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 (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. (b) (4) 3. (b) (4) 4. (b) (4)
Recommended:	*1. Complete response* *2.* (b) (4) *3.* (b) (4) *4.* (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 (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.

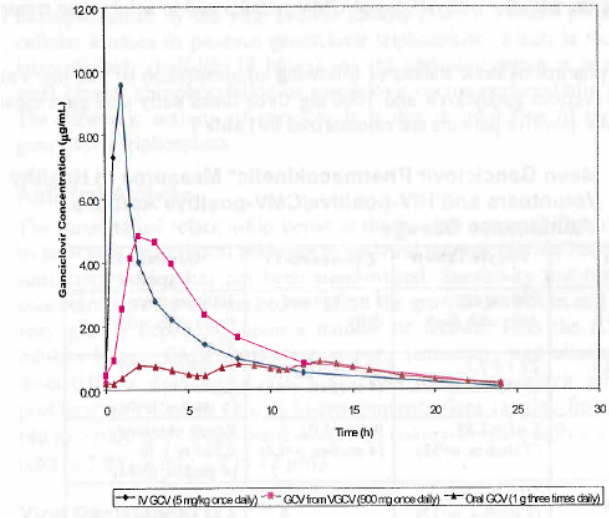
2. Background

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

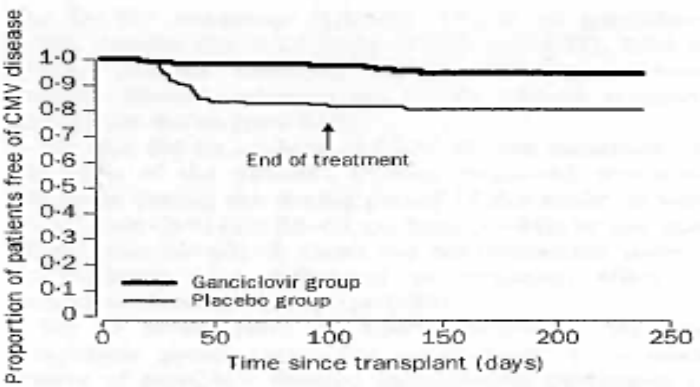


Figure 2: **Kaplan-Meier curves for the cumulative probability of freedom from cytomegalovirus (CMV) disease with time after transplantation**

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.

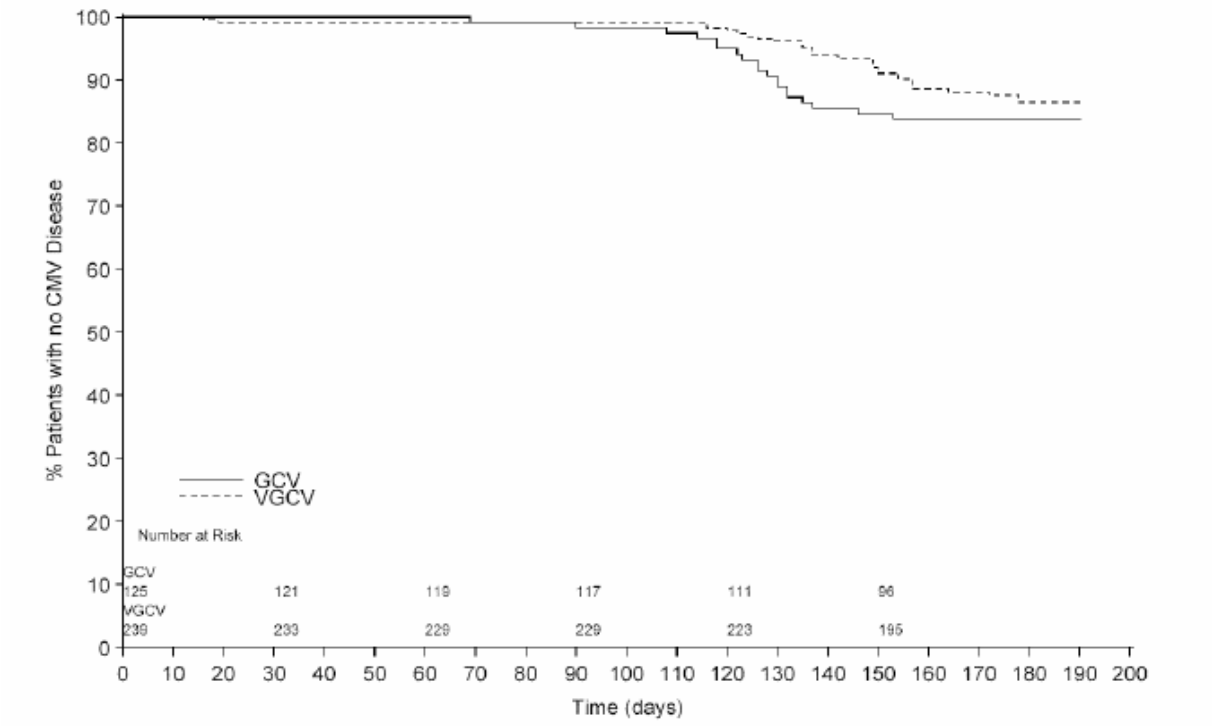
Table 4 - Incidence of Tissue-Invasive CMV Disease at Day 180 in Solid Organ Transplant Recipients by Transplant Type

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, (b) (4) VGCV was approved for prevention of CMV disease in heart, kidney and kidney-pancreas transplant recipients at high risk, (b) (4) based on these post-hoc sub-group analyses.

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)

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

- (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 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.*
- (b) (4) *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

(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, suggest GCV (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)

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)

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 (b) (4). Based on these findings, the plasma concentration data from study WP16726 are not acceptable as submitted.

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 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.

(b) (4)

In addition, deficiencies were noted by DSI during the analytical inspection of (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 (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)

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) 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) 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
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MEDICAL OFFICER