

1 related to blood chemistry or hematology.

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

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

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

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

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

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

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

9 Thank you.

10 **Statistical Review**

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

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

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

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

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

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

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

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

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

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

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

15 So, in summary, the efficacy results are not
16 consistent between the two studies, and there was no
17 statistical significance in the primary endpoints in study
18 003, in which case the p values for secondary endpoints
19 cannot be validly interpreted.

20 That is all for my presentation. Thanks.

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

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

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

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

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

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

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

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

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

1 multiple chances for significance, which I think is an
2 educational thing as well as just a sense of what is really
3 statistically appropriate to do. When you have five
4 endpoints, say, five objective endpoints and you are saying
5 I would like to have one that is significant and that is my
6 criteria for success, then your p value isn't any longer
7 0.05 for that objective criteria. What actually happens is
8 you have five chances to be significant. So, your p value
9 has to be adjusted downward to 0.01, namely, 0.05 divided by
10 5. So, that is the criteria that would need to be put into
11 place for an adjusted type-1 error.

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

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

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

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

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

1 DR. LU: Right.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

20 DR. FONG: Dr. Matoba?

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

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

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

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

1 exacerbated by topical ophthalmic medications.

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

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

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

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

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

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

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

11 DR. REIS: Yes, it did.

12 DR. SEDDON: Thank you.

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

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

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

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

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

10 DR. FONG: Dr. Herndon?

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

19 DR. REIS: The differences that we have in study
20 003 come back to the fact that we had a greater vehicle
21 response in study 003. I would like to spend just a moment
22 talking about what our vehicle was, and emphasize the fact
23 that this was a vehicle with substantial palliative benefit.
24 This was not a clinical trial that was run against what is
25 the current standard of treatment for these patients, namely

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

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

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

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

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

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

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

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

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

1 which is an effect on the immune component.

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

11 DR. FONG: Dr. Matoba?

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

16 DR. REIS: It is not associated with the
17 persistence of blurred vision. We looked specifically at
18 blurred vision in our Phase II dose-ranging trial as part of
19 the formulation tolerability. While there was increased
20 blurred vision at the 0.4 percent, it was not present at the
21 0.1 and the 0.05 percent.

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

1 DR. FONG: Please, go ahead.

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

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

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

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

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

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

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

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

1 Thank you.

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

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

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

22 DR. REIS: Thank you, Mr. Chairman.

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

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

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

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

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

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

20 The staining that was stipulated in the protocol
21 was that we would have a 3-grade change out of a total of
22 15, assuming, in the absence of any other prior studies to
23 guide us, that we would expect a 1-unit change in each
24 region of the conjunctiva and a 1-unit change in each region
25 of the cornea, or at least a 20 percent change in staining.

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

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

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

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

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

6 DR. PFLUGFELDER: That was the improvement in the
7 0.05 percent.

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

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

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

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

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

1 appear that that really occurred much because that Schirmer
2 test did not improve, but the basal Schirmer test, which is
3 the Schirmer without anesthesia, did significantly, and
4 highly significantly improve in 003, as well as in the
5 composite index, which had not only Schirmer without
6 anesthesia but artificial tears and corneal fluorescein
7 staining, which also significantly improved, almost at the
8 0.01 significance level in both groups.

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

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

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

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

10 DR. FONG: Dr. Cioffi?

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

18 DR. REIS: That is correct.

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

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

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

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

1 therapeutically.

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

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

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

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

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

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

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

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

17 DR. CHAMBERS: Thank you.

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

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

1 differences were more apparent. Is that correct?

2 DR. REIS: Yes, that is correct.

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

7 DR. REIS: Yes --

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

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

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

1 important benefit for those particular dry eye patients.

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

13 DR. FONG: Dr. Herndon?

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

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

25 In study 003, at the month 6 time point there

1 wasn't an improvement in global response to treatment but t
2 here had been at month 3. I have no explanation, in this
3 study, as to why we would see an unusual finding like this
4 at the month 6 time point. I would simply add that working
5 in this area of dry eye disease, it is not unusual to find a
6 very unexplained result at some point in the data set. So,
7 I cannot give you a rationale as to why the results at month
8 6 were different from the results at month 3.

9 DR. LAVIN: Looking at this table, they are not
10 that different at month 3 either for study 003. It is the
11 same kinds of numbers. It is 75 percent, 77 percent for the
12 0.05. It is approximately 70 percent for the 0.1, and for
13 the vehicle it is around almost 80 percent. So, it is not
14 that different.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

6 **Questions to the Committee**

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

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

18 DR. FONG: Okay.

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

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

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

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

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

16 DR. FONG: Dr. Cioffi?

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

1 of medicine -- the definitions aren't static.

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

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

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

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

1 I am bothered not only with the results from study
2 003 but by study 002. I, myself, am not completely
3 convinced that there is a clinically and statistically
4 significant difference between the treatment groups, and I
5 am just concerned about the overall efficacy because of the
6 small treatment effect and the very small statistically
7 significant difference.

8 Any more observations or questions from the
9 committee?

10 DR. HERNDON: I want to know when we will have the
11 12-month data. Any comment on that, an extension phase?

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

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

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

12 DR. FONG: I would like to make an observation.
13 On page 89 of the sponsor's document, if you look at study
14 002 and you look at sort of the change from baseline, the
15 mean change from baseline at month 6, at the very bottom,
16 the 0.5 percent, the 0.1 percent and the vehicle, you see
17 that the standard deviations are very large for each of
18 those measurements. You know, what that usually tells me or
19 what I take from that is that there is a lot of variance in
20 counting those measurements. I know the analysis of
21 variance shows a statistically significant change, and my
22 observation that I made earlier was that, you know, with an
23 analysis of variance and with a correlation coefficient
24 oftentimes you get statistically significant finding but
25 it is really difficult to say that it is clinically

1 significant.

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

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

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

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

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

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

8 DR. FONG: Dr. Seddon?

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

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

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

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

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

6 DR. MATOBA: Not at this time.

7 DR. FONG: Okay. Dr. Lavin?

8 DR. LAVIN: Yes, I think that additional evidence
9 would be needed to support the efficacy. I am concerned by
10 the inconsistency between studies 002 and 003. It would
11 have been one thing had study 001 not been more like study
12 003 than it was like study 002. That is also something that
13 tips the scales, and I feel that because of that they should
14 do additional studies.

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

1 DR. FONG: Ms. Goldberg?

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

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

10 MS. PETERSON: Yes.

11 DR. FONG: Dr. Herndon?

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

21 DR. FONG: What additional studies would you
22 recommend?

23 DR. HERNDON: I defer that at this point.

24 DR. FONG: Dr. Cioffi?

25 DR. CIOFFI: I am going to oppose the populous

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

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

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

1 think additional studies could establish the efficacy of
2 this product.

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

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

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

20 DR. FONG: Dr. Lavin?

21 DR. LAVIN: No issues there.

22 DR. FONG: Ms. Goldberg?

23 MS. GOLDBERG: No issues.

24 DR. FONG: Dr. Herndon?

25 DR. HERNDON: No issues.

1 DR. FONG: Dr. Cioffi?

2 DR. CIOFFI: No to both questions.

3 DR. FONG: No issues to either question.

4 DR. SEDDON: No, I have no issues.

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

7 DR. MATOBA: No.

8 DR. LAVIN: I would agree, no.

9 MS. GOLDBERG: No.

10 DR. HERNDON: No.

11 DR. CIOFFI: No.

12 DR. FONG: No.

13 DR. SEDDON: No.

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

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

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

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

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

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

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

11 DR. FONG: Can you repeat the last part?

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

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

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

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

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

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

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

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

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

8 DR. LAVIN: I would also say no.

9 MS. GOLDBERG: I would also say no.

10 DR. HERNDON: No at this time.

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

12 DR. FONG: No.

13 DR. SEDDON: No.

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

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

20 DR. FONG: We are adjourned.

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

23

C E R T I F I C A T E

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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