# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**22-257s000**

**21-304s007**

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

# CLINICAL PHARMACOLOGY MEMO

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|---|---|
| **NDA:** | 22-257 |
| **Generic Name:** | Valganciclovir hydrochloride |
| **Formulation:** | Powder for oral solution; 50 mg/ml |
| **Sponsor:** | Roche |
| **Submission Date:** | April 30, 2008 |
| **Pharmacometrics Reviewer:** | Kevin M. Krudys, Ph.D. |
| **Pharmacometrics Team Leader:** | Pravin Jadhav, Ph.D. |
| **Clinical Pharmacology Reviewer:** | Vikram Arya, Ph.D. |
| **Clinical Pharmacology Team Leader:** | Kellie S. Reynolds, Pharm.D. |

This memo answers the following key question:

- Is there sufficient data to recommend substitution of tablets for oral solution in children who are able to swallow tablets?

## EXECUTIVE SUMMARY

Valganciclovir tablets and oral solution were used in a clinical trial (Study WV16726) conducted to characterize the pharmacokinetics of ganciclovir in pediatric solid organ transplant (liver, kidney, and heart) recipients aged 4 months to 16 years. (b) (4) (b) (4) The administration of either the tablet or oral solution in the pediatric population is acceptable and supported by the following:

- Valganciclovir tablets and oral solution were used interchangeably in the clinical trial (Study WV16726) which provided evidence of efficacy and safety of valganciclovir in the pediatric population. Of the 63 patients enrolled in the study, 25 patients switched from oral solution to tablet during the study and 3 patients received the tablet throughout the study. No efficacy or safety issues were identified in these patients that would suggest a clinically meaningful difference between tablet and oral solution.
- In Study WV16726, plasma ganciclovir concentrations following administration of the tablet were similar to ganciclovir concentrations following administration of oral solution.

### *Summary of Important Clinical Pharmacology Findings*

In Study WV16726, one or two 450 mg valganciclovir tablets were allowed to be taken if it was stipulated by the dosing algorithm and the child was able to swallow them. A total of 28 patients received tablets at least once during the study. Most patients who were administered the tablets were older than 12 years of age and remained on the tablet for 8 to 14 weeks (Table 1). These results show a reasonable distribution between tablet and oral solution usage in the trial. The fact that Study WV16726 provided evidence of safety and effectiveness of valganciclovir in the pediatric population supports the conclusion that there was not a difference in outcomes due to tablet or oral solution.

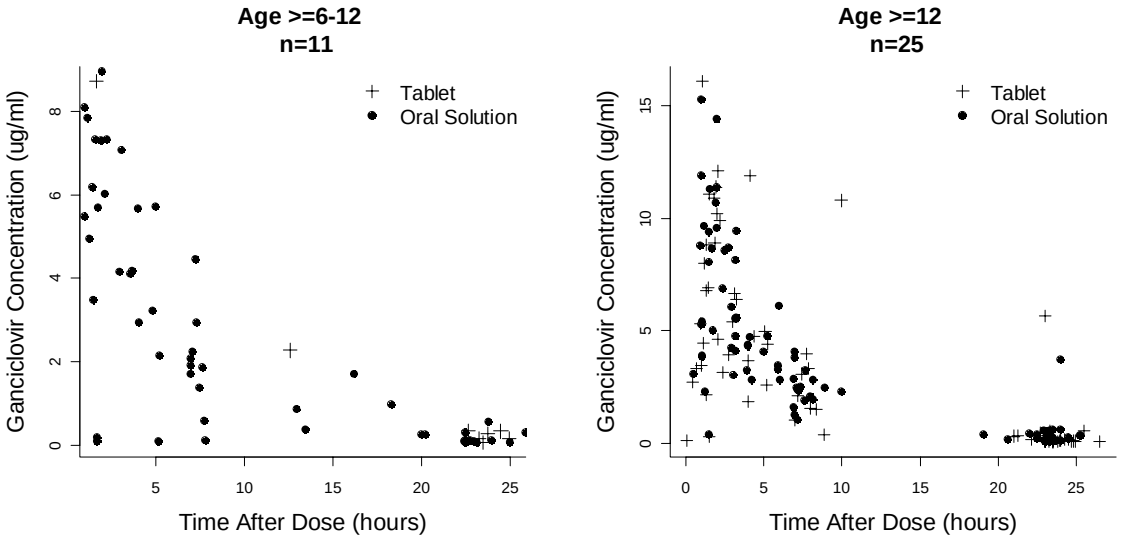
**Table 1: Extent of Exposure to Valganciclovir Tablet in Study WV16726 by Age Group**

| | >2 - < 12 YEARS N = 21 No. (%) | >= 12 YEARS N = 25 No. (%) | TOTAL N = 63 No. (%) |
|---|---|---|---|
| VALGANCICLOVIR MG | | | |
| Treatment Duration (weeks) | | | |
| 0 - 7 | 3 ( 14) | 2 ( 8) | 5 ( 8) |
| 8 - 14 | 3 ( 14) | 20 ( 80) | 23 ( 37) |
| 15 - 21 | - | - | - |
| 22 - 26 | - | - | - |

Percentages are based on N.

Ganciclovir concentrations following dosing with valganciclovir tablet were compared to concentrations following dosing with the oral solution (Figure 1). There were no patients below the age of 6 who received the tablet, so only the two older age groups are shown. In the group of patients 6 to 12 years of age there were 8 ganciclovir concentrations derived from the tablet and 60 from the oral solution. In patients older than 12 years of age there were 77 ganciclovir concentrations following the tablet and 83 concentrations following the oral solution. With the exception of a few outliers in the >12 age group, concentrations derived from the tablet were very similar to those from the oral solution. This provides further evidence that the tablets and oral solution provide similar ganciclovir exposures in the pediatric population.

**Figure 1: Comparison of Ganciclovir Concentrations Following Valganciclovir Tablets and Oral Solution by Age Group in Study WV 16726**




## Listing of Datasets and Analyses Codes

| File Name | Description | Location |
|---|---|---|
| medtpkpd.xpt | Medication for PKPD dataset | \\Fdswa150\nonectd\N22257\N_000\2008-04-30\crt\datasets\wv16726 |
| medtot_e.xpt | Total drug duration dataset | \\Fdswa150\nonectd\N22257\N_000\2008-04- |

| | | |
|---|---|---|
| | | 30\crt\datasets\wv16726 |
| pkpd.xpt | PKPD dataset | \\Fdswa150\nonectd\N22257\N_000\2008-04-30\crt\datasets\wv16726 |
| nmdat.xpt | NONMEM input dataset | \\Fdswa150\nonectd\N22257\N_000\2008-04-30\crt\datasets\wv16726 |
| make.comparison.R | R script for data manipulation and plots | \\cdsnas\pharmacometrics\Valcyte\My_Review\tablet |

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-22257 | ORIG-1 | ROCHE PALO ALTO LLC | VALCYTE |

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/s/

KEVIN M KRUDYS
09/16/2009

VIKRAM ARYA
09/17/2009

PRAVIN R JADHAV
09/17/2009

KELLIE S REYNOLDS
09/17/2009

# CLINICAL PHARMACOLOGY MEMO

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| **NDA:** | 22-257 |
| **Generic Name:** | Valganciclovir hydrochloride |
| **Formulation:** | Powder for oral solution; 50 mg/ml |
| **Sponsor:** | Roche |
| **Submission Date:** | April 30, 2008 |
| **Pharmacometrics Reviewer:** | Kevin M. Krudys, Ph.D. |
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| **Clinical Pharmacology Reviewer:** | Vikram Arya, Ph.D. |
| **Clinical Pharmacology Team Leader:** | Kellie S. Reynolds, Pharm.D. |

This document serves as an addendum to the Clinical Pharmacology Review dated Novermber 25, 2008.

## EXECUTIVE SUMMARY

The sponsor has adequately resolved the outstanding deficiency noted by the Division of Scientific Investigations, namely to:

> "Identify a set of integrations 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 evaluation in studies WV16726 and CASG109."

The original pharmacokinetic analysis using manually integrated data was repeated with automatically integrated data. The results indicated a 0% to 4.4% change in $AUC_{0\text{-}24h}$ and a 0% to 16% change in $C_{max}$ in selected transplant type/age groups. Therefore, the recommendations in the original Clinical Pharmacology Review are final:

- The clinical pharmacology and biopharmaceutics information provided to support the dosing recommendations of valganciclovir powder for oral solution in pediatric (4 months -16 years) solid organ transplant recipients for the prophylaxis of CMV disease is acceptable. The reviewer explored other simplified dosing schemes but they were not superior to the sponsor's proposal. The information provided supports the following dosing recommendation:

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

where

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

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. The calculated dose should be rounded to the nearest 25 mg increment for the actual deliverable powder for oral solution dose. If the calculated dose is between 405 mg and 495 mg, one 450 mg tablet may be taken. If the calculated dose exceeds 900 mg, a maximum dose of 900 mg should be administered.

- The clinical pharmacology and biopharmaceutics information provided to support the dosing recommendations of valganciclovir powder for oral solution in pediatric patients from birth to less than 3 months for the treatment of congenital CMV is acceptable. However, the safety and efficacy of intravenous ganciclovir (reference treatment used in the study) has not been previously established, **(b) (4)** **(b) (4)** The study will be described in section 8.4 (pediatric use) of the package insert to indicate there is similar ganciclovir exposure following administration of 16 mg/kg of valganciclovir and 6 mg/kg IV ganciclovir.
- **(b) (4)**
- **(b) (4)**

***Summary of Important Clinical Pharmacology Findings***

**WV16726**

Automatic re-integration of the chromatograms resulted in one failed run. As a result, 37 pharmacokinetic samples from 9 patients in study WV16726 were excluded from the pharmacokinetic analysis. Two subjects (1101 and 6301) were entirely removed from the pharmacokinetic database. Removal of these 37 samples did not have a significant impact on individual pharmacokinetic parameter estimates in subjects who were affected (Table 1). Similarly in the entire WV16726 population, pharmacokinetic parameters using

automatic integration were similar to the original values estimated with manually integrated data (Table 2).

**Table 1. Individual Pharmacokinetic Parameters (Manual vs. Automatic) in Subjects who had Pharmacokinetic Data Excluded from Analysis**

| ID | Number of PK samples removed | Number of PK samples remaining | CL (manual integration) | CL (automatic integration) | $V_{central}$ (manual integration) | $V_{central}$ (automatic integration) |
|---|---|---|---|---|---|---|
| 1101 | 6 | 0 | 3.30 | - | 16.09 | - |
| 1102 | 6 | 1 | 8.33 | 9.93 | 28.39 | 20.80 |
| 3101 | 3 | 4 | 5.09 | 5.41 | 15.62 | 14.98 |
| 3301 | 4 | 2 | 3.11 | 2.68 | 4.19 | 4.99 |
| 6301 | 4 | 0 | 5.10 | - | 7.69 | - |
| 6401 | 4 | 3 | 11.20 | 12.18 | 23.54 | 29.99 |
| 5101 | 4 | 3 | 9.24 | 9.75 | 17.34 | 18.65 |
| 5102 | 4 | 3 | 8.73 | 9.44 | 18.13 | 22.72 |
| 1103 | 2 | 3 | 5.18 | 4.72 | 10.67 | 10.30 |

**Table 2. Comparison of Pharmacokinetic Parameter Estimates from Study WV16726. (Parameter estimates derived from manually integrated data are in black font; parameter estimated derived from automatically integrated data are below in red font.)**

| | PK Parameter | Age Group (Years) | | |
|---|---|---|---|---|
| | | ≤ 2 (n=2) | > 2 to < 12 (n=12)* | ≥ 12 (n=19) |
| **Kidney** | $AUC_{0\text{-}24h}$ (µg·h/mL) | 65.2 (16.6) | 55.0 (11.9) | 50.0 (11.6) |
| | | 67.6 (13.0) | 55.9 (12.1) | 47.8 (12.4) |
| **(N=33)** | $C_{max}$ (µg/mL) | 10.0 (0.04) | 8.74 (2.49) | 7.85 (2.10) |
| | | 10.4 (0.4) | 8.7 (2.1) | 7.7 (2.1) |
| | $t_{1/2}$ (h) | 3.10 (0.59) | 4.40 (1.41) | 5.67 (1.06) |
| | | 4.5 (1.5) | 4.8 (1.0) | 6.0 (1.3) |
| | | **≤ 2 (n=9)** | **> 2 to < 12 (n=6)** | **≥ 12 (n=2)** |
| **Liver** | $AUC_{0\text{-}24h}$ (µg·h/mL) | 69.4 (35.4) | 58.4 (6.18) | 35.6 (2.76) |
| | | 69.9 (37.0) | 59.4 (8.1) | 35.4 (2.8) |
| **(N=17)** | $C_{max}$ (µg/mL) | 11.7 (3.59) | 9.35 (2.33) | 5.55 (1.34) |
| | | 11.9 (3.7) | 9.5 (2.3) | 5.5 (1.1) |
| | $t_{1/2}$ (h) | 2.72 (1.32) | 3.61 (0.80) | 4.50 (0.25) |
| | | 2.8 (1.5) | 3.8 (0.7) | 4.4 (0.2) |
| | | **≤ 2 (n=6)** | **> 2 to < 12 (n=2)** | **≥ 12 (n=4)** |
| **Heart** | $AUC_{0\text{-}24h}$ (µg·h/mL) | 56.3 (23.2) | 60.0 (19.3) | 61.2 (26.0) |
| | | 55.4 (22.8) | 59.6 (21.0) | 60.6 (25.0) |
| **(N=12)** | $C_{max}$ (µg/mL) | 8.22 (2.44) | 12.5 (1.02) | 9.50 (3.34) |
| | | 8.2 (2.5) | 12.5 (1.2) | 9.5 (3.3) |
| | $t_{1/2}$ (h) | 3.60 (1.73) | 2.62 (0.65) | 5.05 (0.70) |
| | | 3.8 (1.7) | 2.8 (0.9) | 4.9 (0.8) |

* n = 10 for automatic integration.

## CASG109

Pharmacokinetic parameters from study CASG109 using automatic integration were similar to the original values estimated using manually integrated data (Table 3).

**Table 3. Comparison of Relevant Pharmacokinetic Parameters in CASG109**

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

## LABELING RECOMMENDATIONS

As requested by the Division of Anti-Viral Products, the sponsor has updated sections 8.4 and 12.3 (Table 10) of the label to reflect the results using the automatically integrated data. These updates are acceptable and the relevant sections are reproduced below.

### 8.4 Pediatric Use

The pharmacokinetic results showed that in infants > 7 days to 3 months of age, a dose of 16 mg/kg twice daily of Valcyte for oral solution provided ganciclovir systemic exposures (median $AUC_{0-12h}$ = 23.6 [range 16.8 – 35.5] µg h/mL; n = 6) comparable to those obtained in infants up to 3 months from a 6 mg/kg dose of intravenous ganciclovir twice daily ($AUC_{0-12h}$ = 25.3 [range 2.4 – 89.7] µg h/mL; n = 18) or to the ganciclovir systemic exposures obtained in adults from a 900 mg dose of oral Valcyte twice daily.

### 12.3 Pharmacokinetics

**Table 10 Mean (SD) Pharmacokinetics of Ganciclovir by Age in Pediatric Solid Organ Transplant Patients**

| | PK Parameter | Age Group in Years | | |
|---|---|---|---|---|
| | | **≤ 2 (n=2)** | **> 2 to < 12 (n=10)[a,b]** | **≥ 12 (n=19)** |
| **Kidney (N=31)** | $AUC_{0-24h}$ (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) |
| | | **≤ 2 (n=9)** | **> 2 to < 12 (n=6)** | **≥ 12 (n=2)** |
| **Liver (N=17)** | $AUC_{0-24h}$ (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) |
| | | **≤ 2 (n=6)** | **> 2 to < 12 (n=2)** | **≥ 12 (n=4)** |
| **Heart (N=12)** | $AUC_{0-24h}$ (µg·h/mL) | 55.4 (22.8) | 59.6 (21.0) | 60.6 (25.0) |
| | $C_{max}$ (µg/mL) | 8.2 (2.5) | 12.5 (1.2) | 9.5 (3.3) |
| | $t_{1/2}$ (h) | 3.8 (1.7) | 2.8 (0.9) | 4.9 (0.8) |

[a] 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.

[b] 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.

| Linked Applications | Submission Type/Number | Sponsor Name | Drug Name / Subject |
|---|---|---|---|
| NDA 22257 | ORIG 1 | HOFFMAN-LA ROCHE INC | VALCYTE |
| NDA 22257 | ORIG 1 | HOFFMAN-LA ROCHE INC | VALCYTE |

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/s/

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KEVIN M KRUDYS
08/26/2009

VIKRAM ARYA
08/26/2009

PRAVIN R JADHAV
08/26/2009

SARAH M ROBERTSON
08/26/2009
Signing for Kellie Reynolds

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

| | |
|---|---|
| **NDA** | 22-257 |
| **Submission Date** | April 30, 2008 |
| **Brand Name** | VALCYTE ® |
| **Generic Name** | VALGANCICLOVIR HYDROCHLORIDE |
| **OCP Division** | Division of Clinical Pharmacology 4 |
| **OND Division** | Division of Antiviral Products (DAVP) |
| **Sponsor** | Roche |
| **Formulation; Strength** | Powder for oral solution; 50 mg/ml |
| **Indication (Proposed in Pediatric Patients)** | Prevention of CMV disease in kidney and heart transplant patients at high risk |
| **Indication (Approved in Adults)** | Treatment of CMV Retinitis; Prevention of CMV disease in kidney, heart and kidney-pancreas transplant patients at high risk |
| **Dosing Regimen (Approved in Adults)** | 1) Treatment of CMV Retinitis in Patients with HIV (normal renal function): For patients with active CMV retinitis, the recommended dose for induction and maintenance is 900 mg (2X 450 mg tablets administered with food for 21 days) b.i.d and 900 mg q.d., respectively.<br>2) Prevention of CMV Disease in Heart, Kidney, and Kidney-Pancreas Transplant patients at high risk: 900 mg (two 450 mg tablets) once daily with food starting within 10 days of transplantation until 100 days post transplantation. |
| **Submission Type** | 505 b(1), 1P |
| **Reviewer** | Kevin Krudys, Ph.D.<br>Vikram Arya, Ph.D. |
| **Secondary Reviewer** | Pravin Jadhav, Ph.D. |
| **Pharmacometrics Team Leader** | Jogarao Gobburu, Ph.D. |
| **Clinical Pharmacology Team Leader** | Kellie Reynolds, Pharm. D. |

## Table of Contents

# 1 EXECUTIVE SUMMARY

Valganciclovir (Valcyte®) is a valyl ester pro-drug of ganciclovir. Ganciclovir is a synthetic guanine derivative active against cytomegalovirus (CMV). Valganciclovir is currently available as a 450 mg tablet and is approved for the following indications:

1) **Treatment of CMV Retinitis in Patients with HIV:** For patients with active CMV retinitis, the recommended dose for induction and maintenance is 900 mg (2X 450 mg tablets administered with food for 21 days) b.i.d and 900 mg q.d. Dosing regimens are altered for patients with reduced renal function.

2) **Prevention of CMV Disease in Heart, Kidney, and Kidney-Pancreas Transplant patients at high risk:** The recommended dose is 900 mg (two 450 mg tablets) once daily with food starting within 10 days of transplantation until 100 days post transplantation. Dosing regimens are altered for patients with reduced renal function.

In this application, the applicant is seeking dosing recommendations for the use of valganciclovir powder for oral solution:

1) in pediatric solid organ transplant (b) (4) kidney, and heart) recipients aged 4 months to 16 years for CMV prophylaxis

2) (b) (4)

3) (b) (4)

A tutti-frutti flavored powder for oral solution formulation (50 mg/mL) was supported by a relative bioavailability study (WP16302).

To support dosing recommendations in pediatric solid organ transplant recipients, the applicant conducted three pharmacokinetic and safety studies (WP16296, WP16303 and WP16726) to characterize the pharmacokinetics of ganciclovir in pediatric solid organ transplant (liver, kidney, and heart) recipients aged 4 months to 16 years.

The applicant conducted a pharmacokinetic study (CASG 109) in neonates (aged 6-31 days at enrollment and 8-34 days at dosing) to determine dosing recommendations of valganciclovir for the treatment of congenital (birth to <4 months) CMV disease.

The currently approved dose adjustments in patients with different degrees of renal impairment were limited due to the availability of only one strength of the tablet formulation (450 mg) at the time of approval of the original NDA. Therefore, the "dosing interval adjustment" approach was used to provide dosing recommendations. Acceptable dosing recommendations were not possible for the use of valganciclovir tablets in patients on hemodialysis. The (b) (4) dosing recommendations for the powder for oral solution were derived based on extrapolation of pharmacokinetic results from study WP15511, and the approved dosing algorithm for intravenous ganciclovir.

This submission was split into two NDAs for administrative purposes: [redacted] and 2) NDA 22-257 for the indication of valganciclovir for the prevention of CMV disease in pediatric solid organ transplant recipients 4 months to 16 years of age at risk for developing CMV disease [redacted]

Following inspection by the Division of Scientific Investigations the following deficiencies were noted:

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

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

1. Frozen stability data that cover the duration of storage [redacted] of all the plasma samples used for the quantification of ganciclovir in studies WV16726 and CASG109.
2. 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.

## *1.1 Recommendation*

The Office of Clinical Pharmacology (OCP) reviewed the information submitted in this NDA and the information provided supports the following conclusions:

[redacted]

- The clinical pharmacology and biopharmaceutics information pertaining to similarity in systemic exposures of ganciclovir between the tutti-frutti flavored powder for oral solution and tablets is not acceptable. The information does not support approval of the tutti-frutti flavored powder for oral solution.

**NDA 22-257**

The following recommendations are pending the satisfactory resolution of the deficiencies identified by the Division of Scientific Investigations as outlined in the Executive Summary.

- The clinical pharmacology and biopharmaceutics information provided to support the dosing recommendations of valganciclovir powder for oral solution in pediatric (4 months -16 years) solid organ transplant recipients for the prophylaxis of CMV disease is acceptable. The reviewer explored other simplified dosing schemes but they were not superior to the sponsor's proposal. The information provided supports the following dosing recommendation:

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

where

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

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. The calculated dose should be rounded to the nearest 25 mg increment for the actual deliverable powder for oral solution dose. If the calculated dose is between 405 mg and 495 mg, one 450 mg tablet may be taken. If the calculated dose exceeds 900 mg, a maximum dose of 900 mg should be administered.

- The clinical pharmacology and biopharmaceutics information provided to support the dosing recommendations of valganciclovir powder for oral solution in pediatric patients from birth to less than 3 months for the treatment of congenital CMV is acceptable. However, the safety and efficacy of intravenous ganciclovir (reference treatment used in the study) has not been previously established, [redacted] (b) (4) (b) (4) The study will be described in section 8.4 (pediatric use) of the package insert to indicate there is similar ganciclovir exposure following administration of 16 mg/kg of valganciclovir and 6 mg/kg IV ganciclovir.


### *1.2 Phase IV Commitments*

None

### *1.3 Summary of Important Clinical Pharmacology Findings*

Valganciclovir (Valcyte®) is a valyl ester pro-drug of ganciclovir. Ganciclovir is a synthetic guanine derivative active against cytomegalovirus (CMV). Valganciclovir is currently available as a 450 mg tablet and is approved for the following indications:

- Treatment of CMV Retinitis in Patients with HIV: For patients with active CMV retinitis, the recommended dose for induction and maintenance is 900 mg (2X 450 mg tablets administered with food for 21 days) b.i.d and then 900 mg q.d.
- Prevention of CMV Disease in Heart, Kidney, and Kidney-Pancreas Transplant patients at high risk: The recommended dose is 900 mg (two 450 mg tablets) once daily with food starting within 10 days of transplantation until 100 days post transplantation.

The purpose of this review is to use the information from the studies summarized in Table 1 to address the following key questions.

**Table 1 Summary of PK Study Reports**

| Type | Study Number | Report | Population |
|---|---|---|---|
| Bioequivalence, PK, Safety | WP16302 | Bioequivalence comparing valganciclovir oral solution to valganciclovir 450 mg tablet | Adult kidney transplant recipients |
| PK, Safety | WP16303 | Safety and PK of i.v. ganciclovir and valganciclovir oral solution in pediatric liver transplant recipients | Pediatric patients aged 6 months to 16 years |
| PK, Safety | WP16296 | Safety and PK of i.v. ganciclovir and valganciclovir oral solution in pediatric renal transplant recipients | Pediatric patients aged 1 year to 16 years |
| PK, Safety, Efficacy | WV16726 | Safety and PK of valganciclovir syrup formulation in pediatric solid organt transplant recipients | Pediatric patients ages 4 months to 16 years |
| PK, PD, Safety, Efficacy | CASG109 | PK/PD Evaluation of oral valganciclovir in neonates with symptomatic congenital CMV infection | Neonates aged 6 to 31 days at enrollment and 8 to 34 dosing |
| PK, Safety | WP15511 | Effect of renal impairment on pharmacokinetics of ganciclovir following oral administration of valganciclovir | Renally impaired healthy adults and patients with HIV and CMV |

### 1.3.1 Is the exposure ($C_{max}$ and AUC) after oral administration of the powder for oral solution similar to that of the currently approved tablet formulation?

The rate and extent of ganciclovir systemic exposures after administration of the powder for oral solution were similar to those of the tablet formulation. Study WP16302 was a multi-center, open label, randomized, three way crossover study. Patients at a risk of CMV disease, who were being treated prophylactically with Valcyte® (using the commercially available tablets) after their first or second kidney transplant and who had adequate renal and hematological function were eligible for the study. Each patient received all of the following three treatments (treatment A, treatment B, and treatment C):

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

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

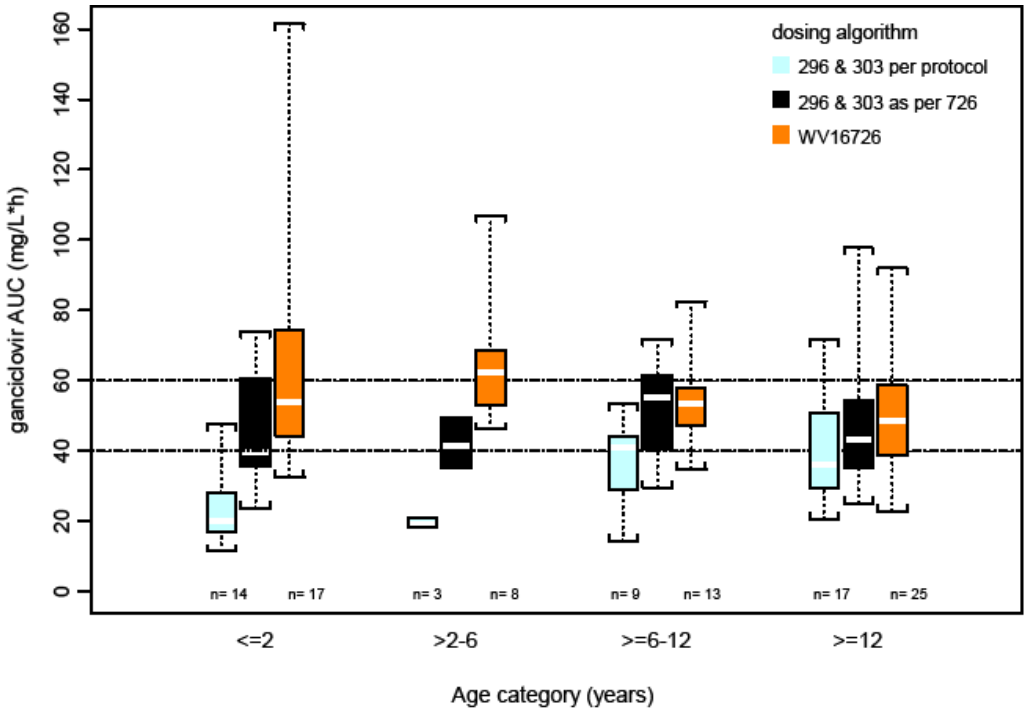
**Treatment C:** Once daily oral dosing (via a syringe) with the valganciclovir strawberry flavored powder for oral solution for 2 days.

The results of study WP16302 showed that the ganciclovir systemic exposures after administration of 900 mg (18 mL) valganciclovir tutti-frutti flavored oral solution formulation (50 mg/mL) were similar to the ganciclovir exposures after administration of 900 mg (2 X 450 mg) valganciclovir tablets.

### 1.3.2 Is the proposed dose recommendation of valganciclovir in pediatric solid organ transplant patients aged 4 months to 16 years who are at risk of developing CMV disease acceptable?

The proposed dose recommendation is acceptable. The proposed pediatric dose of 7×BSA×CrCL (calculated by a modified Schwartz formula) produced ganciclovir exposures close to the target range of 40 – 60 mg h/L in Study WV16726. The formula was derived from population PK analysis of WP16296 and WP16303 which used a different dosing algorithm that provided inadequate exposures. The target exposure was based on an analysis of data from the efficacy study (PV16000) in adult solid organ transplant recipients treated with the approved dose of 900 mg oral valganciclovir. Exposures less than 40 mg h/L are predicted to cause an unacceptable increase in the probability of developing viremia. Exposures greater than 60 mg h/L are predicted to cause a relatively sharp increase in neutropenia and leukopenia. As seen in Figure 1, if the proposed algorithm had been applied in Studies WP16296 and WP16303, predicted exposures would also have fallen within the target range. As opposed to the initial dosing algorithm used in studies WP16296 and WP16303, predicted ganciclovir exposures with the modified algorithm are independent of age, weight and renal function. Simpler, alternative dosing algorithms investigated by the reviewer predicted less optimal distribution of ganciclovir exposures compared to the proposed algorithm.

**Figure 1. Ganciclovir Exposures from Initial and Modified Pediatric Dosing Algorithms**




### 1.3.3 Is the [redacted] (b) (4) dose of 16 mg/kg valganciclovir in pediatric patients less than 3 months of age with symptomatic congenital CMV disease acceptable?

Pharmacokinetic data suggest the dose of 16 mg/kg is acceptable in pediatric patients less than 3 months of age with symptomatic congenital CMV disease. The observed ganciclovir $AUC_{0-12}$ in the neonates receiving 14 mg/kg (n=14) were indistinguishable from those in neonates receiving 16 mg/kg (n=4). However, the results of population pharmacokinetic modeling predict the 16 mg/kg dose would provide exposures closer to the target $AUC_{0-12}$ of 27 mg h/L than the 14 mg/kg dose. The target ganciclovir exposure of an $AUC_{0-12}$ of 27.1 µg h/ml, is chosen to match the exposure achieved in HIV- and CMV-seropositive adult subjects with normal renal function receiving the approved dose of 900 mg once daily oral valganciclovir in study WP15511. Furthermore, a six week study of 6 mg/kg ganciclovir b.i.d. in neonates, which has been shown to achieve an $AUC_{0-12}$ approximately equal to 27 µg h/ml, prevented hearing deterioration at 6 months.

### 1.3.4 Can differences in exposure in either adults or pediatrics explain the observation from a subgroup analysis in adult subjects that showed liver transplant recipients receiving valganciclovir had five times the incidence of tissue-invasive CMV disease compared to the oral ganciclovir group?

The observed increase in tissue-invasive CMV disease in liver transplant recipients can not be explained by differences in exposure of ganciclovir in this population. In the

efficacy trial in adults (Study PV16000), the mean ganciclovir exposure following oral valganciclovir was similar across transplant types and consistently higher than exposure in subjects receiving 1000 mg oral ganciclovir three times daily (Table 2).

**Table 2. Mean Systemic Pharmacokinetic Parameters by Solid Organ Transplant Type in Study PV16000 (N = number of profiles)**

| | Liver | | Heart | | Kidney | |
|---|---|---|---|---|---|---|
| | $AUC_{0-24}$ (mg h/L) | $C_{max}$ (µg/ml) | $AUC_{0-24}$ (mg h/L) | $C_{max}$ (µg/ml) | $AUC_{0-24}$ (mg h/L) | $C_{max}$ (µg/ml) |
| Ganciclovir (1000 mg three times with food) | 24.9 ± 10.2 (N=62) | 1.3 ± 0.4 (N=62) | 26.6 ± 11.6 (N=24) | 1.4 ± 0.5 (N=24) | 31.3 ± 10.3 (N=65) | 1.5 ± 0.5 (N=65) |
| Valganciclovir (900 mg once daily with food) | 46.0 ± 16.1 (N=138) | 5.4 ± 1.5 (N=138) | 40.2 ± 11.8 (N=31) | 4.9 ± 1.1 (N=31) | 48.2 ± 14.6 (N=129) | 5.3 ± 1.5 (N=129) |

Source: Clinical Study Report for PV16000: Page 153

Ganciclovir exposures in pediatric subjects enrolled in Study WV16726 were also similar across transplant type with $AUC_{24}$ (mg h/L) of 51.8 ± 11.9 , 61.7 ± 29.5 and 58.0 ± 21.8 in kidney, liver and heart recipients, respectively. A subgroup analysis in Study WV16726, however, also showed a numerically higher rate of treatment failure in liver transplant recipients compared to kidney and heart recipients, although the sample size is too small to draw any statistical significance (Table 3). Any increase observed in the incidence of tissue-invasive CMV disease in these studies is most likely due to chance or unique physiological characteristics of the liver, rather than differences in pharmacokinetics.

**Table 3. Summary of Treatment Failures in Pediatric Subjects in Study WV16726.**

| **Treatment Failure** | **Liver (N=17)** | **Kidney (N=33)** | **Heart (N=12)** |
|---|---|---|---|
| Patients with treatment failure | 17.6 % | 3 % | 0% |
| Patients with CMV disease requiring treatment | 2 | 1 | 0 |
| Patients discontinued due to lack of efficacy or toxicity | 1 | 0 | 0 |

**1.3.5** (b) (4)

(b) (4)

(b) (4)

**1.3.6** (b) (4)

(b) (4)

(b) (4)

(b) (4)

**SITE INSPECTION**

Following inspections of the clinical sites at the Indiana University Medical Center Indianapolis, IN (7/29–31/08), UCLA Center for Health Sciences, Los Angeles, CA (10/16-21/08) and University of Texas Southwestern Medical Center, Dallas, TX (7/29-31/08) and an inspection of the analytical site at (b) (4) (b) (4) (11/3-7/08) by the Division of Scientific Investigation (DSI), Form 483's were issued. The following were significant findings from the inspections:

Clinical Sites

**Study WP 16302: Indiana University Medical Center, Surgery &** (n=9) **Microbiology/Immunology, Indianapolis, IN.**

**1. Samples of the test drugs were not retained at the clinical site. On 4/26/06 all intact bottles of study drugs were collected by study monitor.**
The clinical site did not retain reserve samples for the bioequivalence study as required by 21 CFR 320.38. Also, the unused drugs were returned to the sponsor. The clinic stated that the sponsor's protocol did not require reserve sample retention, and the unused drugs were returned per protocol. Nonetheless, due to the lack of reserve samples, the authenticity of the test and reference drugs used in the bioequivalence study cannot be confirmed.

*Reviewer's Response: As authenticity of the test and reference products cannot be confirmed, the data from Study WP16302 cannot be used* (b) (4) (b) (4)

**Study WV 16726: UCLA Center for Health Sciences,** (n=5) **Division of Pediatric Nephrology, Los Angeles, CA**

**2. The following pharmacokinetic (PK) assessments were not collected according to the protocol. Specifically, protocol WV 16726 section 5.2.4 titled Pharmacokinetic Assessment (and Appendix 5) required samples to be collected on Day 7 Day 14, Week 6, Week 10 and Day 100. Samples for Week 6, Week 10 and Day 100 were to be collected anytime post dose or at the time of the blood draw for safety assessments.**

| Subject # | PK Time | Dosing Time | Observed PK Sample time |
|---|---|---|---|
| 8601 | Week 6 | 13:30 | 11:21 |
| | Week 10 | 14:00 | 09:30 |
| | Day 100 | 13:30 | 10:02 |
| 8602 | Week 6 | | Not done |
| | Week 10 | 11:00 | 08:59 |
| | Day 100 | | Not done |
| 8603 | Week 6 | 10:30 | 07:00 |
| | Week 10 | 12:00 | 08:00 |
| | Day 100 | | Not done |
| 8604 | Week 6 | | Not done |
| | Week 10 | | Not done |
| 8605 | Week 6 | | Not done |
| | Week 10 | 08:30 | 06:40 |

As indicated in the table, PK samples were either not collected or collected prior to dosing. Section 5.2.4 of the protocol states PK sampling for Weeks 6 and 10, and Day 100 "can be taken at any time after vanganciclovir administration". Nonetheless, review of PK data sets in EDR indicates that the observed PK sampling times were reported at Weeks 6 and 10, and Day 100.

*Reviewer's Response: The deviation of the pharmacokinetic assessments from the protocol shown in the table above should not have an influence on the conclusions reached in the review. The dataset used by the sponsor and reviewer for population pharmacokinetic analysis in NONMEM appears to reflect the actual dosing and sampling times in the table above. The population approach implemented in NONMEM allows for deviation in the timing of pharmacokinetic assessment as long as the actual times of the assessments are recorded.*

**3. Discrepancies in dosing.**
The available source records do not demonstrate the daily doses administered to subjects when they were not hospitalized. The drug dispensing records only indicate the drugs that were dispensed to and returned by the subjects. Also, it is not known whether the entries were contemporaneous as there were no dates and initials of the persons who entered the data, and often the return dates were not known. Since only drug dispensation and return information are available, daily doses can only be estimated for the non hospitalization period assuming the drugs were administered per protocol with no dosing discrepancies. Therefore, the exact daily doses for the non hospitalization periods cannot be confirmed for the five study subjects enrolled at this site.

*Reviewer's Response: The discrepancies in dosing in 5 patients when they were not hospitalized are not expected to influence the conclusions reached in the review. The doses for which pharmacokinetic assessments were used for population pharmacokinetic analysis were all made during hospitalization.*

**Study CASG 109: University of Texas Southwestern Med. Ctr.,** (n=9) **Department of Pediatrics, Dallas, TX.**

**4. Investigation was not conducted in accordance with the investigational plan in that Subject 64 was misdosed.**
According to the home dosing administration diary, subject 0064 received 18.4 mg of ganciclovir for doses 5-12 (May 22-25, 2005) instead of 18 mg, as instructed by **Dr.** Sanchez. Furthermore, doses 13-26 (May 26-June 1, 2005) were not administered because Page 4 of 5 - NDA 22-257, Valcyte® (valganciclovir HC1) Powder for Oral Solution (50 mg/mL, Free Base) the IV line was out and not re-inserted. Because subject 0064 vomited after the oral valganciclovir dose on June 5, 2005, the parent re-dosed the subject, against the written instructions provided to the parent. The OCP reviewer should consider the impact of misdosing on PK assessments for subject 0064.

*Reviewer's Response: The misdosing of subject 0064 should not alter the conclusion that similar ganciclovir exposures are achieved following administration of 16 mg/kg of valganciclovir and 6 mg/kg IV ganciclovir in this population. This was confirmed by the reviewer by reanalyzing the data after excluding subject 0064. The results of the analysis showed that the estimates of the population pharmacokinetic model did not significantly change.*

Analytical Site

**Studies WP16302, WP16726 and CASG109**

**I. Inconsistency in integration of chromatograms.**

**a. Failure to properly integrate several chromatograms. Manual integrations were carried out by modifying parameters from the autointegration.**

The firm automatically integrated chromatograms and modified the integration (i.e. manual integration) of selective chromatograms. The inspection found that the parameters used for automatic integration failed to produce consistent integration in that automatic integrations of similar analyte peaks were inconsistent between chromatograms. Similarly, selection of chromatograms for manual integration was not consistent and modification cannot be justified. In almost all of the chromatograms, the integration parameters chosen to integrate the peak area and the resulting plasma drug concentrations results were not accurate, and possibly overestimated (Exhibit 1). This is because a significant portion of tailing was included, often inconsistently, in integrating chromatographic peaks.

**b. Failure to reject analytical runs in that QCs at a given level were modified by manual integration and brought to acceptance. Several QC chromatograms were modified by manual integration.**

The inspection found that several quality control (QC) chromatograms (20-25%) were modified by manual integration without justification. Particularly, in the analytical runs identified in the table below, duplicate QCs at one or more concentrations or majority of QCs were modified without justification, possibly in an attempt to bring the runs into acceptance. Therefore, the acceptability of the analytical runs cannot be assured. For example, there was no justification for manual integration of both low QCs in analytical

run gan060224 in Study WP16302 (Exhibits 2 and 3). With manual integration, one of the duplicate low QCs barely met QC acceptance (b) (4) ) and the other failed. Failure of both QCs at a given concentration or failure of (b) (4) of total QCs would result in rejection of a run per the firm's procedures.

**II. Storage stability cannot be assured.**
Studies WP16302 and WP16726 were conducted for a period of 1 year, and the study samples were analyzed between 6 months (WP16302) and 1 year (WP16726). Study CASG109 was conducted over a 4 ½ year period and samples were analyzed for 1 ½ years. The firm had frozen stability data for only 3 months. It is not known if this stability period covers the storage period (elapsed time between collection and analysis) of the pharmacokinetic (PK) samples for the above studies. This could not be discerned during the inspection as there was no documentation of sample collection dates at (b) (4) Further, (b) (4) did not receive the PK samples directly from the clinical sites, instead the sponsor collected the samples from the clinical sites and shipped them to (b) (4) in installments.

*Reviewer's Response: Based on these findings, the plasma concentration data from Studies WP16302, WP16726 and CASG109 are not acceptable as submitted in the NDA. Please refer to the Executive Summary for steps that can be taken by the Applicant to assure the accuracy of analytical runs and the resulting drug concentrations.*

Kevin Krudys, Ph.D.
Pharmacometrics Reviewer
Office of Clinical Pharmacology

Vikram Arya, Ph.D.
Clinical Pharmacology Reviewer
Division of Clinical Pharmacology 4

Concurrence:

Pravin Jadhav, Ph.D.
Pharmacometrics Reviewer
Office of Clinical Pharmacology

Kellie S. Reynolds, Pharm. D
Deputy Director
Division of Clinical Pharmacology 4

# 2 Question Based Review (QBR)

## *2.1 General Attributes of the Drug*

Valcyte (valganciclovir HCl tablets) contain valganciclovir hydrochloride (valganciclovir HCl), a hydrochloride salt of the L-valyl ester of ganciclovir. It is a white to off white crystalline powder with a molecular formula of $C_{14}H_{22}N_6O_5$.HCl and a molecular weight of 390.83. Valganciclovir is a polar hydrophilic compound with a solubility of 70 mg/mL in water at 25ºC at pH 7. Valganciclovir is currently approved as a 450 mg tablet.

Valganciclovir powder for oral solution is a granulate with a white to off-white color containing sodium benzoate (b) (4). The proposed dosage form is a powder for oral solution which is reconstituted with 91 mL purified water to make a final volume of 100 mL, containing 5 g per bottle (50 mg/mL) of valganciclovir free base.

Table 4 shows the composition of the valganciclovir powder for oral solution.

**Table 4. Composition of valganciclovir powder for oral solution.**

| Components | Unit Weight mg/ (b) (4) | Filling Mixture g/bottle | Reconstituted Solution mg/mL |
|---|---|---|---|
| Valganciclovir HCl[1] | 55.15 | 5.515 | 55.15 |
| Povidone K30 | (b) (4) | | |
| Fumaric Acid | | | |
| Sodium Benzoate | | | |
| Saccharin Sodium | | | |
| Mannitol | | | |
| Tutti-Frutti Flavour | | | |
| (b) (4) | | | |
| (b) (4) | | | |
| Total | | | |

[1]Equivalent to 50 mg of Valganciclovir on dry basis (HCl salt = MW 390.83; Base = MW 354.36)

(b) (4)

### 2.1.1 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Valganciclovir hydrochloride is a valyl ester prodrug of ganciclovir, an acyclic nucleoside analog of 2'deoxyguanosine. The mechanism of action of valganciclovir is through the virustatic activity of ganciclovir. In CMV-infected cells, ganciclovir is phosphorylated to produce ganciclovir triphosphate which has an intracellular half-life of 18 hours and inhibits viral DNA synthesis.

### 2.1.2 What are the proposed dosage(s) and route(s) of administration?

The proposed dosing recommendations are based on the use of a powder for oral solution formulation.

Dosing in Pediatric Subjects for the Prophylaxis of CMV Disease

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

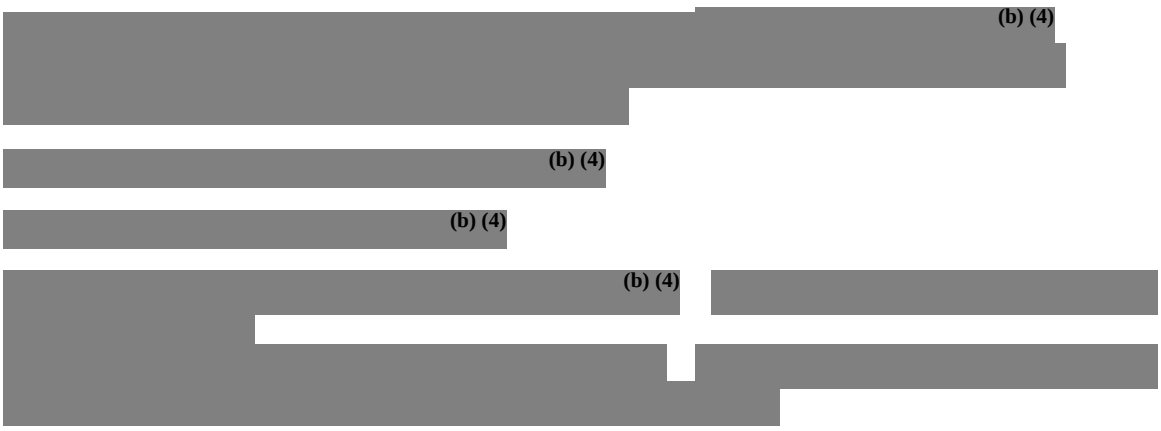
where

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

and

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

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. The sponsor proposes using a value of k = 0.45 for patients aged 1 to < 2 years, whereas the Schwartz formula is typically calculated using a value of k = 0.55 for this age group. The calculated dose should be rounded to the nearest 25 mg increment for the actual deliverable powder for oral solution dose. If the calculated dose is between 405 mg and 495 mg, one 450 mg tablet may be taken. If the calculated dose exceeds 900 mg, a maximum dose of 900 mg should be administered.



[redacted] (b) (4)

## *2.2 General Clinical Pharmacology*

### 2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The applicant designed the clinical pharmacology studies to meet the following four regulatory objectives:

1) Demonstrate similarity in exposures ($C_{max}$ and AUC) after oral administration of the powder for oral solution formulation and the tablet formulation.
2) To seek approval for the use of valganciclovir powder for oral solution for the prophylaxis of CMV disease in pediatric subjects (4 months-16 years). The pharmacokinetic endpoint was $AUC_{0-24}$.
3) [redacted] (b) (4)
4) [redacted] (b) (4)

### 2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics [PD]) and how are they measured in clinical pharmacology and clinical studies?

*Prevention of CMV disease in pediatric solid organ transplant recipients*
It was reasonable to assume similar response to intervention and similar exposure-response relationship between pediatric and adult solid organ transplant populations. Therefore pharmacokinetic studies were conducted in pediatric subjects to determine a dosing regimen that achieves similar ganciclovir exposures (AUC) as in adult subjects at approved doses.

*Treatment of CMV disease in neonates*
The target ganciclovir exposure for treatment of CMV disease is an $AUC_{0-12}$ of 27.1 µg h/ml, which was observed in HIV- and CMV-seropositive adult subjects with normal renal function receiving the approved dose of 900 mg once daily oral valganciclovir in study WP15511. This exposure is also expected to be achieved with a 6 mg/kg i.v. twice daily dose of ganciclovir, which was shown in a separate study to prevent hearing deterioration at 6 months measured by brainstem-evoked response, [redacted] (b) (4) (b) (4)

### 2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

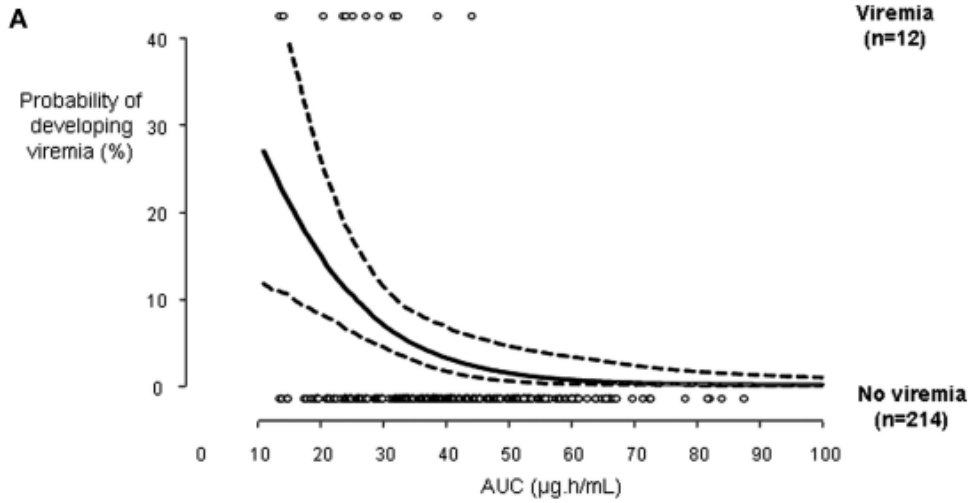
Yes, the sponsor quantified the appropriate moieties in all the clinical pharmacology studies.

### 2.2.4 Exposure-Response

#### 2.2.4.1 What are the characteristics of exposure-response relationships (dose-response, concentration-response) for efficacy in prevention of CMV disease in solid organ transplant recipients?

Systemic exposure to ganciclovir in adults was correlated with antiviral activity during CMV prophylaxis in solid organ transplant recipients. In an adult population at 100 days post-transplant, an AUC of 60 µg h/ml predicted an average incidence of viremia of 1.3%, whereas an AUC of 25 µg h/ml was associated with 8 times this risk. At four months post-transplant, the AUCs associated with a 20% and 10% chance of developing viremia were 33 µg h/ml and 50 µg h/ml, respectively. For ganciclovir AUCs of 33-50 µg h/ml during prophylaxis, the risk of developing CMV disease within one year of transplantion was independent of exposure to ganciclovir during prophylaxis.

**Figure 2. Relationship between systemic ganciclovir exposure and the probability of CMV viremia at the end of prophylaxis in adult solid organ transplant patients.**

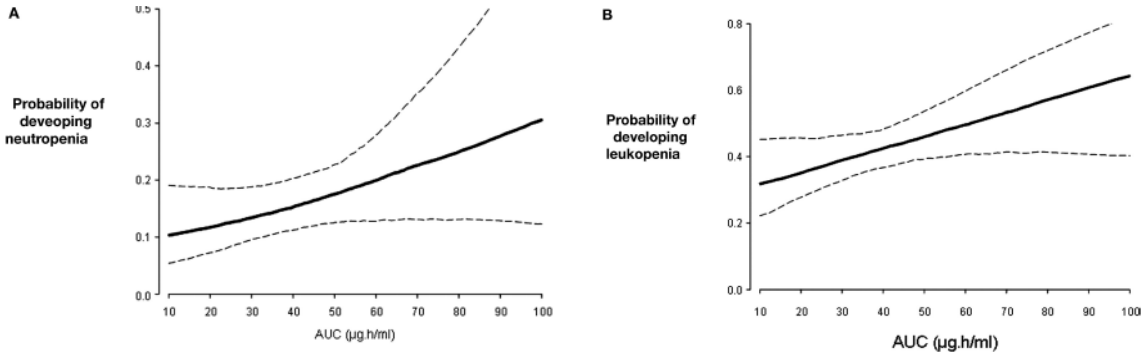



Source: Sponsor's Summary of Clinical Pharmacology Studies P-17.

#### 2.2.4.2 What are the characteristics of exposure-response relationships (dose-response, concentration-response) for safety prevention of CMV disease in solid organ transplant recipients?

Systemic exposure of ganciclovir is correlated with increased neutropenia and leukopenia. In an adult population at four months post-tranplant, median predicted incidences of neutropenia of 15% and 20 % were associated with AUCs of 30 and 61 μg h/ml, respectively. Median predicted incidences of leukopenia of 40% and 50% were associated with AUCs of 34 and 62 μg h/ml, respectively.

**Figure 3. Relationship between systemic ganciclovir exposure and the probability of developing (A) neutropenia and (B) leukopenia up to 4 months post-transplant in adult solid organ transplant recipients.**




Source: Wiltshire et al., *Transplantation* Volume 79, Number 11, June 15, 2005.

#### 2.2.4.3 Does valganciclovir prolong QT or QTc interval?

Not applicable to this NDA.

#### 2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Yes, the dose and dosing regimen is consistent with the known exposure-response relationship. There are no unresolved dosing or administration issues (See section 2.3.1.1).

#### 2.2.4.5 What are the PK characteristics of valganciclovir?

Table 5 (extracted from the Valcyte package insert) shows the PK parameters of ganciclovir after administration of valganciclovir tablets, intravenous ganciclovir, and ganciclovir capsules.

**Table 5. PK characteristics of valganciclovir**

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

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

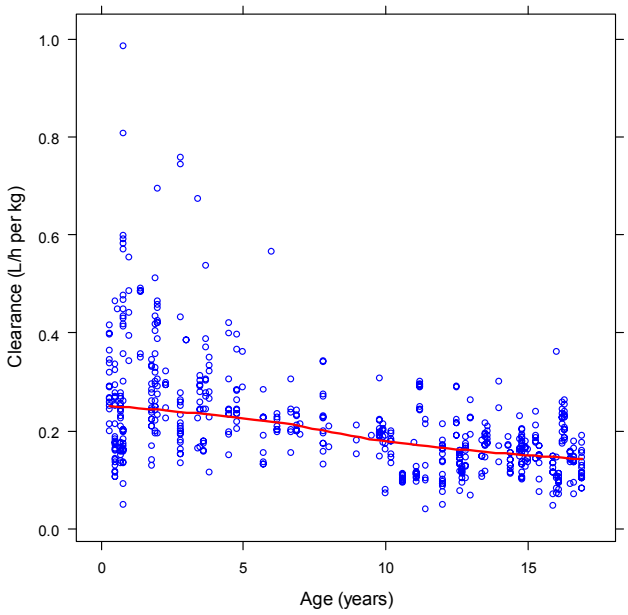
## *2.3 Intrinsic Factors*

**2.3.1 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.**

### 2.3.1.1 Pediatric Patients

Ganciclovir clearance normalized to body weight in pediatric solid organ transplant recipients from studies WP16303, WP16296 and WV16726 shows a small decreasing trend from 4 months to 17 years of age (Figure 4). See Figure 1 for differences in exposure across different age pediatric age ranges. Ganciclovir clearance normalized to body weight in adult subjects in PV16000 was approximately 0.1 L/h per kg, which is consistent with the oldest pediatric subjects, as seen in Figure 4.

**Figure 4. Relationship between clearance normalized for weight and age derived from reviewer's population pharmacokinetic analysis.**




*Dose justification for prevention of CMV disease in pediatric solid organ transplant recipients*

A dose resulting in $AUC_{0-24}$ of 40 – 60 µg hr/mL was targeted for prevention of CMV disease in pediatric solid organ transplant recipients. The lower bound of 40 µg hr/mL is acceptable based on the information provided in Figure 2 which shows that the probability of developing viremia increases rapidly for exposures less than ~ 40 µg hr/mL. This target is also consistent with the exposures achieved in the efficacy study with the approved 900 mg dose in adults (PV16000) which were approximately 46.3 µg hr/mL. The upper bound of 60 µg hr/mL is acceptable based on the data presented in Figure 3. The predicted incidence of neutropenia was 15% and 20% at exposures of 39 and 61 µg hr/mL, respectively. The predicted incidence of leukopenia was 40% and 50% at exposures of 34 and 62 µg hr/mL, respectively.

*Dose justification for treatment of CMV disease in neonates*

A dose resulting in $AUC_{0-12}$ of 27.1 µg hr/mL was targeted for treatment of CMV disease on neonates. An $AUC_{0-12}$ of 27.1 µg hr/mL was observed in HIV- and CMV-seropositive adult subjects receiving the approved dose of 900 mg valganciclovir in study WP15511. This exposure is also expected to be achieved with a 6 mg/kg i.v. twice daily dose of ganciclovir, which was shown in a separate study to prevent hearing deterioration at 6 months measured by brainstem-evoked response, **(b) (4)**



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## *2.4 Extrinsic Factors:*

### 2.4.1 What extrinsic factors influence dose-exposure and/or –response, and what is the impact of any differences in exposure on response?

The applicant did not evaluate any extrinsic factors.

## *2.5 General Biopharmaceutics*

### 2.5.1 What is the relative bioavailability of the proposed to-be marketed formulation to the pivotal clinical trial formulation?

Pivotal clinical trials in adults used the tablet formulation. Use of the powder for oral solution in adults is acceptable based on the results of relative bioavailability study WP16302.

**2.5.2 What is the effect of food on the bioavailability (BA) of ganciclovir from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?**

The currently approved package insert of Valcyte states that valganciclovir should always be administered with food, therefore, a separate food effect assessment was not conducted. The relative bioavailability study and the pediatric studies were conducted under fed conditions.

### *2.6 Analytical Section*

**2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?**

The active moities were identified and measured in the plasma by using validated LC/MS/MS methods.

**2.6.2 Which metabolites have been selected for analysis and why?**

No metabolites were selected for analysis

**2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?**

The analytical methods used measured the total concentrations of ganciclovir

**2.6.4 What bioanalytical methods are used to assess concentrations?**

A validated LC-MS/MS method (b) (4) (b) (4) was used to determine concentration of ganciclovir in human plasma samples. The lower limit of quantification was 0.040 µg/ml and the overall accuracy and precision of the assay was 94.5% – 103% and 4.4% – 6.3%, respectively.

## 3 DETAILED LABELING RECOMMENDATIONS

3 pages of Draft Labeling have been withheld immediately after this page as B4 (CCI/TS).

# 4 APPENDICES

## *4.1* Individual Study Review

### 4.1.1 Safety and Pharmacokinetics in Pediatric Liver Transplant Recipients at Risk of Developing CMV Disease: Study WP16303

#### 4.1.1.1 Objective

The objective of this study was to compare the PK of ganciclovir from i.v. ganciclovir to PK of ganciclovir from valganciclovir oral solution in pediatric liver transplant recipients within the first 14 days of transplantation.

#### 4.1.1.2 Study Design

Enrolled subjects were treated with i.v. ganciclovir twice daily from enrollment (Day 1-4 post-transplant) to Day 12 and then with oral valganciclovir twice daily for Days 13 and 14. Blood samples for measurement of ganciclovir concentrations were obtained on Day 12 pre-dose, 1 h (immediately before end of ganciclovir infusion), and one sample per the following time windows: 2-3 h, 5-7 h and 10-12 h. Blood samples for measurement of ganciclovir and valganciclovir were obtained on Day 14 pre-dose of oral valganciclovir,

0.25-75 h, 1-3 h, 5-7 h and 10-12 h. Patients were evaluated up to Day 42 post-transplant for safety assessments.

*Dosing Algorithm*

The doses of ganciclovir and valganciclovir oral solution were projected to produce a ganciclovir AUC equivalent to that of i.v. ganciclovir at 5 mg/kg in an adult of 70 kg with a BSA of 1.73 $m^2$ adjusted for BSA and creatinine clearance. The pediatric dose is shown below:

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

where,

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

The normalized dose for i.v. ganciclovir was calculated using 5 mg/kg as the reference dose, yielding a value of 200 $mg/m^2$. The normalized dose for valganciclovir oral solution was calculated using 900 mg as the reference dose, yielding a normalized dose of 520 $mg/m^2$. The reference doses are the approved adult doses. The pediatric dose was further adjusted for creatinine clearance (calculated with the Schwartz formula) according to Table 8.

**Table 8 Dose Adjustment Based on Creatinine Clearance**

| Estimated CrCL (mL/min/1.73 $m^2$) | Ganciclovir i.v. dose (mg) | Valganciclovir p.o. dose (mg) |
|---|---|---|
| ≥70 | Full Dose | Full Dose |
| 50 -69 | 50% of Full Dose | 50% of Full Dose |
| 40 – 49 | 25% of Full Dose | 25% of Full Dose |

*Demographics*

A total of 20 subjects were enrolled in the study. There were 9 subjects aged 3 months to 2 years, 6 subjects aged 2 years to 6 years and 5 subjects aged 6 to 16 years. The mean ± s.d. age was 4.0 ± 5.2 years, weight was 18.02 ± 15.71 kg and creatine clearance was 153.37 ± 75.30 mL/min.

*Endpoints*

Pharmacokinetic Parameters: $AUC_{0-24}$, Clearance, Vss, $C_{max}$ and $t_{1/2}$.
Safety: Adverse events and laboratory values.

*Reviewer's comment: $AUC_{0-24}$ was calculated using a population pharmacokinetic analysis where $AUC_{0-24}$ = Dose/Clearance. Dose refers to a single dose and clearance is the individual estimate of clearance. Therefore, the results shown in* Table 9 *do not*

*reflect what actually happened in the study with twice daily dosing, but rather a hypothetical $AUC_{0-24}$ assuming once daily dosing. This approach allows estimates of $AUC_{0-24}$ to be directly compared with those calculated in the WP16296 and WV16726 studies which used once daily dosing.*

#### 4.1.1.3 Results

The pharmacokinetic results are displayed in Table 9.

**Table 9. Summary of Pharmacokinetic Parameters by Age Group in Study WP16303: Mean (Min-Max)**

| PK Parameter | Age Group 0-5 years (N=13) | 6-11 years (N=2) | 12-16 years (N=3) |
|---|---|---|---|
| $AUC_{0-24}$ (mg*h/L) i.v. ganciclovir (200 mg/m$^2$) | 24.3 (14.1-38.9) | 35.2 (27.1-43.2) | 23.4 (19.2-25.8) |
| $AUC_{0-24}$ (mg*h/L) valganciclovir (520 mg/m$^2$) | 23.4 (11.8-40.6) | 46.8 (35.2-58.4) | 25.8 (25-30.9) |
| $C_{max}$ (mg/L) i.v. ganciclovir (200 mg/m$^{2)}$ | 12.2 (9.17-15) | 9.29 (4.73-13.9) | 11.8 (11.6-12.4) |
| $C_{max}$ (mg/L) valganciclovir (520 mg/m$^2$) | 5.51 (2.72-7.18) | 5.29 (3.79-6.79) | 6.9 (5.59-7.04) |
| $t_{½}$ term (h) | 1.65 (1.01-2.57) | 6.8 (3.74-9.87) | 4.35 (4.17-5.04) |

Source: WP16303 Study Report Page 45.

The bioavailability of ganciclovir from valganciclovir oral solution was estimated to be 55% with a 95% confidence interval of 48% - 62%. The $AUC_{0-24}$ of ganciclovir from valganciclovir oral solution was similar to ganciclovir from i.v. administrations. However, ganciclovir exposures were lower than the target exposure (40 – 60 µg h/ml), especially in the 0-5 years and 12-16 years age groups.

Results of population pharmacokinetic modeling are discussed in the Pharmacometrics review.

#### 4.1.1.4 Conclusion

Ganciclovir exposures after i.v. ganciclovir were similar to ganciclovir exposures after valganciclovir oral formulation. However, ganciclovir exposures failed to reach their target, particularly in children less than 5 years of age. This observation is consistent when the youngest age groups is broken into two groups of <2 years and >2 and <6 years of age.

## 4.1.2 Safety and Pharmacokinetics in Pediatric Kidney Transplant Recipients at Risk of Developing CMV Disease: Study WP16296

### 4.1.2.1 Objective

The objective of the study was to determine the once daily dose of valganciclovir oral solution that would achieve a 24 hour ganciclovir exposure similar to that achieved with once daily standard i.v. ganciclovir and identify the pharmacokinetics of ganciclovir in pediatric kidney transplant recipients.

### 4.1.2.2 Study Design

After stabilization of renal function following renal transplant, patients received a once daily dose of i.v. ganciclovir on Days 1 and 2 at a dose equivalent to an adult dose of 5 mg/kg. Blood samples for measurement of ganciclovir were obtained on Day 2 pre-dose, 1 h (immediately before end of infusion), and one sample in the following time windows: 2-3 h, 5-7 h and 10-12 h. On Day 3, patients received a single oral dose of valganciclovir projected to be half the adult dose of valganciclovir tablets (450 mg). On Day 4, patients received a single oral dose of valganciclovir projected to be equivalent to the full adult dose of valganciclovir tablets (900 mg). Both doses of oral valganciclovir were taken within 15 minutes of finishing a breakfast meal. Blood measurements were obtained on Days 3 and 4 for determination of valganciclovir and ganciclovir concentrations at pre-dose, 0.25-0.75 h, 1-3 h, 5-7 h and 10-12 h. On Day 4, an additional PK blood measurement was obtained at 22-24 hours.

*Dosing Algorithm*

The dosing algorithm described in Study WP16303 was also used in Study WP16296.

*Demographics*

A total of 26 subjects between 3 months and 16 years of age were enrolled in the study. There were 6 subjects less than 6 years of age, 19 subjects aged greater than 6 years but prepubescent and one subject 16 years of age and pubescent. The mean ± s.d. age was 10.6 ± 4.5 years, weight was 35.31 ± 19.33 kg and creatinine clearance was 109.90 ± 43.61 mL/min.

*Endpoints*

Pharmacokinetic Parameters: $AUC_{0-24}$
Safety: Adverse events and vital signs

#### 4.1.2.3 Results

The pharmacokinetic results are displayed in Table 10.

**Table 10. Summary of Pharmacokinetic Parameters by Age Group in Study WP16296: Median (Min-Max)**

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

Source: WP16296 Study Report Page 43.

The bioavailability of ganciclovir from valganciclovir oral solution was estimated to be 52% with a 95% confidence interval of 40% - 80%. The $AUC_{0-24}$ of ganciclovir from valganciclovir oral solution was similar to ganciclovir from i.v. administrations. However, ganciclovir exposures were lower than the target exposure (40 – 60 µg h/ml), especially in the 0-5 years age group.

Results of population pharmacokinetic modeling are discussed in the Pharmacometrics review.

#### 4.1.2.4 Conclusion

Ganciclovir exposures after i.v. ganciclovir were similar to ganciclovir exposures after valganciclovir oral formulation. However, ganciclovir exposures failed to reach their target, particularly in children less than 5 years of age. This observation is consistent when the youngest age groups is broken into two groups of <2 years and >2 and <6 years of age.

## 4.1.3 Pharmacokinetics, Efficacy and Safety in Pediatric Kidney, Liver and Heart Transplant Recipients at Risk of Developing CMV Disease: Study WV16726

### 4.1.3.1 Objectives

- Investigate the dafety and tolerability of valganciclovir oral solution in pediatric solid organ transplant recipients
- Determine the pharmacokinetics of ganciclovir following oral administration of valganciclovir solution and tablets in solid organ transplant recipients
- Describe the incidence of CMV disease

### 4.1.3.2 Study Design

Patients began prophylaxis with oral valganciclovir as soon after transplant as possible and continued for a maximum of 100 days post-transplant. Safety assessments occurred on Day 1, Day 7, Weeks 2, 6, 10, 14 (Day 100), 16, 20 and 26 post-transplant. A blood sample was obtained at Day 100 to assess potential viral resistance. Blood measurements were obtained for ganciclovir concentrations during hospitalization and after at least three doses of valganciclovir were administered. The timing of these pharmacokinetic measurements were: pre-dose, 1-3 h, 3-7 h and 7-12 h with at least one hour between the second and third blood draws and at least two hours between the third and fourth blood draws. In addition, a single PK sample was taken during scheduled safety visits at least once during 100 days treatment and on up to a maximum of three occasions.

*Dosing Algorithm*

Based on knowledge from studies WP16296 and WP16303, the once daily dosing algorithm was modified to:

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

where,

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

and,

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

where,

k = 0.45 for ages <2 years
k = 0.55 for boys aged 2 to <13 years and girls aged 2 to 16 years

k = 0.7 for boys aged 13 to 16 years

*Reviewer's comment*: *The sponsor proposes using a value of k = 0.45 for patients aged 1 to < 2 years, whereas the Schwartz formula is typically calculated using a value of k = 0.55 for this age group.*

*Demographics*

A total of 63 solid organ transplant recipients (33 kidney, 17 liver, 12 heart and one kidney and liver) were included in the analysis. There were 17 patients aged less than 2 years, 21 aged 2 to 12 years and 25 aged greater than 12 years. The mean ± s.d. age was 8.1 ± 5.9 years and weight was 29.08 ± 19.94 kg. There were 34 male patients and 29 female patients.

*Endpoints*

Pharmacokinetic Parameters: exposure of ganciclovir $AUC_{0-24}$
Safety: Adverse events, opportunistic infections and laboratory tests
Efficacy: Incidence of CMV disease, treatment failure, episodes of rejection and graft loss

#### 4.1.3.3 Results

The pharmacokinetic results are displayed in Table 11.

**Table 11. Summary of Pharmacokinetic Parameters by Age Group and Transplant Type in Study WV16726: Mean (SD)**

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

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

Source: WV16726 Study Report Page 54.

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

Results of population pharmacokinetic modeling are discussed in the Pharmacometrics review.

There was no incidence of CMV disease reported during the study. CMV viremia was reported for seven patients during the study. Three liver recipients and one kidney recipient had treatment failure. Treatment failure was defined as CMV disease requiring treatment up to day 100 post-transplant or discontinuation of study medication due to lack of efficacy or toxicity. The proportion of subjects with a suspected rejection was higher in the younger patients (47.1% in the ≤ 2 years group, 19.0% in the >2 years to <12 years group and 12.0% in the ≥ 12 years group). Rejections occurred in 8 (47%) of liver recipients, 4 (33%) of heart recipients and 4 (12%) of kidney recipients. Three patients had graft loss during the study.

95% of patients experienced at least one adverse event during the treatment. One patient died due to cardiac rejection 28 days after transplantation, but this was considered unrelated to valganciclovir administration. The proportion of patients who experienced serious adverse events was higher in the <2 years group (65%) than in the >2 to <12 years (38%) and the ≥ 12 years group (32%). Marked laboratory abnormalities were most commonly observed with neutrophils, hemoglobin, transaminases and creatinine.

#### 4.1.3.4 Conclusion

The used of the revised oral valganciclovir dosing algorithm results in ganciclovir exposures within the target range. Furthermore, predicted exposures with the modified algorithm are independent of age, weight and renal function. The overall safety profile is similar to that observed in adult transplant recipients.

#### 4.1.3.5 Site Inspection

Based on the findings from the analytical inspection performed by the Division of Scientific Investigation (DSI) at [redacted] (b) (4), the plasma concentration data from Study WV16726 are not acceptable as submitted in the NDA. Please refer to the Execute Summary for steps that can be taken by the Applicant to assure the accuracy of analytical runs and the resulting drug concentrations.

### 4.1.4 Pharmacokinetics and Tolerability of Valganciclovir Liquid Formulation in a Neonatal Population with Symptomatic Congenital CMV Disease: Study CASG109

#### 4.1.4.1 Objectives

- Determine the pharmacokinetics of ganciclovir after administration of oral valganciclovir solution in neonates with symptomatic congenital CMV disease

- Identify a dose of oral valganciclovir that achieves comparable ganciclovir exposure to 6 mg/kg i.v. (or $AUC_{0-12}$ 27 mg h/L) ganciclovir in neonates with symptomatic congenital CMV disease

#### 4.1.4.2 Study Design

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

*Demographics*

A total of 24 subjects (13 male, 11 female) were enrolled in the study. The median (range) age was 16.5 (6-31) days, birth weight was 2.4 (1.09–4.1) kg and gestational age was 37.5 (34-41) weeks.

*Endpoints*

Pharmacokinetic Parameters: $AUC_{12}$
Safety: adverse events and safety labs

#### 4.1.4.3 Results

In Version 1.0, the median $AUC_{12}$ of ganciclovir after 6 mg/kg i.v. ganciclovir was 24.8 mg h/L on Day 4 and 14.3 mg h/L at Day on Day 34. After 14 mg/kg valganciclovir oral solution, the $AUC_{12}$ of ganciclovir was 23.2 mg h/L on Day 5 and 21.57 mg h/L on Day 36. In Version 2.0/3.0, the median $AUC_{12}$ of ganciclovir after i.v. ganciclovir was 25.5 mg h/L on Day 1. In the 9 subjects who received 14 mg/kg oral valganciclovir, the median $AUC_{12}$ was 23.4 mg h/L on Day 1. In the 4 subjects receiving 20 mg/kg oral

valganciclovir, the median $AUC_{12}$ was 53.3 mg h/L. The 6 subjects who received 16 mg/kg achieved a median $AUC_{12}$ of 23.9 mg h/L.

Results of population pharmacokinetic modeling are discussed in the Pharmacometrics review.

38% of subjects developed Grade 3 or 4 neutropenia. One subject permanently discontinued antiviral therapy due to neutropenia.

#### 4.1.4.4 Conclusion

The observed ganciclovir $AUC_{0-12}$ in the neonates receiving 14 mg/kg (n=14) were indistinguishable from those in neonates receiving 16 mg/kg (n=4). The ganciclovir $AUC_{0-12}$ from 6 mg/kg was similar to the 14 mg/kg and 16 mg/kg oral valganciclovir $AUC_{0-12}$, although both were slightly lower than the 27 mg h/L target.

#### 4.1.4.5 Site Inspection

Based on the findings from the analytical inspection performed by the Division of Scientific Investigation (DSI) at (b) (4) the plasma concentration data from Study CASG109 are not acceptable as submitted in the NDA. Please refer to the Execute Summary for steps that can be taken by the Applicant to assure the accuracy of analytical runs and the resulting drug concentrations.

### 4.1.5 A bioequivalence study comparing ganciclovir from the valganciclovir oral solution and the commercial valganciclovir 450 mg tablet (Valcyte®) at a dose of 900 mg in kidney transplant recipients (pivotal bioequivalence trial).

#### 4.1.5.1 Objectives

The primary objective of this study was to determine the relative bioavailability of ganciclovir from the valganciclovir tutti-frutti oral solution and the 450 mg tablet formulation at a dose of 900 mg administered in the fed state. The secondary objective was to compare the systemic exposure to ganciclovir from the valganciclovir strawberry oral solution with the valganciclovir tutti-frutti oral solution at a dose of 900 mg.

#### 4.1.5.2 Study Design

Multiple center, open label, randomized, three way crossover study. Patients at a risk of CMV disease (D+/R-, D+/R+, D-/R+), who were being treated prophylactically with Valcyte® (using the commercially available tablets) after their first or second kidney

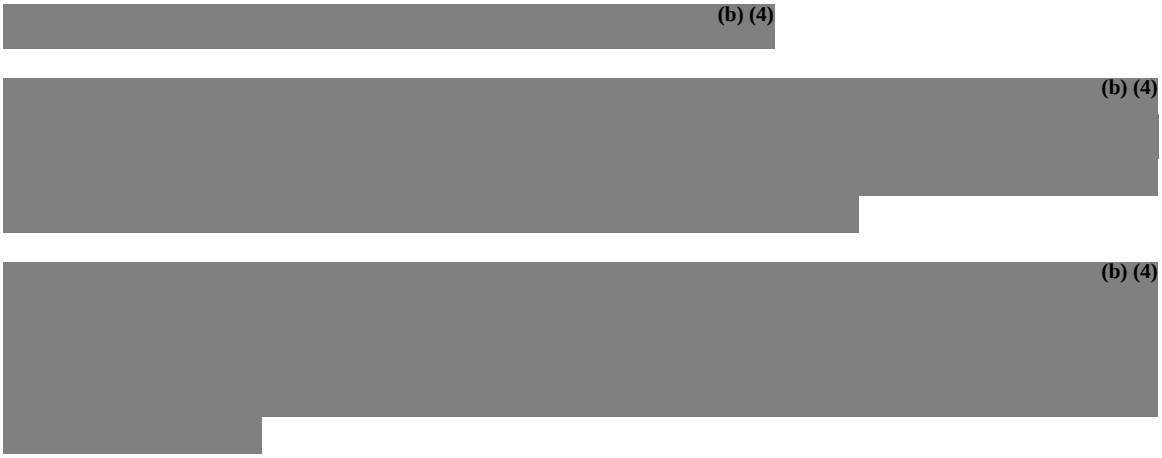
transplant and who had adequate renal and hematological function were eligible for the study. Eligible kidney transplant recipients were screened at any time during prophylaxis with Valcyte® tablets once the transplant had stabilized and provided that the follow-up procedures could be completed during the scheduled time of prophylaxis.

After pre-dose assessments on day 1, the patients were randomized to one of the three treatment sequences (ABC, BCA, and CAB). Each patient received all the three treatments (treatment A, treatment B, and treatment C):

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

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

**Treatment C:** Once daily oral dosing (via a syringe) with the valganciclovir strawberry flavored oral solution for 2 days.




*Reviewer's Note Regarding the Dose Used in the Study*

*The dose of valganciclovir used in this study (900 mg; 2 X 450 mg tablets or 18 mL of 50 mg/mL powder for oral solution) is the approved dose of valganciclovir used for the prophylaxis of cytomegalovirus (CMV) disease in patients with normal renal function.*

After transplantation but prior to study enrollment, valganciclovir (supplied by the center), 2 X 450 mg tablets, was to be administered with food for at least 4 days prior to day 1. From day 1 to day 6, valganciclovir was to be administered within 15 minutes after completion of breakfast. For the powder for oral solution formulation, 18 mL of the reconstituted solution (50 mg/mL) was administered on each dosing occasion directly into the patient's mouth using a syringe to ensure that the full 900 mg of the dose was administered. Each of the three treatments was administered for two consecutive days.

**Sample Collection, Bioanalysis, and Pharmacokinetic Assessments**

*Sample Collection*

On days 2-7, pre-dose plasma samples were collected to determine the trough levels of ganciclovir. Blood samples were collected in EDTA tubes up to 24 hours post dose (at 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 24 hours) to determine the plasma concentrations of ganciclovir on days 2, 4, and 6.

*Bioanalysis*

The plasma concentrations of ganciclovir were determined in human EDTA plasma samples according to a validated LC-MS/MS methods. 50 µL of the plasma sample were injected in the LC-MS/MS system (Perkin Elmer SCIEX® API 3000). The LC-MS/MS system consisted of a pre-column (4 *2 cm ID $C_{18}$ ODS Phenomenex guard column), followed by an HPLC column (Waters C18 symmetry, 15 cm). The mobile phase consisted of acetonitrile: water, 15:85 (v/v) with 1 % (v/v) acetic acid.

The calibration curve was prepared using samples over the range of 0.04 µg/mL to 20 µg/mL (0.04, 0.08, 0.2, 0.4, 0.8, 2, 4, 8, and 20 µg/mL). Of note, the $C_{max}$ observed in the study samples is approximately 7 µg/mL and is therefore covered by the range of the standard curve.

The QC samples were prepared at four different concentrations (0.08, 0.6, 3.2, and 18 µg/mL).
The mean $r^2$ estimate based on the 14 calibration curve was greater that 0.999. The limit of quantification was approximately 0.04 µg/mL. The precision (% CV) of the assay, as determined by the analysis of the quality control samples, ranged from 4.4 % at the highest QC to 6.3 % at the lowest QC. The mean accuracy (%) ranged from 94.5 % to 103 %.

*Reviewer's Note:*

*The assay methodology is acceptable.*

*Pharmacokinetic Assessments*

The pharmacokinetic parameters ($C_{max}$, $t_{max}$, $AUC_{0-t}$, $k_{elim}$, $t_{1/2}$) were computed by non-compartmental analysis using Winnonlin Professional version 5.0.1 (Pharsight corporation, California, USA). The primary parameters for bioequivalence testing were $C_{max}$ and $AUC_{0-24}$. Bioequivalence of the tutti-frutti oral solution and the tablet was to be concluded if the 90 % confidence interval of the mean ratios of $C_{max}$ and AUC of the tutti-frutti powder for oral solution to the oral tablet were entirely within the acceptance region [ 0.8, 1.25] for both parameters ($C_{max}$ and $AUC_{0-24}$).

The systemic exposure to ganciclovir from the strawberry flavored powder for oral solution relative to the tutti-frutti flavored powder for oral solution was statistically compared using ANOVA.

#### 4.1.5.3 Results

*Subject Disposition*

The study planned to enroll 21 kidney transplant recipients; however, 23 patients were actually enrolled. 4 patients were enrolled at a center in New Zealand and 19 patients were enrolled in the United States. All 23 patients completed the study and received two doses each of valganciclovir tablets, strawberry flavored powder for oral solution and tutti-frutti powder for oral solution.

Out of the 23 patients enrolled in the study, pharmacokinetic data were available from 21 patients. 2 patients were excluded from the PK analysis (but included in the safety analysis) for the following reasons: Patient 48713/101 was excluded from the PK analysis because the time of sample collection could not be verified due to conflicting data recorded in the source documentation and CRF across all treatments. For the second patient (48711/302), the blood samples were collected in lithium heparin tubes instead of the tubes containing EDTA and were therefore excluded from the analysis.

Table 1 shows the demographics of subjects enrolled in study WP16302.

**Table 1: Demographics in Study WP16302**

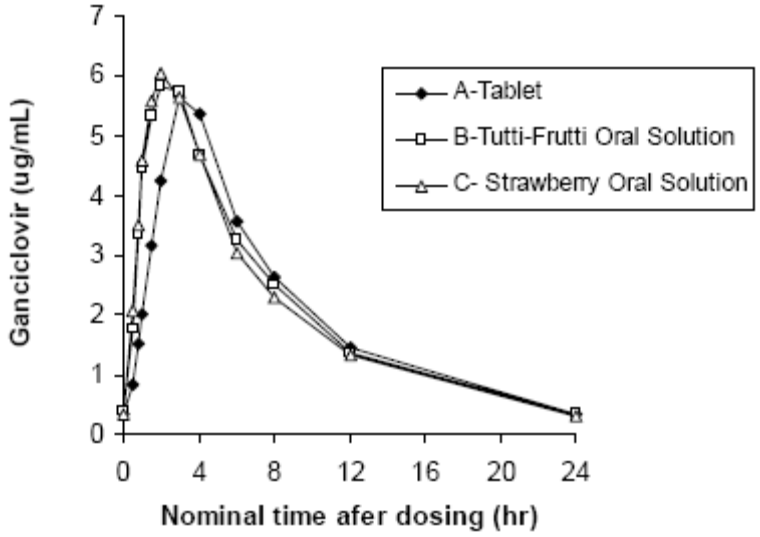
| | All Treatments All Periods N = 23 |
|---|---|
| Sex | |
| MALE | 12 ( 52%) |
| FEMALE | 11 ( 48%) |
| n | 23 |
| Race | |
| CAUCASIAN | 15 ( 65%) |
| BLACK | 5 ( 22%) |
| ORIENTAL | - |
| OTHER | 3 ( 13%) |
| n | 23 |
| Age in years | |
| Mean | 44.2 |
| SD | 12.04 |
| SEM | 2.51 |
| Median | 44.0 |
| Min-Max | 24 - 68 |
| n | 23 |
| Weight in kg | |
| Mean | 88.62 |
| SD | 23.129 |
| SEM | 4.823 |
| Median | 89.40 |
| Min-Max | 49.2 - 128.5 |
| n | 23 |
| Height in cm | |
| Mean | 170.1 |
| SD | 11.97 |
| SEM | 2.49 |
| Median | 172.0 |
| Min-Max | 142 - 191 |
| n | 23 |

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
DM11C 20JUN2006:10:41:51 (1 of 1)

*Pharmacokinetic Analysis*

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

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




The mean concentration-time profiles were comparable for all the three treatments.

Table 2 shows the summary of the pharmacokinetic parameters for ganciclovir after administration of the three treatments.

**Table 2: Summary of the pharmacokinetic parameters for ganciclovir after administration of the three treatments**

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

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

*Reviewer's Comment*

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

*The mean pre-dose concentration ($C_{minss,pre-dose}$ ;ganciclovir plasma concentration 24 hours after administration of valganciclovir on the first day) and the mean 24-hour concentration ($C_{minss,post-dose}$ ;ganciclovir plasma concentration 24 hours after administration of valganciclovir on the first day) were similar, irrespective of the formulation administered. The short half life of the drug (~ 4 hours) and the similarity in $C_{minss,pre-dose}$ and $C_{minss,post-dose}$ suggests that the majority of ganciclovir was eliminated within one dosing interval (24 hours). Further, the similarity in the $C_{minss, pre-dose}$ and $C_{minss,post-dose}$ concentrations indicates the absence of ganciclovir accumulation.*

*The pre-dose concentration on the second day of treatment were approximately 5-7 % of the $C_{max}$ observed on the second day, therefore, the "pre-dose" concentrations are not expected to have an impact on the statistical comparison of $C_{max}$ in order to establish similarity in systemic exposures between the tutti-frutti flavored powder for oral solution and the tablet.*

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

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

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

Treatment A: valganciclovir tablet formulation (reference formulation)
Treatment B: valganciclovir tutti-frutti flavored powder for oral solution formulation (test formulation).

Table 4 shows the statistical analysis of the pharmacokinetic parameters computed after administration of the strawberry flavored powder for oral solution formulation and the tutti-frutti- flavored powder for oral solution formulation.

**Table 4: Statistical analysis of the pharmacokinetic parameters computed after administration of the strawberry flavored powder for oral solution formulation and the tutti-frutti- flavored powder for oral solution formulation.**

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

Treatment A: valganciclovir strawberry flavored powder for oral solution formulation (test formulation)
Treatment B: valganciclovir tutti-frutti flavored powder for oral solution formulation (reference formulation).

#### 4.1.5.4 Conclusion

- The rate and extent of ganciclovir systemic exposures after administration of 900 mg (18 mL) valganciclovir tutti-frutti flavored powder for oral solution formulation (50 mg/mL) were similar to the rate and extent of ganciclovir systemic exposures after administration of 900 mg (2 X 450 mg) valganciclovir tablets.
- The rate and extent of ganciclovir systemic exposures after administration of 900 mg (18 mL) valganciclovir strawberry flavored powder for oral solution formulation (50 mg/mL) were similar to the rate and extent of ganciclovir systemic exposures after administration of 900 mg (18 mL) valganciclovir tutti-frutti flavored powder for oral solution.

#### 4.1.5.5 Site Inspection

The inspection at the Indiana University Medical Center Indianapolis, IN by the Division of Scientific Investigation (DSI) found that the clinical site failed to retain the reserve samples from Study WP16302. The retention of the reserve samples is required as per 21 CFR 320.38 and is critical for assuring the authenticity of the test and reference products used in this pivotal bioequivalence study. As authenticity of the test and reference products cannot be confirmed, the data from Study WP16302 cannot be used (b) (4)

(b) (4)

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- (b) (4)

#### 4.1.6.2 Site Inspection

The inspection at the Indiana University Medical Center Indianapolis, IN by the Division of Scientific Investgation (DSI) found that the clinical site failed to retain the reserve samples from Study WP16302. The retention of the reserve samples is required as per 21 CFR 320.38 and is critical for assuring the authenticity of the test and reference products used in this pivotal bioequivalence study. As authenticity of the test and reference products cannot be confirmed, the data from Study WP16302 cannot be used (b) (4)

(b) (4)

## *4.2 Pharmacometric Review*

### 4.2.1 Summary of Findings

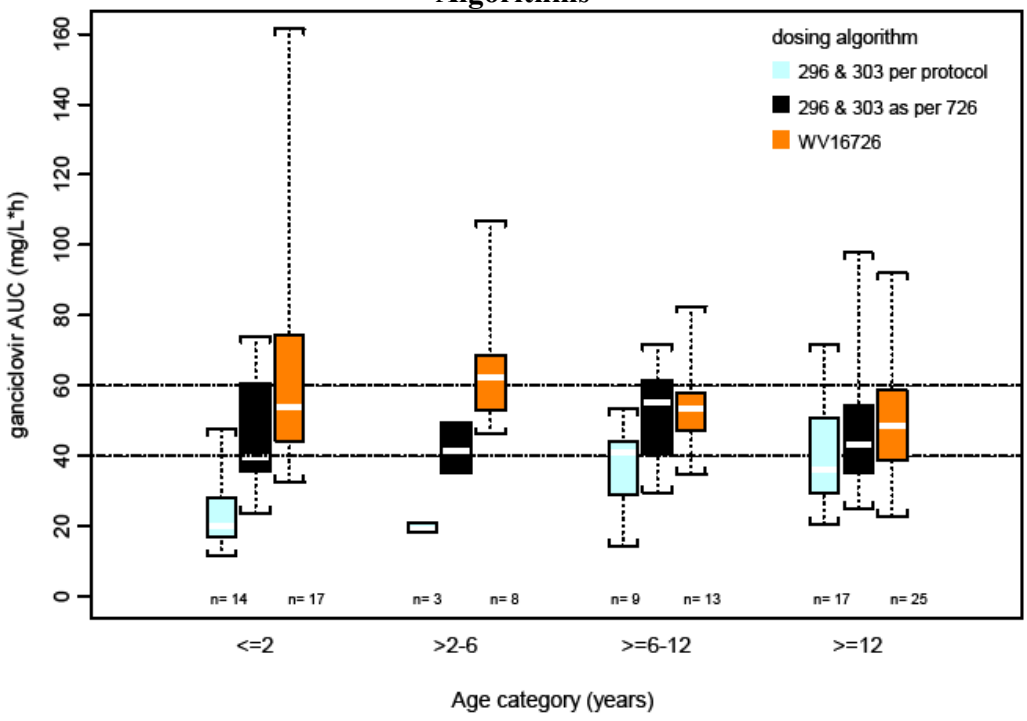
#### 4.2.1.1 Key Review Questions

The purpose of this review is to address the following key questions.

##### *4.2.1.1.1 Is the proposed dose recommendation of valganciclovir in pediatric solid organ transplant patients aged 4 months to 16 years who are at risk of developing CMV disease acceptable?*

The proposed dose recommendation is acceptable. The proposed pediatric dose of 7×BSA×CrCL(calculated by Schwartz formula) produced ganciclovir exposures close to the target range of 40 – 60 mg h/L in Study WV16726. The target exposure is based on an analysis of data from Study PV16000 in adult solid organ transplant recipients treated with the approved dose of 900 mg oral valganciclovir. Furthermore, as seen in Figure 5, if the proposed algorithm had been applied in Studies WP16296 and WP16303, predicted exposures would also have fallen within the target range. As opposed to the initial dosing algorithm used in studies WP16296 and WP16303, predicted ganciclovir exposures with the modified algorithm are independent of age, weight and renal function. Simpler, alternative dosing algorithms investigated by the reviewer predicted less optimal distribution ganciclovir exposures compared to the proposed algorithm.

**Figure 5. Ganciclovir Exposures from Initial and Modified Pediatric Dosing Algorithms**



#### *4.2.1.1.2 Is the recommended dose of 16 mg/kg valganciclovir in pediatric patients less than 3 months of age with symptomatic congenital CMV disease acceptable?*

Pharmacokinetic data suggest the dose of 16 mg/kg is acceptable in pediatric patients less than 3 months of age with symptomatic congenital CMV disease. The observed ganciclovir $AUC_{0-12}$ in the neonates receiving 14 mg/kg (n=14) were indistinguishable from those in neonates receiving 16 mg/kg (n=4). However, the results of population pharmacokinetic modeling predict the 16 mg/kg dose would provide exposures closer to the target $AUC_{0-12}$ of 27 mg h/L than the 14 mg/kg dose (Figure 22). The target ganciclovir exposure of an $AUC_{0-12}$ of 27.1 µg h/ml, is chosen to match the exposure achieved in HIV- and CMV-seropositive adult subjects with normal renal function receiving the approved dose of 900 mg once daily oral valganciclovir in study WP15511.

#### *4.2.1.1.3 Can differences in exposure in either adults or pediatrics explain the observation from a subgroup analysis in adult subjects that showed liver transplant recipients receiving valganciclovir had five times the incidence of tissue-invasive CMV disease compared to the oral ganciclovir group?*

The observed increase in tissue-invasive CMV disease in liver transplant recipients can not be explained by differences in exposure of ganciclovir in this population. In the efficacy trial in adults (Study PV16000) the mean ganciclovir exposure following oral valganciclovir was similar across transplant types and consistently higher than exposure in subjects receiving 1000 oral ganciclovir three times daily (Table 12).

**Table 12. Mean Systemic Pharmacokinetic Measures by Solid Organ Transplant Type in Study PV16000 (N = number of profiles)**

| | Liver | | Heart | | Kidney | |
|---|---|---|---|---|---|---|
| | $AUC_{0-24}$ (mg h/L) | $C_{max}$ (µg/ml) | $AUC_{0-24}$ (mg h/L) | $C_{max}$ (µg/ml) | $AUC_{0-24}$ (mg h/L) | $C_{max}$ (µg/ml) |
| Ganciclovir (1000 mg three times with food) | 24.9 ± 10.2 (N=62) | 1.3 ± 0.4 (N=62) | 26.6 ± 11.6 (N=24) | 1.4 ± 0.5 (N=24) | 31.3 ± 10.3 (N=65) | 1.5 ± 0.5 (N=65) |
| Valganciclovir (900 mg once daily with food) | 46.0 ± 16.1 (N=138) | 5.4 ± 1.5 (N=138) | 40.2 ± 11.8 (N=31) | 4.9 ± 1.1 (N=31) | 48.2 ± 14.6 (N=129) | 5.3 ± 1.5 (N=129) |

Source: Clinical Study Report for PV16000: Page 153

Ganciclovir exposures in pediatric subjects enrolled in Study WV16726 were also similar across transplant type with $AUC_{24}$ (mg h/L) of 51.8 ± 11.9 , 61.7 ± 29.5 and 58.0 ± 21.8 in kidney, liver and heart recipients, respectively. A subgroup analysis in Study WV16726, however, also showed a numerically higher rate of treatment failure in liver transplant recipients compared to kidney and heart recipients, although the sample size is too small to draw any statistical significance (Table 3). Any increase observed in the incidence of tissue-invasive CMV disease in these studies is most likely due to chance or

unique physiological characteristics of the liver, rather than differences in pharmacokinetics.

**Table 13. Summary of Treatment Failures in Pediatric Subjects in Study WV16726.**

| Treatment Failure | Liver (N=17) | Kidney (N=33) | Heart (N=12) |
|---|---|---|---|
| Patients with treatment failure | 17.6 % | 3 % | 0% |
| Patients with CMV disease requiring treatment | 2 | 1 | 0 |
| Patients discontinued due to lack of efficacy or toxicity | 1 | 0 | 0 |

*4.2.1.1.4* (b) (4)


### 4.2.1.2 Recommendations

- The dosing recommendations of valganciclovir powder for oral solution in pediatric (4 months -16 years) solid organ transplant recipients for the prophylaxis of CMV disease is acceptable. The reviewer explored other simplified dosing schemes but they were not superior to the sponsor's proposal to get better handle on ganciclovir exposures. 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

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

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. The calculated dose should be rounded to the nearest 25 mg increment for the actual deliverable powder for oral solution dose. If the calculated dose is between 405 mg and 495 mg, one 450 mg tablet may be taken. If the calculated dose exceeds 900 mg, a maximum dose of 900 mg should be administered.

- The dosing recommendations of valganciclovir powder for oral solution in pediatric patients from birth to less than 3 months of age for the treatment of congenital CMV is acceptable. However, the safety and efficacy of intravenous ganciclovir (reference treatment used in the study) has not been previously established. (b) (4) (b) (4) The study will be described in section 8.4 (pediatric use) section of the package insert to reflect better match in exposures for 16 mg/kg of valanciclovir and 6 mg/kg IV ganciclovir.

- (b) (4)

- (b) (4)

### 4.2.2 Pertinent regulatory background

Intravenous ganciclovir was approved in 1992 for the prevention of CMV disease in transplant recipients at risk for CMV disease. In 1996, oral ganciclovir was subsequently approved for the prevention of CMV disease in solid organ transplant recipients. In 2005, oral valganciclovir, a prodrug of ganciclovir was approved for the prevention of CMV disease in kidney, heart and kidney-pancreas transplant patients at high risk. Valganciclovir was not indicated for use in liver patients due to a subgroup analysis showing a significantly higher rate of tissue-invasive CMV disease in this population.

### 4.2.3 Results of Sponsor's Analysis

#### 4.2.3.1 Dose Recommendation in Pediatric Solid Organ Transplant Recipients for Prevention of CMV Disease

The sponsor conducted a population pharmacokinetic analysis to determine the pharmacokinetics of ganciclovir following i.v. administration of ganciclovir and oral administration of valganciclovir oral solution or tablets and investigate the covariates which might influence the pharmacokinetics of ganciclovir. Initially the sponsor conducted a population pharmacokinetic analysis with data from study WP16303. Subsequently, an integrated analysis with data from studies WP16303 and WP16296 was performed in order support a new dosing algorithm for study WV16726 for prevention of CMV disease in pediatric solid organ transplant recipients. This review will focus on the population pharmacokinetic model incorporating all three studies.

The dataset used for population pharmacokinetic analysis consisted of 924 plasma concentrations from 106 patients enrolled into studies WP16296, WP16303 and WV16726 (Table 14). For details regarding the sampling schemes in the three studies, consult the Individual Study Review section in the Clinical Pharmacology Review.

**Table 14. Description of Studies Used in Population Pharmacokinetic Analysis**

| Type | Study Number | Report | Population | N |
|---|---|---|---|---|
| PK, Safety | WP16303 | Safety and PK of i.v. ganciclovir and valganciclovir oral solution in pediatric liver transplant recipients | Pediatric patients aged 6 months to 16 years | 18 |
| PK, Safety | WP16296 | Safety and PK of i.v. ganciclovir and valganciclovir oral solution in pediatric renal transplant recipients | Pediatric patients aged 1 year to 16 years | 25 |
| PK, Safety, Efficacy | WP16726 | Safety and PK of valganciclovir syrup formulation in pediatric solid organ transplant recipients | Pediatric patients ages 4 months to 16 years | 63 |

The structure of the basic pharmacokinetic model was a two compartment model with first order formation for valganciclovir with a lag time parameterized in terms of formation rate constant ($K_a$), clearance (CL), central volume ($V_{central}$), peripheral volume ($V_{peripheral}$), inter-compartment clearance (Q), lag time (ALAG) and bioavailability (F1) for ganciclovir concentrations after valganciclovir administration relative to i.v. ganciclovir administration. Inter-subject variability on $K_a$, CL, $V_{central}$, $V_{peripheral}$ and F1 was modeled as exponential. A combined additive and proportional error structure model was used to describe residual error. NONMEM FOCE estimation method with interaction

was used. A summary of the parameter estimates for the basic model is provided in Table 15 and Table 16.

**Table 15. Summary of Population PK Parameters for Basic Model**

| PK parameter | VALUE |
|---|---|
| $K_a$ (h) | 0.585 |
| CL (L/h) | 5.19 |
| $V_{central}$ (L) | 8.05 |
| $V_{peripheral}$ (L) | 12.6 |
| Q (L/h) | 5.71 |
| F1 | 0.598 |
| Lag time (h) | 0.22 |
| Multiplicative error (%) | 0.332 |
| Additive error (mg/L) | 0.0637 |

Source: Clinical Study Report for WV16726: Page 1479

**Table 16. Summary of Inter-Individual Variability for Basic Model**

| PK parameters | IIV % | Final Estimates (variance) |
|---|---|---|
| ω_Ka | 47.1 | 0.222 |
| ω_CL | 42.1 | 0.177 |
| ω_V2 | 78.7 | 0.62 |
| ω_V3 | 71.1 | 0.506 |
| ω_F1 | 43.8 | 0.192 |

Source: Clinical Study Report for WV16726: Page 1479

The covariates investigated for influence on inter-individual variability were: gender, age, height, puberty, body weight, BSA, solid organ transplantation type, creatinine clearance derived from Cockroft-Gault formula and Schwartz formula, and liver function parameters. Stepwise generalized additive modeling in Xpose 3.102 was used initially to identify significant covariates to be tested in NONMEM. A forward addition step and backward deletion step at significance level of 0.01% were conducted within NONMEM to identify covariates to be retained in the final model. The final model included creatinine clearance (calculated with the Cockroft-Gault equation) and height as covariates of CL and height as covariate of $V_{central}$ and $V_{peripheral}$. A summary of the parameter estimates for the basic model is provided in Table 17 and Table 18. The equation for clearance of ganciclovir is:

$$CL(l/h) = 5.3 \times \left(\frac{CrCL(ml/\min)}{70.42(ml/\min)}\right)^{0.8} \times \left(\frac{Height(cm)}{121(cm)}\right)^{0.7}$$

*Reviewer's comment: Inclusion of height as a covariate of clearance does not have a physiological basis. Body weight is a better descriptor of body size which has a basis for explaining variation in clearance based on allometric principles.*

**Table 17: Summary of Population PK Parameters for the Final Model**

| PK parameter | VALUE | SE | CI 5% | CI 95% |
|---|---|---|---|---|
| $K_a$ (h) | 0.68 | 0.075 | 0.53 | 0.83 |
| CL (L/h) | 5.3 | 0.24 | 4.8 | 5.8 |
| CL~CRCLC | 0.82 | 0.11 | 0.6 | 1 |
| CL~HGT | 0.7 | 0.13 | 0.45 | 0.95 |
| $V_{cent}$ (L) | 11 | 1.8 | 7.5 | 15 |
| $V_{periph}$ (L) | 12 | 1.3 | 9.5 | 15 |
| $V_{cent\ \&\ periph.}$ V ~HGT | 2.2 | 0.13 | 1.9 | 2.5 |
| Q (L/h) | 5.4 | 1.3 | 2.9 | 7.9 |
| F1 | 0.57 | 0.026 | 0.52 | 0.62 |
| Lag time (h) | 0.22 | 0.0071 | 0.21 | 0.23 |
| Multiplicative error (%) | 0.32 | 0.019 | 0.28 | 0.36 |
| Additive error (mg/L) | 0.077 | 0.017 | 0.044 | 0.11 |

Source: Clinical Study Report for WV16726: Page 1486

**Table 18. Summary of Inter-Individual Variability for the Final Model**

| PK parameters | IIV (%) | IIV CI 5% | IIV CI 95% | Variance | SE |
|---|---|---|---|---|---|
| ω_Ka | 51 | 30 | 65 | 0.26 | 0.086 |
| ω_CL | 28 | 20 | 33 | 0.076 | 0.018 |
| ω_$V_2$ | 35 | 0 | 55 | 0.12 | 0.095 |
| ω_$V_3$ | 31 | 0 | 54 | 0.094 | 0.1 |
| ω_F1 | 20 | 13 | 25 | 0.04 | 0.012 |

Source: Clinical Study Report for WV16726: Page 1487

*Reviewer's comment: The sponsor provided goodness-of-fit plots, including dependent variable vs. population/individual prediction and weighted residuals vs. time/prediction. The model showed a tendency to overpredict at high observed concentrations, but was otherwise acceptable.*

Posthoc estimates of F1 and CL were used to compute AUC values for each individual. AUC was computed each time a change in BSA an/or creatinine clearance derived from Schwartz formula lead to a change in the dose according to the dosing algorithm in Study WV16726. The exposure was calculated as:

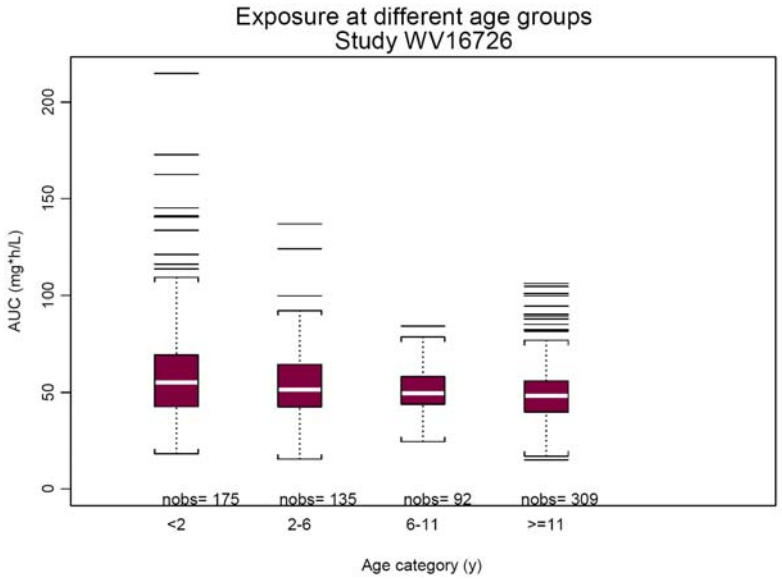
$$AUC = Dose_{ganciclovir} \times \frac{F1}{CL}$$

where,

$Dose_{ganciclovir}$ = Dose of valganciclovir × (molecular weight of valganciclovir/molecular weight of ganciclovir) × F1

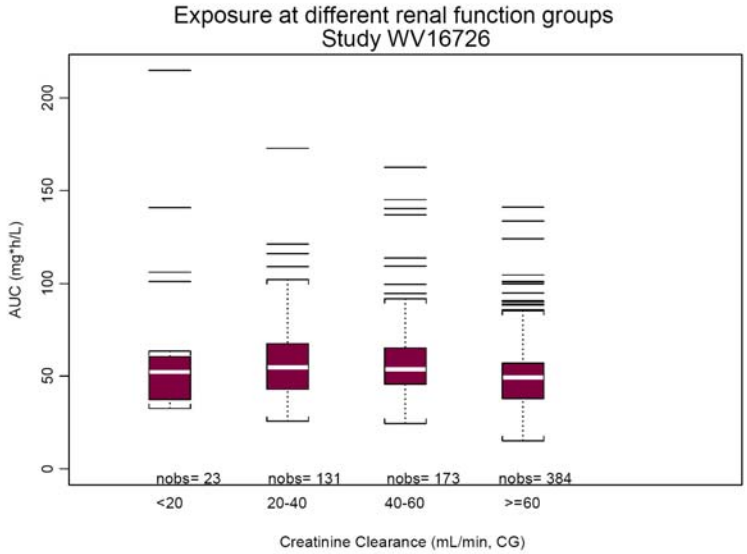
The boxplots in Figure 6 to Figure 9 show the calculated exposures in StudyWV16726 using the sponsor's proposed dosing algorithm displayed by age, renal function, weight and solid organ transplant type. There were 5 subjects who had 12 $AUC_{0-24}$ values >120 mg h/L, with one of the subjects contributing 7 of the 12 values. This was attributed to the result of the higher doses used in WV16726 as well as the influence of extreme post hoc estimates of clearance in these subjects due to the sparse sampling employed in the study.

**Figure 6. Exposure to Ganciclovir in Study WV16726 for Different Age Groups**



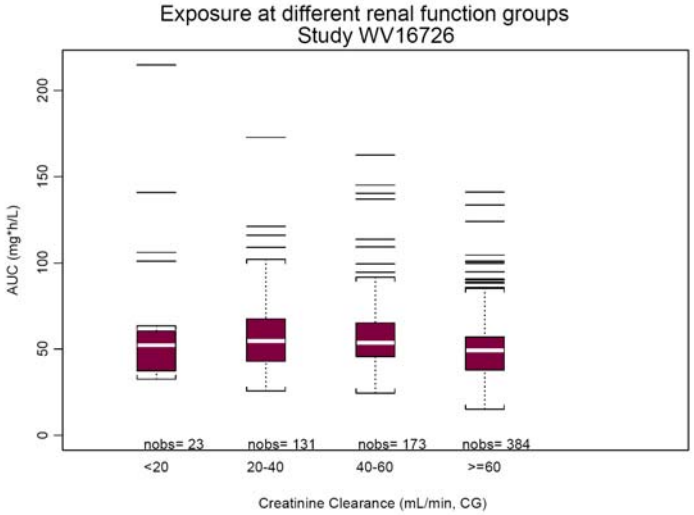

Source: Clinical Study Report for WV16726: Page 1491

**Figure 7. Exposure to Ganciclovir in Study WV16726 for Different Renal Function Groups**



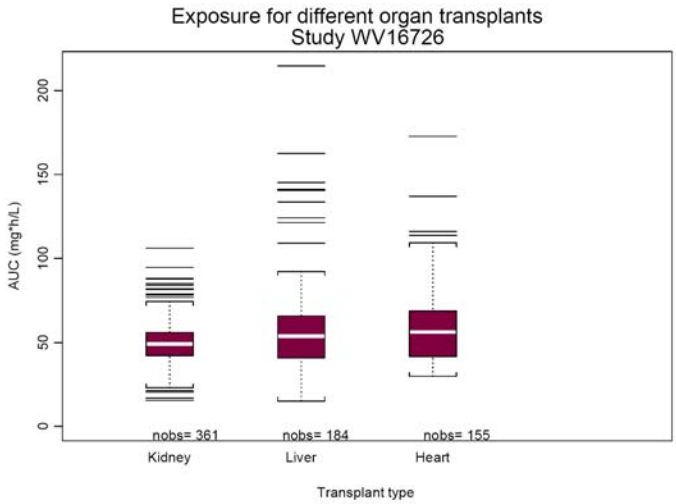
Source: Clinical Study Report for WV16726: Page 1492

**Figure 8. Exposure to Ganciclovir in StudyWV16726 for Different Weight Groups**




Source: Clinical Study Report for WV16726: Page 1492

**Figure 9. Exposure to Ganciclovir in StudyWV16726 for Different Solid Organ Transplant Types**




Source: Clinical Study Report for WV16726: Page 1493

Figure 1 shows the effects of the two dosing algorithms by age category in the three studies. The light blue boxes on the left in each age group summarize the AUCs achieved using the original dosing algorithm proposed in the WP16296 and WP16303 studies. The orange boxes on the right in each dose group summarize the AUCs achieved using the modified dosing algorithm proposed in Study WV16726. The black boxes in the middle of each age group are the predicted AUCs achieved if the modified dosing algorithm had been used in the WP16296 and WP16303 studies. The two horizontal dotted lines represent the lower and upper target for exposure (40 – 60 mg h/l).

#### 4.2.3.2 Dose Recommendation in Neonates for Treatment of Symptomatic Congenital CMV Disease

The sponsor conducted a population pharmacokinetic analysis to determine the pharmacokinetics of ganciclovir following i.v. administration of ganciclovir and oral administration of valganciclovir oral solution and investigate the covariates which might influence the pharmacokinetics of ganciclovir. (b) (4)

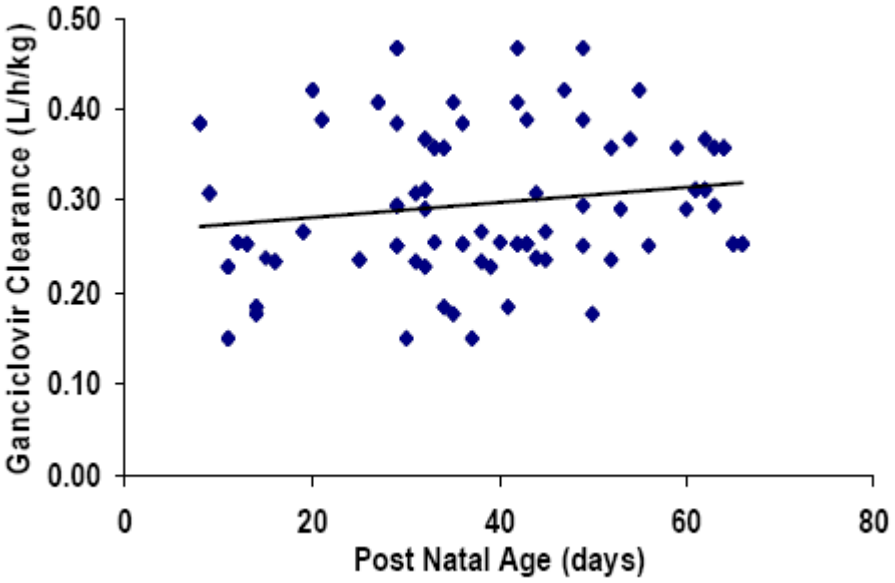
The dataset used for population pharmacokinetic analysis consisted of 350 observations collected from the 24 subjects enrolled in all versions of Study CASG109. For details regarding the sampling scheme in the study, consult the Individual Study Review section in the Clinical Pharmacology Review. The structure of the basic pharmacokinetic model was a one compartment model with first order formation for valganciclovir parameterized in terms of formation rate constant ($K_a$), clearance (CL), volume of distribution and bioavailability fraction (F1). The estimated bioavailability fraction included molecular weight differences between ganciclovir and valganciclovir and the fraction absorbed. Inter-subject variability on CL and F1 was modeled as exponential. A proportional error structure model was used to describe residual error. NONMEM FOCE estimation method with interaction was used in NONMEM version VI beta, level 1.0. The covariates investigated for influence on inter-individual variability were weight, BSA, sex and postnatal age. A covariate was included in the final model if it its inclusion resulted in a drop in the objective function value of 3.8, which corresponds to an $\alpha = 0.05$.
A summary of the parameter estimates for the final model are presented in Table 19. Weight was included as a covariate for CL and V.

**Table 19. Summary of Population Pharmacokinetic Parameters of the Final Model.**

| Parameter | Estimate | 95 % CI |
|---|---|---|
| CL (L/h) = $\theta_1 \times WT^{\theta_2}$ | | |
| $\theta_1$ | 0.146 | 0.0698 – 0.222 |
| $\theta_2$ | 1.68 | 1.24 – 2.12 |
| V (l/kg) | 1.15 | 0.866 – 1.43 |
| Ka ($h^{-1}$) | 0.591 | 0.436 – 0.746 |
| F | 0.536 | 0.434 – 0.638 |
| Inter-Individual Variability in CL (%CV) | 28.4 | 21.7 – 33.8 |
| Inter-Individual Variability in F (%CV) | 12.4 | 0 – 21.0 |
| Residual Variability (%) | 45.4 | 41.5 – 49.0 |

Figure 10 shows the relationship between posthoc estimates of clearance and postnatal age. Although there appears to be a positive relationship between the two, the inclusion of postnatal age in the model did not significantly improve the model.

**Figure 10. Posthoc Estimates of Weight Normalized Ganciclovir Clearance vs. Postnatal Age.**




The sponsor also reported the results of a simpler model with a linear relationship between clearance and body weight. The resulting parameter estimates were: CL = 0.287 l/h/kg; V = 1.131 l/kg; F = 0.486.

### 4.2.4 Reviewer's Analysis – dose recommendation in pediatric solid organ transplant recipients for prevention of CMV disease

#### 4.2.4.1 Introduction

The original dosing algorithm used in Studies WP16303 and WP16296, based on BSA and creatinine clearance failed to achieve target exposures of ganciclovir ($AUC_{0-24}$ = 40 – 60 mg h/L), especially in patients less than 2 years of age. A modified algorithm, also including BSA and creatinine clearance and supported by the results of a population pharmacokinetics analysis, was employed in Study WV16726. The results of a population pharmacokinetic analysis integrating all three studies showed the modified algorithm achieved target exposures in Study WV16726 and also would have achieved target exposures in the first two studies had it been used.

#### 4.2.4.2 Objectives

Analysis objectives are:

1. Assess the ability of the sponsor's algorithm to achieve target therapeutic exposures based on information from Studies WP16303, WP16296 and WV16726.
2. Investigate the use of simpler dosing algorithms to achieve the target exposures.

#### 4.2.4.3 Methods

##### *4.2.4.3.1 Data Sets*

Data sets used are summarized in Table 20.

**Table 20. Analysis Data Sets**

| Study Number | Name | Link to EDR |
|---|---|---|
| WP16303 | nmdat.xpt | \\Fdswa150\nonectd\N22257\N_000\2008-04-30\crt\datasets\wp16303 |
| WP16296 | nmdat.xpt | \\Fdswa150\nonectd\N22257\N_000\2008-04-30\crt\datasets\wp16296 |
| WV16726 | nmdat.xpt | \\Fdswa150\nonectd\N22257\N_000\2008-04-30\crt\datasets\wv16726 |

##### *4.2.4.3.2 Software*

NONMEM Version VI with FOCE with interaction was used for parameter estimation. Xpose 4.0.1 and R were used for plots, data manipulation and calculations.

##### *4.2.4.3.3 Model Results*

The structure of the basic pharmacokinetic model was a two compartment model with first order formation for valganciclovir with a lag time parameterized in terms of formation rate constant ($K_a$), clearance (CL), central volume ($V_{central}$), peripheral volume ($V_{peripheral}$), inter-compartment clearance (Q), lag time (ALAG) and bioavailability (F1) for ganciclovir concentrations after valganciclovir administration relative to i.v. ganciclovir administration. Inter-subject variability on $K_a$, CL, $V_{central}$, $V_{peripheral}$ and F1 was modeled as exponential. A combined additive and proportional error structure model was used to describe residual error. Parameter estimates are summarized in Table 21.

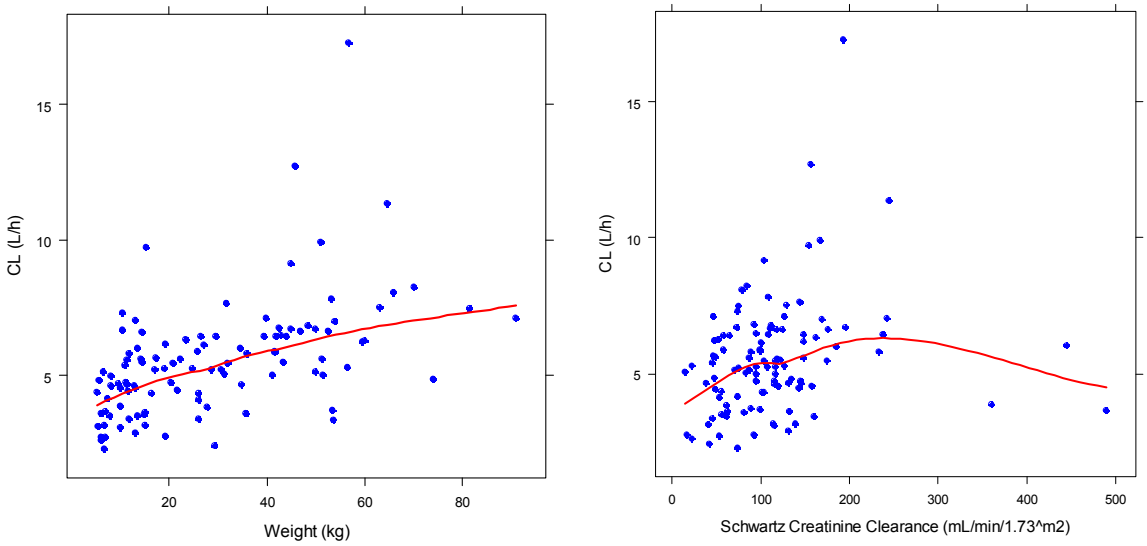
**Table 21. Pharmacokinetic Parameter Estimates for Basic Model**

| Parameter | Parameter Estimate | Parameter Relative SE (CV%) | IIV Estimate (CV%) | IIV Relative SE (CV%) |
|---|---|---|---|---|
| CL (L/h) | 5.23 | 1.95 | 42.4 | 24.3 |
| $K_a$ (h) | 0.581 | 6.27 | 47.4 | 39.1 |
| $V_{central}$ (L) | 8.2 | 14.8 | 78.4 | 31.1 |
| $V_{peripheral}$ (L) | 12.5 | 8.48 | 72.9 | 31.8 |
| Q (L/h) | 5.48 | 14.7 | | |
| F1 | 0.604 | 6.21 | 42.8 | 30.9 |
| Lag Time (h) | 0.22 | 0.0042 | | |
| Multiplicative Error (%) | 0.331 | 6.68 | | |
| Additive Error (mg/L) | 0.0631 | 27.4 | | |

*Reviewer's comment: The parameter estimates from the reviewer's model do not exactly match those of the sponsor from* Table 15. *It is possible the reviewer used a different version of NONMEM than the sponsor. The difference between the final parameter estimates from the sponsor's and reviewer's data sets, however, is negligible.*

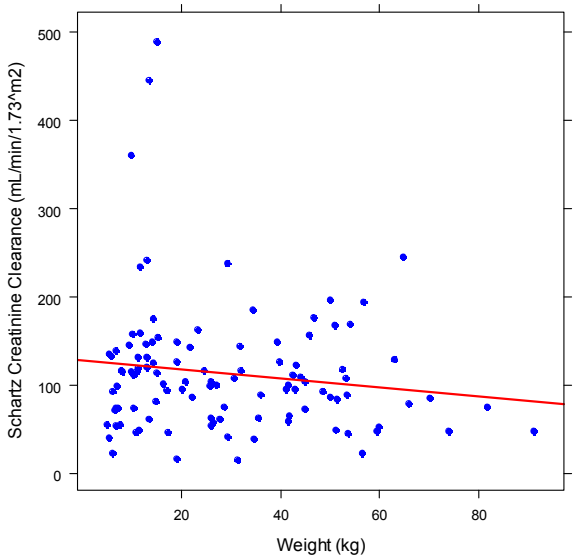
Figure 11 shows the relationship between post-hoc estimates of clearance and body weight and creatinine clearance calculated by the Schwartz formula.

**Figure 11. Relationship between body weight and Schwartz creatinine clearance and clearance. The red line represents the loess fit to the data.**



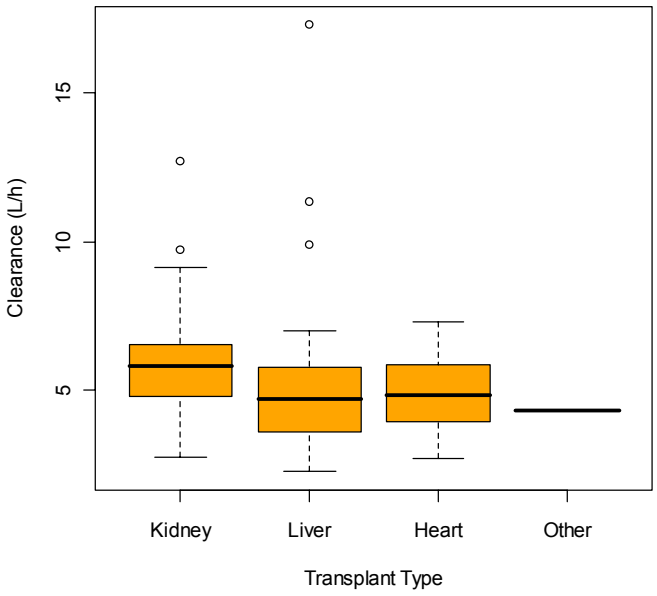

Typically body weight and renal function are strongly correlated, which would imply that inserting only one of the two covariates into the model would be sufficient. Figure 12, however, shows the lack of correlation between the two covariates ($R^2 = 0.019$). In kidney transplant recipients, this disconnect between body weight and renal function as measured by the Schwartz formula may be due to the disconnect between the transplanted kidney and the size of the recipient. In other transplant recipient, the disconnect may be attributed to comedications altering renal function.

**Figure 12. Relationship Between Schwartz Creatinine Clearance and Body Weight. The solid line represents the linear best fit.**




There was no observed relationship between transplant type and ganciclovir clearance. The slightly higher clearance observed in kidney transplant recipients in Figure 13 is explained by the influence of Study WP16296 which enrolled older and heavier subjects compared to the other studies.

**Figure 13. Relationship between Transplant Type and Clearance**




In the first step of the covariate building process, weight was included as a covariate on clearance and central and peripheral volumes of distribution based on physiological principles of allometric scaling. Schwartz creatinine clearance and age were also

investigated as covariates on clearance. The results of the covariate selection process are displayed in Table 22.

**Table 22. Run Record for Model Adjustment**

| Model | Objective Function Value (OFV) | Δ in OFV from Base model |
|---|---|---|
| Basic Model | 598.512 | - |
| CL~WT; $V_{central}$, $V_{peripheral}$ ~WT | 392.819 | 205.693 |
| CL~WT + AGE; $V_{central}$, $V_{peripheral}$ ~WT | 391.187 | 207.325 |
| CL~WT + CrCL; $V_{central}$, $V_{peripheral}$ ~WT (Final Model) | 285.519 | 312.993 |

The addition of age did not improve the model including weight as a covariate on clearance and volumes of distribution. The addition of creatinine clearance, however, was significant and CrCL is included in the final model. Clearance of ganciclovir is therefore given by the following equation:

$$CL(h/l) = 5.61 \times \left(\frac{Weight(kg)}{26kg}\right)^{0.624} \times \left(\frac{CrCL}{117ml/\min/1.73m^2}\right)^{0.788}$$

The parameter estimates of the final model are shown in Table 23. Inter-individual variability for $V_{peripheral}$ could not be estimated in the final model, even though it was included in the base model. Similar to the sponsor's analysis, body size and renal function were important descriptors of clearance.

**Table 23. Pharmacokinetic Parameter Estimates for the Final Model**

| Parameter | Parameter Estimate | Parameter Relative SE (CV%) | IIV Estimate (CV%) | IIV Relative SE (CV%) |
|---|---|---|---|---|
| CL (L/h) | 5.61 | 4.4 | 27.3 | 21.7 |
| Influence of weight | 0.624 | 7.9 | | |
| Influence of creatinine clearance | 0.788 | 15.4 | | |
| $K_a$ (h) | 0.695 | 11.2 | 52.5 | 32.2 |
| $V_{central}$ (L) | 10.6 | 17.1 | 48.5 | 43 |
| $V_{peripheral}$ (L) | 11.7 | 8.55 | | |
| Influence of weight | 0.943 | 4.7 | | |
| Q (L/h) | 5.99 | 19.9 | | |
| F1 | 0.575 | 4.43 | 21.3 | 28 |
| Lag Time (h) | 0.222 | 2.89 | | |
| Multiplicative Error (%) | 0.323 | 6.01 | | |
| Additive Error (mg/L) | 0.0792 | 22.9 | | |

#### 4.2.4.4 Dose Recommendation Results

In order to evaluate the modified dosing algorithm proposed by the sponsor, the "ideal" dose producing an $AUC_{0-24}$ of 50 mg h/L based on model-derived individual post-hoc estimates of clearance and bioavailability was calculated. Figure 14 shows the

relationship between the "ideal" dose and the one calculated from the sponsor's algorithm. The blue points are clustered around the line of unity, without any major deviations, suggesting the sponsor's dose is a close approximation of the ideal dose. The maximum dose was set to the adult dose of 900 mg, which explains the points at the extreme top and right of the plot.

**Figure 14. Comparison between Sponsor's Recommended Dose and "Ideal" Dose. The red line is the line of unity.**

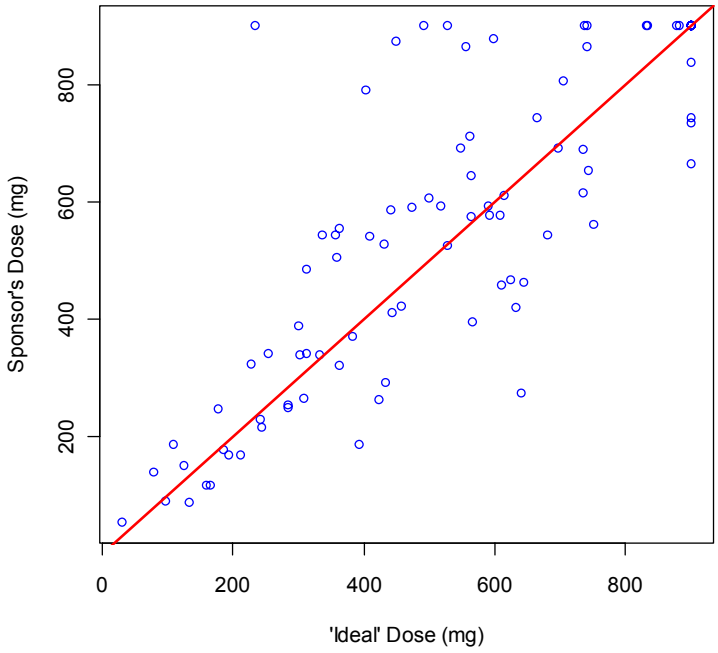



Figure 15 displays the exposures to ganciclovir in all three studies using the sponsor's algorithm and the reviewer's model. 30% of calculated AUCs fell above the 60 mg h/L threshold and 19% fell below. Given that the exposure-effect relationship is steeper at the lower end of the target range (40 mg h/L) than the safety relationship is at the upper end of the target range (60 mg h/L), it is more important to have fewer subjects achieving ganciclovir exposures less than 40 mg h/L than exposures greater than 60 mg h/L.

**Figure 15. Exposure to Ganciclovir Using Sponsor's Dosing Algorithm and Reviewer's Model.** The horizontal red lines refer to the therapeutic target (40 – 60 mg h/L)

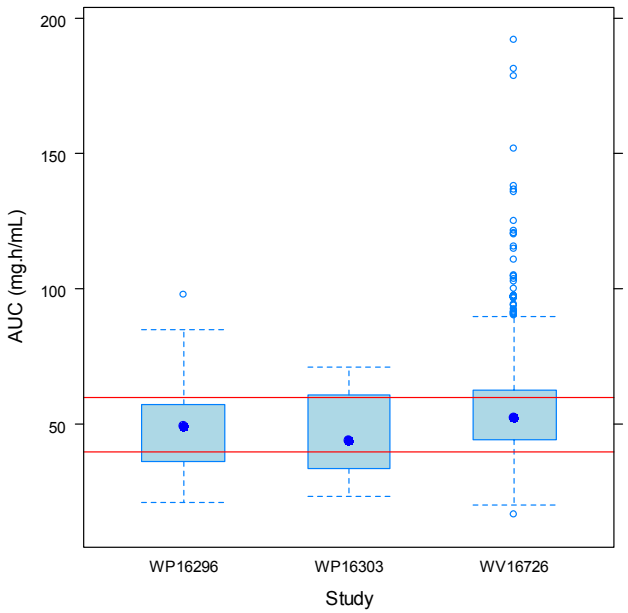



Figure 16 to Figure 18 show the ganciclovir exposure using the sponsor's algorithm and the reviewer's modeling analysis by different age, weight and renal function groups. The absence of a trend across groups confirms the sponsor's conclusion that the modified dosing algorithm provides consistent exposures independent of these factors.

**Figure 16. Exposure to Ganciclovir Using Sponsor's Dosing Algorithm and Reviewer's Model by Weight Group.**

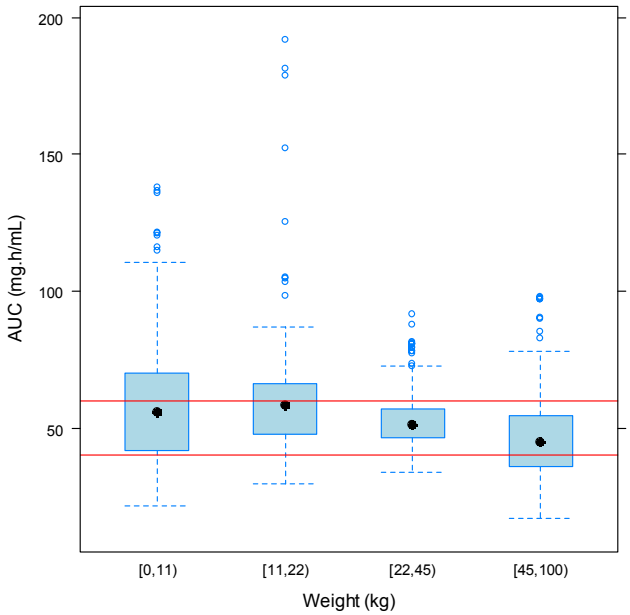



**Figure 17. Exposure to Ganciclovir Using Sponsor's Dosing Algorithm and Reviewer's Model by Age Group.**

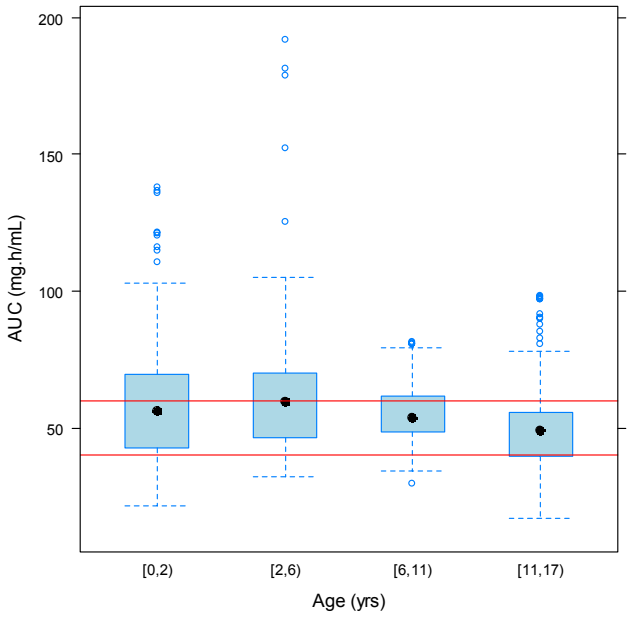
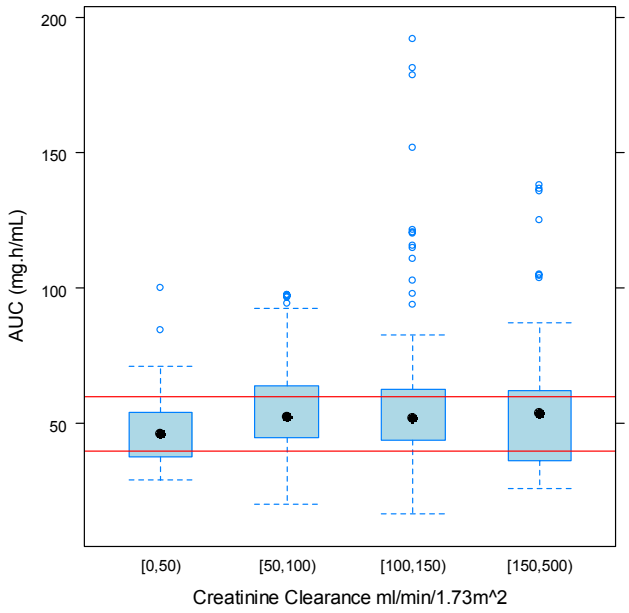


**Figure 18. Exposure to Ganciclovir Using Sponsor's Dosing Algorithm and Reviewer's Model by Renal Function.**

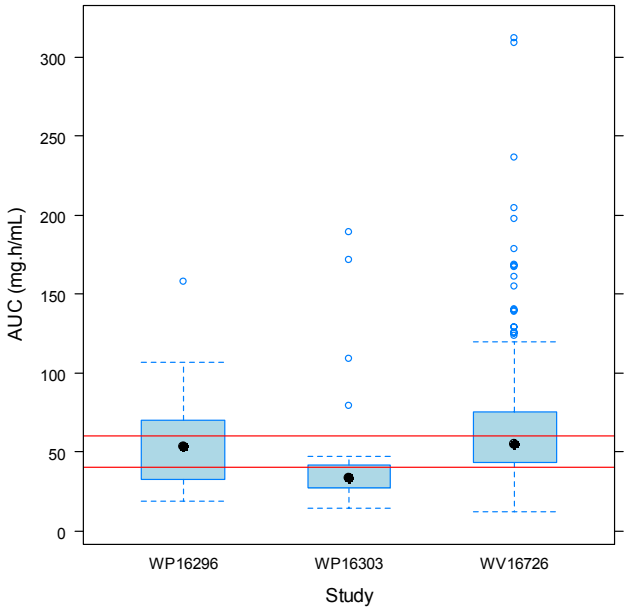



Based on the modeling analysis performed by the reviewer, simpler dosing regimens were investigated. Presented here is a dosing recommendation based solely only body weight:

| Weight Group | Pediatric Valganciclovir Dose |
|---|---|
| < 25 kg | 25 mg/kg |
| >25 kg and <50 kg | 625 mg |
| >50 kg | 900 mg |

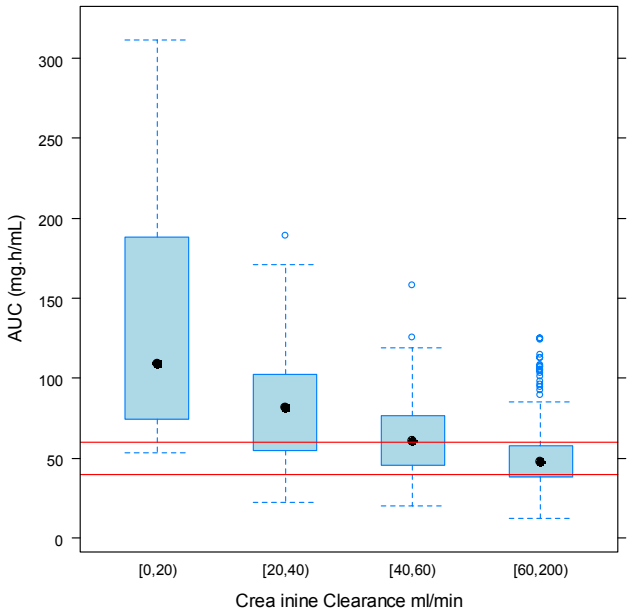
The predicted exposures in the three studies using this alternative dosing algorithm are shown in Figure 19. 40% of predicted exposures fell above 60 mg.hr/l and 21% fell below 40 mg h/L, which is inferior to the results from the sponsor's dosing algorithm.

**Figure 19. Exposure to Ganciclovir Using Reviewer's Explored Dose**




Furthermore, as seen in Figure 20, the alternative dosing proposal results in overexposure in patients with low creatinine clearance and underexposure in patients with high creatinine clearance. Therefore, this dosing algorithm provides no advantages compared to the sponsor's proposed algorithm. Other dosing algorithms investigated by the reviewer included a dose of 14 mg/kg in all subjects, a dose of 200 mg in patients less than 2 years of age and 520 for patients older than 2 years. None achieved ganciclovir exposures that were more optimal than the sponsor's algorithm.

**Figure 20. Exposure to Ganciclovir Using Reviewer's Explored Dose by Renal Function.**

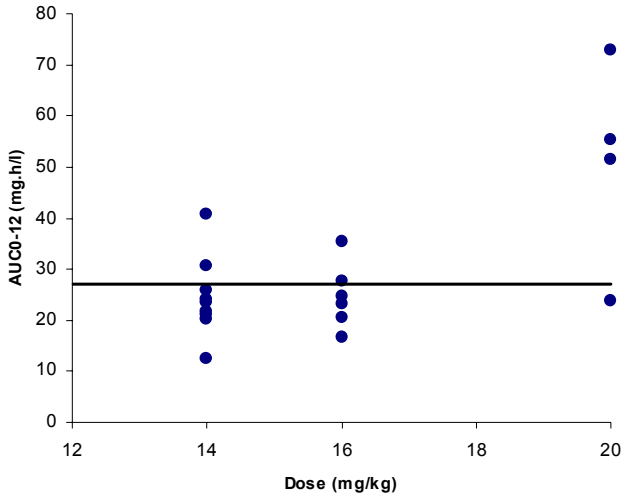



### 4.2.5 Reviewer's analysis – dose recommendation in neonates for treatment of symptomatic congenital CMV disease

#### 4.2.5.1 Introduction

A population pharmacokinetic approach to Study CASG109 was used to support the dose recommendation of 16 mg/kg in neonates for treatment of symptomatic congenital CMV disease. In the original study, the 14 mg/kg dose was judged to be too small to reach the target exposure of 27 mg h/L and was subsequently increased to 20 mg/kg in the next cohort of four subjects. The calculated exposures in these subjects were much higher than target exposure, so the next cohort received 16 mg/kg, which was declared the recommended dose. The raw data, however, do not differentiate between the 14 mg/kg and 16 mg/kg dose as illustrated in Figure 21.

**Figure 21. Ganciclovir $AUC_{0-12}$ after Oral Valganciclovir by Dose**




#### 4.2.5.2 Objectives

Analysis objectives are:

1. Derive oral valganciclovir dosing algorithm for treatment of symptomatic congenital CMV disease in neonates.

#### 4.2.5.3 Methods

##### *4.2.5.3.1 Data Sets*

Data sets used are summarized in Table 24.

**Table 24. Analysis Data Sets**

| Study Number | Name | Link to EDR |
|---|---|---|
| CASG109 | nmdat.xpt | \\Fdswa150\nonectd\N22257\N_000\2008-04-30\crt\datasets\casg109 |

##### *4.2.5.3.2 Software*

NONMEM Version VI with FOCE with interaction was used for parameter estimation. Xpose 4.0.1 and R were used for plots, data manipulation and calculations.

##### *4.2.5.3.3 Models*

Based on the modeling results from the sponsor, the initial pharmacokinetic model was a one compartment model with first order formation for valganciclovir parameterized in terms of formation rate constant ($K_a$), clearance (CL), volume of distribution (V) and bioavailability fraction (F1). A two compartment model was also tested. The data set was modified so that the dose included molecular weight differences between ganciclovir and valganciclovir to be consistent with the pediatric modeling analysis. Inter-subject variability on CL and F1 was modeled as exponential. Weight was included as a covariate on clearance and volume of distribution. Age was also tested as a covariate on

clearance. A combined proportional and additive error structure model was used to describe residual error.

#### 4.2.5.4 Results

The basic pharmacokinetic model was a one compartment model with inter-subject variability on CL. Inter-individual variability on F was poorly estimated and did not significantly improve the performance of the model. A summary of parameters of the basic model is provided in Table 25.

**Table 25. Pharmacokinetic Parameter Estimates of the Basic Model**

| Parameter | Parameter Estimate | Parameter Relative SE (CV%) | IIV Estimate (CV%) | IIV Relative SE (CV%) |
|---|---|---|---|---|
| CL (L/h) | 0.778 | 12.9 | 37.4 | 26.3 |
| $K_a$ (h) | 0.557 | 11 | | |
| V (L) | 2.97 | 11.1 | | |
| F | 0.602 | 0.0574 | | |
| Multiplicative Error (%) | 0.491 | 4.38 | | |
| Additive Error (mg/L) | 0.101 | 20 | | |

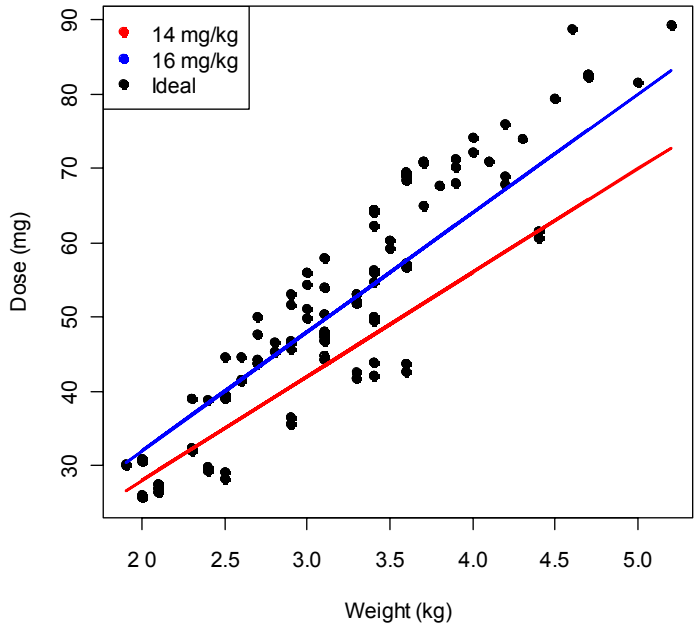
Table 26 shows the effects of the addition of covariates into the base model. The addition of weight on CL and V significantly improved the model and decreased the inter-individual variability in CL from 37.4% to 28.1%. The further addition of post-natal age decreased the objective function value by 16.882 points and decreased inter-individual variability in CL from 28.1% to 26% and was therefore included in the final model. The bioavailability fraction was estimated to be 0.733 with a 95% confidence interval of 0.632 to 0.834.

**Table 26. Tested Clearance Models**

| Model | Description | Parameters | Estimates (%SE) | IIV (CV%) | Objective Function Value |
|---|---|---|---|---|---|
| 1 (base) | $CL = \theta_1$ | $\theta_1$ | 0.778 (12.9) | 37.4 | 304.84 |
| 2 | $CL = \theta_1 \cdot (WT/2.4)^{\theta_2}$ | $\theta_1$<br>$\theta_2$ | 0.618 (10.4)<br>1.63 (12.6) | 28.1 | 206.574 |
| 3 (final) | $CL = \theta_1 \cdot (WT/2.4)^{\theta_2} \cdot (AGE/19)^{\theta_3}$ | $\theta_1$<br>$\theta_2$<br>$\theta_3$ | 0.653 (9.82)<br>1.05 (17)<br>0.245 (23.1) | 26 | 189.692 |

The final model was used to calculate the "ideal" dose that would achieve the target exposure of 27 mg h/L. These "ideal" doses are compared to the 14 mg/kg and 16 mg/kg doses in Figure 22. The 16 mg/kg dose more closely matches the "ideal" doses. It overpredicts at very low weights and underpredicts at the high range of weights due to the linear approximation to a nonlinear relationship.

**Figure 22. Comparison of "Ideal" Dose to 14 mg/kg and 16 mg/kg Doses**




### 4.2.6 Listing of Analyses Codes and Output Files

| File Name | Description | Location in \\cdsnas\pharmacometrics\ |
|---|---|---|
| run1.mod | Reviewer's base model for prevention of CMV disease in pediatric solid organ transplant recipients (NONMEM control file) | NDA22257_valcyte\NM |
| run1.lst | Reviewer's base model for prevention of CMV disease in pediatric solid organ transplant recipients (NONMEM output file) | NDA22257_valcyte\NM |
| run15.mod | Reviewer's final model for prevention of CMV disease in pediatric solid organ transplant recipients (NONMEM control file) | NDA22257_valcyte\NM |
| run15.lst | Reviewer's final model for prevention of CMV disease in pediatric solid organ transplant recipients (NONMEM output file) | NDA22257_valcyte\NM |
| run129.mod | Reviewer's base model for treatment of congenital CMV disease (NONMEM control file) | NDA22257_valcyte\NM\neonates |
| run129.lst | Reviewer's base model for treatment of congenital CMV disease (NONMEM output file) | NDA22257_valcyte\NM\neonates |
| run126.mod | Reviewer's final model for treatment of congenital CMV disease (NONMEM control file) | NDA22257_valcyte\NM\neonates |
| run126.lst | Reviewer's final model for treatment of congenital CMV (NONMEM output file) | NDA22257_valcyte\NM\neonates |

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