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RESEARCH**

*APPLICATION NUMBER:*

**22-257s000**

**21-304s007**

**SUMMARY REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	August 29, 2009
<b>From</b>	Kendall A. Marcus, M.D.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	22-257/Original-1 Valcyte® for Oral Solution pediatric indication for kidney and heart transplant recipients <div style="background-color: black; width: 100%; height: 20px; margin-top: 5px;"></div> <div style="text-align: right; font-size: small;">(b) (4)</div> 21-304 S-007 Valcyte® Tablets pediatric indication for kidney and heart transplant recipients
<b>Applicant</b>	Roche Palo Alto LLC
<b>Date of Submission</b>	April 30, 2008
<b>PDUFA Goal Date</b>	August 29, 2009
<b>Proprietary Name / Established (USAN) names</b>	Valcyte® for Oral Solution, Valcyte® Tablets valganciclovir
<b>Dosage forms / Strength</b>	
<b>Proposed Indication(s)</b>	1. CMV prophylaxis in pediatric kidney and heart transplant recipients at high risk <div style="background-color: black; width: 100%; height: 20px; margin-top: 5px;"></div> <div style="text-align: right; font-size: small;">(b) (4)</div>
<b>Recommended:</b>	1. Approval <div style="background-color: black; width: 100%; height: 20px; margin-top: 5px;"></div> <div style="text-align: right; font-size: small;">(b) (4)</div>

### 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, VGCV for oral solution, and for a pediatric indication for VGCV tablets for the prevention of CMV disease in pediatric solid organ transplant recipients at high risk. 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 and for (b) (4)

This memo will review the regulatory history of ganciclovir products for the prevention of CMV disease in solid organ transplant recipients and an important study previously conducted with IV ganciclovir for the treatment of congenital CMV disease. The pharmacokinetic, safety

and efficacy data submitted from studies to support the proposed pediatric indications will be summarized. Finally, inspections conducted by the Division of Scientific Investigation (DSI) found multiple deficiencies in sample handling and analyses, resulting in issuance of a Complete Response (CR) action; the Applicant's response to the CR letter will also be summarized.

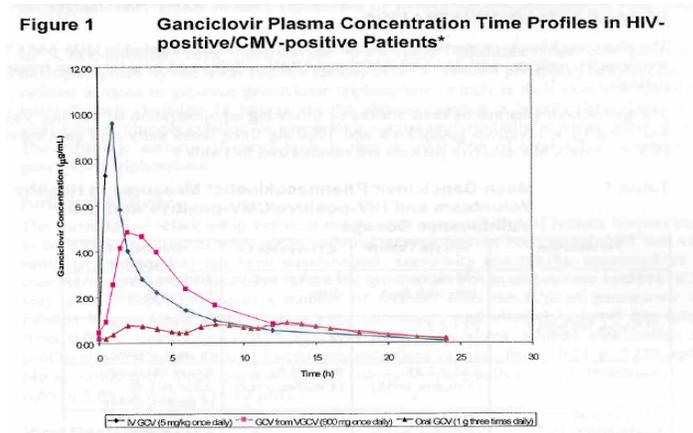
## 2. Background

### Prevention of CMV Disease in Solid Organ Transplant Recipients

Solid organ transplant recipients are at risk for numerous 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 following the cessation of prophylaxis (post-transplant Day 180).

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 C<sub>max</sub> 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.



**IV ganciclovir**

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 °C 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 considered to be 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)

**Ganciclovir Capsules**

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

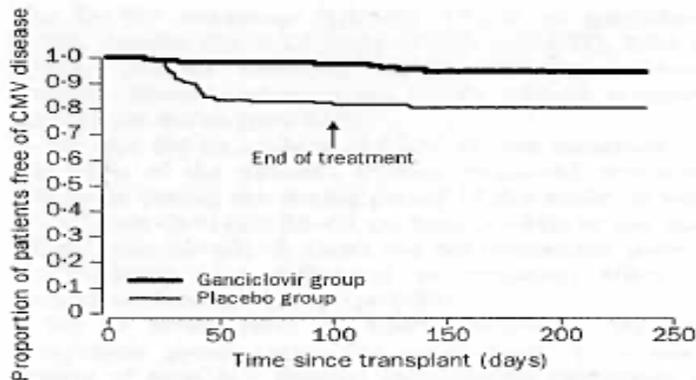
were administered from post-transplant Day 10 through post-transplant Day 100. The incidence of CMV disease was evaluated at Day 180. The incidence of CMV disease observed in this study is summarized in Table 2.

**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 early post-transplant period; 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**

**Valganciclovir Tablets**

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 <sup>†</sup>	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.

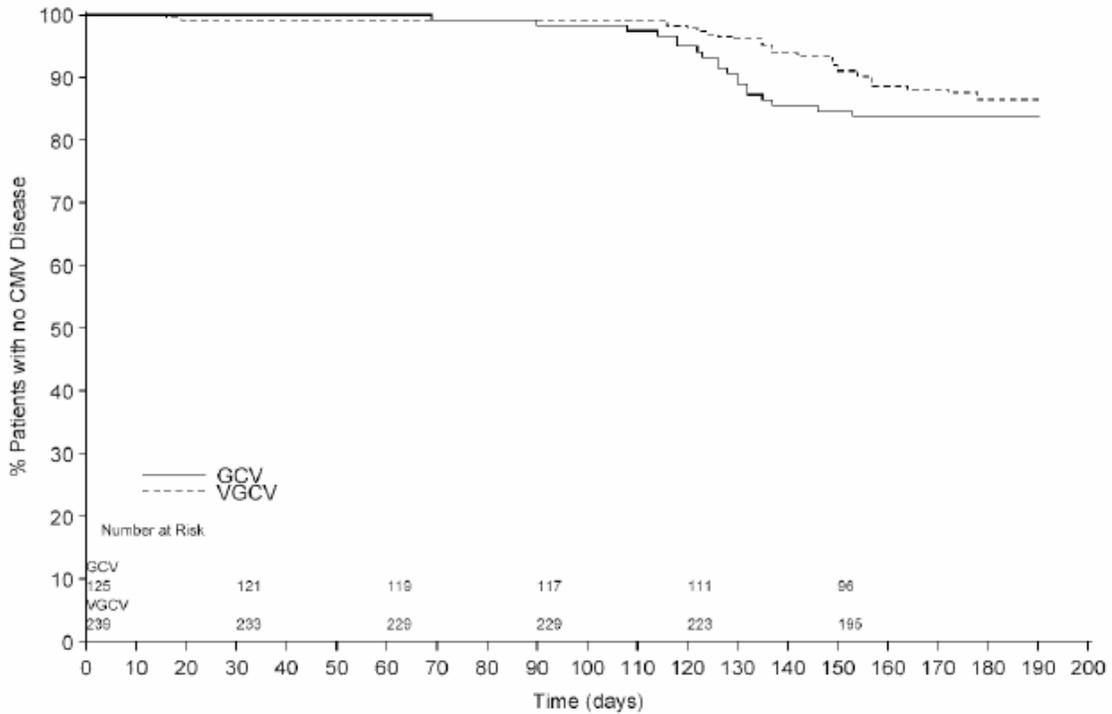
**Table 4 - Incidence of Tissue-Invasive CMV Disease at Day 180 in Solid Organ Transplant Recipients by Transplant Type**

Organ	GCV (N=125)	VGCV (N=239)	2 one-sided 97.5% CI <sup>†</sup>	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, (b) (4) (b) (4) VGCV was approved for prevention of CMV disease in heart, kidney and kidney-pancreas transplant recipients at high risk, (b) (4)

As a result, activity of anti-CMV drugs is now generally considered (b) (4) 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. (b) (4)

**Secondary Reviewer Comment:** *I do not agree with the action taken on the valganciclovir application for prevention of CMV disease in solid organ transplants recipients for the following reasons.*

- [REDACTED] (b) (4) 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 the incidence of CMV disease at this timepoint seeks to address the concern that prophylaxis only delays the onset of CMV disease to the post-prophylaxis period, this strategy overlooks the apparent potent efficacy of the drug during the administration period.
- 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 post-hoc subgroup analyses increases the likelihood of making Type I statistical errors.
- [REDACTED] (b) (4), VGCV appeared superior to GCV in preventing CMV disease in kidney transplant recipients. No plausible explanation has been proposed as to why contradictory findings were observed in these two transplant types, further supporting that these post-hoc subgroup analyses reflect random variation rather than real observed differences regarding VGCV efficacy in these different transplant types.

### **Congenital CMV Disease**

[REDACTED] (b) (4) 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, [REDACTED] (b) (4)

[REDACTED] (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 the baseline and 6-month follow-up visit or retained normal hearing. The treatment group 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 the untreated group. 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) (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 this application. Please refer to the original approval of Valcyte® Tablets (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 pediatric transplant patients at high risk for development of CMV disease, and neonates congenitally infected with CMV.

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

To support dosing recommendations and an indication for 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 data submitted in these NDAs supported the Applicant's dosing recommendations of VGCV for oral solution and tablets 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:

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

where

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

and

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

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.

[REDACTED] (b) (4)

### **Site Inspections/CR Letter and Applicant's Response**

At the request of the Division of Antiviral Drug Products, the Division of Scientific Investigations 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 [REDACTED] (b) (4)

The inspection of the above sites revealed several serious deficiencies. The most important ones are as follows:

Inspection at [REDACTED] (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 originally submitted in the NDA and a CR letter was issued. The sponsor was asked to provide the following information:

- Frozen stability data that cover the duration of storage [REDACTED] (b) (4)  
[REDACTED] (b) (4)  
[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 sponsor provided frozen stability data covering the duration of storage and repeated 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. These changes did not result in a change to the final dosing recommendations for this pediatric population. The submitted data was considered acceptable in support of calculating dosing recommendations.

**Pediatric (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 VGCV 14 mg/kg and 16 mg/kg provide GCV exposures close to the target AUC. The GCV  $AUC_{0-12}$  in neonates receiving 14 mg/kg is indistinguishable from the  $AUC_{0-12}$  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  $AUC_{0-12}$  than the 14 mg/kg dose. As a result of the deficiencies noted above during analytical inspection by DSI, the Applicant repeated the pharmacokinetic analysis using automatically integrated data. The automated analysis did not change the final dosing recommendation.

(b) (4)

## 6. Clinical Microbiology

No issues with respect to Clinical Microbiology are noted in the Applicant's response to the CR letter.

## 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)

(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-pancreas transplant recipients at high risk. The submitted pediatric study was not required to demonstrate superiority of VGCV 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, the study does provide supportive activity data.

Study WP16726 is an open-label, multicenter, non-comparative safety and pharmacokinetic study of VGCV for oral solution and VGCV tablets 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 Day 100 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.

## **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 and 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. Seven (7) 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.

## **11. Other Relevant Regulatory Issues**

None.

## **12. Labeling**

The labeling for Valcyte® for Oral Solution and Valcyte® Tablets was submitted in PLR format. The major changes in the revised label are as follows:

- A new indication for Valcyte® for Oral Solution and Valcyte® Tablets for the prevention of CMV disease in pediatric kidney and heart transplant patients at high risk was added.
- The Dosing and Administration section was changed to add dosing recommendations for pediatric patients and to provide information on the preparation of Valcyte® for Oral Solution.
- Clinical trial information from study WP16726 was added to the Adverse Reactions, Use in Specific Populations and Clinical Studies sections of the label.
- Clinical trial information from CASG 109 was added to the Use in Specific Populations section of the label.

### 13. Recommendations/Risk Benefit Assessment

These applications provided data to support the approval of Valcyte® for Oral Solution and Valcyte® Tablets for the prevention of CMV disease in pediatric kidney and heart transplant recipients at risk for the development of CMV disease. These approvals will provide much needed pediatric formulations for pediatric heart and kidney transplant recipients, enabling most of them to utilize an oral formulation as opposed to IV ganciclovir.

The deficiencies noted during DSI inspections during the first review cycle of this application have been adequately addressed by the Applicant. Reanalysis of pharmacokinetic data from study WV16726 and study CASG 109 did not change any conclusions or dosing recommendations made from these studies.

I agree with the primary reviewer's conclusions. I recommend approval of Valcyte® for Oral Solution and Valcyte® Tablets for the prevention of CMV disease in pediatric kidney and heart transplant patients from ages 4 months to 16 years. (b) (4)

(b) (4)  
Safety and efficacy of valganciclovir for the prevention of CMV disease in adult liver transplant patients has not been demonstrated; therefore, efficacy cannot be extrapolated from adults.

(b) (4)  
(b) (4). The submitted study established that 16 mg/kg of valganciclovir oral solution twice daily provided ganciclovir exposures similar to exposures observed in infants up to age 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 and no similar disease occurs in adults; therefore, efficacy cannot be extrapolated from IV ganciclovir to support the (b) (4) Valcyte® for Oral Solution for congenital CMV infection.

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Kendall Marcus, M.D., Deputy Director for Safety, 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/

KENDALL A MARCUS  
08/28/2009