there a further question on that?

DR. STOLLER: The baseline frequency, the dropout rate for exacerbations.

DR. SHAH: Right. I mean, the other thing on retrospect is that I think we may have affected the overall withdrawal rate for exacerbation differences between these and other studies that have been done. We actually had criteria for lack of efficacy, which was up to physician discretion. We didn't really have good control on what the physicians may have considered was appropriate for lack of efficacy. However, it was, unfortunately, a remnant from our asthma studies and it was there, and we did have physicians withdraw patients for those reasons and there was an imbalance across the treatment groups, with more people in the placebo group being withdrawn for that compared to certainly the high dose FP and Advair groups.

We actually prespecified as part of this program a term that we called COPD-related conditions. So, withdrawals due to COPD-related conditions, which included patients who would have withdrawn for exacerbations; people who withdrew for lack of efficacy; people who withdrew for these other types of reasons. When we actually looked at

the integrated data -- you know, in individual studies we just didn't have enough numbers of patients to look at exacerbations with any kind of statistical comparisons. And, these are all, obviously, post hoc; they are exploratory types of analyses. But we clearly showed when you look at the COPD-related conditions withdrawals, which includes exacerbations and lack of efficacy and adverse events that were related to respiratory conditions, clear evidence of treatment effect with almost all groups, except for the FP 250, achieving p values less than 0.05.

So, there were clear suggestions of effects on the respiratory-related withdrawals in this program but again, as I indicated, we didn't optimize these studies to look at that. Hence, I think the results reflect that.

DR. STOLLER: May I just ask a follow-up just to clarify? I understand that you didn't query these individuals about the baseline frequency of exacerbations. Was there any retrospective attempt to ask individuals as the study was progressing if they could recall, recognizing the limitations of recall bias in those measures?

DR. SHAH: Actually no, because, to be frank, we obviously expected to see some effects on all endpoints. So, we didn't have any reason to believe that there was a need to do that. Clearly, on retrospect, I think we would do it differently.

DR. STOLLER: Then just in response to your comment, I understood your comment that the prevalence of dropouts for exacerbations during the run-in period was 15 percent to 20 percent.

DR. SHAH: Fifteen to 30 across the three trials.

DR. STOLLER: Was that mal-distributed among the placebo versus the individual drug groups?

DR. SHAH: Well, remember, these were at screening so they were not on any treatment. These were basically people coming into the screening period.

DR. STOLLER: But I presume randomization was also obtained prior to that --

DR. SHAH: No, the randomization would have been after screening.

DR. STOLLER: Oh, after it? Fine.

DR. DYKEWICZ: Dr. Fink?

DR. FINK: Yes, this is probably for Dr.

Shah. Since you were dealing with a group of patients with severely impaired pulmonary function at baseline, what would the average FEV1 percent change be if expressed as a change in percent predicted for the patient rather than a change from baseline?

DR. SHAH: In terms of a treatment response?

DR. FINK: Yes, the treatment response.

DR. SHAH: In terms of our program, the FP response, as I said, we averaged in two of those studies about 100-plus milliliter difference as change in FEV1 over baseline. The percent predicted was about 40 percent at baseline. So, that degree of change I think would correspond to about a five percent predicted improvement in FEV1, and with Advair it represents about eight to ten percent predicted improvement over baseline.

DR. FINK: And if you, in your analysis, stratified the change in FEV1 for those patients whose baseline was above 50 percent was the data driven predominantly by those patients who had very low values at baseline, where a two to three percent change in FEV1 would be a ten percent change?

DR. SHAH: No. Actually, we did look at the results by different severity in terms of FEV1 percent predicted at baseline, and what we did see was that across that spectrum of severity, like from 30 to 50 percent because -- recall, the cut-off we had was 65 percent or less in the study -- what we see across all those subtypes of patients is that the response is fairly constant in each of those groups as a magnitude. Obviously, as a percent that would be different because if the magnitude is similar you would expect percent to be greater.

DR. DYKEWICZ: Dr. Atkinson?

DR. ATKINSON: When you were noting the adverse events -- you may have said this, but there were four deaths in the placebo group. I know it wasn't an outcome measure but was there any effort to ascertain the cause of death? Was it respiratory in any of the cases?

DR. SHAH: No, they were all related to other causes. Three of them were, I believe, malignancy and one, I believe, was a cardiac event.

DR. DYKEWICZ: Dr. Apter?

DR. APTER: Dr. Shah, I have three questions. One is just to clarify. You said that

converting the 100 ml change in FEV1 corresponds to about a five percent change in predicted?

DR. SHAH: Yes, in that range. Again, I am estimating this and my math skills have clearly gone down-hill since the advent of the computer but I think that is roughly right. We can get those data for you if that would be useful.

DR. APTER: It would. Secondly, you gave the mean age of the patients as about 64. Do you have any information about the range of standard deviation frequencies? In other words, with respect to Dr. Bone's comment, how many were actually very elderly?

DR. SHAH: Very elderly? Well, as I said, the mean age was about 65 and so about half the patients were over that age compared to, you know, younger. I would say that about 25, 30 percent were about 75, in that order. Again, I don't have those data at the top of my head but we did have a fairly large proportion of patients who were over 65 in this program, and we did look at both the efficacy and safety in that population and the results were comparable to the overall results.

DR. APTER: Actually, a question for Dr. Wise, are asthma patients who are minority affected

more adversely? Do we have information on that in COPD? Because this population was virtually all white. A second question is, of course, that more and more women are smoking and this population has a minority of women. Do you have anything to say about the choice of the population to study?

DR. WISE: The issue of COPD in African-Americans is one that is of interest. There seems to be a protective effect, if anything, at least in terms of the diagnosis of COPD among African-Americans. This has sometimes been called the COPD paradox because African-Americans who smoke have higher rates of lung cancer than Caucasians but lower rates of COPD. Emphysema deaths, at least from death certificate data -- only eight percent of those deaths are African-American. So, there seems to be a paucity of COPD in African-Americans, and this has been borne out in some of the large NIH-sponsored clinical trials, for example, Lung Health Study I, and I believe it was around six percent African-Americans. In Baltimore, where we recruited in the inner city with a majority of African-Americans, screening for early COPD, we had approximately 12 percent African-Americans; similar

numbers in Detroit. So, there does seem to be a protective effect, if anything, in contrast to asthma, as you pointed out, where there is an increased risk.

Gender -- I think Dr. Donohue implied that each year, each study that comes out with COPD shows increasing prevalence of COPD among women, and there is an increasing, although not incontrovertible, body of evidence suggesting that women may be more susceptible to the adverse events of cigarette smoke in terms of developing obstructive lung disease. The prevalence of COPD in the general population, men versus women, is probably around 60-40 or 65-35, in that order.

DR. DYKEWICZ: Dr. Joad?

DR. JOAD: Yes, my question is for Dr. Shah. I want you to address the statistically significant differences that you got in your questionnaires, the symptom and quality of life questionnaires, versus the lack of clinically significant differences for all of them except the Advair 550. Do you have any arguments with those questionnaires that you chose, or any arguments with what was said as a clinically difference that you were looking for?

DR. SHAH: Yes, I think if we look at the two questionnaires -- well, we had three, we had the one for dyspnea, the TDI, and I will say that we have more experience in general in COPD with that instrument because there are numerous clinical trials that have looked at that instrument in terms of evaluating pharmacological agents. As we showed you, the results on that instrument were actually some of the most robust effects we have seen up to date with any currently available drug that has evaluated that instrument with treatment with both FP as well as Advair.

As you know, there are two quality of life health questionnaires that are currently used in assessing COPD. There is the SGRQ, the St. George's Respiratory Questionnaire which was reviewed by Dr. Johnson. That was a study that was done in Europe. At the time we designed this program it had not been validated in the U.S., hence, was not available for us to use in the U.S. at that time. Clearly, now we do use that questionnaire in assessing treatment response.

We had CRDQ with which we did have some experience. As you saw, we had used that questionnaire in a previous clinical program with

Serevent MDI inhalation aerosol, and in that study we saw small trends for effects with the MDI, which is currently approved, but we did not see any evidence of a statistically significant difference. The numbers of patients were very similar in those studies to what we have in our own studies with FP. Whereas, in the FP studies we actually showed evidence of statistical significance or p values less than 0.05 on those measures.

What we didn't achieve is the threshold of what the instrument has defined to be clinically significant. But we have to remember that those thresholds were defined as a change from baseline, not as a between treatment group difference. We have no knowledge currently of what degree of change between two treatment groups would constitute a clinically significant difference. I think, you know, the developers of those instruments would confirm that view. However, we had no other basis to make some determinations of what would be a clinically significant difference between these treatment groups. So, we used the same value that has been defined as a change from baseline as a value or threshold for showing differences between treatment groups.

I think we have to realize that those thresholds for between treatment groups may be unattainable. You know, we don't have a lot of experience and certainly we have not seen any evidence up to now, at least in the published literature and in our own experience, where those degrees of differences have been achieved between treatment comparisons in studies in COPD. So, we did see statistical differences favoring FP on that instrument.

Again, with Advair the mean change from baseline on the CRDQ at both doses achieved a value over 10, which the developer of the instrument would regard to be a clinically important change for these patients. That is how clinical significance was defined in the development of this instrument.

We have to be careful because the clinically significant difference values for these instruments were not defined to be assessed in comparing treatment responses between two treatments. They were defined as individual patient and group responses, how did they change from baseline and is that change from baseline clinically meaningful for those patients.

So, you know, without having much other evidence, we used the same threshold but I think we have to be careful because that may be a threshold that is unattainable in COPD based on the current evidence that we have.

DR. DYKEWICZ: A last question from Ms. Schell.

MS. SCHELL: I am not quite sure who to direct this question to but I was wondering about airway remodeling and the effects of the inhaled corticosteroids on that. There has been some research that reverses airway remodeling and I just wondered if anyone has looked at that, or if you have any studies on COPD effects.

DR. SHAH: Yes, I think I would have to defer to maybe Dr. Johnson to speak to that and maybe Dr. Pauwels could add some comments as well.

DR. JOHNSON: That is a very good question, and it reflects I think the issue that very few studies have been carried out in COPD comparing to asthma, and we are only now beginning to understand what we even mean by the term remodeling in asthma. When you compare that to remodeling in COPD it is a very much more difficult situation.

These studies take a long time to carry out, and we are, again, missing what we could take as acceptable surrogate endpoints for remodeling. Clearly, it is difficult to do biopsy studies over 10, 15 years in any patient population.

I think what we are seeing though is, as I have presented, particularly in terms of the evidence at the biopsy level, is at least a potential for inhaled steroids to influence some of the inflammatory cells and some of the processes that we know could contribute to a remodeling process. So, the potential is there; the proof is not as yet. And, it represents, I think, a key area for further study of any intervention of this disease. You know, has it the capacity to slow down the remodeling process or even, probably more importantly, to try and reverse the remodeling process? I think you raise a very important question, I just wish we had some better data. That also applies to asthma.

DR. DYKEWICZ: One last question by Dr. Malozowski.

DR. MALOZOWSKI: I have a series of questions. Can I ask them or just one?

DR. DYKEWICZ: Let's try to play it by

ear.

DR. MALOZOWSKI: I will try to focus on your slide A106, please. This is the slide that shows the mean percent change in lumbar spine bone mineral density and I would like to make some comments. I cannot really comment about COPD but I can comment on issues related to safety and how to look at safety information.

In this particular slide, if you don't pay attention to the first three columns at week 24, and also if you don't pay attention to the column that is in yellow that represents a dose that doesn't have anything to do with this particular study, what you see is that patients on placebo tended to have positive bone mineral density, while patients that received this medication -- at least the estimates, the mean and the standard deviation are going negative. Okay?

When you look at safety information you cannot look at data in this manner because this really hides what is going on in the patient population. If this were a drug that was developed to treat osteoporosis or a condition such as this, this depiction of the data would be adequate, but here we are looking at signals for adverse events

and what we need to look at is outliers. And, we don't have this because the only information we have is depicted as mean and standard deviation. But the directions in which these columns are going suggest that probably there are some patients that are losing bone mineral density to a larger extent in those receiving fluticasone or the combination therapy versus those patients on placebo.

DR. SHAH: Can I comment on that?

DR. MALOZOWSKI: Please.

DR. SHAH: First I will walk you through the response we see. In any clinical study you have variability around the mean. That is the nature of clinical research. So, you look at the response with the high dose FP, which is in orange. Let's just follow what happens to these patients over the course of the two years of treatment.

You see essentially at six months not much of a difference. Now you go to one year, a slight suggestion of a decrease but, again, given the state of deviation, not much of an effect. Now look at what happens at a year and a half. It has now flipped the other way. You have now what clearly suggests a treatment benefit. If I believe what you were saying, if a low value means a

significant negative effect, obviously a plus value would mean there is a positive effect. Now it flips back down at the two-year time point.

I will also say that prospectively in these studies we defined a value of a five percent change from baseline to be clinically significant over the two years, and we have two patients in the placebo group and two to three patients in the FP 500 group who achieved that degree of change over the two years of treatment.

So, I appreciate the comment that we are looking for signals here, but I think we have to be very careful that we look at the data relatively objectively and make conclusions based on data and not perception.

DR. MALOZOWSKI: I am saying that you cannot look at safety data as mean and standard deviation. This is my point. And, this particular slide does not show what really happened with patients. You don't show the outliers. You just take that unifying as five percent.

Also, you define, for example, hyperglycemia as 175. The American Diabetes Association defines diabetes as equal to or above 126. Therefore, you know, this particular

definition -- I don't know what weight it has, but the point I am trying to make is that it is very difficult to capture outliers that somehow depict what really happens in a clinical study when you try to compress everything to the mean and the standard deviation.

DR. SHAH: Sure and, as I say, we did look for outliers as part of this program and we didn't see a difference. We had about the same proportion of patients who achieved a prespecified change of five percent in bone marrow density in both groups.

DR. MALOZOWSKI: Okay --

DR. SHAH: We actually picked 175 because that is what we have traditionally been doing which previously, by the FDA, has been acceptable. We reanalyzed the data and, actually, we can show you the data for the glucose by using a 120 value and, again, I think the data will speak for themselves.

[Slide]

At these doses of FP, here is the result on mean glucose in our program which we just reviewed. This is for the integrated data for the treatment groups. Here are the screening values for the mean results. Here are the values at week 12. This is using a cut-off now of 120 in change

in glucose. What you see is that at screening we had a reasonable proportion of patients, slightly higher in this group on Advair who achieved greater than 120 or had a 120 change in glucose compared to the other groups, but fairly similar. At week 12 you see that clearly there isn't a suggestion of a signal here in terms of the effects on glucose as the proportion of patients who had a value over 120 change. Here is week 24. Again, there certainly doesn't appear to be any significant signal suggestive of a treatment effect on these measures.

So, clearly, we have looked at these data. We are more than willing to look at the data any way that, you know, you would feel would be best to make an assessment but the results are very reassuring. We don't see concerns on glucose with these doses of FP, which is what we have traditionally shown in our experience in asthma.

DR. DYKEWICZ: We will now take a break. In view of the time, let's resume at 10:45.

[Brief recess]

DR. DYKEWICZ: Please take your seats. We will next begin the segment of our presentations by the FDA. The first presentation will be by Dr. Charles Lee.

FDA Presentations

Flovent Diskus for COPD

DR. LEE: I am Charles Lee, medical reviewer for the Division of Allergy and Pulmonary Drug Products for the FDA.

[Slide]

This morning we will be discussing the new drug application for Flovent Diskus, NDA 20-833 for a COPD indication.

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The proposed labeling states that Flovent Diskus is indicated for the long-term, twice daily maintenance treatment of COPD, including emphysema, and chronic bronchitis.

[Slide]

This is the dosage and administration section of the proposed COPD label. The starting dosage for adults is one inhalation, 250 mcg, twice daily. For patients who do not respond adequately to the starting dose, increasing the dose to 500 mcg twice daily may provide additional control.

[Slide]

In this presentation I will cover a review of efficacy and a review of safety for this application. The sponsor submitted three pivotal

studies in support of efficacy. Safety is supported by data from these three pivotal studies and from additional supportive studies.

[Slide]

In our view, there were key efficacy and safety issues in this application. The treatment effects noted for the primary efficacy endpoint were small and did not appear to be dose related across studies. There were small differences from placebo for secondary endpoints in patient-reported outcomes. The majority of COPD patients in the pivotal studies had reversibility with bronchodilator.

In addition, there were concerns raised in the pivotal studies and in other studies submitted in support of safety. These included respiratory infections, upper and lower, and systemic effects such as adrenal effects and effects on bone.

[Slide]

We would like to have you consider these data in light of the following questions: How clinically relevant is the change observed in the primary efficacy endpoint where there is a small amount of support from secondary endpoints and patient-reported outcomes?

How typical is the COPD population studied in these trials? And, how would this impact the ability to generalize the results from these studies to all COPD patients, specifically with regards to reversibility with bronchodilator, in the presence of chronic bronchitis and emphysema?

How sufficient is the safety database to support the use of the product for long-term maintenance treatment of COPD? Finally, is the risk-benefit profile suitable for approval of this product for this indication?

[Slide]

As you have heard, there were three pivotal studies. Fluticasone 500 twice a day was studied in this study and in this study. Fluticasone 250 twice a day was studied in this study and in this study. Increasing the dose in patients who do not respond to fluticasone 250, as proposed in the labeling, was not studied.

These studies, as you have heard, had similar design; were randomized, double-blind, placebo-controlled, parallel group studies of 24 weeks in duration in patients with an established history of COPD. All patients had chronic bronchitis and patients could have self- or

physician-reported emphysema.

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The primary efficacy variable for fluticasone was the pre-dose FEV1. The primary efficacy endpoint was change from baseline in FEV1 at study endpoint. Secondary efficacy variables included measures of symptoms of chronic bronchitis; measures of symptoms of dyspnea; peak flows; measures of albuterol use; and COPD exacerbations. Patient-reported outcomes or, so-called, health related quality of life, was measured by the Chronic Respiratory Disease Questionnaire, an instrument developed by Guyatt.

[Slide]

Safety variable included adverse events, serious adverse events, withdrawals, vital signs, physical exam and oropharyngeal exam. Physical exams and oropharyngeal exams were performed and any abnormalities were recorded as adverse events. ECGs, hematology and chemistry studies were also performed. Serum cortisols were measured in one study and standard dose cosyntropin stimulation testing with 250 mcg of cosyntropin was performed per package insert in the other two pivotal studies. Bone mineral density or ophthalmologic

examinations were not performed. These studies were performed over a six-month period and were not likely to be have been sufficiently long to detect any bone or ocular effects.

[Slide]

We will look at demographics and baseline characteristics of the population of the pivotal studies next. Demographics and baseline characteristics were similar in the three pivotal studies. Approximately 65 percent of patients were of male gender, with a mean age of approximately 63 years. Ninety-four percent of patients were of Caucasian race. Non-Caucasian races were not well represented in the pivotal studies, with about five percent of patients being Black race and about two percent of "other" race. Approximately 25-30 percent of patients were using inhaled corticosteroids at the time of screening, and about 47 percent of patients were smokers at the time of screening.

[Slide]

Randomization was stratified based on patient response to bronchodilator. Reversible patients were those who had a 12 or more percent increase in FEV1 with bronchodilator or an absolute

change in FEV1 of 200 ml or greater with bronchodilator. There was a high percentage of patients, a majority, who were reversible, ranging from between 54 percent and 59 percent. The ATS standards for the diagnosis and treatment of patients with COPD mention that up to 30 percent may have an increase of 15 percent or more in FEV1 with use of beta-agonists.

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Here we are looking at the mean response to bronchodilator or the degree of reversibility of the population -- the reversible group, the non-reversible group and overall. They were similar among the studies. The amount of reversibility in the reversible group ranged from 30 percent to 32 percent increase in FEV1 with bronchodilator. The non-reversible group had a 9 percent increase in FEV1 with bronchodilator. Overall the degree of reversibility is shown here, with between a 20 and 23 percent increase in FEV1 with bronchodilator.

[Slide]

Next we will look at measures of efficacy in the pivotal studies.

[Slide]

Here we are looking at the primary efficacy endpoint, mean change from baseline in the pre-dose FEV1. Values are in liters. Differences from placebo are displayed. Baseline values are displayed in parentheses, and statistically significant values have an asterisk.

For fluticasone 250 an increase in FEV1 was noted of 27 ml in this study and 108 ml in this study. For fluticasone 500 there was a 50 percent increase in FEV1 at study endpoint and 113 ml increase in this study. Statistical significance was replicated for fluticasone 500 only. Statistical significance was not replicated for fluticasone 250. Across studies there was not strong evidence of a dose-related effect.

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In general relatively small differences from the placebo group were noted for secondary endpoints in patient-reported outcomes. We will cover COPD exacerbations, total daily albuterol use and CRDQ, the Chronic Respiratory Disease Questionnaire, the patient-reported outcome instrument. Total daily albuterol use and CRDQ are representative of the small changes noted for the other secondary endpoints. COPD exacerbations

showed no effect.

[Slide]

Here we are looking at percentage of patients with one or more exacerbations of COPD in each of the three studies. There were fewer COPD exacerbations in fluticasone-treated patients in this study, with an appearance of a dose-related effect. However, in the other two studies the numbers went the other way. In the fluticasone group a higher percentage of patients had COPD exacerbations. These are actually the studies that had the largest change in the primary efficacy endpoint. Overall, there seems to be no evidence of a treatment effect of fluticasone on COPD exacerbations. There were similar results in the percentage of patients who had moderate to severe COPD exacerbations.

[Slide]

Here we are looking at the change from baseline in daily albuterol use. Again, mean change from baseline and the difference from plasma is shown. Decreases in daily albuterol use range from a decrease of 0.3 puffs per day to 0.9 puffs per day over a baseline of about five puffs per day.

[Slide]

Here we are looking at the Chronic Respiratory Disease Questionnaire, the health reported outcomes instrument. We are looking at change from baseline in the overall score. Again, the difference from placebo is displayed. The minimum clinically important change is 10. The baseline ranges from 84 to 89. The amount of change attributed to active drug ranged from a negative 0.2 in one study to a high of 8.1 in this study. There was very little difference from placebo in the study that had the largest effect size in the primary efficacy endpoint. In summary, improvements were noted for active treatment but the differences between the active treatment group and the placebo group were small, and less than the minimal clinically important change.

[Slide]

A subgroup analysis of efficacy was provided for the non-reversible group. As we mentioned, the non-reversible group were those patients with an increase in FEV1 with bronchodilator of less than 12 percent or those patients who had less than 0.2 liter increase in absolute volume with bronchodilator.

[Slide]

Here we are looking at subgroup analysis for the non-reversible group of the primary efficacy endpoint, mean change from baseline in pre-dose FEV1. Again, the difference from placebo is displayed. Baseline measurements are in parentheses. Improvement or increase in FEV1 at baseline ranged from 2 ml to 101 ml in the non-reversible group. Overall there was a smaller amount of change noted for the non-reversible group than was seen in the overall group.

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In summary of efficacy, we see an effect on the primary efficacy endpoint, change from baseline in FEV1, that is statistically significant, and replicated for fluticasone 500 but is not replicated for fluticasone 250. A small effect was noted in the non-reversible group. Secondary endpoints and patient-reported outcomes showed small differences from the placebo group.

[Slide]

Next we will be looking at the safety data from the pivotal studies.

[Slide]

In general, the types of adverse events

reported in the pivotal studies were similar to those noted in current labeling for Flovent products. These will be integrated data and display adverse events that occurred more commonly in fluticasone-treated patients than in placebo-treated patients.

There was a higher percentage of patients treated with fluticasone who had adverse events and this appeared to be dose related. There was also a higher percentage of patients treated with fluticasone who had upper respiratory infections and viral respiratory infections.

[Slide]

The rate of candidiasis was high, 13 percent in the fluticasone 500 group, 7.3 percent in the fluticasone 250 group. Obviously, it would appear to be a dose-related effect. There was a higher percentage of fluticasone-treated patients who reported dysphonia and a slightly higher percentage of fluticasone-treated patients who had pneumonia.

[Slide]

Adrenal effects were measured in the pivotal clinical studies. Serum cortisols were measured at the end of week one in this study, and

cosyntropin stimulation testing, per package insert, was performed in the other two pivotal studies.

[Slide]

Here we are looking at serum cortisol data after treatment compared with the placebo group. AUC 12 represents an integrated measure of serum cortisol or serum sampling over a 12-hour period. There appears to be a dose-related suppression of serum cortisol. For the fluticasone 250 group values were 10 percent less than those of the placebo group. For the fluticasone 500 group values were 21 percent less than those of the placebo group. A similar pattern was seen with lowest cortisol concentration, or the Cmin. The value in the fluticasone 250 group was 5.2 percent lower than the placebo group, and in the 500 group 30.7 percent lower than the placebo group. In summary, we see a treatment effect that appears to be dose related.

[Slide]

Cosyntropin stimulation testing was performed in the other two pivotal studies. There was no evidence of adrenal insufficiency that was observed. However, this test may not be

sufficiently sensitive to conclude that there were no adrenal effects at all.

[Slide]

Next I will present pertinent safety data, submitted in support of this application, from other studies.

[Slide]

This is a Phase I pharmacokinetics and pharmacodynamic study. It was a single center, open-label, randomized, four-way crossover design in which 1000 mcg of fluticasone was administered with different dosage strengths of the Diskus device. Dose proportionality of the different dosage strength devices was the objective of this study. There was a five-day washout period between the study periods.

[Slide]

Here we are looking at mean 24-hour urinary cortisol excretion. Values are the pre-dose measurements, post-dose measurements and percent change from the pre-dose measurement. Each of these groups received 1000 mcg of fluticasone as a single dose, with each of the different dosage strength devices noted there. The post-dose 24-hour urinary cortisol excretion ranged from 35

percent less than the pre-dose to 59 percent of the pre-dose measurement after these single doses of 1000 mcg of fluticasone.

It should be noted that this study was performed in normal volunteers, and inhaled fluticasone appears to have a lower degree of bioavailability in patients with COPD. Despite this, the results do show clear evidence of adrenal effects. We should note that the higher of the two proposed daily doses for fluticasone, 500 mcg twice a day, is the same total daily dose that is administered in this study.

[Slide]

This is a multicenter, double-blind, randomized, placebo-controlled study of Flovent metered dose inhaler, 500 mcg twice a day for three years in patients with COPD, also known as the ISOLDE study. It was published in the British Medical Journal in 2000.

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Here we are looking at notable adverse events that occurred during the inhaled treatment phase of the study. Nearly all of the patients reported adverse events in both treatment groups. There was a higher percentage of

fluticasone-treated patients who reported respiratory adverse events as seen in the pivotal studies. These included lower respiratory infection, upper respiratory infection, viral respiratory infection, as well as pneumonia. There was also a higher rate of serious adverse events due to pneumonia. The numbers aren't displayed here but they are five percent versus two percent, and that data was not included in the paper.

[Slide]

Adverse events that could be contributed to systemic activity of inhaled fluticasone are displayed in this slide. There was a higher percentage of fluticasone-treated patients who had decreased cortisols compared with placebo. These are patients who had laboratory abnormalities that were considered to be clinically significant and, therefore, were reported as adverse events.

The adrenal effects were reported, in a somewhat different fashion than the paper, as mean serum cortisol levels listed and presented in the table. There was a higher percentage of fluticasone-treated patients who were reported as having diabetes. There was also one fluticasone-treated patient who was reported as

having Cushing's syndrome, and one fluticasone-treated patient who was reported as having adrenal hypofunction. Although it is unclear whether this is an adverse event due to adrenal hypofunction or a laboratory abnormality, the paper does state that no decreases in cortisol were associated with symptoms of hypoadrenalism. It should also be noted that the MDI formulation which was used in this study is more bioavailable than the Diskus formulation, but one notes similar concerning patterns.

[Slide]

This was a multicenter, randomized, double-blind, placebo-controlled, parallel group study of 1000 mcg twice a day of fluticasone by the metered-dose inhaler for a four-week period in patients who had an acute COPD exacerbation. In this group of 126 fluticasone-treated patients there was one fluticasone-treated patient who was reported as having a serious adverse event due to a decreased cortisol level, although I have no other details about that patient. The study used the MDI formulation and the dose in the study is twice the proposed dose in this application.

[Slide]

Data on bone mineral density was submitted in support of this application. Data was from two two-year studies of asthma patients. Patients ranged from 18-50 years, and females were premenopausal. The study population may be at lower risk for osteoporosis than the population proposed in this NDA.

[Slide]

In the first study a slight numerical decrease in bone mineral density for the fluticasone 440 mcg dose was noted at the lumbar spine, but an increase in bone mineral density for the 88 mcg dose and placebo make it difficult to interpret these data. The sponsor reported no changes for the proximal femur or total body. In the next study, decreased bone mineral density was noted at the femoral neck, although this data was retrospectively QA'd.

As noted previously, these studies were performed in younger asthma patients, a study population who may be at lower risk for osteoporosis than those proposed in this application. These studies raise some concerns, and I would like to point out that bone mineral density has not been studied in the COPD population

with the proposed drug product.

[Slide]

In conclusion, a statistically significant treatment effect for the primary efficacy endpoint was replicated only for fluticasone 500; was not replicated for fluticasone 250. There were small differences from placebo for the secondary endpoints and patient-reported outcomes. These findings were in a study population in which a majority of the patients were reversibly and may not be representative of the COPD population at large. Non-Caucasian patients were also under-represented.

Safety concerns noted in the pivotal studies and supporting studies included respiratory infections, upper, lower and pneumonia; adrenal effects; and bone density, which has not been studied in the COPD population for this product. We question if the degree of benefit justifies the potential risk in light of these safety concerns, particularly with long-term use in an older, more fragile population.

I will conclude my presentation and then Dr. McClain will be presenting, and I think we are going to entertain questions after the three of us

all present. Thank you.

Advair Diskus for COPD

DR. GILBERT-MCCLAIN: Good morning.

[Slide]

I am Lydia Gilbert-McClain, a medical reviewer for the Advair Diskus product. My objective during this talk is to present to you the Pulmonary Division's perspective on the safety and the efficacy of the Advair Diskus product as it relates to the indication for COPD. During this presentation I will bring out all the issues that raised some concern within the Division as they relate to the applicability of the Advair Diskus product for COPD indication.

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One of our concerns is with respect to the clinical relevance of the efficacy data; secondly, the applicability of the data from these trials to the general COPD population. In other words, if these products are deemed to be approvable, should this approval be generalized to the COPD population, or should it be for a subpopulation of COPD populations? Thirdly, are the safety data adequate to support approval?

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As you are aware, Advair is a combination drug product of fluticasone propionate and salmeterol. Advair Diskus was approved in August of 2000 for long-term maintenance treatment of asthma. Salmeterol, as an inhalation aerosol, was approved in 1998 for the relief of bronchospasm associated with COPD. Fluticasone propionate has not been approved for use in COPD in the United States. Therefore, with respect to Advair for a COPD indication the critical issue is the addition of fluticasone propionate, an inhaled corticosteroid.

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The sponsor has already gone through their develop program and I will not do that in this talk. But just to set the background for my presentation, I would just like to highlight the two trials that I will be discussion, the SFCA3006 and 3007, which evaluated the two strengths of Advair, Advair 500/50 and Advair 250/50. During my talk I will be referring to these products simply as Advair 500 and Advair 250. The corresponding treatment arms are shown here, fluticasone 500 and 250 and the salmeterol and placebo arms. The dosing administration was one inhalation twice

daily.

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The sponsor-stated objectives were to evaluate the efficacy and safety of these Advair products compared to the individual components, fluticasone and salmeterol, and placebo in COPD patients treated over 24 weeks. Additionally, the sponsor's third objective was actually to compare, to use the sponsor's own words, the quality of life in COPD subjects using these Advair products compared to subjects using the individual components, fluticasone and salmeterol and placebo, over 24 weeks of treatment. More recently, the agency has been using the term patient-reported outcomes instead of quality of life. During my talk I will also use the term patient-reported outcomes.

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Given that Advair is a fixed combination drug, the studies were designed to make the fixed combination drug's policy. This policy, stipulated in the Code of Federal Regulations 21 CFR 300.50, states that two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects of the

combination, and the combination is safe and effective for the patient population requiring such therapy. In this regard, the two Advair trials, 3006 and 3007, were adequately designed to fulfill the efficacy requirements of the combination drug policy.

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Just to highlight some key entry criteria, all subjects had to fulfill all the inclusion criteria to be eligible for these studies. They had to have a diagnosis of COPD as defined by ATS. They must have a history of cough, productive of sputum on most days, for at least three months of the year for at least two years, that was not attributable to another disease process; baseline FEV1 of less than 65 percent and FEV1/FVC ratio of less than 70 percent.

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The biometric indices indicate that the subjects enrolled in these studies did have airflow limitation. Their mean FEV1 ranged from 40 percent to 42 percent, and the mean FEV1/FVC ratio ranged from 47 percent to 51 percent. The percentage of subjects across studies with a 12 percent improvement in FEV1 and a greater than 200 ml

absolute change in FEV1 post-bronchodilator therapy was 54 percent to 55 percent. The demographics of this patient population mirrored the demographics that we see in the COPD population in general in that most of the patients were of Caucasian origin, and the majority of the patients were male. This is pretty typical of the COPD population in general and the FDA acknowledges that.

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One of the concerns we have with the patient population in these trials is that the patient population was made up of only persons who met the stringent clinical symptomatic definition of chronic bronchitis. While it is well understood that chronic bronchitis and emphysema can occur together, the entry criteria eliminated patients who did not have chronic bronchitis who would have otherwise met the definition of COPD. The sponsor did report that 75 percent of patients had emphysema, but this was based on patient self-reporting without objective criteria.

The COPD symptoms of cough frequency, cough severity, sputum production and chest symptoms were evaluated on a Chronic Bronchitis Symptom Questionnaire, and the baseline scores

ranged from 6.9 to 7.5 out of a maximum possible score of 16. At baseline most patients had a dyspnea score of about 2, a moderate dyspnea, on the 5-point scale of the Modified Medical Research Council Dyspnea Scale.

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This bargraph depicts the percentage of patients discontinuing from the study for any reason. Shown in purple is Advair; green, placebo; teal, salmeterol; and gold, fluticasone. I will use this color code in subsequent bargraphs.

The percentage of discontinuations in both studies was relatively high. In the Advair 250 study 30 percent of subjects discontinued from the study. In the Advair 500 study the discontinuation was 35 percent. Looking at the Advair group compared to the placebo group, the percentage of discontinuation in the Advair and placebo groups is quite similar. Thirty percent of subjects in the Advair group discontinued compared to 32 percent in the Advair 250 study, and 32 percent of subjects in the Advair group compared to 38 percent of subjects who discontinued in the Advair 500 study.

There are two concerns with these data. The discontinuation rate for Advair is quite

similar to the discontinuation rate for placebo in both studies. One might expect in a clinical trial with an active treatment that the discontinuation rate in the active treatment would be much less than the discontinuation rate in the placebo group. Secondly, such a high dropout rate complicates the interpretation of the effect size.

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As Dr. Meyer pointed out in his introductory remarks, the agency agreed with the prespecified primary endpoints chosen by the sponsor to evaluate Advair. Again just to refresh, pre-dose FEV1 was the endpoint chosen to evaluate the contribution of fluticasone in the combination, and for this evaluation the comparison of interest is Advair versus salmeterol. The two-hour post-dose FEV1 was selected to evaluate the contribution of salmeterol in the combination, and for this evaluation the comparison of Advair versus fluticasone is the comparison of interest.

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Depicted on this table are the results for the pre-dose FEV1, in other words, the evaluation of fluticasone in the combination. Shown here are the results for the Advair 250 study, and here are

the results for the Advair 500 study. This first line depicts the mean FEV1 baseline values for Advair -- quite similar in both studies. The second line depicts the mean FEV1 at baseline for salmeterol -- again, quite similar results. The mean change from baseline at endpoint between Advair and salmeterol, in the Advair 250 group was an adjusted mean difference of 69 cc. In the Advair 500 group the adjusted mean difference was 67 cc. These numbers had statistically significant p values.

Not, however, that in the Advair 500 group the result is almost identical for the Advair 250 group. This is noteworthy given that the dose of fluticasone being evaluated here is twice the dose evaluated here.

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Looking at the two-hour post-dose FEV1, or in other words, the contribution of salmeterol to the combination, again, shown in the first row is the mea

baseline FEV1 for Advair which was seen before in the previous table. The mean FEV1 at baseline for fluticasone is shown here in this table, and they are fairly similar. At endpoint the mean change from baseline in two-hour post-dose

FEV1 between Advair and fluticasone is 124 cc adjusted mean difference for the Advair 250 product and 129 cc adjusted mean difference for the Advair 500 product. Again, the results are quite similar and have statistical significance but, as opposed to the previous study, these similarities are not unexpected because in this situation we are evaluating the same dose of salmeterol.

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Looking at the overall efficacy of the Advair product, that is, the comparison of Advair versus placebo mean change from baseline at endpoint, looking at the primary endpoint, pre-dose FEV1, the overall ITT population, both for the Advair 250 product and the Advair 500 product, had a similar treatment effect, 164 cc for the Advair 250 product compared to 160 cc for the Advair 500 product.

When these results are broken down by the reversible and non-reversible population we see that in the reversible population the treatment effect is greater than in the non-reversible population. We did not perform inferential statistics on these data, however, looking at the Advair 250 product, the effect in the reversible

population is numerically about two-fold the effect in the non-reversible population. Looking at the Advair 500 product, the effect is about one and a half times in the reversible population compared to the non-reversible population. Again, these are numerical differences.

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Looking at the overall efficacy, Advair versus placebo for the two-hour post-dose FEV1, again the results in the overall population indicate that both the Advair 250 and the Advair 500 products had a similar treatment effect, 223 cc for the Advair 250 product and 233 cc for the Advair 500 product. Again, the reversible population had a greater treatment effect than the non-reversible population, and these are numerical differences. Inferential statistics were not done on these data.

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As stated earlier, one of the sponsor's stated objectives of this program was to compare patient-reported outcomes or quality of life in COPD patients receiving Advair compared to patients receiving fluticasone, salmeterol or placebo.

We do agree that evaluation of

patient-related outcomes may be helpful in assessing the clinical relevance of FEV1 changes and assessing whether pharmacotherapy is of benefit. The sponsor used the Chronic Respiratory Disease Questionnaire in both studies to evaluate this. The minimally important clinical change was defined as improvement of ten or greater in the overall score. This was based on the 0.5 point per item improvement in minimally clinically important change that has been previously described in the literature. So, in our assessment this definition for the minimal clinically important change was appropriate. For treatment comparisons, a difference in the mean change from baseline at endpoint between treatment groups of at least ten in the overall score was considered clinically meaningful.

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This table gives the results for the overall score for the disease questionnaire. What we are looking at is the treatment difference in change from baseline at endpoint between treatment groups. Compared to placebo and compared to its individual components, neither the Advair 250 product nor the Advair 500 product achieved a

difference that was clinically meaningful. For the Advair 250 product and the Advair 500 product, compared to placebo, the amount of change attributable to Advair was 5. Similarly, compared to salmeterol and fluticasone, the amount of change was less than the minimal clinically important change.

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Additionally, in neither of the four domains -- dyspnea, fatigue, emotional function and mastery -- did Advair achieve a clinically meaningful important change at endpoint or at any other time point between its comparators, placebo or other individual components. For example, in the dyspnea domain, where the minimal clinically important change was defined as 2.5, again based on the 0.5 point per item improvement criterion, compared to placebo the amount of change attributable to Advair 250 was 1.2, and for Advair 500 2.1. Compared to its individual components, the amount of change attributable to Advair was even smaller.

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One of the purported benefits of inhaled corticosteroids in the literature is reduction in

COPD exacerbations. As you have heard before, one of the recommendations in the recently published NIH GOLD document for the use of inhaled corticosteroids in COPD patients is for patients who have repeated exacerbations. Therefore, we feel that it is important to look at these data.

The sponsor evaluated four secondary endpoints related to COPD exacerbations. They were severity of exacerbations, time to first exacerbation, time to first moderate or severe exacerbation, and number of withdrawals due to COPD exacerbations.

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This bargraph depicts the percentage of subjects with COPD exacerbations of any severity. Again for the color code purple represents Advair; green, placebo; teal, salmeterol; and gold, fluticasone. The percentage of exacerbations was relatively similar across treatment groups for the Advair 250 product and for the Advair 500 product. In the Advair 250 study, Advair had 40 percent of subjects with COPD exacerbations compared to 39 percent in the placebo group. In the Advair 500 group, 41 percent of subjects on Advair reported exacerbations compared to 44 percent in the placebo

group.

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Looking at the percentage of subjects with moderate of severe exacerbations -- and you have heard the definition of moderate and severe exacerbations before. It was based on treatment. Patients treated with antibiotics were defined as having moderate exacerbations. Patients treated with corticosteroids or patients who were hospitalized for an exacerbation were defined as having a severe exacerbation.

Again, the results are quite similar for the Advair 250 product and the Advair 500 product. In fact, in the Advair 250 study they were identical. Thirty-four percent of subjects in the Advair group and in the placebo group reported exacerbations. In the Advair 500 study 37 percent of subjects receiving Advair, compared to 35 percent of subjects receiving placebo, reported moderate exacerbations.

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Looking at the percentage of withdrawals due to COPD exacerbations -- and subjects were withdrawn from the study for a COPD exacerbation if they had a severe exacerbation or if they had more

than two exacerbations requiring antibiotic therapy, in other words, if they had severe exacerbations or if they had more than two moderate exacerbations.

The results were low across both studies and they were quite similar for the Advair 250 study and the Advair 500 study. In both studies the percentage of subjects withdrawing due to COPD exacerbations was about eight percent in the Advair 250 and the Advair 500 groups, with similar percentages in the placebo group.

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The sponsor assessed COPD symptoms using a modified bronchitis symptoms questionnaire, which is a modified version of the Thomas Pettit questionnaire. The sponsor evaluated the symptoms of cough frequency; cough severity; chest discomfort and sputum production. Each symptom was graded on a scale of 0-4, and 0 denotes no symptoms and 4 denotes worst symptoms. Individual scores were added to give what was called a global assessment score, or GS.

To define the minimal clinically important change for this questionnaire, the sponsor matched changes from the baseline GS with a separate

measure of change in chronic bronchitis symptoms called the global rate of change. The global rate of change, as you are aware, is described in the literature and scoring goes from minus 7 to plus 7, where 0 denotes no change, negative numbers denote deterioration and positive numbers denote improvement. With this assessment, the sponsor defined a minimal clinically important change for this questionnaire as 1.4 or greater. With this evaluation, we feel that this was a reasonable assessment.

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This table shows the results for the Chronic Bronchitis Questionnaire, the differences from baseline endpoint, treatment comparisons for the two studies, Advair 250 and Advair 500. Compared to placebo neither in the Advair 250 study nor the Advair 500 study did Advair achieve a minimal clinically important change of 1.4. In other words, with respect to symptom improvement there was no difference when the patients in the Advair group were compared to the placebo group. Similarly, compared to the individual components Advair did not appear to have a treatment advantage for chronic bronchitis symptoms either in the

Advair 250 product nor the Advair 500 product.

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The sponsor also evaluated the impact of Advair on dyspnea using the Transitional Dyspnea Index. In this instrument the minimal clinically important change is defined as 1 or greater. For the Advair 250 study compared to placebo, salmeterol and fluticasone, the Advair 250 product did not achieve the minimal clinically important change. However, for the Advair 500 product compared to placebo, Advair 500 had a change of 1.7 which is greater than the minimal clinically important change of 1.0. Also, compared to salmeterol, the Advair 500 product had a change of 1.2, greater than the minimal clinically important change. Compared to fluticasone there was really no change.

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Moving on to talk about safety, the sponsor conducted an extensive assessment of cardiovascular safety using ECGs and Holter monitoring. The pattern of adverse events did not suggest that COPD patients taking the combination of salmeterol and fluticasone were at increased risk for cardiovascular events. The incidence of

cardiovascular events was similar across treatment groups. There was no clinically significant change in heart rate. There were no drug-related QTc changes. On Holter monitoring there was one case of heart block identified with Advair 500, but there were other Holter monitoring changes in other treatment groups.

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A relatively high percentage of patients reported adverse events during these two studies. However, this finding is not unusual in studies of this duration. In these studies a higher percentage of subjects in the Advair groups reported adverse events compared to placebo. For the Advair 250 product, 70 percent compared to 64 percent in the placebo group, and for the Advair 500 product, 78 percent compared to 69 percent in the placebo group.

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The profile of adverse events noted that were at a higher frequency in the Advair group compared to the placebo group was similar to the profile of adverse events seen with inhaled corticosteroids. For example, for the Advair 250 product ten percent of patients reported

candidiasis of the throat and mouth compared to one percent in the placebo group. Five percent reported hoarseness and dysphonia compared to no reporting in the placebo group. Three percent reported viral respiratory infections.

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With the Advair 500 product 17 percent reported upper respiratory tract infections compared to 10 percent in the placebo group; 8 percent reported viral respiratory infections compared to 3 percent in the placebo group; and candidiases reporting here was 7 percent for Advair 500 compared to 1 percent in the placebo group. There were less differences for placebo and Advair for hoarseness and dysphonia.

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Looking at other adverse events, across the studies fractures were rarely reported and there was no clear signal. No cataracts were reported in these two studies. There were two reports of ocular pressure disorders in the Advair 500 group and one in the placebo group. Elevated blood glucose was reported as being similar in the Advair and placebo groups, but the cut-off for that was fasting blood glucose over 175 mg/dl.

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In looking at HPA axis effects, the mean AM cortisol levels were comparable in the Advair and placebo groups on treatment day one and endpoint. No adrenal insufficiency was observed with the ACTH stimulation testing but, as you heard before in Dr. Lee's talk, ACTH stimulation is less than a sensitive method to evaluate for less than complete adrenal insufficiency.

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Summarizing, Advair 250 and Advair 500 both meet the efficacy criteria for combination drugs and the primary endpoints. The efficacy for Advair 250 and Advair 500 was very similar, and almost identical in some evaluations. Numerically the effect size in reversible subjects was greater than the effect size of the non-reversible subjects.

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Of clinical importance is the observation that no clear treatment advantage with Advair was noted for COPD-related quality of life or patient-reported outcomes, COPD symptoms or COPD exacerbations. It is also not clear whether there is a treatment advantage for improvement in

dyspnea. There was a clinical significant improvement at endpoint with the TDI instrument for the Advair 500 product, however, there was no clinically significant improvement in dyspnea compared to Advair 500 and its components in the dyspnea domain of the Chronic Disease Questionnaire, a well validated instrument.

Taken together, these overall efficacy findings form the basis of our concern regarding the clinical relevance of the FEV1 findings since the efficacy of Advair on airflow limitation did not translate into a clear clinical benefit.

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With respect to safety, the adverse events that were seen that were higher in the Advair group compared to the placebo group were similar events that have been previously noted with inhaled corticosteroids -- candidiasis, viral strain infections, hoarseness and dysphonia with both Advair products, and in the case of Advair 500 a higher incidence of upper respiratory tract infections.

Again, no adrenal insufficiency was observed in these two studies but bear in mind that this method of testing for adrenal insufficiency

might not be able to determine subtle changes in adrenal function. Finally, the studies were not designed, nor were they of significant duration, to evaluate bone mineral density or ocular effects. This concludes my talk. We will now have Dr. Mary Purucker who will summarize and then we will have questions.

Summary and Issues for PADAC

DR. PURUCKER: Good morning, everyone -- I guess it is almost noon.

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I am Mary Purucker, a medical team leader in the Division of Pulmonary and Allergy Drug Products.

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I would like to present a brief summary of our review of the two applications submitted for the indication of maintenance treatment of COPD, starting with efficacy. This will be followed by a safety summary, primary from the perspective of the corticosteroid moiety common to the two products, fluticasone propionate. I will cover the information submitted with the two applications but will also briefly discuss some relevant non-application safety data. I will then proceed

with a wrap-up and discussion points I would like to have the advisory committee consider.

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With regard to efficacy, statistical significance was not replicated for the primary endpoint, change from baseline in pre-dose FEV1 for Flovent 250 mcg BID. It was replicated for the 500 mcg BID dose, with an effect size of 50 cc and 113 cc. This effect size, seen at 24 weeks in trial 3025 was similar in magnitude to that seen in the ISOLDE study at three months, that is, 70 cc and 100 cc.

The combination product, Advair, also replicated the finding of efficacy for both primary endpoints. I show only pre-dose FEV1 versus placebo comparison because this endpoint measures the contribution of the fluticasone moiety to the drug product, and it is this moiety that is novel in COPD. Also, it is the fluticasone that varies with the strength of this product, not the salmeterol. Therefore, it is important to repeat the finding that was discussed earlier by Dr. McClain, that is, there is no dose response evident for the two doses of Advair in this analysis, 165 cc and 160 cc.

Also, as you have heard, we have raised several concerns related to the robustness of the finding of efficacy. In particular, there is a failure to demonstrate clinically significant differences from placebo with the quality of life or patient-reported outcome instrument. There is also a failure to demonstrate clinically significant differences in COPD exacerbation between active treatment and placebo. We also have concerns about the generalizability of this finding to the overall COPD population.

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With regard to safety, our primary concern is with the corticosteroid moiety that is common to the two products, fluticasone. The safety of the moiety salmeterol at the proposed doses has been previously established in this population and FDA's review disclosed no new or unique toxicities that could be attributed to the long-acting beta-agonist component in the combination product.

With regard to fluticasone, steroid-related adverse events were observed in a dose-related manner in the three pivotal trials -- oral candidiasis and dysphonia, for example,, as you have just heard.

Fluticasone is systemically available in the relevant population in a dose-dependent manner, as demonstrated by stead state PK sampling conducted during pivotal trial 3025.

Moreover, there was a dose-related effect on the HPA axis, as shown by a 10 and a 21 percent reduction in serum cortisol AUC relative to placebo. The potential for the corticosteroid system effects should, therefore, be assume, in particular on bone, eyes, connective tissue and metabolism. If approval is granted, then the products ought to be labeled for these effects as accurately as possible.

Unfortunately, the pivotal and supportive studies submitted with the package were not designed or powered to detect a difference in many endpoints that correlate with corticosteroid systemic safety in the population of interest. I will return to this issue momentarily.

Let me add that the long-term safety is important in this application. Contrary to the five-year 50 percent mortality cited earlier today for severe COPD, the patients in these three studies had an annualized mortality rate of 0.4 percent. Also, I think that while the observation

that FP levels in patients with COPD may be less than in patients with asthma is irrelevant since the PK/PD relationship is not necessarily the same.

[Slide]

This slide shows the results of a search by indication of the FDA adverse event database for all reports submitted for any inhaled corticosteroid, including fluticasone, for the indications of COPD, emphysema and chronic bronchitis. The search was performed by Dr. Joyce Leber, of the Office of Drug Safety, who used a cut-off of November 15 of last year.

A total of 206 cases were retrieved, all but 14 from the past three years, accounting for a total of 213 adverse events. Patients were in general elderly; about half were women; and the doses of ICS ranged from 80 to about 8000 mcg per day and varied with moiety. About half of all adverse events were reports of lack of efficacy or worsening of COPD. Several of the remainder adverse events are notable for systemic corticosteroid events, as shown on this slide. At least one of the cataracts was reported as a posterior subcapsular cataract. The bone events included pathological fractures, osteoporosis and

aseptic necrosis. Adrenal events were equally divided between insufficiency and hypocorticism, and skin adverse events included bruising and easy bruisability.

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Let me now return to the issue of specific systemic effects or corticosteroids starting with bone. Chronic systemic corticosteroids may lead to osteoporosis through a variety of mechanisms, including inhibition of osteoblasts, inhibition of GI calcium absorption and its effect on collagen synthesis. There is also individual susceptibility related to activity level, gender, menopausal status, genetics and smoking history.

On a population basis, therefore, bone effects may occur with chronic ICS, particularly at high doses. Ideally, these bone effects should be quantified by a proper risk-benefit assessment. Although bone mineral density was not specifically studied in the three pivotal trials of this supplemental NDA submission for the population in question, summary data from two two-year supportive trials of asthmatics, 3001 and 3017, was provided. I might add that we were not provided with the primary data from 3001 to review, only with data

summary.

Other considerations with regard to this data is that this is a different population, and that they were generally younger. They were asthmatic and the women were all premenopausal. Given these caveats by sponsor report, trial 3001 did find a decrement in bone mineral density in the lumbar spine at the high dose, and trial 3017 reported decreased bone mineral density in measurements of the femur. The latter site was not prospectively validated however.

[Slide]

I might add that the published bone density trials involving fluticasone cited by Dr. Shah in his presentation earlier today, in particular in slide 108A, were very small, with the Ns per treatment arm typically less than 30. The patients were generally young asthmatics and treatment duration was one year or less. This provides no reassurance of the safety of fluticasone on bone in the COPD population. With this in mind, we should turn to additional evidence in the published literature.

This slide provides additional information regarding the long-term effects of ICS on bone.

Important caveats include the fact that a different moiety and ICS formulation was used for the Lung Health Study, and multiple different ICS moieties were used by patients in the two asthma trials. The latter two trials also studied a different patient population than COPD.

Nevertheless, I believe it is important to recall the results of the Lung Health Study II, reported a little over a year ago, which showed that treatment of a population of COPD patients with 1200 mcg per day of the ICS triamcinolone over the three-year period was associated with a statistically significant decrement in bone mineral density at both the femur and the lumbar spine.

The first of the two asthma studies was published in The New England Journal last year, and was authored by Eliot Israel and his colleagues. This study was a three-year prospective cohort study of 109 premenopausal women with generally mild to moderate asthma. A statistically significant dose-related decline in bone mineral density at the total hip and trochanter was found, which persisted even after the exclusion of women who had received oral or parenteral corticosteroids.

The second study, by Wong and colleagues, was published in Lancet and was a cross-sectional study of 196 young asthmatics between the ages of 20 and 40 years. Of this group, a little over half were women. The mean duration of ICS use was six hears, and BDP and fluticasone were the ICS moieties used. The study showed a statistically significant cumulative dose-related decrement in bone mineral density at the hip, the trochanter, Ward's triangle and the lumbar spine.

An accompanying editorial by Philip Sanbrook used data from this study to estimate that seven years of treatment with a dose of ICS that is equivalent to 2000 mcg per day of BDP would result in a decrement of one standard deviation in bone mineral density or one T-score. This approximately doubles the risk of fracture.

While we need to be cautious about applying the results of these studies to the products under consideration today, given the caveats that I have identified earlier, we must also be cautious in the other direction in that these data imply a class effect of ICS on bone. It is, therefore, important to quantify this effect for a given ICS for a given population whenever

possible.

[Slide]

This slide summarizes the HPA axis information on fluticasone provided in the submission from the three pivotal trials and supporting studies. To review, in study 3025 there is a dose-related effect on the HPA axis as demonstrated by a 10 percent and a 25 percent reduction in serum cortisol AUC for Flovent 250 and 500 mcg BID respectively.

The other two pivotal trials conducted cosyntropin stimulation testing in a subset of about 20-25 percent of the participants. No renal insufficiency was reported but, as noted earlier, the test is not designed or validated to quantify levels of adrenal suppression.

The ISOLDE study measured AM cortisol at baseline, then at three-month intervals for the duration of the three-year study. As reported by the sponsor in the submission, there was a 10-15 percent reduction in mean AM cortisol for the fluticasone group in comparison to placebo at all post-baseline time points. Further analysis by shift tables disclosed that 20 percent of the fluticasone group had a shift from normal cortisol

values to low cortisol values compared to nine percent of the placebo group.

Finally, the clinical pharmacology study, 1003, was a single dose PK/PD crossover study of 1000 mcg of fluticasone, proposed total daily dose, administered to normal volunteers. There was a 35-59 percent reduction from baseline in 24-hour urinary cortisol that was observed in these subjects.

[Slide]

This slide covers the epidemiological evidence that draws an association between the dose and duration of ICS use in the occurrence of cataracts or posterior subcapsular cataracts in one of the studies in a middle aged and elderly population.

Again, to be fair, I want to point out at the start that these studies are not randomized controlled trials. Several different ICS moieties were used in the populations in question and, in fact, fluticasone may not even have been approved in these two countries at the time that the studies were conducted, which was the early and mid-90s.

Nevertheless, I believe that we have established that fluticasone is systemically

available at the doses proposed and in the population of interest, and has measurable systemic effects and, therefore, an association of posterior subcapsular cataracts with chronic use of fluticasone-containing drug products should not be unexpected.

The first study, by Cumming and colleagues, was a cross-sectional study of about 3700 subjects in Australia. Among the 370 ICS users identified, PSC was found at a two-fold greater prevalence among the ICS users than non-users, and prevalence was higher among subjects with a higher cumulative lifetime dose.

The second, or the Canadian study, was a case control study. They selected cases based on a history of surgical cataract extraction using the Provincial Insurance Health Database. The study determined that the use of ICS for greater than three years was significantly associated with undergoing cataract extraction, for an odds ratio of slightly greater than 3. For high average daily doses the risk was elevated after only two years.

In conclusion, given the limitations of this analysis based upon the above caveats, the possibility of ocular adverse events should be

considered in the overall risk-benefit assessment of Advair and Flovent proposed for the indication of maintenance treatment of COPD.

[Slide]

In conclusion, efficacy has been very well studied in these applications. There is substantial data that is open to clinical interpretation. If approval is recommended for one or both of these products there would be labeling issues remaining with regard to efficacy, but they would not be insurmountable.

In contrast, the safety database for this population is limited in describing long-term risks. One of the questions that we posed for the advisory committee is whether there are adequate data from which to construct a label for the potential long-term effects in the COPD population, particularly with regard to bone.

The potential for other systemic corticosteroid effects must be assumed, and we must ask ourselves whether there are sufficient data to write an informative label so that the practitioner may make a reasoned choice as to safely and effectively using these drugs in the COPD population if they are, indeed, to be recommended.

[Slide]

Which brings us to the specific issues for consideration by the committee to which I have already alluded. First as it relates to product efficacy, we would like you to discuss the patient population with regard to the generalizability of the findings to the COPD population as a whole. Factors to consider may include the degree of reversibility and the presence of chronic bronchitis. Bear in mind that the proposed indication is for long-term twice daily maintenance treatment of COPD, including chronic bronchitis and emphysema.

Second, also as it relates to product efficacy, we would like you to discuss the primary endpoint, change from baseline in FEV1, with regard to its clinical relevance to the treatment of COPD.

[Slide]

Finally with regard to safety, we would like to ask the committee to consider whether the data are sufficient with regard to the potential long-term impact on bone or other relevant systemic corticosteroid safety endpoints.

[Slide]

Thank you for your attention. I would

like to acknowledge my colleagues who contributed professionally to the thorough and timely review and presentation of these applications. Thank you.

DR. DYKEWICZ: Thank you. I am going to allow only about five minutes for questions at this point because I think this afternoon there will be plenty of time for discussion and for posing any questions. So, for members of the committee, do we have any questions at this point that are kind of burning issues that you would like to get off your chest? Dr. Fink?

DR. FINK: Just a question for FDA in general as regards interpreting this data, is it the FDA's concern that inhaled corticosteroids have a worse safety profile, both in COPD and asthma, than initially was apparent, or is the concern solely that the risk-benefit ratio in COPD is worse than in asthma?

DR. PURUCKER: I don't mean to imply that inhaled corticosteroids are not safe or effective for asthma. At this point what we are trying to ascertain is what the safety profile is; what the long-term risks are so that if they are, indeed, recommended for approval how to construct the label, or how, indeed, to weigh the risk-benefit.

Some of what I presented is the fact that there is an absence of data for the long-term use of fluticasone in the population of interest, the COPD population. That is one of the issues that we have. There are probably safety issues and we can't quantify them.

DR. MEYER: Let me just follow on to that. I agree with what Dr. Purucker said. I think we have, as an agency and as a scientific community or medical community, better appreciated some of the long-term systemic effects of corticosteroids in recent years, although I think the agency has known about such issues for a long time, particularly with regard to our experience with the spontaneous adverse event reports.

But I think the main question here is not that issue so much as it is specific to COPD, whether we even know enough to say whether this population is particularly sensitive to some of these safety issues, number one and, number two, given the differences in the efficacy seen in these studies and perhaps other studies compared to the kind of efficacy you see in asthma, are the safety issues that we know about or don't know about -- how do they factor into the risk-benefit equation?

DR. DYKEWICZ: Thank you. Maybe just one more question before we break for lunch.

DR. STOLLER: My question is also procedural. Bob can address this. In assessing the efficacy outcome measure, obviously the pre-dose FEV1 for fluticasone and the two-hour post for the salmeterol dimensions have been selected and agreed upon. Clearly, there are at least four randomized trials that have assessed delta FEV1 over time about which we have, obviously, heard nothing as an efficacy measure. The question is in assessing efficacy versus safety outside the parameters reflected here, how relevant is that to the conversation of the committee to an assessment of efficacy?

DR. MEYER: Are you asking about essentially whether any improvement in baseline FEV1 continues over time?

DR. STOLLER: I am asking about the change in slope of FEV1 --

DR. MEYER: Right.

DR. STOLLER: -- not being assessed in these studies, but available from antecedent literature but not being negotiated a priori as a primary outcome measure. So, is it off the table

as a relevance issue, or is it a consideration? It is a procedural question.

DR. MEYER: We certainly had this kind of discussion with the sponsor beforehand, and in our mind it is somewhat a different issue as to whether there is shorter-term benefit that you might see in a six-month trial versus preservation of lung function over time, which would require much larger and longer trials. Even with asthma where it is quite clear that the inhaled corticosteroids have a short-term effect that is durable, it is still not entirely clear to me that there is a lung preservation effect. If you look at the CAMP data, for instance, that is not entirely clear, and I don't think it is entirely clear or, in fact, very well supported by the data in the literature to date for COPD either. But I think what you need to focus on today is the sort of shorter-term but durable response that was studied in these studies.

DR. DYKEWICZ: Thank you. Let's now adjourn for lunch and reconvene at 1:10 p.m.

[Whereupon, the proceedings were recessed for lunch, to be resumed at 1:20 p.m.]

AFTERNOON PROCEEDINGS

DR. DYKEWICZ: What I am first going to do, because we broke off for lunch just shortly after the FDA presentations, is to give an opportunity to members of the committee to pose questions to the FDA presenters. Would anyone like to be recognized at this time? Dr. Joad?

DR. JOAD: I am curious for the FDA to answer the same question that I asked to the sponsor, which is to go over why the statistically significant differences in the three questionnaires didn't impress you, and how confident you are about these numbers that have been given as clinically important.

DR. MEYER: I think the easiest one to speak to is the Chronic Respiratory Disease Questionnaire that Guyatt and Juniper developed. I think the bronchitis questionnaire, as the sponsor said, was a relatively new modification of an instrument that is not as well validated. So, I think we can sort of put that one aside.

The CRDQ, as with perhaps all instruments that Juniper and Guyatt have developed, they defined a meaningful clinical difference by an actually non-interventional setting, looking at a

cohort of patients over time, finding patients who change in a global scale of "how do you feel," or sort of a global, broad one question quality of life assessment, and correlate that to changes in their particular instrument over time. Based on the results of how the patient has fared in the global question, then determine what would be a clinically important difference, something meaningful to the patient that they might be able to detect, or might mean a change in therapy for their particular instrument.

So, it is strictly true that these are not to look at between treatment differences, but it is also true that it is not really meant to assess -- it wasn't developed and validated specifically to assess treatment effects at all. This important minimal difference was looked at and derived from spontaneous change over time, not change in response to intervention.

All those caveats aside, I think we go with what seems to be the best assessment of what might be a clinically meaningful difference to a patient, which is what Juniper and Guyatt have determined and what the sponsor prespecified. So, I think that on the CRDQ you would want to see not

only that change from baseline in a particular therapy, but you would want to see that the attributable effect in reference to placebo was meaningful as well.

I think the TDI is also a very well validated instrument. I think a meaningful difference in that is less well validated. I think the sponsor did a reasonable job of identifying what they thought it would be based on speaking to the developer of the instrument, and I think we felt it was reasonable a priori as well.

DR. BONE: Could I just pursue this a little bit? I guess sometimes we need to make sure we are applying the same scientific rigor to the selection of our tools as we are to what we are trying to measure. I am trying to understand here, have these instruments, specifically these minimal significant differences, been shown to be strongly correlated with, let's say, other harder outcomes in clinical trials, such as survival or other indices of morbidity, or other measures where we can say, okay, a difference of so much in this scale predicts a better outcome over a period of time?

DR. MEYER: I think most of such

instruments do have some level of correlation with those kinds of endpoints. That is generally done as part of the validation of the instruments. Of course, if you take FEV1, for example, that correlation is not particularly high but you wouldn't expect it to be because it is not measuring the same thing. It is really measuring the patient's perception of their disease which is multifactorial, and lung function is only a part of that. I don't know the specifics actually of the CRDQ as far as follow to morbidity and mortality, or at least major morbidity, but I think that those kinds of looks are generally done with these instruments, and CRDQ is a reasonably well validated instrument.

DR. DYKEWICZ: Dr. Wise?

DR. WISE: I think I would like to follow-up on that a little bit, and the notion of clinically meaningful changes, particularly in looking at the mean of a population since these have been validated in terms of what is important to an individual or perceptible to an individual in terms of a change in status. Very commonly we see mean changes in populations that seem small but have important clinical effects at the ends of the

population. It is kind of a multiplier effect where people out at the ends, if it is a broad distribution or a skewed distribution, can show remarkable benefits. Sometimes people have looked at percentage of people in one group versus another group who have a clinically meaningful response. I wonder what your views are on that, and whether that data has been available in this.

DR. MEYER: Let me make two observations about that. I think that is certainly true and I think that neither the agency nor necessarily other parties have fully settled on the best way to assess the clinical interpretation of these results. One thing that that raised in my mind -- this sort of gets back to Dr. Joad's question a little bit -- is that it is important to understand that the statistical experience or the experience we have with these instruments, particularly the instruments of Juniper and Guyatt, is that the numbers that you would need to enroll in a trial should the difference between the treatments that you are comparing reach that clinically significant difference, or clinically important difference, is only about 30-35 patients. It is not very many.

So, in fact, just as the sponsors caveated

some of the observations about secondary endpoints, that the trials were not designed to specifically do differential testing on all those, I think, that one of the design issues for interpreting these statistically significant results that don't meet the prespecified clinically important difference between groups is the fact that these studies are, in fact, very much overpowered for looking at the statistics of these instruments.

DR. DYKEWICZ: Dr. Fink?

DR. FINK: From an FDA standpoint, could you give us some perspective, particularly for quality of life or patient-reported outcomes, how this data compares with previously approved drugs, such as salmeterol and ipratropium where they clearly showed a pulmonary function effect, were those drugs capable of showing patient-reported outcome effects?

DR. MEYER: I really hesitate to do that based on cross-study comparisons. I can say that if you look at the labeling for ipratropium it specifically mentions the use of a patient-reported outcome instrument and specifically states that there were not significant differences found. So, I can say that.

I would also emphasize, however, that those drugs have a very specific indication for the relief of bronchospasm associated with COPD. They are not for the maintenance treatment of COPD, which is a rather different kettle of fish.

DR. DYKEWICZ: Dr. Stoller?

DR. STOLLER: I think Dr. Wise's question raises for me a follow-up that I guess I would appreciate your comment on, and it has to do with looking at mean values in a dichotomous way. As I understand the issues put on the table, and I agree, if there is a mean delta of the pre-bronchodilator FEV1 of 100 ml in aggregate, as a group, it might be relevant, to my understanding of efficacy, to have that stratified by different subsets. Admittedly, not done a priori but even in an ad hoc way after the fact, to have it stratified by baseline FEV1 strata and then to look at the percentage of individuals who experienced an increment of a certain defined value stratified by those subsets. So, dichotomously analyzing the data by subsets, which is characteristically a dangerous business after the fact but, nonetheless, it would speak a little bit to the issue I think you have put on the table with which I agree, which

is, is there a segment of the population, given the relatively paltry overall FEV1 rise of 100 ml, 70 ml -- can one one ask to see data around the dichotomous analysis in subsets? Have I made myself clear? It is kind of a procedural question I suppose. That is why I put it forward.

DR. PURUCKER: We looked at subsets post hoc really only based on reversibility, and we found that the patients who were highly reversible contributed numerically more to the effect size than those who were not reversible. Similarly with cigarette smoking, although I believe the effect size was more in clinical trial 3025 than it was in the salmeterol trials, but we did look at those particular variables.

DR. DYKEWICZ: Dr. Bone?

DR. BONE: To pursue this, were responder analyses done as secondary analyses by either the sponsor or the agency, looking at the minimum significant differences as the criterion for response?

DR. GILBERT-MCCLAIN: No, we didn't do those.

DR. BONE: Did the sponsor do that?

DR. SHAH: Yes.

DR. BONE: Were those data submitted to the NDA?

DR. SHAH: They were for some.

DR. BONE: Well, they were or they weren't?

DR. SHAH: Again, we did submit as part of our integrated summary of efficacy, which is part of an NDA submission, analyses for subgroups by responder analysis. Those data were there, but I don't believe they were done at the individual study level but we certainly have those data here if it would be of any use for the committee to see.

DR. DYKEWICZ: I think they would be, and maybe I will give you an opportunity later to respond to that. Dr. Malozowski?

DR. MALOZOWSKI: I am not familiar with this condition, therefore I don't know how common it is to see in a 24-week study this 40 percent patient withdrawal from the study. This is either for the FDA or for the sponsor. How can you assess data integrity applicability of the outcomes that are measured when 40 percent of the patients did not complete the study?

DR. MEYER: Actually, I would say, at least from the Division of Pulmonary and Allergy

Drugs standpoint, that we don't have a lot of experience with six-month trials. More commonly we see three-month trials and I don't think it was entirely unanticipated that there would be some dropouts certainly and I think it does raise some issues, particularly not whether there is an effect or not but really nailing down what the effect size is. But this was discussed with the company and I think that we chose the endpoint analysis basically as a way to try to deal with that.

DR. DYKEWICZ: Dr. Bone?

DR. BONE: This is a relatively specific question for Dr. Lee. You referred to a patient who had a low cortisol value -- if I understood correctly; it went by pretty quickly -- who was reported to have suffered a serious adverse event. I was a little surprised to have a serious adverse event without any clinical information because the criteria for severity are clinical. So, could you explain that further? I am sure there was an SAE report to be reviewed.

DR. LEE: No, there was no case report form for that patient. It was supportive data, not in the pivotal clinical trials and there was no case report form.

DR. PURUCKER: We didn't have the primary data from that trial; we just had summary data and a patient was reported as having had a serious adverse outcome. We don't have any other details.

DR. DYKEWICZ: Dr. Parsons?

DR. PARSONS: There has been a lot of data presented on the group of patients that had a reversible process versus the non-reversible group. On my reading through, the study was not designed to look at those two groups independently. Is that correct? It was initially all-comers and it was a post hoc analysis to look at those two groups.

DR. MEYER: Clearly, the overall analysis was going to be the primary analysis. I think it was understood that we would have an interest in looking at the results in those two separate populations but that was not the primary interest.

DR. PARSONS: Are the two populations large enough to draw conclusions versus one versus the other?

DR. MEYER: As I think Dr. McClain mentioned, we were really not paying attention to the inferential statistics there because we weren't trying to draw inferential conclusions on this data.

DR. DYKEWICZ: Dr. Joad?

DR. JOAD: Since asthmatics appear to respond well to these drugs, how confident are you that this group that has COPD and does not have a fair number of asthmatics also included in this study group -- since asthma can now be defined as non-reversible -- have a non-reversible component? It would just confound the data if there were a group that were highly responding that really maybe should be called asthma instead of COPD.

DR. LEE: Well, patients with a diagnosis of asthma were a priori excluded. Could there be some overlap? It is probably true, there may be some patients whom some people might define as being asthma in the population but, you know, I feel relatively confident with the figures that were presented.

DR. GILBERT-MCCLAIN: Just to add one thing to follow-up on Dr. Lee, also the mean FEV1/FVC ratio that we saw across those studies was 47-51 percent, which is much lower than what we have seen in the all the asthma studies. So, we felt that overall the population was representative of obstruction.

DR. DYKEWICZ: Dr. Bone?

DR. BONE: I am sorry to belabor this point, but how can you not have an SAE report? If it was from another trial, you would still have the report.

DR. LEE: This was supportive data in a study reported and, you know, I did not have the entire case report forms for all the withdrawals. It was not a pivotal study.

DR. BONE: But SAEs are still reported from any clinical trial. You have to report them in ten days.

DR. PURUCKER: This was an old trial that was submitted as supportive data, and perhaps we should direct the question to the sponsor. Perhaps they could tell us what the SAE was.

DR. SHAH: We usually provide case narratives. We may not have provided a case report form because it was a study that was done several years ago and it was done for Europe, not U.S. The case narrative should have most of the information that I think you may be looking for. We are trying to see if we can dig it up and if we find it, we will be happy to share that with this committee.

DR. DYKEWICZ: Dr. Fink?

DR. FINK: Was there anything in the

design of the trials, since we didn't get the total design of the inclusion/exclusion criteria, or in the conduct of these trials that would with any probability have led to a bias toward responders versus non-responders at enrollment, since we have heard that clinically 50-60 percent responders from the COPD population is not surprising? I believe Dr. Donohue, from North Carolina, said that he was actually quoting 60 percent of patients who have reversibility.

DR. GILBERT-MCCLAIN: Just to respond to that, in the papers that Dr. Donohue referred to, reversibility in all of those studies was defined as 12 percent or 15 percent response with bronchodilator. It was not 12 percent and 200 or more cc change in FEV1. So, I think that needs to be taken in the context of those percentages.

DR. FINK: Weren't these studies either 12 percent or 200 ml?

DR. PURUCKER: No, 12 percent and 200 cc.

DR. GILBERT-MCCLAIN: Just to clarify, the studies that Dr. Donohue referred to were 12 percent or 15 percent. There was no absolute change in FEV1 as part of the criteria as opposed to the reversibility here.

DR. FINK: But if FEV1 was below 0.7 L the 200 ml requirement was dropped?

DR. PURUCKER: No.

DR. FINK: No?

DR. SHAH: Can I just clarify? Well, maybe Dr. Donohue can speak to that.

DR. DONOHUE: In the IPB trial, just for everyone's benefit, if you stratify COPD into, let's say, level three where the FEV1 is 1000 ml or 700 ml, you know, 100 cc can be 20 percent or a very, very large response. So, in people with very high lung volumes, they respond primarily with volume.

The IPB -- what originally was reported in The Annals of Internal Medicine was 15 percent. In all the recent studies we really tried to include the 12 percent and the 200 ml so we can take in those two extremes. I presented at the American College of Chest Physicians and also at ERS in an evidence-based symposium and we tried to get at this question, because it is so key, about reversibility and the preponderance of the evidence is that it falls out anywhere around from 50 to 60, 65 percent that do respond with about 12 percent and 200 ml.

The European studies use a different standard, and they use, of course, percent of predicted FEV1. So, we have been interested in looking at a lot of the United States studies against that standard from Europe. In fact, the majority of our patients really would meet the European standard of non-reversibility.

So, again, those of us who work in the field, we appreciate the difficulty in trying to deal with this question, separating asthma from COPD, but our believe is that most patients do exhibit reversibility and we teach all the doctors that if you are giving a bronchodilator to a patient, give it for a month, two months or three months. You can't go by this acute reversibility. Many of the patients that we saw, let's say, in the salmeterol study that seemed to be irreversible at baseline, over the course of a month, two months, you will see a response.

So, that is sort of the caveat but I appreciate the difficulty we are all having with that question. It is a tough one, but it does seem that if you use 12 and 200 a little over half seem to respond at baseline to albuterol two puffs. The difficulty in these studies and the salmeterol

study, of which I am a co-author with Mahler, we used two to four puffs of albuterol. In other studies we have used 15 percent. So, again, it is a very, very difficult subject to tackle. Did I answer the question?

DR. DYKEWICZ: Thank you. First Dr. Wise and then Dr. Stoller.

DR. WISE: I wanted to clarify was the reversibility measured after two or four puffs of albuterol, and if it was four, did that have influenced the percent?

DR. DONOHUE: Yes, it is up to four in this study. Maybe Tushar should answer this -- I was involved in the Mahler studies and in that one the majority of the people responded to two. Only a small extra increment needed four puffs to reach the 12 percent and 200. Do you have the specifics for this?

DR. SHAH: In this program it was prespecified to be four puffs of albuterol. So, we were really trying to get the reversible patients fully defined and, clearly, we know that there is some dose response between 200 and 400. We get the maximal effect at the two puffs but there is an additional effect that we do see with going up to

four. As Dr. Donohue alluded to, in studies that we have done in the past and other sponsors have done it is usually two puffs and occasionally they do go up to four puffs.

DR. DYKEWICZ: Dr. Stoller?

DR. STOLLER: I would like to make a comment just really regarding clarification of the generalizability of reversibility from these data. The issues, as they appear, have to do with the dose -- I am glad Dr. Wise clarified that because that was my follow-on question, but four puffs BID is characteristically higher than most of the baseline reversibility studies of which I am aware. I am not sure what the conclusion of that is but it is an observation.

The second would be that as I remember the Anthonisen data which used the 15 percent criterion, the presence or absence of reversibility was measured over time with up to seven serial spirometries. It was not a single baseline assessment. So, in aggregate over time, as has been pointed out, most of these individuals will over time demonstrate reversibility. The question then defaults, in my mind, to how generalizable is the experience of reversibility regarding a single

baseline measurement in which 56 percent of patients demonstrate 12 percent and 200 ml rise in the post-bronchodilator FEV1, with a dose of albuterol that is higher characteristically than was used in any of the other studies that characterized reversibility? Now, I am not sure how to interpret that but I think, for the sake of clarity, we should understand that phenomenon.

I would make one other point with regard to the presence of reversibility in emphysema, which is clearly a prevalent phenomenon, and perhaps data from the alpha-1 antitrypsin deficient subset of patients, with which I have some familiarity, bears here. When we looked at this experience using 12 percent and 200 ml with FEV1, not with FVC and I presume FVC was not the reversibility criterion here, again, over serial examinations, up to three serial spirometries, and a cohort of FEV1 is about 43 percent of predicted and an N of 1129 individuals, up to 55 percent of these individuals with two puffs BID of albuterol or a comparable drug would satisfy the 12 percent and 200 ml criterion. But, again, that was serialized over at least three serial spirometries. In any given test in a run-in period the prevalence

would not have been anywhere near as high as the 50-55 percent that is being reported here.

Again, I am not sure what the conclusion of that is, but I hope that that lends some clarity to the question posed to us about how representative, with regard to the reversibility of this population, is it of the COPD population at large, with perhaps alpha-1 being the quintessential example of emphysema, not asthma or not chronic bronchitis.

DR. DYKEWICZ: Thank you. Any other questions for the FDA at this point? Dr. Wise and then Dr. Parsons.

DR. WISE: Whoever wants to take this, I was impressed with the prevalence of thrush, oral candidiasis at around 12 percent, which seems more than a clinical experience would warrant. I wondered how that compared to the trials with the fluticasone MDI in asthma. Is that comparable?

DR. LEE: Yes, I think the label mentions about five percent, five percent in both the formulations.

DR. MEYER: I think the thing that complicates that answer, however, is that most of the pivotal trials done for the fluticasone program

were 12 weeks, and I believe the corticosteroid-sparing trials were 16 weeks; they were not 24 weeks. So, this is a higher percentage than we saw pretty much for the asthma trials. I think the highest dose of the oral corticosteroid-sparing trial had a significant amount of thrush but, of course, many of those patients were also on oral corticosteroids. I think this is higher but it is also a longer time period. Commonly adverse events get called incidents but we don't commonly correct for the amount of time that you are looking at. So, you are not true incidents.

DR. DYKEWICZ: Dr. Parsons?

DR. PARSONS: I actually have the same question but I want to take it one step further. Some of the other issues independent of candidiasis were increased incidence of viral respiratory infections and upper respiratory tract infections. Are those also similar percentages to what you saw in the asthma trials? Even accounting for the difference in time, is there any way to equate those at all?

DR. MEYER: I think we would actually have to look back at the data. I don't think that we,

in my mind, had that as an issue. I don't know if the sponsor would have better recollection of those data than I do. I was the primary medical review officer on Flovent but I don't know the data offhand.

DR. DYKEWICZ: Dr. Shah?

DR. SHAH: Thank you. Yes, in asthma, again, remember that the studies we did with fluticasone were very differently designed. Because they were placebo-controlled and we were withdrawing patients who were having worsening of their condition, we did have very significant differences in exposure between treatment groups, meaning that people in the FP groups were treated for a lot longer durations. So, if you were to look at just the overall results, the trends in the placebo versus the active groups were suggestive of a higher number on the actives but, as Dr. Meyer indicated, you know, when you have a study design which was designed to withdraw patients in potentially one group you do have to look at the adjusted results. Though it is not easy to find a good way to adjust for this phenomenon, I think clearly the experience would be that in asthma we don't see any concerns when you try to adjust

between the active and placebo for these various things.

DR. MEYER: Let me just follow-up on that because I think that that is an important point. There really was a very striking difference in most of those fluticasone trials because of wanting to protect the placebo patients in the amount of time that the patients spent in the trials. So, the placebo patients had a much shorter time as a mean exposed to the study and, therefore, able to report study-related adverse events than did the fluticasone. The recollection, without citing the specific data, is that we looked at the data and did not feel that any trends seen were significant given the differences in exposure time. So, that is not an issue here in terms of the amount of time that the groups were exposed. It looks relatively well balanced across the groups.

DR. DYKEWICZ: Dr. Atkinson?

DR. ATKINSON: I think my question is for Dr. Gilbert-McClain. Did I understand, as you were speaking, that the patient selection criteria would have excluded patients with emphysema primarily?

DR. GILBERT-MCCLAIN: There were no objective criteria to define emphysema. I know it

is difficult to define emphysema, but emphysema was by patient self-reporting. As I mentioned earlier, they had strict criteria for chronic bronchitis but not for emphysema.

DR. DYKEWICZ: Dr. Apter?

DR. APTER: I guess this is for Dr. Shah. We were told that GlaxoSmithKline has an ongoing three-year international study to evaluate the effect of Advair Diskus 550 mcg BID and fluticasone 500 mcg BID on the survival of COPD patients, and also there is an evaluation of bone mineral density and ophthalmologic effects over a three-year period. What we are hearing today is that the time of these studies is long by FDA standards but not long at all for such a chronic disease. Where are we on those ongoing studies, and when will the results be available?

DR. SHAH: Yes, this was a study we initiated about a year ago because we recognized, clearly, the high morbidity and mortality in this population and the need for treatment that may actually improve those outcomes. So, that was the primary objective of these studies. In the international study there are going to be over 5000 patients enrolled in the study, but we are planning

to do a subgroup of those patients looking at various safety measures such as bone density, eye exams, as well as HPA axis assessments. But that study has just started so we are looking at almost at least four more years before we will have results from those studies.

DR. DYKEWICZ: Dr. Joad?

DR. JOAD: This question can be for either group. I am just curious. As a pediatrician, I am used to everything being presented as predicted because an absolute amount of change in FEV1 is meaningless to us because it would depend on the size of the child. Now, I would imagine that adults differ enough in size, in height and also effects difference so that it is odd to me that everything is done in absolute milliliters as the primary endpoint.

DR. DYKEWICZ: Any response from the FDA on that?

DR. MEYER: I guess I would just say that in pediatric trials we do look primarily at percent predicted or change in percent predicted for the reasons cited. I think, as you say, adults come in different shapes and sizes and there, of course, are differences but in trials of this size they