CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-304

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-304 **Submission Dates**: 09/28/00, 01/19/01, 01/31/01, 02/07/01, 02/15/01, 03/15/01.
Product: Valganciclovir HCl or VGAN (Valcyte®)
Applicant: Roche Global Development
Formulation: Film-coated Tablets **Strength**: 450 mg valganciclovir
Reviewer: **Robert O. Kumi, Ph.D. Team Leader**: Kellie Reynolds, Pharm.D.
Draft Review Dates: 01/25/2001, 03/14/2001

Executive Summary

Ganciclovir (GAN) is a synthetic guanine derivative active against cytomegalovirus (CMV). CMV treatment requires induction and maintenance therapy. Intravenous GAN (Cytovene®-IV) is indicated for the treatment of CMV retinitis in immunocompromised patients and for the prevention of CMV disease in transplant patients at risk for CMV disease. Oral GAN (Cytovene®) capsules are indicated for prevention of CMV disease in patients with advanced HIV infection at risk for CMV disease, for maintenance treatment of CMV retinitis in immunocompromised patients, and for prevention of CMV disease in solid organ transplant recipients. Oral GAN administration provides adequate GAN serum levels, but the poor oral bioavailability (BA = 6- 9 % under fed conditions) of this formulation necessitates the use of high doses (3000 mg/day). Valganciclovir or ganciclovir valinate hydrochloride (VGAN), is a prodrug of GAN that is rapidly and extensively converted to GAN after oral administration. The absolute BA of GAN is approximately 60 % following oral VGAN administration. According to the applicant, increasing the BA of GAN may increase its efficacy and simplify dosing, while retaining GAN's safety profile. VGAN is being proposed for induction and [redacted] of CMV disease in AIDS patients.

Pharmacokinetic (PK), safety and efficacy (one pivotal study) studies with VGAN and an exposure response (PK/PD) analysis with GAN (maintenance therapy) were conducted in support of the VGAN application. In all PK studies, VGAN systemic exposure was low compared to GAN systemic exposure. Administration of the proposed 900 mg oral VGAN dose and the approved 5 mg/kg IV GAN dose in induction (twice-daily) and maintenance (once-daily) regimens produced comparable GAN AUC. On the other hand, GAN C_{max} following VGAN administration was 40 % lower than following IV GAN administration, but was 30-fold higher than the C_{max} produced by oral GAN administration. An exposure-response relationship for GAN during maintenance therapy could not be validated, because GAN pharmacokinetic measures could not be determined accurately. Consequently, comparisons between oral VGAN and GAN (IV and oral) plasma concentration-time profiles and PK measures were made to support VGAN use in maintenance therapy. The comparisons indicate that GAN plasma concentrations following VGAN administration are approximately bracketed by the GAN plasma concentrations following administration of approved GAN products. Thus, the comparison supports the use of VGAN during maintenance therapy.

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II. Major Questions/Issues

1. Has an adequate exposure-response relationship for GAN been developed? If so, what is its utility with respect to VGAN dose selection? *(Page 4)*

2. In the absence of an adequate exposure-response relationship, what additional evidence is available to support the use of VGAN? *(Page 5)*

3. Are VGAN dosing adjustments required for patients in special populations, particularly patients with impaired renal function? *(Page 11)*

III. Introduction and Background

CMV Retinitis

Human cytomegalovirus (CMV) is a herpes virus that is an important pathogen in immunocompromised patients, particularly patients with advanced HIV infection and organ transplant recipients receiving immunosuppressant agents. CMV retinitis (CMVR) is an ocular manifestation of systemic viral infection and appears as lesions in the retina that destroy retinal tissue, ultimately leading to a permanent loss of vision in the involved area. The goal of CMVR therapy is to prevent or delay progression into healthy retinal tissue. Treatment of CMV disease is divided into a 3-week induction phase followed by a maintenance phase of indefinite length. Presently available induction treatments for CMVR are IV ganciclovir, IV foscarnet, or IV cidofovir. Additionally, two local intraocular treatments are available, fomivirsen and a ganciclovir implant.

Successful induction is achieved when no further lesion enlargement (progression) is observed. However, if therapy is stopped and the patient is still immunocompromised, progression occurs. Induction may be repeated in a cyclic manner to stop the progression, but with each progression, additional retinal tissue is destroyed. Maintenance therapy may prevent or delay progression following a satisfactory response to induction treatment. The success of maintenance therapy is measured by the time from the start of therapy to the next progression of retinitis (time to progression). Time to progression may be assessed by retinal photography or by an ophthalmologist.

Dosing Regimens and Difficulties with Current GAN Treatments

Ganciclovir (GAN) is a synthetic guanine derivative that is active against CMV. During induction, intravenous GAN is given twice daily (BID) as a 5 mg/kg 1 hour infusion for 3 weeks. In the maintenance phase, GAN is given as an IV infusion 5 mg/kg once daily (QD), or orally as GAN 1000 mg capsules three-times daily (TID) or 500 mg six-times daily. Due to the low absolute BA of oral GAN (6-9 % in the fed state), a large oral GAN dose is required for effective maintenance treatment, and oral GAN can not be used for induction treatment. The highest strength of GAN capsules available is 500 mg; thus, patients have a relatively high pill burden.

Clinical Considerations in VGAN Development

The applicant developed valganciclovir (VGAN), an oral prodrug of GAN, with the following potential advantages over current GAN therapy in mind:

- orally administered therapeutic alternative to IV GAN for induction and maintenance treatment of CMV retinitis
- avoidance of morbidity associated with long term venous access required for IV GAN
- a simple oral regimen with reduced tablet count that could improve adherence to long term maintenance treatment

The VGAN development program relies heavily on the assumption that the activity of VGAN is due solely to the activity of its metabolite, GAN. Consequently, the applicant indicates that the VGAN

development program is abbreviated and builds on the extensive efficacy and safety experience with GAN. The major toxicities of GAN are granulocytopenia, neutropenia, anemia and thrombocytopenia.

Clinically, CMV induction therapy is considered a bigger therapeutic hurdle to overcome than maintenance therapy. Hence, the applicant hypothesizes that if VGAN induction efficacy is comparable to IV GAN, one can reasonably infer that VGAN will be efficacious during maintenance therapy. The applicant also indicates that the exposure-response relationship for GAN (Study2226) supports the use of VGAN for maintenance therapy.

Studies Reviewed
The clinical division reviewed controlled safety and efficacy data (Study 15376) for VGAN induction treatment. Bioavailability, bioequivalence, food effect and dissolution studies were submitted and reviewed by the Office of Clinical Pharmacology and Biopharmaceutics. The dissolution study results have been previously reviewed (Re: IND 48106 SN 089, June 1999). A pharmacometrics consult was obtained for Study 2226, which was submitted in support of the use of VGAN during the maintenance phase. The pharmacometrics review is included in the Appendix to this review.

IV. Physico-Chemical Characteristics for VGAN and Bioanalytical Methods

Physico-Chemical Characteristics

1. Chemical Name: L-Valine, 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxyl]-3-hydroxypropyl ester, monohydrochloride
2. VGAN is a valine monoester prodrug of the active moiety GAN. *In vitro* VGAN is hydrolyzed ($t_{1/2}$ = 11 hr) to GAN and valine at neutral pH, but hydrolysis is slower at lower pH
3. Molecular Formula: $C_{14}H_{22}N_6O_5 \bullet HCl$
4. VGAN Molecular Weight: 390.83 (free base 354.3); GAN Molecular Weight: 255.23
5. Stereochemistry- two diastereomers exist as a racemic, almost equal mixture of R and S stereoisomers in the **solid state** (52:48)
6. Interconversion (epimerization) of diastereomers in **solution**- process is fairly rapid at neutral pH, $t_{1/2}$ = 1 hr but is much slower at lower pH (at pH = 3.8 $t_{1/2} \approx$ 500 hr)
7. Absorption and epimerization of isomers ***in vivo***- rates of interconversion, and hydrolysis to GAN are the same for both isomers
8. Solubility at pH 6.8 = 68 mg/mL and solubility > 200 mg/mL at pH < 6
9. Appearance: white to off-white crystalline powder; two polymorphic forms, but only one form manufactured

Bioanalytical Methods

Validated bioanalytical methods for the analysis of VGAN and GAN from plasma were provided and considered acceptable. Plasma concentrations of GAN and VGAN were measured by [redacted] respectively. Features of the assays included:

- **For GAN**

Excitation λ = [redacted], Emission λ = [redacted]
Linear Range: [redacted]
Interassay precision: [redacted]
Interassay Accuracy: [redacted]
LLOQ: [redacted]
Specificity: [redacted]

APPEARS THIS WAY
ON ORIGINAL

- **For VGAN**

UV λ = [redacted]
Linear Range: [redacted]
Precision: [redacted]
Accuracy: [redacted]
Specificity: [redacted]

[redacted]

V. Efficacy Study and its Pharmacokinetic Implications

Evaluation of Safety and Efficacy (Study 15376)

Induction efficacy of VGAN was evaluated in one controlled pivotal clinical efficacy study, WV 15376, in which oral VGAN and IV GAN were administered to HIV+ patients with CMV retinitis. The study was underpowered, but considered acceptable by DAVDP (see Medical Reviewer's review for details).

In the maintenance phase of Study 15376 all patients received VGAN, therefore a comparison to IV GAN can not be made. Due to the lack of a suitable control for VGAN during maintenance therapy, the applicant proposes that the use of VGAN in maintenance therapy can be supported by exposure-response analyses using oral GAN and IV GAN data obtained during maintenance therapy (Study 2226). Findings from the exposure-response analyses are presented in Section on Exposure-Response Relationship for GAN. The applicant indicates that the range of exposure ($AUC_{0\text{-}24\ hr}$) provided by IV ($AUC_{0\text{-}24\ hr}$ = 25 μg hr/mL) and oral GAN ($AUC_{0\text{-}24\ hr}$ ≈ 15 μg hr/mL) administration during maintenance therapy, represent the highest safe and minimum effective concentrations for GAN efficacy and tolerability, respectively.

VI. Review

Has an adequate exposure-response relationship for GAN been developed? If so, what is its utility with respect to VGAN dose selection?

Exposure-Response (PK/PD) Relationship for GAN

The applicant did not conduct exposure-response studies using VGAN; however, the applicant concluded that an exposure-response relationship existed between GAN AUC_{ssavg} (exposure or PK measure) and time to first photographic progression (response or PD measure) during GAN maintenance therapy. For this study, PK data were collected at weeks 2 and 6 from HIV+ patients with newly diagnosed CMV retinitis receiving oral GAN (1000, 1500 and 2000 mg TID) or IV GAN (5 mg/kg QD). PK samples were also collected when an adverse event or CMVR progression occurred. In addition, the time to first photographic progression (FPP) was determined.

According to the applicant's analyses, C_{min} had no significant correlation with the time to FPP; alternatively, C_{max} and AUC_{ssavg} both correlated with time to FPP. The applicant notes that when AUC and C_{max} were tested in the same model, C_{max} no longer correlated with time to FPP. Consequently, the applicant concluded that neither C_{max} nor C_{min} add any predictive value over AUC to the exposure-response relationship and can be omitted. The OCPB pharmacometrics reviewer, Dr. Sue-Chi Lee, could not validate the applicant's exposure-response analyses (see Appendix for Pharmacometrics review).

Dr. Lee concluded that the dosing time records were not sufficient enough to perform the population pharmacokinetic analysis needed for further exposure-response assessment. Specifically, the dosing time was recorded only for the one dose administered prior to blood sample collection. The scheme used in determining dosing times for the two doses before the recorded dose event appears to be clinically

reasonable; however, it relies heavily on assumptions that are not supported by any data. Since errors in dosing times will result in errors in PK parameter estimates, the exposure-response analysis is not acceptable. Another point of concern is 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 is unknown.

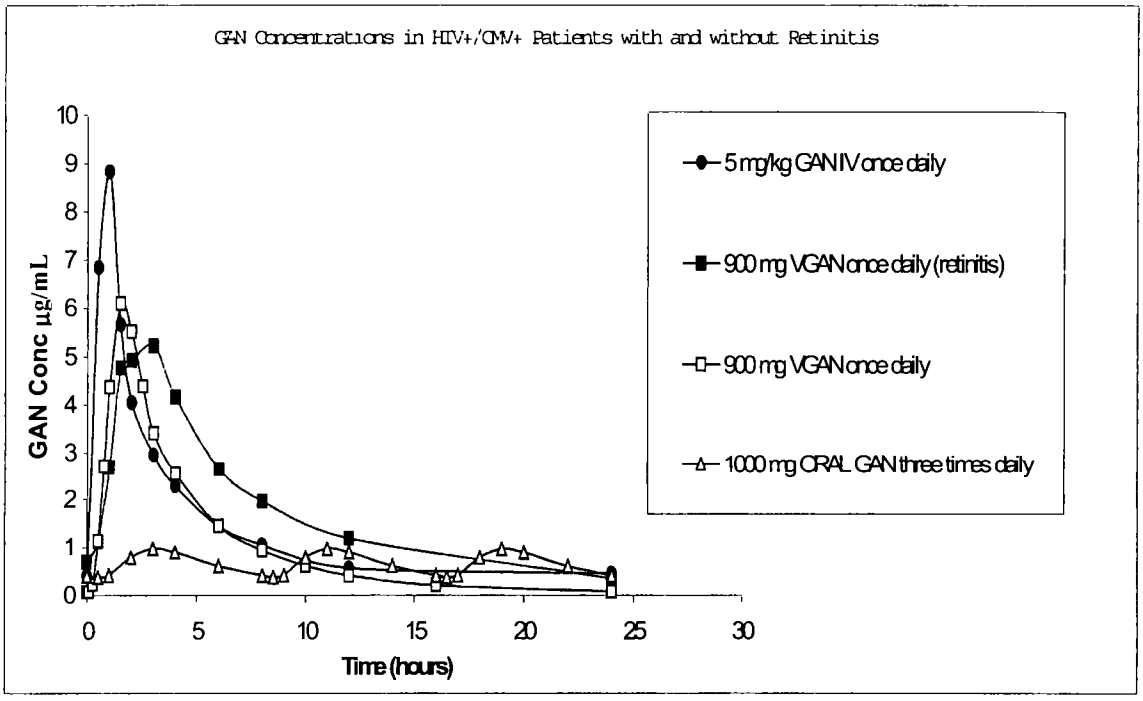
In the absence of an adequate exposure-response relationship, what additional evidence is available to support the use of VGAN during maintenance therapy?

Pharmacokinetic Profile Comparisons

Due to the concerns with the exposure-response analysis (see Exposure-Response Relationship for GAN), alternative methods were explored to support VGAN use during maintenance therapy. Ultimately, pharmacokinetic comparisons (VGAN vs. IV and oral GAN) were considered to be a more appropriate predictor of VGAN safety and efficacy in maintenance therapy than the submitted exposure-response analysis. Consequently, these pharmacokinetic comparisons were used during the review.

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

Figure 1: Delivery of GAN to HIV+/CMV+ Patients



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 VGAN once daily, GAN AUC was comparable to the AUC produced by the approved 5 mg/kg IV GAN dose ($AUC_{0\text{-}24} \approx 28$ µg·hr/mL). The main difference in GAN exposure between VGAN and IV GAN is the higher C_{max} value following IV GAN. However, beginning one to two hours after dosing, GAN plasma concentrations following VGAN administration exceeded GAN concentrations following IV GAN administration. Although C_{max} following VGAN is lower than following IV GAN, it is much higher than the C_{max} observed following oral GAN. Empirically, it appears

that the C_{max} value may not contribute significantly to GAN efficacy during maintenance therapy, because the C_{max} of IV GAN (5 mg/kg once daily) is almost 10-fold higher than the C_{max} of oral GAN (1000 mg q 8 hr), yet oral GAN efficacy is acceptable. Thus, the above plasma concentration-time profile comparisons suggest that VGAN efficacy for CMV maintenance treatment should be comparable to the efficacy of the approved IV and oral GAN regimens. Using this line of reasoning, the exposure-response model is not needed to support VGAN use during maintenance therapy.

Theoretical Considerations

The applicant contends that the short duration of high (C_{max}) and low (C_{min}) GAN concentrations (peak to trough fluctuations) does not appear to have significant impact on GAN efficacy. This observation supports the theory that GAN is converted intracellulary to an active triphosphate form that has a longer intracellular $t_{1/2}$ than GAN plasma $t_{1/2}$. If GAN activity is driven by the formation of an active intracellular triphosphate, systemic exposure, expressed as AUC, would be a more important determinant of active triphosphate concentration than C_{max}. However, it must be noted that none of the above observations regarding the active intracellular triphosphate form have been confirmed experimentally. Consequently, the active triphosphate theory is not acceptable from a regulatory standpoint.

How was the VGAN Dose selected?

According to the applicant, the proposed exposure-response relationship served as a guide in determining VGAN dose selection. Target $AUC_{0\text{-}24\ hr}$ was ≈ 25 μg hr/mL, because that was the AUC value obtained following IV administration (5 mg/kg) of GAN. Results from studies GAN 2661 and WV 15347 were used to select the VGAN dose.

Table II: Pharmacokinetic Data Used in Selecting VGAN Dose

Study #	Formulation and Dose	GAN $AUC_{0\text{-}24\ hr}$* in μg hr/mL	Bioavailability
2661	Oral VGAN solution, 360 mg	10.8 ± 1.92	60.9
	IV GAN, 5 mg/kg	25.1 ± 3.8	NA
15347	Oral VGAN tablet, 875 mg	24.8 (15)	ND

NA- not applicable; ND- not determined, * values reported as mean ± SD or mean (% CV)

Are the VGAN clinical trial and proposed market formulations bioequivalent/equivalent?

Bioequivalence (BE) between the VGAN clinical trial and proposed market formulations could not be established in the pivotal BE study. However, the nature of the formulation differences between the clinical and proposed market formulations did not require that a bioequivalence study be conducted; thus, equivalence between the formulations was established on the basis of *in vitro* dissolution studies.

Bioequivalence

The *in vivo* bioequivalency study was conducted in HIV positive volunteers (Study No.: W-144111; Protocol WP 15509). Subjects received VGAN after a meal, which is contrary to the current regulatory recommendation that BE studies be conducted in the fasted state. Because the study was conducted in the fed state, it is possible that potential formulation differences may not have been adequately identified.

Table III: Geometric Mean Ratio (GMR, Market: Clinical) and 90 % Confidence Interval (CI) for GAN

Relative GAN Exposure Measure	GMR	90 % CI
$AUC_{0\text{-}24\ hr}$ (μg hr/mL)	101	97 – 105
C_{max} (μg/mL)	114	101 - 128

The GMR and 90 % confidence intervals for AUC were within the required range to establish BE, but the C_{max} slightly exceeded the upper limit. The increase in C_{max} with the to-be-marketed formulation is unlikely to pose additional safety concerns, because GAN concentrations following IV administration are

almost two-fold higher than concentrations produced by VGAN and are tolerated in the target population. Thus, the study results do not preclude approval of the market formulation.
Prior to submission of the NDA, internal (within FDA) and external discussions (FDA and applicant) were held to discuss possible ways to establish equivalence between the formulations. Based on these discussions it was determined that *in vitro* dissolution data may be sufficient to demonstrate equivalence of the two formulations, without conducting an *in vivo* bioequivalence study in the fasted state.

Dissolution Studies
The nature of the changes (similar to level 2, SUPAC IR Solid Oral Dosage Form Guidance) in the VGAN formulation indicated that *in vitro* dissolution data comparing the two formulations in three media (12 tablets each) should be submitted. The two formulations can be declared equivalent because dissolution profiles for the two formulations in a given medium were similar:

- both formulations exhibit ——% dissolution in ——minutes
- differences in mean percent dissolved between the two formulations were ≤ 5% at all time points in all media,
- percentage of VGAN dissolved reached plateau within ——minutes for both formulations.

Therefore, results from the dissolution study, coupled with the BE study in the fed state, were sufficient to establish equivalence between the clinical trial and proposed market formulations.

What are the Clinical Pharmacology and Pharmacokinetic Characteristics of VGAN and GAN?
The VGAN clinical pharmacology program enrolled healthy subjects and subjects from 5 different patient groups. PK data were obtained from all of the subject groups. Subsequent discussion of VGAN and GAN PK will encompass data from all of these groups, unless otherwise indicated.

Table IV: Study Populations- Number of Subjects Enrolled in VGAN Clinical Pharmacology Studies

	Healthy Volunteers	HIV +	HIV + CMV +	HIV +/CMV + retinitis	Renally Impaired	Liver Transplant Recipients
Study ID	WP 15511	WP 15509	GANS 2661 and WP 15511	WV 15376	WP 15511	WV 15711
Randomized	12	18	65	160	24	28
PK evaluable	12	18	58	51	23	28

Values for GAN and VGAN pharmacokinetic measures obtained in the efficacy study are presented in Table V as a point of reference for the subsequent PK discussion. Data in Table V are from HIV +, CMV retinitis patients, who tended to have higher GAN plasma concentrations than other populations (see GAN Pharmacokinetics in the Target Patient Population Compared to Other Populations, page 11)

Table V: Arithmetic Mean ± SD (CV %) VGAN and GAN PK Parameters at Week 4 during Efficacy trial

Pharmacokinetic Measure	900 mg VGAN Administered QD in Week 4	
	GAN	VGAN
T_{max} (hr)	2.49 ± 0.98 (39.4); n = 25	1.46 (43.8); n = 20
C_{max} (µg/mL)	5.87 ± 1.46 (24.9); n = 25	0.162 (42.5); n = 20
$AUC_{0\text{-}24\ hr}$ (µg hr/mL)	34.9 ± 13.3 (38.1); n = 25	0.347 (57.3); n = 20
$T_{1/2}$ (h)	4.12 ± 0.86 (20.9); n = 25	2.33 (91.5); n = 9

Absolute Bioavailability of GAN

- **Oral VGAN**

The absolute BA of GAN following oral VGAN administration was approximately 60 % in all populations studied. BA was assessed in subjects with different disease states, but normal renal function.

Each subject received single oral doses of 900 mg VGAN and 5 mg/kg IV GAN in a crossover fashion. Results from selected studies in which absolute BA was assessed are presented in Table VI.

Table VI: Absolute BA of GAN (fed state) when administered as VGAN CT Formulation

GMR	Population	Dose (mg)	F (%)	95 % CI
WP 15509	HIV +, CMV +	900	59	56 – 62
	HIV +, CMV +	900*	59	56 – 62
WP 15511	Healthy volunteers	900	59	54 – 64
	HIV +, CMV +	900	61	55 – 67
WV 15711	Liver Transplant Recipients	450	60	56 – 64
	Liver Transplant Recipients	900	59	55 – 63

* given as to-be-marketed formulation

What are the Absorption, Food Effect, Accumulation, and Dose Proportionality Characteristics of VGAN and GAN following VGAN Administration?

Absorption

VGAN

VGAN is well absorbed from the GI tract, and undergoes the following reaction in the GI tract

Oral VGAN ----------> GAN + valine
(intestinal and hepatic esterases)

The reaction is rapid and extensive, with VGAN AUC < 4 % relative to GAN AUC. For all studies and study populations, formulations and doses, VGAN T_{max} < 2 hours.

GAN

Following VGAN administration, GAN T_{max} occurred between 2 and 3 hours and GAN C_{max} was more than 30 times greater than VGAN C_{max}. The rate of appearance of GAN following oral VGAN administration was more rapid than following oral GAN administration. Approximately 60 % of the administered VGAN dose reaches the systemic circulation as GAN when corrected for the differences in molecular weight. The relatively high bioavailability (BA) and low systemic VGAN exposure indicate that VGAN is highly effective in delivering GAN to the systemic circulation.

Food Effect (Study WP15347)

A food effect was observed on GAN BA when different VGAN doses were administered to fasted and fed HIV + CMV + subjects.

Table VII: Relative GAN Exposure Following Oral Administration of VGAN to fed and fasted individuals

Relative Exposure Measure	Dose (mg)	Point Estimate	95 % Confidence Interval
AUC_{24}	450	1.24	1.07 – 1.44
	875	1.30	1.12 – 1.51
(µg hr/mL)	1750	1.37	1.18 – 1.59
	2625	1.56	1.35 – 1.81
C_{max}	450	1.06	0.89 – 1.26
	875	1.14	0.95 – 1.36
(µg mL)	1750	1.15	0.96 – 1.37
	2625	1.26	1.05 – 1.50

A statistically significant increase in GAN AUC (20 – 56 %) was observed following administration of a high fat meal (total calories = 569; fat 31.1 g) relative to the fasted state, but the increase in mean GAN C_{max} was statistically significant only at the highest studied dose. Median T_{max} and $t_{1/2}$ appeared to increase

with increasing dose, but no difference between the fasted state and fed state were observed with these pharmacokinetic measures. The study design employed by the applicant was not ideal because:

- A parallel study design was used in the comparison, which might not account for intraindividual variability
- Study drug was administered only one hour after a meal in the fasted treatment. This may not represent a true fasted state as food may still be present in the GI tract and affect drug absorption.

Because the drug will be administered in the fed state and was administered in the fed state in clinical trials, determination of the absolute magnitude of the food effect is not critical.

At the recommended dose, GAN AUC following oral GAN administration resulted in a 20 % increase in AUC, slight increase in C_{max}, and longer T_{max}. VGAN administration at the proposed dose resulted in a similar trend in food effect as with oral GAN (GAN AUC increased 30 %).

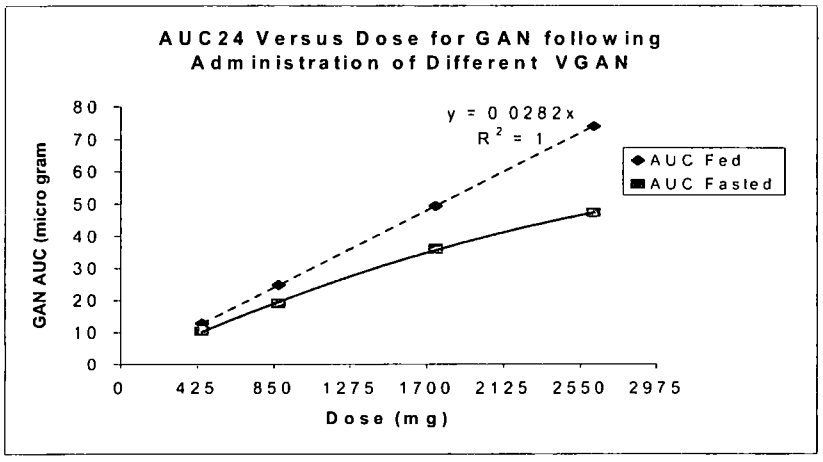
Accumulation

A multiple dose pharmacokinetics study (WP 15347) indicated that VGAN does not accumulate following once daily dosing over the dose range 450 – 2625 mg. VGAN levels could not be quantified beyond 6 hours, even at the highest dose levels. Accumulation is not expected for GAN following VGAN administration, based on the short GAN half-life (< 4 hr) and the proposed BID and QD dosing regimens.

Dose Proportionality of GAN and VGAN

Following multiple dose administration of oral VGAN, GAN PK were dose proportional in the fed state but non-dose proportional in the fasted state, as shown in Figure 2.

Figure 2: Dose Proportionality of GAN Following VGAN Administration



In the fed group, no significant deviation from dose proportionality was found ($p = 0.997$) whereas, in the fasted group, significant deviation from dose proportionality was observed ($p \leq 0.001$). Less than dose proportional increases in AUC and C_{max} were observed with increasing dose for the fasted group. Based on these study results, the applicant recommends that VGAN be given with food. Considering the results from this study, the applicant's proposal is acceptable.

What are the Distribution, Metabolism, and Elimination Characteristics of VGAN and GAN following VGAN Administration?

Distribution

No studies were conducted with VGAN to assess VGAN distribution. GAN volume of distribution at steady-state ($V_{ss} \approx 50$ L) following IV administration in the VGAN program were comparable to volume

of distribution estimates in previous IV GAN studies. Additionally, the V_{ss} estimates of GAN following oral VGAN administration are consistent with distribution of GAN in total body water, as observed in previous oral GAN studies. Other features of GAN distribution that were not explored following VGAN administration include:

- CSF penetration (24 –67 % of plasma concentrations)
- Intra-ocular penetration (40 – 88 % of plasma concentrations, with half-life between 13 and 19 hours)
- Protein binding (< 2 %)

Metabolism
Following oral administration VGAN undergoes rapid and extensive presystemic conversion to GAN, and GAN is not metabolized further. In preclinical studies using human and animal intestinal and hepatic S9 fractions, VGAN was metabolized exclusively to GAN. No other VGAN metabolites have been identified.

Elimination
VGAN is eliminated primarily by metabolism to GAN, which is eliminated renally. Difficulty was encountered in estimating VGAN half-life in VGAN PK studies because VGAN levels diminished rapidly after VGAN administration. In general, VGAN was not detectable in plasma 6 hours after drug administration. GAN half-life ranged from 3 – 5 hours following oral VGAN administration, which was similar to values obtained after IV GAN administration. On the other hand, the GAN half-life following oral GAN administration at the recommended dose is approximately 7 hours. The difference in GAN half-lives following oral VGAN and oral GAN administration appears to indicate different absorption kinetics (flip-flop with oral GAN) for GAN using these two modes of GAN delivery.

Renal clearance of GAN is by both glomerular filtration and net active tubular secretion. Approximately 80 % of systemic GAN CL was attributed to renal CL in all the populations studied.

Table VIII: Mean (% CV) Systemic and Renal Clearance of GAN in Different Patient Groups

		N	CL_{IV} (mL/min/kg)	CL_R (mL/min/kg)
GANS 2661	HIV, CMV seropositive	18	3.39 (15)	nc
WP 15509	HIV seropositive	17	2.77 (23)	nc
WP 15511	Healthy volunteers	8	3.38 (16)	2.88 (20)
	HIV, CMV seropositive	7	3.34 (13)	3.11 (23)
WV 15376	HIV seropositive, CMV retinitis	17	2.97 (44)	1.96 (42)
	HIV seropositive, CMV retinitis	18	2.82 (23)	2.14 (44)

nc- not calculated

In general, CL of GAN following IV GAN administration and VGAN administration were comparable at similar doses in subjects with normal renal function. It is noteworthy that patients with HIV and newly diagnosed CMVR participating in the efficacy trial appeared to have lower GAN CL, particularly CL_R, than other HIV + patients without CMV retinitis.

Are GAN Pharmacokinetics in the Target Patient Population Comparable to GAN Pharmacokinetics in Other Subject Populations?

Pharmacokinetics of GAN following oral VGAN and GAN IV administration were evaluated in the target patient population under presumed steady-state conditions.

Table IX: Mean ± SD GAN Pharmacokinetic Measures in Target Population during Efficacy Trial

	IV GAN		Oral VGAN	
	GAN (week 1)	GAN (week 4)	GAN (week 1)	GAN (week 4)
Pharmacokinetic Measure	N = 18	N = 18	N = 25	N = 25
$AUC_{0\text{-}12\ or\ 24}$* (μg hr mL)	28.6 ± 9.02	30.7 ± 7.69	32.8 ± 10.1	34.9 ± 13.3
$AUC_{0\text{-}\infty}$ (μg hr/mL)	31.9 ± 10.7	31.3 ± 7.95	38.1 ± 13.1	35.9 ± 14.0
C_{max} (μg/mL)	10.4 ± 4.9	9.86 ± 3.14	6.71 ± 2.12	5.87 ± 1.46
C_{ss} (μg mL)	2.4 ± 0.75	1.28 ± 0.32	2.74 ± 0.84	1.46 ± 0.56
T_{max} (hr)	0.89 ± 0.26	0.98 ± 0.21	2.31 ± 0.93	2.49 ± 0.98
$T_{1/2}$ (hr)	3.99 ± 0.85	4.32 ± 0.69	3.94 ± 1.10	4.12 ± 0.86

C_{ss} = $AUC_{0\text{-}12}$ Dosing Interval or C_{ssavg}; * $AUC_{0\text{-}12}$ for week 1, and $AUC_{0\text{-}24}$ for week 4

Analyses of the PK data indicated that VGAN systemic exposure was low in HIV+ patients with CMV retinitis, as was seen in other studies for different patient populations. Neither 4-week nor 1-week PK data were available for other study populations; therefore the comparisons with other populations are not direct comparisons (non-steady state data). However, numerically GAN AUC, and plasma concentrations (see figure 1, page 5) appeared to be higher in these patients compared to other patient populations. The reason for the apparently increased GAN exposure may be attributed to the apparently lower renal clearance in these subjects. The applicant indicates that the CL_R values obtained in the efficacy trial may not be accurate because the experimental conditions, such as accurate urine collection, were not as controlled as in other studies (see Tables VIII and X for comparisons).

Were any drug-drug interactions between VGAN and other drugs observed?

Drug-drug Interactions

No pharmacokinetic drug-drug interaction studies were submitted for the VGAN NDA. The applicant indicates that drug interactions observed with GAN are likely to occur with VGAN. This assumption is reasonable, because of the following two observations

- VGAN levels are low systemically and are unlikely to be affected by or affect other drugs
- VGAN produces only GAN; GAN produced by VGAN administration is present in a sufficiently large quantity to be involved in drug-drug interactions

Potential Transporter-based Drug-Drug Interactions

VGAN is a substrate for the human hpepT1 transporter with a K_m of approximately 4 mM in Caco-2 cells overexpressing the hpepT1 transporter. The K_m falls within the range of VGAN clinical concentrations in the gut ($C_{max,intestine}$ 10 mM) following administration of 900 mg VGAN; consequently, this transport system may partially contribute to the mechanism of absorption.

Are VGAN dosing adjustments required for patients in special populations, particularly patients with impaired renal function?

Meta Analyses

The applicant conducted meta analyses to determine which demographic factors may affect GAN PK following VGAN administration. Demographic factors studied included disease state, gender, age, and race. No definitive conclusions could be made from the analyses regarding age, gender and race, because patient numbers in each category were insufficient. However, the applicant's analyses indicated that AIDS patients with CMV retinitis and normal renal function (CL_{CR} > 70 mL/min) had approximately 30 % higher GAN AUC compared to HIV +/CMV+ patients. In this reviewer's analysis, the mean AUC values were approximately 25 % higher in CMVR patients than in HIV+/CMV+ patients, but the difference did not appear to be statistically significant.

Special Populations

Pediatric Development

VGAN has not been tested in pediatric patients.

Elderly

VGAN has not been studied in adults over the age of 65.

Renal Impairment

A decrease in GAN renal clearance and apparent oral CL was observed with decreasing renal function. VGAN and GAN PK were evaluated in healthy volunteers with normal renal function, HIV+/CMV patients with normal renal function, and otherwise healthy patients with varying renal function. Based on the study results a dosing algorithm for VGAN in patients with varying renal function was proposed by the applicant.

Pharmacokinetics of GAN in Renal Impairment Study

All subjects received a single 900 mg dose of oral VGAN. In addition, 8 out of 12 healthy subjects (Group 2) and 8 HIV+/CMV+ subjects (Group 1) received a single dose of 5 mg/kg IV GAN. PK results from groups 3-6 were compared to the PK of healthy individuals with normal renal function, excluding subjects who received IV GAN before oral VGAN.

Table X: Effect of Renal Impairment on Mean (% CV) GAN PK Measures following oral VGAN Administration (900 mg)

		Mean Ganciclovir Pharmacokinetic Parameters (% CV)					
Group	CL_{CR} (mL/min)	$AUC_{0-\infty}$ ^ (μg hr/mL)	C_{max} (μg/mL)	T_{max} * (hr)	$t_{1/2}$ (hr)	CL_{po} (mL/min)	CL_R
1	> 70	27.1 (13)	5.68 (19)	2.0	3.83 (13)	404 (13)	ND
2^G	> 70	27.8 (25)	5.56 (29)	2.0	3.46 (19)	413 (28)	209 (21)
3	51 – 70	50.5 (46)	6.88 (37)	2.0	4.85 (28)	249 (40)	145 (41)
4	21 – 50	99.7 (55)	7.08 (23)	3.0	10.2 (43)	136 (48)	67.1 (40)
5	11 – 20	252 (25)	8.54 (14)	3.0	21.8 (24)	45 (25)	21.4 (38)
6^D	< 10	407 (20)	10.5 (18)	6.0	67.5 (50)	12.8 (62)	nc

Where: Treatment A = 900 mg VGAN PO; Treatment B = 5 mg/kg IV GAN; * = median values

^ $AUC_{0-\infty}$ was not more than 11 % greater than AUC_{last}

2^G – healthy subjects who received VGAN before IV GAN or received only VGAN

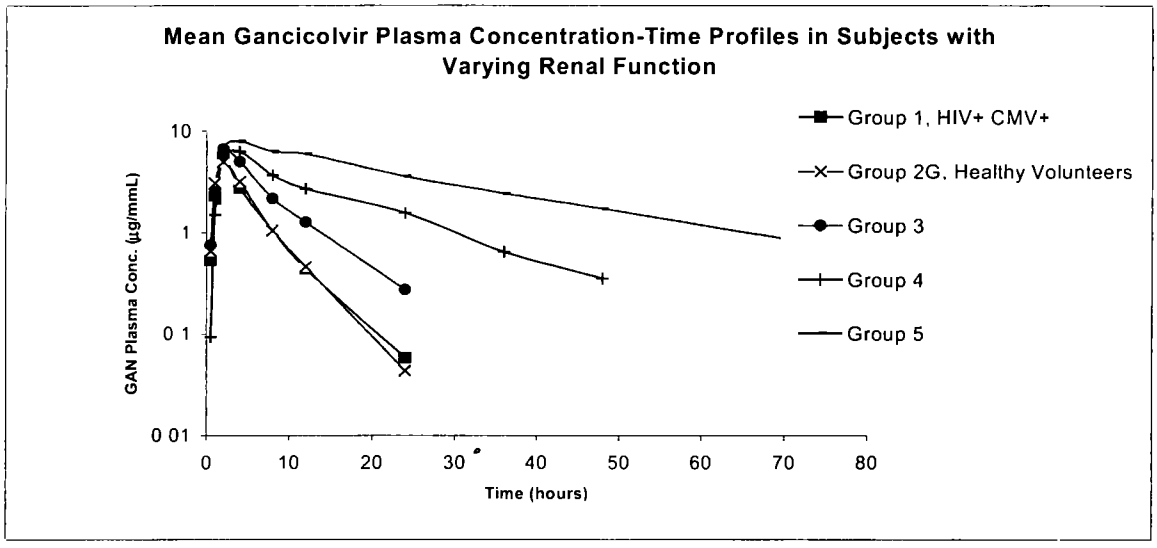
6^D- subjects received dialysis during VGAN dosing

Overall, renal impairment had no clinically significant effect on exposure to VGAN. VGAN PK parameters were comparable between healthy volunteers and HIV+/CMV+ patients. GAN PK parameters were also comparable between these two patient groups following administration of oral VGAN and IV GAN, respectively. The similarity in PK between these two patient groups was also reflected in their similar absolute GAN BA (healthy BA = 59 % and HIV+/CMV+ BA = 61 %).

Subjects with decreasing renal function (Groups 3-6), assessed by calculated creatinine CL, had longer GAN half-life and higher AUC than healthy volunteers. The higher AUC was attributed to the decreased renal CL in these study groups. C_{max} increases were not as profound as the AUC increases. Dialysis removed approximately 50 % of the GAN amount present at the onset of dialysis, as was observed in previous studies with GAN; however, this value was obtained from only 3 out of 6 patients and did not account for the rebound in plasma concentration at the end of dialysis. Consequently, interpretation of the dialysis results is not considered reliable. The sponsor indicates that VGAN will not be administered to patients requiring hemodialysis due to lack of an appropriate tablet strength. However, if VGAN will

ultimately be administered to these patients, an additional PK study will be required to provide more accurate GAN PK estimates in this patient population.

Figure 4: Mean GAN Plasma Disposition Following Administration of oral VGAN to patients with varying renal function



VGAN Dosing Algorithm in Patients with Impaired Renal Function, but Not Requiring Hemodialysis

The applicant proposed a dosing algorithm for VGAN based on the observed approximately linear relationship between CL_{CR} and CL_{po} of GAN, and predicted steady state AUCs for a given CL_{CR} after VGAN administration.

The relationship between CL_{CR} and GAN CL_{po} was based on data from groups 2- 5, which comprised healthy subjects receiving oral VGAN with varying degrees of renal function. The applicant's model is shown in equation 1

$$CL_{po} = 2.33 \times CL_{cr}^{1.13} \exp(\varepsilon), \varepsilon \sim N(0, 0.078) \qquad \text{equation 1}$$

Where, ε is the random deviation in CL_{CR} value and N is the number of subjects, CL_{R} is apparent renal clearance and CL_{CR} creatinine clearance This model was derived by using a logarithmic regression model, which is equivalent to a multiplicative model.

A simpler linear relationship, equation 2, without an error component was developed by this reviewer

$$CL_{po} = 4.58 \times CL_{CR} - 23.37 \qquad \text{equation 2}$$

However, the multiplicative model has a greater ability to predict apparent oral clearance from CL_{CR} than the linear model (see Individual Study Review for more details).

Using the multiplicative model, the applicant generated simulated data for GAN AUC_{ss}. Relevant selected sections of the simulated data are in the appendix to this review. In the clinical trial, the average GAN AUC achieved in the target population (CL_{CR} > 75 mL/min; mean $CL_{CR} \cong$ 130 mL/min) was ≈ 32 µg hr/mL following multiple dosing of IV GAN (5 mg/kg) or VGAN (900 mg) at week 4. The applicant indicated that the target $AUC_{0\text{-}24\ hr}$ was 26 µg hr/mL.

The proposed dosing algorithm (Table XI) is unacceptable for groups 1 and 2 because mean AUC values will exceed the mean target AUC by almost two fold.

Table XI: Applicants Proposed Oral VGAN Dose Modifications for patients with Impaired Renal Function

CL_{CR} (mL/min)	Daily AUC During Maintenance Dosing		Dose	
	Mean AUC * (µg hr/mL)	AUC Range* (µg hr/mL)	Induction	Maintenance
60 – group 1 100	46 26	41 – 52 22 - 31	900 mg BID	900 mg QD
40 – group 2 59	36 23	32 – 41 20 – 26	450 mg BID	450 mg QD
25 – group 3 39	31 18	27 – 36 16 – 20	450 mg QD	450 mg every 2 days
10 – group 4 24	50 18	39 – 63 15 - 20	450 mg every 2 days	450 mg twice weekly

* AUC was obtained by using mean 95 % CI values for CL_{po} (applicant's model) and back-calculating for AUC. The mean AUC and AUC range represent the AUC value and 95 % CI associated with the mean AUC for the CL_{CR} value

This reviewer proposes the following dosing algorithm.

Table XII: Oral VGAN Dose Modifications for patients with Impaired Renal Function

CL_{CR} (mL/min)	Daily AUC During Maintenance Dosing		Dose	
	Mean AUC * (µg hr/mL)	AUC Range* (µg hr/mL)	Induction	Maintenance
70 – group 1 100	39 26	34 – 44 22 - 31	900 mg BID	900 mg QD
50 – group 2 69	28 19	25 – 32 17 - 22	450 mg BID	450 mg QD
25 – group 3 49	31 15	27 - 36 13 – 16	450 mg QD	450 mg every 2 days
10 – group 4 24	50 18	39 – 63 15 - 20	450 mg every 2 days	450 mg twice weekly

* AUC was obtained by using mean 95 % CI values for CL_{po} and back-calculating for AUC. The mean AUC and AUC range represent the AUC value and 95 % CI associated with the mean AUC for the CL_{CR} value

The modifications proposed in this review will be more in line with the current recommendations for oral and IV GAN dosing in patients with impaired renal function and provide AUCs close to the target AUC.

Patients on Hemodialysis

The applicant recommends that patients on hemodialysis not take oral VGAN, but should take IV GAN in accordance with the labeled dose-reduction algorithm for Cytovene-IV®. This recommendation is based on the fact that administration of the available oral VGAN tablet, 450 mg strength, will result in unacceptably high exposures in these patients (exposure level 20 fold greater than in other patients given a similar dose). The applicant's recommendation is acceptable, but should be revised in the label to indicate that VGAN should not be administered in these patients.

Discussion: Applicability of Dosing Algorithm to other Patient Populations

The renal impairment study was conducted in subjects who had varied renal function, but were otherwise healthy (HIV seronegative and CMV seronegative). Because HIV+/CMV+ patients had comparable GAN PK to healthy volunteers with CL_{CR} > 70 mL/min it may be reasonable to assume that the same relationship between GAN PK in these two populations may hold true as renal function decreases. Therefore the proposed dosing algorithm may be applied to HIV+/CMV+ patients. However, extrapolation of this algorithm to other patient groups such as AIDS patients with CMV retinitis may not be straightforward because of the observed differences in CL_R of GAN in these two patient groups. In general, the GAN CL_R in these patients (HIV +, CMV retinitis) was lower than the GAN CL_R in other populations (e.g. HIV+/CMV+ and healthy subjects), who had similar (normal) renal function (CL_{CR} > 70

mL/min) measured by CL_{CR}. The effect of increased exposure (AUC) in these patients may pose a significant safety concern.

In general the mean AUC in HIV+ patients with CMV retinitis with normal renal function was approximately 25 % higher than those of other populations. If one assumes that the 25 % relative increase in GAN AUC will remain constant as renal function decreases, the dosing regimen proposed in this review is acceptable in this population. Currently, VGAN is available in only one strength, 450 mg tablet; therefore arriving at a suitable dose in these patients may be problematic if further dosage adjustments are required.

VGAN Formulations

The clinical trial and commercial formulations are similar except for minor changes in the amount of excipients and the addition of a film coat. The film coat was introduced in light of potential safety concerns for people coming into contact with VGAN tablets, because VGAN is a potent antiviral agent that may be teratogenic and carcinogenic.

Table IV: Commercial and Clinical Formulations for VGAN Film-Coated Tablets, 450 mg

Tablet Core Ingredients	Commercial Formulation		Clinical Formulation	
	Weight per tablet (mg)	% (w/w)	Weight per tablet (mg)	% (w/w)
Valganciclovir Hydrochloride	[redacted]			
Povidone K-30.				
Intragranular Crospovidone				
Extragranular Crospovidone				
Microcrystalline Cellulose				
Stearic Acid Powder				
Total Theoretical Weight				
Purified Water				
Coating Ingredients				
Opadry Pink				
Purified Water				

Dissolution

All clinical trial dosage formulations had similar *in vitro* dissolution characteristics. The proposed dissolution methodology is acceptable.

Apparatus: USP Apparatus 2 at 50 rpm
Medium: 900 mL 0.1 N HCl, pH =1 at 37° C
Assay: [redacted]
Specifications: Q = [redacted] in 30 minutes

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Recommendations
Data submitted to the Human pharmacokinetics and Biopharmaceutics Section of NDA 21-304 for valganciclovir satisfy the requirements for the Office of Clinical Pharmacology and Biopharmaceutics

The dissolution data indicate that the 450 mg valganciclovir capsules manufactured at [redacted] are similar to those manufactured at [redacted] consequently, *in vivo* bioavailability studies are not required for capsules manufactured at [redacted]

Labeling
In general, the applicant's proposed label is acceptable. However, a change should be made to the proposed dosing of VGAN in patients with impaired renal function, as presented in this review. In addition, the findings from the exposure-response evaluation should not be included in the label.

Proposed Phase IV Commitment or Traditional Approval Requirement
Evaluation of the effect of gender on ganciclovir pharmacokinetics following valganciclovir administration.

Robert O. Kumi, Ph.D.
Reviewer, Pharmacokinetics
Division of Pharmaceutical Evaluation III

Concurrence:

Kellie Schoolar Reynolds, Pharm.D.
Pharmacokinetics Team Leader
Antiviral Drug Products Section

cc:
HFD-530 NDA [redacted]
/MO/Toerner
/PM/Stephens
HFD-880 /Kumi, R.
/TL/Reynolds
HFD-340 /Viswanathan

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Study No. and RS No.: GANS2661 and RS-79070-194 volume 40
Investigator and Study Center: [redacted]
Study Period: July 1995- August 1995

Title: First-in humans study: single dose –pharmacokinetics and absolute and relative bioavailability of RS-79070-194 in HIV-and CMV-Seropositive subjects

Objective:
The objectives of this study were to investigate the fasting, single-dose pharmacokinetics and relative bioavailability of RS-79070-194 (in ganciclovir equivalents) administered orally, compared to intravenous and oral ganciclovir in asymptomatic human-immunodeficiency-virus-seropositive (HIV-1) subjects

Study Design: An open-label, randomized, single-dose, three-way crossover study design was employed. Single doses were administered under fasting conditions, with a one-week washout period between treatments. Treatment was for 15 days. All subjects completed the study.

Demographic Characteristics
Subjects: HIV-positive and CMV-seropositive
Gender: 15 male and 3 female
Race: 7 Black and 11 Caucasian
Age in years: Mean ± SD = 35.2 ± 8.0; Range = 22-51
Weight in kg: Mean ± SD = 74.7 ± 9.8; Range = 55.4 – 89.9
In addition, subjects had estimated CL_{CR} > 70 mL/min, platelet count ≥ 100,000 µL, absolute neutrophil count ≥ 1200 cells/µL and CD4 lymphocyte count ≥ 100 cells/µL

Formulations
Valganciclovir (VGAN) free base aqueous solution: 30 mg/mL Formulation [redacted], Batch No. 79070-194-1403471
Ganciclovir (GAN) IV free base lyophilized powder for solution: Formulation [redacted] Batch No. 21592-000-102821
Ganciclovir (GAN) capsules: 250 mg [redacted] Batch No. 21592-000-12232

Treatment Regimens
Regimen A: 5 mg/kg GAN given as IV infusion over 1 hour
Regimen B: 1000 mg GAN given orally
Regimen C: 360 mg VGAN

Pharmacokinetic Analyses
GAN bioavailability, measured using GAN equivalents, was determined.

Results

VGAN Pharmacokinetics
Absorption of VGAN was poor following administration of the oral VGAN solution. Mean VGAN AUC was < 3 % that of GAN AUC. This finding indicates that VGAN is almost completely converted to GAN. VGAN pharmacokinetic measures will not be presented in this study report because this formulation was not pursued by the applicant and was not administered at the proposed clinical dose (see Appendix for VGAN PK data)

GAN Pharmacokinetics

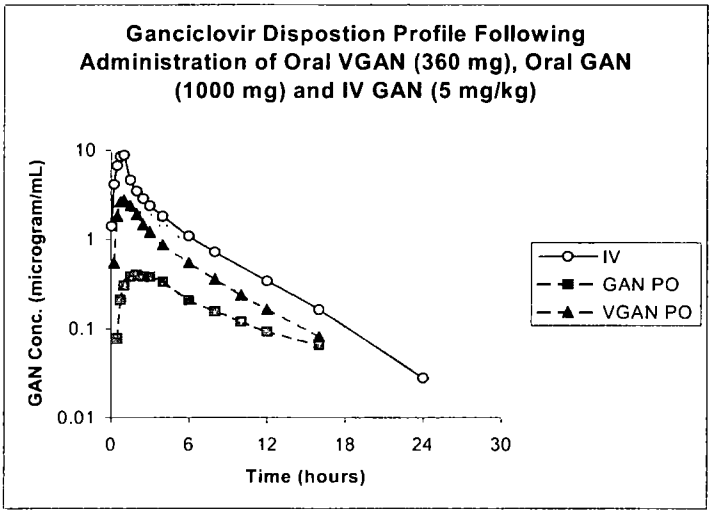
The pharmacokinetic (PK) measures for ganciclovir following Treatments A, B, and C are summarized in Table I, and the plasma concentration profiles for the treatments are shown in Figure 1.

Table I: GAN pharmacokinetic measures following administration of IV GAN (5 mg/kg), oral GAN (1000 mg) and oral VGAN (360 mg) to patients (HIV+ and CMV+)

GAN Pharmacokinetic* Measures	Treatment		
	5 mg kg IV GAN	1000 mg PO GAN	360 mg PO VGAN
T_{max} (hr)	0.93 ± 0.12	2.15 ± 0.99	1.03 ± 0.34
C_{max} (µg/mL)	9.36 ± 0.83	0.47 ± 0.17	2.98 ± 0.77
AUC (µg hr/mL)	25.1 ± 3.8	3.78 ± 1.21	10.8 ± 1.92
F (%)	NC	5.57 ± 1.81	60.9 ± 9.10
Half-life	3.66 ± 0.60	7.02 ± 1.98	3.69 ± 0.623

*Data from two subjects (No. 109 in Regimen A and No. 106 in Regimen C) were not included in the PK analyses because of a large number of missing observations

Figure 1: GAN Plasma Concentration-Time Profile after oral and IV GAN and oral VGAN Administration



The GAN AUC and C_{max} resulting from oral GAN and VGAN administration demonstrated that GAN is absorbed to a greater degree and is more bioavailable following VGAN administration than GAN administration. In addition, the rate of absorption of GAN from VGAN is more rapid than following GAN administration.

As expected, the mean AUC produced by IV GAN was greater than the two oral treatments. It is noteworthy that the $t_{1/2}$ following oral GAN administration was almost twice as long as the half-life for GAN after IV GAN or oral VGAN. This finding suggests that the absorption of GAN following oral GAN administration is different from the absorption following oral VGAN administration. Considering the rate constants and the plasma concentration-time plots (IV GAN and oral GAN), it is likely that a flip-flop between absorption and elimination rate constants occurs. Therefore the half-life reported for oral GAN is not purely an elimination half-life.

As expected, statistically significant differences existed in all tested pharmacokinetic measures among the various treatments.

Safety

Most adverse events were moderate in severity, except for a fever reported by one subject. Adverse events included pain (dental, abdominal, and chest), diarrhea, headache, syncope, hypertension, dizziness, dyspnea, and rash. Of these adverse events, only hypertension and pain were believed to be related to the study drug.

Conclusion

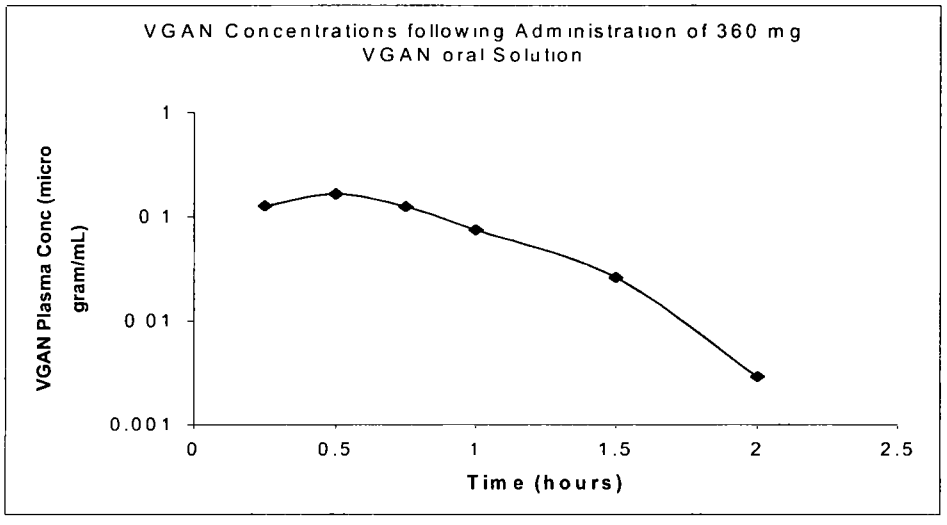
GAN bioavailability following administration of oral VGAN solution is much greater (≈ 10-fold) than GAN bioavailability following administration of oral GAN capsules

Appendix

Table A1: VGAN pharmacokinetic measures following administration of oral VGAN solution (360 mg) to patients (HIV+ and CMV+)

VGAN Pharmacokinetic Measures	N = 18
T_{max} (hr)	0.528 ± 0.283
C_{max} (μg/mL)	0.196 ± 0.069
AUC (μg·hr/mL)	0.171 ± 0.025
Half-life	0.465 ± 0.175

Figure A1: VGAN Plasma Concentration-Time Profile following 360 mg VGAN Dose



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Study No. Protocol WP15347 volume 41

Study Centers: [redacted]

Study Period: July 1996- November 1996

Title: The pharmacokinetics of four different doses of Ro 107-79070 following multiple oral dosing (with and without food).

Objectives:
The objectives of this study were to investigate the steady state pharmacokinetics of four different doses of VGAN following multiple oral dosing (with and without food)

Study Design: An open-label, 4-way randomized crossover study design was employed. Two groups of subjects (A and B) received the four treatments. Group A subjects received all doses in the fasted state, an hour before food; whereas, Group B subjects received all doses following food (see Appendix for meal content). The washout period between treatments was 5 days.

Comment
The applicant considered administration of study drug one hour after a meal to be in the fasted state; however, this may not represent a true fasted state as food may still be present in the GI tract and affect drug absorption. Determination of the absolute magnitude of the food effect using a true fasted state as a reference is not critical, because the drug will be given after meals. Hence, the absence of a true "fasted" state is acceptable in this study, but results will be considered in a qualitative manner rather than in a quantitative manner.

Demographic Characteristics
Subjects: 39 HIV-positive and CMV-seropositive subjects received treatment, but only 32 subjects completed the study (had PK data for four doses)

Table I: Summary of demographic characteristics

	Fasted- Group A	**Fed- Group B**
Sex	N = 19	N = 18
Females	0	2
Males	19	18
Race		
Caucasian	8	13
Black	9	6
Hispanic	2	1
	Mean ± SD (range)	
Weight	75.5 ± 10.6 (60 – 97)	73.4 ± 9.4 (58 – 95)
CL_{CR}	114.2	116.1
Age	34 ± 6.2 (20 –47)	34 ± 7.8 (23 – 46)

Formulations
Valganciclovir (VGAN) hydrochloride salt tablet: 450 mg Batch No. 1504801
875 mg Batch No. 1504791

Treatments
Treatment 1: VGAN 450 mg PO once daily for 3 days
Treatment 2: VGAN 875 mg PO once daily for 3 days
Treatment 3: VGAN 1750 mg PO (2 x 875 mg) once daily for 3 days

Treatment 4: VGAN 2625 mg PO (3 x 875) once daily for 3 days

Pharmacokinetic (PK) Analyses
VGAN and GAN PK parameters were calculated: $AUC_{0\text{-}24\ hr}$, C_{max}, T_{max}, T_{lag}, $t_{1/2}$, AUC, and C_{max}. Parameters were analyzed using ANOVA, with a model appropriate for a crossover design using log-transformed data. Factors in the analyses were group (A and B), subject, period and dose.

RESULTS

VGAN pharmacokinetics
VGAN PK measures following the four doses under fasted and fed conditions are presented in the appendix to this study. VGAN was rapidly absorbed following VGAN administration. Mean plasma concentrations for VGAN increased with increasing dose, but VGAN concentrations were much lower than those observed for GAN. The VGAN concentrations were below the LOQ within 2-4 hours after dosing. The systemic exposure of VGAN was low at all doses: AUC and C_{max} were both < 6 % of the GAN exposure.

GAN pharmacokinetics
Ganciclovir PK measures obtained following administration of VGAN are summarized in Table II.

Table II: Arithmetic mean (CV %) pharmacokinetic measures for GAN following VGAN administration

	Fed (n=16)				Fasted (n=16)			
Dose	450	875	1750	2625	450	875	1750	2625
$AUC_{24\ hr}$ (μg hr/mL)	12.7 (15)	24.8 (15)	49.4 (18)	74.1 (17)	10.3 (25)	19.0 (20)	36.0 (26)	47.3 (25)
C_{max} (μg/mL)	3.28 (33)	6.07 (28)	11.2 (25)	15.4 (28)	3.10 (17)	5.33 (20)	9.73 (18)	12.3 (24)
T_{max}* (hr)	1.5	1.5	2.0	2.0	1.0	1.5	1.5	1.75
$t_{1/2}$ (hr)	3.80 (22)	4.08 (17)	4.25 (14)	4.42 (12)	3.92 (20)	4.10 (16)	4.65 (15)	4.54 (16)

*T_{max} values are median values

Unlike the prodrug, GAN levels were measurable in plasma up to 24 hours post dosing at all doses, except the lowest dose group. Based on T_{max} values for VGAN and GAN, and the low levels of VGAN following oral VGAN administration, it is clear that VGAN is rapidly and extensively converted to GAN.

Food Effect and Relative Bioavailability (BA)
Mean PK measures obtained in Group A (fasted) were numerically lower than those in Group B (fed), however, only GAN AUC_{24} was statistically significantly lower in the fasted group compared to the fed group. A definite conclusion regarding the food effect can not be made due to the inappropriate study design. It is noteworthy that GAN exposure levels were increased approximately 25 % when oral GAN (at the recommended dose) was administered with food, which is comparable to the 30 % increase in GAN AUC following administration of 875 mg VGAN with food.

Comment
The food effect assessment in this study is based on a parallel study design. This approach is not ideal for PK comparisons, because interindividual variability may affect the results.

Table III: Point estimates (Fed: Fasted) and 95 % confidence interval for GAN used in food effect evaluation

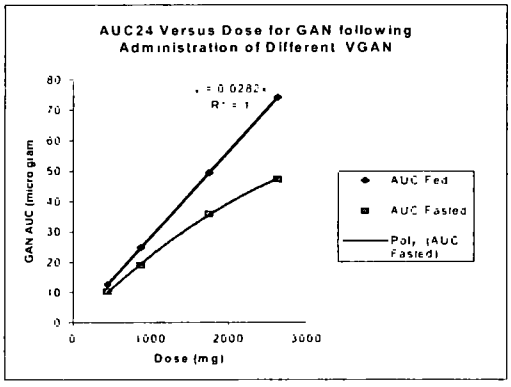
Relative Exposure Measure	Dose (mg)	Point Estimate	95 % Confidence Interval
AUC_{24} (µg hr mL)	450	1.24	1.07 – 1.44
	875	1.30	1.12 – 1.51
	1750	1.37	1.18 – 1.59
	2625	1.56	1.35 – 1.81
C_{max} (µg/mL)	450	1.06	0.89 – 1.26
	875	1.14	0.95 – 1.36
	1750	1.15	0.96 – 1.37
	2625	1.26	1.05 – 1.50

Dose Proportionality

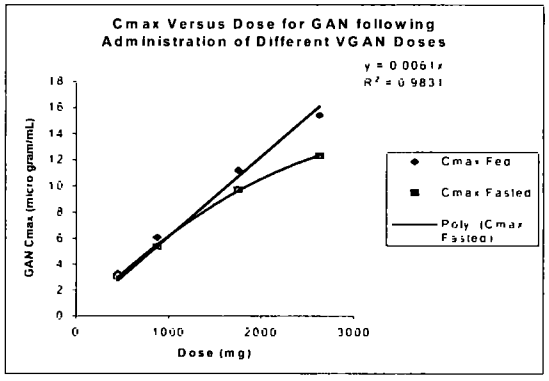
The PK of both GAN and VGAN were not dose-proportional when PK data (log transformed and dose adjusted AUC_{24} and C_{max}) were pooled for the fed and fasted groups. A significant interaction between food and dose group existed for GAN AUC. This finding indicated that the dose-exposure relationships for the two dietary conditions were different. Subsequently, dose-proportionality was assessed for each group separately. In the subsequent analyses, GAN AUC_{24} was dose-proportional in the fed group ($p > 0.997$), but not in the fasted group. A less than dose proportional increase in exposure was observed with increasing dose in the fasted group, as shown in figures 1 a and b.

Figure 1 GAN Dose Proportionality in Fed and Fasted Groups

1 a



1 b



Safety Results

VGAN was well tolerated and was not associated with any unexpected adverse events. The majority of reported adverse events were of mild intensity and consistent with the safety profile of GAN.

Conclusions

- Administration of VGAN in the fed state increased GAN exposure levels.
- Based on dose proportionality, oral administration of 900 mg VGAN under fed conditions should produce mean AUC ≅ 26 µg hr/mL (comparable to 5 mg/kg IV GAN dose).

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Appendix

Table AI Mean and median (n*=16) pharmacokinetic parameters for VGAN

	Mean and Median Parameter Values								
	Dose (mg)	450		875		1750		2625	
PK Par.		**Fed**	**Fasted**	**Fed**	**Fasted**	**Fed**	**Fasted**	**Fed**	**Fasted**
AUC_{24}	Mean	0.167	0.163	0.393	0.328	0.825	0.737	1.30	1.14
(µg hr mL)	Median	0 181	0.149	0.376	0.312	0.806	0.726	1.28	1.13
C_{max}	Mean	0.152	0.184	0.264	0.291	0.462	0.505	0.642	0.725
(µg mL)	Median	0.172	0.192	0.290	0.300	0.510	0.500	0.663	0.707
T_{max} (h)	Mean								
	Median	1.0	0.5	1.0	0.5	1.0	0.75	1.5	1.25
$t_{1/2}$	Mean	0.59	0.37	0.51	0.45	0.56	0.49	0.63	0.48
(h)	Median	0.60	0.39	0.49	0.42	0.53	0.51	0.61	0.50

* n =16 for all treatment groups except for half-life determinations which ranged from n = 9 (lowest dose)-14 (higher doses): CV were ≤ 31 % for all parameters in the fasted group except for the AUC_{24} at the 450-mg dose that was 36 %. For the fed group half of the calculated parameters, particularly the C_{max} and $t_{1/2}$ had CV > 36 % (range ———).

Standardized Breakfast

- 3 strips of bacon
- 2 scrambled eggs
- 1 x slice of whole wheat toast with pat of butter and tablespoon grape jelly
- 180 mL fresh orange juice
- 160 mL decaffeinated tea or coffee
- 1 tablespoon grape jelly

Total number of calories is 569 of which 31.1 g is fat. The total calories are less than the calories recommended in the test meal described in the *Draft Guidance to Industry: Food-Effect Bioavailability and Bioequivalence Studies*. However the standardized breakfast has the same relative proportion of the food types and is similar to the meal used in oral ganciclovir studies.

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Study No. and RS No.: Report W-144128 Protocol WP 15511 volume 43
Investigators and Study Centers:
[ ]
Study Period: April 1998- February 1999

Title: The effect of renal impairment on the pharmacokinetics of valganciclovir and ganciclovir following oral administration of valganciclovir

Objectives:
- To investigate the effect of renal impairment on the PK of VGAN and GAN following oral administration of VGAN
- To provide a dosing algorithm for use of VGAN in renally impaired subjects
- To investigate the effects of hemodialysis on GAN PK
- To compare the absolute bioavailability from VGAN in healthy and HIV-infected subjects

Study Design:
Groups 1 and 2G: Open-label, randomized, 2-way crossover, in which each subject received a single dose of Treatment A and Treatment B, with a washout period of at least 6 days between each treatment.
Group 2UK and Groups 3-6: Open label parallel design, in which each subject received a single dose of Treatment A
Patients received a standardized breakfast (see Appendix) and standard lunch and dinner on all dosing days. All 44 subjects that entered the study completed the study.

Treatments:
Treatment A: VGAN 900 mg P.O. as a single dose after a meal
Treatment B: GAN 5 mg/kg intravenously as a single 1 hour infusion

Groups
Group 1 (n = 8): HIV+/CMV+ subjects with normal renal function, CL_{CR} > 70 mL/min
Group 2G (n = 8): Healthy subjects with normal renal function, CL_{CR} > 70 mL/min
Group 2UK (n = 4): Healthy subjects with normal renal function, CL_{CR} > 70 mL/min
Group 3 (n = 6): Mildly renally impaired subjects, CL_{CR} 51 – 70 mL/min
Group 4 (n = 6): Moderately renally impaired subjects, CL_{CR} 21 – 50 mL/min
Group 5 (n = 6): Severely renally impaired subjects, CL_{CR} 11 – 20 mL/min
Group 6 (n = 6): End-stage renally impaired subjects receiving hemodialysis, $CL_{CR} \leq 10$ mL/min
CL_{CR} was assessed by 24 hour urine collection for all subjects, but serum creatinine was used if subjects were anuric

Demographic Characteristics
Demographic characteristics of the subjects are listed in the appendix to this study review. The majority of subjects in the study were Caucasian males. The net effect of the predominance of males may be an increase in average height and weight values.

Formulations
Valganciclovir hydrochloride salt 450 mg tablets – clinical trial formulation CT 450. Ro 107-9070-194, Batch No. 1630621
Ganciclovir sodium for IV administration sterilized lyophilized powder. Batch No. B636

Pharmacokinetic Analyses

VGAN and GAN PK parameters were calculated: AUC_{∞}, C_{max}, T_{max}, F, CL_{IV}, CL_{PO}, CL_R, k_e, and $t_{1/2}$ (for all subjects), CL_d (dialysis clearance), FR (fraction removed during dialysis), and k_d (dialysis rate constant).

Results

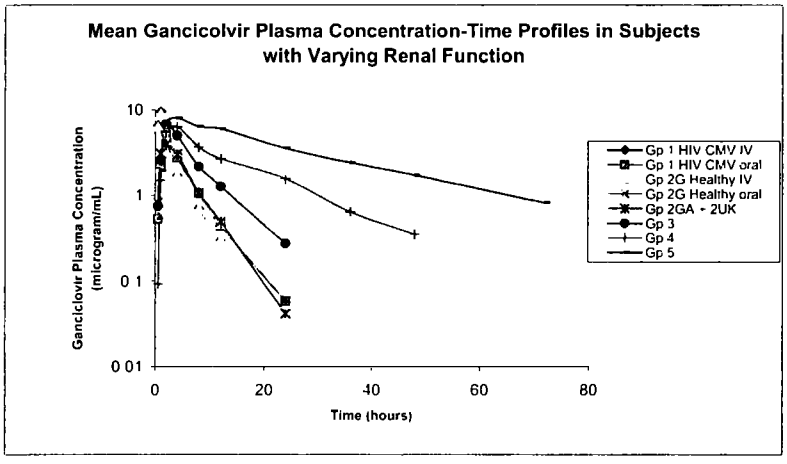
VGAN Pharmacokinetics

Systemic VGAN exposure was low in all study groups. Mean AUC and C_{max} values for VGAN were < 5 % of GAN exposure.

GAN Pharmacokinetics

Pharmacokinetics and absolute BA (≈ 60 %) were comparable in healthy volunteers and HIV-subjects with normal renal function, and were similar to results from other studies.

Figure 1: GAN Plasma concentration time profiles for subjects with varying renal function



Renal CL of GAN was similar following administration of IV GAN and oral VGAN (Groups 1 and 2G). GAN CL_R and CL_{PO} decreased with decreasing renal function after administration of VGAN. Terminal half-life increased with decreasing renal function. Similarly, C_{max} increased, but to a lesser extent. T_{max} also increased with increasing renal impairment.

Table I: Mean GAN pharmacokinetic parameters (% CV) following single doses of IV GAN (5 mg/kg) or oral VGAN (900 mg) administration

Group	Treat*	AUC_{last} (µg hr/mL)	$AUC_{0-\infty}$ (µg hr/mL)	C_{max} (µg/mL)	T_{max}* (hr)	$t_{1/2}$ (h)	CL_{IV} (mL/min)	CL_{PO} (mL/min)	CL_R (mL/min)
1	B	24.4 (16)	25.4 (14)	9.58 (11)	1.0	3.18 (12)	252 (11)	NA	230 (23)
2G	B	24.8 (18)	25.4 (17)	9.03 (14)	1.0	3.32 (14)	238 (16)	NA	203 (21)
1	A	26.6 (14)	27.1 (13)	5.68 (19)	2.0	3.83 (13)	NA	404 (13)	236 (16)
2G	A	27.1 (26)	27.8 (25)	5.56 (29)	2.0	3.46 (19)	NA	413 (28)	209 (21)
2UK	A	27.4 (11)	28.6 (10)	6.14 (32)	2.0	3.57 (28)	NA	380 (9)	289 (16)
3	A	49.5 (45)	50.5 (46)	6.88 (37)	2.0	4.85 (28)	NA	249 (40)	145 (41)
4	A	91.9 (48)	99.7 (55)	7.08 (23)	3.0	10.2 (43)	NA	136 (48)	67.1 (40)
5	A	223 (21)	252 (25)	8.54 (14)	3.0	21.8 (24)	NA	45 (25)	21.4 (38)
6	A	366 (18)	407 (20)	10.5 (18)	6.0	67.5 (50)	NA	12.8 (62)	NC

Treat*: Treatments, A = 900 mg VGAN PO, Treatment B = 5 mg/kg IV GAN, T_{max}* are median values.
NC- not calculable, NA bot applicable

CL_{PO} is approximately proportional to CL_{CR}. The applicant established a relationship between creatinine clearance and apparent oral clearance as shown in equation (1) below:

$$CL_{PO} = 0.703 \times CL_{cr}^{1.41} \exp(\varepsilon), \varepsilon \sim N(0, 0.272) \qquad \textbf{equation 1*}$$

equation 1*- variables used in the equation: where, ε is the random deviation about a CL_{CR} value, and N is the number of subjects. Model was derived by using a logarithmic regression model that is equivalent to a multiplicative model.

In deriving equation (1) the sponsor used data from Groups 2UK, 2GA, 3, 4, 5, and 6. Group 1 data were excluded because the patients were both HIV and CMV positive, whereas the remaining subjects were neither HIV + nor CMV +. The applicant excluded data from subjects in Group 2G who received IV GAN before oral VGAN to keep the population consistent with 2UK. Estimated variance of the residual error using equation 1 is equivalent to a CV of 55.9 % for CL_{PO}.

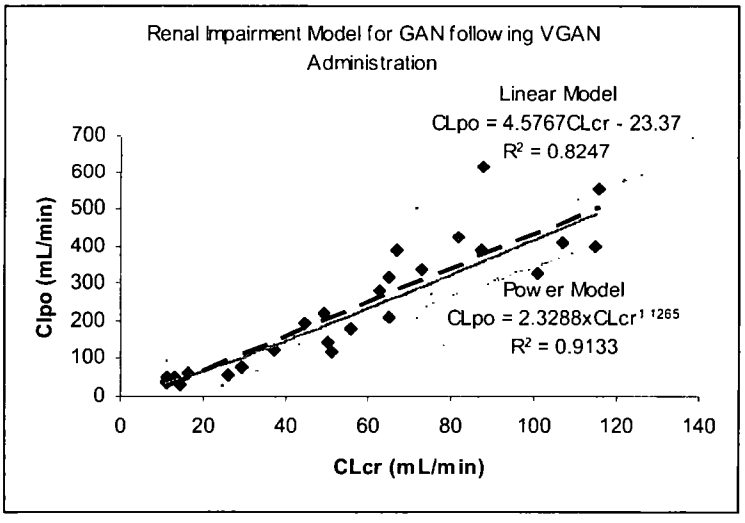
$$CL_{PO} = 2.33 \times CL_{cr}^{1.13} \exp(\varepsilon), \varepsilon \sim N(0, 0.078) \qquad \textbf{equation 2}$$

Equation (2) was derived excluding subjects noted for equation (1) derivation, as well as dialysis subjects. Subjects undergoing dialysis were excluded because these subjects exhibited higher variation in their CL_{PO} than other groups, and their relationship between CL_{CR} and CL_{PO} was unclear. For equation 2, the residual variance was equivalent to a CV of 28.5 % for CL_{PO}, which was less than with equation 1. The model proposed to describe the relationship between CL_{CR} and CL_{PO} appears acceptable, but can be approximated by a simpler linear regression model such as in equation (3) that was proposed by this reviewer.

$$CL_{PO} = 4.58 \times CL_{CR} - 23.37 \qquad \textbf{equation 3}^{\#}$$

equation 3 was derived excluding data from subjects in Group 1, 2GB and Group 6 Reasons for these exclusions were explained previously for equations 1 and 2

Figure 2: Renal Impairment Model for Subjects Receiving oral VGAN



An error component was not included in the linear model; thus the model differs from the applicant's proposed multiplicative model. The linear and power models are presented in figure 2. As can be seen from figure 2 in spite of the absence of an error component, the regression lines for the multiplicative and linear models are nearly superimposable, indicating that the models will give similar results. However, the linear model accounts for approximately 80 % of the correlation between CL_{CR} and CL_{R}, whereas the

multiplicative model accounts for approximately 85 % of this correlation. Introduction of an error component into the linear model may improve the correlation, but is not likely to render the linear model superior to the multiplicative model.

Comment
The applicant's model (equation 2) showing the relationship between CL_{CR} and CL_{PO} is acceptable, with the exclusion of the noted groups. The linear model proposed by this Reviewer is also acceptable (equation 3) because the power in equation 2 is approximately equal to one, which would simplify the applicant's model to a linear model with an error component.

Patients Receiving Dialysis
Six patients underwent dialysis after administration of oral VGAN; however, CL_d could be calculated in only 3 of these patients based on GAN measurement in the dialysate samples. Two of the 3 remaining subjects did not have measurable GAN in their dialysate sample. In the last remaining subject, GAN concentrations in the dialysate samples were greater than those in the plasma precluding calculation of CL_d. Half-life during dialysis ($t_{1/2d}$ = 3.47 hours) was much shorter than during intra-dialysis periods ($t_{1/2p}$ = 67.5 hours). The $t_{1/2d}$ was similar to the half-life seen in patients with normal renal function. Dialysis removed approximately 50 % (———, of GAN; however, this value does not take the rebound in plasma concentration at the end of dialysis into account. A reliable estimate for the amount of rebound could not be obtained because the first blood sample was taken 12 hours after the completion of dialysis. The mean CL_{dtot}/F (clearance with dialysis) was 27.5 mL/min and CL_{PO} (clearance without dialysis) was 12.8 mL/min.

Comment
Due to the scarcity of data from dialysis subjects (n = 3 out of possible 6) in this study and the numerous mathematical manipulations and assumptions required to obtain parameter estimates, the interpretation of GAN PK data in this population should be done cautiously.

Dosing Algorithm for Valganciclovir in Patients with Impaired Renal Function, excluding patients on dialysis
The applicant used the relationship established between CL_{CR} and CL_{PO} (multiplicative model) and the observed VGAN dose proportionality to predict expected mean daily ganciclovir AUC_{ss} for different CL_{CR} levels and different daily VGAN doses (see Appendix). It is noted that the applicant has only developed 450 mg tablet strengths, which limits the dosing algorithm. According to the applicant, the target GAN AUC_{ss} is 26 µg hr/mL per day at the 5 mg/kg IV GAN standard dose; therefore, the objective of the proposed dosing regimen would be to achieve this target level. This value was selected because the range of AUCs achieved following IV GAN administration in previous studies was 19 to 32 µg hr/mL.

Table II: Applicant's proposed dosing regimen with VGAN for patients with renal impairment

Creatinine Clearance	Induction Regimen	Maintenance Regimen
≥ 60	900 mg BID	900 mg QD
40-59	450 mg BID	450 mg QD
25-39	450 mg QD	450 mg every 2 days
10-24	450 mg every 2 days	450 mg twice weekly

Discussion
The applicant's proposal for the dose reduction algorithm is not acceptable based on the available information, if a targeted AUC of 26 µg hr/mL is used. In particular, target AUC is exceeded in the group with $CL_{CR} \geq 60$ mL/min. For a subject with CL_{CR} = 60 mL/min (lower boundary) receiving a 900 mg dose the AUC = 46 µg hr/mL. The exposure values, measured in AUC are almost 2-fold higher than the targeted exposure; thus there is an increase in the likelihood of adverse events. It is not clear from the

present study, if a particular exposure level has been associated with an increased incidence in adverse events. In a subsequent submission and teleconference with the FDA the applicant presented data on the safety and efficacy of different GAN exposure levels in the target population. Particularly, the applicant indicated that in the efficacy study (WV15376), the AUC values were: 22 – 44 μg hr/mL for 5 mg/kg IV GAN and 16 – 63 for VGAN. According to the applicant subjects with relatively high AUC values (> 30 μg hr/mL) did not have an increased incidence of adverse events.

However, due to the previously mentioned concerns with increased GAN exposure (above target AUC), this reviewer proposes the following dosing algorithm for VGAN in patients with impaired renal function.

Table III: Reviewer's proposed dosing regimen with VGAN for patients with renal impairment:

Creatinine Clearance (CL_{CR})	Induction Regimen	Maintenance Regimen
> 70	900 mg BID	900 mg QD
50-70	450 mg BID	450 mg QD
25-49	450 mg QD	450 mg every 2 days
10-24	450 mg every 2 days	450 mg twice weekly

The VGAN dosing algorithm for renal impairment proposed by this reviewer is comparable to that for IV GAN in patients with renal impairment, and is likely to minimize dosing errors in patients with renal impairment switching from IV GAN to VGAN. During the previously mentioned teleconference, the applicant indicated that they were reluctant to change the IV dosing algorithm to the algorithm they proposed for VGAN. However, the reason for the applicant's reluctance to this change was not clear because GAN exposures following VGAN administration and IV GAN are similar.

Patients Requiring Hemodialysis

Patients on hemodialysis should use IV GAN rather than VGAN, because the 450 mg tablet does not allow appropriate dose reductions for patients requiring hemodialysis. The GAN exposure produced by administration of the 450 mg VGAN tablet is more than 20 times higher than those produced in other patient groups.

Patients with CMV Retinitis

Patients with AIDS, CMV retinitis and normal renal function at baseline (CL_{CR} > 70 mL/min) had AUC values that were 25 % higher than in healthy subjects with normal renal function, based on a cross-study comparison. CL_{Cr} was also recorded in the subjects prior to PK assessment in Weeks 1 and 4, with all patients having CL_{Cr} > 70 mL/min. If the patients with CMV retinitis indeed had greater GAN exposure than other patient populations with the same renal function, this reviewer's proposed dosing algorithm is acceptable provided the same relative increase in exposure occurs as renal function decreases.

Comment

Ideally, a study should have been conducted in the target population, AIDS patients with CMV retinitis, because renal function in these patients fluctuates (generally declines) upon treatment initiation. However, the availability of patients from this target population is limited. It will be advisable to closely monitor the renal function of these patients once treatment with VGAN begins, as is recommended in the Cytovene label.

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Appendix

Table A1: Demographic data for study groups

	Subject Groups						
	HIV-CMV Seropositive	Healthy Volunteers	Healthy Volunteers	Mildly Renally Impaired	Moderately Renally Impaired	Severely Renally Impaired	End Stage Renally Impaired
	1	2G	2GA+2UK^	3	4	5	6
Sex Male Female	7 1	4 4	6 2	3 3	6	6	6
Race Caucasian Black	8	8	6 2	6	5 1	5 1	6
Age in yrs Mean (SD) Range	36.9 (6.01) 29-48	44.5 (13.5) 22-56	38.3 (13.0) 22-56	59.5 (5.4) 52-67	46.3 (19.1) 26-73	52.0 (4.7) 46-60	44.0 (13.1) 27-58
Weight in kg Mean (SD) Range	74.7 (7.4) 63.7-85.1	71.3 (12.4) 52.4-88.5	79.3 (11.3) 68.3-101.9	68.1 (6.0) 61.3-79.0	78.7 (9.4) 67.5-89.5	74.1 (3.7) 68.8-77.7	66.1 (7.4) 57.6-79.6
Height in cm Mean (SD) Range	179.6 (3.89) 174-185	171.3 (13.35) 155-187	180.1 (5.7) 172-188	166.8 (6.2) 159-177	174.5 (8.0) 166-188	175. (3.9) 170-181	169.7 (9.2) 157-180
CL_{CR} in mL/min Mean (SD) Range	104.3 (17.3) 71-121	88.1 (16.4) 71-116	96.3 (15.9) 73-116	61.2 (6.3) 51-67	39.3 (10.3) 26-50	12.7 (2.1) 11-16	5.2 (6.9) 0.3-10*

* The CL_{CR} is for n = 2, because the other 4 patients were anuric precluding CL_{CR} calculation

^ 2GA+2UK- healthy volunteers who received only treatment A (2UK) and healthy volunteers who received treatment A before treatment B

Standardized Breakfast

- 1 x bowl of cereal (Cornflakes) with 100 mL of whole milk
- 2 x rashers lean bacon
- 2 fried eggs
- 2 x slices toast with butter
- 100 mL fresh orange juice
- 150 mL decaffeinated tea or coffee

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Table AII: Predicted daily GAN AUC_{ss} for different CL_{CR} based on applicant's model (Equation 2)

CL_{CR} (mL/min)	Dose Regimen	Predicted Mean Daily AUC (μg·hr/mL)	Assumed AUC* in CMV Retinitis Patients
100	900 mg QD	25.9	33.67
900	900 mg QD	29.1	37.83
80	900 mg QD	33.3	43.29
70	900 mg QD	38.7	50.31
70	450 mg QD	19.3	25.09
65	900 mg QD	42.0	54.6
65	450 mg QD	21.0	27.3
60	900 mg QD	46.0	59.8
60	450 mg QD	23.0	29.9
50	450 mg QD	28.3	36.79
50	450 mg every 2 days	14.1	18.33
40	450 mg QD	36.3	47.19
40	450 mg every 2 days	18.2	23.66
35	450 mg QD	42.2	54.86
35	450 mg every 2 days	21.1	27.43
30	450 mg QD	50.2	65.26
30	450 mg every 2 days	25.1	32.63
20	450 mg every 2 days	39.7	51.61
20	450 mg twice weekly	22.7	29.51
15	450 mg twice weekly	31.3	40.69
15	450 mg once weekly	15.7	20.41
10	450 mg twice weekly	49.5	64.35
10	450 mg once weekly	24.7	32.11

* AUC value obtained by assuming AUC in this population is 30 % higher than in studied population

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ON ORIGINAL

Study No. and RS No.: Research Report W-144125 (Protocol 15376) Volumes 53 and 54
Study Centers: Multinational and multicenter study conducted at 42 Centers (22 centers in USA, 3 centers in Canada, 3 centers in Mexico, 1 center in Brazil, 2 centers in Australia, and 11 centers in Europe)
Investigators: Multiple investigators
Study Period: January 1997- September 1999

Title: A randomized controlled comparison of the safety and efficacy of Ro 107-9070 (VGAN) vs. IV GAN as induction therapy for the treatment of newly diagnosed CMV retinitis

Objectives:
- to investigate the efficacy of VGAN when used as induction therapy in patients with newly diagnosed retinitis
- to investigate the safety profile of VGAN in this indication
- to assess the effects of induction and maintenance level dosing of VGAN on CMV viral load, estimated by plasma CMV PCR
- to assess the pharmacokinetics of GAN following administration of VGAN in the target population

Study Design: An open-label, parallel study design was used (n = 160). Patients were randomized to receive induction therapy with VGAN or IV GAN. After the 4-week randomized phase, all patients received oral VGAN during maintenance therapy. Multiple cycles of reinduction therapy with VGAN were permitted upon recurrence of CMV retinitis.

Treatments
Initial Therapy (Induction Therapy, weeks 1-3 and Maintenance therapy week 4)
- Oral VGAN: 900 mg twice-daily (BID) for 3 weeks followed by 900 mg once-daily (QD) for 1 week
- IV* GAN: 5 mg/kg BID for 3 weeks followed by 5 mg/kg QD for 1 week

Maintenance Therapy
- Oral VGAN: 900 mg QD

All oral VGAN doses were given after a meal
* IV GAN given as IV infusion over a 1 hour period

Study Procedures
Unblinded ophthalmologic assessments and blinded assessments of retinal photographs were conducted throughout the study. Serial blood samples were collected at the end of week 1 and week 4 for quantification of VGAN and GAN. Safety and laboratory assessments were made throughout the study.

Subjects in Pharmacokinetics Substudy and their Demographic Characteristics
Fifty-one subjects were recruited for the pharmacokinetic component of the study. Distribution of these subjects into the two treatment groups is shown in Table I.

Table I: Evaluable subjects participating in the efficacy trial

Subject Evaluability	IV Ganciclovir		Oral Valganciclovir	
	Week 1	Week 4	Week 1	Week 4
Evaluable	18	18	25	21
Non-evaluable	4	4	4	8

According to the medical reviewer, patients in the VGAN oral treatment group may have had a slightly more advanced disease progression than subjects receiving IV GAN at baseline. The impact of this finding on GAN PK was not identified by the applicant nor explored in this review.

Table II: Demographic data for study groups: HIV-positive and newly diagnosed CMV retinitis

	Subject Groups	
	N = 23	N = 28
	IV GAN VGAN	VGAN/VGAN
Sex		
Male	21	27
Female	2	1
Race		
Caucasian	15	19
Black	2	5
Other	6	4
Age in years		
Mean (SD)	37.0 (7.8)	41.0 (7.7)
Range	23 - 54	30 – 61
Weight in kg		
Mean (SD)	72.30 (12.64)	70.78 (12.39)
Range	50.2 – 107.0	47.6 – 95.5
CL_{CR} in mL/min		
Mean (SD)	123.3 (28.2)	119.9 (27.3)
Range	77.0 – 180.0	76.0 – 182.0

Formulations

Valganciclovir hydrochloride (VGAN) salt 450 mg tablets – clinical trial formulation F 79070-013, Batch No. 1522401, 1504801, 1539301, 1552991, 1558571, 1630621, 1546691, 1638021, 1630641, 1657881, 1649971, and 1671051

Ganciclovir (GAN) sodium for IV administration sterilized lyophilized powder F 21592-087. Batch numbers 1495011, 1505831, 1533951, 1632931 and 1653521

Pharmacokinetic and Pharmacodynamic Assessments

Pharmacodynamics- reduction in viral load, using CMV PCR

Pharmacokinetics- VGAN and GAN PK parameters were calculated: AUC_{∞}, AUC_{ss}, C_{max}, T_{max}, CL_{IV}, CL_{PO}, A_e, CL_R, k_e, and $t_{1/2}$.

RESULTS

Pharmacokinetics

Several patients in both IV GAN and oral VGAN groups were excluded from the PK analyses for reasons including:

- Absence of plasma data on week 1 or week 4
- Improbably high plasma concentrations that may have been due to sampling through same arm as IV infusion
- Incomplete profile

Exclusion of data from these patients in the PK analyses is acceptable.

VGAN Pharmacokinetics

As in previous studies, administration of VGAN resulted in low VGAN systemic exposure (AUC and C_{max} < 2 % that of GAN), with rapid elimination of VGAN from the plasma.

Table III: Arithmetic mean (CV %) VGAN PK parameters at the end of Week 1 and 4 during efficacy trial

Pharmacokinetic Measure	900 mg VGAN BID in Week 1	900 mg VGAN QD in Week 4
T_{max} (h)	1.36 (52.6); n = 25	1.46 (43.8); n = 20
C_{max} (µg/mL)	0.181 (32.5); n = 25	0.162 (42.5); n = 20
$AUC_{0\text{-}12 \text{ or } 24 \text{ hr}}$ (µg hr/mL)	0.369 (62.3); n = 25	0.347 (57.3); n = 20
$T_{1/2}$ (h)	1.99 (123.8); n = 11	2.33 (91.5); n = 9
k_{el} (hr^{-1})	0.638 (55.8); n = 11	0.444 (47.8); n = 9

VGAN PK appeared to be comparable at week 1 and week 4.

GAN Pharmacokinetics

Apart from C_{max}, all GAN PK measures were comparable for IV GAN and oral VGAN for a given dosing regimen and week, as shown in Table IV.

Table IV: Mean ± SD GAN pharmacokinetic measures during efficacy study

	IV GAN		Oral VGAN	
	GAN (week 1)	GAN (week 4)	GAN (week 1)	GAN (week 4)
Pharmacokinetic Measure	N = 18	N = 18	N = 25	N = 25
$AUC^*_{0\text{-}12 \text{ or } 24 \text{ hr}}$ (µg hr/mL)	28.6 ± 9.02	30.7 ± 7.69	32.8 ± 10.1	34.9 ± 13.3
C_{max} (µg/mL)	10.4 ± 4.9	9.86 ± 3.14	6.71 ± 2.12	5.87 ± 1.46
C_{ss} (µg/mL)	2.4 ± 0.75	1.28 ± 0.32	2.74 ± 0.84	1.46 ± 0.56
T_{max} (hr)	0.89 ± 0.26	0.98 ± 0.21	2.31 ± 0.93	2.49 ± 0.98
$T_{1/2}$ (hr)	3.99 ± 0.85	4.32 ± 0.69	3.94 ± 1.10	4.12 ± 0.86

C_{ss} = $AUC_{0\text{-}12 \text{ or } 24 \text{ hr}}$/Dosing Interval, * for week AUC is for 12 hours and week 4 AUC is for 24 hours

Differences in C_{max} following oral VGAN and IV GAN administrations are anticipated, due to the different routes of administration. Peak to trough fluctuation (measured by C_{max}/C_{min} ratio) of GAN concentrations was greater following IV GAN administration than following oral VGAN. The average fluctuation for IV GAN was 28 at week 1 and 119 at week 4, whereas for VGAN the average fluctuation was 17 at week 1 and 43 at week 4.

Ganciclovir AUC Comparability Between IV GAN and oral VGAN Treatments in Efficacy Trial

Based on AUC values at steady state, systemic exposure of GAN was comparable for both IV administered GAN and orally administered VGAN during induction (BID) and maintenance (QD) level dosing.

Table V: Treatment comparisons based on point estimates and 90 % confidence intervals (non-log-transformed data)

	Geometric Mean Ratio (Oral VGAN/IV GAN)	
Relative Exposure Measure	Point Estimate	90 % CI
$AUC_{0\text{-}12}$ (week 1)	1.16	0.98 – 1.36
$AUC_{0\text{-}24}$ (week 4)	1.09	0.91 – 1.31

Systemic and Renal Clearance of GAN During Efficacy Trial

Renal clearance of GAN was comparable for the two treatments (IV GAN and oral VGAN).

Table VI: Mean urinary GAN pharmacokinetic measures during efficacy trial

GAN Clearance	Week 1 IV GAN	Week 4 IV GAN	Week 1 Oral VGAN	Week 4 Oral VGAN
CL_{IV}	213 ± 84.6	204 ± 63.8	NA	NA
CL_R	149 ± 76.9	159 ± 79.8	226 ± 79.0	198 ± 87.4
CL_{CR}	121 ± 33	126 ± 33	130 ± 27	140 ± 52

NA – not applicable

The renal clearance accounted for 72 to 80 % of the total systemic CL of GAN, based on data from subjects receiving IV GAN. Systemic CL of GAN was comparable following IV GAN on weeks 4 and 1. Similarly, mean CL_R was comparable for a given treatment at weeks 1 and 4. It is noted that CL_R in the IV GAN group was highly variable (CV approx. 50 %). The GAN CL_R following oral VGAN administration was higher than that following IV GAN administration. The applicant attributes the difference in GAN CL_R between the IV GAN and oral VGAN treatment arms to the intrinsic variability associated with estimations of renal CL rather than a true difference between the two treatment groups.

Comment
The applicant's explanation for the observed differences in CL_R and A_e appear to be reasonable based on urinary PK results from other studies. In the renal impairment study, cumulative amounts of drug excreted (A_e) in HIV+, CMV patients without retinitis were 182 – 445 mg for IV dose and 344 – 412 mg for VGAN, and each patient received each treatment. In the efficacy study at week 1, the ranges of A_e were: 70 – 459 mg for IV and 289 – 579 mg for oral VGAN, but these values are obtained from a parallel design. Despite the potential limitations of using data from a parallel study, the results suggest that the amount of GAN excreted in HIV+/CMV+ patients is comparable to that in HIV+/CMV retinitis patients, thus the applicant's claim is supported.

Numerically, AUC values obtained in HIV+/CMV retinitis ($AUC_{IV\ GAN}$ 28.6 ± 9.02 and AUC_{VGAN} 32.8 ± 10.1) subjects were approximately 25 % higher than the AUC values in HIV+/CMV+ ($AUC_{IV\ GAN}$ = 24.4 µg hr/mL and $AUC_{V\ GAN}$ = 26.6 µg hr/mL) subjects following both IV GAN and oral VGAN administration. However this difference did not appear to be statistically significant. This finding suggests that PK differences may exist in these two patient populations, but the cause of the differences is not certain.

Absolute BA
The absolute BA of VGAN was 64 % and 59 %, following administration of VGAN BID and VGAN QD, respectively. These findings are consistent with other study results. However, the applicant states the study was not intended to evaluate BA and was not sufficiently powered to validate these BA results.

Conclusion
In AIDS patients with CMV retinitis, systemic exposure (AUC_{ss}) of GAN from oral VGAN was comparable to that from IV GAN, while the GAN C_{max} from VGAN was approximately 67 % of that obtained after dosing with IV GAN.

APPEARS THIS WAY
ON ORIGINAL

Study No.: W-144111 (Protocol WP 15509) Volume 46
Investigator and Study Center:

Study Period: September 1998 - November 1998

Title: A bioequivalence study of the clinical trial versus market formulations of valganciclovir tablets in HIV positive volunteers

Objectives:
- To demonstrate the bioequivalence of ganciclovir following single oral doses of clinical trial and market formulations of valganciclovir tablets in HIV positive patients
- To establish the absolute bioavailability of ganciclovir following single oral doses of clinical trial and market formulations of valganciclovir tablets

Study Design: An open-label, randomized, balanced, three-way crossover study design was employed. A one-week washout period was observed between treatments. Seventeen of the 18 subjects receiving treatment were evaluable for pharmacokinetic analyses. One subject did not complete the study due to an adverse event (urticaria). The subject did not receive the to-be-marketed formulation, and the subject was not replaced. Subjects received the specified treatments after completion of a standard breakfast (see Appendix for meal contents).

Demographic Characteristics
Subjects: HIV-positive and CMV-seropositive
Gender: 18 male
Race: 18 Caucasian
Age in years: Mean ± SD = 34.6 ± 8.8; Range = 22 - 53
Weight in kg: Mean ± SD = 78.4 ± 9.0; Range = 69 – 97
Estimated CL_{CR} = 124.4 ± 20.6 mL/min
CD4 lymphocyte count ≥ 100 cells/μL

Formulations
Ganciclovir (GAN) IV free base lyophilized powder for solution: Batch No. 066
Valganciclovir (VGAN) tablets: 450 mg market formulation, Batch No. 1652541
Valganciclovir (VGAN) tablets: 450 mg clinical trial formulation Batch No. 1630621

Treatment Regimens
Regimen A: 900 mg PO VGAN clinical trial formulation
Regimen B: 900 mg PO VGAN market formulation
Regimen C: 5 mg/kg IV GAN, given as 1-hour infusion

Pharmacokinetic Analyses
Relative bioavailability of VGAN was measured using GAN equivalents.

Results

VGAN Pharmacokinetics
As observed in other studies, systemic exposure to VGAN was low, with AUC and C_{max} of VGAN < 4 % of systemic GAN exposure. In general, similar VGAN pharmacokinetic measures were obtained following administration of the two oral VGAN formulations.

Table I: Arithmetic mean (%CV) VGAN pharmacokinetic measures following administration VGAN (900 mg) to HIV+ patients

VGAN Pharmacokinetic Measures	Treatment	
	Clinical Trial Formulation (n=18)	Market Formulation (n=17)
T_{max}* (hr)	1.25	1.00
T_{lag}	0.25	0.25
C_{max} (µg/mL)	0.20 (83.6)	0.22 (65.7)
AUC_{0-24} (µg hr/mL)	0.37 (69.8)	0.39 (80.2)
Half-life (hr)	1.33 (70.7)	1.35 (57.9)^

* t_{max} values are expressed as medians
^ n = 12

GAN Pharmacokinetics

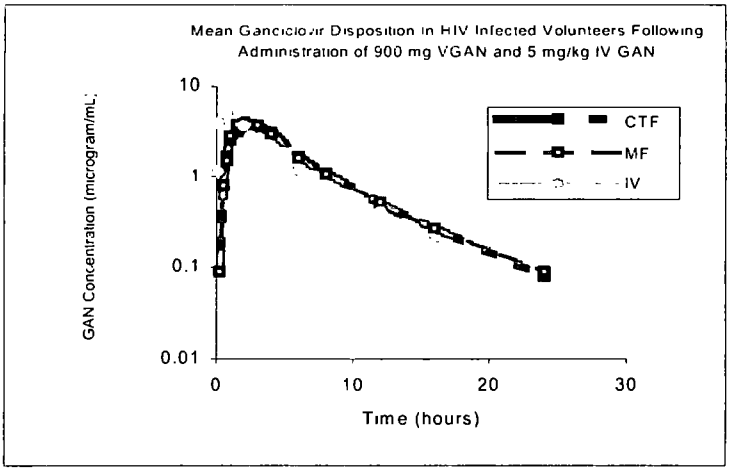
GAN PK measures following Treatments A, B, and C are summarized in Table I.

Table II: Arithmetic mean (%CV) GAN pharmacokinetic measures following administration of IV GAN (5 mg/kg) and two oral VGAN (900 mg) formulations to HIV+ patients

	Treatment		
GAN Pharmacokinetic Measures	Clinical Trial Formulation (n=18)	Market Formulation (n=17)	IV Ganciclovir (n = 18)
Dose	900 mg	900 mg	5 mg/kg
T_{max}* (hr)	2.75	2.00	1.0
C_{max} (µg/mL)	4.63 (29)	5.15 (22)	9.31 (22)
AUC_{0-24} (µg hr/mL)	24.4 (17)	24.9 (18)	25.6 (20)
$AUC_{0-\infty}$ (µg hr/mL)	24.9 (18)	25.5 (19)	26.0 (21)
$F_{abs\ nominal}$ (%)	59	58	
$F_{abs\ actual}$ (%)	48	48	
CL/F or CL (mL/min)	445.6 (16.5)[@]	437.7 (18.8)[@]	216.1 (21.6)[$]
V_{ss} (L/kg)	NA	NA	0.64
Half-life (hr)	4.35 (16)	4.43 (12)	3.94 (17)

* t_{max} values are expressed as medians; [@] Clearance = CL/F; [$] Systemic clearance

Figure 1: GAN disposition following IV GAN and oral VGAN administration in BE Study



GAN PK measures obtained following administration of each of the two oral VGAN formulations were comparable. The mean value of systemic GAN exposure, measured as AUC_{0-24}, was comparable among

all three treatments. However, as expected, GAN C_{max} following IV administration was higher than GAN C_{max} following oral VGAN administration. GAN T_{max} following oral VGAN was comparable to results in other studies. .

Absolute Bioavailability
The absolute BA of GAN was 58 % when nominal IV dose was used and 48 % when the actual IV dose was used. It is not clear why the applicant did not use actual doses in all absolute BA calculations. The findings suggest that the BA of GAN following VGAN in other studies may have been overestimated, because nominal rather than actual doses of IV GAN were used in the calculation. Although, the observed calculated difference may impact the magnitude of the absolute BA, it does not alter the study conclusion or objective.

Bioequivalence*
The VGAN to be marketed formulation did not satisfy the BE criteria, as shown in Table III.

Table III: Geometric mean ratio (VGAN Market: VGAN Clinical) and 90 % confidence interval

GAN Relative Exposure Measure	GMR	90 % Confidence Interval
$AUC_{0\text{-}24\ hr}$ (μg hr. mL)	101	97 - 105
C_{max} (μg mL)	114	101 - 128

The GMR and 90 % confidence intervals for AUC were within the required BE range, but the C_{max} slightly exceeded the upper limit of 125 %. The increase in C_{max} with the to-be-marketed formulation is unlikely to pose additional safety concerns, because GAN concentrations following IV administration are two-fold higher than the oral to be marketed formulation, and are well tolerated in the target population. Maximum increases in individual AUC and C_{max} ratios (Market formulation relative to clinical formulation) were < 30 % for AUC and approximately 80 % for C_{max}.

Two important points to note about the pivotal BE study are:
- The treatments were given in the fed state
- Dissolution studies were conducted to compare the two formulations before study initiation and following study completion (see Discussion below and Dissolution Results)

Discussion
Because the study was conducted in the fed state, it is possible that potential formulation differences may not have been adequately identified in this study. The current regulatory recommendation is that pivotal BE studies be conducted in the fasted state. Prior to submission of this NDA, internal (within FDA) and external discussions (FDA and applicant) were held to discuss possible ways to establish BE between the two formulations. It was agreed that dissolution studies could be conducted in lieu of conducting a fasted BE study. Results from the dissolution study, coupled with the BE study in the fed state, would be sufficient to support approval of the marketed formulation.

Dissolution Results
In both HCl and water, the market formulation and clinical formulation exhibited similar dissolution characteristics. Within 30 minutes [redacted] of the VGAN had dissolved and both formulations reached their plateau in [redacted] Based on these results the formulations can be considered equivalent.

Safety Results
In general VGAN administration was well tolerated. The most common adverse events were headache and events related to the GI system. The proportion of subjects experiencing at least one adverse event

was similar for the three treatments. In general, the adverse events reported were in line with those expected based on the GAN safety profile.

Appendix

Standardized Breakfast

- Cornflakes with 150 mL semi-skimmed milk
- 3 slices of toast with butter (2 sachets)
- Jam (2 sachets)
- 150 mL orange juice

APPEARS THIS WAY
ON ORIGINAL

Study No. and RS No.: Report W-144127 Protocol WP 15711 volume 48
Investigators and Study Centers: Multiple investigators. US and UK sites
Study Period: April 1998- October 1998

Title: The pharmacokinetics of ganciclovir following oral valganciclovir, oral ganciclovir and intravenous ganciclovir in liver transplant patients

Objective:
To determine a dose of valganciclovir given once daily to liver transplant recipients that will provide a ganciclovir exposure, measured as AUC, bracketed by the exposure provided by IV ganciclovir given at 5 mg/kg/day and oral ganciclovir given at 3000 mg/day.

Study Design: An open-label, randomized, 4-way crossover study design was employed. Each subject received the following four treatments:
Treatment A: ganciclovir 3000 mg PO as 3 divided doses after a meal
Treatment B: Valganciclovir 450 mg PO as a single dose after a meal
Treatment C: Valganciclovir 900 mg PO as a single dose after a meal
Treatment D: ganciclovir 5 mg/kg IV as a single 1 hour infusion
The washout period between treatments was 3-7 days. Subjects received a standardized breakfast (see Appendix) and standardized meals throughout the study.

Demographic Characteristics
Subjects: liver transplant recipients who are CMV+ and 45-90 days post transplant or CMV-, received an organ from a seronegative donor and are 21-90 days post transplant
Gender: 21 male and 7 female
Race: 1 Black, 2 Hispanic, 1 Other, and 24 Caucasian
Age in years: Mean ± SD = 47.2 ± 8.3 ; Range = 20 - 60
Weight in kg: Mean ± SD = 88.2 ± 18.3 ; Range = 61 – 121
In addition, subjects had estimated mean CL_{CR} = 92.7 ± 20.8 mL/min (62 – 143), platelet count ≥ 100,000 µL, absolute neutrophil count ≥ 1200 cells/µL and CD4 lymphocyte count ≥ 100 cells/µL

Formulations
Valganciclovir hydrochloride salt 450 mg tablets – clinical trial formulation CT 450. Ro 107-9070-194, Batch No.. 1630621
Ganciclovir capsules 250 mg, Batch No. B014 (UK) and 995731 (USA)
Ganciclovir sodium for IV administration sterilized lyophilized powder. Batch numbers 1632931 and 2080

Pharmacokinetic Analyses
VGAN and GAN PK parameters were calculated: AUC_{∞}, AUC_{24}, C_{max}, T_{max}, CL_{IV}, CL_{PO}, CL_R, k_e, and $t_{1/2}$. The applicant used one-sided equivalence testing with the regions 80 %-∞ for the comparison of $AUC_{0\text{-}24\ hr}$ of Treatments A and B, and 0-125 % for the comparison of $AUC_{0\text{-}\infty}$ of Treatments D and C. In addition the applicant calculated 90 % confidence intervals (CIs) for:

- effect of Treatment A relative to Treatment D
- effect of Treatment B relative to Treatment D
- effect of Treatment C relative to Treatment A

The applicant indicates that the 90 % CIs were interpreted in an exploratory sense only.

Comment
The use of one-sided equivalence testing for PK data is not recommended according to the current regulatory guidelines, whereas use of 90 % CIs is recommended for PK comparisons. Consequently, in this review the 90 % CI will be used for PK comparisons.

Results

Valganciclovir Pharmacokinetics
As in studies in other populations, administration of VGAN resulted in low VGAN systemic exposure. The mean VGAN C_{max} and AUC were 0.172 µg/mL and 0.435 µg·hr/mL after administration of 900 mg VGAN (Treatment C). The elimination of VGAN from the plasma was rapid ($t_{1/2}$ = 1.5 hr), and VGAN plasma levels were undetectable by 4 hours post dose.

Ganciclovir

Table I: Selected mean (CV %) GAN PK measures following oral VGAN, oral GAN and IV GAN administration

Formulation Dose	IV GAN 5 mg/kg	Oral VGAN 450 mg	Oral VGAN 900 mg	Oral GAN 1000 mg TID
GAN PK Measure				
C_{max} (µg/mL)	12.2 (24)	3.01 (27)	6.18 (30)	1.46 (23)
AUC (µg·hr/mL)	48.2 (36)	21.1 (23)	41.7 (24)	20.7 (22)
$T_{1/2}$ (hr)	5.17 (27)	5.22 (20)	5.10 (22)	
CL_R (mL/min)	125 (30)	126 (31)	137 (31)	137 (30)
T_{max} (hr)	-	3.0	3.0	NA

NA- not applicable because oral GAN is administered three times daily

The GAN concentrations observed following 900 mg VGAN were approximately 10-fold greater than the GAN concentrations obtained after oral GAN administration (1000 mg TID), as seen in other patient populations. GAN CL_R was comparable for all treatments. Terminal half-lives following oral VGAN administration and IV GAN administration were comparable.

GAN AUC Comparability among Treatments
GAN AUC_{24} following administration of 450 mg VGAN and 3000 mg GAN were comparable. Similarly, GAN AUC_{24} following administration of 900 mg VGAN was comparable to that following administration of 5mg/kg IV GAN.

Table II : Treatment comparisons based on point estimates and 90 % confidence intervals (non-log-transformed data)

AUC (µg·hr/mL)	Test*	Reference*	Point Estimate	90 % CI
$AUC_{0-\infty}$	C	D	90	83 - 97
AUC_{0-24}	B	A	102	95 - 109
AUC_{0-24}	A	D	44	38 - 50
AUC_{0-24}	C	A	202	186 - 220
$AUC_{0-\infty}$	B	D	45	42 - 49

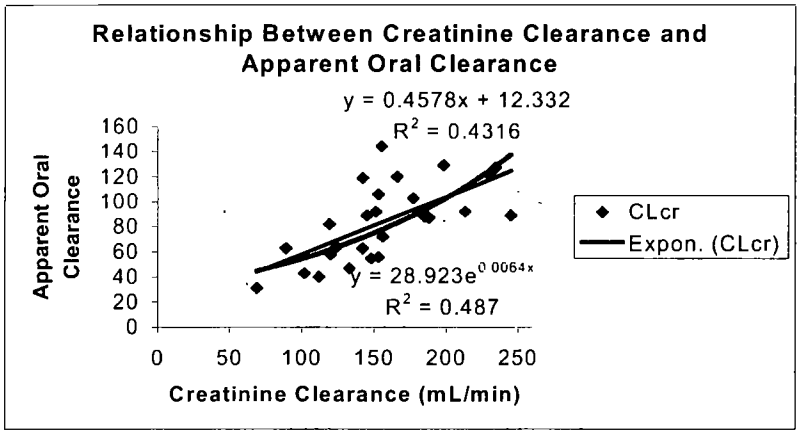
* Treatment A: ganciclovir 3000 mg PO as 3 divided doses after a meal, Treatment B: Valganciclovir 450 mg PO as a single dose after a meal, Treatment C: Valganciclovir 900 mg PO as a single dose after a meal
Treatment D: ganciclovir 5 mg/kg IV as a single 1 hour infusion

It is noteworthy that variability of GAN AUC, assessed by % CV, was greater in IV GAN treatment than in oral treatments. Based on the AUC similarities, results from the current study indicate that 900 mg oral VGAN may be used in place of 5 mg/kg IV GAN, and the 450 mg oral VGAN may be used in place of

3000 mg oral GAN in this patient population. This substitution is possible if the exposure-response relationships produced by the substitute regimens are similar to those for the reference regimens.

AUC in Liver Transplant Recipients vs. Other Patient Populations
In HIV subjects IV GAN given at 5 mg/kg provides drug exposure of ≈ 25 μg hr/mL; whereas, in the same subjects, the AUC produced by 1000 mg oral GAN TID is 15 μg hr/mL. The AUCs in transplant recipients were higher than in other patient populations. According to the applicant, the range of exposure provided by IV and oral GAN administration represent the highest safe and acceptable concentrations, and the minimum effective concentrations for GAN efficacy and tolerability, respectively.

Clearance of GAN
Renal clearance of GAN was comparable for all four treatments. However, the CL_R in this population was 30 % lower than in other populations (e.g. HIV+/CMV+ and healthy volunteers). A weak linear correlation appeared to exist between the GAN apparent CL and CL_{CR}. It will be difficult to establish a dosing algorithm in this patient population with the given data, because data were available only for subjects with CL_{CR} > 60 mL/min. Most of the absorbed GAN was excreted in the urine as unchanged drug over a 24 hour period. From the IV data, total systemic CL was determined, and it was shown that the majority of the CL is due to renal excretion.



Period effects and crossover effects were not statistically significant in this study.

Safety Results
VGAN was well tolerated and not associated with any unexpected adverse events (AEs). Reported AEs were consistent with those associated with GAN administration. The most common AEs were headache and GI related events, such as nausea and diarrhea. The pattern of AEs was comparable among all four treatments. The Medical Reviewer agrees with the applicant's assessment.

Conclusions
In liver transplant patients, the following conclusions can be made:

- A 900 mg dose of oral VGAN provides comparable $AUC_{0-\infty}$ to the 5 mg/kg IV dose
- A 450 mg dose of oral VGAN provides a comparable $AUC_{0-24\ hr}$ to that provided by 3000 mg oral GAN (1000 mg TID)
- VGAN was well tolerated and has a safety profile consistent with the safety profile of GAN

Appendix

Standardized Breakfast

- 1 x bowl of cereal (Cornflakes) with 100 mL of whole milk
- 2 x rashers lean bacon
- 2 fried eggs
- 2 x slices toast with butter
- 100 mL fresh orange juice
- 150 mL decaffeinated tea or coffee

APPEARS THIS WAY
ON ORIGINAL

Research Report W-143167 Volume 30
Title: *In vitro* evaluation of the metabolism of the ester prodrug valganciclovir, in man, mouse and dog

Objectives:
- To determine the tissue location and rate of hydrolysis of valganciclovir to ganciclovir in man
- To determine the metabolic profile of valganciclovir in man

Methodology: varying concentrations of valganciclovir were incubated with liver (pooled from 10 males) and intestine (one male) S9 fractions and whole blood (one male) for up to 60 minutes at 37 ^{O}C. Incubations were carried out in duplicate. A NADPH regenerating system was added to S9 fractions to facilitate metabolism by oxidation pathways. In addition, protein concentrations were varied in the S9 fractions. Enzyme kinetic parameters were determined for the S9 systems.

Drugs*
^{14}C valganciclovir solution (Lot 7364-MK-9)
Valgancilcoivr powder (Lot 1654661)
Ganciclovir solution (Batch 686-237)
* ^{14}C VGAN Solutions were prepared by adding aliquot of ^{14} C solution to solid VGAN powder

Sampling scheme: samples were taken at 5, 10, 15, 30, and 60 minutes. The reaction was stopped with trichloroacetic acid (TCA).

Assay: HPLC assay with radiochemical detection was used to analyze samples

Results
Stability Study:
VGAN stability was determined by measuring the amount of GAN present, as shown in Table I.

Table 1: Percent of GAN in different solutions of VGAN buffer (pH 7.4) stored in the dark

Storage time	VGAN Concentration	
	10 µg mL	100 µg/mL
Freshly made	2.2	1.3
16 hours	13	nd
1 week	42	26

nd- not done

Because VGAN was unstable in the buffer (pH 7.4) after a week of storage, alternative media were evaluated. According to the applicant, VGAN solutions in TCA at pH 3 were stable for 1 week, and could be added as small aliquots to the incubation medium without affecting the pH (data were not supplied).

Hydrolysis Study
The hydrolysis of VGAN in whole blood and plasma were determined.

Table 2: GAN (%) formed by hydrolysis in human, dog, and mouse whole blood and in buffer

	VGAN 10 µg/mL				VGAN 100 µg/mL			
Time (mins)	Human	Dog	Mouse	Buffer	Human	Dog	Mouse	Buffer
0	12.1	13.4	8.4	2.2	8.1	8.4	5.2	1.3
5	10.5	12.8	7.2		7.1	10.2	7.9	
10	10.7	12.3	14.1		6.7	9.5	8.8	
15	10.0	17.8	15.6		6.2	9.4	9.0	
30	11 2	22.0	16.2		10.1	14.6	13.7	
60	14.0	19.2	28.9	7 4	10 7	12.8	23.2	8.4

It is noteworthy that samples at t = 0 had GAN present. The GAN present at time t = 0 in the buffer is more likely to be due to impurities than to immediate hydrolysis. On the other hand, data from whole blood systems suggested that enzymatic hydrolysis was immediate. According to the sponsor, in a subsequent study the apparent immediate hydrolysis was shown to be dependent on the order of addition of reagents. When TCA was added to the S9 fractions before VGAN was added there was no hydrolysis at time zero and GAN concentrations were comparable to those in buffer at t = 0. With this caveat in place, these data indicate that compared to the buffer, minimal hydrolysis occurred in human and dog whole blood, but a small amount of hydrolysis occurred in mouse blood. Only GAN and unchanged VGAN were detected following incubation with the whole blood.

Metabolism Study

The metabolism of VGAN in human liver and intestinal S9 fractions was determined.

Table 3: GAN (%) formed after incubations of VGAN with liver S9 from man

	10 microgram/mL VGAN		100 microgram/mL VGAN	
Time (mins)	Man (low*)	Man (high^)	Man (low*)	Man (high^)
0	4.2	22.8	4.2	19.4
5	37.5	98.9	38.3	95.1
10	49.4	100.0	54.5	100.0
15	61.5	100.0	64.6	100.0
30	78.9	99.0	88.8	99.3
60	95.2	100.0	100.0	100.0

* low = 1 mg/mL protein and ^high = 16 mg/mL protein

At a maximal protein concentration of 16 mg/mL hydrolysis of VGAN was completed within 5 minutes, therefore lower protein concentrations were used in subsequent studies. As observed in other studies, samples at time t = 0 contained some amount of GAN. Initial rates of hydrolysis (GAN formed/time) were similar at the two VGAN incubation concentrations, suggesting that the enzymes were not saturated at a concentration greater than those expected *in vivo*. The hydrolysis reaction was complete within 60 minutes, as indicated by GAN concentrations of 100 %. Similar hydrolysis results were obtained in dog and mouse S9 fractions (data not shown in this review), but the rate of hydrolysis in the animal tissues was not as rapid as in human tissues. In all tested S9 fractions, GAN was the only metabolite detected following VGAN incubation. Based on the study results, it appears that the esterase hydrolysis reaction (removal of valyl group from VGAN) is the predominant metabolic pathway.

The results from incubation of VGAN with intestinal S9 fractions mirrored those found with liver S9 fractions in all species tested; therefore, a discussion on these results will not be repeated.

Table 4: GAN (%) formed after incubations of VGAN with intestinal S9 from man

	10 microgram/mL VGAN		100 microgram/mL VGAN	
Time (mins)	Man (low)	Man (high)	Man (low)	Man (high)
0	8.5	14.3	2.0	12.9
5	28.2	79.5	19.7	74.0
10	39.3	92.4	33.9	91.7
15	48.7	99.1	49.9	98.0
30	65.6	98.7	83.7	100.0
60	89.0	100.0	91.5	100.0

Enzyme Kinetics in Human Hepatic and Intestinal S9 fractions

The initial rates of formation of GAN from various incubations were calculated using the blank values for the buffer and 5 minute GAN concentrations (Table 5)

Table 5: Initial rates of GAN formation (nmoles/min/ mg protein) for S9 fractions

	10 µg/mL, VGAN			100 µg mL VGAN		
S9 tissue	Human	Dog	Mouse	Human	Dog	Mouse
Liver	2.0	1.5	1.1	18.9	16.6	14.7
Intestine	1.3	ND	ND	9.4	ND	ND

ND- not determined

Table 6: Initial Rate of hydrolysis* of VGAN by human hepatic and intestinal S9 (0.5 mg/ml protein)

	Ganciclovir Produced (nmoles/min/mg protein)	
VGAN Conc. (µM)	Hepatic	intestinal
77	8.93	4.35
256	24.41	13.67
769	47.66	22.15
1537	66.82	38.74
2562	90.63	50.75
3843	95.31	53.62
5124	105.69	74.20
7686	124.60	96.33
12810	161.98	133.92

* In this study, the order of addition of reagents was optimized to yield accurate GAN concentrations at t = 0

Based on initial rates, the rate of VGAN hydrolysis in hepatic S9 is twice as fast as in intestinal S9 tissues and does not appear to be saturated at the concentrations tested.

Table: Enzyme kinetic parameters for VGAN

	Hepatic S9	Intestinal S9
V_{max} (nmoles min^{-1} mg protein)	178	237
K_m (mM)	2.7	10.6

Overall Summary and Conclusions

- VGAN is rapidly hydrolyzed to GAN in human liver and intestinal cells, which supports the finding of low bioavailability and low plasma concentrations of VGAN *in vivo* following oral VGAN administration.
- In both liver and intestinal fraction, the enzymes responsible for hydrolysis have a high capacity and low affinity. Based on the K_m values they are unlikely to be saturated at clinical or supra clinical doses
- VGAN is converted to GAN by chemical hydrolysis in phosphate buffer at pH 7.4, indicating that unabsorbed VGAN may undergo chemical as well as enzymatic hydrolysis to GAN
- The metabolism of VGAN to GAN, and the location and rate of metabolism were comparable in man, dog, and mouse.

APPEARS THIS WAY
ON ORIGINAL

Research Report W-143208 Volume 31

Title: Mechanistic and Inhibitor studies on valganciclovir permeability in rat intestine and tissue culture systems

Objectives

To determine the mechanism of absorption of valganciclovir

To investigate the effects of coadministered drugs on valganciclovir permeability

Study Procedures

Four types of tests were conducted.

Test A: Permeability measurements in *in situ* rat intestinal segments

Test B: Transport measurements across Caco-2 cells

Test C: Uptake measurements in Caco-2 cells overexpressing hpepT1 transporter

Test D: Permeability interaction studies in *in situ* rat intestinal segments

General Methods

General methods for the 4 test categories are summarized in the following section.

Phase I (Studies 1, 2, and 3)

In situ Permeability Studies

- Animal Model: Fasted rats with free access to water. Suitable jejunal segment cannulated and rinsed.
  Study 1 (n = 4)
  Study 2 (n = 3)
  Study 3* (n = 2)
- Perfusate or Perfused Buffer:
  Study 1 - 50 mL of perfusate collected per rat and perfusates pooled; perfusate fractions were adjusted to pHs 5.0, 6.5 or 7.5, respectively. VGAN added to perfusate to give concentration of 1 mM VGAN, and perfusate solution incubated in a shaking water bath for 90 minutes at 37 ^{O}C.
  Study 2 - pH 6.5; VGAN at 4 concentrations (0.01 – 10 mM) with and without 20 mM glycine-proline (Gly-Pro) an inhibitor* of the human dipeptide transporter, hpepT1, ^{14}C-PEG 4000, which is a non-absorbable marker for measuring water efflux
  * Future references to inhibitor in this review refer to Gly-Pro
- Attainment of Steady State (*Studies 2 and 3*):
  Inlet and outlet concentrations of radiolabeled PEG 4000 were monitored to assess steady state. When these two concentrations are equivalent, steady state is attained.
- Sampling Times and Sample Treatment
  Study 1 - blank at time 0, 15, 30, 45, 60 and 75 minutes after drug addition; trichloroacetic acid (TCA) was added to acidify and stop the reaction, and samples were flash frozen with dry ice and ethanol immediately after collection.
  Study 2 - after steady state was attained samples were taken every ten minutes until 1 hour after steady state. Additionally, a 0.5 mL aliquot taken for measurement of water flux before freezing; subsequently samples were acidified with TCA as in study 1

* Study procedures for Study 3 were similar to those in Study 2, thus study procedures for Study 3 were not repeated

Phase II (Study 4 and 5)

In vitro Cell Culture Studies

Study 4

- Transport Cell Model: Caco-2 cell monolayer
- Media: Three media were used. Regular medium, Transport medium (pH 6.0 or 7.4), and Incubation medium were added in a standard sequence to the apical and basolateral chambers, which were separated by preincubated monolayer filters.

- Spiking: Varying VGAN concentrations (n = 7, from 0.05 to 25 mM) were added to the appropriate medium alone, or with inhibitor (20 mM Gly-Pro)
- Sampling Times and Sample Treatment: 0, 5, 10, 15, 20, 25, and 30 min; drug solution was acidified with TCA at each time point

Study 5
- Uptake Transfection Model: Caco-2 cells were transfected with adenovirus containing hpepT1 (Ad.RSVhept1). Cells incubated for a total of 4 days to allow for optimal expression of hpepT1
- Media: standard media were used for growing cells and preincubation (uptake buffer)
- Spiking: One mL of uptake buffer containing varying VGAN concentrations (0.5 – 10 mM) alone or in the presence of inhibitor (20 mM) added to cells at 37 ^{O}C for 1 – 30 minutes.
- Sampling Times and Sampling Procedures:
  cells washed (cold PBS) and drug extracted (methanol: buffer mixture) using standard procedures; samples subsequently acidified and frozen (n = 3 per time point)

Phase III
Study 7*
In situ Permeability Studies for Drug-drug Interactions
- Animal Model: Rats with cannulated jejunal segments
- Perfusate: segments perfused at a flow rate of 0.2 mL/min in buffer containing 10 mM VGAN alone, or with one of six inhibitors, and ^{14}C-PEG 4000.
- Sampling: samples were taken in 10 minute intervals after steady state was reached

* Procedures were similar to those in Studies 1-3 (see General Methods: Phase I studies)

Results
Results from the tests were categorized into three phases as previously described.

Phase I
Study 1: Stability of VGAN in intestinal perfusate

Table 1: pH dependent stability of VGAN at 1 mM (n = 3)

	Mean VGAN Concentration (µg/mL)			Mean GAN Concentration (µg/mL)		
Time	pH 5.0	pH 6.5	pH 7.5	pH 5.0	pH 6.5	pH 7 5
0	433	428	431	2.78	2.83	3.50
15	451	428	420	3.05	3.55	7 24
30	447	425	401	3.08	4.33	10.82
45	449	427	401	3.29	4.95	14.17
60	454	424	394	3.39	5.58	16.80
75	448	431	388	3.43	6.20	21.17
90	417	426	394	3.36	6.76	23.87

CV less than 10 % in all studies

Degradation of VGAN in perfusate was low (< 10 %) under the test conditions. However, VGAN degradation increased as pH increased, as shown by the increased GAN levels as pH increased. For example the concentration of GAN at the 90 minute time point was 7-fold higher in pH 7.5 than in pH 5.0

Conclusion: Amount of VGAN degradation in perfusate is low and not likely to affect permeability study results at pH ≤ 6.5.

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Study 2: Measurement of effective intestinal permeability of VGAN in rat jejunum at pH 5- varying VGAN concentrations with or without Gly-Pro inhibitor

Table 2: VGAN permeability as a function of concentration in the presence and absence of a transporter inhibitor, Gly-Pro

Mean Permeability, Pe x 10^{-4} (cm/sec) ± SEM			
0.01 mM	0.1 mM	1.0 mM	10 mM
0.162 ± 0.036	0.253 ± 0.044	0.208 ± 0.025	0.308 ± 0.051
Mean Permeability with 20 mM Gly-Pro, Pe x 10^{-4} (cm/sec) ± SEM			
0.017 ± 0.016	0.133 ± 0.043	0.335 ± 0.061	0.126 ± 0.042

In the absence of the inhibitor, VGAN permeability did not appear to have a significant concentration dependence over the concentration range 0.01 – 10 mM at pH 6.5 . According to the applicant, VGAN permeability was decreased in the presence of transporter inhibitor only at high VGAN concentrations (no effect at concentrations ≤ 1.0 mM). The applicant did not provide a statistical test to support their conclusion. However, in this reviewer's opinion, the data at the 0.01 and 0.1 mM concentrations suggest that Gly-Pro inhibited VGAN permeability even at the low concentrations. A definitive conclusion regarding these study results can't be made because data are inconsistent across the concentration range.

Study 3: Intestinal permeability as a function of site, pH and concentration in *in situ* rat perfusion model

Table 3: Mean permeability ± SEM VGAN concentration

	Mean Permeability Pe x 10^{-4} (cm/sec) ± SEM at pH 6.5		Mean Permeability Pe x 10^{-4} (cm/sec) ± SEM at pH 7.5	
	1.0 mM	10 mM	1.0 mM	10 mM
Duodenum	0.368 ± 0.205	0.328 ± 0.328	0.105 ± 0.068	0.226 ± 0.188
Jejunum	0.127 ± 0.021	0.195 ± 0.163	0.142 ± 0.027	0.280 ± 0.106
Ileum	0.220 ± 0.074	0.069 ± 0.069	0.112 ± 0.035	0.144 ± 0.067

The applicant indicated that technical problems were encountered at pH 6.5 and 10 mM VGAN concentration, resulting in high variability. Consequently, an accurate assessment of the pH effect at 10 mM can not be made. In addition the applicant indicated that the high variability in duodenal permeability may be due to the varying levels of duodenal secretions, subsequently affecting VGAN permeability. Due to the study limitations noted by the applicant it is difficult assess the effect of pH and site on VGAN *in situ* permeability. Therefore, this reviewer did not make a conclusion on this study.

Phase II

Study 4: VGAN transport in Caco-2 cells

Table 4: VGAN Permeability in Caco-2 monolayers

VGAN alone			VGAN with Inhibitor		
Conc. (mM)	Perm (µm/sec)	Velocity (nmoles/min)	Conc. (mM)	Perm (µm/sec)	Velocity (nmoles/min)
0.05	Nc	Nc	0.05	Nc	Nc
0.1	Nc	Nc	0.1	Nc	Nc
0.6	1.21 E-02	0.20	0.6	1.99 E-02	0.003
1.1	1.33 E-02	0.42	1.1	3.58 E-02	0.113
5.2	Nr	Nr	5.7	9.61 E-04	0.155
11.2	4.55 E-03	1.4	11.3	2.79 E-03	0.895
29.9	1.94 E-03	1.64	28.1	1.27 E-03	1.01

Nr- not reported due to technical difficulties

Nc – not calculated because transported VGAN and GAN were below LOQ; CV less than 20 %

With a fifty-fold increase in VGAN concentrations (0.6 to 30 mM) VGAN permeability decreased approximately 10-fold, indicating that VGAN permeability in the Caco-2 monolayer system is dependent on concentration to some degree. The applicant indicates that the findings suggest that at high VGAN concentrations (25 mM) the carrier is saturated, thus the passive component is responsible for the majority of the VGAN transport. The data presented support the applicant's claim. VGAN permeability appeared to decrease in the presence of the inhibitor.

Transport data (not included in this review) were also generated in this study and these data were used to calculate VGAN kinetic parameters.

Table 5: VGAN Kinetic characteristics calculated by nonlinear regression analysis

	Km (mM)	J_{max}* (nmoles min)
Without inhibitor	4.04 ± 0.41	1.9 ± 0.0
With inhibitor	7.27 ± 3.99	1.3 ± 0.2

* J_{max} is the maximal velocity of the hpepT1 carrier in the monolayer system

The VGAN K_m (4.04 ± 0.41 mM) was in the range of expected intestinal concentrations (10 mM*). In the Caco-2 cells, K_m for VGAN increased almost 2 fold (4 to 7.3 mM) in the presence of the inhibitor, while J_{max} was fairly constant (1.9 and 1.3 moles/min). The Caco-2 cell kinetic results suggest that competitive inhibition may occur.

*This concentration will only be achieved at the 900 mg dose (900 mg / 359 g x 250 mL approx. = 10 mM).

Conclusions:

- The hpepT1 transporter appears to be saturated at VGAN concentrations ≥ 11 mM
- The kinetic and concentration data in the presence and absence of inhibitor indicate that the hpepT1 transporter plays a role in VGAN transport.

Study 5: Kinetics of VGAN uptake in Caco-2 cells with overexpressed transporter
The uptake of VGAN was determined in the absence and presence of Gly-Pro.

Table 5: VGAN uptake into Caco-2 cells with cells overexpressing hpepT1

No inhibitor		Inhibitor Present (20 mM Gly-Pro)		
Conc. (nM)	Uptake (nmoles/min)	Conc. (nM)	Uptake (nmoles/min)	Ratio
0.05	0.15 ± 0.01	0.05	BDL	
0.10	0.33 ± 0.04	0.10	0.01 ± 0.003	24.8
0.50	1.13 ± 0.02	0.51	0.06 ± 0.009	17.5
1.10	2.00 ± 0.22	1.10	0.01 ± 0.021	19.4
10.2	6.32 ± 0.31	11.1	0.02 ± Nr	28.4
Kinetic Measures				
mM	nmoles/min			
Km = 3.44 ± 0.19	J_{max} = 8.44 ± 0.16		nd	nd

BDL below detection limit; Nr not reported as single point; nd- not determined

The K_m values in Caco-2 cells with overexpressed transporter (K_m = 3.44 ± 0.19) and regular Caco-2 cells (K_m = 4.04 ± 0.41) were comparable, but the J_{max} was approximately 4-fold higher in cells with overexpressed transporter. The increased J_{max} value is expected because of the overexpression of hpepT1. Uptake of VGAN in Caco-2 cells with overexpressed transporter was inhibited by greater than 15-fold in the presence of Gly-Pro

Phase III
Study 7: Evaluation of potential drug interactions

The applicant identified certain drugs that were likely to be coadministered with VGAN, therefore these drugs may interfere with VGAN during absorption.

Table 6: VGAN Permeability in the presence and absence of selected drugs

	Permeability ± SEM
VGAN alone	0.181 ± 0.057
VGAN + 4 mg/mL valacyclovir*	0.246 ± 0.058
VGAN + saturated nelfinavir	0.335 ± 0.049
VGAN + 0.75 mg/mL didanosine	0.228 ± 0.081
VGAN + saturated cyclosporine A	0.287 ± 0.021
VGAN + saturated mycophenolate mofitel	0.152 ± 0.051
VGAN + saturated omperazole	0.168 ± 0.058

* valacyclovir is a substrate for hpepT1

VGAN permeability in the rat *in situ* model did not appear to be altered significantly by coperfusion of VGAN with most of the studied drugs; although, nelfinavir and cyclosporine appeared to increase VGAN permeability. The mechanism of the apparent permeability enhancement was not elucidated in this study. No conclusion can be made regarding the applicability of these results in rats to humans, because the model has not been validated.

Summary and Overall Conclusions from Phase I, II and III studies

- **Permeability:** VGAN permeability in Caco-2 cells and rat intestinal segments decreased when co-incubated or co-perfused with 20 mM Gly-Pro.
- **Transporter:** VGAN is transported by the human dipeptide transporter hpepT1. According to the applicant, the transporter will be involved at concentrations of ≈ 10 mM.
- **Drug interaction potential** based on rat *in situ* model: unknown

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APPENDIX

Market Formulation

Formulation	MF450(F79070-019) VGAN film coated tablets, 450 mg free base	
Ingredients	mg/tab	% (w/w)
RS-79070-194 Ganciclovir valinate hydrochloride	[redacted]	
Microcrystalline Cellulose [redacted]		
Povidone K-30, USP		
Crospovidone NF, [redacted]		
Crospovidone NF, [redacted]		
Stearic Acid, powder, NF		
Total Core Tablet Weight		
Purified Water, USP		
Coating Ingredients		
Opadry Pink, [redacted]		
Purified Water, USP		

() water is dried off during the coating process

Proposed Dissolution Testing Specification for VGAN tablet

Apparatus: USP Apparatus 2
Media: 900 mg of 0.1 N HCl
Rotation Speed: 50 rpm
Sampling Times: 15, 30, 45, and 60 minutes
Specification: Q = [redacted] of label strength dissolved in 30 minutes

The proposed dissolution method and specification are acceptable.

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Clinical Trial and to be Marketed VGAN Formulations*

	CT450 (F79070-013) VGAN tablets, 450 mg free base		CT875 (F79070-014) VGAN tablets, 875 mg free base		MF450 (F79070-019) VGAN film coated tablets, 450 mg free base		Solution (F79070-003) VGAN oral Solution, 30 mg/mL
Ingredients	mg/tab	% (w/w)	mg/tab	% (w/w)	mg/tab	% (w/w)	Conc. (mg/mL)
RS-79070-194 Ganciclovir valinate hydrochloride							
Microcrystalline Cellulose NF							
Povidone K-30, USP							
Crospovidone NF,							
Crospovidone NF,							
Stearic Acid, powder, NF							
Total Core Tablet Weight							
Purified Water, USP							
Coating Ingredients							
Opadry Pink,							
Purified Water, USP							

1 N hydrochloric acid solution and/or 1 N sodium Hydroxide solution to adjust pH to 3.3 ± 0.3

* CT prefix indicates clinical trial formulation and MF prefix indicates market formulation

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/s/

Robert Kumi
6/27/01 05:32:50 PM
BIOPHARMACEUTICS

Kellie Reynolds
7/10/01 10:18:06 AM
BIOPHARMACEUTICS

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CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 21-304 **SUBMISSION DATES:** 9/28/2000
PRODUCT: ——— (Valganciclovir HCl) Tablets 450 mg 1/19/01, 1/31/01, 2/7/01
SPONSOR: Roche
TYPE OF SUBMISSION: NME, 1P **REVIEWER:** Sue-Chih Lee, Ph.D.

NOTE: This review concerns only the PK/PD analyses included in the NDA. Dr. Robert Kumi is the primary reviewer for the Clinical Pharmacology and Biopharmaceutics section of the NDA.

SYNOPSIS

The sponsor conducted a PK/PD analysis and concluded that AUC is the exposure measure that best predicts 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 oral ganciclovir dosing regimens. A PK/PD analysis was previously carried out and submitted to the Ganciclovir NDA. The current analysis differs from the previous one in that it includes the
following:

(i) A review of actual treatment details (dose and time) for the population PK analysis
(ii) Simultaneous modeling of oral and IV data
(iii) Derivation of exposure parameters: AUC_{0-24}, Cmax and Cmin using treatment information on the day prior to photographic progression of CMV retinitis and individual PK parameters estimated on that day
(iv) Derivation of exposure parameters of average AUC_{0-24}, Cmax and Cmin using the entire dosing history to first photographic progression
(v) Investigation of the relationship between average AUC_{0-24}, Cmax and Cmin and time to first photographic progression.

We conclude 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 and there were no records for missing doses. In order to perform population PK analysis, assumptions were made to determine dosing times for the two doses before the recorded dose event.

Since errors in dosing times will result in errors in PK parameter estimates, the PK/PD analysis is not acceptable. Another point of concern is 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 is unknown.

POPULATION PK AND PK/PD ANALYSES

RR W-144207: Additional Pharmacokinetic Analysis of a Phase III study comparing three doses of oral ganciclovir to intravenous ganciclovir for the maintenance treatment of CMV retinitis in AIDS patients (GANS2226)

The objective of the analysis was to investigate if any individual exposure measurements (Cmax, Cmin and/or AUC) of ganciclovir had an influence on the time to progression of CMV retinitis. To attain this goal, a population PK modeling was conducted to obtain individual estimates of exposure measurements. However, inadequacy of dosing time records precludes meaningful interpretations of the PK/PD analyses especially when individual parameter estimates are heavily relied upon in the analyses. Nevertheless, further review of the PK/PD analyses was conducted because the NDA will be discussed in an advisory committee meeting.

POPULATION PK ANALYSIS

Data

The population PK analysis included data from Study GANS2226 and GAN2300. In all, 244 subjects were included in the analysis.

Study GANS2226 was a multicenter, open-label, randomized, parallel study to compare the clinical efficacy, safety, and tolerance of three oral doses (1000 mg tid, 1500 mg tid and 2000 mg tid) and one IV dose (5 mg/kg qd) of ganciclovir during 26 weeks of maintenance treatment in subjects with AIDS and stable CMV retinitis. All oral doses were to be taken with a meal and at least 3 hours apart. Any subject who had or developed renal impairment (CrCL < 70 mL/min, estimated or measured), on ganciclovir treatment (i.v. or oral), received adjusted dosing. Blood samples were collected routinely for all subjects at Weeks 2 and 6 of the study and additionally when adverse event or progression of CMV retinitis occurred. Of the 230 subjects, 49 had one sample, 105 had 2 samples, 56 had 3 samples and 20 had more than 3 samples collected for analysis of ganciclovir.

The date and time of dose administration was only available for the dose administered prior to sample collection at each visit. 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).

Subjects were evaluated every 2 weeks for progression of retinitis (both ophthalmologically and photographically). If CMV retinitis progression was identified by the ophthalmologist at any time during maintenance treatment, subjects were to undergo a 3-week reinduction course of i.v. ganciclovir twice a day for 14 days followed by 5 mg/kg qd for 7 days. The subject was then to resume ganciclovir maintenance treatment with the originally assigned maintenance dose. Any subject who experienced a second progression of retinitis during maintenance treatment was to be terminated from the study.

Study GAN2300: Data from GAN2300 was included in the population PK analysis to avoid flip-flop. This was a drug-drug interaction study with intensive sampling (11 samples/subject) in HIV-positive and CMV-positive patients. Only data for IV ganciclovir alone was included in the analysis. (*Note*: These patients did not have CMV retinitis. According to Dr. Robert Kumi, patients with CMV retinitis had higher plasma ganciclovir concentrations compared to those without CMV retinitis. Therefore, including this study in the population PK analysis might bias the PK parameter estimates.)

PK Model

A two-compartment model with first order absorption and elimination was simultaneously fit to the combined oral and IV data using NONMEM (primarily with FOCE estimation method). The covariates investigated included age (23-68 yrs.), body weight (40-116 kg), height (137-198 cm) and estimated creatinine clearance (36-190 mL/min). Concomitant medication effects were not investigated. Stepwise addition/deletion procedures were used in the model building process. Covariates were retained in the final model based on improvement in log Likelihood Ratio Test and precision of parameter estimates.

Results

The population parameter estimates for the base model and final model are listed in the table below. It is unclear why intersubject variability for central compartment volume was not included in the final model. Additionally, it is noted that creatinine clearance was truncated to 120 mL/min. Ganciclovir clearance was found to be dependent of both body weight and estimated creatinine clearance although the effect of body weight was weak. Based on the model, total plasma ganciclovir clearance decreased approximately 20% in patients with a creatinine clearance of 50 mL/min compared to patients with a CL_{CR} of 100 mL/min.

Table: Population Parameter Estimates for Base Model and Final Model

	Base Model			Final Model	
Parameter	Population value (SEE*)	%CV**		Population value (SEE*)	%CV**
Ka (h^{-1})	0.0937 (0.0142)	80.8		0.0945 (0.0147)	80.5
CL (L/h)	11.3 (0.477)	34.5	$CL = \theta 1 \bullet (CLcr/93.7)^{\theta 2} \bullet (BM***/70.3)^{\theta 3}$	$\theta 1$ = 11.3 (0.421) $\theta 2$ = 0.374 (0.118) $\theta 3$ = 0.428 (0.208)	30.7
V2 (L)	17.3 (0.455)	12.0		17.3 (0.456)	-
V3 (L)	25.9 (1.25)	-		26.0 (1.27)	12.1
Q (L/h)	13.0 (0.797)	-		12.9 (0.799)	-
F	0.0639 (0.00374)	-		0.063 (0.00344)	-
ε_1(proportional)	0.00443 (0.000926)	-		0.177 (0.015)	-
Study 2226				0.00444(0.000926)	-
Study 2300 ε_2 (additive)	0.000338	-		0.00033 (0.000176)	-

	(0.000183)	

*SEE: standard error of estimate; **Intersubject variability; ***BM: body weight

PK/PD ANALYSES

The objective of the analysis was to investigate if individual exposure measurements (Cmax, Cmin and/or AUC) of ganciclovir had an influence on the time to progression of CMV retinitis. Only Study GANS2226 was included in the analyses.

Bayesian estimates of the steady state parameter values from the population PK analysis were used to determine individual exposure parameters. Exposure parameters were computed in two ways: (1) exposure on the day prior to first photographic progression, and (2) mean exposure before first photographic progression which took into account changes in dosing regimen, periods during which subjects were off drug and changes in clearance for each subject. The summary statistics of the exposure parameters are listed in the tables below.

Table: Summary of $AUC_{0\text{-}24}$, C_{max} and C_{min} on Day Prior to First Photographic Progression

Parameters		Randomized Treatment			
		5 mg/kg i.v.	1000 mg t.i.d. p.o.	1500 mg t.i.d. p.o.	2000 mg t.i.d. p.o.
$AUC_{0\text{-}24}$ (mcg h/mL)	Mean	32.9	17.9	24.8	32.0
	SD	10.5	5.1	8.7	12.4
	Median	30.2	16.9	22.9	30.3
	Minimum	18.3	8.8	7.2	13.6
	Maximum	81.4	33.7	50.9	108.3
C_{max} (mcg/mL)	Mean	11.78	0.94	1.32	1.71
	SD	2.02	0.22	0.36	0.56
	Median	11.59	0.92	1.25	1.66
	Minimum	8.36	0.54	0.79	0.66
	Maximum	17.28	1.55	2.41	4.91
C_{min} (mcg mL)	Mean	0.09	0.50	0.69	0.87
	SD	0.19	0.22	0.35	0.50
	Median	0.04	0.45	0.59	0.79
	Minimum	0.01	0.15	0.02	0.30
	Maximum	1.25	1.23	1.76	4.02

Table: Summary of Average $AUC_{0\text{-}24}$, C_{max} and C_{min}

Parameters		Randomized Treatment			
		5 mg/kg i.v.	1000 mg t.i.d. p.o.	1500 mg t.i.d. p.o.	2000 mg t.i.d. p.o.
$AUC_{0\text{-}24}$ (mcg h/mL)	Mean	30.7	17.3	23.1	30.5
	SD	10.3	5.9	8.4	12.5
	Median	28.8	16.7	21.3	28.3
	Minimum	15.8	7.8	11.5	15.6
	Maximum	73.7	45.8	50.6	108.6
C_{max} (mcg/mL)	Mean	11.0	0.89	1.24	1.56
	SD	2.43	0.28	0.58	0.53
	Median	10.9	0.86	1.12	1.45
	Minimum	6.10	0.40	0.54	0.80
	Maximum	17.2	2.13	4.61	4.69
C_{min} (mcg/mL)	Mean	0.09	0.47	0.60	0.80
	SD	0.18	0.25	0.30	0.48
	Median	0.04	0.42	0.54	0.69
	Minimum	0.01	0.12	0.09	0.26
	Maximum	1.16	1.74	1.66	3.83

The time to first photographic progression was considered to be the PD end point. However, various situations were encountered in the clinical trial and the sponsor made up some rules to assign PD end point as indicated in the table below. According to Dr. Joseph Toerner, Medical Officer of HFD-530, these changes are reasonable.

Table: Categories of PD Endpoint

Rule	PD Endpoint set to:	Actual · Censored	5 mg kg i.v.	1000 mg t.i.d p.o.	1500 mg t.i.d p.o.	2000 mg t.i.d p.o.	*Total*
Date of First Progression on or before Date of reinduction	Date of First Progression	Actual	29	48	41	47	*165*
Date of First Re-induction prior to Date of First Progression	Date of First Re-induction	Actual	5	6	3	5	*19*
Only Date of First Re-induction available	Date of First Re-induction	Censored	2	2	2	3	*9*
Neither Date of First Progression or Date of First Re-induction available	Last Assessment	Censored	11	9	10	6	*36*
Total	-	-	*47*	*65*	*56*	*61*	*229*

Table: Summary of Time to First Photographic Progression (days) by Randomized Treatment Group

Statistics	Treatment			
	5 mg/kg i.v.	1000 mg t.i.d. p.o.	1500 mg t.i.d. p.o.	2000 mg t.i.d. p.o.
Mean	67.0	50.6	65.3	65.6
SD	53.3	42.6	55.0	49.7
Median	43	34	37	52
Minimum	15	12	9	13
Maximum	202	203	194	211

Reviewer's note: This summary serves only to provide a glimpse of the PD data. One has to bear in mind that there are censored data.

Survival analyses was conducted using both Cox and Weibull models to determine which exposure parameter was significant based on Wald statistics at an α-level of 0.10. The association between individual parameters on both the day prior to progression and the average parameter values for the duration of the study to the time to first photographic progression was investigated.

Results:

The results obtained from the Weibull model paralleled those observed using the Cox model. The following discussed the results from Cox regression. For the exposure measures on the day prior to first progression, Cmin was not significant but both AUC and Cmax were found to be significant in predicting time to first progression with a p-value of 0.023 and 0.065, respectively. When both AUC and Cmax were included in the model, the overall likelihood ratio test was significant but none of the measures came out significant based on Wald test. The sponsor stated that neither $AUC_{0\text{-}24}$, nor Cmax was a better predictor than the other. (Reviewer's note: This suggests that AUC and Cmax may be highly correlated.) For the mean exposure measures, average $AUC_{0\text{-}24}$ was highly significantly (p=0.0019) associated with the time to first progression and that the average Cmax (p=0.6) did not have any predictive value over average $AUC_{0\text{-}24}$ when

included in the same model. The sponsor concluded that average AUC_{0-24} is the PK parameter most predictive of efficacy.

The sponsor also performed a Kaplan-Meier analysis to demonstrate that higher average AUC values are associated with a longer median time to progression of CMV retinitis. Patients were divided into three groups based on their individual AUC values. It was found that the group with AUC values between 15-20 μg.h/mL had a similar survival curve compared to the group with AUC values below 15 μg.h/mL. On the other hand, the group with AUC values above 20 μg.h/mL showed a survival curve different from the other two groups. It should be noted that most (~62%) patients had AUC values above 20 μg.h/mL.

Reviewer's Comments:

1. As indicated above, inadequacy of dosing time records precludes meaningful interpretations of the PK/PD analysis. Nevertheless, further review of the analyses was conducted because the NDA will be discussed in an advisory committee meeting.
2. The PK/PD analysis attempted to establish a relationship between individual exposure measure and time to first photographic progression. In GANS2226, 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 parameter estimates is unknown.
3. In the population PK analysis, IV data from Study GAN2300 with intense sampling were included to avoid flip-flop in the structural model. However, GAN2300 was a study in HIV-positive CMV-positive patients without retinitis. According to Dr. Robert Kumi of DPE3/OCPB, the target patient population (as in GANS2226 with positive CMV retinitis) had higher plasma ganciclovir concentrations than patients without CMV retinitis. Therefore, inclusion of GAN2300 in the population PK analysis may bias the results.
4. It is unclear why intersubject variabilities for central compartment volume and bioavailability (F) were not incorporated into the PK model.
5. The PK analysis predicted that total plasma ganciclovir clearance decreased approximately 20% in patients with a CL_{CR} of 50 mL/min compared to those with a CL_{CR} of 100 mL/min. This finding is not consistent with the previous findings in a renal impairment patients.
6. Diagnostics for goodness of fit with Cox regression and Weibull model were not provided.
7. For the exposure measures on the day prior to first progression, Cmin was not significant but both AUC and Cmax were found to be significant in predicting time to first progression when tested separately. When both AUC and Cmax were included simultaneously in the model, the overall likelihood ratio test indicated the model was significant but surprisingly neither AUC nor Cmax came out to be statistically significant. The sponsor stated that this meant neither AUC_{0-24}, nor Cmax was a better predictor than the other. It should be noted that this suggested AUC and Cmax might be highly correlated with either one being a good predictor of the PD outcome.

Sue-Chih Lee, Ph.D.
Division of Pharmaceutical Evaluation III

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/s/

Sue Chih Lee
10/10/01 11:59:17 AM
BIOPHARMACEUTICS

Hard copy of this PK/PD review was signed-off as an attachment to Robe rt's review in February 2001. Robert informed me that I need to bring this review into DFS separately. Please sign off electronically.

Kellie Reynolds
10/12/01 09:18:19 AM
BIOPHARMACEUTICS

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