

Memorandum

From: Valganciclovir Review Team
Division of Antiviral Drug Products

Through: Debra Birnkrant, M.D.
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To: Members, consultants and guests of the Antiviral Drugs Advisory
Committee

Subject: Background information for NDA 21-304

On February 27, 2001, we will ask you to consider NDA 21-304, the new drug application (NDA) for valganciclovir, a prodrug of ganciclovir. The applicant is seeking indications for induction and maintenance treatment of CMV retinitis in AIDS patients.

Regulatory Background

1. Development of valganciclovir

The development of valganciclovir coincided with the development of HAART. The rapid decline of CMV retinitis in AIDS patients significantly impeded the applicant's plan to conduct phase 3 studies to support this indication. The applicant therefore abandoned their plans to pursue an indication for therapy of CMV retinitis in 1997.

However, based upon the public health need for a potent oral therapy for treatment of CMV disease, DAVDP encouraged the applicant to continue the development of valganciclovir, in a more limited fashion. To the applicant's credit, they agreed to expand an ongoing phase 2 study in order to provide clinical data to support the CMV retinitis indication. Both the applicant and DAVDP recognized that the study would be significantly underpowered to demonstrate equivalence. Other evidence to support the safety and anti-CMV activity of valganciclovir would include the extensive experience with ganciclovir, the pharmacokinetic data from valganciclovir, and perhaps the future results from a second clinical study (of prophylaxis of CMV disease in solid organ transplant patients).

In order to provide an historical perspective for review of this NDA, the following table summarizes the efficacy data that supported approval of previous antivirals for induction and maintenance treatment of CMV retinitis. The studies included in NDA 21-304 are also provided.

Efficacy studies used to support approval of anti-CMV agents

Anti-CMV Agents	Type of Study Design for Induction, and Total Number of Patients	Primary Endpoints	Results of the Primary Endpoint Analysis	Studies Used in Support of Maintenance Therapy
Ganciclovir, intravenous Approved June 23, 1989	1. Randomized, controlled, immediate vs. delayed therapy N=35 2. Non-randomized, retrospective, immediate vs. delayed therapy N=41	1. Time to progression of CMV retinitis 2. Time to progression of CMV retinitis	1. Mean time to progression of 66 days for immediate vs. 19 for delayed. 2. Mean of 105 days for immediate vs. 35 days for delayed	Subsequent studies supported maintenance therapy
Ganciclovir, capsules Approved December 22, 1994	Not an approved indication for induction due to poor bioavailability, approved for maintenance therapy			Three open-label, comparative, randomized studies for maintenance, total N=519 Pooled discontinuation rates due to unsatisfactory treatment response: 30% receiving oral ganciclovir, 14% receiving IV ganciclovir
Foscarnet, intravenous Approved September 27, 1991	Randomized, controlled immediate vs. delayed therapy N=24	Time to progression of CMV retinitis	Mean of 53.3 days for immediate vs. 21 days for delayed	Open-label maintenance of three different dosing regimens N=64
Cidofovir, intravenous Approved June 26, 1996	Randomized, controlled, immediate vs. delayed therapy N=48	Time to progression of CMV retinitis	Mean of 120 days for immediate vs. 21.5 days for delayed	Open-label maintenance of two different dosing regimens N=100
Valganciclovir, NDA 21-304 submitted September 2000	Randomized, active-controlled, IV ganciclovir vs. oral valganciclovir N=160	Proportion of patients with disease progression at week 4	7 in IV ganciclovir arm and 7 in oral valganciclovir arm had disease progression	Open-label maintenance, N=212

Clinical Studies:

The applicant submitted the results from two clinical studies, WV 15376 and WV 15705. In addition, the NDA contained data from several pharmacokinetic studies. The NDA also contained a review of the clinical data supporting the approval of ganciclovir for the treatment of CMV retinitis in AIDS patients.

WV15376

Study WV 15376 enrolled 160 patients with newly diagnosed CMV retinitis; 80 received induction therapy with intravenous ganciclovir and 80 received induction therapy with oral valganciclovir. Retinal photographs were obtained at baseline, week two and week four; a masked reviewer evaluated these. After week four, all patients in the study received open-label valganciclovir maintenance at 900 mg once daily; HAART therapy could be changed after week four. Most patients had zone 3 or 3 retinitis, but 24% in each arm had zone 1 retinitis. The mean (median) CD4 cell count at baseline was 54 (26) cells/mm³ in the IV ganciclovir arm, and 58 (20) cells/mm³ in the valganciclovir arm. The median HIV RNA at baseline was 4.9 log₁₀ copies/mL in the IV ganciclovir arm, and 4.8 log₁₀ copies/mL in the valganciclovir arm.

Analysis of the primary endpoint revealed that seven patients in each treatment arm had progression of retinitis after four weeks as determined by the masked ophthalmology reviewer. Of note, the mean time to progression of CMV retinitis was substantially longer (219 days in the ganciclovir arm and 226 days in the valganciclovir arm) than the times observed in studies before the introduction of HAART.

Comments: The weaknesses of the study include its open-label design and the small sample size. The strengths of the study include the fact that subjects were not allowed to change antiretroviral therapy from the time of screening to the week four endpoint, thus minimizing the effect of new antiretroviral regimen on response to study treatments. Another strength was the inclusion of patients with zone 1 retinitis. The pivotal trials used in the past to support the approval of antivirals for the induction therapy of CMV retinitis included only patients with zone 2 or 3 retinitis, and lacked data on the efficacy of the new agent in patients with more advanced CMV retinitis. WV 15376 represents the first pivotal study of induction therapy that included patients with more advanced, zone 1 CMV retinitis.

The primary endpoint of study WV 15376 was the proportion with progression of CMV retinitis at week four. Previous studies of therapies for CMV retinitis usually utilized the endpoint of time to treatment failure. However, the availability of HAART made use of this endpoint no longer tenable for the following reason. Development of a new OI usually indicated failure of antiretroviral treatment and the need for a change in antiretroviral therapy. The impact of a successful new regimen would be to significantly influence the response to treatment and delay the time to failure, making the traditional endpoint of time to CMV retinitis progression impractical, if not impossible.

A discordant drop out rate occurred between weeks four and twelve in this study. Fourteen patients discontinued therapy in the valganciclovir group and four in the IV

ganciclovir group. A preliminary review of the case report forms indicate that four patients (one in the i.v. ganciclovir arm and three in the valganciclovir arm) were already recorded with CMV retinitis progression in the week 4 analysis. Eight patients were recorded with non-progression with CMV retinitis, and six patients were not evaluable because of missing photographs or an incorrect diagnosis of CMV retinitis. Of those who were recorded with non-progression, only one patient in the valganciclovir arm in this review may be considered to have CMV retinitis progression at the week 4 primary endpoint. Further analyses of the results of this study will be presented.

WV 15705

Study WV 15705, enrolled 212 patients who received open-label valganciclovir for the maintenance treatment of CMV retinitis. Patients who were receiving intravenous ganciclovir for the maintenance treatment of CMV retinitis were eligible for enrollment, which began on April 29, 1998. The study was designed primarily as a safety study. The results of the study provide support for the safety profile of valganciclovir in AIDS patients with CMV retinitis. Due to the low number of clinical events, a mean time to CMV retinitis progression could not be calculated.

Safety

Lastly, studies WV 15705 and WV 153765 provided the safety database for 372 patients who received valganciclovir. Review of the safety database demonstrated that in general, valganciclovir's adverse event profile was similar to ganciclovir. An equal proportion of patients (approximately 54%) in each arm of study WV 15376 maintained hemoglobin levels above 9.5 g/dL. However, although all patients were receiving open-label valganciclovir after week four, 29% of patients who received valganciclovir for induction developed hemoglobin levels below 8.0 g/dL versus 16% who received i.v. ganciclovir. In study WV 15705, 12% of patients receiving open label valganciclovir developed hemoglobin levels below 8.0 g/dL.

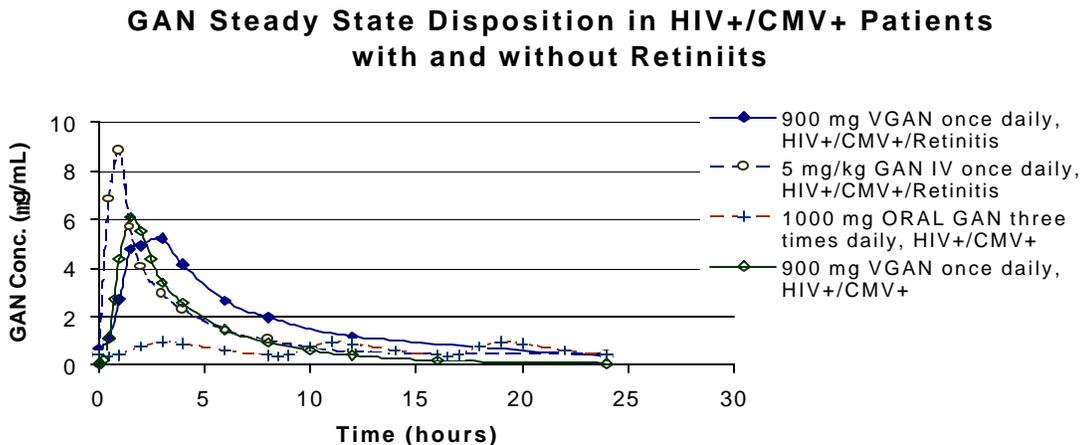
Pharmacokinetic Data that Support Valganciclovir Use in Maintenance Therapy:

The pivotal study WV15376 assessed the efficacy of oral valganciclovir as induction therapy for CMV retinitis. Because all patients received oral valganciclovir after week 4, it was not possible to use study WV15376 results to compare valganciclovir to IV ganciclovir for CMV maintenance therapy. The applicant provided pharmacokinetic data to support the use of valganciclovir for CMV maintenance therapy.

Pharmacokinetic studies conducted with valganciclovir indicated that administration of valganciclovir resulted in insignificant valganciclovir exposure levels and a ganciclovir bioavailability of approximately 60 %. Relative ganciclovir exposure from IV ganciclovir, oral ganciclovir and valganciclovir were consistent across different patient populations, including the target patient population (AIDS patients with CMV retinitis). It was noted that ganciclovir exposure in the target population during the efficacy trial tended to be higher than previously observed in other patient populations.

Ganciclovir concentration vs. time profiles obtained following administration of valganciclovir and the two approved ganciclovir regimens, IV ganciclovir and oral ganciclovir, are presented in figure 1.

Figure 1: Ganciclovir Plasma Concentration-Time Profiles



Data Sources: Study WV15376 for HIV+/CMV+/Retinitis (IV ganciclovir and valganciclovir), Study WP15347 for HIV+/CMV+ (valganciclovir), and Study GANS2638 for HIV+/CMV+ (oral ganciclovir).

At the proposed maintenance dose of 900 mg valganciclovir once daily, ganciclovir exposure (AUC) was comparable to the exposure produced by the approved 5 mg/kg IV ganciclovir dose. The main difference in ganciclovir exposure between valganciclovir and IV ganciclovir is the higher C_{max} value following IV ganciclovir. However, beginning one to two hours after dosing, ganciclovir plasma concentrations for valganciclovir exceeded ganciclovir concentrations following IV ganciclovir. Although C_{max} following valganciclovir is lower than following IV ganciclovir, it is much higher than the C_{max} observed following oral ganciclovir. Empirically, it appears that the C_{max} value may not contribute significantly to ganciclovir efficacy, because the efficacy of oral ganciclovir dosed 1000 mg q 8 hr is comparable to the efficacy of IV ganciclovir dosed once daily. Thus, the above plasma concentration-time profile comparisons indicate that valganciclovir efficacy for CMV maintenance treatment should be comparable to the efficacy of the approved IV and oral ganciclovir regimens.

PK/PD Analyses

The sponsor conducted a PK/PD analysis and concluded that AUC was the exposure measure that best predicted time to first photographic progression during maintenance therapy, and C_{max} has little added value in this regard.

The PK/PD analysis used data from a Phase 3 study conducted during the clinical development of ganciclovir (Study GANS2226). In this study, patients received IV ganciclovir or one of several ganciclovir dosing regimens. We concluded that there were insufficient dosing time records to perform the population PK analysis needed for further PK/PD assessment. Specifically, the dosing time was recorded only for the one

dose administered prior to blood sample collection. In order to perform a population PK analysis, assumptions were made to determine dosing times for the two doses before the recorded dose event, according to the following scheme:

Regimen	Time of Previous Dose	Time of Dose - 1	Time of Dose - 2
TID	03:00 – 10:59	14 h earlier	19 hr earlier
	11:00 – 15:59	5 h earlier	19 hr earlier
	16:00 – 2:59	5 hr earlier	10 hr earlier
BID	03:00 – 10:59	12 hr earlier	24 hr earlier
	11:00 – 15:59	16 hr earlier	24 hr earlier
	16:00 – 2:59	8 hr earlier	24 hr earlier
QD	Any time	24 hr earlier	48 hr earlier

Example: For a TID regimen, if the dosing time right before blood sample collection was 2:00 p.m. (or 14:00) today, then the dose before that (prior dose #1) was assumed to be 5 hrs earlier (or at 9 am today), and the dose before that (prior dose #2) was 19 hrs earlier (or at 7 p.m. yesterday).

Since errors in dosing times will result in errors in PK parameter estimates, the PK/PD analysis was not acceptable. Another point of concern was that only one blood sample per dose was collected, with most patients having a total of two samples for analysis. Under this circumstance, the accuracy of individual PK parameter estimates obtained from the population PK analysis was unknown.

Due to these concerns, the pharmacokinetic comparisons (valganciclovir vs. IV and oral ganciclovir) served as a more appropriate predictor of valganciclovir use in maintenance therapy than the submitted PK/PD analyses.

Draft Questions to the Committee:

1. Do the data submitted in this NDA support the safety and efficacy of valganciclovir for induction therapy of CMV retinitis?
 In your discussion, please consider the effects of the study size, the four-week endpoint, and the differential dropouts between weeks 4 and 12.
2. Has the applicant provided sufficient pharmacokinetic and clinical information to support the use of valganciclovir for the maintenance therapy of CMV retinitis?
3. If the answers to questions #1 and #2 are yes, please discuss how valganciclovir should be used in relationship to other available therapies for CMV retinitis.
4. What additional clinical information, if any, would you recommend that we request of the applicant to answer questions about the safety or efficacy of valganciclovir for the treatment of CMV retinitis in patients with AIDS?