in our previous analyses, and so therefore, we focused our attention on those patients who were counted in the analyses as having no evidence of CMV progression.

And in order to understand this chart, it's important to remember that patients were being treated by the ophthalmologist and did not have knowledge of where their patient was fitting in the four-week endpoint category.

So we asked the question: are disproportionate dropouts failures of induction therapy?

And we still found that even after accounting for the week four progressors and the week four dropouts, there was still a disproportionate dropout rate with two in the intravenous ganciclovir arm and seven in the valganciclovir arm.

We also sought to evaluate the retinal photography that was taken between weeks four and 12 to see if any of these patients were having evidence of CMV progression during this time period because patients were still contributing retinal photographs in the study.

We also looked for reasons why people were discontinuing from the study, and again, to emphasize that the ophthalmologist was making on-study treatment

decisions, and that the photographic scoring was not provided in real time. So we sought to look at the ophthalmologist's clinical diagnosis.

We were somewhat reassured to find that -- and again, we had asked Dr. Boyd to review the retinal photographs that were submitted, and we were somewhat reassured to find that only one patient -- and it was a patient in the valganciclovir arm -- had evidence of CMV progression between weeks four and 12.

The reasons for discontinuation included four deaths. There were three deaths in the valganciclovir arm during this time period, one death in the intravenous ganciclovir arm. There were three voluntary withdrawals. All three were in the valganciclovir arm, and finally, three requested ganciclovir ocular implant, one in each arm.

Furthermore, we found that the treating ophthalmologists were more likely to classify patients in the valganciclovir arm as CMV progressors regardless of the photographic determination, and therefore, we feel that the disproportional dropout rate was driven by the open label study design, and that the differential dropout rate does not represent a failure of induction.

We were also interested to see how

patients performed in the study who had Zone 1 retinitis, and about a quarter of patients in each arm had evidence of Zone 1 retinitis. And the reason we looked at this is that previous registrational trials have excluded patients with Zone 1 retinitis, and we found that the outcomes were very similar to the overall patient population in this study.

And Dr. Pomerantz raised this question this morning. We also raised this question during our review of what was the impact of protease inhibitors on the primary endpoint in this study.

And as Dr. Stempien had mentioned the protocol required that patients not change their heart regimen during the first four weeks, but because patients were receiving a new diagnosis of CMV retinitis, we thought that a change in heart therapy might occur commonly in this study, and so we sought to do a review to find patients who had changed their heart therapy during the induction phase, and we found that nine patients changed heart therapy, four patients in the valganciclovir arm and five patients in the intravenous ganciclovir.

So we're somewhat reassured that the impact of protease inhibitors on the week four endpoint was minimal in this study. At week four, we

found that a majority did change their heart therapy, and that likely this change had a significant impact on the time to progression. In the study, this time to progression was much longer in comparison to historical studies.

So in summary, we found that the proportion of patients having evidence of CMV retinitis progression is similar between the treatment groups. The maximum lower bound of the 95 percent confidence interval in our sensitivity analyses is minus 13 percent.

The results of our primary endpoint was confirmed by an FDA masked review of the retinal photographs, and as the applicant had presented this morning, the visual acuity scores were similar between the treatment groups.

And now I'll move on to the safety database in the study. Again, the three studies provided safety information. The induction study, which enrolled 160 patients, but two patients did not receive study drug just after enrollment; so 158 patients contributed to the safety database.

The safety study enrolled 212 patients, and as you recall, this is a single arm, open label study of valganciclovir for the maintenance therapy in

patients with a previous diagnosis of CMV retinitis.

And finally, the PV-16000 study, which is a study of oral ganciclovir versus valganciclovir for the prevention of CMV disease in solid organ transplant recipients that's an ongoing study and which has enrolled 121 patients thus far, and because I still have a captive audience of ophthalmologists, I'll refer to this as a masked study, and the data are still masked.

This slide represents the number of patients contributing to the safety database, and you can see that 293 patients have completed at least six months of therapy with valganciclovir. Two hundred and thirty-eight patients have completed at least 12 months of therapy with valganciclovir in the two, the induction study and the safety study.

And the induction study provides a comparison between the treatment arms, and gastrointestinal adverse events were the predominant class of adverse events seen in the study.

There was a somewhat higher proportion of patients with diarrhea who were randomized to the valganciclovir arm, and a somewhat higher proportion of patients had nausea who were in the intravenous ganciclovir arm, but overall the gastrointestinal

adverse event rate appears comparable between the treatment groups.

As well, during the first four weeks the hematologic adverse events, and these are all great adverse events, were comparable between the treatment groups. We did note the difference in this Grade 4 anemia that was seen further out in the study.

We also sought to find an explanation as to why this was occurring, and it's important to remember that all patients were receiving open label valganciclovir at this point in the study.

We found that a somewhat higher proportion of patients were taking concurrent zidovudine who had evidence of anemia. There were seven patients with anemia in the valganciclovir arm and three patients with anemia in the intravenous valganciclovir arm who were taking concurrent zidovudine at the time of anemia, and I showed you earlier the data on disseminated mycobacterium avium complex infection, and we're not sure if those two factors were involved in the difference in the rate of anemia, but we feel that that may be a contributing factor as to why further out in the study a difference in the rate of severe anemia was seen.

And the only clinically meaningful

difference in other adverse events that were reported in the study during the first four weeks is catheter associated infection, which occurred at a much higher proportion in patients in the intravenous ganciclovir arm.

We looked at deaths that occurred in the study, and in the first four weeks there were three deaths, two in patients who were randomized to intravenous ganciclovir, one in patients who were randomized to valganciclovir.

At the week 12 time point, there were ten deaths, five in each arm, and these deaths are all primarily due to underlying AIDS.

At one year there were 28 deaths, 18 in the intravenous ganciclovir arm, ten in the valganciclovir arm, but again, all patients were on open label valganciclovir. So it's difficult to draw any firm conclusions. And, again, the 28 deaths were primarily due to underlying AIDS.

We also pooled the adverse event rate for both the induction and the safety study, and we found that gastrointestinal and hematologic adverse events were the predominant classes of adverse events, and we also found that the adverse event rate was very comparable to that of the formulations of the approved

ganciclovir.

And finally, in the PV-16000 study, CMV prevention in solid organ transplant recipients, again, the total number of patients as of August 2000 that have enrolled is 121. It's a 100-day course of therapy, and 39 have completed the 100-day course of therapy.

And, again, the data are still masked. Forty-one patients have reported 60 serious adverse events. In the four-month safety update in this NDA, only the serious adverse events were included, and we see that hematologic and gastrointestinal adverse events were reported. Six percent reported postoperative infectious complications. Three percent reported increased creatinine, and four percent with graft rejection.

So other than graft rejection, we find that these are an expected type of adverse events to be seen in ganciclovir.

So, in conclusion, the safety database of patients completing at least six months of therapy is just under 300 patients. Hematologic and gastrointestinal adverse events were the predominant classes of adverse events, and we found the adverse event profile to be similar to that of ganciclovir.

And I'd like to acknowledge the valganciclovir review team. The medical officer team leader, Dr. Cvetkovich. Dr. Breazna and Dr. Soon provided the statistical support for my talk. I'd like to thank Dr. Boyd, whose tremendous amount of work I had summarized in just one or two sentences. And Dr. Reynolds of the biopharmaceutics team.

And now I'd like to introduce Dr. Robert Kumi, and Dr. Kumi will be presenting the pharmacokinetic data that will provide support for the maintenance therapy in the treatment of CMV retinitis.

DR. KUMI: Good morning.

The primary focus of my talk will be on the pharmacokinetic information submitted to support valganciclovir use in maintenance therapy for CMV retinitis.

Next slide, please.

The outline of my talk will be as follows. I'll give a background on the delivery systems available for systemic delivery of ganciclovir. This will be followed by studies and analysis conducted to support valganciclovir use during maintenance therapy, a summary of these study results, and then I'll offer conclusions.

There are two formulations of ganciclovir

that deliver ganciclovir systemically. These are the IV formulation and the oral formulation. The oral capsule has a poor bioavailability with a value of less than ten percent in the presence of food.

And presently for this NDA, we're considering valganciclovir hydrochloride, which is a pro drug of ganciclovir, and it is an alternative formulation to the IV formulation.

Next slide.

Valganciclovir is a pro drug of ganciclovir, which is rapidly and extensively converted to ganciclovir and valine upon oral administration. Following its administration, the ganciclovir bioavailability in the presence of food is approximately 60 percent, and this represents a substantial increase in the bioavailability relative to the oral ganciclovir formulation.

Furthermore, the pro drug has very low systemic exposure with a value of less than five percent of ganciclovir exposure.

Two studies and analyses were conducted to support valganciclovir use during maintenance therapy. These were the exposure response or PK/PD analysis and the pharmacokinetic comparisons of the ganciclovir delivery systems.

The applicant concluded that in study GANS-2226 that AUC average of ganciclovir was the best predictor of time to first photographic progression. I'll present more details on these two studies in the next series of slides.

The primary objective of the PK/PD analysis was to determine if there were any ganciclovir PK parameters that would predict response during maintenance therapy, and this response was measured as the time to first photographic progression.

The methodology comprised of administering three oral ganciclovir dose regimens and one IV ganciclovir dose regimen to patients with CMV retinitis.

In the PK analysis, PK parameter estimates are obtained using the population approach, and then in the subsequent PK/PD analysis, the population pharmacokinetic parameter estimates were used to evaluate the PK/PD relationship.

However, there were limitations in the PK/PD analysis, the primary one being that there were errors anticipated in the pharmacokinetic parameter estimates due to the insufficient dosing time records.

The second limitation was in the

uncertainty of the accuracy of individual parameter estimates, and this was because of the sampling scheme used.

So we concluded that the population pharmacokinetic analysis results cannot be used for further PK/PD analysis.

Due to the limitations in the PK/PD analysis, we sought an alternative to determine how useful valganciclovir would be during maintenance therapy. This involved plasma concentration time profile comparisons. We looked at the three ganciclovir delivery systems, at the recommended and proposed doses, and we looked particularly at during maintenance, and these formulations were intravenous ganciclovir, valgan. and oral ganciclovir.

The next series of slides I'll show the pharmacokinetic profiles obtained following administration of these delivery systems.

Here we have the ganciclovir plasma concentration time profiles in HIV positive, CMV positive patients. On the Y axis is the ganciclovir concentration in microgram per mL versus the time in hours, and here is plotted on a linear scale.

This first profile, IV ganciclovir was given as a one hour long infusion once daily during

the efficacy trial, and we obtain a typical pattern for an IV infusion.

The next slide I've included the ganciclovir profile resulting from administration of valganciclovir at its proposed dose of 900 milligrams. Here we see there are three main points I would like us to look at for this plot.

Basically the C-max for ganciclovir resulting from valganciclovir administration is lower than that of IV. However, the AUC, which is the measure of the total systemic exposure is comparable for the two profiles.

And finally, approximately three hours after dosing the ganciclovir levels due to valgan administration are actually greater than that of IV ganciclovir.

The final slide on the pharmacokinetic comparisons has included the maintenance dose for oral ganciclovir, which is administered as 1,000 milligrams three times daily, and the two main points from here are that we do not have as much concern with the lower C-max for valganciclovir because this C-max is actually greater than that obtained with oral ganciclovir.

And, secondly, IV ganciclovir and

valganciclovir have higher levels relatively of ganciclovir for a similar proportion of time relative to the oral formulation.

So now the conclusions of these two studies. We conclude that the ganciclovir plasma concentration time profile comparisons of valganciclovir to the two approved ganciclovir regimens, which are IV and oral ganciclovir, support the use of valganciclovir for CMV retinitis maintenance therapy.

And secondly, the PK/PD model, though it's useful, is not needed to support valganciclovir use during maintenance therapy.

I'd like to acknowledge the valganciclovir review team and Dr. Sue-Chi Lee, who performed the pharmacometrics consult.

This concludes the FDA presentation and we'll be willing to entertain any questions you have.

Thank you.

CHAIRMAN POMERANTZ: Thanks to Dr. Toerner and Dr. Kumi.

And we do now open the questions to the Committee. Dr. Bertino.

DR. BERTINO: For Dr. Kumi, before you leave the podium -- I try to get you before you ran

off.

DR. KUMI: Okay.

DR. BERTINO: Did you guys repeat the GANS-2226 PK/PD analysis?

DR. KUMI: I guess, no, essentially we did not. We looked -- basically we looked at the applicant's procedure and saw these I would say limitations in terms of the dosing scheme. I mean the sampling scheme and the recording of dose records, and we concluded that they would not be appropriate.

DR. BERTINO: Yeah. I mean, I guess I got from the FDA briefing material that the FDA's conclusion was that the one point population pharmacokinetic estimates were not accurate.

DR. KUMI: Right.

DR. BERTINO: And therefore, that data couldn't be used, which then goes back to raising the question about the relationship of the area under the curve to efficacy.

How many patients had total pharmacokinetic profiles, more than one point? Do you know?

DR. KUMI: During the GANS-2226, I think basically it was just the IV data, which had complete profiles, and that was from actually a different

study, but during the actual PK/PD part, it was just like one or two samples per patient on two different occasions at week two or week six, and if there was an event like progression and retinitis or an adverse event, I think for those they might have taken the complete profile. I'm not sure.

DR. BERTINO: Okay, and Dr. Pomerantz may want to defer this until this afternoon with the sponsor to ask more about this PK/PD analysis that was done since --

CHAIRMAN POMERANTZ: Why don't you do it now?

DR. BERTINO: Okay. Okay. I guess the question --

CHAIRMAN POMERANTZ: This afternoon we would like to do mainly in voting.

DR. BERTINO: Okay. Could the sponsor kind of walk us through their PK/PD analysis and how they came up with this relationship of AUC to efficacy?

Because I thought what I heard from Dr. Kumi -- and correct me if I'm wrong -- is that the FDA did not believe that the data that was obtained was useful data for doing population pharmacokinetics. Did I misquote you? I think that's what you said.

DR. KUMI: I don't know if the applicant has maybe the table with the dosing time scheme and the how the assumptions were made.

DR. STEMPIEN: I'm sure that we could speak to this and take you through some of the data if that is considered important for your deliberations. My sense though is that the agreement is that this analysis, although it may be useful, it has limitations, and that we can just set it aside and make -- well --

DR. BERTINO: I mean, I think that's fine. My concern actually goes back to what Dr. Wong raised this morning about toxicity because I see at the dose that's being recommended for maintenance, you're actually giving about almost a little more than 50 percent more maintenance dose per day orally versus IV. Even when you correct for bioavailability, you're looking at five mgs. per kg. IV versus I came up with 7.8 mgs. per kg. in a 70 kilo person, which was your average weight in the study and an average bioavailability of 60 percent. That's one question.

The other question has to do with did you look at exposure in induction versus maintenance where they handle differently.

DR. STEMPIEN: Yes, yes. Actually in our

376 study we have pharmacokinetic profiling during maintenance therapy, and that might be the best data to show you.

If I could go back to the primary presentation. Hang on. The 376 PK data, P-78, please. Yes, slide up.

Here are the data that we obtained in our 376 study. At the end of week one, which reflects induction level dosing, patients were receiving twice daily dosing, and at the completion of week four, which reflects maintenance dosing, 900 milligrams once daily and five mgs. per kilogram once daily.

And for comparative purposes the AUCs as represented as dosing interval AUCs, and you can see at both under induction level dosing conditions and during maintenance dosing conditions that the AUCs are comparable.

So the maintenance dose that we are recommending of valganciclovir is providing a systemic ganciclovir exposure that is comparable to the ganciclovir exposure that patients are seeing now when they receive the approved IV ganciclovir maintenance dose.

DR. WONG: But how much data --

CHAIRMAN POMERANTZ: Dr. Wong wants to.

MR. WONG: -- goes into these numbers? I mean, do we have multiple points on multiple patients?

DR. STEMPIEN: These are full profiles. These are full PK profiles on 18 to 25 patients. This is not a modeling exercise. This is full PK profiling conducted during our pivotal efficacy and safety study.

CHAIRMAN POMERANTZ: Are you guys all right with this thing?

DR. BERTINO: I think Dr. Rodvold --

CHAIRMAN POMERANTZ: We'll get to Dr. Mindel in a minute. All right. One of you.

DR. REYNOLDS: My question is that when you look at this data in the week one, you're using area under the curve for 12 hours. So during the day you double it, and when do that, you double the differences between areas, which is about 4.2 there, which means right now there's a 4.2 different in micrograms per hour per mL for 12 hours, which means there's an eight micrograms per mL difference between -- there's a pretty big difference when you look at 24 hours there.

And then when you go multiple days because you're going to daily dose this for three weeks, that's a bigger exposure. So my question comes back

to is that exposure giving you -- driving this dose a little bit higher. It comes back to this question on the table. Is this the right dose, necessarily truly equivalent?

And I like your outcome data, and so I'm not worried about that, but I think you've got to be a little cautious here of saying this is equivalent on AUCs. I think that you are a reasonably amount higher over there.

DR. STEMPIEN: Please take into account the coefficient of variations on these.

DR. BERTINO: But they're equal. So the coefficient of variation is fairly equal between those two groups. So you can work around the means unless your median data is different.

In fact, those are almost identical. So the standard deviation around those numbers is fairly safe, and so that's why I'm using that as a difference there.

CHAIRMAN POMERANTZ: Dr. Mindel.

DR. MINDEL: There were some patients at entry that didn't have CMV retinitis. Were those patients diagnosed on ophthalmologic grounds as having CMV retinitis in Zone 3? By what criteria were you determined not to have CMV retinitis?

DR. STEMPIEN: I'm going to ask Dr. Martin to speak to that in just a moment, but when we say that the photos could not confirm CMV retinitis, that is precisely what we mean, and there are about five different reasons, some of them related to the technical aspects of the photo that I'll ask Dr. Martin to speak to, that can explain that.

We are aware of two patients in this trial that the ophthalmologist felt during the course of the study that a lesion that they felt represented CMV retinitis at study entry over time; they altered their judgment in that regard, but those are the only two that I'm aware of.

So the others that are simply a matter of the photo being unable to confirm retinitis, and there are reasons for that, and I'll ask.

Oh, Dr. Martin doesn't feel he needs to add.

DR. BRESSLER: Could I clarify it then? You said that -- you both said that there were six cases in one group and five in the other that had no photos or no CMV retinitis. So I think Joel was asking how many of those actually had photos, but there was no CMV retinitis noted on them?

Because those obviously could progress.

They could go from zero to something.

DR. MARTIN: The answer is none of them had CMV by photographically, and when we started this trial, the full effect of HAART was just becoming known, and what we were seeing for the first time, sometimes patients coming in with scars in the peripheral that were inactive that sort of looked like old CMV. People weren't sure what it was, and there were a couple of cases like that that in retrospect probably weren't CMV.

There were a couple of -- I continue periodically to see a patient who is thought to have CMV retinitis because of a color change in the RPE out in the mid-periphery when you add a little microangiopathy, a little dot hemorrhage. That can be mistaken for CMV.

We believe that happened a couple of times in this study, and then the other reasons why CMV wasn't seen on the photograph had probably to do or may have had something to do with the execution of the protocol, the photographic protocol.

DR. MINDEL: Well, sort of a related question also is at the end of the study there were some diagnoses of CMV retinitis that you felt caused people to drop out of the study that were

ophthalmologically driven, I think was the phrase that was used. Were those patients also in Zone 3 that caused this relief of progression?

DR. STEMPIEN: No. Everyone came into the study with CMV retinitis diagnosed by an ophthalmologist. During that period of time where we had differential withdrawal rates, there were a number of patients where the ophthalmologist diagnosed a progression, and that that prompted the patient to withdraw from the study.

But I do not believe that they were Zone 3 lesions involved in those patients.

CHAIRMAN POMERANTZ: Dr. Yogev.

DR. YOGEV: You said in the conclusion that patients completed at least six months have similar RS profile to ganciclovir. Looking at the data for the four weeks, for example, neutrophil less than 750 went up from 11, 12 percent to 30 percent; anemia from nine percent to 16 percent. Is that statement refer to historical data on ganciclovir more than six months? Because in this data none of them got the IV ganciclovir, So where that comparison of those who got at least six months came from?

DR. TOERNER: We, as well, pooled the safety data from the two studies, the safety study and

the induction study because all patients were receiving open label valganciclovir after week four, and so the only comparative data we have in this NDA package is the first four weeks of the induction study.

DR. YOGEV: If you compare, it's much higher. It's triple -- sorry -- double in the valganciclovir group in the maintenance, and you're suggesting they are similar. That's why I'm asking.

DR. TOERNER: You mean there's about a quarter of patients having evidence of immunoneutropenia.

DR. YOGEV: Correct.

DR. TOERNER: And that's about what you would see intravenous and oral ganciclovir.

DR. YOGEV: In other studies, not that were represented today.

DR. TOERNER: In other studies that are included in the ganciclovir labeling.

DR. YOGEV: Okay. So we can put the other one. The other question I have is you mentioned out of the possibility of the anemia was patient on AZT. I just share with you my personal experience. You mentioned that most of the patient changed therapy at four weeks. Usually on the second and third salvage

will have less patient on AZT because they already got it.

Is it still true that in the maintenance anemia might have been because of AZT?

DR. TOERNER: It's possible. Actually I have a back-up slide that describes this difference in anemia that I found as well, and it's back-up slide number four.

And, again, it's hard to draw any firm conclusions that there was a true difference between the treatment groups because, again, all were receiving open label valganciclovir, but we found that severe anemia occurred in ten percent overall during the study in those who were originally randomized to intravenous ganciclovir, and 18 percent in those who were randomized in the original first four weeks to valganciclovir,

And again, all anemia was a little bit more proportional between the treatment group, and the proportion with concurrent zidovudine use at the time of anemia, there were three patients, intravenous ganciclovir, and seven patients in valganciclovir, and I also mentioned MAC infection at baseline. I sought to look at those patients who did have MAC and to see if they were contributing more data to the

severe anemia in the valganciclovir arm, but unfortunately my hypothesis didn't pan out to be true. I did not find that all patients who were -- I did not find that the MAC infection at baseline drove the difference in the rates of severe anemia.

CHAIRMAN POMERANTZ: Yes.

DR. HANNUSH: I'd like to switch gears a little bit here, but I think it's appropriate for the morning session. With Dr. Pomerantz's permission, I'd like to make a comment and then ask a question probably to the sponsor, to the applicant.

I've been involved in this panel or a similar panel for the past several years, and when we reviewed the applications for intravitreal ganciclovir implant, as well as for intravitreal formaversin injections, the infectious disease experts on the panel, and if my memory serves me correctly, Dr. Kumar may have been there, constantly warned us that we are concentrating on an end organ, and perhaps by doing so, we would be ignoring the other manifestations of an otherwise systemic disease.

With that comment in mind, I'd like to know from maybe Dr. Stempien: was there any evaluation of collateral benefit from the use of the drug as opposed to this exhaustive discussion of side

effects? Was there any evaluation of other manifestations, any beneficial manifestations of the drug which may be behind your great interest in getting this drug approved?

DR. STEMPIEN: With respect to the uninvolved eye at baseline for patients who had unilateral retinitis coming into the study, we found that the occurrence of bilateral retinitis was comparable in the two treatment groups. So that's another measure of comparable efficacy.

In addition, we did follow all patients for the development of extraocular CMV disease, and within our 376 study, we had only one patient who developed extraocular CMV, and that was a patient who developed gastrointestinal CMV.

Now, you have to put that into context.

CHAIRMAN POMERANTZ: And just to follow that up, nobody came into it with extra intestinal CMV?

DR. STEMPIEN: We had one patient who came in at baseline, one patient who came in at baseline who had both CMV retinitis and also had CNS CMV disease, had polyridiculopathy, and that patient did not do well at all. That patient really was not appropriate to be enrolled.

The patient only received two doses of study drug and withdrew because they needed combined agents for their CMV CNS disease, and that's the only other patient that came into the study that we know of.

CHAIRMAN POMERANTZ: Thank you.

DR. HANNUSH: So I can understand this correctly, are you saying that of all the 160 patients that were enrolled in the study, the only manifestation of CMV disease was their ocular manifestation with the exception of these two? There were no other manifestations of disease that may have been controlled or arrested?

DR. STEMPIEN: Yes, that's correct. That's what I'm saying.

CHAIRMAN POMERANTZ: That's actually fairly common, Dr. Hannush.

DR. KUMAR: Can I ask a question?

CHAIRMAN POMERANTZ: Yes, Dr. Kumar.

DR. KUMAR: Dr. Stempien, can I ask in reference to this question that was raised how did you collect the extraocular manifestations? Was it systematically looked for for each presentation or was it collected ad hoc?

DR. STEMPIEN: No, it was not a rigorous

surveillance as we employed in our ganciclovir prevention study where we had specific criteria for every diagnosis of CMV. That was not the main concern of this study.

This was a retinitis treatment study, but we did collect all diagnoses of extraocular CMV. So this is per the investigator's report to us, and we did not collect biopsy information, culture data to verify that.

DR. KUMAR: May I just follow-up on that question?

Were most of your investigators ophthalmologists or were they infectious disease attendings?

DR. STEMPIEN: We had a mixture.

DR. KUMAR: Could you give us a --

DR. STEMPIEN: Usually --

DR. KUMAR: -- a proportion of who was what? I'm just interested in that.

DR. STEMPIEN: I would have to look that up, Dr. Kumar, but most of the principal investigators were infectious disease working closely with ophthalmologists.

CHAIRMAN POMERANTZ: Are there any other burning questions?

You're burning over there, Dr. Fletcher. Yeah, I know you're going to.

DR. FLETCHER: Just back to that about no other manifestations of disease. Just to clarify, you mean of end organ CMV disease; is that correct? Because certainly some proportion -- I think it was over half -- had CMV in their urine.

DR. STEMPIEN: Yes.

DR. FLETCHER: So when you say no other manifestations --

DR. STEMPIEN: No, no, no.

DR. FLETCHER: -- you mean end organ.

DR. STEMPIEN: Yeah, I'm not talking about viremia or shedding. I'm talking about end organ, yes.

CHAIRMAN POMERANTZ: All right. For the sake of time, let me just very quickly review what we've heard this morning because it's a very interesting application.

We've heard for one of the first times the use of an anti-opportunistic agent to affect in this case CMV in the setting of HAART. HAART has changed everything. We've talked about this. This is an important paradigm not only for CMV, but for the future.

But we have a couple of questions that have come up. Certainly the issues of whether this is useful for induction has been well characterized, and we will discuss it more this afternoon, but maintenance is a separate issue with this, and whether we are dealing with efficacy or whether we have to deal with only PK data and the changes in chart regimen that really confound the analysis of maintenance at least for efficacy.

There's been a lot of discussion from my pharmacological colleagues about whether AUC is a proper parameter, and that will certainly be part of the discussion this afternoon, and safety as well, in particular, anemia and some discordance in the two groups will come up, I'm sure, this afternoon.

So I see four or five major issues that will be tightened into these four questions that we're going to ask and answer this afternoon. Just so you know what we're going to do, we're going to ask each question separately. I will ask for discussion from the Committee. Everyone will not have to give a blurb though. So you're not going to be forced, but everyone is going to have to vote of the voting members on each issue, except for the last.

I thank you. I'm going to take Chairman's

prerogative and take five minutes off of our lunch hour, and ask you to come back at five after one.

Thank you.

(Whereupon, at 12:10 p.m., the meeting was recessed for lunch, to reconvene at 1:05 p.m., the same day.)

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

(1:07 p.m.)

CHAIRMAN POMERANTZ: All right. So we have an afternoon of digesting a few things.

We're going to start before we get into the digestion of our classic open public hearing. What I'm going to do, there's one person signed up. We will then ask if there are others since it is an open public hearing, and the first person for this open public hearing is Mike Marco of the Treatment Action Group.

Michael.

DR. MARCO: Thank you, Dr. Pomerantz.

I just wanted to say that I'm Michael Marco from the Treatment Action Group. I'm the Director of Infections and Oncology, and I am pleased to finally be able to be in front of all of you to discuss valganciclovir.

I'm glad this day has come. TAG does support the approval of valganciclovir for induction and maintenance for CMV retinitis in people with AIDS, and, Dr. Pomerantz, I appreciate your comment that said that while HAART had delayed getting valganciclovir to this point and it's been problematic for the sponsor, it has been good for the patients.

I want my comments to be brief because I know we all want to get out of here soon. So I'd like for all of you to remember me for my brevity and not my astute comments.

(Laughter.)

DR. MARCO: There is a position paper from the Treatment Action Group that's out on the table. It's been passed out to all of you on the Committee, and I want to draw your attention to it. I promise that I will not go over it word by word. It's pretty self-explanatory.

I do want to point out one typo that I find sort of interesting. It's under valganciclovir's pivotal CMV study section. It's the second sentence. I say, "In 1997, the FDA would approve valganciclovir solely on pharmacokinetic data." It should say "would not approve valganciclovir solely on pharmacokinetic data."

In retrospect, I actually think that the FDA probably should have. I think that we have IV ganciclovir and we have oral ganciclovir, and I think the comparable PK data could have warranted the approval for this drug.

Just quickly I'm going to steal some of the thunder of the Committee, and I want to go through

the questions.

As far as the first question, do the data submitted for the NDA support safety and efficacy, and I say yes. I want you all to remember that this is basically more data than we've ever had for other CMV drugs. CMV drugs after valganciclovir were basically approved using immediate versus deferred design. That was basically placebo controlled.

And so it's possibly the Agency to not do their job years ago when they should have had certain drugs like foscarnet or cidofovir compared against cyclovir.

So I do take my hat off to the sponsors for taking their oral drug and comparing it to IV, which is the gold standard. That has not been done before in a registrational study.

And you should also pay attention to the FDA's analysis. They did an excellent job, and I truly believe that they showed that they were both comparable as far as safety and efficacy, at least in the induction.

As far as the second question, I do believe that this has enough information for maintenance therapy. Oral ganciclovir is approved for maintenance therapy. Hoffman LaRoche will know that

I'm probably the harshest critic when it comes to oral ganciclovir. I don't like the drug.

I don't like the drug because I'm not sure how effective it is at least for prophylaxis. For maintenance therapy you need at least 12 tablets a day. There are investigators who think you should almost take 16 to 20.

I think all of you know that HAART regimens have a myriad of pills that patients have to take. So if somebody has CMV retinitis, adding 12 to 16 pills extra is just too much. Resistance is easy to this drug, and so if we can just bring it down to two pills a day hopefully that will help out with resistance.

I fear that the Committee has gotten a little too stuck on the anemia question and the problems with anemia. For those of us who have been doing this work for a great deal of time, and I know many of you have who see patients, Dr. Kumar, Dr. Owens, we all know that IV ganciclovir does cause anemia, and I know that most every clinician is aware of it and knows how to treat it.

So putting somebody on valganciclovir, I think clinicians will be monitoring anemia and all of the cytopenias that come along with it.

I, lastly, just wanted to say that I'd like to see Roche work hard and even harder on getting this drug approved for prophylaxis. Oral ganciclovir I do not find effective at all for prophylaxis of CMV, but I do think that valganciclovir will be an excellent drug and should do well in studies, and they should help support the ACTG team if they need to find additional site.

And if valganciclovir is approved and also approved later on for prophylaxis, they can take oral ganciclovir off the shelves.

Thank you.

CHAIRMAN POMERANTZ: Thank you, Michael.

This is an open microphone right now. So is there anyone else or any other group that would like to make comments on the drug before us today? Speak now or forever hold your peace.

(No response.)

CHAIRMAN POMERANTZ: Okay. We will close the open public hearing and move right to the Committee's discussion and votes.

As I said in the morning, what I'd like to do is deal with each question obviously separately for a discussion from the Committee, and then at the end of the discussion, we'll have a person-by-person vote

which will be tallied by Tara.

All right. So can we have the slides with the questions up there now?

Okay. So we're in revised questions to the Committee, not the first one in your handout.

Do the data submitted in this NDA support the efficacy of valganciclovir for induction therapy of CMV retinitis? If the answer to this question is yes, in your discussion please consider the limited sample size in a study with an equivalence design and the clinical significance of the lower bound of the 95 percent confidence interval of minus 13 percent.

If the answer to the question is no, in addition to the above considerations, please comment on what further clinical data should be required.

This question is open for discussion. Someone has to say something.

DR. BRESSLER: I'll start.

CHAIRMAN POMERANTZ: Neil.

DR. BRESSLER: I'll start. I would say the answer answer for me would be yes. The long answer is that although the data is limited because of the size, that's nothing that you can ever overcome, although the data is limited because of some people lost to follow-up. That's data you can't overcome.

The important thing to do me is that the effect on progression was so close between the two sides, despite the limited numbers and that even the details shown for border activity was so close despite the small numbers that were done that it seems logical to present this data to physicians, let them use that if they believe it's the best way to induce the patient, and they are not confined to only using this drug if they see some progression.

And although once there's progression, there's permanent loss of visual acuity in that peripheral field. It's usually not going to be so fast that the physician couldn't necessarily switch to some other regimen, and so because the effects see so similar, because the totality of the evidence seems to suggest that it's okay, for me it overcomes any of the design limitations, which there are and which physicians should recognize when they decide, okay, I'm going to try this. It has a few limitations, but I'm comfortable.

CHAIRMAN POMERANTZ: Yes, Dr. Mindel.

DR. MINDEL: I'd say no. I think there's basic flaws in the way the study was formulated. Dr. Martin's first patients showed progress at two weeks, and he said this is not uncommon, and it's true. It's

not uncommon that you can get progression at two weeks.

So I think a four-week study is too short.

And also the criterion then of 750 microns necrosis is a fair amount of necrosis in a short amount of time. So just on that basis, I don't think the data are convincing.

CHAIRMAN POMERANTZ: Yes.

DR. PULIDO: Point of clarification. Maybe I didn't hear Dr. Martin properly, but I didn't hear anything about progression of the case that he showed.

PARTICIPANT: That is correct. He showed that it failed to completely resolve.

CHAIRMAN POMERANTZ: Hold it, hold on.

Dr. Martin, could you clarify that, please?

DR. MARTIN: That is absolutely correct. There was no progression at two weeks or at four weeks or eight weeks.

CHAIRMAN POMERANTZ: Neil, Dr. Bressler?

DR. BRESSLER: I was just going to say it just didn't completely resolve at two weeks. So there was still evidence of that whitish retinitis. It was less than before. It hadn't progressed beyond its

original area.

DR. MARTIN: Typically when one starts induction therapy, it takes several weeks before the border of pacification to clear. Very common at two weeks to still have some border of pacification. The important thing is that there was no expansion of the lesion during that period of time.

CHAIRMAN POMERANTZ: Dr. Mindel, you had some comments.

DR. MINDEL: No, other than it's my impression though that it isn't unusual for there to be continued progression in the initial few weeks of therapy. Is that incorrect?

DR. MARTIN: There can be continued movement beyond 750 microns during that time point. That is correct, but it did not happen in that patient.

CHAIRMAN POMERANTZ: Neil.

DR. BRESSLER: Perhaps it would be useful, and, Joel, this might be helpful to address your concerns as well. The 750 microns can be important if it wipes out your foveal center. The sponsors and the FDA said that the visual acuity outcomes were not different between the two groups or they were similar, and they didn't show any large deteriorations in that

first two to four weeks for most of the patients, and the deteriorations were similar.

It might be helpful to have more detailed visual acuity analysis to confirm since we have such little data. You know, we're working with very small numbers, to have the actual visual acuities because the ranges that were used were, you know, your 20-40 or better or your 20-50 to 21-20 or your 2200 or worse, and those are quite broad in a way.

But it implied at least to me that whatever progression did occur didn't necessarily cause more vision harm in one than the other, and this was important since this study did look at the Zone 1 cases, which are the ones that would impact visual acuity, which we wouldn't see with other cases where there isn't a lot of Zone 1 disease being looked at, where peripherally it has to come a long way to impact visual acuity.

CHAIRMAN POMERANTZ: Dr. Ram Yogev.

DR. YOGEV: I'm struggling between academia and practicality, and I have to say yes at the end because if you look at what we approved in the past, not specifically as a Committee, but the FDA, and the n of patients it was approved on and we accept today that the ganciclovir IV, five milligram is the

drug of treatment, this data that were presented to us to me are sufficient to say that at least for the induction I would support that this drug should be approved.

CHAIRMAN POMERANTZ: Other comments?

Yeah, Dr. Fong.

DR. FONG: I agree with everything that everybody has said this morning. I agree with you with the use of HAART nowadays. It's very difficult to do studies with CMV, and it's particularly difficult to sort of look at the time to progression. So I think given all of these limitations, I'm very convinced that there is equivalence between valganciclovir and IV ganciclovir. So I would vote yes for approval.

CHAIRMAN POMERANTZ: For induction approval, yeah.

DR. FONG: For induction.

CHAIRMAN POMERANTZ: Other comments?

(No response.)

CHAIRMAN POMERANTZ: We're going to get to a quick vote here.

I have one comment, and that is I understand Dr. Mindel's feelings. Four weeks is short and worrisome, and there is a lot of confounding

variables that can get into this, even with all of the very nice work the group did to alleviate my concerns, and I am more comforted now that HAART did not have a lot of problems in affecting this analysis at least in the first four weeks.

But that being said, there is the question of a real world component here, and although I remain somewhat concerned, I, too, would vote yes knowing that this is a bit of a paradigm shift, but so was HAART development and the change in the epidemic.

Other -- yeah.

DR. FLETCHER: A point where I need some statistical clarification is on the issue of equivalence. From the data we have, can we really conclude that these are equivalent or is it more appropriate that valganciclovir is not inferior?

Now, maybe that's splitting a fine hair, but perhaps someone from the FDA would want to comment on what the most correct interpretation of the data are, equivalence or not inferior.

DR. YOGEV: What's the difference? I mean there's either equivalence --

CHAIRMAN POMERANTZ: If you're going to talk, talk in -- hold on, hold on. We're not recording of that. You've got to talk into the

microphone.

DR. YOGEV: I don't understand. What's -- if it's not equivalent, it's either inferior or superior, what other levels are there?

DR. FLETCHER: I'm not sure there's a difference either, but the sponsors seemed to take care in their presentation to say that the design was a not inferior design, and in the question that the Committee is being asked it says it's an equivalence design, and I'm looking for some guidance.

Are those, indeed, the same?

CHAIRMAN POMERANTZ: Are there some comments from the FDA?

DR. BIRNKRANT: Dr. (unintelligible) will be answering for the FDA.

PARTICIPANT: Yeah, there really are no difference between the inferiority and equivalence, you know, for analysis. Both of they use the lower bound of 95 percent confidence interval. That's the number we should be looking at for the inference to describe similarity of the two drugs.

CHAIRMAN POMERANTZ: Final discussion points? Yeah, FDA.

DR. CVETKOVICH: If I could just clarify one maybe, I don't know if this will help you or not,

but the reason we emphasize our analysis and looked at the lower limit of the confidence interval was, you know, the question is if it's as -- you know, on one hand it could be better, and on the other hand, it could be worse based on the confidence intervals.

What we're really concerned about it, would it be worse? If it's better, super. But the clinical relevance of being potentially 11 to 13 percent worse than proven therapy, and that's really what we're here to decide, whether that is okay, whether there are limitations to that, what we think about that.

I don't know if that helps. I think whether it's a noninferiority or -- the name of it is probably not going to change the way you think about it.

CHAIRMAN POMERANTZ: Courtney.

DR. FLETCHER: It does because I'm wondering how would you contemplate translating that into the label. How do you communicate then that to the patients or the physicians that prescribe the drug, the patients, you know, that will take this drug?

Is there a way then to say it is no worse than -- I'm trying to find the -- you know, it's not

more than 13 percent worse.

DR. FONG: Drugs aren't compared to each other on the label in general. Isn't that so?

DR. CVETKOVICH: Yeah, we knew from the outset that we would have trouble or this would not be exactly the same as other studies because of its size limitations, and we knew it would be under powered to really demonstrate equivalence. And I guess what we'll come down to is adequately qualifying it, and what we had envisioned would be to provide the confidence interval, and that should indicate both by the width and the directions, you know, the amount of uncertainty that's there.

If you think it doesn't, I guess we need to hear that, but that's what we have.

CHAIRMAN POMERANTZ: So you're going to provide it on the label to let physicians decide what they can make of that?

DR. BIRNKRANT: If labeling is developed for this drug, then we will put in a description of the clinical studies, as well as the analyses, which will include the 95 percent confidence intervals.

CHAIRMAN POMERANTZ: Thank you.

Yeah, Ram.

DR. YOGEV: I think that when you discuss

that you have to pay attention also there are four times more side effects which are life threatening. I'm talking about catheter induced, and if you put that into it, it would be more than minus 13 on the ganciclovir IV as worse, as a whole for the patient -- and that's why I say it's academia versus practical.

And I think when you put those together, I feel relatively comfortable with minus 13 as the worst scenario. That does not mean that that's what would happen.

CHAIRMAN POMERANTZ: Thank you.

Yes, Dr.Dr. Hannush.

DR. HANNUSH: This may be a little bit of elaboration on what Dr. Yogev just said. Again, having done this for several years, I'd just like to make a couple of comments.

First of all, this being the seventh drug to be approved for this indication, I don't think the FDA would be coming to us if the science was clear, meaning this may have been approved internally if the science was clear.

Therefore, they're coming to us because the science is not clear, and that's why we're having this discussion, and I feel that if you'll excuse the pun, we have to make an inductive leap here in making

a decision where we make a decision based on the human factor, based on other factors we're trying to take into consideration as to what is in the best interest of our patients.

Do we want another option for our patients considering many factors?

With that in mind, I think it's reasonable, and I find myself in a situation where we are like a jury ignoring the judge's recommendations, so the Judge being the science here. The science is clearly -- with a four-week study, the science is clearly not conclusive here.

But I think we need to take all of that into account and make a decision in the interest of our patients, and with that in mind, the answer to the first question in my mind is yes.

Now, historically also I have been accosted after the meeting, and with all due respect to the statisticians and to the doctors of pharmacology, they would come to us after the meeting, and one person I remember specifically who I had an encounter with after the meeting who after many explicatives says to me, "You M.D.s are always negating the science and making decision based on factors that were not presented at the meeting."

Well, we are the ones taking care of the patients, and we have to take the human factor into consideration, and I think that plays a big role.

So in my mind if there's not significant harm done, and I think the safety data is equivocal, I think it's reasonable to err in favor of giving the patients another options.

CHAIRMAN POMERANTZ: Our one nay vote, Dr. Mindel, so far.

DR. MINDEL: Well, does the FDA want us to answer the question or does the FDA want us to answer a question should this drug be approved?

CHAIRMAN POMERANTZ: The FDA is asking you to answer this particular question right now.

DR. MINDEL: This particular question. So if you look at that question, how are you going to answer it?

I mean, it seems to me a lot of this discussion is answering a different question, and I might vote in favor of approving this drug even though I might say that the data doesn't support it. I want that option left open.

CHAIRMAN POMERANTZ: We don't approve drugs here. We make recommendations based on the data.

DR. MINDEL: No, but I'm saying I might vote for approval, even though I might vote no on every one of these questions.

CHAIRMAN POMERANTZ: Well, you're not going to be asked that though.

DR. MINDEL: Okay. Well --

CHAIRMAN POMERANTZ: I mean, it's like a study section at the NIH. You're not asked whether you're going to fund the grant. You're asking what you think of questions on the science.

So if you want to answer this question as no, then your answer is no.

Dr. Wong.

DR. WONG: I guess I disagree on the issue of the science, and in my mind the sponsor has demonstrated the efficacy of this drug in the induction phase.

The four weeks doesn't bother me. It seems to me the results are clear, and I guess as an additional comment, I think that the old study design under which the previous CMV drugs have been analyzed probably is unethical in 2001 to do. So that some other design has to be derived, and I think this one was fine.

CHAIRMAN POMERANTZ: Dr. Mindel.

DR. MINDEL: I would agree that the results of the study are clear, but the question is whether the premises on which it was based are reasonable. That is a four-week study and 750 microns of necrosis, additional necrosis within that period to show a difference.

CHAIRMAN POMERANTZ: Are there any other comments? Dr. Fong.

DR. FONG: I'd like to hear how you'd follow up with that. If you don't think the study design is good, what would you recommend?

DR. MINDEL: I would recommend -- I wouldn't -- I understand the difficulties that the FDA is facing. You can't change your therapy, your heart therapy. You have to keep your basic therapy the same, and you're adding another drug. If the disease is going to progress, how long are you going to -- but when you don't know the answer, a month is a reasonable study.

It's not that I disagree with that. It's just a question of whether you accept the data as answering the question. I don't know how else to say it.

CHAIRMAN POMERANTZ: No, that's a very important point. Are there other -- in particular,

I'm asking ophthalmologists here who feel that the data does not answer that question to support efficacy.

There are other ophthalmologists here. Comments?

DR. BRESSLER: You can get progression in these cases within four weeks, and the fact that the progression by careful photograph analysis was so similar between the two and that the reduction in activity was so similar between the two suggests to me that there was a true induction effect by the drug to a level that appears to be safe enough to attempt for the patient at this time.

CHAIRMAN POMERANTZ: Other comments?

DR. FONG: I think -- I'm sorry.

CHAIRMAN POMERANTZ: Yeah, Dr. Fong.

DR. FONG: Well, I think given the use of HAART therapy, I just think you would just have to follow these patients for too long a period of time to do the kind of study that would satisfy, you know, what you're looking for.

CHAIRMAN POMERANTZ: And importantly, no one is going to not change HAART therapy in the setting of a new opportunistic infection obviously with some caveats.

We're going to have a vote on this question. Do the data submitted in this NDA support the efficacy for valganciclovir for induction therapy of CMV retinitis?

There are some people who are nonvoting guests: Dr. Chan, Dr. Piscitelli, Dr. Sun, Dr. Crittenden, and obviously everyone at the table from the FDA.

But I will go around the room and ask for a yea or nay without comment vote at this time.

Dr. Wong.

DR. WONG: Yes.

DR. YOGEV: Yes.

CHAIRMAN POMERANTZ: Turn on your mics, yeah. Okay. Dr. Yogev?

DR. YOGEV:

CHAIRMAN POMERANTZ: Dr. Pulido?

DR. PULIDO: Yes.

CHAIRMAN POMERANTZ: Dr. Rodvold?

DR. RODVOLD: Yes.

CHAIRMAN POMERANTZ: Dr. Mathews.

DR. MATHEWS: Yes.

CHAIRMAN POMERANTZ: Dr. Mindel.

DR. MINDEL: No.

CHAIRMAN POMERANTZ: Dr. Bressler.

DR. BRESSLER: Yes.

CHAIRMAN POMERANTZ: I vote yes.

Dr. Kumar.

DR. KUMAR: Yes.

CHAIRMAN POMERANTZ: Dr. Fong.

DR. FONG: Yes.

CHAIRMAN POMERANTZ: Dr. Hannush.

DR. HANNUSH: Yes.

CHAIRMAN POMERANTZ: Dr. Fletcher.

DR. FLETCHER: Yes.

CHAIRMAN POMERANTZ: Dr. Bertino.

DR. BERTINO: Yes.

CHAIRMAN POMERANTZ: Okay. All yeas with one nay.

We will now move on to the next discussion. That's actually the way that it happens here a lot. So that's okay.

Do the data submitted in this NDA support the efficacy -- that you for putting that slide up -- efficacy of valganciclovir for the maintenance therapy of CMV retinitis? Maintenance therapy.

If the answer to this question is no, please comment on what further clinical data should be required.

This question is now open for discussion.

Dr. Yogev.

DR. YOGEV: Well, I think everybody would agree we don't know because most of the patients were on ganciclovir, all of them. So you get a curve, which looks nice, but what I'm comparing it to? So unless I resort to historical data, which were not exactly presented over here, I have a problem to answer yes or no because the honest answer would be I don't know.

CHAIRMAN POMERANTZ: So right now you're going to abstain courteously?

DR. YOGEV: Yeah, unless somebody can give us some data. What type of a maintenance without the drug? You see, I'm impressed that ganciclovir oral is approved for maintenance when if we look at the PK, I'd be fascinated if somebody would show me the maintenance --

CHAIRMAN POMERANTZ: Yeah, but you can't do a therapy with induction without maintenance. That I think by anyone's idea would be unethical.

DR. YOGEV: I'm just trying to raise the point the data presented both by this company and the FDA did not allow us to make a decision because all of the curves you saw were valganciclovir alone doing something.

It would be nice if somebody can show us what ganciclovir oral maintenance did, some comparison. Otherwise I'm not sure that's enough.

CHAIRMAN POMERANTZ: That's a reasonable question. If there are historical controls, we'd like to talk about, here that maybe the FDA or the applicant would like to talk about, comparing to historical ganciclovir controls? A reasonable question.

DR. FONG: Well, can I make one observation before they speak?

CHAIRMAN POMERANTZ: Please, Dr. Fong.

DR. FONG: I mean, in the presence of HAART therapy there are people who talk about not using any treatment at all, assuming the CD4 count, the T cell count is up. So I think that comparing to history may or may not be useful.

I think that, you know, if we believe that this drug is good enough to do induction, certainly reached high enough levels, and it certainly in terms of the pharmacokinetics looks better than the oral drugs, and the oral drug is approved for maintenance.

I would have to say that, yes, I would advocate that valganciclovir be approved for maintenance.

CHAIRMAN POMERANTZ: So you've given your discussion and your vote there. Thank you.

DR. FONG: Yes.

CHAIRMAN POMERANTZ: Ram.

DR. YOGEV: I just want to -- you hit the nail on its head. See, I'm very concerned that this I heard from the FDA was not presented by the company. Most of the patients change HAART at four weeks. So I look at it as two different studies, one which was without change of the HAART, which obviously didn't work if you look at the viral load of five or four log, if you look at the CD4 are low, and then most of them are changing therapy, and then you see a curve which comes down.

As I mentioned before, it's very reminiscent of population curve of what happened to CMV in the population without valganciclovir and so forth. That's why I'm trying to suggest that this combination of changing HAART, which we know will have an effect within the next six to -- eight to 12, 16 weeks, and that's what we've got, versus is it really valganciclovir what we saw, or is it the HAART.

And that's why if you agree with that, I have a problem to say that valganciclovir is doing good.

DR. CVETKOVICH: Can I just may --

CHAIRMAN POMERANTZ: Please, please.

DR. CVETKOVICH: -- help to address that issue?

I think that it sounds as though at least for you we have not adequately made explicit why we believe that the approach of approval based on pharmacokinetic supported by safety data is a reasonable approach for the maintenance therapy.

We never viewed the continuation part, the maintenance part of the induction study or the open label safety study because they were single arm studies. Certainly we looked at them and were there anything alarming we would have taken note, but in truth, without a comparison, as you say, we can't draw any conclusions about the efficacy, clinical efficacy in maintenance.

However, we didn't believe that that was necessary because we have a very adequate pharmacokinetic argument, as well as adequate safety data, and I think Robert could maybe clarify for you what our position on the pharmacokinetics is, and then, Dr. Stempien, if there's anything you want to add, we'll do that.

Is there anything you want to add at the

moment?

DR. STEMPIEN: I'll follow.

DR. CVETKOVICH: Okay, great.

DR. YOGEV: Just before I get answered, I did want an answer to the Question 3, which you raised, but that's what my major concern is. I don't think that we don't have a different toxicity.

CHAIRMAN POMERANTZ: We're not going to talk about safety now.

DR. YOGEV: No, just because you mentioned --

CHAIRMAN POMERANTZ: I know, but we're not going to do that because we'll get to it, and we can deal with it. Let's deal with what we just asked about.

DR. YOGEV: But to me the PK being above doesn't always mean it's okay. If you try to ignore --

DR. CVETKOVICH: No, and we wouldn't think that either. You have to understand that it's bracketed. The ganciclovir levels that are achieved with the administration of valganciclovir are bracketed by two approved doses or formulations and doses of ganciclovir, the IV and the oral.

And maybe, Robert, you could explain that

a little further.

CHAIRMAN POMERANTZ: Robert.

DR. KUMI: I don't know if it's possible to have the slide from before. I think it's number 11.

All right. There's the IV profile which has the highest C-max, as you can see, and that's an improved regimen, and then there's the oral ganciclovir, which is kind of the lowest profile, which is also an approved regimen.

And from the plots, the ganciclovir concentrations are basically between those of the two approved regimens. So we have some -- I guess we have less concern about the concentrations being so different between valganciclovir and the oral ganciclovir, it's like kind of closer to IV, if anything, than to oral ganciclovir.

DR. CVETKOVICH: Could I --

CHAIRMAN POMERANTZ: No, we haven't gotten to our application.

Sure, please. You have comments?

DR. STEMPIEN: I just wanted to add a few clinical comments to the discussion. You know, the dose of IV ganciclovir has always been limited more by tolerability issues than by a maximum efficacy, if you

will, and that's how we settled on the dose of IV ganciclovir in the past. It was we dosed as high as we could, and we ran into tolerability issues, and we ended up with the approved dose that we have.

We believe that the PK profile of valganciclovir is about as close as we can get to matching an IV formulation with an oral medication, and even with this similar PK profile, if I could have the slide up, even coming fairly close to matching systemic exposures -- this was from my primary presentation -- you can see that even delivering IV ganciclovir exposures with valganciclovir, this was my -- the curve from the 376 study, which showed that patients were still progressing.

Now, keep in mind after four weeks everyone is on valganciclovir getting systemic exposures comparable to IV, and patients are still progressing over time. This is regardless of modifications to their underlying HIV regimens because after four weeks, physicians were able to modify HAART or any other HIV medication that patients were on.

And if I could have the next table, slide up. C-25, please.

Well, the point that I wanted to make with the next table that I was calling for was the -- here

it is. This is the table from which that Kaplan Meier was generated.

I just want to point out that when you follow time to progression out to clinical cutoff in our study, half of the patients are progressing, and this is over about ten to 12 months of study conduct, and the median times to progression, while they are somewhat longer than what we've seen in pre-HAART studies, nonetheless, I don't think we should be satisfied with this. The median time to progression of 160 days.

So I would hate to see us dismiss or deemphasize the importance of maintenance dosing in patients who really may need it for a period of time, and I do think that the treating community has such a good experience with ganciclovir, which has been on the market for 12 years, that they will be able to manage the safety profile of valganciclovir.

And if I could just have that slide up.

Here's the slide of adverse event withdrawals in our 376 study, and this shows you the reasons for a patient to withdraw, safety reasons, all the way out to clinical cutoff.

I just want to point out we only had one patient in each group who left our 376 study because

of anemia. So I just don't want to see too much emphasis being put on the anemia issue.

Thank you.

CHAIRMAN POMERANTZ: I'll tell you my feelings on this for just a second, and I'll get to everybody.

I understand what Ram is saying all too well. I personally feel that the maintenance is the most troublesome arm simply because I like to see efficacy data, and I don't believe you can interpret as the applicant has alluded to at times that HAART was allowed to be changed.

Once you change HAART, everything is off, I would say, on efficacy. You could have the immune reconstitution syndrome in some patients. You could have people who were not on HAART getting started. That had dramatic changes in their immune function.

There are a whole panoply of things that confound that. That being said, this is in my mind going to be the coin of the realm in the era of HAART, meaning you will have to allow this to happen in a variety of anti-opportunistic infections because you have this large anti-retroviral armamentarium, and unfortunately we do have to rely -- I'm not a pharmacologist -- unfortunately you do have to rely

only on PK data.

I am not putting much to the -- I mean, it's nice that the efficacy looked like it was okay, but there's enough there so that I agree with Ram. I can't scientifically say that there isn't enough black boxes there to confound it.

That being said, the PK data is extra ordinary, and I think for what we have so far, it makes sense and will continue to be unfortunately, or fortunately for the patients, what we have to do in the post-HAART era.

Yeah, Dr. Mathews.

DR. MATHEWS: I agree with what you've just said, and I think for the intellectual integrity of the Committee's functioning we should request that the question be reformulated because I think very clearly we don't have data to answer the question based on demonstrated efficacy. There was no comparative group for that part of the study.

On the other hand, if you -- and the historical controls are not particularly relevant here because the historical controls have progression, median time to progression, I think about half of what this observed is.

So really the question is: do we think

they're pharmacokinetically equivalent, and the answer is --

CHAIRMAN POMERANTZ: I mean that's a very big thing. Let me ask the FDA if they want anything to be changed in the semantics of the question.

DR. BIRNKRANT: We would be willing to amend the question to clarify it so that it could read, "Do the pharmacokinetic data submitted in this NDA support the efficacy for maintenance therapy?" given that we do not have any comparative efficacy data.

CHAIRMAN POMERANTZ: So it would read as what? So tell me again.

DR. BIRNKRANT: Just substitute the word "pharmacokinetic" before "data." Do the pharmacokinetic data?

DR. YOGEV: Can you take away the word "efficacy"?

(Laughter.)

CHAIRMAN POMERANTZ: I think she --

DR. YOGEV: Because the PK support maintenance therapy, but we cannot discuss the efficacy.

CHAIRMAN POMERANTZ: I mean then you --

DR. BIRNKRANT: I'm willing to do that, as

well.

CHAIRMAN POMERANTZ: Hold on. So you would say do the pharmacokinetic data submitted in this NDA support the use? The what?

DR. BIRNKRANT: The use of valganciclovir as maintenance therapy.

CHAIRMAN POMERANTZ: Does that make Dr. Ram happier?

DR. YOGEV: Much happier because I would say yes by the PK. I don't know the efficacy.

CHAIRMAN POMERANTZ: What about Dr. Mathews, who brought this up?

DR. MATHEWS: Yeah, you know, if this drug had a much more adverse toxicity profile, it would be a more significant question. So if it were much more toxic and long-term use so that someone could make an argument, well, it's a great drug for inducing, but you wouldn't want to use it long term.

But that's not the case here. We're not seeing anything new in the longer term exposure.

CHAIRMAN POMERANTZ: No, those are good points. Once again, would you be happy with those changes as outlined by the FDA?

DR. MATHEWS: Yes.

DR. BRESSLER: But I'll just point out

that is a different question because as you had mentioned earlier, you said there was no efficacy data.

DR. BIRNKRANT: There's no comparative.

DR. BRESSLER: I understand.

CHAIRMAN POMERANTZ: There's just no good efficacy data.

DR. BRESSLER: Okay.

CHAIRMAN POMERANTZ: There's efficacy data.

DR. BRESSLER: All right. Because the efficacy data that was given in the briefing by the sponsors is not what you are saying is efficacy data. You know, there was something that they put under the title of efficacy, and then you were stating that, well, that's not efficacy. So asking this question is a different question then.

CHAIRMAN POMERANTZ: Let the FDA respond.

DR. BIRNKRANT: I think the applicant would agree, and they can speak to this as well, that the data to support the maintenance use of valganciclovir is being driven by the pharmacokinetic data, as well as the safety data that's been provided.

CHAIRMAN POMERANTZ: Does the applicant have a comment on that one?

DR. STEMPIEN: We're satisfied with that. We feel we do provide efficacy data, but the point is well taken. We have no direct comparative efficacy data beyond that four-week period. So that's absolutely fine.

CHAIRMAN POMERANTZ: Do you have a question there, Dr. --

DR. BERTINO: I do.

CHAIRMAN POMERANTZ: Yeah.

DR. BERTINO: Oh, sorry. Could we pull up Dr. Kumi's slide number 11 again? I just want to --

CHAIRMAN POMERANTZ: That's impressive. You memorized the slides.

(Laughter.)

DR. BERTINO: He actually passed me a note.

I just want to throw this out, and just food for thought, which is if you look at -- we all remember what his slide looks like -- so if you look at this slide here for oral ganciclovir, that gram three times a day dose, the AUC average is 13. So if the -- you know, based on what we heard this morning where an AUC for efficacy is related to an AUC of 26 to 30, this data for oral ganciclovir in terms of efficacy was produced back in the early '90s before

HAART therapy, and it's approved for maintenance.

So I'm going to bring this up again with safety, Dr. Pomerantz, but my concern about the efficacy in maintenance has to do with the dose. Is the dose -- can we go better with side effects?

I understand we're saying, well, you know, the side effect profiles for IV and oral weren't different, but I'm asking the question: can we go better with side effects by using a reduced dose?

And does the old data for oral ganciclovir at a gram three times a day back before HAART support lower exposures being more effective for maintenance therapy?

And, once again, we'll bring that up with safety.

CHAIRMAN POMERANTZ: Roche's response?

DR. STEMPIEN: Yeah, I'd like to speak to that point.

CHAIRMAN POMERANTZ: Please.

DR. STEMPIEN: The IV ganciclovir and oral ganciclovir formulations are both approved for efficacy, but we have a big black box warning in our label with the oral formulation warning the treating physician that patients who take oral ganciclovir will progress earlier.

So oral ganciclovir has never been positioned as equivalent to IV. It does not match IV ganciclovir efficacy in maintenance therapy.

And now we have an oral agent that can provide systemic exposure comparable to IV. There is no reason to compromise on efficacy in a maintenance setting anymore. We have a formulation that can match IV ganciclovir exposure. This is what the treating ophthalmologists want.

DR. BERTINO: I understand that, but I'm still asking the question: do you need that dose for maintenance therapy of valganciclovir? Could you use less?

DR. STEMPIEN: No. I feel we should dose --

DR. BERTINO: You're shaking your head, but that wasn't done.

DR. STEMPIEN: IV ganciclovir, if we could give more IV ganciclovir, we would have. The dose of IV ganciclovir has been limited by tolerability issues, and that is just -- it's primarily neutropenia and anemia. So the efficacy, if we could push for more efficacy, we absolutely would.

Half of the patients are progressing. They're still progressing despite HAART. So it's not

a matter of do we have adequate efficacy. We want maximum efficacy within tolerability limits, and we can deal with neutropenia and anemia today much better than we could several years ago.

So we feel that our objective is to drive the efficacy here. We feel that the treating community understands the safety of ganciclovir, and they will understand valganciclovir, and they'll be able to manage it. That's our belief. We're confident in that.

CHAIRMAN POMERANTZ: There was a question for Dr. Piscitelli and then Dr. Wong.

DR. PISCITELLI: So getting back to the PK issues, I think the pharmacology people agree that this AUC analysis wasn't acceptable. So we don't know what's important here. Is AUC? Is C-min? Is C-max?

Now, if I understand this correctly from Dr. Kumi, the AUC of this drug, it's higher than the oral, and it's equal to the IV. The C-min is greater than the IV, but less than the oral. The C-max is greater than the oral, but less than the IV.

So there's no magic statistics here. It's more of an eyeball approach. It follows in there, and I'm just clarifying. Are you comfortable with that sort of eyeballing of the data?

DR. KUMI: Yes.

CHAIRMAN POMERANTZ: Dr. Wong.

DR. WONG: I guess the comment that I would want to make is with your reformulated question, it's very easy to answer it, but I would go back and suggest that that's really not the right question, that what we're being asked to consider here is prolonged use of a drug to prevent a clinical outcome, and to my mind the sponsor has not addressed that question in the studies presented in that there are no clinical outcomes shown beyond four weeks.

So that, you know, to me there should be some demonstration of a favorable clinical outcome long term. Otherwise the answer is no.

CHAIRMAN POMERANTZ: Comments from the FDA.

DR. BIRNKRANT: Well, I don't really think to be able to please everyone we should have two questions. I think that could be confusing as well.

CHAIRMAN POMERANTZ: It would confuse me.

DR. BIRNKRANT: I think the bottom line is the data are what the data are for maintenance. This is what we have in this particular application.

So the question we're asking you is: is this in the end effective for maintenance therapy for

CMV retinitis? Do the pharmacokinetic data support the use and efficacy of valganciclovir for maintenance?

CHAIRMAN POMERANTZ: No, there's no "efficacy" word in this question.

DR. BIRNKRANT: Okay.

DR. BRESSLER: But if you put it back in, then it makes it a much harder question to answer because the suggestion is that we don't have evidence so far that the maintenance therapy is efficacious in progression compared to maintenance therapy that's used right now.

But if there is data to that effect, then I think we should have it quickly reviewed because that would affect the efficacy question.

DR. BRESSLER: Right, and if I can come back, I mean, I think for maybe not specifically for this drug, but you know, a lot of people are going to consider the decisions that the agency makes for this drug in designing how they approach things in the future, and I think it would be very dangerous, you know, as a long-term statement to let everyone know that we as a Committee or the agency is prepared to draw conclusions about clinical outcomes in the long term based on clinical outcomes in the short term,

plus pharmacology.

I mean, I don't think that that is very wise.

CHAIRMAN POMERANTZ: Roche has a comment.

DR. STEMPIEN: We don't have comparative data in a maintenance setting between valganciclovir and ganciclovir, but if you would be interested, we could show you data on how time to progression with valganciclovir maintenance compares to time to progression with ganciclovir maintenance, although the ganciclovir would be more historical data.

Would you --

CHAIRMAN POMERANTZ: That's what we talked about a few minutes ago. Why don't we throw that up there?

DR. STEMPIEN: Okay. I'm going to ask -- maybe Rebecca can help me -- I'm going to ask the slide up, please.

Okay. So here is a time to progression, Kaplan Meier analysis, photo documented progression, and this is 376, both arms combined because recall after four weeks everyone is on valganciclovir, and this compares our data to previous ganciclovir time to progression curves that were gleaned from four prior ganciclovir studies.

And so here is the ganciclovir time to progression curve. So this is historical data. Some of it is pre-HAART, but here is the valganciclovir time to progression curve.

Don't know if that helps you in any way.

DR. YOGEV: Is that all --

CHAIRMAN POMERANTZ: Welcome to the post-HAART era. This is what we've been talking about. You can compare before and after, and I don't fault Roche at all. We kept prodding you to show this. So there it is.

DR. STEMPIEN: Yeah.

CHAIRMAN POMERANTZ: And the data is the data.

DR. STEMPIEN: I'd also just like to make the point that the way that we approached this, knowing that we couldn't do a direct comparison and maintenance study, was that we felt that if we could establish efficacy in the induction setting, which is recognized as the highest hurdle for efficacy for a CMV retinitis therapy; that if we could show you that valganciclovir is efficacious in that setting, that given that efficacy data, which is a direct comparison to standard of care, and then coupling that with our PK profile information, that you would feel reasonably

comfortable that there's no reason to expect that valganciclovir would not have efficacy in maintenance.

I mean, there's nothing magical about the maintenance setting. It's just a question of dose. So the same disease process is going on. You're treating the same lesion, the same virus. So we felt that that combination might give you some comfort that although we did not have direct comparative data, that you could conclude that valganciclovir should be efficacious in that setting.

CHAIRMAN POMERANTZ: One thing that I should say as a virologist is that induction and maintenance therapy have taught us are different, and even though it's the same virus, it's not always the same disease.

We know that HIV maintenance therapy, except in newly configured regimens, doesn't work, while the same approach cannot be said for induction.

So it is a question. I see your point. I don't disagree with it, but I think we get into this because the data is not as robust as we might like to start talking around the issue, but this is it.

Courtney, you have comments.

DR. FLETCHER: Yeah. I'm wondering if anyone else other than myself may want to draw an

analogy to the Cidofovir data, which at least in terms of when the trial was done was at the very early era of HAART and showed a median time to progression of 120 days.

So while I don't know all of the details of that study and where regimen change is allowed, it nevertheless may be some closer historical data within the era or HAART, probably very early HAART, that would have a very similar time to progression as to the valganciclovir data.

CHAIRMAN POMERANTZ: Comments on that? Yeah.

DR. MATHEWS: Well, I think that's a more relevant historical comparison than what we were just shown, but you know, I think we ought to put in the context that this was a drug whose development at least for this indication was close to being dead in the water a few years ago, and it's unquestionable that there's a very definite need for it.

And so I don't agree that this is setting some kind of precedent that's going to be regretted subsequently. You know, it's impossible to get the kind of data that we would like to hold for the standards that we've used in other contexts.

But, on the other hand, I don't think we

should give the impression that a reasonable person wouldn't conclude that this drug is very efficacious not only for induction, which we've seen good data for, but very likely for maintenance based on the pharmacokinetic data and the historical data with all of the caveats that have to go with that.

So I would like to just say --

CHAIRMAN POMERANTZ: We're going to go to the F -- sorry.

DR. MATHEWS: -- that I think both the agency and the sponsor should be commended for pushing this development program along because it's going to make a big different in patient care to be able to avoid having to put in central catheters even for three to four weeks.

CHAIRMAN POMERANTZ: A comment from the FDA?

DR. REYNOLDS: I just wanted to point out that using the PK data really isn't setting that much of a precedent. Since the oral and IV are both approved for maintenance therapy, if this formulation were identical to oral for maintenance therapy, we wouldn't be asking our question, and if this were identical to IV, we wouldn't be asking our question, and it's in between, and that's why we're calling for

-- PK data are used to approve generic drugs all the time.

CHAIRMAN POMERANTZ: In the setting of antivirals? In the setting of an anti-retroviral?

DR. REYNOLDS: If they were identical, the generic would be approved.

CHAIRMAN POMERANTZ: Has it ever happened?

DR. REYNOLDS: I don't think they're off patent yet. We have new formulations that have been approved.

CHAIRMAN POMERANTZ: See, that's why HIV is always different, and it really is. I mean, we don't usually use that as the paradigm because there are two viruses interacting here. There's enough that make everybody nervous in setting, as Dr. Wong said, a precedent that may come back to bite you.

I personally fall on the side, as I've alluded to, of approval for this maintenance indication, but I do understand the worries.

DR. REYNOLDS: We have had changes in formulations approved based on PK data for anti-retrovirals.

DR. CVETKOVICH: Can I just add to what Dr. Reynolds is saying? What we're trying to tell you is that -- and perhaps it's confusing that we asked

the question, but I think we believe we need to. You know, we're here to explore the data and hear what you think about it, and maybe we should have asked the question in somewhat of a different fashion because we do do this. We approve -- you can approved drugs without clinical data.

Say this was absolutely bioequivalent to the IV. We would have no requirements for clinical data. This is bracketed by two approved products so that we don't feel that we're in much of a bind here with this one.

You know, there's no way that you can know because we've not dealt with this, as you say, in the anti-retroviral arena very often, and in fact, a lot of these decisions would be made without ever bringing it here. So you may not be as aware of how these things work.

But we don't have a big problem with this.

CHAIRMAN POMERANTZ: Unfortunately obviously the Committee has.

DR. CVETKOVICH: Yeah, what's wrong with you guys?

(Laughter.)

CHAIRMAN POMERANTZ: Now, I'm going to ask for two final comments, and then we're going to decide

what the question is and then we're going to vote Ram.

DR. YOGEV: Let me tell you what's wrong with us guys.

(Laughter.)

DR. YOGEV: Okay. With me.

CHAIRMAN POMERANTZ: You did start it.

DR. YOGEV: My problem is the separation between Question 2 and 3 and why the sponsor would allow itself to show it as a response. My problem is exactly what my good friend Dr. Fletcher showed, is the minute we use HAART, everything moved to a longer period of time.

How much of local efficacy here is because of the change of HAART and how much we are paying with safety issue? And to me, it's very surprising that 25 patients had less than 6.5 hemoglobin, gram percent, and yet only one was removed from the study. That's where the toxicities are.

So do we need such a high dose? Do we need a lower dose for the maintenance because we have everything to avoid toxicity, and I don't have an answer for that, but that's where my concerns are.

If you look at the IV ganciclovir, we have to take a lot of patient maintenance just because of

toxicity, and interesting enough, they have the same rate of progression, which suggests to me that the five milligram IV is not enough also.

So we're comparing it to something which is not perfect on something which showed to me at least increased toxicity in maintenance. Am I doing the right decision? And that's why the whole argument when you don't have clear-cut efficacy data.

CHAIRMAN POMERANTZ: Yes, sir.

DR. BERTINO: Looking at it from the point of view just presented, is it at least as efficacious as oral ganciclovir for maintenance therapy???

I would have to say yes because oral ganciclovir for maintenance therapy has such poor efficacy that it's hard for me to believe that with this PK data we wouldn't even have better efficacy than oral ganciclovir.

CHAIRMAN POMERANTZ: Why don't we cut it there?

DR. BIRNKRANT: So then question number two then becomes -- the wording for that is: do the data submitted in this NDA support the use of valganciclovir for the maintenance therapy of CMV retinitis?

CHAIRMAN POMERANTZ: So we are now on

version 3.0.

DR. BIRNKRANT: Exactly.

CHAIRMAN POMERANTZ: So let me read it again. Do the data submitted in this NDA support the use of valganciclovir for the maintenance therapy of CMV retinitis.

DR. BIRNKRANT: Understanding that the data are pharmacokinetic and safety, for the most part.

CHAIRMAN POMERANTZ: But that's parenthetical. That's not in the question.

All right. So do the data submitted in this -- now we're going to do this. Okay?

DR. BIRNKRANT: Right.

CHAIRMAN POMERANTZ: So get ready to vote. Listen to me.

Do the data submitted in this NDA support the use of valganciclovir for the maintenance therapy of CMV retinitis, question mark, et cetera?

And we're going to go clockwise this time and start with Dr. Bertino.

DR. BERTINO: I was afraid you were going to do that.

CHAIRMAN POMERANTZ: Yes or no.

DR. BERTINO: Filling in at Palm Beach

County.

Yes.

CHAIRMAN POMERANTZ: Is the chad dangling? Oh, okay.

DR. BRESSLER: Yes.

CHAIRMAN POMERANTZ: Dr. Fletcher.

DR. FLETCHER: Yes.

CHAIRMAN POMERANTZ: Dr. Hannush.

DR. HANNUSH: Yes.

CHAIRMAN POMERANTZ: Dr. Fong.

DR. FONG: Yes.

CHAIRMAN POMERANTZ: Dr. Kumar.

DR. KUMAR: Yes.

CHAIRMAN POMERANTZ: I vote yes.

Dr. Bressler.

DR. BRESSLER: Yes.

CHAIRMAN POMERANTZ: Dr. Mindel.

DR. MINDEL: Yes.

CHAIRMAN POMERANTZ: Dr. Mathews.

DR. MATHEWS: Yes.

CHAIRMAN POMERANTZ: Dr. Rodvold.

DR. RODVOLD: Yes.

CHAIRMAN POMERANTZ: Dr. Pulido.

DR. PULIDO: Yes.

CHAIRMAN POMERANTZ: Dr. Yogev.

DR. YOGEV: Yes.

CHAIRMAN POMERANTZ: And Dr. Wong.

DR. WONG: Yes.

CHAIRMAN POMERANTZ: It was much easier when we voted, wasn't it?

(Laughter.)

DR. MINDEL: Well, it's much easier when you rephrase the question.

(Laughter.)

CHAIRMAN POMERANTZ: The rephrase for the Committee is we got rid of the word "efficacy." "Use" can be construed in a variety of ways that we'll leave to our FDA colleagues.

Okay. Shall we press on?

All right. Now we get to Ram's favorite one.

DR. FONG: Dr. Pomerantz.

CHAIRMAN POMERANTZ: Yes.

DR. FONG: For Question 2, there was also if the answer -- well, actually can I comment?

CHAIRMAN POMERANTZ: No, that's part of the discussion. This is a yes or no vote. You had that time to discuss it.

DR. FONG: Can I just add something?

CHAIRMAN POMERANTZ: You want to put

something in the record? Sure, go.

DR. FONG: Well, if there's always a discussion about whether the dose is too high, why don't we, you know, have the sponsor consider doing a study with a lower dose?

CHAIRMAN POMERANTZ: So your suggestion, and we may get to that in further trials.

DR. FONG: Yeah, could make some data.

CHAIRMAN POMERANTZ: But you might suggest that.

Yeah, now do you want a counterpoint then?

DR. MARTIN: I want to provide a little perspective then that may be being missed here a little bit. You know, intravenous ganciclovir is a great drug, but most clinicians really aren't even happy with that dose.

And that's the whole reason why we moved to the ganciclovir implant and other treatments. And so at least for me, I would never even consider moving to a lower dose provided that there aren't egregious toxicities, which I think we've shown you that there is not.

For me if there's a higher exposure, great, bonus. I mean, we're trying to treat CMV retinitis. That was the reason why you started

therapy, and the blood-ocular barrier is such that you can't forget that. If you're going to get drugs into the eye, you can't drop the dose. You don't want to. There's no scientific reason to want to do that.

So I just want to keep that perspective in mind.

CHAIRMAN POMERANTZ: Thank you.

Dr. Bertino.

DR. BERTINO: Just one comment to the FDA then, since we've answered one and two, which is that when you work on the label, I think it's imperative to put in that the drug should be take with a high fat meal.

DR. STEMPIEN: Well, I just want --

DR. BERTINO: I was sure there'd be a comment.

DR. STEMPIEN: Yeah, I'm sorry. But I just want to make sure you understand that although in our clin-pharm studies we gave them the high fat standard FDA breakfast, in our clinical trial we simply said, "Please dose with food." So the actual clinical data that was generated here is not high fat. It's just dose with some food.

CHAIRMAN POMERANTZ: Give only with McDonald's cheeseburgers. Is that what you're trying

to say?

DR. STEMPIEN: It should be comparable to what we have in our ganciclovir labeling, which we conducted it the same way.

DR. FLETCHER: But you can't have it both ways. You can't have it an indication for maintenance based upon PK and the PK coming through a well designed, well controlled, pharmacokinetic studies where the patients got a high fat meal, and that is what shows pharmacokinetic equivalence, and then say in the label, "But you can take it for maintenance and you don't have to take it with food."

You're trying to have it both ways, and you can't do that.

CHAIRMAN POMERANTZ: But there's a difference in my way of thinking between a high fat meal and take it with food. What are you saying?

DR. FLETCHER: Well, I'm saying, if I understand what the sponsor said, when we saw the pharmacokinetic data from week one and week four, we asked what was the meal, and they said, "That's the standard FDA meal for those studies."

DR. STEMPIEN: No. So there is a misunderstanding. Let me set the record straight. One of our earlier clinical pharmacology studies did

dose with a high fat standard breakfast. The full PK profiling that I showed you from the 376 study where we had 20 patients with full PK profiles at week one and week four, we did not dose it with a high -- it was not standardized that way. We simply suggested, "Please take your dose with food or snack."

So we did it exactly the same way as we've done our prior oral ganciclovir studies, and so the label should look just like ganciclovir, oral ganciclovir. That's truly what we did.

DR. FLETCHER: I don't know what the label looks like for oral ganciclovir. Does it say "with food"?

DR. STEMPIEN: Yes, it does.

DR. FLETCHER: Okay.

CHAIRMAN POMERANTZ: All right. We've gotten rid of the fat, and we're leaving food. Why don't we move on?

Do the data submitted in this NDA support the safety of valganciclovir for the treatment of CMV retinitis? This is Question 3.

If the answer to this question is no, please comment on additional safety studies that should be required.

Question is open for discussion. Sir?

DR. PULIDO: I have a question for my colleagues on the panel. I'm still concerned about what happens to the valyl ester in the presence of diarrhea where the intestinal esterases may not be functioning properly or in the presence of hepatic toxicity, which by the way there was, as I had mentioned before, 14 percent incidence of lab abnormalities showing some hepatic toxicity from this drug.

It looks to me like there is no data to show what happens in these cases. Should we be worried about toxicity of the valynated form?

CHAIRMAN POMERANTZ: Any comments to that question from either side?

DR. BERTINO: I think a couple of questions though to think about. One would be I think we heard from the sponsor that about 25 percent of the drug is cleaved in the liver. Is that --

PARTICIPANT: No, 15 percent.

CHAIRMAN POMERANTZ: Turn on the mic.

DR. BERTINO: Fifteen percent in the liver.

And so the question is: can the liver do moire?

I guess the other question is if the drug

is being absorbed in the upper part of the small intestine, what happens to esterases there based on diarrhea? Do we know?

One of the things that I always think about when the liver is involved is the liver has got enormous reserve, and the gastroenterologist's definition of liver disease and the pharmacologist's definition of liver disease really are pretty different.

CHAIRMAN POMERANTZ: Well, before you say that, that brings up a point that I wanted to bring up in the morning, in that more and more HIV CMV is being complicated by Hepatitis C virus, and the tripartite viral infection is a big problem, and the question is: if you're going to look for liver dysfunction, is there any data on the use of this in someone who has Hepatitis C?

DR. STEMPIEN: I don't think we have any clinical data on that.

CHAIRMAN POMERANTZ: Because if there's going to be one problem in HIV infected individuals that might give you liver dysfunction, that might get you into trouble with those hypothetical questions, it's more and more becoming Hep. C.

DR. STEMPIEN: We don't have clinical

data, but we do have some preclinical data that addresses the intestinal and hepatic esterase, and Dr. Sue Malcolm, preclinical, can take you through that.

DR. MALCOLM: We were concerned with the effect as to impairment or competing activity for the esterases in both the intestine and the liver. So we did conduct some in vitro studies to look at this problem.

And what we found is that the capacity of these enzymes is so high that you can knock them out by a long way before you see much of an effect. As a result of the in vitro studies that we conducted, we developed a model which actually predicted quite well to the in vivo situation, and from that model we could then say, well, if we knocked out the esterases in the intestine, what would the effect be.

And perhaps I could just show you a quick slide of the results of that. If I could have NC-11, please. Slide up, please.

What you've got here is a series of bar charts representing ganciclovir in green and valganciclovir in orange, where it's on a log scale because I tried to let you see this little tiny blip here for the bioavailability of valganciclovir.

This is what we see measured in vivo.

From the model this is what we predict, and this has given us some confidence in the model that we've developed.

So if you say, "Well, I'm going to knock out the esterases to 80 percent in the intestine," what's the effect on bioavailability, which is what I think your concerns are?

Obviously our major concerns are on valganciclovir, and you can see that the change in bioavailability, the reduction is really quite small because of the high capacity of this system, and if you knock out in the intestine, if you knock out in the liver, and in this worst case scenario where you knock out in both the intestine and the liver, the actual effect on ganciclovir is quite small.

Obviously there is a rise in the exposure to valganciclovir because the original bioavailability is quite low.

Slide off.

CHAIRMAN POMERANTZ: I'm sorry. I missed that. That was in what animal model?

DR. MORGAN: The original result, the original data were generated from human in vitro studies, in both the human intestinal S-9 and human liver S-9.

CHAIRMAN POMERANTZ: So you've never done anything like this in an animal setting of any type except for the in vitro human cells, right?

DR. MORGAN: No. We just looked at the human metabolic capacity.

CHAIRMAN POMERANTZ: Courtney?

DR. FLETCHER: An area of safety there I have some concern, individuals that have renal insufficiency. So we talked a little this morning, you know, about the data showing the need for dose adjustment and a dose adjustment algorithm that you've proposed.

If my understanding from the two studies is right, all of the patients in those trials had creatinine clearances great than 50 mLs per minute. So that with the data we have right now, we really don't have experience in dosing the drug with individuals that have creatinine clearances less than 50 where the need for adjustment becomes much more important.

So I'm wondering. I don't know. If it's in the briefing package I must have missed it, about the study in organ transplant patients that's going on, and in particular, in renal transplant patients, if you have any information there on how this dose

adjustment algorithm is working. Is it really providing the areas, you know, the exposures that you're looking for or not?

DR. STEMPIEN: We don't have any data of that type available to us yet. That study is in an enrollment phase, and, no, I'm sorry. We don't.

DR. FLETCHER: I'd just add I think that in a label there will be some need for some caution about dosing and renal insufficiency while the algorithm can be, you know, made based upon creatinine clearance. Whether it's really going to work or not is another thing, and is it going to provide the same type of safety profile?

I think that's going to be something that can be very important to make sure that that's communicated.

CHAIRMAN POMERANTZ: I think that's a good point. Clearly, sort of the elephant in the room here is how this is going to be used for transplantation, and one that we've stayed away from on purpose at this committee at this point. Maybe we'll hear more about that at a later meeting.

Other comments on safety? Yes.

DR. PISCITELLI: Just a question getting back to the anemia and neutropenia. Just a

clarification. Three, seventy-six, did that protocol allow for growth factors, like GCSF or EPO? And what kind of use was that in the two groups?

DR. STEMPIEN: The protocol did allow for that, and let me just get that slide up for you.

Slide up.

Now, we've looked at the use of colony stimulating factors after baseline up until week four. So this would reflect induction level dosing, and then from baseline all the way out to the data cut. So that would be the total experience.

Regarding support for neutropenia, 13 percent of the IV patients and 15 percent of the valgan patients required did received GCSF or GMCSF, and that percentage did increase over time comparable between the two groups.

When you look at blood products and EPO use across those two time periods balanced during induction, and then you see blood product use was balanced all the way out, this does go along with the anemia finding that we found based on lab data.

So patients had more severe anemia. Now, we don't know how this is related. It may be that the patients who we identified as having more severe anemia required support for that, and so they utilized

more EPO. So the two bits of data travel along together, and so they do support the presence of an anemia difference in that study.

But we don't have -- this does not explain why, of course, and we don't know if it will end up being a real difference or not because all patients were on valganciclovir maintenance at the time that they developed the anemia.

CHAIRMAN POMERANTZ: For the sake of discussion, I'll be one second. Is there anyone who's shading towards no on this question? Because there's another part of the discussion for those noes here to at least address before we go on with it.

Dr. Yogev.

DR. YOGEV: Well, it's not an absolute no, but I think it's very important to realize if you can put this slide back again, the clinical 205. Is that the one?

PARTICIPANT: Pretty good.

DR. YOGEV: Thank you.

CHAIRMAN POMERANTZ: Another one who memorizes slides.

(Laughter.)

DR. YOGEV: If you look at it, what's so fascinating to me, and this is, by the way, a smaller

study because just to point the original point, the 11 patients who got it, when out of 370 patients, 57 of them on maintenance had less than eight grams hemoglobin. So it depends when you start erythropoietin. Some of us like to start it even earlier not to get to that point.

So I wonder if you go to nine or something like that, you might get even higher, but if you compare four weeks versus whenever that is cut off, which we don't know exactly, is that 12 weeks or longer? There's a continuous increase in --

DR. STEMPIEN: Oh, I'm sorry. I didn't mean to interrupt. Go ahead.

DR. YOGEV: -- an increase in toxicity that whether it's compared to ganciclovir or not, it's secondary, and I think we need to mention that's where the patient is going to pay on our lack of understanding the efficacy in Question 2 with toxicity that to be left open to the physician to take the balance and make the patient aware of it, and that's where it's not an absolute no, but I need to see something done in that direction.

CHAIRMAN POMERANTZ: No, that's why I opened it up that way.

Yeah, there is a comment from the

applicant.

DR. STEMPIEN: Oh, no, I just wanted to point out you were asking about the length of time from baseline to data cut, and that would represent a median of approximately ten months of drug exposure.

CHAIRMAN POMERANTZ: Yes, now Dr. Bertino.

DR. BERTINO: Before you take that slide down, because I haven't memorized the number on it, when you say "blood products," I assume that just means packed red cells, not platelets, not fresh frozen plasma, things --

DR. STEMPIEN: Oh, exactly. It's red, red cells.

DR. BERTINO: And the other question then is patients that got EPO, could they also receive blood products? And do you know what the crossover is? Are these separate patients?

DR. STEMPIEN: These are independent measures. So, yes, indeed, it could have been one patient who may have receive both. They would be counted in both categories.

DR. BERTINO: Okay.

CHAIRMAN POMERANTZ: I think that's important because if you look at blood products in EPO and you just add up to the two right-hand columns, it