CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-304 / S-001

Trade Name: Valcyte

Generic Name: valganciclovir

Sponsor: Hoffman La Roche

Approval Date: September 12, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-304 / S-001

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-304 / S-001

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-304/S-001

Hoffman-La Roche Inc.
Attention: Charles Lee
Sr. Program Manager
Drug Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Mr. Lee:

Please refer to your supplemental new drug application dated November 11, 2002, received November 12, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Valcyte™ (valganciclovir hydrochloride) 450 mg Tablets.

We acknowledge receipt of your submissions dated:

November 11, 2002 (2)	March 6, 2003	July 18, 2003	August 29, 2003
January 17, 2003	April 11, 2003 (2)	July 21, 2003 (2)	September 4, 2003 (6)
January 29, 2003 (2)	April 17, 2003	August 1, 2003	September 5, 2003 (3)
February 5, 2003	April 22, 2003	August 8, 2003 (2)	September 9, 2003 (3)
February 10, 2003	May 7, 2003	August 11, 2003	September 10, 2003
February 11, 2003	May 9, 2003	August 21, 2003	September 11, 2003 (4)
February 14, 2003	May 23, 2003	August 22, 2003	
February 28, 2003	July 3, 2003	August 27, 2003	

This supplemental new drug application provides for the use of Valcyte™ (valganciclovir hydrochloride) 450 mg Tablets for the prevention of cytomegalovirus (CMV) disease in kidney, heart, and kidney-pancreas transplant patients at high risk (Donor CMV seropositive/Recipient CMV seronegative).

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and text for the patient package insert submitted September 10, 2003).

Please submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 21-304/S-001." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments in your submission dated September 11, 2003. These commitments are listed below.

1. Perform UL54 gene sequencing for all day 100 and suspected CMV disease samples from study PV16000, previously analyzed by UL97 sequencing and not found to contain UL97 resistance or novel mutations.

Study Start:	Ongoing
Submission of sequencing results:	Within 10 months of the date of this letter

2. Analyze the six novel UL97 mutations observed in study PV16000 via marker transfer experiments.

Study Start:	Ongoing
Submission of experimental results:	Within 18 months of the date of this letter

3. Perform resistance testing in an open randomized study to evaluate the efficacy and safety of oral valganciclovir versus intravenous ganciclovir for the treatment of CMV disease in adult solid organ transplant recipients. Samples for the investigation of emergence of drug resistance will be collected pre-treatment, at end-of-treatment (pre-maintenance) and at end of maintenance therapy.

Protocol Submission:	Within 2 months of the date of this letter
Study Start:	Within 5 months of the date of this letter
Final Report Submission:	Within 40 months of the date of this letter
Submission of Resistance Analysis:	Within 51 months of the date of this letter

4. Perform resistance testing in a study to assess the safety and pharmacokinetics of valganciclovir syrup formulation when administered as prophylaxis for CMV disease in pediatric solid organ transplant recipients. Samples for the investigation of emergence of drug resistance will be collected from all patients on day 100 (end of study drug prophylaxis) and from those patients presenting with suspected CMV disease.

Protocol submission:	Within 2 months of the date of this letter
Study start:	Within 5 months of the date of this letter
Final study report:	Within 30 months of the date of this letter
Submission of Resistance Analysis:	Within 34 months of the date of this letter

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."

FDA's Pediatric Rule [at 21 CFR 314.55/21 CFR 601.27] was challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. Therefore, we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage of legislation or the success of the third party appeal. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

The pediatric exclusivity provisions of FDAMA as reauthorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. We also remind you of the amended Pediatric Written Request issued on November 6, 2001.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

As stated in your submission dated September 11, 2003, we expect that you will distribute the agreed-upon "Dear Health Care Provider" letter within three weeks of the date of this letter. We request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Nitin Patel, R.Ph., Regulatory Project Manager, at (301) 827-2335.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosures: Final Printed labeling (product package insert and patient package insert)

Enclosures: Final Printed labeling (product package insert and patient package insert)

See next page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Debra Birnkrant
9/12/03 05:55:55 PM
NDA 21-304

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-304 / S-001

LABELING

Roche

VALCYTE™
(valganciclovir hydrochloride tablets)

R_x only

WARNING

THE CLINICAL TOXICITY OF VALCYTE, WHICH IS METABOLIZED TO GANCICLOVIR, INCLUDES GRANULOCYTOPENIA, ANEMIA AND THROMBOCYTOPENIA. IN ANIMAL STUDIES GANCICLOVIR WAS CARCINOGENIC, TERATOGENIC AND CAUSED ASPERMATOGENESIS.

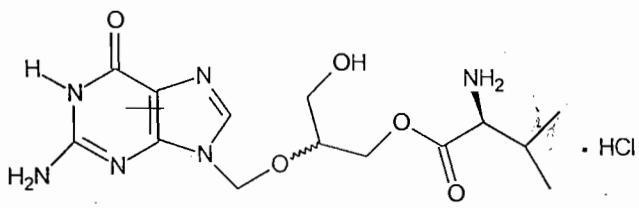
DESCRIPTION

Valcyte (valganciclovir HCl tablets) contains valganciclovir hydrochloride (valganciclovir HCl), a hydrochloride salt of the L-valyl ester of ganciclovir that exists as a mixture of two diastereomers. Ganciclovir is a synthetic guanine derivative active against cytomegalovirus (CMV).

Valcyte is available as a 450 mg tablet for oral administration. Each tablet contains 496.3 mg of valganciclovir HCl (corresponding to 450 mg of valganciclovir), and the inactive ingredients microcrystalline cellulose, povidone K-30, crospovidone and stearic acid. The film-coat applied to the tablets contains Opadry Pink®.

Valganciclovir HCl is a white to off-white crystalline powder with a molecular formula of $C_{14}H_{22}N_6O_5 \cdot HCl$ and a molecular weight of 390.83. The chemical name for valganciclovir HCl is L-Valine, 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy]-3-hydroxypropyl ester, monohydrochloride. Valganciclovir HCl is a polar hydrophilic compound with a solubility of 70 mg/mL in water at 25°C at a pH of 7.0 and an n-octanol/water partition coefficient of 0.0095 at pH 7.0. The pKa for valganciclovir HCl is 7.6.

The chemical structure of valganciclovir HCl is:



All doses in this insert are specified in terms of valganciclovir.

VIROLOGY

Mechanism of Action

Valganciclovir is an L-valyl ester (prodrug) of ganciclovir that exists as a mixture of two diastereomers. After oral administration, both diastereomers are rapidly converted to ganciclovir by intestinal and hepatic esterases. Ganciclovir is a synthetic analogue of 2'-deoxyguanosine, which inhibits replication of human cytomegalovirus in vitro and in vivo.

In CMV-infected cells ganciclovir is initially phosphorylated to ganciclovir monophosphate by the viral protein kinase, pUL97. Further phosphorylation occurs by cellular kinases to produce ganciclovir triphosphate, which is then slowly metabolized intracellularly (half-life 18 hours). As the phosphorylation is largely dependent on the viral kinase, phosphorylation of ganciclovir occurs preferentially in virus-infected cells. The virustatic activity of ganciclovir is due to inhibition of viral DNA synthesis by ganciclovir triphosphate.

Antiviral Activity

The quantitative relationship between the in vitro susceptibility of human herpesviruses to antivirals and clinical response to antiviral therapy has not been established, and virus sensitivity testing has not been standardized. Sensitivity test results, expressed as the concentration of drug required to inhibit the growth of virus in cell culture by 50% (IC_{50}), vary greatly depending upon a number of factors. Thus the IC_{50} of ganciclovir that inhibits human CMV replication in vitro (laboratory and clinical isolates) has ranged from 0.02 to 5.75 μg/mL (0.08 to 22.94 μM). Ganciclovir inhibits mammalian cell proliferation (IC_{50}) in vitro at higher concentrations ranging from 10.21 to >250 μg/mL (40 to >1000 μM). Bone marrow-derived colony-forming cells are more sensitive (IC_{50} = 0.69 to 3.06 μg/mL: 2.7 to 12 μM).

Viral Resistance

Viruses resistant to ganciclovir can arise after prolonged treatment with valganciclovir by selection of mutations in either the viral protein kinase gene (UL97) responsible for ganciclovir monophosphorylation and/or in the viral DNA polymerase gene (UL54). Virus with mutations in the UL97 gene is resistant to ganciclovir alone, whereas virus with mutations in the UL54 gene may show cross-resistance to other antivirals that target the same sites on viral DNA polymerase.

The current working definition of CMV resistance to ganciclovir in in vitro assays is $IC_{50} \geq 1.5$ μg/mL (≥ 6.0 μM). CMV resistance to ganciclovir has been observed in individuals with AIDS and CMV retinitis who have never received ganciclovir therapy. Viral resistance has also been observed in patients receiving prolonged treatment for CMV retinitis with ganciclovir. The possibility of viral resistance should be considered in patients who show poor clinical response or experience persistent viral excretion during therapy.

CLINICAL PHARMACOLOGY

Pharmacokinetics

BECAUSE THE MAJOR ELIMINATION PATHWAY FOR GANCICLOVIR IS RENAL, DOSAGE REDUCTIONS ACCORDING TO CREATININE CLEARANCE ARE REQUIRED FOR VALCYTE TABLETS. FOR DOSING INSTRUCTIONS IN PATIENTS WITH RENAL IMPAIRMENT, REFER TO DOSAGE AND ADMINISTRATION.

The pharmacokinetic properties of valganciclovir have been evaluated in HIV- and CMV-seropositive patients, patients with AIDS and CMV retinitis and in solid organ transplant patients.

The ganciclovir pharmacokinetic measures following administration of 900 mg Valcyte and 5 mg/kg intravenous ganciclovir and 1000 mg three times daily oral ganciclovir in HIV-positive/CMV-positive patients are summarized in Table 1.

Table 1 Mean Ganciclovir Pharmacokinetic* Measures in Healthy Volunteers and HIV-positive/CMV-positive Adults at Maintenance Dosage

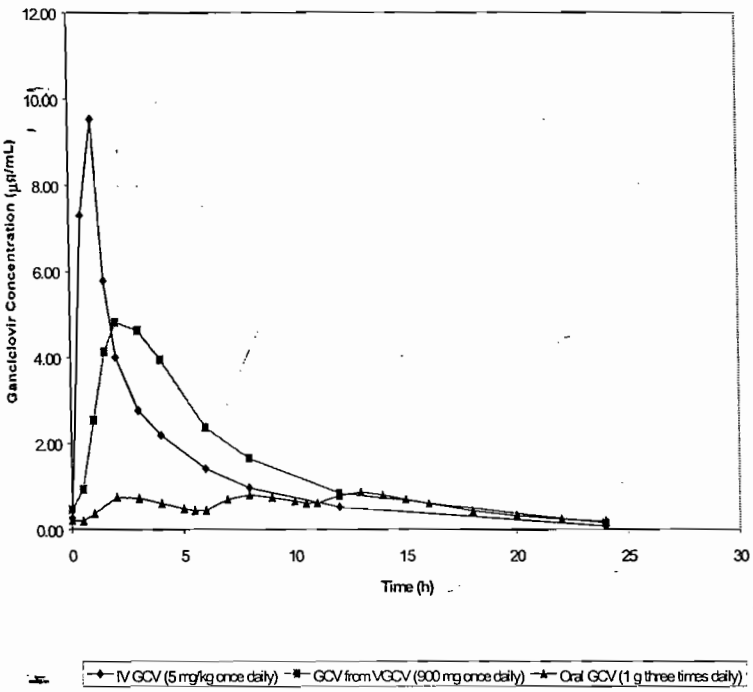
Formulation	Valcyte Tablets	Cytovene®-IV	Cytovene®
Dosage	900 mg once daily with food	5 mg/kg once daily	1000 mg three times daily with food
$AUC_{0\text{-}24\ hr}$ (μg·h/mL)	29.1 ± 9.7 (3 studies, n=57)	26.5 ± 5.9 (4 studies, n=68)	Range of means 12.3 to 19.2 (6 studies, n=94)
C_{max} (μg/mL)	5.61 ± 1.52 (3 studies, n=58)	9.46 ± 2.02 (4 studies, n=68)	Range of means 0.955 to 1.40 (6 studies, n=94)
Absolute oral bioavailability (%)	59.4 ± 6.1 (2 studies, n=32)	Not Applicable	Range of means 6.22 ± 1.29 to 8.53 ± 1.53 (2 studies, n=32)
Elimination half-life (hr)	4.08 ± 0.76 (4 studies, n=73)	3.81 ± 0.71 (4 studies, n=69)	Range of means 3.86 to 5.03 (4 studies, n=61)
Renal clearance (mL/min/kg)	3.21 ± 0.75 (1 study, n=20)	2.99 ± 0.67 (1 study, n=16)	Range of means 2.67 to 3.98 (3 studies, n=30)

*Data were obtained from single and multiple dose studies in healthy volunteers, HIV-positive patients, and HIV-positive/CMV-positive patients with and without retinitis. Patients with CMV retinitis tended to have higher ganciclovir plasma concentrations than patients without CMV retinitis.

The area under the plasma concentration-time curve (AUC) for ganciclovir administered as Valcyte tablets is comparable to the ganciclovir AUC for intravenous ganciclovir. Ganciclovir C_{max} following Valcyte administration is 40% lower than following

intravenous ganciclovir administration. During maintenance dosing, ganciclovir $AUC_{0\text{-}24\ hr}$ and C_{max} following oral ganciclovir administration (1000 mg three times daily) are lower relative to Valcyte and intravenous ganciclovir. The ganciclovir C_{min} following intravenous ganciclovir and Valcyte administration are less than the ganciclovir C_{min} following oral ganciclovir administration. The clinical significance of the differences in ganciclovir pharmacokinetics for these three ganciclovir delivery systems is unknown.

Figure 1 Ganciclovir Plasma Concentration Time Profiles in HIV-positive/CMV-positive Patients*



*Plasma concentration-time profiles for ganciclovir (GCV) from Valcyte (VGCV) and intravenous ganciclovir were obtained from a multiple dose study (WV15376 n=21 and n=18, respectively) in HIV-positive/CMV-positive patients with CMV retinitis. The plasma concentration-time profile for oral ganciclovir was obtained from a multiple dose study (GAN2230 n=24) in HIV-positive/CMV-positive patients without CMV retinitis.

In solid organ transplant recipients, the mean systemic exposure to ganciclovir was 1.7 x higher following administration of 900 mg Valcyte tablets once daily versus 1000 mg ganciclovir capsules three times daily, when both drugs were administered according to their renal function dosing algorithms. The systemic ganciclovir exposures attained were comparable across kidney, heart and liver transplant recipients based on a population pharmacokinetics evaluation (see Table 2).

Table 2 Mean Ganciclovir Pharmacokinetic Measures by Organ Type (Study PV16000)

Parameter	Cytovene Capsules	Valcyte Tablets
Dosage	1000 mg three times daily with food	900 mg once daily with food
Heart Transplant Recipients	N=13	N=17
$AUC_{0\text{-}24\ hr}$ (µg·h/mL)	26.6 ± 11.6	40.2 ± 11.8
C_{max} (µg/ml)	1.4 ± 0.5	4.9 ± 1.1
Elimination half-life (hr)	8.47 ± 2.84	6.58 ± 1.50
Liver Transplant Recipients	N=33	N=75
$AUC_{0\text{-}24\ hr}$ (µg·h/mL)	24.9 ± 10.2	46.0 ± 16.1
C_{max} (µg/ml)	1.3 ± 0.4	5.4 ± 1.5
Elimination half-life (hr)	7.68 ± 2.74	6.18 ± 1.42
Kidney Transplant Recipients*	N=36	N=68
$AUC_{0\text{-}24\ hr}$ (µg·h/mL)	31.3 ± 10.3	48.2 ± 14.6
C_{max} (µg/ml)	1.5 ± 0.5	5.3 ± 1.5
Elimination half-life (hr)	9.44 ± 4.37	6.77 ± 1.25

* Includes kidney-pancreas

In a pharmacokinetic study in liver transplant patients, the ganciclovir $AUC_{0\text{-}24\ hr}$ achieved with 900 mg valganciclovir was 41.7 ± 9.9 µg·h/mL (n=28) and the $AUC_{0\text{-}24\ hr}$ achieved with the approved dosage of 5 mg/kg intravenous ganciclovir was 48.2 ± 17.3 µg·h/mL (n=27).

Absorption

Valganciclovir, a prodrug of ganciclovir, is well absorbed from the gastrointestinal tract and rapidly metabolized in the intestinal wall and liver to ganciclovir. The absolute bioavailability of ganciclovir from Valcyte tablets following administration with food was approximately 60% (3 studies, n=18; n=16; n=28). Ganciclovir median T_{max} following administration of 450 mg to 2625 mg Valcyte tablets ranged from 1 to 3 hours. Dose proportionality with respect to ganciclovir AUC following administration of Valcyte tablets was demonstrated only under fed conditions. Systemic exposure to the

prodrug, valganciclovir, is transient and low, and the AUC_{24} and C_{max} values are approximately 1% and 3% of those of ganciclovir, respectively.

Food Effects

When Valcyte tablets were administered with a high fat meal containing approximately 600 total calories (31.1 g fat, 51.6 g carbohydrates and 22.2 g protein) at a dose of 875 mg once daily to 16 HIV-positive subjects, the steady-state ganciclovir AUC increased by 30% (95% CI 12% to 51%), and the C_{max} increased by 14% (95% CI -5% to 36%), without any prolongation in time to peak plasma concentrations (T_{max}). Valcyte tablets should be administered with food (see DOSAGE AND ADMINISTRATION).

Distribution

Due to the rapid conversion of valganciclovir to ganciclovir, plasma protein binding of valganciclovir was not determined. Plasma protein binding of ganciclovir is 1% to 2% over concentrations of 0.5 and 51 µg/mL. When ganciclovir was administered intravenously, the steady-state volume of distribution of ganciclovir was 0.703 ± 0.134 L/kg (n=69).

After administration of Valcyte tablets, no correlation was observed between ganciclovir AUC and reciprocal weight; oral dosing of Valcyte tablets according to weight is not required.

Metabolism

Valganciclovir is rapidly hydrolyzed to ganciclovir; no other metabolites have been detected. No metabolite of orally administered radiolabeled ganciclovir (1000 mg single dose) accounted for more than 1% to 2% of the radioactivity recovered in the feces or urine.

Elimination

The major route of elimination of valganciclovir is by renal excretion as ganciclovir through glomerular filtration and active tubular secretion. Systemic clearance of intravenously administered ganciclovir was 3.07 ± 0.64 mL/min/kg (n=68) while renal clearance was 2.99 ± 0.67 mL/min/kg (n=16).

The terminal half-life ($t_{½}$) of ganciclovir following oral administration of Valcyte tablets to either healthy or HIV-positive/CMV-positive subjects was 4.08 ± 0.76 hours (n=73), and that following administration of intravenous ganciclovir was 3.81 ± 0.71 hours (n=69). In heart, kidney, kidney-pancreas, and liver transplant patients, the terminal elimination half-life of ganciclovir following oral administration of Valcyte was 6.48 ± 1.38 hours, and following oral administration of Cytovene was 8.56 ± 3.62.

Special Populations

Renal Impairment

The pharmacokinetics of ganciclovir from a single oral dose of 900 mg Valcyte tablets were evaluated in 24 otherwise healthy individuals with renal impairment.

Table 3 Pharmacokinetics of Ganciclovir From a Single Oral Dose of 900 mg Valcyte Tablets

Estimated Creatinine Clearance (mL/min)	N	Apparent Clearance (mL/min) Mean ± SD	AUC_{last} (μg·h/mL) Mean ± SD	Half-life (hours) Mean ± SD
51-70	6	249 ± 99	49.5 ± 22.4	4.85 ± 1.4
21-50	6	136 ± 64	91.9 ± 43.9	10.2 ± 4.4
11-20	6	45 ± 11	223 ± 46	21.8 ± 5.2
≤10	6	12.8 ± 8	366 ± 66	67.5 ± 34

Decreased renal function results in decreased clearance of ganciclovir from valganciclovir, and a corresponding increase in terminal half-life. Therefore, dosage adjustment is required for patients with impaired renal function (see PRECAUTIONS: General).

Hemodialysis

Hemodialysis reduces plasma concentrations of ganciclovir by about 50% following Valcyte administration. Patients receiving hemodialysis (CrCl <10 mL/min) cannot use Valcyte tablets because the daily dose of Valcyte tablets required for these patients is less than 450 mg (see PRECAUTIONS: General and DOSAGE AND ADMINISTRATION: Hemodialysis Patients).

Patients with Hepatic Impairment

The safety and efficacy of Valcyte tablets have not been studied in patients with hepatic impairment.

Race/Ethnicity and Gender

Insufficient data are available to demonstrate any effect of race or gender on the pharmacokinetics of valganciclovir.

Pediatrics

Valcyte tablets have not been studied in pediatric patients; the pharmacokinetic characteristics of Valcyte tablets in these patients have not been established (see PRECAUTIONS: Pediatric Use).

Geriatrics

No studies of Valcyte tablets have been conducted in adults older than 65 years of age (see PRECAUTIONS: Geriatric Use).

INDICATIONS AND USAGE

Valcyte tablets are indicated for the treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS) (see CLINICAL TRIALS).

Valcyte is indicated for the prevention of cytomegalovirus (CMV) disease in kidney, heart, and kidney-pancreas transplant patients at high risk (Donor CMV seropositive/Recipient CMV seronegative [(D+/R-)]).

Valcyte is not indicated for use in liver transplant patients (see CLINICAL TRIALS and WARNINGS).

The safety and efficacy of Valcyte for the prevention of CMV disease in other solid organ transplant patients such as lung transplant patients have not been established.

CLINICAL TRIALS

Induction Therapy of CMV Retinitis

Study WV15376

In a randomized, open-label controlled study, 160 patients with AIDS and newly diagnosed CMV retinitis were randomized to receive treatment with either Valcyte tablets (900 mg twice daily for 21 days, then 900 mg once daily for 7 days) or with intravenous ganciclovir solution (5 mg/kg twice daily for 21 days, then 5 mg/kg once daily for 7 days). Study participants were: male (91%), White (53%), Hispanic (31%), and Black (11%). The median age was 39 years, the median baseline HIV-1 RNA was 4.9 $\log_{10}$, and the median CD_4 cell count was 23 cells/mm^3. A determination of CMV retinitis progression by the masked review of retinal photographs taken at baseline and week 4 was the primary outcome measurement of the 3-week induction therapy. Table 4 provides the outcomes at 4 weeks.

Table 4 Week 4 Masked Review of Retinal Photographs in Study WV15376

	Cytovene-IV	Valcyte
Determination of CMV retinitis progression at Week 4	N=80	N=80
Progressor	7	7
Non-progressor	63	64
Death	2	1
Discontinuations due to Adverse Events	1	2
Failed to return	1	1
CMV not confirmed at baseline or no interpretable baseline photos	6	5

Maintenance Therapy of CMV Retinitis

No comparative clinical data are available on the efficacy of Valcyte for the maintenance therapy of CMV retinitis because all patients in study WV15376 received open-label Valcyte after week 4. However, the AUC for ganciclovir is similar following administration of 900 mg. Valcyte tablets once daily and 5 mg/kg intravenous ganciclovir once daily. Although the ganciclovir C_{max} is lower following Valcyte administration compared to intravenous ganciclovir, it is higher than the C_{max} obtained following oral ganciclovir administration (see Figure 1 in CLINICAL PHARMACOLOGY). Therefore, use of Valcyte as maintenance therapy is supported by a plasma concentration-time profile similar to that of two approved products for maintenance therapy of CMV retinitis.

Prevention of CMV Disease in Heart, Kidney, Kidney-Pancreas, and Liver Transplantation

A double-blind, double-dummy active comparator study was conducted in 372 heart, liver, kidney, and kidney-pancreas transplant patients at high-risk for CMV disease (D+/R-). Patients were randomized (2 Valcyte: 1 oral ganciclovir) to receive either Valcyte (900 mg once daily) or oral ganciclovir (1000 mg three times a day) starting within 10 days of transplantation until Day 100 posttransplant. The proportion of patients who developed CMV disease, including CMV syndrome and/or tissue-invasive disease during the first 6 months posttransplant was similar between the Valcyte arm (12.1%, N=239) and the oral ganciclovir arm (15.2%, N=125). However, in liver transplant patients, the incidence of tissue-invasive CMV disease was significantly higher in the Valcyte group compared with the ganciclovir group. These results are summarized in Table 5.

Mortality at six months was 3.7% (9/244) in the Valcyte group and 1.6% (2/126) in the oral ganciclovir group.

Table 5 Percentage of Patients with CMV Disease and Tissue-Invasive CMV Disease by Organ Type: Endpoint Committee, 6 Month ITT Population

	CMV Disease[1]		Tissue-Invasive CMV Disease		CMV Syndrome	
Organ	VGCV (N=239)	GCV (N=125)	VGCV (N=239)	GCV (N=125)	VGCV (N=239)	GCV (N=125)
Liver (n=177)	19% (22 / 118)	12% (7 / 59)	14% (16 / 118)	3% (2 / 59)	5% (6 / 118)	9% (5 / 59)
Kidney (n=120)	6% (5 / 81)	23% (9 / 39)	1% (1 / 81)	5% (2 / 39)	5% (4 / 81)	18% (7 / 39)
Heart (n=56)	6% (2 / 35)	10% (2 / 21)	0% (0 / 35)	5% (1 / 21)	6% (2 / 35)	5% (1 / 21)
Kidney / Pancreas (n=11)	0% (0 / 5)	17% (1 / 6)	0% (0 / 5)	17% (1 / 6)	0% (0 / 5)	0% (0 / 6)

GCV = oral ganciclovir; VGCV = Valcyte

[1] Number of Patients with CMV Disease = Number of Patients with Tissue-Invasive CMV Disease + Number of Patients with CMV Syndrome.

CONTRAINDICATIONS

Valcyte tablets are contraindicated in patients with hypersensitivity to valganciclovir or ganciclovir.

WARNINGS

THE CLINICAL TOXICITY OF VALCYTE, WHICH IS METABOLIZED TO GANCICLOVIR, INCLUDES GRANULOCYTOPENIA, ANEMIA AND THROMBOCYTOPENIA. IN ANIMAL STUDIES GANCICLOVIR WAS CARCINOGENIC, TERATOGENIC AND CAUSED ASPERMATOGENESIS.

Hematologic

Valcyte tablets should not be administered if the absolute neutrophil count is less than 500 cells/μL, the platelet count is less than 25,000/μL, or the hemoglobin is less than 8 g/dL. Severe leukopenia, neutropenia, anemia, thrombocytopenia, pancytopenia, bone marrow depression and aplastic anemia have been observed in patients treated with Valcyte tablets (and ganciclovir) (see PRECAUTIONS: Laboratory Testing and ADVERSE EVENTS).

Valcyte tablets should, therefore, be used with caution in patients with pre-existing cytopenias, or who have received or who are receiving myelosuppressive drugs or irradiation. Cytopenia may occur at any time during treatment and may increase with

continued dosing. Cell counts usually begin to recover within 3 to 7 days of discontinuing drug.

Impairment of Fertility

Animal data indicate that administration of ganciclovir causes inhibition of spermatogenesis and subsequent infertility. These effects were reversible at lower doses and irreversible at higher doses (see PRECAUTIONS: Carcinogenesis, Mutagenesis and Impairment of Fertility). It is considered probable that in humans, Valcyte at the recommended doses may cause temporary or permanent inhibition of spermatogenesis. Animal data also indicate that suppression of fertility in females may occur.

Teratogenesis, Carcinogenesis and Mutagenesis

Because of the mutagenic and teratogenic potential of ganciclovir, women of childbearing potential should be advised to use effective contraception during treatment. Similarly, men should be advised to practice barrier contraception during, and for at least 90 days following, treatment with Valcyte tablets (see PRECAUTIONS: Carcinogenesis, Mutagenesis and Impairment of Fertility, and Pregnancy: Category C).

In animal studies, ganciclovir was found to be mutagenic and carcinogenic. Valcyte should, therefore, be considered a potential teratogen and carcinogen in humans with the potential to cause birth defects and cancers (see DOSAGE AND ADMINISTRATION: Handling and Disposal).

Tissue Invasive CMV Disease in Liver Transplant Patients

In liver transplant patients, there was a significantly higher incidence of tissue-invasive CMV disease in the Valcyte-treated group compared with the oral ganciclovir group (see CLINICAL TRIALS).

PRECAUTIONS

General

Strict adherence to dosage recommendations is essential to avoid overdose.

The bioavailability of ganciclovir from Valcyte tablets is significantly higher than from ganciclovir capsules. Patients switching from ganciclovir capsules should be advised of the risk of overdosage if they take more than the prescribed number of Valcyte tablets. Valcyte tablets cannot be substituted for Cytovene capsules on a one-to-one basis (see DOSAGE AND ADMINISTRATION).

Since ganciclovir is excreted by the kidneys, normal clearance depends on adequate renal function. IF RENAL FUNCTION IS IMPAIRED, DOSAGE ADJUSTMENTS ARE REQUIRED FOR VALCYTE TABLETS. Such adjustments should be based on measured or estimated creatinine clearance values (see DOSAGE AND ADMINISTRATION: Renal Impairment).

For patients on hemodialysis (CrCl <10 mL/min) it is recommended that ganciclovir be used (in accordance with the dose-reduction algorithm cited in the Cytovene®-IV and Cytovene® Capsules complete product information section on DOSAGE AND ADMINISTRATION: Renal Impairment) rather than Valcyte tablets (see DOSAGE AND ADMINISTRATION: Hemodialysis and CLINICAL PHARMACOLOGY: Special Populations: Hemodialysis).

Information for Patients (see Patient Information)

Valcyte tablets cannot be substituted for ganciclovir capsules on a one-to-one basis. Patients switching from ganciclovir capsules should be advised of the risk of overdosage if they take more than the prescribed number of Valcyte tablets (see OVERDOSAGE and DOSAGE AND ADMINISTRATION).

Valcyte is changed to ganciclovir once it is absorbed into the body. All patients should be informed that the major toxicities of ganciclovir include granulocytopenia (neutropenia), anemia and thrombocytopenia and that dose modifications may be required, including discontinuation. The importance of close monitoring of blood counts while on therapy should be emphasized. Patients should be informed that ganciclovir has been associated with elevations in serum creatinine.

Patients should be instructed to take Valcyte tablets with food to maximize bioavailability.

Patients should be advised that ganciclovir has caused decreased sperm production in animals and may cause decreased fertility in humans. Women of childbearing potential should be advised that ganciclovir causes birth defects in animals and should not be used during pregnancy. Because of the potential for serious adverse events in nursing infants, mothers should be instructed not to breast-feed if they are receiving Valcyte tablets. Women of childbearing potential should be advised to use effective contraception during treatment with Valcyte tablets. Similarly, men should be advised to practice barrier contraception during and for at least 90 days following treatment with Valcyte tablets.

Although there is no information from human studies, patients should be advised that ganciclovir should be considered a potential carcinogen.

Convulsions, sedation, dizziness, ataxia and/or confusion have been reported with the use of Valcyte tablets and/or ganciclovir. If they occur, such effects may affect tasks requiring alertness including the patient's ability to drive and operate machinery.

Patients should be told that ganciclovir is not a cure for CMV retinitis, and that they may continue to experience progression of retinitis during or following treatment. Patients should be advised to have ophthalmologic follow-up examinations at a minimum of every 4 to 6 weeks while being treated with Valcyte tablets. Some patients will require more frequent follow-up.

Laboratory Testing

Due to the frequency of neutropenia, anemia and thrombocytopenia in patients receiving Valcyte tablets (see ADVERSE EVENTS), it is recommended that complete blood counts

and platelet counts be performed frequently, especially in patients in whom ganciclovir or other nucleoside analogues have previously resulted in leukopenia, or in whom neutrophil counts are less than 1000 cells/μL at the beginning of treatment. Increased monitoring for cytopenias may be warranted if therapy with oral ganciclovir is changed to Valcyte, because of increased plasma concentrations of ganciclovir after Valcyte administration (see CLINICAL PHARMACOLOGY).

Increased serum creatinine levels have been observed in trials evaluating Valcyte tablets. Patients should have serum creatinine or creatinine clearance values monitored carefully to allow for dosage adjustments in renally impaired patients (see DOSAGE AND ADMINISTRATION: Renal Impairment). The mechanism of impairment of renal function is not known.

Drug Interactions

Drug Interaction Studies Conducted With Valcyte

No in vivo drug-drug interaction studies were conducted with valganciclovir. However, because valganciclovir is rapidly and extensively converted to ganciclovir, interactions associated with ganciclovir will be expected for Valcyte tablets.

Drug Interaction Studies Conducted With Ganciclovir

Binding of ganciclovir to plasma proteins is only about 1% to 2%, and drug interactions involving binding site displacement are not anticipated.

Drug-drug interaction studies were conducted in patients with normal renal function. Patients with impaired renal function may have increased concentrations of ganciclovir and the coadministered drug following concomitant administration of Valcyte tablets and drugs excreted by the same pathway as ganciclovir. Therefore, these patients should be closely monitored for toxicity of ganciclovir and the coadministered drug.

Table 6 Results of Drug Interaction Studies With Ganciclovir: Effects of Coadministered Drug on Ganciclovir Plasma AUC and C_{max} Values

Coadministered Drug	Ganciclovir Dosage	n	Ganciclovir Pharmacokinetic (PK) Parameter	Clinical Comment
Zidovudine 100 mg every 4 hours	1000 mg every 8 hours	12	AUC ↓ 17 ± 25% (range: -52% to 23%)	Zidovudine and Valcyte each have the potential to cause neutropenia and anemia. Some patients may not tolerate concomitant therapy at full dosage.
Didanosine 200 mg every 12 hours administered 2 hours before ganciclovir	1000 mg every 8 hours	12	AUC ↓ 21 ± 17% (range: -44% to 5%)	Effect not likely to be clinically significant.

Coadministered Drug	Ganciclovir Dosage	n	Ganciclovir Pharmacokinetic (PK) Parameter	Clinical Comment
Didanosine 200 mg every 12 hours simultaneously administered with ganciclovir	1000 mg every 8 hours	12	No effect on ganciclovir PK parameters observed	No effect expected.
	IV ganciclovir 5 mg/kg twice daily	11	No effect on ganciclovir PK parameters observed	No effect expected.
	IV ganciclovir 5 mg/kg once daily	11	No effect on ganciclovir PK parameters observed	No effect expected.
Probenecid 500 mg every 6 hours	1000 mg every 8 hours	10	AUC ↑ 53 ± 91% (range: -14% to 299%) Ganciclovir renal clearance ↓ 22 ± 20% (Range: -54% to -4%)	Patients taking probenecid and Valcyte should be monitored for evidence of ganciclovir toxicity.
Zalcitabine 0.75 mg every 8 hours administered 2 hours before ganciclovir	1000 mg every 8 hours	10	AUC ↑13%	Effect not likely to be clinically significant.
Trimethoprim 200 mg once daily	1000 mg every 8 hours	12	Ganciclovir renal clearance ↓ 16.3% Half-life ↑15%	Effect not likely to be clinically significant.
Mycophenolate Mofetil 1.5 g single dose	IV ganciclovir 5 mg/kg single dose	12	No effect on ganciclovir PK parameters observed (patients with normal renal function)	Patients with renal impairment should be monitored carefully as levels of metabolites of both drugs may increase.

Table 7 Results of Drug Interaction Studies With Ganciclovir: Effects of Ganciclovir on Plasma AUC and C_{max} Values of Coadministered Drug

Coadministered Drug	Ganciclovir Dosage	N	Coadministered Drug Pharmacokinetic (PK) Parameter	
Zidovudine 100 mg every 4 hours	1000 mg every 8 hours	12	AUC_{0-4} ↑ 19 ± 27% (range: -11% to 74%)	Zidovudine and Valcyte each have the potential to cause neutropenia and anemia. Some patients may not tolerate concomitant therapy at full dosage.
Didanosine 200 mg every 12 hours when administered 2 hours prior to or concurrent with ganciclovir	1000 mg every 8 hours	12	AUC_{0-12} ↑111 ± 114% (range: 10% to 493%)	Patients should be closely monitored for didanosine toxicity.
Didanosine 200 mg every 12 hours	IV ganciclovir 5 mg/kg twice daily	11	AUC_{0-12} ↑70 ± 40% (range: 3% to 121%) C_{max} ↑49 ± 48% (range: -28% to 125%)	Patients should be closely monitored for didanosine toxicity.
Didanosine 200 mg every 12 hours	IV ganciclovir 5 mg/kg once daily	11	AUC_{0-12} ↑50 ± 26% (range: 22% to 110%) C_{max} ↑36 ± 36% (range: -27% to 94%)	Patients should be closely monitored for didanosine toxicity.
Zalcitabine 0.75 mg every 8 hours administered 2 hours before ganciclovir	1000 mg every 8 hours	10	No clinically relevant PK parameter changes	No effect expected.
Trimethoprim 200 mg once daily	1000 mg every 8 hours	12	Increase (12%) in C_{min}	Effect not likely to be clinically significant.
Mycophenolate Mofetil (MMF) 1.5 g single dose	IV ganciclovir 5 mg/kg single dose	12	No PK interaction observed (patients with normal renal function)	Patients with renal impairment should be monitored carefully as levels of metabolites of both drugs may increase.

Carcinogenesis, Mutagenesis and Impairment of Fertility‡

No long-term carcinogenicity studies have been conducted with Valcyte. However, upon oral administration, valganciclovir is rapidly and extensively converted to ganciclovir. Therefore, like ganciclovir, valganciclovir is a potential carcinogen.

Ganciclovir was carcinogenic in the mouse at oral doses that produced exposures approximately 0.1x and 1.4x, respectively, the mean drug exposure in humans following

the recommended intravenous dose of 5 mg/kg, based on area under the plasma concentration curve (AUC) comparisons. At the higher dose there was a significant increase in the incidence of tumors of the preputial gland in males, forestomach (nonglandular mucosa) in males and females, and reproductive tissues (ovaries, uterus, mammary gland, clitoral gland and vagina) and liver in females. At the lower dose, a slightly increased incidence of tumors was noted in the preputial and harderian glands in males, forestomach in males and females, and liver in females. Ganciclovir should be considered a potential carcinogen in humans.

Valganciclovir increases mutations in mouse lymphoma cells. In the mouse micronucleus assay, valganciclovir was clastogenic. Valganciclovir was not mutagenic in the Ames Salmonella assay. Ganciclovir increased mutations in mouse lymphoma cells and DNA damage in human lymphocytes in vitro. In the mouse micronucleus assay, ganciclovir was clastogenic. Ganciclovir was not mutagenic in the Ames Salmonella assay.

Valganciclovir is converted to ganciclovir and therefore is expected to have similar reproductive toxicity effects as ganciclovir (see WARNINGS: Impairment of Fertility). Ganciclovir caused decreased mating behavior, decreased fertility, and an increased incidence of embryolethality in female mice following intravenous doses that produced an exposure approximately 1.7x the mean drug exposure in humans following the dose of 5 mg/kg, based on AUC comparisons. Ganciclovir caused decreased fertility in male mice and hypospermatogenesis in mice and dogs following daily oral or intravenous administration. Systemic drug exposure (AUC) at the lowest dose showing toxicity in each species ranged from 0.03 to 0.1x the AUC of the recommended human intravenous dose. Valganciclovir caused similar effects on spermatogenesis in mice, rats, and dogs. It is considered likely that ganciclovir (and valganciclovir) could cause inhibition of human spermatogenesis.

Pregnancy

Category C‡

Valganciclovir is converted to ganciclovir and therefore is expected to have reproductive toxicity effects similar to ganciclovir. Ganciclovir has been shown to be embryotoxic in rabbits and mice following intravenous administration, and teratogenic in rabbits. Fetal resorptions were present in at least 85% of rabbits and mice administered doses that produced 2x the human exposure based on AUC comparisons. Effects observed in rabbits included: fetal growth retardation, embryolethality, teratogenicity and/or maternal toxicity. Teratogenic changes included cleft palate, anophthalmia/microphthalmia, aplastic organs (kidney and pancreas), hydrocephaly and brachygnathia. In mice, effects observed were maternal/fetal toxicity and embryolethality.

Daily intravenous doses administered to female mice prior to mating, during gestation, and during lactation caused hypoplasia of the testes and seminal vesicles in the month-old male offspring, as well as pathologic changes in the nonglandular region of the stomach (see WARNINGS: Teratogenesis, Carcinogenesis and Mutagenesis). The drug exposure in mice as estimated by the AUC was approximately 1.7x the human AUC.

Data obtained using an ex vivo human placental model show that ganciclovir crosses the placenta and that simple diffusion is the most likely mechanism of transfer. The transfer was not saturable over a concentration range of 1 to 10 mg/mL and occurred by passive diffusion.

Valganciclovir may be teratogenic or embryotoxic at dose levels recommended for human use. There are no adequate and well-controlled studies in pregnant women. Valcyte tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

‡**Footnote:** All dose comparisons presented in the Carcinogenesis, Mutagenesis and Impairment of Fertility, and Pregnancy subsections are based on the human AUC following administration of a single 5 mg/kg infusion of intravenous ganciclovir.

Nursing Mothers

It is not known whether ganciclovir or valganciclovir is excreted in human milk. Because valganciclovir caused granulocytopenia, anemia and thrombocytopenia in clinical trials and ganciclovir was mutagenic and carcinogenic in animal studies, the possibility of serious adverse events from ganciclovir in nursing infants is possible (see WARNINGS). Because of potential for serious adverse events in nursing infants, **mothers should be instructed not to breast-feed if they are receiving Valcyte tablets.** In addition, the Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV.

Pediatric Use

Safety and effectiveness of Valcyte tablets in pediatric patients have not been established.

Geriatric Use

The pharmacokinetic characteristics of Valcyte in elderly patients have not been established. Since elderly individuals frequently have a reduced glomerular filtration rate, particular attention should be paid to assessing renal function before and during administration of Valcyte (see DOSAGE AND ADMINISTRATION).

Clinical studies of Valcyte did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Valcyte is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. In addition, renal function should be monitored and dosage adjustments should be made accordingly (see PRECAUTIONS: General, CLINICAL PHARMACOLOGY: Special Populations: Renal Impairment, and DOSAGE AND ADMINISTRATION: Renal Impairment).

ADVERSE EVENTS

Experience With Valcyte Tablets

Valganciclovir, a prodrug of ganciclovir, is rapidly converted to ganciclovir after oral administration. Adverse events known to be associated with ganciclovir usage can therefore be expected to occur with Valcyte tablets.

Treatment of CMV Retinitis in AIDS Patients

As shown in Table 8, the safety profiles of Valcyte tablets and intravenous ganciclovir during 28 days of randomized therapy (21 days induction dose and 7 days maintenance dose) in 158 patients were comparable, with the exception of catheter-related infection, which occurred with greater frequency in patients randomized to receive IV ganciclovir.

Table 8 Percentage of Selected Adverse Events Occurring During the Randomized Phase of Study WV15376

Adverse Event	Valcyte Arm N=79	Intravenous Ganciclovir Arm N=79
Diarrhea	16%	10%
Neutropenia	11%	13%
Nausea	8%	14%
Headache	9%	5%
Anemia	8%	8%
Catheter-related infection	3%	11%

Tables 9 and 10 show the pooled adverse event data and abnormal laboratory values from two single arm, open-label clinical trials, WV15376 and WV15705. A total of 370 patients received maintenance therapy with Valcyte tablets 900 mg once daily. Approximately 252 (68%) of these patients received Valcyte tablets for more than nine months (maximum duration was 36 months).

Table 9 Pooled Selected Adverse Events Reported in ≥5% of Patients in Two Clinical Studies in CMV Retinitis

Adverse Events According to Body System	Patients with CMV Retinitis (Studies WV15376 and WV15705)
	Valcyte (N=370) %
Gastrointestinal system	

Adverse Events According to Body System	Patients with CMV Retinitis (Studies WV15376 and WV15705)
	Valcyte (N=370) %
Diarrhea	41
Nausea	30
Vomiting	21
Abdominal pain	15
Body as a whole	
Pyrexia	31
Headache	22
Hemic and lymphatic system	
Neutropenia	27
Anemia	26
Thrombocytopenia	6
Central and peripheral nervous system	
Insomnia	16
Peripheral neuropathy	9
Paresthesia	8
Special senses	
Retinal detachment	15

Table 10 Pooled Laboratory Abnormalities Reported in Two Clinical Studies in the Treatment of CMV Retinitis

	CMV Retinitis Patients (Studies WV15376 and WV15705)
Laboratory Abnormalities	Valcyte (N=370) %
Neutropenia: ANC/μL	
<500	19
500 – <750	17
750 – ≤1000	17
Anemia: Hemoglobin g/dL	
<6.5	7
6.5 – <8.0	13
8.0 – <9.5	16

	CMV Retinitis Patients (Studies WV15376 and WV15705)
Laboratory Abnormalities	**Valcyte (N=370) %**
Thrombocytopenia: Platelets/μL	
<25000	4
25000 – <50000	6
50000 – <100000	22
Serum Creatinine: mg/dL	
>2.5	3
>1.5 – 2.5	12

Prevention of CMV Disease in Selected Solid Organ Transplantation

Table 11 shows selected adverse events regardless of severity and drug relationship with an incidence of ≥5% from a clinical trial, PV16000 (up to 28 days after study treatment) where heart, kidney, kidney-pancreas and liver transplant patients received Valcyte (N=244) or oral ganciclovir (N=126). The majority of the adverse events were of mild or moderate intensity.

Table 11 Percentage of Selected Grades 1-4 Adverse Events Reported in ≥5% of Selected Solid Organ Transplant Patients in Study PV16000

Adverse Event	Valcyte (N=244) %	Oral Ganciclovir (N=126) %
Diarrhea	30	29
Tremors	28	25
Graft rejection	24	30
Nausea	23	23
Headache	22	27
Insomnia	20	16
Hypertension	18	15
Vomiting	16	14
Leukopenia	14	7
Pyrexia	13	14

Laboratory adverse events are those reported by investigators.

Adverse events not included in Table 11, which either occurred at a frequency of ≥5% in clinical study PV16000, or were selected serious adverse events reported in studies WV15376, WV15705, or PV16000 with a frequency of <5% are listed below.

Allergic reactions: valganciclovir hypersensitivity

Bleeding complications: potentially life-threatening bleeding associated with thrombocytopenia

Central and peripheral nervous system: paresthesia, dizziness (excluding vertigo), convulsion

Gastrointestinal disorders: abdominal pain, constipation, dyspepsia, abdominal distention, ascites

General disorders and administration site disorders: fatigue, pain, edema, peripheral edema, weakness

Hemic system: anemia, neutropenia, thrombocytopenia, pancytopenia, bone marrow depression, aplastic anemia

Hepatobiliary disorders: abnormal hepatic function

Infections and infestations: pharyngitis/nasopharyngitis, upper respiratory tract infection, urinary tract infection, local and systemic infections and sepsis, postoperative wound infection

Injury, poisoning and procedural complications: postoperative complications, postoperative pain, increased wound drainage, wound dehiscence

Metabolism and nutrition disorders: hyperkalemia, hypokalemia, hypomagnesemia, hyperglycemia, appetite decreased, dehydration, hypophosphatemia, hypocalcemia

Musculoskeletal and connective tissue disorders: back pain, arthralgia, muscle cramps, limb pain

Psychiatric disorders: depression, psychosis, hallucinations, confusion, agitation

Renal and urinary disorders: renal impairment, dysuria, decreased creatinine clearance

Respiratory, thoracic and mediastinal disorders: cough, dyspnea, rhinorrhea, pleural effusion

Skin and subcutaneous tissue disorders: dermatitis, pruritus, acne

Vascular disorders: hypotension

Laboratory abnormalities reported with Valcyte tablets in one study in solid organ transplant patients are listed in Table 12.

Table 12 Laboratory Abnormalities Reported in Selected Solid Organ Transplant Patients in Study PV16000

Laboratory Abnormalities	Valcyte (N=244) %	Oral Cytovene (N=126) %
Neutropenia: ANC/μL		
<500	5	3
500 – <750	3	2
750 – <1000	5	2
Anemia: Hemoglobin g/dL		
<6.5	1	2
6.5 – <8.0	5	7
8.0 – <9.5	31	25
Thrombocytopenia: Platelets/μL		
<25000	0	2
25000 – <50000	1	3
50000 – <100000	18	21
Serum Creatinine: mg/dL		
>2.5	14	21
>1.5 – 2.5	45	47

Experience With Ganciclovir

Valganciclovir is rapidly converted to ganciclovir upon oral administration. Adverse events reported with Valcyte in general were similar to those reported with ganciclovir (Cytovene). Please refer to the Cytovene product information for more information on postmarketing adverse events associated with ganciclovir.

OVERDOSAGE

Overdose Experience With Valcyte Tablets

One adult developed fatal bone marrow depression (medullary aplasia) after several days of dosing that was at least 10-fold greater than recommended for the patient's estimated degree of renal impairment.

It is expected that an overdose of Valcyte tablets could also possibly result in increased renal toxicity (see PRECAUTIONS: General and DOSAGE AND ADMINISTRATION: Renal Impairment).

Since ganciclovir is dialyzable, dialysis may be useful in reducing serum concentrations in patients who have received an overdose of Valcyte tablets (see CLINICAL PHARMACOLOGY: Special Populations: *Hemodialysis*). Adequate hydration should be maintained. The use of hematopoietic growth factors should be considered (see CLINICAL PHARMACOLOGY: Special Populations: *Hemodialysis*).

Overdose Experience With Intravenous Ganciclovir

Reports of overdoses with intravenous ganciclovir have been received from clinical trials and during postmarketing experience. The majority of patients experienced one or more of the following adverse events:

Hematological toxicity: pancytopenia, bone marrow depression, medullary aplasia, leukopenia, neutropenia, granulocytopenia

Hepatotoxicity: hepatitis, liver function disorder

Renal toxicity: worsening of hematuria in a patient with pre-existing renal impairment, acute renal failure, elevated creatinine

Gastrointestinal toxicity: abdominal pain, diarrhea, vomiting

Neurotoxicity: generalized tremor, convulsion

DOSAGE AND ADMINISTRATION

Strict adherence to dosage recommendations is essential to avoid overdose. Valcyte tablets cannot be substituted for Cytovene capsules on a one-to-one basis.

Valcyte tablets are administered orally, and should be taken with food (see CLINICAL PHARMACOLOGY: Absorption). After oral administration, valganciclovir is rapidly and extensively converted into ganciclovir. The bioavailability of ganciclovir from Valcyte tablets is significantly higher than from ganciclovir capsules. Therefore the dosage and administration of Valcyte tablets as described below should be closely followed (see PRECAUTIONS: General and OVERDOSAGE).

For the Treatment of CMV Retinitis in Patients With Normal Renal Function

Induction:

For patients with active CMV retinitis, the recommended dosage is 900 mg (two 450 mg tablets) twice a day for 21 days with food.

Maintenance:

Following induction treatment, or in patients with inactive CMV retinitis, the recommended dosage is 900 mg (two 450 mg tablets) once daily with food.

For the Prevention of CMV Disease in Heart, Kidney, and Kidney-Pancreas Transplantation

For patients who have received a kidney, heart, or kidney-pancreas transplant, the recommended dose is 900 mg (two 450 mg tablets) once daily with food starting within 10 days of transplantation until 100 days posttransplantation.

Renal Impairment

Serum creatinine or creatinine clearance levels should be monitored carefully. Dosage adjustment is required according to creatinine clearance as shown in Table 13 (see

PRECAUTIONS: General and CLINICAL PHARMACOLOGY: Special Populations: Renal Impairment). Increased monitoring for cytopenias may be warranted in patients with renal impairment (see PRECAUTIONS: Laboratory Testing).

Table 13 Dose Modifications for Patients With Impaired Renal Function

CrCl* (mL/min)	Induction Dose	Maintenance Prevention Dose
≥60	900 mg twice daily	900 mg once daily
40 – 59	450 mg twice daily	450 mg once daily
25 – 39	450 mg once daily	450 mg every 2 days
10 – 24	450 mg every 2 days	450 mg twice weekly

*An estimated creatinine clearance can be related to serum creatinine by the following formulas:

$$\text{For males} = \frac{(140 - \text{age [years]}) \times (\text{body weight [kg]})}{(72) \times (\text{serum creatinine [mg/dL]})}$$

For females = 0.85 x male value

Hemodialysis Patients

Valcyte should not be prescribed to patients receiving hemodialysis (see CLINICAL PHARMACOLOGY: Special Populations: Hemodialysis and PRECAUTIONS: General).

For patients on hemodialysis (CrCl <10 mL/min) a dose recommendation cannot be given (see CLINICAL PHARMACOLOGY: Special Populations: Hemodialysis).

Handling and Disposal

Caution should be exercised in the handling of Valcyte tablets. Tablets should not be broken or crushed. Since valganciclovir is considered a potential teratogen and carcinogen in humans, caution should be observed in handling broken tablets (see WARNINGS: Teratogenesis, Carcinogenesis and Mutagenesis). Avoid direct contact of broken or crushed tablets with skin or mucous membranes. If such contact occurs, wash thoroughly with soap and water, and rinse eyes thoroughly with plain water.

Because ganciclovir shares some of the properties of antitumor agents (ie, carcinogenicity and mutagenicity), consideration should be given to handling and disposal according to guidelines issued for antineoplastic drugs. Several guidelines on this subject have been published (see REFERENCES).

There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

Valcyte (valganciclovir HCl tablets) is available as 450 mg pink convex oval tablets with "VGC" on one side and "450" on the other side. Each tablet contains valganciclovir HCl equivalent to 450 mg valganciclovir. Valcyte is supplied in bottles of 60 tablets (NDC 0004-0038-22).

Storage

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP controlled room temperature].

REFERENCES

1. Recommendations for the Safe Handling of Cytotoxic Drugs. US Department of Health and Human Services, National Institutes of Health, Bethesda, MD, September 1992. NIH Publication No. 92-2621
2. American Society of Hospital Pharmacists technical assistance bulletin on handling cytotoxic and hazardous drugs. Am J Hosp Pharm. 1990; 47:1033-1049
3. Controlling Occupational Exposures to Hazardous Drugs. US Department of Labor. Occupational Health and Safety Administration. OSHA Technical Manual. Section VI - Chapter 2, January 20, 1999

PATIENT INFORMATION

Read the Patient Information that comes with Valcyte before you start using it and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider.

What is the most important information I should know about Valcyte?

- **Valcyte can affect your blood cells and bone marrow causing serious and life-threatening problems.** Valcyte can lower the amount of your white blood cells, red blood cells, and platelets. Your doctor may do regular blood tests to check your blood cells while you are taking Valcyte. Based on these tests, your doctor may change your dose or tell you to stop taking Valcyte.

- **Valcyte may cause cancer.** Valcyte causes cancer in animals. It is not known if Valcyte causes cancer in people.

- **Valcyte may cause birth defects.** Valcyte causes birth defects in animals. It is not known if Valcyte causes birth defects in people. Valcyte should not be used during pregnancy. **Tell your doctor right away if you get pregnant while taking Valcyte. If you can get pregnant, you should use effective birth control during treatment with Valcyte. Men should use a condom during treatment with Valcyte, and for 90 days after treatment, if their partner can get pregnant.** Talk to your doctor if you have questions about birth control. Valcyte may lower the amount of sperm in a man's body and cause fertility problems.

- **Valcyte changes into the medicine ganciclovir once it is in your body.** Ganciclovir is also the active ingredient in Cytovene® Capsules and Cytovene-IV®. Do not take Valcyte and Cytovene at the same time. The dose of medicine in Valcyte Tablets and Cytovene Capsules is different. **One tablet of Valcyte has more medicine than one capsule of Cytovene. This means that one Valcyte tablet cannot be substituted for one Cytovene Capsule. You could overdose and become very sick.** Talk to your doctor or pharmacist if you have questions about your medicine.

What is Valcyte?

Valcyte is an "antiviral" medicine used:

- to treat cytomegalovirus (CMV) retinitis in people who have acquired immunodeficiency syndrome (AIDS). When CMV virus infects the eyes, it is called CMV retinitis.
- to prevent cytomegalovirus (CMV) disease in people who have received a **heart, kidney, or kidney-pancreas** transplant and who have a chance for getting CMV disease.

Valcyte may:

- slow the growth of CMV virus in your body. CMV is an infection caused by a herpesvirus called cytomegalovirus. If CMV retinitis isn't treated, it can cause blindness. Valcyte may protect your eyesight from damage due to CMV disease. CMV can also infect other parts of the body.
- prevent CMV disease for up to 6 months after **heart, kidney, or kidney-pancreas** transplant. Valcyte may prevent CMV virus from spreading into healthy cells.

Valcyte does not cure CMV retinitis. You may still get retinitis or worsening of retinitis during or after treatment with Valcyte. Therefore, it is important to stay under a doctor's care and have your eyes checked regularly.

Valcyte has not been studied in children or in adults older than age 65.

Who should not take Valcyte?

Do not take Valcyte if you:

- **are receiving hemodialysis.** The use of ganciclovir (Cytovene Capsules) rather than Valcyte tablets is recommended. Valcyte does not come in the right dose for people on hemodialysis.
- **are allergic to any of its ingredients or if you have ever had a serious reaction to ganciclovir (Cytovene Capsules or Cytovene-IV).** See the end of this leaflet for a list of the ingredients in Valcyte.

In addition, Valcyte is not for use in prevention of CMV disease in patients who have received a liver transplant. More research is needed before Valcyte can be recommended for use in the prevention of CMV disease in other organ transplant patients such as liver or lung transplant patients.

Before taking Valcyte, tell your doctor:

- **if you are pregnant or plan to become pregnant.** Valcyte may cause birth defects. (See "What is the most important information I should know about Valcyte?")
- **if you are breast-feeding.** It is not known if Valcyte passes into your milk and if it may harm your baby. You should not breast-feed if you are HIV-positive because of the chance of passing the HIV virus to your baby through your milk.
- **if you have kidney problems.** Your doctor may give you a lower dose of Valcyte, or check you more often if you are taking Valcyte.
- **if you have blood cell problems**
- **if you are having radiation treatment**
- **about all the medicines you take,** including prescription and non-prescription medicines, vitamins and herbal supplements. **Do not take Cytovene Capsules if you**

are taking Valcyte tablets. Valcyte and other medicines may affect each other. These interactions may cause serious problems. The following medicines may need dose changes if you are also taking Valcyte:

- Videx® (didanosine, ddI)
- Retrovir® (zidovudine, ZDV, AZT)
- Probenecid

Tell your doctor if you take medicines such as chemotherapy medicines that can lower your bone marrow function.

How should I take Valcyte?

- Take Valcyte exactly as your doctor prescribes it. Your dose of Valcyte will depend on your medical condition. If you have kidney problems or are over age 65, your doctor may give you a lower dose of Valcyte.
    - the usual dose for adults to get active CMV retinitis under control (induction therapy) is two 450 mg tablets twice a day for 21 days.
    - the usual dose for adults to help keep CMV retinitis under control (maintenance therapy) is two 450 mg tablets once a day.
    - the usual dose to prevent CMV in adults who have had a **heart, kidney, or kidney-pancreas** transplant is two 450 mg tablets once a day starting within 10 days of transplant and continuing until 100 days after the transplant.
- Take Valcyte with food.
- Do not break or crush Valcyte tablets.
- If you miss a dose of Valcyte, take the missed dose as soon as you remember. Then, take the next dose at the usual scheduled time. However, if it is almost time for your next dose, **do not take the missed dose.**
- Do not let your Valcyte run out. The amount of virus in your blood may increase if your medicine is stopped, even for a short time.
- If you take too much Valcyte, call your local poison control center or emergency room right away. You may need treatment in a hospital.
- Do not substitute Valcyte tablets for Cytovene capsules. Talk to your doctor, nurse or pharmacist if you have questions about your medicine.

What should I avoid while taking Valcyte?

- **Do not get pregnant.** Valcyte causes birth defects in animals. It is not known if Valcyte causes birth defects in people. Valcyte should not be used during pregnancy. **Tell your doctor right away if you get pregnant while taking Valcyte. If you can get pregnant, you should use effective birth control during treatment with Valcyte. Men should use a condom during treatment with Valcyte, and for 90 days after treatment, if their partner can get pregnant.** Talk to your doctor if you have questions about birth control. Valcyte may lower the amount of sperm in a man's body and cause fertility problems.

- **Do not breast-feed.** Valcyte may harm your baby. You should not breast-feed if you are HIV-positive because of the chance of passing the HIV virus to your baby through your milk.

- **Do not drive a car or operate other dangerous machinery until you know how Valcyte affects you.** Valcyte can cause seizures, sleepiness, dizziness, unsteady movements, and confusion.

- **Do not break or crush Valcyte tablets.** Avoid contact with broken Valcyte tablets on your skin, mucous membranes or eyes. If contact occurs, wash your skin well with soap and water or rinse your eyes well with plain water.

What are the possible side effects of Valcyte?

See "What is the most important information I should know about Valcyte?" for details on the most serious side effects. **Valcyte can also cause the following serious side effects:**

- **kidney problems.** Valcyte may affect your kidney function. Your doctor may do regular blood tests called serum creatinine levels to check your kidney function while you are taking Valcyte.

- **brain and nerve problems.** Valcyte may cause seizures, sleepiness, dizziness, unsteady movements, and confusion.

Common side effects of Valcyte include diarrhea, nausea, vomiting, stomach pain, fever, headache, shaky movements (tremors), graft rejection, swelling of the legs, constipation, back pain, trouble sleeping, and high blood pressure.

Common changes in blood tests for people taking Valcyte include low white blood cells (neutropenia or leukopenia), low red blood cells (anemia), increased blood creatinine levels, increased calcium in the blood, and abnormal liver function.

Talk to your doctor about side effects that bother you or that won't go away.

These are not all the side effects of Valcyte. For more information, ask your doctor or pharmacist.

How do I store Valcyte?

- Store Valcyte at room temperature, 59° to 86° F (15° to 30° C.)
- **Keep Valcyte and all medicines out of the reach of children.**

General information about Valcyte

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use Valcyte for a condition for which it was not prescribed. Do not give Valcyte to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about Valcyte. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Valcyte that is written for health professionals. Information about Valcyte is also available at 1-800-526-6367 (toll-free).

What are the ingredients in Valcyte?

Active Ingredient: Valganciclovir HCl

Inactive Ingredients: microcrystalline cellulose, povidone K-30, crospovidone, and stearic acid. The film-coating applied to the tablets contains Opadry Pink®.

Cytovene is a registered trademark of Hoffmann-La Roche Inc.

Videx is a registered trademark of Bristol-Myers Squibb Company.

Retrovir is a registered trademark of GlaxoSmithKline.

Valcyte tablets are manufactured by Patheon Inc., Mississauga, Ontario, Canada L5N 7K9

Distributed by:

Roche Pharmaceuticals

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

27898607

Revised: September 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-304 / S-001

MEDICAL REVIEW

Team Leaders Memorandum

NDA:	21-304/SE1-001
Drug Name:	Valcyte™ (valganciclovir) 450 mg tablets
Indication:	Prevention of cytomegalovirus (CMV) disease in kidney, heart, and kidney-pancreas transplant recipients at high risk (Donor CMV seropositive/Recipient CMV seronegative)
Dose:	900 mg once daily
Submission Received:	November 12, 2002
Date of MO Review:	September 11, 2003
Date of Memorandum:	September 11, 2003

Roche submitted a supplemental New Drug Application (NDA) requesting approval for valganciclovir for the prevention of CMV disease [redacted] In support of this request, the applicant submitted data from one multicenter study, PV16000, and two pharmacokinetic studies.

PV16000 was a double-blind, double-dummy active comparator study conducted in 372 heart, liver, kidney, and kidney-pancreas transplant patients. Patients were randomized 2:1 valganciclovir (VGCV): oral ganciclovir (GCV) to receive either valganciclovir 900 mg once daily or oral ganciclovir one gram three times daily, starting within ten days of transplantation and continuing until Day 100 post-transplant. The study was designed to test for non-inferiority between the two treatment arms. The primary endpoint was the proportion of patients who developed CMV disease, defined as CMV syndrome and/or tissue invasive disease, during the first six months post-transplant. The proportion of patients who developed CMV disease during the first six months post-transplant was similar between the VGCV group (29/239, 12%) and the GCV group (19/125, 15%). However, in liver transplant patients the incidence of tissue invasive CMV disease was significantly higher in the VGCV group (16/118, 14%) compared with the GCV group (2/59, 3%). Mortality at six months was greater in the VGCV group (nine deaths, 3.7%) compared to the GCV group (two deaths, 1.6%).

The review team recommends that valganciclovir be approved for prevention of CMV disease in heart, kidney, and kidney-pancreas transplant patients, but not in [redacted]. The safety and efficacy of valganciclovir for prevention of CMV

(p=0.04). This difference was statistically significant, which is particularly noteworthy given the study was a non-inferiority study and was neither designed nor powered to detect statistically significance.

Labeling discussions focused on:

1. The description of study results regarding [redacted] nts and its placement in the label. Valganciclovir for the [redacted]
2. Limited data regarding CMV resistance was removed from the label.
3. Carcinogenicity data was updated and put in language recommended by the FDA Toxicology reviewers.
4. The table and text regarding adverse events from study PV16000 were reformatted.

I am in agreement with the proposed Phase IV commitments included in the approval letter. In the approval letter, the FDA encouraged the sponsor to conduct another study of valganciclovir [redacted]

Harry W. Haverkos, M.D.
Medical Officer, HFD-530

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
Harry Haverkos
9/12/03 01:37:08 PM
MEDICAL OFFICER

Debra Birnkrant
9/12/03 01:46:28 PM
MEDICAL OFFICER

NDA 21-304
S-001

Medical Officer's Review
NDA 21-304
Supplement 001

Date Submitted:	November 11, 2002
Date Received:	November 12, 2002
Date Assigned:	November 22, 2002
Date Review Completed:	September 12, 2003
Applicant:	Hoffman-La Roche, Inc. 340 Kingsland Street Nutley, New Jersey 07110
Drug:	Generic: valganciclovir HCL Trade: Valcyte™
Route of Administration:	Oral
Formulation:	Tablets 450 mg
Proposed Indication:	Prevention of CMV disease in [redacted]
Related IND's:	[redacted]
Related NDA's:	19-661 Cytovene®-IV (ganciclovir sodium) Sterile Powder) 20-460 Cytovene® (ganciclovir capsules) 21-304 Valganciclovir HCl
Medical Division:	Division of Antiviral Drugs and Products (HFD-530)
Medical Reviewer:	Andreas Pikis, M.D.

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Clinical Review for NDA 21-304

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Based on the efficacy and safety analyses of study PV16000, valganciclovir for the prevention of cytomegalovirus (CMV) disease in heart, kidney, and kidney-pancreas transplant patients at high risk [donor CMV seropositive/recipient CMV seronegative (D+/R-)] is recommended for approval

[redacted]

In this submission the applicant sought approval of valganciclovir for the prevention of CMV disease in [redacted] CMV disease was defined in this study as symptomatic CMV infection and included both CMV syndrome and tissue-invasive CMV disease; outcomes were assessed by a blinded endpoint committee. Although the proportion of patients who developed CMV disease during the first six months post-transplant was similar between the valganciclovir arm (12.1%) and the oral ganciclovir arm (15.2%), analyses by organ transplant group revealed significant differences.

In kidney transplant patients, valganciclovir performed better than oral ganciclovir in preventing CMV disease. Valganciclovir was also favored in heart and kidney-pancreas transplant patients.

[redacted]

The overall adverse event profile up to six months post-transplant was comparable between the two arms of the study (valganciclovir versus ganciclovir) and consistent with the known adverse events profiles of each of these drugs.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

As part of their postmarketing commitments the applicant agreed to:

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

This submission reports the results of study PV16000, a randomized, double-blind, double dummy, active comparator controlled multinational study comparing the efficacy and safety of valganciclovir versus oral ganciclovir for the prevention of CMV disease in solid organ transplant recipients at high risk (D+/R-). Three hundred sixty four (364) D+/R- recipients of heart (56), kidney (120), kidney-pancreas (11), and liver (177) allografts were stratified by allograft type and randomized 2:1 at each study center to receive either valganciclovir 900 mg q.d. or oral ganciclovir 1000 mg t.i.d. as soon as they were able to tolerate oral medication (but not later than 10 days post-transplant). Treatment with study drugs continued until day 100 post-transplant. The primary endpoint of this study

was the incidence of CMV disease (CMV syndrome and/or tissue invasive CMV disease) at six months post-transplant.

B. Efficacy

Study PV16000, showed that the proportion of patients who developed CMV disease during the first 6 months post-transplant was similar between the valganciclovir treated arm (12.1%) and the oral ganciclovir arm (15.2%). However, significant differences were observed between the two arms when the data were analyzed by organ transplant group and by specific CMV outcome. In kidney transplant patients, valganciclovir performed better than oral ganciclovir in preventing CMV disease, whereas in liver transplant patients ganciclovir performed better than valganciclovir.

group compared with the incidence observed in the ganciclovir group. Valganciclovir was also favored in heart and kidney-pancreas patients.

C. Safety

Overall, there were no new or unexpected adverse events with the use of valganciclovir in study PV16000. The adverse event profile up to six months of the study was comparable between the two arms (valganciclovir versus ganciclovir) and consistent with the known adverse event profiles of each of these drugs. The percentage of patients withdrawn from the study due to adverse events was similar between treatment arms (5% in each arm). The most serious laboratory toxicities attributed to valganciclovir use were granulocytopenia, thrombocytopenia, and anemia; these adverse events are already described in the valganciclovir label.

Although not statistically significant, mortality was higher in the valganciclovir arm. A total of 7 patients died while on treatment (2 on the ganciclovir arm, 5 on the valganciclovir arm). Mortality at 6 months was 3.7 % (9/244) in the ganciclovir group and 1.6% (2/126) in the ganciclovir group. All deaths were considered by the investigators not related to study drugs.

D. Dosing

Dosing was evaluated during the original NDA review. In study WP15711, it was shown that in liver transplant patients a 900 mg dose of oral valganciclovir provides comparable results to the 5 mg/kg i.v. dose of ganciclovir.

In the current sNDA submission, the applicant provided the results of a population pharmacokinetic study of ganciclovir in heart, kidney, and liver transplant recipients after oral administration of valganciclovir and ganciclovir.

They demonstrated that systemic ganciclovir exposure was ~1.7 times higher after oral administration of 900 mg q.d. valganciclovir compared with oral administration of 1000 mg t.i.d. ganciclovir. Moreover, they demonstrated that systemic ganciclovir exposures were comparable across heart, kidney, and liver transplant patients

E. Special Population

Pediatrics: The applicant did not include any pediatric patients in study PV 16000.'

[ ]

Geriatrics: Study PV16000 did not include sufficient number of patients over 65 years of age; therefore, no conclusions can be reached regarding the efficacy and safety of valganciclovir in this group of patients.

Race: Analysis of efficacy according to race and ethnicity is confounded by an inbalance in the race of participating patients. The study mainly involved Caucasian patients.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Valganciclovir, an L-valyl ester prodrug of ganciclovir, exists as a mixture of two diastereomers. After oral administration it is rapidly and extensively hydrolyzed by gastrointestinal and liver esterases into ganciclovir. Only 1-2% of the absorbed drug appears in plasma as valganciclovir, while the remainder is found as ganciclovir. Ganciclovir is a nucleoside analog which inhibits the replication of human CMV in vitro and in vivo. Ganciclovir must be phosphorylated to its triphosphate form in CMV-infected cells to exercise its antiviral activity by inhibiting viral DNA replication. In CMV-infected cells ganciclovir is initially phosphorylated to ganciclovir monophosphate by the viral protein kinase UL97. Further phosphorylation to its triphosphate form occurs by cellular kinases.

Valganciclovir is currently approved by the Food and Drug Administration for the treatment of CMV retinitis in AIDS patients. The current application seeks the supplemental indication of valganciclovir for the prevention of CMV disease in [redacted]. The recommended dose is 900 mg once daily starting within 10 days of transplantation until 100 days post-transplantation. The submitted study was conducted in men and women at least 13 years of age.

B. State of Armamentarium for Indication(s)

CMV is the single most frequent pathogen in solid organ transplant recipients, contributing significantly both to patient morbidity and mortality. Three forms of infections are recognized:

- primary infection
- reactivation of autologous virus
- superinfection (when a seropositive patient is infected with exogenous virus, usually from the allograft

The risk of developing CMV disease after transplantation depends on different factors; the CMV serologic status of both donor and recipient and immunosuppressive therapy are considered the most significant factors. The lowest rate of CMV infection (<5%) occurs in D-/R- recipients and the highest (> 50%) in D+/R- recipients. The incidence of CMV disease in D+/R+ or D-/R+ recipients is estimated at 10 – 15%.

Because of the increased morbidity and mortality associated with CMV infection in solid organ transplant recipients, it has been recognized that prevention of CMV infection may be a better strategy rather than treatment of established infection. Prophylactic therapy and preemptive therapy are the two major strategies used for prevention. Although during the last decade many investigators have focused on the value of preemptive therapy (therapy that is administered only to those patients who have been shown to have evidence of CMV replication), most of transplant physicians use the prophylactic therapy (therapy that is administered to all patients at risk for developing CMV disease) for transplant patients who are D+/R-.

Intravenous ganciclovir was the first antiviral drug approved for the treatment of CMV infection which was also used for the prevention of CMV disease in solid organ transplant recipients. Unfortunately, the long-term use of intravenous ganciclovir was found to be generally impractical and of limited benefit due to the requirement of an indwelling catheter to deliver the drug and the increased risk of potentially life-threatening catheter-related infections. Oral ganciclovir has also been used for the prevention of CMV disease in solid organ transplant patients, however, this option has been limited because of its low bioavailability and the subsequent large number of capsules required to achieve a minimum effective level. In fact, valganciclovir was developed because of the poor bioavailability of

oral ganciclovir. It was shown that in liver transplant patients a dose of 900 mg q.d. provides comparable results to the 5 mg/kg i.v. dose of ganciclovir and a daily dose of 450 mg valganciclovir provides results comparable to 1000 mg t.i.d dose of oral ganciclovir. The overall ganciclovir concentration-time profile obtained with 900 mg valganciclovir was similar to that obtained with 5 mg/kg i.v. ganciclovir, except that the ganciclovir C_{max} was 60-70% of that provided by the i.v. formulation.

C. Important Milestones in Product Development

October 1999: DAVDP Closed Advisory Committee to discuss study for the prevention of CMV disease in [redacted]

December 2001: Teleconference regarding statistical analysis plan and Division's acceptance of Endpoint Committee adjudication of the primary endpoint.

July 2002: Pre-sNDA meeting to discuss plans for submission of an sNDA for valganciclovir for the prevention of CMV [redacted]

D. Other Relevant Information

Valganciclovir was approved by the FDA in March 2001 for the treatment of CMV retinitis in AIDS patients. It has since been approved for the same indication in another 22 countries.

E. Important Issues with Pharmacologically Related Agents

None noted.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Review

There are no new clinically relevant findings from chemistry and pharmacology/toxicology pertinent to this supplement. The current submission does contain new virology data, which have been reviewed by Dr. Nilambar Biswal. Efficacy data have been reviewed by the Mathematical Statistical Reviewer Dr. Fraser Smith. Consultation was requested from the Division of Special Pathogens and Immunologic Drug Products (Drs. Arturo Hernandez and Marc Cavaille-Coll) for additional expertise on transplant-related issues. Their review comments were taken into consideration during the review process and label discussions.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

The current sNDA submission includes two pharmacokinetic studies with valganciclovir in solid organ transplant recipients:

1. A pharmacokinetic study in liver transplant recipients (study WP15711)

   This study was also submitted in the original NDA submission and was reviewed by Dr. Robert Kumi. The objective of this study was to determine a daily dose of valganciclovir in liver transplant patients that would provide systemic exposure of ganciclovir similar to a single dose of 5 mg/kg intravenous ganciclovir and 1000 mg t.i.d. oral ganciclovir.

   In brief, the study showed that in liver transplant recipients:
   a) A 900 mg dose of oral valganciclovir provides comparable results to the 5 mg/kg i.v. dose of ganciclovir
   b) A 450 mg dose of oral valganciclovir provides comparable results to the 1000 mg t.i.d. dose of ganciclovir
   c) Valganciclovir was well tolerated and had a safety profile consistent with the safety profile of ganciclovir.

2. A population pharmacokinetic study of ganciclovir in solid organ transplant recipients after oral administration of valganciclovir and ganciclovir (PV16000)

The objective of this study was to compare ganciclovir plasma levels after oral administration of 900 mg q.d. valganciclovir or 1000 mg t.i.d. ganciclovir in different organ recipients (heart, kidney, and liver transplant recipients). It showed that:

a) The mean systemic exposure to ganciclovir was ~1.7 times higher after oral administration of 900 mg q.d. valganciclovir compared with oral administration of 1000 mg t.i.d. ganciclovir.
b) The systemic ganciclovir exposures were comparable across heart, kidney, and liver transplant allograft recipients.

Please see the review by Dr. Derek Zhang for further details.

B. Pharmacodynamics

No pharmacodynamic studies were submitted with this application.

IV. Description of Clinical Data and Sources

A. Overall Data

The initial submission contained 27 volumes in paper incorporating data from the 6 month follow-up of clinical study PV16000 (the pivotal study for the sNDA) and the pharmacokinetic study WP15711 (Index, volume 1; labeling, volume 2; human pharmacokinetics and bioavailability, volumes 3-5, clinical and statistical data, volumes 6-27). Case report forms and case report tabulations of patient profiles were submitted electronically. Another 8 volumes were submitted during the review containing data from the 12 month follow-up of study PV16000.

In addition to the above data, the applicant submitted 20 volumes containing safety data from the

B. Tables Listing the Clinical Trials

This application contains data from only one clinical study (PV16000). This was a worldwide, multi-center trial conducted at 57 centers. It included sites in North America (United States, 35 centers; Canada , 5 centers), Europe (11 centers), and Australia/New Zealand (6 centers).

C. Postmarketing Experience

Information on postmarketing data on valganciclovir through November 17, 2002 was submitted.

D. Literature Review

The applicant provided a literature review consisting primarily of articles and book chapters discussing the impact of CMV infection in solid organ transplant recipients and the different methods used for the prevention or treatment of CMV infection in this group of patients.

V. Clinical Review Methods

A. How the Review was Conducted

Study PV16000 was reviewed for both safety and efficacy. The sponsor's conclusions regarding safety and efficacy were confirmed by independent FDA analysis of the data. Dr. Fraser Smith performed the statistical analysis confirming

the primary endpoint and selected secondary endpoints using SAS version 8.2. The MO reviewed study design, patient demographics, adverse events, and laboratory safety monitoring data. Dr Nilambar Biswal reviewed the virology methods and data. In this review, tables derived from the sponsor's presentation of the data are cited as to source in the table footnotes, while tables derived from review-generated results are not referenced.

B. Overview of Materials Consulted in Review

The 27 volumes documenting the 6-month follow-up data regarding study PV16000 and the pharmacokinetic study WP15711 were the primary source of the review.

In addition, the following materials were reviewed:

[ ]

C. Overview of Methods Used to Evaluate Data Quality and Integrity

The Good Clinical Practice Branch, Division of Scientific Investigations, FDA, conducted clinical inspections of 3 study sites in the USA: Indianapolis, IN; Rochester, MN; and Omaha, NE. No major deficiencies were noted in the three inspected sites that would compromise the integrity of the study. For more details please see Clinical Inspection Summary by Antoine El- Hage, Ph.D.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The applicant states that the study was conducted according to accepted ethical standards based on the precepts established by the Declaration of Helsinki. According to applicant, it was the responsibility of the individual investigators to ensure that subjects were given adequate information to assess the potential risks and benefits of study participation. A copy of sample Informed Consent Form was included in the submission.

E. Evaluation of Financial Disclosure

The sponsor submitted financial disclosure information and this was reviewed in this sNDA. One of the clinical investigators disclosed financial arrangements with the applicant.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Study PV16000, showed that the proportion of patients who developed CMV disease (including CMV syndrome and/or tissue-invasive CMV disease) during the first 6 months post-transplant was similar between the valganciclovir treated arm (12.1%) and the oral ganciclovir arm (15.2%). However, significant differences were observed between the two arms when the data were analyzed by organ transplant group and by outcomes. In kidney transplant patients, valganciclovir performed better than oral ganciclovir in preventing CMV disease, whereas in liver transplant patients ganciclovir performed better than valganciclovir. The incidence of tissue-invasive CMV disease in liver transplant patients was five times higher in the valganciclovir group compared with the incidence observed in the ganciclovir group.

Although not statistically significant, mortality at six months was greater in the valganciclovir (3.7%) group compared with the ganciclovir group (1.6%)

B. General Approach to Review of the Efficacy of the Drug

The primary endpoint was the proportion of patients who developed CMV disease within the first six months post-transplant (as assessed by the endpoint committee). The six month endpoint was selected to include the period of highest risk (first 3 months when patients are receiving intensive immunosuppression) and the 3 months after completion of prophylaxis.

All cases of suspected CMV disease reported by the investigators were submitted to a blinded Endpoint Committee for review and adjudication prior to data analysis. The Endpoint Committee identified those CMV disease events to be included in the primary efficacy analysis based on review of the signs, symptoms and laboratory criteria of CMV disease, as defined in the protocol, and through review of supporting clinical and laboratory documentation. The committee also assessed whether each event was CMV syndrome and/or tissue-invasive CMV disease, determined the date of onset of CMV disease, and provided the rationale for their decision.

The Intent to Treat (ITT) population was the primary efficacy analysis population. The ITT population included patients who were randomized and who were D+/R-.

If a patient received no study treatment or was included in the ITT population but had insufficient follow-up data, he/she was listed as 'unevaluable', unless he/she had the event in question (for example, CMV disease). For the ITT population, 'unevaluable' patients were included in the denominator for the calculation of proportions and one-sided 97.5% confidence intervals.

If a patient missed a visit but then completed the subsequent visit and was still CMV disease free at that subsequent visit, it was assumed that the patient was event-free at the missing visit.

C. Detailed Review of Trials by Indication

Study PV 16000

Study design

This was a randomized, double-blind, double dummy, active comparator controlled multi-center study. Recipients of heart, liver, kidney, or kidney-pancreas allograft who met the inclusion criteria were stratified by allograft type and randomized 2:1 at each study center to receive either valganciclovir 900 mg q.d. or oral ganciclovir 1000 mg t.i.d. as soon as they were able to tolerate oral medication (but no later than 10 days post transplant). Treatment with study drugs continued until day 100 post transplant.

Study objective

The primary objective of the study was to determine the comparative efficacy of valganciclovir (900 mg q.d.) relative to oral ganciclovir (1000 mg t.i.d.) when given for the prevention of CMV disease in high-risk (D+/R-) heart, liver, kidney, and kidney-pancreas allograft recipients.

Study population

Enrollment included 372 patients. Eight patients were found to be non- D+/R- after enrollment leaving the number of patients who met the inclusion criteria to 364 (valganciclovir arm =239, ganciclovir arm =125). Approximately half (177) of the 364 patients had liver transplants, followed by a third with kidney transplants (120). The remaining had heart (56) and kidney/pancreas (11) transplants.

Inclusion criteria

- Patient received within the preceding 10 days his/her 1) first heart, liver, kidney, or kidney-pancreas allograft, 2) first kidney-liver or kidney-heart allograft, or 3) second kidney allograft.
- Patient was seronegative for CMV (confirmed within 30 days pre-transplant) and has received allograft from a CMV seropositive donor. A donor who was seropositive solely based on having received a CMV seropositive transfusion immediately prior to organ donation was not considered to be a seropositive donor in this study.

- Patient ≥ 13 years of age
- Patient had adequate hematological and renal function defined as:
  ANC > 1000 cells/μL
  Platelet count > 25,000 cells/μL
  Hgb > 8 gm/dL
  Estimated creatinine clearance 1) >25 mL/min (liver and heart recipients) or 2) >15 mL/min with evidence of improving renal function manifested by a decreasing serum creatinine (kidney and kidney-pancreas recipients)
- Patient agreed to use an effective contraception method during the study period and for 90 days following discontinuation of the study drug.
- Negative pregnancy test at screening
- Patient able to tolerate oral medication within 10 days post transplantation.
- Patient and/or patient's guardian, if appropriate, understood and signed the informed consent form.

Exclusion criteria

- Patient had a history of CMV infection or CMV disease.
- Patient had received anti-CMV therapy within the past 30 days (treatment with acyclovir, valacyclovir, or famciclovir for acute HSV or HZV prior to enrollment is not considered to be an anti-CMV therapy).
- Patient had severe uncontrolled diarrhea or evidence of malabsorption.
- Patient was simultaneously participating in another clinical trial.
- Patient had exhibited in the past an allergic or other significant reaction to acyclovir, ganciclovir, or valacyclovir.
- Patient required the use of any prohibited medication
- Patient was a lactating female who would not discontinue nursing prior to study entry.

Primary endpoint

The primary endpoint was the proportion of patients who developed CMV disease within the first 6 months post transplant (as assessed by the endpoint committee).

CMV disease was defined as symptomatic CMV infection and included both CMV syndrome and tissue-invasive CMV disease.

CMV syndrome was defined as clinical evidence of CMV viremia accompanied by fever and signs or symptoms of CMV infection (such as fever, leukopenia, thrombocytopenia, fatigue etc.)

Tissue-invasive CMV disease was defined as: evidence of localized CMV infection in a biopsy or other appropriate specimen accompanied by relevant signs and symptoms of organ dysfunction

Secondary efficacy variables

- Time to CMV disease
- Time to treatment failure where treatment failure is defined as development of CMV disease, death, or discontinuation of treatment with study drug because of a drug related adverse event.
- Incidence of acute graft rejection at 6 months post transplant.
- Incidence of patient survival at 6 months post transplant.
- Incidence of herpes virus infections and other opportunistic infections at 6 months post transplant.

Efficacy results

Study population

1. Baseline characteristics.
   a) Patient demographics are shown in Table 1.

Table 1. Summary of demographic data (all patients)

Patient Characteristics	VGCV N = 245	GCV N = 127
Sex		
Male	179 (73%)	95 (75%)
Female	66 (27%)	32 (25%)
N	245	127
Race		
Caucasian	218 (89%)	115 (91%)
Other	27 (11%)	12 (7%)
N	245	127
Age (years)		
Mean	46	45
SD	13	13
SEM	0.8	1.2
Median	48	46
Min-Max	14 - 71	16 – 71
N	245	127
Weight in kg		
Mean	81	84
SD	18	22
SEM	1.2	2.0
Median	81	80
Min-Max	31 – 135	41 – 154
N	239	126
Height in cm		
Mean	172	173
SD	11	10
SEM	0.7	0.9
Median	173	173
Min-Max	122 – 195	145 – 193
N	243	125

Source: CSR Vo. 7 - P. 50

n represents number of patients contributing to summary statistics.

Percentages are based on n (the number of valid values).

Percentages are not calculated if n < 10.

Comment: The study includes more males than females and more Caucasians than people of other races. The two treatment groups appear to be balanced.

b) The major disease categories leading to transplant were also well balanced in the two groups. Ischemic cardyomyopathy was the most common reason for heart transplant (62% ganciclovir, 40% valganciclovir), chronic hepatitis C (34% ganciclovir, 28% valganciclovir) and primary sclerosing cholangitis (16% ganciclovir, 15% valganciclovir) were the most common reason for liver transplant, and diabetes mellitus (28% ganciclovir, 25% valganciclovir) was the most common reason for kidney transplant.

2. Disposition of subjects

Most patients in both arms (ganciclovir 73%, valganciclovir 74%) received their first dose within 5 days of their transplant surgery.

Time on study medication is summarized in Table 2.

Table 2. Summary of treatment duration (all patients)

	GCV N=127	VGCV N=245	Total N=372
TREATMENT DURATION (DAYS)			
1 - 1 0	3 (2.4%)	6 (2.4%)	9 (2.4%)
11 - 2 0	1 (0.8%)	4 (1.6%)	5 (1.3%)
21 - 3 0	3 (2.4%)	2 (0.8%)	5 (1.3%)
31 - 4 0	1 (0.8%)	2 (0.8%)	3 (0.8%)
41 - 5 0	2 (1.6%)	2 (0.8%)	4 (1.1%)
51 - 6 0	1 (0.8%)	2 (0.8%)	3 (0.8%)
61 - 7 0	0	2 (0.8%)	2 (0.5%)
71 - 8 0	2 (1.6%)	6 (2.4%)	8 (2.2%)
81 - 9 0	4 (3.1%)	11 (4 .5%)	15 (4.0%)
91 - 1 00	100 (78.7%)	200 (81.6%)	300 (80.6%)
>100	9 (7.1%)	7 (2.9%)	16 (4.3%)
NOT DOSED	1 (0.8%)	1 (0.4%)	2 (0.5%)
N	126	244	370
MEAN (s.d.)	90.6 (21.3)	90.3 (20.5)	90.4 (20.8)
MEDIAN	97.0	97.0	97.0
MINIMUM	1.0	2.0	1.0
MAXIMUM	117.0	115.0	117.0

Source: CSR Vol. 7 - P. 52
Treatment duration is defined as the number of days between treatment start date and treatment end date + 1.

Comment: The mean duration of treatment was similar in the two arms. The majority of patients received anti-CMV prophylaxis for 91-100 days

Study drug discontinuation. Study drug discontinuations are summarized in Table 3.

Table 3. Summary of patient withdrawals from trial treatment at six months.

Reason for withdrawal	GCV N=127 No (%)	VGCV N=245 No (%)
Safety	8 (6)	16 (7)
Adverse event	6	12
Death	2	4
Non-safety	8 (6)	19 (8)
Insufficient therapeutic response	2	5
Violation of selection criteria at entry	1	5
Other protocol violation	0	1
Refused treatment	5	3
Other	0	5
Total	16 (13)	35 (14)

Source: CSR Vol 8. - P. 93

Comment: A total of 51 patients discontinued study drugs with a comparable proportion of patients from the ganciclovir and valganciclovir groups. Adverse events were the most frequent reason for withdrawal.

3. **Primary study endpoint.** The primary endpoint was time to CMV disease during the 6-month post-transplant period. The results are summarized in Table 4.

Table 4. Summary of CMV disease up to six months post-transplant (Endpoint Committee, ITT Population)

No. of Patients	Ganciclovir (N=125)		Valganciclovir (N=239)		Weighted Difference in Proportions (95% CI)	
	N	%	N	%	Difference	95% CI *P*-value
Patients with CMV disease	19	15.2	29	12.1	+0.034	-0.042, +0.110* *P*=0.38
CMV syndrome	13	10.4	12	5.0	+0.06	-0.01, +0.12 *P*=0.08
Tissue-invasive CMV disease+	6	4.8	17	7.1	-0.02	-0.07, +0.03 *P*=0.41
Hepatitis	1		6			
Pneumonia	1		2			
GI	4		12			
Retinitis	0		0			
Other	0		1			
Patients unevaluable	7	5.6	12	5.0		

Source: CSR Vol. 7 - P. 55 with additional statistical analysis performed by F. Smith, FDA Statistical Reviewer

*If lower limit of the 97.5% CI > -0.05 then VGCV is non-inferior to GCV
If lower limit o the 97.5% CI > 0 then VGCV is superior to GCV

+Few patients had more than one type of tissue-invasive CMV disease

If a patient had insufficient visits up to 6 months he was considered unevaluable unless the patient had CMV disease

95% CI and P-value from the stratified Z test

Comment: The proportion of patients who developed CMV disease was comparable between the two groups (GCV 15.2%, VGCV 12.1%). Of note is the higher incidence of CMV syndrome in the GCV group (GCV 10.4%, VGCV 5.0%). The incidence of tissue-invasive CMV disease was higher in the valganciclovir group (GCV 4.8%, VGCV 7.1%). The lower bound of the 95% confidence interval exceeded –0.05 for CMV disease, the pre-specified non-inferiority boundary. Based on these

findings the applicant concluded that valganciclovir was non-inferior to oral ganciclovir for the prevention of CMV disease in solid organ transplant recipients. This assumption depends on the consistency of the primary endpoint across all organ types which was not the case in this study. A Breslow Day test of treatment by organ interaction was statistically significant (*P*=0.036, Table 5).

Table 5. Incidence of CMV disease up to six months post-transplant by organ transplant (Endpoint Committee, ITT population)

Organ	VGCV (N=239)	GCV (N=125)	2 one-sided 97.5% CI+	*P*-value	Treatment Favored
Heart (n=56)	6% (2 / 35)	10% (2 / 21)	-0.12, +0.20	0.63	VGCV
Liver (n=177)	19% (22 / 118)	12% (7 / 59)	-0.18, +0.04	0.29	GCV
Kidney (n=120)	6% (5 / 81)	23% (9 / 39)	+0.02, +0.31	0.01*	VGCV
Kidney/ Pancreas (n=11)	0% (0 / 5)	17% (1 / 6)	-0.24, +0.57	1.00	VGCV

Source: F. Smith, Statistical Reviewer
+Noninferiority is demonstrated for Valganciclovir if the lower bound of the 97.5% CI is >-0.05
*Superiority is demonstrated if *P*<0.05
P values not adjusted for multiple secondary endpoints
Breslow Day test of treatment by organ interaction: *P*=0.036
(The Breslow-Day test of treatment by organ interaction at 12 months was not statistically significant: *P*=0.25)

Comment: The efficacy of valganciclovir compared with oral ganciclovir was not the same in each organ transplant group (*P*=0.036). Valganciclovir performed better than ganciclovir in kidney transplant patients. On the other hand, the incidence of CMV disease was numerically higher among patients randomized to valganciclovir treatment compared with ganciclovir.

Table 6. Incidence of tissue-invasive CMV disease up to six months post-transplant by organ transplant (Endpoint Committee, ITT population)

Organ	GCV (N=125)	VGCV (N=239)	2 one-sided 97.5% CI[+]	*P*-value	Treatment Favored
Heart (n=56)	5% (1/21)	0% (0/35)	-0.07, +0.16	0.38	VGCV
Liver (n=177)	3% (2/59)	14% (16/118)	-0.18, -0.02	0.04*	GCV
Kidney (n=120)	5% (2/39)	1% (1/81)	-0.04, +0.12	0.25	VGCV
Kidney/ Pancreas (n=11)	17% (1/6)	0% (0/5)	-0.24, +0.57	1.00	VGCV

*Superiority is demonstrated if $P<0.05$
Breslow-Day test for treatment by organ interaction: $P=0.028$
P values not adjusted for multiple secondary endpoints
(The Breslow-Day test of treatment by organ interaction was not statistically significant at 12 months: $P=0.17$)
Weighted difference in proportions = -0.02, 95% Confidence Interval = (-0.07, +0.03), *P*-value =0.41

Comment: Significantly different treatment effects were observed in heart, liver, kidney, and kidney/pancreas transplant patients ($P=0.028$). The rate of tissue-invasive CMV disease in valganciclovir liver transplant patients (14%) was almost five times higher than it was in oral ganciclovir patients who received liver transplants (3%) This finding is of concern since tissue-invasive CMV disease is the most serious complication of infection with cytomegalovirus which can lead to organ graft rejection.

Table 7. Incidence of CMV syndrome up to six months post-transplant by organ transplant (Endpoint Committee, ITT population)

Organ	GCV (N=125)	VGCV (N=239)	2 one-sided 97.5% CI+	*P*-value	Treatment Favored
Heart (n=56)	5% (1/21)	6% (2/35)	-0.14, +0.13	1.00	GCV
Liver (n=177)	8% (5/59)	5% (6/118)	-0.05, +0.12	0.51	VGCV
Kidney (n=120)	18% (7/39)	5% (4/81)	-0.00, +0.26	0.04*[1]	VGCV
Kidney/ Pancreas (n=11)	0% (0/6)	0% (0/5)	N/A	N/A	Neither

*Superiority is demonstrated if $P<0.05$
[1]*P* value is from Fisher's Exact test (not from the weighted means test, which corresponds to the 95% CI and is not quite statistically significant)
P values not adjusted for multiple secondary endpoints
Breslow Day test of treatment by organ interaction: $P=0.41$

Comment: For the endpoint of CMVsyndrome, there was no statistically significant treatment effect by organ transplant type interaction ($P=0.41$). Valganciclovir was superior to oral ganciclovir in kidney transplant patients. Valganciclovir also appeared more effective in liver transplant patients, but this difference was not statistically significant.

Tissue-invasive CMV disease and liver transplant patients

The increased incidence of tissue-invasive CMV disease in liver transplant patients in the valganciclovir arm compared with the incidence observed in the ganciclovir arm raised concerns regarding the efficacy of valganciclovir in this group of patients. A number of factors were investigated in order to find a possible explanation for this difference.

a) Baseline characteristics of liver transplant patients (shown in Table 8).

Table 8. Summary of Demographic Data in Liver Transplant Patients.

	VGCV N = 124	GCV N = 61
Sex		
Male	88 (71%)	43 (70%)
Female	36 (29%)	18 (30%)
N	124	61
Race		
Caucasian	116 (94%)	56 (92%)
Other	8 (6%)	5 (8%)
N	124	61
Age		
Mean	48	47
SD	11	12
SEM	0.9	1.5
Median	50	48
Min-Max	17 – 70	18 – 70
N	124	61
Weight in kg		
Mean	83	86
SD	18	24
SEM	1.7	3.2
Median	84	87
Min-Max	40 – 135	49 – 154
N	120	60
Height in cm		
Mean	173	172
SD	10	10
SEM	0.9	1.3
Median	175	173
Min-Max	147 – 195	150 – 191
N	123	60

n represents number of patients contributing to summary statistics. Percentages are based on n (the number of valid values). Percentages are not calculated if n < 10.

Comment: The baseline characteristics in the two arms in liver transplant patients appear to be well balanced.

b) HLA histocompatibility. Table 9 summarizes HLA histocompatibility between donor/recipient in all patients, and Table 10 in liver transplant patients.

Table 9. HLA histocompatibility between donor/recipient in all patients

Number of Mismatches	Valganciclovir (n=245)	Ganciclovir (n=127)
0 (n=16)	4% (n=11)	4% (n=5)
1 (n=9)	3% (n=8)	1% (n=1)
2 (n=17)	4% (n=11)	5% (n=6)
3 (n=47)	11% (n=27)	16% (n=20)
4 (n=43)	11% (n=27)	13% (n=16)
5 (n=38)	11% (n=28)	8% (n=10)
6 (n=39)	10% (n=25)	11% (n=14)
Unobtainable (n=163)	44% (n=108)	43% (n=55)

Source: CSR Vol. 8 - P. 101.

Table 10. HLA histocompatibility between donor/recipient in liver transplant patients

Number of Mismatches	Valganciclovir (n=124)	Ganciclovir (n=61)
0 (n=3)	1% (n=1)	3% (n=2)
1 (n=1)	1% (n=1)	0% (n=0)
2 (n=1)	0% (n=0)	2% (n=1)
3 (n=6)	4% (n=5)	2% (n=1)
4 (n=12)	6% (n=8)	7% (n=4)
5 (n=15)	8% (n=10)	8% (n=5)
6 (n=17)	10% (n=12)	8% (n=5)
Unobtainable (n=130)	70% (n=87)	70% (n=43)

Source: F. Smith, Statistical Reviewer.

Comment: No differences between number of mismatches were apparent between the two treatment groups, although HLA antigens were not obtained in most liver transplant patients.

c) Incidence of CMV disease and tissue-invasive CMV disease by country and center.

Table 11. Incidence of CMV disease in liver transplant patients, by country (Endpoint Committee, six month results)

Country	Ganciclovir (n=59)	Valganciclovir (n=118)
Australia (n=4)	0% (0/1)	0% (0/3)
Canada (n=28)	0% (0/10)	17% (3/18)
France (n=7)	0% (0/2)	0% (0/5)
Great Britain (n=15)	20% (1/5)	0% (0/10)
New Zealand (n=2)	0% (0/0)	0% (0/2)
USA (n=121)	15% (6/41)	24% (19/80)

Breslow-Day test for treatment by country interaction: P =0.09

Table 12. Incidence of tissue-invasive CMV disease in liver transplant patients by country (Endpoint Committee, six month results).

Country	Ganciclovir (n=59)	Valganciclovir (n=118)
Australia (n=4)	0% (0/1)	0% (0/3)
Canada (n=28)	0% (0 / 10)	17% (3/18)
France (n=7)	0% (0/2)	0% (0/5)
Great Britain (n=15)	20% (1/5)	0% (0/10)
New Zealand (n=2)	0% (0/0)	0% (0/2)
USA (n=121)	2% (1/41)	16% (13/80)

Breslow-Day test for treatment by country interaction: P =0.01

Table 13. Incidence of tissue-invasive CMV disease in liver transplant patients by center (Endpoint Committee, six month results).

US liver transplant patients

Center	Ganciclovir (n=41)	Valganciclovir (n=80)
26452 (n=19)	14% (1/7)	17% (2/12)
26453 (n=4)	0% (0/1)	33% (1/3)
26454 (n=1)	0% (0/0)	0% (0/1)
26455 (n=9)	0% (0/3)	33% (2 / 6)
26458 (n=7)	0% (0/2)	20% (1/5)
26460 (n=2)	0% (0 / 1)	100% (1/1)
26461 (n=3)	0% (0/1)	0% (0/2)
26464 (n=9)	0% (0/3)	0% (0/6)
26466 (n=1)	0% (0/0)	0% (0/1)
26471 (n=1)	0% (0/1)	0% (0/0)
26473 (n=3)	0% (0/1)	0% (0/2)
26476 (n=3)	0% (0/1)	0% (0/2)
26492 (n=7)	0% (0/3)	75% (3/4)
26493 (n=4)	0% (0/1)	33% (1/3)
26495(n=17)	0% (0/6)	0% (0/11)
26496 (n=1)	0% (0/0)	0% (0/1)
26783 (n=4)	0% (/2)	50% (1/2)
26784 (n=2)	0% (0/1)	0% (0/1)
26785 (n=2)	0% (0/0)	0% (0/2)
26786 (n=3)	0% (0/1)	0% (0/2)
26788 (n=6)	0% (0/2)	0% (0/4)
26789 (n=1)	0% (0/0)	0% (0/1)
26790 (n=12)	0% (0/4)	13% (1/7)

Breslow-Day test for treatment by center interaction: p=0.75

Canadian liver transplant patients

Center	Ganciclovir (n =10)	Valganciclovir (n =18)
25966 (n=12)	0% (0/4)	25% (2 / 8)
25967 (n=1)	0% (0 / 0)	0% (0/1)
25968 (n=2)	0% (0/1)	0% (0/1)
25969 (n=10)	0% (0/4)	17% (1/6)
25970 (n=3)	0% (0/1)	0% (0/2)

Breslow-Day test for treatment by center interaction not computed: data are too sparse.

Comment: All but one of the cases with CMV disease in liver transplant patients were

diagnosed in North America. Within the United States and Canada, there were no statistically significant treatment effects by center interactions.

d) Immunosuppression

Neutropenia can lead to increased risk of CMV infection. Neutropenia could also be the result of CMV infection or an adverse event of study drugs.

Table 14. Association between CMV Disease up to 6 months post-transplant and neutropenia in liver transplant patients (ITT population)

	Neutropenia (n=15)	No Neutropenia (n=161)
CMV Disease: Endpoint Committee (n=29)	13% (2/15)	17% (27/161)

Table 15. Association between tissue-invasive CMV disease up to 6 months post-transplant and neutropenia in liver transplant patients (ITT population)

	Neutropenia (n=15)	No Neutropenia (n=161)
Tissue-Invasive CMV Disease: Endpoint Committee (n=18)	6% (1/15)	11% (17/161)

Source: F. Smith, Statistical Reviewer.

Comment: There appears to be no association between the incidence of CMV disease or tissue-invasive CMV disease and neutropenia.

Acute graft rejection is associated with increased immunosuppression and therefore increased risk of acquiring CMV infection. It is also true that CMV infection, particularly tissue-invasive CMV disease, can lead to acute graft rejection. The results of any association between these two entities are shown in Table 16.

Table16: Summary of acute graft rejection up to six months post-transplant

Organ	Ganciclovir	Valganciclovir
All Patients	36% (45 / 125)	30% (71 / 239)
Heart (n=56)	71% (15 / 21)	57% (20 / 35)
Liver (n=177)	36% (21 / 59)	27% (32 / 118)
Kidney (n=120)	23% (9 / 39)	21% (17 / 81)
Kidney/Pancreas (n=11)	0% (0 / 6)	40% (2 / 5)

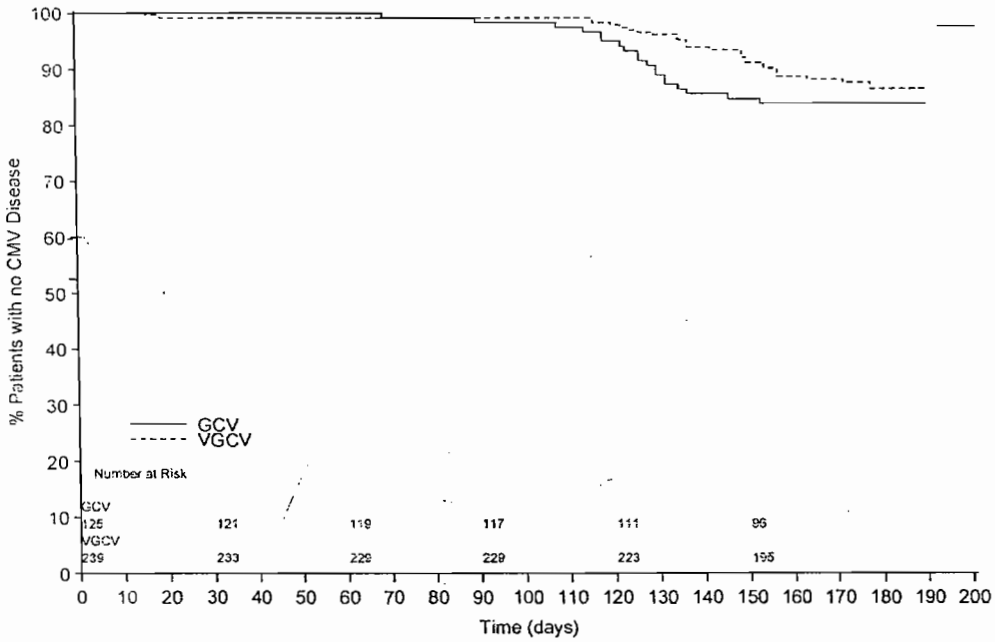
Comment: No association between the incidence of acute graft rejection and CMV disease was apparent. The incidence of acute graft rejection appeared to be at least as high or higher in oral ganciclovir patients than in valganciclovir patients in the three major organ transplant groups.

Immunosuppression: The two treatment arms in the liver allograft recipient group appeared to be relatively well balanced, although data on the exact dosing were not available. Several immunosuppressive regimens were used during the study. The most common immunosuppressive regimen on day 100 post-transplant was the combination of prednisolone and tacrolimus (35.6% ganciclovir, 38.1% valganciclovir). A slightly higher proportion of patients in the valganciclovir arm was receiving a triple therapy of mycophenolate mofetil, tacrolimus and prednisolone at day 100 post-transplant, but this difference was not statistically significant (22.0% ganciclovir, 27.1% valganciclovir).

4. Secondary endpoints

a) Time to CMV disease up to six months post-transplant. The time to first incidence of CMV disease through six months post-transplant as assessed by the endpoint committee (ITT population) is summarized in Fig 1.

Fig. 1. Time to CMV disease (days) up to six months post-transplant - Endpoint Committee (ITT population)



Source:CSR Vol 7- P. 58.

Similar trends were apparent for time to CMV disease. Valganciclovir appeared to have a lower incidence of CMV disease than oral ganciclovir. However these differences were not apparent until >100 days post-transplant, when patients were off treatment.

Comment: The majority of cases of CMV disease occurred after the end of treatment. Overall, the findings were comparable between the two arms.

b) Incidence and time to treatment failure (Table 17 and Figure 2).

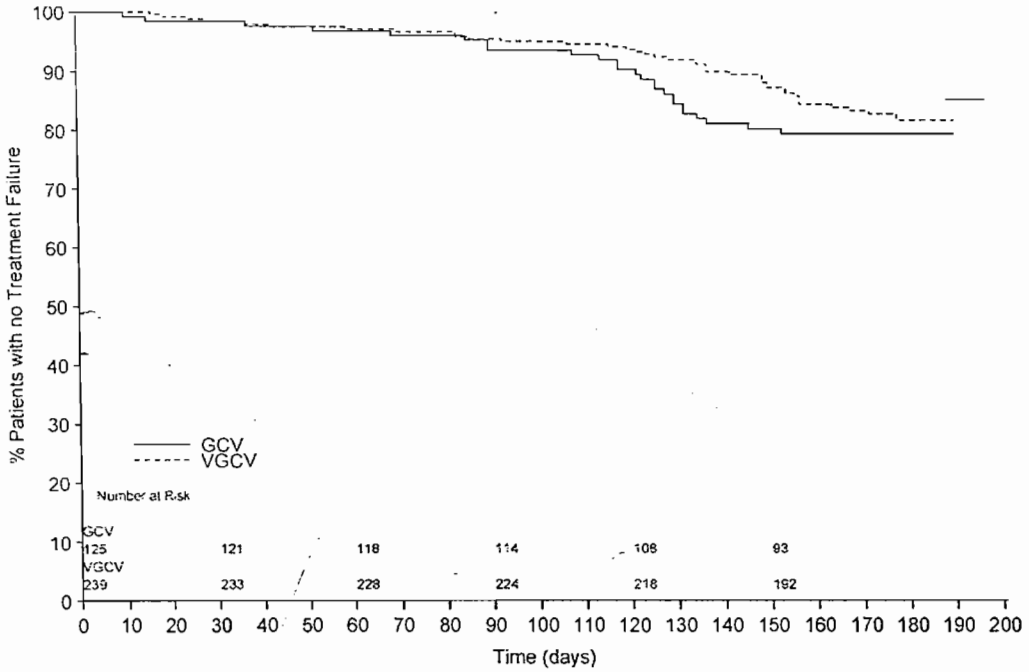
Table 17. Summary of treatment failure up to 6 months post-transplant (Endpoint Committee, ITT population).

	GCV N=125	VGCV N=239	WEIGHTED DIFFERENCE IN PROPORTIONS (95% CI)
Treatment failure			
Patients with treatment failure	25 (20%)	41 (17.2%)	0.035 (-0.053, 0.122)
Patients with no treatment failure	96 (76.8%)	193 (80.8%)	
Patients unevaluable	4 (3.2%)	5 (2.1%)	
Reason for treatment failure			
CMV disease (Endpoint Committee)	19 (15.2%)	29 (12.1%)	
Death	2 (1.6%)	9 (3.8%)	
Discontinuation due to drug-related AE	4 (3.2%)	6 (2.5%)	

Source: CSR Vol. 7 - P. 62
Notes: If a patient has insufficient visits up to 6 months he was considered "Unevaluable" unless the patient had treatment failure
Treatment failure was defined as CMV disease, death, or discontinuation of study drug due to drug related adverse events
If a patient had CMV disease, discontinued from study drug due to drug-related AE and then died, the event was counted only once in the row 'Treatment Failure'. The patient was counted in all three rows,'CMV Disease','Death' and 'Discon. due to a drug-related AE.'

Comment: The incidence of treatment failure (defined as development of CMV disease, death, or discontinuation of treatment with study drug because of a drug-related adverse event) up to 6 months post-transplant was comparable between the two arms (20% ganciclovir, 17.2% valganciclovir). CMV disease was the most common reason for discontinuation.

Fig. 2. Time to treatment failure (days) up to 6 months post-transplant (Endpoint Committee, ITT population).



Source:CSR Vol 7-P. 63.

Comment: Although the treatment failure up to 6 months post-transplant during the post-treatment phase was comparable between the two arms, time to treatment failure appeared shorter on the ganciclovir arm (there were insufficient number of events to calculate a median time to treatment failure on either arm of the study).

c) Acute graft rejection at six months post-transplant. No association between the incidence of acute graft rejection and CMV disease was apparent. The incidence of acute graft rejection appeared to be at least as high or higher in oral ganciclovir patients than in valganciclovir patients in the three major organ transplant groups (please see Table 16).

d) Patient survival at six months post-transplant. A total of 11 patients died through six months post-transplant. Nine of 244 (3.7%) in the valganciclovir group and 2 of 126 (1.6%) in the ganciclovir group. Seven of the 11 patients died while on treatment (2 on the ganciclovir arm, 5 on the valganciclovir arm). All deaths were considered by the investigators not to be related to study drugs. The 2 ganciclovir deaths occurred in liver transplant patients, while 7/9 of the valganciclovir deaths occurred in liver transplant patients. The remaining 2 deaths occurred in heart transplant patients. A detailed description of deaths up to 6 months post-transplant is presented in the section of "Safety Analysis" (Table 23).

e) Opportunistic infections. The incidence of opportunistic infections up to six months post-

transplant was comparable between the two treatment groups (9.6% ganciclovir, 9.2% valganciclovir). There was no difference between the two treatment groups in the incidence of the various opportunistic infections analyzed.

D. Efficacy Conclusions

In this double-blind, double-dummy, active comparator study including 372 heart, liver, kidney, and kidney-pancreas transplant patients the incidence of CMV disease (CMV syndrome or tissue-invasive CMV disease) between the valganciclovir and the oral ganciclovir arm was similar (12.1% versus 15.2%). However, although the overall treatment effect was similar between the two treatment groups, the relative treatment effect between the two arms differed by organ transplant type (*P* value =0.036) and by outcomes. In liver transplant patients, the largest group of patients in this study, the incidence of tissue-invasive CMV disease was five times higher in the valganciclovir group compared with the incidence observed in the ganciclovir group. Although this difference was concerning, the study was neither powered nor designed to detect statistical significance in this subgroup analysis. With regards to kidney transplant patients, valganciclovir performed better than ganciclovir in preventing CMV disease. Valganciclovir was also favored in heart and kidney-pancreas patients.

The absence of a clear explanation for the higher incidence of tissue-invasive CMV disease in liver transplant allograft recipients who received valganciclovir

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

During study PV16000, no new or unexpected adverse events were identified with the use of valganciclovir. Overall, the proportion of patients with any serious adverse event appeared to be higher for the valganciclovir-treated patients (50%) than for ganciclovir-treated patients (41%). Similarly, the percentage of valganciclovir-treated patients with any drug-related serious adverse events (7%) was slightly higher than that for ganciclovir-treated patients (5%); however, these differences were not statistically significant. The most serious laboratory toxicities observed in study PV16000 were granulocytopenia, thrombocytopenia, and anemia; these drug-related adverse events are already described in the valganciclovir label. The percentages of patients withdrawn from the study due to adverse events were similar between treatment arms (5% in each arm).

A total of 7 patients died while on treatment (2 on the ganciclovir arm, 5 on the valganciclovir arm). Mortality at 6 months was 3.7 % (9/244) in the ganciclovir

group and 1.6% (2/126) in the ganciclovir group. All deaths were considered by the investigators not related to study drugs.

B. Description of Patient Exposure

Three hundred seventy two (372) patients were enrolled in study PV16000 (ganciclovir 127; valganciclovir 245). The duration of drug exposure for each patient enrolled in the study is shown in Table 2. Two patients (one in each arm) did not receive any dose of study drug. The mean duration of treatment was about 90 days in each treatment arm. Approximately 80% of patients in each treatment arm received study drug between 91 – 100 days (median duration 97 days).

C. Methods and Specific Findings of Safety Review

The safety population included patients who received at least one dose of study drug and who had at least one safety assessment.

1. Adverse events and serious adverse events.

An overall summary of adverse events that occurred between the first day through the end of study treatment plus 28 days (defined as "on treatment") is shown in Table 18.

Table 18. Overall summary of adverse events occurring on treatment (safety population)

Up to end of study treatment plus 28 days	VGCV N=244	GCV N=126
Any AE	243 (99.6%)	125 (99.2%)
Any drug related A E	99 (40.6%)	43 (34.1%)
Any serious AE	123 (50.4%)	51 (40.5%)
Any drug related serious AE	17 (7.0%)	6 (4.8%)
Withdrawal from study drug due to any AE	12 (4.9%)	7 (5.6%)
Withdrawal from study drug due to any drug related AE	6 (2.5%)	4 (3.2%)
Deaths (all causes)	5 (2.0%)	2 (1.6%)

Source: CSR Vol. 7 - P. 85

Comment: As expected, given the serious underlying medical condition of the study population, almost all patients experienced at least one adverse event. The proportion of patients experiencing any serious adverse event was higher in the valganciclovir arm (50%) than for the ganciclovir arm (41%). Similarly, the proportion of patients experiencing serious adverse events related to study drugs

was higher in the valganciclovir arm (valganciclovir arm 7%, ganciclovir arm 5%).

Table 19 displays all adverse events, which occurred up to 6 months post-transplant, by decreasing frequency.

Table 19. Abbreviated summary of all adverse events occurring up to six months post-transplant by decreasing frequency (safety population)

Adverse Event	GCV N = 126 No. (%)	VGCV N = 244 No. (%)
DIARRHOEA NOS	38 (30.2)	77 (31.6)
GRAFT REJECTION	40 (31.7)	65 (26.6)
TREMOR NOS	32 (25.4)	68 (27.9)
HEADACHE NOS	35 (27.8)	57 (23.4)
NAUSEA	30 (23.8)	56 (23.0)
OEDEMA LOWER LIMB	24 (19.0)	51 (20.9)
CONSTIPATION	25 (19.8)	49 (20.1)
INSOMNIA	21 (16.7)	49 (20.1)
BACK PAIN	20 (15.9)	49 (20.1)
HYPERTENSION NOS	21 (16.7)	45 (18.4)
VOMITING NOS	19 (15.1)	41 (16.8)
PYREXIA	19 (15.1)	39 (16.0)
ABDOMINAL PAIN NOS	19 (15.1)	37 (15.2)
FATIGUE	20 (15.9)	35 (14.3)
HYPERKALAEMIA	19 (15.1)	34 (13.9)
ANAEMIA NOS	19 (15.1)	32 (13.1)
POST-OPERATIVE PAIN	11 (8.7)	35 (14.3)
DYSPNOEA	14 (11.1)	29 (11.9)
LEUCOPENIA NOS	9 (7.1)	34 (13.9)
DYSPEPSIA	13 (10.3)	29 (11.9)
BLOOD CREATININE INCREASED	17 (13.5)	24 (9.8)
POST-OPERATIVE COMPLICATIONS NOS	10 (7.9)	31 (12.7)
HEPATIC FUNCTION ABNORMAL NOS	14 (11.1)	25 (10.2)
OEDEMA NOS	11 (8.7%)	28 (11.5)
URINARY TRACT INFECTION NOS	12 (9.5)	26 (10.7)
DIZZINESS (EXC VERTIGO)	8 (6.3)	25 (10.2)
POST-OPERATIVE WOUND INFECTION	7 (5.6)	26 (10.7)
RENAL IMPAIRMENT NOS	15 (11.9)	18 (7.4)
ABDOMINAL PAIN UPPER	9 (7.1)	23 (9.4)
ASCITES	9 (7.1)	23 (9.4)
HYPOMAGNESAEMIA	11 (8.7)	21 (8.6)

Table 19 (continued): Abbreviated summary of all adverse events occurring up to six months post-transplant by decreasing frequency (safety population)

Adverse Event	GCV N = 126 No. (%)	VGCV N = 244 No. (%)
UPPER RESPIRATORY TRACT INFECTION NOS	9 (7.1)	22 (9.0)
HYPOKALAEMIA	10 (7.9)	19 (7.8)
HYPOPHOSPHATAEMIA	7 (5.6)	22 (9.0)
MUSCLE CRAMPS	15 (11.9)	14 (5.7)
ARTHRALGIA	10 (7.9)	18 (7.4)
DEPRESSION NOS	9 (7.1)	18 (7.4)
DYSURIA	8 (6.3)	19 (7.8)
PLEURAL EFFUSION	10 (7.9)	17 (7.0)
COUGH	10 (7.9)	16 (6.6)
HYPERTENSION AGGRAVATED	6 (4.8)	19 (7.8)
PRURITUS	6 (4.8)	19 (7.8)
WOUND DRAINAGE INCREASED	11 (8.7)	14 (5.7)
ABDOMINAL DISTENSION	9 (7.1)	15 (6.1)
NEUTROPENIA	4 (3.2)	20 (8.2)

Source: :CSR Vol. 7 - P. 86
Multiple occurrences of the same adverse event in one individual counted only once.
Laboratory adverse events are those reported by the investigators.

Comment: Compared to ganciclovir patients, the incidence of leucopenia, neutropenia, post-operative pain, post-operative complications, oedema, post-operative wound infections, dizziness, hypophosphataemia, aggravated hypertension and pruritus appeared to be higher in valganciclovir-treated patients. On the other hand, the incidence of graft rejection, renal impairment, muscle cramps and increased creatinine levels appeared to be higher in the ganciclovir group.

Eight percent (8%, 20/244) of the valganciclovir-treated patients had neutropenia compared with only 3% (4/126) of the oral ganciclovir-treated patients. The incidence of leucopenia in the valganciclovir arm (14%, 34/244) was nearly double the incidence of leucopenia NOS (34/244=14%) observed in the ganciclovir arm (7%, 9/126).

Table 20: Abbreviated summary of all Serious adverse events occurring on treatment by decreasing frequency (safety population)

Adverse Event	GCV N = 126 No. (%)	VGCV N = 244 No. (%)
GRAFT REJECTION	9 (7.1)	14 (5.7)
HEPATIC FUNCTION ABNORMAL NOS	3 (2.4)	8 (3.3)
BLOOD CREATININE INCREASED	3 (2.4)	6 (2.5)
NEUTROPENIA	1 (0.8)	8 (3.3)
PNEUMONIA NOS	0	8 (3.3)
URINARY TRACT INFECTION NOS	3 (2 .4)	5 (2.0)
DEHYDRATION	1 (0.8)	6 (2.5)
PYREXIA	3 (2.4)	4 (1.6)
VENOUS THROMBOSIS DEEP (LIMBS)	2 (1.6)	5 (2.0)
CHOLANGITIS NOS	2 (1.6)	4 (1.6)
CYST NOS	2 (1.6)	4 (1.6)
ASCITES	2 (1.6)	3 (1.2)
HEPATIC ARTERY THROMBOSIS	1 (0.8)	4 (1.6)
POST-OPERATIVE COMPLICATIONS NOS	1 (0.8)	4 (1.6)
POST-OPERATIVE WOUND INFECTION	1 (0.8)	4 (1.6)
VOMITING NOS	0	5 (2.0)
BILIARY TRACT DISORDER NOS	0	4 (1.6)
WOUND DEHISCENCE	3 (2.4)	1 (0.4)

Multiple occurrences of the same adverse event in one individual counted only once.

Comment: The pattern of serious adverse events was comparable between the two treatment arms with the exception of neutropenia and pneumonia which were more common in the valganciclovir treated group.

2. Selected laboratory abnormalities occurred on treatment are summarized in Table 21.

Table 21. Selected laboratory abnormalities occurring on treatment (safety population)

	Solid Organ Transplant Patients (PV16000)	
Laboratory Abnormalities	**Oral ganciclovir (N=126) %**	**Valganciclovir (N=244) %**
Neutropenia: ANC/µL		
<500	3	5
500 – <750	2	3
750 – <1000	2	5
Anemia: Hemoglobin g/dL		
<6.5	2	1
6.5 – <8.0	7	5
8.0 – <9.5	25	31
Thrombocytopenia: Platelets/µL		
<25000	2	0
25000 – <50000	3	1
50000 – <100000	21	18
Serum Creatinine: mg/dL		
>2.5	21	14
>1.5 – 2.5	47	45

Comment: Neutropenia appeared to be higher in the valganciclovir group compared with that of ganciclovir group. Thirty one (31) of 244 (13%) patients in the valganciclovir group had neutropenia, whereas 10 of 126 (8%) patients of the ganciclovir group had neutropenia. This difference was not statistically significant and less significant than the one reported in Table 18. (Table 18 summarizes adverse events reported at the discretion of the investigator as to the definition of neutropenia. On the other hand, Table 21 summarizes the actual laboratory findings analyzed in the central laboratory).

3. Withdrawals

Table 22. Summary of patient withdrawals

Reason	GCV N = 127 No. (%)	VGCV N = 245 No. (%)
Total	16 (13)	35 (14)
Safety	8 (6)	16 (7)
- Abnormal Lab Test	0	0
- Adverse Event	6	12
- Death	2	4
Non-Safety	8 (6%)	19 (8%)
- Insufficient Response	2	5
- Violation / Deviation	1	6
- Refused Treatment	5	3
- Other	0	5

Comment: There were no differences between the two treatment groups with respect to withdrawals due to safety reasons.

4. Deaths

Table23. Listing of deaths up to six months post-transplant (all patients)

Treatment/ Organ Transplant	Age(Yrs)/ Sex	Wt (Kg)	Race	Cause of Death	Last Trt Day	Day of Death	Autopsy
GCV/Liver	52/M	75	C	SEPTICAEMIA NOS	10	11	YES
GCV/Liver	59/M	106	C	SEPSIS NOS	1	28	NO
VGCV/Liver	47/F	72	C	PNEUMONITIS NOS	99	178	NO
VGCV/Liver	49/F	90	C	CARDIAC FAILURE CONGESTIVE	39	39	YES
VGCV/Heart	50/M	78	C	PULMONARY OEDEMA	19	19	YES
VGCV/Liver	25/M	52	C	THROMBOSIS NOS	76	76	YES
VGCV/Liver	45/M	86	C	RENAL FAILURE CHRONIC	12	162	NO
VGCV/Heart	37/F	73	C	CARDIAC ARREST	91	97	NO
VGCV/Liver	54/M	82	C	CARDIAC ARREST	31	33	NO
VGCV/Liver	58/M	78	C	CEREBRAL INFARCTION	96	151	NO
VGCV/Liver	49/M	119	C	HEPATIC FAILURE	97	164	NO

Source: CSR Vol. 7 - P. 101
Abbreviation: C, caucasian

Comment: A total of 11 patients died through six months post-transplant. Nine of 244 (3.7%) in the valganciclovir group and 2 of 126 (1.6%) in the ganciclovir group. Seven of the 11 patients died while on treatment (2 on the ganciclovir arm, 5 on the valganciclovir arm). All deaths were considered by the investigators not to be related to study drugs. The 2 ganciclovir deaths occurred in liver transplant patients, while 7/9 of the valganciclovir deaths occurred in liver transplant patients. The remaining 2 deaths occurred in heart transplant patients.

D. Adequacy of Safety Testing

Safety monitoring performed during this study was considered adequate.

E. Summary of Critical Safety Findings and Limitations of Data

In summary, the safety profile of valganciclovir was consistent with that reflected in the current product label. The overall adverse event profile up to six months post-transplant was comparable between the two arms of the study (valganciclovir versus ganciclovir). We should point out the difference in mortality rates even

though it was not statistically significant. A total of 11 patients died up to 6 months post-transplant. Two of them belonged to the ganciclovir group and the remaining 9 to the valganciclovir group. As mentioned earlier, neutropenia, thrombocytopenia, and anemia were the most serious laboratory abnormalities potentially related to study drugs.

VIII. Dosing, Regimen, and Administration Issues

Dosing was evaluated during the original NDA review. In study WP15711, it was shown that in liver transplant patients a 900 mg dose of oral valganciclovir provides comparable results to the 5 mg/Kg i.v. dose of ganciclovir.

In the current sNDA submission, the applicant provided the results of a population pharmacokinetic study of ganciclovir in solid organ transplant recipients after oral administration of valganciclovir and ganciclovir. They demonstrated that systemic ganciclovir exposure was ~1.7 times higher after oral administration of 900 mg q.d. valganciclovir compared with oral administration of 1000 mg t.i.d. ganciclovir. Moreover, they demonstrated that systemic ganciclovir exposures were comparable across heart, kidney, and liver transplant patients.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The results of gender analysis are provided in Table 24.

Table 24. Summary of CMV disease up to six months post-transplant – Endpoint Committee by gender (ITT population)

Gender	Ganciclovir (n=125)	Valganciclovir (n=239)	2-sided 95% CI[+]	*P*-value	Treatment Favored	Conclusion
Female (n=97)	19% (6/32)	20% (13/65)	-0.18, +0.15	0.86	Ganciclovir	
Male (n=267)	14% (13/93)	9% (16/174)	-0.03, +0.14	0.29	Valganciclovir	Noninferiority[+]

+Noninferiority is demonstrated for Valganciclovir if the lower bound of the 95% CI is >-0.05
Breslow-Day test of treatment by gender interaction: P =0.41

Comment: Clearly, valganciclovir was noninferior to ganciclovir in males. Since the treatment effect by gender interaction was not statistically significant (P =0.41), there was insufficient evidence to conclude that valganciclovir treatment effect

differs between males and females.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

The results of analysis by race and age are shown in Tables 25 and 26, respectively.

Table 25. Summary of CMV disease up to six months post-transplant – Endpoint Committee by race (ITT population)

Race	CMV disease		2-sided 95% CI+	*P*-value	Treatment Favored	Conclusion
	Ganciclovir (n=125)	Valganciclovir (n=239)				
Caucasians (n=325)	17% (19/113)	12% (25/212)	-0.03, +0.14	0.19	Valganciclovir	Noninferiority+
Others (n=39)	0% (0/12)	15% (4/27)	-0.40, +0.06	0.16	Ganciclovir	

+Noninferiority is demonstrated for Valganciclovir if the lower bound of the 95% CI is >-0.05
Breslow-Day test of treatment by race interaction: P =0.10

Comment: Valganciclovir was clearly noninferior to ganciclovir in Caucasians. The number of non-Caucasians was not large enough to allow us to reach any conclusions about the treatment effect of valganciclovir in other races.

Table ~~2~~6. Summary of CMV disease up to six months post-transplant – Endpoint Committee by age (ITT population)

Age (years)	CMV disease		2-sided 95% CI+	*P*-value	Treatment - Favored	Conclusion
	Ganciclovir (n=125)	Valganciclovir (n=239)				
≤50 (n=221)	14% (11 / 78)	10% (15 / 143)	-0.06, +0.13	0.47	Valganciclovir	
>50 (n=143)	17% (8 / 47)	15% (14 / 96)	-0.10, +0.17	0.64	Valganciclovir	

Breslow-Day test of treatment by race interaction: P =0.81

Comment: There was no evidence of a treatment effect by age interaction, so it can be assumed that valganciclovir treatment effects are consistent in younger and older patients. However, it should be pointed out that the applicant did not include

sufficient number of patients over the age of 65 to conclude if this patient population has a different safety or efficacy profile.

C. Evaluation of Pediatric Program

[ ]

D. Comments on Data Available or Needed in Other Populations

Study PV16000 did not include sufficient number of patients over 65 years of age. It is therefore difficult to conclude on the efficacy and safety of valganciclovir in this group of patients. The study was also conducted in a predominantly Caucasian male patients.

X. Conclusions and Recommendations

A. Conclusions

In this submission, the applicant sought approval of valganciclovir for the prevention of CMV disease (CMV syndrome and tissue-invasive CMV disease) in [redacted] he proportion of patients who developed CMV disease during the first six months post-transplant (primary endpoint) was similar between the valganciclovir arm (12.1%) and the oral ganciclovir arm (15.2%). Based on these findings the applicant concluded that valganciclovir was non-inferior to oral ganciclovir for the prevention of CMV disease in solid organ transplant recipients. However, this hypothesis is based on the assumption of consistency of the primary endpoint across all organ types which was not the case in this study. Analyses by organ transplant group by specific outcomes (CMV syndrome and tissue-invasive CMV disease) revealed significant differences.

In kidney transplant patients, valganciclovir performed better than was oral ganciclovir in preventing CMV disease. Valganciclovir was also favored in heart and kidney-pancreas transplant patients. [redacted]

[redacted] This difference was of concern even though the study was neither powered nor designed to detect statistical significance in this subgroup analysis. It is therefore evident that using the overall

rates would give the misleading impression that valganciclovir is non-inferior to oral ganciclovir in all solid organ transplant recipients, including liver transplant patients.

No new or unexpected adverse events were identified with the use of valganciclovir. The overall adverse event profile up to six months post-transplant was comparable between the two arms of the study (valganciclovir versus ganciclovir). The most serious adverse events observed in study PV16000 were granulocytopenia, thrombocytopenia, and anemia; these drug-related adverse events are already described in the valganciclovir label. A total of 7 patients died while on treatment (2 on the ganciclovir arm, 5 on the valganciclovir arm. Mortality at 6 months was 3.7 % (9/244) in the ganciclovir group and 1.6% (2/126) in the ganciclovir group. All deaths were considered by the investigators not related to study drugs.

B. Recommendations

Based on the efficacy and safety analyses of study PV16000, valganciclovir for the prevention of CMV disease in heart, kidney, and kidney-pancreas transplant patients at high risk (D+/R-) is recommended for approval.

[redacted]

Andreas Pikis, M.D.
Medical Reviewer

Concurrences:
HFD-530/MO/Haverkos
HFD530/DivDir/Birnkrant

CC:
HFD530/DepDir/Murray
HFD725/Stats/Smith
HFD530/Micro/Biswal
HFD530/Biopharm/Zheng
HFD530/Pharm/Farrelly
HFD590/TL/Cavaille-Colle
HFD590/MO/Hernandez

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Andreas Pikis
9/12/03 05:41:18 PM
MEDICAL OFFICER

Medical Officer's Review of NDA 21-304/S-001

Harry Haverkos
9/12/03 05:44:50 PM
MEDICAL OFFICER

Debra Birnkrant
9/12/03 05:53:20 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-304 / S-001

CHEMISTRY REVIEW(S)

SUPPLEMENTAL NDA CHEMIST'S REVIEW	DUE DATE 9/12/03	1. ORGANIZATION HFD-530	2. NDA NUMBER 21-304

3. NAME AND ADDRESS OF APPLICANT
Hoffmann-La Roche, Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199
Attn: Melanie Bishop, Program Director
Tel: (973) 562-2764, Fax: (973) 562-3700

4. TYPE OF SUPPLEMENT
Efficacy supplement

5. DOCUMENT(S)

NUMBERS	DATED	RECEIVED
SEI-001	11/11/02	11/12/02

6. NAME OF DRUG
VALCYTE™

7. NONPROPRIETARY NAME
Valganciclovir Hydrochloride (Ro 107-9070)

8. SUPPLEMENT PROVIDES FOR:
VALCYTE™ tablet for the prevention of CMV disease in [redacted]

9. AMENDMENTS/DATES
N/A

10. PHARMACOLOGICAL CATEGORY
Anti-HIV

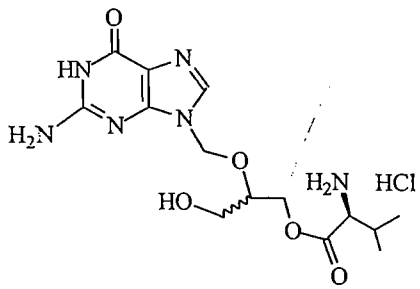
11. HOW DISPENSED
|X| Rx | | OTC

12. RELATED IND/NDA/DMF(s)
N/A

13. DOSAGE FORM(S)
Tablet

14. POTENCY (CIES)
450 mg

15. CHEMICAL NAME AND STRUCTURE
L-Valine, 2-[(amino-1,6-dihydro-6-oxo-9H-purin-9-yl) -methoxy]-3-hydroxypropyl ester, monohydrochloride



16. MEMORANDA
N/A

17. COMMENTS
This efficacy supplement provides VALCYTE™ tablet for the prevention of CMV disease in [redacted] patients at risk. There are no CMC changes provided in this supplement. However, a categorical exclusion from the requirements to prepare an environmental assessment in accordance with 21 CFR 25.31(b) is claimed. Although the use of the active moiety is expected to increase upon approval of this supplemental NDA, the estimated concentration of the substance at the point of enter into the aquatic environment will be below [redacted] The firm also claims that no extraordinary circumstances exist that would significantly affect the quality of the human environment as a result of the proposed action.

18. CONCLUSIONS AND RECOMMENDATIONS
The request for a categorical exclusion from the requirements to prepare an environmental assessment is reasonable. There are no other CMC changes. Therefore, this supplement is recommended for approval from a CMC perspective.

19. REVIEWER

NAME	SIGNATURE	DATE OF DRAFT REVIEW
Zi-Qiang Gu, Ph.D.	*[signed electronically in DFS]*	8/27/03

20. CONCURRENCE: HFD-530/SMiller *[signed electronically in DFS]*

DFS CC LIST								
L = Action Letter	R	L	ZGu		L	Med:		PharmTox
R = Review	R	L	SMiller	R	L	PM: NPatel		Micro
	R	L	CChen			Biopharm		

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Zi-Qiang Gu
8/28/03 02:51:52 PM
CHEMIST

Stephen Paul Miller
9/2/03 03:27:12 PM
CHEMIST

CLAIM FOR CATEGORICAL EXCLUSION FROM THE ENVIRONMENTAL ASSESSMENT REQUIREMENT FOR VALCYTE™ (Valganciclovir hydrochloride) TABLETS (450 mg) SUPPLEMENTAL NEW DRUG APPLICATION

Hoffmann-La Roche Incorporated claims a categorical exclusion from the requirement to prepare an environmental assessment in accordance with 21 CFR 25.31(b). The proposed action, approval of a supplemental NDA, will increase the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion. No extraordinary circumstances exist that would significantly affect the quality of the human environment as a result of the proposed action.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-304 / S-001

PHARMACOLOGY REVIEW

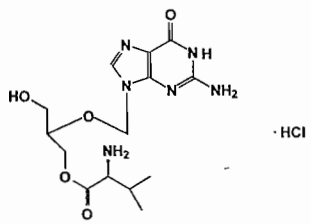
PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 21-304
Sequence number/date/type of submission: SEI-001
Information to sponsor: Yes ( ) No (x)
Sponsor and/or agent:Hoffmann-La Roche
Drug manufacturer: Roche Global Development

Reviewer name: James G. Farrelly
Division name: DAVDP
HFD #: 530
Modified review completion date: 9/2/03

Drug:

Trade name: Valcyte™
Established name: Valgancyclovir HCl
Code name: Ro 107-9070
Chemical name: L-Valine, ester with 9-[[2-hydroxy-1-(hydroxymethyl)-ethoxy]methyl]guanine, monohydrochloride
CAS Number: 175865-59-5 (hydrochloride)
Molecular formula/molecular weight: 390.83
Structure:



Relevant INDs/NDAs: IND 66,429/21-304

Drug class: Prodrug of a nucleoside analog

Indication: Prevention of cytomegalovirus (CMV) disease [redacted] patients at risk

Clinical formulation: Tablet

Route of administration: Oral

Executive Summary

Valcyte is a drug approved for the treatment of CMV retinitis in patients with acquired immunodeficiency syndrome (AIDS). The present supplemental NDA is for the prevention of CMV disease in [redacted] patients at risk. No new pharmacology/toxicology data were submitted with this NDA. There were minor

proposed labeling changes in the pharmacology/toxicology sections of the label to use exposure data rather than nominal dose to relate exposures in animals to that in patients. There are no pharmacology/toxicology issues with this NDA.

Reviewer signature: _____

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/s/

James Farrelly
9/2/03 08:59:12 AM
PHARMACOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-304 / S-001

MICROBIOLOGY REVIEW

MICROBIOLOGY REVIEW
DIVISION OF ANTIVIRAL DRUG PRODUCTS (HFD-530)

NDA 21-304 SE1- 001 **REVIEW DATE: 8/15/2003**

Reviewer: N. Biswal

Date Submitted: 11/11/2002
Date Received: 11/11/2002
Date Assigned: 11/18/2002

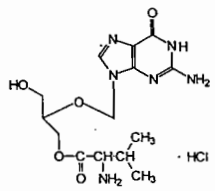
Sponsor: Syntex (USA) LLC.
3401 Hillview Av
Palo Alto, CA 94304

Product Names:

Code Names: VALCYTE™, Valganciclovir hydrochloride, Ro-107-9070/194

Chemical Name: L-Valine, 2-[(2-amino-1, 6-dihydro-6-oxo-9H-purin-9yl) methoxy]-3-hydroxypropyl ester, monohydrochloride

Structural Formula:



Molecular Formula: $C_{14}H_{22}N_6O_5 \bullet HCl$

Molecular Weight: 390.83

Drug Category: Antiviral

Dosage Form/Route of Administration: 450 mg tablets/Oral

Indication: Prevention of Cytomegalovirus (CMV) Disease in [redacted] transplant Patients at Risk

Supporting Documents: IND 48,106, NDA 25-082, NDA 19-661, NDA 20-460

BACKGROUND: Cytomegalovirus (CMV) infections are now the leading causes of morbidity and mortality in solid organ and bone marrow transplant recipients. Transmission and development of CMV disease in such patients is greatly influenced by the patient's immunology and prior history of exposure/infection generally following three recognized patterns: 1) primary infection, 2) reactivated (from latency) infection, and 3) superinfection. Primary infection (as determined by seroconversion) occurs in nearly 100% of CMV negative recipients of CMV positive organs (D+/R-), with symptomatic illnesses occurring in 50 to 70%. Reactivation of latent CMV occurs in approximately 10 to 20% of seropositive recipients. Superinfection is the

infection of a CMV positive recipient by a second strain of CMV of donor origin. Incidence of CMV disease is seen usually twice as often in seropositive recipients of seropositive donor organs (D+/R+) as in seropositive recipients of seronegative organs (D-/R+).

Treatment of ——— transplant (SOT) patients with the FDA approved ganciclovir (GCV) has been effective in reducing the incidence and severity of post transplantation CMV infection among organ-transplant patients at high risk (serology-positive donor or recipient). However, because of the morbidity and mortality associated with CMV infection in transplant patients, it is generally recognized that prevention rather than the treatment of established CMV disease may be a better alternative and should be emphasized. Indeed, antiviral nucleoside analogues such as GCV and to a certain extent, acyclovir (ACV) administered either orally or intravenously have been found to be useful for the prevention of such CMV diseases. However, the long-term use of intravenous (iv) GCV or ACV, has been very impractical in most SOT recipients, and the administration of oral GCV or valaciclovir (VACV), an oral prodrug of ACV, has very inconvenient dosing regimens each requiring three to four times daily intakes over a long period of time. The sponsor has reported that the administration of once daily dosing with 900 mg or 450 mg valganciclovir (VGCV), the oral prodrug of GCV, has been comparable to the plasma concentration of GCV achieved by the administration of 5 mg/kg iv GCV or 3 g oral GCV in HIV infected subjects and liver transplant recipients. With the conviction that "these results represent the possibility of a convenient, oral anti-CMV therapy, which would be highly beneficial for the prevention of CMV disease in SOT recipients," the sponsor has submitted this supplemental new drug application for VGCV for the prevention of CMV disease in SOT patients at risk. A tablet formulation of VGCV has been approved previously for the treatment of CMV retinitis in patients with AIDS, and the sponsor has cross referenced to the original NDA 21-304 for the preclinical information on VGCV.

Valganciclovir

VGCV is a valyl ester prodrug that is rapidly hydrolyzed to GCV and L-valine by intestinal and hepatic esterases after oral administration. Once converted to GCV, the mechanism of antiviral activity is presumed to be the same as has been described for GCV. GCV itself, a nucleoside analog without any intrinsic antiviral activity, must be phosphorylated to an antivirally active triphosphate form in virus-infected cells to inhibit viral DNA replication thus exerting its antiviral activity. In CMV-infected cells, GCV is anabolised to its triphosphate form primarily by 3 enzymes:

1. An unusual protein kinase, UL97 encoded by the CMV *UL97* open reading frame, carries out the critical initial phosphorylation step of GCV to produce GCV-monophosphate.
2. Cellular guanylate kinase phosphorylates the monophosphate to GCV diphosphate.
3. Cellular phospho–glycerate kinase is the principal enzyme to carry out the last phosphorylation to produce the active moiety, GCV-TP. Once phosphorylated, the final antivirally active GCV-TP appears to persist with a half-life >6 to <24 hours in HCMV infected cells.

GCV-TP is both inhibitory to and a substrate for the CMV DNA polymerase, UL54, encoded by the CMV *UL54* open reading frame, thus preferentially (but not exclusively) inhibiting viral DNA synthesis. Experiments have also demonstrated that GCV-TP functions as a competitive inhibitor of the incorporation of deoxyguanosine triphosphate (dGTP) into CMV DNA. GCV-TP is also known to be incorporated into DNA. However, it does not act as an obligate chain

terminator. Incorporation and elongation may occur by virtue of the presence of hydroxyl groups analogous to the natural substrate's 3'- and 5'- hydroxides, thus changing the physico-chemical properties of DNA.

The potency of GCV to inhibit the replication of various laboratory strains or clinical isolates of CMV has been reported to be dependent upon a number of factors including the host cells, virus strain, multiplicity of infection, and assay methods, which are yet to be standardized. Thus, the concentration of GCV that inhibits the replication of human CMV by 50 % (IC_{50}) has ranged significantly from 0.01 μM to 27 μM.

Mutants of CMV resistant to GCV have been isolated from cultured cells *in vitro* as well as from immunocompromised patients undergoing treatment for CMV infection. Serial passage of CMV *in vitro* in the presence of increasing concentrations of GCV has resulted in the emergence of mutants exhibiting IC_{50} values of 10 - fold greater than that of the wild type strain. The current working definition of CMV resistance to GCV is when GCV $IC_{50} \geq 1.5$ μg/ml (≥ 6.0 μM).

As noted earlier, two CMV encoded key enzymes, UL97 and UL54, are recognized thus far to be responsible for the anti-CMV activity by GCV. Therefore, mutations in viral *UL97, UL54*, or both genes are the major mechanisms by which CMV is known to become resistant to GCV. Although the precise mechanism by which a protein kinase UL97 is capable of phosphorylating a nucleoside analog (GCV) is not known, mutations of the *UL97* gene presents the most common (~90%) mechanism for CMV to derive resistance to GCV. The results of various studies demonstrating the GCV mutational hot spots (1 and 2) in the various domains (VIa through XI) of *UL97* and the known amino acid substitutions in UL97 associated with GCV resistance (GCV^r) are compiled in Figure 1. Most of the sites of mutation in the *UL97* gene to date are limited to codons 460, 520, 591-607 and 659 which are currently known to confer resistance to GCV (Lurain et al., 2002, J. Infect Dis 186:760-768).

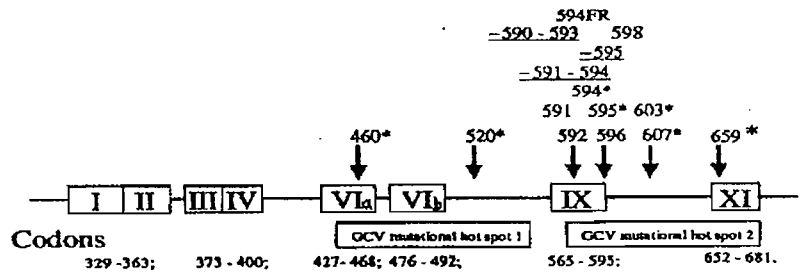


Figure 1. Map of amino acid substitutions in UL97 associated with GCV resistance
Amino acid substitutions in human CMV UL97 associated with reduced sensitivity to GCV are shown relative to conserved regions of the protein. Single amino acid substitutions, frame shift mutations or deletions are shown. Substitutions whose role has been confirmed by marker transfer are denoted *, -, and underlines, denote deletions and FR denotes a frame shift.

Mutations in the *UL54* gene are also responsible for CMV resistance to GCV. Analysis of this viral pol gene has revealed substitutions in the DNA sequence of its conserved regions arising during treatment with GCV and these substitutions have been shown to be associated with GCV^r. A map of the amino acid substitutions in various regions of UL54 associated with GCV^r is reproduced in Fig. 2 below.

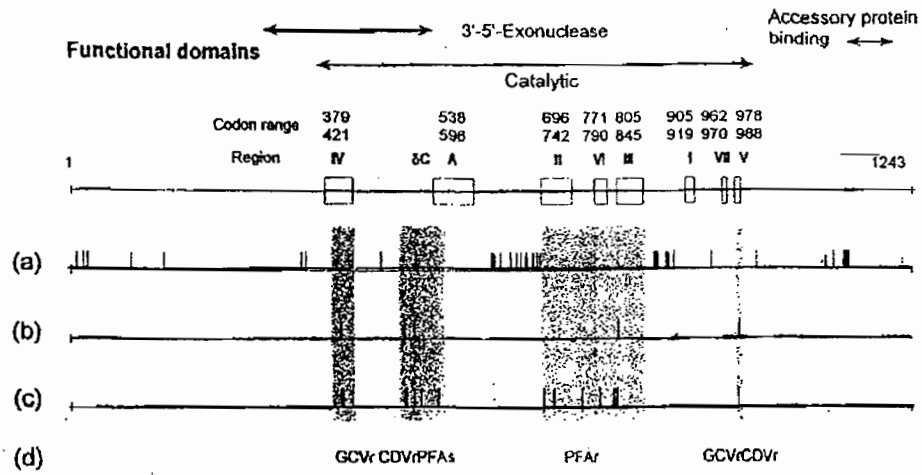


Figure 2. CMV DNA pol mutation map. Shown at top are the conserved functional domains and their codon ranges (boxed). Loci of amino acid changes are mapped below. (a) Codons showing drug sensitive isolates in this study; (b) codons mapped to drug resistance in laboratory strains; (c) codon mapped to drug resistance clinical isolates; (d). drug resistance phenotype associated with drug resistant mutants according to region. Regions known to be associated with drug resistance are shaded. GCV; CDV, cidofovir; PFA, foscarnet (Adapted from Chou et al., 1999, Antimicrob. Agents Chemother. 43:1500-1502).

Analysis of the CMV DNA pol gene coding sequences of clinical isolates thus far have revealed that genotypic assays for resistance may be predominant in the *pol* codon ranges 379 to 421, 492 to 525, 696 to 845, and 978 to 988. However, new mutations in both the *UL54* and *UL97* genes are also being discovered whose clinical and/or biological significance is yet to be elucidated.

CMV strains resistant to GCV have also been isolated from immunocompromised patients who received prolonged courses of the drug. Ordinarily these studies have compared the susceptibilities of the pre- and post-therapy isolates to GCV in cell culture *in vitro.* Incidence of such resistant virus isolates (from the blood or urine of patients, IC_{50} > 6.0 μM) have been observed to be about 11.4% after 6 months of GCV treatment and about 27.5% after 9 months of GCV treatment. However, many clinical investigators have cautioned that the incidence of real GCV resistance may continue to be underestimated as long as the collection and storage of specimens, cell culture and pheontyping methods are not standardized to yield consistently reproducible sensitivity test results from various clinical studies.

A. Clinical Protocol PV16000

PV16000 was a randomized, double-blind, double-dummy, phase III clinical trial designed to determine the comparative efficacy and safety of VGCV versus oral GCV for the prevention of CMV disease in SOT recipients in 57 clinical centers worldwide.

A.1. Objectives of the Clinical Study

The primary objectives of the study were to determine the comparative efficacy and safety of VGCV (900 mg o.d.) relative to oral GCV (1000 mg t.i.d.) when given for the prevention of CMV

disease in high-risk (D+/R-) heart, liver, kidney, and kidney-pancreas allograft recipients.

The secondary objectives included a number of clinical (e.g., the time to CMV disease, the time to treatment failure, incidence of graft rejection, and survival), pharmacokinetic and virologic parameters. The virologic objectives were as follow:

1. Determination of the Incidence of herpesvirus infections (HSV and VZV) and other opportunistic infections.
2. Identification of CMV genotypic changes (e.g., mutation at the UL97 locus) associated with the development of CMV resistance to GCV.

To achieve these objectives, a total of 372 D+/R- recipients of heart (n=56), liver (n=183), kidney (n=120), kidney-pancreas (n=11) or kidney-liver (n=2) were enrolled in this study. There were no lung transplant patients enrolled in this study. Eligibility for enrollment depended upon a number of inclusion and exclusion criteria listed in Table 1.

Table 1. Inclusion and Exclusion Criteria for Study PV16000

Inclusion Criteria	Exclusion Criteria
First heart, liver, kidney, kidney-pancreas, kidney-heart or kidney-liver allograft, or second kidney allograft	History of CMV infection or disease
D+/R- allograft recipients	Received anti-CMV therapy within past 30 days[a]
Age ≥ 13 years	Severe, uncontrolled diarrhea or evidence of malabsorption
Absolute neutrophil count (ANC) > 1000 cells/μL	Simultaneous participation in another study
Platelet count > 25,000 cells/μL	Allergic or other significant adverse reaction to acielovir, ganciclovir or valaciclovir
Hemoglobin > 8 g/dL	Use of prohibited concomitant medications: oral or i.v. acielovir[b], valaciclovir[b], famciclovir[b], cidofovir, oral or i.v. ganciclovir[c], CMV hyperimmune globulin, Foscarnet, Lobucavir, Probenecid
CrCL > 25 mL/min (liver and heart recipients) CrCL > 15 mL/min with improving renal function (kidney and kidney-pancreas recipients)	Previous participation in PV16000
Birth control	Lactating females who intend to continue nursing
Negative pregnancy test	
Able to tolerate oral medication within 10 days post-transplant	
Written informed consent	

[a] except for treatment with acielovir, valaciclovir, or famciclovir for acute herpes simplex or herpes zoster prior to enrollment
[b] except for treatment of acute herpes simplex or herpes zoster
[c] except for up to 4 days if patient unable to tolerate oral medication

As noted in Table 1, all eligible patients must have received within the preceding ten days his/her (1) first heart, liver, kidney, or kidney-pancreas allograft (2) first kidney-heart or kidney-liver allograft, or (3) second kidney allograft. To meet the microbiologic inclusion criteria, these patients must have been evaluated as seronegative for CMV (confirmed within 30 days pre-transplant) and had received an allograft from a CMV seropositive donor. Microbiologic exclusion criteria were defined as follows:

1. A history of, or suspected of having, CMV infection or CMV disease.
2. The patient had received anti-CMV therapy within the previous 30 days (treatment with ACV, VACV, or famciclovir (FCV) for acute herpes simplex or herpes zoster prior to enrollment was not considered to be anti-CMV therapy).

Administration of a number anti-herpes drugs (e.g., ACV, VACV, foscarnet, cidofovir, CMV immunoglobulin), listed in Table 1, were prohibited during the clinical study.

B. Study Procedures

The Clinical Protocol was designed to be executed in four broad phases; the initial screening and randomization phase, the treatment phase (up to post transplant day 100), and two post-treatment follow-up phases lasting up to initial 6 months leading up to 12 months.

B.1. Screening and Randomization

All D+/R- recipients of heart, liver, kidney or kidney-pancreas allografts at each study center who met all the entry criteria (Table 1), and who were able to tolerate oral medication within 10 days after transplantation, were enrolled into the study for a period of 12 months. A summary of the protocol required assessments and procedures during the 12 month study period is provided in Table 2.

Table2. Schedule of Assessments and Procedures

Procedure	Screen	Start Study Drug	Post Transplant Day							Post Transplant Month				Follow-up Post Transplant Month		
			14	28	42	56	70	84	100	4	4.5	5	6[H]	8	10	12
Informed consent	x															
Physical exam	x								x							
Temperature & weight	x	x	x	x	x	x	x	x	x	x		x	x			
Pregnancy test	x[F]															
Medical history & HLA	x															
CMV serology	x[G]															
Study drug		•							•							
For cause CMV virology[A]		•														•
CMV viral load[B]		x	x	x	x	x	x	x	x	x	x	x	x	x		x
Adverse event/Opp Infect.[C]			x	x	x	x	x	x	x	x		x	x	x[C]	x[C]	x[C]
Hematology	x[E]	x	x	x	x	x	x	x	x	x						
Serum chemistries	x[E]	x	x	x[K]	x[K,R]	x	x[K,R]	x[K]	x	x						
Calculate CrCl[D]	x[E]	x[D]	x	x	x	x	x	x								
Urinalysis	x[E]		x						x							
PK assessment[E]			•				•									
Concomitant meds.		x	x	x	x	x	x	x	x	x		x	x			
Record hospital admissions/discharges			x	x	x	x	x	x	x	x		x	x	x	x	x
Ask about CMV disease, rejection, & graft status			x	x	x	x	x	x	x	x		x	x	x	x	x
12-lead electrocardiogram (ECG/EKG)		x[L]		x[M]	x[M]		x[M]	x[M]								

A = If patient was treated for CMV disease, a blood sample was also obtained just prior to onset of treatment and following the end of treatment for CMV disease.
B = Blood samples were assayed for CMV by molecular-based assay at a central laboratory; results were blinded until post-study. If patient was treated for CMV disease, one additional viral load sample was obtained on the last day of treatment.
C = Opp infect = opportunistic infection (OI); all adverse events and OIs were recorded from onset of treatment.
D = For patients with impaired renal function (creatinine clearance < 70 mL/min), serum creatinine was measured at least twice weekly until discharge.

E = Two to 3 blood samples were drawn over a 3-12 hour period on day 28 or 42 and on day 70 or 84.
F = Obtained within 48 h prior to randomization.
G = Obtained prior to transplant.
H = The termination assessment did not occur before month 6 (183 days) post-transplant.
K = Serum creatinine only.
L = 12 lead electrocardiogram was performed in the morning prior to the initiation of study drug (excluding heart transplant recipients).
M = Two ECG/EKGs were performed at just one of the following visits: day 28, day 42, day 70 or day 84.
N = If an ECG/EKG was performed on these days, the serum potassium level was measured within 30 minutes of performing the ECG/EKG.
O = After month 6 post-transplant, only adverse events (either serious or non-serious) considered related to study treatment were to be recorded.

During **the treatment phase** of the study (up to day 100 post-transplant), patients were stratified by allograft type (heart, liver, kidney or kidney-pancreas) and were then randomized 2:1 to receive up to 100 days anti-CMV prophylaxis with either VGCV (900 mg o.d.) tablets or oral GCV (1000 mg t.i.d.) capsules, beginning within 10 days post-transplant. The sponsor has stated that the rationale for VGCV dosage selection was based upon a pharmacokinetic study in liver transplant recipients (Pescovitz M.D. et al., 2000, Antimicrob Agent Chemother. 44:2811-2815), which demonstrated that exposure to GCV comparable to that provided by i.v. GCV (5 mg/kg) and oral GCV (1000 mg t.i.d.) can be provided by 900 mg and 450 mg of VGCV, respectively.

In patients with impaired renal function, the dose of both VGCV and GCV was adjusted according to the reduced renal function based on calculated creatinine clearance (Table 3). If dose modification was required as a result of suspected toxicity related to study drug, the dose of both the tablets and capsules was reduced, since it was not known whether the patient was receiving active VGCV tablets or active GCV capsules.

Table 3. Dose Adjustment for Creatinine Clearance

Creatinine Clearance (mL/min)	Valganciclovir (mg) (450 mg tablets)	Ganciclovir (mg) (250 mg capsules)
≥ 70	2 tablets (900 mg) once daily	4 capsules (1000 mg) t.i.d.
60 - < 70	"	2 capsules (500 mg) t.i.d.
50 - < 60	1 tablet (450 mg) once daily	"
40 - < 50	"	4 capsules (1000 mg) once daily
25 - < 40	1 tablet (450 mg) every other day	"
10 - < 25	1 tablet (450 mg) twice weekly	2 capsules (500 mg) once daily
< 10 or patient on dialysis	**INTERRUPT TREATMENT WITH STUDY DRUG** Treat with i.v. GCV (0.625 mg/kg 3 times per week) or open label oral GCV (500 mg [2 capsules] 3 times per week) following hemodialysis	

After the randomized treatment phase, patients continued on the follow-up phase to be monitored initially up to 6 months, then up to 12 months post transplant period. Patients treated for CMV disease were terminated from the treatment phase of the study, but were followed through to month 12 post-transplant. As elaborated below the clinical and virology efficacy data were collected up to 12 months post-transplant. Pharmacokinetics and safety data were also collected during the treatment phase (up to 4 months post-transplant), with additional follow-up on safety data collected up to 6 and 12 months post-transplant. During the first 6 months post-transplant phase, the proportion of patients who withdrew from the trial treatment,

or from the study, was comparable on the two treatment arms, as was the duration of treatment with study drug, and the duration of the study. A total of 329 patients completed the 12 month study period.

It should be noted that the primary and secondary efficacies, clinical virology, pharmacokinetics, and safety data obtained at 6 months post-transplant timepoint were available for 273 (73%) patients, whilst 99 (27%) patients were still participating in the follow-up phase of the study (between 6-12 months post-transplant) in the 6 Month Clinical Study Report. Once all patients (n=329) had completed the entire study period (or had either died or withdrawn from the study prior to their 12 month study visit), the second 12 Month Clinical Study Report was provided as follow-up data (efficacy, virology and safety) up to 12 months post-transplant, with cross-reference and comparison to the results obtained up to 6 months post-transplant.

C. Efficacy Assessments

Efficacy of the treatment regimens was evaluated on the basis of results obtained through two, clinical and virologic, interrelated assessments.

C.1. Clinical Assessments

Clinical assessment of efficacy was dependent upon both clinical and laboratory evidence of CMV disease, which was defined as symptomatic CMV infection including both CMV syndrome and tissue invasive CMV. The initial diagnosis of CMV disease was made by the physicians at each study center. However, an independent Endpoint Committee of transplantation experts, made the final, retrospective decision regarding the diagnosis of CMV disease.

C.1a. CMV Syndrome was defined as clinical evidence of CMV viremia, accompanied by fever and signs or symptoms of systemic CMV infection as follows.

- Presence of CMV in blood identified by the presence of infectious CMV (shell vial culture), viral protein or viral nucleic acid (FDA-approved DNA/RNA-based assay). A confirmatory test at a central laboratory was required for the positive identification of the CMV markers.
- Fever of ≥ 38^{0}C on two or more occasions separated by at least 24 hours within a 7 day period
- New or increased malaise, leukopenia, atypical lymphocytosis of ≥ 5%, thrombocytopenia, or elevation of hepatic transaminases (ALT or AST).

C.1b. Tissue Invasive CMV was defined as evidence of localized CMV infection in a biopsy or other appropriate specimen accompanied by relevant signs or symptoms of organ dysfunction as follows.

- Evidence of localized CMV infection (CMV inclusion bodies or *in situ* detection of CMV antigen or DNA by immunostain or hybridization, respectively) in a biopsy or other appropriate specimen (e.g. BAL, CSF).
- Relevant clinical symptoms or signs of organ dysfunction, if the affected organ was the allograft, acute rejection had to be excluded as a possible cause for the patient's clinical

findings.

The sponsor has provided the diagnostic criteria for a number of organ-specific tissue-invasive CMV diseases; one example is cited below.

CMV Hepatitis: CMV hepatitis was confirmed by liver biopsy. The biopsy was characterized by the following:

- Presence of cells with positive immunostaining, immunofluorescence, *in situ* hybridization for CMV, CMV inclusions, or a positive viral culture in conjunction with histologic findings compatible with CMV hepatitis.
- At least one liver function test value based on common liver enzymes (AST. ALT, alkaline phosphatase) or bilirubin.

All cases of suspected CMV disease reported by the investigators were submitted to a blinded Endpoint Committee for review and adjudication prior to data analysis.

C.1c. Clinical Assessment of Patients with Suspected CMV Disease

Patients who developed signs or symptoms of possible CMV disease had a blood sample taken for detection of CMV as part of their clinical evaluation. The blood sample was analyzed in two clinical laboratories:

(I) At the local clinical laboratory by [redacted] or FDA-approved DNA/RNA-based assay and
(II) At a central virology laboratory using an FDA-approved or fully validated DNA/RNA-based assay.

The clinical assessment of a patient with suspected CMV syndrome also included appropriate blood cultures to rule out bacterial, fungal and other opportunistic infections as the cause of the patient's fever. Other diagnostic laboratory procedures (e.g. urine cultures, chest x-ray) were performed as warranted by the patient's clinical status and standard medical practices at the study center.

If the patient was found to have either (I) documented CMV viremia (based on assay of the blood specimen at either the local or central laboratory) and met the other criteria for CMV syndrome or (2) documented tissue invasive CMV, the patient was treated for CMV disease in accordance with standard practice at the center. If a patient was treated for CMV syndrome, two additional blood samples were obtained:

- One 'pre-treatment' sample within 12 hours prior to initiation of treatment, and
- One 'CMV treatment end' sample on the last day of treatment for CMV.

The pre-treatment blood sample was sent to the [redacted] for repeat qualitative CMV analysis, determination of CMV viral load, and for possible CMV genotyping. The CMV treatment end sample was processed as a CMV viral load sample. The collection of CMV

treatment end samples was introduced in a late protocol amendment, and as a consequence, treatment end samples were only collected for a minority of patients. Patients who were treated for CMV disease were terminated from the treatment phase of the study, but continued to be followed through post-transplant month 12 in accordance with the schedule of assessments.

Other Clinical Assessments included Acute Allograft Rejection and Opportunistic infections. Acute Allograft Rejection was defined as either (**1**) a biopsy proven rejection episode based on the histologic assessment of the biopsy by the pathologist or investigator at the study center, or (2) a clinical event compatible with an acute rejection episode and for which the patient received a full course of immunotherapy. Opportunistic Infections were diagnosed clinically, based on clinical signs and symptoms in conjunction with culture or biopsy evidence of a specific organism.

C.2. Virology Assessments

As indicated in the previous Section, to support the diagnosis of CMV disease, and as a part of the clinical assessment of the patient, a CMV r FDA-approved DNA/RNA-based assay was performed at each study center to document CMV viremia. This procedure was designated (by the sponsor) variously as ' or ' or ' ll the CMV assay methods at each study center were approved by the sponsor. However, since all the study centers could not use the same qualitative laboratory assay for detection of CMV viremia, for consistency, all ' blood samples were also analyzed for the presence of CMV at a ing an FDA-approved or fully validated DNA/RNA-based method. The sponsor has designated this as Both the d the same CMV assay and adhered to a common laboratory protocol (see below). A positive result was required to fulfill the protocol definition of CMV disease.

Blood Sample Collection: A total of 24 mL of whole blood samples was collected in tubes containing EDTA as anticoagulant, and as provided in each patient kit. The samples were refrigerated and an aliquot was shipped immediately to the central laboratory.

Other CMV Virology Assessments

C.2a. CMV Viral Load: The sponsor has stated that laboratory surveillance for CMV viremia was not a primary component of the clinical study. However, blood samples for assessment of CMV viral load at a (see below) were obtained at baseline. approximately every 2 weeks thereafter beginning at day 14 post-transplant and continuing through day 100 post-transplant (end of treatment), at post-transplant months 4, 4.5, 5, 6, 8, and 12, and if applicable, immediately prior to treatment for CMV disease as noted in Table 2. Results of these CMV measurements were not used for patient management and remained blinded until all patients had completed their post-transplant month 6 assessment. All samples sent to the central laboratory for determination of CMV viral load were assayed using the Cobas Amplicor CMV Monitor® test (Roche Molecular Systems), which detects and quantifies CMV DNA in plasma within a working range 400-100,000 copies/mL.

C.2b. CMV Resistance to GCV: Blood samples collected at the end of treatment with study drug (day 100 post-transplant) were analyzed for genotypic changes associated with the development of CMV resistance to GCV (mutations at the *UL97* or *UL54* loci). Blood samples from patients with suspected CMV disease or CMV viremia were also tested for evidence of genotypic resistance to GCV. If a patient was treated with GCV for CMV disease and did not respond to treatment in the expected manner, an additional blood sample was obtained from the patient for further CMV genotyping. In addition, the investigator provided the sponsor with all laboratory data for this patient regarding CMV sensitivity/resistance testing performed at the study center or at a reference laboratory.

Sample Collection and Preparation Procedure for Day 100 CMV Genotyping and CMV Viral Load Test: A total of 14 mL of whole blood were collected using two 7 mL labeled, EDTA containing tubes provided in each "End of Treatment" collection kit. Samples were refrigerated and shipped immediately to the central laboratory.

Comments:

1. In the original submission of this supplemental NDA, there was no description of any of the virologic assay methods on genotyping mentioned to have been used by either the local and/or the central laboratories. After the initial review of this submission, the sponsor was requested to provide a detailed description of the sensitivity and specificity of each of all of these methods and to define how the results from these methods were standardized at various clinical laboratories to detect CMV infection.
2. Since blood samples were collected for the determination of CMV viremia throughout the entire course of the treatment regimens, the sponsor was also requested to evaluate the relatedness of the virus load with the clinical outcome of CMV disease in patients undergoing Valcyte treatment.

These comments were communicated to the sponsor on April 8, 2003. The sponsor has adequately responded to the comments in an amendment (SE1-001/BI dated April 11, 2003) and detailed description of all the virology tests, the laboratories performing the tests and the location of the individual test methods in four different appendices (Table 4). It should be noted that most of the results presented as "CMV Viral Load" was the number of copies of CMV DNA/mL as determined at the central laboratories.

D. Efficacy Measurements

The primary efficacy endpoint in protocol PV16000 was the difference in the proportion of D+/R- patients developing CMV disease on each treatment arm within the first 6 months post-transplant, as assessed by the Endpoint Committee. The same analysis was also conducted on all data up to 12 months post-transplant, but was considered secondary to the analysis of the 6

month data. This analysis included all the signs, symptoms and laboratory criteria for CMV disease and the date of' onset of CMV disease. This endpoint was referred to in this document as "CMV Disease Endpoint Committee."

Table 4. Virology tests and methods used in Protocol PV1600

Test	Laboratory	Methods	Reference
CMV viremia	Central (required)	[redacted]	Appendix 1
	Local (optional)*	[redacted]	Appendix 2
Viral Load	Central	Roche COBAS Amplicor CMV Monitor Test	Appendix 3
CMV Genotyping	Central	[redacted]	Appendix 4

*Results not used by Endpoint Committee for adjudication of CMV disease.

In addition to this nomenclature of the efficacy endpoint, the sponsor has two more definitions based on the way the efficacy was evaluated. When the primary parameter was evaluated based solely on events which met the protocol definition of CMV disease without any adjudication by the Endpoint Committee, it was referred to as 'CMV Disease - All Signs. Symptoms and Laboratory Criteria Fulfilled.' When the primary endpoint was analyzed based solely on investigator-treated CMV disease events, regardless of whether all the clinical criteria for CMV disease had been met, this clinical analysis of the primary endpoint was referred to as 'CMV Disease -Investigator Treated' throughout this submission.

D.1. Primary Efficacy Results

The incidence of CMV disease at 6 months or at 12 months were comparable on the two treatment arms, whether assessed by the independent Endpoint Committee (18.4% GCV, 17.2% VGCV), by the clinical signs and symptoms defined in the protocol (15.2% GCV, 15.1% VGCV), or by those events treated by investigators (28.0% GCV, 30.5% VGCV). The majority of CMV disease events occurred between the end of treatment and 6 months post-transplant. Because there was no significant comparative difference between the oral GCV and VGCV arms in the assessments by various groups noted above, the results assessed by the Endpoint Committee only are described below.

A total of 16 patients (4 on the GCV arm, 12 on the VGCV arm) developed CMV disease between the 6 - 12 month post-transplant time points. Thus the proportion of patients who developed CMV disease in the GCV arm (18.4%) was comparable to that of the VGCV arm

(17.2%) by 12 months post-transplant (Table 5), as assessed by the Endpoint Committee. These results on the incidence of CMV disease were also very similar to those obtained for the primary efficacy parameter at 6 months post-transplant (Table 6).

While the overall incidence of CMV disease was comparable in the two treatment arms, the incidence of CMV syndrome remained more common in the GCV arm (12.0% GCV, 7.9% VGCV), and the incidence of tissue-invasion was more common in the VGCV arm (6.4% GCV, 9.2% VGCV) (Table 5), due mainly to tissue-invasive CMV disease events which occurred during the first 6 months post-transplant (Table 6). The majority of tissue-invasive CMV disease was experienced by liver transplant recipients (3/8 on the GCV arm, and 17/22 on the VGCV arm) (Table 5), and occurred in the gastrointestinal tract (73.3%). It should be noted that in heart and kidney transplant recipients, the incidence of CMV disease remained higher in the GCV arm, whilst in liver transplant recipients it remained higher in the VGCV arm (due to the higher incidence of tissue-invasive disease). Only one kidney-pancreas transplant recipient (on the GCV arm) developed CMV disease by the 12 month post-transplant timepoint.

Table 5. Summary of CMV Disease up to 12 Months Post-Transplant-Endpoint Committee (from Table 8, Vol. 1, page 47 of this submission)

NO. OF PATIENTS	GCV N=125	VGCV N=239	TOTAL N=364	Weighted difference in proportions (95% CI)
Patients with CMV disease	23 (18.4%)	41 (17.2%)	64 (17.6%)	0.015 (-0.068, 0.098)
Patients with no CMV disease	90 (72.0%)	176 (73.6%)	266 (73.1%)	
Patients unevaluable	12 (9.6%)	22 (9.2%)	34 (9.3%)	
CMV syndrome	15 (12.0%)	19 (7 .9%)	34 (9.3%)	
Tissue-invasive CMV	8 (6.4%)	22 (9.2%)	30 (8.2%)	
Hepatitis	2	6	8	
Pneumonia	2	3	5	
Gastrointestinal	5	17	22	
Retinitis	0	0	0	
Other	0	1	1	

95% CI FROM THE STRATIFIED Z TEST
Patients can have more than one more type of tissue-invasive CMV disease
If a patient has insufficient visits up to 12 months they are unevaluable unless the patient had CMV disease

Table 6. Summary of CMV Disease up to 6 Months Post-Transplant -Endpoint Committee (From Table 9, Vol. 1, page 47 of this submission)

No. of patients	GCV N=125	VGCV N=239	Total N=364	Weighted difference in proportions (95% CI)
Patients with CMV disease	23 (18.4%)	41 (17.2%)	64 (17.6%)	0.015 (-0.068, 0.098)
Patients with no CMV disease	90 (72.0%)	176 (73.6%)	266 (73.1%)	
Patients unevaluable	12 (9.6%)	22 (9.2%)	34 (9.3%)	
CMV syndrome	15 (12.0%)	19 (7 .9%)	34 (9.3%)	
Tissue-invasive CMV	8 (6.4%)	22 (9.2%)	30 (8.2%)	
Hepatitis	2	6	8	
Pneumonia	2	3	5	
Gastrointestinal	5	17	22	
Retinitis	0	0	0	
Other	0	1	1	

95% CI FROM THE STRATIFIED Z TEST
Patients can have more than one more type of tissue-invasive CMV disease
If a patient has insufficient visits up to 12 months they are unevaluable unless the patient had CMV disease

When these six month data are tabulated on the basis of organ type, the higher incidence of tissue invasive CMV disease in liver transplant patients in the VGCV arm (13.6%) becomes more obvious compared to those in the GCV arm (3.4%)(Table 7).

Table 7. Summary of CMV Disease up to 6 Months Post-transplant by Organ type--Endpoint Committee (ITT Population) (Adapted from Table 5 of the revised package insert).

	Liver Patients (N=177)		Heart Patients (N=56)		Kidney Patients (N=120)		Kidney-Pancreas Patients (N=11)	
	GCV (N=59)	VGCV (N=118)	GCV (N=21)	VGCV (N=35)	GCV (N=39)	VGCV (N=81)	GCV (N=6)	VGCV (N=5)
Patients with CMV disease	7 (11.9%)	22 (18.6%)	2 (9.5%)	2 (5.7%)	9 (23.1%)	5 (6.2%)	1 (16.7%)	0
Patients with no CMV disease	48 (81.4%)	90 (76.3%)	19 (90.5%)	30 (85.7%)	28 (71.8%)	74 (91.4%)	4 (66.7%)	4 (80.0%)
Tissue-invasive CMV	2 (3.4%)	16 (13.6%)	1 (4.8%)	0	2 (5.1%)	1 (1.2%)	1 (16.7%)	0

*If a patient had insufficient visits up to 6 months, they were unevaluable unless they had CMV disease.

Comment: The apparent heterogeneity in the results between the different allograft types, and the higher incidence of tissue-invasive CMV disease in liver transplant recipients in the VGCV arm is of major clinical concern. The medical officer may wish to comment on the possibility of resolving these issues by a well designed phase IV clinical study.

The sponsor has, however, stated that the current clinical study was only designed and powered to investigate all allograft types combined, and was not powered for sub-group analyses, including analyses by individual allograft type. The clinical course for patients with CMV syndrome or tissue-invasive disease was very similar, and the median day of onset of syndrome or tissue-invasion was comparable (137.0 days vs. 149.5 days, respectively). For detailed evaluation and clinical implication of these results, please refer to the medical officer's review.

D.1a. Other Clinical Efficacy Endpoints included CMV disease or death, treatment failure or discontinuation of treatment, acute graft rejection and acute graft rejection following CMV disease, graft loss or death. The sponsor has also provided the Time to Events Parameters including efficacy and safety endpoints in the 6 month and 12 month data analysis. Time to Efficacy Endpoints included the following:

- Time to CMV disease
- Time to first treatment for CMV disease
- Time to CMV disease or death,
- Time to treatment failure (defined as CMV disease, death or discontinuation of treatment due to a treatment-related adverse event),
- Time to acute rejection,
- Time to death. (The occurrence and timing of CMV disease events was as assessed by the Endpoint Committee.
- Time to neutropenia (defined as an ANC < 1,000 cells/μL)
- Time to thrombocytopenia (defined as a platelet count < 50,000/μL)
- Time to anemia (defined as a hemoglobin reading < 8 g/dL
- Time to elevated serum creatinine (defined as a serum creatinine reading> 2.5 mg/dL)

D.1b. Time to CMV Disease - Endpoint Committee

The time to first incidence of CMV disease up to 12 months post-transplant is presented graphically in Figure 3. The majority of CMV disease events occurred between the end of the treatment phase and 6 months post-transplant, with a relatively small number of events occurring between 6-12 months post-transplant. Although the overall incidence of CMV disease by 12 months post-transplant was comparable on both treatment arms, during the post-treatment phase, the sponsor believes that the average time to CMV disease may be shorter in the GCV arm of the study, and that the anti-CMV prophylaxis with VGCV may delay the onset of CMV disease compared to prophylaxis with oral GCV.

Similar results were obtained for time to CMV disease (Endpoint Committee) or death, time to investigator-treated CMV disease, and time to treatment failure up to 12 months post-transplant. The incidence of CMV disease (Endpoint Committee) or death, and the incidence of treatment failure up to 12 months, also remained comparable on the oral GCV and VGCV treatment arms.

The incidence of acute graft rejection up to 12 months post-transplant remained slightly higher in the GCV arm of the study (36.0%, versus 32.6% on the VGCV arm), and patients who received anti-CMV prophylaxis with oral GCV also experienced acute graft rejection earlier than those who received VGCV. As with the 6 month data, there appeared to be no strong or obvious correlation between treatment for acute rejection and the subsequent development of CMV disease by 12 months post-transplant. The incidence of graft loss by 12 months post-transplant was low on both treatment arms (1.6% GCV, 1.3% VGCV), as was the incidence of graft loss or death (8.0% GCV, 7.5% VGCV). There were insufficient numbers of events to enable a meaningful comparison of time to first treatment for CMV disease up to 12 months post-transplant in the two treatment arms. For more detailed information on these clinical events, however, please refer to the medical officer's review.

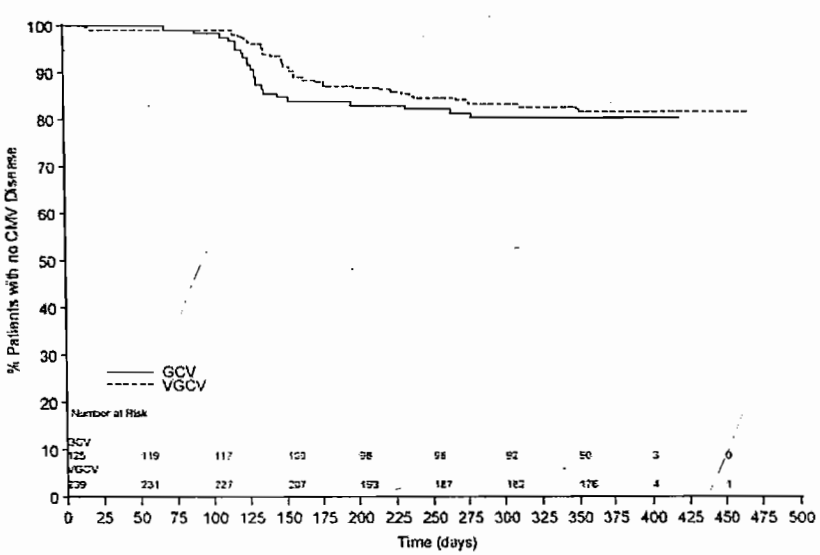


Figure 3. Time to CMV Disease (Days) up to 12 Months Post-Transplant - Endpoint Committee (ITT Population) (from Fig 2, Vol. 1, page 52 of this submission).

The proportion of patients in the ITT population who experienced CMV disease (as assessed by the Endpoint Committee) or death within 12 months post-transplant was also comparable in the two treatment arms [16.8% ganciclovir, 15.1% valganciclovir by 6 months post-transplant, compared with 24.0% GCV, 22.6% VGCV by 12 months post-transplant. However, the incidence of CMV disease or death by 6 months or 12 months post-transplant remained higher for liver transplant recipients in the VGCV arm, and higher for kidney transplant recipients in the GCV arm. The time to CMV disease or death appeared slightly shorter on the GCV arm (due to the CMV disease events).

The incidence of treatment failure were comparable in the two treatment arms (20.0% GCV, 17.2% VGCV by 6 months post-transplant, compared with 27.2% GCV, 24.7% VGCV by 12 months post-transplant, and with the most common reason for treatment failure being CMV disease. As at 6 months post-transplant, the incidence of treatment failure by 12 months post-transplant remained slightly higher for liver transplant recipients in the VGCV arm, and higher for kidney transplant recipients in the GCV arm (pages 131-132 of this submission).

D.1c. Opportunistic Infections

Results presented in Table 8 show the number of patients who experienced at least one opportunistic infection (OI) within the first 6 months post-transplant for the ITT population. The table also includes the individual incidences of the OIs: aspergillus, candida, pneumocystis carinii, cryptococcus, listeria monocytogenes, herpes simplex and herpes zoster. The incidence of opportunistic infections up to 6 months post-transplant was comparable in the two treatment arms (9.6% GCV, 9.2% VGCV), and no treatment-group difference was detected in the incidence of the various OIs analyzed. The number of patients experiencing OIs in the different allograft groups was too low to enable any meaningful comparison.

Table 8. Summary of Opportunistic Infections up to 6 Months Post-Transplant (From Table 37, Vol. 8, page 128)

	GCV N=125	VGCV N=239	TOTAL N=364
Opportunistic infections			
Patients with opportunistic infections	12 (9.6%)	22 (9.2%)	34 (9.3%)
Patients with no opportunistic infection	106 (84.8%)	205 (85.8%)	311 (85.4%)
Patients unevaluable	7 (5.6%)	12 (5.0%)	19 (5.2%)
Type of opportunistic infection			
Aspergillus/mucor	3 (2.4%)	2 (0.8%)	5 (1.4%)
Candida	7 (5.6%)	14 (5.9%)	21 (5.8%)
Pneumocystic Carinii	0 (0%)	0 (0%)	0 (0%)
Cryptococcus	1 (0.8%)	2 (0.8%)	3 (0.8%)
Listeria monocytogenes	0 (0%)	0 (0%)	0 (0%)
Herpes simplex	2 (1.6%)	3 (1.3%)	5 (1.4%)
Herpes zoster	0 (0%)	3 (1.3%)	3 (0.8%)

If a patient has insufficient follow-up visits to 6 months post-transplant they are unevaluable unless the patient had an opportunistic infection.

D.1d. Duration of Therapy with Selected Immunosuppressants

In this clinical study the most frequently administered Immunosuppressants used up to 6 months were: mycophenolate mofetil, ciclosporin, azathioprine, prednisolone, tacrolimus, daclizumab, and sirolimus with exception of daclizumab, which was used < 2 months in some patients. The sponsor has stated that the two treatment arms appeared well balanced with respect to the duration of treatment with each individual immunosuppressant. However, please refer to the biopharmacist's review for more details.

D.2. Virology Efficacy Results

To evaluate the virology efficacy results, the sponsor has analyzed the following virology endpoints at 6 and 12 months post-transplant:

- Incidence and time to first occurrence of CMV DNA load> below the lower limit of quantification (BLQ) (400 copies /mL)
- Proportion of patients with CMV DNA load> BLQ prior to a CMV disease event (Endpoint

Committee)

- Proportion of patients with CMV DNA load > BLQ prior to acute rejection
- Incidence and time to peak CMV DNA load
- Proportion of patients with peak CMV DNA load prior to a CMV disease event (Endpoint Committee)
- Proportion of patients with peak CMV DNA load prior to acute rejection
- Incidence of CMV *UL97* and *UL54* GCV resistance mutations

As discussed earlier in Section C2, a CMV , or FDA-approved DNA/RNA-based assay was used by each study center to document CMV viremia and routine blood samples for the assessment of CMV viral (DNA) load were analyzed at the central laboratory only. The results were not used for patient management, and remained blinded until all patients had completed their post-transplant month 6 assessment.

It should be noted again that on some occasions, routine viral load samples and samples were taken on or around the same day. The sponsor has stated that in most situations, the viral loads for the two samples were comparable, however, in a small number of cases, there were significant discrepancies between the results. The cause of these discrepancies is unknown, as sample re-tests gave similar results. For consistency, the highest viral load recorded (whether routine or was used in all analyses of peak viral load, and the first value > BLQ was used for all analyses of time to viral load > BLQ.

D.2a. Incidence and Time to CMV DNA Load > BLQ

Results summarized in Table 9 show the proportion of patients with viremia, defined as a CMV viral DNA load > BLQ (400 copies /mL), and the time to first occurrence of viremia, within the first 12 months post-transplant.

Table 9. Incidence and Time to CMV DNA Load > BLQ up to 12 Months Post-transplant (From Table 22, Vol. 1, page 66 of this submission)

	GCV N=125	VGCV N=239
Incidence of CMV viral load > BLQ up to 12 months post-transplant		
At least one CMV viral load > BLQ	61 (48.8%)	116 (48.5%)
No CMV viral load > BLQ	63 (50.4%)	122 (51.0%)
CMV viral loads not done	1 (0.8%)	1 (0.4%)
Time to CMV viral load > BLQ Kaplan Meier Analysis		
Number of patients with CMV viral load > BLQ	61 (48.8%)	116 (48.5%)
Number of censored observations	64 (51.2%)	123 (51.5%)
Mean (days)	240.7	257.7
Standard Error (days)	11.7	7.7
Lower Quartile (days)	120.0	142.0
95% CI for Lower Quartile (days)	112.0 to 130.0	133.0 to 147.0
Median time to CMV viral load > BLQ (days)	282.0	357.0
95% CI for within group median (days)	145.0 to #	207.0 to #
Upper Quartile (days)	#	#
95% CI for Upper Quartile (days)	# to #	# to #
Range (days)	1.0 to 410.0	1.0 to 387.0

BLQ is defined as <400 copies/mL

The proportion of patients experiencing viremia was almost identical in the two treatment arms (48.8% GCV, 48.5% VGCV). These results were also similar to those previously submitted for 6 months post-transplant patients (43.2% GCV, 39.7% VGCV). However, by 12 months post-transplant, the estimated time by which 25% patients had experienced viremia (lower quartile), and the median time to viremia, were both shorter on the GCV arm [lower quartile, 120 days GCV vs. 142 days VGCV; median, 282 days GCV vs. 357 days VGCV (Table 9). When the results are presented graphically (Figure 4), time to viremia also appears shorter on the GCV arm. These results, therefore, suggested to the sponsor that anti-CMV prophylaxis with VGCV delays the onset of CMV viremia compared to prophylaxis with oral GCV, and are therefore consistent with the results obtained for time to CMV disease (see Section D.1b). At 6 months post-transplant there were insufficient numbers of events to enable a comparison of the median time to viremia on the two treatment arms. The results obtained for the individual allograft types were generally consistent with those obtained for all allograft types combined.

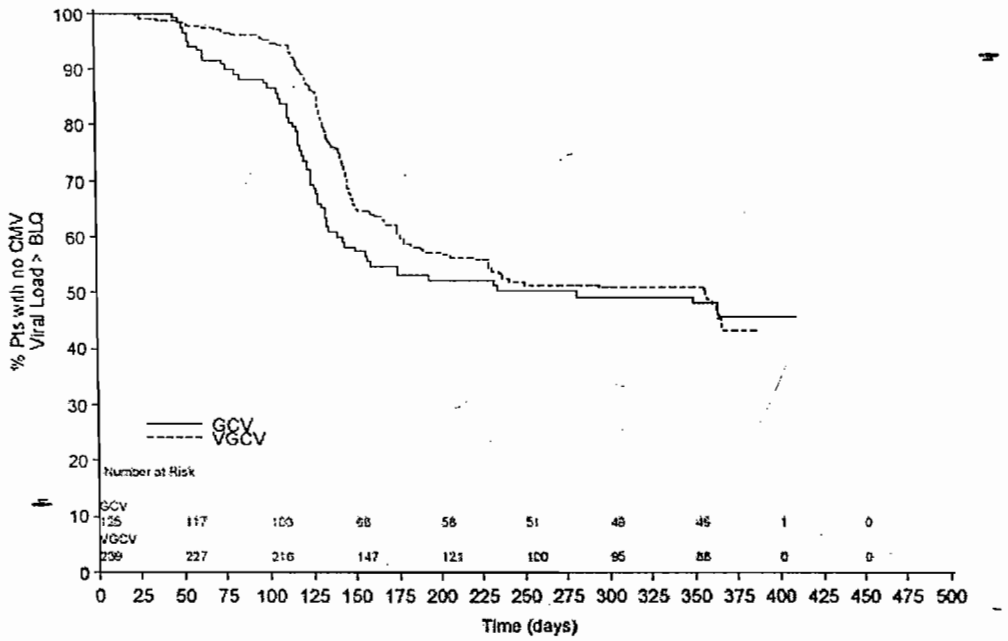


Figure 4. Time to CMV DNA load >BLQ by 12 months Post-Transplant (From Fig. 7, Vol. 1, page 67 of this submission)

D.2b. Incidence and Time to Peak CMV DNA Load

The results presented in Table 10 show the range of peak CMV DNA loads recorded up to 12 months post-transplant. The peak viral DNA loads were similar on the two treatment arms, (50.4% in GCV arm and 51.% in VGCV arm) although there was a tendency for reduced viral loads on the VGCV arm (2.1%) compared with the GCV arm (4.8%), especially for very elevated viral DNA loads (> 50,000 copies/mL). The results were very similar to those obtained up to 6 months post-transplant

Table 10. Summary of Peak CMV Viral DNA Load* up to 12 Months Post-Transplant (From Table 23, Vol. 1, page 68 of this submission)

Peak CMV viral load (copies/mL) up to 12 MONTHS POST-TRANSPLANT	GCV N=125	VGCV N=239
All CMV viral loads < BLQ	63 (50.4%)	122 (51.0%)
400 - 1000	3 (2.4%)	13 (5.4%)
1001 - 5000	14 (11.2%)	31 (13.0%)
5001 - 10000	7 (5.6%)	16 (6.7%)
10001 - 25000	13 (10.4%)	23 (9.6%)
25001 - 50000	9 (7.2%)	18 (7.5%)
50001 - 75000	6 (4.8%)	5 (2.1%)
75001 - 100000	5 (4.0%)	4 (1.7%)
> 100000	4 (3.2%)	6 (2.5%)
CMV viral load not done	1 (0.8%)	1 (0.4%)

BLQ is defined as < 400 copies/mL

*The CMV DNA load is interchangeably mentioned as CMV viral load

Time to peak CMV DNA load > BLQ up to 12 months post-transplant is presented in Table 11. The results were consistent with those obtained at 6 months post-transplant, with the median time to peak CMV viral load being shorter on the GCV arm (282 days, versus 358 days on the VGCV arm). These results therefore remained consistent with those obtained for time to CMV viremia and time to CMV disease (see Section D.1b).

Table 11. Time to Peak CMV Viral Load > BLQ up to 12 Months Post-Transplant (From Table 24, Vol. 1, page 68 of this submission)

	GCV N=125	VGCV N=239
Incidence of CMV viral load up to 12 months post-transplant		
At least one CMV viral load > BLQ	61 (48.8%)	116 (48.5%)
No CMV viral load > BLQ	63 (50.4%)	122 (51.0%)
CMV viral loads not done	1 (0.8%)	1 (0.4%)
Time to Peak CMV viral load Kaplan Meier Analysis		
Number of patients with Peak CMV viral load	61 (48.8%)	116 (48.5%)
Number of censored observations	64 (51.2%)	123 (51.5%)
Mean (days)	247.0	261.6
Standard Error (days)	11.1	7.5
Lower Quartile (days)	129.0	147.0
95% CI for Lower Quartile (days)	122.0 to 144.0	142.0 to 150.0
Median time to Peak CMV viral load (days)	282.0	358.0
95% CI for within group median (days)	154.0 to #	222.0 to #
Upper Quartile (days)	#	#
95% CI for Upper Quartile (days)	# to #	# to #
Range (days)	1.0 to 410.0	1.0 to 387.0

BLQ is defined as < 400 copies/mL

D.2c. Association Between Viral Load and CMV Disease

The peak CMV DNA loads remained generally higher for patients with Endpoint Committee defined CMV disease (median peak viral load $\log_{10}$ 4.3, versus $\log_{10}$ 2.6 for patients without Endpoint Committee defined CMV disease) (Table 12). However, there were examples of very high viral loads being recorded for patients who did not develop CMV disease (page 207 of this

submission), and conversely, of low viral loads being recorded for patients who did develop CMV disease (p203 of this submission).

Table 12. Summary of Peak Viral Loads up to 12 Months Post-Transplant for Patients With/Without CMV Disease . Endpoint Committee (From Table 25, Vol. 1, page 71 of this submission)

	ENDPOINT COMMITTEE CMV DISEASE		
Peak CMV viral load (copies/mL) up to 12 MONTHS POST-TRANSPLANT	GCV	VGCV	TOTAL
Categories of CMV Viral Loads			
All CMV viral loads < BLQ	5 (21.7%)	5 (12.2%)	10 (15.6%)
400 - 1000	0 (0%)	4 (9.8%)	4 (6.3%)
1001 - 5000	0 (0%)	5 (12.2%)	5 (7.8%)
5001 - 10000	1 (4.3%)	4 (9.8%)	5 (7.8%)
10001 - 25000	5 (21.7%)	8 (19.5%)	13 (20.3%)
25001 - 50000	4 (17.4%)	4 (9.8%)	8 (12.5%)
50001 - 75000	4 (17.4%)	3 (7.3%)	7 (10.9%)
75001 - 100000	3 (13.0%)	4 (9.8%)	7 (10.9%)
> 100000	1 (4.3%)	4 (9.8%)	5 (7.8%)
CMV viral load not done	0 (0%)	0 (0%)	0 (0%)
Untransformed Values			
N	23	41	64
MEAN (s.d.)	38555.0 (34180.0)	31541.5 (36498.6)	34062.0 (35570.8)
MEDIAN	31400.0	15900.0	20150.0
MINIMUM	399.0	399.0	399.0
MAXIMUM	100001	100001	100001
Log10 Values			
N	23	41	64
MEAN (s.d.)	4.2 (0.9)	4.0 (0.9)	4.0 (0.9)
MEDIAN	4.5	4.2	4.3
MINIMUM	2.6	2.6	2.6
MAXIMUM	5.0	5.0	5.0

	WITHOUT ENDPOINT COMMITTEE CMV DISEASE		
Peak CMV viral load (copies/mL) up to 12 MONTHS POST-TRANSPLANT	GCV	VGCV	TOTAL
Categories of CMV Viral Loads			
All CMV viral loads < BLQ	58 (56.9%)	117 (59.1%)	175 (58.3%)
400 - 1000	3 (2.9%)	9 (4.5%)	12 (4.0%)
1001 - 5000	14 (13.7%)	26 (13.1%)	40 (13.3%)
5001 - 10000	6 (5.9%)	12 (6.1%)	18 (6.0%)
10001 - 25000	8 (7.8%)	15 (7.6%)	23 (7.7%)
25001 - 50000	5 (4.9%)	14 (7.1%)	19 (6.3%)
50001 - 75000	2 (2.0%)	2 (1.0%)	4 (1.3%)
75001 - 100000	2 (2.0%)	0 (0%)	2 (0.7%)
> 100000	3 (2.9%)	2 (1.0%)	5 (1.7%)
CMV viral load not done	1 (1.0%)	1 (0.5%)	2 (0.7%)
Untransformed Values			
N	101	197	298
MEAN (s.d.)	10126.4 (23000.3)	6485.5 (14860.7)	7719.5 (18078.7)
MEDIAN	399.0	399.0	399.0
MINIMUM	399.0	399.0	399.0
MAXIMUM	100001	100001	100001
Log10 Values			
N	101	197	298
MEAN (s.d.)	3.2 (0.8)	3.1 (0.7)	3.1 (0.7)
MEDIAN	2.6	2.6	2.6
MINIMUM	2.6	2.6	2.6
MAXIMUM	5.0	5.0	5.0

BLQ is defined as <400 copies/mL

Results presented in Tables 26 and 27 of this submission show that the peak viral loads, and peak viral loads recorded up to 12 months post-transplant were generally similar in patients diagnosed with CMV syndrome or tissue-invasive CMV disease (median log_{10} peak viral loads being 4.2 vs. 4.4, respectively, and median log_{10} peak viral loads being 4.0 for patients with CMV syndrome and tissue-invasive CMV disease). However, the number of patients with CMV syndrome versus tissue-invasion was too low to enable any meaningful comparison of the data.

It should be pointed out that a total of 108 patients (35 on the GCV arm, 73 on the VGCV arm) were treated for CMV disease during the first 12 months post-transplant. Results presented in Table 28 of this submission show that the peak viral loads were higher for patients with investigator-treated CMV disease than for patients without investigator-treated CMV disease (median log_{10} values being 4.1 vs. 2.6, respectively). For the clinical significance of these clinical results, please refer to the medical officer's review.

D.2d. Incidence of CMV Viral Load > BLQ Prior to CMV Disease / Acute Graft Rejection

The proportion of patients with / without at least one CMV viral load > BLQ prior to CMV disease or acute graft rejection was assessed by the Endpoint Committee. Results summarized on page 220 and page 221 of this submission show that there were no significant differences between the GCV and VGCV arms of the study. There appeared to be no strong link between the onset of viremia and the development of CMV disease or acute graft rejection, although a slightly higher proportion of patients developed CMV disease following viremia, whilst conversely, a higher proportion of patients experienced acute graft rejection prior to viremia. An individual patient listing which compares the first date recorded for CMV viral load > BLQ with the date recorded for the last episode of CMV disease and/or acute graft rejection, is provided on page 222 of this submission.

D.2e. Peak CMV Viral Load Prior to CMV Disease / Acute Graft Rejection

The peak CMV viral load recorded for patients prior to CMV disease (as assessed by the Endpoint Committee) or acute graft rejection is summarized on page 239 and page 240, respectively. There were no significant differences between the two arms (GCV and VGCV) of the study. Most cases of CMV disease, and acute graft rejection, occurred prior to CMV reaching maximal (peak) levels. An individual patient listing which compares the date recorded for peak CMV viral load with the date recorded for the last episode of CMV disease and/or acute graft rejection is provided on page 241 of this submission.

E. Drug Resistance

As indicated earlier in Section C.2b, blood samples from all patients were collected at the end of the randomized treatment phase (up to day 100 post-transplant) for analysis of mutations in the *UL97* gene of CMV which confers resistance to GCV. In addition, blood samples taken from patients with suspected CMV disease during the first 6 months and then at 12 months post-transplant were also analyzed for the possible emergence of GCV resistance mutations.

As noted earlier, the location of CMV *UL97* mutations was assessed directly in leukocytes by nested polymerase chain reaction followed by restriction fragment length polymorphism (RFLP) and *UL97* DNA sequencing. Since mutations in the *UL54* gene usually follows *UL97* mutations,

sequencing of the *UL54* gene was performed only for samples containing either a known *UL97* resistance mutation or a novel *UL97* mutation not previously reported in the literature. If a GCV resistance mutation was found in the *UL97* gene, then the *UL54* gene was also sequenced. Phenotypic nature of any of the clinical isolates was not analyzed.

E.1. Incidence of Ganciclovir-Resistant CMV During the Treatment Phase of the Study

Day 100 samples from 103 patients on the GCV arm, and 198 patients on the VGCV arm of the study were available for testing. On the GCV arm of the study, 5 CMV isolates with a mutation in the *UL97* gene were observed. One mutation (Q449K) was a known wild-type variant, two (A594V and C607Y) were known GCV-resistance mutations, and two (A427V and M550I) were of unknown significance, and were considered not to be resistance mutations. On the VGCV arm of the study, 2 samples with a mutation in the *UL97* gene were observed: one (H469Y) was a known wild-type variant and one (Y617H) was of unknown significance.

Samples from 4 patients (3 GCV treated, 1 VGCV treated) had mutations in the *UL54* gene. However, the sponsor has stated that these were all known polymorphisms and were not associated with drug resistance. Thus, the sponsor has concluded that the incidence of resistance by the end of treatment with study drug was 2/103 (1.9%) on the GCV arm versus 0/198 (0%) on the VGCV arm of the study.

E.2. Incidence of GCV-Resistant CMV in Patients with Suspected CMV Disease During the First 6 Months Post-Transplant

According to the initial protocol, all patients who developed signs or symptoms of possible CMV disease were to have an [redacted] blood sample taken for detection of CMV as part of their clinical evaluation. Patients with CMV viremia who also met the protocol definition of CMV syndrome, were to have a further 'pre-treatment [redacted] blood sample taken within 12 hours of initiation of treatment for CMV disease, and this sample was also to be tested for the presence of ganciclovir resistant virus. A late protocol amendment also stated that on the last day of CMV treatment, a final 'end of treatment [redacted] blood sample was to be taken. However, as this amendment was implemented after the majority of patients had completed the treatment phase of the study, 'end of treatment' samples were only obtained for a minority of patients. In order to be confident of detecting all cases of resistance, [redacted] or 'pre-treatment' [redacted] samples were tested for all patients with suspected CMV disease events who had CMV viremia.

Samples from 79 patients with suspected CMV disease were available for testing (29 GCV patients, 50 VGCV patients). On the GCV arm of the study, 5 samples with a mutation in *UL97* were observed. One mutation (H469Y, observed in two cases) is a known wild-type variant, two (C592G and C607Y) are known GCV resistance mutations, and one (P405L) is of unknown significance, but was considered not to be a resistance mutation. The C607Y mutation observed was from the same patient who carried virus with a C607Y mutation at the end of the treatment phase of the study. As the two samples were taken only 2 weeks apart, they are considered to represent the same case of resistance. This patient is included as having developed GCV resistant CMV in both the treatment phase of the study and in the first 6 months post-transplant (in patients with suspected CMV disease events).

On the VGCV arm of the study, 9 samples with a mutation in *UL97* were observed. Seven mutations, H469Y (5 cases) and Q449K (2 cases), are known wild-type variants, and two mutations (A582V and A674T) are of unknown significance, but were considered not to be resistance mutations. Samples from 4 patients (2 GCV treated, 2 VGCV treated) had mutations in the *UL54* gene. However, these were known polymorphisms and were not associated with drug resistance. Thus, the incidence of GCV-resistant mutations for patients with suspected CMV disease up to 6 months post-transplant was 2/29 (6.9%) for patients on the GCV arm versus 0/50 (0%) for patients on the VGCV arm of the study.

CMV disease [illegible] samples were sometimes taken from patients with suspected CMV disease who were subsequently shown not to have CMV viremia. These samples were unlikely to provide any useful information regarding resistance (lack of symptoms and no evidence of viral presence), and hence were not intended for analysis. However, when a small number of these samples were inadvertently tested, none contained virus with resistance mutations.

As the collection of 'end of treatment' samples was introduced into the protocol at a late stage, the number of samples actually taken was very low. Furthermore, most samples were inadvertently frozen, preventing the preparation of the [illegible] required for analysis. End of treatment samples were therefore not analyzed because useful data could not be generated from such a small sample set.

E.2a. Assessment of Mutations Detected in the UL97 Gene

The following mutations in the CMV *UL97* gene were observed in this study: P405L (mixed population with wild-type virus), A427V, Q449K, H469Y, M550I, A582V, C592G, A594V, C607Y, Y617H and A674T. Without presenting any experimental evidence for it, the sponsor has speculated on the nature of these mutations as follows:

Wild Type Mutations: Mutations Q449K and H469Y are known wild type variants. Since these mutations are found in naturally occurring CMV strains, they are unlikely to have been of clinical consequence.

Mutations of Unknown Significance: Mutations P405L, A427V, M550I, A582V, Y617H and A674T have not been previously cited in the literature, and therefore, the nature of these mutations is unknown. However, without providing any experimental evidence for it, the sponsor has suggested that it is unlikely that these mutations are associated with GCV resistance as they are either 1) outside of the documented region for UL97 resistance mutations, or 2) were not associated with CMV disease, or 3) were detected when CMV viral loads were low.

GCV Resistance Mutations: In this study, 3 known GCV resistance mutations in the *UL97* gene were detected from samples collected from patients on the GCV arm: C592G, A594V, and C607Y. No mutations in the *UL54* gene were observed. No resistance was observed for patients treated with VGCV.

During the first 6 months post-transplant, 2 patients with suspected CMV disease (both on the GCV) were found to be carrying GCV resistant CMV, with both mutations detected on or prior to day 100 post-transplant (end of study drug prophylaxis). By 12 months post-transplant, samples from a total of 88 patients (33 GCV patients, 55 VGCV patients) with suspected CMV disease had been tested, but no additional GCV resistance mutations were detected.

Therefore, the incidence of GCV-resistant mutations for patients with suspected CMV disease up to 12 months post-transplant with samples available for testing was 2/33 (6.1%) for patients on the GCV arm versus 0/55 (0%) for patients on the VGCV arm of the study. If only those samples which were PCR positive for CMV are included in the resistance calculations, as opposed to all samples tested, then the incidence of resistance up to 12 months post-transplant for patients with suspected CMV disease was 2/32 (6.3%) in the GCV arm, versus 0/47 (0%) in the VGCV arm.

E.2b. Association Between GCV Resistance Mutations and CMV Disease

The sponsor has stated that no GCV resistant mutant isolated from any of the patients with Endpoint Committee defined CMV disease. Therefore the sponsor has speculated that there appeared to be no correlation between the emergence of genotypic resistance and either the development of CMV disease (as defined by the Endpoint Committee) or the occurrence of acute graft rejection within the first 12 months post-transplant. However, one clinical sample from 1 of the 26 patients treated for CMV disease on the GCV arm of the study may be resistant to GCV.

Comments: Recognizing that there are a number of virologic deficiencies in the design and execution of the clinical protocol to define the incidence and character of GCV resistant mutants expected to emerge during the course of the suppressive VGCV therapeutic measures, the following virology concerns were communicated to the sponsor on June 27, 2003.

1. CMV strains resistant to GCV can emerge by selection of mutations in either the viral *UL97* gene and/or in the viral *UL54* gene. Mutation in the *UL97* gene usually, but not always, leads to the development of GCV resistant mutants; therefore mutation in *UL54* gene may or may not follow mutation in *UL97* gene, especially in immunocompromised patients. Experiments should have been conducted to map mutations in both the CMV *UL97* gene and the *UL54* genes to detect the emergence of GCV-resistant mutants of CMV. Current published data (though limited) indicate different antiviral susceptibility pattern depending upon whether the CMV strains contain mutations only in *UL97*, only in *UL54* or in both genes.
2. A number of mutations noted in the current clinical study were considered as wild-type variants or speculated as of unknown significance. The phenotypic nature of all the CMV isolates containing these mutations should have been evaluated to unambiguously establish their resistance to GCV.
3. The sample size tested for the determination of CMV resistance to GCV or VGCV was too small to derive any meaningful conclusion.

The sponsor's response to these comments may be summarized as follows.

Additional resistance testing as a Phase IV study commitment will be conducted as follows:

i) *UL54* Sequencing

Since the testing strategy adopted in PV16000 would have potentially missed detection of isolates with GCV resistance mutations in the *UL54* gene, "we now propose to sequence the *UL54* gene for all day 100 and suspected CMV disease samples which were previously

sequenced for mutations in the *UL97* gene and were found to not contain either CMV resistance or novel mutations (and hence were previously not tested for *UL54* resistance mutations)."

ii) Novel *UL97* Mutations

F. CMV Seroconversion

The sponsor has responded to a request from the medical officer on the rates of CMV seroconversion (according to organ transplant group) in patients with or without developing CMV disease as follows.

Serology data were not collected as part of the main study PV16000 and hence this was not submitted as part of the NDA. However, CMV serology data were collected retrospectively on a sub-set of patients in the trial. It should be noted that these data were not collected, cleaned or analyzed to the normal Roche data collection standards and should be viewed as preliminary/draft at present.

F.1. Summary of Results

Baseline seroconversion data were not included in the analysis to exclude the effect of antibodies (IgG) transmitted via blood/blood product transfusion. There were a significant number of patients who had only IgG seroconversion at baseline. Positive IgG and negative IgM

at baseline can be due to either passive transmission of IgG via transfusion or previous infection with CMV. However, previous infection with CMV disease was unlikely since virtually all patients were tested as R- prior to study start. Also recent infection was unlikely due to the lack of IgM seroconversion at baseline. Only one patient had IgG and IgM seroconversion at baseline. This patient had positive IgM and IgG at day ten, most likely this represent a primary response to CMV.

F.1a. Seroconversion IgG

The overall rate of seroconversion (IgG) in patients with CMV disease (Endpoint Committee) up to 12 months post-transplant was 54/64 = 84.4%. This includes seroconversion (IgG) prior to or after CMV disease onset.

Of the 64 patients who had CMV disease (Endpoint Committee) up to 12 months post-transplant, 12/64 (18.8%) seroconverted (IgG) before the CMV disease onset, 42/64 (65.6%) seroconverted (IgG) at the same visit or after the CMV disease onset and 10/64 (15.6%) did not seroconvert (IgG) at all. Note that there may be patients in the last category who had limited IgG seroconversion data collected and analyzed.

F.1b. Seroconversion IgM

The overall rate of seroconversion (IgM) in patients with CMV disease (Endpoint Committee) up to 12 months post-transplant was 46/64 = 71.9%. This included seroconversion (IgG) prior to or after CMV disease onset.

Of the 64 patients who had CMV disease (Endpoint Committee) up to 12 months post-transplant, 4/64 (6.3%) seroconverted (IgM) before the CMV disease onset, 42/64 (65.6%) seroconverted (IgM) at the same visit or after the CMV disease onset and 18/64 (28.1%) did not seroconvert (IgM) at all. Note that there may be patients in the last category who had limited IgM seroconversion data collected and analyzed.

Comment: As the sponsor has stated, the experiments presented for seroconversion are very preliminary to meaningfully interpret the results.

G. Package Insert

The VIROLOGY section of the Package Insert, already approved for the original NDA 21.304 for Valcyte, was revised and continues to be revised by the sponsor for this sNDA 21-304 SE1-001. The Viral Resistance subsection was initially revised as follows:

G.1a. The last part of first sentence, First Paragraph of Viral Resistance Subsection

Currently it reads as follows:

.....and/or in the viral polymerase gene (*UL54*)

It should be corrected to read

.....and/or in the viral **DNA** polymerase gene (*UL54*)

G.1b. The Last sentence, First Paragraph of Viral Resistance Subsection

Currently it reads as follows:
.....show cross-resistance to other antivirals that target the viral polymerase.

It should be corrected to read

.....show cross-resistance to other antivirals that target **the same sites on** viral **DNA** polymerase.

G.2. The last two paragraphs added to the "Viral Resistance" subsection of the VIROLOGY Section of the label should be deleted for the reasons already cited under Section E.2b. as "Comments." These reasons were:

1. CMV strains resistant to ganciclovir can emerge by selection of mutations in either the viral protein kinase (*UL97*) gene and/or in the viral DNA polymerase gene (*UL54*). Mutation in *UL97* gene usually, but not always, leads to the development of GCV resistant mutants; therefore mutation in *UL54* gene may or may not follow mutation in *UL97* gene, especially in immunocompromised patients. Experiments should have been conducted to map mutations in both the CMV *UL97* gene and the *UL54* genes to detect the emergence of GCV-resistant mutants of CMV. Current published data (though limited) indicate a different antiviral susceptibility pattern depending upon whether the CMV strains contain mutations only in *UL 97*, only in *UL54* or in both genes.
2. A number of mutations noted in the current clinical study were considered as wild-type variants or speculated as of unknown significance. The phenotypic nature of all the CMV isolates containing these mutations should have been evaluated to unambiguously establish their resistance to GCV.
3. The sample size tested for the determination of CMV resistance to GCV or VGCV was too small to derive any meaningful conclusion.

G.3. On the basis of these comments, the sponsor has revised the two sentences in the first paragraphs and deleted the last two paragraphs In the Viral Resistance subsection as suggested.

G4. In a very recent version of the Package Insert submitted on August 14, 2003, the sponsor has revised the IC_{50} values of GCV presented under the Subsection on Antiviral Activity. The IC_{50} values of 0.02 to 5.75 µg/mL (0.08 to 22.94 µM) are replaced by 0.02 to 3.5 µg/mL (0.08 to 14 µM).

Comment: The range of IC_{50} values of GCV [0.02 to 5.75 µg/mL (0.08 to 22.94 µM)] against various strains and clinical isolates of CMV published in the Package Insert for the original NDA 21-304 was based upon the results published by various investigators included (by the sponsor) in Appendices 2 (page 77) and 3 (page 83) of Section 7 of the NDA 21-304. If deemed necessary at this time, and contrary to the revision suggested by the sponsor, the IC_{50} values should be revised to 0.02 to 6.4 µg/mL (0.08 to 27 µM) on the basis of three references: References 7638 (cited in page 77) and 7571 (cited in page 83) of Section 7, NDA 21-304. The 3rd reference by Snoeck et al., 1992, Eur. J. Clin. Microbiol Infect. Dis. 11:1144-1155.

H. Conclusions

1. The sponsor has requested approval of VGCV tablets for the prevention of CMV disease in patients at risk. A tablet formulation of VGCV has been approved for the treatment of CMV retinitis in patients with AIDS, and the sponsor has cross referenced to the original NDA 21-304 for the preclinical information on VGCV.
2. To justify the approval, a randomized, double-blind, double-dummy, phase III clinical trial, PV16000, was conducted to determine the comparative efficacy, safety and pharmacokinetics of VGCV (900 mg o.d.) versus oral GCV (1000 mg t.i.d.) for the prevention of CMV disease in 372 high-risk (D+/R-) recipients of heart, liver, kidney, and kidney-pancreas allograft in 57 clinical centers worldwide. No lung transplant patients were enrolled in this study.

   patients at risk requested by the sponsor.
3. A number of clinical and laboratory tests were performed to determine the eligibility and efficacy of VGCV compared to oral GCV. Virologic tests included ... or FDA-approved DNA/RNA-based assay. Drug resistance was analyzed by locating the CMV *UL97* mutations by nested polymerase chain reaction followed by restriction fragment length polymorphism (RFLP) and *UL97* DNA sequencing.
4. The overall incidence of CMV disease was comparable on the two treatment arms (18.4% in GCV arm and 17.2% in VGCV arm). The incidence of CMV syndrome, however, was more common on the GCV arm (12.0% GCV, 7.9% VGCV), and the incidence of tissue-invasion was more common on the VGCV arm (6.4% GCV, 9.2% VGCV) due mainly to tissue-invasive CMV disease events which occurred during the first 6 months post-transplant.
5. The majority of tissue-invasive CMV disease was experienced by liver transplant recipients, and the incidence of tissue invasive CMV disease in liver transplant patients was higher in the VGCV arm (13.6%) compared to those in the GCV arm (3.4%)(Table 7). The apparent heterogeneity in the results between the different allograft types, and the higher incidence of tissue-invasive
6. The proportion of patients who experienced CMV disease (as assessed by the Endpoint Committee) or death was comparable on the two treatment arms (16.8% in GCV arm and 15.1% VGCV arm) by 6 months post-transplant, compared with 24.0% GCV, 22.6% VGCV by 12 months post-transplant. However, the incidence of CMV disease or death by 6 months or 12 months post-transplant remained higher for liver transplant recipients on the VGCV arm, and higher for kidney transplant recipients on the GCV arm. The time to CMV disease or death appeared slightly shorter on the GCV arm (due to the CMV disease events).
7. The incidence of opportunistic infections (due to aspergillus, candida, pneumocystis carinii, cryptococcus, listeria monocytogenes, herpes simplex and herpes zoster) up to 6 months post-transplant was comparable on the two treatment arms (9.6% GCV, 9.2% VGCV), and no treatment-group difference was detected in the incidence of the various OIs analyzed. However, the number of patients experiencing OIs in the different allograft groups was too low to enable any meaningful comparison.
8. The proportion of patients experiencing viremia was almost identical in the two treatment arms (48.8% GCV, 48.5% VGCV). However, by 12 months post-transplant, the estimated time by which 25% patients had experienced viremia (lower quartile), and the median time to viremia, were both shorter on the GCV arm [lower quartile, 120

days GCV arm vs. 142 days VGCV arm; median, 282 days GCV arm vs. 357 days VGCV arm.

9. The peak CMV DNA loads remained generally higher for patients with Endpoint Committee defined CMV disease (median peak viral load $\log_{10}$ 4.3, versus $\log_{10}$ 2.6 for patients without Endpoint Committee defined CMV disease). However, there were examples of very high viral loads being recorded for patients who did not develop CMV disease (p207 of this submission), and conversely, of low viral loads being recorded for patients who did develop CMV disease (p203 of this submission).
10. There appeared to be no strong link between the onset of viremia and the development of CMV disease or acute graft rejection, although a slightly higher proportion of patients developed CMV disease following viremia, whilst conversely, a higher proportion of patients experienced acute graft rejection prior to viremia. In addition, there were no significant differences between the patients enrolled in the two arms (GCV and VGCV) of the study.
11. Experiments designed to identify and characterize GCV resistant mutants were incomplete. As discussed in Section E earlier, mutations in both the CMV *UL97* gene and the *UL54* gene of CMV isolates should have been mapped, and the phenotypic nature of all the CMV isolates containing these mutations should have been evaluated to unambiguously establish their resistance to GCV. The sponsor has been advised to propose a Phase IV clinical study to address the critical issues related to the incidence and appropriate characterization of all the GCV-resistant mutants emerging from this group of special patients.
12. At the request from the medical officer on the rates of CMV seroconversion (according to organ transplant group) in patients with or without developing CMV disease, the sponsor has submitted very preliminary raw CMV serology data. The overall rate of seroconversion (IgG) in patients with CMV disease (Endpoint Committee) up to 12 months post-transplant was 54/64 = 84.4%. This included seroconversion (IgG) prior to or after CMV disease onset. The overall rate of seroconversion (IgM) in patients with CMV disease (Endpoint Committee) up to 12 months post-transplant was 46/64 = 71.9%. This includes seroconversion (IgG) prior to or after CMV disease onset. However, as the sponsor has stated, the significance of these preliminary results are yet to be critically evaluated.
13. The Package Insert was adequately revised as suggested; however, in the latest version submitted on August 14, 2003, the range of IC_{50} values of GCV has been revised. As discussed earlier in Section G3, the IC_{50} values previously approved for the original NDA 21,304 should be reinstated.
14. Depending upon the following two conditions, this supplemental NDA is approved with respect to microbiology.

RECOMMENDATIONS: 1. The Phase IV study should be based upon the microbiology comments and recommendations communicated facsimile on August 14, 2003. These comments and recommendations were as follows.

As a Phase IV study commitment, please submit a proposal to monitor and characterize the GCV-resistant mutants of CMV emerging from patients undergoing preventive Valcyte therapy. To accurately assess the emergence of CMV mutants resistant to ganciclovir in this patient population, the study should address the following virologic concerns.

- The proposal to sequence the *UL54* gene for all day 100 and suspected CMV disease samples (which were not tested for *UL54* resistance mutations) is not sufficient. The phenotypic nature of these clinical isolates with regard to their susceptibility to ganciclovir should be clearly defined.

2. The IC_{50} values of GCV [0.02 to 5.75 µg/mL (0.08 to 22.94 µM)] against various strains and clinical isolates of CMV previously approved for the original NDA 21,304 should be reinstated. If deemed necessary at this time, the IC_{50} values should be revised to 0.02 to 6.4 µg/mL (0.08 to 27.0 µM) on the basis of three references: References 7638 (cited in page 77) and 7571 (cited in page 83) of Section 7, NDA 21-304. The 3rd reference is by Snoeck et al., 1992, Eur. J. Clin. Microbiol Infect. Dis. 11:1144-1155.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-304 / S-001

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-304 / SE1-001
Drug Name:	Valcyte™ (valganciclovir HCl, Ro 107-9070) 450 mg tablets
Indication(s):	Prevention of cytomegalovirus (CMV) disease in [redacted] patients at risk
Applicant:	Syntex (U.S.A.) LLC
Dates:	Submitted: November 11, 2002 Received: November 11, 2002 Draft Review Completed: September 10, 2003 Final Review Completed: September 10, 2003
Review Priority:	Standard review
Biometrics Division:	Division of Biometrics III (HFD-725)
Statistics Reviewer:	Fraser Smith, Ph.D.
Concurring Reviewers:	Greg Soon, Ph.D.
Medical Division:	Division of Antiviral Drug Products (HFD-530)
Clinical Team:	Andreas Pikis, M.D.; Medical Reviewer.
Project Manager:	Nitin Patel, RPh; Regulatory Project Manager

Keywords: CMV retinitis, seropositive donors / CMV seronegative recipients —(D+/R-) (6-month data), valganciclovir, oral ganciclovir, treatment by organ interaction, Phase III.

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1. EXECUTIVE SUMMARY

1.1. Conclusions and Recommendations

The relative treatment effect of valganciclovir vs. oral ganciclovir differed by organ transplant type (p-value=0.036 and 0.016 using the Breslow-Day statistic and Zelen's exact test to compute the significance of the treatment by organ interaction). In particular, oral ganciclovir treatment was statistically superior to valganciclovir for the treatment of tissue-invasive CMV disease in liver transplant patients at 6 months (p=0.04). This is a [redacted] because approximately half of the patients in the study had liver transplants. Hospitalization and mortality rates were also numerically higher in liver transplant patients that received valganciclovir.

CMV disease was higher for heart, kidney and kidney/pancreas patients for oral ganciclovir patients than valganciclovir patients. Valganciclovir was statistically superior to oral ganciclovir in kidney patients for the treatment of CMV Disease at 6 months (p=0.01).

Valganciclovir should probably be indicated for the treatment of CMV disease in kidney and heart transplant patients but [redacted]

1.2. Brief Overview of Clinical Studies

PV16000: Prevention of CMV Disease in Heart, Liver and Kidney Transplant Patients

A double-blind, double-dummy active comparator study was conducted in 372 heart, liver and kidney transplant patients at high-risk for CMV disease (D+/R-). Patients were randomized (2 Valcyte: 1 oral ganciclovir) to receive either Valcyte (900 mg once daily) or oral ganciclovir (1000 mg three times a day) starting within 10 days of transplantation until Day 100 post-transplant. Patients were stratified by center and organ type (heart, liver or kidney allograft).

The primary objectives of this study was to determine the comparative efficacy and safety of valganciclovir (900 mg q.d.) relative to oral ganciclovir (1000 mg t.i.d.) when given for the prevention of CMV disease in high risk D+/R-, heart, liver, kidney, and kidney-pancreas allograft recipients.

Patients were to be randomized to receive drug as soon as they are able to tolerate oral medication (but no later than 10 days post-transplant). Treatment was continued through day 100 post-transplant. A post-treatment follow-up period continued through post-transplant months 4, 5 and 6. As additional follow-up period continued through post-transplant months 8, 10 and 12.

The primary endpoint was the proportion of patients who developed CMV disease, including CMV syndrome and/or tissue-invasive disease during the first 6 months post-transplant.

All cases of suspected CMV disease reported by the investigator were to be submitted to the Endpoint Committee for review and adjudication prior to data analysis. Based on their review of the signs, symptoms and laboratory criteria of CMV disease (as defined in the protocol) and supporting clinical and laboratory documentation, the Committee was to identify those CMV disease events which should have been included in the primary efficacy analysis. The Committee was also supposed to assess whether the CMV disease was CMV syndrome and/or tissue-invasive CMV disease, the date of onset of CMV disease, and to provide the rationale for their decision.

1.3. Statistical Issues and Findings

The proportion of patients who developed CMV disease, including CMV syndrome and/or tissue-invasive disease during the first 6 months post-transplant was 12.1% in the valganciclovir arm (N=239) compared with 15.2% in the oral ganciclovir arm (N=125). However, there was a statistically significant treatment by organ transplant type interaction (p-value from Breslow-Day test = 0.036 and p-value from Zelen's exact test=0.016).

Oral ganciclovir treatment was superior to valganciclovir for the treatment of tissue-invasive CMV disease in liver transplant recipients (p=0.04), where nearly five times as many valganciclovir patients developed tissue-invasive CMV disease (14%, 16/118) as oral ganciclovir patients (only 3%, 2/59).

Valganciclovir was statistically superior to oral ganciclovir for the treatment of CMV disease in kidney transplant recipients (p=0.01). Twenty-three percent (23%, 9/39) of the oral ganciclovir patients who had kidney transplants developed CMV disease compared to only 6% (5/81) of the valganciclovir patients. There were probably an insufficient number of heart and kidney/pancreas transplant recipients in order to demonstrate non-inferiority in favor of valganciclovir for each organ type separately. However, when liver transplant recipients were excluded, there was no statistically significant treatment by organ interaction (Breslow-Day p-value = 0.62) and valganciclovir was superior to oral ganciclovir. The estimated difference in proportions was +0.13, in favor of valganciclovir [95% CI: = 0.02, 0.23; Cochran-Mantel-Haenszel (CMH) p-value stratified by organ type = 0.02].

Mortality at six months was numerically greater in the valganciclovir arm (3.7%, 9/244) compared to the oral ganciclovir treatment group (1.6%, 2/126). Two (2) ganciclovir deaths and most (7 out of 9) of the valganciclovir deaths occurred in liver transplant recipients. The remaining 2 valganciclovir deaths occurred in heart transplant recipients.

Neutropenia, defined as <1000 ANC/μL was reported more frequently in the valganciclovir group for liver, heart and kidney transplant recipients. The frequency of neutropenia among patients who received valganciclovir or ganciclovir, respectively, were; liver transplant recipients (10%, 3%), kidney (7%, 5%), heart (3%, 0%). Overall, neutropenia was higher in valganciclovir patients (8% of valganciclovir patients had neutropenia at 6 months, compared to 3% of the oral ganciclovir patients). This difference approached statistical significance (p=0.06).

Table 1: Summary of Primary and Selected Secondary Efficacy and Safety Endpoints for Liver Transplant Recipients

Endpoint	Ganciclovir (n=127)	Valganciclovir (n=245)
CMV Disease (6 months – Endpoint Committee)	12% (7 / 59)	19% (2 / 35)
Tissue-Invasive CMV Disease (6 months – Endpoint Committee)	3% (2 / 59)	14% (16 / 118)
Mortality (6 months)	3% (2 / 60)	6% (7 / 124)
Neutropenia (6 months)	3% (2 / 60)	10% (13 / 124)
Hospitalization (6 months)	49% (30 / 61)	57% (71 / 124)
Hospitalization (12 months)	61% (37 / 61)	66% (82 / 124)

For hospitalization, the Breslow-Day tests for treatment by organ interactions were 0.08 at 6 months and 0.053 at 12 months. These were not statistically significant at the 0.05 level but were small enough to be indicative of an interaction. Hospitalizations at 6 and 12 months were numerically higher in liver transplant patients that received valganciclovir than in liver transplant patients receiving oral ganciclovir (57% in valganciclovir patients and 49% in oral ganciclovir patients at 6 months; 66% in valganciclovir patients and 61% in oral ganciclovir patients at 12 months).

Hospitatizations were numerically lower in heart transplant patients that received valganciclovir (31% of the valganciclovir patients compared to 48% of the oral ganciclovir patients at 6 months; 54% of the valganciclovir patients compared to 76% of the oral ganciclovir patients at 12 months). In kidney transplant recipients, hospitalization rates appeared to be similar at 6 months and higher in valganciclovir patients at 12 months.

The incidence of serious adverse events was also numerically higher in valganclovir patients. Fifty percent (50%, 123/244) of valganciclovir patients had serious adverse events compared to 41% (51/126) of the oral ganciclovir patients. These differences were not statistically significant, but the trial was neither powered nor designed to detect differences of this magnitude for safety or efficacy endpoints.

2. INTRODUCTION

2.1. Overview

2.1.1. Study Objective and Design

The primary objectives of study PV16000 were to determine the comparative efficacy and safety of valganciclovir (900 mg q.d.) relative to oral ganciclovir (1000 mg t.i.d.) when given for the prevention of CMV disease in high risk D+/R-, heart, liver, kidney, and kidney-pancreas allograft recipients.

PV16000 was a randomized, double-blind, double-dummy, active comparator controlled multi-center study. Patients were randomized in a 2:1 ratio, to either valganciclovir or oral ganciclovir, respectively. Patients were stratified by center and organ type (heart, liver or kidney allograft). That is, the randomization was performed to ensure an approximate allocation ratio of 2:1 (Valcyte : oral ganciclovir) within each organ type group at each center to avoid any imbalance in treatment allocation.

Patients were to be randomized to receive drug as soon as they are able to tolerate oral medication (but no later than 10 days post-transplant). Treatment was to continue through day 100 post-transplant. A post-treatment follow-up period continued through post-transplant months 4, 5 and 6. As additional follow-up period continued through post-transplant months 8, 10 and 12.

The primary endpoint was the development of CMV disease up to 6 months post-transplant. CMV disease incorporates CMV syndrome and/or tissue-invasive CMV disease. Traditionally, studies of the prevention of CMV disease after solid organ transplant have lasted 6 months. Hence the primary analysis for this study was based on data up to 6 months post-transplant. However the applicant noted that an analysis looking at prevention of CMV disease up to 12 months may give a more complete picture by identifying episodes of CMV disease which may occur between 6 and 12 months.

All cases of suspected CMV disease reported by the investigator were submitted to the Endpoint Committee for review and adjudication prior to data analysis. Based on their review of the signs, symptoms and laboratory criteria of CMV disease (as defined in the protocol) and supporting clinical and laboratory documentation, the Committee was supposed identify those CMV disease events

which should be included in the primary efficacy analysis. The Committee also assessed whether the CMV disease was CMV syndrome and/or tissue-invasive CMV disease, the date of onset of CMV disease, and provided the rationale for their decision.

2.2. Data Sources

Approximately 1/2 of the patients had liver transplants, followed by a third with kidney transplants. The remaining had heart or kidney/pancreas transplants. The percentage of patients with each different type of organ transplant was similar in the two treatment groups.

Table 2: Summary of Transplanted Organ Type (All Patients)

ORGAN TYPE	GCV N=127	VGCV N=245
HEART	21 (16.5%)	35 (14.3%)
LIVER	61 (48.0%)	122 (49.8%)
KIDNEY	39 (30.7%)	81 (33.1%)
KIDNEY/PANCREAS	6 (4.7%)	5 (2.0%)
LIVER/KIDNEY	0	2 (0.8%)

For purposes of all other summary tables and analyses, liver/kidney patients will be added to the liver strata.

Table 3: Summary of Serology Status Prior to Transplant (All Patients)

	GCV	VGCV
NO. OF PATIENTS RANDOMIZED	127	245
D+/R-	125 (98.4%)	239 (97.6%)
D+/R+	1 (0.8%)	5 (2.0%)
D-/R-	1 (0.8%)	1 (0.4%)

The vast majority (98%) of transplants consisted of donor positive / recipient negative (D+/R-) patients. Less than 2% of the donors and recipients were both CMV positive (D+/R+) and <1% were both CMV negative (D-/R-).

The two treatment groups were comparable with respect to demographic characteristics and duration of treatment. Approximately ¾ were male, 90% were white, 6% were black, and 4% were other races. The mean age was approximately 45 years, while the mean weight and height was approximately 83 kg and 173 cm. The majority of patients received between 91 and 100 days of treatment. Approximately 90% of the patients were in the study for at least 190 days and over 90% had at least 6 months of post-transplant follow-up data.

Table 4: Summary of Demographic Data (All Patients)

	GCV N = 127	VGCV N = 245
Sex		
Male	95 (75%)	179 (73%)
Female	32 (25%)	66 (27%)
N	127	245
Race		
Caucasian	115 (91%)	218 (89%)
Black	7 (6%)	16 (7%)
Oriental	1 (<1%)	1 (<1%)
Other	4 (3%)	10 (4%)
N	127	245
Age		
Mean	45.3	45.7
SD	12.9	12.5
SEM	1.15	0.80
Median	46.0	48.0
Min-Max	16 – 71	14 – 71
N	127	245
Weight in kg		
Mean	84	81
SD	22	18
SEM	2.0	1.2
Median	80	81
Min-Max	41 – 154	31 – 135
N	126	239
Height in cm		
Mean	173	172
SD	10	11
SEM	0.91	0.68
Median	173	173
Min-Max	145 – 193	122 – 195
N	125	243

n represents number of patients contributing to summary statistics.
Percentages are based on n (the number of valid values).
Percentages are not calculated if n < 10.

Table 5: Summary of Treatment Duration (All Patients)

	GCV N=127	VGCV N=245
TREATMENT DURATION (DAYS)		
1 – 10	3 (2.4%)	6 (2 .4%)
11 – 20	1 (0.8%)	4 (1 .6%)
21 – 30	3 (2.4%)	2 (0 .8%)
31 – 40	1 (0.8%)	2 (0 .8%)
41 – 50	2 (1.6%)	2 (0 .8%)
51 – 60	1 (0.8%)	2 (0 .8%)
61 – 70	0	2 (0 .8%)
71 – 80	2 (1.6%)	6 (2 .4%)
81 – 90	4 (3.1%)	11 (4 .5%)
91 – 100	100 (78.7%)	200 (81.6%)
>100	9 (7.1%)	7 (2 .9%)
NOT DOSED	1 (0.8%)	1 (0 .4%)
N	126	244
MEAN (s.d.)	90.6 (21.3)	90.3 (20.5)
MEDIAN	97.0	97.0
MINIMUM	1.0	2.0
MAXIMUM	117.0	115.0

Treatment duration is defined as number of days between treatment start date and Treatment end date + 1.

Table 6: Summary of Duration in Study up to 6 Months Post-Transplant (All Patients)

	GCV N=127	VGCV N=245
DURATION IN STUDY		
1 – 19	3 (2.4%)	4 (1 .6%)
20 – 39	2 (1.6%)	4 (1 .6%)
40 – 59	1 (0.8%)	3 (1 .2%)
60 – 79	0	2 (0 .8%)
80 – 99	0	1 (0 .4%)
100 – 119	2 (1.6%)	1 (0 .4%)
140 – 159	0	3 (1 .2%)
160 – 179	0	3 (1 .2%)
180 – 190	1 (0.8%)	4 (1 .6%)
> 190	118 (92.9%)	220 (89.8%)
N	127	245
MEAN (s.d.)	333.9 (85.0))	
MEDIAN	364.0	364.0
MINIMUM	5.0	7.0
MAXIMUM	420.0	427.0

Table 7: Summary of Patient Follow-up (All Patients)

Follow-up Time	GCV N=127	VGCV N=245
≥6 months	119 (94%)	227 (93%)
<6 months	8 (6%)	18 (7%)

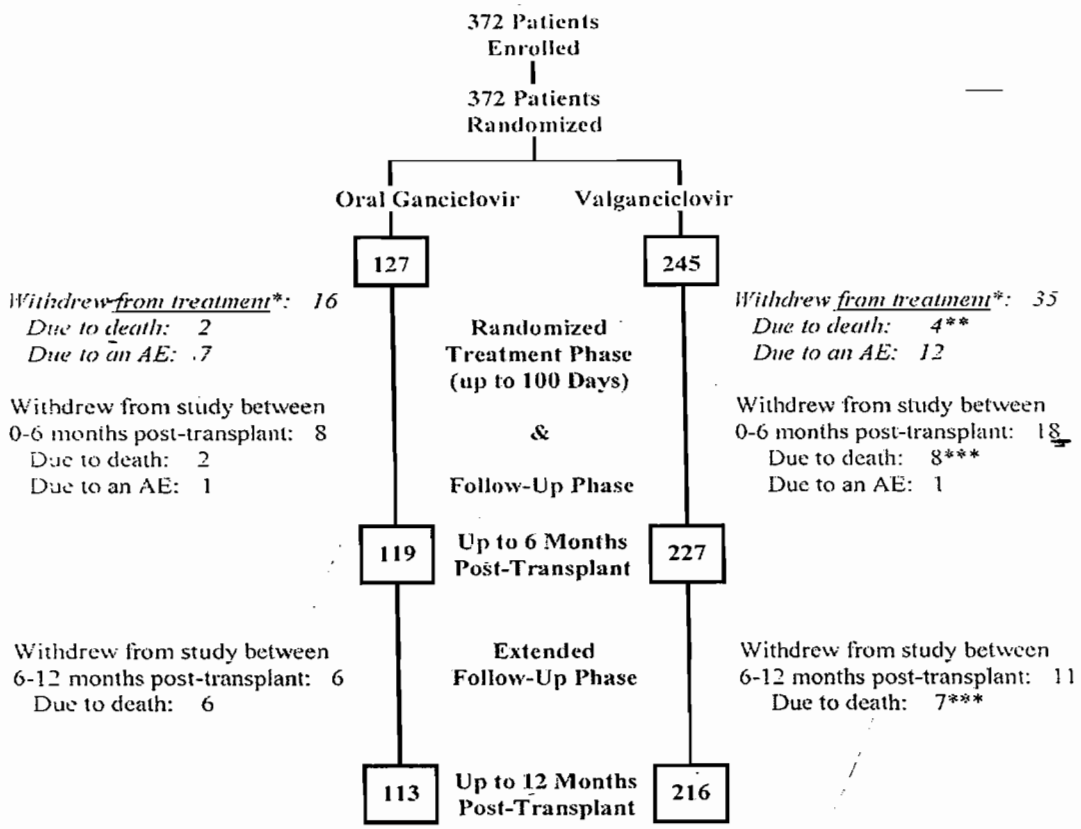
Table 8: Summary of Duration on Study up to 12 Months Post-Transplant (All Patients)

	GCV N=127	VGCV N=245
DURATION IN STUDY		
1 - 3 9	5 (3.9%)	8 (3 .3%)
40 - 7 9	1 (0.8%)	5 (2 .0%)
80 - 1 19	2 (1.6%)	2 (0 .8%)
120 – 159	0	3 (1 .2%)
160 – 199	0	5 (2 .0%)
200 – 239	1 (0.8%)	1 (0 .4%)
240 – 279	1 (0.8%)	0
280 – 319	4 (3.1%)	5 (2 .0%)
320 – 359	14 (11.0%)	29 (11.8%)
360 – 380	86 (67.7%)	175 (71.4%)
> 380	13 (10.2%)	12 (4 .9%)
N	127	245
MEAN (s.d.)	343.7 (82.0)	338.6 (85.9)
MEDIAN	366.0	365.0
MINIMUM	5.0	7.0
MAXIMUM	420.0	469.0

Table 9: Summary of Patient Follow-Up (All Patients)

	GCV N=127	VGCV N=245
No. of patients followed to twelve Months	113 (89.0%)	216 (88.2%)
No. of patients not followed to twelve months	14 (11.0%)	29 (11.8%)

Figure 1: Patient Disposition (up to 12 Months Post-Transplant)



* Patients who withdrew from study treatment did not necessarily withdraw from the study, and could be monitored up to 12 months post-transplant for collection of follow-up efficacy and safety data.
** In addition, one patient (26480/6001), on the valganciclovir arm, died on day 102 post-transplant, after completing the full course of study medication This patient was therefore not included as a withdrawal from study medication due to death, but was included in the total number of deaths (5 deaths) occurring on the valganciclovir arm .on treatment.
*** One patient (25966/4201), on the valganciclovir arm, died on their 6 month study visit (on day 181 post-transplant, or day 178 in relation to study drug dosing). As complete follow-up data up to 6 months post-transplant were collected for this patient, they were categorized as having completed the first 6 months of the study, and were therefore categorized as a withdrawal from study between 6-12 months post-transplant due to death (7 withdrawals). However, it should be noted that this patient was included in the total number of deaths occurring up to 6 months post-transplant (9 deaths), and not in the total number of deaths occurring between 6-12 months post-transplant (6 deaths)

3. STATISTICAL EVALUATION

3.1. Evaluation of Efficacy

3.1.1. Methods of Statistical Analysis of Efficacy Data

The primary analysis compared the proportion of patients who developed CMV disease, as assessed by the Endpoint Committee, within the first 6 months post-transplant. Two one-sided 97.5% confidence intervals and a corresponding two-sided p-value were presented.

The Intent to Treat (ITT) population was the primary efficacy analysis population. The ITT population included patients who were randomized and who were CMV donor positive (D+) / CMV recipient negative (R-).

The study provided an assessment of the non-inferiority of valganciclovir treatment, compared to ganciclovir over a six-month time period. Let π_G and π_V denote the true proportion of patients on ganciclovir and valganciclovir, respectively, who developed CMV disease (as assessed by the Endpoint Committee) up to 6 months post transplant.

A two-stage hypothesis testing approach was used in the analysis of the primary endpoint, testing for non-inferiority and superiority.

The non-inferiority hypothesis was defined as:

$H_0: \pi_G - \pi_V \leq -0.05$

$H_1: \pi_G - \pi_V > -0.05.$ ← Valganciclovir is non-inferior to Ganciclovir

Valganciclovir was deemed non-inferior to ganciclovir if the lower limit of the one-sided 97.5% confidence interval for the difference in proportions of patients with CMV disease up to 6 months (ganciclovir – valganciclovir) was >-0.05.

If valganciclovir was deemed non-inferior to ganciclovir, then at the second stage, the superiority of valganciclovir to ganciclovir, was tested. Superiority was defined as:

$H_0: \pi_G - \pi_V \leq 0$

$H_1: \pi_G - \pi_V > \theta$. ← Valganciclovir is superior to Ganciclovir

For analyses of proportions, two stratified one-sided 97.5% confidence intervals for the differences in proportions were presented. The strata consisted of the heart, liver and kidney transplant groups. The 11 kidney/pancreas recipients were combined with heart transplant recipients (the second smallest stratum) for the weighted analysis used to compute treatment differences (but were not combined for the Breslow-Day or Zelen interaction tests). Center was not included as a stratification variable in the calculation of the confidence interval. This was due to the anticipated small number of patients at each center. However informal checks of consistency of any treatment effects across centers and across countries were performed.

[Reference: Koch, G.G., Carr, G.J., Amara, I.A., Stokes, M.E.. and Uryniak, T.J. (1989). Categorical Data Analysis. Chapter 13 in Berry, D.A. (ed.), Statistical Methodology in the Pharmaceutical Sciences, Marcel Dekker, New York, pp. 414-421.]

Handling patients who received no treatment or have insufficient follow-up data

If patients received no study treatment or were included in the ITT population but had insufficient follow-up data, they were summarized as 'unevaluable', unless they had the event in question (for instance, CMV disease). Patients with insufficient 'follow-up data' were defined as having completed their scheduled 6 month visit. For the ITT population, unevaluable patients were included in the denominator for the calculation of proportions and one-sided 97.5% confidence intervals.

For example, consider a hypothetical patient who died on day 80 post-transplant and had no CMV disease. This patient would be treated as unevaluable for the primary analysis. They would be treated as evaluable for the analyses of CMV disease or death and the analysis of treatment failure because the patient died.

In 'time to event' analyses, unevaluable patients were to be treated as censored at the time of withdrawal.

Patients with missing visits

Due to the nature of the disease and the requirements for reporting CMV disease, if a patient missed a visit but then completed the subsequent visit and was still CMV disease free at that subsequent visit, it was assumed that the patient was event-free at that missing visit.

Patients with more than one occurrence of CMV viral load > BLQ

If patient have more than one occurrence of CMV viral load > BLQ, they were only to be counted once in the summary table and the date of first occurrence of CMV viral load > BLQ was to be used in the calculation of time to event.

3.1.2. Primary Efficacy Analysis

Table 10: Summary of CMV Disease up to 6 Months Post-transplant - Endpoint Committee (ITT Population)

	Ganciclovir (N=125)		Valganciclovir (N=239)		Weighted Difference in Proportions (2-sided 95% CI)	
	N	%	N	%	Difference	2-sided 95% CIs p-value
Patients with CMV disease	19	15.2	29	12.1	+0.03	-0.042, +0.11[+] p=0.38
Patients with no CMV disease	99	79.2	198	82.8		
Patients unevaluable	7	5.6	12	5.0		
CMV syndrome	13	10.4	12	5.0	+0.06	-0.01, +0.12 p=0.08
Tissue-Invasive CMV	6	4.8	17	7.1	-0.02	-0.07, +0.03 p=0.41
Hepatitis	1		6			
Pneumonia	1		2			
Gastrointestinal	4		12			
Retinitis	0		0			
Other	0		1			

2-SIDED 95% CIs IN EFFICACY TABLES WERE COMPUTED USING TWO 1-SIDED 97.5% CIs AND P-VALUE FROM THE STRATIFIED Z TEST.
[+]IF LOWER LIMIT OF THE 1-SIDED 97.5% CI > -0.05 THEN VGCV IS NON-INFERIOR TO GCV.
IF LOWER LIMIT OF THE 1-SIDED 97.5% CI > 0 THEN VGCV IS SUPERIOR TO GCV.
Patients can have more than one type of tissue-invasive CMV disease
If a patient has insufficient visits up to 6 months they are
Unevaluable unless the patient had CMV disease

Fifteen percent of ganciclovir patients and 12% of valganciclovir patients developed CMV disease as adjudicated by the Endpoint Committee within the first 6 months post-transplant. There was insufficient evidence to conclude that valganciclovir was superior to oral ganciclovir (p=0.38). The

estimated weighted difference in proportions was 0.034, in favor of valganciclovir with a 95% confidence interval ranging from –0.042 to 0.110. The lower bound of the 95% confidence interval exceeded -0.05, the pre-specified non-inferiority boundary. Therefore the applicant concluded that valganciclovir was non-inferior to oral ganciclovir for the prevention of CMV disease in SOT recipients.

This statement requires one to assume that there was no difference in treatment effect for each organ transplant type. However there was a statistically significant treatment by organ type interaction (p=0.036 using the Breslow-Day test and p=0.016 using Zelen's exact test), which will be discussed in Section 4 of this review.

The primary (organ-stratified) analysis depends on the assumption of consistency of the primary endpoint across the organ types. This assumption does not hold because there was a qualitative interaction involving liver transplant recipients where the valganciclovir patients had a numerically higher rate of CMV disease compared to oral ganciclovir patients. This was particularly apparent for tissue-invasive CMV disease in liver transplant recipients, where almost five times as many valganciclovir patients developed tissue-invasive disease as oral ganciclovir patients. This difference was statistically significant, which was particularly impressive given the study was a non-inferiority study and was neither designed nor powered to detect statistical significance.

Therefore the "overall rates" no longer pertain to any organ types and should not be used. The use of an overall rate of CMV disease to compared valganciclovir and oral ganciclovir patients would give the misleading impression that valganciclovir was non-inferior to oral ganciclovir in all solid organ transplant patients, including liver transplant recipients.

3.1.2.1. Robustness of Primary Analysis

A similar percentage of patients (approximately 5-6%) were unevaluable in both treatment groups. Compared to valganciclovir, approximately twice as many patients who took oral ganciclovir had CMV syndrome (10% for oral ganciclovir vs. only 5% for valganciclovir) while the percentage of patients with tissue-invasive CMV was a little higher for valganciclovir (7.1% vs. 4.8% for oral ganciclovir). The majority of tissue-invasive CMV disease was evident in liver transplant patients (16/17 for vaganciclovir compared to only 2/6 for oral ganciclovir).

Table 11: Robustness of CMV Disease up to 6 Months Post-Transplant to Missing Data (ITT Population)

	Ganciclovir (N=125)		Valganciclovir (N=239)		Weighted Difference in Proportions (2-sided 95% CI)	
	N	%	N	%	Difference	2-sided 95% CIs p-value
Unevaluables counted as no CMV Disease	19	15	29	12	+0.034	-0.042, +0.11 p=0.38
Unevaluables (UEs) counted as CMV Disease	26	21	41	17	+0.038	-0.048, +0.12[+] p=0.39
VGCV UEs counted as CMV Disease, GCV UEs counted as no CMV Disease	19	15	41	17	-0.018	-0.10, +0.06 p=0.65

When unevaluables were counted as having no CMV disease, valganciclovir was non-inferior to oral ganciclovir (the lower bound of the 95% confidence interval was -.0.042, which was greater than -0.05). When unevaluables were counted as having CMV disease, the lower bound of the 95% confidence interval was 0.048, which still indicated that valganciclovir was non-inferior to oral ganciclovir. The most conservative analysis assigned unevaluables taking valganciclovir as CMV disease and unevaluables taking oral ganciclovir as not having CMV disease. Not surprisingly, in this case the lower bound of the 95% confidence interval was less than -0.05, and oral ganciclovir appeared to be the better treatment. None of these differences were statistically significant.

3.1.3. Secondary Efficacy Analyses

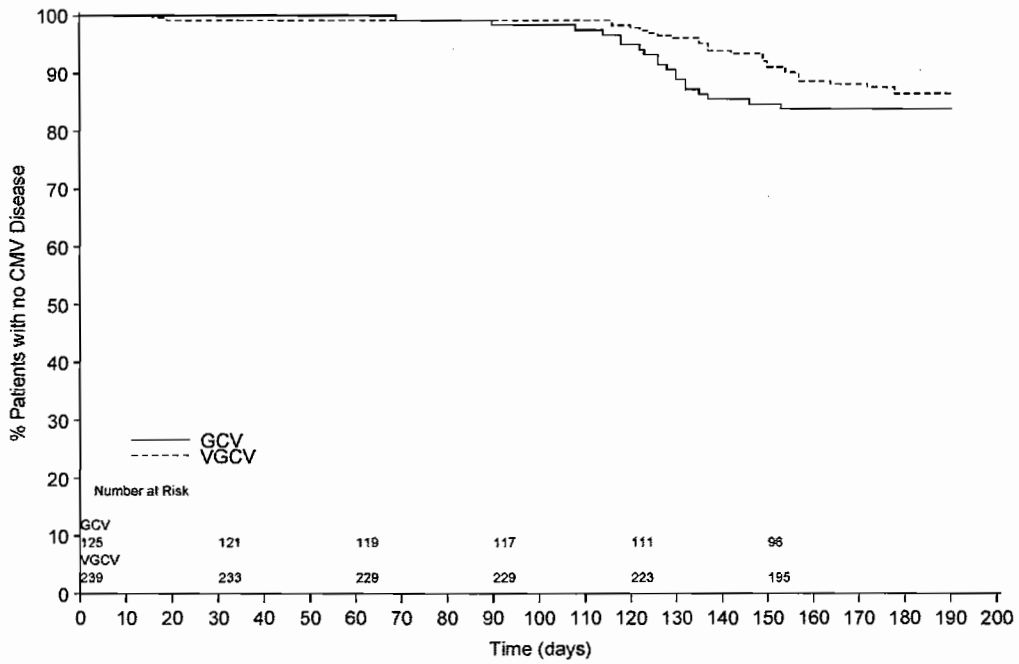
Table 12: Summary of CMV Disease up to 6 Months Post-Transplant. All Signs, Symptoms and Laboratory Criteria Fulfilled (ITT Population)

	GCV N=125	VGCV N=239
PATIENTS WITH CMV DISEASE	16 (12.8%)	27 (11.3%)
PATIENTS WITH NO CMV DISEASE	102 (81.6%)	200 (83.7%)
PATIENTS UNEVALUABLE	7 (5.6%)	12 (5.0%)
CMV SYNDROME	13 (10.4%)	15 (6.3%)
TISSUE-INVASIVE CMV	6 (4.8%)	18 (7.5%)
Hepatitis	1	6
Pneumonia	1	2
Gastrointestinal	4	13
Retinitis	0	0
Other	0	1

Patients can have more than one type of tissue-invasive CMV disease. If a patient has insufficient visits up to 6 months they are Unevaluable unless the patient had CMV disease.

Valganciclovir also appeared to be slightly better than oral ganciclovir for all signs, symptoms and laboratory criteria fulfilled CMV Disease at 6 Months, but worse than oral ganciclovir for tissue-invasive CMV disease.

Figure 2: Time to CMV Disease (Days) up to 6 Months Post-Transplant - Endpoint Committee (ITT Population)



Similar trends were apparent for time to CMV disease. Valganciclovir appeared to have a lower incidence of CMV disease than oral ganciclovir. However these differences were not apparent until >100 days post-transplant, when patients were off treatment.

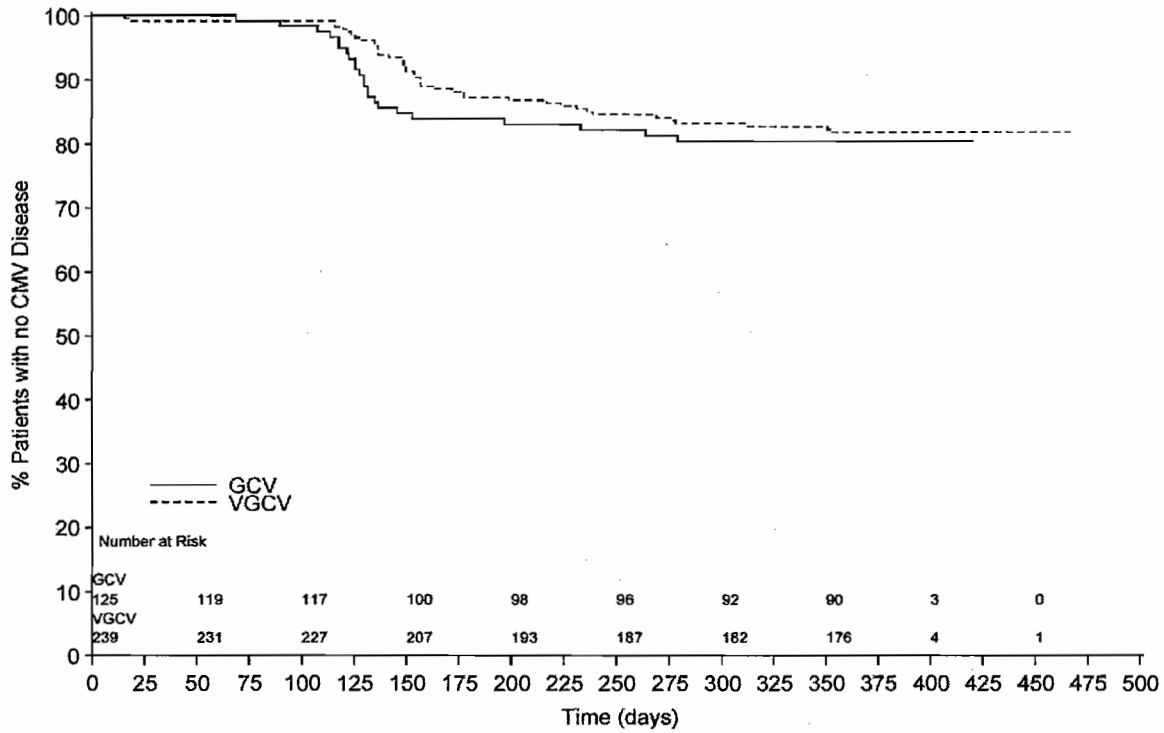
Table 13: Summary of CMV Disease up to 12 Months Post-Transplant - Endpoint Committee (ITT Population)

	GCV N=125	VGCV N=239	WEIGHTED DIFFERENCE IN PROPORTIONS (2-sided 95% CIs)
PATIENTS WITH CMV DISEASE	23 (18.4%)	41 (17.2%)	0.015 (-0.068, 0.098)
PATIENTS WITH NO CMV DISEASE	90 (72.0%)	176 (73.6%)	
PATIENTS UNEVALUABLE	12 (9.6%)	22 (9.2%)	
CMV SYNDROME	15 (12.0%)	19 (7 .9%)	
TISSUE-INVASIVE CMV	8 (6.4%)	22 (9.2%)	
Hepatitis	2	6	
Pneumonia	2	3	
Gastrointestinal	5	17	
Retinitis	0	0	
Other	0	1	

95% CI FROM THE STRATIFIED Z TEST
Patients can have more than one more type of tissue-invasive CMV disease
If a patient has insufficient visits up to 12 months they are Unevaluable unless the patient had CMV disease

The lower bound of the 95% confidence interval was less than –0.05. Therefore non-inferiority was not demonstrated at 12 months for this endpoint.

Figure 3: Time to CMV Disease (Days) up to 12 Months Post-Transplant - Endpoint Committee (ITT Population)



Treatment differences appeared to level off after 6 months and diminished by 12 months.

Table 14: Incidence and Time to CMV Disease (Days) up to 12 Months Post-Transplant . Endpoint Committee (ITT Population)

	GCV N=125	VGCV N=239
Incidence of CMV Disease up to 12 months post-transplant		
CMV Disease	23 (18%)	41 (17%)
No CMV Disease	90 (72%)	176 (74%)
Unevaluable	12 (10%)	22 (9%)
Time to CMV Disease Kaplan Meier Analysis		
Number of patients with CMV Disease	23 (18%)	41 (17%)
Number of censored observations	102 (82%)	198 (83%)
Mean (days)	253	321
Standard Error (days)	5	5
Lower Quartile (days)	N/A	N/A
Range (days)	1 to 420	1 to 469

Censoring date is defined as the last visit date up to 12 months post-transplant
If a patient has insufficient visits up to 12 months they are Unevaluable unless the patient had CMV disease
CMV Disease is as assessed by the Endpoint Committee

Table 15: Summary of Efficacy Results at 6 and 12 months

	Follow-up Period	GCV (N=125)	VGCV (N=239)
Endpoint Committtee	6 months	19 (15.2%)	29 (12.1%)
	12 months	23 (18.4%)	41 (17.2%)
ASSL[1]	6 months	16 (12.8%)	27 (11.3%)
	12 months	19 (15.2%)	36 (15.1%)
Investigator Teated	6 months	27 (21.6%)	55 (23.0%)
	12 months	35 (28.0%)	73 (30.5%)

[1] ASSL=All Signs, Symptoms and Laboratory Criteria Fulfilled

Compared to oral ganciclovir, valganciclovir efficacy appeared less impressive at 12 months than at 6 months. Valganciclovir appeared slightly more efficacious at 6 months than oral ganciclovir with the exception of Investigator Treated CMV disease.

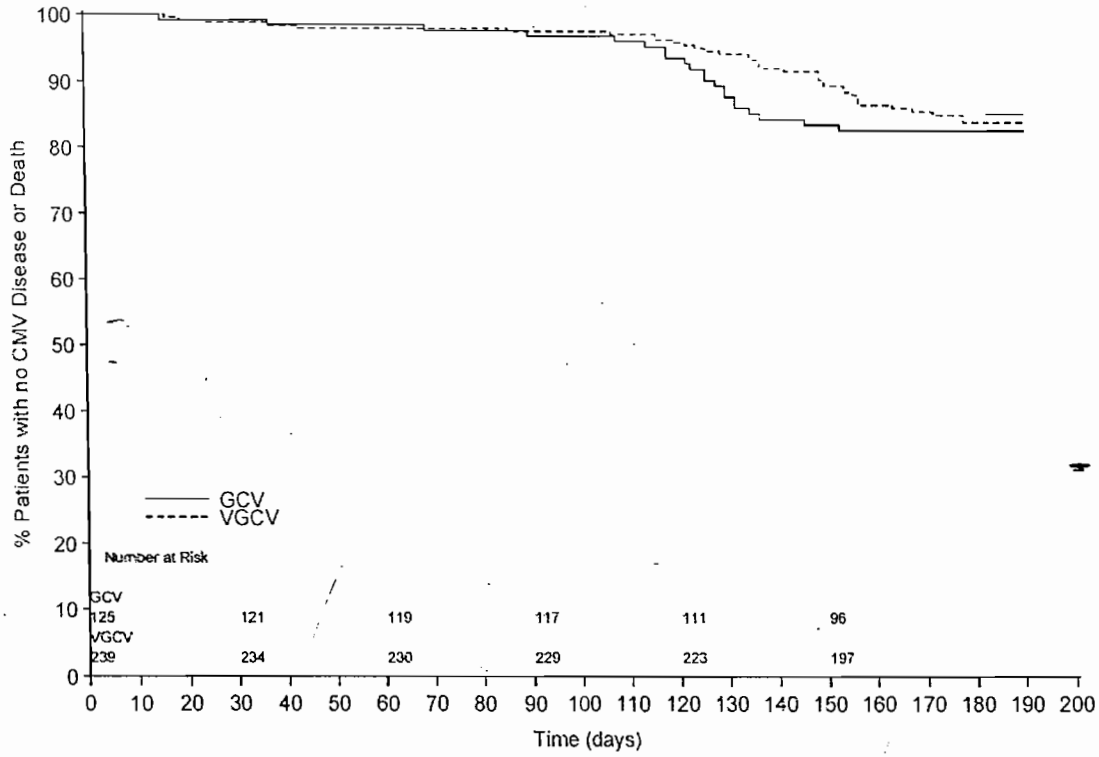
Table 16: Summary of CMV Disease or Death up to 6 Months Post-Transplant - Endpoint Committee (ITT Population)

	GCV N=125	VGCV N=239	WEIGHTED DIFFERENCE IN PROPORTIONS (2-sided 95% CIs)
PATIENTS WITH CMV DISEASE OR DEATH	21 (17%)	36 (15%)	0.020 (-0.061, 0.100)
PATIENTS WITH NO CMV DISEASE OR DEATH	99 (79%)	198 (83%)	
PATIENTS UNEVALUABLE	5 (4%)	5 (2%)	
PATIENTS WITH CMV DISEASE	19 (15.2%)	29 (12%)	
NUMBER OF DEATHS	2 (2%)	9 (4%)	

2-SIDED 95% CIs IN EFFICACY TABLES WERE COMPUTED USING TWO 1-SIDED 97.5% CIs AND P-VALUE FROM THE STRATIFIED Z TEST.
[+]IF LOWER LIMIT OF THE 1-SIDED 97.5% CI > -0.05 THEN VGCV IS NON-INFERIOR TO GCV.
IF LOWER LIMIT OF THE 1-SIDED 97.5% CI > 0 THEN VGCV IS SUPERIOR TO GCV.
If patient had CMV disease and subsequently died, the event will be counted only once in the row 'CMV Disease or Death'.
The patient will be counted in both rows 'CMV Disease' and 'Death'.
If a patient has insufficient visits up to 6 months they are Unevaluable unless the patient had CMV disease or died

CMV disease or mortality had a lower bound of the 95% CI than CMV disease alone. Since it was no longer >-0.05, it could not be concluded that valganciclovir was non-inferior to oral ganciclovir for this endpoint.

Figure 4: Time to CMV Disease or Death (Days) up to 6 Months Post-Transplant - Endpoint Committee (ITT Population)



The Kaplan-Meier plot for this endpoint was similar to the Kaplan-Meier plot for CMV disease alone.

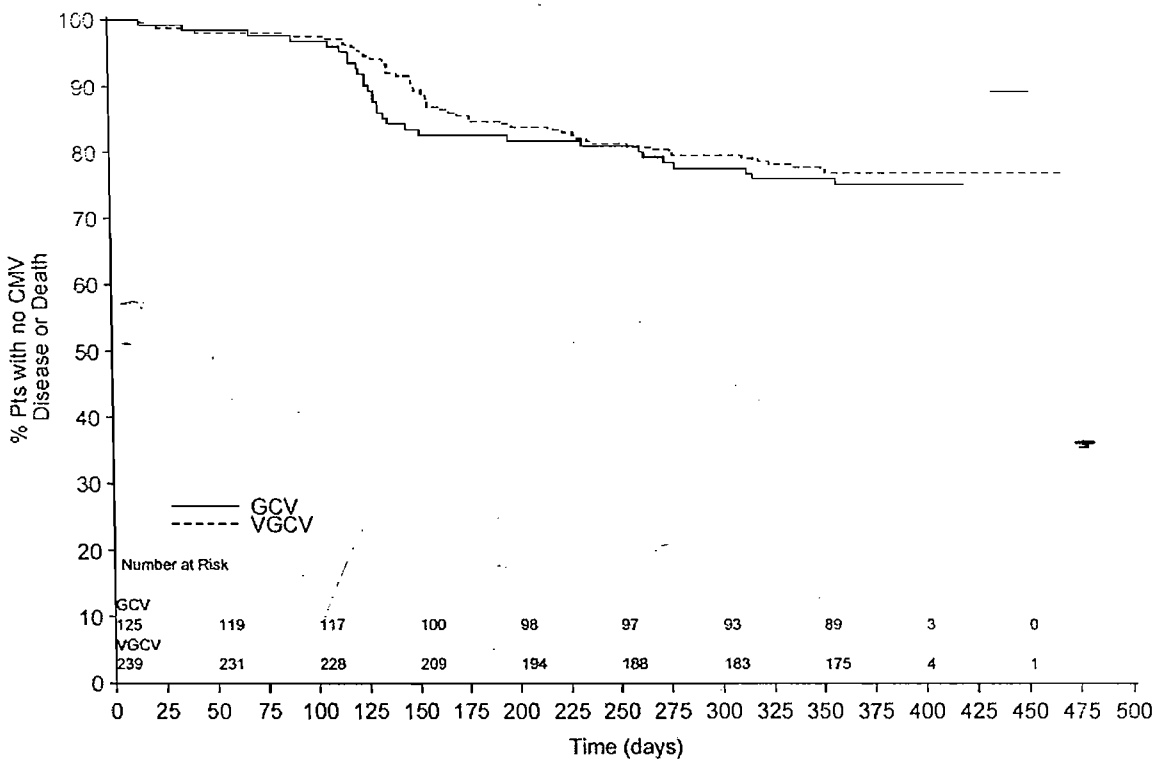
Table 17: Summary of Incidence and Time to CMV Disease or Death (Days) up to Twelve Month Post-Transplant (ITT Population)

	GCV N=125	VGCV N=239
Incidence of CMV Disease or death up to 12 months post-transplant		
CMV Disease or death	30 (24%)	54 (23%)
No CMV Disease or death	90 (72%)	176 (74%)
Unevaluable	5 (4%)	9 (4%)
Time to CMV Disease or death Kaplan Meier Analysis		
Number of patients with CMV Disease or death	30 (24%)	54 (23%)
Number of censored observations	95 (76%)	185 (77%)
Mean (days)	309	312
Standard Error (days)	9	6
Lower Quartile (days)	358	N/A
Range (days)	9 to 420	1 to 469

Censoring date is defined as the last visit date up to 12 months post-transplant. If a patient has insufficient visits up to 12 months they are Unevaluable unless the patient had CMV disease or died.
If patient had CMV disease and subsequently died, the event will be counted only once in the row 'CMV Disease or Death', and the date of CMV disease will be used in this analysis.
CMV Disease is as assessed by the Endpoint Committee.

As for CMV disease, the proportion of patients with CMV disease or death appeared comparable in the two treatment arms at 12 months.

Figure 5: Time to CMV Disease or Death (Days) up to 12 Months Post-Transplant - Endpoint Committee (ITT Population)



The Kaplan-Meier plot for CMV disease or death was similar to the plot for CMV disease alone. Treatment differences were less apparent by 12 months.

Table 18: Summary of Treatment Failure up to 6 Months Post-Transplant – Endpoint Committee (ITT Population)

	GCV N=125	VGCV N=239	WEIGHTED DIFFERENCE IN PROPORTIONS (2-sided 95% CI)
TREATMENT FAILURE			
PATIENTS WITH TREATMENT FAILURE	25 (20%)	41 (17%)	0.035 (-0.053, 0.122)
PATIENTS WITH NO TREATMENT FAILURE	96 (77%)	193 (81%)	
PATIENTS UNEVALUABLE	4 (3%)	5 (2%)	
REASON FOR TREATMENT FAILURE			
CMV DISEASE (ENDPOINT COMMITTEE)	19 (15%)	29 (121%)	
DEATH	2 (2%)	9 (4%)	
DISCON. DUE TO DRUG-RELATED AE	4 (3%)	6 (3%)	

If a patient has insufficient visits up to 6 months they are Unevaluable unless the patient had treatment failure
TREATMENT FAILURE IS CMV DISEASE, DEATH OR DISCONTINUATION OF STUDY DRUG DUE TO A DRUG-RELATED AE.
95% CI FROM THE STRATIFIED Z TEST
If a patient had CMV disease, discontinued from study drug due to drug-related AE and then died, the event will be counted only once in the row 'Treatment Failure'. The patient will be counted in all three rows,'CMV Disease','Death' and 'Discon. due to a drug-related AE.'

Results for treatment failures appeared to be similar to those obtained for the primary endpoint.

Figure 6: Time to Treatment Failure (Days) up to 6 Months Post-Transplant - Endpoint Committee (ITT Population)

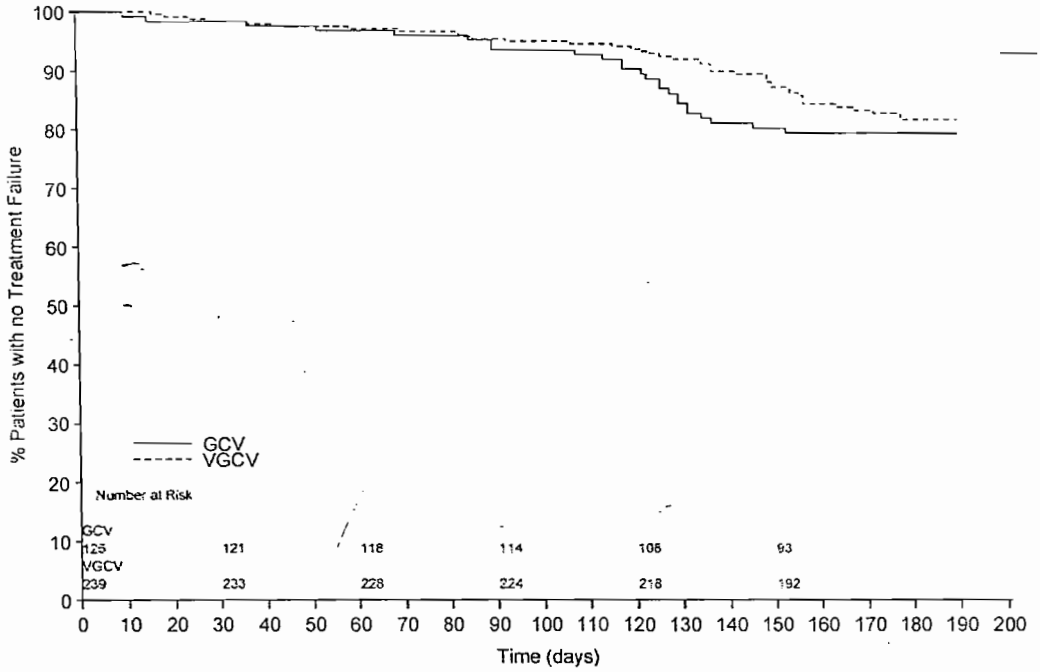
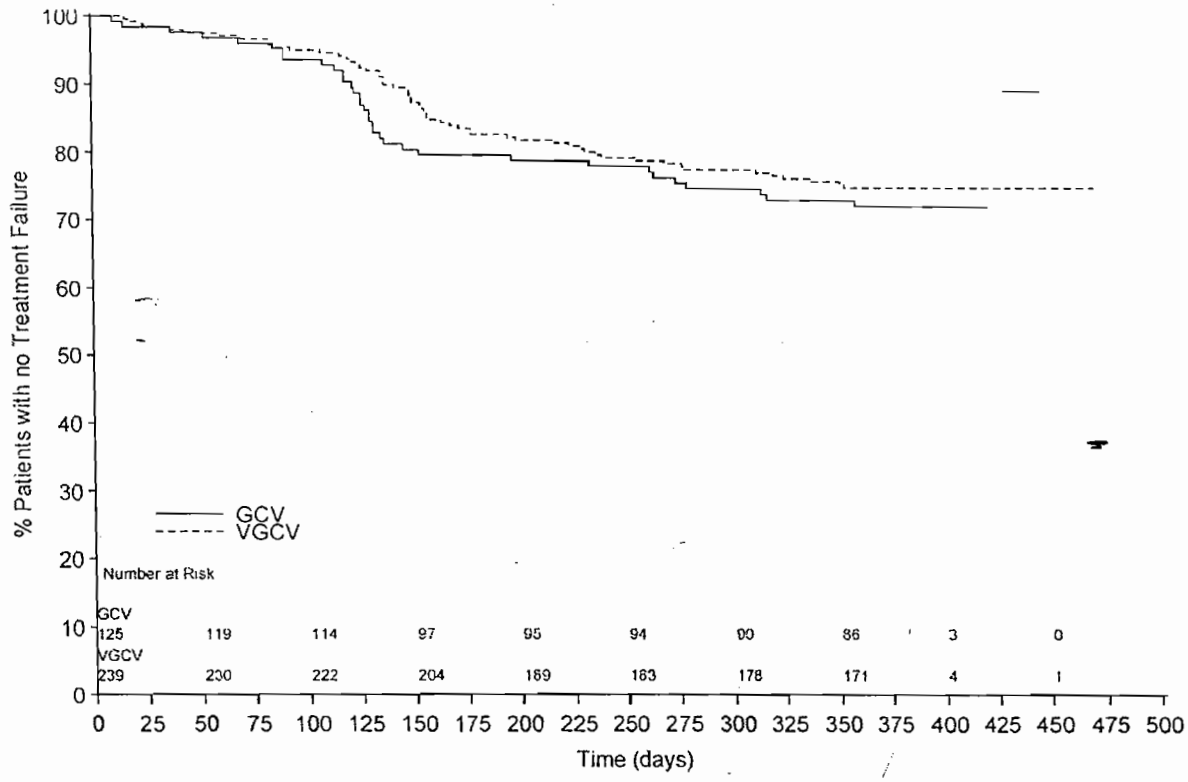


Table 19: Incidence and Time to Treatment Failure (Days) up to 12 Months Post-Transplant – Endpoint Committee (ITT Population)

	GCV N=125	VGCV N=239
Incidence of treatment failure up to 12 months post-transplant		
Treatment failure	34 (27%)	59 (25%)
No treatment failure	87 (70%)	172 (72%)
Unevaluable	4 (3%)	8 (3%)
Time to treatment failure Kaplan Meier Analysis		
Number of patients with treatment failure	34 (27%)	59 (25%)
Number of censored observations	91 (73%)	180 (75%)
Mean (days)	300	306
Standard Error (days)	10	6
Lower Quartile (days)	279	353
Range (days)	9 to 420	1 to 469

Censoring date is defined as the last visit date up to 12 months post-transplant. If a patient has insufficient visits up to 12 months they are Unevaluable unless the patient had treatment failure. TREATMENT FAILURE IS CMV DISEASE, DEATH OR DISCONTINUATION OF STUDY DRUG DUE TO A DRUG-RELATED AE. If a patient has a CMV disease event, discontinues due to a drug-related AE and then subsequently dies, the date of the first event, i.e. CMV disease event, will be used in this analysis, and the patient will only be counted once in the table. CMV disease is assessed by the Endpoint Committee.

Figure 7: Time to Treatment Failure (Days) up to 12 Months Post-Transplant – Endpoint Committee (ITT Population)



The Kaplan-Meier plot of time to treatment failure was similar to the Kaplan-Meier plots for CMV disease alone and other secondary endpoints.

3.2. Evaluation of Safety

3.2.1. Methods of Statistical Analysis of Safety Data

The safety population included patients who were randomized, received at least one dose of study medication and who had at least one safety assessment. This population was used for all standard summaries of safety data (for example adverse events and laboratory data) as well as for analysis of safety endpoints (times to neutropenia, thrombocytopenia, anemia, opportunistic infections, deaths, interaction between valganciclovir/ganciclovir and various drugs).

3.2.2. Adverse Events

Table 20: Overall Summary of Adverse Events Occurring on Treatment (Safety Population)

Up to end of study treatment plus 28 days	GCV N=126	VGCV N=244
Any AE	125 (99.2%)	243 (99.6%)
Any drug related A E	43 (34.1%)	99 (40.6%)
Any serious AE	51 (40.5%)	123 (50.4%)
Any drug related serious AE	6 (4 .8%)	17 (7.0%)
Any AE l/t withdrawal from study drug	7 (5 .6%)	12 (4.9%)
Any drug related AE l/t withdrawal from study drug	4 (3 .2%)	6 (2.5%)
Deaths (all causes)	2 (1 .6%)	5 (2.0%)

The percentage of patients with any serious adverse events appeared to be higher for valganciclovir patients (50%) than for ganciclovir patients (41%). Although the difference was not statistically significant, the study was neither designed nor powered to detect statistical significance for safety data. Similarly, the percentage of valganciclovir patients with any drug-related serious adverse events (7.0%) appeared to be higher than the corresponding ganciclovir-treated patients (4.8%).

Table 21: Abbreviated Summary of All Adverse Events Occurring up to 6 Months Post-Transplant by Decreasing Frequency (Safety Population)

Adverse Event	GCV N = 126 No. (%)	VGCV N = 244 No. (%)
DIARRHOEA NOS	38 (30.2)	77 (31.6)
GRAFT REJECTION	40 (31.7)	65 (26.6)
TREMOR NOS	32 (25.4)	68 (27.9)
HEADACHE NOS	35 (27.8)	57 (23.4)
NAUSEA	30 (23.8)	56 (23.0)
OEDEMA LOWER LIMB	24 (19.0)	51 (20.9)
CONSTIPATION	25 (19.8)	49 (20.1)
INSOMNIA	21 (16.7)	49 (20.1)
BACK PAIN	20 (15.9)	49 (20.1)
HYPERTENSION NOS	21 (16.7)	45 (18.4)
VOMITING NOS	19 (15.1)	41 (16.8)
PYREXIA	19 (15.1)	39 (16.0)
ABDOMINAL PAIN NOS	19 (15.1)	37 (15.2)
FATIGUE	20 (15.9)	35 (14.3)
HYPERKALAEMIA	19 (15.1)	34 (13.9)
ANAEMIA NOS	19 (15.1)	32 (13.1)
POST-OPERATIVE PAIN	11 (8.7)	35 (14.3)
DYSPNOEA	14 (11.1)	29 (11.9)
LEUCOPENIA NOS	9 (7.1)	34 (13.9)
DYSPEPSIA	13 (10.3)	29 (11.9)
BLOOD CREATININE INCREASED	17 (13.5)	24 (9.8)
POST-OPERATIVE COMPLICATIONS NOS	10 (7.9)	31 (12.7)
HEPATIC FUNCTION ABNORMAL NOS	14 (11.1)	25 (10.2)
OEDEMA NOS	11 (8.7)	28 (11.5)
URINARY TRACT INFECTION NOS	12 (9.5)	26 (10.7)
DIZZINESS (EXC VERTIGO)	8 (6.3)	25 (10.2)
POST-OPERATIVE WOUND INFECTION	7 (5.6)	26 (10.7)
RENAL IMPAIRMENT NOS	15 (11.9)	18 (7.4)
ABDOMINAL PAIN UPPER	9 (7.1)	23 (9.4)
ASCITES	9 (7.1)	23 (9.4)
HYPOMAGNESAEMIA	11 (8.7)	21 (8.6)
UPPER RESPIRATORY TRACT INFECTION NOS	9 (7.1)	22 (9.0)
HYPOKALAEMIA	10 (7.9)	19 (7.8)
HYPOPHOSPHATAEMIA	7 (5.6)	22 (9.0)
MUSCLE CRAMPS	15 (11.9)	14 (5.7)
ARTHRALGIA	10 (7.9)	18 (7.4)
DEPRESSION NOS	9 (7.1)	18 (7.4)

Table 22 (continued): Abbreviated Summary of All Adverse Events Occurring up to 6 Months Post-Transplant by Decreasing Frequency (Safety Population)

Adverse Event	GCV N = 126 No. (%)	VGCV N = 244 No. (%)
DYSURIA	8 (6.3)	19 (7.8)
PLEURAL EFFUSION	10 (7.9)	17 (7.0)
COUGH	10 (7.9)	16 (6.6)
HYPERTENSION AGGRAVATED	6 (4.8)	19 (7.8)
PRURITUS	6 (4.8)	19 (7.8)
WOUND DRAINAGE INCREASED	11 (8.7)	14 (5.7)
ABDOMINAL DISTENSION	9 (7.1)	15 (6.1)
NEUTROPENIA	4 (3.2)	20 (8.2)

Multiple occurrences of the same adverse event in one individual counted only once.

Compared to ganciclovir patients, leucopenia and neutropenia appeared to be elevated in valganciclovir patients. The incidence of post-operative pain, post-operative complications, odema, post-operative wound infections, dizziness, hypophosphataemia, aggravated hypertension and pruritus also appeared to be higher in valganciclovir patients.

Eight percent (8%, 20/244) of the valganciclovir patients had neutropenia compared to only 3% (4 / 126) of the oral ganciclovir treatment group. Compared to oral ganciclovir, nearly double the percentage of valganciclovir patients reported leucopenia NOS (34/244=14% of valganciclovir patients compared to only 9/126=7% of oral ganciclovir patients).

Table 23: Abbreviated Summary of All Study Drug Related Adverse Events Occurring On Treatment by Decreasing Frequency (Safety Population)

Adverse Event	GCV N = 126 No. (%)	VGCV N = 244 No. (%)
LEUCOPENIA NOS	5 (4.0)	23 (9.4)
DIARRHOEA NOS	7 (5.6)	18 (7.4)
NAUSEA	4 (3.2)	14 (5.7)
VOMITING NOS	4 (3.2)	11 (4.5)
NEUTROPENIA	1 (0.8)	13 (5.3)
THROMBOCYTOPENIA	4 (3.2)	6 (2.5)
DYSPEPSIA	2 (1.6)	7 (2.9)
ANAEMIA NOS	2 (1.6)	6 (2.5)
WHITE BLOOD CELL COUNT DECREASED	3 (2.4)	5 (2.0)
PANCYTOPENIA	1 (0.8)	6 (2.5)
RENAL IMPAIRMENT NOS	4 (3.2)	3 (1.2)
BLOOD CREATININE INCREASED	2 (1.6)	4 (1.6)
GRAFT REJECTION	2 (1.6)	4 (1.6)
HEADACHE NOS	3 (2.4)	3 (1.2)
ABDOMINAL PAIN NOS	2 (1.6)	2 (0.8)
ABDOMINAL PAIN UPPER	-	4 (1.6)
CONSTIPATION	2 (1.6)	2 (0.8)
HYPERKALAEMIA	-	4 (1.6)
MUSCLE CRAMPS	2 (1.6)	2 (0.8)
OEDEMA LOWER LIMB	1 (0.8)	3 (1.2)
TREMOR NOS	1 (0.8)	3 (1.2)

Multiple occurrences of the same adverse event in one individual counted only once.

Drug-related leucopenia and neutropenia that occurred while patients were on treatment were also higher in valganciclovir patients.

3.2.3. Serious Adverse Events

Table 24: Abbreviated Summary of All Serious Adverse Events Occurring On Treatment by Decreasing Frequency (Safety Population)

Adverse Event	GCV N = 126 No. (%)	VGCV N = 244 No. (%)
GRAFT REJECTION	9 (7.1)	14 (5.7)
HEPATIC FUNCTION ABNORMAL NOS	3 (2.4)	8 (3.3)
BLOOD CREATININE INCREASED	3 (2.4)	6 (2.5)
NEUTROPENIA	1 (0.8)	8 (3.3)
PNEUMONIA NOS	0	8 (3.3)
URINARY TRACT INFECTION NOS	3 (2 .4)	5 (2.0)
DEHYDRATION	1 (0.8)	6 (2.5)
PYREXIA	3 (2.4)	4 (1.6)
VENOUS THROMBOSIS DEEP (LIMBS)	2 (1.6)	5 (2.0)
CHOLANGITIS NOS	2 (1 .6)	4 (1.6)
CYST NOS	2 (1.6)	4 (1.6)
ASCITES	2 (1.6)	3 (1.2)
HEPATIC ARTERY THROMBOSIS	1 (0.8)	4 (1.6)
POST-OPERATIVE COMPLICATIONS NOS	1 (0.8)	4 (1.6)
POST-OPERATIVE WOUND INFECTION	1 (0 .8)	4 (1.6)
VOMITING NOS	0	5 (2.0)
BILIARY TRACT DISORDER NOS	0	4 (1.6)
WOUND DEHISCENCE	3 (2.4)	1 (0.4)

Multiple occurrences of the same adverse event in one individual counted only once.

Compared to ganciclovir, the incidence of serious adverse events due to neutropenia, pneumonia, dehydration, vomiting and biliary tract disorders appeared to be higher in valganciclovir patients.

Table 25: Summary of All Related Serious Adverse Events Occurring On Treatment (Safety Population)

Adverse Event	GCV N = 126 No. (%)	VGCV N = 244 No. (%)
NEUTROPENIA	1 (0.8)	5 (2.0)
LEUCOPENIA NOS	1 (0.8)	2 (0.8)
GRAFT REJECTION	-	2 (0.8)
PANCYTOPENIA	1 (0.8)	1 (0.4)
ANAEMIA NOS	1 (0.8)	-
ANAEMIA NOS AGGRAVATED	-	1 (0.4)
CONVULSIONS NOS	1 (0.8)	-
DRUG INTERACTION NOS	-	1 (0.4)
GRAND MAL EPILEPSY	-	1 (0.4)
HEADACHE NOS	-	1 (0.4)
HEPATITIS NOS	-	1 (0.4)
HYPOAESTHESIA	-	1 (0.4)
MUSCLE WEAKNESS	-	1 (0.4)
PNEUMONIA NOS	-	1 (0.4)
RENAL FAILURE NOS	1 (0.8)	-
THROMBOCYTOPENIA	1 (0.8)	-
VOMITING NOS	-	1 (0.4)

Multiple occurrences of the same adverse event in one individual counted only once.

Compared to ganciclovir, the incidence of all related serious adverse events occurring on treatment due to neutropenia appeared to be higher in valganciclovir patients.

Table 26: Summary of Adverse Events Leading to Discontinuation of Study Drug, by Decreasing Frequency (Safety Population)

Adverse Event	GCV N = 126 No. (%)	VGCV N = 244 No. (%)
LEUCOPENIA NOS	1 (0.8)	3 (1.2)
NEUTROPENIA	1 (0.8)	2 (0.8)
BLOOD BILIRUBIN INCREASED	0	1 (0.4)
CEREBROVASCULAR ACCIDENT	0	1 (0.4)
CONVULSIONS NOS	1 (0 .8)	0
HEADACHE NOS	0	1 (0.4)
HEPATIC ARTERY	0	1 (0.4)
THROMBOSIS	0	0
HEPATIC FUNCTION	0	1 (0.4)
ABNORMAL NOS	0	0
IMPAIRED GASTRIC EMPTYING	0	1 (0.4)
NAUSEA	1 (0 .8)	0
POST-OPERATIVE	0	1 (0.4)
COMPLICATIONS NOS	0	0
RENAL FAILURE NOS	1 (0.8)	0
SEPTICAEMIA NOS	1 (0 .8)	0
WHITE BLOOD CELL COUNT DECREASED	1 (0.8)	0

Multiple occurrences of the same adverse event in one individual counted only once.

Approximately 1% of patients discontinued treatment due to leucopenia or neutropenia in each treatment group.

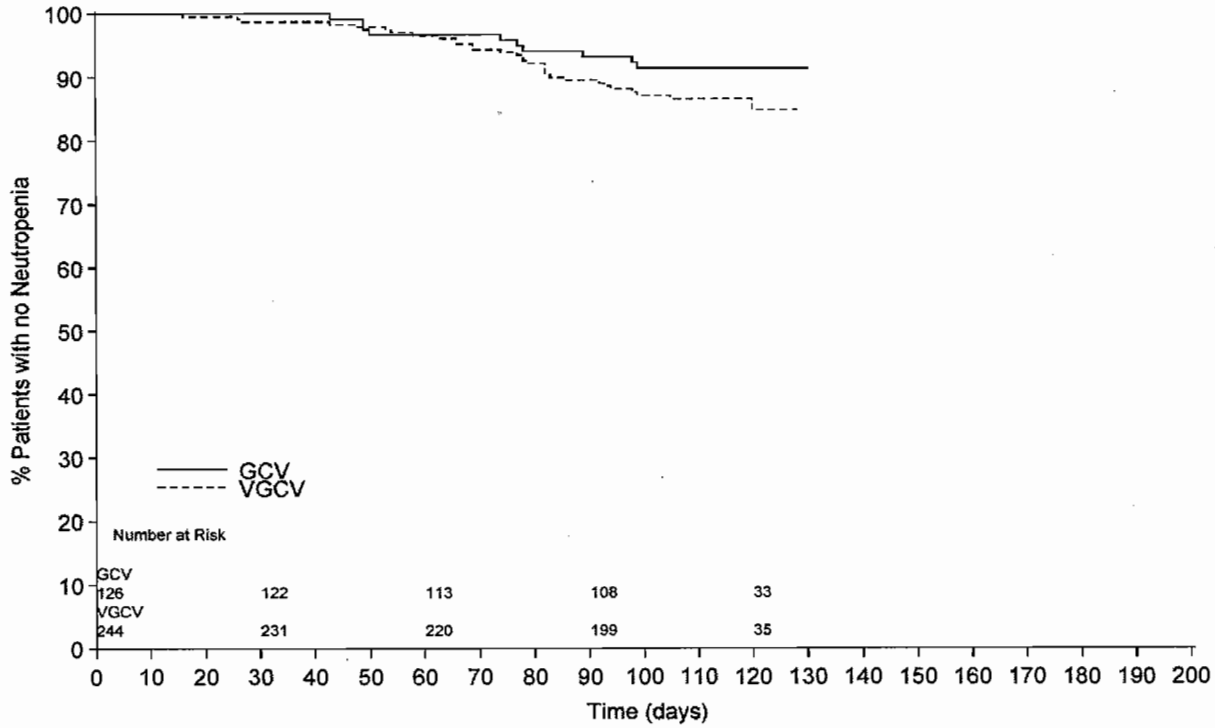
Table 27: Marked Shifts From Baseline in Key Laboratory Parameters On Treatment (Safety Population)

Laboratory Parameter		GCV		VGCV	
		n	%	n	%
Hemoglobin	Low	2	(2%)	6	(2%)
Platelets	Low	1	(1%)	2	(1%)
Neutrophils	Low	5	(6%)	17	(9%)
ASAT (SGOT)	High	2	(2%)	4	(2%)
Alkaline Phosphatase	High	0		0	
ALAT (SGPT)	High	4	(4%)	2	(1%)
Total Bilirubin	High	2	(2%)	4	(2%)
Creatinine	High	0		1	(1%)
Potassium	Low	0		0	
Potassium	High	0		0	

Note: Percentages refer to the number of patients exhibiting an event out of the total number of patients for whom the parameter measurement was available.

Compared to ganciclovir patients, marked shifts from baseline for neutrophils were higher for valganciclovir patients, while ALAT incidence was lower.

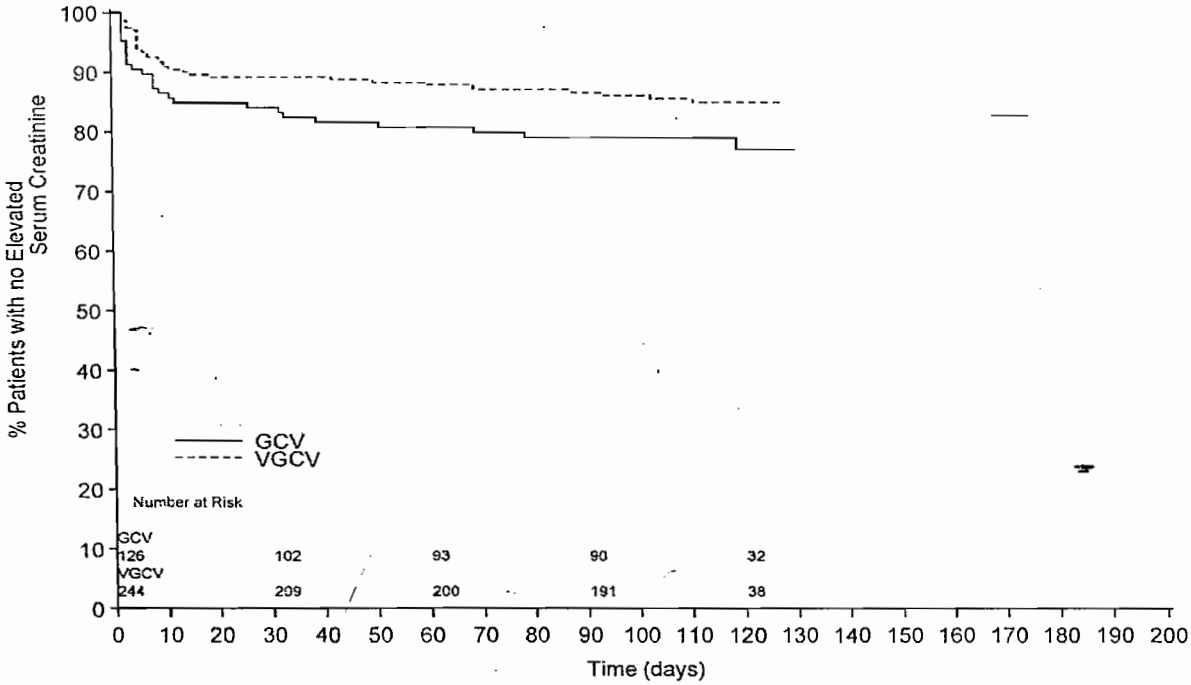
Figure 8: Time (days) to Neutropenia up to End of Study Treatment Plus 28 days (Safety Population)



Neutropenia is defined as Absolute Neutrophil Count < 1000 cells/uL

The Kaplan-Meier plots appear to show a higher incidence of neutropenia and lower incidence of elevated serum creatinine in valganciclovir patients.

Figure 9: Kaplan-Meier Plot for Time (Days) to Elevated Serum Creatinine On Treatment (Safety Population)



Elevated Serum Creatinine is defined as a serum creatinine reading > 2.5 mg/dL

Table 28: Laboratory Abnormalities Reported in One Clinical Study in Transplantation

	Solid Organ Transplant Patients (PV16000)	
Laboratory Abnormalities	**Oral ganciclovir (N=126) %**	**Valganciclovir (N=244) %**
Neutropenia: ANC/μL		
<500	3	5
500 – <750	2	3
750 – <1000	2	5
Anemia: Hemoglobin g/dL		
<6.5	2	1
6.5 – <8.0	7	5
8.0 – <9.5	25	31
Thrombocytopenia: Platelets/μL		
<25000	2	0
25000 – <50000	3	1
50000 – <100000	21	18
Serum Creatinine: mg/dL		
>2.5	21	14
>1.5 – 2.5	47	45

Compared to oral ganciclovir, neutropenia appeared to be consistently higher for valganciclovir patients in each laboratory abnormality elevation category (<500, 500-<750, 750-<1000 ANC/μL). Eight percent (8%, 10/126) of the oral ganciclovir patients and 13% (31/244) for valganciclovir patients had neutropenia (<1000 ANC/μL). These rates were higher than the adverse event rates reported at the discretion of the investigators where there were no definitive criteria as to what the definition of neutropenia was. This was expected as neutrophil counts < 1000 ANC/μL wouldn't necessarily be clinically significant or require treatment (and therefore would not necessarily be an AE).

3.2.3.1. Withdrawals

Table 29: Summary of Patient Withdrawals

Reason	GCV N = 127 No. (%)	VGCV N = 245 No. (%)
Total	**16 (13)**	**35 (14)**
Safety	8 (6)	16 (7)
- Abnormal Lab Test	0	0
- Adverse Event	6	12
- Death	2	4
Non-Safety	8 (6%)	19 (8%)
- Insufficient Response	2	5
- Violation / Deviation	1	6
- Refused Treatment	5	3
- Other	0	5

There were no obvious differences between the two treatment groups with respect to withdrawals due to safety reasons.

3.2.3.2. Deaths

Table 30: Listing of Deaths up to 6 Months Post-Transplant (All Patients)[1]

Treatment Group CRTN/Pt. No.	Age Yr	Sex	Weight Kg	Race	Cause of Death	Last Trt Day	Day of Death	Autopsy
GCV								
25968/4402	52	M	75	CAUCASIAN	SEPTICAEMIA NOS	10	11	YES
26788/2803	59	M	106	CAUCASIAN	SEPSIS NOS	1	28	NO
VGCV								
25966/4201	47	F	72	CAUCASIAN	PNEUMONITIS NOS	99	178	NO
25969/4509	49	F	90	CAUCASIAN	CARDIAC FAILURE CONGESTIVE	39	39	YES
26175/5102	50	M	78	CAUCASIAN	PULMONARY OEDEMA	19	19	YES
26452/2416	25	M	52	CAUCASIAN	THROMBOSIS NOS	76	76	YES
26454/3002	45	M	86	CAUCASIAN	RENAL FAILURE CHRONIC	12	162	NO
26480/6001	37	F	73	CAUCASIAN	CARDIAC ARREST	91	97	NO
26493/0405	54	M	82	CAUCASIAN	CARDIAC ARREST	31	33	NO
26790/3509	58	M	78	CAUCASIAN	CEREBRAL INFARCTION	96	151	NO
26790/3516	49	M	119	CAUCASIAN	HEPATIC FAILURE	97	164	NO

[1]All Deaths were Considered by the Investigators to be Unrelated to Study Drug

Two (2) ganciclovir deaths occurred in liver transplant patients, while 7/9 of the valganciclovir deaths occurred in liver transplant patients. Only 2 deaths occurred in heart transplant patients (26175 and 26480).

Table 3T Listing of Deaths up to 12 Months Post-Transplant (All Patients)[1]

Treatment Group CRTN/Pt. No.	Age yr	Sex	Weight kg	Race	Cause of Death	Last Trt Day	Day of Death	Autopsy
GCV								
25963/4402	52	M	75	CAUCASIAN	SEPTICAEMIA NOS	10	11	YES
26455/0207	44	M	132	CAUCASIAN	HEPATITIS C	97	312	NO
26455/0216	43	M	59	CAUCASIAN	HEPATIC DISEASE NOS	99	272	YES
26495/0807	70	F	74	CAUCASIAN	HEPATITIS C	100	355	NO
26495/0815	59	F	86	CAUCASIAN	SEPSIS NOS	98	319	NO
26495/0819	26	F	73	CAUCASIAN	SEPSIS NOS.	16	312	NO
26783/2803	59	M	106	CAUCASIAN	SEPSIS NOS	1	28	NO
26790/3503	70	M	117	CAUCASIAN	MULTIPLE INJURIES	99	260	NO
VGCV								
25966/4201	47	F	72	CAUCASIAN	PNEUMONITIS NOS	99	178	NO
25966/4205	64	F	74	CAUCASIAN	HEPATIC FAILURE	93	329	NO
25963/4509	49	F	90	CAUCASIAN	CARDIAC FAILURE CONGESTIVE	39	39	YES
26175/5102	50	M	78	CAUCASIAN	PULMONARY OEDEMA	19	19	YES
26452/2416	25	M	52	CAUCASIAN	THROMBOSIS NOS	76	76	YES
26454/3002	45	M	86	CAUCASIAN	RENAL FAILURE CHRONIC	12	162	NO
26471/0106	48	M	81	CAUCASIAN	RESPIRATORY ARREST (EXC NEONATAL)	72	324	NO
26480/6001	37	F	73	CAUCASIAN	CARDIAC ARREST	91	97	NO
26493/0405	54	M	82	CAUCASIAN	CARDIAC ARREST	31	33	NO
26495/0803	50	M	77	CAUCASIAN	HEPATORENAL SYNDROME	97	192	YES
26495/0820	67	M	72	CAUCASIAN	SEPSIS NOS	45	315	NO
26790/3509	58	M	78	CAUCASIAN	CEREBRAL INFARCTION	96	151	NO
26790/3516	49	M	119	CAUCASIAN	HEPATIC FAILURE	97	164	NO
29013/7001	50	M	90	CAUCASIAN	MALIGNANT HEPATIC NEOPLASM	97	223	NO
29501/8001	54	M	86	CAUCASIAN	HEPATIC NECROSIS	94	248	YES

[1]All Deaths were Considered by the Investigators to be Unrelated to Study Drug

A total of 23 patients died within the first 12 months post-transplant (6% on the valganciclovir treatment group and 6% in the ganciclovir treatment group.) with 12 deaths (6 on each arm of the study) occurring between 6-12 months post-transplant. All 23 deaths were considered by investigators to be unrelated to the trial treatment.

Nearly all (7/8) of the ganciclovir deaths occurred in liver transplant patients. (Patient 26790 had a kidney transplant.) The majority of valganciclovir deaths (12/15) occurred in liver transplant patients. (Patients 26175 and 26480 had heart transplants, while patient 26471 had a kidney transplant.)

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1. Gender, Race and Age of Susceptible Partners

Table 32: Summary of CMV Disease up to 6 Months Post-Transplant – Endpoint Committee by Gender (ITT Population)

Gender	Ganciclovir (n=125)	Valganciclovir (n=239)	2-sided 95% CI+	p-value	Treatment Favored	Conclusion
Female (n=97)	19% (6 / 32)	20% (13 / 65)	-0.18, +0.15	0.86	Ganciclovir	
Male (n=267)	14% (13 / 93)	9% (16 / 174)	-0.03, +0.14	0.29	Valganciclovir	Non-Inferiority+

+Non-inferiority is demonstrated for Valganciclovir if the lower bound of the 95% CI is >-0.05
Breslow-Day test of treatment by gender interaction: p=0.41
Zelen's exact test of treatment by gender interaction: p=0.51

Valganciclovir was clearly non-inferior to ganciclovir in males. Since the treatment by gender interaction was not statistically significant (p=0.41), there was insufficient evidence to conclude that the valganciclovir treatment effect differed in males and females.

Table 33: Summary of CMV Disease up to 6 Months Post-Transplant – Endpoint Committee by Race (ITT Population)

Race	Ganciclovir (n=125)	Valganciclovir (n=239)	2-sided 95% CI+	p-value	Treatment Favored	Conclusion
Caucasians (n=325)	17% (19 / 113)	12% (25 / 212)	-0.03, +0.14	0.19	Valganciclovir	Non-Inferiority+
Other (n=39)	0% (0 / 12)	15% (4 / 27)	-0.40, +0.06	0.16	Ganciclovir	

+Non-inferiority is demonstrated for Valganciclovir if the lower bound of the 95% CI is >-0.05
Breslow-Day test of treatment by race interaction: p=0.10
Zelen's exact test of treatment by race interaction: p=0.25

Valganciclovir was non-inferior to ganciclovir in Caucasians but there was a statistically significant treatment by organ interaction. (See Section 4.2.1.) The treatment by race interaction was not statistically significant. The number of non-Caucasians was not large enough to allow us to conclude that valganciclovir was non-inferior to oral ganciclovir in this subgroup.

Table 34: Summary of CMV Disease up to 6 Months Post-Transplant – Endpoint Committee by Age (ITT Population)

Age	Ganciclovir (n=125)	Valganciclovir (n=239)	2-sided 95% CI+	p-value	Treatment Favored	Conclusion
≤50 (n=221)	14% (11 / 78)	10% (15 / 143)	-0.06, +0.13	0.47	Valganciclovir	
>50 (n=143)	17% (8 / 47)	15% (14 / 96)	-0.10, +0.17	0.64	Valganciclovir	

Breslow-Day test of treatment by age interaction: p=0.81
Zelen's exact test of treatment by age interaction: p=1.00

There was no evidence of a treatment by age interaction, so it can be assumed that valganciclovir treatment effects are consistent in younger and older patients.

4.2. Other Special/Subgroup Populations

4.2.1. CMV Disease, Tissue-Invasive CMV Disease and CMV Syndrome by Organ Type

Table 35: Summary of CMV Disease up to 6 Months Post-Transplant – Endpoint Committee by Organ Type (ITT Population)

Organ	Ganciclovir (n=125)	Valganciclovir (n=239)	2-sided 95% CI+	p-value	Treatment Favored /	Conclusion
Heart (n=56)	10% (2 / 21)	6% (2 / 35)	-0.12, +0.20	0.63	Valganciclovir	
Liver (n=177)	12% (7 / 59)	19% (22 / 118)	-0.18, +0.04	0.29	Ganciclovir	
Kidney (n=120)	23% (9 / 39)	6% (5 / 81)	+0.02+, +0.31	0.01*	Valganciclovir	Superiority
Kidney/Pancreas (n=11)	17% (1 / 6)	0% (0 / 5)	-0.24, +0.57	1.00	Valganciclovir	

+Non-inferiority is demonstrated for Valganciclovir if the lower bound of the 95% CI is >-0.05
*Superiority is demonstrated if p<0.05
Breslow-Day test of treatment by organ interaction: p=0.036
Zelen's exact test of treatment by organ interaction: p=0.016
(The Breslow-Day test of treatment by organ interaction at 12 months was not statistically significant: p=0.25)

There was a statistically significant treatment by organ transplant type interaction (p=0.036 using the Breslow-Day test and p=0.016 using Zelen's exact test). Oral ganciclovir treatment was favored in liver transplant patients. This is a possible [redacted] because approximately half of the patients in the study had liver transplants. In liver transplant recipients, there was a 95% probability that oral ganciclovir would be no more than 4% worse than valganciclovir and could be up to 18% better than valganciclovir.

Valganciclovir was statistically superior (and non-inferior) to oral ganciclovir for the treatment of CMV disease in kidney transplant recipients (p=0.01). Twenty-three percent (23%, 9/39) of the oral

ganciclovir patients who had kidney transplants developed CMV disease compared to only 6% (5/81) of the valganciclovir patients.

There were an insufficient number of heart and kidney/pancreas transplant recipients in order to demonstrate non-inferiority in favor of valganciclovir for each organ type separately. However, when liver transplant recipients were excluded, there was no statistically significant treatment by organ interaction (Breslow-Day p-value = 0.62) and valganciclovir was superior to oral ganciclovir. The estimated difference in proportions was +0.13, in favor of valganciclovir [95% CI: = 0.02, 0.23; Cochran-Mantel-Haenszel (CMH) p-value stratified by organ type = 0.02].

Table 36: Summary of Tissue-Invasive CMV Disease up to 6 Months Post-Transplant – Endpoint Committee by Organ Type (ITT Population)

Organ	Ganciclovir (n=125)	Valganciclovir (n=239)	2-sided 95% CI+	p-value	Treatment Favored	Conclusion
Heart (n=56)	5% (1 / 21)	0% (0 / 35)	-0.07, +0.16	0.38	Valganciclovir	
Liver (n=177)	3% (2 / 59)	14% (16 / 118)	-0.18, -0.02	0.04*	Ganciclovir	Superiority
Kidney (n=120)	5% (2 / 39)	1% (1 / 81)	-0.04, +0.12	0.25	Valganciclovir	
Kidney/Pancreas (n=11)	17% (1 / 6)	0% (0 / 5)	-0.24, +0.57	1.00	Valganciclovir	

*Superiority is demonstrated if p<0.05
Breslow-Day test for treatment by organ interaction: p=0.028
Zelen's exact test for treatment by organ interaction: p=0.015
(The Breslow-Day test of treatment by organ interaction was not statistically significant at 12 months: p=0.17)

There was a statistically significant treatment by organ transplant type interaction (p=0.028 using the Breslow-Day test and p=0.015 using Zelen's exact test). Oral ganciclovir was superior to valganciclovir in liver patients. This is a possible [redacted] because tissue-invasive CMV disease is a more severe form of CMV disease. In addition, the rate of tissue-invasive CMV disease in valganciclovir liver transplant recipients (14%) was almost 5 times as higher than it was in oral ganciclovir patients who received liver transplants (3%).

In a July 21, 2003 response to FDA questions, the applicant suggested the diminished valganciclivir treatment effect in liver transplant patients could have been due to the slight imbalance in the combination of triple therapy used in liver transplant patients. The most frequent triple therapy combination was mycophenolate mofetil, tacrolimus and prednisolone. Among liver transplant recipients, this was used in 19% (23/118) of the valganciclovir patients compared to 11.9% (7/59) of the oral ganciclovir patients. The applicant also noted that out of the 16 patients in the valganciclovir arm who developed tissue-invasive CMV disease, 7 were receiving this regimen and 6 patients were receiving tacrolimus and steroids. Similarly one patient out of two patients in the oral ganciclovir arm who developed tissue-invasive disease received the same triple therapy.

However there were other combinations of triple therapy in liver transplant recipients that were used more frequently in oral ganciclovir patients (e.g., ciclosporin, mycophenolate mofetil and

prednisolone).

Table 37: Summary of CMV Syndrome up to 6 Months Post-Transplant – Endpoint Committee by Organ Type (ITT Population)

Organ	Ganciclovir (n=125)	Valganciclovir (n=239)	2-sided 95% CI+	p-value	Treatment Favored	Conclusion
Heart (n=56)	5% (1 / 21)	6% (2 / 35)	-0.14, +0.13	1.00	Ganciclovir	
Liver (n=177)	8% (5 / 59)	5% (6 / 118)	-0.05, +0.12	0.51	Valganciclovir	
Kidney (n=120)	18% (7 / 39)	5% (4 / 81)	-0.00, +0.26	0.04*[1]	Valganciclovir	Superiority
Kidney/Pancreas (n=11)	0% (0 / 6)	0% (0 / 5)	N/A	N/A	Neither	

*Superiority is demonstrated if p<0.05
[1] p-value is from Fisher's Exact test (not from the weighted means test, which corresponds to the 95% CI and is not quite statistically significant)
Breslow-Day test of treatment by organ interaction: p=0.41
Weighted Difference in Proportions = +0.06, 95% Confidence Interval=(-0.01, +0.12), p-value=0.08

There was no statistically significant treatment by organ transplant type interaction for CMV syndrome (p=0.41). Valganciclovir was superior to oral ganciclovir in kidney patients. Valganciclovir also appeared to be a little more effective than oral ganciclovir in liver transplant patients, but the difference was not as great.

The treatment by organ transplant type interaction appears to be most significant for tissue-invasive CMV disease.

4.2.2. Adverse Events by Organ Type

Table 38: Incidence of Mortality (Safety Population)

6 Month Results

Organ	Ganciclovir (n=126)	Valganciclovir (n=244)
Heart (n=56)	0% (0 / 21)	6% (2 / 34)
Liver (n=177)	3% (2 / 60)	6% (7 / 124)
Kidney (n=120)	0% (0 / 39)	0% (0 / 81)
Kidney/Pancreas (n=11)	0% (0 / 6)	0% (0 / 5)

p-value for treatment effect = 0.28, estimated treatment difference= -0.02 in favor of ganciclovir,
95% CI=(-0.06, +0.02)
Breslow-Day test for treatment by organ interaction: p=0.41
Zelen's exact test for treatment by organ interaction: p=1.0

Compared to oral ganciclovir, mortality for heart and liver transplant patients appeared to be higher in the valganciclovir treatment group. Because of small number of deaths and because the study was not designed to compare mortality rates in the two treatment groups, differences in mortality rates were not statistically significant.

Table 39: Incidence of Hospitalization (Safety Population)

6 Month Results

Organ	Ganciclovir (n=127)	Valganciclovir (n=245)
Heart (n=56)	48% (10 / 21)	31% (11 / 35)
Liver (n=177)	49% (30 / 61)	57% (71 / 124)
Kidney (n=120)	59% (23 / 39)	58% (47 / 81)
Kidney/Pancreas (n=11)	17% (1 / 6)	80% (4 / 5)

p-value for treatment effect = 0.57, estimated treatment difference= -0.03 in favor of ganciclovir,
95% CI=(-0.14, +0.08)
Breslow-Day test for treatment by organ interaction: p=0.08
Zelen's exact test for treatment by organ interaction: p=0.10

12 Month Results

Organ	Ganciclovir (n=127)	Valganciclovir (n=245)
Heart (n=56)	76% (16 / 21)	54% (19 / 35)
Liver (n=177)	61% (37 / 61)	66% (82 / 124)
Kidney (n=120)	64% (25 / 39)	70% (57 / 81)
Kidney/Pancreas (n=11)	17% (1 / 6)	80% (4 / 5)

p-value for treatment effect = 0.49, estimated treatment difference= -0.04 in favor of ganciclovir,
95% CI=(-0.14, +0.07)
Breslow-Day test for treatment by organ interaction: p=0.053
Zelen's exact test for treatment by organ interaction: p=0.07

Compared to oral ganciclovir, 6- and 12-month hospitalization rates were higher in the valganciclovir treatment group for liver transplant patients and lower for heart transplant patients. Hospitalization rates in kidney transplant patients were similar at 6 months and higher in the valganciclovir treatment group than in the oral gancyclovir treatment group at 12 months. The

Breslow-Day tests for the treatment by organ transplant interactions at 6 and 12 months were not statistically significant but small enough to be indicative of a possible trend (p=0.08 and p=0.053, respectively using the Breslow-Day test; p=0.10 and 0.07, respectively using Zelen's exact test).

Table 40: Incidence of Neutropenia (Reported Adverse Events, Safety Population)

6 Month Results

Organ	Ganciclovir (n=126)	Valganciclovir (n=244)
Heart (n=56)	0% (0 / 21)	3% (1 / 34)
Liver (n=177)	3% (2 / 60)	10% (13 / 124)
Kidney (n=120)	5% (2 / 39)	7% (6 / 81)
Kidney/Pancreas (n=11)	0% (0 / 6)	0% (0 / 5)

p-value for treatment effect = 0.06, estimated treatment difference=-0.05 in favor of ganciclovir, 95% CI=(-0.10, +0.003)
Breslow-Day test for treatment by organ interaction: p=0.66

The incidence of neutropenia adverse events that were reported by investigators appeared to be higher in valganciclovir patients than in oral ganciclovir patients in the three major organ transplant groups. There were no interaction between treatment group and organ transplant type (p=0.66). The p-value comparing rates of neutropenia in valganciclovir and oral ganciclovir patients (p=0.06) was close to statistical significance. This was particularly impressive for such a small study that was not designed to compare safety endpoints in the two treatment groups.

Table 41: Incidence of Neutropenia (Laboratory Abnormalities)

6 Month Results

Organ	Ganciclovir (n=126)	Valganciclovir (n=244)
Heart (n=56)	0% (0 / 21)	12% (4 / 34)
Liver (n=177)	10% (6 / 60)	12% (15 / 124)
Kidney (n=120)	10% (4 / 39)	14% (11 / 81)
Kidney/Pancreas (n=11)	0% (0 / 6)	20% (1 / 5)

p-value for treatment effect = 0.18, estimated treatment difference=-0.05 in favor of ganciclovir, 95% CI=(-0.11, +0.02)
Breslow-Day test for treatment by organ interaction: p=0.41

The incidence of neutropenia using laboratory abnormality data also appeared to be numerically

higher in valganciclovir patients than in oral ganciclovir patients in the three major organ transplant groups. There were no interaction between treatment group and organ transplant type (p=0.41).

Table 42: Percentage of Solid Organ Transplant Recipients with CMV Disease by Presence or Absence of Neutropenia, 6 Month Adverse Event Data, Safety Population

	Neutropenia (n=24)	No Neutropenia (n=338)
CMV Disease: Endpoint Committee (n=48)	13% (3/24)	13% (45/338)

Table 43: Percentage of Solid Organ Transplant Recipients with Tissue-Invasive CMV Disease by Presence or Absence of Neutropenia, 6 Month Adverse Event Data, Safety Population

	Neutropenia (n=24)	No Neutropenia (n=338)
Tissue-Invasive CMV Disease: Endpoint Committee (n=23)	4% (1/24)	7% (22/338)

There does not appear to be an increased incidence of CMV or tissue-invasive CMV disease among patients with neutropenia.

Table 44: Percentage of Liver Transplant Recipients with CMV Disease by Presence or Absence of Neutropenia, 6 Month Adverse Event Data, Safety Population

	Neutropenia (n=15)	No Neutropenia (n=161)
CMV Disease: Endpoint Committee (n=29)	13% (2/15)	17% (27/161)

Table 45: Percentage of Liver Transplant Recipients with Tissue-Invasive CMV Disease by Presence or Absence of Neutropenia, 6 Month Adverse Event Data, Safety Population

	Neutropenia (n=15)	No Neutropenia (n=161)
Tissue-Invasive CMV Disease: Endpoint Committee (n=18)	6% (1/15)	11% (17/161)

There was a somewhat higher incidence of CMV disease and a slightly lower incidence of tissue-invasive CMV disease among liver transplant recipients with neutropenia compared to liver

transplant recipients without neutropenia.

4.2.3. Histocompatibility and Acute Graft Rejection

Table 46: Histocompatibility between donor / recipients

All transplant patients

Number of Mismatches	Ganciclovir (n=127)	Valganciclovir (n=245)
0 (n=16)	4% (n=5)	4% (n=11)
1 (n=9)	1% (n=1)	3% (n=8)
2 (n=17)	5% (n=6)	4% (n=11)
3 (n=47)	16% (n=20)	11% (n=27)
4 (n=43)	13% (n=16)	11% (n=27)
5 (n=38)	8% (n=10)	11% (n=28)
6 (n=39)	11% (n=14)	10% (n=25)
Unobtainable (n=163)	43% (n=55)	44% (n=108)

Liver Transplant Patients

Number of Mismatches	Ganciclovir (n=61)	Valganciclovir (n=124)
0 (n=3)	3% (n=2)	1% (n=1)
1 (n=1)	0% (n=0)	1% (n=1)
2 (n=1)	2% (n=1)	0% (n=0)
3 (n=6)	2% (n=1)	4% (n=5)
4 (n=12)	7% (n=4)	6% (n=8)
5 (n=15)	8% (n=5)	8% (n=10)
6 (n=17)	8% (n=5)	10% (n=12)
Unobtainable (n=130)	70% (n=43)	70% (n=87)

There were also no discernable differences between number of mismatches in the two treatment groups.

Table 47: Summary of Acute Graft Rejection up to Six Months Post-Transplant

Organ	Ganciclovir	Valganciclovir
All Patients	36% (45 / 125)	30% (71 / 239)
Heart (n=56)	71% (15 / 21)	57% (20 / 35)
Liver (n=177)	36% (21 / 59)	27% (32 / 118)
Kidney (n=120)	23% (9 / 39)	21% (17 / 81)
Kidney/Pancreas (n=11)	0% (0 / 6)	40% (2 / 5)

The incidence of acute graft rejection appeared to be at least as high or higher in oral ganciclovir patients than in valganciclovir patients in the three major organ transplant groups.

4.2.4. Incidence of CMV and Tissue Invasive CMV Disease in Liver Transplant Recipients, by Country

Table 48: Incidence of CMV Disease in Liver Transplant Patients, by Country: Endpoint Committee 6 Month Results

Country	Ganciclovir (n=59)	Valganciclovir (n=118)
Australia (n=4)	0% (0 / 1)	0% (0 / 3)
Canada (n=28)	0% (0 / 10)	17% (3 / 18)
France (n=7)	0% (0 / 2)	0% (0 / 5)
Great Britain (n=15)	20% (1 / 5)	0% (0 / 10)
New Zealand (n=2)	0% (0 / 0)	0% (0 / 2)
USA (n=121)	15% (6 / 41)	24% (19 / 80)

Breslow-Day test for treatment by country interaction: p=0.09
Zelen's exact test for treatment by country interaction: p=0.22

Table 49: Incidence of Tissue-Invasive CMV Disease in Liver Transplant Recipients, by Country: Endpoint Committee 6 Month Results

Country	Ganciclovir (n=59)	Valganciclovir (n=118)
Australia (n=4)	0% (0 / 1)	0% (0 / 3)
Canada (n=28)	0% (0 / 10)	17% (3 / 18)
France (n=7)	0% (0 / 2)	0% (0 / 5)
Great Britain (n=15)	20% (1 / 5)	0% (0 / 10)
New Zealand (n=2)	0% (0 / 0)	0% (0 / 2)
USA (n=121)	2% (1 / 41)	16% (13 / 80)

Breslow-Day test for treatment by country interaction: p=0.010
Zelen's exact test for treatment by country interaction: p=0.11

For tissue-invasive CMV disease, there was a statistically significant treatment by country interaction (p=0.010), primarily because all of the valganciclovir cases of tissue-invasive CMV disease were diagnosed in North America. The only European ganciclovir case was diagnosed in Great Britain. Therefore it appeared that valganciclovir was not a less effective treatment for tissue-invasive CMV Disease in Australia, France, Great Britain or New Zealand. In contrast, the incidence of tissue-invasive CMV disease was 8 times as high for valganciclovir patients in North America as it was for patients treated with oral ganciclovir.

4.2.5. Incidence of Tissue-Invasive CMV Disease by Center in U.S. and Canadian Liver Transplant Recipients

Table 50: Incidence of Tissue-Invasive CMV Disease by Center: Endpoint Committee

6 Month Results

U.S. Liver Transplant Recipients

Center	Ganciclovir (n=41)	Valganciclovir (n=80)
26452 (n=19)	14% (1 / 7)	17% (2 / 12)
26453 (n=4)	0% (0 / 1)	33% (1 / 3)
26454 (n=1)	0% (0 / 0)	0% (0 / 1)
26455 (n=9)	0% (0 / 3)	33% (2 / 6)
26458 (n=7)	0% (0 / 2)	20% (1 / 5)
26460 (n=2)	0% (0 / 1)	100% (1 / 1)
26461 (n=3)	0% (0 / 1)	0% (0 / 2)
26464 (n=9)	0% (0 / 3)	0% (0 / 6)
26466 (n=1)	0% (0 / 0)	0% (0 / 1)
26471 (n=1)	0% (0 / 1)	0% (0 / 0)
26473 (n=3)	0% (0 / 1)	0% (0 / 2)
26476 (n=3)	0% (0 / 1)	0% (0 / 2)
26492 (n=7)	0% (0 / 3)	75% (3 / 4)
26493 (n=4)	0% (0 / 1)	33% (1 / 3)
26495 (n=17)	0% (0 / 6)	0% (0 / 11)
26496 (n=1)	0% (0 / 0)	0% (0 / 1)
26783 (n=4)	0% (0 / 2)	50% (1 / 2)
26784 (n=2)	0% (0 / 1)	0% (0 / 1)
26785 (n=2)	0% (0 / 0)	0% (0 / 2)
26786 (n=3)	0% (0 / 1)	0% (0 / 2)
26788 (n=6)	0% (0 / 2)	0% (0 / 4)
26789 (n=1)	0% (0 / 0)	0% (0 / 1)
26790 (n=12)	0% (0 / 4)	13% (1 / 7)

Breslow-Day test for treatment by center interaction: p=0.75
Zelen's exact test for treatment by center interaction: p=0.60

Canadian Liver Transplant Recipients

Center	Ganciclovir (n=10)	Valganciclovir (n=18)
25966 (n=12)	0% (0 / 4)	25% (2 / 8)
25967 (n=1)	0% (0 / 0)	0% (0 / 1)
25968 (n=2)	0% (0 / 1)	0% (0 / 1)
25969 (n=10)	0% (0 / 4)	17% (1 / 6)
25970 (n=3)	0% (0 / 1)	0% (0 / 2)

Breslow-Day and Zelen tests for treatment by center interaction could not be computed because the data are too sparse

Within the United States and Canada, treatment by center interactions were not statistically significant.

4.2.6. Summary of Demographic Data in Liver Transplant Recipients

Table 51: Summary of Demographic Data in Liver Transplant Recipients

	GCV N = 61	VGCV N = 124
Sex		
Male	43 (70%)	88 (71%)
Female	18 (30%)	36 (29%)
N	61	124
Race		
Caucasian	56 (92%)	116 (94%)
Other	5 (8%)	8 (6%)
N	61	124
Age		
Mean	47	48
SD	12	11
SEM	1.5	0.9
Median	48	50
Min-Max	18 – 70	17 – 70
N	61	124
Weight in kg		
Mean	86	83
SD	24	18
SEM	3.2	1.7
Median	87	84
Min-Max	49 – 154	40 – 135
N	60	120
Height in cm		
Mean	172	173
SD	10	10
SEM	1.3	0.9
Median	173	175
Min-Max	150 – 191	147 – 195
N	60	123

```
n represents number of patients contributing to summary
statistics.
Percentages are based on n (the number of valid values).
Percentages are not calculated if n < 10.
```

Demographic characteristics in the two treatment groups appeared to be similar for liver transplant patients and similar to those observed for all patients.

4.2.7. Estimated Relative Risk of CMV Disease, Tissue-Invasive CMV Disease and CMV Syndrome for Valacyclovir compared to Placebo in Study PV16000

Table 52: Incidence of CMV Disease, Tissue-Invasive CMV Disease and CMV Syndrome in Liver Transplant Patients in Study PV16000 and Historical Controls

Organ	Valganciclovir PV16000 (n=118)	Ganciclovir PV16000 (n=59)	Ganciclovir Historical Controls (n=150)	Placebo Historical Controls (n=154)
CMV Disease, Endpoint Committee	19% (22 / 118)	12% (7 / 59)	5% (7 / 150)	19% (29 / 154)
Tissue-Invasive CMV Disease	14% (16 / 118)	3% (2 / 59)	1% (1 / 150)	6% (10 / 154)
CMV Syndrome	5% (6 / 118)	8% (5 / 59)	4% (6 / 150)	12% (19 / 154)

Table 53: Estimated Relative Risk for Valganciclovir compared to Placebo for Study PV16000

Organ	Valganciclovir PV16000 (n=118)	Estimated Placebo Rate for PV16000[1] (n=154)	Relative Risk (Valganciclovir / Placebo) 95% CI[2]
CMV Disease, Endpoint Committee	19% (22 / 118)	48% (74 / 154)	0.39 (0.3, 0.6)
Tissue-Invasive CMV Disease	14% (16 / 118)	33% (51 / 154)	0.41 (0.3, 0.6)
CMV Syndrome	5% (6 / 118)	26% (40 / 154)	0.19 (0.1, 0.3)

[1] Estimated placebo rate = Placebo rate in previous ganciclovir study × ganciclovir rate in PV16000 / ganciclovir rate in previous ganciclovir study
[2] See Appendix for details

Using historical data from the Valganciclovir label, placebo rates are estimated for study PV16000, using oral ganciclovir rates from the historical data and from PV16000. Relative risks (risk for placebo / risk for valganciclovir) were estimated to be approximately 0.4 for CMV Disease and for Tissue-Invasive CMV Disease and 0.2 for CMV Syndrome.

This table assumed that the historical trial results could be replicated. However it is possible that the active control may not be as efficacious as it was in the past (e.g., due to the development of drug resistance). The results in the following table were computed assuming oral ganciclovir is only half as efficacious as it was in the historical study. Relative risks (risk for placebo / risk for valganciclovir) were estimated to be approximately 0.8 for CMV Disease and for Tissue-Invasive CMV Disease and 0.4 for CMV Syndrome. The upper limit of the confidence interval for CMV

Disease and Tissue-Invasive CMV Disease exceeded one. Only CMV Syndrome appeared to have a statistically significant treatment effect.

Table 54: Estimated Relative Risk for Valganciclovir compared to Placebo for Study PV16000 using twice the historical ganciclovir rate

Organ	Valganciclovir PV16000 (n=118)	Estimated Placebo Rate for PV16000[1] (n=154)	Relative Risk (Valganciclovir / Placebo) 95% CI[2]
CMV Disease, Endpoint Committee	19% (22 / 118)	24% (37 / 154)	0.78 (0.5, 1.1)
Tissue-Invasive CMV Disease	14% (16 / 118)	17% (25 / 154)	0.82 (0.6, 1.2)
CMV Syndrome	5% (6 / 118)	13% (20 / 154)	0.39 (0.3, 0.6)

[1] Estimated placebo rate = Placebo rate in previous ganciclovir study × ganciclovir rate in PV16000 / ganciclovir rate in previous ganciclovir study
[2] See Appendix for details

5. SUMMARY AND CONCLUSIONS

5.1. Statistical Issues and Collective Evidence

There was a statistically significant treatment by organ transplant type interaction (p=0.036 using the Breslow-Day test and p=0.016 using Zelen's exact test). Oral ganciclovir treatment was superior to valganciclovir for the treatment of tissue-invasive CMV disease in liver transplant patients (p=0.04). Valganciclovir was superior to oral ganciclovir for the treatment of CMV disease in kidney patients (p=0.01). There were probably an insufficient number of heart and kidney/pancreas transplant patients in order to demonstrate non-inferiority in favor of valganciclovir.

Hospitalizations at 6 and 12 months were higher in liver transplant patients that received valganciclovir than in liver transplant patients receiving oral ganciclovir (57% in valganciclovir patients and 49% in oral ganciclovir patients at 6 months; 66% in valganciclovir patients and 61% in oral ganciclovir patients at 12 months). Hospitatizations were lower in heart transplant patients that received valganciclovir (31% of the valganciclovir patients compared to 48% of the oral ganciclovir patients at 6 months; 54% of the valganciclovir patients compared to 76% of the oral ganciclovir patients at 12 months). Hospitalization rates appeared to be similar among kidney transplant patients at 6 months and higher in valganciclovir patients at 12 months.

The incidence of mortality and serious adverse events at 6 months was higher in valganclovir patients. By 6 months, nine deaths had occurred in valganciclovir patients (3.7%) compared to only 2 deaths in oral ganciclovir patients (1.6%). Fifty percent (50%, 123/244) of valganciclovir patients had serious adverse events compared to 41% (51/126) of the oral ganciclovir patients. These

differences were not statistically significant, but the trail was neither powered nor designed to detect differences of this magnitude. The majority of deaths occurred in liver transplant patients (9 out of a total of 11). The incidence of mortality at 12 months was comparable in both treatment groups.

Neutropenia was also higher in valganciclovir patients (8% of valganciclovir patients had neurtropenia at 6 months, compared to 3% of the oral ganciclovir patients). This difference approached statistical significance (p=0.06).

On the other hand, acute graft rejection was reported more frequently in the ganciclovir group for liver, heart and kidney transplant patients. The frequencies of acute graft rejections among patients who received Valcyte or ganciclovir, respectively, were; liver transplant patients (27%, 36%), kidney (21%, 23%), heart (57%, 71%).

5.2. Conclusions and Recommendations

Oral ganciclovir treatment was superior to valganciclovir for the treatment of tissue-invasive CMV disease in liver transplant patients. This is because approximately half of the patients in the study had liver transplants. Hospitalization and mortality rates were also higher in liver transplant patients that received valganciclovir. Valganciclovir should probably be indicated for the treatment of CMV disease in kidney and heart transplant patients

6. APPENDICES

Sample size and power calculations

With a 2:1 randomization (valganciclovir : ganciclovir), a sample size of 310 patients was adequate to conclude non-inferiority (a difference of no less than 0.05) in the proportion of patients who developed CMV disease between valganciclovir and ganciclovir with at least 90% power, assuming the true proportion of patients, in the ITT population, who developed CMV disease was 12% for ganciclovir and 5% for valganciclovir.

Assuming a premature termination rate of at least 15% required recruitment of approximately 372 patients to ensure that 310 patients either completed the full course of treatment or reached the primary endpoint (CMV disease).

Rationale for choice of delta and sample size estimates

The sponsor cited a 1997 reference in Lancet by Gan et al where the suggested CMV rate of 12% was reasonable to expect in high risk liver, heart, kidney and kidney-pancreas transplant populations, treated with 1000 mg t.i.d. of oral ganciclovir.

Pharmacokinetic data suggest that 900 mg q.d. valganciclovir and 5 mg/kg i.v. ganciclovir have higher $AUC_{0\text{-}24\ hr}$ and C_{max} than 1000 mg t.i.d. of oral ganciclovir (see Valcyte label). The CMV rate in a 1995 Lancet paper by Winston et al. was 2.4% in high risk liver transplant patients treated with 6 mg/kg of i.v. ganciclovir (administered 5 days a week). To take into account the higher risk of D+/R- patients compared with the mixed serology-based risk population in this study, the estimated valganciclovir CMV rate of 2.4% was doubled to approximately 5%.

The non-inferiority margin of –0.05 was based on the assessment of a clinically meaningful difference from the expected CMV disease rate of 0.12 in ganciclovir patients.

The sponsor did not discuss the placebo response rates in the rationale. Ideally the non-inferiority margin should not just be a clinically meaningful difference but should also represent what the minimal effect size of oral ganciclovir vs. placebo will be. There should be convincing evidence that ganciclovir would be at least 5% better than placebo if placebo were to be included in the trial. From the Cytovene® (ganciclovir) label, 15% (3/21) D+/R- patients on oral ganciclovir had CMV disease at 6 months compared to 44% (11/25) of the placebo patients. The treatment effect of oral ganciclovir was statistically significant {95% confidence interval=(.44-.15) ± 1.96 × [(.15)(1-.15)/21 + (.44)(1-.44)/25]$^{1/2}$ = (+.05, +.55)}.

Estimated confidence intervals for relative risk (risk for placebo / risk for valganciclovir)

The estimated logarithm of the relative risk (risk for placebo / risk for valganciclovir)

= log RR (P/V) = log RR_1 (V/G) × log RR_2 (G/P) = log P_1(V) / log P_1(G) × log P_2(G) / log P_2(P),

where RR (P/V) denotes relative risk (risk for placebo / risk for valganciclovir),

RR_1 (V/G) denotes the relative risk (risk for valganciclovir / risk for oral ganciclovir) from study PV16000,

RR_2 (G/P) denotes the relative risk using data from the historical controls (risk for oral ganciclovir / risk for placebo),

P_1(V) and P_1(G) denote the proportion of valganciclovir and oral ganciclovir patients who developed CMV disease in study PV16000,

P_2(G) and P_2(P) denote the proportion of oral ganciclovir and placebo historical controls who developed CMV disease.

v=variance (log RR) = $[1-P_1(V)]/n_{1V} + [1-P_1(G)]/n_{1G} + [1-P_2(G)]/n_{2G} + [1-P_2(P)]/n_{2P}$,

where n_{1V} and n_{1G} denote the number of valganciclovir and oral ganciclovir patients in study PV16000, and n_{2G} and n_{2P} denote the number of oral ganciclovir and placebo historical controls.

An approximate 95% confidence interval for the RR (P/V)

= $[RR \times \exp(-1.96\ v^{0.5}), RR \times \exp(+1.96\ v^{0.5})]$.

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/s/

Fraser Smith
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Greg Soon
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Mohammad Huque
9/11/03 04:42:38 PM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-304 / S-001

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS TEAM LEADER NOTE

NDA: 21-304, SE1-001
DRUG: Valganciclovir hydrochloride tablets (Valcyte®)
SPONSOR: Roche
TYPE: Efficacy supplement- new indication
INDICATION: Prevention of CMV disease in kidney, heart, and kidney-pancreas transplant patients at high risk
DOSING REGIMEN: 900 mg once daily with food

TEAM LEADER: Kellie Schoolar Reynolds, Pharm.D.
SUBMISSION DATE: November 12, 2002
REVIEW DATE: September 12, 2003

The clinical pharmacology information submitted with this supplemental NDA was reviewed by Derek Zhang, Ph.D. A pharmacometics consult review was completed by Jenny J. Zheng, Ph.D.

As indicated by the sponsor and the clinical pharmacology and pharmacometrics reviewers, the mean exposure to ganciclovir was 1.7 times higher following administration of 900 mg Valcyte tablets once daily versus 1000 mg ganciclovir capsules three times daily. I concur with the conclusion of Drs. Zheng and Zhang that the systemic ganciclovir exposure attained in the pivotal clinical trial (PV16000) was similar across kidney, heart and liver transplant recipients. This conclusion is important because the efficacy results in the pivotal clinical trial, the incidence of invasive CMV disease was higher in liver transplant recipients who received Valcyte compared to those who received ganciclovir. Due to the comparable exposure in recipients of the different organs, it is unlikely the lower efficacy in the liver transplant recipients who received Valcyte is due to pharmacokinetic differences among the transplant recipients.

Dr. Zheng's pharmacometric review includes the following comment-

> Even though the systemic exposure (AUC_{0-24}) to ganciclovir was 68% higher after oral administration of valganciclovir at 900 mg q.d. than oral administration of ganciclovir at 1 g t.i.d., the trough concentration (C_{24}) was higher after oral administration of ganciclovir. E.g. in study WP15711, after a single dose, the mean C_{24} (range) were 0.623 µg/mL (0.266 – 1.17 µg/mL) and 0.2722 µg/mL (0.0914-0.812 µg/mL), respectively, after oral administration of 1 g t.i.d. ganciclovir and oral administration of 900 mg q.d. valganciclovir.

The clinical relevance of the lower trough ganciclovir concentrations in plasma is not known. However, as previously mentioned, due to the comparable plasma ganciclovir exposure in recipients of the different organs, it is unlikely the lower efficacy in the liver transplant recipients who received Valcyte is due to pharmacokinetic differences among the transplant recipients.

Kellie Schoolar Reynolds, Pharm.D.
Pharmacokinetics Team Leader, DPEIII, OCPB

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Kellie Reynolds
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BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICAL REVIEW

NDA: 21-304 SE1-001

TYPE: sNDA
DRUG: Valcyte (valganciclovir hydrochloride)
SPONSOR: Roche
FORMULATION, STRENGTH(S): 450 mg tablets
INDICATION: Prevention of CMV disease in kidney, heart, and kidney-pancreas transplant patients at high risk (Donor CMV seropositive/Recipient CMV seronegative [(D+/R-)])

REVIEWER: Yuanchao (Derek) Zhang
PM REVIEWER: Jenny J. Zheng
TEAM LEADER: Kellie Reynolds
SUBMISSION DATE: 11-11-02
DATE RECEIVED: 11-12-02
DRAFT REVIEW: 08-25-03

Executive Summary

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has reviewed the information submitted and concurred the sponsor's conclusion that the mean systemic exposure to ganciclovir was 1.7 times higher following administration of 900 mg Valcyte tablets once daily versus 1000 mg ganciclovir capsules three times daily, when both drugs were administered according to their renal function dosing algorithms in solid organ transplant recipients. The systemic ganciclovir exposures attained were comparable across kidney, heart and liver transplant recipients based on a population pharmacokinetics evaluation.

Recommendations

The pharmacokinetic information for ganciclovir provided in this submission supports the sponsor's labeling proposal with respect to ganciclovir exposure after oral administration of valganciclovir 900 mg q.d. or ganciclovir 1 g t.i.d. in [redacted] based on a population pharmacokinetic evaluation.

The sponsor needs to incorporate the following changes in the proposed label:

1. CLINICAL PHARMACOLOGY: Pharmacokinetics: Add Table 2 Mean Ganciclovir Pharmacokinetic Measures by Organ Type (Study PV16000). Add a paragraph prior to Table 2, "In solid organ transplant recipients, the mean systemic exposure to ganciclovir was 1.7 x higher following administration of 900 mg Valcyte tablets once daily versus 1000 mg ganciclovir capsules three times daily, when both drugs were administered according to their renal function dosing algorithms. The systemic ganciclovir exposures attained were comparable across kidney, heart and liver transplant recipients based on a population pharmacokinetics evaluation (see Table 2)."
2. CLINICAL PHARMACOLOGY: Pharmacokinetics: Add "In a pharmacokinetic study in liver transplant patients, ..." in the paragraph immediately after Table 2.
3. DOSAGE AND ADMINISTRATION: Add "with food" in the paragraph subtitled, "For the Prevention of CMV Disease in Heart, Kidney, and Kidney-Pancreas Transplantation".

Phase IV Commitments: None

Yuanchao (Derek) Zhang, Ph.D.
Pharmacokinetics Reviewer, DPE III
Office of Clinical Pharmacology and
Biopharmaceutics

Jenny J. Zheng, Ph.D.
Pharmacometrics Reviewer, DPE III
Office of Clinical Pharmacology and
Biopharmaceutics

Concurrence:

Kellie S. Reynolds, Pharm. D.
Pharmacokinetics Team Leader, DPE III
Office of Clinical Pharmacology and
Biopharmaceutics

Summary of Clinical Pharmacology Findings

Valcyte (valganciclovir HCl) is the hydrochloride salt of the L-valyl ester prodrug of ganciclovir. The existing indication for Valcyte is for the treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome. The purpose of this supplement is to extend the Valcyte indication and usage to solid organ transplant recipients at high risk (Donor CMV seropositive/Recipient CMV seronegative [(D+/R-)]) for the prevention of CMV disease. Liver transplant claim was withdrawn by the sponsor during the review cycle due to the fact that there was a significantly higher incidence of tissue-invasive CMV disease in the Valcyte-treated group compared with the oral ganciclovir group in the study the sponsor conducted. The other organs evaluated were kidney, heart, and kidney-pancreas. The modified Valcyte label incorporates the safety, efficacy, and pharmacokinetic information in solid organ transplant patients.

This submission included two pharmacokinetic studies with valganciclovir in solid organ transplant (SOT) recipients: a pharmacokinetic study in liver transplant recipients (study WP15711), and a phase III clinical trial in SOT recipients (study PV16000). Study WP15711 was submitted to the agency in the Valcyte original NDA and reviewed by Dr. Robert Kumi. Study PV16000 was designed to investigate the comparative efficacy and safety of valganciclovir versus oral ganciclovir for the prevention of CMV disease in SOT recipients. Population pharmacokinetic evaluations were performed in Study PV16000 to measure plasma levels of ganciclovir after oral administration of 900 mg q.d. valganciclovir and 1g t.i.d. ganciclovir and to compare systemic exposure to ganciclovir in the recipients of heart, liver and kidney transplants (see Table 2 in the Valcyte label).

Changes related to Clinical Pharmacology and Biopharmaceutics will incorporate the pharmacokinetic information for ganciclovir after oral administration of valganciclovir 900 mg q.d. or ganciclovir 1 g t.i.d. in solid organ transplant recipients based on a population pharmacokinetic evaluation.

The following are proposed labeling changes related to Clinical Pharmacology and Biopharmaceutics:

1. CLINICAL PHARMACOLOGY: Pharmacokinetics: Add the following paragraph and Table 2. "In solid organ transplant recipients, the mean systemic exposure to ganciclovir was 1.7 x higher following administration of 900 mg Valcyte tablets once daily versus 1000 mg ganciclovir capsules three times daily, when both drugs were administered according to their renal function dosing algorithms. The systemic ganciclovir exposures attained were comparable across kidney, heart and liver transplant recipients based on a population pharmacokinetics evaluation (see Table 2)."

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/s/

Derek Zhang
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Jenny Zheng
8/28/03 04:18:52 PM
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Kellie Reynolds
8/28/03 04:35:57 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-304 / S-001

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA # 21-304 SUPPL # S-001

Trade Name VALCYTE™ Generic Name valganciclovir hydrochloride

Applicant Name Hoffman-La Roche Inc. HFD- 530

Approval Date September 12, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /✓/

   b) Is it an effectiveness supplement? YES /✓/NO /___/

      If yes, what type(SE1, SE2, etc.)? SE1

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /✓/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /✓/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Three years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /✓/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /✓/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /✓/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 21-304 Valcyte 450 mg Tablets

NDA # _____ _____

NDA # _____ _____

2. Combination product. Not applicable.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /✓/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /✓/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /✓/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /✓/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # PV16000

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /✓/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /✓/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_1_, Study # PV16000

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # ~~~ YES /✓/ ! NO /___/ Explain: _____

_____

_____

Investigation #2

IND # _____ YES /___/ ! NO /___/ Explain: _____

_____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.) —

YES /___/ NO /✓/

If yes, explain: _____

_____

_____

Nitin Patel
Signature of Preparer
Nitin Patel, R.Ph.
Regulatory Project Manager
Division of Antiviral Drug Products

9/12/03
Date

Debra B. Birnkrant
Signature of Division Director
Debra B. Birnkrant, M.D.
Division Director
Division of Antiviral Drug Products

9/12/03
Date

cc:
Archival NDA 21-304
HFD-530/Division File
HFD-530/RPM/Patel
HFD-530/CRPM/DeCicco
HFD-530/DivDir/Birnkrant
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-304 Supplement Type (e.g. SE5): SE1 Supplement Number: S-001

Stamp Date: November 12, 2002 Action Date: September 12, 2003

HFD 530 Trade and generic names/dosage form: VALCYTE™ (valganciclovir hydrochloride) Tablets

Applicant: Hoffman-La Roche Inc. Therapeutic Class: Antiviral Systemic

Indication(s) previously approved: Cytomegalovirus retinitis in patients with AIDS

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Prevention of cytomegalovirus disease in kidney, heart, and kidney-pancreas transplant patients at high risk

Is there a full waiver for this indication (check one)?

☐ Yes: Please proceed to Section A.

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min	kg	mo. 0	yr.	Tanner Stage	
Max	kg	mo. 3	yr.	Tanner Stage	

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☒ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other: _____

tudies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is nplete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo _____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage _____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Date studies are due (mm/dd/yy):

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Nitin Patel, R.Ph.
Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

CSO Labeling Review

Date of Review:	September 8, 2003
NDA Number:	21-304
Product Name:	Valcyte™ (valganciclovir hydrochloride) Tablets
Sponsor:	Hoffman-La Roche Inc.
Supplement:	SE1-001
Date of Submission:	November 11, 2002
Materials Reviewed: (Submission Dates)	January 17, 2003 (BL) July 3, 2003 (BL, Revised Draft Labeling) August 8, 2003 (BL, Revised Draft Labeling) August 13, 2003 (BL, Revised Draft Labeling) August 22, 2003 (BL, Revised Draft Labeling) September 5, 2003 (BL, Revised Draft Labeling) September 10, 2003 (BL, Final Draft Labeling) March 29, 2001 (Final Printed Labeling approved for NDA 21-304)

I. Background:

This efficacy supplemental application provides for the use of Valcyte™ (valganciclovir hydrochloride) 450 mg Tablets for the prevention of cytomegalovirus disease in kidney, heart, and kidney-pancreas transplant patients at high risk (Donor CMV seropositive/Recipient CMV seronegative). The final draft labeling dated September 10, 2003 was electronically compared to the final printed labeling approved on March 29, 2001 (NDA 21-304). The major revisions to the package insert and patient package insert are described below. Minor revisions such as font changes, formatting changes,

WITHHOLD 13 PAGE(S)

Draft Labeling

~~Ask a health care professional about any concerns about Valcyte. If you want~~These are not all the side effects of Valcyte. For more information, ask your doctor or pharmacist ~~for the labeling for Valcyte that was written for health care professionals~~.
~~Do not use Valcyte for a condition for which it was not prescribed. Do not give Valcyte to other persons.~~

IV. Conclusions/Recommendations:

It should be conveyed to the applicant that the Final Draft labeling dated September 10, 2003 is acceptable, and an approval letter should be sent.

Nitin Patel, R.Ph.
Regulatory Project Manager
Division of Antiviral Drug Products