confidence Intervals by treatment group at 3 and 4 years post randomization will be calculated. AEs will be summarized by type, timing, duration, severity, and device-relatedness.

Valve Removal and Explanted Valve Analysis:
The sponsor stated that clinical sites will be instructed to return any removed and/or expectorated valves back to them and all returned valves will be subjected to examination and analysis for evidence of failure. However, the sponsor has not yet submitted a detailed protocol for the examination and analysis of the removed or expectorated valves.

The sponsor continues to work interactively with FDA to finalize this extended follow-up protocol.

5.2 Long-term Follow-up of Post-Market Cohort Zephyr EBV PAS Protocol (#630-0009-A) Outline

On October 10, 2008, the sponsor submitted an outline for the second PAS with new patients in view of the high lost-to follow-up rate in the extended follow-up of the pre-market cohort.

Study Objective:
The objectives of this study are to evaluate training effectiveness and long-term device safety and effectiveness when EBV is used in a real world setting.

Study Design:
The study is a prospective, observational, open-label, multi-center clinical trial to evaluate the training effectiveness and long-term safety and effectiveness of EBV in subjects with heterogeneous emphysema.

Study Population and Sample Size:
The study population will be subjects evaluated for treatment with EBV. Up to 200 subjects will be recruited at up to 30 sites (maximum of 30 subjects per site) in the United States.

A sample size of 200 patients was calculated by the sponsor based on the following parameters:

- The observed rate of valve expectoration or migration was 7.9% in the VENT trial
- The expected rate of valve expectoration or migration will be 4 - 6% in the PAS
- The upper one-sided 95% confidence limit is less than 10%, i.e., the observed rate is 6% plus 4%.

The sponsor stated that the proposed sample size (n = 200) provides a 95% one-sided exact upper confidence limit of 9.54%. If the observed rate is 5% or 4%, the upper one-sided 95% confidence limits are 8.33% or 7.10%, respectively.

Duration of follow-up:
The duration of follow-up is 3 years.

Study Endpoints:
Proposed study endpoints include the following and all endpoints will be analyzed with descriptive statistics:

i. Training Effectiveness Outcome - Zephyr EBV migration and expectoration rates at 1, 2 and 3 years post-procedure

ii. Effectiveness Outcomes - Post-bronchodilator spirometry at 1, 2 and 3 years post-procedure

iii. Safety Outcomes - Serious adverse event (SAE) rates at 1, 2 and 3 years post-procedure

6. Concluding Remark

This executive summary provides an overview of the data and issues that will be presented to the Advisory Committee at its meeting of December 5th.