UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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ANTIVIRAL DRUG ADVISORY COMMITTEE

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MEETING

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TUESDAY,

FEBRUARY 27, 2001

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The meeting was held in the Grand Ballroom, Gaithersburg Holiday Inn, 2 Montgomery Village Avenue, Gaithersburg, Maryland, Roger J. Pomerantz, M.D., Chairman, presiding.

PRESENT:

ROGER J. POMERANTZ, M.D., Chairman

TARA P. TURNER, Pharm.D., Executive Secretary

PRINCY N. KUMAR, M.D., Member

WM. CHRISTOPHER MATHEWS, M.D., Member

RAM YOGEV, M.D., Member

BRIAN WONG, M.D., Member

PRESENT (Continued):

COURTNEY V. FLETCHER, Pharm.D., Consumer Representative

JOSEPH S. BERNITO, JR., Pharm.D., Consultant (Voting)

NEIL BRESSLER, M.D., Consultant (Voting)

DONALD S. FONG, M.D., M.P.H., Consultant (Voting)

SADEER HANNUSH, M.D., Consultant (Voting)

JOEL MINDEL, M.D., Ph.D., Consultant (Voting)

JOSE PULIDO, M.D., Consultant (Voting)

KEITH RODVOLD, Pharm.D., Consultant (Voting)

NON-VOTING MEMBERS PRESENT:

DAVID CRITTENDEN, D.M.D., Patient Representative

EUGENE SUN, M.D., Industry Representative

CHI-CHAO CHAN, M.D.

STEPHEN C. PISCITELLI, Pharm.D.

WILLIAM BOYD, M.D., FDA

ROBERT KUMI, Ph.D., FDA

KELLIE REYNOLDS, Pharm.D., FDA

JOSEPH TOERNER, M.D., FDA

THERESE CVETKOVICH, M.D., FDA

DEBRA BIRNKRANT, M.D., FDA

ALSO PRESENT:

MARY JEAN STEMPIEN, M.D., M.S.

DR. DANIEL MARTIN

DR. PANAYIOTIS GEORGIOU, Ph.D.

NOEL ROBERTS, Ph.D.

MICHAEL MARCO

C-O-N-T-E-N-T-S

PAGE

P-R-O-C-E-E-D-I-N-G-S

(9:00 a.m.)

CHAIRMAN POMERANTZ: It's nine o'clock, and I think we should get started.

I'm Roger Pomerantz. I'll be your Chairman today as we discuss a very interesting issue of valganciclovir hydrochloride tablets for the treatment of CMV retinitis in the setting of HIV infection.

What we're going to do is start off with an introduction of everyone around the table. Please give your name, your association, and your expertise.

Again, my name is Robert Pomerantz. I'm the Chief of Infectious Disease at Thomas Jefferson University. I'm a virologist.

Can we start at the left-hand all the way down at the end, please?

DR. PISCITELLI: Steve Piscitelli from Virco Laboratories.

DR. SUN: Eugene Sun from Abbott Laboratories.

DR. CRITTENDEN: David Crittenden. I'm a patient representative.

DR. WONG: I'm Brian Wong from the West Haven VA Hospital and Yale University.

DR. YOGEV: Ram Yogev, Children's Memorial Hospital, Chicago.

DR. PULIDO: Jose Pulido, University of Illinois, Department of Ophthalmology.

DR. RODVOLD: Keith Rodvold, Colleges of Pharmacy and Medicine, University of Illinois in Chicago.

DR. MATHEWS: Chris Mathews, University of California, San Diego, Department of Medicine.

DR. MINDEL: Joel Mindel, neuro-ophthalmologist at Mt. Sinai Medical School, and also a member of the Department of Pharmacology.

DR. BRESSLER; Neil Bressler, Johns Hopkins University, and I'm an ophthalmologist specializing in retina there.

DR. TURNER: Tara Turner, Executive Secretary for the Committee.

DR. KUMAR: Princy Kumar, Chief of Infectious Diseases at Georgetown University Medical Center in Washington.

DR. FONG: Donald Fong, and I'm a retina specialist and epidemiologist with Kaiser Permanente in California.

DR. HANNUSH: I'm Sadeer Hannush from the Cornea Service at Willis Eye Hospital in Philadelphia.

DR. FLETCHER: Courtney Fletcher from the Department of Experimental and Clinical Pharmacology at the University of Minnesota.

DR. BERTINO: Joe Bertino. I'm the Section Chief of Clinical Pharmacology at Bassett Health Care in Cooperstown, New York.

DR. BOYD: William Boyd. I'm a medical officer with the FDA.

DR. KUMI: Robert Kumi, pharmacokinetic reviewer, FDA.

DR. REYNOLDS: Kellie Reynolds, pharmacokinetics, FDA.

DR. TOEMER: Joe Toerner. I'm a medical officer at FDA.

DR. CVETKOVICH: Therese Cvetkovich, medical team leader in the Division of Antiviral Drug Products.

DR. BIRNKRANT: Debra Birnkrant, Acting Director, Division of Antiviral Drug Products, FDA.

CHAIRMAN POMERANTZ: Thank you.

As you see by the agenda today, we have a number of things to do this morning, in particular, hearing from the FDA about this drug, as well as the applicant's presentations.

There are going to be four questions that

will be addressed to the Committee, three of which will require an official vote from the voting members later in the afternoon.

So with no further ado, I want to turn it over to Tara Turner, our Executive Secretary, for a conflict of interest statement.

DR. TURNER: Thank you, Dr. Pomerantz.

The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the Committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting with the following exceptions.

In accordance with 18 USC 208(b), full waivers have been granted to Dr. Courtney Fletcher, Dr. Roger Pomerantz, Dr. Brian Wong, Dr. Princy Kumar, Dr. Ram Yogev, Dr. William Christopher Mathews, and DR. Chi-Chao Chan. A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of

the Parklawn Building.

In addition, we would like to disclose for the record that Dr. Joseph Bertino, Dr. Princy Kumar, Dr. Keith Rodvold, and Dr. Neil Bressler have interests which do not constitute a financial interest within the meaning of 18 USC 208(a), but which could create the appearance of a conflict.

The agency has determined, notwithstanding these interests, that the interests of the government in their participation outweighs the concern that the integrity of the agency's programs and operations may be questioned.

Therefore, Dr. Bertino, Dr. Kumar, Dr. Rodvold, and Dr. Bressler may participate fully in today's discussions.

With respect to the FDA's invited guests, Dr. Steve Piscitelli and Dr. Eugene Sun have reported interests which we believe should be made public to allow the participants to objectively evaluate their comments.

Dr. Piscitelli would like to disclose for the record that he is participating in a series of Roche sponsored lectures on therapeutic drug monitoring in HIV.

Dr. Sun would like to disclose for the

record that he is employed full time with Abbott Laboratories.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previously financial involvement with any firm whose products they may wish to comment upon.

Thank you.

CHAIRMAN POMERANTZ: Thanks, Tara.

And let's get right into it then. We're going to start with Debra Birnkrant from the FDA, Acting Director, Division of Antiviral Drug Products, introduction and opening remarks.

Debra.

DR. BIRNKRANT: Thank you very much, and good morning.

I can use an antiviral myself.

(Laughter.)

DR. BIRNKRANT: I'd like to welcome members of the Division of Antiviral Drug Products

Advisory Committee, members of the Ophthalmic Subcommittee of the Dermatologic and Ophthalmic Drugs Advisory Committee, guests, and representatives from Roche.

Today we will be discussing NDA 21304, valganciclovir for the treatment of CMV retinitis. Following my brief opening remarks, Dr. William Boyd of the Division of Anti-Inflammatory Analgesic and Ophthalmic Drug Products will present a regulatory perspective with regard to approvals of CMV treatment.

Then we will proceed with the applicant's presentation. This will be followed by a brief period of questions for clarification purposes, and the FDA will present their regulatory perspective on the safety and efficacy data supported in this application, as well as pharmacokinetic data to support maintenance therapy.

This will also be followed by a brief period for questions for clarification purposes.

In the afternoon, we will have an open public hearing and questions for the Committee to discuss.

Next slide.

To set the stage for today's meeting, I'd like to make a few comments with regard to the

regulatory background of this NDA under discussion today. The development of valganciclovir coincided with the development of highly active anti-retroviral therapy for the treatment of HIV infected subjects.

With the implementation of HAART, we saw a decline in the incidence of CMV retinitis. This had a major impact on Roche's development plan for CMV retinitis for valganciclovir, and in their background document that they supplied to the Committee, they stated that in the early '90s for a clinical trial for CMV retinitis of 160 patients, it would take approximately 15 months at approximately 15 sites, but for that same size trial in the late 1990s, it would take twice as long, and it would have to be conducted at least at twice as many sites.

So because of the impact of the decline of CMV retinitis in the setting of HAART, Roche postponed their plans for development of valganciclovir in 1997. However, the Division of Antiviral Drug Products asked Roche to continue development because of the medical need for an oral drug with greater bioavailability than what was currently on the market or just greater bioavailability for CMV treatment.

Roche then expanded their Phase 2 study of CMV retinitis and agreed to supply additional data to

support a CMV retinitis indication, as well as they agreed to supply data from a solid organ transplant study, as well.

So in the end, agreement was reached that Roche would continue the development of valganciclovir both for CMV retinitis and for prevention of CMV disease in solid organ transplant therapy.

Next slide.

I'd like to represent my previous comments graphically. This graph is taken from an article in the New England Journal of Medicine that appeared in 1998 looking at the declining morbidity and mortality of CMV retinitis in the setting of HAART.

The lead author is Palella in this study.

What you can see is a graph of three major opportunistic infections, CMV, MAC, and PCP. The incidence between the years 1994 and 1997.

Next, next.

With the initiation of HAART following approvals of indinovir, sequinovir, and ritanovir, you can see in red in the next representation a decline in the incidence of CMV retinitis between the years '94 and '97, from 17 per 100 person-years down to less than three per 100 person-years in 1997.

Next slide.

So not only did the implementation and initiation of HAART impact the development plan for valganciclovir, it also had an impact on the primary endpoint in a clinical trial designed to study CMV retinitis with valganciclovir, and that is historically the primary endpoint for CMV retinitis treatment was time to progression, but in the era of HAART this had to change.

It had to change because of the impact of a new HAART regimen on disease progression itself. So Roche sought consultation with outside ophthalmic or ophthalmologic experts, and they proposed an endpoint of the proportion of patients with disease progression at week four, and FDA accepted this endpoint.

Next slide.

With regard to the medical need for another anti-CMV treatment, on this slide you can see that there are six currently available, approved drugs to treat CMV retinitis. We start with ganciclovir intravenous, which was approved in 1989. There are two other intravenous products, foscarnet and cidofovir.

Then we have the ganciclovir implant, and an intraocular injectable.

The medical need relies on the issue

related to a formulation of a drug that would not require an invasive procedure or maintaining an indwelling catheter for patients to receive a particular product, and with the development of valganciclovir, you have an orally bioavailable product that's has tenfold greater bioavailability than the currently approved ganciclovir capsules.

And with that, I'd like to say that the division is looking forward to the deliberations this afternoon and the discussion throughout the day of our Advisory Committee assembled here, and I would now like to introduce Dr. William Boyd, our ophthalmology consultant at the FDA, who will present a regulatory overview of approvals for CMV treatment.

Thank you.

DR. BOYD: Good morning. This will just be a brief presentation on approved products for the treatment of CMV retinitis in immunocompromised patients.

We've already gone through the list of approved products, which are Cytovene IV, Foscavir injection, Cytovene capsules, the Vitrasert implant, Vistide injection, and Vitravene IV injection.

Cytovene IV, which is ganciclovir, was approved on June 23rd, 1989. Two of the clinical data

sources for approval were a randomized controlled trial studying immediate versus delayed treatment in 42 subjects, and a non-randomized retrospective immediate versus delayed treatment study in 41 subjects.

Let me just take a moment to explain what we mean by immediate versus delayed treatment. After randomization, if you were randomized to delayed treatment, you did not receive treatment right away. You were monitored on a weekly basis, and at the first sign of advancement of disease, treatment was initiated.

Next slide.

The primary endpoints for these studies were time to progression of CMV retinitis. The primary endpoint analysis in study number one, and this relied on mask photographic evaluation, was the median time to progression of 50 days for immediate treatment and 14 days for delayed treatment.

In study number two, there was a median time to progression of 71 days for immediate treatment versus 29 days for delayed.

Foscavir injection was approved on September 27th, 1991. Among the clinical data sources for approval was a randomized, open label, controlled

trial studying immediate versus delayed treatment in 24 subjects.

The primary endpoint was a time to progression of CMV retinitis. In the primary endpoint analysis, there was a median time to progression of 93 days for immediate treatment versus 22 days for delayed treatment, and again, this was based on a mask photographic analysis.

Cytovene capsules were approved on December 22nd, 1994. It's not approved for induction therapy due to poor bioavailability. It's only five percent available. The study design for the maintenance indication relied on three randomized open label trials with Cytovene IV as a comparator for a total of 505 subjects.

The Vitrasert implant was approved on March 4th, 1996. Among the clinical data sources for approval were a randomized, parallel, ganciclovir implant versus ganciclovir IV trial in 188 subjects, and the primary endpoint was a time to progression of CMV retinitis.

The primary endpoint analysis demonstrated a median time to progression of 210 days for the implant versus 120 days for IV ganciclovir, and this was based on mask photographic analysis.

Vistide injection was approved on June 26th, 1996. Among the clinical data sources relied upon for approval was a randomized, open label, controlled trial studying immediate versus delayed treatment in 48 subjects. The primary endpoint, again, was time to progression of CMV retinitis.

The primary endpoint analysis demonstrated a median time to progression of 120 days for immediate treatment versus 22 days for delayed treatment, and again, this relied on mask photographic analysis.

Vitravene IV injection was approved on August 26th, 1998, and among the clinical data sources utilized for approval were limited open label, controlled clinical studies studying immediate versus delayed treatment and ADIs. The primary endpoint, again, was time to progression of CMV retinitis.

The primary endpoint analysis demonstrated a median time to progression of 80 days for immediate treatment versus 14 days for delayed treatment, and again, this relied on mask photographic analysis.

Just, again, a brief summary of the approved products: Cytovene IV, Foscavir injection, Cytovene capsules, Vitrasert implant, Vistide injection, Vitravene IV injection.

It's been mentioned before that there's

not an oral agent available for both induction and maintenance therapy. There is morbidity associated with catheter use for the IVs, as well as the need for a surgical procedure for the Vitrasert implant.

That concludes my brief presentation. I did have one other slide. This was a previous version of my presentation for today, and there's a second version you should have on the disk. If we don't, that's okay. I think it's coming.

Okay. All right. Thank you.

CHAIRMAN POMERANTZ: Thank you.

We're remarkably ahead of schedule. We'll see if that continues.

The sponsor will now start. Mary Jean Stempien will give the introduction from Roche, Director of Medical Research.

DR. STEMPIEN: Good morning. I'm Dr. Mary Jean Stempien. I'm one of the physicians on the valganciclovir project team, and I'm very pleased to start off Roche's presentation this morning.

Could I have the projector on, please? Okay. Thank you.

Roche comes before this Committee today seeking a recommendation for approval of valganciclovir, valganciclovir to be indicated for the

treatment of CMV retinitis in patients with AIDS.

Following my brief introduction, Dr. Dan Martin will come up and give the clinical background. Dr. Martin is an ophthalmologist at Emory, and he was the lead principal investigator on our primary efficacy and safety study in our package, and then I will return and discuss the development program for valganciclovir and the study results.

We also have with us two outside experts, Dr. Gary Koch, who is a professor of biostatistics at Chapel Hill, and Dr. Nancy Sambol from UCSF, who's an expert in population PK. They're not presenting, but they're here in case questions come up during Q and A that are relevant, and they would be happy to participate in that.

I'd now like to introduce Dr. Dan Martin.

DR. MARTIN: Good morning. In the next few minutes I'll cover the clinical features of CMV retinitis, the impact that highly active anti-retroviral therapy has had on this disease, and the treatment options currently available for patients who present with CMV retinitis.

This is a photograph of what you see when you look in the back of the eye. This is a photograph of a normal retina. It's the right eye. Here's the

optic nerve, and here is the fovea. These two structures are the most important structures in the back of the eye.

The fovea is the only portion of the retina that is able to resolve visual acuity of 20-20.

Throughout this presentation you will hear us refer to zones of retinal involvement by CMV. When CMV retinitis threatens the optic nerve or the macula, specifically, when it extends to within 1,500 microns from the optic nerve or 3,000 microns from the fovea, we designate that as Zone 1 disease.

If CMV retinitis involves the retina outside this area to this circle, defined by the ampule of the vortex veins seen here and here, that's designated as Zone 2, and then the more peripheral retina is Zone 3.

This patient has active CMV retinitis that involves peripheral Zone 2 and Zone 3.

This is a photograph of the left eye of a patient with active CMV retinitis located in Zone 1 threatening the optic nerve and the fovea. The clinical appearance here is fairly typical. CMV infection of the retina causes a full thickness, white, opaque retinal necrosis with some scattered intraretinal hemorrhage. The area involved by CMV,

the vision in this area is permanently lost.

The CMV can establish itself anywhere in the retina, and once it does, it typically spreads slowly across the back of the eye. People liken it to a brush fire, leaving in its wake atrophic, necrotic retina that is devoid of visual function.

If CMV retinitis is allowed to continue across the eye, it will progress to slowly involve all of the retina, leading to complete loss of vision in the eye.

The goal of therapy then is to prevent or to stop this progression of retinitis and to render this active, white, necrotic lesion completely inactive.

Prior to the development of or the advent of HAART, approximately 30 percent of patients with a CD4 count less than 50 could be expected to develop CMV retinitis. In 1996, with the introduction of sequinovir, ritanovir, and indinovir, we had for the first time the opportunity to profoundly suppress HIV viral load.

Concomitant with that suppression, there can be a rise in the CD4 count, and when that occurred in a large number of patients, it reduced the number of patients at risk for CMV disease, and as a result,

there has been a substantial decline in the incidence of CMV retinitis.

Now, with all of the success that we've had with HAART, one may ask why do we need a new treatment for CMV retinitis, and the answer is as follows.

Despite the success, we continue to see new cases of CMV disease, and this incidence may increase as patients fail their anti-retroviral therapy.

For patients who are on HAART, the development of CMV retinitis represents a failure of their HIV therapy, and those patients require anti-CMV therapy usually consisting of an induction followed by some period of maintenance.

I want to emphasize that point because I think a lot of people have mistaken ideas about how HAART has impacted this disease. Yes, HAART has reduced the risk for CMV disease, reduced the incidence for it, and, yes, HAART impacts potentially the duration of maintenance therapy that may be required in a patient, but for the individual who presents with newly diagnosed CMV retinitis, if they are on HAART, it's almost irrelevant. That patient has failed immunologically to allow this infection to

occur.

You may be able to adjust one's HAART regimen and hopefully result in improvement of their CD4 count, but that event is something that takes place down the road, and at least for three, six months, and sometimes indefinitely, those patients will require anti-CMV therapy. Simply manipulating one's HAART regimen, no one uses that as a primary treatment for CMV retinitis.

Now, you've already heard the available treatment options, and they are presented here. All of them are effective to differing degrees, but none of them are ideal for differing reasons.

Intravenous ganciclovir, followed by intravenous ganciclovir maintenance requires an indwelling catheter which is associated with a negative impact on quality of life and a substantial risk for sepsis.

Oral ganciclovir has limited bioavailability, cannot be used as induction therapy, requires t.i.d. dosing, and has a relatively high daily pill burden.

The ganciclovir implant and usually used in conjunction with oral ganciclovir is quite effective, but is a surgical procedure, and there are

risks, as is true with any surgical procedure.

Intravenous foscarnet has some of the same issues as intravenous ganciclovir in that it requires a catheter, long infusion times, risk of sepsis, a negative impact on quality of life, and there's also the issue of renal toxicity.

Cidofovir, while not requiring daily intravenous infusions, has a substantial risk for renal and, at least in my hands, ocular toxicity, and approximately 50 percent of patients will develop an allergy to probenecid, a medicine that is required to be given concomitant with cidofovir.

Therefore, the development of an oral agent that is effective for both induction and maintenance treatment that has no intravenous catheter requirement, a convenient dosing regimen, and an acceptable safety profile represents a major unmet medical need in the treatment of this disease.

As an investigator in the primary efficacy trial, which Dr. Stempien will be presenting in just a few minutes, I've had the opportunity to treat a number of CMV retinitis patients with valganciclovir.

This is the first patient actually who was enrolled in this study and the first patient ever treated with valganciclovir for CMV retinitis. He had

failed all anti-retroviral therapy presented with a small patch of newly diagnosed CMV retinitis located in Zone 2. You can also see the edge of it here, was randomly assigned to valganciclovir induction, began taking two 450 milligram tablets twice daily; and at two weeks, there was still some retinal opacification, as is typical in most induction scenarios, but by four weeks the lesion was essentially and completely inactive, and by eight weeks there's no sign of active infection.

We were quite excited by this. This was the first time that a patient with newly diagnosed CMV retinitis had had his or her disease rendered inactive by administration of an orally administered compound.

This is another present who presented with newly diagnosed CMV retinitis located in his nasal peripheral retina; was randomly assigned to valganciclovir induction; and at two weeks, as you can see, the border, which is seen here, is now for the most part inactive. There's still some opacification of the retina within the lesion, and by four weeks the entire lesion has cleared. There has been no progression of disease, and now there's a scar in the area of previous infection.

I'll ask Dr. Stempien to return to

continue our presentation.

DR. STEMPIEN: Thank you, Dr. Martin.

IV ganciclovir is a first line treatment for CMV retinitis. It has been approved in the U.S. since 1989. It's currently indicated for the treatment of retinitis in immunocompromised patients and for the prevention of CMV disease in transplant patients at risk, and it has a very well described efficacy and safety profile that has accumulated over 12 years of clinical use.

Oral ganciclovir has been available in the U.S. since 1994. It is indicated for maintenance treatment only of CMV retinitis in immunocompromised patients and for the prevention of CMV disease in solid organ transplant patients and in HIV patients at risk.

And as you have heard, it has been limited by its bioavailability and the fact that it needs to be part of a t.i.d. dosing regimen.

Ganciclovir is preferentially phosphorylated in CMV infected cells via a viral protein kinase, UL-97, and after three phosphorylations it becomes ganciclovir triphosphate, which is the active moiety. And, again, ganciclovir triphosphate inhibits viral DNA polymerase, and the

active moiety has an intracellular half-life of approximately 18 hours.

Valganciclovir is a pro drug of ganciclovir, and it's distinguished from ganciclovir by the presence of this valyl ester group. Here are the key characteristics of valganciclovir.

Most importantly, we can achieve ganciclovir exposures measured as systemic area under the curve following a 900 milligram dose of valganciclovir that are similar to the exposures that we can achieve with standard IV ganciclovir dosing given as five milligrams per kilogram.

The reason we can do this is because of the improved bioavailability. It is tenfold higher than what we can achieve with our current oral ganciclovir formulation. So the bioavailability is approximately 60 percent.

And importantly, just a small amount, less than two percent of the absorbed dose actually appears as parent compound, valganciclovir, in the plasma, and it has a relatively short half-life.

And we have developed valganciclovir as a 450 milligram tablet.

The next few slides will show you the comparative PK profiles of our ganciclovir

formulations and show you how they compared to valganciclovir. Here's a typical IV ganciclovir profile. This is on a semi-log scale, and here is oral ganciclovir, which is dosed three times daily, and as you can see, it has a much lower C-max than IV ganciclovir.

And here I have superimposed the PK profiles for valganciclovir. This is the curve for ganciclovir following a valganciclovir dose, and this is a 900 milligram valganciclovir dose.

Here's the parent compound, valganciclovir, which appears briefly in the plasma and is cleared rather quickly.

The C-max of valganciclovir actually falls between that of IV ganciclovir and oral ganciclovir. Likewise, the C-min is bracketed by that for oral and for IV. And most importantly, the area under the curve for the ganciclovir delivered following a valganciclovir dose is very similar to the area under the curve that we achieve from IV ganciclovir dosing.

Now, here are the PK parameters that go along with the curves that I've just showed you. The IV ganciclovir 24-hour AUC is approximately 26 compared to oral ganciclovir, which is about half that, or 13.

Now, both of these formulations are approved for maintenance therapy, and they are both efficacious, although there is a twofold difference in area under the curve.

If you look at the difference between C-max though for the two formulations, you see a much bigger difference. There's a tenfold difference between IV ganciclovir and oral ganciclovir for both C-max and for C-min.

So based on these PK considerations, it appeared to us that it was most likely that area under the curve was going to be the PK parameter that would best correlate with efficacy.

And, importantly, following valganciclovir dosing, we do achieve an area under the curve that is very similar to what we achieved following IV ganciclovir dosing, and the C-max following valganciclovir is about 60 percent that of IV ganciclovir.

In addition, we did do some PK/PD work from another ganciclovir study. We explored PK/PD in a study GAN-2226, which was a dose ranging maintenance study that included both IV ganciclovir dosing and three different doses of oral ganciclovir ranging from three grams per day to six grams per day.

And we utilized a population PK approach, and while that methodology did have some limitations, the conclusion of the result pointed to area under the curve as being the most important PK parameter to correlate with efficacy, and in that study efficacy was measured as time to progression.

This is completely consistent with our expectations going in simply based on consideration of the PK profiles for oral ganciclovir and IV ganciclovir.

So based on these considerations, we targeted for valganciclovir an AUC of approximately 26, which corresponds to the median AUC that we achieved with IV ganciclovir dosing, and we found in a dose ranging study that we could achieve that target AUC with a 900 milligram dose of valganciclovir.

So that during maintenance treatment, looking for that AUC of 26, that would correspond with a 900 milligram dose of valganciclovir, and then during induction dosing, which is typically given twice daily, that would double the AUC and double the dose of valganciclovir to 1,800 milligrams daily.

Valganciclovir is rapidly hydrolyzed to ganciclovir by intestinal and hepatic esterases, and we have not detected any other metabolite of

valganciclovir, other than ganciclovir.

Therefore, all ganciclovir drug interactions that have been described to date would certainly apply to valganciclovir, and likewise because ganciclovir is predominantly renally cleared, patients with renal impairment would require a dose adjustment if they were using valganciclovir.

So the PK profile of ganciclovir following valganciclovir dosing provided the potential for a therapeutic alternative to IV ganciclovir treatment of retinitis both for induction and for maintenance. It would allow us to avoid the risks associated IV access required for IV ganciclovir therapy, and it would provide a simple oral regimen that could improve patient adherence during longer term maintenance dosing.

Now, as you have already heard, our development program ran into an early challenge when we undertook a pilot study early in our program to explore the potential efficacy of valganciclovir in an induction treatment setting because this had never been done, and we started enrolling this study in January 1997, and that is when we really began to appreciate the full impact of HAART.

This pilot study intended to enroll 70

patients, and in four months utilizing 17 sites we were only able to enroll 11 patients.

You have seen a similar graphical representation from a different reference as to what was happening as a result of the introduction of HAART. This is another reference, but it points to the same phenomenon, and all of the opportunistic infections associated with the HIV were decreasing dramatically after the introduction of HAART.

This is where we were planning our pilot study, and here is where we were when we were starting enrollment, and this represent the decline in CMV retinitis, newly diagnosed CMV retinitis.

So at this point in time, we really had to rethink our development program, and although we had planned a traditional program with a pilot study followed by Phase 3 studies, we realized that that would not be possible in this environment, and we certainly appreciate the collaboration that we enjoyed with FDA in trying to work this through and figure out a reasonable way to proceed and continue development.

This is the program that we ended up with. Our package includes data on nearly 500 patients. We did a standard series of clinical pharmacology studies, and we conducted two therapeutic studies that

enrolled 372 patients.

Our primary efficacy and safety study is WV-15376, and I may simply refer to it as "376" as we go forward.

This was the pilot study. This started out as the pilot study, and we converted it to our primary efficacy and safety study so that we could maximize the contribution of the patients who had already enrolled.

And then to supplement that, we conducted an open label safety study, WV-15705, or I may just refer to it as "705," and that enrolled 212 subjects.

Our 372 patients which we enrolled in our two therapeutic studies enrolled in approximately 26 months utilizing 50 sites and all of the countries pictured on this slide.

The development program for valganciclovir builds on the proven efficacy of ganciclovir, and because of that, we felt that the question of primary interest to the treating community would be how does valganciclovir compare to IV ganciclovir in terms of efficacy and safety.

To answer this question, we decided to study it in the induction setting. We felt that the induction setting would represent the highest efficacy

hurdle for any new CMV retinitis treatment, and we also felt that if we could adequately establish efficacy for valganciclovir in induction, that that information coupled with consideration of the PK profiles would certainly allow us to expect that valganciclovir would have efficacy in maintenance as well.

I'll take you through our studies now and the results. This is our primary efficacy and safety study, 376. We randomized 160 subjects to induction treatment with either IV ganciclovir or valganciclovir. The IV ganciclovir group received standard dosing, five milligrams per kilogram, twice daily for three weeks, and at that time we decreased to once daily, and the valganciclovir group received 900 milligrams of valganciclovir twice daily for three weeks, again, decreasing that to once a day at the completion of three weeks.

The randomized comparison in the study was conducted between baseline and week four. So we measured our primary endpoint at this point, the end of week four, and at that time all patients continued on open label valganciclovir maintenance, receiving 900 milligrams once daily so that we could continue to collect safety information and some secondary

endpoints.

The primary endpoint of this study was the proportion of patients who demonstrated progression of their retinitis by week four, and that progression was defined in a very standard way: movement of the border of the lesion by at least 750 microns along a 750 micron front or the appearance of a new retinal lesion of a certain size, and this was assessed by retinal photography.

And the retinal photography assessment methods were very standard. We utilized the Wisconsin Reading Center. We obtained full field bilateral photographs at each ophthalmology visit, and those photos were archived, sent to the Wisconsin Reading Center. They were scored by an experienced grader who was masked to treatment assignment, and the reading center was not involved otherwise in the conduct of the study.

And the reader scored these photos for progression, distance of border movement, and various measures of border activity.

The next several slides deal with some of our statistical analysis considerations in the 376 study. The question that we were interested in answering was: is the efficacy of valganciclovir

similar to and specifically no worse than IV ganciclovir for induction therapy?

We chose a noninferiority approach to address this. The noninferiority test utilizes the lower bound of the confidence interval. Now, in this trial we were looking at treatment group differences, the proportion of patients in the IV group minus the proportion of patients in the valganciclovir group who progressed, and we were looking at the confidence interval around that difference.

We chose a noninferiority limit D or delta of minus .25, and that was chosen to represent what we felt was a clinically acceptable treatment group difference, and we settled on that D following consultation with several outside experts, ophthalmologists and treating physicians who were helping us to design the study. There were also some sample size considerations that went into that selection.

The next few slides show this in a more visual way that I think will help. Here is the treatment group difference. If the treatment group difference was zero, it would fall along this line. Here is our delta, and so if the lower bound of the confidence interval was to the right of this line, we

would be able to conclude that valganciclovir was no worse than IV ganciclovir in induction treatment.

Here are some hypothetical results just to illustrate our interpretation. In all three of these cases because the lower bound of the confidence interval is to the left of this line, we could not make that conclusion.

With these scenarios, in all three cases because the lower bound of the confidence interval is to the right of this line, we could conclude that valganciclovir was no worse than IV ganciclovir.

And here are the results that we achieved in our 376 study: essentially no treatment group difference and a narrow confidence interval that certainly fulfills our prespecified limit set forth in the protocol.

Now I'll take you through the actual data in more detail. The 376 study randomized 80 patients in each group, predominantly men in their late 30s. This is consistent with previous CMV retinitis studies, and the groups were well balanced with respect to ethnic background.

The groups were also balanced in terms of CD4 count, HIV load, and CMV load at baseline. We did have two imbalanced that are noted here. A higher

percentage of patients in the IV group had a qualitative, positive CMV's PCR in their plasma, and also had positive CMV cultures.

Since culture results were not done in real time, we did not have this information at entry into the study. So although we do have this imbalance in the study, this imbalance could only have been due to chance.

In terms of HIV therapy at baseline, well balanced. Again, the majority of patients were taking protease inhibitors. A certain percentage in each group were protease inhibitor naive, and also a small percentage in each group had not received any anti-retroviral treatment.

The retinitis presented in a very typical way. Twenty-four percent of the patients in each group had Zone 1 involvement at time of entry, and 25 percent of the patients had bilateral disease, and a very high percentage, 89 and 85 percent, had active lesions coming into the trial.

The ITT study population, which was utilized in some of our longer -- some of our analyses that went beyond the four-week time period, utilized all of the randomized subjects, but the primary endpoint and several of our secondary endpoints

utilized a standard efficacy population, which was predefined in the protocol.

We ended up excluding seven patients from each group, and the reasons for exclusion were either that the patient's retinitis could not be confirmed by photo or that subject simply did not contribute any efficacy data after baseline.

Here's the primary endpoint. We found that we had comparable efficacy at week four in both treatment groups. Seven patients in each arm experienced a photo progression by the end of week four.

The proportion who progressed was ten percent in the IV group and essentially ten percent in the valgan group, the difference, .1 percent, and here's the 95 percent confidence interval with the lower bound of the confidence interval well within the boundaries that were set out in the protocol.

I might also say that we did conduct an intend to treat analysis of the same endpoint using all of the randomized patients, and the results are the same.

We looked at progression at week four by the zone of involvement at baseline, and the zone of involvement at baseline did not have an influence.

Patients who had Zone 1 disease coming in, of the 16 who had Zone 1 coming in, 13 percent progressed in the valgan group -- in the IV group; 11 percent progressed in the valgan group. Peripherally they were also balanced if they had a Zone 2 or Zone 3 lesion.

We assessed visual acuity and functional vision. The visual acuity during the first several weeks of the trial were discussed in your backgrounder. Here is a slide that captures visual acuity and functional vision all the way out to study cutoff. So this represents a median of approximately ten months of study drug treatment and a comparable proportion of patients in both groups experienced some decrease in visual acuity or a decrease in functional vision.

Here's the more traditional endpoint for CMV retinitis studies which we did include as a secondary endpoint, the time to progression by photographic assessment. Now, here is the valganciclovir group, and here is the IV group. These curves are similar.

It's important to note that after week four all patients are on valganciclovir. So the only treatment difference is occurring during the first four weeks of the study.

Our conclusion from this set of graphs was that there was no indication -- we took reassurance from this analysis. We felt that there was no indication that valganciclovir induction treatment had in any way had a negative impact on time to progression later in time, and we thought that was very important.

In terms of CMV cultures, as I mentioned before, there was a baseline imbalance, but by the end of week four we had a significant and comparable antiviral effect in both groups, and that also applied to the CMV PCR analysis where a very small percentage were PCR positive at the week four time point.

Now, we did have one issue in the study that we did look at closely after our analysis. When you look at time to withdrawal by Kaplan Meier, it does appear that the curves are separating, and it looked as though it was happening after the completion of the four-week randomized phase of the study, and so we took a closer look at all of the patients who withdrew between week four and approximately week 12 to see, to really understand what was driving those withdrawals and to make sure that those withdrawals did not have any implications on the conclusions of our primary efficacy analysis.

The reasons for withdrawal were varied. They were not all related to safety, and the adverse events that did prompt a withdrawal during this time interval varied.

What we found, our conclusion was that we could not discern a pattern to these withdrawals, and it's also important to note that of the four valganciclovir patients who withdrew because of insufficient response, what was happening here is that the ophthalmologist -- in three of the cases, the ophthalmologist called a progression, and the patient withdrew.

In fact though, those three patients were already counted as primary endpoints in the primary efficacy analysis because they had a documented photo progression that had already been called by the reading center. So they were counted as endpoints.

And just to make certain that we didn't have an issue here, we did a time to progression or withdrawal analysis, and you can see that the curves are very similar. What happened was that the increased number of withdrawals in the valganciclovir arm during that time period ended up being counterbalanced by the increased number of ganciclovir patients who experienced a photographic progression

during the same time interval. So when you do this analysis, the curves come back together.

We collected PK information during this study in a subset of patients, and the next few curves will show you the PK results.

Here are curves for following IV ganciclovir dosing, and then this is ganciclovir from valganciclovir. This is during week one. This reflects induction level dosing, and because we're dosing b.i.d., that's why the curves only go out to 12 hours. So this is the dosing interval during induction.

And during week four, patients were now taking the maintenance level dosing, and so the dosing interval goes out to 24 hours. That's why these curves extend. Again, IV, and then this is valganciclovir.

Now I've put the two curves together, and you can see between week one and week four, the curves are fairly superimposable. This is because there is no accumulation, and I've also added to this slide the parent compound.

So here is valganciclovir appearing again briefly and with a short half-life. These curves should look very similar to the curves that I showed

you earlier in the presentation, and they are, and we're very happy about that.

Here are the numbers that go along with the curves I've just shown you. So at week one, this is induction level dosing. This is maintenance level dosing, b.i.d. and q.d.

The slide shows you the AUCs as dosing interval AUCs so that they'll be easier to compare. So this is a 12-hour AUC. This is a 24-hour AUC. Both at week one and at week four the AUCs that we achieved for IV dosing and valganciclovir dosing were very similar, and they also were similar across the time points because there's no accumulation.

And here are the C-maxes, just what we would have expected: approximately ten with IV and about 60 percent of that with valganciclovir at both time points.

Now I'll cover the safety aspects of our program. During the randomized phase of 376, we had three patients who withdrew because of a safety related reason, two an done. One patient left because of a neutropenia. One patient died of lymphoma, and another patient died from PCP.

And during the randomized phase, the adverse event profile that we found with

valganciclovir was completely consistent with what we know about IV ganciclovir and were the most common events that are associated with IV ganciclovir.

So no new toxicities have been detected to date that have not already been described with ganciclovir. Diarrhea occurred somewhat more frequently in the valganciclovir arm compared to IV, and oral candidiasis was more frequent in the valganciclovir arm compared to IV, and we don't have a ready explanation for that if, in fact, that's a true finding.

Very importantly, intravenous catheter related adverse events were very much reduced in the valganciclovir arm, and this is consistent with what we've seen before when we've compared IV valganciclovir and oral ganciclovir maintenance treatment.

If you can get away with dosing without an IV, you really do reduce some morbidity associated with intravenous catheters.

Since ganciclovir has hematologic toxicity associated with it, we did look at minimum AMC, minimum hemoglobin, and minimum platelet count, and during the randomized phase of the study, the two treatment groups were in good balance for those three

parameters.

Now, I've shown you the safety during the randomized portion of 376 when we had a direct comparison to IV. Beyond this time point, all patients are on valganciclovir. So to give you the most complete picture of valganciclovir;s safety, we have pooled the safety data from the 376 study and from that second safety study that we conducted, 705.

So let me just show you the 705 design, and then I'll show you all of the safety results. Seven, oh, five, didn't randomize, just enrolled 212 patients. It was a single arm study. Everyone received 900 milligrams once daily of valganciclovir, and they were able to receive an induction course of valganciclovir if needed during this study.

In terms of the valganciclovir exposure during both trials all the way out to the clinical cutoff for our NDA, you can see that the median times on treatment are much longer than have been described with previous CMV retinitis studies, and this is because patients are living longer. This is clearly related to HAART.

But it allows us to accumulate safety data over a longer duration of treatment, and so although the total number of patients that we have in our

package's safety database is somewhat less than what you would expect for a new chemical entity, nonetheless because we have these nice, long durations -- and, in fact, these two studies are still running, so we're still continuing to collect safety information -- that gives us a great level of comfort in our safety database.

Here are the adverse events during the maintenance treatment phase out to clinical cutoff, and this column represents the experience of the combined safety database, 370 patients who received valganciclovir during one of the two trials.

Again, the adverse events that you see are adverse events that are associated with ganciclovir. They're the adverse events that we saw during induction treatment.

Now, just to help put this in context a little bit, I have included on this slide some historical information taken from relevant previous ganciclovir studies. It's important to know they were for the most part all pre-HAART, and they were much shorter in duration than our current study. So I think this represents a worst case comparison.

I have added ganciclovir, three gram, information. This is oral ganciclovir, three grams;

IV ganciclovir; and some placebo experience, not truly placebo, but it comes from our 2304 implant study where patients received a local implant and an oral placebo. So we feel comfortable that we can consider these adverse events to represent placebo events in this column.

Just two points to make. Diarrhea, which was more common in the randomized arm in the valganciclovir group, you can see that when you pool the patients, it's about a third of the patients who experienced diarrhea, and that's in line with what we've seen with our oral ganciclovir formulation.

The oral candidiasis, when you pool, is about 17 percent; still looks somewhat higher than the other two ganciclovir formulations, and maybe a little bit closer to previous placebo experience.

Looking at laboratory abnormalities for the combined patient population, they were balanced in terms of these levels of neutropenia, anemia, and thrombocytopenia.

So we've concluded that the safety profile of valganciclovir is comparable to ganciclovir. There have been no unexpected toxicities observed, and the most frequent, severe, or serious events are neutropenia and anemia, and the frequency of

pancytopenia is similar to what we've seen with IV ganciclovir.

During randomized treatment where patients received either IV ganciclovir or valganciclovir, we found that the CMV retinitis progression rates were equal; that there was a clear and comparable antiviral effect, significantly fewer IV catheter related and serious adverse events in the valganciclovir group, and the other adverse event rates were similar.

Valganciclovir provides systemic exposures that are comparable to IV ganciclovir both in the induction and the maintenance treatment setting, and similar long-term rates of retinitis progression and adverse events were seen regardless of the randomized induction regimen.

Valganciclovir is an oral pro-drug of ganciclovir with high bioavailability. It is a better way to give ganciclovir, and it provides an effective and convenient treatment for CMV retinitis.

And that concludes our presentation. Thank you, and we'd be happy to take questions.

CHAIRMAN POMERANTZ: Thank you, and thank you for a very nice overview and presentation.

So we can take questions now for Dr. Stempien or Dr. Martin or any one of the other people

that Roche has brought here from the Committee.

DR. KUMAR: I have a question.

CHAIRMAN POMERANTZ: Sure, Princy.

DR. KUMAR: Can I ask this question of Dr. Martin?

In the data that was provided to us in our booklet there was a marked difference in progression based on fundoscopic examination versus ophthalmological examination. I know this bias was seen in prior studies, and what you had implied was this was all from bias from the ophthalmologist.

My question to you is you chose ophthalmologists that were very well trained in evaluating CMV retinitis. Is there anything other than bias that could explain this difference?

I'm just troubled because if you looked at the fundoscopic evaluation by very trained ophthalmologists, you had 16 percent progression in the valganciclovir versus one percent progression in the IV ganciclovir arm, and you had said in your written statements that that could all be explained on the basis of bias.

DR. MARTIN: We believe, I believe that that observation is primarily due to bias. As you pointed out, that's been observed now in a number of

studies. It was seen in 1653, the original oral ganciclovir trial, and if you look at the SOCA trials, there's always a discrepancy between the SOCA, representing the studies with the ocular complications of AIDS, a very experienced group of ophthalmologists following patients with CMV retinitis. We always miss it.

I mean, when you look at the ophthalmic progression rates, they're always different than the photographic progression rates, and so for that reason and randomized clinical trials, it is the photographic progression -- it's pretty hard to argue with a photograph -- that is the standard.

DR. KUMAR: Can I ask you a follow-up question?

DR. MARTIN: Sure.

DR. KUMAR: Can Zone 3 disease be adequately photographed?

DR. MARTIN: No, it can't.

DR. KUMAR: So can that explain then the difference?

DR. MARTIN: It could.

DR. KUMAR: Can you say how much?

DR. MARTIN: It could, absolutely. In that photo montage, that actually represents more Zone

3 than I think just about I've ever seen. You can get a little bit beyond Zone 2, but most of Zone 3, because of the optics, you can't photograph it.

So, yes, that is one possible explanation, that there were events taking place in Zone 3, but I think that that would be the minority of cases.

DR. KUMAR: Can I ask one more question?

CHAIRMAN POMERANTZ: One more.

DR. KUMAR: Thank you.

(Laughter.)

DR. KUMAR: This is to Dr. Stempien.

How many patients had progression? Do you know where the zone was in Zone 3 in the two groups?

DR. STEMPIEN: I'm sorry. Could you just repeat that question?

DR. KUMAR: Most certainly. My concern again, this is, again, to me as a clinician, when we call up and have a patient when an ophthalmologist tells that there's progression of the disease, we take their word for that, and so I'm concerned in your study because there was such a difference in ophthalmological evaluation versus fundoscopic pictures. How much of your progression was in Zone 3 in the two groups?

DR. STEMPIEN: I think we have a slide

here that will help illustrate that. Yes, I think this would help. Slide up, please.

You know, we didn't distinguish between Zone 2 and Zone 3 in our analysis. We actually put both peripheral -- more peripheral zones together. So I'm not sure that this slide will completely answer your question because it looks like you'd like to know about each zone, and we don't have that.

But if you look at the patients with more peripheral disease -- oh, here -- more peripheral disease, Zone 2-3, we had nine percent of those patients progress in the IV ganciclovir arm versus ten in the valganciclovir arm, and those patients who had Zone 1 coming into the study, 13 percent of them progressed in the IV arm and 11 percent in the valgan arm.

So we feel that both treatment groups showed good efficacy regardless of the zone of involvement coming into the study.

DR. KUMAR: Thank you.

DR. STEMPIEN: Sure.

CHAIRMAN POMERANTZ: Yes, Dr. Bertino.

DR. MARTIN: Actually I'd like to add one other thing, if you don't mind.

Just disease restricted to Zone 3 is

extremely uncommon. The area of retina involved by Zone 3 is very small relative to Zone 2 and Zone 1. So the probability that there would be disease restricted to Zone 3, first of all, there weren't a large number of these patients. There couldn't have been.

And usually when disease progresses, it progresses posteriorally. It doesn't have anywhere to go anteriorally. So if it progresses, it progresses into Zone 2. So it's just highly unlikely that the progressions -- it's a good question, but I think it's highly unlikely that the difference in progressions could be explained, the ophthalmic progressions could be explained solely on the basis of Zone 3 disease. There are just not many cases like that.

CHAIRMAN POMERANTZ: Dr. Bertino, you have a question.

DR. BERTINO: Could you review your food effect data for us, please?

DR. STEMPIEN: Certainly. Dr. Georgiou, clinical pharmacology.

DR. GEORGIOU: Certainly we can do that. What we found with food is we found a 30 percent rise in the area under the curve when we give the therapeutic dose at 900 milligrams, and we also see if

we go higher up in dose, we also see a progressively higher increase in bioavailability.

Can I have the slide up, please?

This is the concentration time curve for ganciclovir and for valganciclovir shown on a linear scale, and as you can see here, here we have the ganciclovir in the fast state, and here we have the concentration time curve in the fed state.

In other therapeutic dose we do see an effect of 30 percent.

DR. BERTINO: What was the meal?

DR. GEORGIOU: It was a high fat, FDA breakfast.

(Laughter.)

DR. BERTINO: Thank you.

Did I misunderstand you? Did you say that as you increase the dose with food, the percentage bioavailability increases?

DR. GEORGIOU: Yes. Can I have the slide up, please? Slide up.

Here we have the data which show the fed versus fasted for the area under the curve. So as you go higher up in dose from 450 to 200,625, you do get an increase in the area under the curve from a mean of 24 percent to 56 percent.

DR. BERTINO: Okay. In your pharmacokinetic data that you presented for 376, the oral data, were those patients studied with or without food at the two time points?

DR. GEORGIOU: If I understand it correctly, what was the dosing recommendation for the studies? Is that what you're saying?

DR. BERTINO: Well, I'm just trying to find out --

DR. GEORGIOU: It was with food.

DR. BERTINO: It was always with food?

DR. GEORGIOU: Yes.

DR. BERTINO: Okay. So the PK data that you present in the packet where you looked at surrogates for efficacy, that was patients dosed with food?

DR. STEMPIEN: That's right.

DR. GEORGIOU: Correct.

DR. BERTINO: So that would be the recommendation then, is to --

CHAIRMAN POMERANTZ: I didn't hear that, but the answer is with food.

DR. STEMPIEN: Yes.

CHAIRMAN POMERANTZ: All right. Just speak into the mic for the record.

DR. STEMPIEN: Thanks.

CHAIRMAN POMERANTZ: I have a question. I had a question when I read your briefing document, as well as when I talked to the FDA about the case studies. You nicely brought up the problem or the issue of HAART in doing a study such as this, which is probably the major problem with doing studies on CMV retinitis, although it's certainly not a problem to the patients who are benefitting by it, but to the researchers.

And one of the things that's the hardest thing to understand is the dynamism of what HAART does in the setting of adding a new antiviral drug. In the briefing document, it states that everyone was on stable HAART, and I use that in quotes because it's not clear what that means.

And then when I looked at your slides, you have some that are naive, some that were not on HAART at present, and there was no question of what you would define as stability, meaning when HAART was -- are they stable after two weeks and they enter this study?

So it may be nitpicking, but it's an important drug, but very little data. Can you tell me, or one of your people tell us, what truly stable

HAART meant in these people and whether you had cases of other entities, such as immune reconstitution disease if HAART was started even after the first four weeks, since you followed them out and showed that data?

DR. STEMPIEN: What the protocol asked for was that patients stay on a stable anti-retroviral regimen during the randomized phase of the study, and after we had assessed the primary endpoint, then we allowed any modification of HIV therapy.

We cannot say specifically how many patients were on HAART because we were not able to define that in the way that we collected concomitant medications. So what we did is we tracked protease inhibitors, and in our study we're using protease inhibitors as a marker for HAART.

The way that we verified that HAART was not influencing the randomized comparison in our study was that we collected CD4 counts and quantified the HIV loads at baseline and at week four in both treatment groups, and I can show you those data if you want, but the data confirm that if HAART was playing a role during the randomized part of the study, it was very small.

There were very minor changes in CD4

counts and in HIV loads during the first four weeks, and those changes did not favor the valganciclovir group in any way.

So we're quite comfortable that HAART was not interfering with our primary efficacy comparison.

CHAIRMAN POMERANTZ: Yeah, let me just discuss that comfort level. When you say HAART was obviously not affecting the CD4 count, the viral load throughout the randomization as determined by the mean or the median, if you look at the cases though, you need very little changes in one to skew the data in this regard.

When you looked at the cases where there -- and there are so few cases that you could look at every case -- were there major differences that were just swallowed up by other patients in the group that were not illustrative?

DR. STEMPIEN: Well, let me show you the CD4 and the HIV load data --

CHAIRMAN POMERANTZ: Okay.

DR. STEMPIEN: -- that we have at those two time points. I think that will help.

Okay. Slide up, please.

Here's the CD4 count at screening, and the median was 26 and 18, and the CD4 in both treatment

groups ranged from two to 365 for IV and two to 296 in the valganciclovir group.

If we -- next slide, please -- if we look at the CD4 count at week four -- slide up -- the median had changed very little. The minimum now ranged to 309 and to 260. We also have a distribution of the CD4 changes at week four.

Yes, that's okay. Slide up.

This shows you the median change in CD4 count in both treatment groups was quite small, and the maximum increase in the two treatment groups was less than 100 cells.

And in terms of the baseline HIV load -- slide up -- the baseline loads were comparable in the two treatment groups, 5.3 logs, mean, and 4.9 median, and they ranged up to about 5.9 logs in each treatment arm.

And at week four -- slide up -- we see that the HIV load had changed very little and still ranged from 1.7 to 5.9 logs.

And here's a distribution of the change in viral load at week four.

Slide up.

There's a fairly even distribution, but most patients, if they did change, they either had a

decrease of no more than a log. Most were up to a half log, or an increase of about a half log. Very few patients had a decrease in their HIV load that was greater than one log, and those changes seem to be balanced in the two treatment groups. They certainly don't favor the valganciclovir arm.

So that's the basis for our feeling that our primary efficacy comparison was not interfered to any great degree by an impact of HAART during the first four weeks.

CHAIRMAN POMERANTZ: Yeah, that's very helpful.

The patients who were naive or not on HAART at present, therefore, they did not get an anti-retrovirals for those four weeks, correct?

DR. STEMPIEN: Yes, that's correct. That's correct.

CHAIRMAN POMERANTZ: Thanks.

DR. MATHEWS: This is for Dr. Stempien.

Could you comment on the management of the ones that had evidence of progression at week four and subsequently? Were they reinduced? Were they switched to other drugs? How are they managed?

DR. STEMPIEN: If patients progressed, and this would have been based on the ophthalmologist's

assessment because the photo results were not known in real time; so if the ophthalmologist called a progression, then that patient could be reinduced with valganciclovir, and they would simply reinduce with the same induction course that they had received coming into the study, and then if they responded to that, they would go back onto valganciclovir maintenance and stay on, continue on.

DR. MATHEWS: Were there patients who were switched to other drugs because of failure even with reinduction?

DR. STEMPIEN: There were some patients who might have been with -- who were withdrawn from the study following a progression, and I discussed a few of them when I talked about the withdrawals between week four and week 12 where there were four patients in the valganciclovir arm who withdrew from the study following the ophthalmologist's detection of a progression.

If they withdrew following a progression, then they were obviously able to receive any other agent that the ophthalmologist deemed suitable.

CHAIRMAN POMERANTZ: Dr. Bressler.

DR. BRESSLER: I would be very comfortable with the photographic data that you have compared to

the ophthalmologist because unfortunately, we as ophthalmologists cannot usually detect these progressions right away, and we see them after they're seen on the photographs.

So I'm comfortable with that, although you could look at your Zone 1 cases where you know you have photographs and you know the ophthalmologists looked and just confirmed that you saw the same sort of discrepancy. I suspect it would be the same there.

That being the case, did the ophthalmologists take photographs in 705? I know you didn't have them graded at the center. Did they take any photographs of that?

DR. STEMPIEN: No, not in that study. That study was primarily for safety and tolerability, and so we didn't incorporated a photographic protocol. So the patients were followed by the ophthalmologist only.

DR. BRESSLER: How do you think we should interpret the progression then that is given for 705, which is based on the ophthalmologist assessment? Should we take it with a grain of salt or say that this is something or what?

DR. STEMPIEN: Well, I think that it could be considered as supportive real world data, but it

certainly wouldn't stand up to the rigor of a photographic assessment.

DR. BRESSLER: And did you have data for the border activity? And was that similar to what you showed for progression?

DR. STEMPIEN: Could you just clarify your question a bit?

DR. BRESSLER: You said that the photographers graded both progression, as you specifically defined it, and border activity, but I only saw the data for progression. Did the border activity also show no significant difference between the two groups?

DR. STEMPIEN: Yes. If you're interested, we could show you border activity data at baseline and also a reduction in border activity over the four weeks, if that data would be of interest.

DR. BRESSLER: If it was the same. Because with all of the limited data, I think you want to use everything you have to show that they appeared equivalent.

DR. STEMPIEN: Okay.

DR. BRESSLER: So that would be helpful.

DR. STEMPIEN: Well, let me tell you that they were balanced at baseline with respect to border

activity, and in fact, both groups showed a similar decrease in lesion activity that you could follow out, week two, week four, week six, in both groups.

DR. BRESSLER: Okay.

DR. STEMPIEN: And it was substantial.

DR. BRESSLER: Okay. That's fine.

DR. TOERNER: Do you have that data?

DR. STEMPIEN: Yes, yes.

DR. TOERNER: Could you show it just for the record for the Committee, please?

DR. STEMPIEN: Oh, sure, and I think I'll ask Dr. Martin to speak to it. Let me get the slide.

DR. BRESSLER: And then while he's coming up, the last question is: how are the visual acuities measured? Were they just routine office practice measurements or were they standardized protocol visual acuity measurements?

DR. STEMPIEN: Well, it was either a Snellin or the early -- I'm sorry --

DR. BRESSLER: ETRS?

DR. STEMPIEN: Yes. Sorry. Yes.

DR. BRESSLER: So it was either one?

DR. STEMPIEN: Yes, yes. But it was consistent. It had to be the same for any given patient throughout the study.

DR. BRESSLER: Thank you. Thank you.

DR. STEMPIEN: Well, let me put this slide up then. This is not the baseline. I've got the reduction, but I think this may be sufficient.

Slide up.

Okay. This shows the lesion activity reduction measuring the greatest reduction in lesion activity in both eyes between week two and week four. So you can follow this.

And the Wisconsin Reading Center used a multiple step scale in determining lesion activity, and you can see that at week two -- and of course, the higher the step reduction, the better result that is.

You can see at week two, there's -- the groups appear fairly well balanced. You have a substantial percentage of patients who have had a one step reduction and then smaller numbers have had two, three, and four step reductions.

And then as you go out to week four, now you're where we assess the primary endpoint. You can see all of the numbers have increased reflecting further reduction in lesion activity so that at week four we had 27 percent of the IV group and 29 percent of the valgan group who had a four step reduction in lesion activity, and seven percent who had a five step

reduction.

Does that help?

DR. BRESSLER: Yes. Very good.

DR. STEMPIEN: Okay. Thank you.

CHAIRMAN POMERANTZ: Dr. Pulido, do you have a question? And then Dr. Yogev.

DR. PULIDO: Actually two. About a third of the patients develop diarrhea on valganciclovir. How did that affect the AUC for those patients?

DR. STEMPIEN: I'm going to ask Dr. Georgiou to comment, but I don't believe -- in our PK subset, we only did full PK profiling on a subset of patients, and I don't believe that those patients experienced much in the way of diarrheas, but Dr. Georgiou will comment.

DR. GEORGIOU: We had a limited PK subset. We had about 42, 43 subjects in the subset, and we have looked to see whether those with lower AUCs had diarrhea, and we only had one patient in the group, and he was actually within the normal range for about 30 micrograms per mL.

Now, diarrhea is a manifestation probably of the lower GI tract, and what we have done is we looked at the absorption profile because we had IV and oral data from a number of studies. So what we have

done is a mathematical term, deconvolution, where we tease out the absorption profile because we know the disposition of the compound and the oral data.

Can I have the slide up, please?

Here is such a curve, where what we have here is the cumulative amount of ganciclovir that appears in plasma, and what you can see here is that for the majority of the patients by four hours after administration we have almost 80 percent absorption, and by six hours, the absorption is almost complete.

So it is unlikely that even with diarrhea that patients will actually suffer in terms of their area under the curve.

DR. PULIDO: The second one is sort of related to the first, and that goes to one of your ending statements. It says as with any new drug, there's a risk that one or more uncommon drug related toxicities associated with the valyl ester modification could be observed as larger numbers of patients are dosed.

And 85 percent of the metabolism of the valyl form occurs in the intestine and 15 percent in the liver. Somewhere about 14 percent had elevated liver function tests while on the medication, and again, a third had diarrhea.

Did you look at the valyl, the amount of the valyl form in those patients with diarrhea or elevated liver function tests to see if they had elevated levels of the valganciclovir form?

DR. STEMPIEN: No, we did not. We measured ganciclovir levels only in the patients who were participating in the PK profiling. We don't have ganciclovir levels on other patients.

We did do a close look at liver function tests, and if I could have the slide up, just for all patients, we weren't able to detect any hepatotoxicity during the randomized phase of the study. We looked at several measures of hepatic function, and there were some small changes between week one and week four, but they were rather small, and they were balanced between treatment groups, and there were no differences between the IV and valganciclovir.

So we have to date within our safety database, we have not been able to discern any toxicity that we could no -- that has not already been described with ganciclovir.

Now, the point that you make is absolutely well taken regarding the presence of valyl, a small amount of the parent compound, but in our database, we have not been able to find any signal of additional

toxicity that might be related specifically to the presence of the valyl valynated compound, the parent compound.

Dr. Yogev.

DR. YOGEV: A couple of questions. One follow-up to Dr. Pomerantz.

Do you have viral load at 12 week or after to show if what we are seeing is so-called maintenance is not affected by the HAART?

DR. STEMPIEN: After the randomized portion of the study we have some limited viral load data, but it rather limited. It was not collected in a rigorous way per protocol. We really focused on the randomized part of the study because we realized that after four weeks patients' regimens were all going to be changing, and that's why our time to progression endpoint in those Kaplan Meier curves need to be interpreted, you know, with that understanding, that patient regimens were changing.

I'd be happy to show you the data that we have, but it's rather sparse, but if you'd like to see it, I'd be happy to show you that now.

DR. YOGEV: The reason I mention it is when I look at the first slide that you showed us about how CMV changed, and the epidemic is almost at

the same rate that your cure of maintenance. Now, if you are asking for induction only, that's fine with me, but for maintenance I'm not sure viral load didn't affect it, the HAART did not affect the whole effect.

The second question is I was a little bit surprised to see how much increase in side effect you have, especially neutropenia, anemia, and platelets, in the longer period of time of follow-up, the 370 patients, and I wondered if the transplant patient that you didn't show any data would help. If you take this medication for a longer period of time, is there really such an increase from, for example, 30 percent of the patients had neutropenia versus only less than 20 percent in the ganciclovir?

Are there any data for a longer period of time to show toxicity is not increasing with time?

DR. STEMPIEN: Well, I'd just like to make a few points about comparing the adverse event data that I've shown you for a valganciclovir package and comparing that to the historical studies.

The historical studies came from a time that was pre-HAART, and studies only ran for six months or perhaps a little longer, and so the duration of time that patients were on the study medication was much shorter, and that definitely has an impact on the

incidence of adverse events in the database.

Our database has almost twice as much data in it, and absolutely the incidence of adverse events is going to go up over time. In fact, we did our NDA data cut, and then we did a four-month safety update beyond that. We're seeing the same adverse events, but each one increased a little bit in terms of incidence because of the longer duration of exposure.

So it's just important to keep that in mind. We feel comfortable that the safety profile that we have described so far is consistent with what we would expect with ganciclovir.

DR. YOGEV: And last, do you have any plans for pediatric formulation?

DR. STEMPIEN: Yes.

CHAIRMAN POMERANTZ: Have to ask that question.

DR. STEMPIEN: Pardon?

Okay. Yes, yes, we do have plans. We're in the process of developing an oral liquid formulation. We have a program planned. We have submitted draft protocols to FDA, and so that's something we look forward to doing.

CHAIRMAN POMERANTZ: Dr. Wong.

DR. WONG: Yes, I have another question

about the safety data. It looks to me from your Table 11 in the briefing document and also Appendix 18, the Kaplan Meier curve, that the patients who got valganciclovir had a substantially higher chance of developing severe anemia than those who got IV ganciclovir.

I mean, is that really true, and why is that? I guess the follow-up is: does that -- should that tell us anything about the dosage level that you're proposed for maintenance therapy? Might that not be too high?

DR. STEMPIEN: Give me just a moment to look for a slide here.

Yeah. I'd like to say, first off, that you're absolutely right. In our briefing package, we do talk about an increased, more severe, more patient sin the valganciclovir arm experience, more significant anemia.

Further out in the study, interestingly, not during the randomized phase when they seem to be balanced and we're both getting the higher induction doses, but the more severe anemia appeared further out.

If that is real, we do not have a ready explanation for it. It certainly isn't what we would

expect. We're providing valganciclovir at similar exposures to IV. So we would not expect that there would be more anemia with valganciclovir. But we certainly recognize that that may be a real finding that we just don't have an explanation for or it may be related to some other factor that we failed to take into account.

We did look at some concomitant medications. The treatment groups were balanced at baseline with respect to their hemoglobin levels. So this was not an imbalance coming in, but I can show you -- slide up -- this Kaplan Meier shows you the time to development of hemoglobin less than eight.

And so I think this curve might be in your backgrounder as well, and so the curves are separate, and there is a difference in our study. Whether that reflects a true difference or whether we just have not found the explanation for it yet, I don't know.

CHAIRMAN POMERANTZ: Dr. Fong.

DR. WONG: Should we take this into consideration when we're thinking about dosage levels in the maintenance phase? Might 900 milligrams be too high?

DR. STEMPIEN: Well, I'm not sure on what basis we could conclude that because we don't -- the

maintenance does that we're proposing for valganciclovir, 900 milligrams a day, delivers a systemic exposure that's comparable to IV ganciclovir, five milligrams per kilogram.

And so given the fact that we're providing similar exposures of ganciclovir with both regimens, you know, we don't have any basis to -- we acknowledge that there is this anemia finding, but we don't have an explanation for it. It was not expected, and at this point it would not cause us to think that the dosing regimen that we suggest for maintenance treatment should be modified.

DR. WONG: All right, but that assumes that one is guided by the exposure as opposed to the observed toxicity. One could certainly look at it the other way.

DR. STEMPIEN: Well, our selection of doses was driven by efficacy considerations, and we targeted our AUC for valganciclovir based on the efficacy that we wanted to achieve.

If it turns out that there is more anemia with valganciclovir, I think the treating physicians who are comfortable with ganciclovir treatment and are aware of its safety profile, which has always included neutropenia and anemia, will understand how to watch

for and manage that particular toxicity. The anemia and neutropenia have always been described with ganciclovir, and so I think the treating physicians will be able to manage that appropriately.

CHAIRMAN POMERANTZ: An important point. Let's move on.

Dr. Fong.

DR. FONG: As an ophthalmologist, I don't look at a lot of this pharmacodynamic data a lot, and I wanted to get some clarification on your use of area under the curve versus the C-max, and I wanted to maybe ask you to clarify for me whether there are any implications of not using C-max to compare the two groups.

For example, is there a risk of, you know, increased mortality or is there a risk of higher development of resistance when we just look at area under the curve versus the C-max?

DR. STEMPIEN: Well, that's a very good question. We have no data that correlates a specific PK parameter with a safety outcome or with a resistance outcome that I'm aware of.

No, we do not. So our view that area under the curve is the most important PK parameter is really based on efficacy considerations and just

consideration of the general shapes of the curves for both IV ganciclovir, oral ganciclovir, and then valganciclovir, which is actually bracketed by both.

And since IV ganciclovir and oral ganciclovir are both approved, efficacious formulations, we feel comfortable that the valganciclovir profile is going to provide good efficacy.

And, no, we can't say that we've established beyond a doubt that AUC is the most important parameter, but it really seems to make the most intuitive sense based on all of the data that we have.

CHAIRMAN POMERANTZ: Do you still have a question, Dr. Kumar? Yeah, Dr. Kumar.

DR. KUMAR: I wanted to follow up on Dr. Wong's issue regarding anemia. When I look through the booklet that you provided, there was one death, and I couldn't figure out whether it was in the 376 or the 705 of a female who died from severe medullary aplasia. I know she got a dose that was higher because of renal failure.

Could you explain and tell us exactly what happened?

DR. STEMPIEN: Well, I can't tell you all

the details. I could get all of the details if you want full details of the case, but I can tell you that she developed -- this is a woman who was severely ill with multiple medical problems, and she developed renal impairment, actually developed acute renal failure, and as her creatinine clearance declined, the dose was not appropriately adjusted, and so, in fact, she ended up with a relative overdose that was reflected about a tenfold higher exposure than what she really should have been receiving based on her creatinine clearance.

And that certainly had to contribute to the events that led to her medullary aplasia and eventual death.

CHAIRMAN POMERANTZ: Dr. Fletcher.

DR. FLETCHER: First, just a comment, again, on Dr. Wong's question about the safety and responses about the systemic exposure of val. and IV being the same.

Well, that's true with area under the curve. That is not true with trough concentrations. The trough concentrations are threefold higher with the valganciclovir form as opposed to the once daily IV form, and it's not at all implausible to believe that you can have two different pharmacodynamic

relationships, one for efficacy that may correlate with area under the curve, and one for toxicity that perhaps may correlate better with a trough concentration.

DR. STEMPIEN: That's a very good point. You're absolutely right, but it's also true that the trough concentration for valganciclovir is actually lower than what we achieve with our oral ganciclovir formulation, and we certainly have not seen increased anemia with our oral ganciclovir formulation.

So you may be right. It's a bit of a puzzle. It doesn't all fit together that way, yeah.

DR. FLETCHER: My second is actually in a sense a follow-up to Dr. Kumar's and your response about the need for adjusting the dose with renal insufficiency. You've provide a table in the background that shows the change in half-life, change in pharmacokinetic parameters with various degrees of renal insufficiency, but you've not laid out at least for us to see an algorithm by which someone would actually adjust the dose of valganciclovir.

So I'd like to see that.

DR. STEMPIEN: Okay. Dr. Georgiou.

DR. GEORGIOU: Would you like me to walk you through the way we've done it?

DR. FLETCHER: I don't know in any great detail. I think can I have, you know, a bottom line table of what you're recommending?

DR. GEORGIOU: Okay.

CHAIRMAN POMERANTZ: I think he's asking for a slide.

DR. FLETCHER: Yeah.

(Laughter.)

DR. FLETCHER: Thank you.

And then also if you would comment. Is that creatinine clearance in your studies a measured or an estimated?

DR. GEORGIOU: Okay. Let me walk you through that and then I'll come to the creatinine clearance. I need to check that, but I think it was an estimated creatinine clearance.

As we can see, we structured the algorithm so that we can match as much as possible that we have for IV ganciclovir within the bounds of flexibility of the 450 milligram tablets, and what we have tried to do is that we tried to maintain a minimum area under the curve of about 26 micrograms hour per mL, and as you can see here from the different groups of creatinine clearance, we can reasonably achieve that for all the groups with the exception of the patients

on hemodialysis, where we cannot use the table formulation to give us the target AUCs that we wanted.

DR. FLETCHER: And then just one last question. Resistance. You haven't made any comments about the emergence of isolates, seeing the isolates that have resistance to ganciclovir following valganciclovir dosing. I wonder if you have any information on that.

DR. STEMPIEN: Yes, we do. We did extensive resistance testing in this study and Dr. Noel Roberts, a virologist, will show you those data.

DR. ROBERTS: Yes, as Dr. Stempien has said, we've done extensive studies for resistance in clinical trial 376. I can show you the data in overview form if you wish, but the bottom line is that we saw no surprises. Both the nature and incidence of resistance that we found was what we would have expected from the previous data that was available for ganciclovir itself.

DR. FLETCHER: Maybe you could humor me and show me a slide. I don't know what no surprises means.

(Laughter.)

CHAIRMAN POMERANTZ: This is sort of the Missouri state today, this show me, yeah.

DR. ROBERTS: Okay. So we look both phenotypically and genotypically for resistance. Phenotypically we saw no isolates with an IC-50 over six micromolar, but we have to say that there were very few culture positive samples well into the maintenance phase when resistance might have emerged.

Most precise data, therefore, comes from our genotypic assessment where we performed a detailed kinetic study looking for changes in UL-97.

Next slide, please.

We took samples from every patient every four weeks, PMNLs, and we looked for the last PCR positive sample in terms of UL-97, and when we got a PCR positive sample, we assayed that for genotype both by sequencing and by a restriction enzyme digest method.

We also looked at every sample where the viral load by quantitative PCR was over 1,000 copies per mL. When we found mutations in UL-97 indicative of resistance, we then backtracked through the four weekly samples to determine the kinetics of emergence of resistance for those patients. So we went back to a stage usually where the resistant virus was in a mixed population with wild type.

Next slide, please.

What we found was we found just 14 instances of mutations in UL-97, six in one arm and eight in the other, but of course, these are all occurring while after all patients are on valganciclovir itself. So that's 14 out of 148 patients who we looked at. So that's a total incidence of a little under ten percent.

The mutations we saw in UL-97, 75 percent of them -- we saw 20 mutations among the 14 patients. Seventy-five percent of those were positions 460, 594, and 595, and that agrees exactly with previous data. The other mutations were at position 520, 603 and 607. Again, that agrees exactly with what has been found with ganciclovir.

Just one of those patients also had a mutation in UL-54, again, which has been a better described position.

The median and mean times to emergence of resistance are as shown there, quite a slow emergence of resistance, and if we compare the rate at which resistance emerged with the previous pre-HAART using phenotyping as the endpoint, you can see that the incidence is certainly no more than has been described from past studies.

So as I said to start with, both

qualitatively and quantitatively we're seeing largely what we might have expected.

CHAIRMAN POMERANTZ: Are there any final burning questions?

Well, hold on. Yeah, at the end?

DR. PISCITELLI: Do you have any data on ocular levels either from animal studies comparing the IV with the valganciclovir or maybe from both selected patients who had procedures or something?

DR. STEMPIEN: No, not following dosing with valganciclovir. We do not.

DR. PISCITELLI: I think this gets back to the issue of is the peak important because of the higher peak.

And the second question is I have a few concerns if the AUC really does correlate with the efficacy. There is the one analyses that you referred to. It looks like they measured one time point and tried to simulate an area under the curve from one sample. I wonder if that procedure was validated at all.

Did you have patients with full curves and pull one out and try to validate that or how that was done?

DR. STEMPIEN: We're confident in the

PK/PD analysis that we did, but the methodology did have some limitations, and I think the FDA has pointed some of them out, and we certainly accept their opinion on that. It had to do with some assumptions that we made regarding missed dosing times and also the amount of data points that we had per patient.

But if you completely set that analysis aside, we view it as supportive, but if you completely set it aside, I think that you can make a reasonably convincing argument just based on PK considerations alone and what we know about our different formulations that it's most likely area under the curve.

We have not absolutely established that, but we feel that that's compatible and consistent with all of the data that we have and what we know about the efficacy of ganciclovir.

Oral ganciclovir works very well in maintenance treatment. Now it has never been equal to IV, but it does work. It has efficacy. Patients usually progress about a week earlier if they're on oral maintenance.

And the C-max of oral ganciclovir is tenfold lower than the C-max for IV ganciclovir. So that amount of difference would not help the argument

that C-max is going to be the most important parameter because there's just too much of a difference, as opposed to AUCs where the oral formulation is about 50 percent of the AUC of the IV formulation.

That seems to make more sense then and explain the efficacy that we see a bit better. So just strictly in PK considerations, that's what we feel.

CHAIRMAN POMERANTZ: Dr. Sun.

I also want to tell the Committee there will be time for other questions after the FDA makes their presentation.

So Dr. Sun.

DR. SUN: Could you comment on the mode of administration in the four-week randomized portion of the study? In other words, were both arms self-administered or was just the oral formulation of val. self-administered?

And then related to that, could you comment on any data on compliance that you have in the two arms with respect to each other?

DR. STEMPIEN: Yes. Just one moment.

I think I understand your question about mode of administration. Are you thinking was the oral formulation, was that somehow directly observed? Is

that what you're getting at?

DR. SUN: Right. Was the IV arm administered by a physician or nurse or was it self-administered, and the same question for the oral?

And depending on the answer, did that have an effect on differential compliance?

DR. STEMPIEN: Yeah. I don't think we had any particular restrictions within the protocol on the setting of administration, and I would imagine that we were fairly flexible in that regard, that the patient could have received their dose in the clinic or at home through a home nurse.

And Dr. Martin indicates that at least at his center they were mostly at home, and the oral administration was provided to the patient, and the patient came back to the clinic and then reported how much they had taken, and we also did capsule, tablet counts.

We do have some information on how many patients completed dosing during the first four weeks.

Slide up.

And in the protocol we wanted patients to complete at least 21 days out of the first 28 days of treatment, and the groups look very comparable with respect to the actual amount of dosing that was

completed, at least 21 days, 20 days or less than 20 days.

Slide off.

CHAIRMAN POMERANTZ: Any final burning questions before we take a break?

DR. RODVOLD: Can I ask one?

CHAIRMAN POMERANTZ: I guess it's burning, yeah.

(Laughter.)

DR. RODVOLD: Considering that AUC, C-min, C-max seem to be the parameters that you're trying to base some of the conclusions and/or recommendations, is there an attempt to do just a simple demographic model that would be able to be predictive of AUC, C-min, C-max based on creatinine clearance, age, gender, simple things, bedside?

And if that does correlate with that, can you then link it to efficacy and toxicity either at a 24-hour marker or a cumulative exposure, in other words, all the way through the trial?

DR. STEMPIEN: Boy, if that's a question for me, I have no idea. I'm sorry.

(Laughter.)

DR. STEMPIEN: It would be certainly worth thinking about, but I do not know if that's possible.

I'm sure there are other people around the table who know more about that than I do.

CHAIRMAN POMERANTZ: Actually I'm not one of them.

Is there a comment on that question from anyone?

DR. RODVOLD: Just in the aspect of other drugs that are simply renal excreted you can do that, quinalones, aminoglycosides, things like that. That way you could estimate an AUC from data of people that you don't have serum concentrations. So subsequently we'll be able to expand that database of all patients enrolled to do that, and it should be a consideration that should probably be done.

CHAIRMAN POMERANTZ: Thank you.

Well, the time is by my watch four minutes to 11. Why don't we go till ten minutes after and take a break? And then we'll come back with the FDA's comments.

Thank you all.

(Whereupon, the foregoing matter went off the record at 10:56 a.m. and went back on the record at 11:11 a.m.)

CHAIRMAN POMERANTZ: Okay. Welcome back. We're now going to go into the FDA

presentation. I believe the starting person is Dr. Jose Toerner.

DR. JOSEPH TOERNER: Good morning.

I would first like to thank the applicant for their clear presentation this morning, and now I would like to present the FDA review of NDA 21304, valganciclovir for the treatment of CMV retinitis in patients with AIDS.

This is how we viewed the valganciclovir NDA. The efficacy portion consisted of study WV-15376, and I'll refer to this as the induction study. As well, multiple pharmacokinetic studies provided support for the maintenance therapy of CMV retinitis. And finally, three studies comprised the safety database in this NDA: the induction study and study WV-15705, and this is a single arm safety study in patients who had a previous diagnoses of CMV retinitis and received open label valganciclovir for the maintenance therapy.

However, we felt that this study provided only safety data, given that there was no comparison group, and the impact of highly anti-retroviral therapy would have on an efficacy endpoint.

And finally, the applicant is conducting currently a study in solid organ transplant

recipients, study PV-16000, and this is a study of oral ganciclovir versus valganciclovir for the prevention of CMV and organ disease in solid organ transplant recipients, and this provides a very small portion of the safety database that was submitted recently in a four-month safety update.

Because the pharmacokinetic profile of ganciclovir after valganciclovir administration is different than that of intravenous ganciclovir, in particular the C-max, the DAVDP requested clinical data in support of efficacy.

And Dr. Birnkrant this morning highlighted some of the regulatory background in terms of valganciclovir development for CMV retinitis, and I just wanted to highlight a few additional points as it pertains to the induction study.

It was generally recognized that an adequately powered study for equivalence would require approximately 200 patients per arm. However, in the current epidemiological climate of CMV retinitis, a feasible study to conduct would be approximately 75 patients per arm, and it was recognized that this would be under powered to demonstrate equivalence.

Therefore, an ongoing Phase 2 study, the induction study, was expanded into a Phase 3 trial,

and outside academic consultants, as well as the FDA concurred with the use of a four-week endpoint of progression of CMV retinitis.

As you heard this morning, the induction study enrolled patients with newly diagnosed CMV retinitis. It was an open label. Twenty-one-day induction therapy was given in a randomized fashion, intravenous ganciclovir, five milligrams per kilogram, twice daily or oral valganciclovir, 900 milligrams twice daily.

And this was followed by maintenance therapy at the assigned treatment regimen for an additional week, and then after week four, all patients received open label valganciclovir.

Just to provide some additional comments about the four week primary endpoint, this was a photographic assessment of CMV retinitis at the week four endpoint compared to baseline. The retinal photography was conducted in a standardized fashion at each of the multiple treatment sites.

This type of photographic assessment was used in previous registrational trials, and the photographic assessment was performed by the University of Wisconsin Fundus Photograph Reading Center, which has a considerable amount of experience

in interpreting these photographs.

We recognize the potential limitations of this study. First of all, it had a small sample size. Agreement was not reached between the applicant and the FDA on the lower bound of the 95 percent confidence interval of minus 25 percent as being a clinically acceptable lower bound.

And finally, the analysis of the primary endpoint was not prespecified.

The applicant in their presentation this morning reviewed the demographic characteristics in the induction study, and as you can see, it is well balanced between the treatment groups.

As well, the baseline HIV characteristics were well balanced between the treatment groups, and you can see that the study consists of patients who are profoundly immune suppressed. An equal proportion had a history of protease inhibitor use, and very similar proportions of patients at enrollment had ongoing use of protease inhibitors.

You can see that a very high proportion of patients in this study had opportunistic infections or opportunistic malignancies other than CMV retinitis, and on this next slide, I wanted to highlight some differences that we found between the treatment

groups.

And I wanted to highlight these differences because it suggests to us that the patients who are randomized to the valganciclovir arm may represent a sicker patient population. We found that 20 patients who were randomized to the valganciclovir arm had at baseline disseminated mycobacterium avium complex infection and 12 patients had this opportunistic infection in the intravenous ganciclovir group.

As well, a higher number of patients, 15 in the valganciclovir group, had esophageal candidiasis in comparison to eight in the intravenous ganciclovir group.

Other than cryptococcal meningitis, for which there were small numbers, the rest of the AIDS defining conditions at baseline were well balanced.

And as well, the characteristics of CMV retinitis were well balanced between the treatment groups with nearly a quarter of patients having Zone 1 retinitis, 25 percent having evidence of bilateral retinitis, and a high proportion having greater than 50 percent border activity at the CMV lesion.

So our analysis of efficacy is as follows. We first sought to evaluate the retinal photography

that was conducted by the University of Wisconsin, and we asked our FDA colleagues, and specifically had asked Dr. Boyd who gave this morning's presentation, to perform a masked review of the original retinal photographs that were submitted with this NDA.

And Dr. Boyd found complete agreement with the result of the University of Wisconsin Eye Center, with the exception of one patient.

The applicant's primary analysis is based on evaluable subjects and excluded deaths and loss to follow-ups. In our analysis we consider a sensitivity analysis, which ranges from a per protocol analysis to an intent to treat analysis and will test the robustness of the 95 percent confidence interval, the lower bound of the 95 percent confidence interval.

Here is how we accounted for patients in the study at the four-week primary endpoint. There were seven patients in each arm who had evidence of CMV progression at the week four endpoint. Those who had non-progression included 63 in intravenous ganciclovir group and 64 in the valganciclovir group.

Three patients died before the four-week endpoint in the study. Three patients discontinued study before week four due to an adverse event and, therefore, did not contribute week four interpretable

data in the study. And finally, one in each arm had failed to return in this study, failed to return before the four-week visit, and 11 patients either did not have baseline photographs that were submitted for evaluation or did not have evidence of CMV retinitis at baseline.

And one patient, who was included in this group is the patient that Dr. Boyd found which was different than the University of Wisconsin Reading Center, and it was a patient who had a previous ocular ganciclovir implant that was discovered after enrollment in the study, and we agreed with the applicant that this person should be excluded from the analysis.

Actually this particular patient had evidence of CMV nonprogression and would have fallen into this category.

Our intent to treat analysis includes those patients who had baseline photographs that were submitted for review, and so therefore, our first analysis highlighted in dark red is the patients that we would like to exclude from our intent to treat analysis. So, in other words, these were patients who either did not have CMV retinitis or did not have baseline photographs.

So, therefore, in our intent to treat analysis, we included only those patients who had baseline photographs that were evaluable.

And four our intent to treat analysis, we'll consider those who died before week four, those who had an adverse event before week four, or those who failed to return. We'll count those as CMV progressors.

So this is our first intent to treat analysis where, in summary, all missing four week photographs equals progression, and we find that 11 out of 74, or 14.9 percent, fall into this analysis in the intravenous ganciclovir group, and valganciclovir group, 14.7 percent, or 11 out of 75. This leaves us a difference of .2 percent and a lower bound of the 95 percent confidence interval of minus 13 percent.

Our next analysis sought to include only those patients who died as CMV progressors. Therefore, we exclude this group of patients here highlighted in dark red. We're excluding patients who discontinued due to an adverse event and discontinued patients who failed to return.

And that leaves us with two additional patients to count as CMV progressors in intravenous ganciclovir and one patient to count as a CMV

progressor in valganciclovir. It leaves us with a denominator of 72 in each of the treatment groups.

And so the second analysis where deaths equal progression, we have 12 percent in the intravenous ganciclovir group and 11 percent in the valganciclovir group, for a difference of one percent, and the lower bound of the 95 percent confidence interval is minus 11 percent.

And finally, we show here the applicant's analysis, which essentially includes all patients who have evaluable baseline and evaluable week four photographs. It leaves us with these denominators: 70 in the intravenous ganciclovir group and 71 in the valganciclovir group.

And so in this analysis seven out of 70, or ten percent, in the intravenous ganciclovir has evidence of CMV progression. Seven out of 71, or 9.9 percent, in the valganciclovir group had evidence of CMV progression. It gives us a difference of .1 percent in a lower bound of the 95 percent confidence interval minus 11 percent.

Let me just back up a bit. So this is a summary of our endpoint evaluation where we find that in a conservative intent to treat analysis where all missing values equal progression, we have a lower

bound of the 95 percent confidence interval of minus 13 percent.

And you can see that with the sensitivity analyses the lower bound of the 95 percent confidence interval is relatively consistent among these analyses.

You heard in this morning's presentation by the applicant that there was a differential dropout rate between weeks four and 12. There were four patients who were counted as dropouts in the intravenous ganciclovir arm, and 14 patients who were counted as dropouts in the valganciclovir arm.

We sought to, first of all, categorize how these patients who dropped out -- where they fit into the four-week endpoint, and we found that four patients, one who was randomized to intravenous ganciclovir and three who were randomized to valganciclovir, were already counted as having evidence of CMV progression by the photographic review, and we accounted for these in our previous analyses.

The discontinuations due to an adverse event or those who did not have a baseline photograph that was submitted for evaluation or did not have evidence of CMV retinitis, those we also accounted for