

QUESTIONS FOR PANEL

1. Evaluation of Effectiveness

Protocol violations and missing data occurred in the VENT study:

- **Inclusion criteria not met in over 19% of subjects** - mostly due to pulmonary function parameters and pulmonary rehabilitation
- **Missing data in over 35% of subjects** - due to missed visits, visits outside the predefined window, or loss to follow-up
- **Statistical analyses on a non-prespecified extended window, despite this data imputed in over 19% of the cases**

Neither subjects nor investigators were blinded.

1. Evaluation of Effectiveness

Q1. Please comment on the interpretability and validity of the statistical results for effectiveness in the VENT study.

2. Evaluation of Effectiveness

- Co-primary effectiveness endpoints achieved statistical significance in the ITT population at 6 months, but threshold level of 15% not achieved for either endpoints
- Clinical magnitude of effects remained similar for FEV₁ and decreased for 6MWT from 6 to 12 months
- Secondary effectiveness endpoints (SGRQ, mMRC, and cycle ergometry) achieved statistically significant changes at 6 months, which decreased at 12 months with no statistical significance

2. Evaluation of Effectiveness

Q2. Please provide your assessment of the results of the co-primary and secondary effectiveness endpoints in the VENT study. Please discuss the clinical significance of these results, if any.

3. Evaluation of Safety

- **Primary Safety Endpoint - Major Complications Composite (MCC; death, empyema, massive hemoptysis, pneumonia distal to a valve, and pneumothorax or prolonged air leak)**
 - **No prior agreement over a MCC delta endpoint**
 - **MCC at 6 months: > 5x higher in Zephyr EBV than control groups**
 - **MCC at 12 months: > 2x higher in Zephyr EBV than control groups**
- **Other Safety Analyses:**
 - **Survival and composite progression to death/lung volume reduction surgery/lung transplantation: similar in Zephyr EBV and control groups**
 - **Rehospitalization: significantly greater in Zephyr EBV than control groups**

3. Evaluation of Safety

- **Adverse and Serious Adverse Events (COPD, pulmonary and valve related) - clinically and statistically significant increases in Zephyr EBV group, which persisted over 12 month follow-up**

Q3. Please discuss and provide your interpretation of the device safety in the VENT study.

4. Evaluation of Safety and Effectiveness

Q4. 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.

Questions 5 & 6

Questions 5 & 6 are intended for Advisory Panel discussion to guide the Agency in the event that the subject device is approved by the Agency. The fact that these questions are included should not be interpreted that the Agency has made a decision or a recommendation on the approvability of this device.

5. Labeling

Q5. With regard to the indications for use, Instructions for Use (IFU), and clinical data, please comment on the following:

- a. The target lobe identification in the IFU is described as a non-specific radiographic assessment of heterogeneity, whereas the VENT trial used a software-based method for analysis of high resolution chest computed tomography. Please comment on whether the IFU adequately instructs the practitioners to choose the target lobe in a way that would produce similar safety and effectiveness results to the VENT trial.**

5. Labeling

Q5. (continued)

- b. Please comment on whether the IFU should limit device use to one lobe, the only use studied in the pivotal trial.**
- c. 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.**

6. Post-Approval Study (PAS)

PAS with New Subjects

The sponsor proposes to conduct a prospective, single-arm, open-label, multi-center, observational study to address training effectiveness and device long-term safety and effectiveness in patients with heterogeneous emphysema. Patients will be followed for 3 years.

- Training Effectiveness: device migration/expectoration rates
- Device Effectiveness: post-bronchodilator spirometry
- Safety: serious adverse event (SAE) rates
- All Endpoints: descriptive statistics

6. Post-Approval Study

Q6. Is the proposed Post-Approval Study appropriate to address training effectiveness and device long-term safety and effectiveness postmarket?

Please discuss the following:

- a. Is this study design appropriate to evaluate device safety and effectiveness postmarket?**
- b. What should be a comparison group against which these data should be evaluated?**
- c. Is it valid to assume that the migration/expectoration rate will be 6% in post-market, which is less than what was observed pre-market (7.9%)?**

6. Post-Approval Study

- d. Is there need for the evaluation of 6MWT in addition to spirometry as effectiveness endpoints?**
- e. What safety endpoints need to be addressed?**
- f. Is a follow-up of 3 years post-procedure sufficient to address device long-term safety and effectiveness?**

Please discuss any additional issues that should be assessed in a Post-Approval Study and provide recommendations.