mechanisms that I think are more than biologically plausible, when we've shrunk down, destroyed very low density lung and we've expanded in a heterogeneous situation higher quality lung, I'm certain that this occurs in lung volume reduction surgery and that that's a component of the benefits that we see in a setting where the bar perhaps needs to be much higher because of the very much stronger adverse events in the lung volume reduction surgery situation.

The fact that we see an association between our mechanistic volume, lobar volume reduction and adjacent lobar expansion with FEV_1, very strong statistical association, supports the fact, and you can't have a placebo effect on volume reduction. I have a hard time understanding how that could happen, and the fact that that's associated with FEV_1 change, to me, confirms that there's truly a mechanistic or a functional component of that mechanistic finding.

DR. RIES: Thank you.

DR. BIRNBACH: Dr. Willsie.

DR. WILLSIE: A couple of questions. Smoking cessation was provided for both groups. Is there a difference between the groups in who quit smoking and who didn't and did that relate anything to responders versus non-responders?

DR. SCIURBA: Charlie's our protocol violation guy here, and nine patients were enrolled who by history had quit smoking but, in fact, the cotarnines were positive. As far as I know, those are the only nine patients who continued to smoke who were enrolled in the trial, and they were equally distributed.

DR. WILLSIE: Okay. And then the last question I have is there was a mention about using CPAP or BiPAP, and I'd like to know who had CPAP or BiPAP added to their usual care and -- okay. I read that in something.

DR. SCIURBA: I think we tried to structure what is appropriate medical management --

DR. WILLSIE: Right.

DR. SCIURBA: -- for these patients.

DR. WILLSIE: Sure.

DR. SCIURBA: And in advanced disease, that is within the guidelines. I believe none of our patients were on CPAP or --

DR. WILLSIE: Okay. Because that was my question. I think that could procedurally make a difference in outcomes if it was added, but nobody had that then. Okay. Thank you.

DR. BIRNBACH: Dr. Halabi.

DR. HALABI: I have two questions, the first one related to the missing visits. Do you have any reasons for the missing visits by the control versus the EBV arms? Did you collect this information during the trial?

DR. STRANGE: Yes. Charlie Strange. The number of missing visits is numerically higher in those individuals that didn't get valves. These were people that traveled a long way to come see us with the hope that they would get the two to one coin flip and get an intervention. And so, you notice the number of individuals that make it into the Completed Cases analysis is only 87 percent for the control population. I think this is pretty good. These were patients that came a long ways. They had bad emphysema, and if you look at comparisons to other interventional trials in this severely morbid cohort, we thought we did a pretty good job with getting patients back to the business.

DR. HALABI: And the other question, I know the trial was designed with only one year of follow-up. Do you have any data beyond the one-year landmark?

MR. McCUTCHEON: We're working with the FDA to continue follow-up. We have not been able to do

that yet. As soon as we have an approved IDE, which is the post-approval S1 that we propose, then we'll continue the follow-up on that.

DR. HALABI: Okay. Thank you.

DR. BIRNBACH: Dr. Vallisiades.

DR. VALLISIADES: Yeah, we're I think trying to understand the step between lung volume reduction surgery and going a non-surgical route, and I think that it's been clear that some of the mechanisms by which patients do poorly or they don't do well or they do better are not completely understood, and there's more to it than just lobar isolation and reducing lung volumes.

But one of the other important differences seems to be the fact that in the cervical NETT study, there were bilateral treatment, and I'm wondering why there wasn't bilateral treatment in this study, and then I'm also wondering what your thoughts are of how this would move forward if it were approved, and would this be a therapy that really would require bilateral therapy in order to show efficacy?

MR. McCUTCHEON: John McCutcheon. So historically when we looked at our pilot data, there was an artifact where the unilateral placements actually did better than bilateral, and that was the

basis of our IDE approval, and this goes back to 2002, 2003. We never really believed that unilateral is better, but that's what the data said, and so that's what we followed.

Now, with the CT follow-up, what we've discovered is when we were doing unilateral, we would do right upper lobe, never touch the middle lobe, or we would do left upper lobe without the lingula. I'm sorry, when we did bilateral, we would do left upper, no lingula, right upper, no middle lobe. When we were doing unilateral, it was random between right and left. They would include the lingula on the left side, and that's what was giving us our response, and it took us a long time to understand that, and most of that understanding came from the CT follow-up.

So I hope that makes sense, but that was the basis of it, and now we believe that we can, and we're doing this in Europe, if we're doing a right upper lobe and there's a missing or incomplete horizontal fissure, when we treat the middle lobe, we get the same sort of results as we get on the left side in this study, and we didn't show this data, but it's in the PMA, we have a much greater response rate on the left upper lobe than we do on the right.

In terms of practice, I think that's up to

you and the FDA in terms of labeling and how you would roll this out. I think in Europe, we're doing more of a staged approach. It's hard to understand a reason why you would do bilateral in one setting because it is so non-invasive. It seems to make more sense to treat one side, see how the patient fairs. If they still need additional treatment, they can come back in, you know, months later or years later and have the other side treated, but I think that really will come down to a labeling discussion in your recommendations.

DR. BIRNBACH: Do you have another one?

DR. VASSILIADES: Just one quick question or clarification from the FDA was that no safety delta was ever agreed upon. Is that correct? That the Sponsor -- my understanding is the Sponsor proposed 30 percent, and the FDA felt that was too high and, you know, there was no other further negotiations that were successful after that. Is that correct?

DR. CHOE: Melanie Choe. Yes, that's correct, and that was during the IDE review process.

DR. BIRNBACH: Dr. Cassiere.

DR. CASSIERE: This question is for the Sponsor. I have a question and just something for

clarification. It's hard to disassociate COPD or emphysema from sputum colonization and bacterial burden. Was there any data generated on sputum production? I know if you're greater than 60 ccs, you're out of the protocol. Was there any attempt to look at sputum colonization? And when you did the bronchoscopic exam, would there be BALs that were sent off for any type of studies in terms of bacterial count? That's the first question.

The second thing is just clarification. The speaker before mentioned that if a valve came out of the segment or was misplaced, it was taken out and then reinserted. So that means that that sterile valve was reused on the same patient?

DR. ERNST: Armin Ernst. To the first part of your question, there was no attempt made at BAL or culture collection. Obviously, as you alluded to, 50 percent of COPD or emphysema patients have tracheal colonization, but what was interesting is when you look back at the MCCs, the actual event rate for post-obstructive pneumonia was actually very low. Actually, surprisingly for most investigators, we would have expected more at the outset. It was a low incidence event.

You can reuse the same valve which you will

do, you know, during the initial procedure, but you probably obviously would not do it if it were expectorated or migrated. You don't know how long it's been some other place.

DR. BIRNBACH: Dr. Domino.

MR. McCUTCHEON: Excuse me. May I follow-up with that, Mr. Chairman?

DR. BIRNBACH: Sure.

MR. McCUTCHEON: John McCutcheon again. It would actually be impossible to reload the device. The way we have the loader, the device is packaged in that, and there's no way you could reload it and once it's coughed out, it's not replaceable. So you could do that intra-procedurally, but never post-procedurally.

DR. BIRNBACH: Dr. Domino.

DR. DOMINO: I had a question about this business of the 15 percent change as being clinically significant, and it goes to both the FDA and the Sponsor. There are two parts of it. First of all, I see the references for the spirometry and the walk test. I'm wondering if any of the secondary endpoints and also if there are any references or literature or history of holding that to a 15 percent difference as being clinically significant.

That's part one, and part two relates to the Sponsor's materials that the supplemental material which they said that the FDA never required this in their previous 2003 meeting. So I'm trying to think of how to deal with that, if it's not been a requirement before.

DR. BIRNBACH: Shall we start with the Sponsor and then go to the FDA, to respond to those.

DR. DOMINO: It's for both.

DR. SCIURBA: So if I can just clarify your question of how did we arrive at MCIDs?

DR. DOMINO: Yeah, I'm trying to find out is there any -- is this 15 percent difference as being held as a standard for clinical relevance, is that a reasonable standard or not? We get it for the primary endpoints. There are a couple of references cited, but in terms of the questionnaires and secondary endpoints, is that relevant or not?

DR. SCIURBA: So for the primaries, FEV_1 and 6-minute walk, we did use 15 percent, winds up giving the baseline average of 300 meters, that 15 percent was actually higher than within the -- paper, the MCID for improvement of 40 meters, it actually exceeded that. So that was a fairly high standard. FEV_1, based on the variation which I think Dr. Shure

addressed very accurately, 15 percent and the ATS has 12 to 15 percent. So that was the high end of that regarding clinically meaningful.

The St. George Respiratory Questionnaire, the ATS, ERS standards are currently four, and you saw the three fairly important questions that required a four. Our standard was eight. This was based on what we used in the NETT to create an unequivocal response, and we used that higher standard of eight. The basis for these MCIDs, I wish, was much stronger. The work is in evolution right now, but I think we based it either on very conservative estimates and the best estimates that there were in the literature.

DR. DOMINO: But your data does not, according to the FDA, meet those standards. Is that correct?

DR. SCIURBA: So MCIDs were intended to use for individual patients in responder analyses. I believe it is not appropriate to require a population to move unless you don't feel that the proportion of patients responding has any meaning, which we would not agree with.

MR. McCUTCHEON: I would just like to clarify one thing. The 15 percent and 17 percent

were the powering equations, using the powering analysis. There was never any a priori requirement to meet that level for either primary endpoint, and it was in the protocol considered other analysis. It was not a primary endpoint nor a secondary endpoint, just other exploratory analysis. There was never hurdles set for those, and there was never any discussion of the hurdle for the other secondary endpoints.

DR. BIRNBACH: Dr. Domino, did you need the FDA also to respond?

DR. DOMINO: Well, I'm curious about this statement from the Sponsor, 2003 there was a General and Plastic Surgery Device Panel that recommended this 15 percent difference, and yet the Sponsor says no, that wasn't the case.

DR. SHURE: Perhaps I could address that -- Deborah Shure. I was actually a member of that 2003 Panel, and there are some things to keep in mind. One is that Panel occurred before the NETT results were published, okay. And the actual recommendation is that these endobronchial devices be used in patients who were not candidates for anything else.

But, in terms of your question about the 15 percent, that's very well recognized as a MCID, and

those sponsor references that I gave you are references we agree with and that are very well recognized in the community. The reason we didn't comment on secondary endpoints is that it didn't come up, and we mention these things but, no, we weren't questioned about the MCIDs for these.

These are also very well established, and the Sponsor has pointed out that these were the same values that they used in NETT for things like the St. George's Respiratory Questionnaire and the mMRC. These are internationally validated indices, and the MCIDs, the minimally important clinical changes are very well established and well recognized for those.

The BODE is a new index, you know, that's just recently come into use and been established, but these, we weren't asked to provide references for that or standards. Minus 8 for the St. George's Respiratory Questionnaire is what was used in NETT, and it's considered a clinically significant difference. In asthma studies, people use minus 4 as a standard. In COPD, people tend to use minus 8, but you can still think about that in terms of, you know, what the actual values were, but minus 8 was specified, we agreed with it, and there are references for that.

But we weren't asked to supply those on the Panel, and I think people would just assume that these are the standard we recognized the changes.

DR. BIRNBACH: Dr. Wiswell.

DR. WISWELL: I had a couple of questions, and I had brought one up before we took the break, and that is you as clinicians and investigators have delineated perhaps the subgroup that may be more likely to respond, the highly heterogeneous. And you in the future as clinicians, should it be approved, I suspect would be more likely to use those kinds of patients should they be identified. And it makes sense that they're more likely to improve. They perhaps have sicker lungs.

But again the data that were brought up beforehand, they may die more or need lung reduction surgery, and what is the other safety profile? Do you have that data because that is concerning?

DR. SCIURBA: So the question I will address is the safety profile, the high heterogeneity group. The FDA cited the analysis that there is a higher death or LVRS rate in the heterogeneity group. That was the only variable that emerged in an analysis. It must be noted that only patients in high heterogeneity groups would go to LVRS. We would

not do LVRS on a patient without that higher level of heterogeneity. So the only option was the high heterogeneity group to have a LVRS event. There was no significant difference in mortality alone between the high and low heterogeneity groups.

So we feel that the death plus LVRS is unfair since that's biased toward the high heterogeneity group.

With regards to other MCCs, there was no difference at all between the high and low heterogeneity group. That analysis is done. So --

DR. WISWELL: I've got two other things if I can ask.

DR. CHIACCHIERINI: Can I make a clarification? This is Dr. Chiacchierini again.

I would like to distinguish the difference between the mortality analysis and the mortality plus LVRS analysis.

The mortality analysis included 11 deaths. The mortality plus LVRS analysis included 13 events, 11 deaths, and 2 LVRS implants. This is a statistical artifact. The fact that two patients could make such a difference in a multivariate analysis, it does stress the bounds of credibility because the total number of high heterogeneity

patients in the mortality population was almost equally balanced between the high and low group. And so it's very difficult to say that this was a true finding because the property of having the LVR surgery, as Dr. Sciurba said, you had to have high heterogeneity. So when you added these two high heterogeneity patients to this analysis, it tipped the balance in favor of statistical significance, but when we did this pure mortality analysis, there was no statistically significant impact of high heterogeneity either by itself as main effect or in combination with treatment as an interaction.

DR. WISWELL: I have two other things I want to address. One is this, and I guess one of my concerns and wholehearted push for obviously is the long-term outcomes, and now you're years beyond the trial. And I particularly am worried about atelectatic areas of the lungs, which you're doing on purpose, of course, with great rationale for. We've got those collapsed areas, and there are a lot of little bits of your data that are pointing to increased infections in your valve group, and I'm just worried over the years that you're more likely to have infections, bronchiectasis, et cetera, and if there are any additional data, I think they're

important, and a group that we haven't talked about today, there have been I believe 66 patients that have gotten compassionate use of the device. How are those patients? What are they doing now? Have they gotten -- is it just a single lobe? Are there people out there that have gotten multiple lobes addressed? Are they being followed at all? Do we have any other information? Especially again long-term data would be important. Granted, they are not in the study meeting all the enrollment criteria. But how are those patients?

DR. STRANGE: The majority of the compassionate use has been for air leak patients, and most of these patients are post-thoracic surgery that have an air leak from their thoracotomies that has lasted more than 14 days and are sitting there with a chest tube in the hospital. Those patients have historically gotten valves to seal their air leak. The air leak stops, chest tubes come out, and then invariably people go back in a few weeks later to either pull those valves or leave them, and so there's really not a lot of long-term data in those individuals, and that's the majority of the use outside of this trial.

DR. ERNST: Armin Ernst again. We have

similar experiences with the compassionate use in the U.S. mainly for bronch flow fistula and the good success associated with that.

I wanted to talk a little bit about the long-term concerns that you have since I actually have been using the valves now for quite a few years also in Europe, and it is exceedingly rare that a patient comes back, even after the valves have been in there for a year, two, or three, from the original cohort with any problems, and we really don't see that. Many of those patients actually do come back on additional trials, you know, when they had their right upper lobe but not their right middle lobe occluded, for additional occlusions rather than anything else.

DR. BIRNBACH: Dr. Brunson.

DR. BRUNSON: This question is for the Sponsor and the FDA. I'm a little bit confused, and when I'm looking at the supplement to the Sponsor's Executive Summary, the statement about the six-minute walk test concerning the six-minute walk test, Agency guidance clearly elaborates limitations of the six-minute walk test and detecting clinically relevant improvements. So my question is are you suggesting that the six-minute walk test isn't clinically

relevant and so, therefore, we shouldn't put much weight on it? And from the FDA, is this a standardized test, and how reliable is it?

DR. SCIURBA: The six-minute walk is actually an area of my research interest, and my group here will put a hook on me if I talk about it to the extent that I would tend to normally do. So I would say these things. Let's say the six-minute walk adds additional information despite its lack of responsiveness in the overall group, and I believe that the BODE score reflects this "or" attribute, not the "and" attribute, in an analysis presented earlier.

It is not as responsive a tool, is almost never responsive in pharma trials for instance. It has a much higher hurdle, yet it does often, the responders may respond independent of the FEV_1 and gives information.

One other aspect of the six-minute walk in this trial is that we did rehab up to the time of randomization, and unlike the NETT, we didn't continue rehab. So the walk distance deteriorated in both groups and, in fact, we saw that difference. It deteriorated, in fact, improved a bit. Despite the significant deterioration in the control group, it

improved in the intervention group. But I believe that added additional noise to the measurement. So I would again come back and say it is an "or" to FEV_1 as additional information, and I believe, and I think the pulmonary community is increasingly believing that the BODE score does reflect that.

DR. SHURE: I just want to clarify about the statements from that guidance. That's a draft guidance from the Office of Drugs. Their view applies to drug trials, which are particularly short-term trials of responses to the medication, not long-term trials. The bulk of the literature, the bulk of the ATS guidelines and reported experience all support the reasonableness of six-minute walk as a performance metric in COPD. Just to be clear, that applied to drugs. It was not a long-term device trial statement, and it was a draft statement from the Office of Drugs, just to be clear about the context there, but it a well-accepted metric.

DR. BIRNBACH: Dr. Wilcox.

DR. WILCOX: I wonder if the Sponsor would comment on the future. Say this device is approved. What are some of the problems you anticipate when you introduce this to the general medical community, make it available to them, and what sort of plans do you

have to address those problems?

DR. CRINER: Gerry Criner. I think one of the most important things to transition a therapy like this out into the public is to make sure it's in the right people's hands, the right patients get its use, and it's done the right way with the right follow-up. So I think the focus of the marketing effects will be focused on controlled dispersion, so that -- and err on the side that more people don't get the device who don't need it rather than a slow rollout and make sure the appropriate people get it in the right way.

So I think that's going to depend upon the Sponsor to have core didactic tools and sessions that are given to the practitioners, that they use a variety of different ways to do that, both didactic proctored sessions and core lectures that are done, and competencies that are assessed, to make sure the operators and practitioners are well versed with that.

I think that the post-approval studies, if this ends up being approved, have to heavily focus on safety and look at the issues of whether distal pneumonia arise or what happens to COPD exacerbation rates.

Although the NETT isn't compared to this therapy, I think there's very profound lessons to learn from the NETT that we still continue to learn. We published a paper, the NETT investigators a year ago, American Journal of Respiratory and Critical Care Medicine, that looked at COPD exacerbation rates, and we found in the NETT, that the exacerbation rate in the lung reduction surgery intervention group compared to medical treatment group was identical or slightly higher in the lung volume reduction surgery group initially after intervention, but after about 200 days through separation, actually the exacerbation rate fell in the group that had lung volume reduction surgery and fell even more in those who had a treatment effect.

So perhaps in this therapy which simulates some features of lung reduction, but with its regional effects may be more than reduction, maybe it's a redistribution of ventilation to better lung that we'll also see similar sort of things that would have bearing on what the long-term safety is and perhaps efficacy.

DR. BIRNBACH: At this point -- I'll let you ask one last question before we move on.

DR. LI: Thank you. I don't mean to beat a

dead horse on this, but this issue about -- I'm still wrestling with the fact that there doesn't seem to be any difference that you could discern between patients that receive nine valves and maybe some that receive one or two valves. So could you possibly explain how that would work, and if there really is no benefit for nine valves, wouldn't you actually then -- that you would basically tell someone don't put in nine because it doesn't get you anything?

DR. STRANGE: So for those of you that haven't been on one side of the bronchoscope, as you go down the airway, the lung is amazingly heterogeneous and the number of airways that you have per lobe, the size of those airways, how long the segments are, and the goal of this study was to take a single lobe of worst emphysema and obstruct every single airway into that one lobe. And remember that the worst emphysema could be in a lower lobe that has nine airway segments or it could be in a right upper lobe that almost always has three that are medium size and will always take three valves.

And so the number of valve differences are really determined by the anatomy. The goal is lobar exclusion at the end of your procedure, and that's where the heterogeneity comes in.

DR. LI: Thank you.

DR. BIRNBACH: Dr. Dominik.

DR. DOMINIK: There was a comment made earlier by the Sponsor about the safety analysis for the high heterogeneity subgroup that the FDA had done, and the comment was that this was somehow a biased analysis because it was done among the high heterogeneity subgroup and they would be more likely to have LVRS. But the comparison is among those treated versus the controls. Their analysis would have been, and maybe they could clarify, it said that high heterogeneity is associated with a higher incidence of death or LVRS, and what they compared here is the incidence of death or LVRS among controls and the device group for the high heterogeneity subgroup. Is that true?

MR. VAN ORDEN: This is Al Van Orden. Yes, this is -- it was a --

DR. DOMINIK: So the controls in that analysis were also high heterogeneity. So they would also be predisposed to a higher risk. So the comparison would not be biased by the fact that it was done in a high heterogeneity setting.

MR. VAN ORDEN: Right. And again, this was the Sponsor's analysis, not FDA.

DR. DOMINIK: Oh, it was actually an analysis done by the Sponsor?

MR. VAN ORDEN: That's correct.

DR. DOMINIK: Okay. It was in your slide but -- okay.

MR. McCUTCHEON: May I clarify. John McCutcheon. There were three deaths in the control group. I believe they were all low heterogeneity, and so the interaction came from -- it seems to just be noise to us. There were -- bear with me. There were eight deaths in the treatment group. Five of those were high heterogeneity. Three of those were low heterogeneity. And there's a two to one balance. So if you have one patient move over from 5 to 3, you have 50/50. It seems random to us, and when you're looking at death only, there was no interaction, there's nothing indicative that high heterogeneity drives any sort of events. It's only when you add the two LVRS patients, which is deterministic. It has to go to high heterogeneity.

DR. DOMINIK: When you select this subgroup and suggest that they have a higher effectiveness, then I think it's important to know what the risk benefit is for that subgroup, and you can't answer that question without doing this sort of analysis.

MR. McCUTCHEON: So the mix model or the -- showed that heterogeneity, not high heterogeneity but heterogeneity has an interaction with treatment. We've been dichotomized at different sets. There is not any cut along the way where you have a significant difference between treatment and control in that measure.

DR. DOMINIK: But have you powered to find an interaction? I mean I think the problem with getting into interactions is if you're saying you didn't have a significant interaction, well, the study wasn't necessarily powered to find a significant interaction for the safety question, but if you're going to be providing effectiveness information for a subgroup, I think it is appropriate to also know what the -- I'm sorry -- if you could provide effectiveness information for a certain subgroup, it's also important to also know what their risks are for that subgroup.

MR. McCUTCHEON: Yeah. So we did a complete analysis on the high heterogeneity versus the low heterogeneity subgroup.

DR. DOMINIK: That's not high versus low. The question is what is treatment versus control among the high heterogeneity.

MR. McCUTCHEON: Exactly. That was the analysis I was alluding to. So in none of those cuts is there any difference between low heterogeneity treatment versus control or high heterogeneity treatment versus control. It's not there, and we have that in the -- it's in the PMA. I'm not sure how much --

DR. DOMINIK: I thought this analysis right here is high heterogeneity, treatment versus control, a safety --

MR. McCUTCHEON: It's a little bit of a misnomer. That .0074 came out of a multivariate analysis that had interaction between treatment and heterogeneity on a continuous scale, not high versus low, and then when you dichotomize it and say, well, let's use the 15 percent that we use for efficacy or take any other cut point that you'd like, there's never a univariate difference between --

DR. DOMINIK: So what is the incidence of this sort of event among the treatment group in the high heterogeneity subgroup and among the control and the high heterogeneity subgroup? What's the incidence in the two groups?

MR. McCUTCHEON: There's five in the high heterogeneity. There's four deaths -- excuse me --

five deaths plus one LVRS in the high heterogeneity and treatment group. I believe there's two and two, one treatment -- excuse me -- one death, one LVRS in the control group, both high and low, and then there three --

DR. DOMINIK: I'm not asking about low right now. I'm asking among those with high heterogeneity, among participants in the study with high heterogeneity, what's the proportion of those in the treatment group who had this sort of event, and what proportion of those in the control group had this sort of event. That would be helpful to know.

MR. McCUTCHEON: I believe it's five to two.

DR. DOMINIK: The percentage is five versus two.

MR. McCUTCHEON: No, the actual, it's five in the treatment group and two in the control group.

DR. DOMINIK: So that seems very inconsistent with this p-value. So what would -- if we're comparing five versus two, we're not going to get .0074.

DR. CHIACCHIERINI: No, the issue is in our statistical analysis plan, we proposed that we would do three multivariate analyses of primary endpoints.

The first multivariate analysis was the MCC endpoint. The next one was mortality, and the next one was mortality or LVRS. Okay.

Now, when we did the mortality analysis, the mortality analysis was done, and we put in that analysis the heterogeneity score, the continuous heterogeneity score as a covariate, okay.

DR. DOMINIK: Uh-huh.

DR. CHIACCHIERINI: Okay. And we put in the interaction of that heterogeneity score with treatment, and that heterogeneity score with treatment was not statistically significant and, in fact, it left the model very early in the exercise. It was slightly lower than halfway. So in the end the only thing that was statistically significant in that analysis was the BODE, and the BODE associated with a one point increase in BODE was associated with a 64 percent higher mortality rate.

Now, we then did the mortality plus LVRS analysis. Who did we add to that analysis? Two patients, two patients who could not have had LVRS if they had low heterogeneity. So these two patients both had high heterogeneity, and the difference between the two populations is that there were five deaths in the high heterogeneity population. Add one

LVRS, that's six. Okay.

We contrast that to one death in the high heterogeneity population in the control plus the one LVRS, and the six versus two was a higher percentage than could be expected by the two to one randomization ratio, and that led to the highly significant statistical interaction. And you said that you didn't believe this was a biased analysis. While on the face of it we had to do this analysis, but by the very fact that a person with low heterogeneity could not have LVRS, it is a somewhat biased analysis.

DR. DOMINIK: I think what would be clearest to see is the event rates for the key safety outcomes that have been talked about for the high heterogeneity subgroup by treatment group, and is that available? I think that would be the most -- because the question is within the high heterogeneity subgroup, what is the difference in --

DR. CHIACCHIERINI: We did.

DR. SCIURBA: We don't have that specific analysis, but the one perspective that I just want to make sure we come back to is, you know, I believe that these subgroups can potentially make the procedure better down the line or can elucidate, but

we're really looking at the overall study right now. We fully acknowledge that these have limitations in going into these subgroups. I believe that they're highly plausible, that there's a lot of hope in there, but in the overall study, I think that we met our marks, and I think that has to be the largest focus, and then we're exploring these and there's exploration to go. We fully acknowledge that. Thank you.

DR. BIRNBACH: At this time, we're going to focus our discussion on the FDA questions. Copies of the questions are in your meeting handout. Could you please put up the first questions?

DR. CHOE: Are you ready?

DR. BIRNBACH: Yes.

DR. CHOE: Okay. The VENT study had protocol violations and missing data as follows: Inclusion criteria were not met in over 19 percent of subjects, mostly due to pulmonary function parameters and pulmonary rehabilitation. Missing data occurred in over 35 percent of subjects due to missed visits, visits outside of predefined window, or loss of follow-up. Statistical analyses were based on a non-prespecified extended window. Despite this, data was imputed in over 19 percent of the cases, and neither

subjects nor investigators were blinded in the event study.

Question 1, Please comment on the interpretability and validity of the statistical results for effectiveness in the VENT study.

DR. BIRNBACH: Okay. So we're going to go around the table and have a little discussion of this question. To summarize this, over 19 percent of the subjects did not meet inclusion criteria, missing data due to missed visits, et cetera, et cetera. Statistical analyses were based on an extended window, and it was not a blinded study.

So I'd like to start with Dr. Dominik, and respond specifically to the FDA question number 1, which is, Please comment on the interpretability and validity of the statistical results for effectiveness in the VENT study.

DR. DOMINIK: So I think what we most have to consider is whether the inclusion of patients with protocol violations or problems with missing data led to a statistical finding of superior effectiveness when, in fact, there isn't one if that were the case. That's what we have to be careful about, and to that, I think it's helpful to consider the issues of protocol violations and missing data separately.

I'm not very worried at all about the inclusion of the protocol violations that were basically baseline characteristics of these participants; that, in general, in randomized trials, I think inclusion of participants with protocol violations based on the inclusion/exclusion criteria are unlikely to lead to conclusion of superior effectiveness for a device that truly has no benefit, but certain patterns of missing this may lead to mistakenly concluding that a product has a benefit when, in fact, it doesn't or exaggerating the benefit, and I think the impact of the missing six-month outcome data needs to be our greatest concern. I think, given how small the observed effect size is and how many observations were outside the planned window or missing altogether, there might have been a small amount of bias.

So I know there were some sensitivity analyses that we didn't actually see in our packets, and I think it would be helpful to see those before concluding there was, in fact, a question about the validity of the findings with respect to a significant improvement for the group who received the device.

DR. BIRNBACH: Dr. Halabi.

DR. HALABI: I concur with Dr. Dominik, and in addition, actually I am also concerned about the protocol violation because at the end of the day you have 59 patients, excuse me, I may be reading the wrong number, we have 57 patients in the control arm, which represent 56 percent of all patients randomized to the control arm, versus 141 patients out of the 220 in the EBV arm. So that represents 64 percent of all the patients randomized to the device arm.

And, it's very difficult to verify missing trend, but there were no reasons collected during the trial that could convince us that the missing patterns between the two arms are similar. I am concerned about the reliability and validity of the results. Obviously, I would have preferred to see results comparing patient characteristics among those missing and not missing data, but that was not provided, and I would have liked to have seen that for not only the missing visit but also the protocol violations.

In addition, going back to the primary endpoint, as specified by the statistical analysis plan in the protocol, the window was extended, but if you look at the original analysis, the p-value wasn't really met. It was 0.025, and because of these

issues, I'm a little bit concerned about the validity of the results from the trial.

DR. BIRNBACH: Okay. Dr. Marcus.

DR. MARCUS: It's a difficult study and, you know, as a practicing clinician, I've had many patients who have asked me about the valve, and patients have gone to centers and have come back and said, no, I didn't get it. Dealing with COPD patients, I mean I think there's a lot of stuff here that we just need to realize, I'm just not sure can be avoided in, you know, the clinical arena. You know, just the last statement of neither patients or investigators were blinded, I mean I think that's a given, and I'm not sure that that is even something that we need to say again. You can't blind somebody as to whether they go for a procedure or not, and you can't blind the investigator. So I'm not sure why that's even here in terms of the evaluation of effectiveness, understanding that there are so-called placebo effects that we may get from things, and I'm still always amazed at 15 percent improvements in FEV_1 when a placebo is given as a bronchodilator.

So we do see these things, but they're short in term, and we're not talking about over six months.

I think it would have been, you know, really nice from a statistical point of view to have all of this data, but my overall feeling is that despite all of this, there still seems to be a gestalt that the device does work.

DR. BIRNBACH: Dr. Ries.

DR. RIES: Well, I certainly agree with Dr. Marcus. There's no such thing as a perfect clinical study, and certainly when you're dealing with sick patients with COPD, you understand that it is very hard to ensure total compliance with a protocol. You know, in hindsight, you know, we always have things we wish we had done differently.

I guess to me this is probably not the key question because, although I think there are some issues and concerns, and I agree that the issue is not so much the violations because those should be sort of equally distributed across the two groups, the issue is whether there's some differential effect of some of the lost data, and, you know, the fact that there was some more lost to follow-up in the control arm which, you know, that negative placebo effect, you know, could have some concern, but I'm not convinced that, you know, sort of the key issues here are really impacted by the absence of data.

I think there is probably a signal here. It's probably a modest signal. You know, the issue is what's the right measure of effectiveness here, and do we accept the FDA's version that it really has to be a combination of both endpoints, or do you sort of accept the, you know, the Sponsor's that it's sort of an either/or. I'm not overly concerned about this particular question.

DR. BIRNBACH: Okay. Dr. Willsie.

DR. WILLSIE: I would concur with what's been said. I have other concerns further down.

DR. BIRNBACH: Dr. Li.

DR. LI: I again agree with the previous speakers. My only comment would be I'm not specifically concerned about the actual shortcomings here other than the fact that it probably means that the results we get would probably be the most favorable view we could get of the data. It's hard to imagine, if we did the study more correctly, the data would be better. So I think, if anything, it biases toward the data being maybe the best look at the data that we could get.

So it's likely, and as with most devices, when you get out of the PMA study, you release it to absolutely everybody. When it gets out to everybody,

typically the device performance goes down just because of the distribution. So I think with all that's going on, I'm not so concerned about these violations, but I think it behooves us to know that this is probably going to be the best set of data we're ever going to see.

So if you're kind of borderline on this data, I would expect the data to decrease as the study expands.

DR. BIRNBACH: Dr. Cassiere.

DR. CASSIERE: I have to agree with my clinical pulmonary colleagues. This is for me not the primary issue, and at best, the statistics, even if it's in favor for the manufacturer, it's not primary.

DR. BIRNBACH: Dr. Wilcox.

DR. WILCOX: I have to confess that I'm statistically challenged. It's a problem for me that we have to strain so hard to approve whatever we're trying to approve here with so many different manipulations, and I wish it could have been clearer. I have an old teacher that used to say, you didn't have to do a -- square on penicillin. I don't think this is penicillin, but I'm not sure we proved one way or the other as to whether this device works.

The blindedness is just an awful problem, a very difficult problem, but it is pretty up front. You take one group of patients and say we're going to keep on doing what we're doing with you, and you know all of them are getting worse anyhow. But we'll take this other group, and we're going to take them back in the back room back here and do all sorts of manipulations on them and so on, and we're going to see which one does better. So I think the blindedness is a major issue, and I wish I had better ways of getting around that other than bronchoscoping everybody, but it's a problem.

DR. BIRNBACH: Thank you. Dr. Vassiliades.

DR. VASSILIADES: Personally I'm not troubled by the protocol violations or the missing data, and overall I think from a statistical standpoint, I think the data is interpretable and valid.

DR. BIRNBACH: Dr. Loeb.

DR. LOEB: I think given the complexity of the study, that protocol violations and missing data are not beyond what would be expected, and I think that the Sponsor provided numerous different statistical manipulations to try to see if this had any impact, and I didn't see any evidence that there

was an impact from that.

DR. BIRNBACH: Dr. Wiswell.

DR. WISWELL: I generally concur with the other members of the Panel. I actually think that using imputed data as described here actually may not have ended up with us seeing the best kind of outlooks because I think they did a pretty good job on how they imputed stuff and entered data there, that it was may actually have saw perhaps a little bit less of a difference than there may have been.

DR. BIRNBACH: Dr. Brunson.

DR. BRUNSON: I think it's obviously a tough patient population with a progressing disease. So looking at the data as I see it, I'm not particularly troubled to the point that I think probably we can't use the data, and I'm not bothered by that.

DR. BIRNBACH: Dr. Domino.

DR. DOMINO: Yeah, I agree with that as well. It's a difficult study to do in a difficult patient population, and I personally would have liked to have seen a blinded bronchoscopy, but I guess maybe that isn't, I don't know, you know, it still might have solved some of the placebo effects, but I'm not bothered by the missing data.

DR. BIRNBACH: Ms. Petersen.

MS. PETERSEN: I think we've had quite a good discussion about a lot of these statistical concerns and other issues, and I think the voting members have ably teased out the questions and concerns.

DR. BIRNBACH: And Mr. Osborn.

MR. OSBORN: I have to agree with Dr. Wilcox. I'm somewhat statistically challenged as well, but I do think that the issues have been well discussed.

DR. BIRNBACH: So to summarize this, although we do not have unanimity of opinion, I believe that the Panel generally believes that there were a lot of protocol violations, but given the complexity of the study and given the nature of clinical studies of this type on this type of patient population, that many of these could not have been otherwise dealt with. They may have been unavoidable, so to speak, and that while they may be an issue, they don't appear to be a major issue.

Does anyone on the Panel disagree with that overall summary of how I read the Panel?

DR. MARCUS: I would agree, and I just would like to just emphasize that this is generally a

desperate group of patients, and we need to realize that.

DR. BIRNBACH: So, Dr. Lin, with regard to question number 1, questioning the validity and reliability, the Panel, although we did not have unanimity, generally believes that the protocol violations were an issue but probably not a major issue and probably one that was unavoidable, and that they are generally okay with the data as we have it as relates to specifically the validity and reliability.

Is that an adequate answer?

DR. LIN: Yes. Thank you.

DR. BIRNBACH: Thank you. We're going to move onto question number 2.

DR. CHOE: In the VENT trial, the two co-primary effectiveness endpoints achieved statistical significance in the ITT population at 6 months, but the threshold level of 15 percent was not achieved for either endpoints. In addition, the clinical magnitude of effects remained similar for FEV_1 and decreased for the 6-minute walk test from 6 to 12 months.

The secondary effectiveness endpoints, SGRQ, mMRC and cycle ergometry, achieved

statistically significant changes at six months. The effects on these three metrics deceased and did not achieve statistical significance at 12 months.

Question 2, Please provide your assessment of the results of the co-primary and secondary effectiveness endpoints in the VENT study. Please discuss the clinical significance of these results, if any.

DR. BIRNBACH: Okay. So while we were anticipating a 15 percent change, we did not actually see that. Although statistically significant findings, we're going to have to come up with an understanding of whether or not they were adequate. So we'll start with Dr. Domino to provide your assessment of the results of the co-primary and secondary effectiveness endpoints in the VENT study. And we're discussing the clinical significance of these results, if any.

DR. DOMINO: Well, while there are some patients who you did say did respond to this 15 percent clinical threshold, I'm not overwhelmed that this is particularly effective or that the effect size is very large. And the other thing that seems to occur is that it goes down with a period of time, perhaps suggesting it's a tangent effect. So I find

it concerning for those two reasons.

DR. BIRNBACH: Dr. Brunson.

DR. BRUNSON: I'm still wrestling with whether or not this is more like a palliative treatment before you get to whatever is going to be an end result down. And if, in fact, you noticed a statistical significant improvement that lasts about six months, is that important to these end-stage patients? But I am troubled that there was not a sustainment of the improvement, but I also don't know if there could have been.

DR. BIRNBACH: Dr. Wiswell.

DR. WISWELL: Yeah, I'm sort of torn, too. I would have loved to have seen, as an investigator and a clinician, you know, that big difference that we all hope for, and we didn't, but we saw some. We saw a glimmer there, and the question in my mind is this good progress and may be leading us down the road to the next thing or in the population that we're going to treat, and maybe by the multiple lobes or however else it's used, maybe it's a further step.

I would have liked to have seen a bigger difference, and I would have liked to have seen a bigger difference in some of the secondary parameters, especially the quality of life

persisting, because in the end it's our patients, and how they're existing and dealing with day-to-day life, and it doesn't look like there's a huge difference in that, that they think is going on in their lives.

DR. BIRNBACH: Dr. Loeb.

DR. LOEB: I have a little different view. I think that what we're seeing in this study is best demonstrated, and I was actually surprised that nobody put this slide up, but on page 132 of our packet, clinical study report, there's a graph with a lot of green dots on it that I think to me was extremely important to look at. And what is seen in that graph is that most of the patients did not have an effect of the therapy, but that there was a subset of patients who clearly benefited, and they seemed to be the ones that had the most lung reduction or the most decrease.

So my conclusion is that when used appropriately in the appropriate patients, there can be a very good effect, but that a lot of the statistical findings were diluted by the fact that either the device wasn't used properly or the wrong patients were chosen or there was some reason why the best effect wasn't obtained.

And so I find it a promising device, but I think a lot more work needs to be done to make sure that it's used to its best advantage.

DR. BIRNBACH: Dr. Vallisiades.

DR. VALLISIADES: My interpretation is that the device is not clinically effective.

DR. BIRNBACH: Dr. Wilcox.

DR. WILCOX: Dr. Loeb expressed my point of view. This is a problem that has been with us for a long, long, long time, and I think we've identified some patients that this will be effective in, but we haven't pinpointed them well enough, and that concerns me a little bit, that this technique would be applied so broadly that we really won't learn anything in the future, but I think it does help some patients, but we haven't learned how to identify those patients.

DR. BIRNBACH: Dr. Cassiere.

DR. CASSIERE: I have to agree. Basically if I saw some data that there was actually lung volume reduction to go along with the theory that this works, I'd be more inclined, but I don't see any of that information. I see this as an interesting technology that is not ready for prime time.

DR. BIRNBACH: Dr. Li.

DR. LI: Actually I have nothing to add to that. I completely agree with that.

DR. BIRNBACH: Dr. Willsie.

DR. WILLSIE: I also agree, you know --

DR. BIRNBACH: Agree with what?

DR. WILLSIE: I'm sorry.

DR. BIRNBACH: Agree with what?

DR. WILLSIE: Well, I'm getting ready to tell you. I agree that there is statistical significance, but clinical significance is completely different, and if I, just for the lay people in the audience, if I had a patient who came in with an 870 cc FEV_1 and later had an 8 percent increase equaling about 60, 70 ccs, I wouldn't see that as being any different. So I agree that the evidence for clinical significance, which we all accept in the pulmonary community, is just not there.

DR. BIRNBACH: Dr. Ries.

DR. RIES: You know, I find this really hard. To me, a critical question is whether there's really effectiveness here, and I think clearly if you accept the way this study was set up, if you accept the way the criteria that the Sponsor used, which are 15 percent changes in these functional measures and the MCIDs that were picked, which were largely picked

off the NETT study which is a surgical trial which was very different, then I think the FDA's analysis is correct. They really haven't met the standard of effectiveness.

The problem I'm having is I really think there's a signal here, and I think this is promising, and I think you found some interesting results, and I've worked many years in rehabilitation, you know, which for 30 years has tried to sort of establish its effectiveness without ever showing changes in lung function, and I think this is more analogous to what we have in rehab, which is, you know, a modest effect with modest risk, and this is not surgery. Surgery, you know, in the NETT study, that was high risk and high reward, and the standards that were applied to that particular patient population, that particular study, I don't know that they really are the applicable standards for this.

So I think there is a signal here. There's probably some subset. I think the technique is not quite, you know, at least how it was applied in this particular trial, is not how it's going to be applied in the future, but there's something worth exploring, and I think there are going to be clinically significant benefits. The problem is for which

patients. So I find this difficult. This is to me the critical question.

DR. BIRNBACH: Dr. Marcus.

DR. MARCUS: I think, going back to something Dr. Ries just said, on NETT, high risk, high reward, but in a selected group of patients, and it wasn't the procedure for everybody in NETT.

And I think even here, we've got a signal. The fact that things get better at 6 months and then at 12 months, is that natural progression of disease? I mean look at all the pharmacological trials that show, you know, no decline in the natural progression of disease, and perhaps maybe that's why we're losing effectiveness at 12 months, and it is natural progression of disease.

I think that we need to learn, if this goes forward, who the right patient is, how to best achieve this deflation, and as we've already heard about incomplete fissures and a lobe and how many segments, this is not as simple as it may sound, but I think it is certainly something that there is significance, there is a signal, and it is something promising for a group of patients.

DR. BIRNBACH: Dr. Halabi.

DR. HALABI: As a statistician, it's very

hard to look at clinical significance, and I concur with my clinical colleagues on the Panel. My biggest struggle here is with the endpoints and whether these really translate to clinical benefits to patients and improvement in quality of life, and I would have liked to see more data beyond the one year, but clearly there is a signal at six months. Whether that's clinically significant is debatable. Thank you.

DR. BIRNBACH: Dr. Dominik.

DR. DOMINIK: Similarly, assuming the data are valid, then there is evidence of a signal here but whether it's clinically significant, I have to defer to the clinicians.

DR. BIRNBACH: Ms. Petersen.

MS. PETERSEN: I think we can agree with others who said that while we see some possibility here, we don't yet identify which patients can benefit, and there are some concerns about the clinical significance and the actual improvements in people's daily life.

DR. BIRNBACH: Mr. Osborn.

MR. OSBORN: As Dr. Loeb was, I was struck with the fact that there does seem to be something here for some patients, and that the real key I think

is how does one identify which patients are going to respond, because fairly clearly some fraction of the patients had a significant clinical improvement. A two to one improvement over the GOLD standard of treatment is not insignificant, but some patients didn't respond. So the question is how does one differentiate ahead of time between those particularly given the low risk and the fact that these patients have almost no other options.

DR. BIRNBACH: Okay. So to summarize, I was quickly jotting down some of the key words that were used around the table. Trouble was said twice, torn, confused, concerned three times, and difficult.

There is, if we're going to go back to the last question, a gestalt here that there may be something here, but there is some difficulty around the table because many of us think that this is promising and interesting, but there is still the looming question of whether or not this is clinically significant.

Would everyone agree that that is overall an assessment of what we said?

(No response.)

DR. BIRNBACH: So, Dr. Lin, in review, in looking specifically at the clinical significance of

these results, the Panel did believe that there was some very promising and interesting data presented. However, there did not look like there was a huge difference. There was a statistically significant difference. That said, the Panel would have liked to have seen the 15 percent mark that the Sponsor was aiming for. At this point, based on evaluation of this data, we are not sure whether or not there is any clinical significance here or not. The other point that had been raised by several people was the fact that there is some troubling information that this may not be a permanent effect but rather that there may be some tangent effect that we're seeing.

Is this adequate to answer that question?

DR. LIN: Yes, but you can keep that in mind when you answer question number 4. When you look at the overall safety and effectiveness, that will be very important information.

DR. BIRNBACH: Yes, we will. Question 3.

DR. CHOE: The primary safety endpoint was the Major Complications Composite. The MCC delta endpoint was not agreed upon. The MCC was more than five times higher in the Zephyr EBV treatment group than the control group at 6 months, and more than two times higher at 12 months.

In addition, other safety analyses were conducted. Survival and composite progression to death/LVRS/lung plantation were similar in the Zephyr EBV and control groups. However, rehospitalization was significantly greater in Zephyr EBV than control groups. In addition, clinically and statistically significant increases in adverse and serious adverse events were observed in the Zephyr EBV group which persisted over the 12 month follow-up.

Question 3, Please discuss and provide your interpretation of the device safety in the VENT study.

DR. BIRNBACH: Okay. So there were some differences of opinion in the presentations we had this morning about the complications and whether or not they were clinically and statistically significant between the two groups.

So I open this up to the Panel. I would like to discuss your interpretation of the device safety as related to the VENT study. And, again, we'll start with Dr. Dominik.

DR. DOMINIK: I just want to first start up by saying I think I'm no longer worried that there was evidence so far of an increased risk of the adverse events we talked about earlier for those

higher heterogeneity patients. I would like to see more data, but I think I now see the relationship with what Dr. Chiacchierini said and the FDA slide, and I'm not especially worried about an increased risk for that subgroup based on what I've seen.

But I think in interpreting the safety data, I think what's important to do is to look at the confidence intervals, and for the primary outcome, the point estimate was about a five percent difference with an upper bound of about nine percent.

So assuming the safety data are valid, I think we can only rule out with reasonable confidence a different in risk of about nine percent or higher with respect to the MCC events, and we don't have the confidence intervals for the secondary safety events, but I think that's what I would focus on. So if there's an 18 percent difference in hospitalizations or so, I think is what it was, that means we can only rule out with high confidence a difference of something a little bit higher than that. So the difference in hospitalization rates might actually be higher.

So I would encourage people to kind of look at the safety data from a non-inferiority perspective, and what are we able to rule out by

thinking about the upper bounds of the confidence intervals for these differences between groups?

DR. BIRNBACH: Dr. Halabi.

DR. HALABI: I concur with Dr. Dominik, although I was a little bit concerned with the increased hospitalization in the device arm. That's beyond the average risk that you would expect.

DR. BIRNBACH: Dr. Marcus.

DR. MARCUS: I think from a statistical point of view, yes, there were differences, but I think from a clinical point of view, the device appears to be safe. I think that as people get experience with it, it probably will get better, and I think the hospitalizations as we heard were largely very short-stay hospitalizations. So I'm not concerned with the safety issue.

DR. BIRNBACH: Dr. Ries.

DR. RIES: Yeah, I agree with Dr. Marcus. I don't have a lot of concerns about the safety issues. I think they're about what you'd expect if you did any kind of intervention in this kind of a patient population. There's always going to be some short-term risks in doing a procedure like this to this patient group, and I think that the critical issue is, is that risk really worth the rewards that

you get? And again going back to the NETT study, you know, where it was high risk, you really had to get a much higher burden of proof in terms of the benefits to justify that risk, and I think this is about what you'd expect. And I was actually heartened looking at the survival, that even though there was even a few extra deaths in the short term, that over a year, that was really balanced out in the two groups. And so I don't really think that the harm is the issue here.

DR. BIRNBACH: Dr. Willsie.

DR. WILLSIE: What I would add to that is that obviously the investigators were chosen because they're extremely accomplished and experienced interventional bronchologists, but I do believe that we have to at least have some concern about what will happen when this is out in the community, when we have all comers using a device that they're not familiar with, and I think that we probably would expect that the adverse events would go up.

DR. BIRNBACH: Dr. Li.

DR. LI: I concur with that, and with one additional comment, that several people have spoken that we don't exactly know what's going on here completely with this device. For instance, there

seems to be a group of patients that does better than others, and several people have commented on, you know, if we could zero in on that patient population, we'd probably get a better clinical effectiveness, but that also means we actually then have no idea what the complication rate is, if you're going to pick a different subset of patients.

So I'll defer to my colleagues' opinion about whether or not the complication rate is clinically relevant now, but I will point out that if we change the patient population or indications, those complication rates may change.

DR. BIRNBACH: Dr. Cassiere.

DR. CASSIERE: I'm going to agree with my clinical colleagues. The short-term safety issues don't seem to be much of an issue. I'm concerned about what would be some of the long-term outcome from keeping an atelectatic lobe in a patient who was going to naturally probably be colonizationed with multi, you know, drug resistant gram negatives over time. If this patient came to the emergency room, and I saw an x-ray like that, I'd bronchoscope that patient to remove the obstruction because the likelihood that that patient's going to develop pneumonia or bronchiectasis long-term is the concern.

So my concern here is not the short-term safety data but the long-term data about what happens with atelectatic lung in this patient population.

DR. BIRNBACH: Dr. Wilcox.

DR. WILCOX: I think the safety record's remarkable, and there's testimony from the folks who were involved. I do worry, as I pointed out earlier, about if this is, and that's something I think we need to discuss, released to the world or should be released in a more controlled way.

DR. BIRNBACH: Dr. Vassiliades.

DR. VASSILIADES: I have no major concerns with safety. I think the device has a favorable ease of use profile, and I think that there seems to be a well thought out plan to translate this into the general community. So while there is some concerns with morbidity, rather than mortality, I think that on balance the question has to be looked at in terms of risk and benefit, which we're going to get to, but independent of that, I think safety in my mind is not a primary concern.

DR. BIRNBACH: Dr. Loeb.

DR. LOEB: I think the risk profile is exactly what I would expect from a device that involves an invasive procedure to insert it, and then

is a foreign body in the body for a prolonged period of time. We have a lot of experience with similar devices, cardiac stents, pulmonary stents. What I see in the data is, yes, most of the decrease in safety or difference in the safety profile is all from the acute procedure, but I did see a difference in the long-term differences in some of the deaths that were presented by the FDA, rehospitalizations and emphysema exacerbations that I think all are related to probably the irritating effect of these devices in the airway and increased mucus production and consequences of that.

So I think it's like any device. It's going to have its side effects, and I'm not particularly troubled, but certainly there is enough side effects that needs to have discrete benefits to outweigh it.

DR. BIRNBACH: Dr. Wiswell.

DR. WISWELL: I echo Dr. Loeb's conclusions. I guess I'm a little more concerned about the deaths just from the FDA interpretation, that they seem to be more COPD-related deaths and six out of the eight EBV patients versus one out of the three. Granted the numbers are small, and it's hard to draw any conclusions there. So I think there

clearly needs to be more work or more follow-up of patients just looking at that particular endpoint, and over time again, the rehospitalizations, potential for infections, et cetera, do worry me some.

DR. BIRNBACH: Dr. Brunson.

DR. BRUNSON: I'm not particularly concerned with any of the issues about safety. I think any time that you're doing an intervention in a diseased lung such as leaving a device in, you would expect to see some of this.

I am a little concerned about what happens further out, which is information we don't have, but as far as the safety of the device, I have no major concerns.

DR. BIRNBACH: Dr. Domino.

DR. DOMINO: Yeah, I'm not particularly concerned in the short-term. I think those risks are expected with the procedure. I think as you've acknowledged, the study is not powered to assess safety, and what the long-term consequences of the device are are unclear to me, and the potential concern for infection, in a long-term situation, I am worried about.

DR. BIRNBACH: Mr. Osborn.

MR. OSBORN: I agree with several of the Panelists who indicate that there does not appear to be a significant short-term safety issue. As was just mentioned, the long-term issue of the study wasn't powered for that. So that's a clear potential issue to look at in a follow-up study where you can have that longer-term data should the device be in commercial distribution.

DR. BIRNBACH: And Ms. Petersen.

MS. PETERSEN: I agree with the Panelists who have suggested that there is not more concerns in the short-term safety, but that the longer-term needs to be looked at because there may be some concerns there.

DR. BIRNBACH: So, in summary, I think this time we have close to unanimity of opinion that there is some concern about the long-term safety, but the studies were underpowered to look at this, but that it also appears to be safe for short term and that we do need more follow-up, especially as relates to death down the road and long-term infections.

Will that be an adequate summary of what we said around the table?

(No response.)

DR. BIRNBACH: So, Dr. Lin, as far as

question number 3 is concerned, the Panel believes that based on the evidence that we were given, it appears to be safe. However, we do need more long-term data, especially as relates to death and long-term infections.

Would that be an adequate answer to question 3?

DR. LIN: Yes. Thank you.

DR. BIRNBACH: Question 4.

DR. CHOE: Question 4, Please provide your overall assessment of the risks and benefits of the Zephyr EBV device for treatment of patients with severe, heterogeneous emphysema who have received optimal medical management.

DR. BIRNBACH: Okay. So question 4 would be the big question. So risk and benefits. Maybe we should begin in the middle this time, although then I'm going to have to have some kind of checklist. Dr. Vassiliades, what do you think about the risks and benefits?

DR. VASSILIADES: Well, as a surgeon, we deal with this every day, and in my mind, while the risks are not huge, they're not insignificant either, and I think that there has to be demonstrated clinical efficacy because that's really what we're

here for is the patient, and the patient needs to benefit, and it doesn't help the patient to tell them they're going to have a statistically improved FEV_1 but they're not going to check the next higher level on their questionnaire for quality of life because it's not going to make any difference to them clinically.

So in my mind, I think that if I have enough information to make my decision about the device, which we can talk about later, but I think that the risks in this case are -- well, to put it another way, I think the benefits are inadequate to overcome the risks.

DR. BIRNBACH: Dr. Wilcox.

DR. WILCOX: I would like to amend our last observation to say that it has been demonstrated that this procedure has been safe in the hands of the investigators.

DR. BIRNBACH: We're going to get to that.

DR. WILCOX: And so I do think in the hands of these particular physicians, it is low risk. I also agree that there's a low predictable benefit and leave it at that.

DR. BIRNBACH: Okay. Let me add a question as the rest of you give your opinions, which is the

risk benefit analysis that we're all doing now. Does that change once this opens to the community and more and more are doing that who might not actually be quite as well trained, as well supervised for the first five and in major institutions where this is a daily event? Dr. Cassiere.

DR. CASSIERE: It seems like most of the significant risks that were studied are up front, and it looks like if you look at the non-clinical significance, that the benefits are up front. What I have a problem with is longer-term; 12 months there's really no difference, and I don't know what the long-term outcome is going to be. So for me, I'd have to say that this doesn't, you know, pass the test for a risk versus benefit.

DR. BIRNBACH: Dr. Li.

DR. LI: On the benefits side, I think, referring to the graph that Dr. Loeb referred to, I think although the big improvement was in the FEV_1 scores, if you look at the actual individual data points, some were between a 1/3 and 40 percent, had actually no improvement with the FEV_1 score, even if there was a reduction of lung volume. So although statistically you could say that there was an increase in the FEV_1 for this group of patients,

fully at least a third of them actually had no improvement in FEV.

So I think that superimposed upon the fact that the difference really, even statistically, wasn't all that big, the benefit, you know, as the non-physician, numerically just doesn't seem like it's very strong.

DR. BIRNBACH: Just to keep you on your toes, Dr. Loeb.

DR. LOEB: I end up with the same conclusion as the other people that the benefit does not outweigh the risk, and I'd do it a little bit more numerically. I think that the, I forget the name of the analysis that was done, the responder analysis quantifies how many people had an improvement in FEV greater than 15 percent, and it looks like there's about 15 percent of the patients had a clinically meaningful benefit, and we saw that between 5 and 10 percent of the patients had some sort of a major adverse event, and I think that's not good enough.

DR. BIRNBACH: Dr. Willsie.

DR. WILLSIE: Yes, thank you. It seems like the high heterogeneity group probably is the group that may, I can't make that assessment on the

basis of this data, may be the one that would respond best, but on the other hand, there was a higher incidence of death and the need for lung volume reduction surgery, statistically significant. So that's an answer to that.

Regarding your question, I alluded to this earlier. I do have concerns about what's going to happen when this goes out in the community and people are using it in all sorts of various ways.

DR. BIRNBACH: Dr. Wiswell.

DR. WISWELL: I share the general kind of feelings people are expressing, not a lot of early clinical benefits, and I have to ask myself what are you going to explain to a patient, you've got, maybe if you use the similar criteria and for your treatment, you've got maybe a 25 percent chance of having a clinical improvement but that means 75 percent not. I recognize that they're sick and they're desperate and they want to improve, but there are some substantial, I think, risks for it, and it doesn't outweigh the relatively low clinical benefits.

DR. BIRNBACH: Dr. Brunson.

DR. BRUNSON: I basically have some of the same conclusion. While I believe that this has some

promise for the future, I don't know if we've gotten to the point yet where it's demonstrated that it is something that we ought to give out to the general public for our physicians to use on their patients. It's a tough circumstance because the patients have no other options, but I think the evidence that we've seen here, for me, doesn't show that we have the clinical benefit or the sustained clinical benefit to outweigh the risk.

DR. BIRNBACH: Dr. Domino.

DR. DOMINO: I agree with that. I'm concerned over the long-term, not a sustainable benefit on the margin, on how important it is. Certainly there may be a subgroup eventually that it is important, and this is an invasive procedure that does carry risk, not an acceptable risk, but it does carry risk. So to me it doesn't have a good benefit for the amount of risk.

DR. BIRNBACH: Dr. Ries.

DR. RIES: Well, I think, you know, that this is a tough decision at this point, but this to me looks like a very promising field. I think the investigators have done a nice job to date. I know the issue is whether we're talking about, you know, currently what we know about effectiveness versus

what the potential is. I think right now we're looking at sort of a modest effect and a modest risk, and I would hate to do anything that would sort of preclude, you know, future development in this field because I think there really is a signal here, an important clinical signal that we haven't quite defined. And I would suspect that in the future, as this field progresses, and hopefully it will, things will change quite a bit, and in defining who the right patients are and improving the risk experience as people get more experienced with the device will improve the balance. And, I do agree, regardless of what the decision is, there needs to be very tight control over how this is -- this is not ready for prime time, but I think it certainly is promising.

DR. BIRNBACH: Dr. Marcus.

DR. MARCUS: I agree a great deal with Dr. Ries. I think that again, coming back and looking at COPD, and we've had this nihilism for many, many years, you know. It's an irreversible disease. What can we really offer these people? And then, you know, we've realized that, you know, we don't even know what the right metric is, and we talk about FEV_1. Sure it's reproducible. It's measurable. We've got 15 percent, and we can say

that's clinically significant or that's statistically significant, but we don't know what clinical significance even means. We can look at five different patients with the same FEV_1 and find a wide range of performance. Some will go to work every day and some can't walk 10 steps with the same FEV_1.

So I think we need to keep a degree of optimism. I think there is definitely some signal that this is going to be good for a select group of patients. I think we just need to better define what that group is, and perhaps we need to be able to have a better objective measurement and whether it's radiographic, I'm not sure if it could be bronchoscopic, but we need something that just tells us that this thing is going to do what we want it to do.

You know, if we look at St. George's Respiratory Questionnaire, we do see it improves. Yes, at 6 months, not at 12 months. You know, so I think a lot of this we need to be careful that we're not throwing out the baby with the bath water, so to speak, in that as you go with time in COPD, you get the further natural decline that no therapy has been shown to change.

DR. BIRNBACH: Dr. Halabi.

DR. HALABI: As a statistician, it is very difficult to assess the risk benefits, and particularly because the data does show a small effect, but somehow beyond minimal risk, but then we have to take this within the context of what other option this special population have. So as a non-clinician, it's very difficult for me to do that, although I am concerned about learning curve and whether we will have or we'll observe a more increased risk among patients treated in academic centers versus community hospitals. So this is something that will require having more follow-up data with regard to both the benefits and the risks.

DR. BIRNBACH: Dr. Dominik.

DR. DOMINIK: I think that the small benefits are not worth the observed risks.

DR. BIRNBACH: Ms. Petersen.

MS. PETERSEN: I think we've seen a pretty consistent view that the benefits don't yet equal the risks. I believe if patients with COPD were here, they might take a more optimistic view of the data that we're looking at today, certainly looking for a more hopeful future. But in light of the transiency of the effect and the sense that we don't really yet well-identify which patients can benefit, I have to

agree that the risks outweigh the benefits.

DR. BIRNBACH: Mr. Osborn.

MR. OSBORN: The troubling part of the study is that we don't seem to be able to figure out ahead of time which patients are going to have the maximal benefit. There was a small subset of patients for whom the benefit was significant. There was a larger set of patients for whom there was no benefit. It's promising. If we could figure out which patients to treat, i.e. those that get the benefit, I'm sure that if they were here, they would say it is very significant because they have very few options, and so that's the conundrum.

DR. BIRNBACH: And the Chair's perspective, I tend to agree with Dr. Ries and Dr. Marcus in that this is a very promising possibility, and it would be a pity to throw out the baby with the bath water. However, I also would agree with the rest of the Panel that, more or less said, this is not ready for prime time because it appears that while there are small risks, there are risks, and the improvement, while statistically significant, may not be clinically significant. Most important, however, is that we need to better define which group would be best served and then use this technique in that

group, at which point the risk benefit analysis would be tremendously different.

Is that an adequate summary of our findings?

(No response.)

DR. BIRNBACH: So, Dr. Lin, there was general agreement around the table, and the best word I could use would be ambivalence because while there was the excitement about the potential for this, there was also the feeling that at this point, with the data that we have, the risks, though not huge, are not insignificant, and the benefits are not clearly enough demonstrated to outweigh those risks that we see.

With that said, if this were done on a patient population that clearly benefited, that analysis would change.

Is that an adequate answer of your question, Dr. Lin?

DR. LIN: Yes. Thank you.

DR. BIRNBACH: Question 5. Well, actually before, we're going to take a break now since we've already been a little past. So we're going to break before we get to question 5. This is going to be a short 10-minute break. It is now 3:02. We'll come

back here at 3:15. So a 13-minute break. And I remind no one on the Panel to talk about it.

(Off the record at 3:02 p.m.)

(On the record.)

DR. BIRNBACH: Question 5.

DR. CHOE: The next questions, 5 and 6, are intended for Advisory Panel discussion to guide the Agency in the event that the subject device --

DR. BIRNBACH: Actually, you better hold on. We do need the Sponsor. Here they come. Okay. Please continue with question 5.

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

Question 5, With regard to the indications for use, Instructions for Use, and clinical data, please comment on the following:

(a) The target lobe identification in the IFU is described as a non-specific radiographic assessment of heterogeneity, whereas the VENT trial used a software-based method for analysis of high

resolution chest computed tomography. Please comment on whether the IFU adequately instructs the practitioners to chose the target lobe in a way that would produce similar safety and effectiveness results to the VENT trial.

DR. BIRNBACH: So questions 5 and 6, rather than poll everyone, we're going to try to get some gestalt from the Panel. So does anyone on the Panel have an opinion about 5? In sum, should we limit this to one lobe as was studied in the pivotal trial or alternatively as was suggested that it would be eventually used in practice, do we need additional warnings for this? Anyone have any -- yes.

Dr. Willsie.

DR. WILLSIE: I would comment that if this product were to be approved, that really you can only recommend the device for use in individuals in whom it's been shown to be effective and have a favorable risk benefit profile. So I would believe that you would need to specify the limitation of one lobe based upon the data.

DR. BIRNBACH: So it would be, from your perspective, limitation on not only where you put it, but of which patients. Is that correct?

DR. WILLSIE: Indeed. Yes, indeed.

DR. BIRNBACH: Dr. Marcus.

DR. MARCUS: But where you put it, the type of patient sort of defines where you put it.

DR. BIRNBACH: The two go hand-in-hand.

DR. MARCUS: Right. I mean you're not going to do it with somebody who's got, you know, the heterogeneous disease. You want somebody who's got a lobe that you can deflate so to speak. So I think the two go in hand-in-hand.

DR. BIRNBACH: Anyone else? Dr. Ries. Dr. Vassiliades. Dr. Ries.

DR. RIES: In terms of this question (a), you know, I think, in response to what I asked earlier, I think it really depends upon how confident they are that they can define heterogeneity in a way that the general, you know, radiologist and the community could interpret.

I think the other issue that ought to be addressed here is the issue of integrity of the fissure which may even be a critical issue and that should be defined, too.

DR. BIRNBACH: Dr. Wiswell.

DR. WISWELL: A couple of thoughts. I don't think we've seen any kind of data showing that there is concordance between a radiographic

assessment of what might be the lobe to put it in comparison to what was used in the trial where you had software look at the high resolution CT scan to point out what is best, and both in trials and clinically, I can tell you that there's often differences in people's opinions on films.

Related to the other two things, the items here in question 5, we've seen absolutely no data that this is more effective, if you're going to go after more than one lobe at a time, and I don't think it should be approved for use in more than one lobe at a time because you haven't shown that it is going to be more effective.

And the last thing, I think there needs to be far more extensive training spelled out in the instructions for use that the individual clinicians have to have before doing this, and whether it's being proctored for X number of successful placements, whether it's meetings that the Sponsor puts together and make sure everybody has this education, but I think it needs to be more extensive.

DR. BIRNBACH: All right. So if I can summarize what I think I'm hearing -- does anyone else have any comments before I summarize what I've heard so far? Dr. Loeb.

DR. LOEB: I would only add that we did hear something from the Sponsor that heterogeneity may be a hot topic, and that there should be, it seems like probably something in the public domain that could be pointed to for use by people who are using this. So one would hope that some judge of heterogeneity that does would be an appropriate domain.

The second thing that I think is very much missing is any instructions about how to evaluate the effectiveness of the therapy after it's placed. We heard that the bronchoscopist rated how effectively they had isolated the lobe, and then see that six months down the road, radiographic evidence says that they didn't isolate the lobe. And so I would hope that there would be earlier identification of whether or not the therapeutic goal had been achieved.

DR. BIRNBACH: So to summarize what I've heard, there were many questions when it comes to labeling, not least of which is who and where, how you monitor this after the fact, and whether you use high resolution CT and which software is or isn't used, how you evaluate effectiveness after placement, and what kind of training will be necessary and how it will be implemented, and does that include

proctors or not. Is that an overall assessment of what we're thinking?

(No response.)

DR. BIRNBACH: Dr. Lin, the Panel believes that we need more data about who should get this, where it should be placed, whether there should be any limitations on, for example, the numbers of devices that are put in. We need more data on high resolution CT and whether that is the be all and end all. Heterogeneity obviously is an issue. Evaluating effectiveness after placement, and last but not least, far more extensive information about training of those who are going to do the procedure, whether or not they're going to need to be proctors or not, and how many you would need to do, et cetera, et cetera.

Is that adequate in response to question 5?

DR. CHIN: Yes.

DR. BIRNBACH: Question 6.

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

information gathered: for training effective as assessed by device migration/expectoration rates; device effectiveness as assessed by a post-bronchodilator spirometry; safety assessed by serious adverse event rates; and all endpoints with descriptive statistics.

Question 6, Is the proposed post-approval study appropriate to address training effectiveness and device long-term safety and effectiveness postmarket?

Please discuss the following:

Is the study design appropriate to evaluate device safety and effectiveness postmarket?

What should be a comparison group against which these data should be evaluated?

Is it valid to assume that the migration/expectoration rate will be 6 percent in postmarket, which is less than what was observed in premarket, which was 7.9 percent?

Is there a need for the evaluation of six-minute walk test in addition to spirometry as effectiveness endpoints?

What safety endpoints needed to be addressed?

Is a follow-up of three years post-

procedure sufficient to address device long-term safety and effectiveness?

Please discuss any additional issues that should be assessed in a post-approval study and provide your recommendations.

DR. BIRNBACH: So question 6, from (a) to (f), does anyone on the Panel have any feelings regarding the proposed post-approval study? In particular, the question of whether three years is adequate and what the comparison group should be. I think we could start with those. Dr. Marcus.

DR. MARCUS: Okay. So I think if we take it step-by-step, first of all, just a question. In terms of spirometry, did the original trial use post-bronchodilator spirometry? I don't remember seeing. Just the FEV_1.

DR. BIRNBACH: Yes, they did.

DR. MARCUS: It was post-bronchodilator.

DR. SCIURBA: Yes.

DR. MARCUS: Okay. So then it's consistent, and then we're fine.

So I think that the design seems to be pretty much appropriate, but I think that in addition to just looking at spirometry, there should be other measures of quality of life, health status, whether

it's a questionnaire, whether it is a six-minute walk, whether it is something else, or just a dyspnea score, I think is important because, you know, if we say all the time it's not all about FEV_1, that there needs to be something else that is showing effectiveness and perhaps radiographic evidence of effectiveness as well.

I'll just take all the questions right down. In terms of a comparison group, I mean I think the comparison group is going to be those who you might have done it and who you didn't. I'm not sure that you have any other comparison group that you really could use. I mean the group of people that are getting true surgery for this disease is so small that I don't think you could find them.

In terms of migration and expectoration, I think we probably see it even higher at the beginning as people are getting their own experience with implanting the device, so that I think we probably expect it to be higher than what was observed premarket.

(d) is sort of, I've already answered, that there needs to be something, and whether it is a six-minute walk or just a questionnaire, but something to indicate that this is benefiting the patient in their

own quality of life.

In terms of other safety endpoints, I think we've already addressed those. I don't think there's anything else I would add except looking long-term at the incidence of true post-obstructive pneumonia as Dr. Cassiere mentioned, secondary to long-term placement of the value.

DR. BIRNBACH: And is three years enough?

DR. MARCUS: I think so. I think three years is probably longer than the survival of most of these patients who are going to be getting this device.

DR. BIRNBACH: Dr. Dominik.

DR. DOMINIK: I had a question. In the packet, where the study was described, it said that this study would be done in subjects with heterogeneous emphysema, whereas, you know, the earlier study had been in subjects with severe heterogeneous emphysema. So would the goal be to change the -- So it would still be those with at least severe emphysema, if it were that I had comment, but since it was different, I wanted to --

DR. BIRNBACH: So -- yes, Dr. Li.

DR. LI: I'm little bit confused how we can talk a little too specifically about the post-

approval study, but it seems like the Sponsor is actually doing a nice job at continually learning about the device and, for instance, better ways to visualize or place the device, and then as we talked over several times, a better selection, a better method to select the patients who would most benefit from that, but as I sit here, I don't really see exactly that those protocols are completely worked out, about exactly how, you know, do we have the best way to place these devices and in what patient population. So with the absence of those two, I'm not exactly sure how to answer these other questions.

And I agree with Dr. Marcus. I know of no example of any medical device whose performance improves when you generally release it.

DR. BIRNBACH: Could anyone on the Panel turn off their BlackBerry if they haven't already or their wireless telephone?

So if I were to summarize what we've heard about question 6, it would be that the study design seems to be appropriate. However, there should be other measures looking at quality of life and perhaps a better look at radiographic evidence, and that three years does seem to be -- yes.

DR. DOMINIK: May I ask that you also add

some kind of clinical functionality measures for patients, for example, are there changes in activities of daily living? Perhaps people who were not able to dress themselves before can now dress themselves or lift light weights or other measures to help the patient evaluate what this might actually mean.

DR. BIRNBACH: Thank you. I think that's a wonderful idea. Yes, Dr. Loeb.

DR. LOEB: Regarding two of the things, item (c), I would just point out that I found the migration/expectoration rate to be very high, and I would hope that it would be lower. So --

DR. BIRNBACH: You're okay as it's stated.

DR. LOEB: I would think that if the rates stayed that high, that would be problematic for long-term use. And then secondly, item (b), not for a direct comparison, but for another group that might be important to look at for comparable safety profile would be other pulmonary stents. So not that they would necessarily match patients but, you know, I guess a postmarket survey would be done versus control group but that the results of that would be evaluated versus other pulmonary studies.

DR. BIRNBACH: Dr. Marcus.

DR. MARCUS: I would think it would be just the opposite. I mean I agree, you know, you're looking at something that's implantable, but from a safety point of view, you're almost looking at opposite endpoints, when you want to keep things open, when you want to keep it closed. So I'm not sure that would be the fairest comparison. And you've got one group of people who are probably all going to have malignancy. So I'm not sure that would be the best comparison.

DR. WISWELL: Just to reiterate one comment here for the proposed postmarket study is just that wording in there, and the wording in here, it's for those with heterogeneous emphysema. I think we need to make sure it's the severe heterogeneous emphysema. That's where it seems to be potentially the most effective, and I think that's where we're going to see potentially that effectiveness or the morbidity in these patients, and I think that has to be in this population.

DR. MARCUS: And I think it all depends on how you're defining severe. If you're using GOLD criteria of FEV_1, then that's the group that this was. So I think we're using the word severe but really meant it all along, from the beginning, that's

the group of patients, the severe and the very severe by FEV_1 criteria.

DR. WISWELL: I've got a different take on things. My understanding of severity was more tied into the software analysis of the imaging studies and defining the population.

DR. BIRNBACH: Dr. Ries.

DR. RIES: Yeah, in terms of this, I think the biggest problem is going to be B, runs the right comparison, and again, going back to experience in the rehab world, you're looking at a modest effect size in a disease which is progressive.

And so as the Sponsors have shown, the real issue is not really the improvement in the treated group. It's the improvement relative to the expected decline because the effect is going to be lost over time, and so I would just wonder, and the problem is, you know, any other kind of non-randomized comparison is going to be problematic.

And I wonder if there is some way of designing possibly a delayed treatment group or, you know, something else which would allow you to get some more observations over time because we're not necessarily making people better. We're helping them be less worse over time.

DR. BIRNBACH: Dr. Willsie.

DR. WILLSIE: That covers what I was going to say.

DR. BIRNBACH: Okay. So, Dr. Lin, if I were to summarize the Panel's viewpoint, it would be that the design for the post-approval study appears to be appropriate, but there should be some additions and clarifications. For starters, there should be some kind of assessment of quality of life, and there should be some kind of clinical functionality included in their assessment. It would be nice to have further radiographic evidence information, and last but not least, we should take care of the wording and make sure that we're looking at the same group, and the Panel believes that it should be severe heterogeneous emphysema, and we ought to do a good job of defining it since the people around the Panel had different take-home messages about how it was defined in the original study.

Is that adequate to answer question 6?

DR. LIN: Yes.

DR. BIRNBACH: We will now proceed with a second open public hearing of this meeting. I will repeat the comments regarding financial disclosure.

Both the Food and Drug Administration, FDA,

and the public believe in a transparent process for information gathering and 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.

Would anyone wish to address the Panel at this time?

(No response.)

DR. BIRNBACH: Being that no one wishes to address it, we will now proceed to the FDA and

Sponsor summations.

We'll start with the FDA. Is there any further comment or clarification from the FDA?

DR. LIN: The FDA, we don't have any further comment.

DR. BIRNBACH: Okay. So being no further comment from the FDA, is there any further comment or clarification from the Sponsor?

DR. SCIURBA: Yes, Mr. Chairman, if you would allow me.

I thank you all really for very thoughtful comments and struggling with a lot of the issues, and that being we found statistical effect technically met our primaries but feel that there is, in fact, too modest of an effect here.

What I'd like to do in two minutes, if it's at all possible, is to bring you from where I was a year ago when I first saw these data to where I honestly am right now in believing that this technology is ready to be delivered, and I'll give you my justification.

First of all, while there is a modest effect, we have identified the subgroups. I urge you to consider a postmarket study that takes advantage of what we've learned. We've learned a lot in this

study. If we were to do it again, we would be able to get much better results. I'm absolutely sure. I believe that we can do this and implement it clinically.

I would start out by saying this was an $80 million study. There will be no resources for this company to complete it, and I fear that this technology will die.

Our heterogeneity group was not a tiny subgroup. This was 50 percent of our patients. This 50 percent had a 12 percent improvement in FEV_1 and a 14 percent improvement in 6-minute walk. While it did not endure 12 months statistically, we weren't powered for a 12-month study with the decline in the loss of numbers.

In addition, with regards to fissure integrity, we've learned so much. Something that hasn't come out in here is when we had a tie in heterogeneity between the left and the right, we defaulted to the right upper lobe, the lobe that only 39 percent of the time had a complete fissure, yet we had 67 percent of the time the left side to go to, that would have unquestionably gotten a better effect.

Lobar exclusion, this is not theoretical.

You ask if we bring this out to the community, will this be worse? Will the results be worse? Well, I would say they would be technically better because we've learned so much about training. We've learned so much about follow-up CT scan to assure lobar exclusion, which occurred in less than 50 percent of the cases.

And then the fact that I have patients in front of me and truly believe that there's a technology that would offer a real choice and that I will not be able to help these desperate people who I know have the potential to respond concerns me.

And, finally, the fact that this is reversible, the fact that we can take these valves out in those that we can find in rather short order do not respond, with very little adverse events, is reassuring to me and I would hope to be reassuring to you.

So I would ask you to consider if it's possible to approve this with your knowledgeable recommendations for postmarketing studies to take care of your concerns because I'm very concerned if we don't come up with this solution, we're going to lose this technology.

So I thank you very much for taking my

concerns.

DR. CRINER: Mr. Chairman, Gerry Criner. So I'd also like to thank the FDA Panel, and I'd also like to thank the FDA for your thoughtful comments and pretty much the commitment of everyone to the care of patients with severe disease. And I think today that you got some glimmer of the insight that this technology may have that's promising, not only to treat patients with this form of less invasive technique, but also trying to select better candidates and also gives us some mechanistic clues that perhaps we don't know everything. In this technology, the benefit isn't just related to volume reduction but may have other changes with improving ventilation to better functioning portion of the lung that challenges our current concepts of improvement with this type of therapy.

I think, though, that with careful consideration and due deliberation between the FDA and Sponsor, that some of the issues that would guarantee that the appropriate patients are selected for this therapy, that would give a greater gain to benefit and also minimize the side effect and ensure the monitoring of safety, may be able to be done in a labeling and post-approval study period. For

example, under labeling, it could be restricted to the patient population who are most likely to be benefited, those with severe heterogeneous emphysema, not only defined by lung function, but define what we learn by CAT scan, the most lobar destruction, and make sure that we basically open up the CAT scan imaging to work out that it's just not related to separate centers, but a functional core could be established that would analyze those scans for the community and then transition that technology to the local site as time moves on.

I think the delineation of complete fissure, high heterogeneity, complete lobar exclusion by CT analysis could all be things that could be done in the labeling and training period of time.

I think that also from a safety standpoint, making sure that the valves are appropriately placed, removed appropriately to prevent the issues with valve migration and hemoptysis also could be done in part of the labeling and training period.

I think one thing I've learned working with the Sponsor, I'm not Mother Teresa and most of these investigators aren't, we're pretty rough with them, but they've been very malleable and geared towards treating severe patients, having been very pliant in

listening to the investigators and changed the protocol to maximize the therapy and learn from it.

I think from the post-approval study period, that we could track several things that have been raised. COPD exacerbations, hemoptysis, expectoration of valves, post-valve implantation pneumonia, quality of life, functional status and performance, radiographic confirmation of sustained improvement and no complication could all be done in post-approval studies.

So I think a lot of the issues that have been raised, targeting the appropriate patient group, making sure what was most effective, making sure that whatever was done in this study that seems highly artificial by select centers could be dealt with, with the training and labeling period and post-approval study to make sure the right patients are treated and the right physicians do it with the right tools.

Thanks very much.

DR. BIRNBACH: Thank you. Before we proceed to the vote, I would like to ask Ms. Petersen, our Consumer Representative, and Mr. Osborn, our Industry Representative, if they have any additional comments? Ms. Petersen.

MS. PETERSEN: Thank you. I'd like to reiterate the Sponsor's appreciate for everyone's investment in reviewing the data and discussing the issues and really trying to find a way to help patients to look beyond questions of statistics and study design and to look for a real answer.

I think it certainly is a concern of patients, particularly those who have very few options, that we try to go forward with something and find a way to make that work.

Having said that, I have to be concerned about approving something that doesn't have some conditions attached to it with regard to how we identify the right patients, how we demonstrate that there really is an effect in patients, not just in a laboratory value but in their function day-to-day in their homes, and I hope you'll take it all into consideration when you take a vote.

Thank you.

DR. BIRNBACH: Mr. Osborn.

MR. OSBORN: Thank you, Mr. Chairman. I don't think I could have said it any better than Ms. Petersen did. There's promise here, but there are substantive issues about the right patient and also following up on those patients. Perhaps one

thing she didn't mention was the need in a protocol of use to ensure that the valves have been effectively placed so that you get a therapeutic effective. Any sort of protocol that would come from this I think needs to include that because if you have a leak as was indicated in the data for half the patients, then you're not going to have the therapeutic effect that you would expect, and that's exactly what the data showed. That in and of itself, if it had been corrected, might have given us a very different result here today. Thank you.

DR. BIRNBACH: Thank you. We're now ready to vote on the Panel's recommendation to the FDA for this PMA. Mr. Patel will now read the Panel recommendation options for premarket approval applications. Panel, please refer to the voting procedure flowchart in your folder. Mr. Patel.

MR. PATEL: The Medical Device Amendments to the Federal Food, Drug and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990, allows the Food and Drug Administration to obtain a recommendation from an expert advisory panel on designated medical device premarket approval applications that are filed with the Agency. The PMA must stand on its own merits, and your

recommendations must be supported by safety and effectiveness data in the application or by applicable publicly available information.

The definitions of safety effectiveness and valid scientific evidence are as follows:

Safety as defined in 21 C.F.R. Section 860.7(d)(1) - There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks.

Effectiveness as defined in 21 C.F.R. 860.7(e)(1) - There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

Valid Scientific Evidence as defined in 21 C.F.R. 860.7(c)(2) is evidence from well-controlled investigations, partially controlled studies, studies

and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness.

Your recommendation options for the vote are as follows:

1. APPROVAL - If there are no conditions attached.

2. APPROVABLE with conditions - The Panel may recommend that the PMA be found approvable subject to specified conditions, such as physician or patient education, labeling changes, or a further analysis of existing data. Prior to voting, all of the conditions should be discussed by the Panel.

3. NOT APPROVABLE - The Panel may recommend that a PMA is not approvable if the data do not provide a reasonable assurance that the device is

safe or the data do not provide a reasonable assurance that the device is effective, under the conditions of use prescribed, recommended, or suggested in proposed labeling.

Following the voting, the Chair will each Panel member to present a brief statement outlining the reasons for his or her vote.

Dr. Birnbach.

DR. BIRNBACH: Are there any questions from the Panel about these voting options before I ask for a main motion for this PMA?

(No response.)

DR. BIRNBACH: Seeing or hearing none, is there a motion for either approval, approvable with conditions, or not approvable from the Panel?

DR. MARCUS: Yes.

DR. BIRNBACH: Dr. Marcus.

DR. MARCUS: I vote that we approve with conditions.

DR. BIRNBACH: Is there a second for this motion?

DR. RIES: Second.

DR. BIRNBACH: Is there any discussion on this motion?

DR. RIES: I have a question. How

realistic, assuming that a number of conditions were put on this in terms of, you know, operators, centers, patients, et cetera, you know, is that a realistic option in terms of how this device will proceed?

DR. VASSILIADES: I'd like to comment. I think the approving and putting a very restricted labeling on a device is not a method to justify continuing doing research on these sorts of devices. Having seen a lot of devices and seeing how that goes, to answer your question, I think it's very ineffective. And I think that if a trial had been done with this particular subgroup of patients that has been identified to benefit from this from the get-go, and we had data, then we could approve it.

But to say we think we know some things, I mean quite honestly a lot of the data is really unsupported and, yes, we have learned a great deal about this disease process and the therapy, but I think it's insufficient and not clinically relevant or proven by this study that you could approve this device and then put a highly restricted label on it simply because you want to see the technology continue.

I think that you're subjecting patients to

undue risks, and I think the ability to be assured that the device is going to be used appropriately under very restrictive conditions is very limited.

So that's my opinion. I don't --

DR. BIRNBACH: Is there any discussion on the motion?

DR. RIES: I mean I think the issue of undue risk needs to be balanced with the perceived benefits and the lack of options. And I think that has to, you know, we have to realize where we are with this disease. As much as we know this disease, there's so much we don't know, and there's so much we can't offer.

DR. BIRNBACH: Dr. Cassiere.

DR. CASSIERE: I have to agree that this is a technology, that once it's approved, the cat's out of the bag, and if you take a look at the drug-eluted stents, if you take a look at how many of those are placed under indication, you'd be shocked to see that the indications are maybe 65 percent of patients who get a drug-eluted stent non-approved. To think that that would happen with another device is, you know, we're not really being realistic.

I tend to agree that approving a product just to continue research is not justified.