

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number** 21-304

**MEDICAL REVIEW(S)**

**Medical Officer Review**  
**NDA 21-304**  
**Valganciclovir for the treatment of CMV retinitis in AIDS**

**Date Submitted:** September 28, 2000  
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**Sponsor:** Syntex, LLC  
Roche Global Development  
3401 Hillview Ave.  
Palo Alto, CA 94304-1397

**Drug:** **Generic:** valganciclovir  
**Trade:** Valcyte  
**Chemical:** L-Valine, 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy]-3-hydroxypropyl ester, monohydrochloride

**Drug Class:** Antiviral Agent

**Route of Administration:** Oral

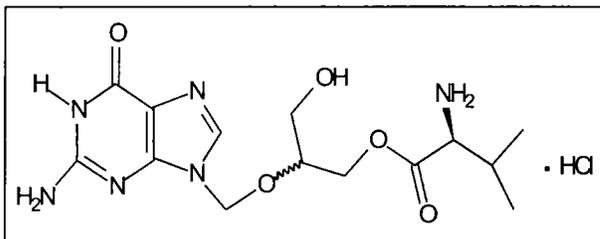
**Proposed Indication:** Treatment of CMV retinitis in patients with AIDS

**Related IND's:** IND 25,082; IND 32,149, IND 48,106

**Related NDA's:** NDA 19-661, NDA 20-460

**Consultation:** William Boyd, MD  
Medical Officer, Division of Analgesic, Anti-inflammatory and Ophthalmologic Drug Products

**Chemical structure:**



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**Executive Summary:**

NDA 21-304 contains the results of an active-controlled, equivalence-designed efficacy study, WV15376, "Randomized, controlled comparison of the safety and efficacy of valganciclovir vs. i.v. ganciclovir as induction therapy for the treatment of newly diagnosed CMV retinitis". One hundred and sixty patients with newly diagnosed CMV retinitis were enrolled to receive induction therapy with either intravenous ganciclovir or oral valganciclovir. The primary endpoint was the proportion of patients with progression of CMV retinitis at week 4. The results of this study showed similar rates of CMV progression at week 4, approximately 10% in each arm, in an intent-to-treat analysis [CI = (-13%, 13%)].

After induction therapy, all patients were treated with open-label valganciclovir 900 mg daily. Results of another single-arm, open-label safety study, WV15705, "Open label study of the safety and tolerability of valganciclovir in subjects with AIDS", were submitted, in which patients with previously diagnosed CMV retinitis changed to maintenance therapy with open-label oral valganciclovir. Data from these studies comprise the safety database of 370 subjects. Two-hundred and ninety-eight subjects received valganciclovir at the marketed dose for prophylaxis for at least six months. Results of these studies demonstrate that the adverse event profile of valganciclovir was comparable to the known adverse event profile of ganciclovir, with hematologic and gastrointestinal adverse events predominating.

The results of pharmacokinetic studies submitted with this application demonstrated that the plasma concentration of ganciclovir after administration of valganciclovir 900 mg was bracketed by plasma levels achieved after administration of intravenous ganciclovir 5 mg/kg and oral ganciclovir 1000 mg TID. The pharmacokinetic profile of oral valganciclovir, and safety, pharmacokinetic, and efficacy of approved formulations of ganciclovir, provided support for the use of valganciclovir in the maintenance therapy of CMV retinitis.

In summary, NDA 21-304 contains the favorable results of one small efficacy study of induction therapy of CMV retinitis; non-comparative data on maintenance therapy that provides longer-term safety data; and pharmacokinetic studies (demonstrating that the pharmacokinetic profile of ganciclovir after valganciclovir administration is between oral and intravenous ganciclovir, both approved therapies for treatment of CMV retinitis). The safety database contained fewer than 400 patients. However, it should be noted that valganciclovir is metabolized to ganciclovir, a drug for which there is considerable safety and efficacy data. In addition, the availability of an oral therapy for the treatment of CMV retinitis represents a substantial public health benefit for patients with AIDS and CMV retinitis. The data submitted by the applicant support the use of valganciclovir for patients with CMV retinitis. Therefore, valganciclovir for the treatment of CMV retinitis in patients with AIDS should be approved.

**Background:**

Human cytomegalovirus (CMV) infects most individuals by person-to-person transmission. Following infection, complex host-virus interactions occur such that CMV persists in a latent form without clinical symptoms. Only patients with immune suppression are susceptible to end-organ diseases due to CMV. CMV end-organ diseases include gastroenteritis, pneumonitis, hepatitis, central nervous system infection, and retinitis. Patients with AIDS are unusually susceptible to CMV retinitis, which occurred rarely before the HIV/AIDS epidemic. The sustained high levels of CMV viremia in AIDS patients is believed to be a contributing factor in the development of retinitis in this patient population.

Intravenous ganciclovir was approved for the treatment of CMV retinitis in the late 1980's. Ganciclovir is a synthetic nucleoside analogue of 2'-deoxyguanosine that inhibits CMV replication. Ganciclovir is metabolized by intracellular kinases to ganciclovir triphosphate, where it inhibits viral DNA synthesis by competitive inhibition of viral DNA polymerases and incorporation into viral DNA resulting in termination of viral DNA elongation. Ganciclovir is also indicated for the prevention of CMV end-organ disease in patients with solid organ transplants or in patients with AIDS. Cytopenias and gastrointestinal adverse events are the principle toxicities of ganciclovir. Other therapies for CMV retinitis include intravenous foscarnet, which received marketing approval in the early 1990's. Intravenous cidofovir and oral ganciclovir (for the maintenance therapy of CMV retinitis) received marketing approval in the mid-1990's. More recently, ocular implants that release ganciclovir and intravitreal injections of fomivirsen have been approved for treatment of CMV retinitis. The studies for approval of these agents contained groups with no or delayed treatment, and during the years that these studies were conducted numerous AIDS patients with CMV retinitis were available to enroll in studies.

Valganciclovir was developed because of the very poor oral bioavailability of ganciclovir. Even though oral ganciclovir was approved for use in maintenance therapy of CMV retinitis, this option has not been widely used because of the large number of capsules required to achieve a minimum effective level of ganciclovir. Intravenous ganciclovir carries the risks associated with placement and maintenance of central or peripheral venous catheters. The other intravenous therapies are more toxic and also require i.v. access. Ocular implants and intravitreal injections treat only the implanted eye and do not offer systemic therapy.

Valganciclovir is dosed orally, and provides plasma levels and area under the curve (AUC) of ganciclovir similar to that achieved with the 5 mg/kg dose of i.v. ganciclovir. However, because of the route of administration, the pharmacokinetic profile of valganciclovir differs from that of either oral or i.v. ganciclovir. The most important difference is that the C<sub>max</sub> is lower after

administration of oral valganciclovir than with i.v. ganciclovir. The clinically relevant pharmacokinetic parameters that are associated with efficacy are unknown. In particular, there are no data to indicate the clinical importance of the higher Cmax that is obtained with i.v. ganciclovir. Therefore, because of concern that a lower Cmax could impact efficacy, during early drug development the applicant was advised that clinical data would be required to support the approval of valganciclovir.

With the advent of HAART therapy the incidence of CMV retinitis in AIDS patients dropped significantly. At the same time, because there was approved effective therapy available for the treatment of CMV retinitis, the small placebo-controlled studies that served for approval of earlier agents were no longer appropriate. When the very slow enrollment in a phase two study of induction therapy of retinitis heralded the difficulties that development of valganciclovir would present, a corporate decision was made to halt further development of valganciclovir. Since the availability of an effective oral therapy for CMV disease represented an important public health benefit, the DAVDP review team initiated discussion with the applicant of approaches to the continued development of valganciclovir, the main one being the design of a retinitis study with a feasible size in this new situation. DAVDP felt that the initial approval of valganciclovir could be supported by the results of a planned large phase 3 study in \_\_\_\_\_, and that a retinitis indication might then be supported by efficacy in induction therapy, with recommendations for maintenance therapy supported by pharmacokinetic data. The applicant agreed to convert an already-open phase 2 study into a phase 3 study of induction therapy of CMV retinitis in AIDS patients. It was felt that efficacy in induction therapy represented a higher hurdle than efficacy demonstrated in maintenance therapy. DAVDP acknowledged that at 75 subjects per arm, the study would be significantly underpowered to demonstrate equivalence.

However, the applicant then decided to submit an NDA package that included only the results of the CMV retinitis study, along with safety data from an open-label study of valganciclovir used for maintenance therapy for CMV retinitis. Because it was never anticipated that efficacy results from a single small study of induction therapy would be submitted to support the initial approval of valganciclovir, DAVDP discussed with the applicant the possibility of granting accelerated approval for the CMV retinitis proposed NDA, \_\_\_\_\_

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**Chemistry Manufacturing and Controls:**

Valganciclovir hydrochloride, the valyl ester of ganciclovir is a type 2 molecular entity. The tablets contain acceptable quantities of the excipients microcrystalline cellulose, povidone K-30, crospovidone, and stearic acid. The impurities that were identified with valganciclovir were in a comparable range to the impurities identified with ganciclovir. Inspections by the field investigators were planned to occur in March 2001, and a preliminary communication with the Office of Compliance has revealed no concerns. Please see Dr. Gu's review for further details.

**Microbiology:**

Valganciclovir is rapidly metabolized to ganciclovir, for which there is considerable information on antiviral activity. The clinical trial WV 15376 specified the collection of urine, plasma, and semen CMV cultures and CMV PCR. The imprecise handling of specimens invalidate the results of the culture and PCR data and therefore no clinical implications from these data can be inferred. In addition, the CMV ~~assay~~ assay is not an approved assay. Please see Dr. N Biswal's review for further details.

**Pharmacology/Toxicology:**

Valganciclovir is rapidly metabolized to ganciclovir and valine. For this reason, pharmacology/toxicology studies were not repeated with valganciclovir. The preclinical studies conducted with ganciclovir demonstrated that ganciclovir is carcinogenic and teratogenic. In addition, ganciclovir appears to arrest spermatogenesis. A Black Box Warning indicating the results of these studies will be incorporated into valganciclovir's product labeling. Please see the composite review organized by Dr. Farrelly for further details.

**Biopharmaceutics:**

The results of clinical pharmacology studies were submitted in volumes 36 to 94, and were reviewed by Dr. Robert Kumi. The results of single-dose, multiple-dose, food-effect, and bioequivalence studies were submitted in support of valganciclovir 900 mg dose with meals. The results of pharmacokinetic studies in patients with renal impairment provided support for dose adjustments according to the level of renal function. Findings with clinical implications include the following:

1. Concern about the potential clinical implications of the C<sub>max</sub>;
2. The maintenance therapy for CMV retinitis was supported by pharmacokinetic data (see Maintenance Therapy. Page 17);
3. Food effect studies demonstrated that valganciclovir should be taken with meals;
4. Patients with renal impairment require dose adjustment.

**Clinical:**

The NDA contains the results of two clinical trials conducted in patients with AIDS and CMV retinitis. The safety update provided preliminary safety results from a third trial conducted in solid organ transplant recipients:

- Study WV15376: "Randomized, controlled comparison of the safety and efficacy of valganciclovir vs. i.v. ganciclovir as induction therapy for the treatment of newly diagnosed CMV retinitis" provided both safety and efficacy data.
- Study WV15705: "Open label study of the safety and tolerability of valganciclovir in subjects with AIDS" provided safety data.
- Study PV 16000: "Randomized, double-blind, double-dummy, multi-center study of the efficacy and safety of valganciclovir versus oral ganciclovir for the prevention of CMV disease in high risk solid organ transplant recipients" provided safety data that was submitted in a four-month safety update.

**Clinical Studies: Study WV15376****Study Design**

This was an open-label, randomized study that enrolled patients with AIDS and newly diagnosed CMV retinitis into one of two treatment arms: valganciclovir 900 mg BID versus i.v. ganciclovir 5 mg/kg BID for an induction period of 21 days. Patients remained on their assigned treatment regimens at a maintenance dose of either valganciclovir 900 mg daily or i.v. ganciclovir 5 mg/kg daily for an additional seven days. Patients randomized to i.v. ganciclovir administered the drug via peripheral or central venous catheter twice daily for three weeks followed by once daily administration for one additional week. The administration of i.v. ganciclovir was consistent with the investigators' usual clinical practice. As such, most patients self-administered i.v. ganciclovir at home after receiving instruction on the care and maintenance of indwelling venous catheters. After the first four weeks of therapy, patients received open-label valganciclovir for maintenance therapy of CMV retinitis at 900 mg daily. Photographs of the retina were performed in a standardized fashion at each study visit; baseline, week 2, week 4, week 6, week 8, and monthly study visits thereafter. The primary endpoint was a masked week 4 photographic determination of progression of CMV retinitis.

**Comments:**

- *Previous therapies for CMV retinitis evaluated efficacy utilizing a time-to-progression endpoint. There has been no previous experience evaluating the use of a week four endpoint. However, now that efficacious therapy for HIV infection is available, the traditional time-to-progression endpoint could not be utilized because patients with newly diagnosed CMV retinitis would ordinarily receive a new HAART regimen as part of standard-of-care treatment. Institution of a new HAART regimen would likely have a favorable impact on*

*the clinical course of CMV retinitis, and might significantly prolong or even prevent the progression of CMV retinitis. Therefore, the time-to-progression endpoint was not useful for evaluation of valganciclovir for the induction or maintenance therapy of CMV retinitis. The 4-week endpoint represented a reasonable endpoint for the determination of CMV progression versus CMV non-progression. The use of a week four endpoint does not account for those patients with initial progression of CMV within the first few weeks of treatment, who then start to respond adequately to treatment. This situation, not uncommonly encountered in clinical practice, would represent a failure of the treatment in the study.*

- *The masked review of the retinal photographs was conducted by \_\_\_\_\_ ophthalmologists at the \_\_\_\_\_, \_\_\_\_\_ who have considerable experience with masked review of retinal photographs.*

The study population consisted of patients with AIDS and newly diagnosed CMV retinitis who were greater than 13 years of age. Screening laboratory values were within a clinically appropriate range. Patients with severe diarrhea were excluded from the protocol. Patients receiving other medications with activity against CMV were excluded. Women of childbearing potential were included in the protocol with use of adequate contraception. Patients with zone 1 retinitis that was not imminently sight-threatening were allowed to enter. Patients likely to require intraocular surgical procedures were excluded from the protocol. Patients received standard-of-care treatment for HIV infection. After week 4, patients were allowed to change HAART.

Comment:

- *HIV RNA and CD4 cell counts were not collected as part of the original phase 2 study. Once the protocol was enlarged into a phase 3 study, plasma samples for HIV RNA were collected at each visit. CD4 cell counts were obtained by the treating physician but were not specified by the protocol. In verbal communication with the applicant, it was determined that CD4 cell counts had been obtained at baseline and at the week 4 timepoint only.*

There was no formal assessment of compliance, other than counting the returned study medication. The study was initially designed as a phase 2 study with a planned duration of four weeks; patients were permitted to remain on open-label valganciclovir as maintenance therapy after four weeks indefinitely.

The primary efficacy variable was the determination of CMV disease progression at the week 4 time point. The \_\_\_\_\_ reviewed retinal photographs in a masked fashion. The week 4 retinal photographs were compared to the baseline retinal photographs. The study defined CMV progression as a movement of the CMV lesion of greater than 750 microns. The results of the photographic determination were not provided to the treating ophthalmologists in real time. Secondary endpoints

included the assessment of retinitis activity by the treating ophthalmologists, the proportion of patients achieving a satisfactory response to induction therapy, the development of contralateral CMV retinitis, changes in visual acuity, and time to first progression of CMV retinitis.

Comment:

- *The definition of CMV progression as lesion movement greater than 750 microns has been used in previous registrational trials. However, the other registrational trials have used this definition in a time-to-progression analysis. The use of this definition as a week 4 endpoint has not been validated, but it appears to be an appropriate endpoint (see Dr. Boyd's review).*

**Results:**

Study population:

One hundred and sixty patients enrolled into the trial between 29 January 1997 through March 31, 1999 at 30 domestic and 26 international study sites. One patient in each arm was enrolled but did not receive study medication.

TABLE 1: Study WV15376, Demographic Characteristics

Demographic Characteristics	IV GCV N=80	Valgan N=80
Race		
Black	9 (11%)	9 (11%)
White	42 (53%)	43 (54%)
Hispanic	24 (30%)	25 (31%)
Other	5 (6%)	3 (4%)
Male	73 (91%)	72 (90%)
Age, mean (median)	38 (37)	40 (39)

Table 2 provides the baseline HIV disease characteristics.

TABLE 2: Study WV16376, Baseline HIV Disease Characteristics

Baseline HIV Disease Characteristics	IV GCV N=80	Valgan N=80
HIV RNA, median	4.9 log <sub>10</sub>	4.8 log <sub>10</sub>
CD4 cell count median (cells/mm <sup>3</sup> )	26	20
History of PI use	64/80 (80%)	64/80 (80%)
Ongoing PI use	47/80 (59%)	53/80 (66%)
Other OI's	57/80 (71%)	63/80 (79%)

Tables 3 and 4 describe the AIDS-defining conditions prior to enrollment, and the characteristics of CMV retinitis, respectively.

TABLE 3: Study WV15376, AIDS Defining Conditions Prior to Enrollment

AIDS-defining Conditions at Baseline	IV GCV	Valgan
	N=80 (%)	N=80 (%)
MAC	12 (15%)	20 (25%)
Esophageal Candidiasis	8 (10%)	15 (19%)
PCP	35 (43%)	32 (40%)
Kaposi's Sarcoma	12 (15%)	13 (16%)
Cryptococcal Meningitis	5 (6%)	1 (1%)
CNS Toxoplasmosis	1 (1%)	3 (4%)
Cryptosporidium	4 (5%)	2 (3%)

TABLE 4: Study WV15376, Characteristics of CMV Retinitis

Characteristics of CMV retinitis at baseline	IV GCV	Valgan
	N=80 (%)	N=80 (%)
Zone 1 retinitis	22 (28%)	19 (24%)
Bilateral retinitis	20 (25%)	20 (25%)
> 50% border activity	65 (81%)	59 (74%)

Comments:

- *The applicant did not provide the total number of patients who were screened for enrollment. Only the data on the 160 patients who actually enrolled were provided.*
- *The baseline HIV disease characteristics were well balanced between the treatment groups.*
- *The baseline demographic characteristics were well-balanced between the two treatment groups and represent primarily a male patient population that was 11% Black and 30% Hispanic, which likely represented the epidemiological profile of the participating study sites.*
- *Greater numbers of patients with MAC infection and esophageal candidiasis were randomized to the valganciclovir arm. This may have indicated an imbalance between the treatment arms of patients who may have had more severe disease at baseline.*
- *Patients with zone 1 retinitis were permitted to enroll into this trial. Although patients with zone 1 retinitis may not have imminently sight threatening retinitis, this zone contains the fovea and optic nerves that are of paramount importance to vision. Most patients who had zone 1 retinitis also had more peripheral zone 2 or zone 3 retinitis. Previous registrational trials of medications used to treat CMV retinitis excluded patients with zone 1 retinitis and included only patients with peripheral zone 2 or zone 3 retinitis. In contrast to the data submitted for marketing approval of other medications for the treatment of CMV retinitis where no data was submitted on the use of the antiviral agent in patients with zone 1 retinitis, this NDA contains clinical data on patients with zone 1 retinitis.*
- *The study population represented in this study may be different in comparison to populations participating in previous studies of CMV retinitis. Many patients in this trial were receiving HAART at the time of a new diagnosis of CMV retinitis. While this likely represents a failure of HAART that may have little impact on the course of CMV retinitis, there is evidence that a lack of virologic response to HAART may not result in a complete lack of clinical benefit.<sup>1</sup> Therefore, the study population in WV15376 may have had somewhat improved immunological function in comparison to populations studied prior to the advent of HAART. This means that an historical comparison may not be relevant, which represents another limitation in the interpretability of the efficacy results of this study.*

<sup>1</sup>Deeks SG, et.al. Virologic and immunologic consequences of discontinuing combination antiretroviral-drug therapy in HIV-infected patients with detectable viremia. *NEJM* 2001;344:472-7.

Table 5 represents the accountability of the patients at the week 4 time point.  
 TABLE 5: Study WV15376, Patient Accountability at Week 4

Week 4 Primary Endpoint	IV GCV	Valgan
	N=80	N=80
<b>Evaluable</b>	70	71
<b>Non-evaluable</b>	10	9

**Reasons for non-evaluable**

• Deaths before week 4	2	1
• Discontinuation due to AE before week 4	1	2
• Failed to return	1	1
• No interpretable baseline photos or no CMV retinitis at baseline	6	5

**Efficacy Results:**

The masked review of evaluable baseline and week 4 photographs identified seven patients in each treatment arm with evidence of CMV retinitis progression at the week 4 time point. There were 63 patients who received i.v. ganciclovir and 64 patients who received valganciclovir without evidence of CMV progression. Based on the applicant's analysis of 141 patients, in which all patients without complete photographic data at baseline and week 4 were excluded, the lower bound of the 95% confidence interval for the difference in proportion with CMV progression is approximately -10%. The applicant did not conduct additional sensitivity analyses that included patients with missing photographic data.

**Comment:**

- *FDA analysis: The FDA analysis included patients without full photographic data at baseline and week 4 who were excluded from the applicant's analysis. This analysis accounts for all persons who had baseline photographs. This analysis excludes those patients who either did not have evidence of CMV retinitis or did not have baseline photographs taken. Therefore, a total of 149 patients are included in an intent-to-treat analysis, as outlined in the following table 6:*

TABLE 6: Modified Intent-to-Treat Analysis

Week 4 Primary Endpoint	IV GCV	Valgan
	N=74	N=75
Non-progressor	63	64
Progressor	11	11

Reason for progressor\*

• Masked photographic review	7	7
• Death before week 4	2	1
• AE before week 4	1	2
• Failed to return before week 4	1	1

\*Deaths and discontinuations treated as progressors. Patients without baseline photographs and patients without evidence of CMV retinitis were excluded.

TABLE 7: Study WV15376, Sensitivity Analyses

Analysis	IV GCV	Valgan	Diff	95% CI*
Modified ITT, Missing = progression	11/74= 14.9%	11/75= 14.7%	0.2%	(-13%, 13%)
Deaths = progression	9/72=12%	8/72=11%	1%	(-11%, 13%)
Applicant's Analysis	7/70=10%	7/71=9.9%	0.1%	(-11%, 11%)

Comment:

- *In the intent to treat analysis, subjects who were missing week 4 photographs (discontinuations due to death, AE, or failed to return) were treated as treatment failures (or CMV progression). Therefore, a total of 11 out of 74 patients are considered progressors in the i.v. ganciclovir arm, and 11 out of 75 are considered progressors in the valganciclovir arm, for a difference of*

0.2%. An analysis that assigns deaths as CMV progressors, and excludes those patients who did not have week 4 photographs due to an adverse event or failure to return leaves 142 patients in the analysis. Nine out of 72 patients on the i.v. ganciclovir group and 8 out of 72 patients in the valganciclovir group are considered progressors, for a difference of 1%. Finally, in an analysis that includes only patients with baseline and week 4 photographs, seven out of 70 in the i.v. ganciclovir group and seven out of 71 in the valganciclovir group had photographic evidence of CMV progression. In a conservative analysis where deaths and discontinuations were considered as failures, the maximum lower bound of the 95% confidence interval is -13%.

#### **FDA Review of Retinal Photographs:**

The retinal photographs were submitted for review in the form of the original slides of the retinal photographs. Dr. William Boyd, a reviewing ophthalmologist with the Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products, evaluated the slides. His masked review of the baseline versus week 4 photographs was in complete agreement with the findings of the \_\_\_\_\_.

\_\_\_\_\_ One subject in the i.v. ganciclovir arm, who reportedly received a ganciclovir ocular implant before enrollment, was excluded from the applicant's analysis. Dr. Boyd concluded that this patient falls in the non-progressor category. Because this patient received a ganciclovir ocular implant before enrollment, the patient's baseline photographs were not interpretable. This patient was excluded from the sensitivity analyses.

Comment:

- *The FDA and the applicant were in complete agreement with the numbers of progressors and non-progressors.*

#### **Additional Efficacy Considerations**

##### **Secondary Endpoint of Week 4 CMV Progression by Ophthalmologists:**

The treating ophthalmologists, in some cases, rated CMV progression differently than the masked reviewers. There were twelve patients with an assessment of non-progression by the ophthalmologist and an assessment of CMV progression by the masked reviewer. In order to evaluate the clinical management of these twelve patients, a review of the case report forms was conducted. All except one patient had CMV disease activity documented at the week 4 visit by the treating ophthalmologist and most had received a re-induction or alternative anti-CMV treatment during the early maintenance period. In addition, ophthalmologists were more likely to designate patients assigned to the valganciclovir arm as treatment failures.

Comments:

- *The \_\_\_\_\_ ophthalmologists had an unlimited amount of time to score the retinal photographs. The treating ophthalmologist, in some*

*cases, may have had very ill patients in his or her office and needed to make rapid decisions about patient management in real-time.*

- Physicians may interpret i.v. therapy to be more efficacious, thereby introducing bias to this open-label study. The incongruent assessment of progression demonstrated why a masked review of the retinal photographs as the primary endpoint was necessary.*
- Finally, patients in this study appeared to be treated appropriately by the ophthalmologists. Nearly all of those patients who were determined by the treating ophthalmologist to be non-progressors at week 4 yet found to be progressors by the masked review had received appropriate reinduction therapy shortly after the week 4 study visit. This reflects the need for prompt and careful follow-up by ophthalmologists experienced in the care of CMV retinitis.*

#### **Evaluation of Immune Function and Changes in HAART During the Initial Four Weeks:**

Immune reconstitution may have one of two effects of CMV retinitis: 1) improvement in CMV retinitis because of improved immune functioning; 2) worsening of CMV retinitis because of enhanced inflammation due to improved immune functioning. Although patients were not supposed to initiate new antiretroviral regimens during the first four weeks of the study, the impact of changes in antiretroviral therapy was evaluated. Data collected on new antiretroviral medications initiated during the first four weeks of the study was evaluated to discern whether changes in antiretroviral therapies occurred. A total of 32 changes in antiviral therapy were captured on the case report forms between weeks 1 and 4. Of these 32, 14 had initiated acyclovir or valacyclovir, seven discontinued protease inhibitors, and one patient each changed from zidovudine to stavudine or changed their indinavir dosing regimen. Therefore, a total of nine patients initiated new protease inhibitor or non-nucleoside analogue (efavirenz) therapy during the first four weeks, four patients in the valganciclovir group and five patients in the i.v. ganciclovir group.

Furthermore, changes in median HIV RNA values between baseline and week four was evaluated in order to provide an indication of whether changes in antiretroviral therapy that might influence study outcomes had occurred. The following table provides the baseline and week 4 HIV RNA determinations.

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TABLE 8: Study WV 15376, HIV RNA Determinations

	IV GCV	Valgan
	Median HIV RNA Copies/ml (N=number of patients)	Median HIV RNA Copies/ml (N=number of patients)
Baseline	75,000 (N=61)	72,326 (N=59)
Week 4	64,383 (N=62)	100,885 (N=61)

The median CD4 lymphocyte counts were well below 50 cells/mm<sup>3</sup> in each arm at baseline. Screening and week 4 CD4 lymphocyte counts were obtained on 100 subjects, 50 in each arm. The majority (65%) of patients had a decrease or no change in CD4 lymphocyte counts. Only 9% of patients had an increase in CD4 lymphocyte counts of greater than 25%.

Finally, in spite of the low incidence of initiation of a new antiretroviral regimen during the first four weeks, it was also possible that new therapies had been initiated in close proximity to enrollment in the study. In order to provide an indirect assessment of patients who may have been diagnosed with CMV retinitis during this immune reconstitution phenomenon, an examination of the baseline viral load was undertaken. Twenty patients had HIV RNA PCR below 400 copies/ml at baseline and thus, may have had CMV retinitis diagnosed in the setting of potential immune reconstitution. Eight patients were randomized to valganciclovir, and twelve patients were randomized to i.v. ganciclovir.

**Comment:**

- *The impact of a change to a new HAART regimen on the week 4 primary endpoint was minimized in this study. Most of the antiviral therapies documented were unlikely to cause significant effects on progression of CMV retinitis.*
- *There were no changes in HIV RNA or CD4 lymphocyte counts to suggest that improved immunologic functioning had an impact on the progression of CMV retinitis.*
- *The small number of patients with baseline HIV RNA below 400 copies/ml was equally distributed between the treatment groups. The impact of the immune reconstitution phenomenon in this study was minimized.*

**Visual Acuity Scores:**

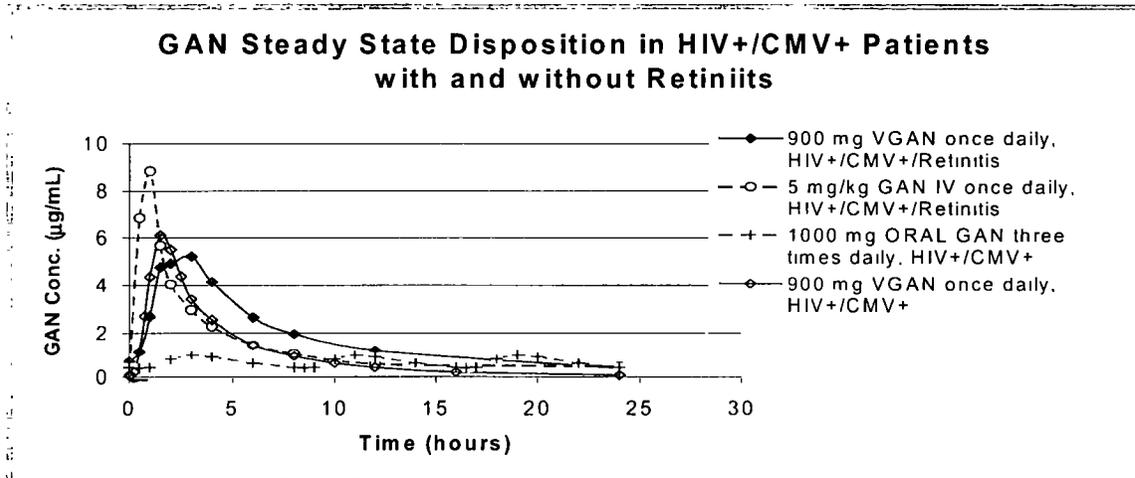
The proportion of patients who maintained visual acuity was comparable between the two treatment arms. In the i.v. ganciclovir arm, 74% maintained visual acuity. In the valganciclovir arm, 69% maintained visual acuity.

### Maintenance Therapy and Time to Progression Analysis:

Patients in study WV15376 received monthly retinal photographs in order to evaluate the secondary endpoint of time to progression. However, since all patients received open-label valganciclovir as maintenance therapy, no comparisons could be made. In addition, patients were permitted to change antiretroviral therapy after the initial four weeks, which likely contributed to the treatment effect. The median time to CMV retinitis progression for all patients in study WV15376 was approximately 220 days.

The support for the use of valganciclovir for the maintenance therapy of CMV retinitis rests on the pharmacokinetic data. The plasma concentration time profiles for ganciclovir following the administration of 900 mg valganciclovir q day, 5 mg/kg i.v. ganciclovir q day, and 1000 mg oral ganciclovir TID are provided in Figure 1. Both i.v. ganciclovir and oral ganciclovir are approved for the use in maintenance therapy for patients with inactive CMV retinitis. At all time points, serum concentrations of ganciclovir following administration of valganciclovir are higher than those provided by oral ganciclovir, which is approved for the maintenance therapy of CMV retinitis. This is demonstrated in Figure 1.

FIGURE 1: Compilation of Plasma Concentration Time Profiles, from Review by Dr. Kumi



#### Comment:

- *No conclusions can be reached on the effect of valganciclovir on the time to CMV retinitis progression because of the lack of a comparator arm.*
- *The pharmacokinetic profile of ganciclovir after administration of valganciclovir is bracketed by pharmacokinetic profiles of i.v. ganciclovir and oral ganciclovir. Because both ganciclovir formulations are approved for the maintenance therapy of CMV retinitis, the pharmacokinetic profiles provide support for the use of valganciclovir for the maintenance therapy of CMV retinitis.*

**Dropouts After Week 4 in Study WV 15376:**

There was a disproportionate dropout rate between weeks 4 and 12 in this study, during the initial eight weeks of maintenance therapy, with a greater number of dropouts occurring in the group originally assigned to valganciclovir induction, 14 versus 4 in the i.v. ganciclovir group. Because some of these patients may have already reached an endpoint of CMV retinitis progression at the week 4 endpoint, but were continued on study after week 4, we examined the results of the masked review of the retinal photographs obtained at week 4 endpoint for the patients who dropped out between weeks 4 and 12, as seen in Table 9.

TABLE 9: Outcome at Week Four for Those Who Discontinued Between Weeks 4 and 12

Week 4 endpoint	IV GCV N=4	Valgan N=14
CMV Progression	1	3
Discontinuations		
Adverse event	1	2
No photos/No CMV	0	2
Non-Progressors	2	7

As Table 9 shows, two patients in the i.v. ganciclovir treatment arm and seven patients in the valganciclovir arm were determined to have CMV disease progression or discontinued treatment, who were already included in the sensitivity analyses. The remaining nine patients who were determined to be non-progressors at week 4 had full evaluations of the case report forms in order to determine if these patients may have represented failures of induction or early maintenance. Only one patient in the valganciclovir group had photographic evidence of progression of CMV retinitis during the time period of weeks 4 to 12. This was confirmed by the FDA ophthalmology review. Two patients requested ganciclovir intraocular implants yet did not have photographic evidence of progression of CMV retinitis. One subject who received an implant was determined by his treating ophthalmologist to have CMV progression, yet the photographic review did not show progression. Four patients died of complications related to AIDS during this time period, and three (all in the valganciclovir group) voluntarily withdrew from the protocol.

**Comment:**

- *One concern was that the differential dropout rate might have represented a failure of induction or early maintenance therapy. After evaluation of the reasons for discontinuation and the retinal photographs taken between weeks 4 and 12, it appeared unlikely that the disproportionate dropouts were due to*

*a failure of therapy with valganciclovir. It appears that the disproportionate dropouts were most likely due to bias introduced by the open-label study design. Treating ophthalmologists made clinical decisions in real time based upon ophthalmologic examinations and without the results of the retinal photography. More patients assigned to valganciclovir were determined to have progression by the treating ophthalmologists, thus it appears that the were influenced by the patients initial treatment assignment of induction therapy.*

**SAFETY:**

Deaths:

There were 10 deaths, 5 in each arm, in study WV15376 during the first 12 weeks of the study.

Table 10: Cause of Death for 10 Patients in Study WV 15376

IV GCV	Valgan
Septic Shock	Wasting syndrome
PCP	PCP
Cardiac Arrest	Lymphoma
CNS lymphoma	Hypovolemic shock
PCP	Unknown (family declined to disclose)

At the one year time point, there were a total of 28 deaths.

Comment:

- The deaths were largely due to underlying AIDS diagnoses, and did not appear to be related to study treatments. The number of deaths (28) at one year is remarkably low given the profound immune suppression described in these patients at baseline. This reflects the improvement in the management of patients with AIDS.*

Serious Adverse Events:

A total of 23 patients reported serious adverse events (SAE's) during the first four weeks of study WV 15376. There were 12 subjects who reported 19 SAE's in the i.v. ganciclovir treatment arm, and 11 subjects reported 15 SAE's in the valganciclovir treatment arm. SAE's in the i.v. ganciclovir treatment arm included 9 reports of opportunistic infections, 5 reports of neutropenia, and one report each of septicemia, cardiac arrest, pancreatitis, mental impairment, and

weakness. SAE's in the valganciclovir treatment arm included 6 reports of opportunistic infections, 3 reports of neutropenia, and one report each of septicemia, lymphoma, death, hypotension, bradycardia, and hypovolemia.

Comment:

- *With the exception of neutropenia, which is known to be associated with ganciclovir therapy, the serious adverse events that were reported could be attributable to the profound immunologic suppression that all patients demonstrated at study entry. There was equal distribution of the types and numbers of serious adverse events between the treatment arms.*

Tables 11 through 13 contain comparative safety data from the first four weeks of study WV15376.

TABLE 11: Study WV15376, Gastrointestinal Adverse Events, All Grades

	IV GCV N=79	Valgan N=79
	%	%
Diarrhea	14%	20%
Nausea	18%	10%
Vomiting	11%	10%
Nausea/vomiting	6%	5%
Abdominal pain	8%	4%

TABLE 12: Study WV15376, Adverse Events Occurring in >5%, All Grades

	IV GCV N=79	Valgan N=79
	%	%
Fever	11%	11%
Oral Candidiasis	6%	10%
Cough	5%	10%
Headache	5%	10%
Rash	8%	5%
Retinal Detachment	6%	1%
Catheter-associated infection	13%	3%

TABLE 13: Study WV15376 Hematologic Adverse Events, All Grades

	IV GCV N=79	Valgan N=79
	%	%
Neutropenia	13%	11%
Anemia	9%	6%
Thrombocytopenia	0	1%

Comments:

- *As expected, the adverse event profiles were comparable, with similar rates of neutropenia and anemia between the treatment groups. There was somewhat more diarrhea occurring in subjects randomized to receive valganciclovir and more nausea in those receiving i.v. ganciclovir. A notable exception was in the rate of catheter –associated infectious complications; 13% in the i.v. ganciclovir arm compared to 3% in the valganciclovir arm. Two patients in the valganciclovir arm required intravenous catheters for chemotherapy and for electrolyte replacement.*
- *Because MAC infection can result in myelosuppression, a greater number of adverse hematologic events might be expected from patients who were randomized to receive valganciclovir. In addition, adverse events might be expected to occur with greater frequency in the valganciclovir arm because of additional concomitant medications due to MAC infection or esophageal candidiasis taken by patients randomized to that arm.*

**Safety and Efficacy Conclusions from Study WV15376:**

Study WV15376 provided comparative data on the efficacy of valganciclovir versus i.v. ganciclovir for the induction treatment of CMV retinitis. The study was not powered to determine statistically significant equivalence and the proportion of patients with progression of CMV retinitis was small (10-15%) in each treatment group. However, the rates were comparable. In a conservative analysis, the maximum difference was –13%, meaning that valganciclovir could be as much as 13% worse than i.v. ganciclovir. This outcome appears to be acceptable when balanced with the advantages associated with the availability of an orally administered drug for the treatment of CMV retinitis. The overall safety profile of valganciclovir during the first four weeks of the study was similar to the safety profile of i.v. ganciclovir. The only clinically meaningful difference was the higher rate of catheter-associated infection in subjects randomized to receive i.v. ganciclovir. Therefore, the applicant has demonstrated that valganciclovir has a comparable safety and efficacy profile to i.v. ganciclovir for the induction therapy of CMV retinitis.

**INTEGRATED REVIEW OF SAFETY:**

In addition to the initial 4 week data from study WV15376, safety data were derived from studies WV15705, an open-label single arm safety study (N=212), and from the open-label maintenance phase of study WV15376 (N=158). All patients received valganciclovir 900 mg daily. Table 16 shows the numbers of patients included in this NDA who were treated with the marketed maintenance dose of 900 mg daily. The safety update provided SAE data from study PV 16000, an ongoing study of valganciclovir prophylaxis in solid organ transplant patients, Data on 41 patients who had completed 100 days of therapy appeared similar to the SAE profile of ganciclovir.

The following table contains the numbers of patients who contributed to the safety database:

TABLE 14: Numbers of Patients Receiving the Marketed Dose for 6 and 12 Months

	WV15376	WV15705	Total
	N	N	N
6 months	115	178	293
12 months	86	152	238

Deaths: There were 21 deaths reported in study WV 15705 over a period of 18 months. The causes of death were primarily related to the patient's underlying immunodeficiency.

Comment:

- *Study medication did not appear to be related to the cause of death for patients in this study.*

Serious Adverse Events: In study WV 15705, there were 182 serious adverse events reported in 95 subjects. The largest proportion of SAE's were hematologic adverse events, with 54 (30%) reports of neutropenia, anemia, or thrombocytopenia. There were 26 SAE reports of opportunistic infections, and 23 SAE reports of gastrointestinal adverse events.

Table 15 shows the selected adverse events that were pooled from studies WV 15376 and WV 15705.

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TABLE 15: Pooled Selected Adverse Events from WV15376 and WV15705 (N=370), All Grades

Gastrointestinal	Diarrhea	41%
	Nausea/vomiting	30%
	Abdominal pain	15%
Hematological	Neutropenia	27%
	Anemia	26%
Other	Fever	31%
	Candidiasis	24%
	Dermatitis	22%
	Headache	22%
	Retinal Detachment	15%
	Abnormal LFT's	9%

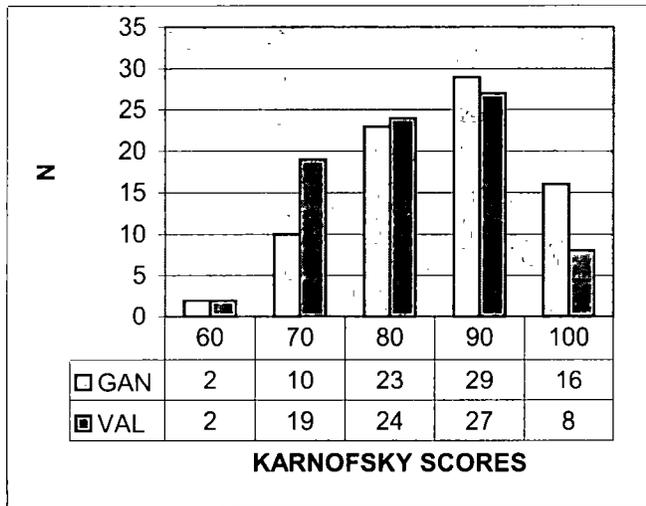
Patients originally randomized to the valganciclovir arm overall had greater numbers of patients with grade 4-4 anemia (hemoglobin less than 8 mg/dl), 12 patients randomized to valganciclovir and eight patients randomized to i.v. ganciclovir. There was greater use of erythropoetin and PRBC transfusions in the patients originally randomized to receive valganciclovir. In addition, seven patients in the valganciclovir group and three in the i.v. ganciclovir group were receiving concurrent zidovudine at the time of severe anemia.

Comment:

- *The pooled safety data from studies WV15376 and WV15705 show that the adverse event profile for valganciclovir was comparable to the adverse event profile described in the ganciclovir label.*
- *As noted above, there were greater numbers of patients with MAC infection at baseline. Figure 2 demonstrates the difference in Karnofsky Scores at baseline. This, along with a greater number of patients treated with zidovudine may provide some explanation for the increased incidence of severe anemia in those initially randomized to valganciclovir arm. However, all patients were receiving open-label valganciclovir at the time of the severe anemia; the rate of severe anemia was comparable to historical trials using i.v. ganciclovir; and the difference between rates of anemia were small. Anemia is readily monitored and managed by clinicians while patients receive ganciclovir.*

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FIGURE 2: Baseline Karnofsky Scores, Study WV 15376



**Safety Conclusions:**

Overall, the adverse event profile of valganciclovir appears comparable to that associated with the approved formulations of ganciclovir. Hematologic and gastrointestinal adverse events were the predominant classes of adverse events judged to be related to valganciclovir treatment. Although the safety database was small, the safety profile of valganciclovir appear similar to that of ganciclovir.. Because valganciclovir is metabolized to ganciclovir, the wealth of safety experience with ganciclovir also supports the safety of valganciclovir.

**Special Populations:**

The applicant did not include sufficient numbers of patients over the age of 65 years to conclude if this patient population has a different safety or efficacy profile. No data on the use of valganciclovir in a pediatric population was submitted. The studies were conducted in a predominantly male patient population. Black and Hispanic populations were well represented in clinical trial WV15376.

**Comments:**

- *The applicant has agreed to examine potential gender differences as a phase 4 commitment.*
- *The applicant has agreed to conduct appropriate pediatric studies, and a Written Request will be issued for valganciclovir and ganciclovir.*

**Pediatric Rule:**

The applicant has requested a waiver of the requirement to conduct studies in pediatric patients with CMV retinitis. The applicant stated that the decreased incidence of opportunistic infections among HIV-infected adults applied to HIV-infected children also. Furthermore, the use of antiretroviral agents to prevent perinatal transmission of HIV has resulted in a substantial decrease in the

number of HIV-infected children in the United States. Under 21 CFR 314.50(g)(3), the FDA can grant a full waiver of the requirement to conduct pediatric studies if the total number of pediatric patients is less than 50,000 per year or the number in a pediatric age group is less than 15,000. Because the number of pediatric patients with CMV retinitis is likely to be less than 50,000, and less than 15,000 for each of the pediatric age groups, a full waiver of the Pediatric Rule will be granted for the indication of CMV retinitis in patients with AIDS.

**Financial Disclosure:**

The applicant submitted a copy of form FDA 3454, which collectively states that none of the clinical investigators disclosed financial interests or financial arrangements with the applicant.

**Labeling:**

The recommended labeling changes were sent to the applicant on March 9, 2001. The label will not contain microbiologic information on viruses other than CMV. The label will include a concise description of drug interactions with ganciclovir and tabular presentation of the clinical study WV15376. The indication will be for the treatment of CMV retinitis in patients with AIDS. Hematologic toxicities are described in the WARNINGS sections. The label will contain appropriate warnings that prevent a one-to-one conversion from oral ganciclovir capsules to valganciclovir tablets could result in overdose. The sponsor initially did not include a Patient Package Insert (PPI) as part of the labeling submitted in the NDA. At our request, the sponsor submitted a PPI with labeling. The PPI will include sufficient warnings about the difference in bioavailability between oral ganciclovir and valganciclovir.

**Conclusions:**

The clinical data from one small equivalence designed study of induction therapy of CMV retinitis, combined with safety and pharmacokinetic data were submitted in the NDA package. The results of the induction study showed comparable proportions of patients with CMV progression in each treatment arm. The maximum lower bound of the 95% confidence interval was -13%. The efficacy of valganciclovir in comparison to i.v. ganciclovir may be up to 13% worse, but this is balanced by the significant improvement in the management of patients with CMV retinitis offered by availability of an oral agent. We believe that the efficacy of valganciclovir demonstrated for the induction therapy of CMV retinitis reached a sufficiently high hurdle. The results of the primary efficacy endpoint of CMV disease progression at four weeks were confirmed by a masked review of the retinal photographs by the FDA ophthalmologists. Pharmacokinetic data was deemed adequate to support the use of valganciclovir for the maintenance therapy of CMV retinitis. The safety database in the NDA package included less than 300 patients receiving valganciclovir for a minimum of six months. Hematologic and gastrointestinal adverse events were the predominate classes of adverse events identified in the safety database. This safety data is similar to

the safety data that is reported in the ganciclovir label. In addition, because valganciclovir is rapidly converted to ganciclovir, the wealth of safety data available from studies of ganciclovir supports the safety of valganciclovir. In summary, the applicant has demonstrated the safety and efficacy of valganciclovir for the treatment of CMV retinitis in patients with AIDS.

**Recommended Regulatory Action:**

This reviewer supports the marketing approval of valganciclovir tablets for the treatment of CMV retinitis in AIDS patients.

**Phase 4 Commitments:**

1. The applicant will commit to the timely completion and submission of study results from study PV 16000, "A Randomized, Double-Blind, Double-Dummy, Active-Comparator Controlled Multi-Center Study of the Efficacy and Safety of Valganciclovir Vs. Oral Ganciclovir for Prevention of Cytomegalovirus Disease in High-Risk Heart, Liver, and Kidney Allograft Recipients". The timing of this submission is estimated to be during the fourth quarter of 2002.
2. At the time that the efficacy supplement outlined above is submitted, the applicant will commit to submission of all available safety data collected in studies WV15376 and WV15705. The timing of this submission is estimated to be during the fourth quarter of 2002.
3. The applicant will commit to an analysis of the gender effects of valganciclovir and ganciclovir in ongoing studies, PV16000, WV15376 and WV15705.

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Joseph G. Toerner, M.D. eso 4/27/01  
Medical Officer, DAVDP

Concurrence:

Therese Cvetkovich, M.D. eso 4/28/01  
Medical Officer Team Leader, DAVDP

Debra Birnkrant, M.D.  
Acting Division Director, DAVDP

CC:

HFD-530/Division File  
HFD-530/Micro/Biswall  
HFD-530/PharmTox/Farrelly  
HFD-530/Chemistry/Gu  
HFD-530/Biopharm/Kumi  
HFD-530/Statistics/Soon  
HFD-530/MO/Toerner  
HFD-530/PM/Stephens

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this page is the manifestation of the electronic signature.**  
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/s/  
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Joe Toerner  
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MEDICAL OFFICER

Therese Cvetkovich  
5/18/01 12:50:36 PM  
MEDICAL OFFICER

Debra Birnkrant  
6/11/01 10:06:00 AM  
MEDICAL OFFICER

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Consult from HFD-530 Division of Antiviral Drug Products to  
HFD-550 Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products

Medical Officer's Review of NDA 21-304  
Retinal Photographs

NDA 21-304  
Medical Officer's Review

Date of Consult: 11/2/00  
Review Completed: 1/26/01

**Proposed Tradename:**

450 mg Tablets

**Generic Name:**

valganciclovir hydrochloride

**Sponsor:**

Roche Global Development – Palo Alto  
Syntex (USA), Inc.  
3401 Hillview Avenue  
Palo Alto, California 94304-1397

**Pharmacologic Category:**

L-valyl ester salt (prodrug) of ganciclovir

**Proposed Indication:**

treatment of cytomegalovirus retinitis in patients  
with acquired immunodeficiency syndrome (AIDS)

**Dosage Form and  
Route of Administration:**

450 mg tablet for oral administration

**Submitted:**

Submitted by the applicant to NDA 21-304 are the original retinal images (slides) for patients from the efficacy study WV15376, "A Randomized, Controlled Comparison of the Safety and Efficacy of RO 107-9070, (Valganciclovir) vs. IV Ganciclovir as Induction Therapy for the Treatment of Newly Diagnosed Cytomegalovirus Retinitis."

**Clinical Study WV15376:**

The study was a randomized, open label, parallel group design conducted in HIV seropositive patients with newly diagnosed CMV retinitis, randomized to receive either intravenous ganciclovir or oral valganciclovir.

Intravenous ganciclovir was administered at 5/mg/kg bid for 3 weeks followed by 5 mg/kg qd for one week. Valganciclovir was administered at 900 mg bid for three weeks then 900 mg qd for one week.

The primary efficacy parameter was the proportion of patients with progression of CMV retinitis by week 4. This endpoint was defined as the movement of retinitis lesion borders  $\geq 750 \mu\text{m}$  (along a front  $\geq 750 \mu\text{m}$  wide) or appearance of a new area of retinitis

$\geq 1/4$  disc area in size at any time between baseline and the week 4 visit. A central reading center, the \_\_\_\_\_ assessed progression by treatment-masked reading and comparison of retinal slides. Readers had no knowledge of patient study drug assignment.

The \_\_\_\_\_ followed the protocol for grading cytomegalovirus (CMV) retinitis from fundus photographs developed by the \_\_\_\_\_ Retinitis progression was classified as “none,” “border movement  $\geq 750 \mu\text{m}$ ,” “new lesion  $\geq 1/4$  disc area,” both movement and new lesion,” or “cannot grade.”

Using wide-angle camera, standardized fundus photography was performed to document the post-equatorial fundus in a set of color slides. Photographers were required to satisfy specific certification requirements. For each eye, the array of nine photographic fields (a non-simultaneous stereoscopic slide pair of the posterior pole of the retina surrounded by eight slightly overlapping non-stereoscopic slides) was mounted in a plastic sheet and examined with a 5X magnifying viewer.

All 160 patients who were randomized were included in the intent to treat population (ITT). Two patients were excluded from the safety analysis population (158 patients) because no safety data was recorded for them.<sup>1</sup> A total of 14 patients were excluded from the standard analysis population (146 patients), seven patients in each treatment arm.

**Table 1 – Patient Listing of Exclusions from Analysis Populations**

Site/Patient	Excluded From	Violation/Deviation
<b>GCV/VGCV Treatment Group</b>		
17840/0602	Standard	Implant OD at entry
17841/0705	Standard	Non-compliance with study therapy in the first 28 study days
17845/1105	Standard	No photographic evidence of CMV at entry
18676/2214	Standard	No efficacy data reported after randomization
18677/2301	Standard	No photographic evidence of CMV at entry
21414/4301	Standard	No photographic evidence of CMV at entry
21422/5102	Standard & Safety	Received no dose of study treatment
<b>VGCV/VGCV Treatment Group</b>		
17840/0613	Standard	Non-compliance with study therapy in the first 28 study days
17841/0703	Standard	Non-compliance with study therapy in the first 28 study days
17845/1101	Standard	No photographic evidence of CMV at entry
17847/1301	Standard	No photographic evidence of CMV at entry
18675/2102	Standard	No efficacy data reported after randomization
21412/4103	Standard	Non-compliance with study therapy in the first 28 study days
21481/5501	Standard & Safety	Non-compliance with study therapy No safety or efficacy data reported after randomization

<sup>1</sup> One patient (21422/5102) withdrew immediately after being randomized to IV ganciclovir and did not receive any study medication; a second patient (21481/5501), randomized to oral valganciclovir, failed to return after his baseline visit.

Based on the analysis of fundus photographic data, no substantial differences between the two treatment groups were noted with respect to CMV retinitis status at baseline. Of the 146 patients in the standard population, 102 (70%) had unilateral CMV retinitis [54 patients (74%) in the ganciclovir arm and 48 patients (66%) in the valganciclovir arm], and 36 patients had bilateral CMV retinitis [16 patients (22%) in the ganciclovir arm, and 20 patients (27%) in the valganciclovir arm].

A total of 8 patients in the standard population were categorized as “unevaluable” at baseline for retinal photographic assessment of unilateral/bilateral disease status.

Photographic assessment of baseline disease status was comparable for patients in the ITT population.

#### Efficacy Results

Based on the masked assessment of fundus photographs in the standard population, the efficacy of valganciclovir was comparable to that of IV ganciclovir as induction therapy for newly diagnosed CMV retinitis. An equal proportion of patients in the two treatment groups (10%) were graded as having progression of CMV retinitis by week 4, and the lower boundary of the 90.4% confidence interval of the between-group difference in progression proportions (-0.082) was above the pre-specified equivalence value of -0.25.

**Table 2 – Analysis of CMV Retinitis Progression by Week 4 Based on Photographic Assessment (Standard Population)**

	GCV/VGCV N=73	VGCV/VGCV N=73
Progression of retinitis by week 4 compared to baseline		
Non-progressor	63 (86%)	64 (88%)
Progressor	7 (10%)	7 (10%)
Unevaluable	3 (4%)	2 (3%)
Type of progression		
Movement	6 (8%)	7 (10%)
New spot	1 (1%)	
Primary efficacy analysis		
Progression proportion	0.100	0.099
No progression proportion	0.900	0.901
Difference in progression proportions		0.001
90.4% confidence interval*		(-0.082, 0.085)

\*90.4% confidence intervals are presented in order to adjust for the interim analysis

Unevaluable = “missing,” “cannot grade,” or “no CMV at baseline”

Unevaluable patients are excluded from the calculations for the primary efficacy analysis

Based on the masked assessment of fundus photographs in the intent to treat population, the efficacy of valganciclovir was comparable to that of IV ganciclovir as induction therapy for newly diagnosed CMV retinitis. An equal proportion of patients in the two treatment groups (9%) were graded as having progression of CMV retinitis by week 4, and the lower boundary of the 90.4% confidence interval of the between-group difference in progression proportions (-0.082) was above the pre-specified equivalence value of -0.25.

**Table 3 – Analysis of CMV Retinitis Progression by Week 4 Based on Photographic Assessment (ITT Population)**

	GCV/VGCV N=80	VGCV/VGCV N=80
Progression of retinitis by week 4 compared to baseline		
Non-progressor	63 (79%)	64 (80%)
Progressor	7 (9%)	7 (9%)
Unevaluable	10 (13%)	9 (11%)
Type of progression		
Movement	6 (8%)	7 (9%)
New spot	1 (1%)	
Primary efficacy analysis		
Progression proportion	0.100	0.099
No progression proportion	0.900	0.901
Difference in progression proportions		0.001
90.4% confidence interval*		(-0.082, 0.085)

\*90.4% confidence intervals are presented in order to adjust for the interim analysis

Unevaluable = "missing," "cannot grade," or "no CMV at baseline"

Unevaluable patients are excluded from the calculations for the primary efficacy analysis

#### Reviewer's Comments:

*A request for consultation was received on November 2, 2000, from HFD-530 Division of Antiviral Drug Products to review retinal photographs submitted to NDA 21-304. This medical reviewer's analysis of CMV retinitis progression by Week 4 based on photographic assessment was performed on the intent to treat population (160 patients).*

*The original retinal images (slides) for 159 of the 160 patients from the efficacy study WV15376 were received and reviewed without knowledge of patient study drug assignment. The protocol for grading cytomegalovirus (CMV) retinitis from fundus photographs developed by the \_\_\_\_\_ was included with the original retinal images, and this protocol was reviewed and utilized in the assessment of the retinal images (slides).*

*Any progression of retinitis by week 4 compared to baseline was noted. A series of graduated standard circles printed on a transparent overlay was utilized for measurements derived from the slides. These standard circles (with diameters of 63, 125,*

250, 375, 500, 750, 1000, and 1500  $\mu\text{m}$ ) were provided by the \_\_\_\_\_ and were identical to those utilized by the \_\_\_\_\_. There were two versions of the standard circles, appropriately scaled for the Canon 60° and Topcon 50° cameras used for photography in study WV15376.

The applicant organized the retinal images (slides) in binders by patient, by eye, and by visit. Visits were separated by tabs within the binders marked: Baseline (BL), week 2, week 4, Extension Visits (EV#), and Termination Visit (Term).

#### Medical Officer's Evaluation of Retinal Photographs

Five subjects were independently evaluated as having no photographic evidence of CMV at baseline and were excluded from the analysis as unevaluable (Table 4).

**Table 4 – Patients with no Photographic Evidence of CMV Retinitis at Baseline**

Site/ Patient Number	Study Treatment*
17845/1105	GCV/VGCV
18677/2301	GCV/VGCV
21414/4301	GCV/VGCV
17845/1101	VGCV/VGCV
17847/1301	VGCV/VGCV

\*study treatment arm unmasked only after all retinal images for study WV15376 evaluated

One subject had no slides submitted and was excluded from analysis as unevaluable (Table 5). Seven subjects had baseline retinal photos only and were excluded from analysis as unevaluable. One subject did not have photos after week 2 and was excluded from the analysis as unevaluable; photos at week 2 for this subject did not show evidence of CMV retinitis progression. One subject did not have baseline slides submitted for his left eye and was excluded from the analysis as unevaluable.

**Table 5 – Patients Excluded from Analysis as Unevaluable (Missing Photos)**

Site/ Patient Number	Study Treatment*	Available Slides for Review
17841/705	GCV/VGCV	Baseline only
18676/2214	GCV/VGCV	Baseline only
21422/5102	GCV/VGCV	Baseline only
21484/5802	GCV/VGCV	Baseline only
17840/613	VGCV/VGCV	Baseline and Week 2 only
17841/703	VGCV/VGCV	Baseline only
18675/2102	VGCV/VGCV	No slides submitted
21412/4103	VGCV/VGCV	Baseline only
21481/5501	VGCV/VGCV	Baseline only
21485/5902	VGCV/VGCV	No Baseline slides for OS

\*study treatment arm unmasked only after all retinal images for study WV15376 evaluated

Three subjects were excluded from analysis as unevaluable based on the quality of the retinal images submitted (Table 6).

**Table 6 – Patients Excluded from Analysis as Unevaluable  
(Inadequate Photographic Quality)**

Site/ Patient Number	Study Treatment*	Comment
17843/906	GCV/VGCV	No peripheral fundus assessments
18009/1802	GCV/VGCV	Poor resolution
21241/3102	VGCV/VGCV	Poor fixation/poor peripheral assessments

\*study treatment arm unmasked only after all retinal images for study WV15376 evaluated

Fourteen subjects were independently graded as having progression of CMV retinitis by week 4 (Table 7). Two of the subjects had missing or incomplete photographic evaluations at Week 4 but were evaluated as progressors based on Week 2.

**Table 7 – Patients with Photographic Evidence of CMV Retinitis Progression by Week 4  
Based on Photographic Assessment**

Site/ Patient Number	Study Treatment*	Comment
17838/404	GCV/VGCV	No Week 4 slides Week 2 shows progression
17840/603	GCV/VGCV	
17840/607	GCV/VGCV	
17842/801	GCV/VGCV	
17847/1304	GCV/VGCV	
18676/2203	GCV/VGCV	
18676/2213	GCV/VGCV	
17837/304	VGCV/VGCV	
17840/604	VGCV/VGCV	Incomplete slides at Week 2 and Week 4 But these slides demonstrate progression
17840/610	VGCV/VGCV	
17840/615	VGCV/VGCV	
17843/903	VGCV/VGCV	
18683/2501	VGCV/VGCV	
21409/3801	VGCV/VGCV	

\*study treatment arm unmasked only after all retinal images for study WV15376 evaluated

Comparing the Medical Officer's photographic assessment of the intent to treat population (Table 8) to the applicant's photographic assessment (Table 3), there is a one-subject difference in the non-progressor and unevaluable groups in the GCV/VGCV treatment arm.

This subject, 17840/602, was excluded from the applicant's standard population as a protocol violator because he had an intraocular implant in the right eye at study entry. This subject was graded as unevaluable in the applicant's intent to treat population.

/s/

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William Boyd  
2/1/01 10:06:07 AM  
MEDICAL OFFICER

Wiley Chambers  
2/1/01 10:17:10 AM  
MEDICAL OFFICER

**APPEARS THIS WAY  
ON ORIGINAL**

Consult from HFD-530 Division of Antiviral Drug Products to  
HFD-550 Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products

**Medical Officer's Review of NDA 21-304  
Retinal Photographs**

NDA 21-304  
Medical Officer's Review #2

Date of Consult: 11/2/00  
Review Completed: 2/6/01

**Proposed Tradename:** ~~\_\_\_\_\_~~ 450 mg Tablets

**Generic Name:** valganciclovir hydrochloride

**Sponsor:** Roche Global Development – Palo Alto  
Syntex (USA), Inc.  
3401 Hillview Avenue  
Palo Alto, California 94304-1397

**Pharmacologic Category:** L-valyl ester salt (prodrug) of ganciclovir

**Proposed Indication:** treatment of cytomegalovirus retinitis in patients  
with acquired immunodeficiency syndrome (AIDS)

**Dosage Form and  
Route of Administration:** 450 mg tablet for oral administration

**Consult Request:**

Ophthalmology Medical Officer's Review #1 identified progression of CMV retinitis by photographs in each treatment group during the first four weeks of Study WV15376. This review will cover the retinal photographs of the eighteen subjects who withdrew from Study WV15376 prior to Week 12.

**Clinical Study WV15376:**

The study was a randomized, open label, parallel group design conducted in HIV seropositive patients with newly diagnosed CMV retinitis, randomized to receive either intravenous ganciclovir or oral valganciclovir.

Intravenous ganciclovir was administered at 5/mg/kg bid for 3 weeks followed by 5 mg/kg qd for one week. Valganciclovir was administered at 900 mg bid for three weeks then 900 mg qd for one week.

On completion of 4 weeks of randomized treatment, patients were able to receive valganciclovir maintenance therapy (valganciclovir 900 mg qd) in an extension of the study designed to provide long term safety and efficacy information. When progression of CMV retinitis was diagnosed during this long term extension phase, re-induction therapy consisting of valganciclovir 900 mg bid for three weeks, followed by valganciclovir 900 mg qd maintenance therapy, could be initiated at the discretion of the investigator.

**Reviewer's Comments:**

*A higher number of subject withdrawals occurred in the valganciclovir treatment arm (14) than in the ganciclovir treatment arm (4) between weeks 4 and 12.*

*The original retinal images (slides) for these eighteen withdrawn subjects were reviewed without knowledge of patient study drug assignment. All available slides for these subjects between baseline and week 12 were evaluated for photographic evidence of CMV retinitis progression.*

**Table 1 - Listing of all Subject Withdrawals after Day 28 (Week 4) and Up to Day 84 (Week 12)**

Pt #	Study Treatment*	Medical Reviewer's Comments	Applicant's Reason for Patient Withdrawal
303	GCV/VGCV	No progression	Death
304	VGCV/VGCV	Progression by wk 4	Insuff. response to therapy
306	VGCV/VGCV	No progression	Failure to return
402	VGCV/VGCV	No progression	Refused tx
607	GCV/VGCV	Progression by wk 4	AE - intercurrent illness
617	VGCV/VGCV	No progression	Refused tx
901	VGCV/VGCV	No progression	AE - intercurrent illness
1110	VGCV/VGCV	No progression	AE - intercurrent illness