study. I mean if you just eyeball from zero to the end of the study, I think they would be much more different and would overestimate the difference.

MS. ANDERSON: Julie Anderson, statistician from GSK.

I agree with Kate. What we have done here is a very conservative analysis, because we haven't taken account of the increase of all the drugs, which you see is still sustained at 24 weeks.

If we had taken it from baseline, the lines would have diverged even more, and there would have been more of a difference, so we have tried to do a very conservative analysis only after the initial increase had been taken account of.

DR. BRANTLY: Dr. Eisner.

DR. EISNER: One thing I wonder if you could clarify. Advair reduced exacerbations overall. One of the definitions of exacerbation was treatment with antibiotics, yet, we are seeing an increase in the risk of pneumonia, so I find these kind of contradictory.

Can you bring any clarity to that

situation?

DR. KNOBIL: The exacerbations treated with antibiotics was not a prespecified analysis that we have done, but you saw that in the FDA's briefing document.

There were two categories - all exacerbations treated with antibiotics whether they were treated with corticosteroids, as well, or exacerbations treated with antibiotics alone.

When you look at the exacerbations, all exacerbations treated with antibiotics, you do see that there is still a statistically significant improvement with Advair over placebo in these exacerbations.

The ones that aren't better than placebo are the ones that are treated with antibiotics alone. When I looked at this analysis, I was trying to figure out, well, what is the clinical relevance of doing it this way, because if you assume that a physician gives antibiotics because they believe that there is an infection going on, you would look at all the exacerbations treated

with antibiotics, not just the ones treated with antibiotics alone.

I am not sure what information this adds over the information that we have from the adverse pneumonia event reporting.

DR. BRANTLY: Dr. Stoller.

DR. STOLLER: In follow-up to that, recognizing that there were no explicit diagnostic criteria for pneumonia in this study, how would I recognize the difference between what was called pneumonia and an acute exacerbation treated with antibiotics alone?

Were there a misclassification of those two, it could have actually an impact I believe on the impact of drug on acute exacerbations depending on whether pneumonias were ascribed to acute exacerbations or vice versa, so how would I recognize the difference between pneumonia based on physician reporting and an acute exacerbation treated with antibiotics alone?

DR. KNOBIL: You mean in the study, the way they were reported in the study?

DR. STOLLER: Yes.

DR. KNOBIL: In the study, if there was an exacerbation that was reported by the investigator, there was a question on the exacerbation form that asked is this also a pneumonia, and for a pneumonia, it was asked is this pneumonia an exacerbation.

So, there was cross-talk in the case report form that specifically asked the investigator, but you are right, there were no diagnostic criteria, so it could just be a clinical diagnosis, so we didn't ask if a chest x-ray was done, we didn't ask if a sputum culture was taken.

DR. BRANTLY: Dr. Reiss.

DR. REISS: I have a couple questions. I will just ask two to start with and then we will move on.

I am still trying to understand about dose selection. When did the 1-year study start relative to the mortality study?

DR. KNOBIL: The TRISTAN study, the 1-year study?

DR. REISS: Yes.

DR. KNOBIL: That study was started and completed before TORCH was started.

DR. REISS: In the same light, can you help us understand a little bit about the safety profile amongst the two doses in the studies in which they were done head to head?

DR. KNOBIL: There were no head-to-head studies of the two doses, so we don't have any head-to-head data of the 250 strength versus the 500 strength.

What we did have in the original clinical program, we had two very similar studies of the 500 strength versus components in one study, and the 250 strength versus components in the other study, and that is where we had the only ability to compare adverse events. In those studies, they were quite similar.

DR. BRANTLY: Dr. Newman and then Dr. Schoenfeld.

DR. NEWMAN: I wanted to come back. I am still trying to get my head around this concept of

the reduction in exacerbations and then the counterpoint that we had this increase in pneumonias.

In looking at the adverse events data that you presented in the summary document, when one looks at other kinds of conditions that as a clinician I might be inclined to use antibiotics, there would appear to me to be not only the issue of the pneumonias in the treatment group, but bronchitis, acute bronchitis, upper respiratory tract infections.

In fact, all of those combined would appear to me at my glance through your data to be conditions where I would be inclined to treat with antibiotics.

I am trying to, and maybe you can just help clarify for me, to understand the shift in what this medication might mean for a patient, because I am seeing, on one side, a reduction that you have shown in exacerbations, but on the flip side, sort of a rising concern for the respiratory tract exacerbations.

DR. KNOBIL: Well, there are a couple of things to remember in the study. First of all, there were 13,000 exacerbation events in TORCH, there were fewer than 1,000 pneumonia events in TORCH.

All of the pneumonia events that were treated with antibiotics and/or systemic corticosteroid would have been classified as an exacerbation. So what we did was, because in the analysis plan, we determined the rate of these things in different ways, so we thought it might be useful to see what the different rates were of exacerbations and pneumonias based on the same way of looking at it.

So, these are the data that I have already shown you with pneumonias with events per 1,000 treatment years. This doesn't include all lower respiratory tract infections, but we do realize that there is an increase in all the lower respiratory tract infections in this patient population.

Just to compare and sort of have an idea

of what the balance is between pneumonias and exacerbations, here is the events per 1,000 treatment years for the exacerbations in the study.

So, you can see that there is many, many more exacerbations events than pneumonia events, but these are incorporated in these rates right here, the pneumonia events, and I know that is confusing, but the increase in pneumonia was a surprise to us, so we didn't--this is the way that we had a priori decided to analyze the data.

DR. NEWMAN: Right, so looking at that now, can you bring in for me the rates for bronchitis? I know you have talked about lower respiratory, but bring in bronchitis but you do report a higher rate of bronchitis as adverse events.

DR. KNOBIL: The rate of bronchitis is higher, but not--there is not as big of a difference in bronchitis between treatment groups when you look at the rates per 1,000 treatment years. If I remember correctly, it is about 70 in the placebo arm and about 85 in the Advair arm.

So, there is an increase. That can have an impact or contribute to the rate of exacerbations, but that is taken into account in these rates that you see here.

DR. NEWMAN: Now add in acute bronchitis.

DR. KNOBIL: When I say "bronchitis," I am including all kinds of bronchitis whether it is acute or chronic.

DR. NEWMAN: Okay, because I was looking at the data and it appears to be reported as a separate condition.

DR. KNOBIL: We did have them separated. I don't have the data right in front of me, but I am just saying that we are not trying to discount that there is not an increase in other lower respiratory tract infections, but what we did with pneumonias was to more fully investigate what was going on with pneumonias because that we felt was the most serious lower respiratory tract infection and could have serious sequelae in patients with COPD.

So, that is why we presented all of these

data today to show that there is not an increase in the risk of pneumonia-related death with Advair when compared with placebo.

DR. SCHOENFELD: I guess I have a question along the same line, which is just what percentage of pneumonias were not included as exacerbations and what percentage of bronchitis, and so on, were not included as exacerbations, or were all pneumonias considered exacerbations?

DR. KNOBIL: Well, pneumonias were only defined as being an exacerbation if they were treated with antibiotics, and it is true that there were pneumonia events reported in TORCH that were not treated with antibiotics.

DR. SCHOENFELD: Do you have any idea what the magnitude is of that, is it just a handful?

DR. KNOBIL: There is about 10 per group.

DR. SCHOENFELD: Ten per group.

DR. KNOBIL: Ten per group, very small.

DR. SCHOENFELD: So, by and large, pneumonias are all included in the exacerbation rate.

DR. KNOBIL: That's right.

DR. SCHOENFELD: And is the same true with bronchitis events, more or less?

DR. KNOBIL: If they were treated with antibiotics, then, they should be included with the exacerbations. I don't have those data at hand right now.

DR. BRANTLY: Dr. Moss.

DR. MOSS: I wanted to switch gears a little bit, so if the questions wanted to stay on this topic of the pneumonia, I am happy to wait.

DR. BRANTLY: Dr. Prussin?

DR. PRUSSIN: No.

DR. MOSS: I have a question about the mortality data and it doesn't have to do with the p-value, which you had brought up. It has more to do with what you considered your control group.

If we think about patients that would meet criteria for the study, based on data, all criteria, most of these people should be on a bronchodilator, and most people would say it might not be cost effective, but they should be on a

long-acting beta agonist.

So, when you talk about your mortality data, you are comparing them and you get the p-value that is on the margin there, compared to the placebo group where they are getting neither of the medications.

Explain to me how I am supposed to interpret that kind of going back to what Polly was saying where, in practice, you would have somebody on a long-acting beta agonist, don't you think that is a better control group to see what your medication, which has two drugs in it, do to what one of the components are that are standardly used in this patient population?

DR. KNOBIL: When we started TORCH, we had very little data on long-acting bronchodilators, long-acting beta agonists, and we didn't know if any of them would have any effect on mortality.

So, at the time that the study was designed, I think that we had the appropriate study groups in the study, and it was based on a previous long-term, 3-year study that we had completed a few

years prior.

So, in hindsight, it probably would have been useful in order to help with these treatment decisions to have an Advair 250 arm or a salmeterol arm alone, but we don't have those things, and now it would be very difficult to run those studies.

DR. MOSS: Well, you do have a salmeterol arm alone.

DR. KNOBIL: Yes, I know, but the study wasn't designed nor powered to show difference between those treatment groups, and we might have done things differently in order to be able to differentiate those groups better.

I think it is important to know or just to reiterate that the Advair arm did go in the right direction compared with salmeterol, and who knows what would have happened over time.

Now, the other thing is, is that remember I told you that the placebo arm withdrew more frequently and could have gone on to other medications, so can you show this slide, please.

We have some limited data about what

medications patients went on to after they withdrew from all of the treatment arms, and actually, this is not just after withdrawal, but this is during the study phase, as well.

We have recorded patients as going onto these medications if they were on that medication for at least 28 days, so this is not just one dose or one week of therapy.

You can see here the placebo arm is shown in black, and they are significantly more likely to go on some of these other medications that we are talking about today including ICS-LABA combinations, long-acting bronchodilators, and inhaled corticosteroids.

We really do believe that this differential taking of other COPD medications could have led to an underestimate of the mortality benefit even in the salmeterol arm, which you can see here, is second after the placebo arm.

DR. BRANTLY: Dr. Prussin.

DR. PRUSSIN: I have a similar question. Oxygen was one of the exclusion criteria. I am an

allergist, so I don't treat these patients on a routine basis, but how many of them would normally be on oxygen therapy, and would that change some of the survival benefits? Then, I would like to follow that up with another pneumonia question.

DR. KNOBIL: Patients who are on long-term oxygen therapy were excluded, because we felt that the mortality would be higher in this group, and they would die early and wouldn't remain in the study long enough to actually detect differences between the treatments.

If patients went on oxygen during the study, they were not taken out of the study. They would just continue into the study. I don't know what patients, the mortality on patients with oxygen, what that normally is.

DR. PRUSSIN: In other words, is the real world benefit of this, would it be less in patients who were being concurrently treated with oxygen, that is the bottom line question.

DR. KNOBIL: Well, we haven't looked at patients who are on oxygen by themselves, but what

we have done is looked at the more severe patients, so patients less than 30 percent predicted, those patients are more likely to be on oxygen, and we still saw a significant survival benefit in that group.

DR. PRUSSIN: Second question. In regard to the pneumonias, right now certainly the public is very apprehensive about issues with drug safety, and certainly this is one that looks like in the future could be looming.

So, can you go in a little more detail how you plan to address the issue of the pneumonias?

I know you had a slide where you mentioned ongoing studies, but is this something that is going to be--you know, how actively are these studies going to be pursued and in what way, because this certainly is something that could be lurking in the background and then once we have many more patients being treated with high-dose fluticasone, it could become much more obvious as a problem.

DR. KNOBIL: Yes. The five observational

studies that I mentioned are all ongoing as we speak, and we have gotten preliminary data from three of them I think, three of them, so we are actively pursuing them, and the other two will be done later this year.

Now, the other thing that we are doing is that we are actively putting these risks in the label, in the medication guide.

DR. JONES: Yes, we do have pneumonia and lower respiratory tract infections in the Precaution Section of the label already. We have actually increased that information in the label, and we have also put the information in the medication guide for patients, so that they recognize the symptoms and seek treatment quickly.

There will be a communications plan associated with that communication of the data.

DR. BRANTLY: Dr. Vollmer.

DR. VOLLMER: Given the differences in how exacerbations are defined in the two trials, I wonder if it is possible, or if it is possible, have you tried to redefine the TORCH exacerbations

more along the lines of how they were defined in TRISTAN and see how those results come out that way, so that they seem a little more accountable?

My recollection, looking over the documents, is there is quite a bit of differences in how they were defined and the time between exacerbations. One exacerbation, I think if you had gone off seven more days between treatments, there was a different exacerbation in the TRISTAN trial, but not necessarily in the other trial.

You had just a lot of vagaries about exacerbations in the TORCH.

DR. KNOBIL: The exacerbation definition for both TRISTAN and TORCH was nearly identical actually, so it was based on whether or not patients received antibiotics or systemic corticosteroids or were hospitalized.

The one difference was that in the protocol in the TRISTAN study, there was a definition that if there was less than 7 days between courses, then, that was called single exacerbation, whereas, that wasn't in the protocol.

However, in the investigator meetings for TORCH, we gave that similar instruction to the investigators to try to get to the same place as with TRISTAN.

The other thing that we did is exactly what you suggested is tried to take the exacerbations in TORCH and exclude the ones that were way long, which some of them are errors in transcribing dates into the case report form and some of them are just the way they were reported, and we don't see any difference in exacerbations when they exclude those.

DR. BRANTLY: We would like to take a break right at this moment and we will get back to our questions. I would like everybody to return by 10:15. Thank you very much for an interesting session so far.

[Break.]

DR. BRANTLY: The next portion of this committee meeting is the FDA presentation. Our first presenter will be Dr. Bosken.

FDA Presentation

History of the Clinical Program for Advair Diskus 500/50 and Introduction to the Efficacy Data

DR. BOSKEN: Good morning. I am Carol Bosken. I am a medical reviewer in the Division of Pulmonary and Allergy Products at the FDA, and I am going to lead off our discussion.

[Slide.]

I will start off with a brief review of the development program for Advair for COPD, have an introduction to the efficacy results, and then I will hand the podium over to Ms. Feng Zhou, who will talk about our efficacy results, and then I will return and talk about the safety results and make a summary.

[Slide.]

To begin with the development program, as you have heard, Advair Diskus 250/50 was approved for the maintenance treatment of airflow obstruction in patients with COPD associated with chronic bronchitis in November of 2003.

The original development program was

designed to demonstrate the contribution of each component of Advair, fluticasone, and salmeterol to the efficacy of Advair in improving lung function.

[Slide.]

Advair was found to be superior to each of the relevant individual components for pre- and post-dose FEV_1 endpoints, but the improvement with the 500/50 mcg dose was not superior to the improvement seen with Advair 250/50.

In addition, other efficacy outcomes, such as patient-reported outcomes, and COPD exacerbation rates were not benefited by either dose of Advair in those studies.

Finally, patients enrolled in the pivotal trials must have had a history of chronic bronchitis by the standard definition.

[Slide.]

For those reasons, the current approval is limited to the 250/50 mcg twice-a-day dose, and is only recommended for patients with COPD associated with chronic bronchitis.

At the time of approval, we agreed to two,

Phase IV commitments. One of these was for a 1-year study to assess the effects of Advair 250/50 on the incidence of COPD exacerbations.

Do not confuse this study with what we are talking about today. The results of the study have not been submitted to the Agency and have not been reviewed. We are only going to be talking about the Advair 500/50 dose.

The other Phase IV commitment was for a 2-year study to assess the effects of Advair 250/50 mcg on bone mineral density.

[Slide.]

At the same time that the original indication was under review at the Agency, the study to assess the effect of Advair on survival was being designed.

The original protocol, this is Study SCO30003, I will refer to the study as Study 03, and you have heard about it so far as the TORCH study. It was of 3 years duration.

The original primary endpoint was all-cause mortality and the key secondary outcomes were

COPD-related mortality and the initiation of long-term oxygen therapy.

Other endpoints included moderate and severe COPD exacerbations, patient-reported outcome measures, and pulmonary function measures.

[Slide.]

The treatments in this trial, as you have heard, were Advair 500/50, fluticasone 500, and salmeterol 50 mcg twice a day.

The original sample size was 3,800 to give an 80 percent power to detect a 5.0 percent difference between Advair and placebo in all-cause mortality.

From a notational point of view, I will be talking about Advair, but I will have on my slides as just SFC, salmeterol fluticasone combination products, FP for fluticasone, SAL for salmeterol, and I have omitted the doses because it's the same dose for all of the studies.

[Slide.]

The Agency reviewed this protocol for the Study 03 in August of 2000. A primary source of

concern was whether a single study would be acceptable for the mortality outcome.

The Agency usually prefers to have two studies to replicate efficacy outcomes in two separate populations, but we agreed that with mortality being a very important outcome, and with the effort that was going to be required to conduct the study, and the length of time, that it would be sufficient if the statistical results were robust and if there were no new safety findings that did not alter the risk/benefit ratio unfavorably.

At the time of those discussions, we also talked about international enrollment, and we also agreed that that was acceptable, but again that we would expect a sufficient U.S. population, so that we could be assured that the trends in efficacy went along in the U.S. population also.

At the time, we did not raise any objection to having one dose of Advair.

[Slide.]

The study was conducted between September of 2000 and through 2002. Over the course of the

study there were two important changes in the study design.

In the first, the moderate and severe COPD exacerbations were raised from another supportive efficacy outcome to the key secondary outcome.

The second change was an increase in the sample size, which finally came up to 6,040. The change in sample size was performed after blinded review of the efficacy data, blinded review of the mortality data, which shows less of a mortality than had been expected at the original planning stage, and the Agency considers this acceptable clinical practices as long as the data is blinded.

At the end of the study, GSK came back for further discussion with the Agency, and at that time, we mentioned that we would expect two studies to support the exacerbation indication even if the survival claim turned out to be convincing.

[Slide.]

So, the submission, as you have already heard, includes two new indications, the increased survival and decreased exacerbation rate, and also

a decreased airflow obstruction.

Again, as you have heard, all of these indications will now apply to the general COPD population without the restriction of being limited to those who have associated chronic bronchitis.

Finally, the recommended dose is to be 500/50 mcg twice a day.

We have to note that in none of the studies was the approved 250/50 mcg dose tested for its effect on these new indications.

[Slide.]

So, to go over this briefly, because you have seen a lot of this already, the three primary trials supporting the new indication, Study 03, the 3-year mortality. This is the only study supporting mortality. It is also being submitted to support the exacerbation rate.

Study SFCB3024, I will refer to it as Study 24, you have heard of it so far as TRISTAN, was a 1-year randomized trial conducted entirely outside of the United States, lung function was the primary efficacy outcome, and exacerbation the key

secondary outcome.

Of note, and we have already said, this study was completed before Study 03 was started, and was conducted without prior consultation with the Agency.

Study SFCA3006, as you have also heard, was submitted with the original application, and was submitted to support the decrease in airflow obstruction indication.

At the time of the original review, the Agency agreed that patients who were treated with 500/50 of Advair had better pulmonary function at the end of the 6-month period than patients treated with either fluticasone, salmeterol, or placebo, and pulmonary function was also measured in Study 03 and Study 24.

In all cases, patients treated with Advair 500/50 had better pulmonary function at the end of the trial than patients treated with either of the components or placebo. Therefore, the Agency agrees that Advair 500/50 is effective in the relief of airflow obstruction. I am not planning

on talking about this outcome further.

[Slide.]

Also, in reference to the St. George's Respiratory Questionnaire, as you have heard, it was administered in both Study 03 and 24. Also, as you have heard, the differences between active treatment and placebo did not reach the minimally important clinical difference of 4 points. This difference has been supported extensively in the literature.

The Agency has used this cutoff in prior regulatory decisions and I was also not planning on discussing this outcome further in this current presentation.

[Slide.]

Now, just some introduction to the efficacy results.

[Slide.]

First, patient populations.

[Slide.]

You have seen a lot about the demographics in these studies. I just wanted to highlight the

differences that we thought were important.

First of all, I said the patient populations were very similar. They all had a mean age around 60, all chronic obstructive lung disease, all heavy smokers.

But in Study 03, there was no requirement for cough or sputum production, there was no requirement for previous exacerbation. This is as compared to Study 24 where the patients were all required to have a history of cough and sputum production, and again this study was designed with exacerbations as the key secondary outcome, and they were all required to have one moderate to severe exacerbation in the 12 months prior to enrollment.

Pulmonary function was moderately reduced in all of the patients. The inclusion criteria for 03 were an FEV_1 percent predicted of less than 60. The mean of the entire group was 40. The inclusion criteria of Study 24 was between 25 and 70 percent predicted, and the actual baseline mean was 45 percent.

Of note, over 700 patients in Study 03 had FEV_1 percent of less than 25 percent of predicted. Both cases we agreed were non-reversible, basically, non-reversible obstructive lung disease.

[Slide.]

Study 24 was international, but it did not enroll patients in Asia, South America, or the United States. This is in contrast to Study 03, which was truly international, and for analytic purposes, the various regions were grouped into patients enrolled in the United States, those enrolled in Asia, Eastern Europe, Western Europe, and Other. This "other" group was quite heterogeneous. It included Canada, South America, South Africa, and Australia.

But the numbers were great enough that you could subdivide them and get some interesting differences in the group. Note that 23 percent were enrolled from the United States.

On this slide I have demographic characteristics. They were not very different, but if you notice, the patients enrolled from Asia had

a slightly higher age. Now, this is percent greater than 65 years of age. There were a few more men. There were a notable number who were underweight by the common criteria of less than 18, and they had the lowest FEV_1 percent predicted.

As you will see in the rest of our efficacy discussion, the response to Advair was related and was better in patients who were younger and patients who had the better FEV_1, or the other way around, it was poorer in those that were older and that had low FEV_1s.

We will also see that the Asian group in particular had a very poor response to Advair.

[Slide.]

We were interested also in the regional variation in medical practice, because as we will talk about, this exacerbation diagnosis, this exacerbation endpoint is really a subjective endpoint. We are measuring medication delivered, which is objective, but the decision when and who to treat was entirely undefined and therefore subjective.

We were thinking what would some of the local practices be that might change the decision to treat and also what might happen to the patients who drop out, how would they be treated and would that differ in the various regions.

The one thing that point showed up was that inhaled corticosteroids were taken by 64 percent of the Western Europeans at baseline in contrast to 45 to 49 percent of the other population.

The other thing that we were wondering about was the technical sophistication of care. Oxygen saturation was taken as a surrogate for that. Oxygen saturation was not a protocol-required measurement. It was included in the case report form if it happened to be in the clinical record.

We noted that 90 percent of the patients enrolled in the U.S. had this measurement as opposed to 48 percent of the Eastern Europeans and 55 to 73 percent of the other populations.

This might be of interest when you are

thinking about this diagnosis of pneumonia because x-rays were not required, and this might have some regional variation. By the way, all these variables were quite similar across the treatment groups.

[Slide.]

Now, just a word about efficacy endpoints.

[Slide.]

The objective of Study 03 was to determine the effect of Advair on survival in patients with COPD, and we can't think of a study that is done that is better.

We started out with all-cause mortality, which is of course an unequivocal endpoint, so there is no diagnostic in this classification, but further than that, as you have already heard, the cause of death was determined.

It was determined by a committee using prospectively defined classification. Not only was the primary cause of death determined, but also an assessment was made as to whether this death was COPD related or not, in addition to which most

survival studies followed patients until they die or are lost to follow-up, whereas, in this study, patients were followed up until the full three years.

Talking about this follow-up, I am sure I only have a guess at how much effort went into all of this. I maybe have looked through 200 case report forms and case narratives, but it was obviously an enormous effort to get all the data in, to correct it. Sometimes the investigators had to be reminded more than once or twice or thrice.

As I understand it, the effort was to continue throughout the long-term follow-up, and to get especially at least the severe adverse events and COPD medications, but the data retrieval dropped off after the first couple of months after the patients were off protocol, if they went off protocol, and it was my understanding that that data was not going to be used for statistical analysis.

But in any event, the follow-up was terrific for the survival outcome and as you have

heard, resulted in almost 100 percent follow-up, and it was even less than 8 percent of the patients did not have a known cause of death.

Also, as you have seen, multiple analyses were performed on this data because of the careful ascertainment of the cause of death.

[Slide.]

Now, we had a little more trouble with the exacerbation endpoint, and you have already heard it was defined as moderate if treated with systemic corticosteroids and/or antibiotics, and severe if hospitalization was required.

There was no definition of the exacerbation itself. While this may be adequate for clinical terms, it becomes difficult in a clinical study where you would like to get a little bit better definition, and I think as we will get into some of the other points I have to make, this will come up again.

There were no required symptoms. We thought it was important that there were no time limits on the duration of the exacerbation or time

limits on the period that you could have between separate exacerbations.

Remember the analysis depends on counts, it is the count of the number of exacerbations.

There was no specific limit on the number of exacerbations although there were suggestions of when it would be appropriate to withdraw a patient because of an excessive exacerbation rate, and also, patients were not supposed to be on systemic corticosteroids for more than 6 weeks.

[Slide.]

The result of this definition was, as you might predict, a highly variable duration of the exacerbation. The median was 12 days with a range of zero to 13. Actually, the shortest mean was in the salmeterol-treated patients, but what was more interesting to us was this range of 1 to 744 days. Twelve percent of the episodes were longer than a month, and we did a random selection of patients who had exacerbations that were greater than 6 months long.

While there might have been some errors in

data entry, there were also a number of patients that had repeated short courses of therapy within this longer 6-month period that was called the exacerbation.

In some cases, the courses of therapy were also separated by several months without therapy, so I am not sure what was going on with those patients.

I assume they weren't doing well is why they were called having the exacerbation, but in terms of analysis, this is compared with other investigators who treated patients with one or two days of corticosteroids every couple of weeks and counted each one of them as different.

Another problem with the definition and we thought might be more worth consideration is that again, treatment with antibiotics and corticosteroids were to define the severity, but there were cases where very severe episodes were not treated with antibiotics or corticosteroids.

One example of this would be an end of life decision where somebody did not want--a family

didn't want to treat the patient. That patient, no matter how severe the exacerbation, even if it resulted in death, it was adjudicated as a COPD-related death, didn't count in the exacerbation count.

Patients who didn't get to the hospital and sometimes other cases where it wasn't clear why a severe pneumonia was not treated with antibiotics, but those did not count in the calculations.

Antibiotics and corticosteroids, either one would define a moderate/severe exacerbation, but patients could have an antibiotic-treated exacerbation during the run-in and still stay in the study. If they had a corticosteroid-treated exacerbation, they had to be withdrawn.

This resulted in a small number of antibiotic-treated exacerbations that started actually before study therapy began.

[Slide.]

We recognize that there is no agreed-upon definition of an exacerbation, but we do know, as

has already been brought up, that even Study 024 had slightly more limits on what was going to be considered an exacerbation.

There were guidelines for symptoms. There must have been 7 days between an exacerbation to call it a separate episode, and exacerbations were supposed to be treated with 10 days of antibiotics or corticosteroids.

That is the end of my introduction, and Ms. Zhou will do the efficacy results.

Efficacy Data for Advair Diskus 500/508

MS. ZHOU: Hi. Good morning. My name is Feng Zhou. I am the statistical reviewer for this application. Dr. Bosken has presented the background information to the other information and now my focus will be the main efficacy results, both mortality and exacerbations.

[Slide.]

First, I will briefly comment on the statistical methods for mortality, and I will talk about the dropout issue and in addition to show you results for primary comparisons of Advair versus

placebo, I will also show you the comparison of Advair versus individual component.

As Dr. Bosken mentioned, we are interested in results for U.S., so we also show results for U.S. versus non-U.S. countries.

Lastly, I will show the exacerbations from two studies 24 and 03, which will include multiplicity issue and results for the U.S. and non-U.S.

[Slide.]

In general, we agree with the sponsor's statistical methods and results. For the mortality, the primary analysis for log-rank test, stratified by smoking status, this test would produce the mortality results for all the arms I am showing today.

Also, I primarily focus on the ITT population where all patients followed for full three years. The primary analysis was Negative Binomial model in the Study 03, and the Poisson model in the Study 24. I will present the results from Negative Binomial model.

All the supportive analysis produced the consistent results.

[Slide.]

Let's look at the survival results, the efficacy results for Study 03. Here is the Kaplan-Meier survival curve using 20 percent scale. The X axis are the treatment days and the Y axis is survival percentage.

The red line is the placebo and the light blue is salmeterol, the pink is fluticasone, and dark blue is the Advair. The primary comparison of the treatment was Advair with a placebo. The absolute difference of Advair with the placebo is 2.6 percent, and hazard ratio is 0.82, and the adjusted p-value for interim analysis was 0.52.

You see Advair have 2.6 survival benefit over placebo in 3 years, but in this study, about 40 percent of patients drop out, so the survival benefit might be impacted by this high dropout rate.

I am going to emphasize here the survival status for all patients except 1 was 3 years

regardless of whether the patient was on treatment or not, so dropout, related baseline characteristic, so I will show you the results for low risk and high risk group, and also show you the U.S. versus non-U.S.

[Slide.]

There were about 1,500 patient enrolled into treatment groups. About 34 to 44 percent of patients dropped out with the primary reason for dropout being adverse event and lack of efficacy.

Note that dropout rate was higher in the placebo group for both those reasons. Overall, there were about 10 percent more patients dropped out in the placebo group than Advair group.

[Slide.]

Now, I am going to address the dropout issue in two ways. First, I will show the dropout pattern for low and high risk groups. In this presentation, the low risk subgroup is defined as a patient who had no MI and no COPD exacerbation during the previous year in enrollment, and the percent predicted bronchodilator, FEV_1 greater than

40 percent.

I will show the mortality results by risk groups, and then I will talk about analysis results for the on-treatment mortality compared with the overall mortality.

[Slide.]

Let's look at the dropout pattern. The Y axis show the percentage of discontinued patients and the X axis show the subgroup by the baseline characteristics. The first two groups of the patients who did or did not use the corticosteroids before the trial.

The second group, the second two are low and high risk as I previously find. The last two groups are defined by age using cutoff at 65.

Here, you can see the patients who used corticosteroids before the trial had higher dropout rates than patients who did not use, and the difference between the placebo and Advair more than about 10 percent.

The same pattern you can see in the low risk group and the high risk group, young age

group, old age group.

Overall, patients who are older and had more severe disease at baseline had higher dropout than patient who might be considered a lower risk. Generally, the difference between the placebo and Advair was 10 percent.

[Slide.]

Let's look at survival result for this subgroup. The graph shows the hazard ratios and 95 percent confidence interval for Advair versus placebo by subgroup.

The Y axis has hazard ratio ranging from 0.4 to 1.4, and the X axis showing the subgroups with percentage of patients in each group. Note that only 7 percent of patients had MIs during the period of enrollment. The other subgroups are the percentage in each patient of each group.

The reference line is hazard ratio over 1. The adult reference line is primary comparison with the placebo for the ITT population.

You can see the patient who has low risk had a better effect than high risk patients. You

see the younger age group, no MI, no COPD.

[Slide.]

This is a Kaplan-Meier curve for the low risk and the high risk subgroups, the red line for the placebo and dark blue for the Advair. About 26 percent of patients had the low risk profile, while the 74 percent was high risk. The treatment group was a balance being the subgroup.

Clearly, you can see the difference between the two graphs. Overall, the death rate was lower in the low risk group than high risk group, but the treatment people was greater.

Among the lowest group, the absolute difference for the death rate at 3 years was 4.2 percent, while it was only about half of that red group, the high risk group, absolute difference about only 1.8 percent.

[Slide.]

Next, you will look at analysis results of the on-treatment deaths. On-treatment deaths was defined as any death occurring on treatment and up to 14 days after treatment stops. So, for the on-

treatment death analysis, only the on-treatment deaths are counted as deaths even.

Patients who die while off treatment were not counted as deaths, instead, were censored at the date of death. Other dropouts was censored at the time of dropout for this analysis. Remember for the overall mortality analysis, patients who did not die on the study were censored at the end of the three years.

Absolute difference for the death rate for on-treatment deaths was 2.4 percent, which was slightly lower than overall result of the 2.6 percent, and also the hazard ratios on-treatment mortality was lower than the hazard ratio for overall mortality.

On my previous slide, you saw the high risk patients were more likely to drop out, and the low risk patient to stay on the treatment, so results for the on-treatment analysis looked similar to low risk subgroup analysis.

[Slide.]

In summary, low risk patients remained on

study longer than the high risk patients regardless of randomized treatment.

Low risk patients show greater benefit from Advair over placebo compared to high risk patients, which were supported by favorable on-treatment mortality results.

I found that the dropouts in both treatment groups were at a higher risk of dying than patients remaining on treatment. Treatment information collected after dropout was not adequate to assess its impact.

[Slide.]

This graph shows a hazard ratio for the five treatment comparison for the all-cause mortality. The estimate I am showing here is unadjusted for the interim analysis. The line is treatment comparison of Advair with the placebo, with the salmeterol, fluticasone, and the two bar was the salmeterol over the placebo and the fluticasone with placebo.

Again, there are two reference lines, the solid line at one, and the dotted line as a

reference compares the primary in comparison to the Advair to the placebo.

The Advair was numerically better than placebo and upper bound of confidence interval indicates without borderline significance.

Under the protocol, the comparison of Advair to its individual component for all-cause mortality are considered exploratory, because salmeterol is approved product for COPD, it is important to understand the contribution of salmeterol to Advair and also to see how salmeterol does against placebo.

Notice that the Advair is similar to salmeterol and is significantly better than fluticasone. Fluticasone was no different from placebo, so fluticasone did not contribute to the survival benefit of the combination product.

Also, due to the side effect of the fluticasone, one may ask whether salmeterol 50 would be as good as combination product of 500/50 in terms of survival benefit.

[Slide.]

This drug is used for COPD patients, so the COPD-related mortality was analyzed as a secondary mortality endpoint. An endpoint committee categorize death by the primary cause and identified which death was considered COPD related.

This graph shows a hazard ratio for the COPD-related mortality on the right, and in order to compare with all-cause mortality overall, I include all-cause mortality on the left.

For COPD-related mortality, comparing Advair to placebo, is similar to the all-cause mortality, however, the comparison to the salmeterol is more favorable to Advair for COPD-related mortality than overall mortality.

Study 03 was conducted at 444 centers in 42 countries, which was grouped into five regions: U.S., Asian, Eastern Europe, Western Europe, and Others. On this slide I will show you how U.S. results fit in with other regions in this multinational study.

[Slide.]

Eastern and Western Europe showed more

benefit, but Advair was Asian showing no survival improvement. U.S. was in between.

You recall from Dr. Bosken's presentation that Asian population might be considered a high risk population due to the age and some baseline characteristics. My next slide will look more closely at U.S. results since these results were considered important by FDA.

[Slide.]

About 23 percent of subjects were from U.S. The absolute difference at 3 years, the 1.6 percent, or the hazard ratio is 0.87 versus the difference of 2.8 percent and hazard ratio of 0.81 in a non-U.S. country.

The main difference between those two populations is in the placebo death rate with the 13.9 percent in the U.S., 15.5 percent for the non-U.S. countries.

[Slide.]

This graph is similar to the graph I just showed you, but it added two lines. The light blue is salmeterol, the pink line is fluticasone. The

Advair with the salmeterol appear to be showing great benefit in U.S. compared to non-U.S., and the opposite appears to be true for the Advair with the fluticasone.

In the U.S., Advair was similar to fluticasone, but in non-U.S. populations, Advair was significantly better than fluticasone. So, we see some inconsistency when we look at the comparison of Advair to its components in this subgroup.

[Slide.]

In summary, Advair showed a marginal benefit over placebo and comparable results to salmeterol.

Advair showed a smaller survival benefit in U.S. compared to other countries.

Advair showed a greater survival benefit for low risk patients compared to higher risk patients.

[Slide.]

Now, I will talk about COPD exacerbation, Study 24 and 03. Study 24 was a 1-year study,

about 1,400 patients, conducted outside the U.S. All patients in Study 24 were required to have at least one exacerbation in previous year. The primary endpoint was pre-dose FEV_1, and exacerbation was the secondary endpoint. There was no adjustment planned for the multiple endpoint.

Study 03 was a larger, longer study with about 6,000 patients in a 3-year duration. As I have already mentioned, about 23 percent patients from U.S., about 57 percent of patients had a history of exacerbation which is similar to those in Study 24.

Study 03 defined a multiplicity adjustment procedure which I will show you now.

[Slide.]

A fixed sequential gatekeeper approach as shown here. The first step says if all-cause mortality, Advair versus placebo, is less than 0.05, go on to exacerbation compared to Advair versus placebo. If this comparison fails to show significance, stop.

Since adjusted p-value for Advair was

compared to placebo, mortality was 0.52.

So, under this procedure, [?] tests for secondary endpoints should not be performed. However, clearly, a p-value of 0.052 would be considered borderline. So, is it reasonable to look at a nominal p-value for the exacerbation endpoint? Also, it is important to see if results for the secondary endpoint support a borderline result for the mortality.

[Slide.]

First, I will show you the moderate and severe exacerbation for Study 24, which is a one-year study.

The X axis shows the treatment comparison in the same order as the other slide. The Y axis is the rate ratio from Negative Binomial model.

Here is the rate ratio over 1, which means [?] to the Advair. Clearly, Advair did not show the benefit of individual component. The Advair did show effect over placebo, as did each component over placebo.

[Slide.]

Here, I am showing the exacerbation results for Study 03. Clearly, in this large study, the Advair is showing effect over placebo and to its individual components.

[Slide.]

In order to compare two studies, this graph is showing a rate ratio of moderate and severe exacerbation for Study 24, and for subgroup of patients who had exacerbation at baseline for the Study 03.

The two studies show a similar trend, but it is clear that the results for the Advair and individual components are less convincing in Study 24.

[Slide.]

For Study 03, I am showing here the exacerbation ratio by region for only the Advair compared to placebo. For this endpoint, we see more variability across region than we saw for the mortality endpoint, so I would like to focus on the U.S.

[Slide.]

Here, I am showing the U.S. non-U.S. result for Study 03, the dotted reference line and the indicated results for the primary comparison of the Advair with the placebo for the ITT population.

The Advair showed a smaller effect in U.S. compared to non-U.S. countries, which is consistent with [?] mortality.

This is interesting to note that in the U.S., a favorable result for the Advair over salmeterol was seen, but the comparison to fluticasone showed essentially no treatment difference.

[Slide.]

In summary, the results shown here had no statistical adjustments for multiple comparisons. Advair showed a benefit in reduction for COPD moderate and severe exacerbation compared to placebo in both studies.

In comparing Advair to salmeterol and fluticasone showed a similar trend in both studies, however, comparison was only significant in Study 03. Advair showed a smaller benefit in U.S.

population compared to non-U.S. population in Study 03, which was consistent with what we saw for mortality.

Thank you for your attention. Now, Dr. Bosken is coming back to show the safety and the summary.

Safety Data for Advair Diskus 500/50 and Summary

DR. BOSKEN: Now, to switch gears a little bit. We are going to talk about the safety endpoints. As has already been discussed, the safety database in Study 03 was extensive. Not only did they collect adverse events in the routine fashion and tabulate them by those that were fatal and those that led to withdrawal, et cetera, they did many, many special studies, some of which you have heard in the respiratory adverse events, and we will talk about that more later, in addition to which they did the studies on the subpopulation of the U.S. population, bone mineral density, ocular exams, and also the cardiac exams.

We have reviewed this data and we agree that there is no new safety concern here, and I am

going to focus the rest of my discussion on these other areas.

[Slide.]

As you have heard also and seen by the dropout slides, follow-up was longer in the active treatment groups and longest in the Advair treatment group. Because this was such a long study, this becomes very important over a three-year period of time, and all of the adverse events were, as you have heard, adjusted by the time on therapy, so that we will be talking about the rate of the event per 1,000 treatment years, as well as the incidence.

Again, as has been pointed out, the overall exposure was much less in Study 24. The spectrum of adverse events was not different, and I will not refer to them again either.

[Slide.]

So, starting with death, just to note that death in Study 03 was both in efficacy and a safety outcome. In the primary efficacy outcome, we looked at all-cause death. It didn't matter if

there was or when there was an adverse event, and death could occur at any time during three years after initiation of treatment.

This, of course, includes deaths that occurred weeks to months after the patient has stopped medication, or one way to adjust for that in the efficacy analysis, was the on-treatment analysis. The safety analysis, we are going to do a little bit differently, and look at the deaths as they relate to the adverse event, and it is the adverse event that is going to be tabulated.

We are specifically interested in the adverse events that occurred during randomized treatment. This will link the event and the death perhaps more closely to treatment, but the death could have occurred at any time after the adverse event.

[Slide.]

On this table, I have included the deaths related to adverse events during treatment. I have included both the incidence and the rates to compare them, and sort of to link this to what we

have heard about efficacy. On the rest of the slides, I will just list the rates.

We can see here that 9 percent of the placebo, 8 percent salmeterol, 10 percent fluticasone, and 7 percent of the Advair patients died at some time after an adverse event that began during randomized treatment.

The rates followed the same pattern. Cause of death was very similar to what was seen in the efficacy analysis. The most common causes were respiratory or cardiac and divided essentially between the two.

Notice, however, though, that in the overall deaths and in the respiratory, the Advair group had the lowest incidence and the lowest rates, and the fluticasone group had the highest incidence and the highest rates.

The adverse events in the cardiac and other areas were distributed widely around, across a very large number of diagnoses where the respiratory events were concentrated and actually we will focus on those from now on.

[Slide.]

These are the respiratory events experienced during active treatment that led to death. COPD, as in the efficacy analysis, was more common in the placebo patients, 9.8 events per 1,000 treatment years, than in the Advair group.

Respiratory failure was the next most common. This listing, by the way, is of all events that occurred in at least 5 patients in any of the active treatment groups. Again, the respiratory failure numbers actually follow the COPD numbers, 3.9, 4.2, 6.2, and 2.1.

Again, both COPD and respiratory failure were lowest in the Advair group and highest in the fluticasone group.

Pneumonia is number 3 on the list and as you have already seen, pneumonia was not a common cause of death, and the rate in the Advair patients was not elevated.

I would just like to add two comments to that finding, however. Number 1 is it has already been commented that many of these patients had

concomitant diseases, many of them presented at death with a concomitant condition, but just as has been pointed out before, all the patients that came in with pneumonia did not receive a diagnosis of COPD.

The reverse happened also, patients who were admitted with COPD might not have had the pneumonia included in their record, so that to the extent that those concomitant or contributing factors to death were not recorded, I think there may be a small underestimation of the overall impact of pneumonia in this population.

I mean we don't disagree that COPD was the underlying cause of death in these patients. They all had end stage lung disease.

The other comment to make is that at least with the CEC, the committee adjudicated death, all of the pneumonia deaths, all but one of the pneumonia deaths occurred in patients who also had a COPD-related death. So, if you look at it from that point of view, the population of interest, the ones that had death-related COPD, the pneumonias

were probably a little more important.

[Slide.]

Going on to serious respiratory adverse events, these are events that occurred on the top of the line are events are occurred in more than 1 percent of the patients in any of the active treatment groups.

COPD, the same pattern, the most in the placebo, the least in the Advair groups. Respiratory failure is similar, but not quite as common, is a serious event as opposed to a fatal event, and the salmeterol and fluticasone groups in this case are in between.

Of note, pneumonia is now the second most common cause. This is a serious respiratory event. This is life-threatening or requiring hospitalization.

The rate in the placebo and the salmeterol group was 28 and 27 events per 1,000 treatment years, whereas, in the fluticasone and Advair group it was 49 and 52. So, there is almost a doubling of the rate of serious pneumonias in patients

treated with the fluticasone-containing regimen.

The bottom line, we have grouped all of the diagnoses that we thought belonged in the lower respiratory tract. These had to have occurred in at least 1 percent of the patients in any of the treatment groups.

This included events that were rarer, but the same pattern, 35 and 33 events per 1,000 treatment years in the placebo and salmeterol groups, 56 and 62 events per 1,000 years in the fluticasone and Advair groups, again almost double the rate in patients treated with fluticasone.

[Slide.]

These are common adverse events. These occurred in more than 5 percent of the patients, and I have tried to list everything here that was infectious or possibly infectious.

Nasopharyngitis, upper respiratory infection, pneumonia, bronchitis, influenza, and candida all occurred in more than 5 percent of one of the active treatment groups.

The reason for listing all these is that

it appeared to us that the rate in the Advair group was consistently higher than the rate in the placebo group for all of the conditions except influenza.

In some of the conditions it wasn't great, it was 97 versus 86, 105 versus 101. With the pneumonias, again double the number of pneumonias. Even bronchitis here, 86 as opposed to 75. Influenza is the one that had a slightly lower incidence, 29 versus 31, and then oral candidiasis, which we would, of course, expect to be elevated.

So, we were impressed that there was an increase in general in respiratory infections. We expect increased candida. We frequently see small elevations in upper respiratory complaints in these studies with the inhaled corticosteroids, so we wanted to focus again on these lower respiratory tract infections.

[Slide.]

This is a Kaplan-Meier curve, cumulative incidence curve of a grouping of lower respiratory tract infection. This is different from the other

group in that it includes both severe and non-severe events. It includes all the events labeled as pneumonia, bronchitis, lower respiratory tract infection.

You can see that this is salmeterol and placebo at the bottom are overlapping. The 3-year cumulative incidence was 26 percent in the placebo and salmeterol group, 30 percent in the fluticasone group, and 34 percent in the Advair group.

The hazard comparing Advair to placebo was 1.38 and the confidence interval excluded 1. Of note, the incidence in the fluticasone group was also higher than in the placebo group, and the incidence in the Advair group was higher than in the fluticasone group.

[Slide.]

As you have already seen, if you pull out the pneumonias from that grouping, and you have seen this graph before, you also have an increased incidence of pneumonia in patients treated with fluticasone-containing regimen.

Again, placebo and salmeterol, salmeterol

is in blue. The 3-year cumulative incidence, 12 and 13 percent, fluticasone 18, salmeterol 20 percent, and the hazard ratio was 1.64 comparing Advair to placebo, and this time fluticasone was the same, very similar. Again, the confidence interval excludes 1.

Looking at these pneumonia graphs, there is clearly a difference between the two, but I would still like to comment that I think we may even yet be underestimating the impact of pneumonia here.

These are all patients who were on treatment at the beginning, when you developed the pneumonia. There was a finite number, and I don't know exactly how many because it would sort of take reviewing all the case records and all the case narratives, but patients who came into the hospital or who developed the exacerbations, study medication was terminated and a day or two later they deteriorated and got pneumonia and died with that pneumonia, that pneumonia would not be included in this analysis, because it was

technically off of treatment.

Again, it is probably not a very large number, but it may be another source of a slight underestimation.

Second, we are also concerned about diagnostic misclassification here. You have already heard that there was no prospective diagnosis or criteria for the diagnosis of pneumonia, and chest x-rays were not required.

Thirdly, we were impressed that it looked like in all the tabulations of adverse events, that the infectious rate was higher in the fluticasone and Advair treated groups.

[Slide.]

So, we took the non-pneumonia lower respiratory tract infections and saw what they looked like. This is just to let you know what we are talking about here. This is bronchitis, acute bronchitis, bacterial bronchitis. I have done some grouping here to make it simpler.

Lower respiratory tract infection with no specification, tuberculosis, pulmonary

tuberculosis, bronchiectasis, fungal infections, there were a couple of Monilia cases, and bronchopulmonary aspergillosis.

This is the number of patients with at least one event. Since there were multiple events in many patients, we will do the statistical analysis to account for that, but just looking at this first grouping, again, there are more Advair patients than placebo, and this appeared to be pretty consistent down the group with fluticasone in this case sort of intermediate.

[Slide.]

So, there is another Kaplan-Meier cumulative incidence curve. Now, this is the non-pneumonia. This is what is left over after you have taken the pneumonias out. In this case, salmeterol, placebo, and fluticasone are overlapping at 15 to 16 percent, a 3-year incidence, compared to Advair at 20 percent.

The hazard ratio was 1.23, and the confidence interval actually did exclude 1 if you take it out to enough decimal points it was 1.02 to

1.5.

So, we think there was evidence that more than just the pneumonias were increased. We repeated this analysis with just the bronchitis group. That was getting to a fairly low number of events. The hazard ratio was the same, but the confidence intervals did not clear 1.

[Slide.]

So, of course, the question has been raised how important is this, what does it mean. We tried to assess the importance by looking at the exacerbations. Now, you have already heard that the steroid-treated exacerbations, and these are exacerbations treated with steroids or steroids and antibiotics, were decreased with Advair and fluticasone treatment.

We looked at the exacerbation-only group in a way trying to focus more on things that would be more likely to be infectious. I am not convinced we always know what is going on with these patients and to know that because--I mean I think a lot of people use steroids and antibiotics,

that is their treatment, that is how they treat a COPD exacerbation, and it doesn't necessarily define an infectious event. I mean that was the logic behind selecting out the antibiotic-only one.

As you can see, the exacerbations, this is a negative binomial like the other exacerbations, events per year, 0.32, 0.31 in the placebo and salmeterol groups, 0.39, 0.37 in fluticasone and Advair group, and the rate ratio was 1.15 comparing Advair to placebo, with the confidence interval again excluding 1.

So, we don't have a good answer as to some of the discussion that has already come up as to why, how could the overall exacerbation rate be low, whereas the infections are high. We certainly all think that infection is important in the pathogenesis here.

I would suggest that the looseness of the definition of exacerbation and infection makes it very difficult to sort out what is going on here, because when you look at the case narratives, the patient is short of breath, has increased sputum,

may or may not be febrile.

They could have been called, for the adverse event, could have been called a COPD exacerbation, it could have been called bronchitis, it could have been called increased phlegm, I mean there was no standardization, so it is a little bit difficult to go back and figure out what was going on, but we will have to leave that with you.

[Slide.]

I am going to summarize what we think we have here. First, for survival, the difference between placebo and Advair in all-cause survival was 2.6 percent over 3 years. There was less benefit in the U.S. population and less benefit in high risk patients.

There was no difference between Advair and salmeterol, the approved product.

COPD-related mortality, the difference between Advair and placebo was only 1.3 percent, and whatever you want to say about the statistics of what looks like an increased risk for fluticasone in the survival curves, it doesn't fit

the pattern we want to see for a combination product.

We don't want to have the combination in the middle of the two components, one making things better and one making it worse. I mean it's a totally different pattern from what we see with pulmonary function where the two components provide a little bit of a benefit, and the combination provides a better benefit. That is what we are looking for.

[Slide.]

For exacerbations, in both Study 03 and 24, Advair decreased the rate of moderate/severe exacerbations when compared to placebo.

In Study 03, but not 24, Advair decreased the rate of moderate/severe exacerbations when compared to the components.

Advair decreased the rate of severe exacerbations in Study 03, but the decrease was not as great as seen with salmeterol treatment.

[Slide.]

COPD exacerbations, reported as adverse

events, were decreased in the Advair-treated patients, however, respiratory tract infections were increased in the patients taking either fluticasone-containing regimen, and antibiotic-treated exacerbations were increased also.

[Slide.]

For a final risk/benefit, the effect of Advair on survival was statistically borderline, not superior to salmeterol, and fluticasone may be exerting a detrimental effect.

One question one might ask is would a lower dose of fluticasone result in a better risk/benefit ratio.

[Slide.]

Advair effect on exacerbations. It was effective in moderate, corticosteroid-treated exacerbations, less effective in severe exacerbations, and not consistently better than the components.

Lastly, we have this increase in antibiotic-treated exacerbations and increased risk of respiratory infections.

Thank you.

DR. BRANTLY: Thank you, Dr. Bosken.

We have some leftover questions from our previous question period. I was wondering if we could go back and address those questions to our sponsor. Dr. Newman was first.

DR. NEWMAN: I had actually two questions, but I will take them one at a time.

One pertained to something that you raised in your comments earlier related to your product labeling. I know it may not be an essential question that has been posed to us, but it is sort of implied in some of the answers we have to give.

I am wondering if you could tell us a little bit more about the reasoning. I read in your documentation what I think is the sum of all of what you have added to your product label.

So, the first question is, is that all that you have added, and if you could explain a little bit of the reasoning for why you took the tack you did with relation particularly to the pneumonia and infection question.

DR. JONES: Actually, that is not all that we have added to the label. The FDA has had the full revised marked-up labeling. We have brought up certain infections. There is already a precaution that talks about low respiratory tract infections and pneumonia. We have now put the data from the TORCH study in the label.

DR. NEWMAN: So, you are saying that it is not just that one page of changes that you put in the document that you provided to us.

DR. JONES: That is the description of the results of the TORCH study. There are other modifications to the label, but that is the specific description of the TORCH study and the results from the pneumonia.

DR. NEWMAN: My second question pertains to the mortality data. I am wondering, from your perspective, how you would define the term "statistically robust."

DR. KNOBIL: Well, we have already talked about what the p-value is. It is 0.052. It is just above the predetermined level of significance

that we said in the protocol and the analysis plan.

It is supported by two other analyses, the Cox analysis and the log-rank that I have already showed you in the core presentation. It is not just the effect of mortality that makes the whole package statistically relevant and clinically relevant, so we believe that the p-value is a guide for what we would believe could occur by chance, so we believe that the mortality benefit, the magnitude of the mortality benefit is clinically relevant.

We found that the secondary endpoints were all highly statistically significant and all went in the same direction including the FEV_1, the exacerbation data, and the health-related quality of life, and those secondary endpoints were not just all in the same direction in the single study, but were also consistent with other studies that we have already done.

So, taking all of those things together, we think that because we only have the single study of mortality, as Dr. Jones discussed already, all

of these other things are going in the same direction and support the relevance both statistically and clinically of the mortality results.

DR. BRANTLY: Dr. Stoller.

DR. STOLLER: I have a couple of questions, one with regard to the FEV_1 slope. If we accept one of the principles of replication of results, I wonder how you interpret this first demonstration of a change in the FEV_1 slope in the context of many other antecedent randomized controlled trials of inhaled corticosteroids that failed to show a change in the FEV_1 slope, the U.S. slope, one health study ISOLDE Copenhagen, et cetera.

It just seems surprising in the context of a large body of antecedent data to now show this difference, and I wonder if you have some mechanistic or other explanation of why this should be discordant with previous results.

DR. KNOBIL: Yes, there are a number of other studies that didn't show a change or a

difference in the rate of decline of lung function between placebo and these are all inhaled corticosteroid studies.

For ISOLDE in particular, which was with FP, the study was actually only 750 patients, so a much smaller study, and there was a high dropout, so if you look at the graph, which I don't have to show you today, there was a difference it seemed over the first two years, but as patients dropped out of the study, the groups came together, so I think a lot of it has to do with the number of patients that you have contributing to your analysis, which is affected by the size of your study, and the dropout rate during the study.

So, we had enough patients left in the analysis to show the difference between the active treatments and placebo.

DR. BRANTLY: Dr. Reiss.

DR. REISS: I just want to go back to safety for a second. In your presentation, you talked about fractures and bone mineral density. I am assuming that the fractures were fractures at

any site. I think there was something in the background document about a spinal BMD, but did you look at vertebral deformities, by any chance, and especially in those patients that had low BMD to begin with, that were at high risk?

DR. KNOBIL: No, we didn't look specifically at vertebral deformities, but the spine BMD followed the same general pattern as the hip BMD with no significant difference between after treatments and placebo.

DR. BRANTLY: Lee.

DR. NEWMAN: i have one last question. A little bit earlier, we were discussing the idea of why there wasn't a comparison between the 250 versus 500, and I appreciated that discussion.

Something that maybe you implied, I just want to get clear, is do you think that it would be unethical to conduct another study?

DR. KNOBIL: Based on the data that we have today, I think it would be very difficult to convince patients and IRBs to do a similar study. Interestingly, when we started TORCH and we were

going to IRBs, even with no data, some IRBs were hesitant to approve the protocol because they thought that Advair already was shown to improve mortality, so now that we have these very strong data, I think it would be nearly impossible to repeat.

DR. BRANTLY: Dr. Reiss.

DR. REISS: Just one last question. Can you speculate on the effect of fluticasone versus Advair in the study, why do you think fluticasone looked a little bit worse numerically?

DR. KNOBIL: That is a question that we have tried to get an answer to, because we were surprised that FP was slightly lower than placebo, and certainly did not follow the observational studies that have been published before.

We dissected all of the data by year and by cause and looked at, well, maybe there was one cause in FP that was more than the other groups, and we couldn't identify any single reason why the FP arm showed the result that it did.

So, it is still something that we would

like to have an answer to, and we are still working on, but it is going to be a very difficult question to answer.

The one thing I did want to address along the same lines is that FP was a little bit below placebo as we didn't expect, and Dr. Bosken brought up the fact that it is causing a detriment in mortality.

I don't know that we can say that in the context of the combination, because if you believe that FP was worsening mortality, then, you would expect that the mortality result in Advair would be less than salmeterol, and not a little bit better, as we showed.

So, it is not as simple as just looking at each arm individually.

DR. BRANTLY: Dr. Moss is next.

DR. MOSS: I have a question for you guys about the gatekeeper concept. What do you guys think of that? I mean what is your opinion about that, because the statistician said we shouldn't go and be talking about anything related to

exacerbations or anything else, so what is your take on all that?

DR. KNOBIL: Well, it is the similar discussion that we had about whether or not you think the result is statistically significant. The p-value was 0.052, which is just above the cutoff that we said it was going to be, and it is a relatively arbitrary number, and probably is not really different from a p-value of 0.048.

Because the reduction in mortality was a clinically relevant reduction and compares favorably to other medicines that we have seen in other therapy areas, we thought that it was completely appropriate to go through the other analyses as we have shown you today, and as I mentioned before, the results of all those analyses on the secondary endpoints were highly statistically significant for FEV_1, exacerbations, and health-related quality of life, which are related to mortality.

So, that leads me to believe that the mortality benefit that we saw was not due to

chance.

DR. BRANTLY: Dr. Prussin.

DR. PRUSSIN: I just want to clarify your answer to Dr. Newman's question. So, you are saying that a trial comparing the combination at 500/50 versus the combination at 250/50 would not be ethical and is not a feasible study to do, is that correct?

DR. KNOBIL: No, that is actually not the question I was answering. If we wanted to repeat this study versus placebo, that would raise ethical considerations.

DR. PRUSSIN: Okay. But a study looking at the two different doses of fluticasone, both in a combination, would be a viable study from an ethics or logistical point of view?

DR. KNOBIL: From an ethical point of view, it would probably be okay, because I think that you have two active treatments, and you wouldn't be asking patients to be on the placebo arm for a long period of time.

Feasible, from an operational standpoint

and a statistical standpoint would be more difficult.

DR. PRUSSIN: Right, because they may be so close, but on the other hand, if we are concerned about the safety signal from fluticasone 500, that might be something that would drop out with the 250, I mean possibly.

The second question I had was essentially the same question I asked earlier, but I would like more detail when you when you are talking about these observational studies and two studies to measure the risk associated with the use of Advair.

I, for one at least, need much more than just repeat of what is here in terms of detail. What are these studies, what are the groups that are proposed or are being actually accrued at present? I would really like to know much more detail about these studies.

DR. KNOBIL: Yes, the studies are ongoing right now, the ones versus Advair, and for further detail on those studies, I will ask Courtney Davis, our epidemiologist, to explain those in more

detail.

DR. DAVIS: Sure. As Kate mentioned, we have a program of work in epidemiology related to the pneumonia signal. That includes five studies. There are three studies which relate to the natural history of pneumonia in COPD patients.

As you probably are aware, there was not a huge literature on this topic when you get into the specific population of COPD patients. There is quite a bit of literature on the epidemiology of pneumonia and the burden of pneumonia, but not in the specific population.

We designed three studies, two of which are based in the GPRD, the General Practice Research Database, which is an electronic medical record database from the UK, and that focuses on both the incidence rates of pneumonia in COPD patients, and non-COPD patients, as well as quantifying the risk factors for pneumonia, specifically in COPD patients.

The third study about natural history is using NIH cohorts specifically the ARIC cohort and

the cardiovascular health study cohort, which focus on again identifying risk factors for pneumonia including lung function and comorbidities. Those studies are completed as of now. We are just finalizing reports and we will get those to the Agency soon.

There are two more studies which are really pharmacoepidemiology studies, which are looking at the risk of pneumonia associated with drug use, and that is where we are trying to take an approach which is more similar to mimicking the trial design from TORCH to see, in patients treated in clinical practice, what is observed.

Again, one of those studies focuses on the GPRD, which has excellent longitudinal records and includes a lot of, well, all the elderly population in the UK in a representative sample.

The second study is a U.S. study which includes patients from four different HMO populations. As I said, those studies are underway. We are expecting results mid-summer.

DR. BRANTLY: Dr. Newman.

DR. NEWMAN: I was convinced that I didn't have any more questions, so I am sorry for that, I do have one more. It pertains to the question of, you know, I understand the idea that you are relying on the body of evidence in terms of other outcomes to bolster the mortality conclusion, and you are pointing out the consistency of that.

Along those lines, I am wondering, though, if you could comment for us on the notion that the improvement in mortality was, in fact, a smaller number in the U.S. portion where we might argue the relevance of what we do here today is most important.

So, if you could comment on the U.S.A. mortality 1.6 percent improvement data and maybe put that in context with the other supporting data that you have used to sort of bolster the mortality conclusion.

DR. KNOBIL: Well, I did kind of touch on this a little bit earlier. I did mention the numbers. Unfortunately, the projector is not working. The difference in the U.S. mortality,

which is 1.6 percent between Advair and placebo, versus the overall population, which was 2.6 percent Advair versus placebo, was something that I looked at much more carefully after looking at some of the documentation that we got for this meeting.

When I looked at it, the mortality rate for Advair in the U.S. population and the overall population was nearly identical at 12.6 percent in the total population and 12.3 percent in the U.S. population.

What really was different, as the statistician mentioned earlier, was that the difference was in the placebo population, having lower mortality in the U.S. than in the rest of the population.

Also, I mentioned earlier that the dropout rate in the placebo arm in the U.S. population was higher in the U.S. population than it was in the overall population. It was 52 percent in the U.S. versus 44 percent in the overall population.

Once a patient drops out of the study, they can take any medication that they would like

including Advair, including anything that is on the market, and they would still be allocated to the placebo arm.

I think the lower effect, even though I think it all goes in the right direction, and there would be some variability when you cut the data into smaller pieces, is mostly due to the placebo arm dropping out and potentially going on to other medication.

I already showed you the graph, the Kaplan-Meier graph of what people went onto in the different treatment arms with the placebo arm going on ICS plus LABA or ICD or LABA more frequently than in the other treatment groups, so I think that this can have a real effect on the results and underestimate what we are seeing.

DR. BRANTLY: Dr. Moss.

DR. MOSS: I want to ask a question I asked earlier, but ask it to the FDA. So, seven years ago they submitted--I might have the process wrong--but they submitted the concept of the study to look at mortalities, the outcome variable,

comparing the placebo group to the combination therapy.

You guys, I think, and this is where I need some clarification, thought that was okay as a primary outcome variable. So, seven years later, what do you guys think about that, is that still okay from your perspective, that we are comparing this to placebo, or in retrospect, do you think it is better that the study would be compared to one of the components, such as the long-acting beta agonist?

DR. BOSKEN: We are talking about the Study 03 now, the survival study, right.

DR. MOSS: The 3003 study.

DR. MEYER: I think that from my perspective, it is still an okay thing to be comparing it overall to the placebo, but I think that having the factorial design where we can look at how it compares to its individual components is important in terms of interpreting the results in terms of what they mean clinically.

So, I think even seven years out that I

would still say that the design of this trial was fine and that it was a well-conducted trial, but I think that having the other arms in there is important in not just making a statistical conclusion, but in the clinical interpretation.

DR. MOSS: For example, looking at trends, you would expect to see, as you said, the inhaled corticosteroid not be on the other side of a placebo arm, is that those sort of issues?

DR. MEYER: Yes, those kind of considerations, and yes, we would not have expected the inhaled corticosteroid to be on the other side.

DR. BRANTLY: Dr. Stoller and then Dr. Vollmer, and then I would like to reserve the last question for myself.

DR. STOLLER: I have one question of clarification to the Agency. In the briefing documents, on page 23, the proposed language for the indication includes a statement that I have not seen represented in the slides, which says an alternative dose is Advair Diskus 250/50 bid.

Am I correct in thinking that that is not

a proposal for the labeling indication? That appears in the briefing document, but I have not seen it anywhere else. On page 23, under the Integrated Review of Efficacy, Section 4.1.

DR. BOSKEN: The alternative dose is Advair 250/50, correct? Yes.

DR. STOLLER: That is true, but is that proposed as part of the new labeling modification?

DR. BOSKEN: Yes.

DR. JONES: The dose for Advair 250/50 and the indication won't change. The purpose of this supplement is just to address the 50/500 dose.

DR. STOLLER: I understand that, but the juxtaposition of the statement an alternative dose, under the language talking about survival and exacerbation, carries with it the implication of the alternative applicable to the 250/50, which as I understand it, has really not been discussed or not compared head to head, so I just want to clarify that, because it has not appeared.

So, I am correct in thinking that that is the text of the labeling indication as proposed?

DR. BOSKEN: That is the proposal, yes, it's not our proposal.

DR. STOLLER: Fair enough. I understand. Thank you. My other question regards the understanding of the survival effect. Dr. Zhou very nicely articulated the several interventions that are available to us in pulmonary medicine, that have been shown to have a favorable impact on survival - smoking cessation and the administration of supplemental oxygen to patients whose resting PO_2 is 55 or less, who have 56 to 59 cor pulmonale.

My question is I think you said that the survival analysis was adjusted for smoking status, but the question is if we look at the strata of patients who actually stop smoking, since they were I think 43 percent active smokers in the cohort at baseline, if we looked at those cohort of individuals who actually stopped smoking through TORCH and the cohort of patients who, by virtue of progression of their lung disease from GOLD stage 2 to 3, which was the baseline group that went on to require supplemental oxygen, are the results about

the Advair impact of survival robust when considered for the substrates of patients who would be benefited from smoking cessation or the administration of supplemental oxygen?

Does that make sense? It's a complicated question.

DR. KNOBIL: I think I understand what you are asking. We did look at mortality by smoking status.

DR. STOLLER: At baseline.

DR. KNOBIL: At baseline, that's correct.

DR. STOLLER: But not around smoking cessation through the course of the study, is that correct?

DR. KNOBIL: That's correct, because the vast majority of patients stayed in the stratum that they were in, so there wouldn't be enough patients to actually look at that endpoint, because very few patients--

DR. STOLLER: Is that right, with 43 percent baseline smoking, there were no smoking stoppers through the trial?

DR. KNOBIL: Not a significant amount, no, unfortunately.

DR. STOLLER: I am surprised.

DR. KNOBIL: Yes.

DR. STOLLER: And what about, you know, clearly, one would expect a relatively high incidence of patients going on to requirement of supplemental oxygen over the course of the three-year study with baseline FEV_1 of 40 to 45 percent predicted.

The question is (a) are you aware of the incidence of that event, (b) are you aware of the administration of the supplemental oxygen to those patients, and (c) if that is the case, were the survival benefits robust around those interventions?

DR. KNOBIL: We did collect long-term oxygen therapy and when patients went on it, and unfortunately, I don't have in front of me the percentages of patients who went on therapy, but I don't have the analysis for you for those who went on therapy to see if that had an additional effect.

My guess would be that again the numbers would be too small to actually have a robust analysis of that effect, but that is something that we could look into.

DR. STOLLER: I think you can understand the potential importance of that situation.

DR. BRANTLY: Dr. Vollmer.

DR. VOLLMER: I have two questions. I understand the discontinuation rates, but while people were on treatment, whatever the treatment was, did you have any objective measures of adherence just to see how well they were adhering to what they were taking at the time?

DR. KNOBIL: We did do dose counts from the discus because there is a dose counter in the discus, and the adherence rate was approximately 90 percent in all groups. So, that is all the data that we have.

DR. VOLLMER: The second question. To get back to this U.S. population and how that may look different, clearly, there is a gender difference and a couple other differences. I can't find the

page, but I am sure I have seen somewhere there was a big difference in comorbidities in the U.S. population versus the other populations.

Relative to the comments that were addressed about the effects of the Advair appearing to be greatest and lower risk than higher risk patients, I am just wondering whether (a) am I remembering right that I read that there was a strong difference in terms of the comorbidity profile of the U.S. population, and when trying to look at similar patients in other countries, was the U.S. experience similar and to what extent did that perhaps explain some of the differences, or did you even look at it?

DR. KNOBIL: I don't recall that there was a huge difference in comorbidities between the U.S. and the other regions. Again, I don't have the tables at hand. We might have that information.

Dr. Bosken?

DR. BOSKEN: Yes, I think you reported a 12 percent incidence of myocardial infarction in the U.S. group compared to the other regions was

like 6 or 7 percent, but the information on myocardial infarction was not obtained until a couple of years after the study had been initiated, and the U.S. enrollment didn't occur until late either, so that a lot of the Europeans that were enrolled did not have that question asked that way. I mean everybody had a question what are your past diseases, but I have forgotten the date of the amendment, when have you had a myocardial infarction was added.

DR. KNOBIL: Yes, and everyone was asked that question. Everyone was asked the same question after the amendment was initiated.

DR. BOSKEN: Correct, but there were a lot of people enrolled in Europe before the amendment was issued.

DR. KNOBIL: Yes, and we went back to the European subjects and asked the same question, so we should have similar data on all the regions.

The data for myocardial infarction is patient reported as much of the data that we have here today, and overall, I guess it was about 7 to

10 percent across the study. I am not sure that that is a huge difference between the regions that would cause one to believe that you would get different results from the different regions.

DR. VOLLMER: I may have just misremembered, I can't find it again, but I was sure that I had seen it when I was reading through all this stuff.

DR. BRANTLY: If it is possible, I would like to take the last question. This is actually a question for Dr. Knobil and Dr. Celli.

I would like to know what percentage of the patients were chronic producers of sputum. This is based on the concept of we are beginning to recognize with CT scans and a number of COPD patients have bronchiectasis as part of it. It is oftentimes one of the explanations for these very prolonged back-to-back treatments that we give patients.

Do you have any data on that?

DR. KNOBIL: No. At the beginning of the study we did not collect whether or not patients

had chronic bronchitis or emphysema, or the level of sputum production, or whether they met the definition of chronic bronchitis as we know it now. So, we don't really have that information for TORCH.

DR. BRANTLY: Is it possible to drill down on the data set of those individuals who had very prolonged and see if you could get more information that might put them into the category of having chronic bronchiectasis?

DR. KNOBIL: I am sorry, more prolonged?

DR. BRANTLY: In that subgroup of individuals that had the prolonged, the 170 days or the 200 or one year exacerbations, if you go back and collect that information to see whether those individuals actually had bronchiectasis.

DR. KNOBIL: It would be very difficult. As Dr. Bosken very sympathetically pointed out, it was hard enough to find out if these patients were alive or dead, so finding a sputum production history, I think would be really very difficult.

DR. BRANTLY: Thank you very much.