We are going to conclude this part of the discussion. We will return at quarter of 1:00. I would like to remind the committee members that discussions regarding the contents of this particular committee meeting should not be discussed during our lunch break.

Thank you very much.

[Whereupon, at 11:47 a.m., the proceedings were recessed, to be resumed at 12:45 p.m.]

A F T E R N O O N  P R O C E E D I N G S

[12:45 p.m.]

MS. WATKINS: Welcome back. As you can see on the agenda, the next item that is listed is the Open Public Hearing, however, we did not have any pre-registered open public hearing speakers, so we are going to proceed with the agenda, but before we do that, Dr. Jones from GSK needs to make a little clarifying statement before we move on.

DR. JONES: Elaine Jones, GSK.

There are a large number of questions that have been raised this morning around the 250/50 strength. I just wanted to clarify that the supplement that GSK has put in to the Agency, and is the subject of today's discussion, is the 5500 strength only.

There is no 250 data in the application and the labeling for the 250/50 strength will not change, and that will only be for the relief of bronchoconstriction. I thought there was some confusion this morning, so I just wanted to clarify that.

Thanks.

DR. BRANTLY: Before we move into the clarifying questions, I just wanted to ask the committee members if there are any further questions of either the FDA or the sponsor that needed to be addressed.

Dr. Gillett.

DR. GILLETT: I am interested in finding out to what extent the company has studied with the 250/50 preparation, how that has fared in nursing homes and other situations where it isn't under as tight a physician control as the study.

By this time they should have some information about that and particularly how it would move from a managed situation in which it is prescribed by a physician to the point where a person is buying it off the Internet and from Canada or wherever and using it in an unmanaged situation. I am particularly looking at that experience to guide us on how this might affect something that might cause an increase in pneumonia among people who are prone to having

pneumonia.

DR. BRANTLY: I would like Dr. Jones to answer, but I have to say that is a little--I think that is a little off the mark regarding, I think the data will be a little slim on that.

Dr. Jones?

DR. JONES: We have seen little in the post-marketing data on the pneumonia. TORCH was really the first study that we actually saw this signal. Dr. Knobil, anything to add?

DR. KNOBIL: No.

DR. JONES: No. So, TORCH was the main purpose of the data set.

DR. BRANTLY: Thank you.

**Committee Discussion and Vote**

Without any other further questions, I think we could go ahead and move into the clarifying questions. Let me begin with the first question. Again, this is the major work of the committee here, so what we will be asking for in each of these questions is a Yes or a No vote or an abstaining, and you will also be expected to

justify your vote.

The first question is: Do the data provide substantial convincing evidence that Advair Diskus (fluticasone/salmeterol inhalation powder) 500/50 mcg increase survival when used in the chronic treatment of patients with COPD?

Let's begin with Dr. Parsons, please.

MS. WATKINS: Before you cast your vote please state your name, so the transcriber can accurately record.

DR. PARSONS: Dr. Polly Parsons. I would vote no. I would substantiate it by although the p-value is close, that is not all I am taking into consideration. I am concerned that not only is the p-value close, but also when you look at the data that was shown by the FDA group, comparing the Advair results to salmeterol, it is not clear that there really is any impressive survival benefit above and beyond what is already available and is highly considered on the market.

So, that is what led to my conclusion of no.

DR. BRANTLY: Dr. Prussin.

DR. PRUSSIN: I would vote no. The marginal p-value, the fact that it is a single study where the endpoint is hugely important, probably needs more weight. Also, the fact that in the U.S., the population did not seem to respond with that same magnitude of survival.

DR. BRANTLY: I have been reminded that we might want to build a little discussion around this as we are talking about it.

Given this particular question, what discussion do we have on this particular issue?

Dr. Schoenfeld.

DR. SCHOENFELD: I have a couple of sort of observations on this. First, it always amazes me that we have all these discussions on subset analyses when we have no statistical sort of tests at all which would indicate that we should treat the subsets in any way different from each other.

So, there is no significant interactions here, nobody has even made the suggestion that there is a suggestion of an interaction. An

interaction would that is a statistical test p equals 0.05, 0.1, 0.2, that, in fact, the U.S. population is different than the European population, that, in fact, patients who are at high risk are different than patients who are low risk in terms of the effect of this treatment.

There is no basically statistical test that shows that this is the case. It is kind of interesting that we make a big deal about p equals 0.052 versus p equals 0.05, and then we go ahead and have all kinds of discussions about things that might very well be completely due to chance.

So, I think that the argument about consistency, robustness, and so on, relative to subset analyses, I find very, very strange, and I kind of basically ignore. That would be the first point I would make. I don't think they are really very interesting analyses.

Now, in terms of the difference between the salmeterol, the other interesting question I think is whether we are talking about the comparison of the combination to salmeterol alone.

I took some notes on this.

What it seems to me we have is that for mortality, we don't really know whether the steroid fluticasone is necessary in the combination, because we don't have a strong signal that the combination is better than salmeterol alone.

The data that would support that assumption is data in the other endpoints, that is, with exacerbations and FEV, the combination does appear to be better than the combinations alone. So, I guess that issue, which is I think an important issue, sort of you have to decide whether or not you can extrapolate from these other things to the mortality question.

That extrapolation is made a little bit more difficult by the fact that the side effect that may be working against the mortality improvement is probably a side effect that has to do with the fluticasone, at least from a mechanistic point of view.

So, that is sort of my perspective on that.

Polly? I will pause.

DR. PARSONS: The reason I was actually using the salmeterol comparison is understanding that statistically it may not have been powered for that, and I understand that, but my biggest concern is that the comparison that we can make statistically is to placebo, and placebo is no longer an adequate treatment for this patient population.

So, that doesn't exist anymore, I mean placebo isn't what we do for those patients, so I was trying then to say is there any way we can make any comparison from this study to what would be considered close to standard of care or some semblance of close to standard of care, because I think that's, you know, it's difficult. We have seen this in other studies that you and I participated in. Things change over time, medicine changes, and you just can't do clinical trials fast enough to keep up sometimes.

But unfortunately, the comparison group of placebo is not a comparison group that we can use

in this day and age, so it doesn't exist right now.

DR. SCHOENFELD: What is standard of care? As a statistician, I am ignorant of that currently for these patients. Assuming not counting Advair as standard of care, because that is sort of is being tested, but what is standard of care if they are not using Advair, is it salmeterol alone, or is there a standard of care?

DR. MOSS: I will put myself out on a limb here. Marc Moss. Just going by the GOLD criteria, you know, a bunch of people sit around a room, smart people trying to do the right thing.

If you look at the inclusion criteria for this study, the first line of therapy would be bronchodilator therapy and possibly long-acting beta agonist therapy with one of the compounds in this drug, and if they don't do well with that, it would be recommended to prevent exacerbations, what it says in the GOLD criteria, to add an inhaled corticosteroid.

So, I think most people--and, please, correct me if you feel differently--would feel that

bronchodilator therapy is a reasonable therapy for people with this degree of COPD.

DR. EISNER: This is Mark Eisner. I would agree with that except to say that there has never been any indication that bronchodilator therapy improves mortality, so if we are looking at mortality as an endpoint, I actually think the placebo is a reasonable comparison because we don't have any medications that improve mortality right now that are approved for use.

DR. BRANTLY: Dr. Reiss.

DR. REISS: I was just going to pose a question actually to the Agency, because this morning it was asked of the sponsors what their concept of a robust result was, and the Agency said that they would accept a robust result and then described what they observed, but really didn't say what they would consider a robust result to be.

I was wondering if that would help the committee in their thinking.

DR. BRANTLY: Bob.

DR. MEYER: This is Bob Meyer. I will try

to tackle that as best I can. First of all, in terms of the language in the question itself, in 1962, when the Food and Drug and Cosmetic Act was amended to put in an efficacy standard, because up until that point, drugs were reviewed just for safety, that standard referred to adequate and well-controlled trials with an "s," which we have always taken since that time to mean that you needed to have statistical findings in more than one trial, two or more trials, to provide substantial evidence of efficacy.

More recently, Congress did put into a revision of the Food, Drug, and Cosmetic Act, the possibility of having a single trial serve as the basis of substantial evidence, but that would be predicated on much evidence leading up to that to allow you to sort of do a Bayesian analysis, if you will, to look at that single trial and say yes, this makes sense with everything else.

If you don't have a lot of that antecedent data, then, I think particularly for something like a mortality trial, where it is indeed hard at times

to do multiple trials, then, the Agency looks to what we might call a robust finding, and that would be I don't think we can give you--I could give you a single number, because it is going to be somewhat situational, but generally, we are not talking about even a p of 0.05. We are talking about something lower than that. 0.01, in some cases, maybe even something like a 0.0025, which statistically it is very similar to doing two trials of 0.05 and winning them both.

So, I don't think there is a single answer from the Agency's standpoint, but in this case, we had in mind something more striking than a 0.05.

DR. BRANTLY: Dr. Newman.

DR. NEWMAN: To follow up on that, what the FDA provided us with included a document, which is this guidance, providing clinical evidence for effectiveness guidance, and I read that with interest.

In particular, you know, you get on page 12 and 13 where it articulates the situations in which a single trial might be used. It is a little

fuzzy, but it does say, uses the timolol example, looking for a low p value, and, in fact, says that without saying what a low p value is.

The other thing that I thought was interesting about that, the reasons for doing a single study were, I thought, important in this context today.

For example, the notion that a second study would be impractical or unethical, or otherwise impossible to do, a question to you in follow-up on this, do you, the FDA, think that it is impossible to do a follow-up study focusing on an endpoint that includes placebo, now that this has been published, is there actually a position that you have, based on the data?

DR. MEYER: I wouldn't say that we have given that specific question thought at this point, but I think if one is not convinced that this statistical finding is absolutely meaningful, then, you are not really moved off of equipoise.

So, from a very strict sense, I don't think it would be unethical to go back and

reexamine this question including placebo. From a practical standpoint whether you can do that I think is another matter.

DR. BRANTLY: Dr. Vollmer next.

DR. VOLLMER: I have got several issues to chime in on here. I would echo the concern about subgroup analyses. They inevitably have less power than do main effect analyses, and so that limits their utility.

It has been interesting that they have actually been argued both ways on the FDA side, pointing out differences in our materials for some subgroups, it seems apparently, less favorable, and on the sponsor side, arguing that we don't see any significant differences.

The same nonsignificant trends are in one way looked at it as being not statistically significant, and in another way looked at as trending towards something else, so it does get into lots of problems.

If we start getting into what is the right comparator, is it versus placebo, is it versus

salmeterol, I would throw out that we probably need to be talking about if we are going against an established drug that is out there, then, you are probably not talking about the conventional trial to see whether something is superior, but you are probably not going to an equivalence trial, which is a whole separate situation, and we have a set of analyses now that are presented for superiority trials, so that complicates things.

That brings me to I guess my main issue for the FDA here is as I look at the questions and try to understand how I am meant to respond to the questions, given that Question 3 specifically addresses the question of salmeterol and do we see any advantage over that, it leaves the implication that what you are asking us implicitly is, in Question 1, is it better than placebo, because unless you are clear with us as to what the comparator is meant to be, it is hard for us to answer that question.

So, I would turn back to you and ask what was the comparator meant to be for Question 1.

DR. MEYER: That was certainly the pre-specified comparison would be the combination product against placebo, and that is what we accepted, and that is what is intended then in Question 1.

DR. BRANTLY: Dr. Schoenfeld.

DR. SCHOENFELD: I would like to briefly comment on the need or lack of need for two studies. On page 10 of the guidance, which we put in our books, which I should I guess quote the source of the guidance. It is the guidance for industry, providing clinical evidence of effectiveness for human drug and biological products.

On page 10, it says, "Studies of different clinical endpoints," and it says, "A demonstration of a beneficial effect in different studies on two different clinically meaningful endpoints could cross-substantiate a claim for efficacy for each outcome. For example, the initial claim for effectiveness of enalapril for heart failure was supported by one study showing symptom improvement

over several months, and the second study showing improved survival in a more severely ill population. There were two different findings, each from an adequate and well-controlled study, led to the conclusion that enalapril was effective in both treating symptoms and improving survival."

So, in a certain sense, that sort of kind of argues against the need for two studies in terms of exacerbation and survival, and we were presented with basically two studies. So, I don't think that is the main issue.

The main issue I see, and it is sort of a little bit of a difficult one is we have sort of set a standard of 0.05 as the conventional standard to use for making these decisions, and we didn't quite hit it.

I think that in a way, it sort of resolves around that, which is how good is the standard, should we stick to the standard, what do we do in situations in which the standard is very close to being met, but just not quite, and how do we interpret that especially in situations where it is

very expensive to repeat the study.

In other words, if it was a 50-patient trial that could be easily repeated, we might say, oh, maybe you should try it again. Unfortunately, to repeat a trial where the p-value is very close to 0.05, you actually have to double the number of patients in the repeat trial, because if you aim for the difference that gave a 0.05 p-value, then, half the time you will get the 0.05 p-value and half the time you will get something less than 0.05 and half the time you will get something more than 0.05, and your power will be 0.5.

So, to repeat the trial, you need to do a much, much bigger trial. If it was a 50-patient trial that we were going to repeat with a 100-patient trial, we would just say go ahead and do it. If it's a 3,000-patient trial that we are going to repeat with a 6,000-patient trial, it's a little harder.

So, I think that is really the most salient issue that is this sort of rule of 0.05, which was sort of a Fisher's aside. Fisher said,

"Well, you know, say 0.05," and sort of we then reified it, and you can argue in favor of that reification on the grounds that it sort of served us well over the last hundred years, but on the other hand, we don't really know how we would have done had we used a different criteria.

DR. BRANTLY: Dr. Vollmer, do you have any comments, because I believe that the point that Dr. Schoenfeld has brought up is critical to this particular question here?

DR. VOLLMER: I guess I would weigh in for myself that there is nothing magical about 0.05, I would absolutely agree with that, and at the end of the day when I assess things, I try to take in the totality of information.

It's a slippery slope. You can go down and then all of a sudden it creates lots of problems and pretty soon as you marginalize here and there, your nominal p-value in practice gets to be a heck of a lot bigger than 0.05, but I wouldn't have any particular qualms in this case about saying it's 0.052 versus 0.05 given the

substantiating evidence, I think that is fair game personally.

DR. BRANTLY: Dr. Prussin.

DR. PRUSSIN: I just wanted to point out that this drug, it is not just a statistical or scientific question. This drug is commercially available, COPD is already on the indications on the package label, and so what we are debating is not whether this drug is going to be available for these patients, but more specifically, the package insert and how is that going to recommend and the impact of that.

So, I think it's a broader question than just what has been, you know, scientifically proven, and again, what level of rigor that scientific proof.

Some of these indications are a little softer and don't have as much weight, but when you tell a patient this drug on the package insert says you are going to live longer, that has a huge impact compared to something that says, well, it is going to make you have fewer exacerbations or have

a better airflow.

So, I think part of the weight of decisionmaking and the stringency of the p-value has to factor that in. It is not just all statistics.

DR. BRANTLY: Dr. Newman.

DR. NEWMAN: I think that is really well said and as you were speaking, I was highlighting one sentence from the guidance document that we have been quoting from, and it is on page 13 where it says, "Reliance on only a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality."

That is just one part of it, but a clinically meaningful effect on mortality, and it's backing up the point that we don't want to be foolishly consistent with a p-value cutoff, but we really want to address in terms of what is clinically meaningful, what we say to our patients about what this is going to do to their life span. I think that is what really feel like the question

is to me on the mortality issue.

DR. VOLLMER: Again, going back to that guidance document, it also points out, though, that--and I think, Dr. Meyer, you also alluded to it--that times have changed and when the policies were written, you didn't have these huge multicenter trials that had people from all over the world, and they were essentially one big trial that was a series of multicenter trials, if you will, and it gives one the opportunity in terms of generalizability to look at what happens.

It is actually interesting as I read the documents that the FDA's take on the robustness of the findings and the stability of the findings was somewhat different from the sponsor's. I actually was somewhat more impressed with the sponsor's presentation of seeing the general tightness of that response as you took out one center after the other one, but that does give you some measure of extra consistency, and so I think that we are not wedded to the one trial only. We do have a large trial. We have a huge representation.

At the same time, I don't know how the FDA deals with this, which makes me also harder to respond to the questions, but there are clearly some differences, as I think documented.

I don't think anybody is going to argue with how patient care happens in this country versus some other countries that were part of the trial, some of the patient mix issues, and the extent to which it is important for the FDA in making decisions in what they want from us is to try to gaze into a crystal ball that we don't necessarily have to say what would happen in the U.S. population versus a different population.

I would like some guidance as to what you are looking for from us in trying to interpret that.

DR. MEYER: I have been trying to think of the best way to address that, because I think that to a large extent, first of all, I would just say that what we are looking for from you all is your expert opinions and we will take your advice and put it into the regulatory context.

So, we are not necessarily looking for you to take on the role today of regulator for a day. You are here because of your scientific expertise, and we will take the advice and put it into our own context.

I think that there is a number of reasons to look at subgroups, understanding that you may not be able to make inferential statistical statements about them, but in a single trial, one of the things that one might find as more convincing or more evidence of the robustness of the trial is consistency across different groups, across different measures, and so on.

So, that is what we were looking at in terms of some of the subgroup analyses that we undertook. I must say while there is some differences between, say, the findings in the U.S. population here and some of the overseas population are all non-U.S., they are not as striking as differences we have seen in some large multinational trials where, in fact, you will find in some cases no effect in the U.S. population,

absolutely none, and all this coming from the overseas site.

I think that is a different sort of conundrum for us, but back to the question. I think what we are looking for is just your best assessment as to whether this single trial, taking into account what the p-value was, and maybe you want to disregard the standard of 0.05 or not. That is up to each and every one of you.

But whether this single trial and its results, taken in context with the other trials presented today, does provide enough substantial evidence to label the drug specifically for, in the case of this question, for survival, an effect on survival.

DR. BRANTLY: Dr. Eisner.

DR. EISNER: Yes. I think we have been spending a lot of time talking about the chance issue and the p-value issue, and, for me, whether it's 0.05 or 0.052 or 0.01, I think is less of an issue than the bias issue, which we haven't spent much time talking about.

I think there are at least two issues that concern me. Number one, there were a lot of dropouts and they vary by treatment group. There were many more dropouts in the placebo group than in any of the active treatment group.

The sponsor makes the argument that that is going to be a conservative bias, but I think that is an assumption that is essentially untestable and unprovable. For example, in the Advair group, if patients developed pneumonia at a higher rate and were dropping out because they had pneumonia, it could actually lead to an overestimate of the treatment effect.

I think the second concern I have is the definition of COPD exacerbations. We are not as tight as they could be, not based on objective criteria in all cases. There is a huge amount of variability in the duration, in the types of things that were classified as exacerbations.

Now, that could all just be noise that is equally distributed among the four groups or there could be something more differential about that,

that could lead to bias.

So, I think that we should at least spend a little bit of time talking about whether those are serious concerns or not.

DR. BRANTLY: Dr. Stoller.

DR. STOLLER: I guess I would like to say a couple of things along those lines. One is I have great appreciation for the magnitude of this trial and the difficulty of conducting it, so I think that shouldn't go unsaid here.

One of my concerns along the same lines around the understanding of survival impact is the analysis of data around other clinical interventions that have been shown to have survival benefit, namely, smoking cessation and supplemental oxygen.

I assume few of these patients had lung volume reduction surgery, which is some contexts would be considered yet another survival enhancing intervention.

So, I think in the assessment of the robustness of the survival benefit, my attention is

less on whether it's a single study, perhaps even less on a p of 0.05, but on the methodologic solidity, if you will, of the understanding of survival impact in the absence of understanding the impacts of these other co-interventions, which have been discussed today, and are clearly well recognized to impact survival.

For example, one could see biases going in both directions. If, by chance, recognizing the statement that few of these patients had stopped smoking over three years, but if, by chance, the number of patients who had stopped smoking were disproportionately distributed among the Advair recipients, that might help explain a difference in survival that would otherwise be ascribed to the use of the study intervention.

Similarly, if there were maldistribution in the prescription of supplemental oxygen for patients who became hypoxemic over the course of three years, which would absolutely be expected in a cohort of these baseline demographics, that, too, could have a confounding effect on our

understanding of the impact of the intervention.

My reservations in understanding the survival benefit have to do with the methodologic understanding of the analysis of the results independent of the multiplicity of trials with a p value. Those are additional issues that we have been grappling with, but represent a separate source of concern.

DR. BRANTLY: Dr. Schoenfeld.

DR. SCHOENFELD: I think one of the issues is that people tend to overinterpret differences. So, the difference in the dropout rate between placebo and treatment I think was something like 30 percent versus 40 percent or 40 percent versus 50 percent.

It is really only 10 percentage points. That is, 30 percent of the people dropped out under both treatments. Most of the dropouts, I think three-quarters of them or maybe more, because I don't have the numbers on my fingertips, would have dropped out under both treatments.

So, I think that there is a tendency to

overinterpret that particular cointervention which is dropping out, but by and large, most of the dropouts were uncommon, so I think you have to remember that, not simply that it was statistically significant the difference in dropout rates, but rather that there were a lot of dropouts in both treatments.

Assessing the effects of cointerventions is very, very difficult because the cointerventions are confounded, that is, interventions that occurred later in the trial are confounded with the treatment effect, as well.

So, it is sort of interesting, but really impossible to analyze whether the survival effect was modified or mediated by people stopping smoking, or people going on oxygen, or people dropping out, which again you can consider it kind of as a co-invention.

That is why I think we tend to try to look at these intent-to-treat trials. So, that is sort of the rationale behind intent to treat. The place where intent-to-treat didn't work was with

exacerbations. I think that is sort of an additional issue, that is, exacerbations are only measured while people are on treatment. It was apparently impossible to do an intent-to-trial there, at least it wasn't done.

So, that is sort of a problem and if, in fact, it was true that the placebo rate of dropouts was twice the treated rate or three times the treated, you know, if there was a real huge difference, that would be very worrisome, but it is not so worrisome when the difference is not that great, albeit statistically significant.

DR. BRANTLY: I would like to go back to the question that Dr. Stoller brought up again regarding other therapies. Embedded in that question suggests that there might be some bias to one group or another in any particular therapy, and I wanted to open the question.

Is there any suggestion, any reason why you might think that, for instance, oxygen therapy, or, for instance, even something like tiotropium or something like that might be in one group rather

than another group given that this is a blinded study?

DR. KNOBIL: At the break, we were able to see how many patients in each treatment group went on to oxygen, and it was the same. It was 5 percent in each treatment group. So, we really didn't see a difference, as I mentioned, in smoking cessation or in oxygen therapy in any of the treatment groups. It was low and very similar between the treatment groups.

DR. JONES: I am sorry. I just have one quick clarification, too. The 5500 strength is not approved for COPD. The only strength that is approved for the use in COPD is the 5250 strength.

DR. BRANTLY: Dr. Stoller, would you like to discuss this further?

DR. STOLLER: No, just one clarification. I take the point that this goes beyond the intention-to-treat strategy, and I take the point that the numbers of patients prescribed supplemental oxygen were equal in both groups.

It begs the question how many patients

actually were appropriate candidates to receive supplemental oxygen in both groups, not how many patients actually did, because as a practicing clinician, I can tell you that there are many patients that I see in my clinical practice who satisfy absolute criteria for prescription supplemental oxygen, who do not actually have it.

If that number were differentially maldistributed between the two groups, it would not ablate the concern that I have about cointerventions, recognizing that it goes beyond the intention to treat, and so on.

I take the point, I think it is well said, but it does materially affect our understanding of the survival impact when, in fact, there are interventions that are known to affect survival, that are not accounted for in the analysis.

DR. BRANTLY: Any further questions? Dr. Vollmer.

DR. VOLLMER: Just in response to that, in terms of baseline characteristics, whether you have it or not, given the size of the population, it

would be extremely unlikely that you would see a marked imbalance, so it would be unlikely to be a confounder.

MS. THORNTON: I am just curious. We talked about other therapies, but did any of the patients, were they involved in any other type of pulmonary rehabilitation at all other than supplemental, but any type of formal pulmonary rehab as they were going through this?

DR. KNOBIL: No.

DR. BRANTLY: In case that couldn't be heard for the recording, it was no known therapies regarding pulmonary rehab.

If there are no further questions, I think we would like to restart the voting again beginning with Dr. Parsons again, if you want to restate your vote.

DR. PARSONS: I still vote no.

DR. BRANTLY: And for the same reasons?

DR. PARSONS: Yes.

DR. BRANTLY: Dr. PRUSSIN.

DR. PRUSSIN: I still vote no, same

reasons.

DR. BRANTLY: Ms. Thornton.

MS. THORNTON: My vote is no.

DR. GILLETT: No.

DR. NEWMAN: Lee Newman. I would vote no and for the reasons that have been stated. Maybe I am a little hung up on the--I am not hung up on the p-value--but I am hung up on two concepts. One, the concept that it should be statistically robust, and secondly, that it should be something that is clinically meaningful, clinically important.

DR. MOSS: Marc Moss. I would say no for the similar reasons that have been mentioned.

DR. STOLLER: Jamie Stoller. I would say no.

DR. EISNER: Mark Eisner. No.

DR. SCHOENFELD: I would say yes. I think this is a tough decision and I must say that I can't really comment on the clinical--whether this is a meaningful clinical difference or not, that is beyond the level of my expertise, but I think that the evidence, when you take the survival

difference, which is very close to our reified 0.05, almost right on it, and the fact that other things line up would make me say that probably that it does impact survival beneficially compared to placebo.

DR. VOLLMER: I would say no although I must admit that I am pretty close to being on the fence on this. My main reason for saying no is my interpretation based on the documents that I have gotten from the FDA, their definition of robust, and it doesn't seem to meet that strict a standard.

DR. BRANTLY: Mark Brantly. I vote yes and the reasons why I vote yes is that I believe that the statistical standard is really met, and particularly the clinical standard, and support including the $FEV_1$ rate of decline is consistent with an expected survival increase.

MS. WATKINS: The total are 2 Yes, 9 No.

DR. BRANTLY: Let's move on to the next question.

That involves a 1(a) part, which is: If not, what additional data would need to be obtained

to meet the evidence that there is a survival benefit?

Discussion around this point?

DR. PRUSSIN: So, not survival, you just said survival benefit?

DR. BRANTLY: Where there is a survival benefit, that's right, around the question of whether there is a survival benefit.

DR. MOSS: Mark, you mean increased COPD exacerbations?

DR. BRANTLY: No, it's 1(a). I am sorry. Maybe I didn't make that clear enough. Do I need to restate it again?

Part 1(a) of this particular question is related to 1. If you voted no, what additional data would be necessary to support the claim of survival benefit?

Discussion? Dr. Moss.

DR. MOSS: I would go back to what Mark Eisner said when we were talking about what is the right control group, and I understand that there is no data out there that bronchodilators, beta

agonists improve outcome, but they are what are used in clinical practice for these patients, and therefore, if that is sort of the standard of care based on other outcome variables, I think that is a reasonable comparison group to see if the addition of inhaled corticosteroids is beneficial to patients on bronchodilator therapy. I am being vague about the bronchodilator therapy as I don't want to get into, at this point, specifically what that should be.

DR. BRANTLY: Let me just try to make that just a little bit more concise.

So, to determine whether there is a benefit or not, you would recommend specifically collecting what data, under what kind of format?

DR. MOSS: I really do appreciate what David Schoenfeld said about cost of studies and time to do larger studies, you are not talking about doing an additional 10 people, the effect size between these two drugs and whether it is an efficacy trial or a true, looking for statistical difference will be different depending on how the

study is designed.

But I think it gets back to what has been talked in other forums about what is the standard of care, and to me, the standard of care for these patients is that they should be, at this level of pulmonary dysfunction based on their $FEV_1$, should be on bronchodilator therapy with beta agonist, and not talking about cost effectiveness here, on a long-acting beta agonist, and I think that would be a more reasonable control group.

To me, the question is does this drug compare to placebo. To me, I realize it's the way the study was set up, and I appreciate the FDA and the sponsor's understanding of that, but I think the question is do the two drugs work better than one of the drugs alone, to me is a much more robust study to be done.

DR. BRANTLY: Other thoughts? Dr. Parsons.

DR. PARSONS: I think the other comparison that would be incredibly helpful is in light of the data that suggested that there was an increase in

infectious complications, not only in the Advair group, but in the fluticasone-alone group potentially. Again, we are getting into subgroup analyses, but if we can find a mortality benefit with Advair, if we could see at the lower dose 250 versus 50 also confers a benefit, may decrease the complication issue.

So, I think a comparison of 50/50 versus 250/50 with placebo group that represents patients being treated in a fairly regimented way based on GOLD criteria, which will be hard in an international study, but I think doable, would give you a much better study.

DR. BRANTLY: Dr. Prussin, did you have a question?

DR. PRUSSIN: No.

DR. BRANTLY: Dr. Vollmer.

DR. VOLLMER: I would concur that given the data that we have currently from TORCH, it would be very difficult, in fact probably impossible, to launch a similar placebo-controlled trial.

If I was sitting on my IRB, I would say it was unethical to do that given the other evidence. Whether or not it is for mortality, it is just another benefit for having some sort of therapy for these people.

Given that that is likely not to happen--and that would have been the evidence that I would like to see, some sort of replicative trial if the comparator is placebo--it seems to me a better solution, I don't know if it's feasible in terms of the way labeling goes, but to indicate that the product, the evidence is suggestive of a mortality effect, my hesitancy is really going out and seeing if there is clear-cut evidence for it.

I would have very little qualms about referring to a suggestive effect, that I think there is enough of positive benefits that it is going to be a positive drug to be using for other reasons.

DR. KNOBIL: I just want to clarify that patients were not only given a placebo inhaler. They could take any medication for COPD except for

the ones under study including long-acting bronchodilators, inhaled corticosteroids, and long-term systemic corticosteroids, so they could be on beta agonists, short-acting beta agonists, beta agonists combined with ipratropium, ipratropium alone, theophylline, mucolytics, whatever.

So, while it may not be what you have stated in the GOLD guidelines, they were allowed to take other medications.

DR. BRANTLY: That is important information to know about. When you are matched with placebo, we think they are taking nothing.

Other comments?

I would like to go around the room and just again, in a bullet, say what suggestions you might have for a design that might either meet or refute the benefit.

Dr. Vollmer.

DR. VOLLMER: Again, I would just say that if the question is the placebo as a comparator, recognizing what Dr. Knobil just said, I don't see that you are going to launch another successful

design. I have given what my statement would be. I would just clarify in the labeling that it is suggestive, because I don't think there is going to be another design that is going to answer this question.

DR. BRANTLY: Before we go any further, I would like to ask Dr. Meyer to address that issue about whether label can be, yes or no, it can be suggestive.

DR. MEYER: The standard for putting something in the labeling, and I can't swear that this has never been gone against, or acted against, but the standard is substantial evidence for anything in the labeling.

DR. BRANTLY: Seems reasonable.

Dr. Schoenfeld. You answered yes, but--

DR. SCHOENFELD: I think one of the reasons I did answer yes is that, you know, of course, whatever you decide, whatever you see there is always uncertainty, so in a way, one of the criterias for how you decide something is whether, in fact, you could get more certain with other

data. If you can get more certain with other data, that you could develop, then, you are more likely to say, well, my uncertainty leads me again something.

If you can't find out anymore, then, sometimes you just have to make a choice with what data you have, and it seems to me that I agree that it would be very hard to repeat this trial given its current results.

In terms of comparing the salmeterol alone, I believe that is Question 3, and I think we have to answer Question 3 separately.

DR. BRANTLY: Dr. Eisner.

DR. EISNER: I think to address the issues that have come up in the discussion, it would have to be a larger trial to satisfy the smaller p-value that people seem to want, and I think there would need to be fewer dropouts, if possible, and more protocolizing of cointerventions with other COPD medications, smoking cessation, other cointerventions to the extent that they can be made more uniform, I think the results would be more

convincing.

DR. BRANTLY: What would you recommend as the study arms?

DR. EISNER: I still think that the basic design of placebo versus--I think the basic factorial design is what is still needed, but I think I would power it to detect each cell against each other, so, in other words, Advair versus the components.

I realize what we are talking about is probably an enormous sample size, it may not be feasible, but if what I am hearing from the group is that it is the way the discussion would go next time around, I think that is what will be needed.

DR. BRANTLY: Dr. Stoller.

DR. STOLLER: Well, regrettably, I share the view that repeating a study would be difficult, if not impossible. Let me clarify that I don't think that on the basis of equipoise about efficacy and survival, but around the practical realities given that TORCH data are published and people have an impression around the other potential published

benefits.

That said, if I review the robustness criteria they have been offered, recognizing what Dr. Meyer said about the room for interpretation, I regrettably don't regard these results as statistically robust, and if one takes the condition of safety findings not altering risk/benefit, I think that a study would probably have to address either a separate study, larger number, and also have a 250/50 comparator around the issue of risk/benefit ratio on complications at the 500 mcg dose.

Having said that, i regrettably recognize that doing that may be nigh impossible, and I say it with some sympathy for the recommendation, but I can't get around that.

I would also like to see again, recognizing Dr. Vollmer's point about the unlikelihood of differences between the two compared groups given the comparableness at baseline. I think we have all seen, you know, I think we believe in the reification of a randomized

controlled trial, but we have all seen how distributions and characteristics downstream from baseline, that in my view require an assessment in TORCH, in 3003, of an assessment of how many patients became hypoxemic and were or not treated with supplemental oxygen, and how many patients achieved smoking cessation in both groups. So, that would be retrospective analytic data that would help inform my level of confidence in the results notwithstanding, taking your point about intention to treat and the unlikelihood of that event.

I think we would be remiss in not wanting to see that given what we know about the efficacy of these other interventions.

DR. BRANTLY: Dr. Moss, could you restate one more time?

DR. MOSS: I basically agree with what other people are saying, Mark, and I agree with what Jamie said, what people are going to ask for maybe can't be done, but I think there is enough concern about the robustness of this trial that, as

Polly said, comparing the different doses I think would be important, having a more regimented standard of care control group.

You don't have to worry about defining the outcome variable in this part of the study. I think that will come up with the discussions on the second question. I really agree with what other people are saying.

DR. BRANTLY: Thank you, Dr. Moss.

Dr. Newman.

DR. NEWMAN: I agree with what other people have been saying here. I think there are just two things that I wanted to mention. One is it doesn't take away from the fact that this was a rather substantial and heroic effort to conduct a study like this.

I also just want to take a minute to comment that I think that the presentations that we received today, in particular I want to compliment the GSK people for giving us, in fact, a rather clear articulation of what this study was about and what the data show.

That being said, it doesn't change my view on this particular point, that I can't see myself saying to a patient take this drug, it is going to make you live longer.

I do think that it is probably an impossibility to imagine the study being done on a larger scale to just answer that one question.

DR. BRANTLY: Thank you, Dr. Newman.

Dr. Gillett.

DR. GILLETT: I agree with that statement. It is a very difficult situation, but I think that they do have to get more data comparing particularly the 250/50 and 500/50, at least at that point.

DR. BRANTLY: Ms. Thornton.

MS. THORNTON: I agree with the comparison for 250/50 and the 500. Definitely need it.

DR. BRANTLY: Dr. Prussin.

DR. PRUSSIN: Two things. One in relation to what Dr. Newman mentioned. I would be fine with the physician telling a patient, look, these are what the data are, this is what this paper shows,

but there is a difference between that act and our codifying this in terms of what downstream could become essentially policy in a package insert. So, that is the difference between a single research paper and what we are doing with that. They are very different endpoints.

The second is in terms of this larger study that we are talking about, I would obviously want to try to simplify and have the minimal number of groups, and as we keep adding different groups, and I think you do want a 250 and a 500 group, but perhaps you don't need a fluticasone by itself group, and people have mentioned the different components.

I think at this point, salmeterol is pretty close to standard of care. I see why people are talking about placebo and arguing for placebo, but I don't think there is as much strong an argument for fluticasone by itself anymore.

DR. BRANTLY: Dr. Parsons.

DR. PARSONS: I agree with all that has been said. I think this was a huge trial. I think

based on the literature that is out there, there will be numbers of patients that get put on this medication, so it is not going to stop that necessarily, but I agree that codifying is concerning based on the data we have.

I would like to see a study done again, which probably won't happen, because I understand all the difficulties with that. I think it should include the 500/50, the 250/50, salmeterol if possible, and then the placebo group will have to be, as Dr. Eisner described it, a fairly well-protocolized group that reflects sort of the current considered standard of care. Probably it was based on GOLD's guideline.

Now, that's a huge trial and I am sure there is a way to sort of maybe eliminate one of those groups, I am not sure which one to eliminate, however. It would be nice to get it down to three arms, that certainly would make it smaller, maybe the placebo arm is one that could be eliminated. I would be reluctant to eliminate any of the others.

DR. BRANTLY: For myself, as I answered

yes, and I made suggestions.

Next question is Part B of the same major question. Is additional dosing information needed, e.g., efficacy of Advair 500/50 versus Advair 250/50?

Any discussion around this first?

DR. MEYER: I was just going to comment. A lot of folks I think already spoke to this point. Not meaning to cut off conversation, but certainly we have heard a lot of advice back on it. If anybody else has something to add, that's fine, but I have heard a lot of people already address this.

DR. BRANTLY: Dr. Vollmer.

DR. VOLLMER: I would just say that while I think many of us would like to see such a comparison, I would categorically say it is not needed to answer the Question No. 1, which is again versus the placebo group, so that is what you are wanting to go ahead and you are wanting to answer the mortality question against placebo, I don't see that relevant whether you are asking the question

is it better than the other product, that is a whole separate issue, but I can't see how it relates to Question 1.

DR. BRANTLY: Okay. Let's move on to Question No. 2. Do the data provide substantial convincing evidence that Advair Diskus (fluticasone/salmeterol inhalation powder) 500/50 mcg provide a clinically meaningful decrease in the incidence of COPD exacerbations when used in the chronic treatment of patients with COPD?

First, let's have some discussion. Dr. Parsons.

DR. PARSONS: I think one of the issues that confounds this question for me this sort of difficulty in defining an exacerbation and the variability of that definition between the two trials that were used as the pivotal ones for this.

I have difficulty, although the results are statistically significant, I have a lot of trouble trying to compare the two trials and putting them together in terms of, like I say, the definitions are just so different and I don't quite

understand why they were so different because they were fairly clearly defined in the first trial and they got a little more nebulous in the second trial.

I think clarity and consistency across would have been helpful to really understand how consistent this finding is.

DR. BRANTLY: Other discussion?

DR. EISNER: I totally agree with you, but despite that, the results were actually remarkable consistent at least for the Advair versus placebo, which does reassure me that it probably is a real result.

I mean there is clearly a lot of noise in the definition of an exacerbation, but we haven't heard any evidence that it is a systematic bias, in other words, that the definition of an exacerbation would differ in a placebo versus the fluticasone versus the Advair group.

As long as it's just randomly distributed among the four groups, all it should do is decrease the statistical power and precision. Given that

there are statistically significant and seemingly clinically significant results, I actually think we are on safer ground with the exacerbation question than we were on the mortality question.

DR. BRANTLY: Other discussion?

Okay. Let's go around the room and vote then. Let me begin with Dr. Vollmer.

DR. VOLLMER: I would answer yes, I concur with the rationale that Dr. Eisner gave.

DR. BRANTLY: And your reasoning?

DR. VOLLMER: I concur with the rationale that Dr. Eisner gave, and I have a problem with the fact that despite some of the differences in how they were defined, I think you have a fairly robust finding there.

DR. BRANTLY: Very good.

Dr. Schoenfeld.

DR. SCHOENFELD: I would say yes on this.

DR. BRANTLY: Dr. Eisner.

DR. EISNER: Yes.

DR. BRANTLY: Dr. Stoller.

DR. STOLLER: I would say yes, I concur

with the view that the results are actually more robust by virtue of different definitions.

Having said that, I think going forward my strong plea would be to use definitions of exacerbations that go beyond operational characteristics, that is to say, physician-prescribing behaviors are highly variable in many settings and then, you know, within small regions, and then to generalize that across many countries, I think creates a daunting interpretative challenge.

So, I do think the results support this and I would vote yes, but my advice going forward in designing new trials would be to be very stringent about the a priori criteria for an exacerbation so as to avoid the possibility that if the results weren't concordant in the two trials, my answer would be distinctly different.

DR. BRANTLY: Thank you.

Dr. Moss.

DR. MOSS: I didn't sleep trying to figure this one out for myself, so this was kind of a

tough call for me. I think the correct answer is yes.

The concern that I have, and I realize we are going to talk about No. 4 later, is that if this is approved, and then we find out that the pneumonia situation is a real problem, there is that perception issue for the FDA that something has been approved and then there is a problem down the road, and that is the concern I have.

I realize Mark will get to that on No. 4, but I think to answer this question alone, you would have to say yes, but I am very concerned about the fourth part of it in terms of the increased pneumonia risk. It's a tradeoff. You are decreasing the number of exacerbations that these people will have where they need steroids definitely, steroids and antibiotics potentially, but that is a tradeoff, and the tradeoff is a risk, an increasing risk of pneumonia, and I think the answer is yes, but I am concerned about that second part of it.

DR. BRANTLY: Thank you, Dr. Moss.

Dr. Newman.

DR. NEWMAN: I had made the same thoughts as Marc Moss just articulated. My answer is yes, but the points I would like to make are, first of all, that if we are going to be saying that as a standard for defining efficacy, that we are going to accept exacerbations, there is going to need to be maybe a stricter definition of what that is, and that won't be easy in conducting these kinds of international studies to hold everyone to the same definitions, but that is going to be needed, but I think the body of the evidence supports a yes answer here.

My second point would be that you can answer this question the way it has been posed to us, and the answer is yes, but there is a big but, and the but has to do with the exacerbations that one can anticipate having related to bronchitis and pneumonia, and maybe other lower respiratory tract infections.

You almost have to say it in the same breath I think although I know I am jumping ahead

to the next part of it, but I don't think you would want to say to a patient take this medicine, it is going to prevent exacerbations, period. There is going to be a comma, and you are going to have to say more.

DR. BRANTLY: Thank you, Dr. Newman.

Dr. Gillett.

DR. GILLETT: Yes.

DR. BRANTLY: For similar reasons?

DR. GILLETT: Yes, for similar reasons.

DR. BRANTLY: Ms. Thornton.

MS. THORNTON: Yes. I want to make sure that pneumonia is not considered an exacerbation, is that correct?

DR. BRANTLY: It is my understanding that pneumonia encompasses an exacerbation. Is that correct?

MS. THORNTON: My answer is yes.

DR. BRANTLY: For similar reasons?

MS. THORNTON: Yes.

DR. BRANTLY: Dr. Prussin.

DR. PRUSSIN: Yes, for multiple studies,

multiple endpoints, all leading in the same direction.

DR. BRANTLY: Dr. Parsons.

DR. PARSONS: Yes, but I want to re-echo some of the concerns that were raised by Dr. Moss and Dr. Newman, just so there is a caveat of yes, but there are potential risks that need to go with the yes.

DR. BRANTLY: Thank you. I also vote yes.

That is 11 Yes, zero No, no abstentions.

Let's move on to Question 2(a), which given the fact that we have all said yes, we don't need to address.

Question 2(b).

DR. MOSS: Can I just saying about that? I mean we did say yes to that, but I think there is interest there because as people have raised maybe, that the dosing might have implications in terms of complication rates, in terms of the higher dose of the inhaled corticosteroids, so you could make a case potentially--I am not saying it's right--that having the different dosing might even be more

beneficial.

So, I think at some point it would be interesting, difficult to answer that question.

DR. BRANTLY: Indeed, 2(b), I think is a separate question, and I think we can get a specific answer to that.

I would like some discussion around this particular issue. Do you think additional dosing information would be needed? Look at the efficacy of Advair 500/50 versus 250/50.

Dr. Reiss.

DR. REISS: I just have a question. It was told in the initial presentations that there is a study going on looking at exacerbations at the 250/50 dose, or how would the Agency see that information in light of the way the committee was just thinking.

DR. MEYER: I don't actually know the details of the study.

DR. BOSKEN: We haven't received the study report for this, so we have not reviewed it yet.

DR. MEYER: But is it true that it is just

of the 250/50?

DR. BOSKEN: Yes, correct.

DR. MEYER: So, it is not going to have a direct comparison, to my understanding. I would say that in the initial data that was presented for the COPD indication that led to the approval, such as it is, for the 250/50, the trials that were done did not find any significant effect on exacerbations, but those trials, as the sponsor pointed out at the time to the advisory committee, were not designed to find an exacerbation effect. They were designed to look at other endpoints.

So, they weren't particularly targeting patients who might have a high propensity for exacerbations, and so on. So, the existing data, I don't think, even though they were across-study comparisons we had to do at that time, they were a very similar trial, but they didn't show an effect. They weren't designed to show an effect, and the ongoing study that is going to fulfill, or the study that will fulfill the Phase IV commitment won't give direct comparative data.

DR. BRANTLY: Dr. Vollmer.

DR. VOLLMER: My sense is again to answer the pure question that is stated, you don't need this, I think it would be highly desirable. I continue to be struck by the statement in the briefing documents that when the approval for the 250/50 formulation was put forward, the statement states, "The higher doses are not recommended due to failure to document additional improvement in pulmonary function as compared to the 250/50."

So, clearly, the Agency had some concern about approving a higher dose that wasn't giving a comparable gain in benefit. So, I think it's an Agency's decision as to how they want to deal with that, and if that is still an issue for them, and they clearly would want that information, but to answer the question as put, which is, is it better than placebo, is it giving you an advantage, I think it seems fairly clear.

DR. BRANTLY: Dr. Meyer, do you have any comment to that?

DR. MEYER: No. I think our concern to

some degree is a little bit theoretic up until the point of seeing this pneumonia signal. Just from the existing database for fluticasone in general, particularly in the dry powder formulation, it is really between a dose of 250 mcg twice a day and 500 mcg twice a day that one begins to see definable systemic effects.

So, when we had to make the decision about the original COPD indication, it just seemed if there were no clear-cut advantages to going above the 250/50 dose, there were at least theoretic advantages why one would not want to give undue systemic exposure.

We didn't have a specific pneumonia issue there, and, of course, we don't know, or at least I don't know sitting here today whether we would have similar findings for 250/50 with regard to pneumonia, fewer, we just don't know that.

DR. BRANTLY: Dr. Parsons.

DR. PARSONS: Putting on my clinician hat, if there is going to be a trial of 250 versus 50 in exacerbations, and we have just said 500/50 works

for exacerbations, I don't see the 500/50 getting tested against 250/50 unless somebody says it would be a really good idea.

As a clinician, I think it would be a phenomenal idea. I would like to know if I am going to use the drug Advair generically for exacerbations in my COPD patients, I would want to know if the lower dose works as well as the higher dose because I am concerned that there is an increased risk of pneumonia and potentially other long-term complications.

So, is there a way that--so, yes, that is why we have all sort of nodded yes, we answered yes to the initial Question 2, but the big but is, is there an advantage to the 250/50 dosing being tested, and I think the answer is yes.

I think a head-to-head comparison of the two doses is the way to do it as opposed to what may happen now is we will have a 250 versus 50 study, and that is going to show that it's better than placebo, okay, and then we are going to have an 500/50 that we have now that is better than

placebo, and one of them is going to be a little bit more better than placebo for lack of poor English there.

So, as a clinician I am going to have to choose between those two doses without really understanding what to do, because they have not been compared head to head in the same patient population.

DR. BRANTLY: Dr. Vollmer.

DR. VOLLMER: The only challenge, and I am speaking as a non-clinician though, is do you want to wait. I mean I totally agree and I think that there is probably not going to be a lot of motivation from the company to do that trial, but do you want to wait however many years it is going to take to have that trial launched and completed before you start telling people that here is a product that is out there now, that we think can give you some benefit, and that is a tough challenge.

DR. SCHOENFELD: I don't think that is the question, is it? The question, we are not arguing

the question as to whether they could have the exacerbation indication before they do a trial of 250 versus 500, I mean I don't know that that is the issue. Is that correct, it is not the issue?

DR. MEYER: I think that is correct considering we have framed this as really being pertinent to the discussion whether you voted yes or not to the sort of parent question here.

DR. SCHOENFELD: Polly has sort of framed the issue, well, it would be useful information to see the comparison to clinicians who use this drug.

DR. VOLLMER: Again, my comments weren't to deny that. It is just that I wanted to make sure, because I wasn't sure what you meant by that, I mean whether you were implying that you would rather wait to see this approved to find that answer or not. That was what I wasn't sure of.

DR. PARSONS: No, I didn't mean to imply that. I just wanted to see if we could be a little proactive about suggesting that the head-to-head competition, since there is already going to be a trial of 250/50 in exacerbations, that my strong

recommendation would be there would be a head-to-head competition in that trial, such that down the road we are not ending up with two trials of two different doses that will show slightly variable amounts of improvement in exacerbation, and then trying as clinicians to figure out which one really is the best one for exacerbations versus complications.

I think it gets tough if you are a clinician, and I think there is an opportunity to prevent that from happening.

DR. BRANTLY: Dr. Newman.

DR. NEWMAN: Polly, I think you have said it really well. Putting on that clinician hat, that is the information we are going to need, and it is really balancing off whether you are going to go with the higher dose, because there is evidence that it is going to improve $FEV_1$ and reduce exacerbations, but carrying with it a 2-fold risk of pneumonia.

So, that is really, for me, the crux of it.

DR. BRANTLY: If we were to do such a study, one of the things that I would like to see is actually stratification by $FEV_1$, because it may be that, as we know, the inflammatory burden in the individual that has fairly severe chronic obstructive pulmonary disease is substantially higher than it is for those that have less $FEV_1$'s, and it may be that it is appropriate as far as targeting to one dose might be more appropriate for people that have a greater inflammatory burden or higher $FEV_1$ as compared to another one.

DR. EISNER: I was just thinking if this is going to be done, it should be linked with Item 4, which is to very rigorously look at pneumonia, because the definition of pneumonia that we have now is very nonspecific. It doesn't require chest x-rays, it doesn't really require any specific criteria.

So, if we are going to do 250/50 versus 500, I am assuming equivalency trial, there should be a very rigorous evaluation for pneumonia.

DR. BRANTLY: I think that we have had a

fair amount of discussion around this. I think we would like to answer 2(b), really in some way separated away from 2, as a totally separate issue? Would that be of interest to the Agency?

DR. CHOWDHURY: Well, I think we don't really need a formal vote here, but discussion is what we are looking for. I think you already had the discussion.

DR. BRANTLY: We are happy to move on.

Let's move on to Question 3. Does the data provide sufficient evidence that Advair Diskus (fluticasone/salmeterol inhalation powder) 500/50 mcg provide substantial advantage for the treatment of patients with COPD when compared to salmeterol alone?

Let's begin with some discussion. Dr. Moss.

DR. MOSS: I had a question about this one. I need some clarification on what people mean by "substantial advantage." I guess to the FDA, because I am not sure--I think I know what you mean, but I am not positive.

DR. CHOWDHURY: There is not really any inner meaning to the word "substantial advantage." It basically is stated as based on the data that you have seen today. We just try to get a general feeling from you if you think that the combination provides anything over the single ingredient, which is salmeterol here in the question.

DR. MEYER: I would just say one other thing to help frame that. I agree with what Dr. Chowdhury said, but I think one of the reasons we raised this is because there does seem to be the signal of concern coming from having the added fluticasone. We saw the fluticasone arm, we saw the Advair arm in terms of pneumonia.

So, then, a natural question from the clinician standpoint is, okay, salmeterol gets me here, Advair gets me here. Is that added advantage a reasonable tradeoff given some of the disadvantages we have seen?

DR. BRANTLY: Dr. Schoenfeld.

DR. SCHOENFELD: So, if everybody had voted--I sort of did my thing before the meeting

and thought what I thought--if everybody had voted yes on 1, then, I would have voted no on 3 clearly. That is, I didn't think there was substantial evidence that the combination was better than salmeterol alone on mortality. I didn't think there was substantial evidence of that.

So, I don't know whether to answer this based on what I voted on 1 or what we voted on 1. If I base it on what we voted on 1, which is no, then, mortality is sort of out of the equation, and if mortality is out of the equation, then, I look back at the data, and that data just to remind people is on page 40 and 41, which is of the FDA's statistical analysis, so the comparison between the combination and salmeterol 50, 0.878 was I guess it's the hazard ratio, and the p-value is 0.002. That is using negative binomial and Poisson is 0.931 with a p-value of 0.004, and the Andersen and Gill is not quite significant, but the two primary analyses are.

That is in regards to exacerbations, and then the difference in $FEV_1$ is 30.9 with a p-value

of 0.002. So, if you ignore the mortality issue, then, I think I would answer 3 yes.

The way I am thinking about this, sort of putting things in the negative, is that it is pretty clear. It is clear that the combination is better than placebo in these two endpoints, and it is pretty clear to me at least that it surely doesn't make survival worse and probably improves it, but we can't make the same statement about survival relative to salmeterol alone.

DR. BRANTLY: Other discussion?

DR. VOLLMER: My recollection, having it in front of me, was that the comparison with salmeterol on the exacerbations was highly significant in one trial, I believe the 003, and not significant in the other trial. It was still trending in the same direction.

There seems to be very clear lung function advantage for the combination products. I would still say that there is a benefit there. I would look to the clinicians to argue as to whether the potential side effects that are associated with

this outweigh the benefits if we are now looking at the somewhat mixed exacerbation finding and the strength of the lung function finding alone, but my inclination is to say yes, there is an advantage.

DR. BRANTLY: Would you like to vote on this? Dr. Chowdhury, is it necessary to vote on this?

DR. CHOWDHURY: Yes.

DR. BRANTLY: So, we are going to vote on Question 3, and we will start with Dr. Vollmer.

DR. VOLLMER: I would vote yes for the reasons that I just gave.

DR. BRANTLY: Dr. Schoenfeld.

DR. SCHOENFELD: Yes.

DR. BRANTLY: Dr. Eisner.

DR. EISNER: I vote yes. I think the weight of the evidence is in favor.

DR. BRANTLY: Dr. Stoller.

DR. STOLLER: Again, I would stratify my responses by the endpoints, taking the comments about survival, which obviously, we have responded to, I think the evidence is compelling about $FEV_1$.

I would vote yes. I would vote yes with less enthusiasm on the exacerbations, but yes in both.

DR. BRANTLY: Dr. Moss.

DR. MOSS: I would reiterate exactly what Dr. Stoller just said, so I would say yes overall, but if you want to stratify it, no according to mortality, yes in terms of exacerbations, and yes in terms of pulmonary function.

Actually, the other thing that hasn't been brought up, but in terms of health-related quality of life, I would say no.

DR. BRANTLY: Thank you.

Dr. Newman.

DR. NEWMAN: I would say yes for the reasons that have already been stated.

DR. BRANTLY: Dr. Gillett.

DR. GILLETT: Yes for the reasons stated.

MS. THORNTON: Yes also.

DR. BRANTLY: Dr. Prussin?

DR. PRUSSIN: Yes.

DR. BRANTLY: Dr. Parsons?

DR. PARSONS: Yes, but with the same exact

caveats that Dr. Moss had, so I would outline it as four votes.

DR. BRANTLY: Excuse me. I have to vote also, and I vote yes, and for the same reasons that have been discussed.

So, we have 11 Yes, zero No, zero abstains.

Let's move on to the last question posed to the committee to address. Does the increased incidence of respiratory infections and pneumonia seen in these studies warrant additional evaluation?

Can we have some discussion around this point.

Dr. Newman.

DR. NEWMAN: I just want to start by saying that I want to thank the presenters from the Agency, because you really helped in your presentation I think to crystallize for me what I was pulling from the documents, and that was very helpful.

I am also glad that in articulating the

question, you have included respiratory infections and pneumonia, that you have treated both of those, because I think this matter, there is noise here about what we are really talking about, whether they are truly pneumonias, what kinds of respiratory infections we are dealing with, but to me, there is a pretty clear signal here that there is a red flag of concern I think that we should have going forward in trying to understand this category of exacerbations.

DR. BRANTLY: Other discussion? Dr. Prussin.

DR. PRUSSIN: We find ourselves in a bit of a catch-22, because we have been shown that the 500/50 dose has efficacy in terms of exacerbations, and don't have any data on the 250/50, and yet that is the only choice we have of what to approve or what to at least to recommend is the 500/50, which is associated at least on the surface with these pneumonias.

So, we really don't have enough data to make the decision, but obviously, we have to make

some kind of recommendation. With that incomplete data set, I guess I would ask the company, how do you put this all together, because it is clearly an incomplete data set, and a lot of that is driven by the fact this happened over the last seven years of investigation and was discovered during that process.

But other than the plans that you have shown, is there anything else that you are doing? Again, I think the bottom line is that even the investigations you have talked about are not going to answer the 250 versus 500 question, or by the time it answers that, it is going to be another 7 to 10 years out.

DR. KNOBIL: We do have the five observational studies that we talked about, that will look at Advair and the different doses of Advair to see if there is any relationship.

DR. PRUSSIN: So, are they going to look at both doses or just the--

DR. KNOBIL: The doses that are available on the market.

DR. PRUSSIN: Okay. So, it's in the practice, the British Practice Consortium is looking sort of free form what people are using in practice.

DR. KNOBIL: That is correct. As long as the people have a diagnosis of COPD, it doesn't matter which strength they have been prescribed, we have it in the database either in the GPRD or in the four HMO databases that Dr. Davis spoke about earlier.

Another question is, well, what is the mechanism, what is going on, and that is a much more difficult question to answer, and we are currently discussing that internally and with experts, and we will be looking further into what studies could be done in the future.

DR. PRUSSIN: And the endpoints in the practice registry in terms of the numbers of patients being treated with the 500, and how the data is actually--I am familiar with the database, the registry, but are you going to be capturing, so we really can tell the difference between a

pneumonia and something that is a surrogate for that?

That is the bottom line is the pulmonologists here are uncomfortable with how pneumonias were diagnosed in this study. Obviously, it is different than this practice registry, but what kind of data are we going to get from that, and are there going to be enough numbers of patients getting the 500 to make something of that comparison.

DR. KNOBIL: You can see behind me I am going to allow Dr. Davis to answer those questions.

DR. DAVIS: I don't have the exact numbers of patients given the different strengths. Remember that in Europe, it is actually the 500 strength that is approved for COPD. So, you do have quite a bit of 500 users in the UK, so we will be able to stratify that.

You also have generic use of other inhaled steroids, which we will be able to look at, as well, in addition. So, we can look for dose/response in dexamethasone, as well as looking

in fluticasone in the U.S.

I guess just to give you an order of magnitude about the size of that study, the cohort is around 40,000 patients roughly, but those aren't all taking inhaled steroids although 60 to 70 percent of them are.

DR. PRUSSIN: 40,000 COPD?

DR. DAVIS: Correct. In the U.S. database study, obviously, we will have a little more of the flip side, which is because 250 is the indicated dose in the United States, you have more 250 users, although because 500 is approved for asthma, it is occasionally used in COPD, and we will be able to see those patients, we will be able to pull them out and look at them separately.

DR. PRUSSIN: What is the time line on those studies? I am referring to the registry studies or the practice registry studies.

DR. DAVIS: Both of those pharmaco-epi studies, the GPRD study, which is the UK-based study, as well as the U.S. study, we expect final reports this summer, so June-July time frame.

I guess to also address your question about pneumonia diagnosis, what we have in the GPRD are codes, diagnosis codes for pneumonia. We can see whether patients had chest x-rays ordered. We can't actually see the chest x-ray, we don't have that scanned, but we can see who had them ordered.

In the U.S., pretty similar. We can see the procedure code for x-ray.

DR. SCHOENFELD: The next question, Dr. Stoller.

DR. STOLLER: By way of discussion, I would say that the response to this question is clouded by definition. It reminds me of the joke about the three umpires.

One guy is standing around saying I am the best umpire, he said I calls them as I sees them. The next guy says, you know, I am the best umpire, I calls them as they is. The third guy says you guys ain't nothing, I am the best umpire. He says they ain't nothing until I calls them.

I think the lesson here independent of what kind of databases we use around understanding

pneumonia, really have to ultimately drill down on what the diagnostic criteria for pneumonia are that go beyond physician behaviors, because clinically, I see every day, as I am sure all of you in practice see every day, patients receiving antibiotics without infiltrates, who don't satisfy the most stringent Anthonisen criteria for exacerbations that would rise to the level of benefit.

On the one hand, you are caught--I am sympathetic to the problem, because you are caught in the signal of pneumonia, and yet I don't believe that the pneumonias you have described in the study rise to the level of definition of pneumonia.

So, I think going forward, on the one hand, I sympathize with that, on the other hand, you can't discount the signal in the study, and I recognize it falls outside of any other experience with any of the other studies that we cited earlier on inhaled steroids in COPD, and yet it is very difficult in a forum like this, or in any clinical forum, to put that back in the bottle.

So, I think that the response to this question, in some ways this question almost is the first question that we, as a committee, should answer, because our responses to the others, as others have said, is predicated upon, in the risk/benefit analysis, is predicated upon the reliability of this observation.

Having said that, I would hope that whatever deliberations the Agency makes, just to I think reiterate the comments I have heard from many of my colleagues, have to be taken in the context of how believable this is.

On the one hand, I am unsure, on the other hand, as a clinician, I am very concerned, and I think that it requires mechanistic understanding, it requires replication in stringently defined prospective studies of pneumonia that will not be satisfied by retrospective database analyses, not only for the point that I am not confident in the diagnostic criteria, but you can't actually analyze the films that would be the underpinnings of the diagnosis.

So, I think that the studies going forward have to be designed rigorously, as do those for acute exacerbations rigorously, to prespecify the criteria for pneumonia, and then to look at the impact of this drug and other dose formulations on that event.

I don't think these data unfortunately inform any opinion that we could have, and yet I share the nonspecific concern of a much higher rate in the inhaled steroid users both in combination and in isolation.

DR. BRANTLY: Dr. Eisner.

DR. EISNER: I actually share your concerns, but I wonder if some of the issues couldn't be addressed in the observational epi studies by a validation study. I don't know, maybe you are planning this, but just to take a random subset of pneumonia cases and actually have a chart review, a validation possibly with review of films, and then maybe a sample of non-pneumonia cases just to look at the false negative rate.

So, it might be possible, with several

very robust cohorts, and perhaps with some of that validation work, it would become more satisfactory to the group here.

DR. BRANTLY: Dr. Newman.

DR. NEWMAN: I think it's answerable, and I think, Jamie, you may be right, that we could learn with cleaning up and perhaps also with a validation study design, that the pneumonias go away the signal--my impression from the data we have seen today is that the signal about respiratory infections is unlikely to go away, but it may not be of the magnitude of pneumonia once we get data that is more critically defined.

I echo what you said about the need to essentially proceed with caution and get the information that would answer the question.

Dr. Jones was kind enough to share that you are doing more in terms of putting information out there about the potential set of complications with the medication, but I have to come back to page 82 of the briefing document that you provided, because for me, the only thing i would want to say

to the company and to the Agency, is that all I have been presented with is this one page of what additional information has been inserted or is being inserted, and I am not reading it as a labeling expert, but as a clinician who reads these things and then decides what to say to a patient.

I am not sure that this right now portrays for me adequately what I think I need to know to communicate to my patients. You know, pneumonia finds its way into a second bullet list as, you know, among the comments with dysphonia, et cetera.

I would just suggest that there be a really more--you are not asking us to do that today, but among yourselves, I think you need to take a hard look at what you are saying back to clinicians and to patients with the labeling.

DR. CHOWDHURY: This comment that you are making is actually very useful for us to hear, because we will take what you are telling us into consideration as we move forward towards the decision for this application.

As for the labeling that you are seeing is

actually proposed labeling that GSK has provided the Agency for us to look at in the context of the submission. When we take an action on an application, between the Agency and the GSK, there will be discussions happening, which partly will be reflective of what we get in here, and we come up with a labeling that will lay out the risk and the benefit.

DR. JONES: Dr. Chowdhury has said it perfectly, yes, this is the draft label that we put forward, and we wanted to put the information from the TORCH study within the label, and we have also put it in the medication guide regarding the identification of the risk.

The Agency and GSK will work to ensure that the labeling, both for physicians and patients, adequately address the issues that you have raised.

DR. BRANTLY: Dr. Schoenfeld.

DR. SCHOENFELD: One of the problems is this is sort of worded, this question is worded sort of like do you like mom and apple pie, because

it is very hard to say oh, don't consider something.

So, I am assuming that the real meaning of this question is, is did we think that the evidence about pneumonia indicates that there were more pneumonias in the combination treatment than there were in the placebo, and if I read it that way, then, the answer I would answer to that is yes, it was convincing that there is a problem with pneumonia.

So, that being said, the question of what to do about it is much more difficult, because the epi studies are not going to be able to have any better definition of pneumonia, any better verification of pneumonias in the clinical trial. In fact, the verification will be worse because it is not in the context of a clinical trial.

Furthermore, if you did a clinical trial, for instance, comparing the 250 to 500, and then did a really careful diagnosis of pneumonia, if you didn't see any difference, it might be that it is simply that the signal on pneumonia is really

mostly due to bad diagnosis, so you really would only be able to draw conclusions if you did see a difference, and a negative difference wouldn't tell you anything, because you would be having a new definition of pneumonia.

So, I think this is not going to be an easy issue to resolve.

DR. BRANTLY: I wanted to make yet another point about a prospective trial to evaluate this particular issue, and that is that it is a relatively low frequency event, so the trick of trying to accumulate these individuals to do a study is difficult.

However, given the fact that it is a safety signal, I think that it is important that we develop strategies to better assess the magnitude of this particular observation.

Dr. Schoenfeld.

DR. SCHOENFELD: I just would make one other point, that, yes, I think it is a safety signal. Suppose we pretend for a minute that the trial was essentially a trial of exacerbation as

the primary endpoint, and not mortality. The fact that the mortality difference went suggestively, I will say, in favor of the active drug would argue that the safety issue is not overriding.

DR. BRANTLY: Any further comments?

Let's go ahead and start our votes. Again, I would like to start with Dr. Vollmer.

DR. VOLLMER: I guess I would echo the comments that it would be nice to gather further information on this given the caveats and leave it at that.

DR. BRANTLY: Is your answer yes?

DR. VOLLMER: Yes.

DR. SCHOENFELD: I would have to say yes to the question as a tautology, and it is also yes in terms of was there a statistically significant effect on pneumonia.

DR. EISNER: I would say yes, but I would start with looking at the five epi studies that are going to be done this summer. I actually think that the UK registry, there may be more uniformity in how pneumonia is diagnosed. It is a single

nation as opposed to a multinational study, and I think based on those results, you can kind of make a decision of whether a prospective study is needed.

DR. BRANTLY: Dr. Stoller.

DR. STOLLER: I would say yes, I think it is very difficult to answer a question posed this way by saying no, particularly when there is a signal as it is. I am just less optimistic that administrative database analyses are going to clarify this, and I do think it requires explicit prospective criteria and analysis, recognizing the points you have made, Dr. Brantly, about the low frequency event.

I think, however, because it is a safety signal, I think that needs to be done.

DR. BRANTLY: Dr. Moss.

DR. MOSS: I would say yes for the reasons that Mark Eisner and Jamie Stoller said.

DR. BRANTLY: Dr. Newman.

DR. NEWMAN: Yes, for the reasons that Mark said which was saying what the rest of the

guys said.

DR. BRANTLY: Dr. Gillett.

DR. GILLETT: I am going to say yes for a slightly different reason. As a layman, given the uncertainties faced in diagnosing whatever it is you guys are calling COPD and/or other respiratory diseases, and/or what you are calling pneumonia, I think the level of uncertainty requires significantly more investigation.

DR. BRANTLY: Ms. Thornton.

MS. THORNTON: Yes, based on just the general comments.

DR. BRANTLY: Dr. Prussin.

DR. PRUSSIN: Yes, and just a separate point. On the package label, you might consider in that language where you mention all the different percentages of pneumonia, just having Advair Diskus and placebo, because having the salmeterol alone and fluticasone alone, it is a bit of a distractor and you sort of lose the actual signal of what the information is when you have so many different drugs being listed.

DR. BRANTLY: Dr. Parsons.

DR. PARSONS: Yes.

DR. BRANTLY: Myself, I also vote yes. I did unfortunately come up with a question actually for the sponsor, though, in the process. That question is, is there any evidence in any of the studies that indicate an increase in immunodeficiency in these individuals?

The second part of that question is do you see a time effect. For instance, the longer you are on Advair, the higher the incidence of pneumonia.

DR. KNOBIL: The answer to your first question is that no, we haven't seen any evidence of immunosuppression, and as I mentioned before, in the sputum cultures that we got, we didn't see any evidence of increased opportunistic infection.

As for increasing over time, no, we haven't seen that either. You saw the Kaplan-Meier curve. We also looked at the risk of having a second pneumonia, and that risk of second pneumonia was not higher in the inhaled corticosteroids

groups versus the other patients in the other groups who got pneumonia.

DR. BRANTLY: Thank you very much.

Let me do the tally of the vote here. We have 11 Yes, no zeros, or zero for No, and zero abstentions.

We have a follow-on question as to what additional data should be obtained. We have talked around this issue and I think that we can probably give some focus recommendations, some discussion about additional data that should be obtained.

DR. MOSS: I think it alludes to the question that you asked. I agree with what David Schoenfeld said about the subgroup analysis, but here is the situation where there might be specific patients who, with the addition of this medication, might be at increased risk, people that have other reasons, be immunocompromised.

So, however this is going to be done, as Mark Eisner said, with databases, it will be very important to look at people that have other immunodeficiencies to see if they are the ones that

are really at increased risk and therefore, maybe would not benefit from this drug.

DR. BRANTLY: Other comments?

Dr. Chowdhury, do you feel that we need to give any more specific recommendations on this issue?

DR. CHOWDHURY: Basically, what we heard of the discussion item on this question is that some thought that the studies that GSK is doing is good thing to do. In addition, we heard the proposal of doing a prospective study to look for pneumonia as a possibility. Is that a correct assessment?

DR. BRANTLY: Let me perhaps reframe it at least the way I understand it at the present time. I think that the general wisdom would be that starting with the epidemiologic studies to help focus things is a very important step, and then the potential of either a prospective study, if it was at least possible, or at least some mechanistic studies, and also further to stratify which risk categories might be.

This may lead to whether it be an immunosuppressed individual, prolonged exposure, or actually different subtypes of COPD, for instance, bronchiectasis versus chronic bronchitis versus emphysema.

Does anybody disagree with that particular summary?

Thank you.

I think that we have accomplished our duty here as a committee. I would like to thank all the committee members, the sponsor, and the Agency for allowing us to have this forum, and I would like to wish you a safe trip home.

This meeting is adjourned.

[Whereupon, at 2:35 p.m., the meeting was adjourned.]

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