

SUMMARY MINUTES**CENTER FOR DEVICES AND RADIOLOGICAL HEALTH
ANESTHESIOLOGY AND RESPIRATORY THERAPY
DEVICES PANEL**

December 5, 2008

**Hilton Washington DC North
620 Perry Parkway
Gaithersburg, MD**

Attendees:**Chairperson**

David J. Birnbach, M.D., M.P.H.
University of Miami School of Medicine
Miami, FL

Voting Members

Claude D. Brunson, M.D.
University of Mississippi Medical Center
Jackson, MS

Hugh A. Cassiere, M.D., FCCP
North Shore University Hospital
Manhasset, NY

Karen B. Domino, M.D., M.P.H.
University of Washington School of Medicine
Seattle, WA

Robert G. Loeb, M.D.
University of Arizona
Tucson, AZ

Thomas E. Wiswell, M.D.
Florida Hospital Orlando
Orlando, FL

Temporary Voting Members

Rosalie Dominik, Ph.D.
University of North Carolina Medical School
Chapel Hill, NC

Susan Halabi, Ph.D.
Duke University
Durham, NC

Stephen Li, Ph.D.
Medical Device Testing and Innovations, LLC
Sarasota, FL

Philip Marcus, M.D., M.P.H.
St. Francis Hospital
Roslyn, NY

Andrew L. Ries, M.D., M.P.H.
University of California, San Diego
La Jolla, CA

Thomas Vassiliades, MD
Emory University School of Medicine
Atlanta, GA

Benson R. Wilcox, M.D.
University of North Carolina Medical School
Chapel Hill, NC

Sandra Willsie, D.O., FACOI, FACP, FCCP
Heartland Health Sciences University
Overland Park, KS

Consumer Representative

Carolyn Petersen, M.S.
Mayo Clinic
Rochester, MN

Industry Representative

David G. Osborn, MEE
Philips Medical Systems
Andover, MA

Executive Secretary

Neel Patel, MEng
Food and Drug Administration
Rockville, MD

CALL TO ORDER

Panel Chairperson David J. Birnbach, M.D., M.P.H., called the meeting to order at 8:02 a.m., noting the presence of a quorum and that the Panel had received training in FDA device law and regulations.

CONFLICT OF INTEREST

Executive Secretary Neel Patel, MEng, read the Conflict of Interest Statement and advised that no conflict of interest waivers had been issued.

He identified the subject of discussion as being the premarket approval application for the Emphasys Zephyr Endobronchial Valve System sponsored by Emphasys Medical, Incorporated.

DEPUTIZATION TO VOTING MEMBER STATUS STATEMENTS

Mr. Patel introduced David Osborn as the industry representative and read into the record the appointment to temporary voting status of Drs. Wilcox, Ries, Li, Vassiliades, Willsie, Marcus, Halabi and Dominik, adding that they had undergone the customary conflict of interest review and had reviewed the material for consideration.

He made general announcements concerning availability of transcripts, purchasing videos, and providing hard copies of remarks and overheads. He indicated that Siobhan DeLancey was the press contact for the meeting.

PANEL INTRODUCTION

Chairperson Birnbach asked the Panel members and FDA staff to introduce themselves.

OPEN PUBLIC HEARING

There were no requests to participate in the open public hearing.

PRESENTATION BY THE SPONSOR

John McCutcheon, President and CEO of Emphasys Medical, Inc., first related the history of the company and gave a brief description of the Zephyr EBV (endobronchial valve), stating that its purpose is to improve FEV₁ and six-minute walk test distance in patients with severe heterogeneous advanced emphysema who have received optimal medical management.

In outlining the presentation, he stated that Dr. Scieurba was the principal VENT investigator; that Dr. Criner's focus would be on outlining the clinical need description of the device and trial design and on the presentation of training and post-approval study proposals; and that Dr. Ernst would be

providing baseline characteristics for the study. He also introduced the advisors, Dr. Geoff McLennan and Dr. Charlie Strange, and also indicated that Dr. Jonathan Goldin, the Imaging Core Lab director, was present along with Dr. Richard Chiacchierini, Dr. Christopher Cooper and Dr. Robert Wise to answer any questions.

Gerard Criner, M.D., FCCP, began his presentation by providing disclosure information, adding that he has been involved in the research and clinical care of patients with COPD and emphysema for over the last 20 years. He indicated that the purpose of his presentation would be to frame the clinical problems of patients with emphysema, the needs that they have for further new treatments, and also to describe the trial design.

He then gave some background statistics on emphysema, pointing out that there are currently 12 million Americans that suffer from COPD and 3.5 million of those are estimated to suffer from emphysema. He went on to cover reasons as to the morbidity and mortality of the disease, citing the pathophysiological effects such as hyperinflation and its effects, including the increase of dyspnea and inactivity, and he explained the staircase ascending treatment plan, which is based on the severity of the underlying lung disease.

In summarizing data from the National Emphysema Treatment Trial (NETT), he reported that over 1,218 patients with follow-up of up to seven years were identified that showed a preferential improvement with lung volume reduction surgery towards survival, improvement in exercise capacity, and quality of life. He added that this was the first study that showed that the heterogeneity of emphysema on high resolution CT scan could predict response to a surgical therapy. He also covered additional data obtained from the NETT study.

He next described the VENT trial, explaining that it was centered on therapy, the vehicle of which was the Zephyr Endobronchial Valve, and he showed schematics of how it works.

Moving on to trial design, he went over four important recommendations made by an FDA advisory panel in 2003, explaining the methodology used to conduct the trial. Using a line diagram, he explained how the NETT was conducted and covered the key entrance inclusion and exclusion criteria.

He then went to state that because of challenges in regard to choosing endpoints, two co-primary efficacy endpoints were chosen by VENT, a percent change in FEV₁ from baseline to six months and percentage change in six-minute walk test distance from baseline to six months, and he discussed secondary efficacy endpoints, relating how BODE was incorporated by VENT to be used as a secondary efficacy outcome. He explained that BODE is calculated by these four indices: body mass index, airway obstruction, dyspnea, and exercise tolerance.

He concluded by discussing the major complications composite (MCC), which was the primary safety endpoint for VENT, and the various

entities involved in study oversight and management throughout the trial.

Armin Ernst, M.D., FCCP, began his presentation by relating that his main interest over the past decade has been in advanced endoscopic procedures in the chest. He provided disclosure information and stated that he would be presenting results regarding the baseline characteristics of the study population and safety data. He pointed out that the trial had met all of its endpoints, the primary ones being efficacy as well as safety.

He went on to cover baseline characteristics of the study population and some important considerations with regard to study conduct, including various timeframes given for follow-up and data analysis. He also related that the sensitivity analyses show the primary endpoints were all met across windows either way. He then discussed eligibility violations, protocol deviations, and the safety data.

The next topics covered were the MCC event rate and particulars related to it, adverse events that were not included in the composite index as well as events that are unique to the treatment, and he addressed the issue of re-hospitalizations. In relating non-MCC events, he included a list of seven that were either statistically significant or trended towards it, noting the ones of specific interest as being COPD exacerbations as well as hemoptysis. Unique events covered included distal pneumonia by migration and expectoration as well as granulation tissue formation. He related, among other things, that re-hospitalizations were higher in the treatment group, 39.7 versus 25.3, noting that it was an active intervention versus non-active control.

In conclusion, he stated that there is definitely no increased mortality in the treatment arm when compared to control, and he further emphasized that it is a removable device, allowing for quicker recovery from complications when removed.

Frank Sciurba, M.D., FCCP, discussed the efficacy results for VENT. He conveyed his belief that the expected pre-specified efficacy criteria had been achieved in the context of this trial, and he went on to address the data, stressing that the primary population pre-specified was an intent to treat population with imputed analyses of missing data and talked about the co-primary pre-specified outcome parameters (FEV₁ and six-minute walk). He related that FEV₁ in the intervention group improved above the control group by 6.8 percent and the six-minute walk distance improved above the control group by 5.8 percent.

He then described pre-specified secondary analyses and emphasized that all of these parameters moved in the right direction with statistical significance and corroborated nominally and statistically with the completed cases analyses. He reported that the BODE index decreased in the trial, and he discussed protocol violations, stating that independent of inclusion/exclusion of these minor and often expected incidences, the results

were not different. He directed the Panel's attention to high resolution CT analysis data with respect to changes in volume in the intervened lobe showing a 200 cc increase in the non-targeted adjacent lobe, and he stressed that these target lobe volume changes correlated very strongly with mechanical changes in the lung or FEV₁.

After covering the topic of responder analysis, he expressed his belief that the pre-specified primary outcomes have been met, and he went on to discuss variables, explaining that from these variables, two highly plausible predictors emerged, heterogeneity of disease and fissure integrity, which he went on to discuss in greater detail.

He described the durability of effect in the procedure, looking at completed case analyses of FEV₁ patients who returned at all three points (three months, six months, and a year), and in summary, he expressed his belief that the primary and secondary efficacy endpoints had been met across all parameters, that target lobe volume reduction had been achieved, that integrative parameters integrating the multiple domains of COPD corroborates these treatments, and that substantial numbers of patients have clinically meaningful responses.

Dr. Criner then gave a brief outline of the training and post-approval studies put forth by the Sponsor.

Beginning with physician training, he presented a variety of different didactic teaching modes and hands-on demonstrations that have worked in other countries, stating that the Sponsor would endorse a similar program in the United States, if approved.

He described two post-approval studies, one with the primary objective to collect and report long-term safety and efficacy data, the other to evaluate training effectiveness of longer-term safety of valve placement when used by clinicians in private practice with a range of underlying experience.

Expounding the reasons why VENT is a landmark study, he pointed out that after NETT, this is the largest interventional trial ever conducted in this group of patients with severe emphysema, and it is the largest interventional study ever done in severe emphysema that has been conducted by industry. He further emphasized that it is the first ever prospective multicenter randomized control trial to evaluate lung volume reduction via endobronchial less-invasive approach and the first to evaluate the regional effects of lobar treatment for severe emphysema in patients with severe to very severe disease and that the high-resolution CAT scan data provides a novel paradigm for patient selection, mechanistic effect of endobronchial lung reduction and outcome assessment that is impervious to the placebo effect.

He then covered study conduct, stating that there is no impact on study outcomes due to protocol or eligibility deviations and that the primary endpoints were met regardless of whether protocol or eligibility deviations were included or excluded from the analysis.

He spoke next of safety issues and asserted that clinical safety efficacy

had been established and that all endpoints have been met. He also spoke of the responder analysis data that show clinically meaningful changes in a significant percentage of heterogeneous disease in the treated cohort with minimal morbidity and mortality.

He indicated where Zephyr EBV would fit in practice and how risk and benefits of treatments in severe emphysema would be assessed.

In summation, he asserted that this therapy is reasonable and the risk can be anticipated and manageable; that it has important clinical benefits in a substantial number of patients who undergo this therapy and the benefits outweigh the risks; and that study safety results demonstrate reasonable assuredness of safety and effectiveness.

SPONSOR Q&A

The Panel members then posed questions to the Sponsor, requesting clarification regarding endpoints being met clinically as well as statistically, who would be the intended operators for the Sponsor's market, and whether training programs and certification had been established. Selection of patients was discussed, and **Jonathan Goldin, M.D.**, explained that all targeting was done following a very pre-specified algorithm for targeting.

Other questions focused on such issues as proctoring of individuals who would be doing the procedure, whether volume reduction had been achieved, how patients with characteristics of heterogeneity and intact fissure would be defined and could be easily determined by radiologists in the community, and the pharmacological management of patients.

The Sponsor was questioned in regard to the materials used in the device, i.e., silicone and nickel, whether there were allergic reactions to the nickel in particular. **Dr. Ernst** responded that there were no allergic reactions during the course of the study as well as, to his knowledge, no reported allergic reactions outside the United States. He also specified that the material used in the device is not nickel, but nickel titanium alloy, which is frequently used in medical devices.

The session ended with questions about whether the research had been published and regarding long-term follow-up and preclinical data.

PRESENTATION BY FDA

Melanie Choe, Ph.D., the review team leader, gave the first presentation, advising that the focus would be on the premarket approval application of the Zephyr Endobronchial Valve System. She informed the Panel that she would be providing a device description and a brief introduction to the clinical study with the preclinical evaluation status; that Mr. Van Orden would be presenting the statistical evaluation, which would be followed by the clinical evaluation by Dr. Shure and post-approval study by Dr. Chen.

She then gave a description of the device, stating that the EBV system is a sterile single-use system consisting of three components and that the valve is intended to prevent airflow into the hyper-inflated regions of the lung distal to the valve while allowing air flow out.

She went over the considerations for premarket approval and the kind of data that is required in determining reasonable assurance as to safety and effectiveness, such as patient population factors, conditions for use as reflected in the labeling or advertisement of the device, benefits of the device versus harm that the device may cause, and the reliability of the device.

She next explained the investigational exemption under which the U.S. clinical study had been conducted, stating that the pivotal study was an unblinded, prospective, randomized, multicenter trial of the Zephyr EBV treatment group compared to optimal medical management control. Describing the specifics of the study, she pointed out that at the time of the pivotal study approval, the Sponsor proposed a 30 percent MCC delta between the treatment and control groups, which had not been agreed upon by the FDA and that the FDA had informed the Sponsor at the time of the pivotal study conditional approval that it intended to evaluate the complication rates for the Zephyr EBV and the control groups based on demonstration of benefit. She added that in vitro, performance and characterization studies, and animal tests had been conducted by the Sponsor, and all had been determined to be satisfactory.

She noted that packaging and sterilization processes were validated according to FDA standards, and a wide variety of specialists had been consulted to review this application due to the complexity of the device.

Alvin Van Orden, M.S., presented a statistical review of the VENT clinical trial that covered the topics of study design, subject accountability and protocol violations, primary and secondary effectiveness results, statistical significance and estimation of the treatment effect, additional analyses, safety results, and the European data.

He began by explaining that both the control and treatment groups received optimal medical management, that multiple endobronchial valves were placed in the target lobe of the treatment patients, and that patients and investigators were not blinded to the treatment received. Relating that patients were randomized in the two-to-one fashion, treatment to control, and the randomization was stratified by target lobe and exercise capacity, he then explained the two co-primary endpoints.

He stated that an original list of nine secondary endpoints had been changed to four: quality of life measure; St. George's Respiratory Questionnaire (SGRQ); the modified Medical Research Council which measures dyspnea; a measure of the exercise capacity, cycle ergometry, and the amount of supplemental oxygen used by subjects. He added that another major change in the study design was the creation of an extended window for the primary endpoint.

He next covered statistics relative to the reported 2,492 protocol violations and then moved on to discuss the primary effectiveness analysis. He spoke of the differences between the treatment and control groups, and results for the secondary endpoints, stressing that differences between the groups were fairly consistent, though most of the secondary endpoints were not statistically significant in the completed cases.

He then identified four important factors that could impact the estimation of the treatment as being lack of blinding, bias resulting from post-hoc extension of the window, missing data, and protocol violations.

He indicated that the Sponsor had conducted a responder analysis plus analyses on residual volume, diffusion capacity, quality of well-being, and relationship between high heterogeneity treatment interaction and death, and LVRS. He then presented the primary safety endpoint major complication composite, a combination of these major adverse events: death, empyema, massive hemoptysis, pneumonia distal to valve, pneumothorax, and respiratory failure.

He also touched briefly on re-hospitalization, stating that it was categorized as a secondary safety endpoint and, on the European data, observing that it is instructive to look at the results of this arm of the clinical trial.

In conclusion, he stated that statistical significance was achieved in the primary effectiveness analysis but advised that the estimates of differences could be impacted by the four factors discussed.

Deborah Shure, M.D., introduced herself and her colleague and co-reviewer, Dr. Julie Swain, representing that neither one had any conflicts of interest.

She began by discussing valve placement, the number of valves chosen in each particular case, target lobe selection, and the software used. Focusing on two aspects of the study design, she stated that the control group was optimal medical management, and she pointed out that during study development, FDA suggested to the Sponsor that LVRS be used as a control, which the Sponsor rejected. FDA then advised that no comparison could be made to LVRS without an LVRS control.

She reminded the Panel that similar entry criteria does not guarantee the same population and that the NETT population, while similar, was slightly worse at baseline in terms of FEV₁, total lung capacity (TLC), residual volume, and diffusing capacity. She also pointed out that the method of patient selection in the NETT trial was different from the software analysis method used in the VENT trial.

She next touched on potential ramifications due to the fact that the study was not blinded, and referring to the entry criteria, she made note that the software used to determine heterogeneity was different from the visual assessment method.

Addressing patient follow-up, she indicated that the

pre-specified windows for assessment visits had been extended with no reasons being given, which could have consequences for the determination of missing data.

Moving on to study endpoints and statistical analysis, she highlighted the two components of the primary effectiveness endpoint, the FEV₁ and the six-minute walk, and then covered certain aspects of the study size determination. She next discussed three of the final four endpoints, the St. George's Respiratory Questionnaire, the MRC score, and cycle ergometry.

She then focused on the primary safety endpoint, the MCC, and others, including death, lung transplantation, re-hospitalization, and adverse events, and she further discussed the co-primary endpoint components. She directed the Panel's attention to the instances and causes of deaths within the valve treated group, concluding that the 12-month death rates were comparable. She noted certain points of interest and then covered the topics of adverse events and hospitalization.

She summed up her presentation and made these points: (1) the method of patient and target lobe selection is not the same in the instructions for use as in the trial; (2) the instructions for use do not specify how many lobes should be treated, pointing out that the VENT trial did not treat more than a single lobe; and (3) training is not included in the instructions for use.

Jiping Chen, M.D., Ph.D., M.P.H., an epidemiologist in the Division of Postmarket Surveillance, Office of Surveillance and Biometrics, spoke next on development of a post-approval study protocol.

Outlining her presentation, she advised that she would be discussing general principles used in the development of post-approval studies, the rationale for postmarket questions, FDA assessment of the PAS, and other related issues. She stressed that the discussion of a post-approval study prior to formal recommendation did not mean that the FDA is suggesting the Panel find the device approvable.

She next identified the main objective of the general principles for post-approval studies as evaluation of device performance and potential device-related problems over an extended period of time after premarket establishment of device safety and effectiveness. She added that post-approval studies are conducted in order to address issues and concerns that the Panel may have. She explained that questions considered are the real world performance of the device, long-term safety and effectiveness postmarket, and the need for postmarket failure analysis of removed or expectorated valves.

She went on to give the FDA assessment of the Sponsor's PAS outline, beginning with study design; is a single-arm study with descriptive statistics the most appropriate design for a PAS? She asked the Panel members to discuss whether there is a need to compare EBV subjects with LVRS subjects and standard of care controls.

Regarding effectiveness endpoints, she posed the question as to whether spirometry alone would be sufficient to address device long-term

effectiveness postmarket. She also asked the Panel to discuss whether or not there is a need for evaluation of the six-minute walk test in addition to spirometry.

Relating to safety endpoints, she stated that all adverse events, including death, should be documented. She related FDA's uncertainty as to whether it is more appropriate to include all adverse events, not just serious ones, to adequately interpret the device's long-term safety profile. She asked the Panel members to discuss what safety endpoints should be addressed in the post-approval study. She then asked if a follow-up of three years is appropriate.

She next addressed the issue of sample size and explained the FDA's concerns. She asked the Panel to discuss the appropriateness of the migration/expectoration rate of 6 percent for the postmarket period and to discuss what would be an appropriate safety hypothesis for the post-approval study. She indicated that the FDA would be asking the Panel to discuss whether the proposed PAS plan for new patients is appropriate to address device long-term safety and effectiveness and make recommendations.

She finished by asking the Panel to discuss any additional issues or questions that can be addressed in the post-approval study and to make recommendations should the device be approved.

FDA Q&A

The Panel posed questions to the FDA on such issues as the European data, whether it was available prior to the start of the U.S. trial and why it was not used as part of that trial, the window extension, and the higher increase in safety issues with regard to the high heterogeneous subgroup.

Questions were raised relating to protocol violations and whether safety data analyses such as MCC, AEs, SAEs, and re-hospitalizations had been made for the high heterogeneous groups. Questioned as to whether data regarding patients who had valves removed or replaced versus clinical outcomes had been broken down, **Mr. Van Orden** responded that those analyses had been looked at and a determination could not be made whether there was a relationship between having the valve removed and the effectiveness of the device.

The FDA's interpretation of protocol violations was discussed, with the clarification being made that there were lots of protocol violations, but the only ones of concern were the ones the Sponsor identified as clinically important and excluded from the protocol.

Discussion ensued on various other topics, such as the objectivity and subjectivity of pulmonary function tests and whether the measuring of PO₂ is included in these tests. **Dr. Shure** answered no, but that there is an assessment of fatigue and dyspnea, relating further that oxygen saturation is often monitored but is not stopped for desaturation unless it becomes dangerous.

SPONSOR RESPONSE TO PANEL QUESTIONS

Before proceeding to the Panel discussion, **Chairperson Birnbach** gave the Sponsor an opportunity to address detailed issues raised during the morning session. **Mr. McCutcheon** first addressed the question which had been raised concerning why the European data had not been pooled. He answered that it was due to a change in the FDA review team when the PMA was first submitted, resulting in a request that the data not be pooled.

In response to questions regarding the extension of windows, he responded that this was addressed in Dr. Scirba's presentation, that there was no impact on outcomes whether narrow or extended windows were used and that it was made asymmetrical because it was felt that it would be a more conservative approach.

Questions on competence intervals for individual adverse events and baseline comparisons of the available data versus the imputed ITT group were discussed, as were correlations of different versions of the device with performance criteria. **Mr. McCutcheon** offered that multivariate analysis using valve version showed no significance, that there was no learning curve identified in operator experience, and that there was no correlation with either safety or outcome measures. The Sponsor also explained that determination of whether the valve is actually working or not can be visually assessed.

PANEL DISCUSSION

Some of the questions directed to the Sponsor by the Panel were whether there was improved efficacy of appropriate placement with increased experience by the operator. **Mr. McCutcheon** responded that over time placements got better and there was evidence of fewer expectorations.

Philip Marcus, M.D., M.P.H., asked if there was any benefit of re-looking at valves a week later to see how they're doing. **Charlie Strange, M.D.**, replied that it had not been looked at, but when the six-month CT data showed that a fair number were misplaced, the possibility of a one-month scan or re-look in a post-approval study was considered.

Questions with regard to protocol, questionnaires, and the quality of well-being scale were discussed, as well as volume reduction and differences, if any, between groups who had quit smoking and those who had not. Questioned as to whether there was any data beyond the one-year landmark, **Mr. McCutcheon** replied that the Sponsor is working with the FDA to continue follow-up, and as soon as there is an approved IDE, there will also be continued follow-up on that as well.

Other issues such as clarification made between the mortality analysis and the mortality plus LVRS analysis were also discussed, along with questions regarding the clinical relevance of the six-minute walk test and event rates for the key safety outcomes of the high heterogeneity subgroup by

treatment group.

PANEL DELIBERATIONS AND FDA QUESTIONS

The following FDA questions were presented to the Panel for deliberation.

Dr. Choe read Question 1 to the Panel: Please comment on the interpretability and validity of the statistical results for effectiveness in light of the extent of protocol violations and missing data.

There was general agreement among the Panel members that this is not the primary issue. It was observed that what needed to be considered most is whether the inclusion of patients with protocol violations or problems with missing data led to a statistical finding of superior effectiveness when there isn't one and that it is helpful to consider the issues of protocol violations and missing data separately. Some concern was expressed regarding the reliability and validity of the results due to the protocol violations and that the P-value was not met in the original analysis with respect to the primary endpoint, even though the window had been extended.

Andrew L. Ries, M.D., M.P.H., expressed his feeling that the issue is not so much the violations but whether there is some differential effect of lost data. Should the FDA's view that a combination of both endpoints is necessary be accepted or the Sponsor's view that it should be either one or the other? **Benson R. Wilcox, M.D.**, stated his view that the blinded-ness is a major issue, and **Thomas Vassiliades, M.D.**, expressed that he is not troubled by the protocol violations or missing data and that, overall, the data is interpretable and valid.

The Panel members, in general, were in consensus that this was a difficult study with a difficult patient population, and they were not particularly troubled by the data.

Chairperson Birnbach summarized that although there was not unanimity, the Panel generally believes that the protocol violations were an issue, but probably not a major issue and one that was unavoidable, and that they are generally okay with the data as it relates specifically to validity and reliability.

The Panel then moved on to Question 2: Please provide your interpretation of the safety data collected in the VENT trial.

Chairperson Birnbach advised that although a 15 percent change had been anticipated, that was not actually seen, and the Panel would have to come to an understanding of whether the findings were adequate or not. He asked for assessment of the results of the co-primary and secondary effectiveness endpoints in the VENT study and discussion of the clinical significance of these results.

Karen B. Domino, M.D., M.P.H., stated that although there were

some patients who did respond to the 15 percent threshold, she had doubts as to the effectiveness or that the effect size is very large; also, the seeming occurrence of it going down over time, suggesting a possible tangent effect. **Claude D. Brunson, M.D.**, observed that improvement was not sustained but was unsure if it could have been.

Robert G. Loeb, M.D., expressed his conclusion that a very good effect can be achieved when the device is used appropriately in the right patients but that much of the statistical findings were diluted due to the fact that it either was not used properly or the wrong patients were chosen, among other reasons, and that although it is a promising device, a lot more work needs to be done to ensure that it is used to its best advantage. Other Panel members expressed agreement. **Dr. Valliades** stated that his interpretation is that the device is not clinically effective.

Another topic of concern in regard to the endpoints was whether they really translate to clinical benefits to patients and improvement in quality of life and that data beyond one year would have been helpful. There was also general consensus that patients who can benefit had not yet been identified.

Chairperson Birnbach summed up by asserting that the Panel does believe some very promising and interesting data had presented; however, there does not seem to be a huge difference and the Panel would have liked to have seen the 15 percent mark that the Sponsor was aiming for. He pointed out that the Panel is not sure whether or not there is any clinical significance; also, there is some troubling information that this may not be a permanent effect, but rather a tangent effect.

The Panel was next presented with Question 3: Please discuss and provide your interpretation of the device safety in the VENT study.

Rosalie Dominik, Ph.D., began the discussion, stating that she was no longer worried that there was evidence of an increased risk of adverse events for higher heterogeneity patients, and she further stated her belief that in interpreting safety data, it is important to look at the confidence intervals. She also encouraged that safety data be looked at from a non-inferiority perspective. **Susan Halabi, Ph.D.**, agreed and shared her concern regarding the increased hospitalization in the device arm.

Dr. Marcus and **Dr. Ries** articulated that they did not have concerns regarding the safety issues. **Sandra Willsie, D.O., FACOI, FACP, FCCP**, added that concern should be focused on what will happen when the device is out in the community and being used by those who are less familiar with it and that adverse effects could be expected to go up. **Stephen Li, Ph.D.**, concurred, stating that complication rates may change with a different patient population or indications. Concerns were also raised about long-term data as opposed to the short-term safety data.

Dr. Vassiliades related that he had no major concerns with safety, and **Dr. Loeb** pointed out that the risk profile is exactly what he would expect from such a device; like any other device, it is going to have its side effects.

Thomas E. Wiswell, M.D., agreed and voiced concern over the fact that the deaths seem to be more COPD-related and more follow-up of patients is clearly needed.

Chairperson Birnbach concluded that the Panel believes, based on the evidence given, that the device appears to be safe, but the Panel needs to see more long-term data especially as it relates to death and long-term infections.

The Panel then moved on to Question 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.

Dr. Vassiliades began the discussion by making the observation that while the risks are not huge, they are not insignificant either, and there has to be demonstrated clinical efficacy, and it is his belief that the benefits are inadequate to overcome the risks. **Dr. Wilcox** reminded the Panel that the procedure has been demonstrated to be safe when done by the investigators and agreed that there is a low predictable benefit.

Chairperson Birnbach also asked the Panel to take into consideration the changes that could occur to the risk benefit analysis once the device is being used in the community in general by operators who may not be as well-trained and supervised.

There was agreement voiced among some of the Panel members that the benefit does not outweigh the risk, and what will happen when the device goes out into the general public and is used in various ways? There was also general agreement that it is a very promising field and there needs to be a better definition of patients who would benefit.

Chairman Birnbach, in summary, described the Panel's feeling as one of ambivalence, pointing out that although there is excitement about the potential, that at this point, with the data provided, the risks, though not huge, are not insignificant and the benefits are not clearly enough demonstrated to outweigh those risks.

Dr. Choe advised the Panel that the final two questions were intended for the Agency's guidance should the device be approved and read Question 5 to the Panel: With regard to the indications for use, instructions for use, 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.

Chairperson Birnbach asked the Panel if there should be a limitation of one lobe and whether additional warnings would be necessary. **Dr. Willsie**

shared her view that the limitation should specify what patients the device should be used on as well as where it would be placed. The other Panel members observed that the two go hand-in-hand, that the type of patient would define where the device would be put.

Dr. Ries pointed out that heterogeneity should be defined in a way that could be generally understood and added that the issue of integrity of the fissure should also be defined.

Following some more discussion, the Panel concluded that there should be more data regarding which patients should receive this device, placement of the device, whether there should be limitations on such things as the number of devices used, and on high-resolution CT. The Panel also placed emphasis on heterogeneity, effectiveness after placement, and the need for far more extensive information regarding training of those individuals who would be performing the procedure.

The final question, Question 6, was then presented to the Panel for deliberation: Is the proposed post-approval study appropriate to address training effectiveness and device long-term safety and effectiveness postmarket? Please discuss the following: Is the study design appropriate to evaluate device safety and effectiveness postmarket? What should be a comparison group against which these data should be evaluated? Is it valid to assume that the migration/expectoration rate will be 6 percent in postmarket, which is less than what was observed in premarket, which was 7.9 percent? Is there a need for the evaluation of six-minute walk test in addition to spirometry as effectiveness endpoints? What safety endpoints needed to be addressed? Is a follow-up of three 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 your recommendations.

Dr. Marcus began the discussion by stating that the design seems appropriate, but in addition to just looking at spirometry, there should be other measures of quality of life and health status showing effectiveness. He was unsure as to how there could be any other comparison group, that he expected to see migration and expectoration higher than at premarket, that there needs to be something to indicate if the device is benefiting patients, and that he did not feel that he could add anything else to the safety endpoints issue, other than looking long-term at the incidence of true post-obstructive pneumonia secondary to long-term placement of the valve. He also stated his belief that three years is long enough.

Dr. Dominik suggested the addition of some kind of clinical functionality measures for patients assessing changes in daily living. **Chairperson Birnbach** agreed it was a good idea. **Dr. Wiswell** also suggested that the wording in the postmarket study should reflect that it is for patients with severe heterogeneous emphysema, the population where it seems to be potentially the most effective. **Dr. Marcus** added that it depends on

how "severe" is defined and that if the criteria of the FEV₁ is being used, then this is the group that it has been intended for from the beginning.

Dr. Ries expressed the opinion that the real issue is not really the improvement in the treated group; it is the improvement relative to the expected decline because the effect is going to be lost over time. Thus, any other kind of non-randomized comparison is going to be problematic. He also suggested the possibility of designing a delayed treatment group for the purpose of obtaining more observations over time.

In summation, the Panel's conclusion was that the design for the post-approval study appears to be appropriate, but there should be some additions and clarifications. For example, there should be assessments of some sort of quality of life and clinical functionality. The Panel would also like to see further radiographic evidence information, that the wording should be severe heterogeneous emphysema and should be well-defined.

SECOND OPEN PUBLIC HEARING

There were no requests to participate in the open public hearing.

FDA AND SPONSOR SUMMATION

The FDA had no further comments.

For the Sponsor, **Dr. Sciurba** began by stating that although there is a modest effect, subgroups have been identified, and he urged the Panel to consider a postmarket study that takes advantage of all that has been learned.

He pointed out that the heterogeneity group was not a tiny subgroup, that it was 50 percent of the patients, and of this 50 percent, there had been a 12 percent improvement in FEV₁ and a 14 percent improvement in the six-minute walk. Regarding fissure integrity, he stated that when there had been a tie in heterogeneity between the left and right lobe, the right upper lobe was defaulted to. He expressed his belief that results concerning lobar exclusion would be technically better due to what had been learned about follow-up CT scan, and he also expressed concerns about not being able to offer desperately ill patients this choice of technology. He also stated that he found the fact that this is reversible, that the valve can be removed, to be reassuring. He then expressed concern about the possible loss of this technology.

Dr. Criner thanked the Panel and stated that he believes that selection of appropriate patients for this therapy can be achieved in a labeling and post-approval study period. He also expressed the belief that the delineation of complete fissure, high heterogeneity, and complete lobar exclusion by CT analysis are all things that could be done in the labeling and training period of time. He added that appropriate placement and removal of valves, to prevent

issues with valve migration and hemoptysis, could also be done in the labeling and training period.

He listed other issues that could be addressed in post-approval studies as COPD exacerbations, hemoptysis, expectoration of valves, post-valve implantation pneumonia, quality of life, functional status and performance, radiographic confirmation of sustained improvement, and no complication.

COMMENTS BY CONSUMER REPRESENTATIVE

Carolyn Petersen, M.S., thanked the Panel and stated her belief that for patients who have very few options, a way should be found to make this technology work, but she stressed her concern about approving a device in which there is uncertainty regarding identification of appropriate patients and of its effect in day-to-day life as opposed to the laboratory.

COMMENTS BY INDUSTRY REPRESENTATIVE

David Osborn, MEE, agreed that while there is promise with the device, there are substantive issues about selection of appropriate patients and also of follow-up measures on those patients. He suggested the need for a protocol of use to ensure that the valves have been effectively placed, observing that any sort of protocol needs to include this because if a leak in the data occurs, as in this case, which was half the patients, that the expected therapeutic effect would not result, and if that had been corrected, there may have been a very different outcome.

PANEL VOTE

Mr. Patel read the Medical Device Amendments to the Federal Food, Drug and Cosmetic Act as amended by the Safe Medical Devices Act of 1990 and informed the Panel that the options for the vote are as follows:

(1) Approval if there are no conditions attached; (2) Approvable with conditions; (3) Not Approvable. The Panel then commenced with the vote.

Dr. Marcus moved for approval with conditions, which was seconded by **Dr. Ries**. Discussion on this motion ensued, with **Dr. Ries** voicing his opinion that the issue of undue risk needs to be balanced with the perceived benefits and the lack of options. He pointed out that there is much that is not known about this disease and much that cannot be offered. **Hugh A. Cassiere, M.D., FCCP**, reiterated that approving a product just to continue research is not justifiable. **Chairperson Birnbach** then asked if anyone wished to recommend a condition. **Dr. Marcus** moved that the post-approval study as outlined in Number 6 in the questions for the Panel be a condition of approval, which was seconded. The Panel voted four in favor, nine opposed.

Dr. Loeb next moved to change the labeling to specify which patients and to evaluate effective placement, which was seconded. **Dr. Ries** then

suggested that as an amendment, these be considered as two requests.

Dr. Loeb acceded. The Panel voted four in favor, nine opposed.

Dr. Loeb moved for adoption of a rigorous educational program associated with the device after approval, which was seconded. The Panel voted seven in favor, six opposed.

The Panel then voted on the main motion, approval with conditions, two in favor, eleven opposed.

Dr. Vassiliades moved that the device be found not approvable, which was seconded. The Panel voted eleven in favor, two opposed, with no abstentions.

PANEL RECOMMENDATION

The Panel recommended that PMA P070025 for the Zephyr Endobronchial Valve System be found not approvable.

PANEL COMMENTS ON RECOMMENDATION

Chairperson Birnbach asked each Panel member to explain the reasons for their votes and also for comments from the industry and consumer representatives.

Dr. Domino stated that she would like to see the CT scanning and selection in the heterogeneous group who might have a greater benefit of effect and also to see follow-up safety data for more than one year; also, that there is promise for this and that there is a subcategory of patients that will benefit. **Dr. Brunson** agreed and added that the Sponsor needs to tighten up selection of the group, which the Sponsor appears to have already gotten a good start on. He stated that he would also like to see more long-term data regarding sustainability when the subset of patients that can benefit is selected.

Dr. Wiswell stated that there was not enough clinical effectiveness for approval of the device, and he would like to see long-term safety data of three years or more. **Dr. Loeb** cited the fact that the data presented did not show an adequate benefit-risk ratio and observed that a trial more limited in scope with better patient selection and earlier evaluation would have shown adequate risk benefit, but there was no data to show that; therefore, he could not, in good faith, vote for approvable with conditions.

Dr. Vassiliades suggested further definition of the subgroups, and **Dr. Wilcox** expressed the opinion that he believes the Sponsor has not provided reasonable assurance that the use of this device is broadly applicable clinically.

Dr. Cassiere was of the opinion that a niche patient population needs to be clearly defined and that the outcomes of these patients after a year should be looked at.

Dr. Li explained that the reason for his no vote was a combination of

clinical results that could have been a lot better but was reinforced by a lack of understanding of how these devices are actually performing. He added that the correlation of FEV₁ with actual patient activity may not be as strong as the Panel would like to see, and seeing that this was the best of the clinical results, he felt he had no option but to vote no.

Dr. Willsie commented that she would like to see a new study looking at a newly defined population that is most likely to respond using lessons learned regarding the fissure, lobe selection, clinical significance for outcome, and to abolish the placebo effect.

Dr. Ries commented that the Sponsors are well on their way to finding the appropriate use of this device in terms of the heterogeneity and the lobar exclusion; also, that the data presented in terms of effectiveness and the balance of effectiveness and safety are not compelling. **Dr. Marcus** agreed, adding that he believes there is still a future for this and that perhaps more studies need to be done.

Dr. Halabi cited the issues of a large proportion of missing data, post-hoc window extension, and multiplicity of analysis as the reason for her no vote, and she added that she would like to see a larger trial with a smaller number of missing data.

Dr. Dominik remarked that if the high heterogeneity subgroup is more likely to have the benefit, changes in the procedures for how the device is placed and followed up immediately may help to improve the effectiveness, and it may not take as large of a study to demonstrate the effect in that group. She observed that a new trial showing effectiveness more definitively in that subgroup plus safety data from the current trial would contribute to the overall evaluation of safety and effectiveness.

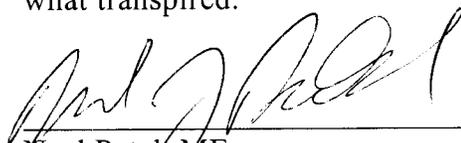
Ms. Petersen commented that she appreciated the Panel voting not to approve and for resisting the temptation to use the approval process to facilitate the research. She reiterated the need to better understand who can be helped by this and what the benefits are.

Mr. Osborn stated that he would like to have seen an analysis of the data breaking apart at the six-month point, those patients that had leakage from those that didn't, which he felt might have correlated with those that had an effect and didn't. In terms of conducting further trials, he stressed that it is very important to focus on the right patient, the proper placement of the valve, and the complete blockage of the desired lobe. He reiterated that the labeling needs work, and a training module needs to be created to reflect that.

ADJOURNMENT

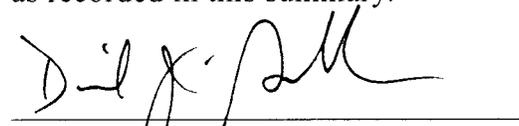
Chairperson Birnbach thanked the Panel, the FDA, and the Sponsor. **Chiu Lin, Ph.D.**, Director, Division of Anesthesiology, General Hospital, Infection Control and Dental Devices, also thanked the Panel and the Sponsor. The meeting was adjourned at 4:30 p.m.

I certify that I attended this meeting on December 5, 2008 and that these minutes accurately reflect what transpired.



Neel Patel, MEng
Executive Secretary

I approve the minutes of this meeting as recorded in this summary.



David J. Byrnbach, M.D., M.P.H.
Chairperson

Summary Prepared by

Karen D. Martini
Free State Reporting, Inc.
1378 Cape St. Claire Road
Annapolis, MD 21409
(410) 974-0947
December 17, 2008