

FDA Questions for Anesthesiology and Respiratory Therapy Devices Advisory Panel

December 5, 2008

P070025

Emphasys Zephyr Endobronchial Valve System

Evaluation of Safety and Effectiveness

The VENT trial for the Emphasys Zephyr Endobronchial Valve (EBV) System was an unblinded, prospective, randomized, multi-center trial to assess the safety (at 6 months and at one year) and effectiveness (at 6 months) of a one-way valve to improve FEV₁ and 6MWT in patients with severe heterogeneous emphysema. All 321 patients enrolled in the study were to have received optimal medical management including pulmonary rehabilitation before randomization.

A large number of protocol violations and missing data were observed in the study as noted in Section 4.3 of the FDA's Executive Summary, and restated below.

- Over 19% of subjects did not meet inclusion criteria, mostly with respect to pulmonary function parameters and pulmonary rehabilitation.
- Missing data due to missed visits, visits outside the predefined window, or loss to follow-up occurred in over 35% of patients. Statistical analyses were based on an extended window, which was not pre-specified, and still resulted in the need to impute data in over 19% of the cases.

1. Please comment on the interpretability and validity of the statistical results for effectiveness, in light of the extent of protocol violations and missing data.

The MCC was more than five times higher in the Zephyr EBV treatment group than the control group at 6 months, and more than two times higher at 12 months. Higher MCC rates in the treatment group were also observed in Zephyr EBV Europe trial with statistical significance.

With respect to the secondary safety endpoints, the study was not powered to look at the component rates of MCC events. The differences in survival or the composite progression to death, lung volume reduction surgery, or lung transplantation were not statistically significant. The proportion of patients rehospitalized was, however, significantly higher in the Zephyr EBV treatment group as shown in Figure 6 of the FDA's executive summary. In addition, there were clinically and statistically significant increases in COPD, pulmonary and valve related adverse and serious adverse events in the Zephyr EBV treatment group, and these increases persisted

over the 12 month follow-up. The data for these are provided in Tables 12 through 16 in the FDA’s executive summary.

2. Please provide your interpretation of the safety data collected in the VENT trial.

In the VENT trial, the two co-primary effectiveness endpoints achieved statistical significance in the ITT population at 6 months. However, the clinical significance level of 15% was not achieved for either co-primary endpoint.

ITT	Δ at 6 months	Confidence Interval	One-sided p-value
FEV ₁	6.8%	2.1, 11.5	0.002
6MWT	5.8%	0.5, 11.2	0.019

The clinical magnitude of the effects on FEV₁ and the 6MWT are similar or lower at 6 and 12 months in both the Completed Cases (CC) and Per Protocol (PP) populations.

	Δ at 6 months	Δ at 12 months
CC FEV ₁	7.2%	8.1%
PP FEV ₁	7.0%	7.0%
CC 6MWT	5.8%	3.6%
PP 6MWT	4.1%	2.8%

Statistically significant changes were also achieved in St. George’s Respiratory Questionnaire (SGRQ), modified Medical Research Council (mMRC) and cycle ergometry at 6 months (secondary effectiveness endpoints). The effects on these three metrics decreased at 12 months and did not achieve statistical significance.

	Δ at 6 months	Δ at 12 months
SGRQ	-3.4	-1.9
mMRC	-0.3	-0.1
Cycle Ergometry	+3.8	+2.2

- 3. Please provide your clinical and statistical interpretation of the results of the co-primary and secondary effectiveness endpoints in the ITT, PP and CC populations.**
- 4. Please provide your overall assessment of the risks and benefits of the Zephyr EBV device for treatment of patients with severe, heterogeneous emphysema who have received optimal medical management, as demonstrated in the premarket approval application.**

Labeling

One aspect of the pre-market evaluation of a new product is the review of its labeling. The labeling must identify which patients are appropriate for treatment, identify potential adverse events with the use of the device, and explain how the product should be used to maximize clinical benefit and minimize adverse events. If you recommend approval of the device, please address the following questions regarding product labeling. Please refer to section 4.5 of FDA's Executive Summary and the proposed Instructions for Use in the Panel Package for further information.

The proposed indication for use of this device:

“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 FEV₁ and six minute walk test distance in patients with severe, heterogeneous emphysema who have received optimal medical management.”

The Zephyr EBV is contraindicated for:

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

4. With regard to the indications for use, Instructions for Use (IFU), and clinical data, please comment on the following:

- a. Please comment as to whether the indications for use adequately reflect the Zephyr EBV study's patient population, and for which the device may be marketed.**
- b. Please comment on whether the IFU should limit device use to one lobe, the only use studied in the pivotal trial.**
- c. The target lobe identification in the IFU is described as a visual assessment of heterogeneity instead of the software-based method used in the VENT trial for heterogeneity determination. Please comment on whether the IFU adequately instructs the practitioners to choose the target lobe.**
- d. Please discuss whether you think that any additional warnings, precautions, or contraindications should be included in the labeling to assist practitioners in using the Zephyr EBV System.**

Post-Approval Study

Note to Panelists: The inclusion of questions on Post-Approval Study should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA device.

- 5. In the Post-Approval Study (PAS) Protocol, the sponsor proposes to continue follow-up of the premarket cohort for up to 4 years. Please note that only 3 and 4 years data will be collected. The proposed effectiveness endpoints include mean changes from baseline in FEV1, FVC, 6MWT, SGRQ, mMRC, and BODE and will be evaluated with descriptive statistics at 3 and 4 years post randomization with 95% Confidence Intervals by treatment group. The sponsor also proposes to track adverse events over the follow-up period and plans to perform analysis on removed or expectorated devices for failure. Is the proposed PAS study design appropriate to address long-term device safety and effectiveness of the device in the post-market phase?**

- 6. The second PAS is proposed to address training effectiveness and device long-term safety and effectiveness. The sponsor proposes to conduct a prospective, observational, open-label, multi-center clinical study of up to 200 patients with heterogeneous emphysema. Training effectiveness will be evaluated by estimating the device migration and expectoration rates at 1, 2 and 3 years post-procedure; device effectiveness will be evaluated by post-bronchodilator spirometry at 1, 2 and 3 years post procedure; and safety will be evaluated by estimating the serious adverse event (SAE) rates at 1, 2 and 3 years post procedure. All endpoints will be evaluated with descriptive statistics. Is the proposed study appropriate to address device long-term safety and effectiveness? Please consider the following study elements in your discussion:**
 - a. Is the proposed study population the most suitable one?**
 - b. What should be the control group against which these data should be evaluated?**
 - c. Are the proposed study endpoints appropriate to address device effectiveness and safety (i.e., SAE only) in the real-world setting?**
 - d. Please discuss whether the 6MWT should be evaluated in addition to spirometry as effectiveness endpoints, and whether all adverse events should be evaluated in this a PAS.**
 - e. Please discuss whether a 3 year follow-up period post-procedure is sufficient to address long-term effectiveness of the device, and to identify potential adverse events.**