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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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ANESTHESIOLOGY AND RESPIRATORY THERAPY
DEVICES PANEL

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December 5, 2008
8:00 a.m.

Hilton Washington DC North
Salons A, B and C
620 Perry Parkway
Gaithersburg, MD 20877

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M E E T I N G

(8:02 a.m.)

DR. BIRNBACH: Good morning. I would like to call this meeting of the Anesthesiology and Respiratory Therapy Devices Panel to order.

I am Dr. David Birnbach, the Chairperson of this Panel. I'm a Professor of Anesthesiology, Obstetrics and Gynecology in Public Health at the University of Miami, Miller School of Medicine, where I'm also Associate Dean and Vice Provost.

If you haven't already done so, please sign the attendance sheets that are on the tables by the doors. If you wish to address this Panel during one of the open sessions, please provide your name to Ms. AnnMarie Williams at the registration table.

If you are presenting in any of the open public sessions today and have not previously provided an electronic copy of your presentation to the FDA, please arrange to do so with Ms. Williams.

I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I'd also like to add that the Panel participating in the meeting today has received training in FDA device law and regulations.

No one from the public or press is allowed

into the Panel area at any time during the breaks or during the conduct of this meeting.

Mr. Patel, the Executive Secretary for the Anesthesiology and Respiratory Therapy Devices Panel, will make some introductory remarks.

MR. PATEL: Thank you, Mr. Birnbach.

I will now read the Conflict of Interest Statement followed by the appointment of temporary voting members statement.

The Food and Drug Administration is convening today's meeting of the Anesthesiology and Respiratory Therapy Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and consultants of this Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act are being provided to participants in today's meeting and

to the public.

FDA has determined that members and consultants of this Panel are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special Government employees who have potential financial conflicts when it is determined that the Agency's need for that particular individual's services outweighs his or her potential financial conflict of interest. Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special Government employees and regular Government employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussions of today's meeting, members and consultants of this Panel who are special Government employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purpose of 18 U.S.C. Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties,

and primary employment.

Today's agenda involves the discussion of a premarket approval application for the Emphasys Zephyr Endobronchial Valve System sponsored by Emphasys Medical, Incorporated. The device is intended to improve forced expiratory volume in the first second FEV_1 and six-minute walk test distance in patients with severe heterogeneous emphysema who have received optimal medical management. This is a particular matters meeting during which specific matters related to this PMA will be discussed.

Based on the agenda for today's meeting and all financial interest reports by the Panel members and consultants, no conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208 and Section 712 of the FD&C Act. A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

Mr. David Osborn is serving as the industry representative, acting on behalf of all related industry, and is employed by Philips Healthcare.

We would like to remind members and consultants that if their discussions involve any other products or firms not already on the agenda for

which the FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Panel of any financial relationships that they may have with any firms at issue.

Pursuant to the authority granted under the Medical Devices Advisory Committee Charter of the Center for Devices and Radiological Health, dated October 27, 1990, and as amended August 18, 2006, I appoint the following individuals as voting members of the Anesthesiology and Respiratory Therapy Devices Panel for the duration of this meeting on December 5, 2008.

Dr. Benson Wilcox, Dr. Andrew Ries, Dr. Stephen Li, Dr. Thomas Vassiliades, Dr. Sandra Willsie, Dr. Philip Marcus, Dr. Susan Halabi and Dr. Rosalie Dominik.

For the record, these individuals are special Government employees and are consultants to this Panel or other Panels under the Medical Devices Advisory Committee. They have undergone the customary conflict of interest review and have reviewed the material to be considered at this

meeting.

This statement was signed by Dr. Daniel G. Schultz, Director for the Center of Devices and Radiological Health, and dated November 24, 2008.

Before I turn the meeting back over to Dr. Birnbach, I'd like to make few general announcements.

Transcripts of today's meeting will be available from Free State Court Reporting, and their phone number is (410) 974-0947.

Information on purchasing videos of today's meeting can be found on the table outside the meeting room.

Presenters to the Panel who haven't already done so should provide FDA with an electronic copy of their remarks.

I would like to remind everyone that members of the public and the press are not permitted in the Panel area at any time during the meeting including the breaks.

The press contact for today's meeting is Siobhan DeLancey, and she's in the back of the room.

I request that reporters wait to speak with FDA officials until after the Panel meeting.

And, finally, please silence your cell

phones. Thank you very much.

Dr. Birnbach.

DR. BIRNBACH: Good morning again. At this meeting, the Panel will be making a recommendation to the Food and Drug Administration, FDA, on the Premarket Approval Application, or PMA, P070025, for the Zephyr Endobronchial Valve System from Emphasys Medical, Incorporated.

Before we begin, I would like to ask our Panel members and the FDA staff seated at this table, to introduce themselves. Please state your name, your area of expertise, your position, and your affiliation. Dr. Lin.

DR. LIN: Good morning. My name is Chiu Lin. I'm the Division Director of Division of Anesthesiology, General Hospital, Infection Control and Dental Devices, FDA.

DR. DOMINO: Karen Domino, Professor of Anesthesiology, University of Washington.

DR. BRUNSON: Dr. Claude Brunson, Professor and Chairman of Anesthesiology and Administrator of Perioperative Services at University of Mississippi Medical Center.

DR. WISWELL: Tom Wiswell. I'm a neonatologist at Florida Hospital Orlando and a

Professor of Pediatrics at the University of Florida.

DR. LOEB: I'm Robert Loeb. I'm an Associate Professor of Anesthesiology at University of Arizona.

DR. VASSILIADES: Tom Vassiliades. I'm an Associate Professor of Cardiothoracic Surgery at Emory University in Atlanta.

DR. WILCOX: I'm Ben Wilcox, a Professor of Surgery at the University of North Carolina in Chapel Hill.

DR. CASSIERE: Hugh Cassiere, Pulmonary Critical Care. I'm the Director of the Cardiovascular and Thoracic Surgery Critical Care Division, North Shore University Hospital, New York.

DR. LI: Stephen Li. I'm President of an independent research and development company, Medical Device Testing and Innovations in Sarasota, Florida.

DR. WILLSIE: Sandra Willsie from Overland Park, Kansas. I'm a Professor of Medicine, Pulmonary Critical Care at Heartland Health Sciences University.

DR. RIES: Andy Ries. I'm a pulmonary critical care physician at the University of California, San Diego, Professor of Medicine and Family Preventative Medicine and Associate Dean of

Academic Affairs.

DR. MARCUS: I'm Phil Marcus from Long Island, New York. I'm the Chief of Pulmonary Medicine at St. Francis Hospital and the Associate Dean of Curriculum Development and Professor of Medicine and Pharmacology at the New York College of Osteopathic Medicine.

DR. HALABI: Susan Halabi, Associate Professor of Biostatistics, Duke University Medical Center.

DR. DOMINIK: Rosalie Dominik, Associate Professor of Biostatistics, University of North Carolina Medical School and Department of Biostatistics.

MS. PETERSEN: I'm Carolyn Petersen. I'm the Consumer Representative. I'm Managing Editor with Mayo Clinic, Global Products and Services, and my medical training is in exercise physiology.

MR. OSBORN: Dave Osborn, Philips Healthcare. I'm the Industry Representative, and I'm also secretary of ISO TC 121 Subcommittee 3, lung ventilation and related equipment.

DR. BIRNBACH: Okay. We will now proceed with the open public hearing portion of the meeting.

Both the Food and Drug Administration, FDA,

and the public believe in a transparent process for information gathering and for decision making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of any individual's presentation. For this reason, FDA encourages you, the open public hearing or industry speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have to the Sponsor, its product, and if known, its direct competitors.

For example, this financial information may include the Sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Prior to the meeting, we received no formal requests to speak during today's open public hearing sessions.

Would anyone wish to address the Panel at

this time?

(No response.)

DR. BIRNBACH: Okay. Seeing no one, we will now proceed to the Sponsor presentation for the Zephyr Endobronchial Valve System.

I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel.

MR. McCUTCHEON: Good morning, Dr. Birnbach, distinguished Panel members. Thanks so much for the time that you've taken to review our PMA, time and energy, and the time that you're taking here today will be greatly appreciated.

I also wanted to briefly thank the FDA review staff who have been working on this together for sometime. The PMA submission is an expedited review and that puts additional pressure on the FDA staff, and we really do appreciate the efforts that they've gone through to help us in that effort.

Let me take just a few minutes to introduce Emphasys Medical, and then I'll introduce our speakers and other advisors and go through our agenda this morning.

Emphasys Medical was founded in June of 2000 on the concept of developing a minimally invasive endobronchoscopic approach to creating volume reduction in patients with advanced heterogeneous emphysema, and to that end, we've developed the endobronchial valve system, Zephyr EBV.

That's our sole product at this point. We're a small medical device company with 48 employees all based in Redwood City, California. We manufacture there, as you can see in the picture here, and we currently have CE Mark and are on the market in Europe in a limited commercial launch.

The Zephyr EBV, or endobronchial valve, the proposed indication based on our VENT results are to improve FEV_1 and six-minute walk test distance in patients with severe, heterogeneous advanced emphysema who have received optimal medical management.

Our speakers today are all of our investigators in that study. Dr. Frank Sciurba was the principal VENT investigator.

We're going to start with Dr. Gerard Criner from Temple University. Dr. Criner will outline the clinical need, the clinical problem that exists today, the unmet need for treating these patients.

He'll also describe the device and system in more detail and go through the trial design.

We'll then ask Dr. Armin Ernst to approach the bench and provide baseline characteristics for the study. He'll also go over the conduct of the study including patient accountability and safety.

And then Dr. Frank Sciurba, from University of Pittsburgh, will provide the efficacy results for VENT.

Finally, Dr. Criner will come back and present the training and post approval study proposals as well as the conclusion to our presentation.

In addition to our speakers, we have additional advisors. Dr. Geoff McLennan and Dr. Charlie Strange are both VENT top enrollers and have a wealth of background in pulmonary medicine. Our imaging Core Lab director, Jonathan Goldin, from UCLA, is here as well. Our primary biostatistician is Dr. Richard Chiacchierini. And then the clinical events committee chairman, Dr. Christopher Cooper, and our data safety monitoring board chairman, Dr. Robert Wise, will be here as well to support any questions.

With that, I'd like to invite Dr. Criner to

come up and begin the presentations. Thank you.

DR. CRINER: Thanks, John. Good morning, Mr. Chairman and Panel members.

In terms of disclosure, I've received travel expenses and lodging by the Sponsor for this meeting. I received no honorarium, and I have no equity in the firm. I was a principal investigator at the Temple site for the VENT trial, and as far as professional background, I'm the Director of Pulmonary and Critical Care Medicine at Temple University. I was one of the principal investigators of the National Emphysema Treatment Trial, which was a study of lung volume reduction surgery versus optimal medical management, and I'm currently a principal investigator at Temple for NIH trials for the COPD Clinical Research Network, a long-term oxygen treatment trial, and for the COPD genetic epidemiology study. I've been involved in the research and clinical care of patients with COPD and emphysema for over the last 20 years.

So my job in this 18 to 20 minutes is really to frame the clinical problem of patients with emphysema, the needs that they have for further new treatments and also describe the trial design.

So for some background for the non-clinical

members of the Panel, emphysema, as most know, is a progressive and debilitating disorder that markedly impairs patients' quality of life. It's estimated by more recent guidelines from the American Lung Association in 2007, there currently are 12 million American that suffer from COPD and approximately 3.5 million of those are estimated to suffer from emphysema.

Pharmacologic intervention is used in patients with predominant emphysema, also like with patients with COPD at large, but it's believed to be of limited value.

In fact, only smoking cessation has been proven to alter the decline in lung function that patients with COPD or emphysema have.

The only medical treatment that we have that has been shown to improve survival of patients with COPD or emphysema is oxygen therapy, and that only benefits a small subgroup who have lower oxygen values.

So why is emphysema so morbid and mortal? Some of it relates to the pathophysiological effects of emphysema. Emphysema is irreversible destruction of lung tissue that involves the alveolus or air sack and the small airway. This causes severe airflow

obstruction, impairs gas exchange, contributes to low oxygen, high carbon dioxide, and the trapping of gas that happens in the lung impairs how the lung works, the chest wall and respiratory muscle mechanics.

It would be if any of you in the room took a big breath in, breathe a little bit out and try and take another big breath in. Some of these patients suffer from the effects of hyperinflation promoting the feeling of suffocation and limits their exercise tolerance.

Now patients who have COPD have significant variability in severity and distribution of the extent of emphysema that they have. It can be more or less severe. It can involve different regions of the lung, and that concept of heterogeneity will be discussed further through the presentation.

This is a paradigm of what are the factors from a pathophysiologic standpoint that contributes to the severe morbidity, mortality and disability and impairment of quality of life that patients with severe emphysema suffer. The severe hyperinflation from the pathophysiological mechanisms that I've showed you increases the patient's dyspnea. It decreases their activity performance. They become further deconditioned. It increases their dyspnea

further and leads to a circle downward spiral of inactivity that leads to greater morbidity and mortality such as in the representative patient that's shown here is now chair bound, is dependent upon others to give his care, and his quality of life is markedly impaired.

So these are the treatment options, the medical treatment options that we have currently for patients with COPD and those who suffer from emphysema. This is based on the GOLD criteria, an international consortium of respiratory experts that represent international societies of pulmonary medicine. In this treatment paradigm, the staircase ascending treatment plan is based on the severity of the underlying lung disease. So as patients become more severe, we treat them with bronchodilators more intensively. We added inhaled and in some cases, systemic steroids, and we have long-term oxygen therapy.

In the patients that we'll be presenting for this therapy, these patients have already received this optimized maximal medical regime.

But even if we do this, the data from the National Emphysema Treatment Trial tells us that these patients not only suffer from significant

morbidity, they suffer from significant mortality. This is data from the National Emphysema Treatment Trial in over 1,000 subjects who received optimized medical treatment, and you can see at two years these patients, despite optimum medical treatment, have an 18 percent mortality and in 5 years have approximately a 40 percent mortality.

Because of this high mortality, despite medical treatment, surgeons since Otto Branagan (ph.) in 1950 have looked at other ways to decrease the size of the thorax to improve patient's physiologic function and hopefully functional status. This was revised by Joel Cooper in 1993 and was coined lung volume reduction surgery, the surgical approach to make the lungs smaller and the thorax smaller by cutting out about 30 percent of both lungs and right size the thorax to a better degree.

After Dr. Cooper presented his results in 1993, this was endorsed by a number of practitioners that led to uncertain outcomes, both in morbidity, mortality, and cost. Because of that, CMS ceased payment in 1995 and worked with the NHLBI, the agency of healthcare policy research, to start the National Emphysema Treatment Trial, which was an unblinded, multicenter, prospective, randomized clinical trial

of bilateral lung volume reduction surgery compared to optimal medical management in patients with severe emphysema.

The primary endpoints of that trial were survival and maximum exercise. Secondary endpoints were lung function, quality of life, six-minute walk test, and cost effectiveness.

In summary, NETT randomized over 1218 patients with follow-up of up to 7 years, and important subgroups were identified that showed a preferential improvement with lung volume reduction surgery towards survival, improvement in exercise capacity, and quality of life.

We also found from that that there was a treatment response or treatment effect that could be predicted by their pattern of emphysema such that in the non-high risk group, those who had upper lobe predominant disease had more pronounced improvements either in mortality for the upper lobe/low exercise group or for the upper lobe group at large for exercise performance and quality of life. So this was the first study that showed that the heterogeneity of emphysema on high resolution CT scan could predict response to a surgical therapy.

NETT had great benefits, but NETT also

carries morbidity and mortality. The 90-day mortality for patients who underwent surgical therapy was approximately 5 percent. The 30-day morbidity included air leaks that were found in 90 percent of patients, 50 percent of those had air leaks that was a week or greater in duration. About 50 percent of these patients suffered from cardiopulmonary morbidity such that in the year 2006, only 120 Medicare beneficiaries received lung volume reduction surgery across the United States. In the year 2007, only 104 Medicare beneficiaries underwent lung volume reduction surgery.

Also, if one looks at the NETT data, at six months, in terms of change in FEV_1 percent and six-minute walk test, you see a marked scatter in the potency of the treatment. Some patients had substantial improvements of a minimal amount. Others had much less extent of improvement in both the FEV_1 percent change and six-minute walk test. So the potency of the treatment wasn't guaranteed to the group at large.

This has led to the perspectives that we think contributes to the lack of the use of this therapy in the public. When patients talk to their physicians, although LVRS has benefits in terms of

improving lung function, exercising and performance, quality of life, and the subgroup with upper lobe disease and low exercise, it decreased in mortality, that it is also counterbalanced by these risks and uncertain potency of treatment of all patients that go through the therapy such that when we look at patient such optimized medical therapy who are severe or very severe due to their disease, that these patients could potentially undergo either a lung volume reduction surgery or lung transplant patient, but currently this is rarely done because of limited access, the perceptions of morbidity and uncertain changes in clinical status. So this results in unmet clinical need for these severely impaired patients who have undergone maximum medical treatment.

That was the reason to move forward to try to investigate more non-invasive techniques who could provide lung reduction but do so in a less morbid and mortal fashion.

So let me describe for you the VENT trial. The VENT trial was centered on therapy, but the vehicle is the Zephyr Endobronchial Valve. It is an implantable one-way valve. It modifies airflow in the lung. It's bronchoscopically delivered and can be delivered under local or general anesthesia, and

in contrast to surgical therapy, it's removable and reversible.

This is the cartoon that shows overall the schematic of how the valve conceptually works. It's a one-way endobronchial valve. It prevents inspiratory airflow, but this one-way valve allows egress of air and fluids from the sealed and vented portion of the lung which it has been treating. Multiple valves can be placed into feeding segmental bronchi into a lobe. It can isolate the diseased targeted lobe with emphysematous destruction and hopefully collapse it.

This is a schematic of what the endoscopist would see. There's windows that helps to size the size of the bronchus so the appropriate valve size could be picked. This valve is then inserted with the crown below the segmental orifice to help anchor it. You can see after this valve was placed, that there's vacuum on the other side, and there's a negative tug on the duckbill that's somewhat bent. You can see it's blocked on inspiration and then on expiration, the valve vents and allows that locked and sealed segment of lung to empty.

So patient -- that was part of the trial that before and one month after chest x-rays were

obtained, this patient had segmental treatment of all three right upper lobes segmental bronchi and had lobe -- of the upper lobe. You can see here that this shows the volume of the lung before treatment. This shows the horizontal fissure after treatment. You can see that there's a decrease in size of the volume of the lung in the thorax and a horizontal fissure shifts up showing that we've isolated and collapsed or partially collapsed that portion of the lung.

This also shows, the cartoon shows the device can be easily removed. Use alligator forceps and pull on a portion of the stent at the crown, and it can be easily removed endoscopically.

So let me move forward and talk to you about the trial design. There was a FDA Panel advisory meeting in 2003 who made four important recommendations to the trial design. The Panel recommended at that time that the targeted population should be similar to NETT, that the endpoints should be physiologic, exercise tolerance and clinical endpoints should be included, and the trial duration should be 6 months for efficacy and 12 months for safety, and the control group should be optimal medical management plus pulmonary rehabilitation and

therefore no sham. These recommendations were all adopted for the design and implementation of the VENT trial.

This is the methodology, the important methodology that was used to conduct the trial. Heterogeneous emphysema was defined by digital high resolution CAT scan imaging. This was scored by a center Core Lab. Target of lobe for treatment was defined by the percent emphysematous destruction from the targeted lobe minus the adjacent lobe in the ipsilateral lung.

Pulmonary rehabilitation was optimized and used per the NETT protocol, 6 to 8 weeks of duration, with 12 to 18 sessions. This included treatments of upper and lower limb strength and endurance.

Optimal medical management also followed the NETT trial, smoking cessation, optimized bronchodilator therapy, vaccination, optimal medical treatment per NETT per GOLD guidelines.

Sample size calculation was based on a pilot trial and based on an assumption of 15 plus or minus 33.7 percent for FEV_1 and 17 plus or minus 41.5 percent for 6-minute walk test, and as you can see based on this pilot data, these had very large variance assumptions for the projections of the

power.

This is overall line diagram of how NETT was conducted. Prospective randomized control trial at 31 U.S. centers, involving 321 patients, with heterogeneous emphysema. Pulmonary rehab and optimal medical treatment was given to all subjects. Patients then had baseline testing, and then were randomized in a 2 to 1 randomization scheme to Zephyr EBV plus continuation of optimal medical management and 220 were optimal medical management alone and 101 participants.

These are the key entrance inclusion criteria and exclusion criteria. These mirrored the NETT criteria. Patients were 40 to 75 years of age, normal body mass index or this window showing here between 31 and 32 or less than that, heterogeneous emphysema, severely obstructed gas trapped hyperinflated.

Exclusion criteria were patients without Alpha-1 antitrypsin deficiency, large bullae, significant respiratory secretions or underlying cardiac morbidity.

There were some challenges to choose the endpoints that have been discussed by others. The NIH has brought up that since COPD is such a protein

or diverse disease, it's hard to get one measure that would look at and say that you've met points of efficacy. Also the FDA has recommended that the six-minute walk test has a substantial amount of noise, and it might be hard to control those factors and find the signal of treatment. And the FDA has further recommended that since some of these signals may be important but relatively small, because of the heterogeneity of the disease, perhaps not one index but two index needs to be the primary endpoints when designing trials in patients with COPD.

Because of that, VENT chose two co-primary efficacy endpoints, a percent change in FEV_1 from baseline to six months, and percentage change in six-minute walk test distance from baseline to six months. And the definition of success is the differences between arms for the percent change from baseline to three months for both FEV_1 and six-minute walk test reached statistical significance with the one-sided test of p less than 0.025 in favor of the treatment group.

For secondary efficacy endpoints, there were originally nine, but to control for multiplicity, these four were prospectively chosen from the original group of nine, and that was these.

St. George Respiratory Questionnaire was chosen to measure disease specific changes in quality of life. Modified Medical Research Council was used to score dyspnea. Max workload on cycle ergometry was used to indicate exercise tolerance, and daily oxygen consumption was the tool to measure supplemental oxygen utilization.

Shortly after the design of VENT was being conducted, BODE was reported by Bart Celli in the New England Journal of Medicine in 2004 to be a multidimensional tool that might have greater sensitivity and specificity to indicate mortality shifts in patients with COPD.

As a result of that, BODE was incorporated by VENT to use as a secondary efficacy outcome. BODE is calculated on these four indices, body mass index, airway obstruction by FEV_1, dyspnea by the mMRC, and exercise tolerance, six-minute walk test with a lower score being better, and as you can see, it also incorporates the two co-primary endpoints of VENT.

This is Bart Celli's data that looks at the 650 subjects with FEV_1 against survival over 5 years, and as you can see, based on the severity of FEV_1, there's not as much change in mortality as you can have with the BODE scale that measures pulmonary and

non-pulmonary factors. You can see here the patients with the highest BODE score are more severe. They have a survival at 5 years of 20 percent, compared to the patients who were less impaired by BODE and have a survival of 90 percent in quartile one.

The primary safety endpoint for VENT was a Major Complications Composite or MCC. This is evaluated at 6 and 12 months. This incorporated death, pneumonia distal to valve implantation, respiratory failure with greater than 24 hours of mechanical ventilation, pneumothorax or air leak that persisted more than a week, massive hemoptysis with more than 300 ml of blood, and empyema. Higher rates were assumed given an active intervention being done in the treated arm versus the non-active control group.

Study oversight and management through the trial was conducted by these entities. Independent Clinical Events Committee adjudicated the severity and relatedness of all adverse events. An independent data safety monitoring board had decision trees to halt the trial or to continue with trial. Independent statistical analysis was conducted, and as I mentioned, the core radiologic labs and there was a core quality of life lab at the University of

California in San Diego.

So with that prelude to the need for treatment of these patients with emphysema through new therapies and also the design of the trial, I'd like to introduce Dr. Armin Ernst who will discuss the conduct of the trial baseline characteristics and safety. Armin.

DR. ERNST: Thank you, Gerry. Good morning, Mr. Chairman and members of the Panel. I somehow have been singled out as the only one who is approaching the bench, but my name is Armin Ernst. I'm the Chief of Interventional Pulmonology, and I direct a multidisciplinary chest disease center at Beth Israel Deaconess Medical Center. I'm an Associate Professor of Medicine and Surgery, and over the last decade, I have been mainly interested in advanced endoscopic procedures in the chest.

I served as an investigator at the BI site for the VENT trial. I have no equity or stock in the company but am being reimbursed for expenses related to today's meeting.

I'm also active in many other device-related trials, some of them related to endoscopic lung volume reduction at this point.

It is my pleasure to really introduce to

you some results about the baseline characteristics about the study population, conduct of the study I want to go into for a few minutes, and mainly the safety data that I'd like to present to you.

It is important in the first slide to just really make the point that this trial met all its endpoints. Primary endpoints were efficacy as well as safety. Dr. Sciurba will talk about the efficacy ones in detail. I will concentrate on the MCC rates, the mortality as well as non-MCC events, and go into those into detail for you.

Before we do that, first of all, the baseline characteristics of the study populations we are going to look at.

You will see that the groups were well matched. There is a small agenda difference between the Zephyr intervention group and the control group, but this was not predictive of outcome in multivariate analyses. Otherwise, as you can see here, very comparable in issues like smoking, height and weight, as well as blood pressure.

When you look at the patients' pulmonary function tests, you see that they are very well matched. These are patients with significant airflow obstruction and hyperdistention as evidenced by their

RV, TLC, and FEV_1 parameters. These are patients that we see in our clinics presenting with significant shortness of breath. These are patient that you'll recognize also in your outpatient setting.

Here are some more variables. As you can see, overall well matched in parameters like six-minute walk test, the cycle ergometry. There is a small but statistically significant difference in the $PaCO_2$, but again this was not predictive of any outcomes in the multivariate analyses.

If you look at the patient population where the -- is exactly where we want it to be, we want it to address GOLD III and GOLD IV patients, and as Dr. Criner told you, these are the patients that despite best medical management continue to have significant trouble with symptoms and have a significant morbidity and mortality associated with that.

So in terms of study conduct, some things are important to realize. When the study was initially conceived, the windows for follow-up, around 6 months, are very narrowly defined as plus or minus 14 days. For all of us who actually do practice clinical medicine, you will realize that

this is very difficult to do, and as a comparator, the NETT study actually for that reason allowed plus or minus 90 days to ensure that there is appropriate follow-up.

There was an extended window chosen before data analysis that allowed for minus 30 to plus 45 days which seems well within reasonable limits, and with that window, the rates of data not obtained at about 20 percent were certainly consistent with other landmark trials that we frequently quote, such as the TORCH, UPLIFT, and OPTIMAL trial.

And also here very important, the sensitivity analyses that were performed really show that the primary endpoints were all met across windows either way.

There were eligibility violations. Twenty-three of them occurred during initial screening, but all of those patients, once they actually were eligible for enrollment, fit the enrollment criteria. So the ones that are important to look at are really the ones that were at baseline which were 39, which is 12 percent of patients, and those eligibility violations were small. They usually accounted for small abnormalities or, you know, discrepancies in blood tests like small variations in $PaCO_2$. Most of

them were within the plethysmography, some in spirometry, and then several others as you can see but again on statistical analyses, all co-primary endpoints were met with or without eligibility violations.

Protocol deviations were present as expected in any such study that goes over more than 30 sites, and the number is more than 2400, but it needs to be put into perspective. This is only 3 percent of all available data fields over the study, and those are almost 80,000. Most of them again were minor, you know, things like an x-ray, for example, at 63 minutes rather than within the 60-minute window after the procedure or, you know, follow-ups that again were some minor variations to the actual protocol, but they were all balanced between arms and there was not one particular site or one particular investigator who collected all of them. And again, all co-primary endpoints, no matter how you looked at it, with or without clinically important deviations, were again all met.

Having said that, I want to present to you the actual safety data, and this is the population we're going to look at. 321 patients were enrolled. The Intention To Treat was 220 in the valve group,

101 in the control group. Obviously a few patients less in the modified intent to treat that actually received the valves. Those were 214. Four in the control group did show up for follow-up. So that data is necessary for the safety analysis or the mITT group was the one that is used for that particular part now that I'm going to show you.

What I want to go through is the MCC event rate and some particulars related to that, but I also want to talk about some adverse events that are not included in that composite index as well as events that are unique to the treatment, and I want to address re-hospitalizations.

Here's the MCC. It's been defined for you already. It's measured at 6 months in the column on the left as well as 12 months on the right. I will concentrate on the 12 months because that is really the aggregate of what happened throughout the whole year.

There is a difference of 5 percent in the MCC at six months that I maintained over time, but you will see that the death rate and mortality is equivalent at about 3.5 percent and it is mainly driven, the difference is mainly driven by pneumonia that occurred distal to the valve, obviously

something that cannot happen in the non-active control. Everything else was not statistically significant.

I would also like to repeat that this is what we expect, in a non-active control compared to an intervention, the intervention group is expected to have a higher event rate than the non-active control.

Now, only for 4 percent of patients, that is 9 patients in total, actually had distal pneumonia, and this is what happened to them. All of them were started on antibiotics, conventional therapy. None of those patients required ventilation or anything like that, and most of those patients, 5 out of 9, just resolved on antibiotics. Three patients did not, and they have the valve removed, continued on antibiotics, and also resolved the -- and the good news here is that the valve removal was easily achieved, and the patients responded to that actually quite quickly. We do not have data on one patient because that happened pretty much exactly at the end of the study and there's no follow-up data available.

We should also look into the details of mortality. Even though it is the same between

treatment and control, this lists all the deaths on the treatment side. As you can see, some of them have really nothing to do with an intervention as they are patients who have, for example, metastatic cancer. Some of them are respiratory failure deaths, and you heard that the 5-year mortality is 40 percent in this patient population. So some of them are expected, and really only one of those deaths, the one with the massive hemoptysis, was adjudicated to be potentially related to the procedure itself, and that is why really in this slide I want to go through some of the details of this death.

This was a patient with proper eligibility who had uncomplicated valve placement, reported some minor hemoptysis from home and was eventually admitted with massive hemoptysis, was intubated, transferred to the ICU, and eventually died three weeks later with evidence of hypoxic brain injury.

The family was gracious enough to allow for a limited autopsy, and during that autopsy, all valves were found in position. There was no trauma identified. The airway walls were in order, and there was also no injury to any vessels reported. So in the end, it is still unclear why the patient did have hemoptysis even after an autopsy, but I think it

is fair and it's the right thing to do to adjudicate this event anyway as possibly procedure and device-related.

This resulted in notification of all sites and a recommendation to be extra careful should any hemoptysis occur in those patients.

But this is the curve that really that really speaks for itself. The Kaplan-Meier survival curve is basically identical between the two groups. This is a low incident event in both groups that we looked at, control as well as treatment, and at 12 months, as I said, there is really absolutely no difference between the two.

Now, having gone through the MCCs, I also want to address the non-MCC events, which includes a list of seven that were either statistically significant or trended towards it. The ones of specific interest I think to us and the Panel will be the COPD exacerbations as well as all hemoptysis that were not massive because those are higher of those groups.

I would like to remind you that we were performing bronchoscopy with intervention placing valves in a patient population that has advanced lung disease in to a large degree all three active

airways. So to have a spike in COPD exacerbation early within the first 30 to 90 days is not surprising and certainly in line with other interventions that we do on that patient population. Forty percent of COPD exacerbations occur very early, and after 90 days, you can see that the lines are completely similar between the two groups. All those COPD exacerbations were easily medically manageable and, as I said, at least in our view anticipated.

Only very few were judged severe, and severe means that you performed either a bronchoscopy, which is a standard intervention really if you do a device trial or the patient was re-hospitalized. Again, this was more common in the first 90 days, and then the curves are similar.

Hemoptysis was qualified as any blood. So any blood-tinged sputum after somebody had a bronchoscopy with valve placement was listed as hemoptysis, and as you can imagine, this is a fair number of patients, but almost all of them really only reported blood-tinged sputum with a spike around the procedure and a significant drop after a short period of time. And most of this you just wait, really no intervention necessary, and it goes away.

There were some SAEs with hemoptysis.

Again just a bronchoscopy to do a look and see what's going on moved you into the SAE area. If you go by sight report, so the physician who actually saw the patient, only three patients were reported to have more than minimal, in this case as severe, hemoptysis but it was not clarified any further. As I said, there was really only one patient with massive hemoptysis, and I showed you the details of that before.

We have lumped the other adverse events because they really have to do with peri-procedural events, nausea, vomiting, some chest pain, anything, you know, of this kind we see frequently after bronchoscopy or anesthesia. All of those disappeared very quickly and made no difference between treatment and control after a short period of time.

I want to spend a minute or two on really going through events that are unique to the treatment, you know, that you would not expect in anything else but this kind of intervention. We talked about the distal pneumonia obviously is one in detail already, by migration and expectoration as well as granulation tissue formation I think are the other ones of interest. There was one case of catheter-induced trauma that healed very quickly

without any intervention, and it was such a low incidence event that I did not include any more details on that.

But this is another picture of the valve, and if you recall what Dr. Criner showed you, this looks slightly different. The knee of the valve is slightly outside the orifice, and you can imagine that this is probably not placed correctly and at risk of migrating, migrating meaning that it moves from one place where you put the valve to another place in the lung over time. Expectoration means that you cough it out. This is probably not a device-related issue but much more often operator-related issue with a first of its kind device where you have to learn to size them properly and place them properly more than anything else.

Those do not go unnoticed by the patient. All patients have some minor symptoms like cough, for example, or blood-tinged sputum, really getting people to look what happened. In the six-month follow-up, there was no evidence that there was any occult migration. All these patients had CTs. There was nobody who was asymptomatic but was found to have his valve in any other place rather than anticipated. Nine migrations, eight expectorations. There were no

long-term sequelae with that.

All the migrations were easily removed. You saw the video. This is actually a quick procedure. It's not a problem, and it really resulted in some retraining as we were going on through the trial to teach people the experiences from others how to really size these valves properly and how to place them so nothing happens.

There were also some product modifications. So you had already seen the sizing device, which is the little green flap, but there was a depth marker added later on, and that obviously really helps you to judge, you know, how you should place your valve in. And if you look at the outside, experience of the United States, and I can speak to that somewhat because I also practice in Europe and, you know, in the last couple of hundred cases that have been done, there were only two cases reported where there was a valve migration. So this is becoming, with increasing experience, really an event that's more and more rare.

Granulation tissue in the airway is something you almost expect to some degree when we place stents into patients, for example. There's always a certain number of patients who develop

granulation tissue. It's a foreign body reaction. Eight percent of patients had some, mostly mild and maybe related to the actual valve placement if it was not quite proper, but all of them easily dealt with usually by removal of the valve, and with that, the granulation tissue usually just goes away. Ninety-four percent of them, almost all of them were rated as mild.

Lastly, I want to address the re-hospitalizations because they were higher in the treatment group, 39.7 versus 25.3. And again this was an active intervention versus non-active control, and it was a first of its kind device. As you can all imagine, this leads to a significant caution on the side of the treating physician, and the primary cause for re-hospitalization as you can see are not unexpected. COPD exacerbations and pneumonia, but valve replacements and hemoptysis, you know, after what I explained to you, played a significant role in the re-hospitalization, and a quarter of all re-hospitalizations were a day or less, really showing that there was a lot of caution, for example, around the hemoptysis where everybody just wanted to be safe and the patient's advocate, and you just admitted them for the day, made sure nothing happened, and

then let the patient go.

Valves we would not place or replace as inpatients anymore. They would not be outpatient procedures, and another reassuring fact is that the EBV length of stay was actually significantly shorter, reflecting I think a lot of cautionary admissions than the 8.6 days for the controls.

So, in conclusion, having done quite a few procedures of these now, there's definitely no increased mortality in the treatment arm when you compare it to control. The events that are peri-procedural and post-procedural are and were all expected. They're usually minor and transient, and they drop off in time, all as you would expect in this patient population with this kind of intervention. Only two SAEs were statistically significant in one year, and they were COPD exacerbations and hemoptysis. We went through that in detail. Again, most of them peri-procedural and easily dealt with.

What I also would like to emphasize again, that this is a removable device. When there were device-related complications such as granulation tissue formation or post-obstructive pneumonia, those devices are removable, and patients recover very

quickly.

With that, I thank you for your attention. I'll pass on the bench to Dr. Sciurba.

DR. SCIURBA: Thank you. Thank you, Dr. Ernst. I appreciate Dr. Birnbach and the committee for your attention to our data today.

I will reveal my conflicts. I was a principal investigator on the VENT trial. I have no equity or ownership and have taken no consulting fees from Emphasys since initiation of this trial. I do have some consulting and investigative relationships with other device companies.

I'm an Associate Professor at the University of Pittsburgh. I've had an interest in COPD for over 20 years. I'm fully funded by the National Institutes of Health at this point. I was one of the early investigators in the early '90s dissecting the mechanisms of lung volume reduction surgery and have participated in other mechanistic and clinical trial studies with the National Institutes of Health.

You've heard the medical need by Dr. Criner and the devastating effects of this disease and the population, who we're addressing, and you heard Dr. Ernst discuss the expected adverse events that we

believe are acceptable and manageable in the context of the severity of this patient population.

I would now like to communicate with you my belief in, after investigating these data, that, in fact, we have achieved our expected, prespecified efficacy criteria in the context of this trial, and not only that, but that, in fact, if you look at the proportion of patients with clinically meaningful responses, that we can offer and actually offer a hope to patients with regards to meaningful therapy in a group of patients with not many other choices.

As we address these data, you will see several populations that we address. It's important to note that the primary population prespecified was an intent to treat population with imputed analyses of missing data. You can see that the interventional group consisted of 220 patients and the control group, 101 patients. We also provide corroborating evidence using our Completed Cases analysis, patients with complete data, both at baseline and 6 months, consisting of 179 patients in the intervention and 75 patients in the control group.

Our co-primary prespecified outcome parameters are FEV_1 and six-minute walk. FEV_1, for those non-clinicians on the Panel, is the most

accepted measure of severity in patients with COPD. It is a very accepted measure with reproducibility, and it's followed and it's executed using very rigorous quality control standards. It is generally not affected in patients with advanced COPD by effort.

Six-minute walk test is a measure of more global exercise function and measures the distance an individual walks in six minutes. It's important to note that this test is executed using very standard American Thoracic Society criteria, but Dr. Criner did address that it does have some unknown issues with regards to its sensitivity and responsiveness to therapies.

What's critical to understand is that COPD is a disease with multiple domains that can respond in different ways and then multiple parameters are important in assessing the outcome of these patients.

To remind us of the prespecified effectiveness outcome for this trial, and to quote the original trial design, "For effectiveness, the difference between arms for the percent change from baseline at 180 days for both FEV_1 and six-minute walk must reach statistical significance (using a one-sided T test at p less than 0.25 significance) in

favor of the treatment group." And I believe these data, using the imputed analysis show, in fact, that we did achieve both the high bar of achieving significance in both of our primaries, FEV_1 in the intervention group improved above the control group by 6.8 percent and 6-minute walk distance improved above the control group by 5.8 percent, both of these statistically significant.

Looking at the Completed Cases, these data corroborate the imputed analysis showing that the difference between the intervention group and the control group was 7.2 percent with regards to FEV_1 and 5.8 percent with regards to 6-minute walk, and you note the usual drop in most COPD trials in the control group as this disease does progress over time.

Importantly because this disease has multiple domains, we specify prespecified secondary analyses. It's important to note that originally we had specified nine secondary analyses. In discussions with the FDA, they suggested adjustment for multiplicity at which time we agreed cutting the number of secondaries to four. These were determined prior to any analyses.

The secondaries included parameters

discussed by Dr. Criner including qualify of life measures, St. George Respiratory Questionnaire, disease specific qualify of life, a four-point dyspnea scale, the Modified Medical Research Council dyspnea scale, incremental cycle ergometry using the NETT protocol which we designed and implemented in the lung reduction surgery trial, and a novel parameter assessing daily supplemental oxygen use.

It's important that just as with the primaries, in the imputed analysis, all of these parameters, all of our parameters moved in the right direction with statistical significance, and they corroborated nominally and statistically with the Completed Cases analyses.

As we've been stating, COPD is a multidimensional disease with many domains, and when we initiated this trial, a parameter that we felt was promising but really not fully validated, the BODE index was included in the secondary parameters.

Subsequently, this parameter has increased acceptance and validity within the pulmonary and COPD community. We feel it's an important integrated parameter, and we present these data.

In our trial, the BODE index decreased, and that's good, in the intervention group relative to

the control group by a half a point, and this was very statistically significant.

You've heard by Dr. Ernst and you will hear in the FDA presentation that there were many protocol violations. Individuals missed the inclusion window, and that the inclusion criteria and that the window was extended. I can tell you that in the context of conducting clinical trials in this severe population, this is not extraordinary. Our window was extraordinarily narrow to start with, and what's very important is to know that these analyses and these windows were determined before any data analyses. And what's further important to note is that regardless of whether we include patients done Per Protocol, patients excluded in analyses who did not meet rigid inclusion/exclusion criteria, no matter how minor, and patients that were in the prespecified window or not, the results are identical. In fact, those patients done purely Per Protocol analyzed despite the loss in power with the numbers were even nominally more substantial.

So independent of inclusion/exclusion of these minor and often expected incidences, the results were not different.

So we've shown you, we've met our

prespecified primaries. We've shown you that this is corroborated by our secondary outcome parameters in a multidimensional disease.

I would now like to show you corroborating evidence that we feel is important with regards to confirming our prespecified mechanism, and also in assessing whether there are more clinically important changes that occur in substantial numbers of patients that offers a realistic hope to individuals.

These data show an analysis that assesses high resolution CT in our Core Lab, changes in volume in the intervened lobe, and here we see a 400 cc volume reduction in the targeted lobe, nearly 400 ccs, a 200 cc increase in the non-targeted adjacent lobe. To keep in context when we describe our subgroups is particularly relevant in a heterogeneous group where we're targeting the most severe disease, and we see that, in fact, the non-targeted lobe with the lesser disease expands. Notice that this is not subjected to a placebo effect, and there's effect in the control group.

Very importantly, these target lobe volume changes correlated very strongly with mechanical changes in the lung or FEV_1.

I would now like to show that going beyond

the statistical ends of our study, which we met, that, in fact, there are substantial portions of patients that do, in fact, have clinically meaningful responses to this therapy. In order to do responder analysis, we have to determine minimally clinically important differences in the population that would be specified. I can tell you that while there's a lot of work, that this is a field in evolution in COPD. We determine these cutoffs based on the available literature and based on our actually very conservative criteria in the NETT trial. And you can see we required a 15 percent change in FEV_1 or 6-minute walk distance and 8 point change in BODE, which is double the American Thoracic, European Respiratory Society Guidelines, and the integrated BODE parameter, we've required a 1 point change.

Looking at the 10,000-foot view, this is a -- plot representing the relative rate of patients achieving clinical important differences in the intervention versus the control group. They are all nominally 1.4 to 2.8 percent more prevalent in the intervention group. You can see that FEV_1, St. George Respiratory Questionnaire very significant, and then the integrated BODE parameter was significant as well.

Looking at the individual responders, we see 42 of 179 or over 23 percent of patients responded with regards to FEV_1 in the intervention, whereas there was only 8 of 75 or just over 10 percent in the control again with a relative rate of 2.2 which was significant. Six-minute walk distance relative rate of 1.4 did not achieve statistical significance. However, if we look at the integrated BODE parameter which looks at several important domains, which may change, or one or the other, we find that, in fact, a substantial proportion of patients achieve the 1 point change in BODE, 64 out of 160 or 40 percent, in contrast to only 11 of 59 or just over 18 percent in the control group with a relative rate of 2.2.

To give some significance to these changes, for instance a 15 percent change or a 130 cc change in FEV_1 would be equivalent to 2 to 3 years of typical decline due to emphysema. It would be equivalent to four years of the improved rate of decline due to smoking cessation. A 1 point BODE score change in a study that Dr. Martinez, Dr. Criner and I recently published showed that a 1 point change resulted in a 6-month decrease in mortality risk of 43 percent. A 4 point change in SGRQ, and you recall

that we required an 8 point change, but a 4 point change in SGRQ required all of these to happen. Patients could wash and dress more quickly, could now walk up stairs without having to stop, and can now go out shopping and entertainment. They had to achieve all of those to get a 4 point change. We required an 8 point change.

So I believe we've shown we've met our prespecified primary outcomes, that, in fact, we have corroborating evidence of mechanism and substantial proportion of patients who this is a realistic choice for patients.

I would like to show you that we can do even better because we've identified statistically important and biologically plausible and meaningful subgroups of patients who respond better.

It needs to be known that this was prespecified in a statistical analysis plan using a multivariate, mixed model analysis to identify these predictors. The subsequent analyses, dichotomization of these continuous variables was dictated by a statistical analysis plan and was designed to identify important predictors of clinical outcomes from a prespecified set of variables.

In the FDA presentation, you will see this

long list of variables, and it's important to note that we prespecified our approach to these variables using a very rigorous and approved on analysis plan.

From this set of variables emerged very comfortably two highly plausible predictors, that being heterogeneity of disease and fissure integrity, and we'll show you what each of these represent.

With regards to heterogeneity, we have patients who have patients who have increased destruction in an intervening lobe versus preservation in the adjacent lobe. Here we've applied a density mask to those lung units achieving a low pixel density, and we use a minus 910 Housefield Unit threshold suggesting and validated using tissue studies to represent emphysema. These analyses were performed in Dr. Goldin's CT Core Laboratory. Heterogeneity was defined as the continuous variable of low density difference between the intervening and non-intervening lobe, and we believe that this mechanism is consistent with the proposed mechanism action if we reduce the volume of the most affected lobe and expand the volume of the higher quality tissue, that this plausibly should result in a better effect.

It's important to note that the only

variable that emerged from the multivariate, mixed model analysis was the continuous variable, and we need it to dichotomize this variable. But you need to know regardless of the cutoff we choose, we would have very strong significance. The advantage and disadvantage of using various cutoffs is this. If we use the 6 percent cutoff, the degree of difference between the high heterogeneity and low heterogeneity group would have been just over 10 percent, and it would have included 75 percent of subjects in the high heterogeneity group. If we used a heterogeneity difference of 25 percent, in other words, more than 25 percent greater destruction in the intervening lobe versus the non-intervening lobe, we would have found a significantly greater difference in response between the intervention and the control.

We chose a parameter that represented the median number of patients so that 50 percent of patients were above 15 percent heterogeneity, 50 percent below. This was both with respect to FEV_1 and six-minute walk, and that reflects these data. The high heterogeneity group representing patients with greater than 15 percent heterogeneity showed a greater response, 12 percent change in FEV_1 or over 100 ccs, in the intervention compared to the control,

and with regards to 6-minute walk distance, a 14.4 percent difference or 50 meters between intervention and control group.

With regard to the responder analysis, again the potential impact of meaningful results for individual patients, we note that 32 of 91 or 35 percent of patients achieved an important difference with regards to FEV_1 and 31 percent with regards to 6-minute walk. These resulted in 2.8 and 2.4, respectively, relative rates in the intervention group versus control of clinically important changes.

The other variable that emerged from the subgroup analysis was fissure integrity and simply identified in this diagram and as analyzed in our CT Core Laboratory. Some patients had absolutely complete fissures. Others had incomplete fissures. We categorized fissures, again simply dichotomously as complete or incomplete. We felt and included this index in the original statistic analysis plan because we felt there was plausibility that this would represent a proxy for inter-lobe or collateral flow.

In other words, if we intervened on a lobe, and there was an incomplete fissure, that the lobe would have less tendency to collapse because of continuous supply of the non-intervening lobe. And,

in fact, we show you these results. The mechanistic results, in fact, do show plausibly that this was a proxy for collateral flow, that, in fact, when the fissure was complete, there was a closed system resulting in targets significantly greater, target flow reduction volume of 700 ccs and an increase in volume of the adjacent lobe of 400 ccs. You can see that the minor fissure, horizontal fissure, had the least likelihood of fissure integrity on the right side compared to the major fissures.

Here you see that these mechanistic results transferred into changes in our primary parameters. Both FEV_1 and six-minute walk were nominally increased with great significant improvement of 16 percent in the FEV_1 and a trend towards significance in the 6-minute walk with regards to the fissure, complete fissure versus or in the complete fissure group, intervening group compared to the control.

Finally, I'd like to discuss the durability of effect of this procedure, and here we look at a Completed Cases analysis of FEV_1 in patients who returned at all points, three, six and one year, and you can see in this case that the dotted yellow line is the control group. The dashed blue line is the intervention group. The dark green bar is the

difference, and you can see maintenance of the difference between intervention and control and Completed Cases and an even greater effect as we had noted both a six months and one year in the high heterogeneity group.

With regards to six-minute walk, there was some drop off, but preservation in the Completed Cases difference and the difference over the entire one year remains statistically significant both in the Completed Cases of all patients and in the high heterogeneity group.

And finally, again, given the fact that we believe that this is a disease with multiple domains and dimensions, we feel the BODE score is a critical measure to discuss and we found -- maintenance of the one year effect compared to six months in all cases and maintenance in the high heterogeneity group of greater than one-half point BODE score change.

So, in summary, I think we have convincingly shown that we met our primary and secondary efficacy endpoints with consistent changes across all parameters, that we achieved the mechanistic effect we had hoped for, target lobe volume reduction; that an integrative parameter integrating the multiple domains of COPD corroborates

these treatments; that substantial numbers of patients have clinically meaningful responses. This is particularly important in the setting of acceptable adverse events in a largely reversible procedure. That, in fact, we can do better effectiveness in the real world than we have shown because of our increased attention to subgroups and high heterogeneity and complete fissures, and that this effect is sustained for at least 12 months.

So I appreciate your attention, and I'd like to hand the podium back to Dr. Criner to give you a perspective on the post-approval studies and a summary.

DR. CRINER: Thanks, Frank. So let me briefly outline the training and post-approval studies that the Sponsor has put forth.

From the standpoint of physician training, and they have this based on their experience with postmarket training of physicians, where they are approved for overseas, is based on a goal of controlled dispersion of the therapy into the places that are post-approval so that they're made sure that the devices are put in the appropriate patients in the appropriate manner.

A variety of different didactic teaching

modes is shown here and hands-on demonstration with the appropriate proctoring of initial cases.

And this has worked with them as they have rolled this out in other countries, and we would endorse a similar program in the United States if approved.

There is two post-approval studies that they have put forth. One is further, longer-term follow-up with the patients who have already been enrolled into VENT, with the primary objective to collect and report long-term safety and efficacy data at three and four years post-enrollment of those already in the VENT trial. And the second post-approval study is a real world sort of assessment of its efficacy and durability of response and complications. Here the primary objective will be evaluate the training effectiveness of longer-term safety of valve placement when used by clinicians in private practice with a range of underlying experience.

These are the details that are in the handout for the Post-Approval Study I and the Post-Approval Study II.

So in conclusion or summary, where does VENT sit as far and what does the study bring forward

for not only potential clinical care but what does it bring to clinical research? And for several different hard rule reasons, I think VENT is a landmark study.

First of all, after the National Emphysema Treatment Trial, which was funded by CMS and NHLBI HRQ, this is the largest interventional trial ever conducted in this group of patients with severe emphysema.

It's furthermore the largest interventional study ever done in severe emphysema that's been conducted by industry.

It's the first ever prospective multicenter randomized control trial to evaluate lung volume reduction via endobronchial less invasive approach.

And it's furthermore the first to evaluate the regional effects of lobar treatment for severe emphysema in patients with severe to very severe disease.

Finally, the high resolution CAT scan data provides novel paradigm for patient selection, mechanistic effect of endobronchial lung reduction, and outcome assessment that is impervious to the placebo effect.

Study conduct, the visit windows were

employed for analysis that's reasonable for this severe and very severe patient population that underwent an intervention and was narrower than that used in the National Emphysema Treatment Trial.

The missing data rates are similar to other landmark studies, as we've shown you, with patients with severe COPD populations especially, this subgroup with severe emphysema.

There's no impact on our study outcomes due to protocol or eligibility deviations, and as Dr. Sciurba showed you, the primary endpoints were met regardless of whether protocol or eligibility deviations were included or excluded from the analysis.

Study summary in terms of safety. The intervention group was equivalent to the standard of care treatment that required no intervention. The complications, peri-procedural increase in events were as expected in the cohort of severe or very severe patients that underwent bronchoscopy at intervention. They are typically minor and transient. The rates as Dr. Ernst showed you decreased over time, and these events were medically manageable with no surgical interventions required.

And finally, this form of endobronchial

therapy was removable with the device being able to be safely removed in cases where either complications arose or lack of efficacy was saved.

We also, I think, established clinical safety efficacy. We met our primary and secondary efficacy endpoints. In fact, we didn't meet one endpoint. We met all endpoints, and we showed a paradigm switch in treatment that favored intervention compared to the control group.

The responder analysis data also shows that we had clinical meaningful changes in a significant percentage of a heterogeneous disease in the treated cohort with minimal morbidity and mortality. And I think based on our data and the National Emphysema Treatment Trial, where we found that a change in BODE signals a change in mortality, that the change in BODE scores as Dr. Sciurba showed you signifies that possibly endobronchial valve treatment for patients with severe emphysema with heterogeneous diseases signifies a disease modifying therapy.

So where would Zephyr EBV fit in practice? This is the GOLD guidelines that you've seen before. Patients with severe impairment, we believe that endobronchial valve placement could potentially join the armamentarium of limited tools that we now have

to treat the severe group of patients who otherwise have been maximally medically treated and are still at severe impairment and a high risk for morbidity and mortality, and it would join LVRS and transplant in the continuum of tools that we would have to potentially treat this patient with.

How would we assess the risk and benefits of treatments in severe emphysema including EBV? Well, the factors that one uses as a clinician to determine whether you do a therapy and which one on a patient is based on the clinical benefit, do you change lung function, dyspnea, other exercise tolerance? Do you make a change in the patient's morbidity or mortality from the underlying disease? And overall, what's the patient preference? No patient comes to me asking me to improve their FEV_1. Every patient that comes to me or any other clinician wants you to improve their symptoms, wants you to alleviate dyspnea, especially in this impaired patient group, and improve their quality of life.

The emphasis is placed on the clinician that have tools and their knowledge that guide the patient to get the patient what they want to improve, their quality of life, in the most effective and the least invasive and safest manner.

So our options would be in this patient group again to continue with medical management, consideration lung volume reduction surgery or lung transplantation, but hopefully EBV would be in this continuum of care to offer the clinician and the patient reasonable options that would improve their clinical status.

So we believe from the risk benefit standpoint, VENT shows that we treat severe emphysematous patients with otherwise limited options. These patients have already been optimized with treatment of maximum medical therapy. We believe this therapy is reasonable and the risk can be anticipated and manageable. We believe it has important clinical benefits in a substantial number of patients who undergo this therapy, that the benefits outweigh the risks.

We believe there are study safety results that demonstrate reasonable assuredness of safety and effectiveness.

Thanks very much.

DR. BIRNBACH: I'd like to thank the Sponsor for that presentation.

Does anyone on the Panel have a question for the Sponsor? Before you start the questions,

please remember that the Panel may also ask the Sponsor questions during the Panel deliberations later today. If anyone on the Panel has extensive questions for the Sponsor, you may ask them now so the Sponsor can be prepared to respond in the afternoon.

DR. VASSILIADES: I have several questions. Would you prefer that I just ask them all right now and give them plenty of time?

DR. BIRNBACH: Sure.

DR. VASSILIADES: One was the primary endpoint clarification. The power analysis was done with data that would look towards using 15 percent and 17 percent difference, respectively, in your two endpoints, and that was based on data that was felt to be clinically significant. So my point is we're generously mixing statistical and clinical significance here in your discussion, and so which is it? You clearly statistically met your endpoints, but did you meet them clinically, and this bears out even more importantly when you start talking about degree of heterogeneity. So I would like some more clarification on that.

The other point to that is on slide 83 where you discussed the change in BODE, I'm wondering

what the Y axis is. Is that the raw number or is that a percentage? Because -- what I'm getting at is that you said that there's a clinically significant difference if there's at least a one point difference and that would transform into some difference in mortality, and so I'm wondering if those are fractions of a point? Is that what that is? So that's my question there.

DR. BIRNBACH: Feel free to answer these --

DR. SCIURBA: So with regard to the first question, power analysis and the numbers that go into that equation, which include a reasonable guess at what would be an important change as well as adjusted for the variants is not the outcome that was specified in this trial. The outcome that was specified is ultimately the significance in the change.

Ultimately if you want to look at the overall impact with regards to clinical important differences, the appropriate analysis there is a responder analysis, and responder analyses as originally determined requires individual MCID responses, not responses in the mean population. And so to me, ultimately the answer comes down that if I have this prespecified MCID in a given -- first of

all, we met our primaries. That was what was prespecified. We never in the original plan, and Dr. Criner showed that and I showed it, said that we needed to meet this difference plus significance, but then I agree, you need to go on further and say what is the clinical impact, and we've shown you that if you use an integrated parameter such as BODE, and I'll come back to your second question, that we see 40 percent of the patients in contrast to less than in the teens in the control group that have a clinically important response. And if the adverse event profiles is exorbitant in all patients, then you may say that's not enough. But if you have an acceptable adverse event, particularly in the setting of reversible valves, then we believe the responder analysis carries the day. We met our primaries, and we see a substantial proportion of patients with no other medical alternatives that have a response.

With regards to your second question, the BODE is the absolute BODE score in the mean of the population. And so while the average is less than 1, we feel a clinically meaningful difference would be one, that, in fact, that was achieved in 40 percent of the intervention group.

DR. VASSILIADES: Okay. I had just a

couple of more questions if I could. One is many times the Sponsor invites one of your patients to come for the open public forum. I'm curious as to why we don't have one. That's one question.

And then I have just one more which was who is your intended operator for your market? Is it -- and what qualifications will they be required to have in terms of bronchoscopic experience, et cetera? Are you looking at internists, pulmonologists, pulmonary surgeons, et cetera? So I'll probably just stop there with those last two questions.

DR. CRINER: Let me just speak to bringing a patient in. You can make an argument that that's a compelling case, to bring a patient in, and they can give their personal experience. But the investigators thought that that was an undue burden on the patient, and we thought that pretty much bringing a patient in to carry the day, whether a device needs to be done or not, isn't the right thing to do. We thought it would be more important to create the need based on the medical literature and show the effectiveness of the device. We feel that, especially me, being the token dumb doctor that presents the clinical case, it's basically depending upon us to carry the medical need for the caring for

this patient group. I think Armin is going to answer the intervention question.

DR. ERNST: I think that's a very important question, who is going to do that procedure. Our experience really has been that the procedure in itself, when someone has been properly trained, is really not that complicated, but I think it is very important to be an experienced thoracic endoscopist. That's how I would frame it, you know. That means that pulmonologists as well as surgeons who are experienced in bronchoscopy could really do that.

It is almost more important to have good systems in place, you know. These are sick patients. You need experienced endoscopists. You need the support, for example, through anesthesia, and you need proper patient selection all coming together, but there would not be in my mind just one specialty or, you know, one person that could potentially do that procedure that I think could be relatively widespread.

DR. WILCOX: It would be almost impossible to have anyone other than pulmonologists, irresponsible of someone else do this, it seems to me, because these patients are in the hands of a pulmonologist, and it's been our experience,

certainly in coronary artery surgery, that once a cardiologist developed a procedure for which they can treat coronary artery disease, the number of patients passing along to surgeons diminished dramatically. How would you overcome that sort of bias to keep it in-house and --

DR. ERNST: I don't know. I think it is obviously an issue that will need to be addressed. Obviously in the thoracic community we like to think of ourselves as really a group of people who work together about the disciplinary, and I have really not observed this to be too much of an issue. I know of many places where pulmonologists refer pretty much all interventional work to their local thoracic surgeon, and it is generally a very good and collaborative teamwork.

This really is more of an issue of where you have to identify who's the best person in any particular setting to do this, and I think, you know, this should be less an issue of it has to be me but more of an issue of, you know, who has the best qualifications, and that is probably the driver here.

DR. WILCOX: And have you established any sort of training programs and given some certification of having --

DR. ERNST: Correct. There should be a training program, a training module that involves, you know, video teaching, you know, instructions on the device, et cetera, but there should be no limitation in that training module that it can only be a pulmonologist. As I said, it should be an experienced thoracic endoscopist who has all the, you know, systems at his or her disposal.

DR. CRINER: Just to add to Dr. Ernst's statement to Dr. Wilcox, this is a tool that would be used by one person. It has to be a member of a multidisciplinary team because, as we showed you, these patients are very sick, and there's other options to consider. Optimized medical therapy, LVRS, transplant, potentially this therapy. So all those potential therapies need to be covered to give the options to the patient, and pretty much what I would envision, this is similar to what LVRS or transplants being done in these sick patients, you bring a multidisciplinary team together, the proceduralist who is probably going to be a pulmonologist or a surgeon or an interventionalist, with the pulmonologist, the surgeon, and other members of the multidisciplinary team to do what's right with the patient. And as you saw with patient

selection, the radiologist is also an important person to bring into this team to make sure you're treating the right patient in the right place at the right time.

DR. WILCOX: Thank you.

DR. BIRNBACH: Any more questions?

DR. WILCOX: Yes, I have one or two questions. It was not clear to me in patient selection exactly how that went out. I read one paragraph from the Executive Summary. It said because prior study for lung resection found the treatment was most effective in the upper lobe in patients with low exercise tolerance, the patients in the VENT pivotal trial with upper lobe/low exercise tolerance, 74 percent or almost 75 percent were randomized to the treatment group and 25 to the control group, suggesting, at least the way I read that, is that we found a group that responds best to this type of therapy. So we overloaded our treatment group with those patients. Is that -- am I misunderstanding that?

DR. SCIURBA: One important thing to note is that we had a two to one randomization in this trial. So twice as many patients were likely to have an intervention compared to the control. One of the

reasons we did that design was to have greater numbers to look at responder or to look at subgroup analyses from this perspective.

I'll let you clarify if I haven't fully answered your question. I mean are you interested in knowing the specifics of how we determined or what the subgroups are?

DR. WILCOX: Well, they look like here, you deliberately went in and picked out the best responders and sent three-fourths of them to the treatment group.

DR. SCIURBA: Oh, no.

DR. STRANGE: Maybe I can answer. My name is Charlie Strange. I work at the Medical University of South Carolina. My disclosure, since this is the first time I've been to the microphone, I've taken travel monies and consultant fees from Emphasys, less than $10,000 over the four years of the study.

I think the target, to answer your question, Dr. Wilcox, is actually that the area of the lung that was most involved with emphysema was the target lobe for valve placement. So if someone had lower lobe emphysema, for instance, that lower lobe could be treated. If the emphysema was equally bad in both upper lobes, then there is a default in

the protocol to treat the right upper lobe. In retrospect, we also know that right upper lobe is the area where that fissure, the minor fissure was most frequently incomplete. And so that's why 52 percent of treatment went to the right upper lobe, and upper lobe emphysema is more prevalent than lower lobe emphysema. So it was really the CT guided targeting was where that --

DR. WILCOX: And it just came out this way.

DR. STRANGE: And it just came out that way.

DR. GOLDIN: By way of introduction, I'm Jonathan Goldin. I'm a thoracic radiologist at UCLA, a Professor of Radiology. My disclosure is I am with Health Core Labs. We receive funding as the Core Lab but in person have received only travel and accommodation, no consulting fees.

I just want to add that the selection bias is not something that happened randomly. All targeting was done by the Core Lab following a very prespecified algorithm for targeting.

DR. WILCOX: Okay. Thank you. If you don't mind, I have one more, at least one more.

Is this basically a feel-good procedure, that is the patient's going to feel better after

this? Mortality was the same after six months. So it didn't impact, at least in this study, mortality. So how do we separate that?

DR. SCIURBA: Well, I think -- well, my patients ask me when I'm meeting them is I'm suffering and can you help me not to suffer, and we didn't test whether there was a beneficial survival effect or not. The magnitude of that study would be pretty much an overwhelming burden for any company to develop a product in emphysema. You recall it took 15 years to prove that tobacco kills people in the lung health study. But what we did show is that, in fact, the things that patients want quality of life, exercise, a multiple domain of potential factors that influence how they feel, that we had a substantial portion of patients who achieved those goals.

And so I would say that palliative symptomatic improvement is a very important outcome for these patients.

DR. WILCOX: I would agree with you.

DR. SCIURBA: Thank you.

DR. BIRNBACH: Dr. Willsie.

DR. WILLSIE: I have a couple of questions. There was mention in the presentation that there would be proctoring of individuals who would be doing

this procedure, and I'd like to know how you plan to handle that. Who would be the individual who would proctor a new physician? Say if I decided I wanted to do this, I watched the videotape, who would be proctoring me?

DR. STRANGE: Yes. I'll just tell you what happened in the VENT trial. There were 31 sites as you know, and the company actually has representatives that have come out and proctored each of the first five cases or so. They're actually very good. At our particular site, we had two endoscopists that were trained. The training module is both on the laptop and has videos associated with it. There's a model that we practice placing valves in, and so it's really a hands-on training that was very effective. And then importantly, sitting there through the first five cases or so the company came out, whether you can actually take five cases to every site in America that might do this I think is an open question, and how that's exactly designed is still not clear until post-approval.

But I think the point that was made earlier is that this is a multimodality approach. You need a physiologist. You need a radiologist. You need a team here to handle this, and members of that team

would have training at rollout sites as they've done in Europe.

DR. WILLSIE: Okay. Several questions, if I could, please. I noticed that clearly the targeting of the treated lobe was according to a very specific protocol with the radiologic Core Lab making that determination. How does that translate to -- how would you plan to handle that? In reading the information for use, I really don't see anything that specifies using any sort of protocol or targeting other than just kind of, you know, the most heterogeneous.

DR. GOLDIN: I think that clearly that's an important question, and our experience on that is the following. First of all, heterogeneity of disease is something that has been done fairly routinely in many centers today for lung volume reduction surgery assessments. And as you've seen, heterogeneity is the predominant CT predictor, and I believe that that can be done, the visual scoring level for the vast majority of these patients.

The other component of this is fissure integrity which again is something that is something that was prespecified as a research question and exploratory analysis and has been shown to be done by

thoracic radiologists who developed a training module and then went on to assess cases independently and then by consensus. And again this is somebody that has been shown that can be trained and, in fact, in the rollout in Europe, a training set was put together both for heterogeneity and fissure integrity, and so certainly I think that you can take this with some training into the field sites fairly comfortably for the vast majority of patients, and as we've done in the lab, as a part of rollout, there's always the potential for cases that may be in a more finer distinction to come to a central lab only for those very small percentage of cases.

DR. WILLSIE: Okay, my final question. We talked about the BODE score, and we talked about the difference between the two groups, but if we look at the change from baseline in the treated group, it was minus .021. I would like to know if you looked at whether or not that changed the quartile, the patient in the quartile according to -- classification? And I guess I'd be referring back to slide number 30, something that showed his classification with the expected mortality by quartile. That's slide 37.

DR. CRINER: Yeah, that's a very good question, but our data is too immature right now to

look at that. Hopefully with the post-approval studies, the longer-term follow-up with these patients, with FDA approval, then we'd be able to look at survival for the events because there really wasn't enough events to, you know, mirror Celli's paper with the study design.

DR. WILLSIE: Well, no, I was just asking if that changed the score, the difference in score would have moved the patient to a different -- to a better quartile, I guess.

DR. CRINER: Yes. So the Celli paper looked at the data on -- but didn't look at movement, but the Martinez paper that looked at the cohort in the National Emphysema Treatment Trial did look at the movement of the change in BODE, and they found with the change in BODE of greater than 1 at one year was associated with about a five percent mortality improvement in the patients whose BODE improved. There was about a two to threefold greater increase in mortality in the medical versus the LVRS groups, in those whose BODE moved in whatever direction that it moved. So we think with longer-term data, we'll be able to look at the movement of the BODE.

DR. WILLSIE: Thank you.

DR. BIRNBACH: Dr. Ries.

DR. RIES: I have two main questions and then a couple of points of clarification. The first question is it seems like the rationale for this is to achieve volume reduction in a non-surgical alternative. Did you achieve volume reduction? I didn't see any data about whether the lung vibs were actually reduced.

DR. SCIURBA: So with regards to lung volume reduction of greater destroyed lobe with expansion of adjacent higher quality lobe resulting in improved lung mechanics and other, sometimes, as I'm sure you know, more difficult to measure attributes that may be reflected in some of the broader parameters, we had success.

With regards to reduction in residual volume, there was not, but recalling the lung volume reduction surgery literature with unilateral procedures, while there were clearly evidence of improvement, that residual volume changes were much less dramatic in that subgroup.

So I believe that we have provided from a mechanistic standpoint, which I think you're interested in, a plausible mechanism, but ultimately those are surrogates for the clinically meaningful differences that I believe we have documented well.

DR. RIES: Same answer for total lung incapacity?

DR. SCIURBA: Total lung capacity was not changed. I know residual volume was not changed across the group.

DR. RIES: And the other main question, maybe Dr. Goldin could address this, but as I understand it, in going forward, a focus on defining patients with characteristics of heterogeneity and also the intact fissure is maybe important, and how much of that determination really relies on an expert, you know, you used the central lab? Is that something could be easily determined by radiologists in the community?

DR. GOLDIN: Yeah, I think that this is some -- will require as we've already heard, these are procedures that are likely to be done where there are multidisciplinary teams. In those sort of settings, I believe that the radiologists have already played a role in determining heterogeneity. The nice, reassuring thing about this heterogeneity is it comes with fix action data which is fairly, in today's world, basic CT data.

So the heterogeneity question I feel is something that can comfortably be translated through

training modules of the sites. Fissure integrity requires that the sites be able to do -- section acquisitions, which again in today's world is the predominant CT platform and again it's a teaching session. Remember that this was done by a group of thoracic radiologists as an initial research question, someone that was trained and has subsequently been trained to people on the field site in Europe with very good effect from the data that we see as part of the ongoing surveillance. So, yes, I think it can be translated to the vast majority.

DR. CRINER: Let me just emphasize what Dr. Goldin said from a clinical center. Since the advent of NETT, close to 13 years ago, we started to look at the heterogeneity of emphysema by CAT scan, and currently we've built our clinical program for patients that are coming in either for this or a lung reduction or transplant, to identify the extent of distribution of emphysema. It's part of a clinical program now. We have one technician who uses a commercially available software program and then www.slice.org, a public domain that's available for anyone to use to quantitate and measure the extent of distribution of emphysema, and we use those as roadmaps for treatment.

So I think it can be widened out with appropriate training and made available to many others.

DR. McLENNAN: Hello. I'm Geoff McLennan, and I'm a pulmonary physician at the University of Iowa. I'm in the Department also of Radiology and in Biomedical Engineering.

I have some disclosures to make in that I'm an investigator for the VENT study at Iowa where I am the Director of Interventional Pulmonology. I haven't received any financial support from any company, although I work with many of the device companies in this field.

As part of my academic duties, I chair a number of national panels. Those panels are looking, in fact, at imaging as an assessment of the lung. So that's the Lung Image Database Consortium. I work with a group which I chair called IDRI, which is a private/public partnership through the foundation of the NIH involving many academic sites and the imaging industry, and most recently I chair a group called RIDER, which is again a National Institutes of Health partnership with industry, the FDA, and the National Institute of Standards, looking at imaging as an outcome assessment.

My disclosure is a financial one as part of my research activities is funded through the NIH. Over the years, we have developed software to interrogate the lung, and that software was used in the NETT study to interrogate those images and to provide quantitative imaging. That software has now gone into a small company called VIDA, which I am a co-owner of and a co-founder of, and that software which will help facilitate this sort of study in the future, including a clinical rollout, is being approved by the FDA for clinical use two weeks ago.

So that's in accordance with this emerging field of image-based analysis of the lung, and I think we can expect to see that out in the field very quickly as approved by the FDA recently, if that helps answer how this will be done in the future.

DR. BIRNBACH: Thank you. Just a note that speaker should wait to be recognized by the Chair before beginning. Dr. Marcus.

DR. MARCUS: I've just a clinical question in terms of the pharmacological management of patients. Were they all uniformly on long-acting beta-agonist, long-acting anti-cold-allergic and inhaled glucocorticosteroids, or is there any effort to at randomization perhaps intensify therapy for the

control group?

DR. CRINER: Yeah, the GOLD guidelines of treatment for optimal medical care was applied evenly to both the patients that were randomized to the intervention group as well as to the control group. So every opportunity was taken to maximize patients' medical care.

DR. MARCUS: And again, not to be nitpicking but, you know, the guidelines says, you know, one or more long-acting bronchodilators. So I guess we would assume that everybody was, one, both a long-acting beta-agonist and a long-acting anti-cold-allergic as many of us would do?

DR. CRINER: Yeah, the appropriate treatment was given to patients based on the GOLD guidelines. So, you're right that most patients would have maximization of long-acting agents, the appropriate use of supplemental oxygen, the appropriate use of inhaled glucocorticosteroids if they are prone to exacerbation.

DR. MARCUS: Thank you.

DR. BIRNBACH: Dr. Brunson. I'm attempting to do it as I saw people trying to jump through their skin, but is this related to that question?

DR. DOMINIK: But you asked if we had

questions initially, and we did have questions.

DR. BIRNBACH: So did they.

DR. DOMINIK: I'm sorry. Where were you going to go?

DR. BIRNBACH: I was going over there.

DR. DOMINIK: Okay. I thought you were summing it up. I'm sorry.

DR. BIRNBACH: Oh, no.

DR. DOMINIK: As long as we get a chance.

DR. BIRNBACH: Far from summing it up.

DR. BRUNSON: Thank you, Dr. Birnbach. This should be brief, but in hearing that there's no reduction in the lung volume or change in total lung capacity, I'm beginning to wonder, is this therapy going to turn out to be palliative before you get LVRS or transplantation? And, if so, would that be appropriate?

DR. SCIURBA: I think it's highly plausible that it will find its place in a complex interaction with lung volume reduction, with lung transplantation in the spectrum of disease progression. We're advocates of lung volume reduction surgery. We've seen it work. We have programs. The fact is, for whatever reason, referring physicians, patients, choose often not to undergo that procedure, and they

have no alternatives and no options. So I think that this is a palliative procedure in a significant number of patients who have no alternatives.

With regards to progressing to lung volume reduction surgery, I think it's a potential option in that proportion who appear not to respond, and admittedly there are a number of them, but in those that do respond, I believe that we can avoid those choices. Certainly in the moderate one.

DR. CRINER: So to answer your question further, is this use this as opposed to using other therapy and that's the end of the therapy line? No, I don't think so. I think this gives us another tool to use in the armamentarium. Some of these patients could be treated -- that they could be treated with EBV, LVRS and then transplant. Currently we have patients -- approximately we've done 30 patients, single lung transplant, double lung transplant for COPD for emphysema after they've received LVRS a couple of years before. So if there's a further decline in disease, then this gives us another approach. We may be able to temporize, improve, palliate until a patient's symptoms are so much that we need to go to the next invasive therapy. So it's part of the chain.

DR. BRUNSON: Thank you.

DR. McLENNAN: And I can just add to that, what's happening here is we're inventing the future, and the future for these patients who have no participant thing that will help them apart from major invasive surgery. The future includes changing the bronchoscopic lab, and in Iowa, we have just rebuilt out bronchoscopic labs to manage the future, which will include the interactive imaging from the powerful modality of CT scanning in that setting.

COPD is a multidisciplinary disease, just like we did with lung cancer 15 years ago. So in our bronchoscopy lab, our thoracic surgeons actually have sessions in the lab, like our laryngologists will come there to do cases, and we communicate regularly between these specialties on behalf of the patient group.

DR. BIRNBACH: We're going to hear from, in this order, Dr. Dominik, Dr. Halabi, and Dr. Domino before we take our break, and then we will have plenty of opportunity to ask more questions this afternoon.

DR. DOMINIK: Okay. I think a few topics. The first one is pretty quick, and I don't expect you to have the information here. If you would present

it to us later, that would be helpful.

I think to fully evaluate safety, it's important to look at the confidence intervals around the differences in proportions of individuals having a certain event in the two groups. So I found that in the clinical study report for the primary endpoint, for the MCC, the confidence interval, about the difference, the point estimate was about 5 with an upper bound of the confidence interval about 9, but I didn't see confidence intervals about differences for any of the other safety events that might be important. So if we had that later, it would be helpful for our overall evaluation of safety.

I'll comment that the subgroup analyses raise -- they raise concerns for me, both in the way they were performed and reported. And I think first that it's a bit misleading I think to refer to subgroup analyses that were performed in this manner as prespecified subgroup analyses. I really think that terminology should be reserved for situations where either there are a very small number of subgroups that have been defined a priori or you've tightly controlled the type 1 air rate across your subgroup analyses, which I don't think was done here.

It's true that you had a planned, prespecified list of covariates that you were going to use to explore potential subgroups of interest, and interactions, but that strategy could lead to an inflated type 1 air rate. I think what you were doing was dropping potential covariates that would affect modifiers from further consideration when they had high p-values in initial models. But that doesn't mean that those looks have no impact on the overall chance of falsely declaring some interaction to be statistically significant.

So in light of that, I would consider any of the conclusions about the subgroup analyses, for example, that the treatment is even more effective than the control among the high heterogeneity subgroup, to be somewhat exploratory in nature.

And also when an interaction between a covariate such as heterogeneity and treatment group is detected by the Sponsor, it appears that you really only reported results for the level of that covariate where the treatment does better. And if, in fact, there are subgroups that truly have a greater benefit than the average patient in the study, then the complement of that subgroup, in this case the subjects without high heterogeneity, must

have a smaller treatment effect than the entire population. And it's possible that there is little or no benefit for the people who are not in the high heterogeneity group.

So I would want to see in order to interpret the subgroup analyses estimates of the treatment of fact and confidence intervals for those who do not have that characteristic, not just for those who do have that characteristic, to fully evaluate the impact of that finding.

With missing data, I didn't see a comparison of baseline characteristics for the complete case population. So I think it would be helpful to see how similar or dissimilar patients who provided data for the complete case analysis and whose data was used to impute the information, how dissimilar and similar those participants were in the two treatment groups.

And I think we need some more clarification about the methods for the multiple imputation method that was applied. It's not clear to me that -- I think in some cases, you dropped covariates that were not significant in doing the multiple imputation, but it doesn't appear that you took into account measurements on outcomes that were available at month

one or three in doing the multiple imputation which some methods would allow you to do. And it seems to me, to eliminate the most bias possible due to the missing data, you wouldn't to do some sort of substitutive analyses that take that information into account.

And finally with respect to missing data, there were a couple of analyses described on page 13 of the statistical analysis plan that were additional sensitivity analyses that were planned, and I didn't see those results reported.

DR. CHIACCHIERINI: Good morning. I'm Richard Chiacchierini. I'm the statistician for Emphasys on this trial.

My disclosure is that my local expenses are not being paid for because I live locally, and I have no equity interest in the company, and I do have a fee for service arrangement with the company as a consultant. Okay.

I will address the last two portions of your question. The others will have to wait until we get some information. But I will address a part of your question about the fact that we only presented the high heterogeneity subgroup. Because the univariant analysis demonstrated an overall effect,

the impact of those patients with low heterogeneity was very small so that the mean, the overall impact was still statistically significant and positive. So one usually takes the univariant analysis and then follows it by a multivariant analysis to determine whether or not statistical significance is overturned by any variable that might be introduced in the multivariant setting. And this could be due to imbalances between the treatment groups in those settings and so forth. And so that's why the multivariant analyses were done.

With respect to the multiple numbers of variables that were included, it is routine for FDA to require in any multivariant analysis any clinically relevant variable. This presents a conundrum for the Sponsor because we have to test the availability of significance for these variables, and under routine circumstances, if all of these variables were independent of each other, there could be a significant erosion in alpha, in type air rate.

And, in fact, what we found in this trial is that approximately 80 percent of the variables that were included in our list were highly correlated. The obstruction scores of the target lobe and the non-target lobe are highly correlated.

Heterogeneity and non-heterogeneity scores are highly correlated. And so the ability to get down and find out what the alpha inflation might be under that situation has not been done, and there certainly will be some.

So I can see that there's probably some alpha inflation.

However, the subgroup definition, the study was designed to treat heterogeneous patients. So a heterogeneity sub-score as a potential subgroup variable would have arisen anyway.

The fissure score is another issue, and we can address that at a different time.

And so while going through this very elaborate and complicated process of trying to screen out things that may or may not affect the overall significance, what we came down to in the final wash is that even those variables that remained in our final model did not modify the impact of the treatment, and that is that the treatment was still statistically significant and it was significant across a very large proportion of the population.

I missed your last question. Would you repeat that please?

DR. DOMINIK: My -- I think my very last

question was the point that there was some sensitivity analysis mentioned at the end of the analysis plan that would be additional sensitivity analysis to address missing data that I didn't see reported.

DR. CHIACCHIERINI: Some of those were preempted by other analyses that were requested by the agency, and so we just didn't do that.

DR. DOMINIK: I think the conventional wisdom is that when there are large amounts of missing data, that the most important thing to do is to do many sensitivity analyses to look at the potential impact.

DR. CHIACCHIERINI: And we did that, and the way we did that was that these data were imputed in three different ways. And, in fact, the initial imputation, we took clinically relevant subgroups and did a random selection within those subgroups of patients.

The FDA reviewer, statistical reviewer, requested that we use the baseline characteristic of six-minute walk or FEV_1, and we attempted to do that in two ways. The first way was unsatisfactory because it didn't adequately address the issue of the baseline characteristic. And so we used a direct