related to blood chemistry or hematology.

The statistically significant primary efficacy variable was foreign body sensation from the scheduled visit query.

Just moving on to an overview of efficacy of the three trials, summarizing protocol 002, the objective sign reaching statistical significance was corneal staining. The subjective symptoms reaching statistical significance were blurred vision, sensitivity to light and itching, refresh use, the composite symptom score, facial expression, subjective scale, the OSDI and the global response to treatment.

In the overview of efficacy in trial 003, the objective signs reaching statistical significance were the categorized Schirmer with anesthesia, and global response to treatment under subjective symptoms reached significance only at month 3.

In protocol 001 the primary efficacy variable that reached statistical significance was foreign body sensation.

Both Phase III studies technically satisfied the criteria for efficacy as set forth in their study reports, and that is that there is a statistically significant difference in one objective sign and one subjective symptom, but it is apparent that the two Phase III studies were not replicative.

Just a brief overview of safety, there are no increases in ocular or systemic infections in the cyclosporine treatment group, and adverse experiences are predominantly mild to moderate ocular events in all three studies.

In conclusion, I have attempted to briefly summarize the three trials submitted to the NDA to establish safety and efficacy for cyclosporine ophthalmic emulsion. Thank you.

Statistical Review

DR. LU: Good morning. I am Laura Lu, the statistical reviewer of this NDA. In this presentation I am going to discuss the efficacy results from a statistical point of view.

First, I am going to discuss the efficacy evaluation at multiple time points. Secondly, I am going to compare the efficacy results in the two pivotal trials, trial 002 and trial 003.

Study 002 and 003 are two identically designed trials. In these two studies most of the endpoints were measured at baseline, month 1, 3, 4 and 6. However, the criteria of efficacy evaluation based on these multiple measurements are not clearly specified.

At this point, you may see a discrepancy between my presentation and the sponsor's presentation. I think the

main confusion is that in the sponsor's study report of the NDA the endpoints with any p value less than 0.05 at any time point were reported as statistical significance. If we just pick up small p values at each of the time points, then there will be multiple chances in claiming a statistical significance and the type-1 error will be inflated.

Since month 6, which is the end of the trial, is considered a reasonable time point for efficacy evaluation by the review team, in these slides I am going to present the ITT efficacy results of studies 002 and 003 at month 6 so we are presenting at the same time point.

In this table the rows correspond to endpoints. The yellow-shaded rows are for the primary endpoints which are the sum of staining and OSDI. The rows below are for the secondary endpoints. The columns list the between group comparisons in the two studies. These between group comparisons are cyclosporine 0.05 percent versus vehicle and cyclosporine 0.1 percent versus vehicle. The numbers listed here are the p values smaller than 0.05.

The first thing I would like to point out is that in study 003 no primary endpoints showed statistical significance, and the only secondary endpoint associated with small p values is categorized Schirmer tear test with anesthesia. But I would like to point out that when the primary endpoint has no statistical significance the p

values for secondary endpoints cannot be validly interpreted. It is not only a multiple issue; there is another issue too.

The second thing I would like to point out is that in study 002 the categorized Schirmer tear test with anesthesia is not associated with small p values. So, there is no common primary endpoint and secondary endpoint with small p values in both studies.

The third thing I would like to point out is that the responders analysis presented by the sponsor, based on corneal staining, Schirmer with anesthesia, blurred vision and use of refresh is not listed in this table since it is not a preplanned analysis. So, the p value is not interpretable in terms of statistical significance.

So, in summary, the efficacy results are not consistent between the two studies, and there was no statistical significance in the primary endpoints in study 003, in which case the p values for secondary endpoints cannot be validly interpreted.

That is all for my presentation. Thanks.

DR. FONG: Questions for the FDA? Dr. Lavin?

DR. LAVIN: Yes, this is a question for Laura. I am a little bit confused looking at what the briefing document pulled together by the sponsor versus what the FDA has said with these primary and secondary endpoints. My

understanding was that the requirement in the protocol was to have one or more of five objective and one or more of five subjective to come in for that to be statistical significance. But now, in Laura's presentation, all I see are just primary and secondary. Could you clarify which it really is?

DR. LU: Yes, I think I would like to first turn to Bill to answer this question.

DR. BOYD: The protocol that was submitted breaks the efficacy measures into primary and secondary variables. The study report that we received breaks it into subjective and objective signs. It is true that there was agreement between the sponsor and the agency that efficacy was one objective sign and one subjective symptom that were statistically significant, but the actual protocols that we received for 002 and 003 specified primary efficacy variables that include the sum of the corneal and conjunctival staining and OSDI. The secondary efficacy variables were facial expression, scale, symptoms of dry eye, the Schirmer tear test, tear breakup time and global evaluation. So there was a difference in the way that the variables were named. In the original protocol it was primary and secondary. In the study reports that we received and reviewed it is objective signs and subjective symptoms.

DR. LAVIN: A follow-up question to that, did the sponsor submit an analysis plan to you prospectively to indicate that they were going to do one of five subjective and one of five objective? Was it a surprise to you when you saw the report, or did you have the knowledge of that before they sent any data in?

DR. CHAMBERS: Let me take you back historically. These studies were planned at a time when we did not have good information as far as what to expect from any of the parameters. There have not been good studies that have looked at the efficacy of products for keratoconjunctivitis sicca or any of the dry eye syndromes in a number of years. Consequently, at the time of the planning there were guesses that were made as far as what would be the best variables to look at, as well as a scale that would need to be validated.

The agency, at that time, was not willing to accept outright the primary variables that were listed as being necessarily okay, necessarily acceptable because they had not yet been validated. So, the agreement that the agency has had for any of these products is a minimum requirement of showing at least one subjective and one objective criterion, and it has been stated as that at numerous meetings with numerous firms.

DR. LAVIN: Okay. One follow-up point on that statistically, this is an interesting issue when you have

multiple chances for significance, which I think is an educational thing as well as just a sense of what is really statistically appropriate to do. When you have five endpoints, say, five objective endpoints and you are saying I would like to have one that is significant and that is my criteria for success, then your p value isn't any longer 0.05 for that objective criteria. What actually happens is you have five chances to be significant. So, you p value has to be adjusted downward to 0.01, namely, 0.05 divided by 5. So, that is the criteria that would need to be put into place for an adjusted type-1 error.

The same kind of reasoning would also apply for the subjective endpoints. Again, five possible subjective endpoints divided into 0.05. So, if you are to accept that criteria of one of five successful for the objective and one of five successful for the subjective, then the p value hurdle in the true statistical perspective should be 0.01 instead of 0.05 as criteria for significance.

Another thing that also has to be talked about here in terms of significance and comparisons is the overall adjustment for the overall global test, and then the test for the individual pair-wise comparisons. While it is acceptable to do it as they have, there are other adjustment procedures that are controversial amongst statisticians. There is Holmgreen's procedure and a Holmes' procedure, each

of which would require a p value smaller than 0.05 for comparison. So, we are really into rather subjective areas of statistical inference in terms of seeing whether or not the treatment comparisons need further adjustment. But I would say that for the purposes of the panel and comparisons I would go with 0.01 as the standard for significance in these studies.

DR. CHAMBERS: From the agency's perspective, there is no disagreement that when we stated we would take one subjective and one objective we were assuming there would be correction for multiplicity depending upon the number of endpoints that were put in. Depending on what the correlation is between those endpoints, as you know, the adjustment will vary. The most conservative is to divide by the number of variables and take 0.01. The assumption was that we would initially look at it as though we were taking that most conservative estimate, recognizing that that may be an overcorrection if there was correlation between the variables, and there is most likely correlation between several of these variables.

DR. FONG: I have a question to Laura. In looking through the documents submitted by the sponsor and from the FDA, it appeared to me that the primary endpoint was three-step change in sum of corneal and conjunctival staining. Is that correct?

DR. LU: Right.

DR. FONG: If that is correct, then shouldn't the results be reported as percent with a three-step change? If so, I am curious to see what the result of that might show, the comparison of three-step change between the vehicle group and the treatment groups.

DR. LU: The sum of staining is from 0-15. I am not exactly sure, what do you mean? Three-step?

DR. FONG: I guess I am concerned that oftentimes in these analyses of variances or correlations very small differences can yield a statistically significant finding but, in fact, the clinical significance is relatively low. So, if we had defined ahead of time that a three-point change in the scale, 1-15, is what you are looking for shouldn't the results be presented as the percent of eyes that had a three-step change in each of the categories?

DR. LU: Yes, actually, in my review I comment that the actual change -- that the point estimation is 1.67, or something, and is really less than the prespecified. Although there is statistical significance, but it doesn't mean clinical significance. So, you know, to judge that I leave it to you.

DR. FONG: Maybe I will ask the sponsor after lunch the same question, you know, what percent of eyes actually had a three-step change. Any other questions?

If not, let's go ahead and break for lunch and we should reconvene at one o'clock. I wanted to remind the committee members not to discuss the issues under discussion outside this room.

[Whereupon, at 11:47 a.m. the proceedings were recessed, to be resumed at 1:05 p.m.]

A F T E R N O O N S E S S I O N

DR. FONG: Good afternoon. We will go ahead and reconvene for the Ophthalmic Drug Subcommittee meeting. I believe we were in the middle of questions for the FDA. Are there any questions for the FDA at this point? Dr. Lavin?

DR. LAVIN: Yes, just one question further, have there been any open-label data submitted on either safety or efficacy to the FDA?

DR. CHAMBERS: Any additional data? Yes, what we have tried to present has been what we felt was the most representative and best controlled information but, as was pointed out by Allergan earlier today, there are still ongoing studies.

DR. LAVIN: Two things that would be of interest from my perspective would be if you doubled the safety information. From the graph that was shown earlier, I think there were at least 300 person years of safety experience between months 6 and 12. Also, it would be real interesting to see whether or not the vehicle data could have improved once those patients started to be treated. I think those could also shed some insight as to whether or not there was just back luck with study 003 or whether or not further improvement could be seen in that vehicle group.

DR. CHAMBERS: I will ask Allergan to comment if I am mistaken but it was my understanding that there is nobody

left on vehicle; that everybody has been switched to active therapy.

DR. REIS: That is correct. The last 6 months of the trial would not be a vehicle-controlled trial. All the vehicle patients were switched to the higher concentration of 0.1 percent.

DR. CHAMBERS: Which is our standard procedure when we are trying to collect additional safety information.

DR. FONG: Other questions for the FDA or the sponsor? Jack?

DR. CIOFFI: This is for t he sponsor, if we are going to go back to that. Actually, we really didn't get any answer earlier on the responder versus non-responder, and you went to your responder analysis and explained that in some detail but I am wondering more about did you ever look back at the demographics of your patient population, not at their disease characteristics but at their demographics to see who this was working in and who it wasn't?

DR. REIS: We did look at that. There is no way to identify based solely upon the demographics of these patients who would be responsive to Restasis therapy. The population that we studied is representative of the heterogeneous group that exists in dry eye. So, we feel that the studies were representative in looking across the

broader spectrum of the patient population. We are still not yet at the point in our learning where we could identify a priori simply based upon demographics, other than what has currently been known, that the postmenopausal female is predisposed to the development of chronic dry eye.

DR. CIOFFI: And you could not separate out any group that responded better based on anything?

DR. REIS: Not based upon the demographics alone, no.

DR. CIOFFI: No. On anything? I didn't say on demographics alone.

DR. REIS: Based upon the subjective signs and symptoms, the objective signs that we had identified in overall disease severity, yes, there we can identify patients that are responsive based on low Schirmer scores and based upon corneal staining, as well as the two symptomatic components. This would be consistent with the way ophthalmologists utilize multiple signs and symptoms to definitively diagnose the disease.

DR. FONG: Dr. Matoba?

DR. MATOBA: I wanted to just ask you to clarify the exclusion criteria that you used for your clinical study. It says here that patients were excluded if they were using concomitantly or had recently used certain topical systemic medications, including general anesthetics,

antihistamines, etc., and then you specifically say topical steroids but you didn't mention systemic steroids. Also, since many of these patients were felt to have Sjogren's syndrome they may have been on anti-metabolites, steroids or some other immunomodulating systemic therapy. Were all those patients specifically excluded, or was that not addressed?

DR. REIS: First of all, let me say that the proportion of Sjogren's syndrome patients enrolled in our trial was approximately 30 percent in each of the two studies. Patients who had systemic autoimmune disease were allowed to use their systemic therapies such as systemic steroids. These are patients, however, who, despite the use of systemic immunomodulating or anti-inflammatory treatment, still had ocular surface disease or chronic dry eye disease. So, we did address, from a systemic use, that it was all right for patients to use these medications as long as they still had the dry eye condition.

With respect to the topical medications, all concomitant topical medications, apart from the artificial tears provided by the sponsor, were not allowed to be used for a variety of reasons, predominantly because these are agents that are known to induce or exacerbate a dry eye condition. Our intent was to study patients who had chronic dry eye disease and not dry eye that was induced or

exacerbated by topical ophthalmic medications.

DR. MATOBA: Did you monitor the level of systemic anti-metabolite or steroid therapy throughout the study to ensure that they did not have significant alterations in their regimen?

DR. REIS: Yes, the use of all concomitant therapies was tracked throughout the study period at each patient visit, with any change in concomitant medication being recorded with respect to dosage and duration of treatment. These data were evaluated and accounted for. Patients who had substantial changes in concomitant medications would have been excluded from efficacy analysis but permitted to be included in the safety analysis.

DR. FONG: Dr. Seddon has a related question.

DR. SEDDON: Related to what Dr. Matoba just said and what Jacquelyn Goldberg said earlier this morning, related to these different factors and variables, did you look to see if they were equally distributed among the three different groups -- vehicle and the two dose groups? I think that would be an indicator that these factors might not play a role if they were equally distributed among the three groups.

DR. REIS: Yes, we did look at the distribution of a variety of factors over the three treatment groups and between the two studies. Things that we looked at

specifically were the incidence of Sjogren's syndrome, the presence or punctal occlusion for these patients, distribution by sex, race, iris color, medication use, and found that these, for the most part, were equally distributed across the treatment groups. The lack of normal distribution or the lack of equivalent distribution had to do with some of the individual criteria for dry eye disease that confounded the results which we have already shown you.

DR. SEDDON: And the medication use included hormonal use?

DR. REIS: Yes, it did.

DR. SEDDON: Thank you.

DR. CIOFFI: Were the four factors that you used in your factor analysis equally distributed?

DR. REIS: Yes, those factors were equally distributed and, indeed, a factor analysis that was done on the baseline data independently from each of the two studies showed the exact same distribution of the signs and the symptoms across the analysis.

DR. CIOFFI: One other more mundane point, in your Phase II and Phase III, under objective criteria, you had meibomian gland health on multiple slides. What is that?

DR. REIS: Meibomian gland health, as we evaluated it in our Phase III program, referred specifically to the patency of the meibomian gland orifices. We had attempted

in our Phase II program to do a more detailed evaluation of meibomian gland health, including things such as meibomian gland dropout, the turbidity and clarity of the expressible meibomian, and found that there was considerable difficulty among investigators in evaluating those things in a standard way. So, the patency of the meibomian glands was the specific measure of meibomian gland health that was evaluated in Phase III, primarily from a safety standpoint, with the use of an emulsion formulation.

DR. FONG: Dr. Herndon?

DR. HERNDON: I have a question dealing with the quality of life. Earlier it was mentioned that with the topical cyclosporine perhaps you could limit the number of drops, refresh drops that your patients had to take over time. I sort of can appreciate that as a glaucoma specialist by increasing compliance and quality of life. But at 6 months the vehicle group is actually using fewer drops than the cyclosporine group. Can you expound on that?

DR. REIS: The differences that we have in study 003 come back to the fact that we had a greater vehicle response in study 003. I would like to spend just a moment talking about what our vehicle was, and emphasize the fact that this was a vehicle with substantial palliative benefit. This was not a clinical trial that was run against what is the current standard of treatment for these patients, namely

an artificial tear. So, I am going to ask Dr. Dan Nelson to speak to why we would see a strong vehicle response in these patients based upon the preponderance of patients with less severe cases in study 003.

DR. NELSON: I am a clinician who specializes and most of the patients I see are dry eye. I have been doing it for about 20 years.

Here is a simplistic way of approaching this. The state of knowledge that we had even three years ago as it relates to dry eye has changed drastically. It has now become apparent, and the data that you have seen today helps substantiate that, that inflammation is the key component as it relates to dry eye. Again, simplistically thinking about it, there are two causes. One is irritation, whether that be environmental, allergens, solutions, mechanical effects or the like, and immune activation.

In the study, those were entered who fell in the mild to severe category. As you can see, there are going to be many more patients in the severe category that might have an immune basis for the disease. In those patients that are up in the high moderate zone, they might respond to treatment that is more related to treating irritation.

So, for example, in patients that come into a study like this and we treat them with a vehicle, they may or may not get better depending on the vehicle. There are

three reasons. One, we can see that patients get better because they are more compliant during the study. Two, it might be sheer chance. They were bad one day; they are good the next. Or, we might actually see a vehicle response.

So, for example, when we look at 002 and 003, we see a vehicle response from baseline in the study group, and this is a much more severe population, and in 003 we see an even more significant vehicle response.

I suggest to you that it is not compliance related because they are only taking the drug twice a day. It is probably not random chance because I wouldn't expect a group of 100 or so patients to sporadically, everybody, improve. It is probably related to true vehicle effect. And, because we are dealing with a more mild population, I would expect the vehicle to have more effect on irritative symptoms. In this particular group we might see some effect as we do from the vehicle because there is a certain irritative component. On the other hand, I would not expect to see anything that might influence immunoreactivity from the vehicle group.

If we look at this slide, which is a similar slide that looked at the baseline Schirmer tests, here we can see that we wouldn't expect the vehicle to have any significant effect on increasing Schirmer's with anesthesia, and that is basically what we see -- minimal vehicle effect but we do see an effect at the 6-month evaluation of the cyclosporine,

which is an effect on the immune component.

So, I think the effect we are seeing here is a true vehicle effect. When you do studies, ideally you would like to have a true placebo. It is not possible in this. The standard might be comparing to an artificial tear; you probably wouldn't see as significant an effect. The vehicle's effect, as has been mentioned before, has a long retention time on the surface of the eye which probably accounts for its beneficial effect that we see in these studies.

DR. FONG: Dr. Matoba?

DR. MATOBA: This is a related question. You mentioned earlier that the vehicle has a prolonged residence on the ocular surface. Is that prolonged residence time associated with persistence of blurred vision from the drop?

DR. REIS: It is not associated with the persistence of blurred vision. We looked specifically at blurred vision in our Phase II dose-ranging trial as part of the formulation tolerability. While there was increased blurred vision at the 0.4 percent, it was not present at the 0.1 and the 0.05 percent.

Mr. Chairman, if I might, I would like to come back and complete some questions that were raised this morning, right before the lunch break, with respect to some of the statistical items, if that would be appropriate.

DR. FONG: Please, go ahead.

DR. REIS: All right. Dr. David Strauss will respond, on our behalf, for the questions that were raised around the demonstration of significance in one sign and one symptom, and there are multiple signs and symptoms, and the adjustments that might be appropriate for that.

DR. STRAUSS: Yes, David Strauss again. The committee raised some important points about multiplicity. I just wanted to add some comments. I thought as an external statistician that might be appropriate.

First of all, just to recap something that was said before regarding multiplicity over time, the statistical analysis plan specifically said 6 months and Dr. Reis's presentation was confined to 6 months. So, there is no issue there.

I think a more challenging question is the one that was raised by Dr. Lavin, which is that if you have, say, five symptoms to look at and you want to do a 5 percent test, then shouldn't you divide that 5 percent by 5? I think this is an important point and I would like to make several comments, if I may.

I think, actually, it would be good if these things could be discussed in an appropriate forum later and perhaps some guidelines be given. First of all, if your objective is to come up with a single global test of the

study and you have five symptoms and any one of them would do, then I would certainly agree with Dr. Lavin that you need to make that adjustment. I am sure Dr. Lavin would agree with me that divided by five might not be the preferred way because that is rather conservative, and particularly if the tests are dependent that should probably be taken into account. But, certainly, that is the kind of analysis that you would want.

On the other hand, I think there is also a case to be made for not doing that under some circumstances. If you want to look at these five symptoms separately and then they could all be tested at the same five percent level, and then it would be up to the panel and the evaluating board to integrate those findings as they thought they were appropriate. My own personal view is that perhaps it would be best in some circumstances to report both since I think both of them have some interest.

The other point I wanted to mention is that for today's purposes the issue really is moot because whether you use a five percent level or one percent level, it turns out you get exactly the same result, namely, the study 002 gives you significance with respect to one sign and one symptom, and study 003 gives you significance with respect to one sign, not a symptom. Just to repeat, that is true whether you use an 0.5 percent level of significance or 0.1.

Thank you.

DR. LAVIN: Yes, I would like to respond to that. I think that there is an issue that I think the panel needs to be aware of, which is basically that one does not know whether these endpoints are all clones of each other or not. We would like to think, from having looked at the data that was presented to us, that those were not clones of each other. So, I would stand by my earlier statement that it is more likely to be 0.01 than 0.05.

The other thing that is also critical is that in our briefing document we see p values that I guess were provided by you, folks, as well as by the FDA that show p values at month 1, month 2, month 4, month 6. So, we do have a multiplicity of time points. So, clearly, it is something that needs to be considered.

I do agree totally with your strategy of emphasizing month 6 outcome, but I think that this is obviously something that is an issue. I do agree with your last point, which is that in study 002 one has achieved significance by that standard and in study 003 one has not. So, I would agree with you on that last point as well.

DR. REIS: Thank you, Mr. Chairman.

DR. FONG: I have another question. Can you refresh my memory again, which are we talking about that has achieved statistical significance in study 002? Was it the

corneal staining? Is that the objective sign that we are talking about as having reached statistical significance?

DR. REIS: In study 002 corneal staining and the total of the corneal and conjunctival staining achieved statistical significance.

DR. FONG: That goes back to my earlier point of statistical significance versus clinical significance. You know, it is a very, very small finding, and I would like to ask again whether the comparison was statistically significant if we look at three-step improvement in the sum of corneal and conjunctival staining.

DR. REIS: I will respond first to the three-step improvement and then I will ask Dr. Pflugfelder to respond to the clinical significance of the changes that we observed in corneal staining.

With respect to your request prior to lunch on the three-step change in corneal staining, we are still waiting for our data to come back from Irvine so I can't provide that to you just yet.

The staining that was stipulated in the protocol was that we would have a 3-grade change out of a total of 15, assuming, in the absence of any other prior studies to guide us, that we would expect a 1-unit change in each region of the conjunctiva and a 1-unit change in each region of the cornea, or at least a 20 percent change in staining.

Due to the difficulty that our investigators encountered with the lissamine staining, the majority of the change that we saw in staining was for the cornea. In study 002 that change was approximately 20 percent, and a little bit less than that in study 003.

I will ask Dr. Pflugfelder to respond to the clinical merit of the change that we observed in corneal staining.

DR. PFLUGFELDER: I feel that the change in corneal staining was significant. It changed about 0.9 units on a 5-point scale in 002, and I believe about 0.8 on a 5-point scale in 003. So, that represents about a 20 percent improvement in each of the two studies. Having looked at, you know, patients with keratoconjunctivitis sicca for years and really just recently, as I showed you in my talk, getting a handle on the significance of that in terms of the quality of a patient's optical system and their complaints of blurred vision, I think that is significant because usually what we find is that keratoconjunctivitis sicca gets better. The central corneal staining, which is over the line of sight which affects vision more, goes away first, and rarely do we ever get rid of the staining at the upper and lower cornea where the eyelid margin rubs on the eye and creates a frictional force. So, you know, if we assume that that may represent about 50 percent of the

staining, getting rid of the central corneal staining certainly should have an impact on the quality of life and a patient's visual function.

DR. FONG: You are talking about the 20 percent, was that the treatment effect between 0.05 and vehicle?

DR. PFLUGFELDER: That was the improvement in the 0.05 percent.

DR. FONG: How was it changed from the vehicle?

DR. PFLUGFELDER: Actually, I don't have those numbers here in front of me.

DR. LAVIN: I think it would be relevant to the mean at baseline as opposed to the full-scale of five units. So, if it was 0.8 relative to 3, that is more meaningful than 0.8 relative to 5.

Also, if I could interject a question for Dr. Pflugfelder, on the Schirmer test with the anesthetic, what would be a clinically meaningful difference there, and did you think that in the study it was attained, especially in study 003 and relative to study 002 as well?

DR. PFLUGFELDER: I think that any improvement in a Schirmer test would be significant for the patient because the problem is that most of these patients don't have any tear production. Most of them lack the ability to reflex tear, which is the eye's way to respond to a stimulus such as a piece of dust getting into the eye, and it didn't

appear that that really occurred much because that Schirmer test did not improve, but the basal Schirmer test, which is the Schirmer without anesthesia, did significantly, and highly significantly improve in 003, as well as in the composite index, which had not only Schirmer without anesthesia but artificial tears and corneal fluorescein staining, which also significantly improved, almost at the 0.01 significance level in both groups.

DR. LAVIN: Yes, I just mean the clinical improvement, not a statistical one. I need to know is that something that you, as an ophthalmologist, would say that is a meaningful difference, and that difference was quite different between the vehicle and the active groups. That is really my question, is that difference meaningful from baseline? I think the answer to that is yes, but is the difference between the vehicle and the active treatments clinically meaningful? It is not a statistical question but a clinical question.

DR. PFLUGFELDER: Yes, it is because, as Dr. Nelson showed you just a second ago, you know, there was almost no improvement in the Schirmer without anesthetic from the vehicle, and a significant improvement with the drug, either the 0.05 percent or the 0.1 percent cyclosporine. I do think that is very significant, and it is reflected -- again, it is a retrospective analysis but it

is reflected in the fact that patients used less artificial tears and complained of less blurred vision.

So, my global understanding of keratoconjunctivitis sicca is that as the corneal surface improves people are going to have less blurred vision complaints and they are going to use less artificial tears, and that is how I think of it as a clinician. So, yes, I really, honestly, feel that it is a significant improvement from a patient's perspective.

DR. FONG: Dr. Cioffi?

DR. CIOFFI: I believe in Dr. Schiffman's presentation he removed the 1-month responders and took a relook, and claimed that the rationale for that was that if the vehicle was lubricating -- correct me if I am wrong here -- that would likely happen quicker, while with the cyclosporine you supposed to be a longer response to take effect?

DR. REIS: That is correct.

DR. CIOFFI: Do you believe that, that actually the cyclosporine takes a ramp-up time, that there is a time between start and relief of symptoms? Do you have any data on that? Could you comment on that?

DR. REIS: Yes, the data that have been generated both for the use of the veterinary ophthalmic ointment in the dog and in cyclosporine use in patients indicate that

you do not get an immediate response, and there is a very specific rationale around the mechanism of cyclosporine's action on the infiltrating T-cells that we believe explains why that therapeutic response has a delay. I will ask Dr. Stern to comment on that.

DR. STERN: The way cyclosporine acts on a T-cell as it comes into the tissue, the T-cell arrives at the tissue intact with topical treatment with cyclosporine, and it diapedeses out of the vessel into the tissue. What happens here is that cyclosporine binds to a complex. Its natural receptor is cyclophilin. There is a complex that is formed in the cytosol of the T-cell and it binds to its cyclophilin here. Now, what happens here is that there is a dephosphorylation normally in T-cell activation that allows translocation of this nuclear factor to the promoter region of the DNA within the nucleus. That promotes synthesis and secretion of the pro-inflammatory cytokines that are involved in this whole thing. What cyclosporine does is it binds to the cyclophilin and prevents this dephosphorylation, thus inactivating this translocation of the nuclear factor. What it is doing here is preventing activation of T-cells. What it does not do is deactivate preactivated T-cells. So, there is a lag time that is required for those T-cells to undergo apoptosis. That is why we feel it takes a while for this to kick in

therapeutically.

DR. REIS: So, while we would accept the palliative benefits of the formulation overall to provide some immediate relief to these patients, it does take a period of time for the therapeutic effect to clearly differentiate the active treatment from the palliative benefits of the vehicle.

DR. CHAMBERS: Can I come back to the issue of blurring? It is my understanding that you would not be able to detect any effects of your vehicle on blurring in these three trials, that any evaluation of blurring would require a comparison between a straight solution and your emulsion vehicle, and that did not occur in any of these three trials we have been discussing today. Is that right?

DR. REIS: That is true, Dr. Chambers. The question that was responded to with respect to blurred vision could be answered, and was answered, solely on the basis of the varying concentrations of the formulations. We have not looked specifically at a difference in blurred vision between our formulation compared to an artificial tear.

DR. CHAMBERS: So it is still possible that the emulsion is causing a blurring effect.

DR. REIS: No, I would say it is not based upon the way we evaluated blurring in our Phase II trial. The

patients were asked about the degree of their blurred vision prior to installation of the drug. Following installation of the drug, immediately post-installation and at 15 minutes and 30 minutes the patients were queried for the occurrence of blurred vision. If the patient did not have an increase in blurred vision prior to installation of the drug our conclusion was that the drop was not contributing to an increase in blurred vision. So, it has not been compared to an artificial tear but it did not increase the blurring of vision beyond the baseline or prior to drop installation which the patient had already had at that moment.

DR. CHAMBERS: But that is a subjective evaluation; that is not an objective evaluation of visual acuity.

DR. REIS: That is correct. It was subjective and did not include an assessment of visual acuity.

DR. CHAMBERS: Thank you.

DR. FONG: Are there more questions for the FDA or for the sponsor? Dr. Seddon?

DR. SEDDON: Just another point of clarification. When I asked this morning about the apparent similarity between the vehicle and the two dose groups in terms of some of the parameters, objective and subjective, the response was that in subgroup analysis, when some of the more mild cases were excluded from the database of the 003 study, the

differences were more apparent. Is that correct?

DR. REIS: Yes, that is correct.

DR. SEDDON: So, is it that the indication for this medication would be for investigators with those more severe parameters rather than the whole general population of the KCS patient population?

DR. REIS: Yes --

DR. SEDDON: Would that be specifically designated by certain objective signs, what that level of severity is?

DR. REIS: There are two questions there. One is the sponsor's opinion about the appropriate target population for the use of Restasis and then, secondly, what might be the criteria that the patient would have that would indicate that they would be a candidate for Restasis treatment.

With respect to your first question, it is our position that Restasis therapy is appropriate for the moderate to severe dry eye patient. We have not studied it in milder cases, and we are not suggesting that it be appropriate for all dry eye patients. For those patients with chronic dry eye disease who have not be adequately managed on conventional therapy, artificial tears and ointments -- and these are usually the patients who fall into what would be described as the moderate to severe category, we propose that Restasis will be a significant and

important benefit for those particular dry eye patients.

With respect to the specific criteria that were defined in moderate to severe patients, because of the heterogeneity of the disease and also because signs and symptoms do not correlate, it is very difficult to stipulate a specific level of aqueous deficiency based on a Schirmer score, a specific level of corneal staining or a specific level of pathology. As frequently occurs in medicine, we would rely on the judgment of the treating eye care provider to determine that their patient is, indeed, a moderate to severe patient and, therefore, an appropriate patient for Restasis treatment.

DR. FONG: Dr. Herndon?

DR. HERNDON: If you would comment on the global response to treatment, as I read it for, I guess, study 003 a full 67 percent of patients had only a slight response, condition unchanged or conditioned worsened. So, that is a pretty significant percentage of these patients who only had a slight improvement or were unchanged or worsened. Could you comment on that? This is on page 52, table 13.

DR. REIS: The global response to treatment was handled as a questionnaire, and in some cases the investigator made that assessment and in some cases the investigators queried the patients.

In study 003, at the month 6 time point there

wasn't an improvement in global response to treatment but t here had been at month 3. I have no explanation, in this study, as to why we would see an unusual finding like this at the month 6 time point. I would simply add that working in this area of dry eye disease, it is not unusual to find a very unexplained result at some point in the data set. So, I cannot give you a rationale as to why the results at month 6 were different from the results at month 3.

DR. LAVIN: Looking at this table, they are not that different at month 3 either for study 003. It is the same kinds of numbers. It is 75 percent, 77 percent for the 0.05. It is approximately 70 percent for the 0.1, and for the vehicle it is around almost 80 percent. So, it is not that different.

DR. REIS: I am sorry, for clarification, Dr. Lavin, could you tell us where you are referring to, please, and if this is the FDA document or the sponsor document?

DR. LAVIN: Yes, this is the FDA document, the same document that has just been referred to, on the same page, page 52.

DR. REIS: If I might have a moment, please? Okay, I have the data in front of me. For month 3, this is where we did have a statistically significant difference, I believe, in study 003. As you will note, there are not, across the board, that many patients that move into the

category of being completely cleared or almost cleared. The majority of the patients move from the categories of condition unchanged, either slight response or moderate response. We are not curing KCS with Restasis treatment. We are providing a management of the disease and a management of the underlying pathology that contributes to the disease. So, I am not surprised that the majority of the patients did not move into the almost cleared or completely cleared categories and remain, however, in the categories that still indicate improvement. You see that very few of these patients moved into conditioned worsened.

DR. LAVIN: About as many who had a marked response at month 3. That is the problem. See, this is a very flat table. You have a 0.03 p value there at month 3 but you don't really have any more than a 10 percent difference in the proportions who had slight response -- you know, condition unchanged or worsened. So, you really don't have an edge there. You may have a significance level but I wouldn't push that too far because I thought we were only limiting p values to month 6, but this is not an impressive result at month 3.

DR. REIS: And, I would add, Dr. Lavin, that this is a subjective assessment of patient response to treatment, and I would not consider a global evaluation of patient response to be as clinically meaningful as changes observed,

for example, in things that can be more objectively measured, such as corneal staining and increases in Schirmer scores.

DR. SEDDON: Were these evaluated by severity of disease within the groups?

DR. REIS: Could you elaborate on your question, Dr. Seddon?

DR. SEDDON: I am talking about the global response to treatment in terms of severity of disease within the groups. For example, you had the analysis performed without some of the more mild cases. Did you also look at that subgroup in regard to these responses?

DR. REIS: The only data that have been looked at removing the milder cases were the endpoints which Dr. Schiffman shared with you this morning. We have not removed the milder cases from the global evaluation response or any of the others. So, we have presented the full data set to you today in our presentation.

DR. FONG: Any more questions for the FDA or sponsor? If not, we can move on -- Dr. Matoba, I am sorry?

DR. MATOBA: I know you talked about treating the underlying pathology with the use of topical cyclosporine, but the inflammatory-cell mediated destruction of a lacrimal gland is not affected by topical cyclosporine, and that would be expected to progress. Right? So, what do you

think is a reasonable time frame in which topical cyclosporine would be helpful or palliative for these patients?

DR. REIS: I heard two questions there, Dr. Matoba, one being what sort of effect, if there is an effect, we might expect on the main lacrimal gland. We do believe that treating the ocular surface will have an effect on reducing the inflammation in the main lacrimal gland, and I will ask Dr. Stern to comment on that.

Then, your second follow-up question, as I understood, is the period of time that would be required for an effect on the underlying pathology of the disease. Is that correct?

DR. STERN: I may have heard your questions a little bit differently, because I thought you had started to talk about the progression of the inflammatory-mediator destruction of the lacrimal gland even with treatment with cyclosporine.

DR. MATOBA: I assume that that would occur since you have not shown any data -- the penetration of the drug into the lacrimal gland is very poor, and you have not shown any lacrimal gland data for humans.

DR. STERN: Right. Well, obviously we can't really get biopsies from lacrimal glands from humans, although the apoptosis data that I did present has been

confirmed in lacrimal glands in Japan, by Dr. Katsosobota, where he has shown destruction of the gland from that perspective.

The shut-down of inflammation by cyclosporine within the ocular surface does penetrate into the accessory lacrimal glands located in the superior conjunctival fornix and the lid just above the meibomian gland. We believe that is the initial response that we are seeing. The response in the main lacrimal gland would, therefore, be a more indirect and longer-term type thing, and what we have hypothesized, since we have not seen any main lacrimal gland data, is that the reestablishment of the neural arc and the elimination of ocular surface inflammation would decrease the T-cell call to the main lacrimal gland over time and subdue the inflammation there. Now, that is a hypothesis on our part since we don't have any main lacrimal gland data and the data we do have is on the accessory lacrimal glands.

It should be noted that Dr. Barman, who is sitting here, on my left, has a population of monkeys in which he has removed the main lacrimal gland. None of these monkeys came down with dry eye, primarily because the accessory lacrimal glandular function is still there, and they are still able to have a normal tear composition, bathing the ocular surface. So, really what we think is happening is that we have accessory secretions returning to normal

initially and that the main lacrimal gland is probably a later phenomenon.

DR. FONG: More questions for the sponsor or FDA? If not, let's go ahead and discuss the questions to the advisory committee.

Questions to the Committee

Dr. Matoba, I am going to start with you first, and it is going to be with the first question: Has sufficient evidence been submitted to support the efficacy of cyclosporine ophthalmic emulsion for the treatment of keratoconjunctivitis sicca? Then the second part of the question is are additional studies needed to establish efficacy for this product?

DR. CHAMBERS: Can I interrupt for a point? It would probably be of benefit to the agency if there was a general discussion about the questions before you ask for specific votes of investigators.

DR. FONG: Okay.

DR. CHAMBERS: So, if I could encourage a general discussion of the questions before you take a vote, I would appreciate it.

DR. FONG: Does anybody want to lead off the discussion on that?

DR. MATOBA: I am still not clear on what exactly we determined the criteria to be that we are supposed to be

judging since the objective and subjective criteria were going to be one out of five -- I don't actually know at this point which criteria did we decide upon to be judged.

DR. CHAMBERS: I will address that. Legally, as far as the law is concerned, safety and efficacy is considered to be determined by the evaluation by experts in the field based on adequate and well-controlled trials. It is not specific criteria that have to be met in order to demonstrate safety and efficacy. It is what experts in the field believe is sufficient based on adequate and well-controlled trials. We obviously have adequate and well-controlled trials. Whether the information has demonstrated to the satisfaction of experts in the field is essentially what the agency is asking each of the individuals here for their opinions.

DR. FONG: Dr. Cioffi?

DR. CIOFFI: In terms of general discussion of question 1, you know, from my standpoint, I agree with the sponsor that this is a difficult, debilitating disease that affects a large population. The problem is that it is difficult to determine endpoints, and I think the sponsors have been given a moving target of sorts, by necessity. They have tried to heighten their awareness and provide us with definitions but those definitions continuously change, and it is not unlike other things in ophthalmology and all

of medicine -- the definitions aren't static.

So, I guess I would just echo that it is going to be our decision, not based on a specific menu or recipe of voting criteria, and I am not sure it is fair to say that there is one objective and one subjective because it sounds like that target is continually moved over the five-year course, or whatever, of planning and implementing this study.

Study 003, on the other hand, is worrisome and I think the sponsor probably realizes that. After completing study 002 I am sure they felt very good. I do like the idea of removal of the 1-month responders that Dr. Schiffman presented, and it may give us some idea of drug versus vehicle but it is a moving target. This is a tough field and I think we are going through this in multiple phases of ophthalmology right now, and we are going to be revisiting this soon, I am sure.

DR. CHAMBERS: There are several diseases where we have clear-cut criteria and it is much easier to determine safety and efficacy. Unfortunately, this is not one that is as easily defined as we would like.

DR. FONG: I agree with Dr. Cioffi that dry eyes are a very difficult disease to study, and I think the sponsor has done a good job in trying to look at the efficacy of the drug.

I am bothered not only with the results from study 003 but by study 002. I, myself, am not completely convinced that there is a clinically and statistically significant difference between the treatment groups, and I am just concerned about the overall efficacy because of the small treatment effect and the very small statistically significant difference.

Any more observations or questions from the committee?

DR. HERNDON: I want to know when we will have the 12-month data. Any comment on that, an extension phase?

DR. REIS: Allergan has provided a 120-day update to the agency on the 12-month safety data. We have not yet had an opportunity to look at the 12-month efficacy data. The 12-month efficacy data will not be vehicle-controlled data; that will be active treatment data only as the vehicle patients were converted to one of the active treatments. So, we would not expect to have any of that data until perhaps later this fall.

DR. CHAMBERS: The 120-day safety information that she was referring to was just recently submitted to the agency, in the last couple of weeks. That is the 120-day time frame. That is where we are with this application. So, obviously we were not able to share it with the committee.

DR. LAVIN: Just one point further about just SOPs and following things, I think that whenever one writes a protocol and the protocol is approved by the FDA that that should be the industry standard. The target shouldn't really be allowed to shift on the sponsors, and I think that one has to really go by the idea if there was a primary and the secondary and you raise your flag on the basis of the primary, otherwise it wouldn't be fair to any sponsor or to any panel to be put in the position to retrospectively judge. So, I think from my perspective, the protocol should be the standard.

DR. FONG: I would like to make an observation. On page 89 of the sponsor's document, if you look at study 002 and you look at sort of the change from baseline, the mean change from baseline at month 6, at the very bottom, the 0.5 percent, the 0.1 percent and the vehicle, you see that the standard deviations are very large for each of those measurements. You know, what that usually tells me or what I take from that is that there is a lot of variance in counting those measurements. I know the analysis of variance shows a statistically significant change, and my observation that I made earlier was that, you know, with an analysis of variance and with a correlation coefficient oftentimes you a get statistically significant finding but it is really difficult to say that it is clinically

significant.

DR. CIOFFI: Might the sponsor comment on their observations on reproducibility of any or all of these measures? There was a little bit of talk about a reading center for the biopsy samples but do you have that sort of data? Have you looked to see how reproducible somebody's corneal staining is? Have you done any of that? These are noted as objective measures but there is a huge subjective component.

DR. REIS: Right, absolutely. I will ask our statistician to speak briefly to the tests that we looked at for investigator interactions around their testing, and then ask one of the ophthalmologists who participated in a Phase III trial to speak to the attempts that were made to try to standardize these tests as best as possible.

DR. K. STERN: As was stated earlier, our tests were stratified by investigator and we did look for by investigator interaction specifically at baseline and at month 6. We did not find any by investigator interactions for either study.

DR. FONG: Are we ready to vote on question 1? I am sorry, go ahead.

DR. PFLUGFELDER: Allergan did an excellent job about having an investigator meeting before the trial where they prepared a brochure on exactly how to perform the

staining, how to evaluate the staining and other relevant objective parameters in the study. But, as many of you are probably aware, even if you take corneal fluorescein staining two different people may interpret the result a little bit differently, and if you wait another minute it may be a little stronger than it was. So, they took every step to try to standardize the methodology.

DR. FONG: Dr. Seddon?

DR. SEDDON: Just one quick comment. I think this is an inherent problem in a lot of studies in ophthalmology and other areas as well, the study is masked and so the investigators know exactly what group the patient is in, plus the fact that it is a randomized study, I think that is really the best way to handle this kind of potential bias.

DR. FONG: So, let me read the question again: Has sufficient evidence been submitted to support the efficacy of cyclosporine ophthalmic emulsion for the treatment of keratoconjunctivitis sicca? Are additional studies needed to establish efficacy for this product? Maybe you could state your name and your answer.

DR. MATOBA: Alice Matoba. Well, each of the two studies, 002 and 003, did show among group differences that were significant for at least one or more of the subjective and objective criteria, but I am troubled by the fact that the two studies were inconsistent and I would have to say

that I do not believe that efficacy was shown in these studies. So, I think further studies are necessary.

DR. FONG: So, the answer to the first question is no. And the second, are additional studies needed, do you want to specify what those additional studies might be?

DR. MATOBA: Not at this time.

DR. FONG: Okay. Dr. Lavin?

DR. LAVIN: Yes, I think that additional evidence would be needed to support the efficacy. I am concerned by the inconsistency between studies 002 and 003. It would have been one thing had study 001 not been more like study 003 than it was like study 002. That is also something that tips the scales, and I feel that because of that they should do additional studies.

I think the key thing that may already be there is the open-label data where seeing how the patients who were on the vehicle performed when they crossed over, using those patients as their own control. I think there may be important information there that can be gleaned not just for safety but the efficacy, and that may well be very telling. The sponsors I think are to be commended on having such an excellent percentage of the patients who made it into the open-label phase. It was like 90 percent who made it into that. So, there may well be some very good data that is beyond that normally seen with open-label trials.

DR. FONG: Ms. Goldberg?

MS. GOLDBERG: As the consumer rep, I see the importance of having a drug for this population but, also as a consumer rep, there are peculiar statistical nuances of this particular set of issues beyond my scope of expertise, so if I could abstain in some way, that is what I am going to do. But I am also troubled by what I see as inconsistencies.

DR. FONG: Is that okay, Jayne, to abstain?

MS. PETERSON: Yes.

DR. FONG: Dr. Herndon?

DR. HERNDON: I was a bit concerned as well, particularly with the global response to treatment. As I understand, the global response to treatment actually asked the patients themselves on how they feel and are they doing better, and that is one way of getting at the clinical significance. And, when we look at all the numbers, I do not see a lot of difference between treatment arms and vehicle. So, at this point I would say that sufficient evidence has not been submitted.

DR. FONG: What additional studies would you recommend?

DR. HERNDON: I defer that at this point.

DR. FONG: Dr. Cioffi?

DR. CIOFFI: I am going to oppose the populous

view here in that I am not sure the sponsor has been given the correct guidelines, or maybe we haven't, but there is statistical significance in both these studies. These were put out in the proposal and accepted as primary and secondary endpoints. Albeit multiple time points; albeit small numbers in terms of significance, they do show significance. So, I will say yes to the first question. Are additional studies needed? I believe that is yes as well.

DR. FONG: I guess it comes to me, Dr. Fong, and as I stated earlier, I think dry eye is a very difficult disease. I think the sponsors have done a very good job in studying this disease. I don't believe that the evidence submitted to the committee is convincing that there is efficacy. I think clearly in study 003 efficacy has not been shown and I am not convinced from the small treatment effect and the statistics that were used that there is a statistically significant difference, let alone a clinically significant difference. So, I don't believe there is sufficient evidence that has been submitted.

As far as whether additional studies are needed, that is a very difficult question. I guess it depends fundamentally on whether you believe that the data suggest that there is some treatment or whether the treatment may not be effective. If the treatment is not effective I don't

think additional studies could establish the efficacy of this product.

DR. SEDDON: I think the data presented so far are insufficient to support the efficacy for treatment of keratoconjunctivitis sicca. However, I think there, indeed, maybe important clinical as well as statistically significant effect for the group classified as severe -- not moderate and severe but perhaps just severe KCS. So, I would like to see additional analyses of these data within the study population available and, pending these results, perhaps additional data collection on a more homogeneous group of severe KCS patients would be helpful.

DR. FONG: Okay. We will go on to the second question: Are there adverse experiences that are of particular concern for this product? The second part of the question, are additional studies needed to further quantify/qualify these experiences? Dr. Matoba?

DR. MATOBA: Alice Matoba. The answer to both the questions is no.

DR. FONG: Dr. Lavin?

DR. LAVIN: No issues there.

DR. FONG: Ms. Goldberg?

MS. GOLDBERG: No issues.

DR. FONG: Dr. Herndon?

DR. HERNDON: No issues.

DR. FONG: Dr. Cioffi?

DR. CIOFFI: No to both questions.

DR. FONG: No issues to either question.

DR. SEDDON: No, I have no issues.

DR. FONG: The third question, are additional studies needed to establish the safety of this product?

DR. MATOBA: No.

DR. LAVIN: I would agree, no.

MS. GOLDBERG: No.

DR. HERNDON: No.

DR. CIOFFI: No.

DR. FONG: No.

DR. SEDDON: No.

DR. FONG: Question four, are there other issues related to the safety or efficacy of the product?

DR. MATOBA: With regard to safety no, with regard to efficacy there may be a benefit to further studies but I would have to defer elaboration on that point.

DR. FONG: I didn't hear the last part.

DR. MATOBA: I can't comment on that at this time.

DR. LAVIN: I have no issue son the safety but I am always perplexed by, you know, who was helped in terms of the efficacy, is it the patients who have very severe affection at baseline or are there other subgroups who could be helped. I think it is very problematic in the situation

where you have the vehicle effect which is pretty much achieving 80 percent at a minimum of the effects that are achieved by the active treatment in the study. So, that represents a clear challenge for doing these types of trials and seeing if there is some subgroup where that difference might have been larger. I think it would be worth pursuing.

MS. GOLDBERG: I have no concerns at this time about safety and, in terms of efficacy, I have the same concerns that other people have expressed but also I would like to see a drug developed for this population.

DR. FONG: Can you repeat the last part?

MS. GOLDBERG: I would just like to reiterate what I said before, that I would like to see an effective drug for the people who need it.

DR. HERNDON: I have no further issues regarding safety, but I do have issues regarding efficacy, as I mentioned earlier.

DR. CIOFFI: I have no issues regarding safety. I would like to comment further on this efficacy question because I think that if we are going to send this sponsor or another sponsor a message, we have to help them in some way determine endpoints, or at least markers of disease, or surrogate markers of disease, and I don't think we have done that for them.

I think this has not been a one-time dialogue with

the agency, and for them to go with guidelines that were proposed and accept them and then for it to be called questionable efficacy when they met those guidelines -- I think that is very confusing. I reiterate, we are going to revisit this; we are going to revisit this soon in glaucoma; we are going to revisit this in every area of ophthalmology, and I would ask that we further some discussion on how sponsors might interact with the agency to determine efficacy in terms of markers, secondary markers, surrogate markers, etc.

DR. FONG: I have no issues with safety, and I disagree a little bit with Jack in that I believe that the primary endpoints were specified, and I think that in looking at the results of this study I am not convinced that there are any objective measures that demonstrated statistically and clinically significant differences. So, I would like to encourage the sponsor to continue work on treatment for dry eyes because dry eyes is a significant problem.

DR. SEDDON: I have no issues at all regarding safety. I think the data demonstrated safety of this product. My issues with efficacy are what I said earlier in response to question number one. There may, indeed, be a subgroup here, particularly the severely affected patients who may benefit and this should be further evaluated.

DR. FONG: Question five, does the committee recommend approval of cyclosporine ophthalmic emulsion for the treatment of moderate to severe keratoconjunctivitis sicca?

DR. MATOBA: Based on my concerns regarding the lack of adequate data to support efficacy, I would have to say no.

DR. LAVIN: I would also say no.

MS. GOLDBERG: I would also say no.

DR. HERNDON: No at this time.

DR. CIOFFI: Surprisingly, I as well would say no.

DR. FONG: No.

DR. SEDDON: No.

DR. FONG: I would like to adjourn the meeting of the ophthalmic drugs subcommittee.

DR. CHAMBERS: Even though you have adjourned it, I do want to thank everybody for their time and effort in coming and for your advice. I would also like to thank Allergan for their presentation and their time and effort.

DR. FONG: We are adjourned.

[Whereupon, at 2:15 p.m., the proceedings were adjourned.]

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CERTIFICATE

I, **PAMELA BRIGGLE,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

Pamela Briggle

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Lawyer's Notes

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