CLINICAL REVIEW

Application Type	Supplemental NDA
Application Numbers	21304/S-11 & 22257/S-5
Priority or Standard	Standard
Submit Date	March 31, 2014
Received Date	March 31, 2014
PDUFA Goal Date	April 30, 2015
Division / Office	Division of Antiviral Products/ Office of Antimicrobial Products
Reviewer Name(s)	Andreas Pikis, M.D.
Review Completion Date	March 20, 2015
Established Name	Valganciclovir
Trade Name	VALCYTE
Therapeutic Class	CMV antiviral
Applicant	Hoffman-La Roche, Inc.
Formulations	Powder for Oral Solution Tablets
Dosing Regimen	Based on body surface area and creatinine clearance
Indications	Prevention of CMV disease
Intended Populations	Pediatric heart and kidney transplant recipients

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

In these supplemental New Drug Applications (sNDAs), 21-304/S-11 and sNDA 22-257/S-5, the Applicant seeks to:

- Extend the dosing regimen of valganciclovir for the prevention of CMV disease in pediatric kidney transplant recipients 4 months to 16 years of age at high risk from 100 days to 200 days post-transplantation; and
- Expand the Indications and Usage of valganciclovir to include heart transplant patients from (b) (4).

Applicant's request to extend the dosing regimen of valganciclovir from 100 days to 200 days for the prevention of CMV disease in pediatric kidney transplant recipients 4 months to 16 years of age (sNDA 21-304/S-11) is based on Study NV25409. This study was conducted in response to the Pediatric Research Equity Act (PREA) post-marketing requirement (PMR#1670-1) issued on August 5, 2010, asking for a tolerability study evaluating up to 200 days of valganciclovir oral solution or tablets in pediatric kidney transplant recipients.

The Division of Antiviral Products (DAVP) determined that based on the safety and efficacy data from Study NV25409, together with the previous study in adult patients which demonstrated that valganciclovir administered within 10 days post-transplantation and until 200 days post-transplantation was superior to valganciclovir administered until 100 days post-transplantation, the dosing regimen of valganciclovir for the prevention of CMV disease in pediatric kidney transplant recipients 4 months to 16 years of age will be extended from 100 days to 200 days post-transplantation. In addition, DAVP agrees that the submitted data fulfilled the requirements for PREA PMR #1670-1.

The Applicant's request to expand the Indications and Usage to include valganciclovir prophylaxis administered within 10 days of transplantation until 100 days post-transplantation for the prevention of CMV disease in heart transplant recipients from (b) (4) of age is based on:

- Study NP22523. This study was conducted in response to PREA PMR # 1533-2 issued on August 28, 2009, asking for a pharmacokinetic and safety study in pediatric heart transplant recipients < 4 months of age in order to determine appropriate valganciclovir dosing in this age group and to submit dosing recommendations for inclusion in the package insert.

- Physiologically based pharmacokinetic (PBPK) model. Because of difficulties in enrolling patients < 6 weeks of age, the Applicant was encouraged to develop a PBPK model based on available pharmacokinetic data from pediatric and adult patients in order to support valganciclovir dosing in children younger than 6 weeks of age.

- Safety data from CASG112 study, "A phase 3, randomized, placebo-controlled, blinded investigation of 6 weeks versus 6 months of oral valganciclovir therapy in infants with symptomatic congenital CMV infection".

Based on the submitted data and extrapolation of efficacy data from adult heart transplant patients, DAVP determined that the submitted data support the use of valganciclovir prophylaxis for the prevention of CMV disease in heart transplant recipients one month to less than four months of age. (b) (4) To this extent, DAVP supports that the submitted data fulfilled the requirements for PREA PMR#1533-2. In addition, DAVP supports the waiver of a study in heart transplant patients less than one month of age because such a study would be impossible given that heart transplantation in patients less than 1 month of age is extremely uncommon.

1.2 Risk Benefit Assessment

The safety profile of valganciclovir is well characterized. Until now, more than 700,000 patients have been exposed to this drug in the context of solid organ transplantation, including approximately 8,800 pediatric solid organ transplant patients. Hematologic adverse events are the major risks associated with the use of valganciclovir and are included in the boxed warning of the package insert. No new safety concerns have been identified with the safety data submitted to support the approval of valganciclovir for the prevention of CMV disease in heart transplant patients less than 4 months of age. The pharmacokinetic data indicated that the pediatric dosing algorithm could achieve AUC exposures similar to the historical adult targeted exposures (40-60 µg • h/mL) for children 1 month to less than 4 months of age. These data, together with the extrapolated efficacy data from the adult studies, support the indication of valganciclovir for the prevention of CMV disease in heart transplant patient 1 month to < 4 months of age. However, it is not clear whether the pediatric dosing algorithm can achieve exposures similar to the adult targeted exposures in neonates due to unverified assumptions in the proposed PBPK model for this age group. Therefore, valganciclovir is not indicated for CMV prophylaxis in heart transplant patients < 1 month of age.

Study NV25409, designed to assess tolerability rather than efficacy, was submitted to support the extension of the valganciclovir dosing regimen from 100 days to 200 days

post-transplantation in pediatric kidney transplant patients 4 months to 16 years of age. Efficacy was extrapolated from the adult study which demonstrated that valganciclovir administered until 200 days post-transplantation was superior to valganciclovir administered until 100 days post-transplantation. Of some concern is the higher rate of severe neutropenia observed in study NV25409 (30%) compared to that observed in a previous pediatric study in solid organ transplant patients treated until 100 days post-transplantation (5%). However, considering that clinicians are highly aware of the adverse reactions associated with the use of valganciclovir and its routine use in transplant centers, we believe that the benefits of extending the dosing regimen to 200 days outweigh the risks.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No specific Risk Management Activities were requested from the Applicant.

1.4 Recommendations for Postmarket Requirements and Commitments

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

- Conduct resistance analysis of pUL97 codons 340-363 for all available clinical samples across all of your clinical studies for which no known resistance substitutions were identified.

Agreement with the Applicant on this post-marketing requirement is pending.

2 Introduction and Regulatory 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%) (b) (4) than that of oral ganciclovir capsules (6-9%).

Established name and trade name: Valganciclovir (Valcyte®)

Pharmacological class: Valganciclovir is a nucleoside analogue (b) (4) However, valganciclovir's unique characteristic is potent inhibition of CMV DNA polymerase.

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

Adult patients:

- 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 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.
- Prevention of CMV disease in kidney transplant patients at high risk for developing CMV disease:
  900 mg once daily starting within 10 days of transplantation until 200 days post-transplantation.

Pediatric patients (4 months to 16 years of age):

- Prevention of CMV disease in kidney or heart transplant patients at high risk for developing CMV disease. Valganciclovir is administered once a day within 10 days of transplantation until 100 days post-transplantation according to the following dosage algorithm:

  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 (b) (4) 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.

Applicant's proposed indication, dosing regimen, and age groups included in these submissions:

In these submissions, the Applicant proposes to:

- Extend the dosing regimen for the prevention of CMV disease in pediatric kidney transplant recipients 4 months to 16 years of age at high risk from 100 days to 200 days post-transplantation; and
- To expand the Indications and Usage to include heart transplant from (b) (4) .

2.2 Tables of Currently Available Treatments for Proposed 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. 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 adults, the lowest rate of CMV infection (< 5%) occurs in donor-negative/recipient-negative (D-/R-) patients and the highest rate (>50%) in donor-positive/recipient-negative (D+/R-) patients. The incidence of CMV disease in D+/R+ or D-/R+ patients is estimated at 10-15%.

The clinical symptoms of CMV infection range from asymptomatic CMV viremia to tissue invasive CMV disease (e.g., CMV hepatitis, colitis, and pneumonia). 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 (drug administered to all patients at risk for developing CMV disease) and preemptive therapy (treatment only of patients with evidence of CMV replication without tissue invasive disease) are the two major strategies used for prevention. Although there have been no large studies comparing the two approaches, prophylaxis with valganciclovir has emerged as the most common strategy. Table 1 summarizes the FDA-approved drugs for prophylaxis against CMV infection in solid organ transplant recipients.

Table 1. Currently approved drugs for CMV prophylaxis in solid organ transplant recipients.

Drug	**Indication and dosage in adult patients**	
Intravenous ganciclovir	Prevention of CMV disease in transplant recipients at high risk for CMV disease	5 mg/kg every 12 hours for 7-14 days, followed by 5 mg/kg once daily, 7 days per week or 6 mg/kg once daily, 5 days per week. The duration of treatment depends upon the duration and degree of immunosuppression.
Oral ganciclovir	Prevention of CMV disease in transplant recipients at high for CMV disease	1000 mg three times daily. The duration of treatment depends upon the duration and degree of immunosuppression. Note that oral ganciclovir is not currently available in the United States.
Oral valganciclovir	Prevention of CMV disease in heart or kidney-pancreas transplant patients at high risk for developing CMV disease (D+/R-) Prevention of CMV disease in kidney transplant patients at high risk for developing CMV disease (D+/R-)	900 mg once daily starting within 10 days of transplantation until 100 days post-transplantation. 900 mg once daily starting within 10 days of transplantation until 200 days post-transplantation.
Drug	**Indication and dosage in pediatric patients**	
Oral valganciclovir	Prevention of CMV disease in kidney or heart transplant patients 4 months to 16 years of age at high risk for developing CMV disease	Dose once a day within 10 days of transplantation until 100 days post-transplantation according to dosage algorithm.

Ganciclovir, in its intravenous formulation, was the (b) (4) 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. These reasons led to the development of oral ganciclovir for the prevention of CMV disease (b) (4)

(b) (4). 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%) (b) (4) greater than the bioavailability of oral ganciclovir capsules (b) (4). 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) administered within 10 days of transplantation until 100 days post-transplantation was approved by FDA for the prevention of CMV disease in kidney, heart, or kidney-pancreas transplant patients at high risk for developing CMV disease.

CMV prophylaxis in solid organ transplant recipients has focused on CMV disease occurring during the first 100 days after transplantation, with the duration of prophylaxis no longer than three months. However, it has been noted that the effects of prophylaxis appear to be limited to the period for which prophylaxis is administered. Late-onset of CMV disease, defined as CMV disease occurring after three months post-transplant, has become an important problem in this setting. Trial NT18435 compared the efficacy and safety of 200 days of valganciclovir prophylaxis with 100 days of prophylaxis for the prevention in CMV disease in adult kidney transplant recipients at high risk. The results of this study demonstrated that fewer patients in the 200 day group developed CMV disease within the first 12 months post-transplant compared to the 100 day group (16.8% versus 36.8%, p< 0.001).Based on the results of this study, the dosing regimen for the prevention of CMV disease in adult kidney transplant recipients was extended from 100 days to 200 days post-transplantation.

In these two sNDAs the Applicant proposes to:

- Extend the dosing regimen for the prevention of CMV disease in pediatric kidney transplant recipients 4 months to 16 years of age at high risk from 100 days to 200 days post-transplantation; and
- To expand the Indications and Usage to include heart transplant from (b) (4)

2.3 Availability of Proposed Active Ingredient in the United States

Valcyte is available in the United States as a tablet and oral solution.

Valcyte tablets: Supplied 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.

Valcyte for oral solution: Supplied as a conventional (b) (4) white to slightly yellow powder containing standard excipients and manufactured using conventional methods. The drug product is packaged in a (b) (4) amber glass bottle containing (b) (4) 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.

2.4 Important Safety Issues With Consideration to Related Drugs

The only approved drugs for CMV prophylaxis in solid organ transplant recipients are ganciclovir and valganciclovir. Valganciclovir is a prodrug which is converted to ganciclovir after oral administration. Valganciclovir's mechanism of action, antiviral spectrum, resistance pattern, and safety profile are the same as those of the parent drug, ganciclovir. The safety profile of valganciclovir and its parent drug, ganciclovir, are well characterized and described in the current drug label. Both drugs have been on the market for a long time. Ganciclovir sodium for injection and ganciclovir capsules were approved more than 20 years ago. The initial approval of valganciclovir was in 2001 for the treatment of CMV retinitis in patients with AIDS. In 2003, it was approved for CMV prophylaxis in kidney, heart, or kidney-pancreas transplant patients and in 2009 for pediatric solid organ transplant recipients.

Adverse events of concern with valganciclovir include those associated with hematologic toxicity. Of great concern is also drug's carcinogenic, teratogenic, and testicular toxicity potential; these potential adverse events are based on animal studies and not on human data.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

March 2001:	Valcyte was approved by FDA for the treatment of CMV retinitis in patients with AIDS.
September 2003:	Valcyte 900 mg once a day within 10 days of transplantation until 100 days post-transplantation was approved for the prevention of CMV disease in kidney, heart, or kidney-pancreas adult transplant patients at high risk.
August 2009:	Valcyte once a day within 10 days of transplantation until 100 days post-transplantation according to dosage algorithm was approved

for the prevention of CMV disease in kidney or heart transplant patients 4 months to 16 years of age.

A PREA PMR (1533-2) was issued asking for a pharmacokinetic and safety study in pediatric heart transplant patients less than 4 months of age in order to determine appropriate dosing in this age group and to submit dosing recommendations for inclusion in the package insert.

August 2010: Valcyte 900 mg once a day within 10 days of transplantation until 200 days post-transplantation was approved for the prevention of CMV disease in kidney adult transplant patients at high-risk for CMV disease.

A PREA PMR (1670-1) was issued asking for a tolerability study for up to 200 days post-transplant of valgaciclovir for oral solution or tablets in pediatric kidney transplant patients

March 2013: FDA extended the timeframe for the final report submission for PREA PMR 1533-2 through March 31, 2015.

July 2013: FDA extended the timeframe for final report submission for PREA PMR 1670-1 through January 31, 2014.

November 2013: A meeting between the Applicant and FDA was held to discuss the format and content of the sNDAs that will be submitted to fulfill the PREA PMRs listed above. During the meeting it was agreed that safety data from Study CASG112 would be acceptable for review (b) (4) [redacted]

January 2014: FDA extended the timeframe for final report submission for PREA PMR 1670-1 through March 31, 2014.

2.6 Other Relevant Background Information

The extended dosing regimen of valganciclovir, 900 mg once daily for up to 200 days for the prevention of CMV disease in adult kidney transplant patients at high risk for CMV disease has been approved [redacted] (b) (4). The extended dosing regimen of valganciclovir (Dose (mg)= 7 x BSA x CrCl) administered once daily for up to 200 days in pediatric kidney transplant recipients 4 months to 16 years of age has recently been approved by the European Medicines Agency. The European Medicines Agency has also recently expanded the indication of valganciclovir (administered once daily within 10 days of transplantation until 100 days post-transplantation) for the prevention

of CMV disease to include heart transplant recipients from birth to less than 4 months of age.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

At the request of the DAVP and the Office of Clinical Pharmacology, the Office of Scientific Investigations (OSI) audited the analytical portion of Study NP22523. No major deficiencies were identified that would compromise the integrity of the study. For more details, please see the inspection summary by Seongeun Cho, Ph.D.

3.2 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.

3.3 Financial Disclosures

In compliance with the rule on Financial Disclosure by Clinical Investigators, the Applicant provided financial interest information for all clinical investigators and sub-investigators who participated in Studies NP22523 and NV25409. According to the Applicant, none of the clinical investigators and sub-investigators had a proprietary interest in the product or a significant equity in the Sponsor as defined in 21 CFR 54.2(b) (see Appendix).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

A new study was undertaken to assess the dose accuracy for dispensing volumes less than 2 mL of valganciclovir for oral solution (50 mg/mL) with the 10 mL oral dispenser. The lowest envisioned dose is 50 mg (1 mL).

Three different operators filled the oral dispenser to the 1 mL mark with valganciclovir oral solution and dispensed the content into weighed beakers. The volume of the dispensed solution was calculated from the density. Each operator repeated this for 30 times, for a total of 90 measurements. The mean dispensed dose was 1.05 mL with a

range of 0.98 to 1.16 mL with a relative standard deviation of 2.7%.These results indicate that the supplied oral syringe can accurately deliver the 50 mg (1 mL) dose. For more details please see the review by Steven Miller, Ph.D., Product Quality reviewer.

4.2 Clinical Microbiology

Cytomegalovirus resistance to ganciclovir/valganciclovir is an emerging problem in transplant patients. The overall incidence of ganciclovir resistance in solid organ transplant recipients is 0% to 13% and this variation depends on the duration of therapy, the type of organ transplant, and host factors. Resistance to ganciclovir can be the result of one or more amino acid substitutions in either the viral pUL97 kinase gene responsible for ganciclovir monophosphorylation and/or in the viral DNA polymerase (pUL54). Of note, CMV pUL54 DNA polymerase mutations can confer cross-resistance to any or all of the current anti-CMV approved drugs (cidofovir and foscarnet).

There are concerns that the prolonged use of valganciclovir may lead to CMV resistance. As a component of their analysis, the Applicant conducted virology substudies to determine whether CMV resistant virus emerged in pediatric kidney transplant recipients who received valganciclovir prophylaxis for 200 days in Study NV25409.

Of the 56 patients dosed with study drug, 10 had asymptomatic CMV viremia as confirmed by the central laboratory with only one subject having > 5000 copies/mL. Sequence analysis revealed that only one patient carried a virus at a single time-point with a known UL97 ganciclovir resistance mutation (L595F). This patient was not treated for CMV infection and at the next visit the virus was undetectable.

It is reassuring that in Study NV25409 only one subject carried a virus at a single time-point with known resistance mutation and that viremia subsided without any treatment. However, despite these reassuring results, resistance to ganciclovir remains a serious public health issue and continuous surveillance monitoring CMV for resistance is needed. Please also refer to Dr. Takashi Komatsu's virology review for more detailed information on the virology resistance data submitted with these sNDAs.

4.3 Preclinical Pharmacology/Toxicology

No new animal pharmacology and toxicology data were submitted with these sNDAs. Please refer to the original NDA reviews for background information.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Valganciclovir is the L-valyl ester of ganciclovir. After oral administration, valganciclovir is rapidly and extensively hydrolyzed by intestinal and hepatic esterases into ganciclovir and the essential amino acid valine. Ganciclovir is a (b) (4) analogue with inhibitory activity against herpes viruses. However, valganciclovir's unique characteristic is potent inhibition of CMV DNA polymerase (pUL54).

Ganciclovir must be phosphorylated to the triphosphate form in viral infected cells to exercise antiviral activity by inhibiting viral DNA replication. In CMV-infected cells ganciclovir is initially phosphorylated to ganciclovir monophosphate by the viral protein kinase (pUL97). Further phosphorylation to the triphosphate form occurs by cellular kinases.

4.4.2 Pharmacodynamics

Not applicable.

4.4.3 Pharmacokinetics

These submissions include pharmacokinetic data from Study NP22523. This was an open-label, pharmacokinetic and safety study of ganciclovir after administration of valganciclovir for oral solution in pediatric heart transplant recipients < 4 months of age. The pharmacokinetic results of this study are described in Section 5.3 together with the safety data.

In addition, these submissions include a physiologically based pharmacokinetic (PBPK) model. The PBPK model was developed at the request of the DAVP because of difficulties in enrolling patients < 6 weeks of age in Study NP22523 (only two patients were enrolled, aged 26 and 37 days, respectively). The development of the PBPK model was based on the available pharmacokinetic data from pediatric and adult patients (see section 5.3).

For more details, about the pharmacokinetic data included in these submissions, please see the review by Dr. Mario Sampson, the Clinical Pharmacology reviewer.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The clinical studies provided in these submissions are summarized in the following table.

Table 2. Studies supporting sNDA 21-304/S-11 & sNDA 22-257/S-05

Indication: To extend the dosing regimen for the prevention of CMV disease in pediatric kidney transplant recipients 4 months to 16 years of age		
Study NV25409	This was an open-label, multicenter, single-arm, non-comparative study designed to assess the safety and efficacy of valganciclovir administered up to 200 days post-transplantation in pediatric kidney transplant patients 4 months to 16 years of age.	N=57
Indication: To expand the Indications and Usage for pediatric heart transplant recipients to include children from (b) (4)		
Study NP22523	This was a an open-label, pharmacokinetic and safety of ganciclovir in pediatric heart transplant patients <4 months of age who received a single dose of valganciclovir oral solution on each of two consecutive days	N=17

N= number of subjects enrolled
*In order to support the approval of valganciclovir prophylaxis for the prevention of CMV disease in heart transplant patients from (b) (4) the Applicant submitted the following additional data: 1) The results of PBPK modeling (b) (4) and 2) Safety data from CASG112 study, "A phase 3, randomized, placebo-controlled, blinded investigation of 6 weeks versus 6 months of oral valganciclovir therapy in infants with symptomatic congenital CMV infection".

5.2 Review Strategy

Study NV25409: This was the pivotal pediatric study to support the extension of the dosing regimen for the prevention of CMV disease in pediatric kidney transplant recipients 4 months to 16 years of age from 100 days to 200 days post-transplantation. The clinical review is focused on the safety and antiviral activity. The Medical Officer reviewed study design, subject demographics, efficacy results, adverse events and laboratory abnormalities.

Study NP22523: The clinical review of this open-label, pharmacokinetic and safety study of ganciclovir in pediatric heart transplant patients less than 4 months of age is focused on the safety and the pharmacokinetic data. The Medical Officer reviewed study design, subject demographics, adverse events and laboratory abnormalities. The

Clinical Pharmacology reviewer focused on the pharmacokinetic data and the population pharmacokinetic model.

Supportive studies:
Study CASG112: The clinical review of this phase 3, randomized, placebo-controlled, blinded investigation of 6 weeks versus 6 months of oral valganciclovir therapy in infants with symptomatic congenital CMV infection is focused only on safety.

Physiologically based pharmacokinetic model (PBPK): The results of the PBPK model intended to support dosing recommendations in pediatric heart transplant patients < 6 weeks of age were reviewed by the Clinical Pharmacology reviewer.

Overview of material consulted in review: The safety, efficacy, and pharmacokinetic data were submitted electronically following the common technical document format.

Please refer to Dr. Mario Sampson's clinical pharmacology review for more detailed information on the pharmacokinetic data submitted with these sNDAs. Please also refer to Dr. Takashi Komatsu's virology review for more detailed information on the virology resistance data submitted with these sNDAs.

5.3 Discussion of Individual Studies/Clinical Trials

Studies submitted to support the extension of CMV prophylaxis with valganciclovir until 200 days post-transplantation in pediatric kidney transplant patients 4 months to 16 years of age:

Study NV25409: Tolerability of up to 200 days of valganciclovir oral solution or tablets in pediatric kidney transplant recipients

This was an open-label, multicenter, single-arm, non-comparative study designed to assess the safety and efficacy of valganciclovir administered up to 200 days post-transplantation in pediatric kidney transplant patients 4 months to 16 years of age for the prevention of CMV disease. The study was conducted at 16 centers across 8 countries, including 4 centers in the United States. The primary objective of the study was to describe the tolerability profile of up to 200 days prophylaxis of valganciclovir oral solution and tablets in pediatric kidney transplant patients. The secondary objectives were to: 1) describe the incidence of CMV infection (viremia) and CMV disease (CMV syndrome or tissue invasive CMV disease) within the first 52 weeks post-transplant, and 2) describe the incidence and nature of CMV resistance to ganciclovir (mutations in pUL97and/or pUL54).

A total of 57 subjects aged 4 months to 16 years of age who received kidney transplant and were at risk for developing CMV disease were enrolled in the study. Patients who met all the entry criteria began prophylaxis with oral valganciclovir (oral solution or

tablets) as soon as possible after transplantation, preferably within 1-2 days but no later than 10 days post-transplantation and continued treatment until a maximum of 200 days post-transplantation. The daily dose of valganciclovir (administered once daily) was determined using the currently approved dosing algorithm for children which is based on body surface area (BSA) and estimated creatinine clearance.

Dose (mg) = 7 x BSA x CrCl

Baseline characteristics and disposition of patients:

A total of 57 kidney transplant recipients were enrolled in this study. All but one of the patients received treatment. Patient 233050/90201 withdrew from study before treatment (the mother changed her mind about her child participating in the study). Thirty-one of the 56 patients were male (55%) and 25 (45%) were female. Thirty (54%) were white, 4 (7%) were black, 2 (4%) were Asian, 3 (5%) unknown, and 18 (32%) of other race. The ethnicity breakdown was 31 (55%) Hispanic or Latino, 23 (41%) not Hispanic or Latino, 1(2%) not reported and 1 (2%) unknown.

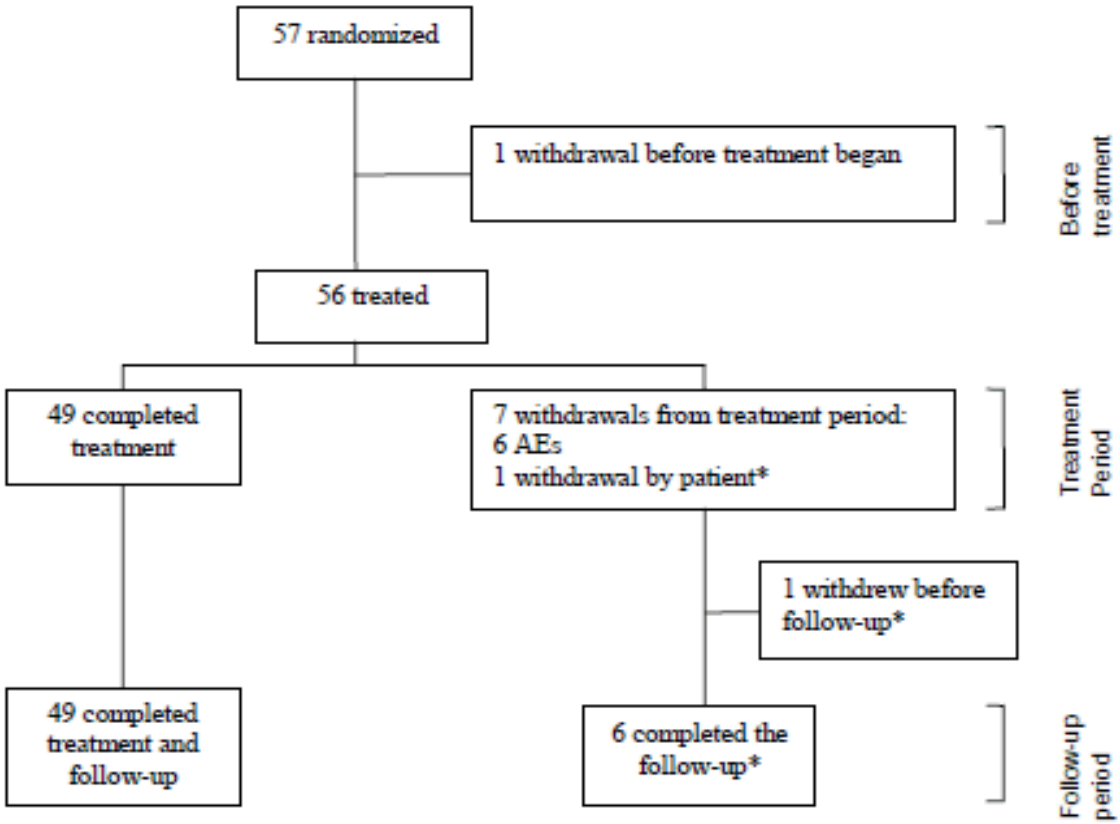
There were 6 patients ≤ 2 years of age, 18 patients > 2 years to ≤ 12 years of age, and 32 patients > 12 years of age. The serology results for CMV status are shown in Table 3.

Table 3. Summary of CMV serology status - Study NV25409

CMV serology status	**N=56**
D+/R+	25 (45%)
D+/R-	22 (39%)
D-/R+	4 (7%)
D-/R-	4 (7%)
Not Done/R+	1 (2%)

Study drug discontinuation: Seven of the 56 subjects who received treatment withdrew from study during treatment (adverse events: 6 subjects; withdrew consent: 1 subject). All of the 49 subjects who completed treatment and 6 of the 7 subjects who withdrew during the treatment, completed the off treatment follow-up period until Week 52 post-transplantation. A summary of disposition is shown in the following figure.

Figure 1. Disposition of subjects enrolled in Study NV25409



Efficacy results:

CMV disease: CMV disease (defined as CMV syndrome or tissue-invasive CMV disease) was not reported in any subject in this study (until Week 52 post-transplantation). CMV viremia confirmed by the central laboratory (CMV DNA levels above the limit of quantification [≥150 copies/mL]) was reported in 10 (18%) patients but none of them fulfilled the criteria of CMV syndrome (CMV replication and fever or any other symptom of CMV disease) or tissue-invasive CMV disease. Eight of the 10 patients had CMV viremia after completing prophylaxis. The remaining two patients had CMV viremia during the treatment phase of the study. The major findings of these 10 patients are summarized in Table 4.

Table 4. Findings in patients with CMV viremia

Patient No	Age at transplantation (years)	Sex	CMV serology status of Donor/Recipient	Time to positive CMV test after initiating prophylaxis	Treated for CMV
234011/90801*	9	M	D+/R-	Week 24 (495 copies/mL)	No
234028/90409*	13	M	D+/R-	Week 24 (180 copies/mL)	No
234011/90803	12	M	D+/R-	Week 44 (3245 copies)	No
234020/91601	1	F	D+/R+	Week 36 (285 copies)	No
234024/92202	3	M	D+/R-	Week 36 (3800 copies/mL)	No
234013/92901	9	M	D+/R+	Week 36 (1452 copies/mL)	No
234013/92902	16	M	D+/R+	Week 28 (318 copies/mL) (8 weeks after prophylaxis which was ended due to adverse event)	No
234013/92904	10	M	D+/R+	Week 36 (11330 copies/mL)	No
233049/90104	12	F	D+/R-	Week 40 (664 copies/mL)	Yes
233041/90602	15	M	D+/R-	Week 48 (343 copies/mL)	Yes

*CMV viremia occurred while patients were receiving valganciclovir for prophylaxis

Comments: Similar to Study WV16726 (study enrolled 63 pediatric solid organ transplant patients [liver, heart, and kidney]) who received valganciclovir prophylaxis for 100 days), none of the patients enrolled in Study NV25409 developed CMV disease. However, the frequency of asymptomatic CMV viremia was higher in Study NV25409 compared to that observed in Study WV16726 (18% vs. 11%). It should be noted that these studies are not directly comparable as they were conducted at different times with some significant differences in study design. Study WV16726 was conducted in 2004-2005, whereas Study NV25409 was conducted in 2011-2013. In study NV25409, blood samples were collected monthly and assays were performed by central laboratory; while only events (CMV viremia) reported by the local laboratory were captured in Study WV16726. The 18% incidence of asymptomatic CMV viremia in Study NV25409 is based on confirmation by the central laboratory. Only 4 of the 56 patients (7%) enrolled in Study NV25409 had CMV viremia events based on local laboratory assays; 3 patients with asymptomatic CMV infection (viremia or

antigenemia) and 1 patient with CMV syndrome. The case with CMV syndrome was not confirmed, because all blood samples tested by the central laboratory were negative for CMV.

CMV viral load testing is not straightforward. Prior to July 5, 2012, there were no FDA–approved laboratory tests for the quantification of CMV DNA. Therefore, most CMV viral load tests were considered laboratory-developed tests that are developed and validated by an individual laboratory to the standard of the laboratory-inspecting agencies. A multicenter study conducted to assess the variability of CMV viral load testing across 33 laboratories in the United States, Europe, and Canada showed that the variability in viral load values for individual samples ranged from 2.0 $\log_{10}$ copies/mL to 4.3 $\log_{10}$ copies/mL (Pang et al., 2009). These findings reinforce the fact that test results from 2 laboratories cannot be directly compared nor can clinically relevant cutoffs developed using 1 test be applied to results from another test, unless the 2 tests have been rigorously compared and the relationship between them is well understood.

CMV viremia by CMV serology status: When patients with CMV viremia were analyzed according to the CMV serology status of the donor and recipient, it was found that 6 of the 10 patients were D+/R-, and 4 of the 10 were D+/R+ (Table 5).

Table 5. CMV serology status of donor/recipient and CMV viremia

CMV serology status	**No of patients (N=56)**	**No of patients with CMV viremia (%)**
D+/R+	25	4 (16%)
D+/R-	22	6 (27%)
D-/R+	4	0
D-/R-	4	0
Not Done/R+	1	0

Comments: Most of the cases of CMV viremia occurred in the D+/R- group, the group at the highest risk for CMV disease after transplantation.

Patients who experienced a biopsy proven graft rejection: Six (11%) patients had biopsy proven graft rejection; 1 of the 6 (16.6%) patients in the ≤ 2 years age group, 1 of the 18

(5.5%) in the > 2 years to < 12 years group, and 4 of 32 (12.5%) in the ≥ 12 years group. Only one of the six patients who experienced biopsy proven graft rejection had CMV viremia (maximum CMV DNA levels: 664 copies/mL).

Patients who experienced graft loss: No patients experienced graft loss in this study.

Patient survival at 12 months post-transplantation: There were no deaths during the course of this study.

Safety results:

All patients experienced at least one adverse event (AE) between the first day through the end of treatment plus 28 days (defined as "on treatment"). An overall summary of AEs that occurred in more than 10% of patients is shown in Table 6.

Table 6. Adverse events reported in more than 10% of patients on treatment by age group

Adverse event	**≤ 2 years (N=6)**	**>2 to < 12 years (N=18)**	**≥ 12 years (N=32)**	**Total (N=56)**
Upper respiratory tract infection	3 (50%)	6(33%)	10 (31%)	19 (34%)
Urinary tract infection	5 (83%)	6 (33%)	8 (25%)	19 (34%)
Diarrhea	3 (50%)	7 (39%)	8 (25%)	18 (32%)
Leukopenia	1 (17%)	2 (11%)	11 (34%)	14 (25%)
Neutropenia	1 (17%)	5 (28%)	7 (22%)	13 (23%)
Headache	-	4 (22%)	8 (25%)	12 (21%)
Abdominal pain	2 (33%)	4 (22%)	4 (13%)	10 (18%)
Dysuria	1 (17%)	3 (17%)	6 (19%)	10 (18%)
Tremor	-	2 (11%)	8 (25%)	10 (18%)
Anemia	-	4 (22%)	5 (16%)	9 (16%)
Hypertension	1 (17%)	6 (33%)	2 (6%)	9 (16%)
Blood creatinine increased	1 (17%)	4 (22%)	4 (13%)	9 (16%)
Pyrexia	3 (50%)	2 (11%)	4 (13%)	9 (16%)
E. coli urinary tract infection	3 (50%)	2 (11%)	2 (6%)	7 (13%)
Vomiting	1 (17%)	3 (17%)	3 (9%)	7 (13%)
Hematuria	1 (17%)	2 (11%)	3 (9%)	6 (11%)

Comment: Upper respiratory tract and urinary tract infections were the most common adverse events followed by diarrhea, leukopenia and neutropenia.

The majority of the adverse events were mild (363 of the total of 577 reported AEs) or moderate (136/577) in intensity. Most of the AEs were considered by the investigators not related to study drug (522/577).

Serious AEs: A total of 106 SAEs were reported by 41 patients during the entire study. The most common SAEs were reported from the SOC infections and infestations (27

patients, 48%), blood and lymphatic system disorders (9 patients, 16%), and renal and urinary disorders (7 patients, 13%). The most common SAEs were urinary tract infection (10 patients, 18%), pyelonephritis (5 patients, 9%), elevated blood creatinine (5 patients, 9%), and neutropenia (5 patients, 9%).

E.coli was the most common etiology of urinary tract infections and pyelonephritis, accounting for 4 of the 10 cases of urinary tract infection and 3 of the 5 cases of pyelonephritis. None of the cases had severe neutropenia during the episodes of urinary tract infection or pyelonephritis.

Eighty-three of the 106 SAEs were reported by 37 patients while on treatment. A similar number of SAEs was reported from Days 1-100 (43 SAEs by 22 patients) and Days 101-228 (40 by 28 patients).

Serious AEs related to study drug: A total of 14 SAEs experienced by 9 patients were considered related to study drug and all these events occurred while on treatment. Four of the 9 patients were in the > 2 to < 12 years group and 5 in the ≥ 12 years group. None of the patients in the ≤ 2 years of age group experienced an SAE related to study drug. Ten of the 14 SAEs were severe in intensity while the remaining 4 AEs were moderate in intensity. The most common SAEs were reported from the SOC blood and lymphatic system disorders, accounting for 10 of the 14 SAEs, were neutropenia 5, leukopenia 2, pancytopenia 2, and bicytopenia 1. A summary of the SAEs related to study drug are shown in Table 7.

Table 7. Treatment related serious adverse events

Adverse event	≤ 2 years (N=6)	>2 to < 12 years (N=18)	≥ 12 years (N=32)	Total (N=56)
Total number of patients with at least one SAE	-	4 (22%)	5 (16%)	9 (16%)
Total number of SAEs	-	5	9	14
Blood and lymphatic disorders				
Total number of patients with at least one event	-	3	5	8
Neutropenia	-	2	3	5
Leukopenia	-	1	1	2
Pancytopenia	-	-	2	2
Bicytopenia	-	1	-	1
Total number of SAEs	-	4	6	10
Gastrointestinal disorders				
Total number of patients with at least one event	-	-	1	1
Nausea	-	-	1	1
Vomiting	-	-	1	1
Total number of SAEs			2	2
Infections and Infestations				
Total number of patients with at least one event	-	1	-	1
Infection	-	1	-	1
Total number of SAEs	-	1	-	1
Nervous system disorders				
Total number of patients with at least one event	-	-	1	1
Headache	-	-	1	1
Total number of SAEs	-	-	1	1

Withdrawals due to AEs: Six (11%) patients withdrew from study treatment because of AEs. Five of the 6 patients withdrew because of blood dyscrasias: 1 patient with neutropenia and anemia, 2 patients with pancytopenia, 1 patient with neutropenia, and 1 patient with bicytopenia. These events were considered related to study drug. The sixth patient withdrew because of abdominal pain, diarrhea, vomiting, and gastrointestinal protozoal infection (these adverse events were considered unrelated to study drug). All AEs that led to withdrawal of study treatment subsequently resolved.

Five of the 6 patients who withdrew from study treatment because of AE were in the ≥12 years age group and the remaining one in the > 2 to < 12 years group.

AEs that led to dose modification: Twenty-two patients had 40 AEs that led to dose modification. Fifteen (27%) of patients had 25 AEs during the first 100 days of study and 13 (23%) patients had 15 AEs during Days 101-128 of the study. In 13 of the 22 patients dose modification was due to AEs from the SOC blood and lymphatic system disorders.

Laboratory abnormalities: The key laboratory findings observed in Study NV25409 are summarized in Table 8, together with findings from the previous pediatric study, WV16726, and the previous adult study in kidney transplant patients (NT18435).

Table 8. Key laboratory findings in Studies NT18435, WV16726, and NV25409

Laboratory abnormalities	Study NT18435 Adult Study (kidney transplant patients)		Study WV16726 Pediatric Day 100 post-transplant (kidney, heart, liver) (N=63) %	Study NV25409 Pediatric Day 200 post-transplant (kidney) (N=56) %
	Valcyte Tablets Day 100 Post-transplant (N=164) %	Valcyte Tablets Day 200 Post-transplant (N=164) %		
Neutropenia: ANC/µL				
< 500	9	10	5	30
500 – < 750	6	6	8	4
750 – < 1000	7	5	5	11
Anemia: Hemoglobin g/dL				
< 6.5	0	1	0	0
6.5 – < 8.0	5	1	14	5
8.0 – < 9.5	17	15	38	29
Thrombocytopenia: Platelets/µL				
< 25000	0	0	0	0
25000 – < 50000	1	0	10	0
50000 – < 100000	7	3	3	2
Serum Creatinine: mg/dL				
> 2.5	17	14	2	5
> 1.5 – 2.5	50	48	11	20

The most remarkable laboratory abnormality was the incidence of severe neutropenia noted in Study NV25409. Seventeen of the 56 patients (30%) enrolled in study developed Grade 4 neutropenia. This incidence was higher than that observed in pediatric solid organ transplant patients treated until Day 100 (3/63, 5%) and as compared to the adult kidney transplant patients treated until Day 100 or Day 200. In 11 of the 17 patients the events of neutropenia occurred during the Days 1-100.

The number of patients experiencing a marked shift in selected laboratory abnormalities (worsening of 3 or 4 grades) is summarized in Table 9.

Table 9. Marked shifts from baseline in key laboratory parameters.

Laboratory parameter	Abnormality	N	Number of patients who had a shift of:	
			Three Grades	Four Grades
Lymphocytes	Low	53	3 (6%)	1 (2%)
WBCs	Low	54	1 (2%)	-
Neutrophils	Low	53	1 (2%)	1 (2%)
Inorganic phosphorus	Low	54	2 (4%)	-
Uric acid	Low	54	4 (7%)	-
Uric acid	High	54	4 (7%)	-
Creatinine	Low	52	2 (4%)	

Comment: Marked laboratory abnormalities were most commonly observed with uric acid. Interestingly, only two patients had marked shift in neutrophils.

Conclusions:

Study NV25409, a tolerability rather than efficacy study, is the pivotal pediatric study submitted to support the extension of the valgancicicloviir dosing regimen from 100 days to 200 days post-transplantation in pediatric kidney transplant patients 4 months to 16 years of age. Efficacy was extrapolated from the adult study which demonstrated that valganciclovir administered until 200 days post-transplantation is superior to valganciclovir administered until 100 days post-transplantation.

Fifty-seven children who received kidney transplant and met the entry criteria entered the study. They received valganciclovir within 10 days after transplantation until a maximum of 200 days. CMV viremia confirmed by the central laboratory was reported in 10 (18%) of patients, but none of these events fulfilled the criteria of CMV syndrome or tissue-invasive CMV disease. The overall safety profile was similar to that observed in pediatric solid organ transplant patients who received valganciclovir for 100 days. However, the incidence of severe neutropenia (ANC < 500/μL) was higher in pediatric kidney transplant patients treated until Day 200 (17/57, 30%) compared to pediatric solid organ transplant patients treated until Day 100 (3/63, 5%). It is notable that the two studies differ in the period for safety monitoring. Safety data for both studies were collected while “on treatment,” which was defined as the treatment period plus 28 days; thus, the period of safety monitoring was 228 days for Study NV25409 and 128 days for Study WV16726. Considering the routine practice in transplant centers and the awareness of adverse reactions associated with the use of this drug, we believe that the benefits of extending the dosing regimen to 200 days outweigh the potential risks.

The DAVP and the Pediatric Review Committee determined that the submitted data fulfilled the requirements for PREA PMR #1670-1.

Studies submitted to support the approval of valganciclovir for CMV prophylaxis in heart transplant patients from birth to less than 4 months of age:

Study NP22523: Pharmacokinetics and safety of valganciclovir in pediatric heart transplant recipients < 4 months of age

This was an open-label, pharmacokinetic and safety study of ganciclovir after administration of valganciclovir for oral solution in pediatric heart transplant recipients < 4 months of age. The initial plan was to enroll a minimum of 16 patients < 4 months of age with at least 4 patients < 6 weeks.

Heart transplant patients who were hemodynamically stable and were already receiving or were eligible to receive CMV preventive therapy with either intravenous ganciclovir or valganciclovir for oral solution underwent screening for study enrollment within two days prior to study drug administration. Enrolled subjects had their preventive CMV therapy interrupted for two days in order to participate in the study. They received oral valganciclovir once daily for two days. Dosing was determined using the currently approved dosing algorithm for children based on body surface area (BSA) and estimated creatinine clearance:

Dose (mg) = 7 x BSA x CrCl.

Blood samples were collected for pharmacokinetic assessments on Dosing Day 2 at the following intervals: pre-dose (within 1 hour prior to valganciclovir administration, 1-3 h, 3-7 h (at least 1 hour after the previous blood draw), 7-12 h (at least 2 hours after the previous blood draw), and 24 h after valganciclovir administration. Following the 24-hour pharmacokinetic blood sample collection, patients continued their usual anti-CMV prophylaxis treatment at their centers. Laboratory samples for safety assessment were obtained at screening, on Day 1 and 2 prior to dosing, on the time of last pharmacokinetic sample and at safety review visit performed approximately 7 days after the second valganciclovir dose.

A total of 17 patients < 4 months of age were enrolled in the study. The age distribution of the enrolled patients was as follows:

< 6 weeks of age: 2 subjects (pharmacokinetic data from 2)
6 weeks to < 4 months of age: 15 subjects (pharmacokinetic data from 14)

Although the initial plan was to enroll at least 4 patients < 6 weeks of age, only 2 patients were enrolled in this age group because of difficulties in recruiting such young patients.

Dose rationale:
The dosing algorithm used in Study NP22523 was the same as that one approved for older children.

Baseline characteristics and disposition of patients:

Of the 17 subjects enrolled in this study, 10 (59%) were male and 7 (41%) were female. Twelve (71%) were white, 4 (24%) were black, and the remaining 1 of other race. The ethnicity breakdown was 2 (12%) Hispanic or Latino and the remaining 15 (88%) were not Hispanic or Latino.

The mean age at the time of the last pharmacokinetic sample of the subjects enrolled in the 6 week to < 4 month age group was 92.8 ± 27.7 days. The two patients in the < 6 week age group were 26 and 37 days old at the time of the last pharmacokinetic sample. The serology results for CMV status are shown in the following table.

Table 10. Summary of CMV serology status – Study NP22523

CMV serology status	**N = 17**
D+/R+	7 (41.2%)
D+/R-	5 (29.4%)
D-/R+	5 (29.4%)

Pharmacokinetic results:
The pharmacokinetic data obtained from the first 14 patients enrolled in this study, together with data from previous pharmacokinetic studies in solid organ transplant recipients (Studies WP16296, WP16303, and WV16726), were used to build a population pharmacokinetic model (PopPK).

A summary of the model-estimated pharmacokinetics of ganciclovir in pediatric solid organ transplant patients by age from Study NP22523 (patients < 4 months of age) and Study WV16726 (age groups 4 months to ≤ 2 years, > 2 to < 12 years, and ≥ 12 years) is shown in Table 11.

Table 11 Model-estimated ganciclovir pharmacokinetics by age in pediatric solid organ transplant patients (Studies NP22523 and WV16726) [a]

Organ	PK Parameter mean (SD)	Age Group < 4 months	4 months to ≤ 2 years	> 2 to < 12 years	≥ 12 years
Heart (N=26)	N	14[b]	6	2	4
	AUC_{0-24h} (µg·h/mL)	66.3 (20.5)[c]	55.4 (22.8)	59.6 (21.0)	60.6 (25.0)
	C_{max} (µg/mL)	10.8 (3.30)	8.2 (2.5)	12.5 (1.2)	9.5 (3.3)
	$t_{1/2}$ (h)	3.5 (0.87)	3.8 (1.7)	2.8 (0.9)	4.9 (0.8)
Kidney (N=31)	N	NA	2	10[d,e]	19
	AUC_{0-24h} (µg·h/mL)		67.6 (13.0)	55.9 (12.1)	47.8 (12.4)
	C_{max} (µg/mL)		10.4 (0.4)	8.7 (2.1)	7.7 (2.1)
	$t_{1/2}$ (h)		4.5 (1.5)	4.8 (1.0)	6.0 (1.3)
Liver (N=17)	N	NA	9	6	2
	AUC_{0-24h} (µg·h/mL)		69.9 (37.0)	59.4 (8.1)	35.4 (2.8)
	C_{max} (µg/mL)		11.9 (3.7)	9.5 (2.3)	5.5 (1.1)
	$t_{1/2}$ (h)		2.8 (1.5)	3.8 (0.7)	4.4 (0.2)

N= number of patients
[a] Pharmacokinetic parameters were estimated by using population pharmacokinetic modeling.
[b] 14 heart transplant patients 26 to 124 days of age were included in the population pharmacokinetic model development.
[c] 19 observations, some patients contributed more than one value.
[d] There was one subject in this age group who received both a kidney and liver transplant. The pharmacokinetic profile for this subject has not been included in this table as it is not possible to determine whether the effects observed are from the kidney/liver transplant or neither.
[e] The pharmacokinetic profiles for two subjects in this age group who received kidney transplants have not been included in this table as the data were determined to be non-evaluable.

Comments: Although the mean AUC_{0-24h} exposure (66.3 µg.h/mL) in heart transplant patients < 4 months of age was within acceptable range,

it was somewhat higher than the targeted historical adult exposures resulting from a valganciclovir dosing 900 mg once daily (targeted $AUC_{0\text{-}24h}$ 40-60 µg.h/mL). The targeted AUC derived from adults is based on efficacy and safety data from Study PV16000 which demonstrated that $AUC_{0\text{-}24h}$ <40 µg.h/mL was associated with higher risk of CMV viremia and $AUC_{0\text{-}24h}$ >60 µg.h/mL was associated with higher risk of leukopenia (neutropenia).

Thus, the Division requested additional analyses of the pharmacokinetic data from all pediatric solid organ transplant patients to investigate whether by changing the dosing algorithm from "7 x BSA x CrCl" to "6 x BSA x CrCl", a greater proportion of patients would have AUC exposures within the targeted AUC range, and fewer patients would have AUC values above the target range. The results of these analyses are shown in the following two tables.

Table 12. Observed ganciclovir AUC_{0-24h} (µg • h/mL) for patients treated with a Valganciclovir Dose (mg) of 7 ×BSA×Schwartz CrCL (Studies NP22523 and WV16726)

	<4 months	≥4 months to ≤2 years	>2 to <6 years	≥6 to <12 years	≥12 to ≤16 years	All Patients
No. patients	14	17	8	12	25	76
No. AUC estimates [a]	19	101	29	56	59	264
Median	61.4	59.5	54.9	53.1	49.0	55.1
Min	33.8	33.3	40.7	30.9	24.2	24.2
Max	123.2	107.1	82.0	93.6	96.6	123.2
P5	33.8	38.4	42.7	38.2	29.1	36.6
P95	123.2	89.7	80.1	77.6	79.8	83.2
Patients AUC <40 µg • h/mL	1 (7%)	1 (6%)	—	—	8 (32%)	10 (13%)
Patients AUC 40–60 µg • h/mL	5 (36%)	8 (47%)	5 (62%)	9 (75%)	12 (48%)	39 (51%)
Patients AUC >60 µg • h/mL	8 (57%)	8 (47%)	3 (38%)	3 (25%)	5 (20%)	27 (36%)

AUC = area under the plasma concentration-time curve; BSA = body surface area; CrCL = creatinine clearance; max = maximum; min = minimum.

[a] Some patients provided more than one set of pharmacokinetic samples (observations) for the estimation.

Table 13. Calculated ganciclovir AUC_{0-24h} (µg • h/mL) for patients projected for a valganciclovir dose (mg) of 6 ×BSA×Schwartz CrCL based on observed PK data for each patient (Studies NP22523 and WV16726**)**

	<4 months	≥4 months to ≤2 years	>2 to <6 years	≥6 to <12 years	≥12 to ≤16 years	All Patients
No. patients	14	17	8	12	25	76
No. AUC estimates [a]	19	101	29	56	59	264
Median	52.6	51.0	47.1	45.5	42.0	47.2
Min	29.0	28.5	34.9	26.5	20.7	20.7
Max	105.6	91.8	70.3	80.2	82.8	105.6
P5	29.0	32.9	36.6	32.7	24.9	31.4
P95	105.6	76.9	68.7	66.5	68.4	71.3
Patients AUC <40 µg • h/mL	1 (7%)	5 (29%)	—	5 (42%)	11 (44%)	22 (29%)
Patients AUC 40–60 µg • h/mL	8 (57%)	9 (53%)	7 (87%)	6 (50%)	10 (40%)	40 (53%)
Patients AUC >60 µg • h/mL	5 (36%)	3 (18%)	1 (13%)	1 (8%)	4 (16%)	14 (18%)

AUC = area under the plasma concentration-time curve; BSA = body surface area; CrCL = creatinine clearance; max = maximum; min = minimum.

[a] Some patients provided more than one set of pharmacokinetic samples (observations) for the estimation.

Comments: These analyses demonstrated that both regimens achieve a similar fraction of patients within the target range of 40-60 µg.h/mL The current formula (7 x BSA x CrCl) results in in fewer patients underexposed (13% vs. 29%) and at higher risk for CMV infection; on the other hand, the current formula results in higher proportion of patients with AUC levels above the upper range (36% vs. 18%).

Considering the routine practice in transplant centers and the awareness of the potential adverse reactions associated with overexposure, it is preferable to keep the currently approved dosing regimen as the most appropriate for pediatric patients.

Efficacy results:

Efficacy data were not obtained in this study.

Safety results:

Adverse events: All safety events were reported as events occurred either during study dosing days or during the follow-up period of the study (Days 3 to 9).

Eight (47%) of the 17 patients included in the safety population experienced 19 adverse events. Five of the 19 adverse events occurred during the dosing period and 14 adverse events during the follow-up period. The most common adverse events were anemia (4) and vomiting (2). The remaining adverse events occurred as a single occurrence. Only one of the adverse events was considered by the investigator possibly related to study drug. This was a case of anemia that was mild in intensity.

Fourteen of the 19 adverse events were mild in intensity, four adverse events were moderate (anemia, hematochezia, dehydration, and thrombocytosis) and one adverse event was considered severe (postoperative wound infection).

Adverse events led to dose modification or to withdrawal of study drug: None

Serious adverse events: Two patients experienced serious adverse events during the follow-up period; one patient with dehydration and one with postoperative wound infection.

Deaths: There was one death which occurred after the study follow-up. This was the case with postoperative wound infection. This 4-month-old male (at the time of screening) had a history of obstructive hydrocephalus, ascites, chylothorax, and renal and respiratory failure. The patient had a heart failure on (b) (6) because of congenital aortic stenosis. The patient was receiving intravenous ganciclovir for CMV prophylaxis after the transplantation. Twelve days after the heart transplant surgery the intravenous ganciclovir was interrupted and the patient was started on study medication after a 48 hour washout period. His standard of care treatment was resumed on Study Day 3. On study Day 4 the patient was diagnosed with postoperative wound infection due to the heart transplant and open chest. He was started on antibiotics on study day 9. On the same day, his clinical condition deteriorated due to renal insufficiency, shock, pleural effusion and ascites. At the time of completion of the study (study Day 9) this event was considered unresolved. (b) (6) after completing the study, the patient died due to this event (b) (6)). The event was considered unrelated to study drug.

Laboratory abnormalities: There were few cases with Grade 3 or Grade 4 laboratory abnormalities. However, in almost all cases there was only one grade shift from baseline.

Comment: The overall safety profile of oral ganciclovir was consistent with that obtained in previous pediatric studies and there were no unexpected findings.

It should be noted that most of the patients enrolled in this study were receiving CMV prevention (predominantly intravenous ganciclovir) prior to study drug as part of the local protocols and continued with CMV prevention after the completion of study drug. Therefore, it is very difficult to distinguish whether the adverse events were due to the anti-CMV medications administered prior and after study drugs or to study drug.

No conclusions with respect to safety can be drawn from this study considering the short duration of the study and the standard of care with CMV prevention drugs prior and after study drug.

Physiologically based pharmacokinetic model

The Applicant submitted a PBPK model to support dosing recommendations of valganciclovir for the prevention of CMV disease in heart transplant patients < 6 weeks of age. The PBPK model was developed at the request of the Division because of difficulties in enrolling patients < 6 weeks of age in Study NP22523 (only two patients were enrolled, aged 26 and 37 days, respectively). The development of the PBPK model was based on the available pharmacokinetic data from pediatric and adult patients.

The PBPK model was initially developed for preclinical species and then adults by incorporating physiological and drug-specific parameters. The model was verified for adults by comparing model predictions to PK data from four studies in adult transplant or CMV-positive patients. The model was scaled from adults to children by incorporating age-specific changes in physiological parameters, and was evaluated in comparison to observed data from three studies in pediatric transplant recipients and one study in infants with congenital CMV disease.

Several drug-specific and physiological parameters had to be “fit” and/or adjusted in order to obtain adequate model PK predictions in adults and children >1 month of age. An additional assumption of very low transporter expression, which was not verified, was required to obtain adequate predictions in neonates. Due to the uncertainty (particularly for neonates) in model predictions, the review team determined that the model is not sufficiently verified to support dosing recommendations in neonates.

For more details, please see the review by Dr. Mario Sampson, the Clinical Pharmacology reviewer.

Study CASG112: A phase 3, randomized, placebo-controlled, blinded investigation of 6 weeks versus 6 months of oral valganciclovir therapy in infants with symptomatic congenital CMV infection

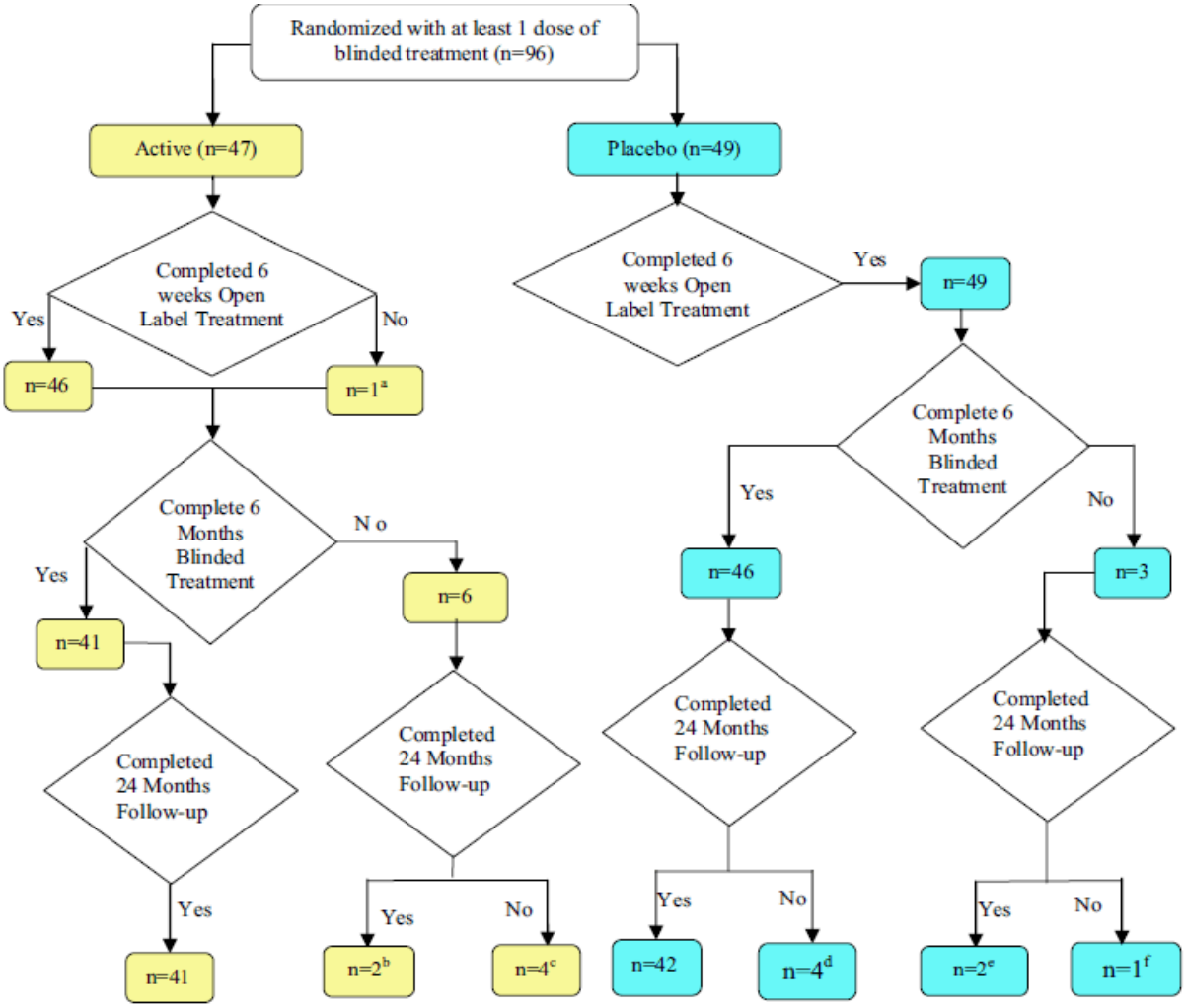
The Applicant submitted safety data from the CASG112 study to support the dosing recommendation of valganciclovir for the prevention of CMV disease in heart transplant patients < 4 months of age. This was a phase 3, multicenter, international, placebo-controlled, randomized blinded study designed to compare 6 weeks versus 6 months of treatment of oral valganciclovir therapy in neonates with symptomatic congenital CMV disease. A total of 109 subjects ≤ 30 days of age who had a confirmed diagnosis of symptomatic congenital CMV infection and fulfilled the entry criteria received 6 weeks treatment with oral valganciclovir (dose: 16 mg/kg/dose b.i.d.). Upon completing the 6-week course, subjects were randomized in 1:1 ratio to continue with oral valganciclovir to complete 6 months or to begin a matching placebo to complete the 6 months.

Dose rationale: The 16 mg/kg b.i.d. dose was based on a previous pharmacokinetic study conducted in 24 neonates with congenital CMV infection involving the central nervous system (CASG109). The pharmacokinetic results showed that in infants greater than 7 days to 3 months of age, a dose of 16 mg per kg twice daily of Valcyte for oral solution provided ganciclovir systemic exposures (median $AUC_{0\text{-}24h}$ = 47.2 [range 33.6 – 71.0] mcg·h/mL; n = 6) comparable to those obtained in infants up to 3 months from a 6 mg per kg dose of intravenous ganciclovir twice daily ($AUC_{0\text{-}24h}$ = 50.6 [range 4.8 – 179.4] mcg·h/mL; n = 18) or to the ganciclovir systemic exposures obtained in adults from a 900 mg dose of Valcyte tablets twice daily.

Disposition of subjects:

A total of 109 subjects were enrolled in the study but only 107 subjects received open-label valganciclovir (two subjects withdrew prior to receiving study drug). Ninety-seven subjects completed the open label treatment. Ninety-six of the 97 subjects began the blinded study treatment: 49 subjects were randomized in the placebo group and 47 subjects in the active arm of the study. Forty-six of the 49 subjects in the placebo group and 41 of the 47 in the active arm completed the 6-month blinded treatment. Disposition of subjects by blinded treatment is summarized in Figure 2.

Figure 2. Disposition of subjects by blinded treatment (CASG112)



Safety results:

Adverse events were collected and reported for subjects throughout the study period, i.e., during the 6 week period of initial treatment with valganciclovir and during the randomized, blinded treatment period in which subjects received valganciclovir or placebo through 6 months. Ninety-two of the 96 randomized subjects experienced at least one AE for a total of 675 AES. Fifty-three percent (347 AEs) of the AEs were from subjects in the placebo group. No significant difference was observed in the number of subjects with AEs between the two treatment groups in any of the body systems. The most common AEs by Body System were: Infections and Infestations (164 AEs), Gastrointestinal Disorders (124 AEs), Blood and Lymphatic System disorders (79 AEs),

Skin and Subcutaneous Tissue disorders (69 AEs), and Investigations (62 AEs). The majority of AEs were mild or moderate in intensity.

Serious AEs: A total of 43 SAEs were reported by 30 randomized subjects. Eleven subjects in the active group (valganciclovir) experienced a total of 18 SAEs and 19 subjects in the placebo group experienced 25 SAEs. The most common SAEs were reported from the SOC blood and lymphatic system disorders (15 SAEs: placebo group 11, active group 4) and infections and infestations (15 SAEs: placebo group 10, active group 5).

Of the 43 SAEs, 9 SAEs were mild in intensity (placebo group 3, active group 6), 17 SAEs were moderate in intensity (placebo group 9, active group 8), 5 SAEs were severe (all of them in the placebo group) and 12 SAEs were life-threatening (placebo group 8, active group 4).

In the initial 6 weeks of treatment, 42 (89%) of subjects who were later randomized to the active group and 39 (80%) of subjects who were later randomized to the placebo group did not experience SAE. During the blinded period, 37 (79%) of subjects randomized to active treatment group and 39 (80%) of subjects randomized to placebo did not experience SAE.

Withdrawals due to AEs: All but two of the AEs that led to withdrawal from study treatment occurred during the initial 6 weeks of treatment. The two AEs (rash and neutropenia) that occurred during the randomization phase of the study belonged to the placebo group.

Deaths: No deaths were reported during the study.

Laboratory abnormalities: There were no clinically significant differences in laboratory abnormalities between the two groups. Grade 3 or 4 neutropenia was experienced by 21 (19%) of the subjects during the first 6 weeks of open-label valganciclovir treatment. During the randomized phase of the study, 10 of the 47 (21%) subjects randomized to the active group and 13 of the 49 (27%) subjects who were randomized in the placebo group demonstrated Grade 3 or Grade 4 neutropenia.

No subjects experienced a marked shift in selected laboratory abnormalities (worsening of 3 or 4 grades). Three subjects had 2 grades worsening in SGPT levels (2 subjects in the active group and 1 subject in the placebo group).

Safety data from patients enrolled in CASG112 study who had ganciclovir $AUC_{0\text{-}24h} \geq 40$ g/μL and received valganciclovir for at least 100 days:

Twenty-one subjects assigned to the active (valganciclovir) treatment group of the study met these criteria. AEs were collected from enrollment until 30 days beyond the final day of study drug administration. None of the patients withdrew from the study as a result of an AE and as previously mentioned no deaths occurred during the study.

Serious adverse events: A total of 9 SAES were reported by 5 patients (ankyloglossia 1, otitis media 1, neutropenia 2, anemia 1, vomiting 1, gastroesophageal reflex 1, head injury 1, and RSV infection 1). Only 3 of the SAEs were considered related to study drug (the 2 cases of neutropenia and the case of anemia). Three of the SAEs were mild in intensity, 3 moderate and 3 were considered life-threatening.

These results indicate that the safety profile of these 21 patients in the active arm who received valganciclovir for at least 100 days and had $AUC_{0\text{-}24h} \geq 40$ g/μL was comparable to that observed in patients randomized to the placebo group.

Conclusions:

The pharmacokinetic and safety data obtained from Study NP22523 and supportive safety data from Study CASG112, together with previous demonstration of efficacy in adult patients, support the use of valganciclovir for oral solution for the prevention of CMV disease in pediatric heart transplant patients > 1 month to < 4 months of age. Due to uncertainty in PBPK model predictions for neonates (< 1 month of age), an appropriate dosing regimen could not be determinated for neonates, and thus valganciclovir is not indicated for prophylaxis in this age group.

It is noteworthy that the DAVP and the Pediatric Review Committee determined that the submitted data fulfilled the requirements for PREA PMR#1533-2. Further, the DAVP and the Pediatric Review Committee support the waiver of a study in heart transplant patients less than one month of age because such a study would be impossible.

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.

In these sNDAs, the Applicant seeks to:

- Extend the dosing regimen of valganciclovir for the prevention of CMV disease in pediatric kidney transplant recipients 4 months to 16 years of age at high risk from 100 days to 200 days post-transplantation; and
- Expand the Indications and Usage of valganciclovir to include heart transplant patients (b) (6)

Applicant's request to extend the dosing regimen from 100 days to 200 days for the prevention of CMV disease in pediatric kidney transplant recipients 4 months to 16 years of age is based on Study NV25409 and extrapolation of efficacy data from the

adult study which demonstrated that valganciclovir administered until 200 days post-transplantation is superior to valganciclovir administered until 100 days post-transplantation. In Study NV25409, 57 children who received kidney transplant and met the inclusion and exclusion criteria entered the study. They received valganciclovir within 10 days after transplantation until a maximum of 200 days. CMV viremia confirmed by the central laboratory was reported in 10 (18%) patents but none of these events fulfilled the criteria of CMV syndrome or tissue-invasive CMV disease. The overall safety profile was similar to that observed in pediatric solid organ transplant patients who received valganciclovir for 100 days. However, the incidence of severe neutropenia (ANC < 500/μL) was higher in pediatric kidney transplant patients treated until Day 200 (17/57, 30%) compared to pediatric solid organ transplant patients treated until Day 100 (3/63, 5%). Considering the routine practice in transplant centers and clinician awareness of adverse reactions associated with the use of this drug, we believe that the benefits of extending the dosing regimen to 200 days outweigh the potential risks.

Applicant's request to expand the Indications and Usage to include valganciclovir prophylaxis administered within 10 days of transplantation until 100 days post-transplantation for the prevention of CMV disease for heart transplant recipients from (b) (6) is based on:

- Study NP22523. This study was conducted in response to PREA PMR # 1533-2 issued on August 28, 2009, asking for 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.
- Physiologically based pharmacokinetic (PBPK) model. Because of difficulties in enrolling patients < 6 weeks of age, the Applicant was encouraged to develop a PBPK model based on available pharmacokinetic data from pediatric and adult patients in order to support dosing in children younger than 6 weeks of age.
- Safety data from CASG112 study, "A phase 3, randomized, placebo-controlled, blinded investigation of 6 weeks versus 6 months of oral valganciclovir therapy in infants with symptomatic congenital CMV infection".

The pharmacokinetic results from Study NP22523 showed that in infants 1 month to < 4 months of age, the currently approved valganciclovir dosing algorithm provides ganciclovir systemic exposures somewhat increased compared to the adult exposures, but within the range considered safe and effective in adults. These data, together with the supportive safety data from the CASG112 study, and extrapolation of efficacy data from adult heart transplant patients, support the expansion for the use of valganciclovir prophylaxis for the prevention of CMV disease in heart transplant recipients 1 month to less than 4 months of age. Due to unverified assumptions in the proposed PBPK model for neonates, DAVP does not recommend the approval of valganciclovir for the prevention of CMV disease in heart transplant patients less than one month of age.

6.2 Labeling Recommendations

Key labeling recommendations as of this writing our outlined below. Please refer to the Cross Discipline Team Leader (CTDL) review by Dr. Mary Singer for any subsequent labeling changes recommended after this review.

INDICATIONS AND USAGE

This section was changed to add information on the use of valganciclovir for the prevention of CMV disease in heart transplant patients one month to less than four months of age. The Pediatric Patients subsection reads as follows:

DOSAGE AND ADMINISTRATION

This section was changed to: 1) extend the dosing regimen from 100 days to 200 days for the prevention of CMV disease in pediatric transplant patients 4 months to 16 years of age, and 2) to expand the use of valganciclovir for the prevention of CMV disease in heart transplant patients one month to less than 4 months of age. The subsection of Pediatric Patients reads as follows:

Pediatric Patients
Prevention of CMV Disease in Pediatric Kidney Transplant Patients: For pediatric kidney transplant patients 4 months to 16 years the recommended once daily mg dose (7 x BSA x CrCl) should start within 10 days of post-transplantation until 200 days post-transplantation.

Prevention of CMV Disease in Pediatric Heart Transplant Patients: For pediatric heart transplant patients 1 month to 16 years of age, the recommended once daily mg dose (7 x BSA x CrCl) should start within 10 days of post-transplantation until 100 days post-transplantation.

CLINICAL PHARMACOLOGY

The subsection of pharmacokinetics of pharmacokinetics was modified to add pharmacokinetic data in heart transplant patients less than 4 months of age. Below is the modified Table 12.

Table 1 Ganciclovir Pharmacokinetics by Age in Pediatric Solid Organ Transplant Patients[a]

Organ	PK Parameter mean (SD)	Age Group < 4 months	4 months to ≤ 2 years	> 2 to < 12 years	≥ 12 years
Heart (N=26)	N	14[b]	6	2	4
	AUC_{0-24h} (µg·h/mL)	66.3 (20.5)[c]	55.4 (22.8)	59.6 (21.0)	60.6 (25.0)
	C_{max} (µg/mL)	10.8 (3.30)	8.2 (2.5)	12.5 (1.2)	9.5 (3.3)
	$t_{1/2}$ (h)	3.5 (0.87)	3.8 (1.7)	2.8 (0.9)	4.9 (0.8)
Kidney (N=31)	N	NA	2	10[d,e]	19
	AUC_{0-24h} (µg·h/mL)		67.6 (13.0)	55.9 (12.1)	47.8 (12.4)
	C_{max} (µg/mL)		10.4 (0.4)	8.7 (2.1)	7.7 (2.1)
	$t_{1/2}$ (h)		4.5 (1.5)	4.8 (1.0)	6.0 (1.3)
Liver (N=17)	N	NA	9	6	2
	AUC_{0-24h} (µg·h/mL)		69.9 (37.0)	59.4 (8.1)	35.4 (2.8)
	C_{max} (µg/mL)		11.9 (3.7)	9.5 (2.3)	5.5 (1.1)
	$t_{1/2}$ (h)		2.8 (1.5)	3.8 (0.7)	4.4 (0.2)

N= number of patients
[a] Pharmacokinetic parameters were estimated by using population pharmacokinetic modeling.
[b] 14 heart transplant patients 26 to 124 days of age were included in the population pharmacokinetic model development.
[c] 19 observations, some patients contributed more than one value.
[d] There was one subject in this age group who received both a kidney and liver transplant. The pharmacokinetic profile for this subject has not been included in this table as it is not possible to determine whether the effects observed are from the kidney/liver transplant or neither.
[e] The pharmacokinetic profiles for two subjects in this age group who received kidney transplants have not been included in this table as the data were determined to be non-evaluable.

CLINICAL STUDIES

The following information was added under the subsection Pediatric Patients:

Prevention of CMV in Pediatric Kidney Transplantation: Fifty-seven children, 1 to 16 years of age, who had a renal transplant and were at risk for developing CMV disease, were enrolled in an open-label, tolerability study of oral Valcyte (Valcyte for oral solution or tablets). Patients received Valcyte once daily within 10 days after transplant until a maximum of 200 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)]*. No case of CMV syndrome or tissue-invasive CMV disease was reported (b) (6)

7 Appendices

7.1 Clinical Investigator Financial disclosure

Clinical Investigator Financial Disclosure
Review Template

Application Number: 21304/S-11 & 22257/S-5

Submission Date(s): March 31, 2014

Applicant: Hoffman-La Roche,

Product: Valganciclovir

Reviewer: Andreas Pikis

Date of Review: March 20, 2015

Covered Clinical Study (Name and/or Number): NP22523 & NV25409

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: Principle investigators: 45; sub-investigators: 108		
Number of investigators who are sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455):		

None		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) None		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Andreas Pikis, M.D.
Medical reviewer, DAVP

Concurrences:
Mary Singer, M.D., Ph.D.,
Medical Team Leader, 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
03/26/2015

MARY E SINGER
03/26/2015
I concur with Dr. Pikis' review and recommendations.