

1 variability within--between individual readers. I can't
2 tell you what the right answer is to know--

3 DR. KILPATRICK: Well, let me let you off that
4 hook, and let me make a statement in my own behalf then.
5 What I'm saying is that, in my opinion, as a statistician I
6 think there is over, undue dependence on p-values in this
7 presentation. And what I hear from your presentation in
8 general is that we, the committee, should consider other
9 sources of variation, not simply random sampling variation.

10 DR. CHAMBERS: I absolutely agree with that.

11 CHAIRMAN WILSON: Ms. Cohen, did you have a
12 question?

13 MS. COHEN: I defer to Dr. Chew.

14 CHAIRMAN WILSON: Dr. Chew?

15 DR. CHEW: This is really a question of
16 philosophy, I guess, listening to all this. The population
17 of patients we're studying is shrinking. It's a smaller
18 number. We're having difficulties mounting these trials.
19 Yet I'm hearing that there are differences between Gary's
20 and Wiley's assessment of this, and this is a question for
21 myself: Why isn't there adjudication? You know, there are
22 other reading centers out there. Could there be other
23 independent adjudications that could have been brought in to
24 see whether the sample size could, you know, improve upon
25 the number of patients that really would be evaluable and

1 whether that would be considered by the agency at any one
2 point?

3 I personally know that there are other--and
4 perhaps FDA itself can fund it rather than the drug company
5 itself so that there would be another independent reviewer
6 of these very important endpoints.

7 DR. CHAMBERS: I guess I don't think that it would
8 make any difference. I mean, I have not-- what I say, I
9 believe that there is consistency between--within individual
10 reviewers. So the way that I evaluated these is the same
11 way that I evaluated Ganciclovir implant, Ganciclovir IV,
12 Foscarnet IV, the Cidofovir. I don't think you'll find much
13 difference between those.

14 So if you want to make the comparisons between
15 those, that can already be done with either just looking at
16 my individual readings all the way across or Gary's readings
17 all the way across. I don't think you'll see much
18 difference.

19 Whether there's difference between us I don't
20 think is as much a factor as that we're consistent across
21 the different products as we look through, and I think
22 that's been the case. Having some third group go and read
23 them and in some cases maybe agree with one or agree with
24 the other on particular cases I don't think is going to make
25 a whole lot of difference.

1 The actual differences as we went through some of
2 these is frequently one week or frequently a progression at,
3 say, two weeks where one person thought it went 150 microns
4 and one person thought it went 120 microns. That is a very
5 small difference, and I don't think that really represents
6 much difference in the thinking that went on as far as
7 evaluating it. It has to do with our current way of calling
8 things makes those relatively big. But the actual
9 difference, if we were to sit down, between the things is
10 not that much different.

11 CHAIRMAN WILSON: Ms. Cohen?

12 MS. COHEN: Did I hear there were different ways
13 of censoring the information? And that was kind of
14 troubling for me because is there--are there criteria that
15 can be established as to how you censor, or is it the nature
16 of the science that you can't do it and it's ad hoc?

17 DR. CHAMBERS: The protocol had a number of
18 different ways--things that were going to get done. It did
19 not include even potential possibility that's there, and
20 what you're seeing are some of the possibilities that were
21 not thought of ahead of time.

22 The other issue is how much you try and--you've
23 heard me say it probably a hundred times at this point. The
24 data set was small, and to the extent that we're trying to
25 use as much as possible, we were picking up things that we

1 might otherwise throw out. If we had a couple hundred
2 patients, we would have readily thrown these people out and
3 not cared about them. It's because we only have a few that
4 we're trying to make the most of the patients that we have.

5 Had these trials gone to their expected
6 completions all the way through, we wouldn't be talking
7 about this at all.

8 MS. COHEN: Okay. So that, in fact, is a
9 reflection of the sample size.

10 DR. CHAMBERS: Correct.

11 MS. COHEN: Okay. Thank you.

12 CHAIRMAN WILSON: Dr. Fong?

13 DR. FONG: I had a question about the failed
14 therapy studies. If we're talking about anti-CMV therapy,
15 should the control group for CS9 be, you know, reinductioned
16 with Ganciclovir or Foscarnet? Wouldn't that make more
17 sense? Weren't you really interested in knowing, you know,
18 is this better than reinduction with the agent that had
19 failed?

20 DR. CHAMBERS: There were a number of questions
21 that have been asked and we would like to go and ask of this
22 particular agent. And you pick and choose with each
23 individual trial to answer some questions as opposed to
24 others. This particular trial, we did not have rationale
25 for the dose regimen that was being used before, so this was

1 an attempt to figure out whether we could alter that dose
2 regimen.

3 I'm not disagreeing at all that it wouldn't also
4 be nice to have an arm that had a standard reintroduction of
5 one of the therapies. It's a matter of the number of
6 patients and that would be a nice design for another trial.

7 DR. FONG: You know, if you were going to--if the
8 FDA considers approving this sort of for failed therapies,
9 then you really want to know whether this new drug is better
10 than, you know, reinduction of the failed agent.

11 DR. CHAMBERS: I agree.

12 CHAIRMAN WILSON: Any further questions from the
13 panel?

14 [No response.]

15 CHAIRMAN WILSON: Wiley, let me just ask one
16 question. It's just more or less a summary, and I just want
17 to make sure I heard you right.

18 A lot was put on the differences in the grading
19 between you and Gary. My understanding from your
20 presentation is that the conclusions, although the strength
21 of the conclusions may have differed between the two
22 interpretations, that your conclusion was still supportive
23 of the fact that there probably is efficacy, particularly in
24 the high-dose group, and questionable in the low-dose first-
25 line therapy group. Is that--

1 DR. CHAMBERS: I would agree. I think the major
2 difference between my analysis and what you've heard from
3 the sponsor is I believe there is efficacy to the 330. I do
4 not see sufficient support for the 165 dose at the present
5 time.

6 CHAIRMAN WILSON: Thank you very much.

7 At the beginning of the sponsor's presentation,
8 they had requested a chance to re-present some of the
9 materials after Dr. Wiley's presentation. I'd like to go
10 ahead and invite them to do that now and to restrict your
11 comments to the differences in the conclusions and in the
12 results that Dr. Chambers got from your earlier
13 presentation.

14 DR. KISNER: The issues that I think you asked me
15 to address have to do with the fundus photography results.
16 The other issue that was raised earlier was the concern
17 about RPE stippling and its potential import. I'm prepared
18 to answer that as well, if you'd like.

19 To start with, one of the reasons that the
20 discussion that we're about to have will focus only on the
21 CS2 protocol is because we received Dr. Chambers' review
22 about three weeks prior to this meeting and the detailed
23 list of classification of these patients just about 15 days
24 prior to this meeting, and there was a lot to do to even
25 reread the photographs associated with the CS2 study.

1 For started, it's worth mentioning to you that
2 what we have done with the analysis of this study and all
3 the studies is to take the data that comes from the fundus
4 photography reading center from Dr. Holland's group,
5 translate those data directly into life tables, take those
6 life tables and put them onto Kaplan-Meier curves. There
7 has been no manipulation of the data in any other way.

8 That's what's been done with the data at the
9 beginning. No qualified patients have been excluded.

10 The initial reading of these photographs was done
11 by Dr. Holland, and I'll let him describe it in as much
12 detail as he'd like, and I think it may be useful to hear
13 his comments after mine; that is, that there are two
14 readers, they're read sequentially, Dr. Holland is one of
15 the readers in every instance, and they are masked to the
16 treatment that the patients are receiving.

17 We did receive Dr. Chambers' review, and as you
18 might imagine, we were immediately interested in attempting
19 to re-evaluate the photographs that represented
20 discrepancies.

21 We went through the listings that Dr. Chambers
22 provided to us and generated a list of patients on whom
23 there were significant discrepancies for the CS2 study. And
24 we sent that list--that list consisted of any patient for
25 whom the FDA review differed by at least one week from that

1 of the fundus photography reading center, plus we added two
2 patients for whom the reading center reading and Dr.
3 Chambers' read were identical so that we then had an
4 admixture. A total of 13 sets of photographs were reread.

5 Of interest, we also went and looked at the
6 clinical evaluations provided by the clinical investigators
7 seeing the patients on a week-to-week basis and found of
8 interest, in fact, that there was not a single episode in
9 any of these discrepant cases in which the clinical
10 investigator identified a clinical progression prior to the
11 fundoscopic reading center.

12 Next slide.

13 Just, again, confining the comments to CS2 because
14 this is all we've had time to do, I'd like to set this slide
15 up. First of all, we have patient numbers. We have
16 categories of patients, delayed and immediate treated and so
17 forth. In this column, we have the time in days to the
18 event listed here by the reading center. The 1 and 2 at the
19 top is to remind me basically to tell you that the reading
20 center rereading these photographic assessments, in no case,
21 in not one single case did they find on a second read any
22 difference from their initial interpretation. The numbers
23 provided here are the same for both reading number 1 by two
24 reviewers and reading number 2 by two reviewers.

25 Here you see the time in days to the event of

1 censor, in this case provided by the Food and Drug
2 Administration, and this means not classified in the case of
3 some by Dr. Chambers, and as a reminder, the clinical
4 investigator's assessment provided in this column.

5 For starters, there are two patients here at the
6 top that Dr. Chambers has already mentioned that were
7 delayed--initially delayed therapy patients who progressed
8 on days 13 and 7 and were crossed over that were
9 inappropriately classified as delayed therapy throughout in
10 Dr. Chambers' first analysis. But, in fact, one of those
11 patients progressed on day 13 and then had disease that
12 inactivated and has been progression-free for a further 684
13 days on the 165-microgram dose level. This patient crossed
14 over and had progression on day 55, and the further patient
15 here that was not classified by Chambers was felt to be
16 classifiable and interpretable by Dr. Holland's group.

17 In immediate therapy, there are three patients
18 here that were not classified by Dr. Chambers at all as a
19 result of his interpretation of photographs, largely
20 baseline photograph problems, as I recall, and these
21 patients, just to remind you that these differences in
22 interpretation have very big differences in terms of the
23 results we get. We're talking here about a patient that in
24 one case was classified by Dr. Holland as having--being
25 censored--was censored on the basis of Dr. Holland's read on

1 day 85, and this patient was not classified at all and not
2 in the analysis done by the FDA. And this patient was
3 censored at the time of his demise on day 183 without
4 progression and was not classified at all. Again,
5 differences in these interpretations, while minor in one
6 sense, perhaps, produce dramatic differences in the results
7 of the study.

8 Next slide.

9 These are patients in the immediate therapy group
10 for which there are additional differences. The slide is
11 the same. The reading center assessment is the same result
12 in two consecutive reads.

13 Again, I just want to focus in this case on the
14 days, the difference in days, and we're talking here 15 days
15 for the reading center, seven for the FDA, 98 to 21, 71 to
16 20, 29 to 8, 267 to 14, down here 57 to 7. In each and
17 every case, the difference between the assessment done by
18 Dr. Chambers resulted in meaningful reduction in the time to
19 event identified for these patients. Fundamentally, all of
20 the long-term responders to fomivirsen have been
21 reclassified as either not classifiable or have a much, much
22 shorter time to event than the FDA analysis.

23 Just to remind you that in every case, in every
24 case, the investigator--multiple investigators seeing these
25 patients, not in one case did they call time to progression

1 in advance of any fundoscopic reading done by the
2 fundoscopic reading center.

3 Next slide.

4 So, in summary, what we've done is take data from
5 the reading center, create Kaplan-Meier tables, and make
6 Kaplan-Meier plots with that. There are 13 patients, a
7 total of 176 sets of photographs that have been re-examined
8 by two masked reviewers a second time at the fundus reading
9 center led by Dr. Holland. There were the two patients
10 previously mentioned by both Dr. Chambers and myself. There
11 was a 100 percent reconfirmation of the time to event as
12 determined by Dr. Holland's reading center in this study,
13 and in each and every case, that was consistent with the
14 clinical investigator's assessment in terms of the patient's
15 progression-free survival to the time of the call by the
16 fundus reading center.

17 Next slide.

18 Our inevitable conclusion is that the UCLA
19 interpretation is correct. It's been done by two readers
20 once. It's been done by two readers a second time. We
21 believe it's correct.

22 We think that the differences--and I'd like Dr.
23 Holland to address this, if the committee permits--are
24 derived from quite possibly a very different level of
25 intensity of efforts made to evaluate difficult-to-read

1 photographs. There was some discussion between Dr. Holland
2 and Dr. Chambers in the phone conversation that we had to
3 suggest that they approach the level of effort to interpret
4 difficult photographs somewhat differently, and differences
5 in interpretation of individual photographs, again,
6 resulting not in subtle but in dramatic differences in the
7 time to event in this study.

8 Again, just to say it, we have good clinical
9 investigators, and not in one case did any of them call the
10 clinical progression prior to the way the fundus reading
11 center did. Our inevitable conclusion is that CS2 is
12 positive as we reported it.

13 With the committee's permission, perhaps Dr.
14 Holland could comment on some of the technical elements of
15 this.

16 CHAIRMAN WILSON: Would the committee members like
17 to hear more about the way the reading center performed?
18 Yes?

19 MR. FROST: Well, I think the committee has
20 probably over the years heard a lot about how fundus
21 photograph reading is done, but with the Chairman's
22 permission, I'd certainly like to address some questions to
23 Dr. Holland.

24 CHAIRMAN WILSON: Okay. Dr. Holland, can you come
25 up? Maybe we'll just address questions to you. Unless

1 there's anybody else on the committee who would like to hear
2 a little bit about any other comments prior to discussion?

3 [No response.]

4 CHAIRMAN WILSON: Okay. Dr. Holland?

5 Mr. Frost, would you like to begin the questions?

6 MR. FROST: Thank you.

7 Dr. Holland, on the second review of the
8 photographs that your center performed, were you masked to
9 treatment assignments?

10 DR. HOLLAND: Yes.

11 MR. FROST: Did you know that you were--which
12 patients you were reading the second time?

13 DR. HOLLAND: No, I did not.

14 MR. FROST: So the fact that you were 100 percent
15 consistent was done even though you didn't know that these
16 were the--I mean, you knew they were the same patients, but
17 you didn't know who was who the second time around. So you
18 were completely masked to therapy, completely masked to
19 treatment assignment, even the second time around?

20 DR. HOLLAND: Well, let me clarify just how that
21 was done. We were given a list of 13 patients, and we still
22 retained all of the slides in the reading center at UCLA.
23 When we were given that list, those slides were pulled, and
24 they were first reread by Dr. Susan Ransom, who's a retina
25 specialist who assisted me on some of the initial readings.

1 She reread the entire sets from baseline to event and
2 identified a time to progression or the last evaluable
3 photograph.

4 I then reviewed her evaluations and compared them
5 to our initial evaluations, so at that point I knew what I
6 had read before. But we didn't know what treatment
7 assignments, and, actually, at that time I didn't know
8 whether these were slides that I disagreed with Dr.
9 Chambers' evaluation or whether they were the random slides
10 just as controls.

11 If we identified a progression on a certain date
12 and that matched the date that we had read progression
13 before, then I went back and reread the previous visit to
14 see whether or not there was any evidence that there had
15 actually been progression on a prior visit and confirmed
16 that there hadn't been. So that's the manner in which this
17 re-review was done.

18 MR. FROST: I see. But when the retinal
19 specialist reread the photographs for the second time, she
20 was not aware of your reading results from the first go-
21 round; is that correct?

22 DR. HOLLAND: Yes. She started from scratch and
23 just reread them.

24 MR. FROST: Just reread them completely. The
25 committee has heard Dr. Chambers' characterization of the

1 differences that can occur between reviewers. Could you
2 comment on that for us and maybe give us some ideas of how
3 you feel such dramatic differences could be achieved?

4 DR. HOLLAND: Sure. I think there's two issues.
5 The first issue is in whether slides were evaluable or not,
6 and I did not keep track of how many slides I felt were
7 evaluable and how many were not. But certainly there were
8 some slides that were not evaluable. And on the data sheets
9 that we used, there was a spot for checking off "unable."
10 So there were some unevaluable photographs even in our
11 reading.

12 It's been alluded to those cases where there may
13 be periods when there was an unevaluable set or a series of
14 unevaluable sets, and what I would do is, if we had a
15 baseline and could follow a patient along, even if there was
16 a period of time when I couldn't evaluate a set of
17 photographs, if the subsequent sets became evaluable and I
18 could make a decision that did not depend on that interval
19 when we didn't have photographs, then I would still score
20 that patient.

21 For example, if the last set of photographs before
22 a period of time that was unevaluable, if that last set of
23 photographs had active disease but the patient did not
24 progress because the border had not advanced to a certain
25 threshold, and the first set after that unevaluable period

1 had active disease and had still not advanced past that
2 threshold, then I'd resume my reading and could determine
3 when it passed the threshold and, thus, the patient has
4 progressed subsequently. So--

5 MR. FROST: From your recollection, can you just
6 tell us, do you have any idea about how long those periods
7 were and how often they occurred?

8 DR. HOLLAND: I really couldn't tell you that
9 accurately. There were some cases where groups of slides
10 became unevaluable, and the last sets of slides were
11 unevaluable and we never resumed reading. There were other
12 sets that were of poor quality, and we sometimes had to do
13 things like going to a more intense light source so that we
14 could see satellites or we could identify landmarks to
15 compare. And so there are some slides perhaps that Dr.
16 Chambers would consider unevaluable that I would not
17 consider unevaluable. So that's the first issue.

18 The second issue is the problem of slides being
19 scored as progressed sooner by Dr. Chambers' evaluation than
20 by mine, and especially in some of the examples where there
21 was a very long lag period, probably the most likely cause
22 is patients who had a small amount of advance, sub-threshold
23 advance, and then became inactive. And that's a phenomenon
24 whereby those patients are classified as progressed by a
25 reader in a patient who, in fact, in responding well to the

1 drug.

2 The SOCA research group and the reading center at
3 Madison has called those false positive reads. It's
4 documented in the literature that this happens. And one of
5 the reasons that this happens is difficulty in identifying
6 the border of a lesion and misinterpreting fill-in of the
7 satellite region, the area between a solid area of whiteness
8 and uninfected retina, there's a region of small white dots.
9 And as those small white dots undergo their evolution to
10 scarring, it becomes more white. That can be misinterpreted
11 as advance because it looks like the solid border is
12 advancing. The Madison reading center has published that
13 about 20 percent of these false positives are attributable
14 to problems with identifying the satellite border.

15 Having read photographs for the past 11 years, I'm
16 very aware of this problem. I train my readers to identify
17 the border at the outside of the satellite region right at
18 the interface between satellites and uninfected retina. So
19 some of those false positives are eliminated because of the
20 accuracy we take in identifying that border.

21 We will, for example, make maps, retinal maps of
22 difficult cases, so I hope that Dr. Chambers didn't leave
23 you with the impression that reading is based on very quick
24 impressions. I don't think he meant to leave you with that
25 impression. It takes a long time to examine a photograph.

1 We don't do it on single photographs. Every sheet--or every
2 visit consists of a sheet of up to 10 photographs.

3 So we took great care to get as much information
4 as we could out of each of those sets of photographs, even
5 if they were difficult to read.

6 MR. FROST: Thank you.

7 CHAIRMAN WILSON: Gary, I want to just follow up
8 on the unevaluable. You had mentioned that if there was a
9 period of time in which the films were not evaluable, but
10 then they became evaluable later, and if you were able to
11 see active disease which had not progressed from baseline,
12 then you resumed examining them as evaluable photos.

13 How would you handle the situation if, after that
14 period of time, the next evaluable photo showed active
15 disease which had progressed? What was used as the time of
16 progression in that situation?

17 DR. HOLLAND: That's an excellent question, and I
18 should clarify that I was not doing an analysis here. I was
19 simply scoring photographs. And I would score--any
20 evaluable photograph I would continue to score even if we
21 had identified advancement of the border past the threshold
22 that defines progression. So it wasn't my decision to
23 identify the date of progression for analysis. I simply
24 gave a distance of advancement of the border.

25 So I was continuing to score those even if there

1 was advancement past the threshold. So it would really be
2 up to the analysts at ISIS to give you the answer to that
3 particular question.

4 CHAIRMAN WILSON: Can I get somebody else to
5 answer that question who analyzed this?

6 DR. KISNER: Yes, the answer to that question is
7 that, first of all, there were relatively few of those
8 patients. But, in fact, what would ordinarily be done at
9 that point would be to censor the patient back at the last
10 evaluable photograph in the primary efficacy analysis.

11 DR. HOLLAND: Dr. Wilson, in reflecting back on
12 Kevin's question, I think there's one part of the question
13 that I didn't answer, and that was I had meant to address
14 the issue of how could there be long periods of delay
15 between interpretations. And I really cannot imagine
16 smoldering disease going for 200 days without either the
17 reading center or the clinician identifying--eventually
18 identifying that smoldering disease. So really the only two
19 possibilities for those discrepancies are that there was
20 advancement that was either just sub-threshold or just over
21 threshold that eventually stopped and then the disease was
22 quiet for the rest of those 200 days.

23 I don't think that's likely. I think it's very
24 unlikely, almost impossible, for there to be smoldering
25 disease for 200 days that was not recognized. Knowing the

1 natural history of the disease, knowing the rates with which
2 borders advance in treated but inadequately treated disease,
3 you would get anywhere from 3 disc diameters to 13 disc
4 diameters of advancement of a border over that length of
5 time, and that would not be missed by the reading center, it
6 would not be missed by the clinicians.

7 MR. FROST: Just one quick follow-up. Regarding
8 the false positives, Gary, in the overall percentage of
9 patients who are early progressions, what percentage of
10 those can be attributed to false positives?

11 DR. HOLLAND: In this data set?

12 MR. FROST: From the literature. You had
13 mentioned the Madison publication. I assume that's Mathews'
14 work. How often do we call early progressions in controlled
15 trials when, in fact, it's just a false positive?

16 DR. HOLLAND: Well, I think the frequency with
17 which that occurs happens less and less as we become
18 familiar with this concept of the satellite border. So I
19 don't think it happens very often now. The data that I
20 quoted was from the first SOCA trial, which was started in
21 1989.

22 I also think that investigators have been made
23 aware of this concept of the satellite border, and I think
24 that that's why investigators are now identifying
25 progression earlier than they did in some of the very early

1 drug trials of Ganciclovir or Foscarnet.

2 CHAIRMAN WILSON: Dr. Kilpatrick?

3 DR. KILPATRICK: Dr. Holland, just a short
4 question. I want to take you back to the initial reading of
5 these photographs.

6 I understand that the readers were masked to the
7 patient and to the patient's assignment in treatment. Were
8 the two readers independent or was there an exchange of
9 information, confirmation as to whether what you saw--

10 DR. HOLLAND: The way we did it was another
11 physician, other than me, read them the first time. Then I
12 read them independent of that reader. We did not read them
13 together. I read it separately. After I established my
14 initial impression of times or of events, then I looked at
15 their assessment. And sometimes we would discuss it if
16 there was a large difference. But my--if there was a large
17 difference, we would discuss it, the two of us, and we would
18 come to consensus.

19 If for some reason we couldn't come to consensus,
20 the final score was mine, and that provided the consistency
21 that has gone over numerous studies over the years.

22 CHAIRMAN WILSON: Ms. Cohen?

23 MS. COHEN: I think it was good to have an example
24 of what Dr. Chambers showed on the slides for us to see, and
25 I think it would be interesting to hear your observations to

1 give us a better sense--I mean, this is all kind of in a
2 vacuum, to tell you the truth. It's a matter of minds or
3 like minds or not like minds.

4 In the presentation that he made of those slides--
5 and I must say they were murky to me, but maybe because I am
6 not capable of judging--would you have had a different
7 analysis of what Dr. Chambers showed versus what he put up
8 there?

9 DR. HOLLAND: Well, he really didn't provide you
10 with an analysis, the kind of analysis that he derived to do
11 his final determination of time to progression or the type
12 of analysis that I did for the type of scoring that I did
13 and provided to ISIS.

14 What he was illustrating for you was the
15 difficulty in establishing a border because the faintness of
16 the whiteness, the fact that the pictures can be slightly in
17 different orientations, and it was because of those problems
18 that we did things like making a map of the fundus. We
19 would actually take those pictures and draw a diagram of
20 where all the vessels are and where in relation to those
21 vessels the white spots were so that we could be very
22 consistent in performing our evaluations.

23 MS. COHEN: But, in essence, what I think you're
24 saying, unless I misconstrue, that, in fact, on face value
25 it was very difficult to determine what those slides really

1 said.

2 DR. HOLLAND: It is. It is difficult, and that's
3 probably why there aren't more reading centers in the
4 country. We take a lot of time to do this. Our experience
5 has been very consistent. The time to progression that was
6 generated from the data that I provided is the same as the
7 time to progression that's been reported in every other
8 study using a deferral design.

9 I read these photographs in the same manner that I
10 read slides for Iliad Sciences, for their studies GS106 and
11 107 when they submitted that information in the New Drug
12 Application. And, in fact, the SOCA research group
13 performed a very similar study of Cidofovir, and the results
14 that I generated were very similar to the results that the
15 Madison reading center generated for those two very similar
16 studies.

17 So I think that facts like that indicate the
18 consistency and the reproducibility of the technique that we
19 use.

20 MS. COHEN: All right. Well, in my naivete, let
21 me ask you this: In plain English, could those slides have
22 been better and clearer? Was that possible

23 DR. HOLLAND: The slides certainly could have been
24 of better photographic quality, but I don't think that the
25 results that I generated were inaccurate because of--

1 MS. COHEN: No, I'm not--I mean, I'm not getting
2 into that. I'm getting into the quality of what was
3 received and the quality of the interpretation and the
4 quality that could be improved. I mean, you know, hindsight
5 is wonderful for all of us. I can be brilliant and say--you
6 know, but what do I know? I'm just trying to determine. We
7 all have to learn. I mean, this is a learning process.

8 DR. HOLLAND: I think it's important to state that
9 if I thought that information could not be provided by the
10 photograph, I scored it as such and turned that in to the
11 pharmaceutical--

12 MS. COHEN: In no way was I questioning your
13 technical, you know, professional--I'm just trying to
14 determine, because we're sitting here as--sitting here
15 trying to make a determination of something that is very,
16 very difficult, and I'm wondering, you know, exactly where
17 this all falls in and our responsibility.

18 Thank you very much.

19 CHAIRMAN WILSON: I think that sometimes there are
20 technical reasons why a photo isn't as good as it should be,
21 but sometimes it's because the condition of the patient--you
22 know, medial opacity and uveitis and so forth may also cause
23 slides to not be quite the quality that you may want. So
24 it's probably a combination of both.

25 MS. COHEN: Again, therefore, can you use it in--

1 if you're using it for a scientific study, for clinical
2 trials, and you're saying it can't be, then can you really
3 use it? If it can't be, should it be used? I don't know if
4 anybody can answer that.

5 MR. FROST: Well, I think he is answering it. I
6 think Dr. Holland is saying that if it couldn't be used, he
7 wouldn't have used it.

8 DR. FONG: Not only that, I mean, if the rate of
9 ungradables is equivalent between the two groups, then
10 you're not going to have a bias. You know, so it's not
11 necessarily--it doesn't really hurt the outcome.

12 MS. COHEN: I think this is a very interesting
13 exercise in science.

14 CHAIRMAN WILSON: Don?

15 DR. FONG: This is the first time that I've served
16 on the Advisory Committee, and I'm just curious. Does Dr.
17 Chambers review photographs of all other CMV trials? And if
18 so, what has been the disagreement rate in the past with the
19 other trials?

20 DR. CHAMBERS: I have reviewed the slides for
21 every CMV retinitis product with the exception of oral
22 Ganciclovir, so IV Ganciclovir, Cidofovir, Foscarnet IV,
23 Ganciclovir implant have all been reviewed in exactly the
24 same manner.

25 The discrepancies that you are seeing here are not

1 any different than what we've typically seen in other
2 studies. The difference you're seeing has to do with the
3 number of patients. If we disagree on a few patients, it's
4 not made a big difference in the past because there have
5 been significantly more patients. And while the dates may
6 be off a little bit and they were--I think you saw in the
7 presentation the sponsor made, Cidofovir has both--the
8 presentation has both the date the sponsor had as far as
9 reading, which, I believe, I guess it was Dr. Holland's, and
10 there was an FDA presentation date. That date is mine.

11 You will also see a difference in days. It's not
12 inconsistent with what's happened before.

13 CHAIRMAN WILSON: Mr. Frost?

14 MR. FROST: I just want to concur with what Dr.
15 Chambers said, and one comment is actually that there were
16 many of us on the committee who wished Dr. Chambers had
17 reviewed the oral Ganciclovir photographs.

18 But having said that, I think that even in the
19 Cidofovir insert--correct me if I'm wrong--there are two
20 sets of dates, one of which belong to the sponsor and one of
21 which belong to Dr. Chambers, and they are quite different.
22 And just in my own opinion, for whatever it's worth, I think
23 having been at most of these hearings over the last ten
24 years, Dr. Chambers' reviews are very conservative reviews.
25 And I think that's appropriate for the agency, but I think

1 we have to put that into the context of understanding
2 efficacy and safety and all of those things.

3 CHAIRMAN WILSON: Other questions from the panel?

4 DR. KILPATRICK: Not for Dr. Holland, no.

5 CHAIRMAN WILSON: Any other questions for Dr.
6 Holland?

7 [No response.]

8 CHAIRMAN WILSON: Wiley, would you like to make
9 any final comments related to this issue before we take any
10 other questions? You don't have to.

11 DR. CHAMBERS: I'm not sure that--it's not--in my
12 mind, it's not unexpected to have differences between the
13 reading centers. I think it's problematic that relatively
14 small calls early on as far as progression versus whether
15 they would not progress in the first couple weeks and have
16 such a profound difference, I think that's problematic of
17 the way we do these analyses.

18 MR. FROST: Can I ask a question to that point,
19 Dr. Chambers? Based on what ISIS has shown here, there were
20 several patients that you called early that they called
21 later. Among those patients, just from your memory, first,
22 did you follow those patients--or did you review the
23 photographs even after the point that you called early
24 progressions? And the reason I'm asking that is because I
25 want to know if, in your opinion, there were patients who

1 responded in those follow-up photographs despite having been
2 called early progressors?

3 DR. CHAMBERS: I did evaluate them all as
4 continuing after work, and I'm not sure about the
5 percentage, but it would not surprise me if there are at
6 least half of those that, while I viewed them as having
7 progressed, progressed no further, essentially stopped and
8 got quiet.

9 MR. FROST: So from an analytical perspective--I
10 mean, we're playing with the differences here between an
11 analysis which says a time to progression, which I think we
12 understand is a fairly arbitrary and I think I'm hearing
13 even perhaps insufficient definition of efficacy, clearly
14 there was a demonstration of activity that may, in fact,
15 differ quite dramatically from what's presented from an
16 analytic perspective in a Kaplan-Meier curve.

17 DR. CHAMBERS: Correct, and that's some of why you
18 are hearing from me that I believe there is pharmacological
19 activity here, because I do not believe that the patients
20 would have reacted the way they did had there not been some
21 kind of pharmacological activity going on. But they don't--
22 the difference comes down to, if you see something
23 progressing 130 microns versus--730 microns versus 750
24 microns, get called entirely differently. And it's a very
25 small difference that you see.

1 CHAIRMAN WILSON: Wiley, the issue of false
2 positives that was brought up by Gary, do you feel like that
3 could in any way explain any of the differences? I would
4 expect you're quite familiar with that issue and probably
5 there were no false positives, at least from the way it was
6 presented. But I'd like to hear your views on that.

7 DR. CHAMBERS: There's absolutely no question that
8 there are--in fact, I showed some of the slides where there
9 are some satellite lesions there. The question comes up,
10 when you have some satellite lesions, is exactly where that
11 border is.

12 Satellite lesions getting slightly bigger I don't-
13 -I'm sure were not called on either--I know they weren't
14 called by me, and I obviously doubt they were called by Dr.
15 Holland's group. The issue happens with some of the fill-in
16 there, and where you--if you see one or two satellite
17 lesions, do you draw a line all the way up at the farthest
18 of the satellite lesions and say any filling-in to there is
19 not considered progression? Or is that line a curved line,
20 and where you see some of the satellite lesions you say
21 filling-in up to that point is not progression, but filling-
22 in next to it may be progress? And I have no doubt that
23 there may be some calls where I said that was progression
24 because there's filling-in--I didn't think that satellite
25 line is a straight line. And my interpretation of where the

1 line was and Dr. Holland's group's interpretation of the
2 line were slightly different. And we're talking small
3 micron differences.

4 CHAIRMAN WILSON: Go ahead, Dr. Holland?

5 DR. HOLLAND: Can I respond to that? I think the
6 committee should understand that there are very clear
7 definitions of what the border is. If satellites have less
8 than 750 microns of normal-appearing retina between them,
9 they're considered all to be in the same--within the same
10 lesion. If the satellites are more than 750 microns from
11 another area of infected retina, it's considered a separate
12 foci of disease.

13 So for our group, it's very clear where the border
14 is, and I think that that's why we get such consistent
15 results and why our results are the same as the results that
16 the Madison reading center gets. The Madison reading center
17 that I've been alluding to is the center that reads the
18 photographs for the SOCA research group, the NIH-sponsored
19 trials, and has read studies for Roche.

20 So our results are very similar to the results
21 that they get, and I think it's because we work off of the
22 same standard definitions. And as far as the clinical
23 relevance of filling-in of the satellite border versus
24 whether there's advancing border, that's not a trivial
25 issue. The region that has satellites in it is destined to

1 be non-functional retina. We know that from histopathologic
2 studies at autopsy. We know from experience, for example,
3 there's a phenomenon where it looks like patients just
4 develop scars but never had white foci of disease. And
5 those scars arise from the evolution of a collection of
6 satellites. The retina is destroyed, but it never goes
7 through that very edematous stage.

8 So it is important to draw the border outside of
9 all of the satellites.

10 CHAIRMAN WILSON: I understand, but, Gary, how
11 standard is that standard technique? I mean, is it beyond
12 just your center and Davis? Would anybody that reads fundus
13 photographs consider that 750 micron to be the standard?
14 And would that be something that Dr. Chambers and anybody
15 else that would be reading would use as a definition?

16 DR. HOLLAND: Well, it's certainly been discussed
17 widely amongst people who deal with CMV retinitis. I don't
18 know how other people would read trials, and I can't say
19 where Dr. Chambers drew his borders or just how he
20 established them.

21 The point I'm trying to make is that our reading
22 is by standard definitions and is very consistent.

23 CHAIRMAN WILSON: I hate to keep--

24 DR. CHAMBERS: I'm just going to make one last
25 comment and go on. Everybody has to remember that the 750-

1 micron border was an arbitrary border that was initially set
2 up purely because you were convinced that it was
3 progressing, and the basic definition we were concerned
4 about is: Is the lesion moving or is it not moving?
5 Whether it's actually 750, 730, 710, was completely
6 arbitrary.

7 CHAIRMAN WILSON: Dr. Kilpatrick, you had a
8 question?

9 DR. KILPATRICK: Yes, I may have a series of
10 questions. I believe Dr. Chandler may be able to answer
11 these questions.

12 I want to return to the design and analysis of
13 these clinical studies. In particular, as I read the
14 information, I can see little difference between CS9 and
15 CS12 apart from location. CS9 is in the Americas, and CS12
16 is in Europe and Asia, I believe.

17 The question I have is: Why were these--since
18 these studies were presented before completion, why were
19 these two studies not combined given the repeated reference
20 to small sample size?

21 DR. KISNER: Yes, Dr. Kilpatrick, I'll answer the
22 question. In fact, these two studies are essentially
23 identical, and they were started at different times, and
24 they were performed in geographically different locations.
25 We gave every consideration to the possibility of combining

1 them and decided ultimately against it.

2 Very clearly, there is no real trend in favor of
3 one treatment group versus the other. In fact, our
4 calculation on the CS9 study suggested there is only maybe a
5 10 percent possibility that if we completed that trial that
6 there would be any difference between those two treatment
7 groups. So we didn't combine them, frankly, because we felt
8 that there might be difficult statistical questions about
9 that procedure, and in the end, our feeling was that these
10 studies wouldn't add anything to their separate
11 presentation.

12 CS9, by the way, did reach the protocol-defined
13 interim evaluation, which is what we reported.

14 DR. KILPATRICK: Thank you. But there is an
15 intent, then, to analyze CS12 at some point and present
16 results to this group or to FDA or to some group?

17 DR. KISNER: We have made a proposal to the FDA
18 that we'll discuss with them in the future, presumably, for
19 a Phase 4 program that will actually modify both the CS9 and
20 CS12 studies to replace the Regimen A, the more intensive
21 regimen, with a regimen that actually contains the 165-
22 microgram induction, and then monthly maintenance at 330.
23 And the reason for that is that the trend in favor of the
24 less intensive regimen with regards to safety was viewed by
25 us as an important signal.

1 DR. KILPATRICK: One follow-up question. Both
2 these studies involved randomization, and yet if I look at
3 your demographic summary on Table 33 of the background
4 information package, I see that all--and I'm only counting
5 three, but all three of the three Asians in CS12 ended up in
6 treatment A, and with regard to CS9, all--that is, three of
7 three blacks ended up in treatment A.

8 Now, this does not look like an effective
9 randomization. Dr. Chambers--these were also in some of his
10 publications, in the report that he presented to the
11 committee. Can somebody explain why we have all the Asians
12 in one group and all the blacks in the same group and no
13 balance there? Or is that simply a statistical anomaly?

14 DR. KISNER: I believe that's a statistical
15 anomaly. Clearly, there was no stratification for those
16 parameters, and I believe we got unlucky with regards to
17 that.

18 DR. KILPATRICK: And yet Dr. Chandler presented,
19 in my view, redundant comparisons of sex differences in
20 these, in CS9, and didn't look at the ethnic division.

21 DR. KISNER: Is your comment that he didn't
22 present details of the ethnic division in those studies?

23 DR. KILPATRICK: Well, I'm somewhat at a loss here
24 because I believe, as has been indicated by Kevin, that if
25 you believe in randomization, you don't then go and do

1 statistical tests to confirm that your randomization worked.
2 You accept, as you are suggesting here, that the things fall
3 as they do. So there's some inconsistency in the treatment
4 of these data. That is the point that I'm making.

5 DR. KISNER: I see.

6 CHAIRMAN WILSON: It's a little past the beginning
7 of lunchtime, so I think we'll break here and resume at 1
8 o'clock

9 [Luncheon recess.]

AFTERNOON SESSION

[1:02 p.m.]

CHAIRMAN WILSON: We'll resume the meeting.

Is there anybody from the public that would like to speak now?

[No response.]

CHAIRMAN WILSON: Okay. We'll go to the open--

MR. SMITH: I'd just like to say a few more things that weren't addressed in my opening talk that people had alluded to.

CHAIRMAN WILSON: Would you introduce yourself again, please?

MR. SMITH: My name is Christopher Smith. I'm one of the patients that was up on one of the slides. And I guess what I want to say is the injections--to demystify some of this stuff, I put my treatment into about a four-hour slot every two weeks, and 15 minutes of that is laying on the injection table. And I can't stand here and say that the injection is not painful, okay? It feels like there is a needle going in your eye, which does not feel any different than a needle going into your arm or a needle going into your butt. It still has that same pinching feeling.

The administration of the drug is so small that you can barely feel that anything is being injected into

1 your eye, and there is enough local anesthetic that you
2 don't feel anything until you get through to the last layer
3 before vitreous.

4 I've had 60 of these injections. I will continue
5 to do this until it fails. I have counseled people who have
6 been patients in the clinic that I go to and also one of the
7 clinics that I work at.

8 It's a manageable thing for quality of life.
9 Right now I'm working full-time in an HIV practice in
10 Chicago as an office manager, and they have no problem
11 letting me go the four hours every two weeks in order to get
12 this done. So it is possible to maintain a highly active
13 life-style and get the injections done and still live.

14 CHAIRMAN WILSON: Thank you, Mr. Smith.

15 MR. SMITH: Okay. Thank you.

16 CHAIRMAN WILSON: Okay. I want to turn the
17 panelists' attention to the questions on page 4 of your
18 agenda. Just keep these in mind as we go along.

19 Any other questions to either the sponsor or to
20 the FDA?

21 DR. MATHEWS: I have a number of questions for the
22 sponsor. I wanted to get some information, if you could
23 just clarify for me, on the covariate predictors of outcome.
24 The protease inhibitor variable is a baseline measurement,
25 not post-treatment.

mc

1 DR. KISNER: That's correct.

2 DR. MATHEWS: Okay. Were viral loads collected on
3 patients?

4 DR. KISNER: They were not.

5 DR. MATHEWS: On none of them. Okay. All right.

6 DR. KISNER: Not as part of this protocol, no.

7 DR. MATHEWS: The point estimate for the effect of
8 the protease inhibitor therapy at baseline in CS2, could you
9 give us what the point estimate was? You reported a p-value
10 in the slides, but because the sample size was so small, one
11 doesn't really know how to interpret it.

12 DR. KISNER: What I'm able to address is the p-
13 value in terms of the difference in baselines. The Cox
14 linear regression with regards to the prognostic value of
15 protease inhibitor use in the treatment outcome and a p-
16 value that is modified for that difference in baseline--

17 DR. MATHEWS: Yes, adjusted--but I wanted to know
18 what the protease--the hazard ratio for the protease effect
19 in the multi-predictor model that you alluded to in--

20 DR. KISNER: We actually have the hazard ratio.
21 Can I see that slide? Maybe if I went up...

22 Now, the specific question was what was the hazard
23 ratio. We do have a slide with the hazard ratio. These are
24 slides that you have seen in the presentation.

25 CHAIRMAN WILSON: While they're looking for the

1 slide--

2 DR. KISNER: It's a specific slide. I'm sorry.
3 We're going to take just a second. Maybe I can help with
4 another question while they're looking for that.

5 CHAIRMAN WILSON: Well, while they're looking for
6 the slide, I was going to ask Dr. Mathews what his concern
7 was regarding viral loads and whether the other panelists
8 had any other concerns related to that.

9 DR. MATHEWS: Well, you know, what I'm concerned--
10 first of all, let me preface this by saying that overall, on
11 balance, I'm impressed that this is a very promising agent,
12 and I believe it's shown an effect. But we're in an era of
13 therapy with HIV where things can change very dramatically.
14 And it's well-known now that people who were diagnosed with
15 CMV retinitis, who were put on potent antiretroviral therapy
16 after going through a standard period of induction, can be
17 taken off therapy and followed for many months with no
18 evidence of reactivation. And both CD4 and viral load are
19 independently predictive of progression, not only in CMV but
20 in other opportunistic infections.

21 So if you don't collect in detail the treatment--
22 the post-baseline treatment experience so that a person can
23 assess at the end of--whenever the patient was censored, are
24 there alternative explanations for why a certain individual
25 did well? And that's why earlier I was alluding to the

1 informativeness of looking at perhaps a responder analysis
2 so that--and there aren't that many patients to talk about,
3 so that we could get a sense, like, how many of the patients
4 who have never progressed on these studies had their
5 therapies changed, had sustained CD4 responses, had viral
6 load drops, those kinds of questions.

7 You know, I think the data that you presented from
8 my own ability to discern possible sources of confounding
9 was incomplete.

10 DR. KISNER: Right. First of all, I think--I
11 agree with many of the things that you said, and for
12 starters, we agree that certainly within the last six months
13 or so, data have been generated to suggest that patients
14 having profound responses to CD2 protease inhibitor-based
15 combinations can be withdrawn from anti-CMV therapy, and
16 there are cohorts now that are being followed to see what
17 the success of that effort is. Keep in mind that these
18 patients were enrolled in these studies beginning in the
19 early part of 1995 and ending with patients enrolled in the
20 roughly mid-third quarter of 1997.

21 So two things are true. One was that at the time
22 we started this, protease inhibitors were not available;
23 routinely performed HIV titers, HIV viral load studies were
24 not being performed. In any case, we didn't do them. And
25 we certainly have not been able to account for recent

1 information.

2 We do have accurate information on the concomitant
3 medications for patients treated in these studies. I think
4 there may have been a misunderstanding about an answer to a
5 question earlier in which it sounded as though we didn't
6 have control of that. We certainly didn't have control over
7 what these patients were being treated for with regards to
8 their antiretroviral therapy, but we have accurate
9 concomitant medication information.

10 The information--the way we chose to--sorry. I
11 have an insect that finds me attractive.

12 The way we chose to deal with this was based upon
13 the fact that protease inhibitor therapies changed very
14 frequently on those patients that were on protease
15 inhibitors. We found ourselves initially trying to find
16 some specific HAART regimen that we should look at as a
17 prognostic factor. In fact, these regimens changed many,
18 many times. Patients went on one protease inhibitor, came
19 off of it, went on to something else, had periods of time
20 when they were on nothing with regards to protease inhibitor
21 therapy. They were on some other antiretroviral program or
22 no antiretroviral program for a period of time.

23 Attempting to do an analysis in a group of
24 patients over a period of months where the antiretroviral
25 therapy might change several times in our view made it very

1 difficult to look for any given regimen or even any given
2 protease inhibitor as a meaningful prognostic indicator.

3 We agree with everything you've said, but this, at
4 least in our practice, was much more difficult than it may
5 have sounded when you said it.

6 What we did do was attempt to identify whether
7 protease inhibitor use was important, and at baseline we
8 were unable to detect that patients on baseline protease
9 inhibitors had longer times to progression in this study.

10 We were very concerned about this panoply of
11 antiretroviral programs that patients were going on and off
12 of throughout the course of these studies, and the only way
13 we could get at that--and it may not be adequate, but--at
14 least we think it is, but it may not be in your mind--was to
15 follow CD4 counts serially in as many patients as we could.

16 So at the time when protease inhibitor therapies
17 became available, we made mandatory serially CD4 counts part
18 of these protocols. At the beginning, when all of these
19 patients had very low CD4 counts and there was no--we
20 followed them sporadically, but there was no therapy that
21 made very much difference on CD4 counts back at the
22 beginning of these studies. We didn't have it in the
23 protocol. We initiated serial CD4 count measurements as
24 soon as it became obvious that there were therapies being
25 used in some of these patients that might make a difference,

1 and we followed CD4 count measurements as opposed to trying
2 to pick one protease inhibitor or some protease inhibitor
3 combination regimen to look at.

4 That was the serial CD4 count information that we
5 showed you, and if you--

6 DR. MATHEWS: That was in CS2; right?

7 DR. KISNER: I thought we were talking--

8 DR. MATHEWS: No, no. That's correct.

9 DR. KISNER: Can I see the CS2 CD4 count, serial
10 CD4 count information again? And, Lisa, when it's up, maybe
11 we can even comment on a few of the individual patients that
12 are here, because some of these patients, as you'll see, if
13 we can get to the slide--I'm sorry.

14 As you can see, this is the majority of the
15 patients in the study, and we did follow CD4 count over
16 time. It's hard to see some of these individual, but the
17 two patients that we censored were patients that started out
18 here and had a bump in CD4 count, and then it came back down
19 and stabilized for a while and then went up and had a
20 sustained increase in CD4 count.

21 It's of interest to point out that this patient
22 had an active CMV retinitis lesion at entry into the study
23 at a CD4 count that's approximately 100. We went back and
24 looked at all the baseline photographs to reassure ourselves
25 that, regardless of whether the CD4 count was above or below

1 50, we had active lesions at entry into the study.

2 That patient had an active lesion at entry into
3 the study. That lesion stayed--was active at entry. That
4 patient had more than 100 days before a change in CD4 count
5 that you and I would probably agree was a meaningful
6 increase.

7 So that, at the very least, this patient had
8 inactivation--and this patient, as I recall, had an inactive
9 lesion shortly after initiating therapy--had at least in our
10 view 100 days, maybe as much as 150 days, before any change
11 in CD4 count might have benefited that patient's CMV
12 retinitis, went on to have an increase, a decrease, an
13 increase, and was one of the two patients that we removed in
14 the sensitivity analysis since because--in an attempt to
15 make sure that the treatment effect that we saw was not
16 related to two long-term responders that happened to do well
17 and have high CD4 counts.

18 We can't preclude high CD4 counts in the study.
19 All we tried to do was to see to it that those patients
20 weren't accounting for the treatment effect that we were
21 seeing, and we demonstrated, I think, that they were not
22 responsible for the treatment effect.

23 When you eliminate those two patients--when you
24 eliminate those two patients with really meaningful changes
25 from baseline, keeping in mind everybody had an active

1 lesion at baseline, remove the patients, the p-value on the
2 comparison is still 0.0003. So our view is that changes in
3 CD4 counts over time--and those are the ones that we think
4 are convincingly different from baseline. Changes in CD4
5 count over time, at least in our view, cannot explain this
6 treatment effect.

7 Can we go to the baseline slide? Go back one.

8 Sorry.

9 You saw this distribution earlier. The same
10 concept applies. We have, in fact--we had, in fact, no way
11 of knowing what the right cutoff level was for CD4 count,
12 but we did see active lesions in patients with CD4 counts
13 from 0 all the way up to the mid-400s. Every single one of
14 these patients had active, newly diagnosed CMV lesions when
15 they came into the study. Half of these patients had CD4
16 counts over 100.

17 When we looked at this analysis, it had seemed to
18 us that, in general, the baseline CD4 counts were quite
19 similar except for two outliers. Just to preclude the
20 possibility that they played a role in the treatment
21 outcome, we did a sensitivity analysis that excluded them
22 and got, again, the p-value of 0.0003, showing that they
23 changed the p-value from 0.001 to 0.0003 when they were
24 removed.

25 DR. MATHEWS: I understand that, and that was a

1 reasonable thing to do. But, you know, the data that was
2 recently published from Freeman's group at San Diego, the 11
3 patients that were withdrawn from maintenance therapy, the
4 median--who did not reactivate--the median CD4 at time of
5 withdrawal was 183 or something like that. So that half of
6 the patients had smaller CD4 rises, and what I'm suggesting
7 is we really don't understand fully how big a CD4 response
8 is required, what is the relationship to the viral load, to
9 take care of this concern about residual confounding by
10 post-baseline treatment effects. And I don't know that you
11 can resolve it right now, but it leaves a certain
12 uncertainty in my own mind about some attenuation of the
13 treatment effect if you actually could adequately control
14 for these factors.

15 DR. KISNER: We clearly were concerned about the
16 same set of issues, and I think there will be a lot more
17 data collected on cohorts of patients whose anti-CMV therapy
18 is removed. It isn't entirely clear to me that it's going
19 to be a routine practice. Maybe it will be. But at the
20 point that these studies were done, I think we did what was
21 feasible. And in terms of the analysis we've done, we've
22 done everything we can think of to try to remove this
23 question mark over the studies.

24 In the end, given everything we've looked at in
25 terms of CD4 count and protease inhibitor use, we still find

1 a very, very strong treatment effect. It's hard to know how
2 much that treatment effect might be diminished by some of
3 the things you're talking about, but, you know, we believe
4 at this point that we've done what we can with this data.

5 CHAIRMAN WILSON: Dr. Kisner, were you able to
6 find the hazard ratio slide?

7 DR. KISNER: Did you find that slide?

8 DR. GRILLONE: Actually, we don't have a slide of
9 it, but I can tell you the hazard ratio of the baseline use
10 of protease inhibitors, the Cox regression analysis that you
11 saw in the presentation, the hazard ratio for that is 0.611.

12 CHAIRMAN WILSON: Does that satisfy your question?

13 Dr. Fong?

14 DR. FONG: Well, I am--I understand the difficulty
15 in identifying all the different protease inhibitors a
16 patient may be on, but it seems like that it would not be
17 too difficult to model in the Cox regression analysis the
18 use--the first-time use of protease inhibitors. There is a
19 time-dependent covariate, and that way, you know, then you
20 have an estimate, at least, as to the effect of protease
21 inhibitors on the treatment effect.

22 DR. KISNER: It's an analysis we haven't done. I
23 frankly am unconvinced that that would be a reliable way to
24 actually determine the impact of protease inhibitors simply
25 because first-time use might--in a patient population that

1 are coming on and off and changing constantly, first-time
2 use seems to me potentially not important enough.

3 DR. FONG: It may not be the ultimate way to look
4 at the treatment effect of protease inhibitors, but it
5 provides an estimate to at least relieve some of the
6 questions that are in my mind and Dr. Mathews' mind about
7 the role that protease inhibitors might play in the
8 treatment effect.

9 DR. KISNER: Again, it would have to imply some
10 role that protease inhibitors play that's independent of CD4
11 counts, as far as I can see.

12 CHAIRMAN WILSON: Dr. Hannush, did you have a
13 question?

14 DR. HANNUSH: Yes, I'd like to make a few comments
15 and then ask questions to the sponsor.

16 First of all, I'd like to thank Drs. Grillone and
17 Kisner for their comments. I'd like to thank Mr.
18 Christopher Smith from Chicago for adding a human dimension
19 to this issue. Although this is a personal report, I think
20 it carries a lot of weight.

21 I think what we're faced today with is trying to
22 make a decision on whether a new class of drugs, antisense
23 drug, should be added to the armamentarium of treatment of
24 CMV retinitis. And we are trying to make an effort to
25 distinguish science from no science, and then trying to

1 decide if science alone should be what we should take into
2 consideration in making this decision.

3 I come from a generation of ophthalmologists
4 trained in the mid-'80s who were taught by Dr. Jack Chandler
5 and his colleagues. And he has made incredible
6 contributions to the training of ophthalmologists in this
7 country and to eye care in general.

8 I also feel that Dr. Gary Holland has an
9 encyclopedic knowledge of uveitis and continues to make
10 great contributions in this regard, and we are very
11 appreciative of that.

12 I've been on this committee for three years, and
13 I've had the good fortune of being on the Ganciclovir
14 implant study, which gave me a lot of perspective on
15 approaching this. I learned a lot about the multi-
16 dimensional aspect of this disease and the human issues
17 relating to that. In this respect, I've been extremely
18 impressed by Kevin Frost's contribution. I feel I've
19 learned so much more from him than I could ever contribute
20 to this panel, and he says he's been on this for ten years,
21 but I've only heard him for three years, and I appreciate
22 his comments very, very much.

23 Now, in trying to make this decision, I have a few
24 questions that I would like to ask the sponsor. I was
25 trying to go through all the data and make a few decisions

1 on what the exit criteria for these patients were. First of
2 all, what the length of follow-up was. I'm looking at Slide
3 19, if you were to look at the revised version, and this one
4 describes overall fomivirsen exposure, and I don't know that
5 this means length of follow-up because I assume that
6 everybody who remained in the study continued to receive
7 injections. But at one year, there were only 2 percent in
8 the 165-mic group and 7 percent in the 330-mic group that
9 were still receiving injections. Does that also mean that
10 that is the length of follow-up for--the longest follow-up
11 for these patients? So this is one question.

12 Secondly, was retinal detachment an exit criteria?
13 Was that an endpoint? Did people who had retinal
14 detachments, then were they a subset of the discontinued
15 patients? I'd like to know something about that.

16 Then if we look at Slides 91 and 92, on the issue
17 of final visual acuities, I would be very curious to know
18 what the definition of final visual acuity was. I mean, I
19 know it means at the last visit, but the median on Slide 89
20 days on fomivirsen is roughly two months. Again, the
21 question is: How long were these patients followed? And
22 how long did they continue to maintain these visual
23 acuities? Unlike Mr. Smith's experience, I'd be very
24 interested to know whether--again, what is the length of
25 follow-up, and the question here is: What percentage of

1 these patients continued to retain their vision throughout
2 the period of follow-up?

3 DR. KISNER: Thank you for those questions. Let's
4 start by examining the slide that you referred to.

5 These numbers do approximate the follow-up periods
6 for these patients. Patients tended to be observed for a
7 short time after they went off study for late onset adverse
8 events and so forth, but for purposes of their treatment
9 period, these are the numbers that we're talking about.

10 DR. HANNUSH: Well, why did they leave the study?
11 What mechanism--how did they leave the study?

12 VOICE: The study ended.

13 DR. KISNER: Sorry, was there another question?

14 Patients left the study because of voluntary
15 withdrawal, adverse events, in large part related to their
16 HIV disease and complications. We gave you information
17 about adverse events related to ocular adverse events in the
18 eye that was treated. Unfortunately, a significant number
19 of our patients died on study, and another number of
20 patients had progressive retinitis and left the study at
21 that point--assuming that the study was one in which they
22 didn't cross over to some other treatment.

23 So those were the categories of reasons for
24 patients to leave the study. One of them was retinal
25 detachment. Patients who had at least unilateral disease

1 and had a retinal detachment had a repair and were no longer
2 considered actually treated. Period of follow-up for those
3 patients extended to the resolution of their adverse event,
4 but in terms of on-treatment follow-up, which is what I
5 think you're trying to get at, these are the numbers that
6 represent the numbers.

7 There's another slide to show the medians and
8 ranges that was in the presentation right before this one,
9 at least at one point.

10 Just to remind you, that last slide showed you 85
11 patients--85 eyes treated for more than six months.

12 Now, these are the numbers of--these are the
13 numbers that relate to median, mean, and maximum times on
14 study that Dr. Chandler presented to you. And as you can
15 see, the medians are in that two-month range that you're
16 talking about. The means are somewhat longer because of a
17 skew in favor of long-term progression-free survivors, and
18 the maximums at the time of last observation--and some of
19 those are observations--these observations, Lisa, are these
20 post-NDA filing observations? Are these current as of today
21 or are they--

22 DR. GRILLONE: These are current.

23 DR. KISNER: So as of today, the longest
24 observation is a patient who is still on uninterrupted
25 treatment for 972 days. And I think that answers the

1 questions except for the one on visual acuity. Can we go to
2 the visual acuity slides that were in the--I mentioned that
3 retinal detachment was an off-study criteria.

4 DR. HANNUSH: That would be Slide 91?

5 DR. KISNER: These are the data for 165
6 micrograms, and they do represent the first and last visual
7 acuity assessments that Dr. Chandler went through for you.
8 So it is the baseline visual acuity and the last visual
9 acuity done before the patient left the study. If it was
10 done on the day the patient left the study, then it's the
11 last day. If it was done a few days before, it's the last
12 one. He already walked you through this slide. Do you have
13 specific questions about--

14 DR. HANNUSH: No, I understand this fine. My
15 question is: Is the median exit point the same as what is
16 described in Slide 89, meaning is the median exit point from
17 the study two months? Is that basically the median length
18 of follow-up where people maintained these excellent visual
19 acuities?

20 DR. KISNER: The median length of follow-up is two
21 months. But this--these data show that 80 percent of
22 patients, including patients that went all the way out to
23 three or four hundred days, also retained visual acuity of
24 20/200 or better.

25 DR. HANNUSH: I understand. Thank you.

1 DR. KISNER: But I think the answer is that the
2 median is in that two-month range.

3 Jack, did you want to comment?

4 DR. CHANDLER: If I may, we'll pull another slide
5 up that may get at your question a little differently with
6 visual--

7 CHAIRMAN WILSON: Jack, would you use the
8 microphone, please?

9 DR. CHANDLER: I'm sorry.

10 MR. FROST: While you're doing that, Dan, are we
11 talking about best corrected visual acuity?

12 DR. CHANDLER: Yes.

13 DR. KISNER: Yes, that's exactly right. Jack's
14 got another slide he wants to show.

15 DR. CHANDLER: Another way to look at this is to
16 look at the two different dose regimens, the 165 on your
17 left, 330, all eyes, on your right, and say over a period of
18 time who maintained 20/40 or better visual acuity. As you
19 can see here, at four months, 120 days, there were 40 eyes
20 at the 165, roughly a quarter of them--I'm sorry, about a
21 third of them were out at that range, and 80 percent still
22 had 20/40 or better vision.

23 The group at 330, of that group, two-thirds of
24 them had 20/40 or better acuity at baseline, and at the
25 four-month visit, it went from 269 down to 131, I believe it

1 is--I'm sorry, I'm not lined up well--and it had dropped
2 from a proportion of two-thirds down to 44 percent. Does
3 that help you, give you a better--

4 MR. FROST: Yes, it does.

5 DR. KILPATRICK: I'd just like to ask Dr.
6 Chandler, are we talking about eyes or patients here?

7 DR. CHANDLER: These are eyes.

8 DR. KILPATRICK: What happens if there's a
9 different experience in different eyes in the same patient?
10 I mean, how would you classify that in terms of visual
11 acuity?

12 DR. CHANDLER: They get visual acuity recorded for
13 each eye separately. As we've told you, the eyes appeared
14 in terms of adverse events and efficacy, appeared to be
15 behaving in an independent fashion.

16 DR. FONG: So this includes multiple eyes from the
17 same patient?

18 DR. CHANDLER: Certainly.

19 DR. FONG: Well, that may be an overestimate of,
20 you know, the visual acuity because, you know, if one
21 happens to see well, the likelihood is that the other eye
22 will probably see well, as well. You know, just for the
23 future, a better way is to pick the worst eye, the worse--

24 DR. CHANDLER: We've looked at that data as well,
25 and it literally mirrors what you see here.

1 DR. KILPATRICK: Dr. Chandler, what was
2 randomized?

3 DR. KISNER: Patients were randomized.

4 DR. KILPATRICK: Thank you.

5 DR. FONG: A quick question to the visual acuity.
6 This shows vision of 20/40 or better. Was there any
7 differences in the frequency of worst vision? Was 20/200
8 the prevalence of that pretty symmetric all along the way as
9 well, pretty similar?

10 DR. KISNER: I didn't understand the question.
11 Jack, maybe you did.

12 DR. FONG: Well, this reports the good visual
13 acuities. I'm looking at what is the distribution of poor
14 visual acuities over time. Was the prevalence of vision of
15 20/200 or worse pretty similar through the follow-up?

16 DR. CHANDLER: Overall, there is a slight trend
17 toward more patients having vision of 20/200, 20/100,
18 whatever you want, or worse over time. As you remember,
19 between the yellow improved, the blue, there are a few over
20 there. But the critical thing is that during that time on
21 therapy and follow-up that we have, in the 165-microgram
22 dose 85 percent who entered at 20/100 or better were still
23 20/100 or better, and--

24 DR. FONG: I guess what I was looking for was
25 whether there might be some transient decrease in vision

1 after the injection.

2 DR. CHANDLER: Oh. There were sporadic reports of
3 decreased visual acuity after injections. Come back the
4 next scheduled visit, and it would be the same as they were
5 prior to the injection.

6 DR. FONG: How severe were these decreases?

7 DR. CHANDLER: Typically, they were--

8 DR. FONG: And how long did they last?

9 DR. CHANDLER: Typically, they were in terms of
10 hours, sometimes a day, usually in the range of two--of the
11 data we have, two lines or so.

12 CHAIRMAN WILSON: Any other questions to visual
13 acuity? Emily?

14 DR. CHEW: Yes, just one more. I wasn't quite
15 clear. You said patient was what you randomized; that was
16 your randomization. But yet you had two eyes. So I know
17 for your CS2 you had only unilateral CMV, but for your CS5,
18 I guess--or is it 7? 9?

19 DR. CHANDLER: 7--9.

20 DR. CHEW: Right, 9. The next one is 9. Was
21 that--if the patient had bilateral disease, how were they
22 randomized then? Is that possible? You had bilateral--you
23 must have had bilateral disease in there.

24 DR. CHANDLER: We had some bilateral disease that
25 came in, and there were some who developed the second eye--

1 DR. CHEW: During the course--

2 DR. CHANDLER: --while on treatment. They were
3 randomized to treatment in CS9 for the eye that most met
4 those criteria. And there were other eyes that weren't
5 eligible to be randomized, people that had bilateral disease
6 or later became positive with CMV retinitis, they were
7 allowed to go into the compassionate CS7 trial and be
8 treated when there weren't other options for them.

9 DR. CHEW: But that other eye was not counted then
10 in--

11 DR. CHANDLER: Was not counted--

12 DR. CHEW: Okay. That's what I wanted to know.

13 DR. KILPATRICK: But this is not what I understand
14 from the statistics on CS9 where there is consistently more
15 eyes than patients. Am I incorrect in that?

16 DR. KISNER: Let me make sure that it's
17 understood. When a patient was entered into CS9, was
18 randomized into CS9, and had pre-existing bilateral disease,
19 both eyes were study eyes.

20 DR. CHANDLER: Oh, I'm sorry. Yes.

21 DR. KISNER: When the patient developed a
22 contralateral lesion in another eye that was not present at
23 diagnosis, that patient was allowed to be treated with the
24 compassionate protocol, and that was not a study eye.

25 Now, we kept track of the information. The reason

1 there's more eyes than there are patients in CS9 is that
2 when a bilateral patient was--a bilateral disease patient
3 was entered, both eyes were treated according to the
4 protocol and counted in the data.

5 CHAIRMAN WILSON: So the randomization was by
6 patient in that case--

7 DR. FONG: How many bilateral eyes were there?

8 DR. KISNER: Four.

9 DR. FONG: Just four.

10 DR. KISNER: There are four. And the
11 randomization was by patient, Dr. Wilson. It was by
12 patient. The complexities of trying to do it the other way
13 were almost unimaginable.

14 CHAIRMAN WILSON: Sure. Any other questions
15 related to this? Dr. Mathews?

16 DR. MATHEWS: A different topic.

17 CHAIRMAN WILSON: Go ahead.

18 DR. MATHEWS: I had a couple of questions about
19 the dosing recommendations for newly diagnosed versus
20 relapse disease.

21 On Slide 61, it looks somewhat paradoxical to me
22 that the time to treatment failure or progression was longer
23 in the previously treated patients, granted that there was a
24 difference in dose intensity, but one might expect that
25 previously treated patients, no matter what they were

1 treated with previously, would tend to progress more
2 rapidly. And so I'm wondering, first of all, whether you
3 think the difference in times to progression between CS2 and
4 CS9 are simply a matter of dose intensity. And, secondly,
5 since the toxicities between Regimen B and the 165-microgram
6 dose on Slide 74 looked quite comparable, why you don't
7 suggest going with Regimen B for all patients.

8 DR. KISNER: Those are very good questions that
9 you can imagine we spent quite a bit of time thinking about.

10 To begin with, the integrated data are shown here,
11 and it is the slide you suggested. But keep in mind that
12 the median time to progression in CS2 for the 165 regimen,
13 newly diagnosed patients, was 71 days. The CS9 study, the
14 interpolated median, meaning the arithmetically modified
15 median to account for the long shoulder, was 90 days in each
16 of the two regimens.

17 I'm personally unconvinced that those are really
18 different numbers. There may be some treatment intensity
19 difference, but I am not prepared to stand here and claim
20 that I believe those are different numbers.

21 So it is--I would answer the question that way.
22 We're not entirely certain that the result is really
23 different.

24 Keep in mind, of course, that the total dose
25 administered to the eye in the 165 regimen is essentially

1 the same as the total dose administered in the 330 Regimen B
2 regimen that--Regimen B, that dose is monthly treatment. So
3 we're not terribly surprised that the safety profile of
4 those two regimens is similar, and I'm not fully convinced
5 that necessarily these results are really different either
6 in terms of efficacy. They're different studies and done,
7 in large part, in different centers and so forth.

8 The other thing to say is that I do believe that
9 we do have data to suggest that patients, for example, with
10 greater than three Ganciclovir prior failures that went into
11 CS9 did have a shorter time to progression than those
12 patients that had two or less. So I believe that that dogma
13 holds up in the study, but I also would point out that we
14 have good solid anti-CMV activity in the CS9 study with many
15 patients in the median number--a mean number of three prior
16 treatments, with many patients who have failed multiple DNA
17 polymerase inhibitors. And we believe we have an agent that
18 is not cross-resistant.

19 So I think maybe that's the best answer I can
20 formulate to those two questions.

21 DR. MATHEWS: Okay. One follow-up on that same
22 point is the CS2 admitted patients who were--who had
23 peripheral retinitis, what about data on zone 1 retinitis,
24 newly diagnosed? Because they would be treated the same
25 way, according to your proposed recommendations.

1 DR. KISNER: Right. We, of course, don't have
2 direct information on zone 1 retinitis except in the
3 previously treated population.

4 CHAIRMAN WILSON: Now might be a good time to
5 answer my initial question from this morning related to the
6 actual number of patients that could be expected to be
7 benefited from this treatment. Because as I mentioned, I am
8 concerned that it's taken a while, and the last several
9 years it's been very difficult to find eligible patients.
10 And the implication is that there will be increased
11 resistance to the currently available treatments. But I
12 don't have enough information on this, and I'm just
13 wondering if sponsors could enlighten me a little bit about
14 this increased resistance and the reemergence of CMV
15 retinitis that is being anticipated.

T4A 16 DR. KISNER: To address the issue of the number of
17 patients who might benefit, at least one factor in that is
18 how many patients there might be. And I think from a
19 variety of sources, I think the best guess is that there may
20 be between 7,000 and 10,000 patients, something like that,
21 in terms of prevalence, who have CMV retinitis in the United
22 States today.

23 There have been several reports related to HAART
24 failure. For example, the University of San Francisco
25 cohort that's been followed for the last year or so in which

1 about 50 percent of the patients have experienced
2 progression and failure on HAART, and they anecdotally
3 reported in a couple of abstracts in the last six months or
4 so that they were beginning to see newly diagnosed CMV
5 retinitis again.

6 We've heard from several sources, anecdotal
7 sources, that CMV--that some new cases of CMV retinitis are
8 now beginning to be seen in places where there hadn't been
9 any for a number of months or a year or more. But, clearly,
10 those are anecdotal data.

11 We do have some information on resistance to CMV
12 and clinical specimens taken and patients treated over
13 periods of time. This comes from Doug Jabs and was
14 presented at the retroviral conference in February, and it
15 shows that under the pressure of treatment with Ganciclovir,
16 Foscarnet, or Cidofovir, that after three months, clinical
17 isolates taken from patients, that about 3 percent of them
18 demonstrate resistance that at zero--at baseline, there's 3
19 percent; at three months, there is already quite a bit of
20 resistance to Cidofovir. That seems to stabilize. And then
21 by nine months of treatment, the incidence of resistant
22 strains isolated from these patients is as high as 25 to--25
23 percent to a third.

24 This is a distinct change from an earlier report
25 that Doug published in which these numbers were quite a bit

1 lower, that I think he reported two years ago. So there is
2 change over time. Whether these are the right numbers or
3 whether a new study would repeat these numbers I think
4 remains to be seen. But there is today, I think, much more
5 information to suggest that resistance to CMV can happen and
6 is happening.

7 Whether it is a large clinical problem in CMV
8 retinitis today is a harder question to answer, and I can't
9 answer that question. But this is not a trend that I think
10 we can afford to ignore.

11 CHAIRMAN WILSON: Just a follow-up question.
12 There has been a number of studies performed, and a lot of
13 them, all the initial ones, were not carried out to its
14 fruition. It seemed like they were terminated for various
15 reasons, and so the sample size never got to the point where
16 they could really be analyzed.

17 Can you give us some feel for why these studies
18 were terminated, particularly since subsequent studies had
19 almost the same protocol--not the same protocol. I'm just
20 trying to get an idea of why you felt that the study should
21 be terminated and another study started as opposed to
22 finishing?

23 DR. KISNER: I'm trying to make sure I understand
24 the question. We presented the two clinical studies, 2 and
25 9, for efficacy purposes. CS--

1 CHAIRMAN WILSON: Yes. I'm referring to the
2 studies that Dr. Chambers presented.

3 DR. KISNER: All of these studies were presented
4 in the New Drug Application pretty much in terms of their
5 status, as Dr. Chambers indicated. The CS3 protocol is
6 ongoing, and the Phase 4 plan that ISIS has submitted to the
7 agency would take all newly diagnosed patients who might
8 otherwise have been eligible for CS2 and put them into the
9 CS3 study, which is the oral Ganciclovir-fomivirsen
10 combination compared against intravenous followed by oral
11 Ganciclovir. So the CS3 study is ongoing. That study has
12 not been terminated.

13 Our Data Safety Monitoring Board suggested we
14 discontinue CS2 on the basis of the efficacy result. They
15 made the suggestion that we change the study design for CS9
16 and 12 to exclude the Regimen A program that we felt had a
17 somewhat higher risk with regard to safety and replace it
18 with a regimen that is 165 micrograms for three weeks
19 induction, much like the CS2 study, but with monthly
20 maintenance at 330.

21 Now, the reason the studies didn't complete I
22 think is an important thing for the committee to hear.
23 During the period of time that these studies were open, as I
24 said to you earlier in my introductory remarks, CMV
25 retinitis went from being an orphan indication to a

1 distinctly rare disease. A distinctly rare disease. Our
2 ability to enroll patients at some point--at one point or
3 another during the course of 19--I would say early and mid-
4 1997, fell to nearly zero and in late '97 remained close to
5 zero.

6 When we reached the formal interim--protocol-
7 directed interim evaluations for CS9 and CS2 and did those
8 analyses and saw the results that we saw and recognized that
9 our enrollment rate for this whole program--for this whole
10 program--was in the range of one to two patients a month, we
11 realized that this was no longer an indication that can be
12 studied using the conventional approaches and using the
13 conventional notions of how many patients should be
14 available to assess the disease.

15 It is my personal belief that this 430-eye
16 experience that we've shown you is the largest experience in
17 CMV retinitis you're going to see for a long time. And we
18 didn't discontinue these studies because it was convenient.
19 We moved mountains to try to get patients into these
20 studies. We added centers. We did IRB-approved television
21 and radio advertising. We did workshops with HIV community
22 groups around the country in an attempt to get this done.
23 These patients--thank heavens, in many ways--disappeared.
24 So we stopped these studies--we stopped these studies in
25 anticipation of a conversion to a Phase 4 program in the

1 case of CS9 and 12. We stopped CS2 on the recommendation,
2 also on the recommendation of our Data Safety Monitoring
3 Board. But the ability to study this disease right now--
4 it's not zero, but it's darn close.

5 CHAIRMAN WILSON: Mr. Frost?

6 MR. FROST: I just want to make a couple of
7 comments to add to something Dr. Kisner has said, and that
8 is that while it is true that this disease went from being
9 orphan to rare, one also has to remember the context in
10 which these studies were doing--were going on, and that is,
11 they were happening at a very time when the development of
12 therapeutics for CMV was exploding. Bristol Meyers Squibb
13 was doing studies of Cyclobute G(?). Glaxo has their
14 polyhalogenated Benzomizols(?). Roche was developing
15 Progam Cyclovir(?). There were oral Ganciclovir prophylaxis
16 studies going on. There was tremendous--and remains even in
17 this environment tremendous competition for patients in
18 clinical centers.

19 So while the overall incidence of disease was
20 diminishing, the capacity for clinical trials was increasing
21 profoundly. And so you add that to an environment in which
22 there were now five approved therapeutics, so that a patient
23 could choose to go into a clinical trial or could choose to
24 get an implant or could choose to get, you know, twice-a-
25 month injections with Cidofovir, and you have a tremendously

1 difficult environment in which you're trying to put patients
2 into a research protocol. And I think that that environment
3 alone made it incredibly difficult and continues to make it
4 incredible difficult to find patients for research studies.

5 The other thing I just wanted to remind the
6 committee is that stopping a study sometimes is actually
7 good, and I think we would all agree, in the same position,
8 to some of the decisions that were made. It's no secret to
9 the committee I was on the Data and Safety Monitoring Board
10 and recommended stopping because there was an answer.

11 When Cidofovir came before the agency it was on
12 the basis of an interim analysis, a study that was stopped
13 because it had an answer. When the implant came before the
14 committee, it was a complete study, but I assure you that,
15 as a member of that DSMB, I had argued very strongly to stop
16 that study nine months before its completion because the p-
17 value was 0.0001. It went on for different reasons.

18 So stopping a study, in my opinion, when you have
19 an answer is not only good, but it's appropriate and the
20 ethical thing to do.

21 So just a few comments.

22 CHAIRMAN WILSON: Yes, I think everybody would
23 agree with that. I think the point I was specifically
24 getting at is the protocol was changed to go from the higher
25 dose, 330, to a lower dose based on some information related

1 to retinal stippling and so forth. And I'm not--do you feel
2 comfortable that the information that you used to change the
3 protocol to a lower dose in retrospect now was enough
4 information? Do you think--for example, the retinal
5 stippling, that doesn't seem to me to be a big problem,
6 whereas I think in your deliberations that was included in
7 terms of why you decided to change.

8 DR. KISNER: Yes. I'm sorry if I misunderstood
9 your question. Very clearly, back in May of 1995--and maybe
10 I can see the slide that describes what happened at that
11 period of time--the CS2 and CS3 protocols were opened with
12 the initial clinical dose of 330 micrograms. After the
13 first 20 eyes among 70 patients were treated--right--it was
14 identified that we saw among those eyes four eyes in four
15 patients in which there was a subjective claim of reduced
16 peripheral vision. That was associated with RPE stippling.

17 The company and Data Safety Monitoring Board at
18 that point assessed the potential importance of that. In my
19 view, what in retrospect was a very, very conservative
20 decision was made, and the decision was made that we
21 couldn't rule out the possibility that this was, in fact,
22 drug-related and that it might represent an adverse event
23 that would continue in what seemed at that point a high
24 frequency to us if we continued the randomization.

25 We had no evidence at that point of any animal

1 data of direct retinal toxicity for fomivirsen, and I want
2 to come back to what we know about RPE stippling and direct
3 retinal toxicity before this is over. But we had no
4 evidence that there was any direct retinal toxicity. We had
5 no way of knowing whether this was drug-related or not. We
6 made a conservative decision to discontinue randomization in
7 the CS2 and CS3 studies at that time and drop back and do a
8 dose escalation effort. Initially--let's see if it's here.
9 Yes, initially evaluating a 75-microgram dose level in a
10 cohort of patients and eyes and then a 150-microgram cohort
11 of patients and eyes.

12 What we saw is that at the end of 16--in 16 eyes
13 treated at 75 micrograms, there was no evidence of
14 peripheral vision loss, and in these patients, we were now
15 doing perimetry, and also no evidence of RPE stippling. And
16 about 40 percent of those patients' eyes remained free of
17 progression at approximately one month. We regarded that as
18 an unacceptable therapeutic outcome. With fully 60 percent
19 of the patients' eyes demonstrating a disease progression in
20 30 days, we decided to escalate the dose to 150 micrograms
21 at that point, and at the end of the evaluation of the 165
22 microgram cohort, 150 and 165 are the same dose. It had to
23 do with a change in the concentration of the vials that we
24 were using. I'm sorry about that confusion.

25 We found that 70 percent of the patients were free

1 of progression at one month, and, again, we had no evidence
2 of any RPE stippling or any objective or subjective
3 peripheral vision problems in that cohort of patients.
4 Maybe that was the wrong number of patients or the wrong
5 size dose escalation study to do. But it was our judgment
6 at that point that we could reinitiate randomization at the
7 165-microgram dose level in CS2 and CS3. The data that
8 we've shown you for CS2 and the data that is in the package
9 but we didn't present to you in CS3, because it's not
10 finished, is based upon all of the data since the initiation
11 of re-randomization.

12 In other words, these patients that we considered
13 to be the definitive analysis for CS2 are patients who were
14 entered into--you know, were in the analysis related to the
15 reopening of that study in a randomized dose form after the
16 dose escalation. The dose escalation work was an attempt to
17 find a safe and effective dose. And at 165, we felt that we
18 had a dose that was inactivating virus. We saw border
19 opacification changes that suggested that we were
20 inactivating virus, and we reopened the studies for those
21 reasons at that time at that dose.

22 Now, we then went on and I think in our clinical
23 program demonstrated in the end of the day that RPE
24 stippling and peripheral vision effects are relatively
25 uncommon events, 2, 3, 4 percent in our assessment in this

1 disease not a terribly big--not a terribly common problem.
2 In patients that have it, it's a problem, but in the total
3 population it's small.

4 We also did a thorough investigation into the
5 potential direct retinal toxicity of fomivirsen, and I won't
6 show you a lot of detail, but fundamentally we demonstrated
7 that the drug in vitro is not directly toxic to RPE cells.
8 Even in tissue culture experiments with the drug exposure at
9 50 micromolar for 14 consecutive days, there were no toxic
10 effects; and, furthermore, that in animals there is no
11 direct toxic effect to the retina that we've been able to
12 demonstrate in any dose in any frequency of administration.

13 So we do not believe that fomivirsen is a direct
14 retinal toxin, and, frankly, it's our view--even though
15 we've reported the information, it's our view that it's
16 unlikely that the drug is actually responsible for the RPE
17 stippling or the peripheral vision effects that we've seen.

18 CHAIRMAN WILSON: Are there any other last-minute
19 questions before we go to answering the questions? Ms.
20 Cohen?

21 MS. COHEN: With the increase in off-label use and
22 with the encouragement now of new legislation, are you
23 anticipating off-label use?

24 DR. KISNER: Is the question--I'm sorry. The
25 question was with--I didn't hear the first part of your

1 question. I'm sorry, Ms. Cohen.

2 MS. COHEN: Well, I'm just interested to know if
3 you're anticipating any off-label use of this medication if
4 it is approved.

5 DR. KISNER: We're certainly not going to
6 encourage off-label use, but as you well know, physicians
7 are perfectly free and legally free to use drugs as they see
8 fit.

9 We are going to provide very careful instructions
10 for the use of fomivirsen in this disease. We intend to do
11 this responsibly and in great detail, and our partners at
12 Ciba Vision will be doing the very same thing.

13 I think it's impossible to preclude off-label use,
14 but we'll do the best we can to make it a very carefully
15 instructed package.

16 CHAIRMAN WILSON: Dr. Kisner, do you have any
17 other information that you feel you want the panelists to
18 know about before we go into the specific questions?

19 DR. KISNER: It's my personal view that hearing a
20 couple of comments from maybe a clinician who has used the
21 drug might be useful. I think clinicians' impression,
22 clinicians' experience with the injections might be helpful,
23 but that's up to you.

24 CHAIRMAN WILSON: If there is a clinician here who
25 would like to speak to that, we'd be willing to hear it.

1 DR. GOLDSTEIN: If I can reach the microphone, I
2 will. Or maybe not. My name is Dr. Debra Goldstein. I am
3 an ophthalmologist at the University of Illinois, and I am
4 one of the principal investigators from ISIS Pharmaceuticals
5 for this drug.

6 I wanted to address--thank you--one of the issues
7 that Ms. Cohen raised, which is how difficult is this to
8 perform the injection and will people be able to give this
9 drug. And I think that in CMV retinitis the most difficult
10 thing is actually diagnosing and following the progression
11 of CMV retinitis. As Dr. Chambers showed us so clearly on
12 the photographs, progression isn't always obvious to see.
13 So I think that the real challenge to the physician taking
14 care of patients with AIDS is actually the diagnosis and
15 following of CMV retinitis.

16 I think that any physician who is capable of doing
17 that is certainly capable of performing the intravitreal
18 injection, which is certainly within the scope of practicing
19 ophthalmologists'--who are surgeons--scope of practice. So
20 that was the first thing I wanted to reassure, that this
21 isn't an earth-shatteringly difficult procedure to perform.

22 The other thing that I'd like to comment on, if I
23 may, is the clinical assessment of CMV retinitis
24 progression, and we all know that there are differences
25 between fundus photography reading centers' diagnosis of

1 progression and the clinician's. I'd like to say that from
2 the patients that I've had on the study and from looking
3 over the rest of the data, which Dr. Kisner may want to
4 show, in all cases in this study the clinician's assessment
5 of the progression was closest to that of our fundus
6 photography reading center, and in no case was clinical
7 progression diagnosed before a fundus photography reading
8 center progression. So I don't think that our reading
9 center was missing progressions.

10 And, ultimately, the use of this drug, if it is
11 approved--and I do pray that it is approved--will be by the
12 clinician, and the diagnosis of progression will be made by
13 the clinician. Oh, you put that up. I think that's
14 important to see, that our clinical efficacy endpoint was
15 very similar to the primary efficacy endpoint of the fundus
16 photography reading center. So that the clinical judgment
17 of progression is very similar to that that we reported in
18 the study which will go along with the way the drug will be
19 used if it is, God willing, approved.

20 Thank you.

21 CHAIRMAN WILSON: Thank you for your comments.

22 I'd like the panelists to--thank you, Dr. Kisner.
23 I'd like the panelists to begin considering the questions
24 that are on page 4, and we'll start with Dr. Mathews on the
25 first question. The first question is: Has sufficient

1 evidence been submitted to support the efficacy of
2 fomivirsen sodium intravitreal injectable against CMV
3 retinitis? Dr. Mathews?

4 DR. MATHEWS: Yes, very briefly, I think yes, it
5 has. I have a lot of reservations, and my level of
6 confidence in terms of ascertainment bias and these
7 covariate issues that I talked about are still leaving me
8 with some hesitancy. But I doubt that even those issues
9 could have totally explained the treatment effects. So I
10 think efficacy has been demonstrated

11 CHAIRMAN WILSON: Okay. Dr. Hannush?

12 DR. HANNUSH: I think yes, efficacy has been
13 established.

14 CHAIRMAN WILSON: Dr. Chew?

15 DR. CHEW: I would agree that I think it has been
16 established, even with the small numbers, as we all talked
17 about and some of the problems with it, but I do think that
18 it has been established.

19 CHAIRMAN WILSON: Dr. Fong?

20 DR. FONG: Well, I think that efficacy, the way
21 that it was demonstrated, is not of the highest standards
22 because there was no analysis of covariates. But I think
23 that even considering that issue, I don't think the
24 covariates could explain the treatment effect.

25 CHAIRMAN WILSON: Dr. Kilpatrick?

1 DR. KILPATRICK: The committee and audience should
2 recognize that Kevin Frost, Mrs. Cohen, and I have been
3 segregated over here--

4 [Laughter.]

5 DR. KILPATRICK: --as the non-M.D. portion of the
6 committee. It follows, therefore, that the views that I, at
7 least--I can't speak for the others--may be different from
8 the clinicians.

9 I'm speaking as a statistician, and my
10 understanding is that the FDA requires several well-
11 conducted, randomized, blind clinical trials of a new
12 treatment such as Vitravene against an existing standard
13 treatment such as Ganciclovir. We have not had these, and
14 the ones that we've had--I've suffered several--some
15 confusion in trying to absorb the material that's being
16 presented to us lately. And with the changes--and I've made
17 some of my points obvious to you in talking, and so I'm
18 ducking the question in the sense that I'm grossly
19 dissatisfied with the standard of the clinical trials as
20 reported.

21 CHAIRMAN WILSON: Ms. Cohen?

22 MS. COHEN: Yes, I think it comes to consumer
23 protection. I need a little definition. Efficacy, I
24 understand efficacy, and I understand "against," but does it
25 mean that the efficacy cures it, prevents it? What do they

1 mean by "against"? Does it delay it? Does it make someone
2 more comfortable? Does it get rid of it? What does it mean
3 "against"?

4 CHAIRMAN WILSON: I will presume that the sponsors
5 mean delays the progression of the CMV retinitis.

6 MS. COHEN: Well, then, I don't like the word
7 "against." I'm sorry. I don't--I'm not comfortable with
8 that word, nor am I comfortable with the clinical trials.
9 But I'm not--to me, "against" means--

10 CHAIRMAN WILSON: Cure. Okay. Well, let's change
11 it to: Does the evidence support the efficacy of this drug
12 in delaying the progression of CMV retinitis? Is that a
13 reasonable--

14 MS. COHEN: I mean, I don't want to pick words,
15 but I have problems with the word "against."

16 CHAIRMAN WILSON: If we change the word--

17 MS. COHEN: Wiley, do you see where I'm coming
18 from?

19 DR. CHAMBERS: Yes. CMV retinitis is--I'm sorry,
20 CMV is present in a large number of people in the
21 population. Whether it actually is active within the body
22 is what varies. And so the assumption of the question was
23 that it--did the drug stop it from causing its harmful
24 effect in the body?

25 MS. COHEN: Well, I think that that meets(?)

1 against--I have problems with the clinical trials. I really
2 do. The sample--even the diversity I have problems with.

3 CHAIRMAN WILSON: Mr. Frost?

4 MR. FROST: Dr. Kilpatrick being a statistician
5 will probably remember the words of Thomas Chalmers, who
6 said, "There are lies, damn lies, and statistics." In this
7 particular case, he might have included statisticians since
8 all of this seems so terribly confounding.

9 In my mind, efficacy is a pretty well defined
10 term. Is fomivirsen sodium effective against CMV? And I
11 think the evidence is pretty overwhelming, both from the
12 agency and from the sponsors, that it does.

13 CHAIRMAN WILSON: I want to follow up before I
14 give my view on this question. Does anybody--would
15 everybody agree that it's for both first-line and failed, or
16 would anybody like to modify their statements based on
17 first-line versus failed? If we went through both, would
18 you still keep the same view, Dr. Mathews, if we considered
19 each separately?

20 DR. MATHEWS: Well, you know, I was grappling with
21 this because I don't think--the level of hesitancy because
22 of the scientific issues that I don't think have been
23 elucidated in large part because of factors not under the
24 sponsor's control, the sample size, in particular, that that
25 level of certainty of efficacy, the actual magnitude of the

1 treatment effect, is somewhat uncertain. And while I don't
2 think putting on the label secondary therapy is the optimal
3 way to approach it, I don't feel comfortable, based on the
4 evidence, stating that it is first-line therapy and
5 equivalent to other agents that are well studied and, in
6 fact, have not been compared back to back.

7 You know, the problem is, in my mind, that if we
8 were not in an era where there were immuno-restorative
9 therapies you could rely on historical data when--you know,
10 what would be the expected progression rates. But it's a
11 moving target. It's very difficult to capture, as the
12 sponsor has pointed out, what regimens people are on and
13 what their impact are post-randomization. And you certainly
14 cannot restrict antiretroviral therapy in this day and age
15 on these kinds of trials.

16 So I think additional postmarketing studies are
17 going to be required to--perhaps Phase 3 studies, to lead to
18 the equivalence of this to other agents.

19 CHAIRMAN WILSON: That's going to be one of the
20 questions, but I'm not sure I got your answer. What I'm
21 really trying to figure out is whether or not your belief in
22 the efficacy of this drug would be modified if we were to
23 split it up into first-line versus use only in failed.
24 Would you still say that it's the same in both situations?
25 Understanding that there's a level of uncertainty there,

1 would it make you more uncertain to include first-line
2 therapy also, or are you comfortable enough with that?

3 DR. MATHEWS: I'm not comfortable stating that the
4 evidence convinces me it's--when you say first-line therapy,
5 that implies to me it is equivalent to other already
6 approved agents.

7 CHAIRMAN WILSON: Yes.

8 DR. MATHEWS: And I don't consider that the
9 evidence presented to date is convincing of that.

10 CHAIRMAN WILSON: Dr. Hannush?

11 DR. HANNUSH: I agree with Dr. Mathews. I think
12 we should separate these two questions, even though that may
13 make all of our afternoon a little bit longer. But I think
14 we should address them separately. And if Dr. Wilson would
15 indulge me a little bit, at the risk of philosophizing here--
16 --and if my wife was sitting in the audience, she'd close her
17 eyes and say, "Here he goes again." But basically what
18 we're trying to decide tonight--today--hopefully it's not
19 tonight--is: Is this drug going to help more people see
20 longer with an acceptable safety profile? And is it
21 relatively equivalent to current acceptable methods of
22 treatment?

23 One epidemiological note that should be mentioned
24 is that although the eye is a major target of CMV, there are
25 other organs in the body that are targeted by the drug. I

1 do have a concern because of the precious nature of vision
2 that people, patients who are afflicted with this condition
3 may seek eye treatment, which is local, and not be diagnosed
4 or seek treatment to other organs of the body through
5 systemic medication. Even though the systemic medication
6 may be toxic in nature, there is a concern that the type of
7 patients seeking this treatment is so dependent on their
8 vision that they may ignore treatment of other organs and,
9 thus, their life expectancy may be limited. So that's one
10 note.

11 As far as the eye treatment itself, I feel that--
12 and we're going to talk about the safety profile in a
13 second--that it has been shown to be efficacious whether
14 clearly--clearly, the numbers presented are less than ideal,
15 and I think we should decide on these two questions
16 separately so that we do not forego an established treatment
17 just because the patient and their doctor may perceive this
18 treatment as easier to deliver and more acceptable than
19 other established treatments.

20 CHAIRMAN WILSON: Dr. Chew?

21 DR. CHEW: I have to ask Wiley, is it necessary
22 for us to decide this decision--we've never done that before
23 in past--I don't think for the AIDS studies. You know, the
24 implant study was passed through. I don't think that was
25 ever decided it should be a primary, a secondary, as well as

1 Cidofovir was the same way. So, I mean, the studies that
2 were presented did not look at that specific issue, so we
3 don't have the data to really say whether it should be
4 first-line or not. So I think we're put in a position to
5 answer things that we have no data for.

6 DR. CHAMBERS: Well--

7 DR. CHEW: Aside from the clinical, you know.

8 CHAIRMAN WILSON: I think that the data presented
9 is enough to give your impression of what you would prefer,
10 and I think that that information might be useful to the FDA
11 in terms of what--how we feel about this. It's certainly
12 not a requirement that they've asked us to perform, but I
13 think it could be useful to them. So if you can just give
14 your impression based on the data, the FDA can make their
15 own determination.

16 DR. CHAMBERS: Yes, this is Wiley Chambers. We're
17 clearly interested in whatever opinions you have at the
18 present time. Obviously, in Question 6, we are directly
19 headed toward whether you think that's a first-line therapy
20 or whether it's additional.

21 DR. CHEW: Sure.

22 DR. CHAMBERS: So, I mean, patients were studied
23 that had received previous treatments before, so the
24 population has been looked at. The question is: What do
25 you think about that?

1 DR. HANNUSH: I think we're asked to make a
2 reasonable judgment here, and although this may not have
3 come up with previous CMV drugs, it has come up with other
4 drugs, and I have been on this panel when we looked at
5 Zylotan, and many of you were here as well. And Zylotan,
6 for people in the audience who are not familiar with this,
7 is an anti-glaucoma drug. And based on the safety profile
8 exhibited by the sponsor, we felt that it should not be a
9 primary drug used for the treatment of glaucoma. And even
10 though Mrs. Cohen's comments are very well taken, physicians
11 are notorious for off-label use or what is called the
12 practice of medicine. That is something to be left to
13 physicians to decide.

14 And I think it is reason--I mean, you cannot
15 control every aspect of this through a regulatory mechanism.
16 I think the job of the FDA and the patient advocate is to
17 protect the public, but within reasons. And I think we
18 should be allowed to exercise judgment in this regard.

19 DR. CHEW: Well, I think in my opinion the data
20 that's been presented shows efficacy, and we have seen that,
21 I believe, in the primary untreated cases. Whether one
22 would use it would be another question because other issues
23 which we talked about, briefly elucidated, in terms of
24 systemic aspects of the whole disease. So that may not be
25 the first choice, just as implants may not be the first

1 choice if you're concerned about systemic disease.

2 So I think in deciding whether it's a primary or a
3 secondary line of attack, I would not probably put this as a
4 primary attack for main CMV retinitis.

5 CHAIRMAN WILSON: Dr. Fong?

6 DR. FONG: Well, this is--as I mentioned before,
7 this is the first time that I've served on this panel, and I
8 guess I'm not completely sure how to answer the question.
9 You know, if I was reviewing the data presented to me, you
10 know, for a paper--you know, for publication in a journal--
11 I'm not sure that I would recommend publication without
12 significant revisions. And so, you know, although--you
13 know, I think it's suggestive that it works. I'm not sure,
14 you know, how strongly I feel about it.

15 CHAIRMAN WILSON: I'm going to go to Mr. Frost
16 since, Dr. Kilpatrick, you were on the opposite view,
17 anyway. So I think it's--

18 MR. FROST: Well, I'm actually going to make a
19 shameful appeal directly to the agency not to do this. And
20 I want to explain why.

21 In my mind, I don't think it serves any useful
22 function. I think Dr. Hannush is right to point out that
23 physicians are notorious for off-label use, and I think the
24 agency has a long history of recognizing off-label use and
25 its appropriate position within medical treatment. And I

1 think we all recognize that it certainly has a place within
2 proper medical treatment.

3 My fear is that by doing this the only real
4 function that it will serve is to set up hurdles that
5 patients will have to overcome in order to access a
6 potentially useful therapy. There is nothing to prevent a
7 physician from prescribing something off-label first-line if
8 they believe it's appropriate for their patient. There is,
9 however, enormous incentive within the third-party payer and
10 the insurance industry not to reimburse for products that
11 are used in an off-label environment. So that you create
12 hurdles from a regulatory environment in which patients
13 cannot access a therapy despite the fact that their
14 physician may decide this is the best and appropriate
15 therapy for you.

16 You are an ex-IV drug user and cannot get a
17 Hickman catheter. You cannot take Ganciclovir because you
18 don't have any white blood cells. Foscarnet is ruled out
19 because of nephrotoxicity. Cidofovir is ruled out for the
20 same reason. And an implant in your case is inappropriate
21 because we already know you are resistant to Ganciclovir.

22 I can think of and create for you plenty of
23 scenarios in which this product might be considered as a
24 first-line therapy. We should clarify that first-line in
25 this environment does not mean, should not mean, and

1 shouldn't be construed to mean it is equivalent to other
2 therapies. That's not the job here. This product hasn't
3 been compared to other therapies, and one cannot make a
4 judgment of the relative efficacy of this product compared
5 to other products based on the data that's been presented
6 today. One can, however, understand that in this context
7 first-line therapy means patients who have not otherwise
8 been treated.

9 If you cannot in your mind as a committee member
10 construct a scenario in which a patient might or a doctor
11 might want to prescribe this product in a patient who has
12 never been treated before, then, of course, vote that they
13 should be broken up and this should be salvage therapy.

14 I, on the other hand, think that by doing that and
15 creating that scenario on the part of the agency from a
16 regulatory environment, the only real purpose you serve is
17 to prevent patients from accessing it. Because it is the
18 third-party payers and it is the insurance industry that
19 will step in and say unless you've failed something else, we
20 won't pay for this. And I don't particularly think that in
21 the environment in which we are talking about that's a
22 particularly useful outcome or a role that the agency should
23 play.

24 I think that traditionally we've approved products
25 for CMV retinitis on the basis of two things: Is it

1 effective, and is it safe? And I think that's what we
2 should do today.

3 CHAIRMAN WILSON: Ms. Cohen?

4 MS. COHEN: Just I want to draw your attention to
5 some new rules and regulations, the dissemination of
6 information on unapproved/new uses for marketed drugs,
7 biologics, and devices. And I think everybody should read
8 it, and I am very concerned about the off-label use of
9 drugs. So I just think this is for people to look at and to
10 study.

11 CHAIRMAN WILSON: Well, to wrap up this first
12 question, let me just give my views. I have certain
13 uncertainties related to the methodology, particularly with
14 respect to the sample size. And my uncertainties are even
15 more so for the first-line use as opposed to failed
16 treatments.

17 On the other hand, I think that the study of AIDS
18 has other issues that are different than, for example,
19 glaucoma where the quality of life issues are much bigger,
20 although I agree with Dr. Fong in terms of the--some of the
21 methodological shortcomings. AIDS is different. It's not
22 the same as studying a disease where the side effects of the
23 disease itself are minimal and the side effects of the
24 treatment becomes much more paramount. Here the side
25 effects of the disease in many cases is much more so than

1 the side effect of the treatment. So there are some
2 different issues here. And I think that the data does
3 support efficacy, enough so that I feel comfortable in
4 supporting it from both the failed and the first-line,
5 simply because I don't--I agree with Mr. Frost. I just
6 don't see any basic purpose to separate the two out.

7 Let's move on to the second. If I may just
8 summarize, besides my view, the view that I think that I've
9 received from everybody--or at least the majority, is that
10 there is some uncertainty but from a clinical standpoint, at
11 least the clinicians feel relatively comfortable in moving
12 forward was the recommendation of efficacy being supported.

13 Okay. Moving onto Question 2, what additional
14 efficacy studies should be performed? Phase 3 studies or
15 Phase 4 studies? Mr. Frost, do you want to start off with
16 that one?

17 MR. FROST: Well, I'll just say quickly that I
18 think it's entirely appropriate in a Phase 4 context to
19 perform studies in which we try to establish how a
20 particular therapeutic fits into the context of standard of
21 care. And so with that in mind, I think one could look for
22 or hope for studies that would try to place this into an
23 appropriate context in terms of standard of care. And so I
24 would hope that even independent groups like the SOCA Group
25 might look to do studies where this intravitreal injection

1 could be compared, for example, to an intravitreal implant,
2 two local therapies, try to understand the differences. I
3 think the efficacy differences have been well established,
4 but safety, visual acuity changes, many of those things
5 might be sorted out in a Phase 4 environment.

6 So those would be the kinds of studies--
7 understanding where it fits in a therapeutic context--I
8 think would be the studies I'd like to see done.

9 I see that safety is another question further
10 down, so I'll save my comments on safety for then.

T4B 11 CHAIRMAN WILSON: Ms. Cohen?

12 MS. COHEN: I would be concerned, again, how
13 slides--what we're going to do with slides. I think that's
14 something that has to be resolved as to how we're going to
15 interpret them, because we've been having problems in
16 interpretation of slides, so whatever is presented.

17 The other thing that Dr. Mathews explained far
18 more eloquently than I can is those people whose immune
19 systems have been improved versus those who have not. And I
20 think you can state--or you stated it before better than I
21 can in terms of the study. Am I interpreting what you said
22 correctly?

23 DR. MATHEWS: Yeah. I mean, I think--I don't
24 think there'd be any question that the sponsor would
25 probably agree that in 1998 you simply have to collect all

1 of the immune and viral parameters that have already been
2 shown to be prognostic for disease progression and control
3 for them. I don't think, you know, unless the situation
4 changes drastically in terms of the epidemiology of CMV
5 disease, that you'll ever see an equivalence trial of the
6 size that would be convincing with other agents.

7 MS. COHEN: And I don't know if the word
8 "censored" can be defined better or not, also, as to who's
9 excluded and who the FDA might think should be excluded,
10 because it seemed as though there was some diversity of
11 opinion on the word "censored."

12 CHAIRMAN WILSON: Okay. Dr. Kilpatrick?

13 DR. KILPATRICK: Well, we've been asked to respond
14 to the science and not to the politics, and my view is
15 consistent with regard to this question with my prior point
16 of view. I think that prior to approval a worldwide study
17 should be conducted of the efficacy of Vitravene. I brought
18 up in the past, this morning, the fact that the agency--the
19 sponsor had but did not choose to include an analysis of
20 CS12, I believe it was, with CS9, and I did not find the
21 answer to my question convincing as to why that was not done
22 given the standard of the statistical analysis in other
23 aspects of the report.

24 I'm not an epidemiologist, but I am aware that
25 there is a great deal of AIDS and HIV in other countries,

1 and I appreciate that the standard of care of patients in
2 those countries is not that of the United States. But this
3 committee has seen other companies going abroad to locate
4 certain types of patients who are not resident in the United
5 States.

6 Thank you.

7 CHAIRMAN WILSON: Dr. Fong?

8 DR. FONG: I think it's clear from my comments
9 earlier that I think that there is some significant
10 shortcomings to the design of the study, execution of it,
11 sample size, and analysis of covariates. But I think that
12 given the epidemiology of CMV now that it's going to be
13 really difficult to do a well-powered study. I mean, it
14 would be really nice to have a good study demonstrating
15 efficacy with adjustment for covariates and also to look at
16 equivalence studies, but I'm just not sure that it's
17 possible. So, you know, I guess I wouldn't feel comfortable
18 with recommending additional studies other than just maybe
19 some additional analysis of their data.

20 CHAIRMAN WILSON: So you would recommend not even
21 a Phase 4 study, just--

22 DR. FONG: I just think it's going to be, you
23 know, so difficult to do, you know, to carry out in a timely
24 fashion.

25 CHAIRMAN WILSON: Emily?

1 DR. CHEW: I would agree. I think given the
2 population that we have now, unless--there's going to be a
3 lot of resistance that you're going to see, and you're going
4 to develop a new increased incidence, I think it would be
5 very hard to get equivalency studies. It would be nice to
6 see. We're not going to, I think, amount that. That would
7 be nice to have if we had that, and the covariate analyses
8 obviously are very important if you can get that. But I
9 think the Phase 4 studies is probably more likely to deal
10 with the ongoing safety and, again, what Kevin suggested,
11 where does it fit in in the regimens of all these different
12 types of treatments that we have. So I would suggest Phase
13 4's to look at that as well as safety.

14 CHAIRMAN WILSON: Dr. Hannush?

15 DR. HANNUSH: Just a couple comments regarding Dr.
16 Kilpatrick's comment that we're being charged with a
17 decision based on science, not politics.

18 I just want to say that I don't think this is
19 science versus politics. I think there's a human issue to
20 this, as Dr. Wilson suggested, that is of immense
21 proportion, and it doesn't necessary involve politics. But
22 science alone should be taken into consideration, but should
23 not be the only factor that motivates us to make a decision.

24 Regarding Mr. Frost's comments that--and he
25 described it as a shameless appeal to the agency not to put

1 restrictions on this--I think that appeal is very
2 legitimate, and I don't think you should encumber it by the
3 adjective "shameless." I mean, it's a great appeal. I just
4 don't quite agree with that obstacle that you think will be
5 created.

6 First of all, I think what we're trying to do is
7 to make the physician who is going to use this drug perhaps
8 think a little bit more than to use it as an immediate
9 option, perhaps document the chart, as I do when I use
10 something that has been labeled differently, as to why I am
11 planning to use cyanoacrylate adhesive or Zylotan or
12 cyclosporin and so on.

13 It may be interesting to find out that as far as
14 the insurers are concerned, this may be a much less
15 expensive--I mean, if they are motivated by finances, this
16 may be a much less expensive alternative for them than
17 intravenous injections or IV piggybacks so many times. So
18 this may be more attractive to insurers, and the obstacle
19 may not necessarily be there, depending on how ISIS plans to
20 price this.

21 So as far as Question 2, I agree with what has
22 been said already. I don't know whether it should be--
23 whether the word Phase 4 is appropriate. I think continued
24 collection of data is appropriate. Whether it's under the
25 guise of a study or not is up to the FDA to decide.

1 CHAIRMAN WILSON: Prior or after approval?

2 DR. HANNUSH: After.

3 CHAIRMAN WILSON: Dr. Mathews?

4 DR. MATHEWS: Well, I think in Phase 4 studies
5 there needs to be further exploration of the appropriate
6 dosing regimen. We really don't know whether people with
7 central retinitis should receive Regimen B or the 165, and I
8 think there's a lot of room for further exploration of the
9 proper dosing regimens. And, also, perhaps when some of the
10 ongoing studies are fully accrued, the treatment effect will
11 be--the precision of the treatment effect will be more
12 defined.

13 I think ideally subset analyses probably across
14 trials could be very informative. Like in CS9 we were
15 presented aggregate data, but it would be interesting to
16 know what was the treatment effect among those who had viral
17 loads of over 750,000 and no CD4 response compared to those
18 who had good responses.

19 So I think a lot of this work will involve cross-
20 study analyses, but the dose comparisons I think probably
21 would involve formal studies.

22 One last comment regarding extraocular CMV. I
23 have talked, every time I come at this meeting, about
24 extraocular CMV disease, so I didn't say it again this time.
25 But it's really I don't think an issue anymore in 1998.

1 Most clinicians are very much aware of the risk of
2 extraocular disease, and I think it's rather hazardous to
3 rely solely on intraocular therapy, especially since it's so
4 much more difficult to diagnose CMV in the gut and other
5 sites.

6 CHAIRMAN WILSON: Well, I'm hearing a majority
7 consensus that, first of all, there should be additional
8 studies and that Phase 4 is probably the most appropriate.
9 And some of the suggestions that were given for Phase 4 was
10 to look at dosing and to specifically look at how it fits
11 into the armamentarium of other treatments. I think I would
12 basically agree with that majority consensus.

13 Going on to No. 3, are there adverse experiences
14 which are of particular concern for this product? Are
15 additional studies needed to further quantify or qualify
16 these experiences?

17 Let's start with the middle. Dr. Chew?

18 DR. CHEW: The one thing that we talked about was
19 the peripheral visual--subjective peripheral visual loss and
20 the field defects. That seemed to be less with the lower
21 doses. And you did say that the first Phase 1 study was
22 stopped because of some of the pigmentary changes. It would
23 be nice to have some electrophysiological studies that
24 studied, you know, any toxic effects to the retina from that
25 and whether there's reversibility as well. So I think

1 that's the sort of thing I would like to see in Phase 4, but
2 as I see it, it's a very low percentage that develops it,
3 but if it does, it would be very important to document that,
4 I think.

5 CHAIRMAN WILSON: Dr. Fong?

6 DR. FONG: I agree with Dr. Chew that there's
7 still some issues about the peripheral retinal stippling and
8 detritus that might need further study.

9 DR. HANNUSH: Dr. Chambers, do you know off the
10 top of your head what the incidence of retinal detachment
11 was in the Ganciclovir implant study as well as what is the
12 average number of implants a patient received in their
13 lifetime?

14 DR. CHAMBERS: The range of retinal detachment
15 runs somewhere around 20 percent, is what was reported at
16 the time. There is a huge variation around that, anywhere
17 between 5 and 40, but most people report somewhere in the
18 20s.

19 As for the number of implants, the average at the
20 time of the submission was somewhere between three and four.

21 DR. HANNUSH: In answer to Question 3, I have very
22 limited concerns about the safety profile of this product.

23 CHAIRMAN WILSON: Dr. Kilpatrick?

24 DR. KILPATRICK: I'm sorry, I was sleeping. Which
25 number are we--

1 CHAIRMAN WILSON: This is No. 3, and basically are
2 there any adverse experiences which are of particular
3 concern?

4 DR. KILPATRICK: No comment. I'm not a clinician.

5 CHAIRMAN WILSON: Ms. Cohen, do you want to
6 comment?

7 MS. COHEN: Well, I just noticed the things that
8 were listed. The retinal pigment change, I don't think
9 that's been mentioned, the intraocular inflammation, and the
10 pressure, intraocular pressure, I don't know if these have
11 been--for those of you who know, that this has been
12 satisfactorily answered.

13 CHAIRMAN WILSON: Mr. Frost?

14 MR. FROST: I think Dr. Chew's comments are well
15 placed. I think that, you know, one can almost combine
16 Questions 3 and 4 from a safety perspective and just ask are
17 there safety questions, and I think there's always the
18 concern with a small sample size or a smaller sample size
19 that there could be rare events that we've missed. And so I
20 think a postmarketing database--I'm not so sure I'd qualify
21 this as a study, but certainly a postmarketing database
22 sufficient to really track and catch those kinds of safety
23 issues as they may arise, much like we do in expanded access
24 protocols, would probably be really important to try to
25 understand, maybe something to go with the kinds of ERG or

1 EOG studies that you were referring to, Dr. Chew.

2 So I think those would be appropriate kinds of
3 things, and the answer, I guess, from me is yes, there's
4 still much more I'd like to know about safety, much more
5 that I think we will learn about safety in a postmarketing
6 environment, provided we have the proper ways to catch that
7 I place.

8 I do want to make one quick comment, however,
9 about something Dr. Hannush said, and that is, I think that
10 when--and I'm sorry to go backwards, but I'm hammering away
11 at a dead horse here. That is, in the issue of obstacles
12 for patients' accessing this product, it may not be that you
13 as an individual physician are faced with this question and
14 this difficulty. But I can assure you that patients are,
15 and I think we sometimes, in order to understand this in the
16 proper context, have to take a step back and look at the
17 broader perspective. I can assure you at a national agency
18 we deal with these problems all the time.

19 In the State of Texas, do you know that Medicaid
20 will pay for three antiretrovirals? It can be any three you
21 want, but just three. So if your physician prescribes AZT,
22 3TC, and Ratonivir Sequenivir(ph), one of those you've got
23 to pay for yourself, because they have good reason to say
24 it's only going to be three because three is the standard of
25 care.

1 In the State of Tennessee, the AIDS Drug
2 Assistance Program has two drugs on it that they'll
3 reimburse for.

4 So while you as an individual physician may not
5 have to deal with this or maybe your patients won't even
6 have to deal with this, I can assure you that agencies like
7 Medicaid and Medicare and ADAP programs and in an
8 environment in which the politics are constantly pressuring
9 states to cut back and cut back and cut back, large third-
10 party payers need very little excuse not to reimburse for
11 something or to put it onto the formulary. And when we
12 separate a product like this, which we will be doing if we
13 break out the indications, we give those third-party payers
14 an excuse to do that. We give them an excuse not to put it
15 on their formulary. We give them an excuse not to reimburse
16 for it in Medicaid or Medicare programs or any of a number
17 of other programs like ADAP. And that's my real concern
18 here.

19 CHAIRMAN WILSON: Dr. Mathews, can we hear your
20 response to No. 3?

21 DR. MATHEWS: I don't have any comments since I'm
22 not an ophthalmologist.

23 CHAIRMAN WILSON: I agree that there are further
24 data collection that's necessary because the sample size is
25 so small to make sure that there are rare events that