CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-257s000

21-304s007

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA 22-257/Original-1 (b) (4)
Submission Number	000
Submission Code	000
Application Type	sNDA 21-304
Submission Number	07
Submission Code	Pediatric Efficacy Supplement
Letter Date	April 30, 2008
Stamp Date	May 1, 2008
PDUFA Goal Date	August 29, 2009
Reviewer Name	Andreas Pikis, M.D.
Review Completion Date	August 20, 2009
Established Name	Valganciclovir
Trade Name	VALCYTE
Therapeutic Class	CMV Antiviral
Applicant	Hoffmann-La Roche, Inc.
Priority Designation	P
Formulation	Powder for Oral Solution Tablets
Dosing Regimen	Based on body surface area and creatinine clearance
Indication	Prevention of CMV disease in solid organ transplant recipients at risk
Intended Population	Children 4 months to 16 years of age

This review amends the Clinical review for NDA 22-257/SN00 submitted to this NDA on November 25, 2008. This review is also a cross-reference to NDA 21-304/SN07.

Of note, NDA 22-257/SN00 was split into two NDAs for administrative purposes; NDA 22-257/Original-1 for the indication of CMV prophylaxis in pediatric kidney and heart transplant patients at high risk and (b) (4)

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

These New Drug Applications (NDAs) were initially submitted on April 30, 2008, and included pharmacokinetic and safety data from four pediatric studies conducted in response to the Pediatric Written Request for the use of valganciclovir for the prevention or treatment of CMV disease in children. Based on these studies, the Applicant sought the following:

- Approval of valganciclovir for oral solution and valganciclovir tablets for the prevention of cytomegalovirus (CMV) disease in pediatric solid organ transplant recipients 4 months to 16 years of age at risk for developing CMV disease, and
- (b) (4)

After a thorough review and based on the deficiencies noted during the inspection by the Division of Scientific Investigations, the Division decided valganciclovir is not recommended for approval for any of the above indications. A complete response letter outlining the deficiencies that needed to be addressed by the Applicant was issued on November 25, 2008. The deficiencies noted during the inspection were as follows:

Based on the findings from the analytical inspection at (b) (4) (b) (4) the plasma concentration data from WP16726 (A safety and pharmacokinetic study of valganciclovir in pediatric solid organ transplant recipients) and CASG109 (A phase I/II pharmacokinetic and pharmacodynamic evaluation of valganciclovir in neonates with symptomatic congenital CMV infection) are not acceptable as submitted. To assure the accuracy of analytical runs and the resulting drug concentrations, the Applicant needs to provide the following information:

- Frozen stability data that cover the duration of storage (b) (4) (b) (4) (b) (4) of all the plasma samples used for the quantification of ganciclovir in studies WV16726 and CASG109.
- Identify a set of integration parameters and re-integrate all the chromatograms within a run in a consistent manner. This procedure should be repeated for all the chromatograms generated in studies WV16726 and CASG109. Use the resulting concentrations to repeat the pharmacokinetic and/or pharmacodynamic evaluations in studies WP16726 and CASG109.

The Applicant addressed the deficiencies stated in the November 25th, 2008, complete response letter by providing frozen stability data covering the duration of storage and repeating the pharmacokinetic analysis using automatically integrated data. Pharmacokinetic analysis using

automatically integrated data compared to that using manually integrated data revealed insignificant changes in $AUC_{0\text{-}24h}$ and C_{max} values.

Based on the review of the four pediatric studies and the Applicant's resubmissions addressing the deficiences noted by the Division of Scientific Investigations, the Division determined the submitted data, together with the previous demonstration of efficacy for the prevention of CMV disease in adult transplant patients, support an indication for valganciclovir (oral solution and tablets) for the prevention of CMV disease in pediatric kidney and heart transplant recipients, ages 4 months to 16 years. The proposed pediatric dose (Dose [mg] = 7 x BSA x CrCl [calculated using the modified Schwartz formula]) administered once daily achieved ganciclovir exposures similar to those observed in adult solid organ transplant recipients receiving valganciclovir 900 mg once daily (b) (4) (b) (4) (b) (4) Valganciclovir is not approved in adults for the prevention of CMV disease in liver transplant patients; therefore, extrapolating efficacy data from adults to this population is not possible.

(b) (4) (b) (4) In neonates and infants ages 8 days to 3 months, 16 mg/kg of valganciclovir oral solution twice daily provided ganciclovir exposures similar to exposures observed in infants up to 3 months receiving 6 mg/kg of IV ganciclovir twice daily and to ganciclovir exposures observed in adults receiving 900 mg dose of valganciclovir twice daily. However, the safety and efficacy of IV ganciclovir have not been established for the treatment of congenital CMV infection in infants and no similar disease occurs in adults; therefore, efficacy cannot be extrapolated from IV ganciclovir to support the (b) (4) valganciclovir for oral solution for the treatment of congenital CMV infection. (b) (4)

The overall safety profile of Valcyte in children appears similar to that observed in adults. No new or unexpected safety findings were observed. However, the rates of certain adverse events and laboratory abnormalities such as upper respiratory tract infection, pyrexia, anemia, and neutropenia were reported more frequently in pediatric patients than in adults.

1.2 Recommendation on Post-marketing Actions

1.2.1 Risk Management Activity

No specific risk management activities were requested from the Applicant.

1.2.2 Required Phase 4 Commitments

As part of their post-marketing requirements the Applicant agreed to:

- Analyze the phenotypic nature of ganciclovir resistant viruses isolated during the clinical study CASG 109. The results will be submitted in a SAS transport file dataset by June 30, 2010.
- Perform a pharmacokinetic and safety study in pediatric heart transplant recipients <4 months of age in order to determine appropriate dosing in this age group and submit dosing recommendations for inclusion in the package insert. The results will be submitted by March 31, 2013.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Description: Valganciclovir is the L-valyl ester of ganciclovir. After oral administration, valganciclovir is rapidly and extensively hydrolyzed by gastrointestinal and liver esterases into ganciclovir and the essential amino acid valine. Its mechanism of action, antiviral spectrum, resistance pattern, and safety profile are the same as those of its parent drug ganciclovir. The absolute bioavailability of ganciclovir from oral valganciclovir tablets (~60%) is up to 10 times greater than that of oral ganciclovir capsules (6-9%).

Established name and trade name: Valganciclovir (Valcyte®)

Pharmacological class: Valganciclovir is a nucleoside analogue with inhibitory activity against herpes viruses. However, valganciclovir's unique characteristic is potent inhibition of CMV DNA polymerase.

Indications, dosing regimens, age groups: Currently, Valcyte® is approved for adults for the following indications:

- Treatment of CMV retinitis in patients with AIDS:
  Induction: 900 mg twice daily for 21 days
  Maintenance: following induction treatment, or in patients with inactive CMV retinitis, the recommended dose is 900 mg once daily
- Prevention of CMV disease in kidney, heart, or kidney-pancreas transplant patients at high risk for developing CMV disease:
  900 mg once daily starting within 10 days of transplantation until 100 days post-transplantation.

Applicant's proposed indications, dosing regimens, and age groups included in this submission:

- Prevention of CMV disease in pediatric solid organ transplant recipients, aged 4 months to 16 years of age, at risk for developing CMV disease:
  Pediatric Dose (mg) = 7 x BSA x CrCl (calculated using the modified Schwartz formula)

where

$$Mosteller\ BSA\,(m^2) = \sqrt{\frac{Height\ (cm)\ x\ Weight\ (kg)}{3600}}$$

$$Schwartz\ Creatinine\ Clearance\ (mL/\min/1.73m^2) = \frac{k\ x\ Height\ (cm)}{Serum\ Creatinine\ (mg/dL)}$$

where k =

0.45 for patients aged < 1 year,

0.45 for patients aged 1 to < 2 years (note k value is 0.45 instead of the typical value of 0.55),

0.55 for boys aged 2 to < 13 years and girls aged 2 to 16 years, and

0.7 for boys aged 13 to 16 years.

All calculated doses should be rounded to the nearest 25 mg increment for the actual deliverable dose. If the calculated dose exceeds 900 mg, a maximum dose of 900 mg should be administered. The oral solution is the preferred formulation since it provides the ability to administer a dose calculated according to the formula above; however, Valcyte tablets may be used if the calculated doses are within 10% of available tablet doses. For example, if the calculated dose is between 405 mg and 495 mg, one 450 mg tablet may be taken.

- [redacted] **(b) (4)**

2.2 Currently Available Treatment for Indications

Prevention of CMV disease in solid organ transplant recipients:
Cytomegalovirus is the single most frequent pathogen in solid organ transplant recipients, contributing significantly both to patient morbidity and mortality: Three forms of infection 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. However, CMV serologic status of both the donor and recipient and immunosuppressive therapy are considered the most significant factors. In adult patients, the lowest rate of CMV infection (< 5%) occurs in D-R- recipients and the highest rate (>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 than treatment of established infection. Prophylactic therapy and preemptive therapy are

the two major strategies used for prevention. During the last 15 years many investigators have focused on the value of preemptive therapy (treatment only of patients with evidence of CMV replication); however, at the present time, most transplant physicians use prophylactic therapy (prophylaxis administered to all patients at risk for developing CMV disease) for solid organ transplant recipients.

IV ganciclovir was the first antiviral drug approved for prevention of CMV disease in solid organ transplant recipients. Unfortunately, the long-term use of IV ganciclovir is generally impractical due to the requirement of an indwelling catheter to deliver the drug and, in addition, places the patient at increased risk of acquiring potentially life-threatening catheter-related infections. Oral ganciclovir is also approved for the prevention of CMV disease in solid organ transplant patients, however, this formulation has poor bioavailability and prophylaxis requires that patients take four capsules three times daily, making compliance challenging.

The poor bioavailability of oral ganciclovir and the limitations for the use of IV ganciclovir led to the development of valganciclovir, a more orally bioavailable form of ganciclovir. The absolute bioavailability of ganciclovir from oral valganciclovir tablets (~60%) is up to 10 times greater than the bioavalability of oral ganciclovir capsules (6-9%). In a population pharmacokinetic study of ganciclovir in solid organ transplant recipients, the mean systemic exposure to ganciclovir was ~1.7 times higher after oral administration of 900 mg q.d. valganciclovir compared with ganciclovir systemic exposure after oral administration of 1 gram t.i.d. ganciclovir. In liver transplant patients 900 mg of valganciclovir provides comparable exposures to 5 mg/kg of IV ganciclovir, and a 450 mg dose of oral valganciclovir provides comparable ganciclovir exposures to the 1000 mg t.i.d. dose of ganciclovir. Based on the results of a Phase 3 non-inferiority study comparing valganciclovir to oral ganciclovir, oral valganciclovir (900 mg once daily) was approved by FDA for the prevention of CMV disease in kidney, heart, and kidney-pancreas transplant patients at high risk for developing CMV disease.

Of note, none of these drugs (IV ganciclovir, oral ganciclovir, or oral valganciclovir) is approved for use in pediatric patients.

Congenital CMV infection:
The incidence of congenital CMV infection ranges from 0.2% to 2.2% of live births worldwide. In the United States, it is estimated that approximately 40,000 infants are born each year with congenital CMV infection (Stagno S, Britt W. Cytomegalovirus infections. In Remington JS, Klein JO, Wilson CB, Baker CJ, eds. Infectious Diseases of the fetus and newborn infant. 6th ed. Philadelphia: Elsevier-Saunders, 2006:739-772). Approximately 10% of infected newborns are symptomatic at birth. Mortality in these infants is about 12% and approximately 90% of symptomatic survivors experience significant morbidity from the infection. Survivors can have mental retardation, sensorineural hearing loss, microcephaly, seizures, and other medical problems (Boppana SB et al. Symptomatic congenital cytomegalovirus infection: neonatal morbidity and mortality. Pediatr Infect Dis J 1992;11:93-99). Children with asymptomatic congenital CMV infection rarely have neurologic sequelae and their long-term outcome is much better. However, about 10-15% of these asymptomatic infants are at risk for developing

neurologic sequelae such as sensorineural hearing loss, microcephaly, motor defects, mental retardation, and other abnormalities.

Currently, no drugs are approved for antiviral therapy of congenital CMV infection. However, results from a recent clinical trial suggest ganciclovir (b) (4) (b) (4) (Kimberlin DW et al. J Pediatr 2003;143:17-26). This was a randomized, non-blinded controlled trial of ganciclovir for newborns with symptomatic congenital CMV disease involving the CNS. The trial was sponsored by the NIH-NIAID Collaborative Antiviral Study Group (CASG) and enrolled 100 newborns. Enrolled newborns were assigned to receive either IV ganciclovir 6 mg/kg bid for 6 weeks or no treatment. The primary endpoint was brainstem-evoked response (BSER) audiometry improvement by one gradation (e.g., from severe to moderate) between baseline and the 6-month follow-up or retained normal hearing. The major secondary endpoints included evidence of laboratory (thrombocytopenia, hepatitis) and clinical (organomegaly, chorioretinitis) improvement and growth rate. Treated subjects had a greater incidence of improved hearing or maintenance of normal hearing at 6 months of age and lack of hearing deterioration at 6 months and 1 year as compared to untreated subjects. Between the two groups no statistically significant difference was observed in the time to resolution of organomegaly, CMV retinitis, thrombocytopenia or hyperbilirubinemia. Median weight gain and median increase in head circumference between baseline and 6 weeks were higher in the ganciclovir treatment group. These differences were not sustained at the 6 month follow-up. Almost two thirds of ganciclovir-treated patients developed severe neutropenia. Fourteen of the 29 patients with neutropenia required dose modification and two patients received granulocyte colony-stimulating factor. One newborn developed gram-negative sepsis.

Several deficiencies were noted in this study. Less than half of the patients (42/100) had evaluable data at both entry and 6 months raising the possibility of follow-up bias that could influence the results of the trial. Moreover, non-evaluable ganciclovir recipients were more likely to be black and premature compared to the non-evaluable infants in the non-treatment group. Considering these deficiencies, the adverse events related to this drug, including potential long-term gonadal toxicity and carcinogenicity, some investigators raised questions on the impact of study's findings on hearing (Demmler GJ. Congenital cytomegalovirus infection treatment. Pediatr Infect Dis J 2003; 22:1005-6). The Committee on Infectious Diseases of the American Academy of Pediatrics states the following in the 2006 edition of the Red Book, "One study of ganciclovir therapy of congenitally infected newborn infants with central nervous system disease suggested that treatment decreases progression of hearing impairment. However, because of the potential toxicity of long-term ganciclovir therapy, additional study is necessary before a recommendation can be made" (Red book 2006. Report on the Committee on Infectious Diseases, 27th Edition. Pickering LK, ed. American Academy of Pediatrics; 2006).

2.3 Availability of Proposed Active Ingredient in the United States

Valcyte is available in the United States as a 450 mg pink convex oval tablet with "VGC" on one side and "450" on the other side. 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. Valcyte is supplied in bottles of 60 tablets.

2.4 Presubmission Regulatory Activity

March 2001: Valcyte was approved by FDA for the treatment of CMV retinitis in patients with AIDS.

June 2001: To obtain needed pediatric information on ganciclovir and valganciclovir, the FDA issued a formal Written Request, pursuant to Section 505A of the Federal Food, Drug and Cosmetic Act, to submit information from the following four pediatric studies. Final study reports were to be submitted to the Agency on or before January 1, 2004.

Study 1: Single-dose, open-label, dose-escalation pharmacokinetic and safety study of valganciclovir in pediatric renal transplant recipients.

Study 2: Single-dose, open-label, non-comparative pharmacokinetic and safety study of valganciclovir in pediatric liver transplant recipients.

Study 3: Multicenter, open-label, single-dose, non-comparative safety and pharmacokinetic study in pediatric patients with solid organ transplants.

Study 4: Single-dose and multiple-dose pharmacokinetic and tolerability study of valganciclovir liquid formulation in a neonatal population with congenital CMV disease.

November 2001: The Pediatric Written Request was amended to change the number of patients required and to modify the statistical assessments for Study 1, to add requirements for labeling and format of reports, and to extend the timeframe for submitting all clinical study reports to December 31, 2004. The modified studies read as follows:

Study 1: An open-label, dose-escalation pharmacokinetic and safety study of valganciclovir in pediatric renal transplant recipients.

Study 2: An open-label, non-comparative pharmacokinetic and safety study of valganciclovir in pediatric liver transplant recipients.

Study 3: Multicenter, open-label, single-dose, non-comparative safety and pharmacokinetic study in pediatric patients with solid organ transplants.

Study 4: Single-dose and multiple-dose pharmacokinetic and tolerability study of valganciclovir liquid formulation in a neonatal population with congenital CMV disease.

December 2004: The Pediatric Written Request was amended to extend the timeframe for submitting all clinical study reports to December 31, 2007.

June 2007: The Pediatric Written Request was amended to modify the pharmacokinetic study endpoints of Studies 2 and 3, to change the title of Study 2, and to extend the timeframe for submitting all clinical study reports to December 31, 2007. The modified Study 2 reads as follows:

Study 2: An open-label, comparative pharmacokinetic and safety study of valganciclovir in pediatric liver transplant recipients.

March 2008: The Pediatric Written Request was amended to extend the timeframe for submitting all clinical study reports to December 31, 2008.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 Chemistry Manufacturing and Control

As part of the Pediatric Written Request, the Sponsor was asked to develop a commercially marketable age-appropriate formulation for children. The Sponsor's attempts were successful and the product proposed for marketing is a powder reconstituted with purified water to provide an oral solution.

The Valcyte for oral solution is a conventional granulate formulation of white to slightly yellow powder containing standard excipients and manufactured using conventional methods. The drug product is packaged in a (b) (4) glass bottle containing (b) (4) dried powder (5 gram drug substance). Prior to dispensing to the patient, Valcyte for oral solution must be prepared by the pharmacist in 91 mL of purified water to make 100 mL of 50 mg/mL oral solution. The preparation is as follows:

- Measure 91 mL of purified water in a graduated cylinder.
- Shake the Valcyte bottle to loosen the powder. Remove the child resistant bottle cap and add approximately half the total amount of water for constitution to the bottle and shake the closed bottle well for about 1 minute. Add the remainder of water and shake the closed bottle well for about 1 minute. This prepared solution contains 50 mg of valganciclovir free base per 1 mL.
- Remove the child resistant bottle cap and push the bottle adapter into the neck of the bottle.
- Close bottle with child resistant bottle cap tightly. This will assure the proper seating of the bottle adapter in the bottle and child resistant status of the cap.
- Store constituted oral solution under refrigeration at 2°C to 8°C (36°F to 46°F) for no longer than 49 days. Do not freeze.
- Write the date of expiration of the constituted oral solution on the bottle label.

For further details regarding the chemistry and manufacturing of the Valcyte for oral solution please refer to the review by Ted Chang, Ph.D., the Chemistry reviewer.

3.2 Animal Pharmacology/Toxicology

No new animal pharmacology and toxicology data were submitted with this NDA. Please refer to the original approval of Valcyte (NDA 21-304) for background information.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

This review is primarily based on data from four studies (WP16303, WP16296, WV16726, and CASG109), conducted in response to the final amended Pediatric Written Request, to support dosing recommendations for the prevention of CMV disease in pediatric solid organ transplant recipients (b) (4)

4.2 Data Quality and Integrity

The Good Clinical Practice Branch, Division of Scientific Investigations, FDA, conducted clinical inspections of three study sites in the United States that enrolled a relatively large number of subjects for Study WV16726 and Study CASG109: UCLA Medical Center, Los Angeles, CA (Dr. Robert Ettinger) and Washington University School of Medicine, St. Louis, MO (Dr. S. Paul Hmiel) for Study WV16726; UT Southwestern Medical Center, Dallas TX (Dr. Pablo Sanchez) for Study CASG109. No major deficiencies were identified in the three inspected sites that would compromise the integrity of the studies. For more details, please see Clinical Inspection Summary by Antoine El-Hage, Ph.D.

At the request of the Division of Antiviral Drugs and Products, the Division of Scientific Investigations also audited the pharmacokinetic and analytical portions of Studies WV16726, and CASG109. The following studies were audited: UCLA center for Health Sciences, Division of Pediatric Nephrology, Los Angeles, CA for study WP16726; and University of Texas Southwestern Medical Center, Department of Pediatrics, Dallas, TX for Study CASG109. The analytical portion of the studies was inspected at (b) (4)
The inspection of the above sites revealed several serious deficiencies. The most important ones are as follows:

Inspection at (b) (4):

- Inconsistency in integration of chromatograms.
- Storage stability cannot be assured.

Based on the findings from the analytical inspection, the concentration data for Studies WP16726, and CASG109 were considered not accurate and not acceptable as submitted in the NDA.

To assure the accuracy of analytical runs and the resulting drug concentrations, the Applicant was asked to provide the following information:

- Frozen stability data that cover the duration of storage (b) (4) (b) (4) (b) (4) of all the plasma samples used for the quantification of ganciclovir in studies WV16726 and CASG109.
- Identify a set of integration parameters and re-integrate all the chromatograms within a run in a consistent manner. This procedure should be repeated for all the chromatograms generated in studies WV16726 and CASG109. Use the resulting concentrations to repeat the pharmacokinetic and/or pharmacodynamic evaluations in studies WP16726 and CASG109.

The Applicant addressed the deficiencies stated in the November 25th, 2008, complete response letter by providing frozen stability data covering the duration of storage and repeating the pharmacokinetic analysis using automatically integrated data. Pharmacokinetic analysis using automatically integrated data compared to that using manually integrated data revealed insignificant changes in AUC_{0-24h} and C_{max} values.

For more details, please see Inspection Summary by C.T. Viswanathan, Ph.D.

4.3 Compliance with Good Clinical Practices

The Applicant states the studies were conducted according to accepted ethical standards based on the precepts established by the declaration of Helsinki. All studies were conducted with the approval of Ethics Committees or Institutional Review Boards and informed consent was obtained from all subjects.

4.4 Financial Disclosures

In compliance with the rule of Financial Disclosure by Clinical Investigators the Applicant provided financial interest information for clinical investigators participating in studies WP16303, WP16296, WV16726, and CASG109. Based on available financial data, the $25,000 threshold was exceeded by (b) (6)

(b) (6) participated in the following studies:

Study WP16303: He served as the Principle Investigator for the study center (b) (4). He received payments exceeding the $25,000 threshold from Roche towards consulting fees and honoraria in his position at the (b) (4)

Study WP16303 is a multicenter, open-label, non-comparative study to investigate the pharmacokinetics and safety of IV ganciclovir and valganciclovir oral solution in pediatric liver transplant

recipients. (b) (6) site enrolled (b) of the 20 subjects enrolled in this study. This site is not expected to potentially bias the outcome of the study because the objectives of the study (primary and secondary pharmacokinetic parameters) are non-subjective. Moreover, the results of this study were consistent with the results observed at the other two study sites and for the overall outcome of the study.

Study WP16296: He served as the Principle Investigator for the study center (b) (4) He received payments exceeding the $25,000 threshold from Roche towards consulting fees and honoraria in his position at the (b) (4)

Study WP16296 is a multicenter, open-label pharmacokinetic and safety study to investigate the pharmacokinetics and safety of IV ganciclovir and valganciclovir oral solution in pediatric kidney transplant recipients. There were six participating centers and a total of 26 patients were enrolled in this study (b) (6) site enrolled (b) (4) of the 26 subjects in Study WP16296. This site is not expected to potentially bias the outcome of the study because the objectives of the study (primary and secondary pharmacokinetic parameters) are non-subjective. The results of the patients enrolled in this site were consistent with the results observed at the other five study sites and with the overall outcome of the study.

Study WP16726: (b) (6) served as the Principle Investigator for the study center (b) (4) He received payments exceeding the $25,000 threshold from Roche towards consulting fees and study investigator payment in his position at the (b) (4)

Study WP16726 is a multicenter, open-label, single-dose, non-comparative pharmacokinetic, safety, and efficacy study of the valganciclovir oral solution in pediatric solid organ transplant recipients. There were 18 participating centers and a total of 63 patients were enrolled in this study. (b) (6) site enrolled (b) (4) in Study WP16726. This site is not expected to potentially bias the outcome of the study.

(b) (6), sub-investigator of (b) (6), participated in Studies WP16303 and WP16296. He received payments exceeding the $25,000 threshold from Roche towards an investigator initiated research support in his position at the (b) (4)

5 REVIEW OF CLINICAL STUDIES

5.1 Review Methods

The clinical review is focused on the pharmacokinetic and safety data from four pediatric studies conducted in response to the Pediatric Written Request. The Applicant's conclusions regarding safety (and efficacy when indicated) were confirmed by independent analyses of data. The Medical Officer reviewed study design, patient demographics, adverse events and laboratory abnormalities, pharmacokinetic data and efficacy data when indicated. The safety data were evaluated either with the use of JMP Statistical Discovery software or manually. In this review,

tables derived from the Applicant's presentation of the data are cited as to source in the table footnotes, while tables derived from review-generated results are not referenced.

Overview of materials consulted in review: The safety and pharmacokinetic data from all studies were submitted electronically following the common technical document format.

Please also refer to Dr. Vikram Arya's and Dr. Kevin Krudys's reviews for more detailed information on the pharmacokinetic data submitted with this NDA.

5.2 Study design, Pharmacokinetics, Efficacy, Safety, and Conclusions

Study WP16296: **The pharmacokinetics and tolerability of IV ganciclovir and oral valganciclovir syrup formulation in pediatric renal transplant recipients**

This is an open-label, pharmacokinetic and tolerability study of IV ganciclovir and oral valganciclovir syrup formulation in pediatric renal transplant patients conducted at six centers in the United States. Twenty-six subjects between the ages of 3 months and 16 years who had received their first kidney transplant, had stable renal function, and were at risk for developing CMV disease (including all transplant patients except those who were D-/R-) were eligible for enrollment.

Following renal transplantation, patients received anti-CMV prophylaxis according to local protocol. After stabilization of renal function, patients received a once daily dose of IV ganciclovir on Days 1 and 2 at a dose equivalent to the adult dose of 5 mg/kg (adjusted for BSA and renal function). On Day 3, patients received a single oral dose of valganciclovir syrup formulation projected to be equivalent to half the adult dose of valganciclovir tablets (450 mg, adjusted for BSA and renal function). On dosing Day 4, patients received a single dose of oral valganciclovir syrup formulation projected to be equivalent to the full adult dose of valganciclovir tablets (900 mg, adjusted for BSA and renal function). Doses of oral valganciclovir were taken within minutes of finishing a breakfast meal. After completion of this study, patients continued their usual anti-CMV prophylaxis treatment at their centers.

Blood samples for pharmacokinetic analysis were obtained on Day 2 before dosing and at 1 h (immediately before end of infusion), 2-3 h, 5-7 h, and 10-12 h after infusion. On Day 3 and Day 4, blood samples for pharmacokinetic analyses were obtained at pre-dose, 0.25-0.75 h, 1-3 h, 5-7 h, and 10-12 h. On Day 4, an additional blood sample was obtained at 22-24 hrs after dosing. Optional pharmacokinetic blood samples were taken 34-36 h and 46-50 h post-dose on Dosing day 4. Laboratory samples for safety assessment were obtained at Screening, on Day 1 before dosing, on the day of last pharmacokinetic sample and at safety review visit performed 28 days after the cessation of study drug.

A total of 26 subjects between the ages of 3 months and 16 years were enrolled in this study. The age distribution of the enrolled subjects was as follows:

≤ 6 years of age: 6 subjects (pharmacokinetic data from 5)
> 6 years of age (but prepubescent): 19 subjects (pharmacokinetic data from 19)
16 years of age and pubescent: 1 subject (pharmacokinetic data from 1)

Pharmacokinetic and safety data were reviewed during two interim analyses to ensure patients are not overexposed to ganciclovir from either IV ganciclovir or oral valganciclovir. The first interim analysis was performed when eight patients had completed treatment and the second when 18 patients had completed treatment in this study and eight patients had completed treatment in a pediatric liver transplant study (Study WP16303).

Complete pharmacokinetic data are available from 25 of the 26 enrolled subjects. One patient withdrew from the study after receiving the two doses of IV ganciclovir. Data from this patient were included in the safety analyses but excluded from the pharmacokinetic analyses.

Dose rationale:

Doses of IV ganciclovir and valganciclovir oral solution formulation were calculated using BSA for adjusting adult doses to pediatric doses. Pediatric doses of IV ganciclovir and valganciclovir oral solution were projected to provide ganciclovir systemic exposures similar to those obtained in adults after 5 mg/kg of IV ganciclovir and 900 mg of oral valganciclovir adjusted for child's BSA and creatinine clearance. The targeted ganciclovir systemic exposure was $AUC_{0\text{-}24}$ = 40–60 mg.h/L and was based on analysis of data from an adult study in solid organ transplant recipients treated with the approved valganciclovir dose of 900 mg once daily (Study PV1600). Ganciclovir exposures < 40 mg.h/L were predicted to have an unacceptable rate of CMV viremia, whereas exposures > 60 mg.h/L were predicted to have an unacceptable rate of neutropenia and leukopenia.

The pediatric dose is shown below:

$$\text{Pediatric Dose} = \text{BSA } (m^2) \times \text{Normalized Dose } (mg/m^2)$$

where,

$$BSA(m^2) = \sqrt{\frac{height(cm) \times weight(kg)}{3600}}$$

The normalized dose for IV ganciclovir was 200 mg/m^2 and was calculated based on a standard adult dose of 5 mg/kg in an adult of 70 kg and a BSA of 1.73^2 (i.e., 5 mg/kg x 70 kg [adult BW] ÷ 1.73^2 [adult BSA] = 200 mg/ m^2).

The normalized dose for oral administration was 520 mg/m^2 and was calculated using the 900 mg as the reference dose (i.e., 900 mg ÷ 1.73^2 [adult BSA] = 520 mg/ m^2).

The pediatric doses were further adjusted for creatinine clearance (calculated with the Schwartz formula) according to Table 1.

Table 1. Dose adjustment based on creatinine clearance.

Estimated CrCL (mL/min/1.73 m^2)	**Ganciclovir IV dose (mg)**	**Valganciclovir p.o. dose (mg)**
≥70	Full dose	Full dose
50 -69	Full dose	Full dose
40 – 49	25% of full dose	25% of full dose

Baseline characteristics and disposition of patients:

Of the 26 subjects enrolled in this study, 17 (65%) were male and 9 (35%) were female. Thirteen (50%) subjects were white, 5 (19%) were black, and the remaining 8 (31%) of other race. The ethnicity breakdown was not recorded in this study.

The mean age of the enrolled subjects was 10.6 ± 4.5 years (range 1 to 16 years). The majority of the enrolled subjects were D+/R+ for CMV disease. Two subjects were CMV D-/R- but were enrolled in the study because at this center all patients are considered at risk for CMV disease. The CMV serologic status of both donors and recipients was as follows: D+/R+: 16 subjects (62%), D+/R-: 6 subjects (23%), D-/R+: 2 subjects (8%), and D-R-: 2 subjects (8%).

All enrolled subjects had adequate renal function with a creatinine clearance of at least 45 mL/min/1.73 m^2 (mean 109.9 mL/min/1.73 m^2, range 45.5-232.9 mL/min/1.73 m^2). The primary reasons for kidney transplant were diverse; however, the most common reason was renal dysplasia, counting for almost 40% of the cases.

Pharmacokinetic results:

A summary of the pharmacokinetic parameters by age group is displayed in Table 2. The

AUC_{0-24} and C_{max} were calculated under steady state conditions for the nominal dose of 200 mg/m^2 IV ganciclovir and the higher nominal dose of 520 mg/m^2 of valganciclovir.

Table 2. Summary of pharmacokinetic results by age group in Study WP16296.

PK Parameter	Age Group	Arith Mean	CV [%]	Geom. Mean	Median	Min	Max
AUC_{0-24} (mg.h/L) i.v. ganciclovir (200 mg/m^2)	0-5	22.15	20	21.82	22.18	17.13	27.1
	6-11	34.43	37	32.89	37.86	15.78	43.59
	12-16	41.57	38	38.98	38.58	21.01	89.29
AUC_{0-24} (mg.h/L) valganciclovir (520 mg/m^2)	0-5	21.28	19	21.02	22.22	16.15	24.52
	6-11	39.54	49	36.68	43.78	14.45	55.07
	12-16	41.61	32	39.75	39.88	20.95	70.64
C_{max} (mg/mL) i.v. ganciclovir (200 mg/m^2)	0-5	10.46	12	10.40	10.19	9.17	12.29
	6-11	9.07	17	8.97	9.03	6.79	11.28
	12-16	9.99	43	9.21	9.40	3.51	25.26
C_{max} (mg/mL) valganciclovir (520 mg/m^2)	0-5	5.72	32	5.51	5.10	4.20	8.50
	6-11	5.94	37	5.64	6.01	3.37	9.08
	12-16	5.32	21	5.22	5.40	3.56	7.92
$t_{½}$ term (h)	0-5	3.71	57	3.33	3.28	1.97	6.31
	6-11	6.28	52	5.64	4.41	3.06	12.77
	12-16	7.29	52	6.25	5.62	3.32	27.04

Source: CSR Vol. 13 – p. 42

The bioavailability of ganciclovir from valganciclovir oral solution was estimated at 53% with a 95% confidence interval of 40 to 80%, similar to the value predicted in adults.

Comments: Ganciclovir systemic exposures after IV ganciclovir were similar to ganciclovir systemic exposures after valganciclovir oral solution across all age groups.

Average ganciclovir systemic exposures in children ≤ 5 years of age were significantly lower than the targeted historical adult exposures resulting from a valganciclovir dosing 900 mg once daily (targeted AUC_{0-24} = 40-60 mg.h/L). Even for the age groups 6-11 and 12-16 years of age, the ganciclovir exposures were at the lower levels of the target AUCs.

Efficacy results:

Efficacy data were not obtained in this study.

Safety results:

As previously stated, 25 of the 26 subjects enrolled in the study received the complete course of study treatment. This includes a single dose of IV ganciclovir equivalent to the adult dose of 5 mg/kg on Days 1 and 2, a single dose of valganciclovir oral solution equivalent to half the adult dose of valganciclovir (450 mg) on Day 3, and a single dose valganciclovir oral solution equivalent to the full adult dose of valganciclovir (900 mg). The remaining patient received the first two doses of IV ganciclovir on Days 1 and 2 but not the doses of oral valganciclovir on Days 3 and 4.

Adverse events: All safety events were reported as events occurred either "on treatment" or "off treatment". Events occurred "on treatment" refer to those that occurred while the patients were taking study medication and are divided to those occurred while patients were receiving IV

ganciclovir or to those occurred while patients were receiving oral valganciclovir. The "off treatment" phase of the study refers to the follow-up period and could have been attributed to either study drug.

During the treatment phase of the study, a higher proportion of patients experienced at least one adverse event while receiving IV ganciclovir (13, 50%) compared with those receiving valganciclovir (8, 32%). The most common adverse events were diarrhea, nausea, and vomiting. The incidence of vomiting was higher during treatment with valganciclovir than during treatment with IV ganciclovir (12.0 % vs. 0%). The incidence of all other adverse events was comparable during treatment with both study medications. During the follow-up period (off treatment), the pattern of adverse events remained the same with gastrointestinal disorders being the most common.

Only four adverse events were considered by the investigator as severe (a case of sepsis during treatment with valganciclovir oral solution, and abdominal pain, vomiting, and wound dehiscence that occurred off treatment. The rest of the other events were considered by the investigators mild or moderate in severity

Three patients had adverse events considered by the investigators related to study drugs. These patients experienced four related adverse events (headache, nausea, and vomiting) during treatment with valganciclovir oral solution.

No deaths were reported during the study and no subject experienced adverse event leading to premature withdrawal from the study. Four patients experienced serious adverse events: one patient during treatment (sepsis); two patients during the follow-up period (lymphocele and transplant rejection 1, urinary tract infection 1); the fourth patient had two serious adverse events, one during treatment (deep vein thrombosis) and one during the follow-up period (wound dehiscense).

Laboratory abnormalities: There were 4 patients who exhibited a worsening of 2 grades and one patient with a worsening of 3 grades.

Worsening of 2 grades: elevated SGOT 1, elevated SGPT 1, elevated creatinine 1, and a decrease in hemoglobin levels 1.

Worsening of 3 grades: one patient with neutropenia. This is a 15-year-old male who underwent kidney transplantation for obstructive uropathy. On study day 36 (follow-up period), the patient exhibited significant decrease in neutrophil count (from 6.1 x 10^9 cells/L at baseline to 0.7 x 10^9 cells/L on Day 36).

Comments: The overall safety profile of IV ganciclovir and oral valganciclovir was consistent with that obtained in adult solid organ transplant patients and there were no unexpected safety findings.

It should be noted that most of the patients enrolled in this study were taking ganciclovir (20 [77%]) or valganciclovir (2 [8%]) prior to study drugs as part of the local protocols and continued with these drugs after the last dose of study drug. Therefore, it is impossible to distinguish whether the adverse events are due to the anti-CMV medications administered prior and after study drugs or to the study drugs. Even for adverse events that occurred during Days 3 and 4, it is very

difficult to determine whether they are due to oral valganciclovir or to IV ganciclovir which was administered on Days 1 and 2 or to the anti-CMV drugs administered prior to study initiation.

Conclusions:

Pharmacokinetic results showed that ganciclovir exposures after IV ganciclovir were similar to ganciclovir exposures after valganciclovir oral formulation. However, ganciclovir exposures were lower than the mean exposures in adults receiving IV ganciclovir 5 mg/kg, particularly in children ≤ 5 years of age. Therefore, this BSA-based dosing algorithm cannot be used in children.

The IV ganciclovir and oral valganciclovir were tolerated in pediatric kidney transplant patients with an overall safety profile similar to that observed in adult solid organ transplant recipients.

Study WP 16303: **Safety and pharmacokinetics of IV ganciclovir and valganciclovir oral solution formulation in pediatric liver transplant recipients receiving treatment with IV ganciclovir for prevention of cytomegalovirus disease**

This is an open-label, pharmacokinetic and tolerability study of IV ganciclovir and valganciclovir oral solution formulation in pediatric liver transplant patients conducted at three centers in the United States. Twenty subjects between the ages of 3 months and 16 years who had received their first liver transplant, had stable renal function (estimated creatinine clearance > 45 mL/min/1.73 m^2), and were at risk for developing CMV or EBV disease (including all transplant patients except those who were D-/R- for CMV and EBV) were eligible for enrollment.

Enrolled subjects were treated with IV ganciclovir twice daily from enrollment (Day 1-4 postransplant) to Day 12, and then with oral valganciclovir twice daily for Days 13 and 14. After completion of this study, patients continued their usual anti-CMV prophylaxis treatment at their centers. The doses of IV ganciclovir and valganciclovir oral solution were projected to produce a ganciclovir AUC equivalent to that of IV ganciclovir 5 mg/kg in an adult of 70 kg with a BSA of 1.73 m^2 (adjusted for BSA and renal function). Doses of oral valganciclovir were taken within minutes of finishing a breakfast meal. After completion of this study, patients continued their usual anti-CMV prophylaxis treatment at their centers.

Blood samples for pharmacokinetic analysis were obtained on Day 12 before dosing and at 1 h (immediately before end of infusion), 2-3 h, 5-7 h, and 10-12 h after infusion. On Day 14, blood samples for measurements of ganciclovir and valganciclovir concentrations were obtained at pre-dose, 0.25-0.75 h, 1-3 h, 5-7 h, and 10-12 h after dosing. Laboratory samples for safety assessment were obtained at Screening (Day 1-4 posttransplant), on Day 8, Day 13, during the follow-up examination which took place between 28-32 days posttransplant, and during the safety review visit which took place on Day 42 (± 4 days) posttransplant.

A total of 20 subjects between the ages of 3 months and 16 years were enrolled in this study. The age distribution of the enrolled subjects was as follows:

< 2 years of age: 9 subjects
≥ 2 years but < 6 years: 6 subjects
≥ 6 years but ≤ 16 years: 5 subjects

Sixteen of the 20 enrolled patients completed the study. Three patients withdrew from the study before receiving valganciclovir oral solution and one patient received valganciclovir oral solution for one day before being withdrawn from the study.

Dose rationale:

The dosing algorithm used in Study WP16303 was the same as in Study WP16296.

Baseline characteristics and disposition of patients:

Of the 20 subjects enrolled in this study, 11 (55%) were male and 9 (45%) were female. Eighteen (90%) subjects were white, and the remaining 2 (10%) were black. The ethnicity breakdown was not recorded in this study.

The mean age of the enrolled subjects was 4.0 ± 5.23 years (range 6 months to 16 years). The serology results of CMV and EBV status are shown in the following table. Three patients were both CMV and EBV D-/R- but were enrolled in the study because at these centers all patients are considered at risk for CMV or EBV disease (from blood transfusions) regardless of their CMV and EBV serologic status.

Table 3. Summary of CMV and EBV serology status

Serology status	**CMV (n=20)**	**EBV (n=20)**
D+/R+	4 (20%)	5 (25%)
D+/R-	6 (30%	6 (30%)
D-/R+	2 (10%)	2 (10%)
D-/R-	8 (40%)	6 (30%)
D (not done)/R+	-	1(5%)

All enrolled subjects had adequate renal function with a creatinine clearance of at least 45 mL/min/1.73 m^2, except one patient who had a creatinine clearance 41.7mL/min/1.73 m^2 at baseline (mean 153.37 mL/min/1.73 m^2, range 41.7-357.8 mL/min/1.73 m^2). The most common

reasons for liver transplant were biliary atresia (9, 45%) and alpha-1 antitrypsin deficiency (3, 15%).

Pharmacokinetic results:

A summary of the pharmacokinetic parameters by age group is displayed in Table 4. The

AUC_{0-24} and C_{max} were calculated under steady state conditions for the nominal doses of 200 mg/m^2 IV ganciclovir and 520 mg/m^2 valganciclovir oral solution adjusted by Schwartz creatinine clearance.

Table 4. Summary of pharmacokinetic parameters by age group in Study WP16303: Median (min-max)

Pharmacokinetic parameter	Age group		
	0-5 years* (N=13)	**6-11 years (N=2)**	**12-16 years (N=3)**
AUC_{0-24h} (mg.h/L) IV ganciclovir (200 mg/m^2)	24.3 (14.1-38.9)	35.2 (27.1-43.2)	23.4 (19.2-25.8)
AUC_{0-24h} (mg.h/L) valganciclovir (520 mg/m^2)	23.4 (11.8-40.6)	46.8 (35.2-58.4)	25.8 (25-30.9)
C_{max} (mg/L) IV ganciclovir (200 mg/m^2)	12.2 (9.17-15)	9.29 (4.73-13.9)	11.8 (11.6-12.4)
C_{max} (mg/L) valganciclovir (520 mg/m^2)	5.51 (2.72-7.18)	5.29 (3.79-6.79)	6.9 (5.59-7.04)
t½ term (h)	1.65 (1.01-2.57)	6.8 (3.74-9.87)	4.35 (4.17-5.04)

*All children in 0-5 years group were < 3 years of old.
Source: CSR Vol. 9- p.45

The bioavailability of ganciclovir from valganciclovir oral solution was estimated at 55% with a 95% confidence interval of 48 to 62%, similar to the value predicted in adults.

Comments: Ganciclovir systemic exposures after IV ganciclovir were similar to ganciclovir systemic exposures after valganciclovir oral solution across all age groups.

Average ganciclovir systemic exposures in children ≤ 5 years of age and 12-16 years of age were significantly lower than the targeted historical adult exposures (targeted AUC_{0-24} = 40-60 mg.h/L).

Efficacy results:

Efficacy data were not obtained in this study.

Safety results:

Fourteen (14) of the 20 subjects enrolled in the study received the complete course of valganciclovir oral solution for 2 days. Three patients withdrew from the study before receiving valganciclovir oral solution; 1 patient received 3 doses of valganciclovir oral solution; 1 patient received 2 doses; and 1 patient received valganciclovir for 3 days.

Adverse events: All safety events were reported as events occurred either "on treatment" or "off treatment". Events occurred "on treatment" refer to those that occurred while the patients were taking study medication and are divided into those that occurred while patients were receiving IV ganciclovir or those that occurred while patients were receiving oral valganciclovir. The "off treatment" phase of the study refers to the follow-up period and could have been attributed to either study drug. It should be noted that after the last dose of study drug most of the patients continued taking ganciclovir or valganciclovir as part of the local protocols. For adverse events occurring on Days 13 and 14, it is very difficult to determine whether they are due to oral valganciclovir or to IV ganciclovir which was administered on Days 1 through 12. Moreover, the term "off treatment" is not accurate because almost all patients continued to take anti-CMV drugs (ganciclovir or valganciclovir) as part of the local protocols.

During the treatment phase of the study, a higher proportion of patients experienced at least one adverse event while receiving IV ganciclovir (90%) compared with those receiving valganciclovir (12%). The most common adverse events by patients receiving IV ganciclovir were adverse events associated with gastrointestinal disorders (55%), infections and infestations (40%), and vascular disorders (30%). Hypertension was the most frequent adverse event experienced by 30% of the patients. The remaining adverse events were experienced by one or two patients. The two adverse events reported by the two patients while receiving valganciclovir were ascites and back pain.

Twelve patients experienced 22 AEs considered severe and one patient experienced two AEs (two episodes of post-procedural hemorrhage) considered life-threatening. The two AEs reported in the valganciclovir oral solution treatment phase were considered mild (back pain) and moderate (ascites) in intensity.

Three patients experienced six adverse events considered by the investigators related to study drug during treatment with IV ganciclovir: rash 1 patient, anemia and renal impairment 1, vomiting, diarrhea and elevated hepatic enzymes 1 patient).

Ten patients experienced 14 serious adverse events during treatment with IV ganciclovir and 9 patients experienced a total of 17 SAEs during the follow-up period, while only 1 patient experienced an SAE during treatment with valganciclovir oral solution. Two SAEs (vomiting and elevated hepatic enzymes) experienced by one patient during treatment with IV ganciclovir were considered related to study drug.

No deaths were reported during the study. However, two patients were withdrawn prematurely from the study secondary to AEs (ascites and sepsis 1 patient, peritonitis 1).

Laboratory abnormalities: There was only one patient who experienced a worsening of 3 or more grades. This is a 7-month-old male who underwent liver transplantation for biliary atresia.

On study Day 2 the patient developed severe hepatic artery thrombosis and peritonitis resulted in re-transplant. Transaminases were elevated. The shift from baseline was Grade 0 to Grade 4 for ALT and Grade 0 to Grade 3 for AST. Elevated transaminases improved by Day 11 and returned to normal at the follow-up visit.

Comments: The overall safety profile of IV ganciclovir and oral valganciclovir was consistent with that obtained in adult solid organ transplant patients and there were no unexpected safety findings.

Conclusions:

Pharmacokinetic results showed that ganciclovir exposures after IV ganciclovir were similar to ganciclovir exposures after valganciclovir oral formulation. However, ganciclovir exposures were lower than the mean exposures in adults receiving IV ganciclovir 5 mg/kg, particularly in children ≤ 5 years and 12-16 years of age. Therefore, this BSA-based dosing algorithm cannot be used in children.

The IV ganciclovir and oral valganciclovir were tolerated in pediatric liver transplant patients with an overall safety profile similar to that observed in adult solid organ transplant recipents.

Study WP16726: Safety and pharmacokinetics of valganciclovir syrup in pediatric solid organ transplant recipients

This is an open-label, single-dose, multicenter, non-comparative safety and pharmacokinetic study of valganciclovir oral formulation in pediatric solid organ transplant recipients. The objectives of the study were to: 1) investigate the safety and tolerability of valganciclovir oral solution in pediatric solid organ transplant recipients, 2) determine the pharmacokinetics of ganciclovir following oral administration of valganciclovir solution and tablets in solid organ transplant recipients, and 3) describe the incidence of CMV disease.

A total of 63 children, 4 months to 16 years of age, who received solid organ transplants and were at risk for developing CMV disease were enrolled in this study. Patients who met all the entry criteria began prophylaxis with oral valganciclovir once daily (valganciclovir oral solution or tablets) as soon as possible after transplantation and continued treatment until a maximum of 100 days post-transplant. Patients were followed until Week 26 (Day 180) post-transplant

The design of this study is similar to Study PV1600 (study in adult solid organ transplant recipients). The major difference between the two studies was the CMV serologic status of donors and recipients. In the adult study, patients were seronegative for CMV and received allografts from CMV seropositive donors. In study WP16726, the serologic status of donors and recipients was as follows:

Table 5. Summary of CMV serology status of donors and recipients in Study WP16726.

Serology status	**CMV (n=63)**
D+/R+	24 (38%)
D+/R-	25 (40%)
D-/R+	12 (19%)
D-/R-	2 (3%)

Dose rationale:

The proposed pediatric dose was projected to provide ganciclovir exposures at the range of 40 – 60 mg.h/L. The target exposure is based on analysis of data from an adult study in solid organ transplant recipients treated with the approved valganciclovir dose of 900 mg once daily (Study PV1600). Ganciclovir exposures < 40 mg.h/L were predicted to have an unacceptable rate of CMV viremia, whereas exposures > 60 mg.h/L were predicted to have an unacceptable rate of neutropenia and leukopenia.

The calculation of the once daily dose of oral valganciclovir used in Study WP16726 was based on the knowledge from studies WP16296 and WP16303 and was modified as follows:

Dose (mg) = 7 x BSA x CrCl (calculated using the modified Schwartz formula)

where,

$$Mosteller\ BSA(m^2) = \sqrt{\frac{height(cm) \times weight(kg)}{3600}}$$

and,

$$\text{Schwartz } CrCL(mL/\min/1.73m^2) = \frac{k \times height(cm)}{SerumCreatinine(mg/dL)}$$

where,
k = 0.45 for ages < 1 year,
k = 0.45 for ages 1 to < 2 years (note k value is 0.45 instead of the typical value of 0.55),
k = 0.55 for boys aged 2 to < 13 years and girls aged 2 to 16 years, and
k = 0.7 for boys aged 13 to 16 years

(Most of the enrolled subjects received the valganciclovir powder for oral solution)

Safety assessments occurred on Day 1, Day 7, Weeks 2, 6, 10, 14 (Day 100), 16, 20 and 26 post-transplant. Blood samples for safety laboratory tests (chemistry and complete blood counts) were obtained at each visit. A blood sample was obtained at Day 100 to assess potential viral resistance and at any time when patient experienced CMV disease.

Blood sampling for ganciclovir concentrations were obtained from each subject on at least 2 occasions and at least 4 weeks apart. Subjects had at least three doses of valganciclovir before pharmacokinetic sampling. The timing of these pharmacokinetic measurements were: pre-dose, 1-3 h, 3-7 h and 7-12 h with at least one hour between the second and third blood draws and at least two hours between the third and fourth blood draws. In addition, a single PK sample was taken during scheduled safety visits at least once during 100 days treatment and up to a maximum of three times on three separate days.

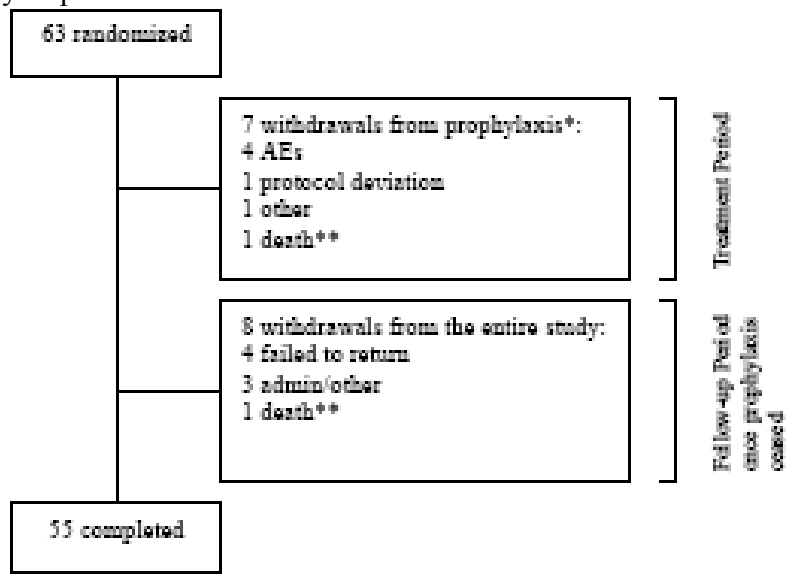
Baseline characteristics and disposition of patients:

A total of 63 solid organ transplant recipients enrolled in this study. There were 33 kidney recipients, 17 liver recipients, 12 heart recipients, and 1 kidney/liver recipient. Thirty-four (54%) were male and 29 (46%) were female. Fifty-one (81%) were white, 1 (2%) was black, 2 (3%) Asian, 1 (2%) Arabic, 1 (2%) Aboriginal, 2 (3%) American Indian/Alaska Native, and 5 (8%) Latin American. The ethnicity breakdown was 22 (35%) Hispanic or Latino and the remaining 41 (65%) not Hispanic or Latino.

There were 17 patients ≤ 2 years of age, 21 patients > 2 years to <12 years of age, and 25 patients ≥ 12 years of age. The mean age was 8.1 ± 5.9 years and mean weight was 29.08 ± 19.94 kg. The serology results for CMV status are shown in Table 5. Two patients were D-/R- but were enrolled in the study because at these centers all pediatric patients are considered at high risk for CMV disease.

Study drug discontinuation: A total of 55 patients completed the study (completed prophylaxis and follow-up to Week 26). Study drug discontinuations are shown in Figure 1.

Figure 1. Summary of patient withdrawals from trial treatment.



*Two of the seven patients who were withdrawn from study treatment were classified as completing the study as they continued to have their safety assessments. These two patients are not included in the list of withdrawal from the study
**One patient died in the study
Source: CSR Vol. 15 – p. 45

Pharmacokinetic results:

Automatic re-integration of the chromatograms resulted in one failed run. As a result, 37 pharmacokinetic samples from 9 patients in study WV16726 were excluded from the pharmacokinetic analysis. Two subjects (1101 and 6301) were entirely removed from the pharmacokinetic database. Removal of these 37 samples did not have a significant impact on individual pharmacokinetic parameter estimates in subjects who were affected. Similarly in the entire WV16726 population, pharmacokinetic parameters using automatic integration were similar to the original values estimated with manually integrated data (Table 6).

Table 6. Summary of pharmacokinetic parameters by age group and transplant type in Study WV16726: Mean (SD) (Parameter estimates derived from manually integrated data are in black font; parameter estimated derived from automatically integrated data are below in red font.)

	PK Parameter	Age Group (Years)		
		≤ 2 (n=2)	**> 2 to < 12 (n=12)***	**≥ 12 (n=19)**
Kidney	$AUC_{0\text{-}24h}$ (µg·h/mL)	65.2 (16.6) 67.6 (13.0)	55.0 (11.9) 55.9 (12.1)	50.0 (11.6) 47.8 (12.4)
(N=33)	C_{max} (µg/mL)	10.0 (0.04) 10.4 (0.4)	8.74 (2.49) 8.7 (2.1)	7.85 (2.10) 6.6 (1.3)
	$t_{1/2}$ (h)	3.10 (0.59) 4.5 (1.5)	4.40 (1.41) 4.8 (1.0)	5.67 (1.06) 6.0 (1.3)
		≤ 2 (n=9)	**> 2 to < 12 (n=6)**	**≥ 12 (n=2)**
Liver	$AUC_{0\text{-}24h}$ (µg·h/mL)	69.4 (35.4) 69.9 (37.0)	58.4 (6.18) 59.4 (8.1)	35.6 (2.76) 35.4 (2.8)
(N=17)	C_{max} (µg/mL)	11.7 (3.59) 11.9 (3.7)	9.35 (2.33) 9.5 (2.3)	5.55 (1.34) 5.5 (1.1)
	$t_{1/2}$ (h)	2.72 (1.32) 2.8 (1.5)	3.61 (0.80) 3.8 (0.7)	4.50 (0.25) 4.4 (0.2)
		≤ 2 (n=6)	**> 2 to < 12 (n=2)**	**≥ 12 (n=4)**
Heart	$AUC_{0\text{-}24h}$ (µg·h/mL)	56.3 (23.2) 55.4 (22.8)	60.0 (19.3) 59.6 (21.0)	61.2 (26.0) 60.6 (25.0)
(N=12)	C_{max} (µg/mL)	8.22 (2.44) 8.2 (2.5)	12.5 (1.02) 12.5 (1.2)	9.50 (3.34) 9.5 (3.3)
	$t_{1/2}$ (h)	3.60 (1.73) 3.8 (1.7)	2.62 (0.65) 2.8 (0.9)	5.05 (0.70) 4.9 (0.8)

*There was one subject who received both kidney and liver transplant. The PK profile for this subject has not been included in the pharmacokinetic analysis as it is not possible to determine whether the affects observed are from the kidney/liver or neither. In addition, the PK profile of another two patients in this age group was not included in the estimates derived from automatic integration.

The bioavailability of ganciclovir from valganciclovir oral solution was estimated to be 57% with a 95% confidence interval of 52% - 62%.

Comments: Pharmacokinetic analysis using automatically integrated data compared to that using manually integrated data revealed insignificant changes in $AUC_{0\text{-}24h}$ and C_{max} values.

The proposed pediatric dose of valganciclovir (Dose [mg] = 7 x BSA x CrCl [calculated using the Schwartz formula]) administered once daily achieved ganciclovir exposures similar to those observed in adult solid organ transplant patients receiving valganciclovir 900 mg once daily.

The pharmacokinetics of ganciclovir were similar across organ types and age ranges.

Efficacy results:

CMV disease: CMV disease (defined as CMV syndrome or tissue-invasive CMV disease) was not reported in any subjects in this study. Seven patients reported CMV viremia/antigenemia but none of them fulfilled the definition of CMV syndrome or disease (presence of fever plus any other symptoms of CMV disease). Four patients had CMV viremia/antigenemia after completing prophylaxis. Another patient discontinued study medication on Day 35 due to an intestinal obstruction, and had CMV viremia on Day 86. The remaining two patients had CMV positive test during the treatment phase of the study. Five of the seven cases with positive CMV test were treated with ganciclovir. It is noteworthy that the majority of the cases (5 of the 7 patients) had CMV viremia/antigenemia after the end of treatment. The major findings of these seven patients are shown in Table 7.

Table 7. Findings in patients with CMV viremia/antigenemia

Patient No	Age at transplantation (months)	Sex	Organ Transplant	CMV serology status of Donor/Recipient	Time to positive CMV test after initiating prophylaxis (days)	Treated for CMV
8604	150	F	kidney	D+/R+	143	Yes
8801	6	F	heart	D+/R-	38	No
8802	195	M	heart	D+/R-	173	Yes
1101	133	F	kidney	D+/R-	169	Yes
5205*	43	M	liver	D+/R-	86	Yes
6104	9	F	liver	D+/R-	8	Yes
1106	203	F	heart	D+/R-	160	No

*This patient discontinued valganciclovir prophylaxis on Day 35.

CMV viremia/antigenemia by CMV serology status: When patients with CMV viremia/ antigenemia were analyzed according to the CMV serology status of the donor and recipient, it was found that 6 of the 7 patients were D+/R- (Table 8).

Table 8. CMV serology status of donor/recipient and CMV viremia/antigenemia

CMV serology status of donor/recipient	No of patients	No of patients with CMV viremia/ antigenemia (%)
D+/R+	24	1 (4)
D+/R+	25	6 (24)
D-R+	12	0
D-/R-	2	0

Comments: Of note, in Study PV1600, 12.1% of patients in the valganciclovir arm had CMV disease (CMV syndrome 5%, tissue-invasive CMV disease 7.1%). As with Study WP16726, most of the cases of CMV disease occurred after the end of treatment. However, as mentioned previously, none of the 7 patients from Study WP16726 who had CMV viremia/antigenemia met the criteria for CMV syndrome or tissue-invasive CMV disease.

It is noteworthy that most of the cases of CMV viremia/antigenemia occurred in the D+/R- group, the group at the highest risk for CMV disease after transplantation.

Treatment failure defined as either the development of CMV disease (viremia, antigenemia,or test positive) requiring treatment up to Day 100 post-transplant or discontinuation of study medication due to lack of efficacy or to toxicity: A total of four patients had failure: two had CMV viremia/antigenemia (both of them were liver transplant recipients) and two had toxicity (one liver transplant with elevated transaminases and one kidney transplant with severe neutropenia). It should be noted that one of the patients with CMV viremia/antigenemia, valganciclovir discontinued on Day 35 due to an intestinal obstruction. He developed CMV viremia on Day 86). Below is a brief description of patients who had treatment failure:

Patient 6104: This is a 9-month-old CMV seronegative girl who underwent liver transplantation from a CMV seropositive donor for biliary atresia. She was started on valganciclovir prophylaxis six days after transplant. On Day 8 of treatment a routine blood test was CMV antigen positive. Valganciclovir was stopped and patient was treated with IV ganciclovir. The next day she experienced convulsions and radiologic images revealed leukoencephalopathy. She was treated with antiepileptic drugs. On Day 15, repeat blood tests were negative for CMV and study drug was restarted. The patient's course was also complicated with a biliary tract infection.

Patient: 5205: This is a 43-month-old CMV seronegative boy who underwent liver transplant from a CMV seropositive donor for Alagille syndrome. Seven days after transplantation he was started on valganciclovir for CMV prophylaxis. On Day 35 he experienced abdominal pain and he was diagnosed with intestinal obstruction. Study drug was discontinued and he underwent surgery on Day 56. He had a second episode of intestinal obstruction requiring laparotomy on

Day 86. During the same time he was found to have CMV antigenemia for which he was treated with 10 days of IV ganciclovir.

Patient 8805: This is a 10-month-old CMV seropositive girl who underwent liver transplant from a CMV seropositive donor for alpha-1-antitrypsin deficiency. She was started on valganciclovir for CMV prophylaxis the next day. On Day 3 she had significantly elevated transaminases and she was treated with steroids for a presumed acute rejection. Because LFTs remained elevated, a liver biopsy was performed on Day 32 which showed no evidence of acute rejection. Valganciclovir was discontinued on Day 39 and LFTs decreased (Day 48). On Day 108 the patient was hospitalized for fever and rash and she was treated with ampicillin and cefotaxime. Blood cultures were negative and the fever resolved in 4 days. The episode of increased transaminases was considered possibly related to study drug and the liver transplant.

Patient 3301: This is a 42-month-old CMV seropositive boy who underwent kidney transplant from a CMV seronegative donor for congenital nephrotic syndrome. Valganciclovir was started two days after transplant. His major complications were as follows:
Study Day 3: Diarrhea and dehydration.
Study Day 34: He was hospitalized for probable asthma. Asthma was not confirmed and he was discharged with the diagnosis of nasopharyngitis.
Study Day 38: Hospitalized for asthma.
Study Day 76: His ANC was 408 and valganciclovir was discontinued. ANC remained low until Day 83. Tests for CMV were negative.
Study Day 95: He experienced mild fever with neutropenia. The fever resolved in five days.
Day 104: He was diagnosed with EBV infection. The neutropenia resolved by Day 112. The investigator considered the neutropenia related to study drug, as well as to mycophenolate and trimethoprim/sulfamethoxazole.

Patients who experienced a biopsy proven graft rejection: A total of 9 (14.3%) patients had a biopsy proven graft rejection; 5 of the 17 (29.4%) patients in the ≤ 2 years group, 2 of the 21 (9.5%) in the > 2 years to < 12 years group, and 2 of the 25 (8%) in the ≥ 12 years group (Table 9). None of the patients who experienced biopsy proven and treated rejection had CMV positive test.

Table 9. Summary of patients with biopsy proven graft rejection.

Organ	Age Group		
	≤ 2 years (n=5)	> 2 years to < 12 years (n=2)	≥ 12 years (n=2)
Kidney	-	1	2
Liver	5	1	-
Heart	-	-	-

Patients who experienced graft loss: Three patients had graft loss during the study before Day 100): one heart transplant in the ≤ 2 years group, one liver transplant in the >2 years to < 12 years group, and one kidney transplant in the ≥ 12 years group.

Patient survival at six months posttransplant: Only one patient (1.6%) died during the study due to cardiac rejection on Day 28 posttransplant and after taking study medication for 25 days. This was a 2-year-old boy who underwent cardiac transplantation for end stage heart disease. Both the donor and recipient were CMV seronegative. The patient was started on valganciclovir prophylaxis two days after transplant. On study Day 25 the patient had vomiting and decreased urine output. Blood cultures were negative. The patient was admitted to the intensive care unit for treatment with dobutamine, sodium bicarbonate, amilrinone, and pulse steroids. His cardiac function deteriorated and the patient was intubated. He developed progressive heart failure and metabolic acidosis and he died on Study Day 26. An autopsy was not performed. The investigator considered the death as unrelated to study drug but as a result of graft rejection. Notably, the mortality rate in Study PV1600 in adults was 3.7% (9 of 244) in the valganciclovir arm and 1.6% (2 of 126) in the ganciclovir arm.

Safety results:

An overall summary of adverse events that occurred in more than 10% of patients between the first day through the end of study treatment plus 28 days (defined as "on treatment") is shown in Table 10.

Table 10. Adverse events reported in more than 10% of patients on treatment by age group

Adverse Event	<= 2 YEARS N = 17 No. (%)	>2 - < 12 YEARS N = 21 No. (%)	>= 12 YEARS N = 25 No. (%)	TOTAL N = 63 No. (%)
DIARRHOEA	6 (35)	8 (38)	6 (24)	20 (32)
PYREXIA	5 (29)	8 (38)	2 (8)	15 (24)
HYPERTENSION	3 (18)	3 (14)	8 (32)	14 (22)
UPPER RESPIRATORY TRACT INFECTION	4 (24)	3 (14)	7 (28)	14 (22)
VOMITING	3 (18)	4 (19)	6 (24)	13 (21)
ANAEMIA	7 (41)	2 (10)	-	9 (14)
NEUTROPENIA	4 (24)	2 (10)	2 (8)	8 (13)
CONSTIPATION	-	5 (24)	2 (8)	7 (11)
NAUSEA	-	2 (10)	5 (20)	7 (11)
TRANSPLANT REJECTION	3 (18)	-	3 (12)	6 (10)

Source: CSR Vol. 15 – p. 62

Comment: Diarrhea was the most common adverse event followed by pyrexia and upper respiratory tract infection, vomiting, hypertension, anemia, and neutropenia.

The majority of AEs were mild or moderate in intensity and were considered by the investigator not related to study drug (371 out of 400)

Table 11 compares the adverse events observed in Study WV16726 (pediatric solid organ transplant recipients) and Study PV1600 (adult solid organ transplant recipients). Of note, the reported adverse events in adults cover the period up to 180 days post-transplant, whereas the reported adverse events in children cover the period up to 128 days post-transplant.

Table 11. Most common adverse events in Study WV16726 (pediatric patients) and Study PV1600 (adult patients)

Adverse Event	Most Common AEs (>10%) in **Pediatric** Data from SOT Study WV16726 (on treatment)		**Adult** Data from SOT Study PV16000 (6 months)	
	N=63		N=244	
	N	No. (%)	N	No. (%)
Diarrhea	20	32	73	30
Pyrexia	15	24	32	13
Upper Respiratory Tract Infection	14	22	16	7
Vomiting	13	21	40	16
Hypertension	14	22	43	18
Anemia	9	14	28	12
Nausea	7	11	55	23
Neutropenia	8	13	20	8
Constipation	7	11	49	20
Cough	7	11	15	6
Hypomagnesaemia	6	10	19	8
Nasopharyngitis	4	6	10	4
Pruritus	5	8	18	7
Transplant Rejection	6	10	59	24
Urinary Tract Infection	6	10	26	11

Comment: The rates of certain adverse events such as pyrexia, upper respiratory tract infection were higher in pediatric patients than in adults. On the other hand, transplant rejection was more frequent in adults.

Serious AEs: Sixty-six SAEs were reported by 32 patients during the study. Fifty SAEs were reported by 27 patients while on treatment. The most common were infections and infestations (9 patients, 14%), and gastrointestinal disorders (7 patients, 11%). The overall pattern of SAEs was comparable among the three organ transplants. However, a higher proportion of SAEs was noted in patients ≤ 2 years of age.

SAEs related to study drug: A total of seven SAEs were considered related to study drug. All these SAEs occurred during treatment. There were two cases with increased transaminases and single cases of anemia, CMV antigenemia, diarrhea, neutropenia, and febrile neutropenia.

Withdrawals due to AEs: Three patients were withdrawn due to AEs. One kidney transplant due to severe neutropenia (probably related to study drug), one liver transplant due to elevated transaminases (probably related to study drug), and one liver transplant due to an intestinal obstruction (unrelated to study drug).

Laboratory abnormalities: the number of patients experiencing a marked shift in selected laboratory abnormalities (worsening of 3 and 4 grades) is summarized in Table 12.

Table 12. Marked shifts from baseline in key laboratory parameters.

Laboratory Parameter	Abnormality	N	Number of Patients who had a Shift of			
			Three Grades (e.g. from 0 to 3)		Four Grades (e.g. from 0 to 4)	
			n	%	n	%
Hemoglobin	Low	63	6	10	0	0
White Blood Cell (WBC)	Low	59	3	5	1	2
Lymphocytes	Low	54	3	6	3	6
Neutrophils	Low	54	7	13	4	7
Alkaline Phosphatase	High	40	1	3	0	0
ALAT (SGPT)	High	48	1	2	0	0
Total Bilirubin	High	38	1	3	0	0
Potassium	Low	56	4	7	0	0
Potassium	High	57	4	7	2	4
Sodium	Low	58	2	3	0	0
Sodium	High	57	0	0	1	2
Calcium	Low	46	1	2	3	7
Phosphate	Low	43	2	5	0	0
Fasting Glucose	Low	39	1	3	0	0
Uric Acid	High	21	2	10	2	10

Source: CSR Vol. 15 – p. 77

Comment: Marked laboratory abnormalities were most commonly observed with neutrophils and hemoglobin.

A comparison of marked shifts from baseline in key laboratory abnormalities between children and adult solid organ transplant recipients treated with valganciclovir for prophylaxis of CMV infection is shown in the following table.

Table 13. Comparison between marked shift from baseline in key laboratory abnormalities between children and adult solid organ transplant recipients treated with valganciclovir for prophylaxis of CMV infection.

Laboratory parameter	Abnormality	Percentage of patients with worsening of 3 or 4 grades	
		Pediatric Study WP16726 %	Adult Study PV1600 (Valganciclovir arm) %
Hemoglobin	Low	10	2
Neutrophils	Low	20	9
ALT	High	1	2
Total bilirubin	High	3	2
Alkaline phosphatase	High	3	0
Potassium	High	11	0
Potassium	Low	7	0

Comment: A higher rate of pediatric patients had a marked shift in neutrophil count, hemoglobin, and potassium levels.

Conclusions:

The proposed pediatric dose of valganciclovir (Dose [mg] = 7 x BSA x CrCl [calculated using the modified Schwartz formula]) administered once daily achieved ganciclovir exposures similar to those observed in adult solid organ transplant patients receiving valganciclovir 900 mg once daily. The ganciclovir exposures were similar across organ transplant types and age ranges. No case of CMV disease was reported during the study. However, there were 7 (11%) patients with CMV viremia/antigenemia; none of these events fulfilled the definition of CMV syndrome. Based on the pharmacokinetic, safety, and efficacy data from this study and extrapolated efficacy data from the adult study, valganciclovir is indicated for the prevention of CMV disease in kidney and heart transplant recipients ages 4 months to 16 years at risk for developing CMV disease. Valcyte is not approved in adults for CMV prophylaxis in liver transplant patients; therefore, Valcyte is not recommended for CMV prophylaxis in pediatric liver transplant patients because efficacy cannot be extrapolated from adults.

Study CASG 109: A phase I/II pharmacokinetic and pharmacodynamic evaluation of oral valganciclovir in neonates with symptomatic congenital cytomegalovirus (CMV)

This is an open-label, pharmacokinetic, and safety study of valganciclovir oral formulation in neonates and infants up to three months with symptomatic congenital CMV infection. This study was sponsored by the National Institutes of Health and conducted in 8 centers in the United States by the Collaborative Antiviral Study Group. The objectives of this study were to: 1) determine the pharmacokinetics of ganciclovir after administration of oral valganciclovir solution in neonates with symptomatic congenital CMV disease, and 2) identify a dose of oral valganciclovir that achieves comparable ganciclovir exposure to 6 mg/kg IV (or AUC_{0-12} 27 mg h/L) ganciclovir in neonates with symptomatic congenital CMV disease

A total of 24 neonates with symptomatic congenital CMV infection involving the central nervous system were enrolled in the three versions of this protocol. All patients were treated for 6 weeks with a combination of IV ganciclovir 6 mg/kg b.i.d. or valganciclovir powder for oral solution with doses ranging from 14 mg/kg to 20 mg/kg twice daily.

In Version 1.0 of the protocol subjects received 6 weeks of twice daily 6 mg/kg IV ganciclovir therapy interrupted on Days 5-6 and 35-36 at which time subjects received twice daily 14 mg/kg valganciclovir oral solution. Blood measurements of ganciclovir were obtained at pre-dose, 1 h, 3-5 h, 5-7 h and 10-12 h on Days 4, 6, 34, 35 and 36. In Versions 2.0/3.0 subjects received one dose of oral valganciclovir on Day 1. Twelve hours later, 6 mg/kg IV ganciclovir was begun and continued every 12 hours. Blood measurements of ganciclovir were obtained at 0.25-0.75 h, 1-3 h, 5-7 h and 10-12 h after the oral valganciclovir dose on Day 1 and the second IV ganciclovir dose. In addition to pharmacokinetic sampling, anti-CMV activity was evaluated by viral load measurements between Day 1 and Days 7, 14, 28, 42 and 56. IV therapy was continued for approximately two weeks while pharmacokinetic specimens were sent for analysis. After the two weeks, the subject's oral valganciclovir dose changed based on the pharmacokinetic results. One and two weeks after re-initializing oral therapy, blood samples were obtained at 0.5 and 3 h post-dose. As groups of four subjects were enrolled, oral valganciclovir dose increased from 14 mg/kg to 20 mg/kg and then decreased to 16 mg/kg. Dose changes were based on AUC calculations from previous cohorts.

Dose rationale:

The dose(s) of valganciclovir powder for oral solution was selected to provide comparable systemic exposures to those obtained in infants up to 3 months from a 6 mg/kg dose of IV ganciclovir twice daily (AUC_{0-12h} = 25.5 µg.h/mL) or to the ganciclovir exposures obtained in adults from a 900 mg dose of oral valganciclovir twice daily (AUC_{0-12} =27 mg.h/L). Of note, the 6 mg/kg dose of IV ganciclovir administered twice daily was used in another trial sponsored by the National Institutes of Health and conducted by the Collaborative Antiviral Study Group (CASG12; J Pediatr 2003;146:16-250). The results of that study showed that ganciclovir may

[redacted] (b) (4) (see Subsection 2.2).

Baseline characteristics and disposition of patients:

Of the 24 subjects enrolled in this study, 13 (54%) were male and 11 (46%) were female. Nineteen (79%) subjects were white, 4 (17%) were black, and the remaining one of other race. The ethnicity breakdown was Hispanic or Latino 6 (25%) and not Hispanic or Latino 10 (42%). For the remaining 8 (33%) subjects ethnicity was not recorded.

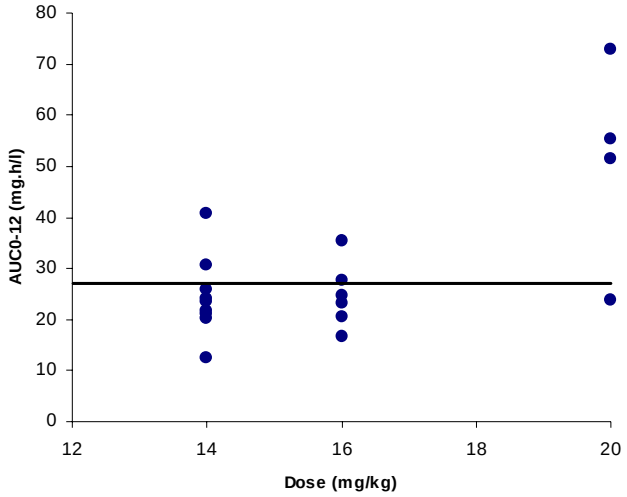
The median age of all subjects was 16.5 days (range 6 to 31 days). The median birth weight of these neonates was 2.4 kg (range 1.09 to 4.1 kg), and the median gestational age was 37.5 weeks (range 34 to 41 weeks).

The baseline clinical and laboratory characteristics of the enrolled neonates were similar to those reported in the published literature on symptomatic congenital CMV infection.

Pharmacokinetic results:

In Version 1.0, the median AUC_{0-12} of ganciclovir after 6 mg/kg IV ganciclovir was 24.8 mg.h/L on Day 4 and 14.3 mg.h/L on Day 34. After 14 mg/kg valganciclovir oral solution, the AUC_{0-12} of ganciclovir was 23.2 mg.h/L on Day 5 and 21.57 mg.h/L on Day 36. In Version 2.0/3.0, the median AUC_{0-12} of ganciclovir after IV ganciclovir was 25.5 mg h/L on Day 1. In the 9 subjects who received 14 mg/kg oral valganciclovir, the median AUC_{0-12} was 23.4 mg.h/L on Day 1. In the 4 subjects receiving 20 mg/kg oral valganciclovir, the median AUC_{0-12} was 53.3 mg.h/L. The 6 subjects who received 16 mg/kg achieved a median AUC_{0-12} of 23.9 mg h/L. The ganciclovir AUC_{0-12} after the different doses of oral valganciclovir is shown in Figure 2.

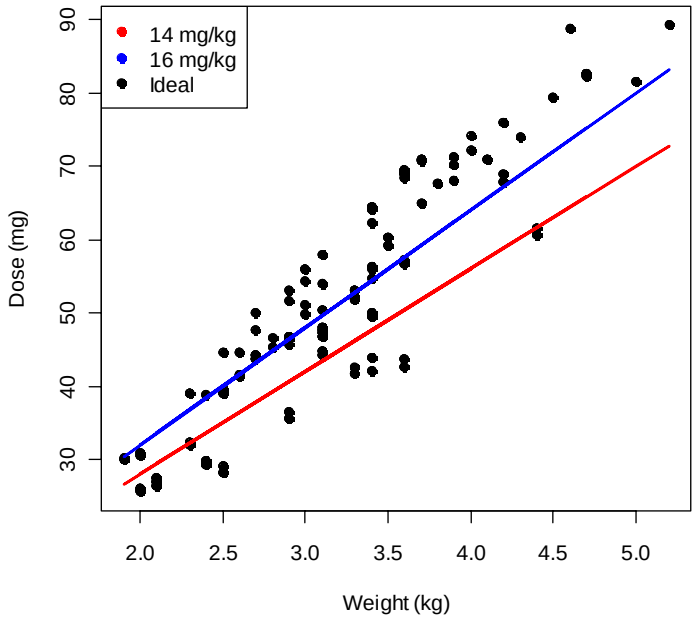
Figure 2. Ganciclovir AUC_{0-12} after Oral Valganciclovir by Dose



Comments: The pharmacokinetic results showed that in pediatric patients up to 3 months of age with symptomatic congenital CMV infection, doses of 14 mg/kg and 16 mg/kg, respectively, provide ganciclovir exposures close to the target AUC_{0-12} of 27 mg.h/L.

The ganciclovir exposures (AUC_{0-12}) in neonates receiving 14 mg/kg are indistinguishable from the AUC_{0-12} observed in neonates receiving 16 mg/kg. However, the results of a population pharmacokinetic modeling predicted that the 16 mg/kg dose would provide exposures closer to the target AUC_{0-12} than the 14 mg/kg dose (Figure 3)

Figure 3. Comparison of "ideal" valganciclovir dose to 14 mg/kg and 16 mg/kg doses



Of note, pharmacokinetic parameters from study CASG109 using automatic integration were similar to the original values estimated using manually integrated data (Table 14).

Table 14. Comparison of Relevant Pharmacokinetic Parameters in CASG109.

Dosing Regimen	**AUC_{0-12} (manual integration) Median [range]**	**AUC_{0-12} (automatic integration) Median [range]**
16 mg/kg Valcyte	23.9 [16.7 – 35.4]	23.6 [16.8 – 35.5]
6 mg/kg iv ganciclovir	25.5 [2.45 – 191]	25.3 [2.4 – 89.7]

Efficacy results:

Hearing and neurologic assessments: The results of hearing evaluation were similar to those observed in Study CASG 102. (b) (4)

Because study CASG 109 is not a comparable trial, definitive assessments on the effect of treatment on hearing cannot be made.

Safety results:
An overall summary of adverse events occurred in more than 15% of patients is shown in Table 15.

Table 15. Most common adverse events (> 15%) in Study CASG109

Adverse Event	**No (%)**
Anemia	10 (42)
Neutropenia	10 (42)
Rash	6 (25)
Agitation	5 (21)
Fever	5 (21)
Emesis	4 (17)
Head lag	4 (17)
Thrush	4 (17)
Skin irritation	4 (17)

Comment: Neonates and young infants with symptomatic congenital CMV infection enrolled in Study CASG109 comprise a unique population which can explain the differences in the safety profile between Study CASG109 and WV16726.

Severe adverse events: Eleven patients experienced 16 AEs considered severe. Five of these severe AEs experienced by four patients were considered probably related to study drug (3 patients had neutropenia and 1 patient had neutropenia and anemia). Two patients experienced life-threatening AEs (one patient had Gram negative sepsis and the other elevated potassium). These life-threatening events were considered as not related to study drug.

Below is a brief description of the two cases with life-threatening events:

Patient 0054: At one month of age, this neonate with congenital CMV infection and CMV-associated hepatitis, presented with fever and irritability and a history of mild diarrhea over the last few days. The patient was admitted to the hospital and a full sepsis work up was done. The patient remained afebrile during hospitalization but blood cultures from the central line grew *Klebsiella pneumoniae* and *Citrobacter*. The central line was removed and the patient was

treated with intravenous antibiotics for seven days. The patient did not have neutropenia during this time period.

Patient 0065: This 2-month-old infant with congenital CMV infection involving the central nervous system and severe hearing loss in the left ear was noted to have hyperkalemia (6.3 meq/L). Repeated tests showed potassium levels of 6.8 and 6.1 mEq/L, respectively. A nephrologist was consulted and determined that the hyperkalemia was secondary to thrombocytosis.

Serious AEs: Twelve SAEs were reported by eight patients during the study. These SAEs were: anemia (1), gram-negative bacteremia/sepsis (1), hyperkalemia (1), fever (1), upper respiratory infection (1), ear infection (1), neutropenia (1), pneumonia (2), bilateral hearing loss (1), reflux (1), and RSV infection (1).

Serious AEs related to study drug: Only one SAE was considered by the investigator possibly related to study drug. This patient was switched from IV ganciclovir to oral ganciclovir according to the protocol. Four days after oral valganciclovir the patient was discharged from the NICU. Two days following discharge the patient was noted to have an ANC 750 cells/mm^3 and the patient was hospitalized because of the neutropenia. The next day the patient was given a dose of GCSF. The same day a repeat test showed ANC 500 cells/mm^3 and the valganciclovir dose was decreased by half. The next day another dose of GCSF was given and the ANC increased to 2000 cells/$mm^3$and subsequently the valganciclovir resumed to the full dose.

Laboratory abnormailities: The most significant safety concern observed in Study CASG 109 was the occurrence of neutropenia. Almost 40% of the enrolled subjects developed Grade 3 or Grade 4 neutropenia. One subject permanently discontinued antiviral therapy due to neutropenia.

Conclusions:

This study was (b) (4) to provide pharmacokinetic and safety data (b) (4) of valganciclovir oral solution for the treatment of neonates and infants up to 3 months with symptomatic congenital CMV infection. Study CASG 109 was designed to provide comparable ganciclovir exposures to those obtained in infants up to 3 months from a 6 mg/kg dose of IV ganciclovir (used in a previous CASG trial to evaluate the effect of IV ganciclovir on symptomatic congenital CMV infection) and to ganciclovir exposures obtained in adults from a 900 mg dose of oral Valcyte twice daily.

Although the pharmacokinetic results showed that in neonates and infants > 7 days to 3 months of age, a dose of 16 mg/kg twice daily of valganciclovir powder for oral solution provided ganciclovir exposures similar to those obtained in infants up to 3 months from a 6 mg/kg dose of IV ganciclovir twice daily and to ganciclovir exposures obtained in adults from a 900 mg dose of oral Valcyte twice daily, (b) (4) (b) (4) The safety and efficacy of IV ganciclovir have not been established for the treatment of congenital CMV infection and no similar disease occurs in adults; therefore, efficacy cannot be extrapolated from IV ganciclovir to support the

[redacted] valganciclovir powder for oral solution for the treatment of congenital CMV infection.

6 OVERALL ASSESSMENT

6.1 Conclusions

Pediatric use information for many of the approved drugs, including antiviral drugs against cytomegalovirus, is needed. Children have fewer treatment options than adults due to lack of pediatric formulations and information to guide clinicians in dosing children.

These NDAs were initially submitted on April 30, 2008, and included pharmacokinetic and safety data from four studies conducted in response to the Pediatric Written Request for the use of valganciclovir for the prevention or treatment of CMV disease in children. Based on these studies, the Applicant sought the following:

- Approval of valganciclovir for oral solution and valganciclovir tablets for the prevention of cytomegalovirus (CMV) disease in pediatric solid organ transplant recipients 4 months to 16 years of age at risk for developing CMV disease, and
- [redacted]

After the first review cycle for these NDAs and because of deficiencies noted during the inspection by the Division of Scientific Investigations, the Division decided valganciclovir was not recommended for approval for any of the above indications. A complete response letter outlining the deficiencies that needed to be addressed by the Applicant was issued on November 25, 2008. The deficiencies noted during the inspection were as follows:

Based on the findings from the analytical inspection at [redacted] the plasma concentration data from WP16726 (A safety and pharmacokinetic study of valganciclovir in pediatric solid organ transplant recipients) and CASG109 (A phase I/II pharmacokinetic and pharmacodynamic evaluation of valganciclovir in neonates with symptomatic congenital CMV infection) are not acceptable as submitted. To assure the accuracy of analytical runs and the resulting drug concentrations, the Applicant needs to provide the following information:

- Frozen stability data that cover the duration of storage [redacted] of all the plasma samples used for the quantification of ganciclovir in studies WV16726 and CASG109.
- Identify a set of integration parameters and re-integrate all the chromatograms within a run in a consistent manner. This procedure should be repeated for all the chromatograms generated in studies WV16726 and CASG109. Use the resulting concentrations to repeat the pharmacokinetic and/or pharmacodynamic evaluations in studies WP16726 and CASG109.

The Applicant addressed the deficiencies stated in the November 25th, 2008, complete response letter by providing frozen stability data covering the duration of storage and repeating the pharmacokinetic analysis using automatically integrated data. Pharmacokinetic analysis using automatically integrated data compared to that using manually integrated data revealed insignificant changes in AUC_{0-24h} and C_{max} values.

Based on the review of the four pediatric studies and the Applicant's response to address the deficiencies noted by the Division of Scientific Investigations, the Division decided the submitted data, together with the previous demonstration of efficacy for the prevention of CMV disease in adult transplant patients, support an indication for valganciclovir (oral solution and tablets) for the prevention of CMV disease in pediatric kidney and heart transplant recipients, ages 4 months to 16 years. The proposed pediatric dose (Dose [mg] = 7 x BSA x CrCl [calculated using the modified Schwartz formula]) administered once daily achieved ganciclovir exposures similar to those observed in adult solid organ transplant recipients receiving valganciclovir 900 mg once daily. (b) (4) (b) (4) Valganciclovir is not approved in adults for the prevention of CMV disease in liver transplant patients; therefore, extrapolating efficacy data from adults to this population is not possible.

(b) (4) Although the pharmacokinetic results showed that in neonates and infants > 7 days to 3 months of age a dose of 16 mg/kg of valganciclovir oral solution twice daily provided ganciclovir exposures similar to those obtained in infants up to 3 months from a 6 mg/kg dose of IV ganciclovir twice daily and to ganciclovir exposures obtained in adults from a 900 mg dose valganciclovir twice daily, (b) (4) (b) (4) The safety and efficacy data of IV ganciclovir have not been established for the treatment of congenital CMV infection and no similar disease occurs in adults; therefore, efficacy cannot be extrapolated from IV ganciclovir to support the (b) (4) valganciclovir powder for oral solution for the treatment of congenital CMV infection.

The overall safety profile of Valcyte in children appears similar to that observed in adults. No new or unexpected safety findings were observed. However, the rates of certain adverse events and laboratory abnormalities such as upper respiratory tract infection, pyrexia, anemia, and neutropenia were reported more frequently in pediatric patients than in adults.

6.2 Required Phase 4 Commitments

As part of their post-marketing requirements the Applicant agreed to:

- Analyze the phenotypic nature of ganciclovir resistant viruses isolated during the clinical study CASG 109. The results will be submitted in a SAS transport file dataset by September June 30, 2010.
- Perform a pharmacokinetic and safety study in pediatric heart transplant recipients <4 months of age in order to determine appropriate dosing in this age group and submit dosing recommendations for inclusion in the package insert. The results will be submitted by June 30, 2012.

6.3 Labeling Review

The proposed label submitted with these NDAs has been reviewed by all disciplines involved in the review. Modifications of the proposed label have been discussed with and agreed upon by the Applicant. The major changes in the modified label involve the following sections

INDICATIONS AND USAGE

This section was changed to add information on the use of Valcyte for CMV prophylaxis in children. The 'Pediatric Patients' subsection reads as follows:

Pediatric Patients

Prevention of CMV disease: [redacted] (b) (4)

DOSAGE AND ADMINISTRATION

This section was changed to add information on the use of Valcyte in pediatric solid organ transplant recipients and to provide information on the preparation of Valcyte for oral solution.

The Pediatric Patients subsection reads as follows:

Prevention of CMV Disease: For pediatric patients 4 months to 16 years of age who have received a kidney or heart transplant, the recommended once daily dose of Valcyte starting within 10 days of transplantation until 100 days post-transplantation is based on body surface area (BSA) and creatinine clearance (CrCl) derived from a modified Schwartz formula, and is calculated using the equation below:

Pediatric Dose (mg) = 7 x BSA x CrCl (calculated using a modified Schwartz formula), where

$$Mosteller\ BSA\,(m^2) = \sqrt{\frac{Height\ (cm)\ x\ Weight\ (kg)}{3600}}$$

$$Schwartz\ Creatinine\ Clearance\ (mL/\min/1.73m^2) = \frac{k\ x\ Height\ (cm)}{Serum\ Creatinine\ (mg/dL)}$$

where k =

0.45 for patients aged < 1 year,

0.45 for patients aged 1 to < 2 years (note k value is 0.45 instead of the typical value of 0.55),

0.55 for boys aged 2 to < 13 years and girls aged 2 to 16 years, and

0.7 for boys aged 13 to 16 years.

All calculated doses should be rounded to the nearest 25 mg increment for the actual deliverable dose. If the calculated dose exceeds 900 mg, a maximum dose of 900 mg should be administered. Valcyte for oral solution is the preferred formulation since it provides the ability to administer a dose calculated according to the formula above; however, Valcyte tablets may be used if the calculated doses are within 10% of available tablet strength (450 mg). For example, if the calculated dose is between 405 mg and 495 mg, one 450 mg tablet may be taken.

The Preparation of Valcyte for Oral Solution reads as follows:

Prior to dispensing to the patient, Valcyte for oral solution must be prepared by the pharmacist as follows *[see How Supplied/Storage and Handling (16)]*:

- Measure 91 mL of purified water in a graduated cylinder.
- Shake the Valcyte bottle to loosen the powder. Remove the child resistant bottle cap and add approximately half the total amount of water for constitution to the bottle and shake the closed bottle well for about 1 minute. Add the remainder of water and shake the closed bottle well for about 1 minute. This prepared solution contains 50 mg of valganciclovir free base per 1 mL.
- Remove the child resistant bottle cap and push the bottle adapter into the neck of the bottle.
- Close bottle with child resistant bottle cap tightly. This will assure the proper seating of the bottle adapter in the bottle and child resistant status of the cap.
- Store constituted oral solution under refrigeration at 2°C to 8°C (36°F to 46°F) for no longer than 49 days. Do not freeze.
- Write the date of expiration of the constituted oral solution on the bottle label.

The patient package insert, which includes the dosing instructions for patients and 2 oral dispensers, should be dispensed to the patient *[see Patient Counseling Information (b) (4)]*.

ADVERSE REACTIONS

The following information was added under the section of Clinical Trial Experience in Pediatric Patients subsection:

Valcyte for oral solution and tablets have been studied in 109 pediatric solid organ transplant patients who were at risk for developing CMV disease (aged 4 months to 16 years) and in 24 neonates with symptomatic congenital CMV disease (aged 8 to 34 days), with duration of ganciclovir exposure ranging from 2 to 100 days. The overall safety profile was similar in pediatric patients as compared to adult patients. However, the rates of certain adverse events and laboratory abnormalities, such as upper respiratory tract infection, pyrexia, nasopharyngitis,

anemia, and neutropenia were reported more frequently in pediatric patients than in adults *[see Use in Specific Populations (8.4), Clinical Studies (14.2)]*.

USE IN SPECIFIC POPULATIONS

The following was added under the subsection of Pediatric Use:

Valcyte for oral solution and tablets are indicated for the prevention of CMV disease in kidney and heart transplant pediatric patients 4 months to 16 years of age at risk for developing CMV disease *[see Indications and Usage (1.2), Dosage and Administration (2.3)]*.

The use of Valcyte for oral solution and tablets for the prevention of CMV disease in pediatric patients 4 months to 16 years of age with kidney or heart transplant is based on pharmacokinetic, safety, and efficacy data from an open-label trial with oral Valcyte (Valcyte for oral solution or tablets) in pediatric solid organ transplant recipients at risk for developing CMV disease. The results of this study were supported by previous demonstration of efficacy in adult patients *[see Adverse Reactions (6.2), Clinical Pharmacology (12.3), Clinical Studies (14.2)]*.

The safety and efficacy of Valcyte for oral solution and tablets have not been established in children for:

- Prevention of CMV disease in liver transplant patients
- Prevention of CMV disease in solid organ transplants other than those indicated
- Prevention of CMV disease in pediatric solid organ transplant patients < 4 months of age
- Treatment of congenital CMV disease

The pharmacokinetic profile and safety of Valcyte for oral solution in children were studied in two open-label studies.

Study 1 was an open-label trial with oral Valcyte (Valcyte for oral solution or tablets) in pediatric solid organ transplant recipients at risk for developing CMV disease *[see Clinical Pharmacology (12.3), Clinical Studies (14.2)]*.

Study 2 was a pharmacokinetic and pharmacodynamic evaluation of Valcyte for oral solution in neonates with congenital CMV infection involving the central nervous system. Twenty-four neonates were enrolled in this study. All patients were treated for 6 weeks with a combination of intravenous ganciclovir 6 mg/kg twice daily and Valcyte for oral solution at doses ranging from 14 mg/kg to 20 mg/kg twice daily. The pharmacokinetic results showed that in infants > 7 days to 3 months of age, a dose of 16 mg/kg twice daily of Valcyte for oral solution provided ganciclovir systemic exposures (median $AUC_{0\text{-}12h}$ = 23.6 [range 16.8 – 35.5] μg·h/mL; n = 6) comparable to those obtained in infants up to 3 months from a 6 mg/kg dose of intravenous ganciclovir twice daily ($AUC_{0\text{-}12h}$ = 25.3 [range 2.4 – 89.7] μg·h/mL; n = 18) or to the ganciclovir systemic exposures obtained in adults from a 900 mg dose of Valcyte tablets twice daily.

The safety and efficacy of intravenous ganciclovir have not been established for the treatment of congenital CMV infection in infants and no similar disease occurs in adults; therefore, efficacy cannot be extrapolated from intravenous ganciclovir use in adults.

CLINICAL STUDIES

The following was added under the subsection of Pediatric Patients:

Pediatric Patients

Prevention of CMV in Pediatric Solid Organ Transplant Recipients: Sixty-three children, 4 months to 16 years of age, who had a solid organ transplant (kidney 33, liver 17, heart 12, and kidney/liver 1) and were at risk for developing CMV disease, were enrolled in an open-label, safety, and pharmacokinetic study of oral Valcyte (Valcyte for oral solution or tablets). Patients received Valcyte once daily as soon as possible after transplant until a maximum of 100 days post-transplant. The daily doses of Valcyte were calculated at each study visit based on body surface area and a modified creatinine clearance *[see Dosage and Administration (2.3)]*.

The pharmacokinetics of ganciclovir were similar across organ transplant types and age ranges. The mean daily ganciclovir exposures in pediatric patients were comparable to those observed in adult solid organ transplant patients receiving Valcyte 900 mg once daily *[see Clinical Pharmacology (12.3)]*. No case of CMV disease was reported during the study. CMV viremia was reported in 7 (11%) patients during the study; however, none of these events fulfilled the definition of CMV syndrome. Based on the pharmacokinetic, safety, and efficacy data from this study and extrapolated efficacy data from the adult study, oral Valcyte is indicated for the prevention of CMV disease in kidney and heart transplant children 4 months to 16 years of age at risk for developing CMV disease. Valcyte is not approved in adults for CMV prophylaxis in liver transplant patients; therefore, Valcyte is not recommended for CMV prophylaxis in pediatric liver transplant patients because efficacy cannot be extrapolated from adults.

Andreas Pikis, M.D.
Medical Reviewer, DAVP

Concurrences:
KMarcus/SafetyDepDir/DAVP

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 21304	SUPPL 7	ROCHE PALO ALTO LLC	VALCYTE(VALGANCICLOVIR HYDROCHLORIDE)450
NDA 22257	ORIG 1	HOFFMAN-LA ROCHE INC	VALCYTE
NDA 22257	ORIG 1	HOFFMAN-LA ROCHE INC	VALCYTE
NDA 22257	(b) (4)	HOFFMAN-LA ROCHE INC	VALCYTE
NDA 22257	(b) (4)	HOFFMAN-LA ROCHE INC	VALCYTE

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/s/

ANDREAS PIKIS
08/28/2009

KENDALL A MARCUS
08/28/2009

Cross-Discipline Team Leader Review

Date	November 25, 2008
From	Kendall A. Marcus, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	22-257 Valcyte for oral solution pediatric indication [redacted] (b) (4)
Applicant	Roche
Date of Submission	April 30, 2008
PDUFA Goal Date	October 31, 2008
Proprietary Name / Established (USAN) names	Valcyte® for Oral Solution valganciclovir
Dosage forms / Strength	
Proposed Indication(s)	1. CMV prophylaxis in pediatric solid organ transplant recipients at high risk 2. [redacted] (b) (4) 3. [redacted] (b) (4) 4. [redacted] (b) (4)
Recommended:	*1. Complete response* *2.* [redacted] (b) (4) *3.* [redacted] (b) (4) *4.* [redacted] (b) (4)

1. Introduction

Valganciclovir (VGCV) tablets are currently approved in the United States for the treatment of cytomegalovirus (CMV) retinitis in adult patients with acquired immunodeficiency syndrome (AIDS) and for the prevention of CMV disease in adult kidney, heart, and kidney-pancreas transplant patients at high risk (donor CMV seropositive/recipient CMV seronegative [D+/R-]). These New Drug Applications (NDAs) provide data in support of the registration and approval of a new formulation of VGCV for oral solution. The Applicant submitted data from a bioequivalence study to support approval of the oral solution for the currently approved adult indications for VGCV tablets. In addition, the Applicant provided data from 4 pediatric trials requested under the Best Pharmaceuticals for Children Act in support of an indication for VGCV for the prevention of CMV disease in solid organ transplant recipients from 4 months to 16 years of age [redacted] (b) (4)

This memo will review the regulatory history of ganciclovir products for the prevention of CMV disease in solid organ transplant recipients, as well as an important study previously

conducted with IV ganciclovir for the treatment of congenital CMV disease. The pharmacokinetic, safety and efficacy data submitted to support proposed pediatric indications and the bioequivalence study submitted (b) (4) will be summarized. Finally, inspections conducted by the Division of Scientific Investigation (DSI) which found multiple deficiencies in sample handling and analyses, resulting in a Complete Response action on these applications, will be noted.

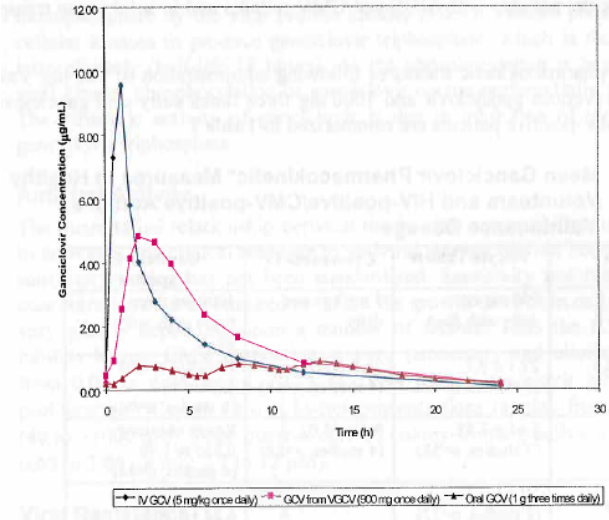
2. Background

Prevention of CMV Disease in Solid Organ Transplant Recipients
Solid organ transplant recipients are at risk for a multitude of infections following transplantation, due to the administration of immunosuppressive drugs used to prevent rejection of the transplanted organ by the transplant recipient. Various strategies are employed to prevent infections that may occur during the post-transplant period. Prior to the advent of prophylaxis for CMV disease, the period of highest risk for development of CMV disease was post-transplant Day 10 through post-transplant Day 100. Because of concerns that prophylaxis for CMV disease would merely shift the period of risk of CMV disease to the post-prophylaxis period, the clinical endpoint of incidence of CMV disease has been typically measured about three months (post-transplant Day 180) following the cessation of prophylaxis.

Ganciclovir is a synthetic analogue of 2'-34 deoxyguanosine, which inhibits replication of CMV both *in vitro* and *in vivo*. Currently, three formulations of ganciclovir are marketed, IV and oral ganciclovir and oral VGCV. IV ganciclovir (GCV) is parenterally administered. GCV capsules are orally administered, however, poor bioavailability results in exposures significantly lower than observed with IV GCV. Valganciclovir is an L-valyl ester, a prodrug, of GCV. After oral administration, VGCV is rapidly converted to GCV by intestinal and hepatic esterases. Systemic exposure to the prodrug, VGCV, is transient and low, with the AUC and Cmax being about 1% and 3% of GCV levels.

Because of its improved bioavailability, VGCV provides GCV AUCs that are comparable to those achieved with administration of IV GCV. The following figure from the VGCV package insert displays concentration-time profiles for GCV following administration of IV GCV, oral GCV and oral VGCV from a multiple dose study in HIV/CMV positive patients with CMV retinitis.

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



IV GCV was the first GCV product approved. In 1992, marketing approval was granted for the prevention of CMV disease in transplant recipients at risk for CMV disease. Three trials formed the basis for approval, one conducted in heart transplant recipients and two studies conducted in bone marrow transplant recipients. The heart transplant study is reviewed briefly here.

The heart transplant study was a randomized double-blind, placebo-controlled study of heart transplant recipients (D+R-, D+R+, D-R+) who received IV GCV for 28 days and were followed for 120 days post-transplant for CMV disease. Patients received IV GCV or placebo for 28 days. The incidence of CMV disease was measured at Day 120.

In clinical development trials, "CMV disease" has been defined as:

- **CMV Syndrome**
  - CMV viremia
  - Fever > 38 ºC on at least two occasions, plus at least one of the following
    - Malaise
    - Leucopenia
    - Elevation of transaminases
    - Thrombocytopenia
    - Atypical lymphocytosis

OR

- **Tissue Invasive CMV Disease**
  - Symptoms or signs of organ dysfunction
  - Evidence of localized CMV infection in a biopsy or other specimen

FDA review of the data demonstrated a statistically significant reduction in the incidence of CMV disease in study patients as a whole, however, no treatment effect was observed in a subgroup analysis of patients at highest risk for developing CMV disease.

Table 1 - Incidence of CMV Disease at Day 120 in Adult Heart Transplant Recipients

CMV Disease at Day 120	IV ganciclovir	Placebo
Overall	16% (12/76)	43% (31/73)
D+R-	42% (5/12)	40% (4/10)

GCV capsules for oral administration were approved in 1996 for prevention of CMV disease in solid organ transplant recipients. This approval was based on a single, randomized, double-blind, placebo-controlled study of orthotopic liver transplant recipients who were CMV seropositive or recipients of an organ from a seropositive donor. GCV capsules or placebo were administered from post-transplant Day 10 through post-transplant Day 100. The incidence of CMV disease was evaluated at Day 180. The incidence of CMV disease observed in this study is summarized in Table 2.

Table 2 – Incidence of CMV Disease at Day 180 in Adult Liver Transplant Recipients

CMV Disease at Day 180	Oral GCV	Placebo
Overall	5% (7/150)	19% (29/154)
D+R-	15% (3/21)	44% (11/25)

A Kaplan-Meier curve of the time to CMV disease in this study appears to confirm that the period of highest risk for development of CMV is during the first 100 days post-transplant; prophylaxis in this study did not appear to shift the incidence of CMV disease to the post-prophylaxis period.

Figure 1
Liver Transplant Study
Ganciclovir versus Placebo
Kaplan-Meier Curve of Time to CMV Disease

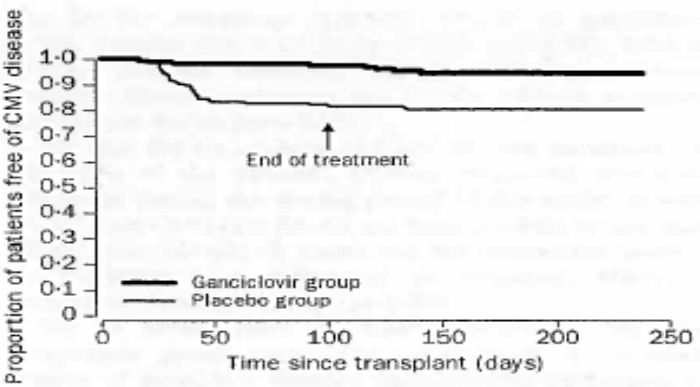


Figure 2: **Kaplan-Meier curves for the cumulative probability of freedom from cytomegalovirus (CMV) disease with time after transplantation**

VGCV tablets were approved in 2003 for prevention of CMV disease in heart, kidney and kidney-pancreas transplant recipients at high risk [D+/R -]. This approval was based on a single, randomized, double-blind, double-dummy, GCV-controlled study of D+/R- solid organ transplant recipients. Recipients of kidney, liver, heart, and kidney-pancreas transplants were enrolled. VGCV tablets or GCV capsules, each with corresponding placebo, were administered from post-transplant Day 10 through post-transplant Day 100. The incidence of CMV disease was evaluated at Day 180. Overall, the proportion of subjects who developed CMV disease was similar between the two groups (GCV 15.2%, VGCV 12.1%) and met the protocol definition of non-inferiority for VGCV. However, subgroup analyses demonstrated differences in the incidence of CMV disease by transplant type, and, in particular, in the subgroup of patients who developed tissue-invasive CMV disease. The incidence of CMV disease observed in this study by transplant type is summarized in Table 3.

Table 3 - Incidence of CMV Disease at Day 180 in Solid Organ Transplant Recipients by Transplant Type

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: MOR NDA 21-204 S-001

The incidence of tissue-invasive CMV disease observed in this study by transplant type is summarized in Table 4.

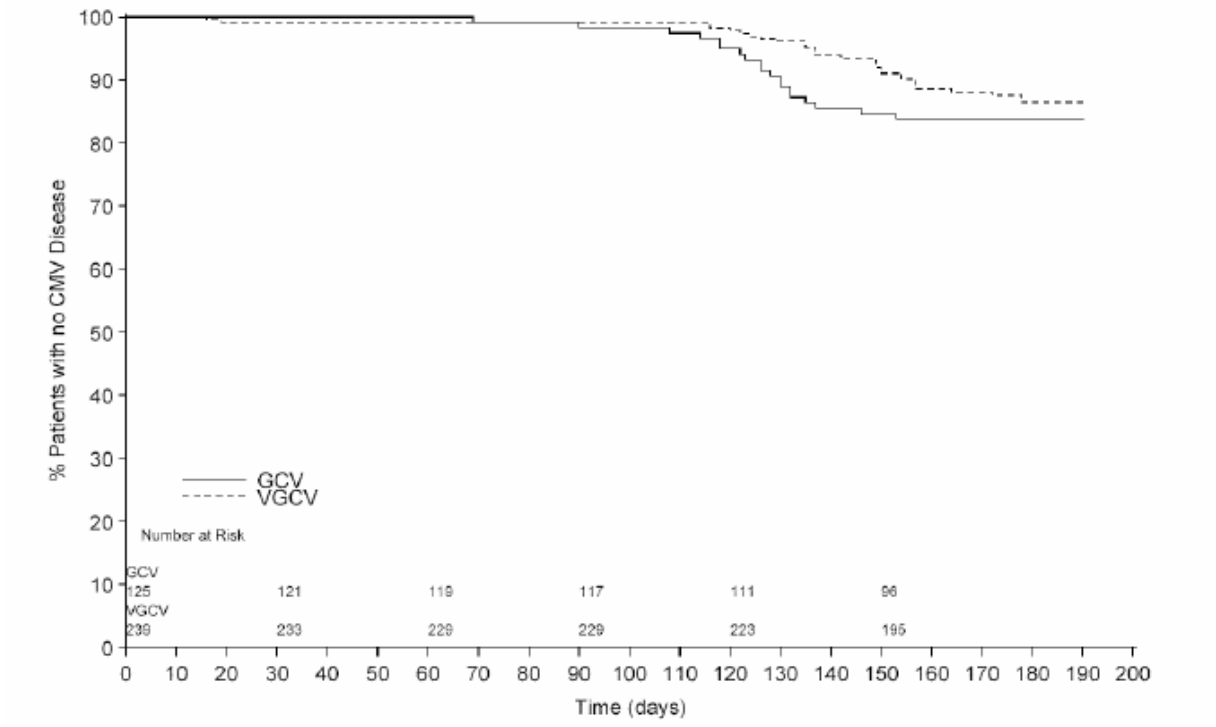
Table 4 - Incidence of Tissue-Invasive CMV Disease at Day 180 in Solid Organ Transplant Recipients by Transplant Type

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

Source: MOR review NDA 21-304 S-001

A Kaplan-Meier curve of time to CMV disease demonstrates that almost all endpoints were reached after discontinuation of study drugs.

Figure 2 - Time to CMV Disease up through Day 180



Source: MOR review NDA 21-304 S-001

Based on the observed differences between transplant types in the incidence of CMV disease between VGCV and GCV-treated subjects, [redacted] VGCV was approved for prevention of CMV disease in heart, kidney and kidney-pancreas transplant recipients at high risk, [redacted] based on these post-hoc sub-group analyses.

As a result, activity of anti-CMV drugs is now generally considered [redacted] by organ transplant type. Because VGCV was not approved for prevention of CMV disease in adult liver transplant recipients, efficacy data in this population cannot be extrapolated to pediatric liver transplant patients. [redacted]

Team Leader Comment: *I do not agree with the action taken by the Division for the following reasons.*

- [redacted] *Clinical trials supporting activity of anti-CMV drugs have all utilized the same strategy of measuring the endpoint of CMV disease about 3 months after drug is discontinued. While evaluation of this endpoint seeks to potentially address the concern that prophylaxis only delays the onset of CMV disease to the period of time after drug is discontinued, it ignores the obvious and potent efficacy of the drug when it is administered.*
- *This study was not adequately powered to discern treatment differences in transplant sub-groups or in endpoint sub-groups. In my opinion, making decisions based on these types of pos-hoc subgroup analyses increases the likelihood of making Type I statistical errors.*
- [redacted], *VGCV appeared superior to GCV in preventing CMV disease in kidney transplant recipients. No plausible explanation exists as to why contradictory findings were observed in these two transplant types, further supporting that these post-hoc sub-group analyses reflect random variation rather than real observed differences regarding VGCV efficacy in these different transplant types.*

Congenital CMV Disease

[redacted] In the United States, it is estimated that approximately 40,000 infants are born each year with congenital CMV disease. Approximately 10% of infected newborns are symptomatic at birth. Mortality in these infants is about 12% and approximately 90% of symptomatic survivors experience significant morbidity from the infection. Survivors can have mental retardation, sensorineural hearing loss, microcephaly, seizures, and other medical problems. In contrast, only 10-15% of infected, asymptomatic infants are at risk for development of neurologic sequelae.

Currently, no drugs are approved for antiviral therapy of congenital CMV disease. However, results from an NIH-NIAID Collaborative Antiviral Study Group (CASG) clinical trial, CASG 102, suggest GCV (b) (4) (b) (4) This randomized, open-label, controlled trial of GCV enrolled 100 newborns with symptomatic congenital CMV infection involving the CNS. Enrolled newborns were assigned to receive either IV GCV 6 mg/kg twice daily for 6 weeks or no treatment. The primary endpoint was brainstem-evoked response (BSER) audiometry improvement by one gradation (e.g., from severe to moderate) between baseline and the 6-month follow-up or retained normal hearing. Treated subjects had a greater incidence of improved hearing or maintenance of normal hearing at 6 months of age and lack of hearing deterioration at 6 months and 1 year as compared to untreated subjects. However, no significant difference was observed in the time to resolution of organomegaly, CMV retinitis, thrombocytopenia or hyperbilirubinemia. Median weight gain and median increase in head circumference between baseline and 6 weeks were higher in the GCV treatment group, but these differences were not sustained at the 6 month follow-up. Importantly, this study has been noted to have several deficiencies, including poor follow-up. Less than half of the patients (42/100) had evaluable data at both entry and 6 months raising the possibility of follow-up bias that could influence the results of the trial. (b) (4)

3. CMC/Device

Please see Dr. Ted Chang's review for additional details. As part of the Pediatric Written Request, the Applicant was asked to develop a commercially marketable age-appropriate formulation for children. The Applicant's attempts were successful and the product proposed for marketing is a powder reconstituted with purified water to provide an oral solution.

Valcyte for oral solution is a conventional granulate formulation of white to slightly yellow powder containing standard excipients and manufactured using conventional methods. The drug product is packaged in a (b) (4) glass bottle containing (b) (4) dried powder (5 gram drug substance). Prior to dispensing to the patient, Valcyte for oral solution must be prepared by the pharmacist in 91 mL of purified water to make 100 mL of 50 mg/mL oral solution.

4. Nonclinical Pharmacology/Toxicology

No new animal pharmacology and toxicology data were submitted with these applications. Please refer to the original approval of Valcyte (NDA 21-304) for background information.

5. Clinical Pharmacology/Biopharmaceutics

Please see the clinical pharmacology/Biopharmaceutics review for additional details. The Applicant conducted a number of studies and analyses to support indications and dosing recommendations of Valcyte for oral solution for:

- (b) (4)
- (b) (4)
- pediatric transplant patients at high risk for development of CMV disease, and
- (b) (4)

(b) (4) (b) (4) (b) (4) This was a multi-center, open-label, randomized, three-way crossover study comparing the bioavailability of Valcyte tablets to 2 oral solution formulations of VGCV in 23 kidney transplant recipients with stable renal function (estimated creatinine clearance 60 mL/min). The study demonstrated that GCV systemic exposures after administration of 900 mg (18 mL) of VGCV tutti-frutti flavored oral solution formulation (50 mg/mL) were similar to the GCV exposures after administration of 900 mg (2 X 450 mg) VGCV tablets. However, inspection of one clinical site that conducted this study and enrolled 9 subjects, Indiana University Medical Center, Indianapolis, IN, revealed that the site failed to retain reserve samples, thus making it impossible to confirm study results. The retention of the reserve samples is required as per 21 CFR 320.38 and is critical for assuring the authenticity of the test and reference products used in the pivotal bioequivalence study. As the authenticity of the test and reference products could not be confirmed, the data from the bioequivalence study cannot be used (b) (4) (b) (4)

(b) (4)

Pediatric (b) (4) – Prevention of CMV Disease in Solid Organ Transplant Recipients

To support dosing recommendations and an indication in pediatric solid organ transplant recipients for the prevention of CMV disease, the applicant conducted three pharmacokinetic and safety studies (WP16296, WP16303 and WP16726) to characterize the pharmacokinetics and safety of GCV in pediatric solid organ transplant (liver, kidney and heart) recipients aged 4 months to 16 years. Study WP16726 is discussed further in Section 7 – Efficacy. For additional information regarding studies WP16303 and WP16296, please see the clinical pharmacology/Biopharmaceutics review.

In summary, review of the information submitted in this NDA supported the Applicant's dosing recommendations of VGCV for oral solution in pediatric (4 months -16 years) kidney and heart transplant recipients for the prophylaxis of CMV disease. The clinical pharmacology reviewer explored other simplified dosing schemes but they were not superior to the Applicant's proposal. The information provided supports the following dosing recommendation:

$$\text{Pediatric Dose (mg)} = 7 \times BSA \times CrCL$$

where

$$\text{Mosteller BSA } (m^2) = \sqrt{\frac{Height(cm) \times Weight(kg)}{3600}}$$

and

$$\text{Modified Schwartz Creatinine Clearance } (mL/\min/1.73m^2) = \frac{k \times Height(cm)}{SerumCreatinine(mg/dL)}$$

where k = 0.45 for patients < 2 years, 0.55 for boys ages 2 to < 13 years and girls ages 2 to 16 years, and 0.7 for boys ages 13 to 16 years.

Unfortunately, inspection of the investigative site responsible for analyzing clinical study samples found multiple deficiencies that preclude approval of Valcyte for oral solution for this indication. The Division received a report from DSI describing multiple deficiencies observed during the analytical inspection at [redacted] (b) (4) Based on these findings, the plasma concentration data from study WP16726 are not acceptable as submitted.

Pediatric [redacted] (b) (4) **– Treatment of Congenital CMV Disease**

A pharmacokinetic study (CASG 109) in neonates (aged 6-31 days at enrollment and 8-34 days at dosing) congenitally infected with CMV was conducted to determine dosing recommendations of VGCV for treatment of CMV disease. A total of 24 neonates with symptomatic congenital CMV disease involving the central nervous system were enrolled in three versions of the protocol. All enrolled subjects were treated for 6 weeks with a combination of IV GCV 6 mg/kg twice daily or VGCV for oral solution with doses ranging from 14 mg/kg to 20 mg/kg twice daily. Doses of VGCV for oral solution were selected to provide comparable systemic exposures to those obtained in infants up to age 3 months from 6 mg/kg dose of IV GCV twice daily or GCV exposures obtained in adults from a 900 mg dose of VGCV tablets twice daily. Of note, IV GCV 6 mg/kg twice daily was used in CASG102, the congenital CMV study described in the background section of this document.

Pharmacokinetic results showed that doses of 14 mg/kg and 16 mg/kg provide GCV exposures close to the target AUC. The GCV $AUC_{0\text{-}12}$ in neonates receiving 14 mg/kg is indistinguishable from the $AUC_{0\text{-}12}$ observed in neonates receiving 16 mg/kg. However, the results of population pharmacokinetic modeling predicted the 16 mg/kg dose would provide exposures closer to the target $AUC_{0\text{-}12}$ than the 14 mg/kg dose.

[redacted] (b) (4)

In addition, deficiencies were noted by DSI during the analytical inspection of (b) (4) (b) (4) Based on these deficiencies, the plasma concentration data from study CASG109 are not acceptable as submitted.

6. Clinical Microbiology

No issues with respect to Clinical Microbiology are noted; however. See Dr. Nilambar Biswal's review for additional details.

7. Clinical/Statistical- Efficacy

(b) (4)

Pediatric (b) (4) - Congenital CMV Disease

The study submitted (b) (4) for congenital CMV disease is CASG 109. The study was sponsored by the National Institutes of Health and conducted in 8 centers in the United States by the Collaborative Antiviral Study Group. This is an open-label, pharmacokinetic, and safety study of IV GCV and VGCV for oral solution in neonates and infants up to three months of age with symptomatic congenital CMV disease. A total of 24 neonates with symptomatic congenital CMV disease involving the central nervous system were enrolled in this protocol. All patients were treated for 6 weeks with a combination of IV GCV 6 mg/kg twice daily or VGCV for oral solution with doses ranging from 14 mg/kg to 20 mg/kg twice daily.

Efficacy was assessed through hearing and neurologic assessments at baseline, at the end of treatment and at multiple timepoints after treatment. The results of hearing evaluation were similar to those observed in Study CASG 102, described in the background section of this document. (b) (4)

(b) (4)

Pediatric (b) (4) – CMV Prophylaxis in Pediatric Solid Organ Transplant Recipients at High Risk

As previously discussed, the efficacy of GCV, the active metabolite of VGCV, is well established for the prevention of CMV disease in adult solid organ transplant recipients. IV GCV and GCV capsules for oral administration have demonstrated efficacy for this indication in placebo-controlled trials. As discussed in the background section of this document, VGCV tablets are indicated for the prevention of CMV disease in kidney, heart and kidney-transplant recipients at high risk. The submitted pediatric study was not required to demonstrate

superiority of VGCV for oral solution to a placebo control or to demonstrate non-inferiority to an active control, as efficacy of VGCV for kidney, heart or kidney-pancreas recipients can be extrapolated from adult data; however, it does provide supportive activity data.

Study WP16726 is an open-label, multicenter, non-comparative safety and pharmacokinetic study of VGCV for oral solution in pediatric kidney, heart and liver transplant recipients. The objectives of the study were to:

1) Investigate the safety and tolerability of VGCV for oral solution in pediatric solid organ transplant recipients, and

2) Determine the pharmacokinetics of GCV following oral administration of VGCV solution and tablets in solid organ transplant recipients, and

3) Describe the incidence of CMV disease.

A total of 63 children, 4 months to 16 years of age, who received solid organ transplants and were considered at risk for developing CMV disease were enrolled in this study. Thirty-three (33) kidney recipients, 17 liver recipients, 12 heart recipients, and 1 kidney/liver recipient were enrolled. Liver transplant recipients were allowed to enroll despite non-approval of VGCV tablets for this population because the Division believed the Applicant could submit new data supporting activity of VGCV in adult liver transplant recipients. Of note, in the VGCV adult transplant study, patients were seronegative for CMV and received allografts from CMV seropositive donors, while in this study, enrolled subjects were not required to be CMV seronegative and donors were not required to be CMV seropositive. Patients who met entry criteria began prophylaxis with oral VGCV once daily (VGCV for oral solution or tablets) as soon as possible after transplantation and continued treatment until a maximum of 100 days post-transplant. Patients were followed until Week 26 (Day 180) post-transplant.

During the study, 7 subjects reported CMV viremia/antigenemia, however, none fulfilled the definition of CMV disease, either CMV syndrome or tissue-invasive CMV disease. Five (5) patients developed CMV viremia/antigenemia after completing or discontinuing prophylaxis. One of these patients discontinued study medication on Day 35 due to an intestinal obstruction, and developed CMV viremia on Day 86. The remaining two patients had CMV positive tests during the treatment phase of the study. Of note, 6 of the 7 subjects were D+R-, the transplant group considered to be at highest risk for development of CMV disease. Two (2) of the subjects were liver transplant recipients. Five (5) of the 7 subjects who developed a positive CMV test were treated with GCV. Of the highest risk subjects enrolled (D+R-), 6/25 (24%) developed CMV viremia/antigenemia; by comparison, in the adult solid organ transplant study, 29/235 (12.1%) of D+R- subjects receiving VGCV developed CMV disease. Importantly, however, as was stated previously, none of the pediatric patients met criteria for CMV disease and conclusions based on this cross-study comparison should be made with caution.

Also noted previously, inspection of the investigative site responsible for analyzing clinical study samples found multiple deficiencies that preclude approval of VGCV for oral solution for this indication. The Division received a report from DSI describing multiple deficiencies

observed during the analytical inspection at [redacted] (b) (4)
Based on these findings the plasma concentration data from study WP16726 are not acceptable as submitted. As a result of this report, the Division determined that the data submitted with this NDA does not support approval of VGCV for oral solution for the prevention of CMV disease in pediatric kidney and heart transplant recipients ages 4 months to 16 years at risk for developing CMV disease.

8. Safety

No new safety issues were identified during review of these applications.

In Study WP16726, the open-label, non-comparative safety and pharmacokinetic study of VGCV in pediatric kidney, heart and liver transplant recipients, diarrhea was the most common adverse event followed by pyrexia, upper respiratory tract infection, vomiting and hypertension. The majority of AEs were mild or moderate in intensity and were considered by the investigator not related to study drug. When compared to adult solid organ transplant recipients receiving VGCV for CMV prophylaxis, pediatric subjects reported higher rates of certain adverse events such as pyrexia, upper respiratory tract infection. In addition, neutropenia and anemia were laboratory abnormalities observed more frequently in pediatric subjects as compared to adults. Transplant rejection was more frequent in adults.

Serious adverse events (SAEs) were most commonly due to infections or gastrointestinal related disorders. A total of seven SAEs were considered related to study drug, all occurring during treatment. These included increased transaminases, anemia, CMV antigenemia, diarrhea, neutropenia, and febrile neutropenia. Three patients withdrew due to AEs. One kidney transplant recipient due to severe neutropenia (probably related to study drug), one liver transplant recipient due to elevated transaminases (probably related to study drug), and one liver transplant recipient due to an intestinal obstruction (unrelated to study drug).

In Study CASG 109, neonates congenitally infected with CMV received IV GCV or VGCV for oral solution for 6 weeks. Anemia and neutropenia were the most common adverse events reported; however only one subject discontinued for neutropenia. Rash, agitation, fever and emesis were other frequently reported adverse events. The common occurrence of rash likely represents susceptibility of the treatment population to rash; no subject discontinued study for rash development.

9. Advisory Committee Meeting

\No advisory committee was held for these applications.

10. Pediatrics

The pediatric studies submitted with these applications were also submitted in support of fulfillment of the Pediatric Written Request, originally issued in June 2001, and amended on multiple occasions, most recently in March 2008. On September 10, 2008, the Pediatric

Exclusivity Board determined that the submitted studies fulfilled the requirement of the pediatric written request and pediatric exclusivity was granted. The deficiencies noted in the DSI inspections have not changed the outcome of this assessment.

11. Other Relevant Regulatory Issues

Please see DSI inspection reports for additional details. Inspection of one clinical site that conducted the adult bioequivalence study and enrolled 9 subjects, Indiana University Medical Center, Indianapolis, IN, revealed that the site failed to retain reserve samples, thus making it impossible to confirm study results. The retention of the reserve samples is required as per 21 CFR 320.38 and is critical for assuring the authenticity of the test and reference products used in the pivotal bioequivalence study. As the authenticity of the test and reference products could not be confirmed, the data from the bioequivalence study cannot be used (b) (4) (b) (4)

12. Labeling

Because Valcyte for oral solution cannot be approved at this time, no final agreement was reached on labeling.

13. Recommendations/Risk Benefit Assessment

These applications provided data to support the approval of Valcyte for oral solution for (b) (4) the prevention of CMV disease in pediatric kidney and heart transplant recipients at risk. This formulation would have provided a much needed pediatric formulation for pediatric heart and kidney transplant recipients, enabling most of them to utilize an oral formulation as opposed to IV GCV. (b) (4)

Unfortunately, after a thorough review and based on deficiencies noted during inspections by the Division of Scientific Investigations, the Division determined Valcyte for oral solution is not recommended for approval for any of the proposed indications. The deficiencies noted during the inspection are as follows:

(b) (4) Inspection of one clinical site that conducted the adult bioequivalence study and enrolled 9 subjects, Indiana University Medical Center, Indianapolis, IN, revealed that the site failed to retain reserve samples, thus making it impossible to confirm study results. The retention of the reserve samples is required as per 21 CFR 320.38 and is critical for assuring the authenticity of the test and reference products. As the authenticity of the test and reference products cannot be confirmed, the data from the bioequivalence study cannot be used to (b) (4)

NDA 22-257: Based on the findings from the analytical inspection at (b) (4) (b) (4) the plasma concentration data from WP16726 and CASG109 are not acceptable as submitted.

Complete response letters will be issued for both NDAs. A new bioequivalence study will need to be conducted to address the deficiencies noted for (b) (4) To address the deficiencies noted for NDA 22-257, the Applicant will need to provide the following data and analyses:

- Frozen stability data that cover the duration of storage (b) (4) (b) (4) of all the plasma samples used for the quantification of ganciclovir in studies WV16726 and CASG109.
- Identify a set of integration parameters and re-integrate all the chromatograms within a run in a consistent manner. This procedure should be repeated for all the chromatograms generated in studies WV16726 and CASG109. Use the resulting concentrations to repeat the pharmacokinetic and/or pharmacodynamic evaluations in studies WP16726 and CASG109.

Kendall Marcus, M.D., Medical Team Leader, DAVP

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/s/

Kendall Marcus
11/25/2008 04:15:40 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA 22-257 & (b) (4)
Submission Number	000
Submission Code	000
Letter Date	April 30, 2008
Stamp Date	May 1, 2008
PDUFA Goal Date	November 1, 2008
Reviewer Name	Andreas Pikis, M.D.
Review Completion Date	October 20, 2008
Established Name	Valganciclovir
Trade Name	VALCYTE
Therapeutic Class	CMV Antiviral
Applicant	Hoffman- La Roche, Inc.
Priority Designation	P
Formulation	Powder for oral solution
Dosing Regimen	Based on body surface area and creatinine clearance
Indication	Prevention of CMV disease in solid organ transplant recipients at risk
Intended Population	Children 4 months to 16 years of age

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This New Drug Application (NDA) includes pharmacokinetic and safety data from five studies; one bioequivalence study assessing the bioequivalence of ganciclovir from the new valganciclovir for oral solution with the marketed valganciclovir 450 mg tablet at a dose of 900 mg and four pediatric studies conducted in response to the Pediatric Written Request for the use of valganciclovir for the prevention or treatment of CMV disease in children. Based on these studies, the Applicant seeks the following:

- (b) (4)
- (b) (4)
  (b) (4)
- Approval of valganciclovir for the prevention of cytomegalovirus (CMV) disease in pediatric solid organ transplant recipients 4 months to 16 years of age at risk for developing CMV disease, and
- (b) (4)

Of note, this submission was split into two NDAs for administrative purposes: (b) (4)
(b) (4) 2) NDA 22-257 for the indication of valganciclovir for the prevention of CMV disease in pediatric solid organ transplant recipients 4 months to 16 years of age at risk for developing CMV disease (b) (4)
(b) (4)

After a thorough review and based on the deficiencies noted during the inspection by the Division of Scientific Investigations, the Division decided valganciclovir is not recommended for approval for any of the above indications. The deficiencies noted during the inspection are as follows:

(b) (4) The clinical site failed to retain the reserve samples from the pivotal bioequivalence study. The retention of the reserve samples is required as per 21 CFR 320.38 and is critical for assuring the authenticity of the test and reference products used in the pivotal bioequivalence study. As the authenticity of the test and reference products cannot be confirmed, the data from the bioequivalence study cannot be used (b) (4)
(b) (4)

NDA 22-257: Based on the findings from the analytical inspection at (b) (4)
(b) (4), the plasma concentration data from WP16726 (A safety and pharmacokinetic study of valganciclovir in pediatric solid organ transplant recipients) and CASG109 (A phase I/II pharmacokinetic and pharmacodynamic evaluation of valganciclovir in neonates with

symptomatic congenital CMV infection) are not acceptable as submitted. To assure the accuracy of analytical runs and the resulting drug concentrations, the Applicant needs to provide the following information:

- Frozen stability data that cover the duration of storage (b) (4) (b) (4) of all the plasma samples used for the quantification of ganciclovir in studies WV16726 and CASG109.
- Identify a set of integration parameters and re-integrate all the chromatograms within a run in a consistent manner. This procedure should be repeated for all the chromatograms generated in studies WV16726 and CASG109. Use the resulting concentrations to repeat the pharmacokinetic and/or pharmacodynamic evaluations in studies WP16726 and CASG109.

A complete response letter will be issued outlining the deficiencies needed to be addressed by the Applicant.

1.2 Recommendation on Post-marketing Actions

1.2.1 Risk Management Activity

No specific risk management activities were requested from the Applicant.

1.2.2 Required Phase 4 Commitments

No phase 4 commitments are requested from the Applicant at this time.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Description: Valganciclovir is the L-valyl ester of ganciclovir. After oral administration, valganciclovir is rapidly and extensively hydrolyzed by gastrointestinal and liver esterases into ganciclovir and the essential amino acid valine. Its mechanism of action, antiviral spectrum, resistance pattern, and safety profile are the same as those of its parent drug ganciclovir. The absolute bioavailability of ganciclovir from oral valganciclovir tablets (~60%) is up to 10 times greater than that of oral ganciclovir capsules (6-9%).

Established name and trade name: Valganciclovir (Valcyte®)

Pharmacological class: Valganciclovir is a nucleoside analogue with inhibitory activity against herpes viruses. However, valganciclovir's unique characteristic is potent inhibition of CMV DNA polymerase.

Indications, dosing regimens, age groups: Currently, Valcyte® is approved for adults for the following indications:

- Treatment of CMV retinitis in patients with AIDS:
  Induction: 900 mg twice daily for 21 days
  Maintenance: following induction treatment, or in patients with inactive CMV retinitis, the recommended dose is 900 mg once daily
- Prevention of CMV disease in kidney, heart, or kidney-pancreas transplant patients at high risk for developing CMV disease:
  900 mg once daily starting within 10 days of transplantation until 100 days post-transplantation.

Applicant's proposed indications, dosing regimens, and age groups included in this submission:

- Prevention of CMV disease in pediatric solid organ transplant recipients, aged 4 months to 16 years of age, at risk for developing CMV disease:
  Pediatric Dose (mg) = 7 x BSA x CrCl (calculated using the modified Schwartz formula)

where

$$Mosteller\ BSA\,(m^2) = \sqrt{\frac{Height\ (cm)\ x\ Weight\ (kg)}{3600}}$$

$$Schwartz\ Creatinine\ Clearance\ (mL/\min/1.73m^2) = \frac{k\ x\ Height\ (cm)}{Serum\ Creatinine\ (mg/dL)}$$

where k =

0.45 for patients aged < 1 year,

0.45 for patients aged 1 to < 2 years (note k value is 0.45 instead of the typical value of 0.55),

0.55 for boys aged 2 to < 13 years and girls aged 2 to 16 years, and

0.7 for boys aged 13 to 16 years.

All calculated doses should be rounded to the nearest 25 mg increment for the actual deliverable dose. If the calculated dose exceeds 900 mg, a maximum dose of 900 mg should be administered. The oral solution is the preferred formulation since it provides the ability to administer a dose calculated according to the formula above; however, Valcyte tablets may be used if the calculated doses are within 10% of available tablet doses. For example, if the calculated dose is between 405 mg and 495 mg, one 450 mg tablet may be taken.

- [redacted] **(b) (4)**

2.2 Currently Available Treatment for Indications

Prevention of CMV disease in solid organ transplant recipients:
Cytomegalovirus is the single most frequent pathogen in solid organ transplant recipients, contributing significantly both to patient morbidity and mortality. Three forms of infection 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. However, CMV serologic status of both the donor and recipient and immunosuppressive therapy are considered the most significant factors. In adult patients, the lowest rate of CMV infection (< 5%) occurs in D-R- recipients and the highest rate (>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 than treatment of established infection. Prophylactic therapy and preemptive therapy are the two major strategies used for prevention. During the last 15 years many investigators have focused on the value of preemptive therapy (treatment only of patients with evidence of CMV replication); however, at the present time, most transplant physicians use prophylactic therapy (prophylaxis administered to all patients at risk for developing CMV disease) for solid organ transplant recipients.

IV ganciclovir was the first antiviral drug approved for prevention of CMV disease in solid organ transplant recipients. Unfortunately, the long-term use of IV ganciclovir is generally impractical due to the requirement of an indwelling catheter to deliver the drug and, in addition, places the patient at increased risk of acquiring potentially life-threatening catheter-related infections. Oral ganciclovir is also approved for the prevention of CMV disease in solid organ transplant patients, however, this formulation has poor bioavailability and prophylaxis requires that patients take four capsules three times daily, making compliance challenging.

The poor bioavailability of oral ganciclovir and the limitations for the use of IV ganciclovir led to the development of valganciclovir, a more orally bioavailable form of ganciclovir. The absolute bioavailability of ganciclovir from oral valganciclovir tablets (~60%) is up to 10 times greater than the bioavalability of oral ganciclovir capsules (6-9%). In a population pharmacokinetic study of ganciclovir in solid organ transplant recipients, the mean systemic exposure to ganciclovir was ~1.7 times higher after oral administration of 900 mg q.d. valganciclovir compared with ganciclovir systemic exposure after oral administration of 1 gram t.i.d. ganciclovir. In liver transplant patients 900 mg of valganciclovir provides comparable exposures to 5 mg/kg of IV ganciclovir, and a 450 mg dose of oral valganciclovir provides comparable ganciclovir exposures to the 1000 mg t.i.d. dose of ganciclovir. Based on the results of a phase 3 non-inferiority study comparing valganciclovir to oral ganciclovir, oral

valganciclovir (900 mg once daily) was approved by FDA for the prevention of CMV disease in kidney, heart, and kidney-pancreas transplant patients at high risk for developing CMV disease.

Of note, none of these drugs (IV ganciclovir, oral ganciclovir, or oral valganciclovir) is approved for use in pediatric patients.

Congenital CMV infection:
The incidence of congenital CMV infection ranges from 0.2% to 2.2% of live births worldwide. In the United States, it is estimated that approximately 40,000 infants are born each year with congenital CMV infection (Stagno S, Britt W. Cytomegalovirus infections. In Remington JS, Klein JO, Wilson CB, Baker CJ, eds. Infectious Diseases of the fetus and newborn infant. 6th ed. Philadelphia: Elsevier-Saunders, 2006:739-772). Approximately 10% of infected newborns are symptomatic at birth. Mortality in these infants is about 12% and approximately 90% of symptomatic survivors experience significant morbidity from the infection. Survivors can have mental retardation, sensorineural hearing loss, microcephaly, seizures, and other medical problems (Boppana SB et al. Symptomatic congenital cytomegalovirus infection: neonatal morbidity and mortality. Pediatr Infect Dis J 1992;11:93-99). Children with asymptomatic congenital CMV infection rarely have neurologic sequelae and their long-term outcome is much better. However, about 10-15% of these asymptomatic infants are at risk for developing neurologic sequelae such as sensorineural hearing loss, microcephaly, motor defects, mental retardation, and other abnormalities.

Currently, no drugs are approved for antiviral therapy of congenital CMV infection. However, results from a recent clinical trial suggest ganciclovir (b) (4) (b) (4) (Kimberlin DW et al. J Pediatr 2003;143:17-26). This was a randomized, non-blinded controlled trial of ganciclovir for newborns with symptomatic congenital CMV disease involving the CNS. The trial was sponsored by the NIH-NIAID Collaborative Antiviral Study Group (CASG) and enrolled 100 newborns. Enrolled newborns were assigned to receive either IV ganciclovir 6 mg/kg bid for 6 weeks or no treatment. The primary endpoint was brainstem-evoked response (BSER) audiometry improvement by one gradation (e.g., from severe to moderate) between baseline and the 6-month follow-up or retained normal hearing. The major secondary endpoints included evidence of laboratory (thrombocytopenia, hepatitis) and clinical (organomegaly, chorioretinitis) improvement and growth rate. Treated subjects had a greater incidence of improved hearing or maintenance of normal hearing at 6 months of age and lack of hearing deterioration at 6 months and 1 year as compared to untreated subjects. Between the two groups no statistically significant difference was observed in the time to resolution of organomegaly, CMV retinitis, thrombocytopenia or hyperbilirubinemia. Median weight gain and median increase in head circumference between baseline and 6 weeks were higher in the ganciclovir treatment group. These differences were not sustained at the 6 month follow-up. Almost two thirds of ganciclovir-treated patients developed severe neutropenia. Fourteen of the 29 patients with neutropenia required dose modification and two patients received granulocyte colony-stimulating factor. One newborn developed gram-negative sepsis.

Several deficiencies were noted in this study. Less than half of the patients (42/100) had evaluable data at both entry and 6 months raising the possibility of follow-up bias that could influence the results of the trial. Moreover, non-evaluable ganciclovir recipients were more likely to be black and premature compared to the non-evaluable infants in the non-treatment group. Considering these deficiencies, the adverse events related to this drug, including potential long-term gonadal toxicity and carcinogenicity, some investigators raised questions on the impact of study's findings on hearing (Demmler GJ. Congenital cytomegalovirus infection treatment. Pediatr Infect Dis J 2003; 22:1005-6). The Committee on Infectious Diseases of the American Academy of Pediatrics states the following in the 2006 edition of the Red Book, "One study of ganciclovir therapy of congenitally infected newborn infants with central nervous system disease suggested that treatment decreases progression of hearing impairment. However, because of the potential toxicity of long-term ganciclovir therapy, additional study is necessary before a recommendation can be made" (Red book 2006. Report on the Committee on Infectious Diseases, 27th Edition. Pickering LK, ed. American Academy of Pediatrics; 2006).

2.3 Availability of Proposed Active Ingredient in the United States

Valcyte is available in the United States as a 450 mg pink convex oval tablet with "VGC" on one side and "450" on the other side. 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. Valcyte is supplied in bottles of 60 tablets.

2.4 Presubmission Regulatory Activity

March 2001: Valcyte was approved by FDA for the treatment of CMV retinitis in patients with AIDS.

June 2001: To obtain needed pediatric information on ganciclovir and valganciclovir, the FDA issued a formal Written Request, pursuant to Section 505A of the Federal Food, Drug and Cosmetic Act, to submit information from the following four pediatric studies. Final study reports were to be submitted to the Agency on or before January 1, 2004.

Study 1: Single-dose, open-label, dose-escalation pharmacokinetic and safety study of valganciclovir in pediatric renal transplant recipients.

Study 2: Single-dose, open-label, non-comparative pharmacokinetic and safety study of valganciclovir in pediatric liver transplant recipients.

Study 3: Multicenter, open-label, single-dose, non-comparative safety and pharmacokinetic study in pediatric patients with solid organ transplants.

Study 4: Single-dose and multiple-dose pharmacokinetic and tolerability study of valganciclovir liquid formulation in a neonatal population with congenital CMV disease.

November 2001: The Pediatric Written Request was amended to change the number of patients required and to modify the statistical assessments for Study 1, to add requirements for labeling and format of reports, and to extend the timeframe for submitting all clinical study reports to December 31, 2004. The modified studies read as follows:

Study 1: An open-label, dose-escalation pharmacokinetic and safety study of valganciclovir in pediatric renal transplant recipients.

Study 2: An open-label, non-comparative pharmacokinetic and safety study of valganciclovir in pediatric liver transplant recipients.

Study 3: Multicenter, open-label, single-dose, non-comparative safety and pharmacokinetic study in pediatric patients with solid organ transplants.

Study 4: Single-dose and multiple-dose pharmacokinetic and tolerability study of valganciclovir liquid formulation in a neonatal population with congenital CMV disease.

December 2004: The Pediatric Written Request was amended to extend the timeframe for submitting all clinical study reports to December 31, 2007.

June 2007: The Pediatric Written Request was amended to modify the pharmacokinetic study endpoints of Studies 2 and 3, to change the title of Study 2, and to extend the timeframe for submitting all clinical study reports to March 31, 2008. The modified Study 2 reads as follows:

Study 2: An open-label, comparative pharmacokinetic and safety study of valganciclovir in pediatric liver transplant recipients.

March 2008: The Pediatric Written Request was amended to extend the timeframe for submitting all clinical study reports to December 31, 2008.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 Chemistry Manufacturing and Control

As part of the Pediatric Written Request, the Sponsor was asked to develop a commercially marketable age-appropriate formulation for children. The Sponsor's attempts were successful

and the product proposed for marketing is a powder reconstituted with purified water to provide an oral solution.

The new oral solution was evaluated in a bioequivalence study (WP16302; see Subsection 5.2) comparing ganciclovir pharmacokinetics from the valganciclovir oral solution formulation to the commercial Valcyte tablets 450 mg formulation administered as a dose of 900 mg to kidney transplant patients. It was established that the oral solution formulation is bioequivalent with respect to ganciclovir $AUC_{0\text{-}24h}$ and C_{max} to the marketed 450 mg tablet formulation.

The Valcyte for oral solution is a conventional granulate formulation of white to slightly yellow powder containing standard excipients and manufactured using conventional methods. The drug product is packaged in a (b) (4) glass bottle containing (b) (4) dried powder (5 gram drug substance). Prior to dispensing to the patient, Valcyte for oral solution must be prepared by the pharmacist in 91 mL of purified water to make 100 mL of 50 mg/mL oral solution. The preparation is as follows:

- Measure 91 mL of purified water in a graduated cylinder.
- Shake the Valcyte bottle to loosen the powder. Remove the child resistant bottle cap and add approximately half the total amount of water for constitution to the bottle and shake the closed bottle well for about 1 minute. Add the remainder of water and shake the closed bottle well for about 1 minute. This prepared solution contains 50 mg of valganciclovir free base per 1 mL.
- Remove the child resistant bottle cap and push the bottle adapter into the neck of the bottle.
- Close bottle with child resistant bottle cap tightly. This will assure the proper seating of the bottle adapter in the bottle and child resistant status of the cap.
- Store constituted oral solution under refrigeration at 2°C to 8°C (36°F to 46°F) for no longer than 49 days. Do not freeze.
- Write the date of expiration of the constituted oral solution on the bottle label.

For further details regarding the chemistry and manufacturing of the Valcyte for oral solution please refer to the review by Ted Chang, Ph.D., the Chemistry reviewer.

3.2 Animal Pharmacology/Toxicology

No new animal pharmacology and toxicology data were submitted with this NDA. Please refer to the original approval of Valcyte (NDA 21-304) for background information.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

This review is primarily based on data from four studies (WP16303, WP16296, WV16726, and CASG109), conducted in response to the final amended Pediatric Written Request, to support

dosing recommendations for the prevention of CMV disease in pediatric solid organ transplant recipients and the treatment of neonates and infants with congenital CMV infection.

In addition, pharmacokinetic and safety data from Study WP16302 were reviewed. This was a bioequivalence study comparing ganciclovir pharmacokinetcs from the new valganciclovir for oral solution formulation to the commercial Valcyte tablets 450 mg formulation at a dose of 900 mg.

4.2 Data Quality and Integrity

The Good Clinical Practice Branch, Division of Scientific Investigations, FDA, conducted clinical inspections of three study sites in the United States that enrolled a relatively large number of subjects for Study WV16726 and Study CASG109: UCLA Medical Center, Los Angeles, CA (Dr. Robert Ettinger) and Washington University School of Medicine, St. Louis, MO (Dr. S. Paul Hmiel) for Study WV16726; UT Southwestern Medical Center, Dallas TX (Dr. Pablo Sanchez) for Study CASG109. No major deficiencies were identified in the three inspected sites that would compromise the integrity of the studies. For more details, please see Clinical Inspection Summary by Antoine El-Hage, Ph.D.

At the request of the Division of Antiviral Drugs and Products, the Division of Scientific Investigations also audited the pharmacokinetic and analytical portions of Studies WP16302, WV16726, and CASG109. The following studies were audited: Indiana University Medical Center, surgery and Microbiology/Immunology, Indianapolis, IN for Study WP16302; UCLA center for Health Sciences, Division of Pediatric Nephrology, Los Angeles, CA for study WP16726; and University of Texas Southwestern Medical Center, Department of Pediatrics, Dallas, TX for Study CASG109. The analytical portion of the studies was inspected at (b) (4) (b) (4) The inspection of the above sites revealed several serious deficiencies. The most important ones are as follows:

Study WP16302: The clinical site failed to retain the reserve samples from this study. The retention of the reserve samples is required as per 21 CFR 320.38 and is critical for assuring the authenticity of the test and reference products used in this study.

Inspection at (b) (4):

- Inconsistency in integration of chromatograms
- Storage stability cannot assured

Based on the findings from the analytical inspection, the concentration data for Studies WP16302, WP16726, and CASG109 are not accurate and not acceptable as submitted in the NDA. For more details, please see Inspection Summary by C.T. Viswanathan, Ph.D.

4.3 Compliance with Good Clinical Practices

The Applicant states the studies were conducted according to accepted ethical standards based on the precepts established by the declaration of Helsinki. All studies were conducted with the approval of Ethics Committees or Institutional Review Boards and informed consent was obtained from all subjects.

4.4 Financial Disclosures

In compliance with the rule of Financial Disclosure by Clinical Investigators the Applicant provided financial interest information for clinical investigators participating in studies WP16302, WP16303, WP16296, WV16726, and CASG109. Based on available financial data, the $25,000 threshold was exceeded by (b) (4)

(b) (4) participated in the following studies:

Study WP16302: He served as the Principle Investigator for the study center (b) (4). He received payments exceeding the $25,000 threshold from Roche towards grants and honoraria in his position at the (b) (4)

Study WP16302 is a multicenter, open-label, randomized, 3-way cross-over bioequivalence study comparing ganciclovir exposure from the valganciclovir oral solution and the commercial valganciclovir 450 mg tablet at a dose of 900 mg in kidney transplant recipients. (b) (4) site enrolled (b) (4) of the 23 subjects enrolled in this study. This site is not expected to potentially bias the outcome of the study because the objectives of the study (primary and secondary pharmacokinetic parameters) are non-subjective. Moreover, the results of this study were consistent with the results observed at other study sites.

Study WP16303: He served as the Principle Investigator for the study center (b) (4). He received payments exceeding the $25,000 threshold from Roche towards consulting fees and honoraria in his position at the (b) (4)

Study WP16303 is a multicenter, open-label, non-comparative study to investigate the pharmacokinetics and safety of IV ganciclovir and valganciclovir oral solution in pediatric liver transplant recipients. (b) (4) site enrolled (b) of the 20 subjects enrolled in this study. This site is not expected to potentially bias the outcome of the study because the objectives of the study (primary and secondary pharmacokinetic parameters) are non-subjective. Moreover, the results of this study were consistent with the results observed at the other two study sites and for the overall outcome of the study.

Study WP16296: He served as the Principle Investigator for the study center (b) (4) He received payments exceeding the $25,000 threshold from Roche towards consulting fees and honoraria in his position at the (b) (4)

Study WP16296 is a multicenter, open-label pharmacokinetic and safety study to investigate the pharmacokinetics and safety of IV ganciclovir and valganciclovir oral solution in pediatric kidney transplant recipients. There were six participating centers and a total of 26 patients were enrolled in this study (b) (4) site enrolled (b) (4) of the 26 subjects in Study WP16296. This site is not expected to potentially bias the outcome of the study because the objectives of the study (primary and secondary pharmacokinetic parameters) are non-subjective. The results of the patients enrolled in this site were consistent with the results observed at the other five study sites and with the overall outcome of the study.

Study WP16726 (b) (4) served as the Principle Investigator for the study center (b) (4) He received payments exceeding the $25,000 threshold from Roche towards consulting fees and study investigator payment in his position at the Indiana (b) (4)

Study WP16726 is a multicenter, open-label, single-dose, non-comparative pharmacokinetic, safety, and efficacy study of the valganciclovir oral solution in pediatric solid organ transplant recipients. There were 18 participating centers and a total of 63 patients were enrolled in this study. (b) (4) site enrolled (b) (4) in Study WP16726. This site is not expected to potentially bias the outcome of the study.

(b) (4), sub-investigator of (b) (4) participated in Studies WP16303 and WP16296. He received payments exceeding the $25,000 threshold from Roche towards an investigator initiated research support in his position at the (b) (4)

5 REVIEW OF CLINICAL STUDIES

5.1 Review Methods

The clinical review is focused on the pharmacokinetic and safety data from four pediatric studies conducted in response to the Pediatric Written Request and on the pharmacokinetic and safety data from one bioequivalence study conducted in adult kidney transplant recipients. The Applicant's conclusions regarding safety (and efficacy when indicated) were confirmed by independent analyses of data. The Medical Officer reviewed study design, patient demographics, adverse events and laboratory abnormalities, pharmacokinetic data and efficacy data when indicated. The safety data were evaluated either with the use of JMP Statistical Discovery software or manually. In this review, tables derived from the Applicant's presentation of the data are cited as to source in the table footnotes, while tables derived from review-generated results are not referenced.

Overview of materials consulted in review: The safety and pharmacokinetic data from all studies were submitted electronically following the common technical document format.

Please also refer to Dr. Vikram Arya's and Dr. Kevin Krudys's reviews for more detailed information on the pharmacokinetic data submitted with this NDA.

5.2 Study design, Pharmacokinetics, Efficacy, Safety, and Conclusions

Study WP16302: A bioequivalence study comparing ganciclovir from the valganciclovir oral solution formulation and the commercial valganciclovir tablet (Valcyte®) at a dose of 900 mg in kidney transplant recipients

This is an open-label, randomized, three-way, crossover, bioequivalence study designed to determine the relative bioavailability of ganciclovir from the valganciclovir oral solution and the commercial Valcyte 450 mg tablet when given as a dose of 900 mg in kidney transplant recipients. The primary objective of the study was to determine the relative bioavailability of ganciclovir from the valganciclovir tutti-frutti oral solution and the 450 mg tablet formulation at a dose of 900 mg administered in the fed state. The secondary objective was to compare the systemic exposure to ganciclovir from the valganciclovir strawberry oral solution with the valganciclovir tutti-frutti oral solution at a dose of 900 mg.

The study was conducted at four centers in the United States and one center in New Zealand. Twenty-three adult subjects who had their first or second kidney transplant, had stable renal function (estimated creatinine clearance ≥ 60 mL/min) and were at risk for developing CMV disease (including all transplant patients except those who were D-/R-) were eligible for enrollment. Eligible subjects had been receiving CMV prophylaxis with Valcyte (900 mg once daily) prior to enrollment.

After pre-dose assessments on Day 1, the patients were randomized to one of three treatment sequences (ABC, BCA, and CAB). Study drug (either two 450 mg tablets q.d. or 900 mg [18 mL] of valganciclovir oral solution q.d.) was administered within 15 minutes of completing breakfast. Each patient received all the three treatments (treatment A, treatment B, and treatment C):

Treatment A: Once daily oral dosing (900 mg) with the 450 mg tablet formulation (2 X 450 mg once a day) for 2 days.

Treatment B: Once daily oral dosing (18 mL of 50 mg/mL; administered via a syringe) with the valganciclovir tutti-frutti flavored oral formulation for 2 days.

Treatment C: Once daily oral dosing (18 mL of 50 mg/mL; administered via a syringe) with the valganciclovir strawberry flavored oral solution for 2 days.

Follow-up was 7-14 days after the last dose of study drug.

On Days 2-7 blood samples were obtained to determine trough levels of ganciclovir. Blood samples were obtained up to 24 hours post dose (at 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 24 hours) to determine the plasma concentrations of ganciclovir on Days 2, 4, and 6. Laboratory samples for safety assessment were obtained at Screening, on Day 1 before dosing, on Day 7, and at safety review visit.

All patients completed the study and received two doses each of Valcyte tablets, strawberry and tutti-frutti oral solutions. However, complete pharmacokinetic data were available for 21 of the 23 enrolled subjects. All patients were included in the safety analysis.

Comment: (b) (4)

(b) (4)

Dose rationale: The standard dose of valganciclovir for CMV prophylaxis in solid organ transplant recipients is 900 mg once daily. However, the dose of valganciclovir is reduced in patients with renal impairment. Limiting enrollment to only those patients with CrCl ≥ 60mL/min avoided dose modifications during the clinical trial.

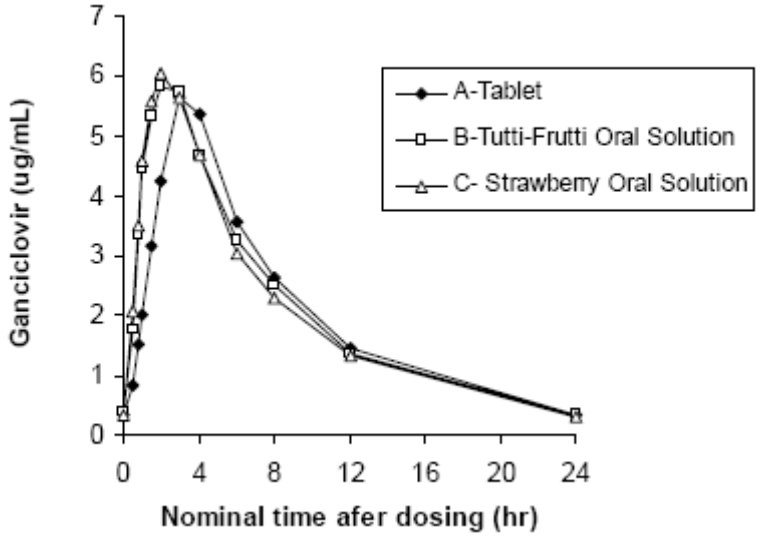
Baseline characteristics and disposition of patients:

Of the 23 subjects enrolled in this study, 12 (52%) were male and 11 (48%) were female. Fifteen (65%) subjects were white, 5 (22%) black, and the remaining 3 (13%) of other race. The mean age of the enrolled subjects was 44.2 ± 12.04 years (range 24 to 68 years). The most common reasons for transplant were focal segmented glomerulosclerosis (6, 26%) and polycystic kidney disease (5, 22%).

Pharmacokinetic results:
As previously stated, pharmacokinetic data were available from 21 of the 23 enrolled subjects. The two patients were excluded from the pharmacokinetic analysis (but included in the safety analysis) for the following reasons: One patient was excluded because the time of sample collection could not be verified due to conflicting data recorded in the source documentation and CRF across all treatments. For the other patient, the blood samples were collected in lithium heparin tubes instead of the tubes containing EDTA and were therefore excluded from the analysis.

Figure 1 shows the mean plasma concentration-time profile of ganciclovir after administration of the tablet, tutti-frutti flavored powder for oral solution formulation, and strawberry flavored powder for oral solution formulation.

Fig 1: Mean plasma concentration-time profile of ganciclovir after administration of the tablet, tutti-frutti flavored powder for oral solution formulation, and strawberry flavored powder for oral solution formulation



Source: CSR Vol. 7 – Study WP16302, p. 35

Comment: The mean concentration-time profiles were comparable for all 3 treatments.

Pharmacokinetic parameters for ganciclovir after administration of the 3 treatments is displayed in Table 1.

Table 1. Summary of the pharmacokinetic parameters for ganciclovir after administration of the three treatments

Treatment A - Tablet (n=21)[a]	**T_{max} (h)**	**C_{max} (µg/mL)**	**$C_{min,ss}$ (pre-dose) (µg/mL)**	**$C_{min,ss}$ (post-dose) (µg/mL)**	**$t_{1/2}$ (h)**	**AUC_{0-24h} (µg.h/mL)**
N	21	21	21	21	21	21
Mean (SD)	-	6.90 (1.49)	0.427 (0.244)	0.425 (0.234)	5.71 (1.40)	52.2 (10.0)
Min	1.00	4.08	0.0771	0.0766	3.04	33.1
Median	3.00	7.03	0.411	0.430	5.74	54
Max	4.00	9.43	0.991	0.927	8.92	65.1
Geometric Mean	-	6.73	0.346	0.352	5.55	51.2
Treatment B - Tutti-Frutti Oral Solution (n=21)[a]	**T_{max} (h)**	**C_{max} (µg/mL)**	**$C_{min,ss}$ (pre-dose) (µg/mL)**	**$C_{min,ss}$ (post-dose) (µg/mL)**	**$t_{1/2}$ (h)**	**AUC_{0-24h} (µg.h/mL)**
N	21	21	21[b]	21[b]	21	21
Mean (SD)	-	6.60 (1.8)	0.51 (0.418)	0.394 (0.23)	5.67 (1.34)	52.3 (10.3)
Min	1.00	3.90	0.0993	0.0844	3.28	35.4
Median	2.00	6.17	0.436	0.41	5.75	52.5
Max	6.03	10.8	2.01	0.944	8.58	72.2
Geometric Mean	-	6.39	0.391	0.327	5.51	51.2
Treatment C - Strawberry Oral Solution (n=21)[a]	**T_{max} (h)**	**C_{max} (µg/mL)**	**$C_{min,ss}$ (pre-dose) (µg/mL)**	**$C_{min,ss}$ (post-dose) (µg/mL)**	**$t_{1/2}$ (h)**	**AUC_{0-24h} (µg.h/mL)**
N	21	21	21[b]	21[b]	21	21
Mean (SD)	-	6.72 (1.85)	0.42 (0.247)	0.371 (0.21)	5.77 (1.50)	51.0 (10.2)
Min	0.75	4.64	0.0987	0.087	3.46	33.2
Median	2.00	5.97	0.372	0.365	5.86	53.7
Max	4.00	12.5	0.961	0.962	10.3	64.7
Geometric Mean	-	6.52	0.345	0.309	5.59	50.0

a. Two patients were excluded from the PK analysis.
b. One patient was excluded from the analysis of trough levels.

Source: CSR Vol. 13 – p. 34

Comments: The mean C_{max} and AUC_{0-24} of ganciclovir observed in this trial after administration of the tablet formulation (6.9 µg/mL and 52.2 µg*hr/mL) is similar to the range of mean C_{max} and AUC_{0-24} of ganciclovir observed in a previous pivotal clinical trial PV16000 (the mean C_{max} ranged from 4.9 to 5.4 µg/mL and AUC_{0-24hr} ranged from 40.2 to 48.2 µg*hr/mL) that established the efficacy of valganciclovir for prophylaxis in solid organ transplant recipients. This suggests that the systemic exposure observed in the reference treatment in this study is a valid comparator to use for comparing the systemic exposure after administration of the tutti-frutti powder for oral solution formulation.

Ganciclovir systemic exposures (AUC_{0-24} and C_{max}) were comparable across all treatments.

Table 2 shows the statistical analysis of the pharmacokinetic parameters computed after administration of the tablet formulation and the tutti-frutti-flavored powder for oral solution formulation.

Table 2: Statistical analysis of the pharmacokinetic parameters computed after administration of the tablet formulation and the tutti-frutti flavored powder for oral solution formulation.

			Mean Effect Ratio (Test / Reference)		
Variable	**Treatment**	**Estimate**	**Estimate (%)**	**90% Confidence Region (%)**	**Conclusion**
AUC_{0-24h}	A	51.57	100	Reference	
	B	51.52	100	[96, 104]	Equivalence
C_{max}	A	6.748	100	Reference	
	B	6.381	95	[89, 101]	Equivalence
Equivalence Region (%):				[80, 125]	

Treatment A: valganciclovir tablet formulation (reference formulation)
Treatment B: valganciclovir tutti-frutti flavored powder for oral solution formulation (test formulation).
Source: CSR Vol. 13 – p. 36

Comment: The tutti-frutti oral solution and the marketed tablet formulation are bioequivalent.

Table 3 shows the statistical analysis of the pharmacokinetic parameters computed after administration of the strawberry flavored powder for oral solution formulation and the tutti-frutti flavored powder for oral solution formulation.

Table 3: Statistical analysis of the pharmacokinetic parameters computed after administration of the strawberry flavored powder for oral solution formulation and the tutti-frutti flavored powder for oral solution formulation.

			Mean Effect Ratio (Test / Reference)	
Variable	**Treatment**	**Estimate**	**Estimate (%)**	**90% Confidence Region (%)**
AUC_{0-24h}	B	51.52	100	Reference
	C	50.28	98	[94, 101]
C_{max}	B	6.381	100	Reference
	C	6.544	103	[96, 109]

Treatment B: valganciclovir tutti-frutti flavored powder for oral solution formulation (reference formulation).
Treatment C: valganciclovir strawberry flavored powder for oral solution formulation (test formulation)
Source: CSR Vol. 13 – p. 37

Comment: The valganciclovir tutti-frutti oral solution and the vaganciclovir strawberry oral solution are bioequivalent.

Efficacy results:

Efficacy data were not obtained in this study.

Safety results:

Adverse events: All three formulations were well tolerated with no observed difference in the incidence of adverse events (AEs) among the three formulations. Most of the AEs were mild in intensity and only two patients experienced three AEs of moderate intensity (alopecia, insomnia, and hypertension).

Three patients experienced AEs of mild intensity considered by the investigator as possibly related to study drugs. Two patients in the strawberry oral solution arm (flatulence 1, headache 1), and one patient in the valganciclovir tablet arm (headache).

There were no deaths, SAEs, ar AEs leading to withdrawal during the study.

Laboratory abnormalities: The incidence of marked laboratory abnormalities was low and included low WBCs (1 patient), low lymphocytes (3 patients), high WBCs (1 patient) low neutrophils (1 patient) high creatinine (1 patient), high fasting glucose (2 patients), low phosphate (3 patients), glucosuria (3 patients), and hematuria (4 patients). There were no Grade 4 laboratory abnormalities and only two Grade 3 laboratory abnormalities (the two patients with high fasting glucose).

Conclusions:

Ganciclovir systemic exposure after administration of 900 mg (18 mL) valganciclovir tutti-frutti flavored oral solution formulation (50 mg/mL) was similar to ganciclovir systemic exposure after administration of 900 mg (2 X 450 mg) valganciclovir tablets.

Ganciclovir systemic exposure after administration of 900 mg (18 mL) valganciclovir strawberry flavored powder for oral solution formulation (50 mg/mL) was similar to ganciclovir systemic exposure after administration of 900 mg (18 mL) valganciclovir tutti-frutti flavored powder for oral solution.

Note: *After completing the review, the Division received on October 24, 2008, the report by the Division of Scientific Investigations stating the clinical site failed to retain the reserve samples from Study WP16302, the pivotal bioequivalence study. The retention of the reserve samples is required as per 21 CFR 320.38 and is critical for assuring the authenticity of the test and reference products used in the pivotal bioequivalence study. As the authenticity of the test and reference products cannot be confirmed, the data from the bioequivalence study cannot be used* [redacted] **(b) (4)**

Study WP16296: **The pharmacokinetics and tolerability of IV ganciclovir and oral valganciclovir syrup formulation in pediatric renal transplant recipients**

This is an open-label, pharmacokinetic and tolerability study of IV ganciclovir and oral valganciclovir syrup formulation in pediatric renal transplant patients conducted at six centers in the United States. Twenty-six subjects between the ages of 3 months and 16 years who had received their first kidney transplant, had stable renal function, and were at risk for developing CMV disease (including all transplant patients except those who were D-/R-) were eligible for enrollment.

Following renal transplantation, patients received anti-CMV prophylaxis according to local protocol. After stabilization of renal function, patients received a once daily dose of IV ganciclovir on Days 1 and 2 at a dose equivalent to the adult dose of 5 mg/kg (adjusted for BSA and renal function). On Day 3, patients received a single oral dose of valganciclovir syrup formulation projected to be equivalent to half the adult dose of valganciclovir tablets (450 mg, adjusted for BSA and renal function). On dosing Day 4, patients received a single dose of oral valganciclovir syrup formulation projected to be equivalent to the full adult dose of valganciclovir tablets (900 mg, adjusted for BSA and renal function). Doses of oral valganciclovir were taken within minutes of finishing a breakfast meal. After completion of this study, patients continued their usual anti-CMV prophylaxis treatment at their centers.

Blood samples for pharmacokinetic analysis were obtained on Day 2 before dosing and at 1 h (immediately before end of infusion), 2-3 h, 5-7 h, and 10-12 h after infusion. On Day 3 and Day 4, blood samples for pharmacokinetic analyses were obtained at pre-dose, 0.25-0.75 h, 1-3 h, 5-7 h, and 10-12 h. On Day 4, an additional blood sample was obtained at 22-24 hrs after dosing. Optional pharmacokinetic blood samples were taken 34-36 h and 46-50 h post-dose on dosing

Day 4. Laboratory samples for safety assessment were obtained at Screening, on Day 1 before dosing, on the day of last pharmacokinetic sample and at safety review visit performed 28 days after the cessation of study drug.

A total of 26 subjects between the ages of 3 months and 16 years were enrolled in this study. The age distribution of the enrolled subjects was as follows:
≤ 6 years of age: 6 subjects (pharmacokinetic data from 5)
> 6 years of age (but prepubescent): 19 subjects (pharmacokinetic data from 19)
16 years of age and pubescent: 1 subject (pharmacokinetic data from 1)

Pharmacokinetic and safety data were reviewed during two interim analyses to ensure patients are not overexposed to ganciclovir from either IV ganciclovir or oral valganciclovir. The first interim analysis was performed when eight patients had completed treatment and the second when 18 patients had completed treatment in this study and eight patients had completed treatment in a pediatric liver transplant study (Study WP16303).

Complete pharmacokinetic data are available from 25 of the 26 enrolled subjects. One patient withdrew from the study after receiving the two doses of IV ganciclovir. Data from this patient were included in the safety analyses but excluded from the pharmacokinetic analyses.

Dose rationale:

Doses of IV ganciclovir and valganciclovir oral solution formulation were calculated using BSA for adjusting adult doses to pediatric doses. Pediatric doses of IV ganciclovir and valganciclovir oral solution were projected to provide ganciclovir systemic exposures similar to those obtained in adults after 5 mg/kg of IV ganciclovir and 900 mg of oral valganciclovir adjusted for child's BSA and creatinine clearance. The targeted ganciclovir systemic exposure was $AUC_{0\text{-}24}$ = 40–60 mg.h/L and was based on analysis of data from an adult study in solid organ transplant recipients treated with the approved valganciclovir dose of 900 mg once daily (Study PV1600). Ganciclovir exposures < 40 mg.h/L were predicted to have an unacceptable rate of CMV viremia, whereas exposures > 60 mg.h/L were predicted to have an unacceptable rate of neutropenia and leukopenia.

The pediatric dose is shown below:

$$\text{Pediatric Dose} = \text{BSA } (m^2) \times \text{Normalized Dose } (mg/m^2)$$

where,

$$BSA(m^2) = \sqrt{\frac{height(cm) \times weight(kg)}{3600}}$$

The normalized dose for IV ganciclovir was 200 mg/m^2 and was calculated based on a standard adult dose of 5 mg/kg in an adult of 70 kg and a BSA of 1.73^2 (i.e., 5 mg/kg x 70 kg [adult BW] ÷ 1.73^2 [adult BSA] = 200 mg/m^2).

The normalized dose for oral administration was 520 mg/m^2 and was calculated using the 900 mg as the reference dose (i.e., 900 mg ÷ 1.73^2 [adult BSA] = 520 mg/ m^2).

The pediatric doses were further adjusted for creatinine clearance (calculated with the Schwartz formula) according to Table 4.

Table 4. Dose adjustment based on creatinine clearance.

Estimated CrCL (mL/min/1.73 m^2)	**Ganciclovir IV dose (mg)**	**Valganciclovir p.o. dose (mg)**
≥ 70	Full dose	Full dose
50 - 69	Full dose	Full dose
40 – 49	25% of full dose	25% of full dose

Baseline characteristics and disposition of patients:

Of the 26 subjects enrolled in this study, 17 (65%) were male and 9 (35%) were female. Thirteen (50%) subjects were white, 5 (19%) were black, and the remaining 8 (31%) of other race. The ethnicity breakdown was not recorded in this study.

The mean age of the enrolled subjects was 10.6 ± 4.5 years (range 1 to 16 years). The majority of the enrolled subjects were D+/R+ for CMV disease. Two subjects were CMV D-/R- but were enrolled in the study because at this center all patients are considered at risk for CMV disease. The CMV serologic status of both donors and recipients was as follows: D+/R+: 16 subjects (62%), D+/R-: 6 subjects (23%), D-/R+: 2 subjects (8%), and D-R-: 2 subjects (8%).

All enrolled subjects had adequate renal function with a creatinine clearance of at least 45 mL/min/1.73 m^2 (mean 109.9 mL/min/1.73 m^2, range 45.5-232.9 mL/min/1.73 m^2). The primary reasons for kidney transplant were diverse; however, the most common reason was renal dysplasia, counting for almost 40% of the cases.

Pharmacokinetic results:

A summary of the pharmacokinetic parameters by age group is displayed in Table 5. The

AUC_{0-24} and C_{max} were calculated under steady state conditions for the nominal dose of 200 mg/m^2 IV ganciclovir and the higher nominal dose of 520 mg/m^2 of valganciclovir.

Table 5. Summary of pharmacokinetic results by age group in Study WP16296.

PK Parameter	Age Group	Arith Mean	CV [%]	Geom. Mean	Median	Min	Max
AUC_{0-24} (mg.h/L) i.v. ganciclovir (200 mg/m^2)	0-5	22.15	20	21.82	22.18	17.13	27.1
	6-11	34.43	37	32.89	37.86	15.78	43.59
	12-16	41.57	38	38.98	38.58	21.01	89.29
AUC_{0-24} (mg.h/L) valganciclovir (520 mg/m^2)	0-5	21.28	19	21.02	22.22	16.15	24.52
	6-11	39.54	49	36.68	43.78	14.45	55.07
	12-16	41.61	32	39.75	39.88	20.95	70.64
C_{max} (mg/mL) i.v. ganciclovir (200 mg/m^2)	0-5	10.46	12	10.40	10.19	9.17	12.29
	6-11	9.07	17	8.97	9.03	6.79	11.28
	12-16	9.99	43	9.21	9.40	3.51	25.26
C_{max} (mg/mL) valganciclovir (520 mg/m^2)	0-5	5.72	32	5.51	5.10	4.20	8.50
	6-11	5.94	37	5.64	6.01	3.37	9.08
	12-16	5.32	21	5.22	5.40	3.56	7.92
$t_{½}$ term (h)	0-5	3.71	57	3.33	3.28	1.97	6.31
	6-11	6.28	52	5.64	4.41	3.06	12.77
	12-16	7.29	52	6.25	5.62	3.32	27.04

Source: CSR Vol. 13 – p. 42

The bioavailability of ganciclovir from valganciclovir oral solution was estimated at 53% with a 95% confidence interval of 40 to 80%, similar to the value predicted in adults.

Comments: Ganciclovir systemic exposures after IV ganciclovir were similar to ganciclovir systemic exposures after valganciclovir oral solution across all age groups.

Average ganciclovir systemic exposures in children ≤ 5 years of age were significantly lower than the targeted historical adult exposures resulting from a valganciclovir dosing 900 mg once daily (targeted AUC_{0-24} = 40-60 mg.h/L). Even for the age groups 6-11 and 12-16 years of age, the ganciclovir exposures were at the lower levels of the target AUCs.

Efficacy results:

Efficacy data were not obtained in this study.

Safety results:

As previously stated, 25 of the 26 subjects enrolled in the study received the complete course of study treatment. This includes a single dose of IV ganciclovir equivalent to the adult dose of 5 mg/kg on Days 1 and 2, a single dose of valganciclovir oral solution equivalent to half the adult dose of valganciclovir (450 mg) on Day 3, and a single dose valganciclovir oral solution equivalent to the full adult dose of valganciclovir (900 mg) on Day 4. The remaining patient received the first two doses of IV ganciclovir on Days 1 and 2 but not the doses of oral valganciclovir on Days 3 and 4.

Adverse events: All safety events were reported as events occurred either "on treatment" or "off treatment". Events occurred "on treatment" refer to those that occurred while the patients were taking study medication and are divided to those occurred while patients were receiving IV

ganciclovir or to those occurred while patients were receiving oral valganciclovir. The "off treatment" phase of the study refers to the follow-up period and could have been attributed to either study drug.

During the treatment phase of the study, a higher proportion of patients experienced at least one adverse event while receiving IV ganciclovir (13, 50%) compared with those receiving valganciclovir (8, 32%). The most common adverse events were diarrhea, nausea, and vomiting. The incidence of vomiting was higher during treatment with valganciclovir than during treatment with IV ganciclovir (12.0 % vs. 0%). The incidence of all other adverse events was comparable during treatment with both study medications. During the follow-up period (off treatment), the pattern of adverse events remained the same with gastrointestinal disorders being the most common.

Only four adverse events were considered by the investigator as severe (a case of sepsis during treatment with valganciclovir oral solution, and abdominal pain, vomiting, and wound dehiscence that occurred off treatment. The rest of the other events were considered by the investigators mild or moderate in severity

Three patients had adverse events considered by the investigators related to study drugs. These patients experienced four related adverse events (headache, nausea, and vomiting) during treatment with valganciclovir oral solution.

No deaths were reported during the study and no subject experienced adverse event leading to premature withdrawal from the study. Four patients experienced serious adverse events: one patient during treatment (sepsis); two patients during the follow-up period (lymphocele and transplant rejection 1, urinary tract infection 1); the fourth patient had two serious adverse events, one during treatment (deep vein thrombosis) and one during the follow-up period (wound dehiscense).

Laboratory abnormalities: There were 4 patients who exhibited a worsening of 2 grades and one patient with a worsening of 3 grades.

Worsening of 2 grades: elevated SGOT 1, elevated SGPT 1, elevated creatinine 1, and a decrease in hemoglobin levels 1.

Worsening of 3 grades: one patient with neutropenia. This is a 15-year-old male who underwent kidney transplantation for obstructive uropathy. On study Day 36 (follow-up period), the patient exhibited significant decrease in neutrophil count (from 6.1 x 10^9 cells/L at baseline to 0.7 x 10^9 cells/L on Day 36).

Comments: The overall safety profile of IV ganciclovir and oral valganciclovir was consistent with that obtained in adult solid organ transplant patients and there were no unexpected safety findings.

It should be noted that most of the patients enrolled in this study were taking ganciclovir (20 [77%]) or valganciclovir (2 [8%]) prior to study drugs as part of the local protocols and continued with these drugs after the last dose of study drug. Therefore, it is impossible to distinguish whether the adverse events are due to the anti-CMV medications administered prior and after study drugs or to the study drugs. Even for adverse events that occurred during Days 3 and 4, it is very

difficult to determine whether they are due to oral valganciclovir or to IV ganciclovir which was administered on Days 1 and 2 or to the anti-CMV drugs administered prior to study initiation.

Conclusions:

Pharmacokinetic results showed that ganciclovir exposures after IV ganciclovir were similar to ganciclovir exposures after valganciclovir oral formulation. However, ganciclovir exposures were lower than the mean exposures in adults receiving IV ganciclovir 5 mg/kg, particularly in children ≤ 5 years of age. Therefore, this BSA-based dosing algorithm cannot be used in children.

The IV ganciclovir and oral valganciclovir were tolerated in pediatric kidney transplant patients with an overall safety profile similar to that observed in adult solid organ transplant recipients.

Study WP 16303: **Safety and pharmacokinetics of IV ganciclovir and valganciclovir oral solution formulation in pediatric liver transplant recipients receiving treatment with IV ganciclovir for prevention of cytomegalovirus disease**

This is an open-label, pharmacokinetic and tolerability study of IV ganciclovir and valganciclovir oral solution formulation in pediatric liver transplant patients conducted at three centers in the United States. Twenty subjects between the ages of 3 months and 16 years who had received their first liver transplant, had stable renal function (estimated creatinine clearance > 45 mL/min/1.73 m^2), and were at risk for developing CMV or EBV disease (including all transplant patients except those who were D-/R- for CMV and EBV) were eligible for enrollment.

Enrolled subjects were treated with IV ganciclovir twice daily from enrollment (Day 1-4 post-transplant) to Day 12, and then with oral valganciclovir twice daily for Days 13 and 14. After completion of this study, patients continued their usual anti-CMV prophylaxis treatment at their centers. The doses of IV ganciclovir and valganciclovir oral solution were projected to produce a ganciclovir AUC equivalent to that of IV ganciclovir 5 mg/kg in an adult of 70 kg with a BSA of 1.73 m^2 (adjusted for BSA and renal function). Doses of oral valganciclovir were taken within minutes of finishing a breakfast meal. After completion of this study, patients continued their usual anti-CMV prophylaxis treatment at their centers.

Blood samples for pharmacokinetic analysis were obtained on Day 12 before dosing and at 1 h (immediately before end of infusion), 2-3 h, 5-7 h, and 10-12 h after infusion. On Day 14, blood samples for measurements of ganciclovir and valganciclovir concentrations were obtained at pre-dose, 0.25-0.75 h, 1-3 h, 5-7 h, and 10-12 h after dosing. Laboratory samples for safety assessment were obtained at Screening (Day 1-4 post-transplant), on Day 8, Day 13, during the follow-up examination which took place between 28-32 days post-transplant, and during the safety review visit which took place on Day 42 (± 4 days) post-transplant.

A total of 20 subjects between the ages of 3 months and 16 years were enrolled in this study. The age distribution of the enrolled subjects was as follows:

< 2 years of age: 9 subjects
≥ 2 years but < 6 years: 6 subjects
≥ 6 years but ≤ 16 years: 5 subjects

Sixteen of the 20 enrolled patients completed the study. Three patients withdrew from the study before receiving valganciclovir oral solution and one patient received valganciclovir oral solution for one day before being withdrawn from the study.

Dose rationale:

The dosing algorithm used in Study WP16303 was the same as in Study WP16296.

Baseline characteristics and disposition of patients:

Of the 20 subjects enrolled in this study, 11 (55%) were male and 9 (45%) were female. Eighteen (90%) subjects were white, and the remaining 2 (10%) were black. The ethnicity breakdown was not recorded in this study.

The mean age of the enrolled subjects was 4.0 ± 5.23 years (range 6 months to 16 years). The serology results of CMV and EBV status are shown in the following table. Three patients were both CMV and EBV D-/R- but were enrolled in the study because at these centers all patients are considered at risk for CMV or EBV disease (from blood transfusions) regardless of their CMV and EBV serologic status.

Table 6. Summary of CMV and EBV serology status

Serology status	**CMV (n=20)**	**EBV (n=20)**
D+/R+	4 (20%)	5 (25%)
D+/R-	6 (30%	6 (30%)
D-/R+	2 (10%)	2 (10%)
D-/R-	8 (40%)	6 (30%)
D (not done)/R+	-	1(5%)

All enrolled subjects had adequate renal function with a creatinine clearance of at least 45mL/min/1.73 m^2, except one patient who had a creatinine clearance 41.7mL/min/1.73 m^2 at baseline (mean 153.37 mL/min/1.73 m^2, range 41.7-357.8 mL/min/1.73 m^2). The most common

reasons for liver transplant were biliary atresia (9, 45%) and alpha-1 antitrypsin deficiency (3, 15%).

Pharmacokinetic results:

A summary of the pharmacokinetic parameters by age group is displayed in Table 7. The

AUC_{0-24} and C_{max} were calculated under steady state conditions for the nominal doses of 200 mg/m^2 IV ganciclovir and 520 mg/m^2 valganciclovir oral solution adjusted by Schwartz creatinine clearance.

Table 7. Summary of pharmacokinetic parameters by age group in Study WP16303: Median (min-max)

Pharmacokinetic parameter	Age group		
	0-5 years* (N=13)	**6-11 years (N=2)**	**12-16 years (N=3)**
AUC_{0-24h} (mg.h/L) IV ganciclovir (200 mg/m^2)	24.3 (14.1-38.9)	35.2 (27.1-43.2)	23.4 (19.2-25.8)
AUC_{0-24h} (mg.h/L) valganciclovir (520 mg/m^2)	23.4 (11.8-40.6)	46.8 (35.2-58.4)	25.8 (25-30.9)
C_{max} (mg/L) IV ganciclovir (200 mg/m^2)	12.2 (9.17-15)	9.29 (4.73-13.9)	11.8 (11.6-12.4)
C_{max} (mg/L) valganciclovir (520 mg/m^2)	5.51 (2.72-7.18)	5.29 (3.79-6.79)	6.9 (5.59-7.04)
t½ term (h)	1.65 (1.01-2.57)	6.8 (3.74-9.87)	4.35 (4.17-5.04)

*All children in 0-5 years group were < 3 years of old.
Source: CSR Vol. 9- p.45

The bioavailability of ganciclovir from valganciclovir oral solution was estimated at 55% with a 95% confidence interval of 48 to 62%, similar to the value predicted in adults.

Comments: Ganciclovir systemic exposures after IV ganciclovir were similar to ganciclovir systemic exposures after valganciclovir oral solution across all age groups.

Average ganciclovir systemic exposures in children ≤ 5 years of age and 12-16 years of age were significantly lower than the targeted historical adult exposures (targeted AUC_{0-24} = 40-60 mg.h/L).

Efficacy results:

Efficacy data were not obtained in this study.

Safety results:

Fourteen (14) of the 20 subjects enrolled in the study received the complete course of valganciclovir oral solution for 2 days. Three patients withdrew from the study before receiving valganciclovir oral solution; 1 patient received 3 doses of valganciclovir oral solution; 1 patient received 2 doses; and 1 patient received valganciclovir for 3 days.

Adverse events: All safety events were reported as events occurred either "on treatment" or "off treatment". Events occurred "on treatment" refer to those that occurred while the patients were taking study medication and are divided into those that occurred while patients were receiving IV ganciclovir or those that occurred while patients were receiving oral valganciclovir. The "off treatment" phase of the study refers to the follow-up period and could have been attributed to either study drug. It should be noted that after the last dose of study drug most of the patients continued taking ganciclovir or valganciclovir as part of the local protocols. For adverse events occurring on Days 13 and 14, it is very difficult to determine whether they are due to oral valganciclovir or to IV ganciclovir which was administered on Days 1 through 12. Moreover, the term "off treatment" is not accurate because almost all patients continued to take anti-CMV drugs (ganciclovir or valganciclovir) as part of the local protocols.

During the treatment phase of the study, a higher proportion of patients experienced at least one adverse event while receiving IV ganciclovir (90%) compared with those receiving valganciclovir (12%). The most common adverse events by patients receiving IV ganciclovir were adverse events associated with gastrointestinal disorders (55%), infections and infestations (40%), and vascular disorders (30%). Hypertension was the most frequent adverse event experienced by 30% of the patients. The remaining adverse events were experienced by one or two patients. The two adverse events reported by the two patients while receiving valganciclovir were ascites and back pain.

Twelve patients experienced 22 AEs considered severe and one patient experienced two AEs (two episodes of post-procedural hemorrhage) considered life-threatening. The two AEs reported in the valganciclovir oral solution treatment phase were considered mild (back pain) and moderate (ascites) in intensity.

Three patients experienced six adverse events considered by the investigators related to study drug during treatment with IV ganciclovir: rash 1 patient, anemia and renal impairment 1, vomiting, diarrhea and elevated hepatic enzymes 1 patient).

Ten patients experienced 14 serious adverse events during treatment with IV ganciclovir and 9 patients experienced a total of 17 SAEs during the follow-up period, while only 1 patient experienced an SAE during treatment with valganciclovir oral solution. Two SAEs (vomiting and elevated hepatic enzymes) experienced by one patient during treatment with IV ganciclovir were considered related to study drug.

No deaths were reported during the study. However, two patients were withdrawn prematurely from the study secondary to AEs (ascites and sepsis 1 patient, peritonitis 1).

Laboratory abnormalities: There was only one patient who experienced a worsening of 3 or more grades. This is a 7-month-old male who underwent liver transplantation for biliary atresia.

On study Day 2 the patient developed severe hepatic artery thrombosis and peritonitis resulted in re-transplant. Transaminases were elevated. The shift from baseline was Grade 0 to Grade 4 for ALT and Grade 0 to Grade 3 for AST. Elevated transaminases improved by Day 11 and returned to normal at the follow-up visit.

Comments: The overall safety profile of IV ganciclovir and oral valganciclovir was consistent with that obtained in adult solid organ transplant patients and there were no unexpected safety findings.

Conclusions:

Pharmacokinetic results showed that ganciclovir exposures after IV ganciclovir were similar to ganciclovir exposures after valganciclovir oral formulation. However, ganciclovir exposures were lower than the mean exposures in adults receiving IV ganciclovir 5 mg/kg, particularly in children ≤ 5 years and 12-16 years of age. Therefore, this BSA-based dosing algorithm cannot be used in children.

The IV ganciclovir and oral valganciclovir were tolerated in pediatric liver transplant patients with an overall safety profile similar to that observed in adult solid organ transplant recipents.

Study WP16726: Safety and pharmacokinetics of valganciclovir syrup in pediatric solid organ transplant recipients

This is an open-label, single-dose, multicenter, non-comparative safety and pharmacokinetic study of valganciclovir oral formulation in pediatric solid organ transplant recipients. The objectives of the study were to: 1) investigate the safety and tolerability of valganciclovir oral solution in pediatric solid organ transplant recipients, 2) determine the pharmacokinetics of ganciclovir following oral administration of valganciclovir solution and tablets in solid organ transplant recipients, and 3) describe the incidence of CMV disease.

A total of 63 children, 4 months to 16 years of age, who received solid organ transplants and were at risk for developing CMV disease were enrolled in this study. Patients who met all the entry criteria began prophylaxis with oral valganciclovir once daily (valganciclovir oral solution or tablets) as soon as possible after transplantation and continued treatment until a maximum of 100 days post-transplant. Patients were followed until Week 26 (Day 180) post-transplant

The design of this study is similar to Study PV1600 (study in adult solid organ transplant recipients). The major difference between the two studies was the CMV serologic status of donors and recipients. In the adult study, patients were seronegative for CMV and received allografts from CMV seropositive donors. In study WP16726, the serologic status of donors and recipients was as follows:

Table 8. Summary of CMV serology status of donors and recipients in Study WP16726.

Serology status	**CMV (n=63)**
D+/R+	24 (38%)
D+/R-	25 (40%)
D-/R+	12 (19%)
D-/R-	2 (3%)

Dose rationale:

The proposed pediatric dose was projected to provide ganciclovir exposures at the range of 40 – 60 mg.h/L. The target exposure is based on analysis of data from an adult study in solid organ transplant recipients treated with the approved valganciclovir dose of 900 mg once daily (Study PV1600). Ganciclovir exposures < 40 mg.h/L were predicted to have an unacceptable rate of CMV viremia, whereas exposures > 60 mg.h/L were predicted to have an unacceptable rate of neutropenia and leukopenia.

The calculation of the once daily dose of oral valganciclovir used in Study WP16726 was based on the knowledge from studies WP16296 and WP16303 and was modified as follows:

Dose (mg) = 7 x BSA x CrCl (calculated using the modified Schwartz formula)

where,

$$Mosteller\ BSA(m^2) = \sqrt{\frac{height(cm) \times weight(kg)}{3600}}$$

and,

$$\text{Schwartz } CrCL(mL/\min/1.73m^2) = \frac{k \times height(cm)}{SerumCreatinine(mg/dL)}$$

where,
k = 0.45 for ages < 1 year,
k = 0.45 for ages 1 to < 2 years (note k value is 0.45 instead of the typical value of 0.55),
k = 0.55 for boys aged 2 to < 13 years and girls aged 2 to 16 years, and
k = 0.7 for boys aged 13 to 16 years

(Most of the enrolled subjects received the valganciclovir powder for oral solution)

Safety assessments occurred on Day 1, Day 7, Weeks 2, 6, 10, 14 (Day 100), 16, 20 and 26 post-transplant. Blood samples for safety laboratory tests (chemistry and complete blood counts) were obtained at each visit. A blood sample was obtained at Day 100 to assess potential viral resistance and at any time when patient experienced CMV disease.

Blood sampling for ganciclovir concentrations were obtained from each subject on at least 2 occasions and at least 4 weeks apart. Subjects had at least three doses of valganciclovir before pharmacokinetic sampling. The timing of these pharmacokinetic measurements were: pre-dose, 1-3 h, 3-7 h and 7-12 h with at least one hour between the second and third blood draws and at least two hours between the third and fourth blood draws. In addition, a single PK sample was taken during scheduled safety visits at least once during 100 days treatment and up to a maximum of three times on three separate days.

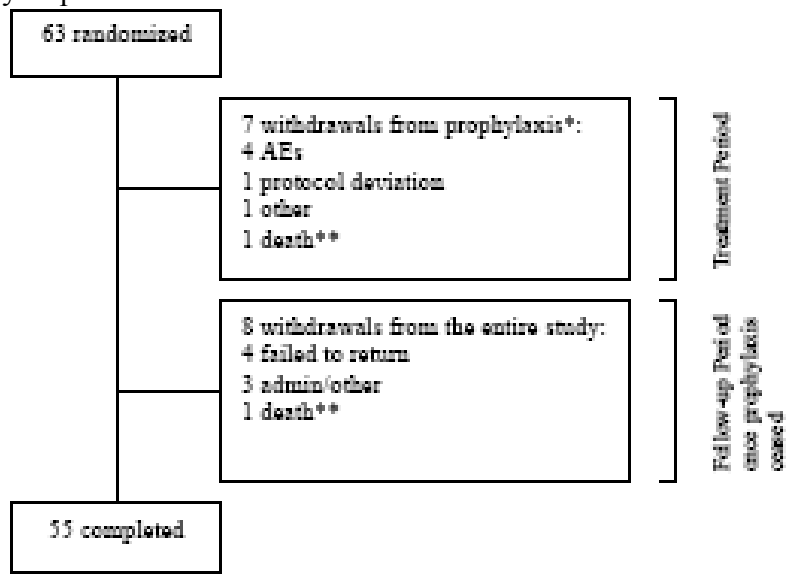
Baseline characteristics and disposition of patients:

A total of 63 solid organ transplant recipients enrolled in this study. There were 33 kidney recipients, 17 liver recipients, 12 heart recipients, and 1 kidney/liver recipient. Thirty-four (54%) were male and 29 (46%) were female. Fifty-one (81%) were white, 1 (2%) was black, 2 (3%) Asians, 1 (2%) Arabic, 1 (2%) Aboriginal, 2 (3%) American Indian/Alaska Native, and 5 (8%) Latin American. The ethnicity breakdown was 22 (35%) Hispanic or Latino and the remaining 41 (65%) not Hispanic or Latino.

There were 17 patients ≤ 2 years of age, 21 patients > 2 years to <12 years of age, and 25 patients ≥ 12 years of age. The mean age was 8.1 ± 5.9 years and mean weight was 29.08 ± 19.94 kg. The serology results for CMV status are shown in Table 8. Two patients were D-/R- but were enrolled in the study because at these centers all pediatric patients are considered at high risk for CMV disease.

Study drug discontinuation: A total of 55 patients completed the study (completed prophylaxis and follow-up to Week 26). Study drug discontinuations are shown in Figure 2.

Figure 2. Summary of patient withdrawals from trial treatment.



*Two of the seven patients who were withdrawn from study treatment were classified as completing the study as they continued to have their safety assessments. These two patients are not included in the list of withdrawal from the study
**One patient died in the study
Source: CSR Vol. 15 – p. 45

Pharmacokinetic results:

The pharmacokinetic results are displayed in Table 9.

Table 9. Summary of pharmacokinetic parameters by age group and transplant type in Study WV16726: Mean (SD)

	PK Parameter	Age Group (Years)		
		≤ 2 (n=2)	> 2 - < 12 (n=12)*	≥ 12 (n=19)
Kidney (N=33)	AUC_{0-24} (μg.h/mL)	65.2 (16.6)	55.0 (11.9)	50.0 (11.6)
	C_{max} (μg/mL)	10.0 (0.04)	8.74 (2.49)	7.85 (2.10)
	$t_{1/2}$ (h)	3.10 (0.59)	4.47 (1.37)	5.69 (1.06)
		≤ 2 (n=9)	> 2 - < 12 (n=6)	≥ 12 (n=2)
Liver (N=17)	AUC_{0-24} (μg.h/mL)	69.4 (35.4)	58.4 (6.18)	35.6 (2.76)
	C_{max} (μg/mL)	11.7 (3.59)	9.35 (2.33)	5.55 (1.34)
	$t_{1/2}$ (h)	2.72 (1.32)	3.61 (0.80)	4.50 (0.25)
		≤ 2 (n=6)	> 2 - < 12 (n=2)	≥ 12 (n=4)
Heart (N=12)	AUC_{0-24} (μg.h/mL)	56.3 (23.2)	60.0 (19.3)	61.2 (26.0)
	C_{max} (μg/mL)	8.22 (2.44)	12.5 (1.02)	9.50 (3.34)
	$t_{1/2}$ (h)	3.60 (1.73)	2.62 (0.65)	5.05 (0.70)

* There was one subject (41468/8702) who received both a kidney and liver transplant. The PK profile for this subject has not been included in this table as it is not possible to determine whether the affects observed are from the kidney/liver transplant or neither.

Source: CSR Vol. 15 – p. 54

The bioavailability of ganciclovir from valganciclovir oral solution was estimated to be 57% with a 95% confidence interval of 52% - 62%.

Comments: The proposed pediatric dose of valganciclovir (Dose [mg] = 7 x BSA x CrCl calculated using the modified Schwartz formula]) administered once daily achieved ganciclovir exposures similar to those observed in adult solid organ transplant patients receiving valganciclovir 900 mg once daily.

The pharmacokinetics of ganciclovir were similar across organ types and age ranges.

Efficacy results:

CMV disease: CMV disease (defined as CMV syndrome or tissue-invasive CMV disease) was not reported in any subjects in this study. Seven patients reported CMV viremia/antigenemia but none of them fulfilled the definition of CMV syndrome or disease (presence of fever plus any other symptoms of CMV disease). Four patients had CMV viremia/antigenemia after completing prophylaxis. Another patient discontinued study medication on Day 35 due to an intestinal obstruction, and had CMV viremia on Day 86. The remaining two patients had CMV positive test during the treatment phase of the study. Five of the seven cases with positive CMV test were treated with ganciclovir. It is noteworthy that the majority of the cases (5 of the 7 patients) had CMV viremia/antigenemia after the end of treatment. The major findings of these seven patients are shown in Table 10.

Table 10. Findings in patients with CMV viremia/antigenemia

Patient No	Age at transplantation (months)	Sex	Organ Transplant	CMV serology status of Donor/Recipient	Time to positive CMV test after initiating prophylaxis (days)	Treated for CMV
8604	150	F	kidney	D+/R+	143	Yes
8801	6	F	heart	D+/R-	38	No
8802	195	M	heart	D+/R-	173	Yes
1101	133	F	kidney	D+/R-	169	Yes
5205*	43	M	liver	D+/R-	86	Yes
6104	9	F	liver	D+/R-	8	Yes
1106	203	F	heart	D+/R-	160	No

*This patient discontinued valganciclovir prophylaxis on Day 35.

CMV viremia/antigenemia by CMV serology status: When patients with CMV viremia/ antigenemia were analyzed according to the CMV serology status of the donor and recipient, it was found that 6 of the 7 patients were D+/R- (Table 11).

Table 11. CMV serology status of donor/recipient and CMV viremia/antigenemia

CMV serology status of donor/recipient	No of patients	No of patients with CMV viremia/ antigenemia (%)
D+/R+	24	1 (4)
D+/R-	25	6 (24)
D-R+	12	0
D-/R-	2	0

Comments: Of note, in Study PV1600, 12.1% of patients in the valganciclovir arm had CMV disease (CMV syndrome 5%, tissue-invasive CMV disease 7.1%). As with Study WP16726, most of the cases of CMV disease occurred after the end of treatment. However, as mentioned previously, none of the 7 patients from Study WP16726 who had CMV viremia/antigenemia met the criteria for CMV syndrome or tissue-invasive CMV disease.

It is noteworthy that most of the cases of CMV viremia/antigenemia occurred in the D+/R- group, the group at the highest risk for CMV disease after transplantation.

Treatment failure defined as either the development of CMV disease (viremia, antigenemia,or test positive) requiring treatment up to Day 100 post-transplant or discontinuation of study medication due to lack of efficacy or to toxicity: A total of four patients had failure: two had CMV viremia/antigenemia (both of them were liver transplant recipients) and two had toxicity (one liver transplant with elevated transaminases and one kidney transplant with severe neutropenia). It should be noted that in one of the patients with CMV viremia/antigenemia, valganciclovir was discontinued on Day 35 due to an intestinal obstruction. He developed CMV viremia on Day 86. Below is a brief description of patients who had treatment failure:

Patient 6104: This is a 9-month-old CMV seronegative girl who underwent liver transplantation from a CMV seropositive donor for biliary atresia. She was started on valganciclovir prophylaxis six days after transplant. On Day 8 of treatment a routine blood test was CMV antigen positive. Valganciclovir was stopped and patient was treated with IV ganciclovir. The next day she experienced convulsions and radiologic images revealed leukoencephalopathy. She was treated with antiepileptic drugs. On Day 15, repeat blood tests were negative for CMV and study drug was restarted. The patient's course was also complicated with a biliary tract infection.

Patient: 5205: This is a 43-month-old CMV seronegative boy who underwent liver transplant from a CMV seropositive donor for Alagille syndrome. Seven days after transplantation he was started on valganciclovir for CMV prophylaxis. On Day 35 he experienced abdominal pain and he was diagnosed with intestinal obstruction. Study drug was discontinued and he underwent surgery on Day 56. He had a second episode of intestinal obstruction requiring laparotomy on

Day 86. During the same time he was found to have CMV antigenemia for which he was treated with 10 days of IV ganciclovir.

Patient 8805: This is a 10-month-old CMV seropositive girl who underwent liver transplant from a CMV seropositive donor for alpha-1-antitrypsin deficiency. She was started on valganciclovir for CMV prophylaxis the next day. On Day 3 she had significantly elevated transaminases and she was treated with steroids for a presumed acute rejection. Because LFTs remained elevated, a liver biopsy was performed on Day 32 which showed no evidence of acute rejection. Valganciclovir was discontinued on Day 39 and LFTs decreased (Day 48). On Day 108 the patient was hospitalized for fever and rash and she was treated with ampicillin and cefotaxime. Blood cultures were negative and the fever resolved in 4 days. The episode of increased transaminases was considered possibly related to study drug and the liver transplant.

Patient 3301: This is a 42-month-old CMV seropositive boy who underwent kidney transplant from a CMV seronegative donor for congenital nephrotic syndrome. Valganciclovir was started two days after transplant. His major complications were as follows:
Study Day 3: Diarrhea and dehydration.
Study Day 34: He was hospitalized for probable asthma. Asthma was not confirmed and he was discharged with the diagnosis of nasopharyngitis.
Study Day 38: Hospitalized for asthma.
Study Day 76: His ANC was 408 and valganciclovir was discontinued. ANC remained low until Day 83. Tests for CMV were negative.
Study Day 95: He experienced mild fever with neutropenia. The fever resolved in five days.
Day 104: He was diagnosed with EBV infection. The neutropenia resolved by Day 112. The investigator considered the neutropenia related to study drug, as well as to mycophenolate and trimethoprim/sulfamethoxazole.

Patients who experienced a biopsy proven graft rejection: A total of 9 (14.3%) patients had a biopsy proven graft rejection; 5 of the 17 (29.4%) patients were in the ≤ 2 years group, 2 of the 21 (9.5%) in the > 2 years to < 12 years group, and 2 of the 25 (8%) in the ≥ 12 years group (Table 12). None of the patients who experienced biopsy proven and treated rejection had CMV positive test.

Table 12. Summary of patients with biopsy proven graft rejection.

Organ	Age Group		
	≤ 2 years (n=5)	> 2 years to < 12 years (n=2)	≥ 12 years (n=2)
Kidney	-	1	2
Liver	5	1	-
Heart	-	-	-

Patients who experienced graft loss: Three patients had graft loss during the study before Day 100): one heart transplant in the ≤ 2 years group, one liver transplant in the >2 years to < 12 years group, and one kidney transplant in the ≥ 12 years group.

Patient survival at six months posttransplant: Only one patient (1.6%) died during the study due to cardiac rejection on Day 28 posttransplant and after taking study medication for 25 days. This was a 2-year-old boy who underwent cardiac transplantation for end stage heart disease. Both the donor and recipient were CMV seronegative. The patient was started on valganciclovir prophylaxis two days after transplant. On study Day 25 the patient had vomiting and decreased urine output. Blood cultures were negative. The patient was admitted to the intensive care unit for treatment with dobutamine, sodium bicarbonate, amilrinone, and pulse steroids. His cardiac function deteriorated and the patient was intubated. He developed progressive heart failure and metabolic acidosis and he died on Study Day 26. An autopsy was not performed. The investigator considered the death as unrelated to study drug but as a result of graft rejection. Notably, the mortality rate in Study PV1600 in adults was 3.7% (9 of 244) in the valganciclovir arm and 1.6% (2 of 126) in the ganciclovir arm.

Safety results:

An overall summary of adverse events that occurred in more than 10% of patients between the first day through the end of study treatment plus 28 days (defined as "on treatment") is shown in Table 13.

Table 13. Adverse events reported in more than 10% of patients on treatment by age group

Adverse Event	<= 2 YEARS N = 17 No. (%)	>2 - < 12 YEARS N = 21 No. (%)	>= 12 YEARS N = 25 No. (%)	TOTAL N = 63 No. (%)
DIARRHOEA	6 (35)	8 (38)	6 (24)	20 (32)
PYREXIA	5 (29)	8 (38)	2 (8)	15 (24)
HYPERTENSION	3 (18)	3 (14)	8 (32)	14 (22)
UPPER RESPIRATORY TRACT INFECTION	4 (24)	3 (14)	7 (28)	14 (22)
VOMITING	3 (18)	4 (19)	6 (24)	13 (21)
ANAEMIA	7 (41)	2 (10)	-	9 (14)
NEUTROPENIA	4 (24)	2 (10)	2 (8)	8 (13)
CONSTIPATION	-	5 (24)	2 (8)	7 (11)
NAUSEA	-	2 (10)	5 (20)	7 (11)
TRANSPLANT REJECTION	3 (18)	-	3 (12)	6 (10)

Source: CSR Vol. 15 – p. 62

Comment: Diarrhea was the most common adverse event followed by pyrexia and upper respiratory tract infection, vomiting, hypertension, anemia, and neutropenia.

The majority of AEs were mild or moderate in intensity and were considered by the investigator not related to study drug (371 out of 400)

Table 14 compares the adverse events observed in Study WV16726 (pediatric solid organ transplant recipients) and Study PV1600 (adult solid organ transplant recipients). Of note, the reported adverse events in adults cover the period up to 180 days post-transplant, whereas the reported adverse events in children cover the period up to 128 days post-transplant.

Table 14. Most common adverse events in Study WV16726 (pediatric patients) and Study PV1600 (adult patients)

Adverse Event	Most Common AEs (>10%) in **Pediatric** Data from SOT Study WV16726 (on treatment)		**Adult** Data from SOT Study PV16000 (6 months)	
	N=63		N=244	
	N	No. (%)	N	No. (%)
Diarrhea	20	32	73	30
Pyrexia	15	24	32	13
Upper Respiratory Tract Infection	14	22	16	7
Vomiting	13	21	40	16
Hypertension	14	22	43	18
Anemia	9	14	28	12
Nausea	7	11	55	23
Neutropenia	8	13	20	8
Constipation	7	11	49	20
Cough	7	11	15	6
Hypomagnesaemia	6	10	19	8
Nasopharyngitis	4	6	10	4
Pruritus	5	8	18	7
Transplant Rejection	6	10	59	24
Urinary Tract Infection	6	10	26	11

Comment: The rates of certain adverse events such as pyrexia, upper respiratory tract infection were higher in pediatric patients than in adults. On the other hand, transplant rejection was more frequent in adults.

Serious AEs: Sixty-six SAEs were reported by 32 patients during the study. Fifty SAEs were reported by 27 patients while on treatment. The most common were infections and infestations (9 patients, 14%), and gastrointestinal disorders (7 patients, 11%). The overall pattern of SAEs was comparable among the three organ transplants. However, a higher proportion of SAEs was noted in patients ≤ 2 years of age.

SAEs related to study drug: A total of seven SAEs were considered related to study drug. All these SAEs occurred during treatment. There were two cases with increased transaminases and single cases of anemia, CMV antigenemia, diarrhea, neutropenia, and febrile neutropenia.

Withdrawals due to AEs: Three patients were withdrawn due to AEs. One kidney transplant due to severe neutropenia (probably related to study drug), one liver transplant due to elevated transaminases (probably related to study drug), and one liver transplant due to an intestinal obstruction (unrelated to study drug).

Laboratory abnormalities: the number of patients experiencing a marked shift in selected laboratory abnormalities (worsening of 3 and 4 grades) is summarized in Table 15.

Table 15. Marked shifts from baseline in key laboratory parameters.

Laboratory Parameter	Abnormality	N	Number of Patients who had a Shift of			
			Three Grades (e.g. from 0 to 3)		Four Grades (e.g. from 0 to 4)	
			n	%	n	%
Hemoglobin	Low	63	6	10	0	0
White Blood Cell (WBC)	Low	59	3	5	1	2
Lymphocytes	Low	54	3	6	3	6
Neutrophils	Low	54	7	13	4	7
Alkaline Phosphatase	High	40	1	3	0	0
ALAT (SGPT)	High	48	1	2	0	0
Total Bilirubin	High	38	1	3	0	0
Potassium	Low	56	4	7	0	0
Potassium	High	57	4	7	2	4
Sodium	Low	58	2	3	0	0
Sodium	High	57	0	0	1	2
Calcium	Low	46	1	2	3	7
Phosphate	Low	43	2	5	0	0
Fasting Glucose	Low	39	1	3	0	0
Uric Acid	High	21	2	10	2	10

Source: CSR Vol. 15 – p. 77

Comment: Marked laboratory abnormalities were most commonly observed with neutrophils and hemoglobin.

A comparison of marked shifts from baseline in key laboratory abnormalities between children and adult solid organ transplant recipients treated with valganciclovir for prophylaxis of CMV infection is shown in the following table.

Table 16. Comparison between marked shift from baseline in key laboratory abnormalities between children and adult solid organ transplant recipients treated with valganciclovir for prophylaxis of CMV infection.

Laboratory parameter	Abnormality	Percentage of patients with worsening of 3 or 4 grades	
		Pediatric Study WP16726 %	Adult Study PV1600 (Valganciclovir arm) %
Hemoglobin	Low	10	2
Neutrophils	Low	20	9
ALT	High	1	2
Total bilirubin	High	3	2
Alkaline phosphatase	High	3	0
Potassium	High	11	0
Potassium	Low	7	0

Comment: A higher rate of pediatric patients had a marked shift in neutrophil count, hemoglobin, and potassium levels.

Conclusions:

The proposed pediatric dose of valganciclovir (Dose [mg] = 7 x BSA x CrCl [calculated using the modified Schwartz formula]) administered once daily achieved ganciclovir exposures similar to those observed in adult solid organ transplant patients receiving valganciclovir 900 mg once daily. The ganciclovir exposures were similar across organ transplant types and age ranges. No case of CMV disease was reported during the study. However, there were 7 (11%) patients with CMV viremia/antigenemia; none of these events fulfilled the definition of CMV syndrome. Based on the pharmacokinetic, safety, and efficacy data from this study and extrapolated efficacy data from the adult study, oral valganciclovir is indicated for the prevention of CMV disease in kidney and heart transplant recipients ages 4 months to 16 years at risk for developing CMV disease. Valcyte is not approved in adults for CMV prophylaxis in liver transplant patients; therefore, Valcyte is not recommended for CMV prophylaxis in pediatric liver transplant patients because efficacy cannot be extrapolated from adults.

Note: *After completing the review, the Division received on November 18, 2008, the report by the Division of Scientific Investigations stating the deficiencies noted during the analytical inspection at* [redacted] **(b) (4)** *Based on these findings the plasma concentration data from study WP16726 are not acceptable as submitted. As a result of this report, the Division decided valganciclovir is not recommended for approval for the prevention*

of CMV disease in kidney and heart transplant recipients ages 4 months to 16 years at risk for developing CMV disease.

A complete response letter will be issued outlining the deficiencies needed to be addressed by the Applicant.

Study CASG 109: A phase I/II pharmacokinetic and pharmacodynamic evaluation of oral valganciclovir in neonates with symptomatic congenital cytomegalovirus (CMV)

This is an open-label, pharmacokinetic, and safety study of valganciclovir oral formulation in neonates and infants up to three months with symptomatic congenital CMV infection. This study was sponsored by the National Institutes of Health and conducted in 8 centers in the United States by the Collaborative Antiviral Study Group. The objectives of this study were to: 1) determine the pharmacokinetics of ganciclovir after administration of oral valganciclovir solution in neonates with symptomatic congenital CMV disease, and 2) identify a dose of oral valganciclovir that achieves comparable ganciclovir exposure to 6 mg/kg IV (or AUC_{0-12} 27 mg h/L) ganciclovir in neonates with symptomatic congenital CMV disease

A total of 24 neonates with symptomatic congenital CMV infection involving the central nervous system were enrolled in the three versions of this protocol. All patients were treated for 6 weeks with a combination of IV ganciclovir 6 mg/kg b.i.d. or valganciclovir powder for oral solution with doses ranging from 14 mg/kg to 20 mg/kg twice daily.

In Version 1.0 of the protocol subjects received 6 weeks of twice daily 6 mg/kg IV ganciclovir therapy interrupted on Days 5-6 and 35-36 at which time subjects received twice daily 14 mg/kg valganciclovir oral solution. Blood measurements of ganciclovir were obtained at pre-dose, 1 h, 3-5 h, 5-7 h and 10-12 h on Days 4, 6, 34, 35 and 36. In Versions 2.0/3.0 subjects received one dose of oral valganciclovir on Day 1. Twelve hours later, 6 mg/kg IV ganciclovir was begun and continued every 12 hours. Blood measurements of ganciclovir were obtained at 0.25-0.75 h, 1-3 h, 5-7 h and 10-12 h after the oral valganciclovir dose on Day 1 and the second IV ganciclovir dose. In addition to pharmacokinetic sampling, anti-CMV activity was evaluated by viral load measurements between Day 1 and Days 7, 14, 28, 42 and 56. IV therapy was continued for approximately two weeks while pharmacokinetic specimens were sent for analysis. After the two weeks, the subject's oral valganciclovir dose changed based on the pharmacokinetic results. One and two weeks after re-initializing oral therapy, blood samples were obtained at 0.5 and 3 h post-dose. As groups of four subjects were enrolled, oral valganciclovir dose increased from 14 mg/kg to 20 mg/kg and then decreased to 16 mg/kg. Dose changes were based on AUC calculations from previous cohorts.

Dose rationale:

The dose(s) of valganciclovir powder for oral solution was selected to provide comparable systemic exposures to those obtained in infants up to 3 months from a 6 mg/kg dose of IV

ganciclovir twice daily (AUC_{0-12h} = 25.5 µg.h/mL) or to the ganciclovir exposures obtained in adults from a 900 mg dose of oral valganciclovir twice daily (AUC_{0-12} =27 mg.h/L). Of note, the 6 mg/kg dose of IV ganciclovir administered twice daily was used in another trial sponsored by the National Institutes of Health and conducted by the Collaborative Antiviral Study Group (CASG12; J Pediatr 2003;146:16-250). The results of that study showed that ganciclovir may [redacted] (b) (4) (see Subsection 2.2).

Baseline characteristics and disposition of patients:

Of the 24 subjects enrolled in this study, 13 (54%) were male and 11 (46%) were female. Nineteen (79%) subjects were white, 4 (17%) were black, and the remaining one of other race. The ethnicity breakdown was Hispanic or Latino 6 (25%) and not Hispanic or Latino 10 (42%). For the remaining 8 (33%) subjects ethnicity was not recorded.

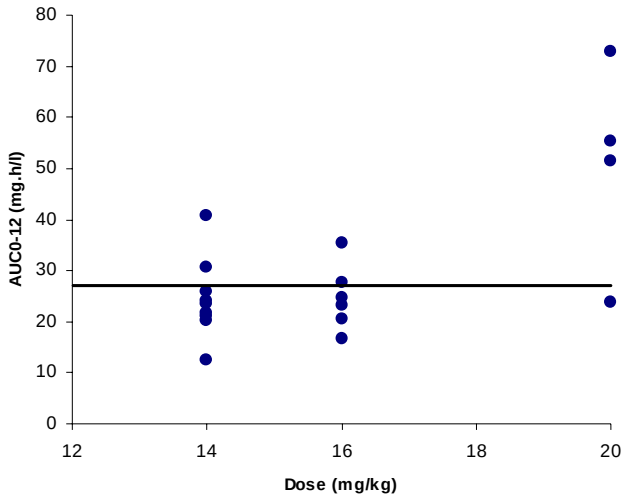
The median age of all subjects was 16.5 days (range 6 to 31 days). The median birth weight of these neonates was 2.4 kg (range 1.09 to 4.1 kg), and the median gestational age was 37.5 weeks (range 34 to 41 weeks).

The baseline clinical and laboratory characteristics of the enrolled neonates were similar to those reported in the published literature on symptomatic congenital CMV infection.

Pharmacokinetic results:

In Version 1.0, the median AUC_{0-12} of ganciclovir after 6 mg/kg IV ganciclovir was 24.8 mg.h/L on Day 4 and 14.3 mg.h/L on Day 34. After 14 mg/kg valganciclovir oral solution, the AUC_{0-12} of ganciclovir was 23.2 mg.h/L on Day 5 and 21.57 mg.h/L on Day 36. In Version 2.0/3.0, the median AUC_{0-12} of ganciclovir after IV ganciclovir was 25.5 mg h/L on Day 1. In the 9 subjects who received 14 mg/kg oral valganciclovir, the median AUC_{0-12} was 23.4 mg.h/L on Day 1. In the 4 subjects receiving 20 mg/kg oral valganciclovir, the median AUC_{0-12} was 53.3 mg.h/L. The 6 subjects who received 16 mg/kg achieved a median AUC_{0-12} of 23.9 mg h/L. The ganciclovir AUC_{0-12} after the different doses of oral valganciclovir is shown in Figure 3.

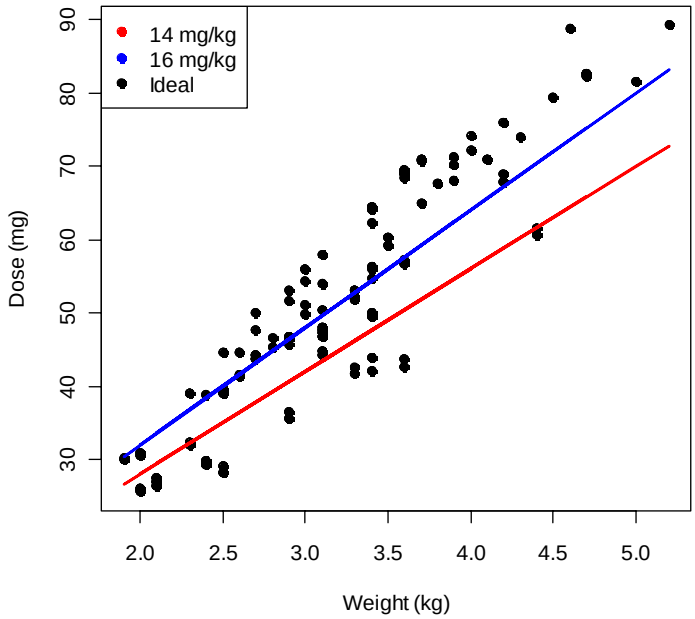
Figure 3. Ganciclovir AUC_{0-12} after Oral Valganciclovir by Dose



Comments: The pharmacokinetic results showed that in pediatric patients up to 3 months of age with symptomatic congenital CMV infection, doses of 14 mg/kg and 16 mg/kg, respectively, provide ganciclovir exposures close to the target AUC_{0-12} of 27 mg.h/L.

The ganciclovir exposures (AUC_{0-12}) in neonates receiving 14 mg/kg are indistinguishable from the AUC_{0-12} observed in neonates receiving 16 mg/kg. However, the results of a population pharmacokinetic modeling predicted that the 16 mg/kg dose would provide exposures closer to the target AUC_{0-12} than the 14 mg/kg dose (Figure 4)

Figure 4. Comparison of "ideal" valganciclovir dose to 14 mg/kg and 16 mg/kg doses



Efficacy results:

Hearing and neurologic assessments: The results of hearing evaluation were similar to those observed in Study CASG 102. (b) (4)

Because study CASG 109 is not a comparable trial, definitive assessments on the effect of treatment on hearing cannot be made.

Safety results:
An overall summary of adverse events occurred in more than 15% of patients is shown in Table 17.

Table 17. Most common adverse events (> 15%) in Study CASG109

Adverse Event	**No (%)**
Anemia	10 (42)
Neutropenia	10 (42)
Rash	6 (25)
Agitation	5 (21)
Fever	5 (21)
Emesis	4 (17)
Head lag	4 (17)
Thrush	4 (17)
Skin irritation	4 (17)

Comment: Neonates and young infants with symptomatic congenital CMV infection enrolled in Study CASG109 comprise a unique population which can explain the differences in the safety profile between Study CASG109 and WV16726.

Severe adverse events: Eleven patients experienced 16 AEs considered severe. Five of these severe AEs experienced by four patients were considered probably related to study drug (3 patients had neutropenia and 1 patient had neutropenia and anemia). Two patients experienced life-threatening AEs (one patient had Gram negative sepsis and the other elevated potassium). These life-threatening events were considered as not related to study drug.

Below is a brief description of the two cases with life-threatening events:

Patient 0054: At one month of age, this neonate with congenital CMV infection and CMV-associated hepatitis, presented with fever and irritability and a history of mild diarrhea over the last few days. The patient was admitted to the hospital and a full sepsis work up was done. The patient remained afebrile during hospitalization but blood cultures from the central line grew Klebsiella pneumoniae and Citrobacter. The central line was removed and the patient was treated with intravenous antibiotics for seven days. The patient did not have neutropenia during this time period.

Patient 0065: This 2-month-old infant with congenital CMV infection involving the central nervous system and severe hearing loss in the left ear was noted to have hyperkalemia (6.3 meq/L). Repeated tests showed potassium levels of 6.8 and 6.1 mEq/L, respectively. A nephrologist was consulted and determined that the hyperkalemia was secondary to thrombocytosis.

Serious AEs: Twelve SAEs were reported by eight patients during the study. These SAEs were: anemia (1), gram-negative bacteremia/sepsis (1), hyperkalemia (1), fever (1), upper respiratory infection (1), ear infection (1), neutropenia (1), pneumonia (2), bilateral hearing loss (1), reflux (1), and RSV infection (1).

Serious AEs related to study drug: Only one SAE was considered by the investigator possibly related to study drug. This patient was switched from IV ganciclovir to oral ganciclovir according to the protocol. Four days after oral valganciclovir the patient was discharged from the NICU. Two days following discharge the patient was noted to have an ANC 750 cells/mm^3 and the patient was hospitalized because of the neutropenia. The next day the patient was given a dose of GCSF. The same day a repeat test showed ANC 500 cells/mm^3 and the valganciclovir dose was decreased by half. The next day another dose of GCSF was given and the ANC increased to 2000 cells/$mm^3$and subsequently the valganciclovir resumed to the full dose.

Laboratory abnormailities: The most significant safety concern observed in Study CASG 109 was the occurrence of neutropenia. Almost 40% of the enrolled subjects developed Grade 3 or Grade 4 neutropenia. One subject permanently discontinued antiviral therapy due to neutropenia.

Conclusions:

This study was (b) (4) to provide pharmacokinetic and safety data (b) (4) of valganciclovir oral solution for the treatment of neonates and infants up to 3 months with symptomatic congenital CMV infection. Study CASG 109 was designed to provide comparable ganciclovir exposures to those obtained in infants up to 3 months from a 6 mg/kg dose of IV ganciclovir (used in a previous CASG trial to evaluate the effect of IV ganciclovir on symptomatic congenital CMV infection) and to ganciclovir exposures obtained in adults from a 900 mg dose of oral Valcyte twice daily.

Although the pharmacokinetic results showed that in neonates and infants > 7 days to 3 months of age, a dose of 16 mg/kg twice daily of valganciclovir powder for oral solution provided ganciclovir exposures similar to those obtained in infants up to 3 months from a 6 mg/kg dose of IV ganciclovir twice daily and to ganciclovir exposures obtained in adults from a 900 mg dose of oral Valcyte twice daily, (b) (4) The safety and efficacy of IV ganciclovir have not been established for the treatment of congenital CMV infection and no similar disease occurs in adults; therefore, efficacy cannot be extrapolated from IV ganciclovir to support the (b) (4) valganciclovir powder for oral solution for the treatment of congenital CMV infection.

Note: *In addition to the above deficiencies, several other deficiencies were noted by the Division of Scientific Investigations during the analytical inspection at* (b) (4) (b) (4)*. Based on these deficiencies (stated in a report dated November 18, 2008) the plasma concentration data from study CASG109 are not acceptable as submitted. A complete response letter will be issued outlining the deficiencies needed to be addressed by the Applicant.*

6 ADDITIONAL CLINICAL ISSUES

6.1 Dosing Regimen in Adult Patients With Renal Impairement

After oral administration, valganciclovir is rapidly and extensively metabolized by gastrointestinal and liver esterases to ganciclovir which is primarily excreted unchanged through the renal route. Therefore, its clearance is highly associated with creatinine clearance and dose modifications are needed for patients with different degrees of renal impairment.

The current dosing recommendations of valganciclovir in adult patients with different degrees of renal impairment are based on the results of a previously conducted study (Study WP15511; reviewed as part of the original NDA [NDA 21-304]) and the single available strength of the 450 mg tablet. The information in Table 18 shows the dosing recommendations in the currently approved package insert.

Table 18. Current valganciclovir dosing recommendations for adult patients with renal impairment.

CrCl (mL/min)	**Induction dose**	**Maintenance/Prevention dose**
≥ 60	900 mg twice daily	900 mg twice 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

For patients with end stage renal impairment who require hemodialysis (CrCl < 10 mL/min), no dosing recommendation is provided with the valganciclovir tablet because the daily required doses are less than 450 mg. In fact, for these patients it is recommended that ganciclovir be used according to the dose reduction algorithm cited in the IV and oral ganciclovir capsules labels.

(b) (4)

[redacted] (b) (4)

To support the [redacted] (b) (4) dosing in patients with different degrees of renal impairment, pharmacokinetic modeling and simulation studies were performed. The results of these studies were reviewed by Dr. Vikram Arya, the Clinical Pharmacology and Biopharmaceutics reviewer, and were considered acceptable.

Note: *After completing the review, the Division received the report by the Division of Scientific Investigations stating the clinical site failed to retain the reserve samples from Study WP16302, the pivotal bioequivalence study. The retention of the reserve samples is required as per 21 CFR 320.38 and is critical for assuring the authenticity of the test and reference products used in the pivotal bioequivalence study. As the authenticity of the test and reference products cannot be confirmed, the data from the bioequivalence study cannot be used to* [redacted] (b) (4)

[redacted] (b) (4)

7 OVERALL ASSESSMENT

7.1 Conclusions

Pediatric use information for many of the approved drugs, including antiviral drugs with activity against cytomegalovirus, is needed. Children have fewer treatment options than adults due to lack of a pediatric formulation and information to guide clinicians in dosing children.

This NDA includes pharmacokinetic and safety data from five studies; one bioequivalence study assessing the bioequivalence of ganciclovir from the new valganciclovir powder for oral solution with the marketed valganciclovir 450 mg tablet at a dose of 900 mg and four pediatric studies conducted in response to the Pediatric Written Request for the use of valganciclovir for the

prevention or treatment of CMV disease in children. Based on these studies, the Applicant seeks the following:

- (b) (4)
- (b) (4)
- Approval of valganciclovir for the prevention of cytomegalovirus (CMV) disease in pediatric solid organ transplant recipients 4 months to 16 years of age at risk for developing CMV disease, and
- (b) (4)

Of note, this submission was split into two NDAs for administrative purposes: (b) (4) (b) (4) (b) (4) and 2) NDA 22-257 for the indication of valganciclovir for the prevention of CMV disease in pediatric solid organ transplant recipients 4 months to 16 years of age at risk for developing CMV disease (b) (4) (b) (4)

Based on the deficiencies noted during the inspection by the Division of Scientific Investigations, the Division decided valganciclovir is not recommended for approval for any of the above indications. The major deficiencies noted during the inspection are as follows:

(b) (4) The clinical site failed to retain the reserve samples from the pivotal bioequivalence study. The retention of the reserve samples is required as per 21 CFR 320.38 and is critical for assuring the authenticity of the test and reference products used in the pivotal bioequivalence study. As the authenticity of the test and reference products cannot be confirmed, the data from the bioequivalence study cannot be used (b) (4) (b) (4)

NDA 22-257: Based on the findings from the analytical inspection at (b) (4) (b) (4) the plasma concentration data from WP16726 (A safety and pharmacokinetic study of valganciclovir in pediatric solid organ transplant recipients) and CASG109 (A phase I/II pharmacokinetic and pharmacodynamic evaluation of valganciclovir in neonates with symptomatic congenital CMV infection) are not acceptable as submitted. To assure the accuracy of analytical runs and the resulting drug concentrations, the Applicant needs to provide the following information:

- Frozen stability data that cover the duration of storage (b) (4) (b) (4) of all the plasma samples used for the quantification of ganciclovir in studies WV16726 and CASG109.
- Identify a set of integration parameters and re-integrate all the chromatograms within a run in a consistent manner. This procedure should be repeated for all the chromatograms generated

in studies WV16726 and CASG109. Use the resulting concentrations to repeat the pharmacokinetic and/or pharmacodynamic evaluations in studies WP16726 and CASG109.

A complete response letter will be issued outlining the deficiencies needed to be addressed by the Applicant.

Andreas Pikis, M.D.
Medical Reviewer, DAVP

Concurrences:
KMarcus/MedTL/DAVP

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
11/25/2008 02:00:50 PM
MEDICAL OFFICER

Kendall Marcus
11/25/2008 02:19:25 PM
MEDICAL OFFICER