CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-257s000

21-304s007

MICROBIOLOGY REVIEW(S)

MICROBIOLOGY REVIEW
DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

NDA 22-257 SN 000 **REVIEW DATE: 10/01/2008**

Reviewer: N. Biswal

Date Submitted: 4/30/2008
Date Received: 5/02/2008
Date Assigned: 5/02/2008

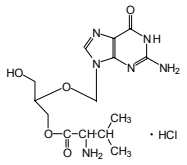
Sponsor: Roche Laboratories Inc
340 Kingsland Street
Nutley, NJ 07110

Product Names:

Code Name: Valcyte™ (Valganciclovir hydrochloride)

Chemical Name: L-Valine, 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9yl) methoxy]-3- hydroxypropyl ester, monohydrochloride

Structural Formula:



Molecular Formula: $C_{14}H_{22}N_6O_5 \bullet HCl$

Molecular Weight: 390.83

Drug Category: Antiviral

Dosage Form/Route of Administration: Powder/Oral Solution

Indication: Treatment of Cytomegalovirus (CMV) Retinitis in Immunocompromised Patients and for the Prevention of CMV Disease in Transplant Patients at Risk for CMV Disease

Supporting Documents: IND 32,149; IND 48,106, IND 63,389; NDA 19-661; NDA 20-460, NDA (b) (4)

BACKGROUND AND SUMMARY: Valcyte™ (Valganciclovir hydrochloride, VGCV) is a valyl ester prodrug that is rapidly hydrolyzed to ganciclovir (GCV) and L-valine by intestinal and hepatic esterases after oral administration. GCV, which by itself is a prodrug without any intrinsic antiviral activity, must be phosphorylated (initially by the viral protein kinase homolog UL97) to GCV

monophosphate then to an antivirally active triphosphate form by cellular kinases in virus-infected cells to inhibit viral DNA polymerase (UL54) thus exerting its antiviral activity. Its potency to inhibit various laboratory strains or clinical isolates of human cytomegalovirus (HCMV) has been reported to be dependent upon a number of factors including the host cells, virus strain, multiplicity of infection, and assay methods, which are yet to be standardized. Thus, the concentration of GCV that inhibits the replication of human CMV by 50 % (EC_{50}) has ranged significantly from 0.01 μM to 27 μM.

Serial passage of HCMV in the presence of increasing concentrations of GCV in cell culture has resulted in the emergence of mutants exhibiting EC_{50} values of 10 - fold greater than that of the wild type strain. However, the degree of HCMV resistance to GCV is not always clearly distinguishable within the normal range of wild-type CMV sensitivity, since there are a number of different assays and endpoints (which are yet to be standardized) used to determine the susceptibility of HCMV to inhibition with GCV. Nevertheless, the current working definition of CMV resistance to GCV is when GCV $EC_{50} \geq 6.0$ μM (≥ 1.5 μg/ml). Mutants of HCMV resistant to GCV have been isolated from immunocompromized patients undergoing treatment for HCMV infection. GCV^r mutants of HCMV usually result from mutations in the two viral genes, *UL97*, *UL54* or both.

VGCV has been approved for the treatment of CMV retinitis in patients with AIDS, and for the prevention of CMV disease in kidney, heart, and kidney-pancreas transplant patients at high risk (D+/R-). In this submission, the sponsor has proposed to:

- Support a new dosage form of Valcyte, powder for oral solution 50 mg/ml, to be administered to patients with varying degree of impaired renal functions, including hemodialysis.
- Make labeling changes for the use the powder formulation for the treatment of pediatric patients

The rationale for the current proposal appears to be based on the sponsor's belief that the oral solution (50 mg/ml) formulation will provide a better flexibility in dosing than the current tablet formulation offers, and an appropriate once-daily oral dosing regimen may achieve target GCV exposures to patients with moderate to severe renal impairment. Thus the sponsor contends that once-daily dosing regimen may also facilitate compliance and hence offers the potential for more reliable anti-CMV effectiveness, leading to fewer CMV infections and greater protection against the development of resistance to GCV.

To advance the two proposals noted above, the sponsor has provided information from five clinical studies conducted with the VGCV powder for oral solution:

- One in adults (Study WP16302) and
- Four in pediatric patients (Studies WP16303, WP16296, WV16726 and CASG 109).

Four (WP16302, WP16303, WP16296 and WV16726) of the five studies were conducted by the sponsor (Hoffmann-La Roche) and one of the pediatric studies (CASG109) was conducted by the

Collaborative Antiviral Study Group (CASG) based at the University of Alabama, and sponsored by the Division of Microbiology and Infectious Diseases, NIAID, NIH. All of these clinical studies were designed to determine the pharmacokinetics, safety and tolerance of VGCV, and to fulfill the Written Request in this application. CASG 109 was the only clinical study which included an additional (secondary) endpoint of monitoring the pediatric patient population for the emergence of GCV resistant mutants and to characterize the phenotypic and genotypic nature of such mutants. The information contained in these clinical study reports, as they relate to the new information on the clinical virology of VGCV, may be summarized as follows.

Note: The sponsor has also referred to the previously submitted and approved NDAs noted above for information on the preclinical and clinical virology of VGCV and GCV.

1. Clinical Study WP16302 was a multicenter, open-label, randomized, 3-way crossover study in 23 adult kidney transplant recipients at risk of developing CMV disease to determine the bioequivalence of GCV from the VGCV tutti-frutti flavored powder for oral (900 mg once-daily) solution formulation and the commercial VGCV 450 mg film-coated tablet. This study was not designed to evaluate any aspect of clinical virology of VGCV.

2. Clinical Study WP16303 was an open-label study designed to assess the safety and pharmacokinetics of the VGCV powder (oral solution formulation) in 20 pediatric liver transplant recipients receiving intravenous (i.v.) GCV for the prevention of CMV disease. All patients were administered ganciclovir (5 mg/kg i.v. b.i.d.) between enrollment (days 1-4) and day 12, and then strawberry flavored VGCV (900 mg powder for oral solution b.i.d.) on days 13 and 14. This study was not designed to evaluate any aspect of clinical virology of VGCV.

3. Clinical Study WP16296 was an open-label study in 26 pediatric kidney transplant recipients requiring anti-CMV prophylaxis. It was designed to determine the pharmacokinetics and safety of the VGCV powder for oral solution. Patients were administered GCV (5 mg/kg i.v. o.d.) for two consecutive days followed by strawberry flavored VGCV powder for oral solution (450 mg o.d.) for one day and then followed by a different dose of the strawberry flavored VGCV powder for oral solution (900 mg o.d.) for one day. This study did not evaluate any aspect of clinical virology of VGCV.

4. Clinical Study WV16726 was a single arm, open-label study in 63 pediatric SOT recipients at risk of CMV disease, which assessed the pharmacokinetics, efficacy, safety, and tolerability of the tutti-frutti flavored valganciclovir powder for oral solution and Valcyte tablets. All patients received once-daily valganciclovir powder for oral solution or tablets for up to 100 days as a prophylaxis for CMV disease. This study was not designed to evaluate any aspect of clinical virology of VGCV.

5. Clinical Trial CASG109 was a multi-center, open-label trial designed to assess primarily the pharmacokinetics, pharmacodynamics, safety and tolerability of the VGCV powder for oral solution (strawberry or tutti-frutti flavored) and intravenous GCV in a total of 24 neonates with symptomatic congenital CMV disease. A secondary endpoint of this trial also included the evaluation of the

potential development of resistance to GCV by analyzing the nucleotide sequences of *UL97* and *UL54* genes of CMV in the blood cells collected at various time points during and after the six week treatment of these patients.

Eligible patients were administered antiviral therapy (VGCV/GCV) for 6 weeks (42 days). The first VGCV oral solution dose was 14 mg/kg b.i.d. for the first 14 patients enrolled in the study but this was increased to 20 mg/kg/dose b.i.d. for four patients (based on the $AUC_{0\text{-}12h}$ values for the first four patients evaluated), and then again per protocol was decreased to 16 mg/kg/dose b.i.d. for the final six patients enrolled. The first dose of i.v. GCV was 6 mg/kg b.i.d. All doses were adjusted weekly by body weight.

Efficacy Parameters in Study CASG109

Primary

- Growth (height, weight, and head circumference).
- Hearing modality.
- Behavioral assessment.
- Change in CMV load during treatment and follow-up period.

Secondary

- Potential development of resistance to GCV during and after the treatment period.

In the initial submission of this NDA, the sponsor had provided information on the change in CMV load, as measured by quantitative PCR, in the blood samples collected from 24 patients enrolled in this study. However, the sponsor was requested and has provided additional information (in three separate amendments) on the quantification of the viral load as well as on the potential development of resistance of CMV during and after the treatment period. The results of these submissions (which have been reviewed earlier) may be summarized as follows.

Of the 24 patients, six had undetectable virus in the blood at baseline and throughout therapy. Of the 18 patients who had detectable CMV in blood at baseline or during therapy, 11 had < 4 $\log_{10}$ copies/mL of viral DNA at baseline and seven had ≥ 4 $\log_{10}$ copies/mL of viral DNA at baseline. The median decline in viral load among all patients was 0.7 $\log_{10}$ copies/mL, with patients starting at higher viral burden experiencing greater declines in viral load (1.8 $\log_{10}$ copies/mL) compared with the decline in viral burden among patients starting at lower viral loads (0.6 $\log_{10}$ copies/mL).

Of the 18 patients with detectable CMV at or after the beginning of antiviral therapy, six were PCR-negative at the completion of 42 days of antiviral therapy (all of whom had < 4 $\log_{10}$ copies/mL of viral DNA at baseline), and 12 remained PCR-positive. Of the six who were PCR-negative at the completion of 42 days of antiviral therapy, two remained PCR-negative at Day 56 and four were PCR-positive. For technical reasons, the DNA samples from a limited number of 7 patients, who

had $\geq 10^4$ copies/ml of viral DNA that appeared to increase even after the end of VGCV/GCV therapy, were analyzed for genotypic resistance.

For genotypic analysis, DNA fragments containing the entire *UL97* and *UL54* genes were amplified by using primers appropriate for each of these two genes through nested PCR procedure utilizing Taq Polymerase Master Mix. All of the amplified DNA sequences were compared with those of a reference laboratory strain CMV (AD169). However, the investigators have stated that some of the DNA samples from this limited number of 7 patients were not easy to amplify to obtain adequate amounts for DNA sequencing, and the amplification procedures failed to generate PCR products of sufficient quantity for DNA sequence analysis." Thus:

- Both *UL97* and *UL54* genes could be sequenced for 3 patients (b) (6)
- Only the *UL54* could be sequenced for two patients (b) (6)
- Only the *UL97* could be sequenced for patient (b) (6)
- No DNA sequence analysis could be performed with specimen collected from patient 0065.

Thus it was concluded by the investigators of this study that the "collected data set is incomplete and reflects the small quantities of DNA remaining in some specimens." Whatever samples could be collected, the investigators could generate sufficient quality and quantity of DNA to yield good quality DNA sequence with at least 100 genomes per reaction corresponding to approximately 10^4 copies/ml.

The results from the sequence analysis of the *UL97* and *UL54* mutations revealing the changes in the inferred amino acid sequences (presented at the right side) observed in blood specimens from six patients noted above is summarized below.

***UL 97* GCV Resistance Mutations (Known):** (b) (4)

Unknown *UL97* Mutations: (b) (4)

***UL97* Polymorphism (Known):** (b) (4)

***UL54* GCV Resistance Mutations:** None Observed

***UL54* Polymorphism (Known):** (b) (4)

Unknown *UL54* Mutations: (b) (4)

Thus there are now five mutations resulting in inferred substitutions in amino acid sequence, three (b) (4) in UL97 and two (b) (4) in UL54 of CMV which are identified as of unknown significance. The sponsor of this NDA application (Roche Laboratories, Inc.) has stated that the phenotypic nature of these GCV resistant mutants will be analyzed and a

"SAS transport file dataset will become available September 2009 due to the extensive nature of the laboratory experiments utilized to phenotype." As discussed at the GAM #4 meeting for NDA 22-257 on August 8, 2008, it was decided that the sponsor may submit the phenotypic data in September 2009 as a post approval commitment.

In an attempt to correlate the clinical significance of the GCV resistance substitution in UL97 (b) (4) identified in patient (b) (6), it was concluded that the clinical data (audiologic and neurodevelopmental) collected during this clinical study "do not appear to suggest a negative clinical correlate to the (b) (4) substitution. However, the investigators of his study have emphasized that "these correlates are extremely limited given that only one subject had documented genotypic resistance and that the sample size of the study was relatively small."

The Package Insert (Label): The VIROLOGY section of the Package Insert should be updated as noted below.

RECOMMENDATIONS: The NDA is approvable under the following conditions.

1. As a post-approval commitment, the sponsor will analyze the phenotypic nature of GCV resistant viruses isolated during the clinical study CASG 109, and the results will be provided as a SAS transport file dataset in September 2009.
2. The Virology Section of the Package Insert for the NDA 22-257 should be updated as follows.

VIROLOGY

Mechanism of Action

Valganciclovir is an L-valyl ester (prodrug) of ganciclovir that exists as a mixture of two diastereomers. After oral administration, both diastereomers are rapidly converted to ganciclovir by intestinal and hepatic esterases. Ganciclovir is a synthetic analogue of 2'-deoxyguanosine, which inhibits replication of human cytomegalovirus in (b) (4) and in vivo.

In CMV-infected cells ganciclovir is initially phosphorylated to ganciclovir monophosphate by the viral protein kinase, pUL97. Further phosphorylation occurs by cellular kinases to produce ganciclovir triphosphate, which is then slowly metabolized intracellularly (half-life 18 hours). As the phosphorylation is largely dependent on the viral kinase, phosphorylation of ganciclovir occurs preferentially in virus-infected cells. The virustatic activity of ganciclovir is due to inhibition of viral DNA synthesis by ganciclovir triphosphate.

Antiviral Activity

The quantitative relationship between the in (b) (4) susceptibility of human herpes viruses to antivirals and clinical response to antiviral therapy has not been established, and virus sensitivity testing has

not been standardized. Sensitivity test results, expressed as the concentration of drug required to inhibit the growth of virus in cell culture by 50% (EC_{50}), vary greatly depending upon a number of factors. Thus the EC_{50} of ganciclovir that inhibits human CMV replication in (b) (4) (laboratory and clinical isolates) has ranged from 0.02 to 5.75 μg/mL (0.08 to 22.94 μM). Ganciclovir inhibits mammalian cell proliferation (b) (4) in (b) (4) at higher concentrations ranging from 10.21 to >250 μg/mL (40 to >1000 μM). Bone marrow-derived colony-forming cells are more sensitive ((b) (4) 0.69 to 3.06 μg/mL (2.7 to 12 μM).

Viral Resistance

Viruses resistant to ganciclovir can arise after prolonged treatment with valganciclovir by selection of mutations in either the viral protein kinase (UL97) gene responsible for ganciclovir monophosphorylation and/or in the viral DNA polymerase (UL54) gene. Virus with mutations in the *UL97* gene is resistant to ganciclovir alone, whereas virus with mutations in the *UL54* gene may show cross-resistance to other antivirals that target the same sites on viral DNA polymerase.

The current working definition of CMV resistance to ganciclovir in *in* (b) (4) assays is $EC_{50} \geq 1.5$ μg/mL (≥ 6.0 μM). CMV resistance to ganciclovir has been observed in individuals (immunocompromized and neonates) receiving prolonged treatment with ganciclovir. The possibility of viral resistance should be considered in patients who show poor clinical response or experience persistent viral excretion during therapy.

Nilambar Biswal, Ph.D.
Microbiologist

CONCURRENCES:

HFD-530/TLMicro/J. O'Rear

CC:
HFD-530/Orig. NDA 22,257
HFD-530/Division File
HFD-530/Araojo, RPM

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MICROBIOLOGIST

MICROBIOLOGY REVIEW
DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

NDA 22-257 SN 000 (BI) **REVIEW DATE: 9/05/2008**

Reviewer: N. Biswal, Ph.D.

Date Submitted: 8/15/2008
Date Received: 8/19/2008
Date Assigned: 8/25/2008

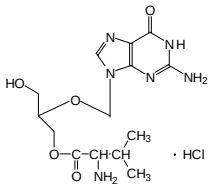
Sponsor: Roche Laboratories Inc
340 Kingsland Street
Nutley, NJ 07110

Product Names:

Code Names. Valcyte™ (Valganciclovir hydrochloride)

Chemical Name: L-Valine, 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9yl) methoxy]-3-hydroxypropyl ester, monohydrochloride

Structural Formula:



Molecular Formula: $C_{14}H_{22}N_6O_5 \bullet HCl$

Molecular Weight: 390.83

Drug Category: Antiviral

Dosage Form/Route of Administration: Powder/Oral Solution

Indication: Treatment of Cytomegalovirus (CMV) Retinitis in Immunocompromised Patients and for the Prevention of CMV Disease in Transplant Patients at Risk for CMV Disease

Supporting Documents: IND 32,149; IND 48,106: IND 63,389;
NDA 19-661; NDA 20-460; [redacted] (b) (4)

BACKGROUND AND SUMMARY: As committed in the last submission (NDA 22-257 BM on 7/29/2008), the sponsor has provided a report on [redacted] (b) (4) (CASG 109)" [redacted] (b) (4) The information provided in this report may be summarized as follows.

Clinical trial CASG 109 was designed to evaluate primarily the pharmacokinetic/pharmacodynamic parameters of valganciclovir (VGCV) and intravenous ganciclovir (GCV) in a total of 24 neonates infected with CMV. A secondary endpoint of this trial also included the evaluation of the potential development of resistance to GCV by analyzing the nucleotide sequences of *UL97* and *UL54* genes of CMV in the blood cells collected at various time points during and after the six week treatment of these patients.

Without providing any details of the experimental protocol and a description of the results, the sponsor has stated that blood samples from 18 out of 24 patients enrolled in this study had detectable levels of CMV DNA at baseline or during the course of treatment (Fig. 1a, also as included in this submission). Although the legend to the figure is missing, the "lower limit detection of CMV viral load" (black solid line in the figure) appears to be 2 $\log_{10}$ copies of CMV DNA.

Eleven (green line with triangles in the figure) out of these 18 patients had less than 10^4 copies/ml of DNA; therefore, according to the investigators, were below the limit of the DNA amplification procedure. The remainder 7 patients (blue and red lines in Fig.1a) had $\geq 10^4$ copies/ml of viral DNA that was detectable and appeared to increase even after the end of VGCV/GCV therapy (Fig.1b). Therefore, the DNAs from these seven patients were analyzed for genotypic resistance.

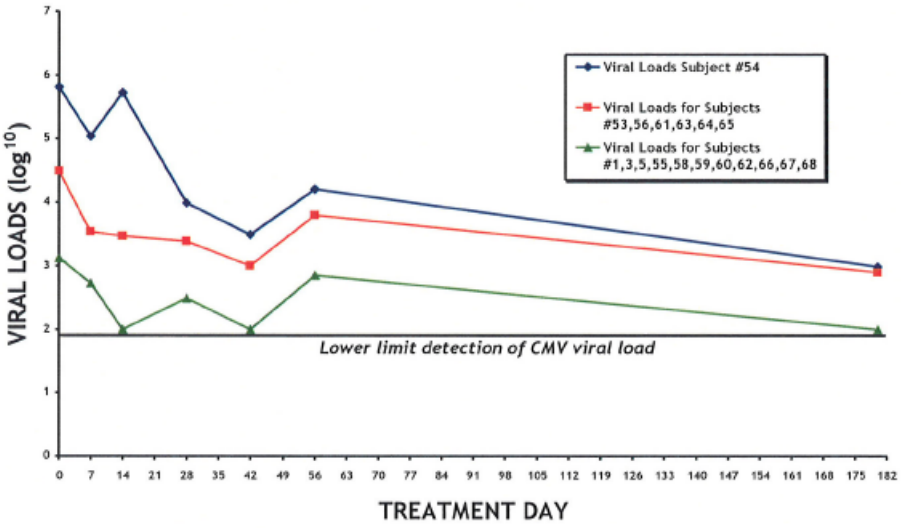


Figure 1a. CASG109 BLOOD VIRAL LOADS vs. TIME: All Subjects with CMV DNA Detected by PCR

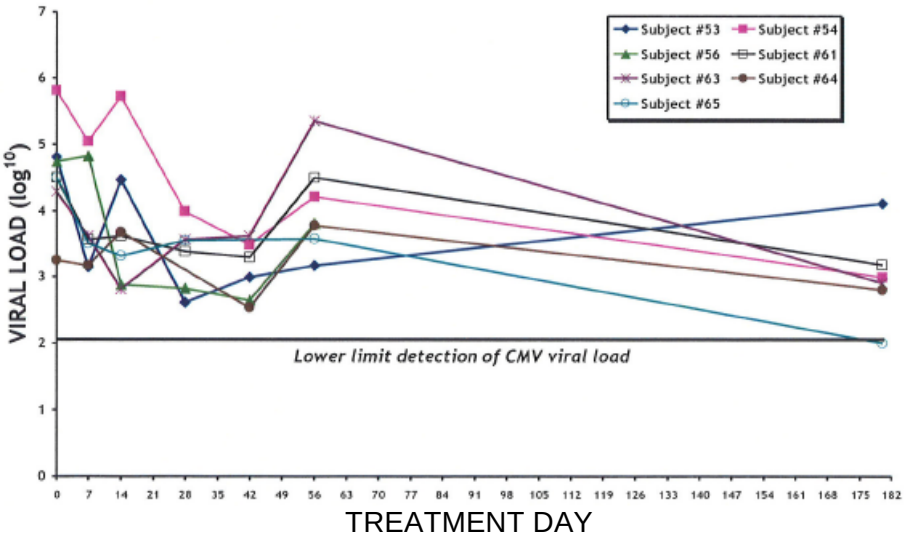


Figure 1b. CASG109 BLOOD VIRAL LOADS vs. TIME: Subjects for Whom Genotypic Resistance Testing Performed

Comments:

1. A description of the experimental protocol to obtain the results presented in the Figures 1a and 1b and the legends to both the figures are missing. The solid straight line labeled as the "lower limit detection of CMV viral load" as 2 $\log_{10}$ should be clearly defined (e.g., as CMV DNA copies/ml). In addition, the lower limit of quantification of CMV DNA in these experiments should be clearly defined.

2. In response to an earlier microbiology request, the sponsor (Division of Microbiology and Infectious Diseases, NIAID, NIH) had committed (on February 13, 2002, IND 63,389 SN 001) to use more recent and advanced PCR methodology sensitive enough to detect <10 copies/5 µl of CMV DNA. In addition, the sponsor had also stated that "a single copy of CMV-DNA-containing plasmid can also be detected in most of the assays." There is no explanation as to why the current experiments were designed to set the limit of detection of CMV load to 2 $\log_{10}$ (Figures 1a and 1b).

3. More importantly, there is no explanation as to why a concentration $\geq 10^4$ copies/ml of CMV DNA (as the limit of detection) was needed for genotypic assay (second sentence, last paragraph, page 6 of 17), especially since the sponsor had committed to use more recent and advanced PCR methodology to detect <10 copies/5 µl of CMV DNA (or a single copy of CMV DNA). It is not clear whether the analysis of GCV resistance would have been limited to seven patients only, if a more advanced and sensitive method of genotypic assay was used.

For genotypic analysis, fragments containing the entire *UL97* and *UL54* genes were amplified by

using primers appropriate for each of these two genes (listed in Table 1 of this submission) through nested PCR procedure utilizing Taq Polymerase Master Mix. All of the amplified DNA sequences were compared with those of a reference laboratory strain CMV (AD169). However, the investigators have stated that some of the DNA samples from this limited number of 7 patients were not easy to amplify to obtain adequate amounts for DNA sequencing. Without providing any information on the exact specimen collection and PCR amplification procedures, the investigators have stated that for some samples, "the amplification procedures failed to generate PCR products of sufficient quantity for DNA sequence analysis." Thus:

- Both *UL97* and *UL54* genes could be sequenced for 3 patients (b) (6)
- Only the *UL54* could be sequenced for two patients (b) (6)
- Only the *UL97* could be sequenced for patient (b) (6)
- No DNA sequence analysis could be performed with specimen collected from patient 0065.

Thus it was concluded by the investigators of this study that the "collected data set is incomplete and reflects the small quantities of DNA remaining in some specimens." Whatever samples could be collected, the investigators could generate sufficient quality and quantity of DNA to yield good quality DNA sequence with at least 100 genomes per reaction corresponding to approximately 10^4 copies/ml. The results from the sequence analysis presented in tabular form (Table 2 in this submission, see below) for six patients (not seven patients as noted above) show the mutations in both the *UL97* and *UL54* genes that resulted in changes in the inferred amino acid sequences.

Table 2. Mutations in the *UL97* and *UL54* genes following VGCV Therapy.

patient	date	copies/ml	*UL97*	*UL54*
(b) (6)	3.21.2005	12704		(b) (4)
	12.6.2004	16258		
	12.13.2004	6452		
	5.31.2005	31008		
	7.1.2005	223922		
	7.13.2005	5950		
	8.1.2005	3752		

a. This mutation has been reported previously to be sufficient to confer resistance to ganciclovir and was present in about 50% of the viral genomes from this patient.
b. Not determined because DNA fragment could not be obtained.
c. Observed as a minor population in a sequenced clone derived from this specimen.

A listing of the nature of the *UL97* and *UL54* mutations resulting in changes in the inferred amino acid sequences observed in blood specimens from six patients presented in Table 2 above is summarized below (and in Appendix 2 of this submission).

UL 97 GCV Resistance Mutations (Known): (b

Unknown UL97 Mutations: (b) (4)

UL97 Polymorphism (Known): (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4)

UL54 GCV Resistance Mutations: None Observed

UL54 Polymorphism (Known): (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4)

Unknown UL54 Mutations: (b) (4)

Thus the analysis of UL97 DNA sequence identified:

(1) One mutation (b) (4) which is known to confer GCV resistance (patient (b) (6).
(2) Three mutations (b) (4) of unknown clinical significance (patients (b) (6) (b) (6), and (b) (6)
(3) Six mutations of UL97 due to polymorphism (known)

Similarly, analysis of the UL54 DNA sequence identified:

(1) No resistance mutation, which has been published
(2) Two mutations (b) (4) of unknown clinical significance (patient 063)
(3) Eleven mutations due to UL54 polymorphism (known)

Thus there are now five mutations resulting in inferred substitutions in amino acid sequence, three (b) (4) in UL97 and two (b) (4) in UL54 of CMV which are identified as of unknown significance. The sponsor of this NDA application (Roche Laboratories, Inc.) has stated that the phenotypic nature of these GCV resistant mutants will be analyzed and a "SAS transport file dataset will become available September 2009 due to the extensive nature of the laboratory experiments utilized to phenotype." As discussed at the GAM #4 meeting for NDA 22-257 on August 8, 2008, it was decided that the sponsor may submit the phenotypic data in September 2009 as a post approval commitment.

In an attempt to correlate the clinical significance of the GCV resistance mutation in UL97 (b) (4) identified in patient (b) (6) the sponsor has summarized the clinical data (audiologic and neurodevelopmental) collected during this clinical study in Appendix 3 (Tables 3 and 4) of this submission with the conclusion that these clinical data "do not appear to suggest a negative clinical

correlate to the (b) (4) mutation. However, these investigators have emphasized that "these correlates are extremely limited given that only one subject had documented genotypic resistance and that the sample size of the study was relatively small." These investigators have further suggested that the clinical significance of the newly discovered 3 mutations in the *UL97* (resulting in inferred amino substitutions (b) (4) and two mutations in *UL54* (resulting in inferred amino substitutions (b) (4) remains to be elucidated.

Comment: While the investigators have concluded that the genotypic data set presented in this report is incomplete "due to small quantities of DNA remaining in some specimens," as well as some technical shortcomings noted above, it is clear that new mutations in both the UL97 and UL54 genes of CMV were discovered during the course of the clinical trial involving a small number of pediatric patient population. While the clinical significance of these mutations remains to be elucidated, this discovery obviates the need for continued surveillance of this patient population for the emergence of CMV mutants resistant to GCV. To meet this goal, the sponsor should be advised to design and conduct new Phase IV clinical studies to monitor pediatric patients for any possible development of CMV resistance to GCV and to characterize the phenotypic and genotypic nature of such mutants.

RECOMMENDATIONS:

1. Please provide a description of the experimental protocol, results and interpretation of the results presented in the Figures 1 (a, b and c). Please include a description of the legends to each of the Figures, and define the "lower limit detection of CMV viral load." In addition, please explain whether the solid line at 2 $\log_{10}$ viral load in these figures represents the lower limit of quantification or detection of CMV DNA.

2. In response to an earlier request (on February 13, 2002, IND 63,389 SN 001), the sponsor of the Clinical Trial CASG 109 (Division of Microbiology and Infectious Diseases, NIAID, NIH) had committed to use more recent and advanced PCR methodology sensitive enough to detect <10 copies/5 µl of CMV DNA, or even "a single copy of CMV-DNA-containing plasmid in most of the assays." Please explain as to why the current experiments were designed to set the limit of detection of CMV load to about 2 $\log_{10}$ (Figures 1a and 1b).

3. Please explain as to why a concentration $\geq 10^4$ copies/ml of CMV DNA (as the limit of detection, second sentence, last paragraph, page 6 of 17 of this submission) was needed for genotypic assay, especially since the sponsor of the Clinical Trial CASG 109 had committed to use more recent and advanced PCR methodology to detect <10 copies/5 µl of CMV DNA or even "a single copy of CMV DNA."

4. The discovery of new mutations in both the CMV *UL97* and *UL54* genes from the blood specimens of a very limited number of pediatric patients obviates the need for continued surveillance of this patient population for the emergence of CMV mutants resistant to GCV. The sponsor should design and conduct new Phase IV clinical studies to monitor pediatric

patients for any possible development of CMV resistance to GCV and to characterize the phenotypic and genotypic nature of such mutants.

Nilambar Biswal, Ph.D.
Microbiologist

CONCURRENCES:

HFD-530/J O'Rear/TLMicro

CC:
HFD-530/Orig. NDA 22-257
HFD-530/Division File
HFD-530/Araojo, RPM

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9/8/2008 01:20:42 PM
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MICROBIOLOGY REVIEW
DIVISION OF ANTIVIRAL DRUG PRODUCTS (HFD-530)

NDA 22-257 SN 000 (BM) **REVIEW DATE: 8/13/2008**

Reviewer: N. Biswal

Date Submitted: 7/29/2008
Date Received: 7/30/2008
Date Assigned: 8/04/2008

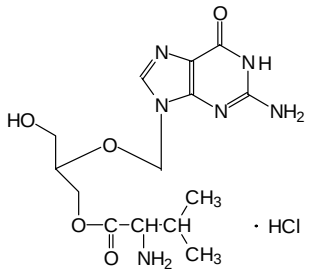
Sponsor: Roche Laboratories Inc
340 Kingsland Street
Nutley, NJ 07110

Product Names:

Code Names. Valcyte™ (Valganciclovir hydrochloride)

Chemical Name: L-Valine, 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9yl) methoxy]-3-hydroxypropyl ester, monohydrochloride

Structural Formula:



Molecular Formula: $C_{14}H_{22}N_6O_5 \bullet HCl$

Molecular Weight: 390.83

Drug Category: Antiviral

Dosage Form/Route of Administration: Powder/Oral Solution

Indication: Treatment of Cytomegalovirus (CMV) Retinitis in Immunocompromised Patients and for the Prevention of CMV Disease in Transplant Patients at Risk for CMV Disease

Supporting Documents: IND 32,149; IND 48,106: NDA 19-661; NDA 20-460, (b) (4)

MICROBIOLOGY REVIEW
DIVISION OF ANTIVIRAL DRUG PRODUCTS (HFD-530)

NDA 22-257 SN 000 (BM) **REVIEW DATE: 8/13/2008**

BACKGROUND AND SUMMARY: In this submission, the sponsor has responded to the microbiology comment (in Italics) communicated on June 30, 2008 as follows.

Microbiology Comment:

Please submit a supplemental study report with the genotypic and phenotypic data obtained in CASG 109 as SAS transport files as soon as both sets of data are available. Please provide a definitive time frame for the submission of these data, so that we can complete our review of NDA 22-257 in a timely manner.

Summary of Sponsor's Response:

The sponsor is currently working with NIH who sponsored protocol CASG 109, conducted under IND 63,389, and proposes the following sequential submission plan for the requested resistance data:

- Genotypic Resistance Data: Submission of the genotypic resistance report and SAS transport file dataset in mid August 2008.

The sponsor has also stated that the genotypic study report (to be submitted in mid August 2008) will include data from 6 subjects, since only samples from these subjects were of sufficient quality and quantity of DNA fragments to allow for genotyping of both the UL54 and UL97 genes. Nine mutations were identified by gene sequencing in study CASG 109 that have not been previously observed. Seven unknown mutations identified by UL54 gene sequencing and 2 unknown mutations identified by UL97 gene sequencing:

- Phenotypic Resistance Data: The phenotypic resistance report (characterizing the previously unobserved mutations from UL54 and UL97 gene sequencing) and SAS transport file dataset will become available September 2009 due to the extensive nature of the laboratory experiments utilized to phenotype.

- Roche would like to discuss with FDA, at the requested teleconference, the acceptability of the proposed submission approach; such that the review of the genotypic resistance data can be completed within the action date while Roche would commit to providing phenotypic data as a post approval commitment (PAC).

Comment: These responses of the sponsor to the microbiology request were discussed with the review team at the GAM #4 meeting for this NDA 22-257 on August 8, 2008. It was agreed at the meeting that the sponsor may submit the genotypic data in mid August 2008, and the phenotypic data as a post approval commitment.

RECOMMENDATION: As discussed at the GAM #4 meeting for NDA 22-257 on August 8, 2008, the sponsor may submit the genotypic data (from Study CASG 109) in mid August 2008, and the phenotypic data as a post approval commitment. With respect to microbiology, no additional

regulatory action is needed at this time.

Nilambar Biswal, Ph.D.
Microbiologist

CONCURRENCES:

HFD-530/ J O'Rear/TLMicro

CC:
HFD-530/Orig. NDA 22-257
HFD-530/Division File
HFD-530/Araojo, RPM

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Nilambar Biswal
8/15/2008 08:29:21 AM
MICROBIOLOGIST

Julian O Rear
8/15/2008 08:58:39 AM
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