These patients are getting those orally, which are likely to be a lot more unsafe for the skeleton but I know that is not a consideration for deliberating on this. I guess I would have to say that overall for considering the lung health of the patient and the skeletal health and what I view as a very slow erosion of their bone density, I would have to say the overall safety profile is good.

DR. DYKEWICZ: From my perspective on the safety I am considering several things. One is we do have an agent for which we do know what the potential side effects would be. We know what the signals would be in terms of adverse effects of corticosteroids on the body. So, it is not a question that we are dealing with a totally unknown entity where we don't know what to look for.

In the case of the studies of fluticasone in asthma which generally are reassuring, of course, that certainly has relevance to a consideration of the use of this agent in COPD. But I am quite conscious that the population of COPD patients may potentially be more vulnerable to certain adverse effects than might occur in a population of asthmatics which will tend to be, among other things, younger for instance.

So, I would like to, of course, ideally see much longer follow-up than just the 24-week study. As Dr. Malozowski has pointed out, there are certain potential side effects that will be perhaps more apparent with longer-term follow-up. However, in the main, with those qualifications, I do believe that there is reasonable safety data that would then have to be judged in a risk-benefit assessment when we finally come to the approvability question.

DR. APTER: Like many of my colleagues, I cannot say that these drugs are safe long-term for chronic obstructive bronchitis. I am concerned also about the large number of dropouts which made the follow-up even shorter. I am concerned, like the others, that this is a different population than the asthmatic population -- older, more morbidities.

DR. DYKEWICZ: Dr. Joad?

DR. JOAD: I am also concerned about this product in this age group for this disease. I think we need more data before we can decide on safety. I just wanted to comment that changing the package insert to saying for the treatment of chronic obstructive bronchitis -- I think what that

will become is long-term therapy of chronic obstructive bronchitis. I don't see how, in practice, people will somehow give it for six months and then stop it, and then give it again sometime later. I think if it is approved for the treatment it is going to be approved for the long-term prevention of symptoms.

DR. DYKEWICZ: Ms. Schell?

MS. SCHELL: On this issue, I have some concern and I can also see the potential benefit. I am trying to weigh the benefit-risk in what I have seen in patients who have been on this drug already for treatment. I do have a problem with the long-term wording because the studies weren't geared towards the COPD patients that demonstrate safety. I appreciate Dr. Bone's remarks and his input on that, but looking at the benefit-risk, again, it is difficult for me to say. I would think as long as we continue to monitor, and maybe that could be in the wording of the labeling, this would be a benefit to the patient.

DR. DYKEWICZ: Let's then begin the formal vote. Again, do the data provide sufficient evidence of safety of Flovent Diskus for treatment of chronic obstructive bronchitis?

DR. PARSONS: No.

DR. DYKEWICZ: Did you want to vote on this question, Dr. Bone?

DR. BONE: I think the overall assessment really belongs to people who work in this area so I will pass on this.

DR. STOLLER: I will say no.

DR. FINK: No.

DR. ATKINSON: Yes.

DR. DYKEWICZ: Yes.

DR. APTER: No.

DR. JOAD: No.

MS. SCHELL: Yes.

DR. DYKEWICZ: The vote on the question is three yes, five no, one abstention.

Moving on to question four, do the data provide sufficient evidence of safety of Advair Diskus for the treatment of chronic obstructive bronchitis? I think we will go back to that side of the table. Some thoughts on that question, Ms. Schell?

MS. SCHELL: Much of my opinion is the same as with the previous question as long as take the "long-term" out and we just say treatment. Also, again, looking at the population studied, I

have concerns about COPD patients compared to asthma patients in this study.

DR. DYKEWICZ: Dr. Joad?

DR. JOAD: With Advair, my concern is the steroid components so my thoughts would be the same as before.

DR. DYKEWICZ: Dr. Atkinson?

DR. ATKINSON: Yes, I am not that concerned about the salmeterol component either so I think my opinion wouldn't change either.

DR. DYKEWICZ: Thank you, Dr. Atkinson. Dr. Apter?

DR. APTER: My concerns are the same as previously for Flovent. I could say "but" and change if the wording included "not for long-term management."

DR. DYKEWICZ: So, if I rephrased it long-term, you would vote no, but if I stated that it was just for treatment you might vote yes?

DR. APTER: That safety has only been established for short-term treatment.

DR. DYKEWICZ: I guess my view is that the data is paralleling that of the safety data for Flovent Diskus because I don't really believe that the addition of the salmeterol component raises any

significant safety issues. Dr. Fink?

DR. FINK: I would agree with that and I think actually there is an additional safety factor for the Advair Diskus in that clinical practice I think it is general knowledge that Advair is only dosed twice a day, and I think the potential that physicians would escalate the dosage of Advair to three or four inhalations a day is far less than for the Flovent 500 Diskus being escalated. So, by being a combination product -- I never would have imagined myself saying this, I think it is probably safer in clinical practice.

DR. DYKEWICZ: Dr. Stoller?

DR. STOLLER: My comments would be as before, although I would say, again, in the interest of being as helpful to the agency as I can with regard to really framing what I think, I think in the context of what we have been shown, as I mentioned before, I don't have huge safety concerns within the scope of the 24 weeks as shown. My concerns are extrapolated to the clinical implications of long-term use which is not satisfied by the data at hand. So, it really defaults to kind of a word-smithing issue. You know, if you are going to write the label so it

says it is approved for the relatively short-term management of chronic obstructive bronchitis and it is safe in that regard, my concerns are less. If it is going to be kind of open-endedly endorsed for the in perpetuity treatment of patients, I have concerns, as I have said before, about its safety. So, I would say that, very simply put, I am not satisfied that long-term safety benefit has been shown by the data at hand. I think within the framework of what we have been shown I have no major immediate concerns about major adverse clinical events right now.

DR. DYKEWICZ: Thank you. Dr. Parsons?

DR. PARSONS: I have the same concerns with this one that I did with the Flovent, which is that the long-term safety has not been established. I think, no matter how we word that, whether it is just simply for treatment of chronic obstructive bronchitis or whatever, it will be used long-term. I think to try to label it that it both has efficacy and is safe for 24 weeks -- I guess that is an option but I think every physician that then treated their patient for 24 weeks, at 24 weeks would have a therapeutic decision to make and I think the patients would stay on the drug. So, I

think we need to look at it as something that is going to be used as long-term persistent therapy, and I think in that use there is not adequate safety data.

DR. DYKEWICZ: Any other general comments from the committee? If not, let's begin the formal vote. Do the data provide sufficient evidence of safety of Advair Diskus for the treatment of chronic obstructive bronchitis? Ms. Schell?

MS. SCHELL: Yes.

DR. JOAD: No.

DR. APTER: Again, no in terms of long term.

DR. DYKEWICZ: Yes.

DR. ATKINSON: Yes.

DR. FINK: Yes.

DR. STOLLER: No.

DR. PARSONS: No.

DR. DYKEWICZ: On the issue of safety of Advair Diskus, the votes were four yes, four no, one abstention. Dr. Meyer?

DR. MEYER: Just before we go on to the next question, I just wanted to really set the stage for this question because I think it is important that here you don't change the wording;

that you use the wording that we have because that is the wording that is proposed by the sponsor. But, I think a yes vote, if the committee will look down below, allows for several options. So, in essence, what we are asking here is any level of yes. In other words, if you are clear that your answer is no, no matter what is done to the labeling or what other kind of Phase IV studies might be recommended, vote no. If you are in any other category vote yes, and then you will have an opportunity to give us advice as to what labeling or other restrictions might be needed, whether only one dose or two doses and what Phase IV studies you might recommend if it is a yes.

DR. FINK: Just a clarification I guess, do we have to consider both products? If we have one product that has clearly higher efficacy with no additional toxicity, I am not sure why we would want to market or approve two different products even if they showed efficacy and safety when you have a product that clearly has better efficacy with no additional safety concerns.

DR. MEYER: I understand your point but we are asking these as separate questions about separate applications and I think we need separate

advice.

DR. DYKEWICZ: A question by Dr. Parsons?

DR. PARSONS: I just have a question about procedure. If the answer is yes but there are Phase IV studies that are recommended, do those studies get completed before the drug gets marketed?

DR. MEYER: No.

DR. PARSONS: Is there a time frame in which they need to be completed?

DR. MEYER: We do agree to a time frame with the sponsors in instances of Phase IV studies. Generally, the kind of studies that are often done in Phase IV, it is two or three years before we get the data in.

DR. DYKEWICZ: Dr. Apter?

DR. APTER: I was just going to comment about Flovent. Some patients will probably use Flovent and Serevent separately. Maybe their insurance won't allow a combination, or things like that.

DR. DYKEWICZ: Dr. Stoller?

DR. STOLLER: Just a procedural question, my understanding is that, obviously, as a hypothetical were it to be approved and were there

to be recommendation for Phase IV studies, and we were two and a half years into the Phase IV studies with clear evidence of higher incidence of fractures in a dose-related way, what implications would that have retrospectively for the indication? In other words, what are the teeth of a Phase IV study from the agency's perspective?

DR. MEYER: In usual approvals -- because there are approvals contingent on a Phase IV study -- it is understood under the actual mechanism of the statute that if it comes out negative you withdraw approval. I think with most of this we would be talking about perhaps very stringent labeling changes.

Bear in mind that in this specific instance these drugs are already on the market and they are, I am sure, being used for COPD now and they will continue to be used for COPD one way or the other after our discussion today. So, I don't think we would be talking about a Phase IV study that would lead us to absolute withdrawal -- certainly the approval, but perhaps not even the indication.

DR. DYKEWICZ: Comment from Glaxo?

DR. WHEADON: Just one or two points of

clarification. I fully respect the vote and the commentary of the committee and we really appreciate the input. I think it is important to note that there are several precedents where drugs have been approved for chronic illnesses. I am a psychiatrist; depression being a prime example of one, where the language can be such that you indicate that the studies were of certain duration. In the case of studies for depression they typically are six to eight weeks duration. So, the labeling clearly can reflect the duration of treatment in the studies that we have presented before you.

Additionally, a number of concerns have been raised by the committee concerning the potential for long-term use. From our perspective certainly, labeling is perhaps the most informative place for physicians to understand what we do know and what we don't know about safety. A number of committee members have sort of been reflecting on just how safe or unsafe these things may be. Clearly, labeling can be a very cogent repository of that state of affairs. I think that is important to keep in mind as we go through the next level of discussion.

DR. DYKEWICZ: Thank you. I guess I would make my personal response that I think oftentimes physicians are remiss in looking at labels and the details in labels. Some of my colleagues have expressed concerns that although one can nuance phrasing in labeling, there still is the concern that when you do give an approval status you have to think that, in fact, physicians won't be reading the fine print. So, that is a consideration.

But just to redirect to Dr. Meyer in terms of the decision about approvability, based upon the statutory language that we are using in our deliberations here, there is the statement that we are making an assessment about substantial evidence of efficacy and safety and, thereby, kind of an implicit assessment of relative benefits versus risks of the drug. So, that is what I am personally going to use in my deliberation but presumably other people will consider that as well.

DR. MEYER: Absolutely. This is the question that really integrates what we know from the efficacy and what we know from the safety, and how you put that together in making your recommendation.

DR. DYKEWICZ: This now is again just

discussion on what your thoughts are about the approvability of Flovent Diskus for the indication of long-term, twice daily maintenance treatment of COPD.

DR. PARSONS: Well, I voted that, yes, it had shown efficacy at the 500 mg dose, but it was a yes, "but" and I thought that there was not adequate safety data. So, I think if I add those together the answer would be no, I would not recommend approval at this time, primarily because of safety concerns, which are not necessarily all that great but the level of efficacy shown also wasn't that great. So, I would err on the side of saying no.

DR. DYKEWICZ: Thank you. Dr. Stoller, your thoughts?

DR. STOLLER: Again, I want to be very explicit in my response to the process, which is to respond to Dr. Meyer's lead that if there is any dimension of yes one has the opportunity to qualify the yes. So, I would say overall yes. I would say that there would need to be very stringent constraints on the labeling regarding the difference between COPD and chronic obstructive bronchitis. I would have to put very specific

language about duration of therapy in regard to what the indication would say, and I do that cognizant of the difference between what it says on the label and how it is used clinically. I live in that world and I understand that world very well, but I think the rules of engagement, if you will, are around the specific endpoints. We are not turning the clock back and saying, you know, could we design the study from first principles. I am sympathetic to the significant amount of work and energy that has gone into trying to evaluate it along those lines.

So, I would say yes, but in terms of long-term for both doses I would have those labeling contingencies on both, and I would say that in Phase IV studies I would absolutely be interested in long-term monitoring, not just on patient-reported data but with regard to the explicit investigation for both bone and ocular manifestations. Given what we know from some of the asthma literature, admittedly what we don't know from the Lung Health Study, and also on a more prolonged examination of survivorship, which I gather will ultimately be forthcoming and which will clearly inform the clinical relevance with

delta FEV1 of 100 or 160 ml. I think all of us, if we were presented with data which showed that there was a 100 ml increment that was reproducible but translated over longer term to no symptomatic benefit, perhaps no survival benefit and a higher frequency of fractures, or even one more cataract, it would be very difficult to clinically embrace the use of these drugs.

So, I would say yes in terms of the overall possibility that there would be benefit, but I would think that yes would have to be very carefully crafted in the labeling around those concerns, and I would have those recommendations on Phase IV monitoring.

DR. DYKEWICZ: Thank you. Dr. Fink?

DR. FINK: I would lean towards saying no with the fact that the relatively modest effect carries with it all of the toxicity and safety concerns, and it would be hard to approve the steroid component alone when you think of the additional benefit with the use of the combination product.

DR. DYKEWICZ: Dr. Atkinson?

DR. ATKINSON: I would recommend yes, but I would also agree with the comments that have been

made previously about specifying that the treatment period for which safety had been shown was only 24 weeks, and that the population that is was most likely to be effective in was chronic bronchitis.

DR. DYKEWICZ: Thank you. I guess I would view a qualified yes, echoing Dr. Stoller and Dr. Atkinson, with some additional consideration about labeling relative to Dr. Bone's discussion earlier about the appropriateness of considering that because the long-term adverse effects of fluticasone and bone density are not well known in COPD patients, are not well characterized in COPD patients, consideration should be made to assessment of periodic bone density measurements. You know, the exact phrasing might be worked out but I think there would be some caution statement that I would put in that would reflect that concern.

DR. APTER: I agree with Dr. Stoller and Dr. Dykewicz, and I would say yes to both doses. I think some patients would use Flovent and Serevent separately. Again, I do think labeling restrictions are needed. I am concerned about the lack of long-term data. Phase IV studies, I agree, should look at both side effects and efficacy

markers like survival, like exacerbations, like prednisone requirements and side effects on bone density findings and adrenal status.

DR. DYKEWICZ: Thank you. Dr. Joad?

DR. JOAD: I know it seems clear I am going to say no but the caveat I think I would like to say is that I think there is potential in both of these products, and my concern is we haven't had the demonstration of them, that they are effective and that they are safe. This is such a large number of patients that will receive it, and they are elderly, and I think now is the time, before you approve it, to show that it really is effective and to show that it really is safe. To me, it would be jumping the gun to approve it now when we could require very carefully controlled studies to satisfy ourselves that it is effective, really changing symptoms, and it really is safe.

DR. DYKEWICZ: Thank you. Ms. Schell?

MS. SCHELL: As to the wording in question five as it is, I still have problems with the wording but I would say yes, and I think the only dose I would approve would be the 500. I would also like to see restriction on labeling, including, as Dr. Bone said, some pretesting on

patients for their bone density and follow-up. Also, I would like to see in the Phase IV studies some pre-exacerbations after they get started on the drug to see if there was a comparison in less frequency, and dose.

DR. DYKEWICZ: Thank you. Now let's take the formal vote on question five, with the provisos that we have. So, do you recommend approval of fluticasone Diskus for the indication of long-term, twice daily maintenance treatment of COPD, including emphysema and chronic bronchitis?

DR. PARSONS: Could I just ask a quick clarification question? Dr. Stoller, I think Dr. Fink and a couple of others, when you are saying yes with specific labeling restrictions, are you thinking of restrictions being yes for 24 weeks in chronic obstructive bronchitis?

DR. DYKEWICZ: I personally was thinking --

DR. PARSONS: I am sorry --

DR. DYKEWICZ: No, that is fine, I think four of us may have been of a similar mind on this -- but that there would be a labeling statement that the studies conducted were of limited duration of 24 weeks. I think, if I am correctly

summarizing, the thought was that we would recommend that Phase IV studies be aggressively pursued about looking at concerns of systemic side effects and particularly bone issues. As I understand it from the charge given to us by Dr. Meyer, if those provisions or provisos or caveats are articulated, if we would then feel we could state yes, then we should vote yes.

DR. PARSONS: I vote no.

DR. DYKEWICZ: Dr. Stoller?

DR. STOLLER: Again, under the rules as I understand them from Dr. Meyer's charge, I would say yes contingent upon all the comments I made.

DR. FINK: No.

DR. ATKINSON: Yes, under the same restrictions.

DR. DYKEWICZ: Yes, with restrictions.

DR. APTER: Yes, with restrictions.

DR. JOAD: No.

MS. SCHELL: Yes.

DR. DYKEWICZ: The formal vote on the Flovent recommendation for approval would be five yes, three no and one abstention.

Last question, number six, do you recommend approval of Advair Diskus for the

indication of long-term, twice daily maintenance treatment of COPD, including emphysema and chronic bronchitis? Let's begin discussion with Ms. Schell.

MS. SCHELL: I would agree to approve this drug with the same reservations I had previously. I would approve both doses with labeling restrictions as well, and a continued Phase IV study with those recommendations.

DR. DYKEWICZ: Dr. Joad?

DR. JOAD: I don't really have anything to add, but I would just like to repeat that I think it is unlikely that people will only give it for 24 weeks, highly unlikely.

DR. DYKEWICZ: Dr. Apter?

DR. APTER: I would vote yes, with the same restrictions and arguments as previously.

DR. DYKEWICZ: I am of a similar mind, yes.

DR. ATKINSON: Yes, as before.

DR. FINK: I would vote yes on this drug, but I would like to see a required Phase IV trial both for Advair and Flovent, if it is approved. I think there should be a required Phase IV dose escalation study to actually provide data on how

many patients would have a suboptimal response at the 250 dose of either drug and have a better response at the 500 dose.

DR. DYKEWICZ: Thank you. Dr. Stoller?

DR. STOLLER: I would say yes, again subject to the same contingencies. I guess I would also perhaps use this as an opportunity to talk about -- I don't see the language about the doubling dose reflected in this commentary and that was, as I remember, Dr. Lee's initial comment, that there was language about doubling the dose for failure to respond. I would say one of the other labeling contingencies that I would create would be to eliminate that as I am not satisfied with the dose responsiveness data and I think that in order to justify that comment it would require evidence that within a single patient, who failed to respond at a lower dose, that there was essentially an inter-patient crossover experience rather than a parallel controlled comparison of two cohorts to show that doubling the dose was justified for non-response to the lower dose. So, I would not be comfortable with language about a higher dose may help in the absence of benefit at the lower dose. So, that is the other qualification of language

that I would apply. I know it is not on the table here because it is not framed in the question, but as I recall it was one of the language indication and I guess I would comment on that probably around both of these doses.

DR. DYKEWICZ: Actually, I am very glad you mentioned that because that would be a concern of mine as well, that the recommendation for dose escalation in an individual patient has not been, obviously, looked at with the data presented. Dr. Parsons?

DR. PARSONS: I have the same concerns regarding this one as I did for Flovent. I would still answer no. I think if Phase IV studies were done they would probably show that this drug is safe. I think that is likely to occur. I think with the limited efficacy that has been shown, it is worth waiting to be sure the drug is safe. So, that would be my recommendation.

DR. DYKEWICZ: Thank you. Now for the formal vote with the rules of engagement that have been articulated, do you recommend approval of Advair Diskus for the indication of long-term, twice daily maintenance treatment of COPD, including emphysema and chronic bronchitis? Ms.

Schell?

MS. SCHELL: Yes, with the stated restrictions.

DR. DYKEWICZ: Dr. Joad?

DR. JOAD: No.

DR. DYKEWICZ: Dr. Apter?

DR. APTER: Yes, with the restrictions and endorsements of Dr. Fink's suggestion for a dose escalating study.

DR. DYKEWICZ: Yes.

DR. ATKINSON: Yes.

DR. FINK: Yes.

DR. STOLLER: Yes, again with the contingencies as stated.

DR. PARSONS: No.

DR. DYKEWICZ: The final vote on question six about recommending approval of Advair Diskus is six yes, two no, one abstention. Are there any final comments that any members of the committee want to make, maybe about stipulations about product labeling, additional safety studies that were recommended, or have you all articulated your concerns previously? Dr. Joad?

DR. JOAD: Was the final labeling going to say chronic obstructive bronchitis? Did we say

that? I thought we had said that with the efficacy part.

DR. DYKEWICZ: Maybe what we should do is get a consensus from the committee, but Dr. Meyer?

DR. MEYER: At the risk of offending folks, I think we heard that, maybe not as a consensus but as a very strong opinion and I think we will take that under very strong advisement.

I did want to make a closing statement. I think I heard some folks earlier talking about framing linguistic "buts." I think we have framed our physical ones here in these seats.

[Laughter]

This has been a very useful discussion. In all seriousness, I thank you very much for all your advice and very careful thought. For our guests, for Dr. Bone, Dr. Wise and for Dr. Malozowski, I am specially thankful for your expertise in these matters, and again thank the committee for their time today.

DR. DYKEWICZ: As chair, I would again like to thank everyone for their attentiveness and for their participation. Have a good evening. We are adjourned.

[Whereupon, at 5:10 p.m., the proceedings

were recessed, to resume on Friday, January 18, 2002 at 8:00 a.m.]

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CERTIFICATE

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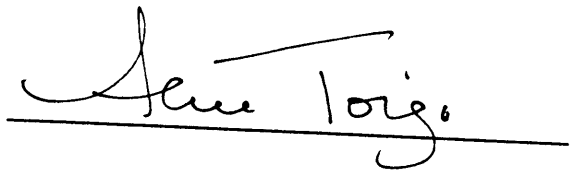

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