

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-304

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

DRUG: VALGANCICLOVIR
NDA#: 21-304
NDA DATE: SEPTEMBER 28, 2000
INDICATION: TREATMENT OF CMV RETINITIS
MEDICAL REVIEWER: JOSEPH TOERNER, MD

STATISTICAL REVIEWER: ANDREI BREAZNA, Ph.D.

BACKGROUND

Cytomegalovirus (CMV) causes important sight- or life-threatening opportunistic disease in immunocompromised subjects. Intravenous medications (ganciclovir, foscarnet and cidofivir) were the first drugs utilized to treat CMV retinitis. Local therapies (intra-ocular implants or intravitreal injections) are available, but they do not provide systemic coverage against the viral infection. The oral ganciclovir medication has low bioavailability. The drug under evaluation is a valyl ester pro-drug of ganciclovir. When given orally, valganciclovir is rapidly hydrolyzed to the active compound ganciclovir, with the majority of hydrolysis thought to occur pre-systemically.

The objectives of the study were:

- a) To investigate the efficacy of valganciclovir when used as induction therapy in patients with newly diagnosed CMV retinitis.
- b) To investigate the safety profile of valganciclovir in this indication.
- c) To assess the effects of induction and maintenance level dosing of valganciclovir on CMV viral load, as measured by CMV PCR.
- d) To assess the pharmacokinetics of ganciclovir following the administration of valganciclovir in the target population.

This review will focus on objective a listed above, i.e., to investigate the efficacy of valganciclovir when used as induction therapy in HIV-infected patients with newly diagnosed CMV retinitis

STUDY DESIGN AND ENDPOINTS

The evaluation of efficacy will be primarily based on Study WV15376. Study WV15376 was a randomized, open label, parallel group design conducted in seropositive patients with newly diagnosed CMV retinitis. Patients were equally randomized by center, in

blocks of four to receive either intravenous ganciclovir or oral valganciclovir. Intravenous ganciclovir was administered at 5mg/kg b.i.d. for 3 weeks followed by 5mg/kg q.d. for 1 week. Valganciclovir was administered at 900-mg b.i.d. for 3 weeks and then 900-mg q.d. for one week. Fundus photographs were obtained at study entry and after 2 and 4 weeks of drug administration. The primary endpoint for this study is CMV retinitis progression at Week 4, as assessed from the fundus photographs. Retinitis progression was defined as a 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 $\geq \frac{1}{4}$ disc area in size. This is based on an agreement reached with the DAVDP since the traditional endpoint of time to progression is not feasible here, in the context of treatment induction.

Confidence intervals of the difference of those proportions were computed in order to assess valganciclovir's non-inferiority to IV ganciclovir. The protocol-specified non-inferiority margin is 25% when using 90% CI. The agency did not commit to a bound (routinely called "delta") for the confidence interval or on the population for this analysis (i.e. treatment of missing or incomplete data).

Given the fact that the trial was started shortly after the introduction of HAART (for treatment of HIV infection), the historical data available has a limited clinical or statistical relevance. Before the introduction of HAART, CMV retinitis was a frequent and hard to contain disease. Under HAART, this condition occurs with a much lower frequency and intensity. HAART has no direct effect on the CMV, but patients treated with HAART have better immune response to a variety of challenges, the CMV infection being one of them. This is why the "pre-HAART" data cannot be properly used to stipulate the margin of non-inferiority.

On completion of 4 weeks of randomized treatment, patients were able to receive valganciclovir maintenance therapy in an extension of the study in order to provide long-term safety and efficacy information. This statistical review will have only minor comments on the extension phase of the trial.

Table 2 Patient accountability

Week 4 Primary Endpoint Or Status	GAN	VAL
	Total=80	Total=80
Progressor	7	7
Non-progressor	63	64
Death	2	1
Discontinued due to AE before Week 4	1	2
Failed to return	1	1
No photos or CMV retinitis at baseline	6	5

We analyzed three cohorts described in Table 3.

Table 3 Study Cohorts

Cohort	Week4 Primary Endpoint Or Status	GAN	VAL	TOTAL
Modified ITT	Progressor, Non-progressor, Death, AE before Week 4, Failed to return	74	75	149
Death = Failure	Progressor, Non-progressor, Death	72	72	144
Per Protocol	Progressor, Non-progressor	70	71	141

The Per Protocol analysis coincides with the applicant’s analysis. It is an idealized model since, in clinical practice one cannot overlook the patient’s death, failure to return for evaluation, or treatment cessation due to adverse events. The Modified Intent-To-Treat cohort may give a more accurate image of the clinical reality, but could bring in the analysis more uncertainty, since some of the failures may be due to other infections or HIV – related conditions. The Death=Failure analysis is a compromise between the Per Protocol and the Modified Intent-To-Treat analyses. A true Intent-To-Treat analysis would have contained the subjects from the Modified ITT cohort and also the 11 patients with Week 4 status of “No photos or CMV retinitis at baseline”. However, we do not have good information that would allow us to claim failure or success in the treatment of the eye ailment for those patients.

Table 4 summarizes the efficacy findings in different cohorts.

Table 4 Efficacy as measured by failure rates, their differences and the confidence intervals of those differences.

Cohort	GAN	VAL	Diff.	95% CI* of Diff.
Modified ITT	11/74=14.9%	11/75=14.7%	0.2%	(-13%,13%)
Death = Failure	9/72=12%	8/72=11%	1%	(-11%,13%)
Per Protocol	7/70=10%	7/71=9.9%	0.1%	(-11%,11%)

* Normal approximation with continuity adjustment

Confidence intervals for the differences of failure rates have also been computed using exact methods and they did not differ in a substantial way. Since the randomization was done by center (in blocks of 4), a correct analysis is supposed to adjust for that factor. An analysis of efficacy with strata adjustments (centers with less than 4 patients included in one stratum) produced results similar to those listed in Table 4.

OPHTHALMOLOGIC EVALUATION AND DROPOUTS BY WEEK 12

The (treatment-unblinded) ophthalmologists appear to detect the progression of disease later than the _____ Moreover, at Week 4, they appear to call many progressions not confirmed by the _____ for patients that are in the valganciclovir arm. Considering the center's readings as the gold standard, one may suspect that a bias could explain the discrepancies. Table 5 details the comparison between the center's readings and the ophthalmologic evaluations at Week 4 (based on the per-protocol cohort). In Table 5, P stands for Progression and NP for non-progression.

**APPEARS THIS WAY
ON ORIGINAL**

models, the odds ratio estimates and their associated p-values. The predictors for the first model includes Week 4 progression status by photos, Week 4 progression status by ophthalmologist, and treatment randomized. Since the treatment does not appear to be a significant predictor, it is dropped in the second model.

Table 7 Predicting withdrawals by week 12 with Week 4 evaluations and treatment arm

Predictor	Odds Ratio Estimate	p-value
Week 4 Progression by Photo	3.1	0.1161
Week 4 Progression by Ophthalmologist	7.0	0.0075
VALGANCICLOVIR	1.7	0.4142

Table 8 Predicting withdrawals by week 12 with Week 4 evaluations

Predictor	Odds Ratio Estimate	p-value
Week 4 Progression by Photo	3.1	0.1180
Week 4 Progression by Ophthalmologist	8.8	0.0015

Even if statistics does not study causality, one can easily imagine that patients that are told at Week 4 that they are failing the assigned treatment will be more likely to withdraw. The previous statistical calculations tend to confirm this explanation.

TIME TO EVENT ANALYSES

The applicant provided several Kaplan Meier models of time-to-failure, where failure was defined in different ways (photographic failure, photographic failure plus withdrawals, etc.). Most of those analyses treated death as a censored event. We strongly object to this description of the trial for three reasons:

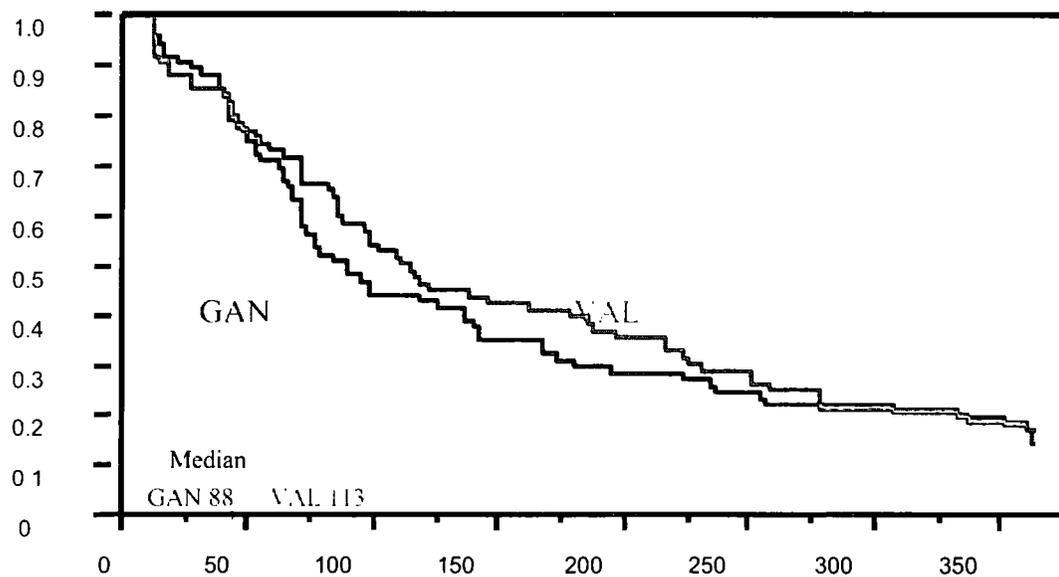
1. Mathematical: the model postulates that censoring is independent from the endpoint, so the joint distribution of censoring and endpoint should be the product of its marginal distributions, therefore it should have a rectangular support. In this case, it would mean that we should be able to observe retinitis progression after death. That is a quite unrealistic assumption.
2. Statistical: It would mean that patients that died are not different from those that experienced the endpoint. In other words, if they did not die,

they would have experienced a similar time-to-failure, as the other subjects in their treatment arm. This is another hard to accept assumption.

3. Ethical: it dilutes the impact of the ultimate negative outcome on the treatment arm.

Given the fact that, after induction, all patients were under the same treatment we doubt that strong conclusions can be drawn from the comparison of the two treatment arms. The possible investigator bias discussed in the previous section may also play a big, but hard to quantify role. We understand that other anti-CMV drugs were tested under the “death=censored event” rule, but we still object to this description. Figure 2 shows the “survival” curves, where failure is photographic progression, withdrawal or death. The median time to failure in the two treatment arms is about 100 days.

Figure 2 Time To Failure



This trial did not test the maintenance therapy. This issue should be addressed for valganciclovir and all other drugs that treat the same condition. We are not aware of a consensus on maintenance therapy for CMV retinitis in the context of HAART.

CONCLUSIONS

Based on Study WV15376, valganciclovir is no more than 13% worse than IV ganciclovir when used as an induction therapy. This assessment is based on CMV retinitis progression at Week 4 as determined by Fundus photograph. The advisory committee and our FDA medical team agreed that a non-inferiority margin of about 13% is appropriate, so valganciclovir is non-inferior to ganciclovir in terms of efficacy.

Subgroup analyses (gender, zone 1 retinitis, etc.) did not reveal anything remarkable. However, given the size of the study, one can find a statistically significant difference in a subgroup analysis only if it is very large.

Andrei Breazna, Ph.D.

Mathematical Statistician, DB III

Concur: Greg Soon, Ph.D.

Acting Team Leader, DB III

**APPEARS THIS WAY
ON ORIGINAL**

/s/

Andrei Breazna
4/6/01 01:00:38 PM
BIOMETRICS

Greg Soon
4/9/01 04:01:43 PM
BIOMETRICS

**APPEARS THIS WAY
ON ORIGINAL**