

FDA Advisory Committee Briefing Document
For
Valganciclovir HCl
in the Treatment of CMV Retinitis in AIDS Patients
NDA 21-304

22 January 2001

Table of Contents

1. Executive Summary	11
2. Background and Scientific Rationale	13
2.1 Pathology of CMV Retinitis	13
2.2 Current Practice for the Treatment of CMV Retinitis and Unmet Medical Need	13
2.3 Development of Valganciclovir	14
3. Preclinical Characteristics of Valganciclovir	15
4. The Valganciclovir Clinical Program	16
4.1 Overview of the Clinical Program	16
5. Design of the Clinical Development Program	19
5.1 Impact of HAART on the Epidemiology of CMV Retinitis	19
5.2 Effect of HAART on the Clinical Course of CMV Retinitis	21
5.3 Design of Efficacy and Safety Study WV15376	21
6. Clinical Pharmacology of Valganciclovir	22
6.1 Evidence of an Exposure Response Relationship for Ganciclovir ..	22
6.2 Pharmacokinetics of Valganciclovir	23
6.2.1 Absorption	23
6.2.2 Distribution	24
6.2.3 Metabolism	24
6.2.4 Elimination	24
6.2.5 Bioavailability	24
6.2.6 Renal Impairment	24
6.2.7 Children and The Elderly	25
6.2.8 Pharmacokinetics in Valganciclovir Therapeutic Study WV15376	25
6.2.9 Drug Interactions	27
7. Efficacy of Valganciclovir Study WV15376	27
7.1 Study Objectives and Design	27
7.2 Ophthalmologic Evaluations and Fundus Photographs	28
7.3 Virology Assessments	28
7.4 Pharmacokinetic Assessments	28
7.5 Primary Efficacy Parameter	28
7.6 Secondary Efficacy Parameters	29
7.6.1 Randomized Phase	29

7.6.2 Extension Phase	30
7.6.3 Exploratory Subgroup Analyses.	30
7.7 Efficacy Data Analysis in Study WV15376	30
7.7.1 Statistical Model.	30
7.8 Measures and Endpoints in Study WV15376	31
7.9 Sample Size Considerations	31
7.10 Active Control Considerations.	32
7.11 Efficacy Results Study WV15376	32
7.11.1 Demographic Data, Baseline Disease Characteristics and Withdrawals	32
7.11.1.1 Demographics.	32
7.11.1.2 Baseline Disease Characteristics	33
7.11.1.3 Withdrawals From Study.	33
7.11.2 Primary Endpoint Proportion of Patients With Progression of CMV Retinitis by Week 4, Photographic Assessment	34
7.11.2.1 Exploratory Subgroup Analyses of Primary Endpoint.	35
7.11.3 Secondary Efficacy Parameters up to Week 4	36
7.11.3.1 Proportion of Patients With Progression of CMV Retinitis by Week 4 Ophthalmological Assessment	36
7.11.3.2 Proportion of Patients Achieving a Satisfactory Response to Induction Therapy by Week 4, Photographic Assessment	36
7.11.3.3 Change in Visual Acuity Between Baseline and Weeks 2, 4 and 6	36
7.11.3.4 Change in Vision Assessment Between Baseline and Weeks 2 and 4	37
7.11.4 Secondary Efficacy Parameters During Extension Phase.	37
7.11.4.1 Incidence and Time to First Progression of CMV Retinitis - Photographic Assessment	37
7.11.4.2 Incidence and Time to Progression or Withdrawal Photographic Assessment	38
7.11.4.3 Incidence and Time to First Progression of CMV Retinitis - Ophthalmological Assessment.	38
7.11.4.4 Incidence and Time to Development of Contralateral CMV Retinitis Photographic Assessment.	39
7.11.4.5 Incidence of Extraocular CMV Disease Between Baseline and Clinical Cut-Off	39
7.11.4.6 Incidence and Time to Deterioration in Visual Acuity Between Baseline and Clinical Cut-Off	39
7.11.5 Virology Results	39
8. Efficacy of Valganciclovir Study WV15705	41
8.1 Study Objectives and Design	41

8.2 Efficacy Parameters	41
8.3 Efficacy Data Analysis in Study WV15705	41
8.4 Efficacy Results Study WV15705	42
8.4.1 Demography Data And Baseline Disease Characteristics.	42
8.4.2 Efficacy Results Summary	42
9. Assessment of Safety in Valganciclovir Clinical Studies	43
9.1 Extent of Exposure to Trial Treatment.	45
9.2 Safety Results	46
9.2.1 Valganciclovir Clinical Pharmacology Studies	46
9.2.2 Adverse Events Reported During Valganciclovir and Ganciclovir Induction Treatment Study WV15376	46
9.2.3 Laboratory Data Reported During Valganciclovir and Ganciclovir Induction Treatment Study WV15376	47
9.2.4 Deaths, Serious Adverse Events and Premature Withdrawals due to Adverse Events Reported During Induction Treatment.	48
9.2.5 Laboratory Data Reported Between Baseline and Clinical Cut-off in Study WV15376	49
9.2.6 Adverse Events Reported During Valganciclovir Studies WV15376 and WV15705	50
9.2.7 Laboratory Data Reported During Valganciclovir Studies WV15376 and WV15705	51
9.2.8 Deaths, Serious Adverse Events and Premature Withdrawals due to Adverse Events Reported During Valganciclovir Studies WV15376 and WV15705.	53
9.2.9 Adverse Events Reported During Valganciclovir Maintenance Treatment, Comparison With Prior Ganciclovir Studies.	54
9.2.10 Laboratory Data Reported During Valganciclovir Maintenance Treatment, Comparison With Prior Ganciclovir Studies	54
9.2.11 Special Safety Considerations.	55
10. Data From 4 Month Safety Update	55
11. Benefit/Risk Summary.	56
12. Conclusion	57
13. References	58

List of Tables

Table 1 Description of Studies in the Clinical Program.	18
Table 2 Summary of Mean (CV%) Ganciclovir Pharmacokinetic Parameters Following Oral Valganciclovir and IV. Ganciclovir (WV15376)	26
Table 3 Progression Data from Ganciclovir Study GAN1697.	32
Table 4 Summary of Baseline Disease Characteristics in Study WV15376	33
Table 5 Analysis of CMV Retinitis Progression by Week 4 Based on Photographic Assessment (Standard Population)	35
Table 6 Overall Status of CMV Cultures at Baseline and Week 4 (ITT Population)	40
Table 7 Summary of Qualitative PCR Data Obtained with the CMV AMPLICOR® Test (ITT Population)	40
Table 8 Description of Ganciclovir Therapeutic Studies Used in the Comparison of the Known Safety Profile of Ganciclovir with the Safety Profile of Valganciclovir	45
Table 9 All Adverse Events Reported During Induction Treatment, by Decreasing Frequency (Overall Incidence \geq 2%)	47
Table 10 Minimum ANC, Hemoglobin and Platelet Levels and Maximum Serum Creatinine Values During Induction Treatment	48
Table 11 Minimum ANC, Hemoglobin and Platelet Levels and Maximum Serum Creatinine Values Reported During Study WV15376	50
Table 12 Adverse Events Reported During Valganciclovir Therapeutic Studies, by Decreasing Frequency (Incidence \geq 10%)	51
Table 13 Marked Shifts From Baseline in Key Laboratory Parameters During Valganciclovir Therapeutic Studies in AIDS Patients	51
Table 14 Minimum ANC, Hemoglobin and Platelet Levels and Maximum Serum Creatinine Values During Valganciclovir Therapeutic Studies in AIDS Patients	53

List of Figures

Figure 1 Mean Steady-State Ganciclovir Concentrations in AIDS Patients Following Administration of I.V. Ganciclovir (5 mg/kg) and Oral Valganciclovir (900 mg) at Induction (b.i.d.; Week 1) and Maintenance (o.d.; Week 4) Level Dosing (Study WV15376)	15
Figure 2 Overview of the Clinical Program	17
Figure 3 Incidence of Selected Opportunistic Infections World-Wide in Patients with HIV Infection, 1992-1997	20
Figure 4 Dose Proportionality of Ganciclovir AUC ₀₋₂₄ Following Administration of Valganciclovir (WP15347)	23
Figure 5 Mean Ganciclovir Plasma Concentrations Following Single Oral Doses of 900 mg Valganciclovir in Subjects With Increasing Renal Impairment (WP15511)	25
Figure 6 Mean Ganciclovir Concentrations Following i.v. Ganciclovir (5 mg/kg b.i.d. Week 1; 5 mg/kg o.d. Week 4) or Oral Valganciclovir (900 mg b.i.d. Week 1; 900 mg o.d. Week 4) (WV15376)	26
Figure 7 Overall Design of Study WV15376	28
Figure 8 Time To First Progression of CMV Retinitis up to Study Day 360 Where Death is a Censored Event, Based on Photographic Assessment (ITT Population)	38
Figure 9 Overall Design of Study WV15705	41
Figure 10 Time to First Progression of CMV Retinitis, Where Death is a Censored Event (All Patients) WV15705	43
Figure 11 Overview of Clinical Studies Discussed in the Integrated Safety Summary for Valganciclovir (n = Number Enrolled)	44

List of Appendices

Appendix 1 Preclinical Characteristics of Valganciclovir	59
Appendix 2 Overview of Valganciclovir Clinical Studies	62
Appendix 3 Valganciclovir Solid Organ Transplant Study PV16000.	66
Appendix 4 Evidence of an Exposure Response Relationship for Ganciclovir (Study GANS 2226)	67
Appendix 5 Absolute Bioavailability of Ganciclovir when Administered as Valganciclovir	69
Appendix 6 Effect of Renal Impairment on Mean (%CV) Ganciclovir Pharmacokinetic Parameters	70
Appendix 7 Inclusion and Exclusion Criteria for Studies WV15376 and WV15705.	71
Appendix 8 Summary of Demographic Data Study WV15376 (ITT Population)	73
Appendix 9 Assessment of the Possible Influence of HAART During the Randomized Phase of Study WV15376	74
Appendix 10 Satisfactory Response to Induction Therapy by Week 4 Based on Photographic Assessment (Standard Population)	78
Appendix 11 Change in Visual Acuity Between Baseline and Weeks 2, 4 and 6	79
Appendix 12 Time to First Progression of CMV Retinitis up to Study Day 360 Where Death is a Censored Event (Based on Photographic Assessment; ITT Population), or Withdrawal	80
Appendix 13 Time to First Progression of CMV Retinitis up to Study Day 360 Where Death is a Censored Event, Based on Ophthalmological Assessment (ITT Population)	81
Appendix 14 Time to First Progression Where Death is a Censored Event Valganciclovir (Ophthalmologic vs Photographic Data, ITT Population)	82
Appendix 15 Time to First Progression Where Death is a Censored Event Ganciclovir (Ophthalmologic vs Photographic Data, ITT Population)	83
Appendix 16 Summary of Quantitative CMV PCR Data (CMV Viral Load) Obtained in CMV PCR Positive Patients.	84
Appendix 17 Summary of Demographic Data Study WV15705 (All Patients)	85
Appendix 18 Kaplan-Meier Plot of Time to First Incidence of Anemia (Hemoglobin < 8.0 g/dL) in Study WV15376.	86
Appendix 19 Summary of Causes of Patient Deaths During Valganciclovir Therapeutic Studies	87



Appendix 20 Adverse Events Reported During Valganciclovir Maintenance Treatment, by Decreasing Frequency (Overall Incidence $\geq 4\%$), Using Data From Previous Ganciclovir Studies for Comparison 88

Appendix 21 Minimum ANC, Hemoglobin and Platelet Levels, and Maximum Serum Creatinine Values During Valganciclovir Maintenance Treatment, Using Data From Previous Ganciclovir Studies for Comparison 89

Appendix 22 Updated Adverse Events Reported During Valganciclovir Studies WV15376 and WV15705, by Decreasing Frequency (Updated Incidence $\geq 10\%$) 90

Appendix 23 Minimum ANC, Hemoglobin and Platelet Levels and Maximum Serum Creatinine Values During Valganciclovir Studies WV15376 and WV15705 91

GLOSSARY OF ABBREVIATIONS

ACTG	AIDS Clinical Trials Group
AIDS	acquired immune deficiency syndrome
ALT	alanine aminotransferase (SGPT)
ANC	absolute neutrophil count
AST	aspartate aminotransferase (SGOT)
AUC	area under the plasma concentration-time curve
b.i.d.	twice daily
CI	confidence interval
CD4	CD4 positive lymphocyte
CL _{iv}	systemic clearance
CL _R	renal clearance
C _{max}	maximum plasma concentration
C _{min}	minimum plasma concentration
CMV	cytomegalovirus
CrCL	creatinine clearance
CSF	cerebrospinal fluid
F	bioavailability
GCV	ganciclovir
GCV-TP	ganciclovir triphosphate
h	hour
HAART	highly active antiretroviral therapy
HIV	human immunodeficiency virus
HIV+	HIV infected
HUS	hemolytic uremic syndrome
i.v.	intravenous
ITT	Intent to treat
kg	Kilogram

GLOSSARY OF ABBREVIATIONS

L	liter
μg	microgram
μm	micrometer
mg	milligram
mL	milliliter
min	minute
o.d.	once daily
PBL	peripheral blood leukocyte
PCP	<i>Pneumocystis carinii</i> pneumonia
PCR	polymerase chain reaction
PD	pharmacodynamic
PK	pharmacokinetic
PMNL	polymorphonuclear leucocyte
p.o.	per os, orally
RBC	red blood cell
t ^{1/2}	half-life
t.i.d.	three times per day
T _{max}	time to maximum plasma concentration
TTP	thrombotic thrombocytopenic purpura
VGCV	valganciclovir
V _{ss}	steady state volume of distribution
WRC	Wisconsin Reading Center

1. EXECUTIVE SUMMARY

The sponsor submitted a New Drug Application (NDA) on 28 September 2000 for valganciclovir HCl 450 mg tablets in the treatment of cytomegalovirus (CMV) retinitis in patients with AIDS. The purpose of this briefing document is to provide an overview of the valganciclovir development program as presented in the dossier submitted to the Food and Drug Administration (FDA).

Unmet Medical Need (Section 2.2): Despite the reduced incidence of new cases of CMV retinitis following the introduction of highly active antiretroviral therapy (HAART), many AIDS patients remain or become severely immunocompromised and at risk of developing CMV retinitis. Initial systemic anti-CMV therapy involves intravenous treatment which is time-consuming, inconvenient and associated with catheter-related morbidity, while use of intraocular implants requires a surgical procedure. Oral ganciclovir has low bioavailability (about 6%) which limits the effectiveness of the capsule formulation to maintenance treatment of CMV retinitis following a satisfactory response to induction treatment. There remains an unmet medical need for a simple oral regimen which could be used for both induction and maintenance treatment of CMV retinitis.

Development of Valganciclovir (Section 2.3): Valganciclovir is a valyl ester prodrug of ganciclovir which is rapidly converted to ganciclovir following oral administration, with an absolute bioavailability of ganciclovir of 60%, a 10-fold improvement over the current oral ganciclovir formulation. A valganciclovir dose of 900 mg (two 450 mg film coated tablets) achieves a ganciclovir exposure comparable to that of 5 mg/kg i.v. ganciclovir. Valganciclovir therefore provides the potential for:

- An orally administered therapeutic alternative to i.v. ganciclovir induction and maintenance treatment of CMV retinitis
- Avoidance of morbidity associated with venous access required for i.v. ganciclovir
- A simple oral regimen with reduced tablet count and frequency that could improve adherence to long term maintenance treatment

Design of the Clinical Program (Section 0): The valganciclovir program was implemented during a period when the natural history of AIDS and associated opportunistic infections was undergoing a dramatic change. Because the use of HAART changed the epidemiology and clinical course of HIV-related CMV retinitis, the ability to conduct large comparative clinical trials was reduced. The clinical development program for valganciclovir is an abbreviated program which builds upon the extensive efficacy and safety experience of ganciclovir. Induction treatment was targeted as the highest hurdle in terms of efficacy. If valganciclovir induction efficacy comparable to i.v. ganciclovir could be demonstrated, efficacy in maintenance therapy could be reasonably inferred based on an established PK/PD relationship for ganciclovir, where ganciclovir exposure, as measured by AUC, correlates with clinical response. Higher exposures of ganciclovir (represented by average AUC_{0-24}) were associated with statistically significantly longer times to progression of CMV retinitis, whilst average C_{max} or C_{min} did not add any further predictive value over AUC (Section 6.1).

Results from Clinical Program (Sections 7, 8, 9): Based on the masked assessment of fundus photographs, the efficacy of valganciclovir was comparable to that of i.v. ganciclovir as induction therapy for newly diagnosed CMV retinitis. Following four weeks of randomized treatment with i.v. ganciclovir (5 mg/kg, b.i.d. for 3 weeks followed by 5 mg/kg o.d. for one week) or oral valganciclovir (900 mg b.i.d. for 3 weeks followed by 900 mg o.d. for one week), an equal proportion of patients in the two treatment groups (7 patients per arm, 10%) had experienced CMV retinitis progression (the primary endpoint, Section 7.11.2), and a similar proportion in each treatment group (77% ganciclovir; 72% valganciclovir) had achieved a satisfactory response to induction therapy (a secondary endpoint, Section 7.11.3.2). The impact of protease inhibitor use during the randomized phase of the study was small and did not influence the primary comparison of oral valganciclovir and i.v. ganciclovir induction therapy. A higher number of withdrawals occurred on the valganciclovir arm between weeks 4 and 12 of the study (14 withdrawals compared to 4 on the ganciclovir arm)(Section 7.11.1.3). These withdrawals occurred during the extension phase of the study (beyond week 4) when all patients were receiving oral valganciclovir. Although this difference in withdrawal rates did not affect the primary efficacy outcome at week 4, it may have influenced time to progression estimates beyond week 4 (a secondary endpoint) (Section 7.11.4.2). Valganciclovir had a pronounced antiviral effect on CMV viremia comparable to that of i.v. ganciclovir, as measured by CMV culture positivity and qualitative and quantitative PCR (Section 7.11.5).

Based on retinal photography, between baseline and clinical cut-off, a comparable proportion of patients in each treatment group had experienced CMV retinitis progression (53% ganciclovir; 51% valganciclovir). The median time to first retinitis progression was 125 days on the ganciclovir arm versus 160 days on the valganciclovir arm (Section 7.11.4.1). Based on unmasked ophthalmological assessment, 45% of patients in the ganciclovir group and 54% in the valganciclovir group experienced progression of retinitis. The median time to first progression was 337 days in the ganciclovir arm and 196 days in the valganciclovir arm. These results imply a degree of bias on the part of the study ophthalmologists in favor of standard i.v. ganciclovir therapy (Section 7.11.4.3). By clinical cut-off, a comparable proportion of patients in each treatment group had developed contralateral CMV retinitis (11% ganciclovir; 12% valganciclovir), and had experienced a deterioration in visual acuity (26% ganciclovir; 31% valganciclovir).

The safety profile of valganciclovir is similar to that of systemic ganciclovir; no new toxicities or clinical observations were reported during treatment with valganciclovir that have not been observed during treatment with i.v. or oral ganciclovir. During induction treatment, the safety profile of valganciclovir is similar to that of i.v. ganciclovir. Valganciclovir is associated with significantly fewer i.v. catheter-related adverse events (Section 9.2.2). Valganciclovir treatment is associated with neutropenia and anemia, consistent with that previously recorded for ganciclovir. However, severe anemia (hemoglobin < 8.0 g/dL) was reported more frequently with valganciclovir (Section 9.2.5).

Summary: Valganciclovir provides systemic ganciclovir exposures comparable to i.v. ganciclovir at both induction and maintenance dosing levels. Study WV15376 demonstrated comparable rates of CMV retinitis progression, both following induction therapy and longer term, and comparable adverse events and survival, regardless of the original randomized induction regimen (i.v. ganciclovir or oral valganciclovir).

Conclusion: Valganciclovir, an oral prodrug of ganciclovir with high bioavailability provides an effective and convenient treatment for CMV retinitis. The safety profile is comparable to that of ganciclovir, with the significant benefit of reduced morbidity associated with i.v. ganciclovir administration.

2. BACKGROUND AND SCIENTIFIC RATIONALE

2.1 Pathology of CMV Retinitis

Human cytomegalovirus (CMV) is a herpes virus recognized to be an important pathogen in individuals with AIDS and in organ transplant recipients. In immunocompromised patients, CMV retinitis is an ocular manifestation of systemic CMV infection. CMV retinitis lesions are characterized by inflammation, retinal necrosis, edema, perivascular cuffing, and varying degrees of hemorrhage. The necrosis of retinal tissue results in irreversible and permanent loss of vision in the involved area. Lesions enlarge by outward movement of the lesion border (termed *progression*). A new lesion can arise in a previously uninvolved area of retina in either eye (also termed *progression*), and multiple discrete lesions may occur in the same eye. The goal of therapy for CMV retinitis is to prevent or delay progression into healthy retinal tissue.

2.2 Current Practice for the Treatment of CMV Retinitis and Unmet Medical Need

Ganciclovir is available as a lyophilized powder for intravenous (i.v.) infusion and is indicated for the treatment of CMV retinitis and for the prevention of CMV disease in immunocompromised patients at risk of CMV disease. Ganciclovir capsules for oral administration are available for maintenance treatment of CMV retinitis in patients with AIDS, and for the prevention of CMV disease in solid organ transplant recipients, and in individuals with advanced HIV infection.

The initial treatment of CMV retinitis involves i.v. administration of one of three currently available antiviral drugs, i.v. ganciclovir, i.v. foscarnet, or i.v. cidofovir. There are also two local intraocular treatments available, fomivirsen and a ganciclovir intraocular implant. Systemic ganciclovir therapy starts with i.v. ganciclovir induction treatment at 5 mg/kg b.i.d. for 14 to 21 days. Eighty to ninety percent of patients will respond with a decrease in hemorrhage and edema, and no further lesion enlargement. This is considered a favorable or *satisfactory response to induction treatment*. What remains after healing is non-functional, scarred retina. If therapy is stopped and if the patient remains immunocompromised, within 2 to 4 weeks the lesion becomes inflamed, hemorrhagic, and a progression occurs. A repeat cycle of induction treatment is effective, but with each progression additional retinal tissue is destroyed. Maintenance treatment is therefore given to prevent or delay progression following a satisfactory response to induction treatment. Maintenance treatment is long term and involves either

i.v. administration of ganciclovir, foscarnet or cidofovir, or oral administration of ganciclovir capsules. Maintenance treatment with ganciclovir comprises i.v. ganciclovir at 5 mg/kg once daily, or oral ganciclovir at 1000 mg t.i.d. (6×500 mg or 12×250 mg capsules daily).

Despite the benefits of standard treatment regimens, intravenous treatment is time-consuming, expensive, inconvenient and associated with catheter-related morbidity, while use of intraocular implants requires a surgical procedure. The advantages of oral administration for long term use are significant, however, oral ganciclovir has low bioavailability (about 6%), which limits the effectiveness of the capsule formulation to maintenance treatment of CMV retinitis following a satisfactory response to induction treatment. Higher doses of ganciclovir (4500 mg and 6000 mg) were studied with a trend towards improved times to progression, but with an unacceptable number of capsules (up to 24 capsules daily).

The development of valganciclovir was thus targeted to address the unmet medical need for a simple oral regimen which could be used for both induction and maintenance treatment of CMV retinitis.

2.3 Development of Valganciclovir

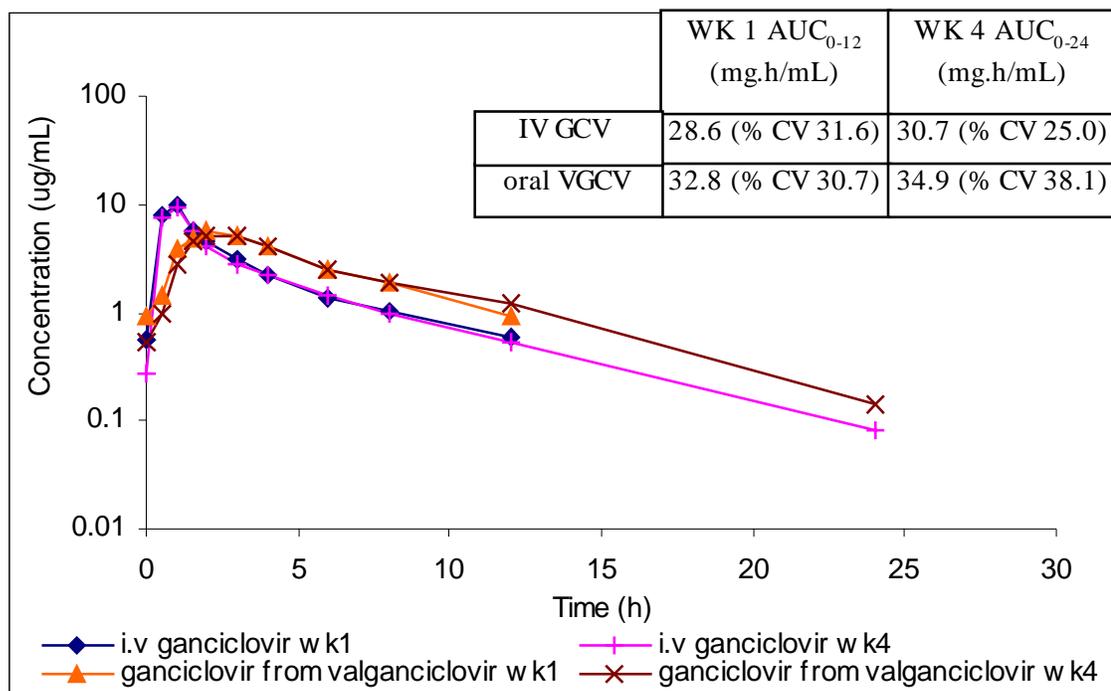
Valganciclovir (Ro 107-9070) is a valyl ester prodrug of ganciclovir that is rapidly hydrolyzed to ganciclovir following ingestion. Only 1-2% of absorbed valganciclovir appears as valganciclovir in the plasma, the remainder being found as ganciclovir. The absolute bioavailability of ganciclovir from valganciclovir is approximately 60%, a 10-fold improvement over the approximate 6% bioavailability of the current oral ganciclovir formulation.

A previous clinical study investigating the comparative efficacy of three oral ganciclovir treatment regimens (3 g/day, 4.5 g/day and 6 g/day) against that of i.v. ganciclovir (5 mg/kg/day), showed that the area under the plasma concentration time curve (AUC), a measure of systemic ganciclovir exposure, is the pharmacokinetic parameter that best correlates with clinical efficacy (see Section 6.1). A dose of 900 mg of valganciclovir (two 450 mg film-coated tablets) taken twice a day after food achieves a ganciclovir plasma AUC_{0-12} comparable to that of the standard i.v. ganciclovir induction dose of 5 mg/kg b.i.d.; 900 mg once daily achieves a ganciclovir AUC_{0-24} comparable to that of the standard i.v. ganciclovir maintenance dose of 5 mg/kg once daily (Figure 1). Given this understanding of a PK/PD relationship for ganciclovir, and based on the ganciclovir exposure achieved following oral administration of valganciclovir, the safety and efficacy of valganciclovir was hypothesized to be similar to that already known with ganciclovir.

The pharmacokinetic profile and improved oral bioavailability of ganciclovir from valganciclovir therefore provides the potential for:

- An orally administered therapeutic alternative to i.v. ganciclovir induction and maintenance treatment of CMV retinitis
- Avoidance of morbidity associated with intravenous access required for i.v. ganciclovir
- A simple oral regimen with reduced tablet count and frequency that could improve adherence to long-term maintenance treatment

Figure 1 Mean Steady-State Ganciclovir Concentrations in AIDS Patients Following Administration of I.V. Ganciclovir (5 mg/kg) and Oral Valganciclovir (900 mg) at Induction (b.i.d.; Week 1) and Maintenance (o.d.; Week 4) Level Dosing (Study WV15376)



3. PRECLINICAL CHARACTERISTICS OF VALGANCICLOVIR

The preclinical characteristics of valganciclovir, comprising:

- Antiviral activity and mechanism of action
- Preclinical pharmacokinetics, mechanism of absorption and conversion to ganciclovir
- Preclinical toxicology

are presented in Appendix 1.

4. THE VALGANCICLOVIR CLINICAL PROGRAM

4.1 Overview of the Clinical Program

An overview of the clinical studies which form the basis of the clinical development program for valganciclovir in the treatment of CMV retinitis is provided in Figure 2. This information is supplemented further in Table 1 and Appendix 2.

The first clinical study conducted with valganciclovir was GANS 2661, a phase I clinical pharmacology study which demonstrated that in HIV+, CMV+ patients, valganciclovir is rapidly and extensively hydrolyzed to ganciclovir [1]. The absolute bioavailability of ganciclovir from valganciclovir was approximately 10-fold greater than from oral ganciclovir, and ganciclovir appeared so rapidly in the circulation after valganciclovir dosing that it appeared likely that the *in vivo* effects of valganciclovir would be comparable to those of ganciclovir. A subsequent phase I clinical pharmacology study in HIV+, CMV+ subjects, study WP15347, demonstrated that under fed conditions, the ganciclovir exposure (AUC_{0-24}) obtained with valganciclovir was dose proportional [1]. By interpolation of the data obtained in study WV15347, it was possible to calculate the doses of valganciclovir which would provide ganciclovir exposures comparable to those obtained with i.v. ganciclovir at induction and maintenance level dosing. Thus, the recommended dosage of valganciclovir for induction treatment of CMV retinitis is 900 mg b.i.d. for 21 days followed by maintenance treatment with 900 mg once daily. These valganciclovir doses were studied in several clinical pharmacology studies (WP15511, WP15711, WP15509 [1]), and were also utilized in the controlled phase II/III efficacy and safety study WV15376 [2], and in the uncontrolled phase II/III safety study WV15705 [3].

Although this application seeks approval for valganciclovir in the treatment of CMV retinitis, the NDA submission also included preliminary safety data from an ongoing study in solid organ transplant recipients (study PV16000) to further describe the safety profile of valganciclovir. A brief outline of the design and endpoints of study PV16000 is provided in Appendix 3.

Figure 2 Overview of the Clinical Program

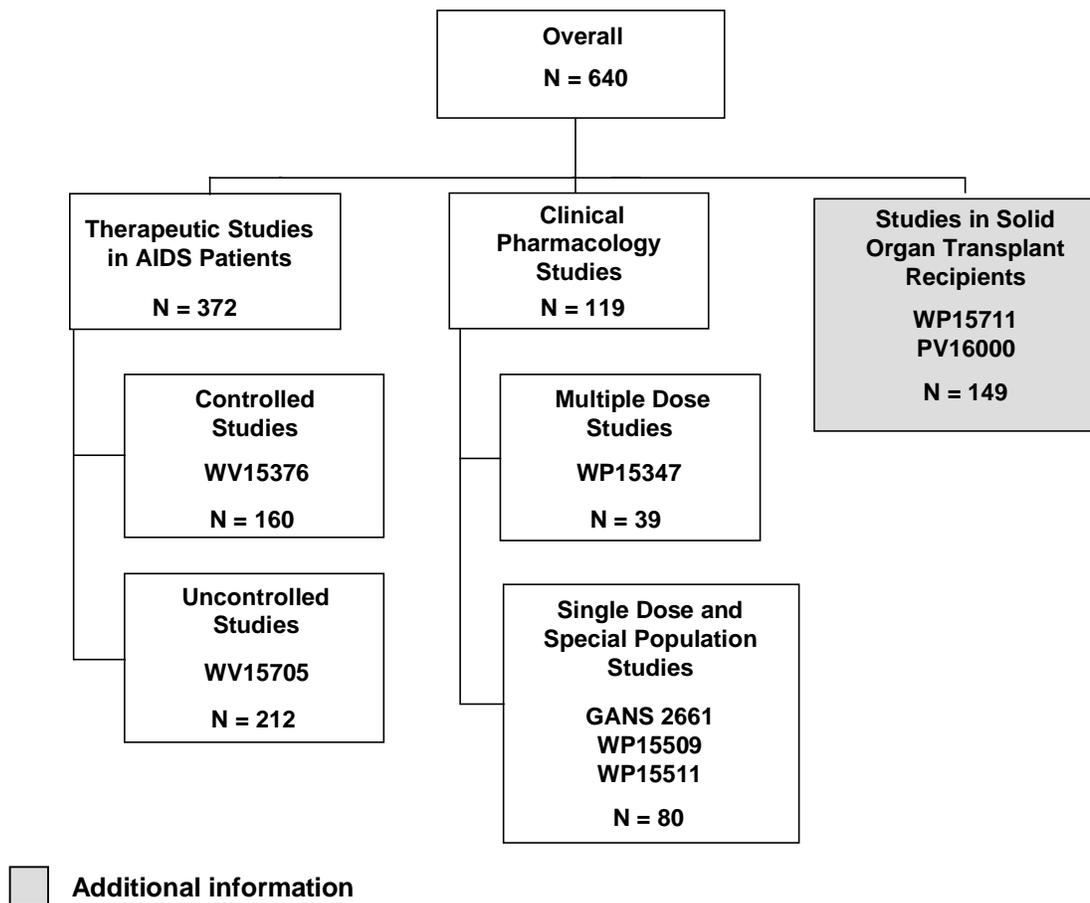


Table 1 Description of Studies in the Clinical Program

Protocol	Description
Valganciclovir Clinical Pharmacology Studies	
GANS 2661	Single dose pharmacokinetics and absolute and relative bioavailability of valganciclovir in HIV+ and CMV+ subjects
WP15347	The pharmacokinetics of four different doses of valganciclovir following multiple oral dosing (with and without food)
WP15511	The effect of renal impairment on the pharmacokinetics of valganciclovir and ganciclovir following oral administration of valganciclovir
WP15509	A bioequivalence study of the clinical trial versus market formulations of valganciclovir tablets
Valganciclovir Therapeutic Studies in AIDS Patients	
WV15376	A randomized, controlled comparison of the safety and efficacy of valganciclovir vs i.v. ganciclovir as induction therapy for the treatment of newly diagnosed CMV retinitis
WV15705	An open label study of the safety and tolerability of valganciclovir, an oral prodrug of ganciclovir, for the treatment of CMV retinitis in subjects with AIDS
Valganciclovir Studies in Solid Organ Transplant Recipients	
WP15711	The pharmacokinetics of ganciclovir following oral valganciclovir, oral ganciclovir and intravenous ganciclovir in liver transplant recipients
PV16000	A randomized, double-blind, double-dummy, active-comparator, controlled, multicenter study of the efficacy and safety of valganciclovir vs oral ganciclovir for the prevention of CMV disease in high-risk heart, liver and kidney allograft recipients

5. DESIGN OF THE CLINICAL DEVELOPMENT PROGRAM

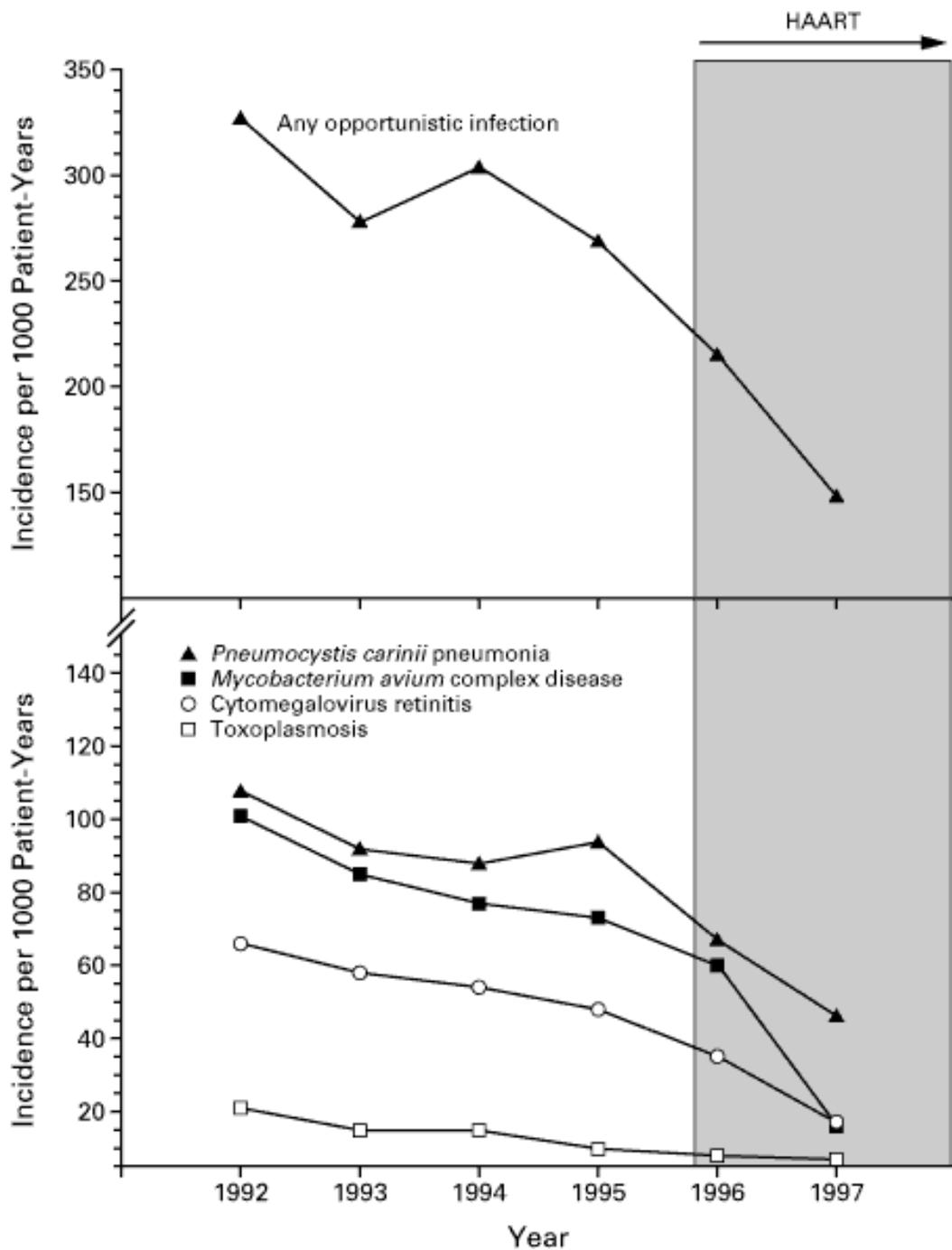
Valganciclovir is rapidly converted to ganciclovir, and provides ganciclovir systemic exposures comparable to i.v. ganciclovir. The valganciclovir clinical program builds upon the already large volume of efficacy and safety data available for ganciclovir. The submission focuses primarily on the results of two therapeutic studies: one primary efficacy and safety study (WV15376) in the induction treatment of patients with newly diagnosed CMV retinitis, and one long-term safety study (WV15705) in the maintenance treatment of patients with previously treated CMV retinitis, in addition to pharmacokinetic and pharmacodynamic data.

In addition, the valganciclovir program was implemented during a time when the natural history of AIDS and associated opportunistic infections was undergoing a dramatic change as a consequence of newly available, highly active antiretroviral therapy (HAART). HIV-infected individuals treated with HAART began to achieve varying degrees of immune reconstitution and to experience substantially fewer opportunistic infections, including CMV retinitis. The decreased number of cases of newly diagnosed CMV retinitis had a significant impact on the valganciclovir development program.

5.1 Impact of HAART on the Epidemiology of CMV Retinitis

Because the use of HAART changed the epidemiology and clinical course of HIV-related CMV retinitis, the ability to conduct large comparative clinical trials was reduced. The number of new cases of CMV retinitis decreased to 20% or less of the pre-HAART numbers in both the U.S. and Europe (Figure 3). In the early 1990's a typical trial of newly diagnosed CMV retinitis enrolled 161 patients at 15 locations in 15 months (0.72 patients/month/location). Study WV15376, the primary randomized study of valganciclovir, enrolled 160 patients at 42 locations in 28 months (0.14 patients/month/location).

Figure 3 Incidence of Selected Opportunistic Infections World-Wide in Patients with HIV Infection, 1992-1997



Kovacs JA and Masur H. Prophylaxis against opportunistic infections in patients with human immunodeficiency virus infection. N Engl J Med. 2000; 342: 1416-1429.

5.2 Effect of HAART on the Clinical Course of CMV Retinitis

In spite of the decrease in new cases of CMV retinitis, many AIDS patients remain or become severely immunocompromised, and are at risk of developing CMV retinitis. The diagnosis of CMV retinitis during HAART reflects a failure of the current antiretroviral drug regimen, and requires treatment. Other patients may develop CMV retinitis and later respond to HAART. In these patients, the clinical course of the disease is altered. The number of progressions of CMV retinitis is lower, and the time to progression is longer than seen prior to the introduction of HAART.

Thus, the use of HAART has resulted in patients with CMV retinitis across a broad spectrum of HIV disease:

- One population consists of patients with newly diagnosed CMV retinitis, continued severe immunosuppression in spite of HAART, a low CD4 count ($< 100/\mu\text{L}$), a high HIV viral load, and multiple opportunistic infections. These patients, even if receiving HAART, are not responding to the anti-HIV therapy. They are not unlike patients diagnosed with CMV retinitis in the pre-HAART era.
- The second population has CMV retinitis and has responded to HAART with an increased CD4 lymphocyte count and few, if any, active opportunistic infections. These patients have predominantly inactive and healed retinitis, with a lower rate of progression of CMV retinitis relative to patients in the pre-HAART era.

5.3 Design of Efficacy and Safety Study WV15376

Originally, a traditional development program of phase III randomized clinical trials was planned to assess the efficacy of valganciclovir. However, the changes in the epidemiology and natural history of CMV retinitis, made it apparent that conducting large comparative phase III studies would be prohibitively difficult.

The sponsor met with FDA in September 1997 to explore ways to move forward in this difficult research environment. This meeting and subsequent discussion with the Division led to the current development program for valganciclovir. Study WV15376 had already been initiated as a phase II proof of concept study in 70 patients with non sight-threatening, newly diagnosed CMV retinitis and it was agreed that this trial would be expanded to form the primary efficacy study for the valganciclovir clinical program. The study was enlarged to enroll 150 patients, 75 patients per arm, in order to provide an acceptable balance between what was practical in the current environment, and the evidence required to conclude that treatment with valganciclovir was within an acceptable range of efficacy compared to i.v. ganciclovir. The primary efficacy objective was to halt the progression of CMV retinitis during the first 4 weeks of treatment. Following an early masked assessment of efficacy by an external panel of expert ophthalmologists, the inclusion criteria were broadened to allow for the enrollment of patients with sight-threatening CMV retinitis. The study was also expanded to include virological assessments, including CMV culture and PCR.

Study WV15376 compared induction treatment with valganciclovir to induction treatment with i.v. ganciclovir. As induction treatment represents the highest hurdle in

terms of efficacy of an anti-CMV drug, it was postulated that if valganciclovir induction efficacy comparable to i.v. ganciclovir could be demonstrated, the efficacy of valganciclovir in maintenance therapy could be reasonably inferred, based on the established PK/PD relationship for ganciclovir, and the ganciclovir exposure achieved following oral administration of valganciclovir. Consultation with external expert physicians made it clear that a study design requiring long-term i.v. ganciclovir maintenance treatment was not feasible in the current environment, and it was therefore decided that after 4 weeks of randomized treatment with either i.v. ganciclovir or oral valganciclovir, all patients would receive maintenance therapy with valganciclovir in an extension of the study designed to capture as much long-term efficacy and safety data with valganciclovir as possible.

Study WV15376 provides randomized, comparative efficacy data for induction treatment, uncontrolled efficacy data for the maintenance treatment of CMV retinitis, and safety and comparative pharmacokinetics in the target population. To expand the amount of safety data with valganciclovir, a second therapeutic study, WV15705 was designed to investigate the safety and tolerability of long-term treatment with valganciclovir in patients with previously treated, mostly stable CMV retinitis. WV15705 also provided uncontrolled but supportive efficacy data for long-term maintenance treatment.

6. CLINICAL PHARMACOLOGY OF VALGANCICLOVIR

Evaluation of the human pharmacokinetics of valganciclovir focused on:

1. Determination of a dose of valganciclovir that would result in a systemic drug exposure similar to i.v. ganciclovir
2. Characterization of the repeat dose pharmacokinetics and dose proportionality of valganciclovir and its antiviral metabolite ganciclovir (Study WP15347)
3. Assessment of the effect of food on the pharmacokinetics of valganciclovir and ganciclovir (Study WP15347)
4. Determination of the absolute bioavailability of ganciclovir from valganciclovir (Studies GANS 2661, WP15347, WP15509, WP15511, WP15711, WV15376)
5. Investigation of the influence of renal impairment on the pharmacokinetics of valganciclovir and ganciclovir in order to enable the derivation of a dose adjustment algorithm in patients with varying degrees of renal dysfunction (Study WP15511)

6.1 Evidence of an Exposure Response Relationship for Ganciclovir

A study conducted during the clinical development of ganciclovir, GANS 2226, had demonstrated that plasma AUC is the pharmacokinetic parameter which best correlates with clinical response. In this study, higher exposures of ganciclovir (represented by average AUC_{0-24}) were associated with statistically significantly longer times to progression of CMV retinitis, whilst average C_{max} or C_{min} did not add any further predictive value over AUC (Appendix 4).

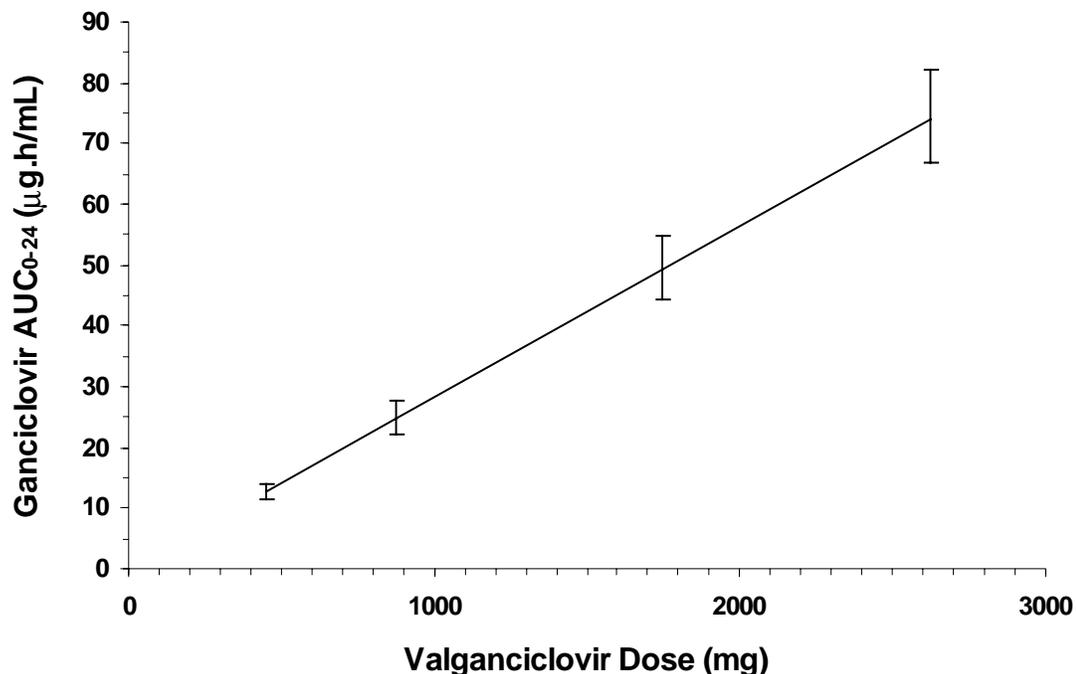
6.2 Pharmacokinetics of Valganciclovir

The pharmacokinetics of valganciclovir have been studied in a total of 190 subjects. The population of subjects recruited for the valganciclovir clinical program consisted predominantly of subjects who were HIV/CMV seropositive (n = 83) and HIV positive patients with CMV retinitis (n = 43; study WV15376). In addition, the compound was studied in otherwise healthy, renally impaired subjects (n = 24), liver transplant recipients (n = 28) and healthy volunteers (n = 12).

6.2.1 Absorption

Valganciclovir is well absorbed from the gastrointestinal tract and is then rapidly and extensively converted by intestinal and hepatic esterases to ganciclovir. Following valganciclovir administration, plasma concentrations of ganciclovir reach maximal concentrations in 2-3 hours, and exceed those of valganciclovir by a wide margin (30-fold or over). Approximately 60% of the administered dose reaches the systemic circulation as ganciclovir, a figure which is consistent across doses and patient populations. Food increases the extent of exposure to ganciclovir (AUC_{0-24}) by 30% at 900 mg. When valganciclovir is given with food, the resulting exposure to ganciclovir (AUC_{0-24}) is dose proportional over the dose range of 450 to 2625 mg (Study WP15347).

Figure 4 Dose Proportionality of Ganciclovir AUC_{0-24} Following Administration of Valganciclovir (WP15347)



6.2.2 Distribution

The volume of distribution at steady state (V_{ss}) of valganciclovir has not been determined. The volume of distribution following intravenous administration of ganciclovir is 0.680 ± 0.161 L/kg (n=114). Estimates of the V_{ss} of ganciclovir appear independent of the patient population and are consistent with distribution of ganciclovir in total body water.

6.2.3 Metabolism

Valganciclovir given orally undergoes rapid and extensive conversion to ganciclovir. Systemic exposure to valganciclovir is low at all doses with an AUC ratio of valganciclovir to ganciclovir of 0.009 ± 0.005 (n=319) and a C_{max} ratio of 0.031 ± 0.015 (n=320). *In vitro* studies using human and animal (dog and mouse) intestinal and hepatic S9 fractions show that valganciclovir is metabolized to ganciclovir and no other metabolites can be identified. Hydrolysis in human blood could not be detected over a 1 hour incubation period. Extracellular ganciclovir is not metabolized in humans and is excreted essentially unchanged in the urine.

6.2.4 Elimination

Valganciclovir is eliminated rapidly by metabolism to ganciclovir. Post peak plasma concentrations of valganciclovir decline with a half-life of 0.4 to 2.0 h, and in subjects with normal renal function the post-peak plasma concentrations of ganciclovir following administration of valganciclovir decline with a half-life of 3.5 to 4.5 hours.

Estimates of renal clearance were obtained in study WP15511 following administration of i.v. ganciclovir and oral valganciclovir in both healthy subjects and HIV+/CMV+ subjects. The mean renal clearance was comparable across the two subject groups and across treatments. When renal clearance was expressed as a ratio of the systemic clearance in the two groups, it accounted for 85-90% of the systemic clearance.

6.2.5 Bioavailability

The absolute bioavailability of ganciclovir from orally dosed valganciclovir is approximately 60%, and is much greater (approximately 10-fold) than that seen with the existing ganciclovir capsule formulation. The bioavailability of ganciclovir from valganciclovir appears to be independent of the patient population studied (Appendix 5).

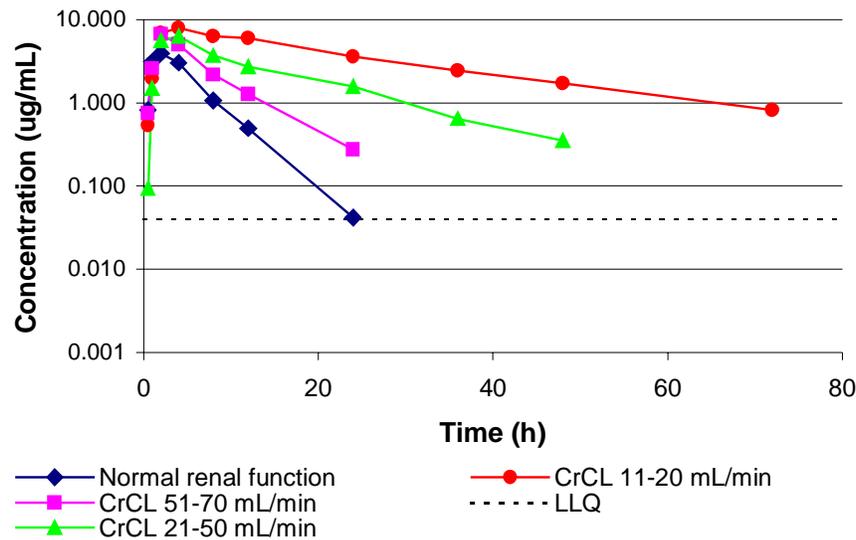
6.2.6 Renal Impairment

The effect of renal impairment on the pharmacokinetics of ganciclovir and valganciclovir following valganciclovir dosing was examined in study WP15511. The study was conducted in 44 subjects separated into groups with varying degrees of renal impairment: creatinine clearance of ≥ 70 , 51-70, 21-50, 11-20, and ≤ 10 mL/min (the latter group requiring dialysis treatment ≤ 3 times per week).

Decreasing renal function as assessed by creatinine clearance, resulted in decreased renal and apparent clearance of ganciclovir administered as valganciclovir, and corresponding increases in terminal half-life and AUC. C_{max} values were also increased to a lesser

extent. The effect of renal impairment on mean ganciclovir pharmacokinetic parameters is illustrated in Figure 5 and summarized in Appendix 6.

Figure 5 Mean Ganciclovir Plasma Concentrations Following Single Oral Doses of 900 mg Valganciclovir in Subjects With Increasing Renal Impairment (WP15511)



The study showed that renal impairment has no clinically relevant effect on exposure to valganciclovir. Based on the almost linear relationship between CrCL and apparent clearance of ganciclovir, dose reduction algorithms were derived for the use of valganciclovir as induction and maintenance treatment in renally impaired patients. For patients receiving hemodialysis, it was not possible to arrive at a suitable dose reduction algorithm using a unit dose of 450 mg. It is recommended that these patients receive i.v. ganciclovir in accordance with the dose reduction algorithm cited in the approved product label.

6.2.7 Children and The Elderly

No studies using valganciclovir have been conducted in children or in adults over the age of 65 years.

6.2.8 Pharmacokinetics in Valganciclovir Therapeutic Study WV15376

Study WV15376 compared the pharmacokinetics of valganciclovir in a randomized, controlled comparison study of the efficacy and safety of valganciclovir versus i.v. ganciclovir as induction therapy for the treatment of patients with newly diagnosed CMV retinitis. Steady state pharmacokinetic profiles were obtained at week 1 (induction level dosing) and week 4 (maintenance dosing) in a subset of patients in both groups.

Plasma concentrations for ganciclovir obtained after administration of i.v. ganciclovir and oral valganciclovir are presented in Figure 6. The main pharmacokinetic parameters for ganciclovir are summarized in Table 2.

Figure 6 Mean Ganciclovir Concentrations Following i.v. Ganciclovir (5 mg/kg b.i.d. Week 1; 5 mg/kg o.d. Week 4) or Oral Valganciclovir (900 mg b.i.d. Week 1; 900 mg o.d. Week 4) (WV15376)

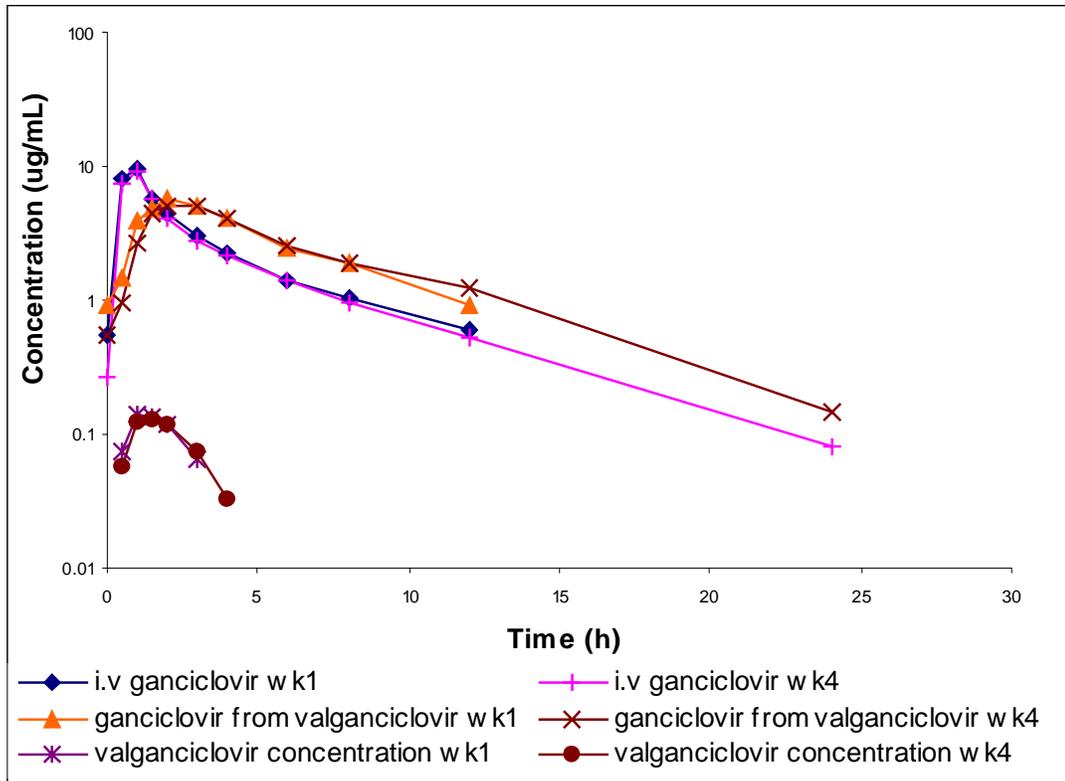


Table 2 Summary of Mean (CV%) Ganciclovir Pharmacokinetic Parameters Following Oral Valganciclovir and IV. Ganciclovir (WV15376)

	AUC* ($\mu\text{g}\cdot\text{h}/\text{mL}$)	C_{max} ($\mu\text{g}/\text{mL}$)	t_{max} (h)	$t_{1/2}$ (h)	k_{el} (h^{-1})	CL_r ($\text{mL}/\text{min}/\text{kg}$)
VGCV Week 1	32.8 (30.7) (n=25)	6.71 (31.6) (n=25)	2.31 (40.1) (n=24)	3.90 (28.4) (n=24)	0.190 (24.3) (n=24)	3.06 (37) (n=15)
VGCV Week 4	34.9 (38.1) (n=20)	5.87 (30.9) (n=21)	2.49 (39.5) (n=21)	4.12 (20.9) (n=20)	0.176 (23.5) (n=20)	2.71 (47) (n=14)
GCV Week 1	28.6 (31.6) (n=18)	10.4 (47.0) (n=18)	0.893 (28.9) (n=18)	3.99 (21.3) (n=18)	0.184 (27.2) (n=18)	1.96 (42) (n=14)
GCV Week 4	30.7 (25.0) (n=18)	9.86 (31.8) (n=18)	0.977 (21.9) (n=18)	4.32 (16.0) (n=18)	0.165 (16.6) (n=18)	2.18 (44) (n=16)

*AUC₀₋₁₂ for Week 1, AUC₀₋₂₄ for Week 4

Similar ganciclovir systemic exposures (AUC_{0-12} and AUC_{0-24}) were seen with each treatment group for both weeks. As expected, higher mean maximum concentrations were observed following dosing with i.v. ganciclovir compared to oral valganciclovir.

Systemic exposure of the prodrug (valganciclovir) compared to the metabolite (ganciclovir) was low. Mean values for the ratio of AUC and C_{max} of prodrug to metabolite were less than 1% and at 2% respectively, after adjusting for molecular weights.

6.2.9 Drug Interactions

As valganciclovir is rapidly converted to ganciclovir, the drug interactions applicable to ganciclovir will also be applicable to valganciclovir.

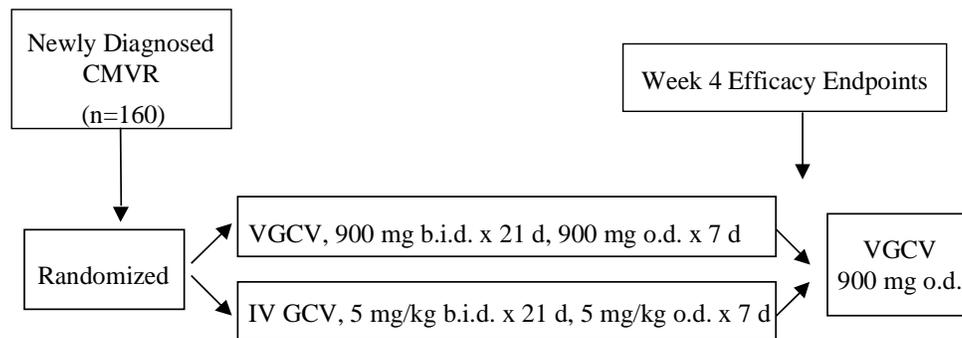
7. EFFICACY OF VALGANCICLOVIR – STUDY WV15376

7.1 Study Objectives and Design

The primary purpose of this study was to compare the efficacy of valganciclovir to i.v. ganciclovir for induction treatment of patients with AIDS and newly diagnosed CMV retinitis. The study enrolled male and female HIV seropositive patients, 13 years of age or older who had new, untreated CMV retinitis, diagnosed by an experienced ophthalmologist, and confirmed photographically. Further details of the study inclusion and exclusion criteria are provided in Appendix 7.

Additional objectives of this study were to investigate the safety profile of valganciclovir in this indication, to determine the antiviral effect of valganciclovir as measured by CMV culture and qualitative and quantitative CMV DNA PCR, and to assess the pharmacokinetics of ganciclovir following administration of valganciclovir in the target population. The schema for the study is shown in Figure 7.

Masked reading of bilateral, full-field fundus photographs was used to determine the response of retinitis to treatment. After completion of the first 4 weeks of randomized therapy, patients were able to receive valganciclovir maintenance therapy in an extension of the study designed to provide long term safety and uncontrolled efficacy information. During this extension phase, subjects with progression of CMV retinitis could receive multiple cycles of valganciclovir induction and maintenance therapy, according to best medical judgment.

Figure 7 Overall Design of Study WV15376

7.2 Ophthalmologic Evaluations and Fundus Photographs

In study WV15376, fundus photographs were taken at baseline (day 0), at week 2 and week 4, and then every two weeks through first progression of CMV retinitis or week 16, whichever occurred first. Photographs were then taken monthly until second progression of retinitis, unless an intravitreal implant or injection was provided, in which case fundus photography ceased. Photographs were sent to the Wisconsin Reading Center (WRC) for assessment by an experienced photograph grader, who remained masked to subject treatment assignment. Assessment by indirect ophthalmoscopy was also performed and recorded (unmasked), along with visual acuity and a patient questionnaire regarding subjective visual functioning.

Progression of retinitis was defined as any new lesions of CMV retinitis ($\geq \frac{1}{4}$ disk area in size), or advancement of the border of any pre-existing lesion by $\geq 750 \mu\text{m}$, along a front of $\geq 750 \mu\text{m}$ wide.

7.3 Virology Assessments

Blood samples for plasma CMV PCR analysis were collected at screening, weeks 1, 2, 3 and 4, then every two weeks until week 16, and then monthly until second progression or termination, whichever occurred first. Urine samples for CMV culture were collected at screening, weeks 4, 12, 24 and termination. Blood samples for CMV culture were taken at every visit until second progression of CMV retinitis and at termination. At one site only, semen samples for CMV culture were collected at screening, week 2 and week 4.

7.4 Pharmacokinetic Assessments

Pharmacokinetic evaluations were conducted in selected centers in study WV15376, consisting of 12 and 24 hour profiles at weeks 1 and 4.

7.5 Primary Efficacy Parameter

The primary efficacy parameter was the proportion of patients in study WV15376 with photograph defined progression of CMV retinitis between baseline and Week 4. Although patients received induction treatment for 3 weeks, assessment of induction efficacy was performed at week 4 (a delay or lag time of 1 week) to allow the clinical appearance of the retina to fully reflect the therapeutic effect.

7.6 Secondary Efficacy Parameters

7.6.1 Randomized Phase

Secondary efficacy parameters during the randomized phase of study WV15376 included the following:

- Proportion of patients achieving satisfactory induction therapy by week 4 and week 6. A satisfactory response to induction therapy was assessed on the basis of retinal photographs obtained at the week 4 and week 6 visits. Satisfactory response to induction therapy was considered to have been attained at week 4 / week 6 if there had been:
 - No movement of retinitis lesion borders by $\geq 1500 \mu\text{m}$ (along a front $\geq 750 \mu\text{m}$ wide) or appearance of a new area of retinitis ≥ 1 disc area in size between baseline and the week 4 / week 6 visit.
 - No movement of retinitis borders by $\geq 750 \mu\text{m}$ (along a front $\geq 750 \mu\text{m}$ wide) or appearance of a new area of retinitis $\geq 1/4$ disc area in size between week 2 and the week 4 / week 6 visits.
 - No increase in lesion activity between week 2 and week 4 / week 4 and week 6.
 - In comparison to baseline photographs, a decrease in retinitis lesion border activity of greater than or equal to two steps (where such a reduction was possible) on the Wisconsin Fundus Photo Reading Center 6-step grading scale by the week 4 / week 6 visit.
- Proportion of patients achieving satisfactory induction therapy by week 4 and week 6 who also achieved each of the following:
 - No retinitis lesion activity (atrophic or questionably active) at the week 4 / week 6 visit.
 - Less than 5% retinitis lesion border activity at the week 4 / week 6 visit.
 - A decrease in retinitis activity of ≥ 3 steps (where such a reduction was possible) on the Wisconsin Fundus Photo Reading Center 6-step grading scale between baseline and the week 4 / week 6 visit.
- Proportion of patients developing contralateral CMV retinitis by week 4 and week 6
- Ophthalmological assessments
- Comparison of ophthalmological assessments and photographic readings
- Patients' vision assessment
- Development of extraocular CMV disease
- Virological parameters. Analysis of plasma CMV PCR (both qualitative and quantitative) at screening and at weeks 1 to 4, analysis of CMV cultures at screening and week 4.

7.6.2 Extension Phase

Secondary efficacy parameters during the extension phase of study WV15376, when all patients received valganciclovir, included:

- Incidence and time to first progression of CMV retinitis at any time compared to baseline, calculated separately for the photographic and ophthalmological data.
- Incidence and time to second progression of CMV retinitis, calculated separately for the photographic and ophthalmological data.
- Incidence and time to development of contralateral CMV retinitis, calculated separately for the photographic and ophthalmological data.
- Incidence of extraocular CMV disease.
- Incidence and time to deterioration in visual acuity.
- Change from baseline in patients' vision assessment.
- Incidence of positive and negative CMV cultures.
- Emergence of viral resistance to ganciclovir (genotypic)
- Patient weights and Karnofsky performance scores.

7.6.3 Exploratory Subgroup Analyses

In an attempt to examine the possible effects of previous and concomitant antiretroviral therapy, and of immune reconstitution on study endpoints, a number of exploratory analyses of the primary efficacy endpoint were performed for specific patient subgroups. These subgroups were based on protease inhibitor use and CD4 count at baseline, and between baseline and week 4, and degree of CMV retinitis lesion activity at baseline.

7.7 Efficacy Data Analysis in Study WV15376

7.7.1 Statistical Model

A comparison between randomized treatment groups for both the primary and secondary parameters was performed.

The intent of the analysis was to test whether valganciclovir had a similar effect to (was no worse than) i.v. ganciclovir.

The primary efficacy measure, the proportion of patients who progressed photographically at week 4, was used to compare the two treatment groups. Using these two proportions, the difference between them (D_p) was calculated. D_p was the proportion of patients with Week 4 progression in the i.v. ganciclovir group minus the proportion in the valganciclovir group. If more i.v. ganciclovir patients progressed than valganciclovir patients, D_p would be positive, and if more valganciclovir patients progressed, D_p would be a negative number. A confidence interval could also be calculated for D_p .

As specified in the protocol, valganciclovir induction therapy was defined as an acceptable therapeutic option relative to i.v. ganciclovir, if the difference in proportions (i.v. ganciclovir minus valganciclovir) of patients progressing at Week 4 and its confidence interval was greater than delta (Δ), the non-inferiority margin.

The non-inferiority margin was chosen to be -0.25 and this represents the largest clinical difference that is considered acceptable by the sponsor.

If the resultant difference in proportions (D_p) and its 95% confidence interval lie entirely to the right of -0.25 , a conclusion that valganciclovir is no worse than i.v. ganciclovir can be drawn.

7.8 Measures and Endpoints in Study WV15376

Trials of CMV retinitis have traditionally used “time to” methods of survival analysis to calculate the time from the start of study treatment to the first progression of CMV retinitis for a group of patients. This usually includes the maintenance phase of treatment, which is of variable length because patients progress at different times. However in study WV15376 the sponsor chose a primary endpoint which was measured at the end of the randomized treatment phase and at a common time point for all patients (Week 4). A group of expert ophthalmologists and clinical trial specialists was convened to define an endpoint for this ‘induction study’, and to provide a definition of ‘satisfactory induction’ to be utilized as a secondary endpoint. This panel agreed on the definitions of progression and satisfactory induction used in WV15376. These definitions were subsequently endorsed as clinically relevant by investigators working on the study.

The most important secondary endpoint in study WV15376 was the proportion of patients with *satisfactory response* to induction treatment at Week 4. (Briefly, satisfactory induction was defined as no progression, no increase in lesion activity, and a reduction in retinitis border activity). This was a quantitative derivation of a more subjective endpoint originated from early studies of treatment of CMV retinitis which used observed healing and clearing of the retinal lesions as a measure of response.

Time from start of treatment to progression of CMV retinitis was also measured in study WV15376. However, the interpretation of the data must take into account the absence of a comparison treatment for the maintenance phase of the study, as patients receiving i.v. ganciclovir during the first 4 weeks crossed over to valganciclovir maintenance treatment after Week 4.

7.9 Sample Size Considerations

The sample size for study WV15376 was based partly upon the number of patients that could be enrolled over a practical time period (~2 years), and the need for progression proportion estimates with standard errors that were not inappropriately large. This was estimated to be 75 patients per arm. It was also estimated from prior ganciclovir studies that the proportion demonstrating progression at Week 4 would be about 0.20 (20% of patients).

The protocol defined the non-inferiority margin as follows: valganciclovir was to be considered to be clinically effective relative to i.v. ganciclovir if, on comparison, the lower bound of the confidence interval for D_p was above -0.25. This lower bound is larger than usually seen in these types of trials. However, based on a previous study of i.v. ganciclovir compared to delayed treatment (GAN1697), in which untreated patients had a 4 week progression rate of 86% compared to 23% with i.v. ganciclovir, this choice did not seem unreasonable. Table 3 shows the results of GAN1697 when the data are expressed as the photographic progression proportions at 28 days.

Table 3 Progression Data from Ganciclovir Study GAN1697

Treatment	Progressions by day 28 / no. on arm	Proportion Progressed by day 28	95% CIs*
I.V. ganciclovir	3/13	0.23	(0.05, 0.54)
Delayed treatment	19/22	0.86	(0.65, 0.97)
I.V. ganciclovir minus delayed treatment	-	-0.63	(-0.87, -0.30)

* Confidence intervals calculated using exact methods.

7.10 Active Control Considerations

An inherent critical question in active control trials is whether the trial is capable of distinguishing active from inactive treatments.

In the absence of a placebo arm (or delayed treatment arm in the context of CMV retinitis trials), the efficacy of the active control (i.v. ganciclovir) relies on implicit historical evidence and the assumption that this efficacy has not changed. Comparative trials of i.v. ganciclovir (the active control) have consistently distinguished active from inactive therapy in similar patient populations and under similar conditions of use. Intravenous ganciclovir is widely used for treatment of CMV retinitis. It has consistently demonstrated reduced progression rates in patients when compared to delayed treatment. As such, the sponsor believes that this study design is valid for this active control and disease setting.

7.11 Efficacy Results Study WV15376

7.11.1 Demographic Data, Baseline Disease Characteristics and Withdrawals

7.11.1.1 Demographics

Demographic data for the 160 patients enrolled into study WV15376 are presented in Appendix 8. The two treatment arms in WV15376 were comparable with respect to their overall baseline demographics. The majority of patients in the study were males (91%), with a mean age of approximately 39 years, a mean Karnofsky performance score of greater than 80, a mean creatinine clearance (CrCL) rate of approximately 120 mL/min, and a mean CD4+ T-cell count at screening of approximately 56 cells/ μ L (median 22 cells/ μ L).

7.11.1.2 Baseline Disease Characteristics

Based on the analysis of fundus photographic data, no substantial differences were noted between the two treatment groups in WV15376 with respect to CMV retinitis disease status at baseline. Of the 160 patients (80 in each treatment group) in the ITT population, 20 patients (25%) in each treatment group had bilateral CMV retinitis. The majority of patients in both arms had zone 2/3 as the most posterior zone affected by retinitis at baseline. Nineteen patients (24%) in each arm had retinitis in zone 1. The majority of patients had at least 90% retinitis lesion border activity at baseline. A similar proportion of patients on each treatment arm were receiving protease inhibitor therapy at baseline. There was an imbalance between the groups with respect to CMV culture and plasma CMV PCR positivity at screening; a higher proportion of patients in the ganciclovir arm were CMV culture and CMV PCR positive compared with the valganciclovir arm.

The ophthalmologist's fundoscopic assessments showed balance similar to the photographic assessments.

Table 4 Summary of Baseline Disease Characteristics in Study WV15376

Parameter	GCV/VGCV (n = 80)	VGCV/VGCV (n = 80)
No. with zone 1 retinitis	19 (24%)	19 (24%)
No. with bilateral retinitis	20 (25%)	20 (25%)
Lesion border activity:		
≥ 90% active	57 (71%)	50 (63%)
≥ 50% active < 90%	8 (10%)	9 (11%)
≥ 10% active < 50%	5 (6%)	7 (9%)
< 10% active	1 (1%)	2 (3%)
Questionably active	2 (3%)	1 (1%)
Atrophic	2 (3%)	2 (3%)
Cannot grade/Unevaluable	5 (6%)	9 (11%)
PI use duration:		
> 1 year	25 (31%)	23 (29%)
3 to 12 months	18 (23%)	17 (21%)
0 to 3 months	16 (20%)	14 (18%)
not on PI at entry	33 (41%)	27 (34%)
CD4 mean/median (cells/μL)	54 / 26	58 / 20
HIV viral load mean/median (log ₁₀)	4.5 / 4.9	4.5 / 4.8
CMV viral load mean/median (log ₁₀)	3.5 / 3.4	3.6 / 3.6
CMV positive culture	65% (46/71)	46% (33/71)
Positive plasma CMV PCR	51% (39/80)	40% (31/80)

7.11.1.3 Withdrawals From Study

A total of 93 patients terminated the study prior to the clinical cut-off date of 30 September 1999; 46 patients on the ganciclovir arm (58%) and 47 patients on the

valganciclovir arm (59%). Thirty percent of the ganciclovir withdrawals, and 23% of the valganciclovir withdrawals were for reasons of safety. A total of six patients, 3 per treatment arm withdrew during the randomized phase of the study. In the ganciclovir group, the 3 patient withdrawals occurred as a result of a patient death (due to lymphoma), an adverse event (neutropenia) and one patient refused treatment. In the valganciclovir group, one patient died during the randomized phase (death due to cardio-respiratory arrest, secondary to *Pneumocystis carinii* pneumonia), one patient refused treatment, and one patient failed to return after his baseline visit.

A higher number of withdrawals occurred on the valganciclovir arm between weeks 4 and 12 (14 withdrawals compared with 4 on the ganciclovir arm), with no obvious explanation for this difference. More patients on the valganciclovir arm withdrew during this time period due to adverse events/intercurrent illness (5 valganciclovir patients; 1 ganciclovir patient), refusing treatment/failure to return (4 valganciclovir patients; 1 ganciclovir patient), or insufficient therapeutic response (4 valganciclovir patients; 0 ganciclovir patients). There were also 3 withdrawals due to death between weeks 4 and 12 (1 valganciclovir patient; 2 ganciclovir patients). Three of the four patients who withdrew due to insufficient therapeutic response to therapy withdrew as a result of CMV retinitis progression diagnosed by the study ophthalmologist. This difference in withdrawal rates did not affect the primary efficacy outcome at week 4 (Section 7.11.2) since the number of withdrawals during the first 4 weeks were comparable for the two treatment arms, but it may have influenced time to progression estimates beyond week 4 (Section 7.11.4.2).

7.11.2 Primary Endpoint – Proportion of Patients With Progression of CMV Retinitis by Week 4, Photographic Assessment

The proportion of patients with first CMV retinitis progression by week 4 according to the photographic data is summarized for the predefined standard population in Table 5. The standard analysis population included all patients who were randomized **and** who received at least one dose of study medication **and** for whom efficacy data was recorded after randomization **and** who had no major protocol violations.

Based on the photographic analyses, there was no difference in the proportion of patients with CMV retinitis progression between the ganciclovir and valganciclovir treated patient groups. Ten percent of patients (7/70 evaluable patients for ganciclovir and 7/71 evaluable patients for valganciclovir) in each treatment group were assessed as having progression of CMV retinitis by week 4.

The difference in progression proportions (i.v. ganciclovir minus valganciclovir) was 0.001, with a 95% confidence interval of -0.097 to 0.100 (Table 5). As the lower boundary of the 95% confidence interval (-0.097) is well above the pre-specified equivalence value of -0.25, it can be concluded that the efficacy of valganciclovir is comparable to that of i.v. ganciclovir as induction treatment for newly diagnosed CMV retinitis.

The majority of patients in both arms (78% ganciclovir; 76% valganciclovir) had a reduction in CMV retinitis activity (on the WRC 6-grade scale) of 2 or more grades



between baseline and week 4. Five percent of ganciclovir patients, and 7% of valganciclovir patients, did not demonstrate a reduction in retinitis lesion activity.

Comparable results were also obtained for the ITT population. In this population, analysis of CMV retinitis progression by week 4 based on photographic assessment showed there was no difference in the number of patients with CMV retinitis progression between the ganciclovir and valganciclovir treated patient groups. Nine percent of patients (7/80) in each treatment group were assessed as having progression of CMV retinitis by week 4. The difference in progression proportions (i.v. ganciclovir minus valganciclovir) for the ITT population was 0.001, with a 95% confidence interval of -0.097 to 0.100.

Table 5 Analysis of CMV Retinitis Progression by Week 4 Based on Photographic Assessment (Standard Population)

Ro 107-9070 WV15376 FINAL DATA
Analysis of First CMV Retinitis Progression, based on Photographic Data - 95% Confidence Intervals
(Standard Population)

	GCV/VGCV N = 73	VGCV/VGCV N = 73
PROGRESSION OF RETINITIS BY WEEK 4 COMPARED TO BASELINE		
NON-PROGRESSOR	63 (86%)	64 (88%)
PROGRESSOR	7 (10%)	7 (10%)
UNEVALUABLE	3 (4%)	2 (3%)
TYPE OF PROGRESSION		
MOVEMENT	6 (8%)	7 (10%)
NEW SPOT	1 (1%)	
PRIMARY EFFICACY ANALYSIS		
PROGRESSION PROPORTION	0.100	0.099
NO PROGRESSION PROPORTION	0.900	0.901
DIFFERENCE IN PROGRESSION PROPORTIONS		0.001
95% CONFIDENCE INTERVAL		(-0.097, 0.100)

Unevaluable = 'Missing', 'Cannot Grade' or 'No CMV at Baseline'
Unevaluable patients are excluded from the calculations for the primary efficacy analysis

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\$PROD/cdp01269/i15376b/reports/progs95T21.s17
09FEB2000 13:54 Page 1 of 1

7.11.2.1 Exploratory Subgroup Analyses of Primary Endpoint

Exploratory subgroup analyses found no notable treatment group difference in the proportion of patients who progressed by week 4 according to use of HIV protease inhibitors (PI) at baseline, duration of PI use at baseline, or receipt of new PI therapy during the first 4 weeks of the study. In addition, the possible influence of HAART has been addressed by evaluating changes in three related parameters during the first 4 weeks of the study (analyses were based on the standard population):

- Antiretroviral medication use
- CD4 lymphocyte counts
- HIV viral load

The results are presented in Appendix 9. Overall, any impact of HAART during the randomized phase of the study is generally small, and does not influence the primary comparison of oral valganciclovir and i.v. ganciclovir induction therapy. The noted imbalance between groups in the proportion of patients with HIV load increases versus decreases does not favor the valganciclovir group.

7.11.3 Secondary Efficacy Parameters up to Week 4

7.11.3.1 Proportion of Patients With Progression of CMV Retinitis by Week 4 – Ophthalmological Assessment

In contrast to the masked assessment of fundus photographs, the unblinded examination performed by the study ophthalmologists identified a substantially higher proportion of patients in the valganciclovir arm (12 patients; 16%) with CMV retinitis progression by week 4 compared to the ganciclovir arm (1 patient; 1%). Given the more precise and unbiased nature of the retinal photographic assessment method, the unmasked results imply a degree of bias on the part of the study ophthalmologists in favor of i.v. ganciclovir therapy. This is not surprising given the fact that the ophthalmologist was aware of the patient's treatment assignment, and may well have been more conservative in the diagnosis of progression for patients receiving oral valganciclovir, an unproven therapy, than in their determination of progression for patients receiving i.v. ganciclovir, the standard induction therapy for CMV retinitis. This phenomenon has been consistently observed in randomized trials of CMV retinitis using the masked reading of fundus photographs.

7.11.3.2 Proportion of Patients Achieving a Satisfactory Response to Induction Therapy by Week 4, Photographic Assessment

A similar proportion of patients in each treatment group were considered to have achieved satisfactory induction by week 4 [47/61 (77%) in the ganciclovir group; 46/64 (72%) in the valganciclovir group] (Appendix 10). The most common reason for an unsatisfactory response to induction therapy was a failure to decrease lesion activity by two or more grades from baseline on the WRC 6-step grading scale [13/63 patients (21%) in the ganciclovir group; 17/65 patients (26%) in the valganciclovir group].

Of those patients in each treatment group who achieved a satisfactory response to induction therapy, 64% of patients in the ganciclovir group, and 70% patients in the valganciclovir group exhibited no retinitis lesion activity at week 4, $\leq 5\%$ retinitis lesion border activity, and a decrease of at least 3 steps on the WRC grading scale between baseline and week 4, suggesting that the retinitis had responded well to therapy and had become essentially inactive.

7.11.3.3 Change in Visual Acuity Between Baseline and Weeks 2, 4 and 6

The valganciclovir treatment group included more patients with impaired/severely impaired visual acuity at baseline. In both treatment groups, there were patients with improvement and patients with deterioration in visual acuity through week 6 (Appendix 11). There did appear to be a treatment difference early in the induction phase; by week 2, a higher proportion of patients in the valganciclovir group (12%)

experienced deterioration in visual acuity compared to the ganciclovir group (1%), which may reflect baseline differences between the two treatment groups. This treatment group difference had decreased by week 4, and diminished further by week 6 (proportion of patients with deterioration at week 6: 5% for ganciclovir arm and 10% for valganciclovir arm). The majority of patients in both treatment groups experienced either no deterioration or improvement in their visual acuity between baseline and week 6.

7.11.3.4 *Change in Vision Assessment Between Baseline and Weeks 2 and 4*

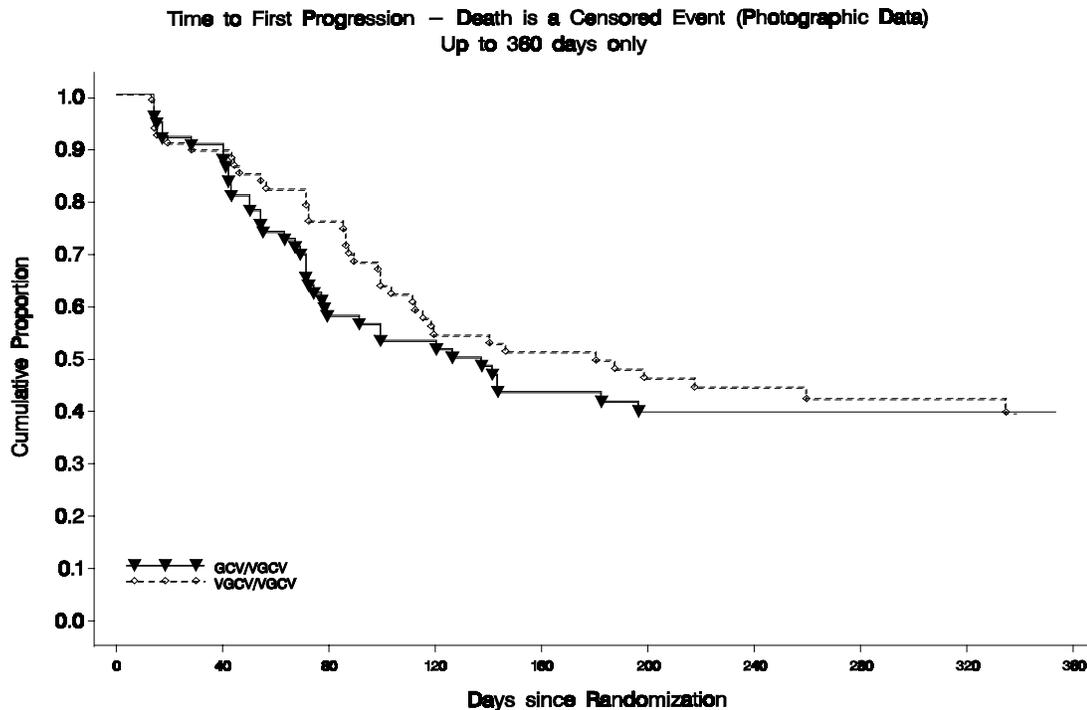
At baseline, the majority of patients in both treatment groups rated their general vision category as 'very good' or 'good' and reported having 'no trouble' or 'a little trouble' with their eyesight. Overall, no marked between-group differences were identified in the number of patients reporting either an improvement or a deterioration in their general vision between baseline and weeks 2 and 4.

7.11.4 Secondary Efficacy Parameters During Extension Phase

7.11.4.1 *Incidence and Time to First Progression of CMV Retinitis - Photographic Assessment*

The masked photographic assessment of retinitis progression demonstrated that 53% of patients originally randomized to i.v. ganciclovir (42/80), and 51% of patients originally randomized to valganciclovir (41/80), experienced progression by the date of clinical cut-off when death prior to photographic progression was censored at the date of the last photographic assessment. The mean (median) time to first progression was 219 (126) days on the ganciclovir arm, and 226 (180) days on the valganciclovir arm. Results of the Kaplan-Meier analyses of the time to first progression (up to a 360 day cut-off) are provided in Figure 8. It should be noted that the medians given above for time to progression in the i.v. ganciclovir randomized patients fell on a plateau portion of the Kaplan-Meier survival curve, and thus have to be considered imprecise. Using a linear interpolation method which allows for the apparent plateau in the survival curves, the estimated median time to progression was 125 days on the ganciclovir arm and 160 days on the valganciclovir arm.

Figure 8 Time To First Progression of CMV Retinitis up to Study Day 360 Where Death is a Censored Event, Based on Photographic Assessment (ITT Population)



Ro 107-9070 WY16796 FINAL DATA
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7.11.4.2 Incidence and Time to Progression or Withdrawal – Photographic Assessment

In an attempt to determine the influence on time to progression estimates of the greater proportion of withdrawals between weeks 4 and 12 observed for the valganciclovir patients (Section 7.11.1.3), an additional analysis calculated the mean/median time to progression (as detected by masked photographic assessment) or withdrawal from study. Seventy-four percent of patients originally randomized to i.v. ganciclovir (59/80) and 76% of patients originally randomized to valganciclovir (61/80) experienced either progression or withdrawal by the date of clinical cut-off when death prior to photographic progression was censored at the date of last photographic assessment. The mean (median) time to first progression or withdrawal was comparable for the two treatment groups: 192 (102) days on the ganciclovir arm and 184 (112) days on the valganciclovir arm. Results of the Kaplan-Meier analyses (up to a 360 day cut-off) are provided in Appendix 12.

7.11.4.3 Incidence and Time to First Progression of CMV Retinitis - Ophthalmological Assessment

Based on unmasked ophthalmological assessment, 36/80 patients (45%) in the ganciclovir group and 43/80 patients (54%) in the valganciclovir group experienced

progression of retinitis between baseline and clinical cut-off. The mean (median) time from randomization to first retinitis progression was 233 (337) days in the i.v. ganciclovir arm and 221 (196) days in the valganciclovir arm. Results of the Kaplan-Meier analyses of the time to first progression (up to a 360 day cut-off) are provided in Appendix 13. These results imply a degree of bias on the part of the study ophthalmologists in favor of i.v. ganciclovir therapy. This can be seen clearly when the Kaplan-Meier analyses for time to first progression by photography and ophthalmology are presented in the same graphic. There is good agreement between the times to progression as assessed by photographs and by ophthalmology for the valganciclovir group (Appendix 14), while the ophthalmologists generally diagnosed time to progression after photographic assessment for the ganciclovir group (Appendix 15).

7.11.4.4 Incidence and Time to Development of Contralateral CMV Retinitis – Photographic Assessment

By photographic assessment, a comparable proportion of patients in each treatment group with unilateral CMV retinitis at baseline went on to develop contralateral CMV retinitis during the study [6/54 (11%) in the ganciclovir arm; 6/52 (12%) in the valganciclovir arm]. Due to the low numbers recording development of contralateral CMV retinitis, a median time to occurrence of this event could not be calculated for either treatment group.

7.11.4.5 Incidence of Extraocular CMV Disease Between Baseline and Clinical Cut-Off

Only one patient was diagnosed with new extraocular CMV disease between baseline and clinical cut-off. This patient, who had originally been randomized to valganciclovir, developed CMV esophagitis on study day 240.

7.11.4.6 Incidence and Time to Deterioration in Visual Acuity Between Baseline and Clinical Cut-Off

A total of 21/80 (26%) patients in the ganciclovir arm and 25/80 (31%) patients in the valganciclovir arm experienced a deterioration in visual acuity by at least one category [with the categories defined as normal (up to and including 20/40), impaired (20/50 to 20/120), and severely impaired (20/200 and beyond)] between baseline and clinical cut-off. Ten patients (13%) in the ganciclovir arm, and 12 patients (15%) in the valganciclovir arm, exhibited a deterioration in visual acuity by 1 category. Eleven patients (14%) in the ganciclovir arm, and 13 patients (16%) in the valganciclovir arm, exhibited a 2-category deterioration in visual acuity. Kaplan-Meier analyses revealed that patients originally randomized to valganciclovir experienced a slightly faster time to deterioration in visual acuity by at least one category than their counterparts originally randomized to i.v. ganciclovir.

7.11.5 Virology Results

At screening, 65% of patients randomized to ganciclovir, and 46% of patients randomized to valganciclovir, were culture positive for CMV in either blood, urine or semen (predominantly urine). After 4 weeks of randomized therapy, the proportion of



CMV culture positive patients had decreased to 6% in the ganciclovir treatment group, and 7% in the valganciclovir group (Table 6). According to qualitative CMV PCR, 51% patients in the ganciclovir arm, and 40% patients in the valganciclovir arm, had CMV viremia by plasma assay at screening, but by week 4, this had reduced to 3% patients in the ganciclovir arm, and 4% in the valganciclovir arm (Table 7). Among those patients positive by qualitative assay, the median CMV viral load decreased in the ganciclovir arm from 3.4 log/mL at screening to 2.6 log/mL at week 4, and decreased in the valganciclovir arm from 3.6 log/mL at screening to 2.6 log/mL at week 4 (Appendix 16). After week 4, qualitative PCR detected only a few CMV positive patients (a maximum of 4 per arm) at any one visit.

Table 6 Overall Status of CMV Cultures at Baseline and Week 4 (ITT Population)

bcmvciT02/cmvc4iT02 Ro 107-9070 WV15376 FINAL DATA			
Summary of Urine, Blood and Semen CMV Cultures at Baseline and Week 4 (ITT Population)			
	GCV/VGCV N = 80		VGCV/VGCV N = 80
BASELINE: URINE, SEMEN OR BLOOD CMV CULTURE			
POSITIVE	46 (65%)		33 (46%)
NEGATIVE	25 (35%)		38 (54%)
NOT KNOWN	9		9
WEEK 4: URINE, SEMEN OR BLOOD CMV CULTURE			
POSITIVE	4 (6%)		4 (7%)
NEGATIVE	60 (94%)		54 (93%)
NOT KNOWN	16		22

A patient is recorded as positive if they return a positive result for at least one of the tests for Urine, Blood or Semen. If no positive tests occur then they are similarly recorded as negative if they have at least one negative test result for Urine, Blood or Semen. Percentages are calculated using the total number of negative and positive results for the treatment group & visit.

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\$PROD/cdp01269/i15376b/reports/bcmvciT02.pdrd/cmvc4iT02.pdrd
17APR2000 7:14 Page 1 of 1

Table 7 Summary of Qualitative PCR Data Obtained with the CMV AMPLICOR® Test (ITT Population)

Summary of Qualitative Plasma Results (RMS) for CMV Viral Load (ITT Population)

Study Visit	GCV/VGCV	GCV/VGCV	GCV/VGCV	VGCV/VGCV	VGCV/VGCV	VGCV/VGCV
	Pos N = 80	Neg N = 80	Not Done N = 80	Pos N = 80	Neg N = 80	Not Done N = 80
Screening	39 (51%)	37 (49%)	4	31 (40%)	46 (60%)	3
Week 1	21 (31%)	47 (69%)	12	18 (24%)	57 (76%)	5
Week 2	11 (16%)	57 (84%)	12	11 (16%)	57 (84%)	12
Week 3	6 (9%)	63 (91%)	11	6 (9%)	60 (91%)	14
Week 4	2 (3%)	68 (97%)	10	3 (4%)	68 (96%)	9

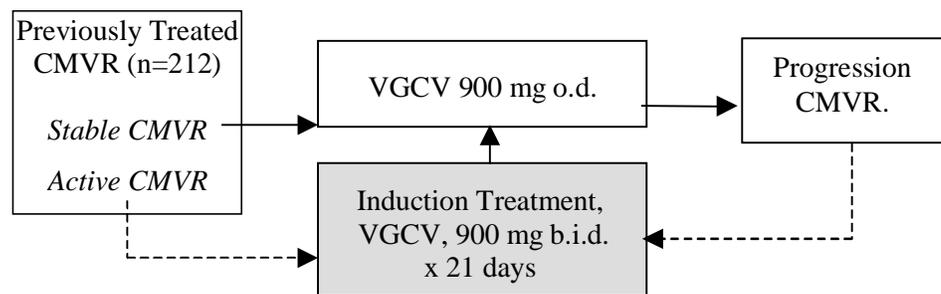
Note: Percentages are calculated by dividing by the total number of Pos and Neg results for the visit. Program : /plasma.sas / Output : \$PROD/cdp01269/i15376b/reports/plasmaT01.pdrd

8. EFFICACY OF VALGANCICLOVIR – STUDY WV15705

8.1 Study Objectives and Design

This is an open-label, non-comparative study, to evaluate the safety and tolerability of valganciclovir when given as treatment for previously treated CMV retinitis. The study also includes the collection of uncontrolled efficacy data, comprising ophthalmology assessments and measures of vision, but retinal photographs were not taken. Patients with progression of CMV retinitis could receive multiple cycles of induction and maintenance therapy, according to best medical judgment. The overall design of study WV15705 is represented schematically in Figure 9.

Figure 9 Overall Design of Study WV15705



8.2 Efficacy Parameters

Study WV15705 provides the following supportive efficacy data, derived by unblinded ophthalmological assessment:

- Incidence and time to first progression of CMV retinitis.
- Incidence and time to second progression of CMV retinitis.
- Incidence and time to development of contralateral CMV retinitis (in those patients with unilateral CMV retinitis at baseline).
- Incidence and time to extraocular CMV disease.
- Incidence and time to deterioration in visual acuity.

As in study WV15376, progression of retinitis was defined as any new lesions of CMV retinitis ($\geq \frac{1}{4}$ disk area in size), or advancement of the border of any pre-existing lesion by $\geq 750 \mu\text{m}$, along a front of $\geq 750 \mu\text{m}$ wide.

8.3 Efficacy Data Analysis in Study WV15705

Due to the single arm, exploratory nature of the study, no statistical tests were planned and no hypothesis testing was undertaken. All analyses performed were of a descriptive nature.

8.4 Efficacy Results Study WV15705

8.4.1 Demography Data And Baseline Disease Characteristics

The overall demographics were similar to study WV15376 for the 212 patients enrolled into study WV15705 (Appendix 17), with the majority of patients being male (91%), with a mean age of 41 years, a mean Karnofsky score of 89, and a mean creatinine clearance (CrCL) rate of 108 mL/min. The only notable demographic differences between the two studies were in race and CD4+ T-cell count, with study WV15376 having a higher proportion of Caucasian patients, and with patients in WV15705 having a higher CD4+ T-cell count at study entry (mean 171 cells/ μ L) than their counterparts in WV15376 (mean 56 cells/ μ L).

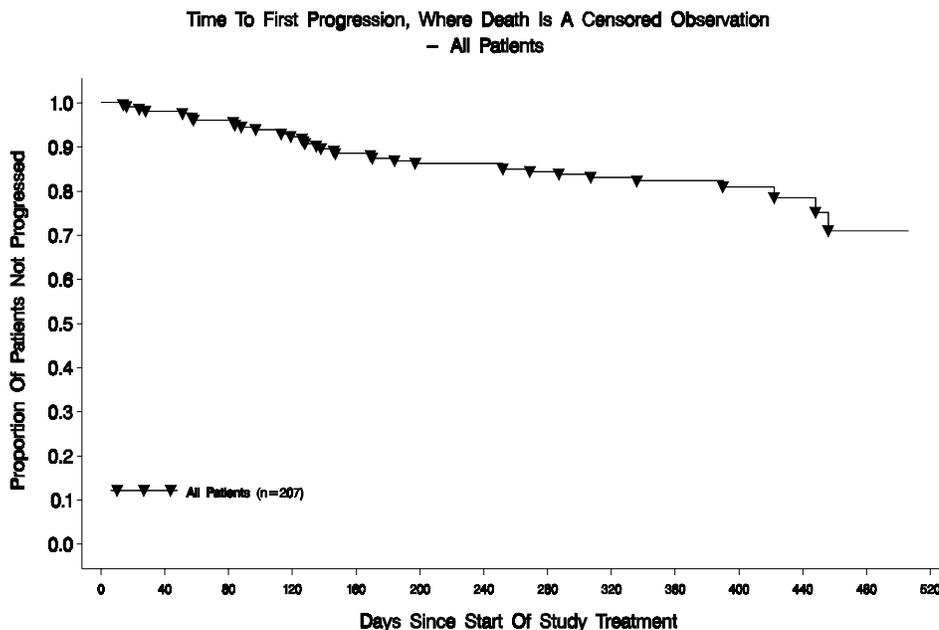
As expected, a higher proportion of patients in WV15705 had bilateral CMV retinitis and zone 1 involvement at study entry compared with patients in WV15376. Funduscopy assessment indicated that of the 212 patients in WV15705, 53% had unilateral, and 43% had bilateral retinitis at screening. Thirty-five per cent of patients had CMV retinitis involving zone 1 in at least one eye. In contrast to WV15376, only 15 patients (7%) had active lesion borders at screening. Thirty-eight patients (18%) had a ganciclovir intraocular implant in at least one eye at screening, and 31 patients (15%) had a history of extraocular CMV disease, including CMV esophagitis, gastroenteritis, colitis and pneumonia.

8.4.2 Efficacy Results Summary

WV15705 was primarily designed as a safety study, to assess the safety and tolerability of long-term exposure to valganciclovir. However, uncontrolled, supportive efficacy data was also collected.

Based on funduscopy by the evaluating ophthalmologist, 36 of the 212 patients (17%) experienced CMV retinitis progression during the study period. The time at which an estimated 25% of patients had progressed (first quartile; Kaplan-Meier estimate) was 456 days (15 months). Of the 113 patients with unilateral retinitis at study entry, 7 patients (6%) developed contralateral CMV retinitis. Thirty-six of the 212 patients (17%) showed deterioration in visual acuity from study entry by one category (normal, impaired or severely impaired) at two consecutive visits, or at their last visit. Fourteen patients (7%) experienced deterioration by two categories. A median time to deterioration could not be calculated due to the low number of events. According to the patient subjective vision assessment, there was no apparent difference in vision at study entry and at the last visit prior to clinical cut-off. Five patients (2%) developed extraocular CMV disease during the course of the study.

Figure 10 Time to First Progression of CMV Retinitis, Where Death is a Censored Event (All Patients) – WV15705



Deaths prior to progression have been censored
Unevaluable patients have been excluded from the graph

Ro 107-9070 WV15705 Clinical Out-01 : 26th September 1999
Treatment : Valganciclovir
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9. ASSESSMENT OF SAFETY IN VALGANCICLOVIR CLINICAL STUDIES

The safety of valganciclovir was assessed in three ways. First, safety outcomes were compared in the two randomized treatment arms of study WV15376 during the first 4 weeks of treatment. Second, all safety data from the two valganciclovir therapeutic studies WV15376 and WV15705 were pooled (including data from the first 4 weeks in study WV15376) to provide the overall safety profile of valganciclovir in the target population. Third, longer term safety was evaluated during maintenance level dosing of valganciclovir in both studies. The valganciclovir maintenance safety data were compared to the maintenance safety data gathered from prior clinical studies of i.v. and oral ganciclovir. An overview of the studies included in the safety assessment is provided in Figure 11. The previous ganciclovir studies are further described in Table 8.



Figure 11 Overview of Clinical Studies Discussed in the Integrated Safety Summary for Valganciclovir (n = Number Enrolled)

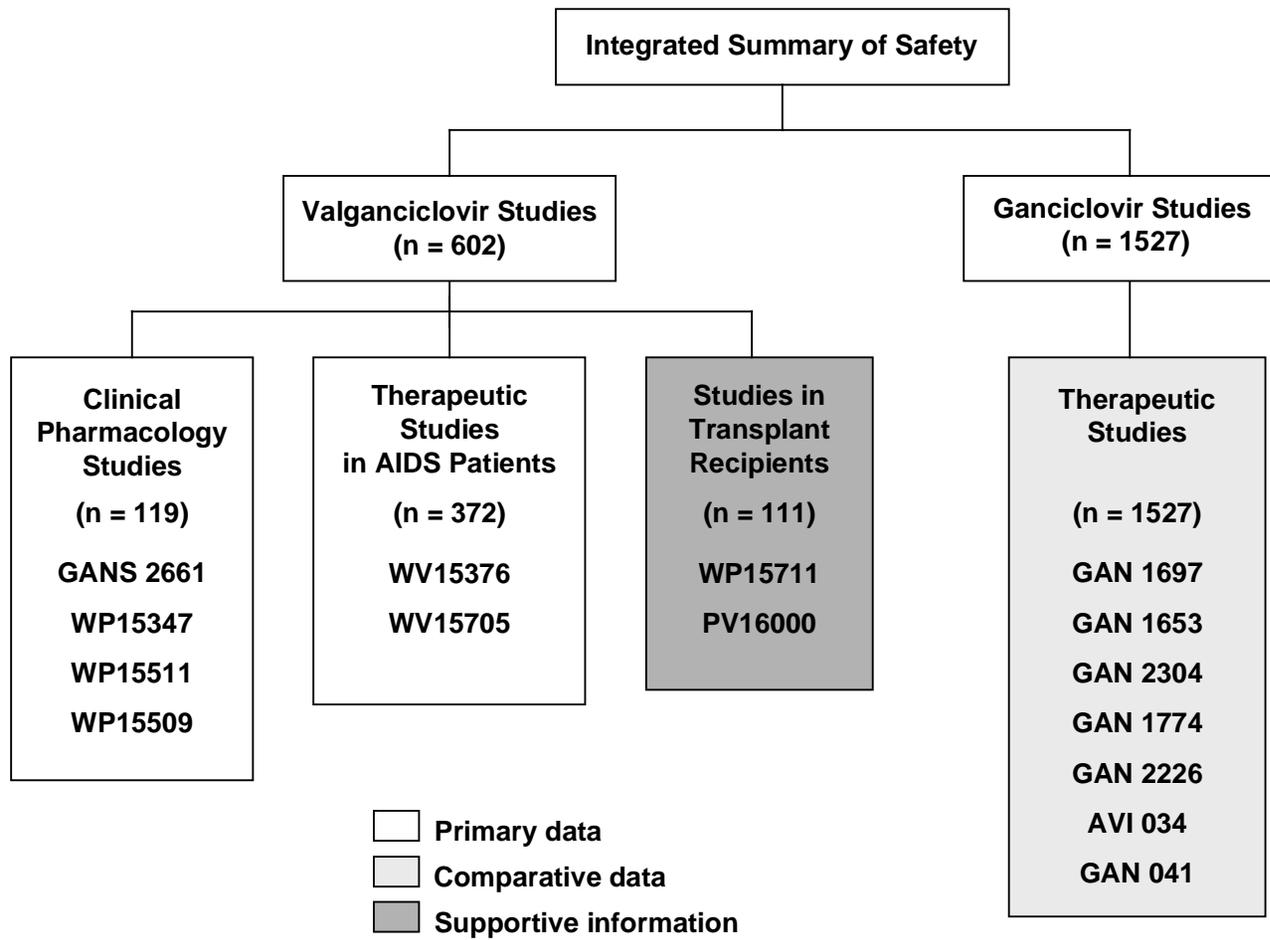


Table 8 Description of Ganciclovir Therapeutic Studies Used in the Comparison of the Known Safety Profile of Ganciclovir with the Safety Profile of Valganciclovir

Protocol	Description
Ganciclovir Therapeutic Studies for Comparison	
GAN 1697	A randomized, controlled study of intravenous ganciclovir therapy for peripheral CMV retinitis in patients with AIDS (ACTG 071) Study conduct: February 1989 – December 1990
GAN 1653	A randomized, controlled study of the efficacy and safety of maintenance treatment with oral ganciclovir for newly diagnosed CMV retinitis in people with AIDS Study conduct: March 1991 – November 1992
AVI 034	A multicenter randomized, controlled study of the efficacy and safety of maintenance treatment with intravenous and oral ganciclovir in the prevention of recurrence of CMV retinitis in AIDS patients Study conduct: June 1991 – February 1993
GAN 1774	A randomized study comparing the safety and efficacy of two regimens of oral ganciclovir to intravenous ganciclovir maintenance therapy for CMV retinitis in people with AIDS who have received prior ganciclovir therapy Study conduct: June 1991 – August 1993
GAN 041	A multicenter, randomized, double-blind study of the efficacy and safety of maintenance treatment with oral ganciclovir (3g versus 6g a day) for CMV retinitis in AIDS patients Study conduct: December 1993 – July 1995
GAN 2226	A randomized study comparing the safety and efficacy of three doses of oral ganciclovir to intravenous ganciclovir for the maintenance treatment of CMV retinitis in people with AIDS Study conduct: February 1994 – October 1995
GAN 2304	A randomized, controlled study of the safety and preventive efficacy of oral ganciclovir when used in conjunction with an intravitreal ganciclovir implant in the treatment of CMV retinitis Study conduct: May 1994 – October 1997

9.1 Extent of Exposure to Trial Treatment

A total of 160 patients were recruited into study WV15376 over a 26 month enrollment period, with the first patient entering the study on 29 January 1997 and the last patient on 31 March 1999. Data from 32 months of study conduct, from enrollment of the first patient on 29 January 1997 to the clinical cut-off on 30 September 1999, are summarized. At the clinical cut-off, 70% patients in WV15376 had received more than 6 months trial treatment, and approximately 15% patients had received more than 18 months of treatment. The duration of exposure to trial treatment was greater for patients who were randomized to the ganciclovir arm [mean 346 days (median 310 days)] than for those randomized to the valganciclovir arm of the study [mean 278 days (median 245 days)].

The median time to withdrawal between study start and clinical cut-off was shorter on the valganciclovir arm of the study (376 days, versus 419 days on the i.v. ganciclovir arm), probably as a result of the higher number of withdrawals on the valganciclovir arm between weeks 4 and 12 (14 withdrawals compared with 4 on the ganciclovir arm) (Section 7.11.1.3).

A total of 212 patients were recruited into study WV15705 over a 7 month enrollment period; with the first patient entering the study on 29 April 1998 and the last patient on 24 November 1998. Data from 17 months of study conduct, from enrollment of the first patient in April 1998 to the clinical cut-off on 30 September 1999, are reported. At clinical cut-off, 81% patients in WV15705 had received at least 6 months treatment with valganciclovir. The average duration of treatment in WV15705 [mean 333 days (median 372 days)] was longer than in WV15376.

Exposure times in previous ganciclovir studies were in the range of 60 to 200 days (0.16-0.55 years per patient), considerably shorter than those in the valganciclovir trials (about 350 days; 0.88 years per patient).

9.2 Safety Results

9.2.1 Valganciclovir Clinical Pharmacology Studies

Valganciclovir was generally well tolerated and was not associated with any unexpected adverse events. The most frequently reported adverse events were headache and gastrointestinal disorders: diarrhea, nausea, dyspepsia, abdominal pain, flatulence. The majority of adverse events in all studies were considered to be either mild or moderate in intensity.

9.2.2 Adverse Events Reported During Valganciclovir and Ganciclovir Induction Treatment – Study WV15376

Table 9 presents the adverse events reported during the first 4 weeks of study WV15376 for valganciclovir compared to i.v. ganciclovir. Diarrhea and oral candidiasis was more common in the valganciclovir group, and nausea was more common in the i.v. ganciclovir group.

The most notable difference between the valganciclovir and i.v. ganciclovir treatment groups during induction treatment in study WV15376 was the greater incidence of i.v. catheter-related events reported by the i.v. ganciclovir patients. A total of 9 patients (11%) in the i.v. ganciclovir group compared to 2 patients (3%) in the valganciclovir group had one or more adverse events involving venous access. These events included injection site infection, inflammation, burning, edema of the injection site or line sepsis.



Table 9 All Adverse Events Reported During Induction Treatment, by Decreasing Frequency (Overall Incidence ≥ 2%)

Summary of Adverse Events With an Incidence Rate of at Least 2 % by Trial Treatment
 All Adverse Events
 Protocol(s): WV15376
 Analysis: SAFETY Center: ALL CENTERS
 SUMMARY OF ALL AEs BY FREQUENCY INDUCTION
 Adverse Event Onset between Study Day 1, Clock Time 00:00 and Study Day 9999, Clock Time 23:59

Adverse Event	VGCV		IV GCV	
	N = 79		N = 79	
	No.	(%)	No.	(%)
PYREXIA	10	(13)	9	(11)
DIARRHOEA NOS	13	(16)	8	(10)
NEUTROPENIA	9	(11)	10	(13)
HEADACHE NOS	7	(9)	4	(5)
FATIGUE	6	(8)	3	(4)
NAUSEA	6	(8)	11	(14)
ANAEMIA NOS	6	(8)	6	(8)
VOMITING NOS	6	(8)	8	(10)
COUGH	5	(6)	4	(5)
NIGHT SWEATS	2	(3)	-	
ABDOMINAL PAIN NOS	3	(4)	4	(5)
DERMATITIS NOS	4	(5)	6	(8)
ORAL CANDIDIASIS	9	(11)	5	(6)
APPETITE DECREASED	4	(5)	2	(3)
INSOMNIA	2	(3)	2	(3)
VITREOUS FLOATERS	2	(3)	3	(4)
DEPRESSION NOS	3	(4)	1	(1)
DYSPNOEA	2	(3)	-	
INJECTION SITE INFECTION	2	(3)	3	(4)
LEUCOPENIA NOS	1	(1)	4	(5)
VENOUS PHLEBITIS AND THROMBOPHLEBITIS NOS	-		5	(6)
CONSTIPATION	2	(3)	2	(3)
PERIPHERAL NEUROPATHY NOS	-		-	
VISION BLURRED	1	(1)	-	

Percentages are based on N. Percentages not calculated if N < 10.
 Multiple occurrences of the same adverse event in one individual counted only once.
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9.2.3 Laboratory Data Reported During Valganciclovir and Ganciclovir Induction Treatment – Study WV15376

Laboratory data obtained during induction treatment were largely comparable between the valganciclovir and i.v. ganciclovir induction groups in study WV15376 (Table 10). However, a higher incidence of anemia (hemoglobin < 8.0 g/dL) was apparent in patients originally randomized to valganciclovir as the study continued beyond week 4 (Section 9.2.5).

Table 10 Minimum ANC, Hemoglobin and Platelet Levels and Maximum Serum Creatinine Values During Induction Treatment

ae203a24, a25, a26, and a27 - Induction from WV15376

	VGCV N=79	IV GCV N=79
ANC (cells/ul)		
Unevaluable	1	
< 500	5 (6.4%)	5 (6.3%)
500 to < 750	12 (15.4%)	10 (12.7%)
750 to < 1000	13 (16.7%)	19 (24.1%)
>= 1000	48 (61.5%)	45 (57.0%)
Hemoglobin (g/dl)		
Unevaluable	1	
< 6.5		
6.5 to < 8.0	4 (5.1%)	2 (2.5%)
8.0 to < 9.5	8 (10.3%)	17 (21.5%)
>= 9.5	66 (84.6%)	60 (75.9%)
Platelets (cells/mm3)		
Unevaluable	1	1
< 25000		
25000 to < 50000	1 (1.3%)	
50000 to < 100000	4 (5.1%)	8 (10.3%)
>= 100000	73 (93.6%)	70 (89.7%)
Creatinine (mg/dl)		
Unevaluable	1	
<= 1.5	78 (100%)	76 (96.2%)
> 1.5 to 2.5		2 (2.5%)
> 2.5		1 (1.3%)

Note: percentages refer to number of patients exhibiting event out of number of patients for whom a parameter measurement was available and not total patient number

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9.2.4 Deaths, Serious Adverse Events and Premature Withdrawals due to Adverse Events Reported During Induction Treatment

Two deaths occurred during the randomized phase of study WV15376, one patient in the ganciclovir treatment group died as a result of lymphoma, and one patient in the valganciclovir group died as a result of cardio-respiratory arrest (secondary to *Pneumocystis carinii* pneumonia). Both deaths were considered unrelated to study drug.

A total of 42 serious adverse events were reported during the randomized phase of the study. Of these events, 29 were reported by 19 (24%) patients in the ganciclovir treatment group, and 13 were reported by 8 (10%) patients in the valganciclovir group. The most common serious adverse events were infections and infestations (experienced by 11 patients in the ganciclovir group, and 1 patient in the valganciclovir group), general disorders (6 patients in the ganciclovir group, and 3 in the valganciclovir group) and disorders of the blood and lymphatic system (3 patients in the ganciclovir group, and 1 in the valganciclovir group).

In the ganciclovir treatment group, there were 4 treatment-related serious adverse events: 1 due to sepsis (considered probably related), 2 due to neutropenia (both considered probably related), and 1 due to pancytopenia (considered possibly related). In the

valganciclovir treatment group, 8 serious adverse events occurred which were considered related to trial treatment. One of these events (neutropenia) was considered probably related to treatment with valganciclovir, whilst 4 were considered possibly related (hypoesthesia, pain in limb, hypoglycemia, and collapse), and 3 were considered remotely related (depression, hypotension, and bradycardia).

Only 1 patient withdrew from the study during the randomized phase as a result of an adverse event. The patient was randomized to i.v. ganciclovir and withdrawal was due to neutropenia, severe in intensity and possibly related to treatment with ganciclovir.

9.2.5 Laboratory Data Reported Between Baseline and Clinical Cut-off in Study WV15376

The minimum ANC, hemoglobin level and platelet count recorded in study WV15376 between baseline and clinical cut-off is summarized by randomized treatment group in Table 11. The distributions of minimum ANC and minimum platelet count were similar between the two randomized treatment arms, however, a higher proportion of patients originally randomized to valganciclovir had a minimum hemoglobin level of < 8.0 g/dL compared with patients originally randomized to i.v. ganciclovir.

A total of 36 (23%) patients experienced anemia (defined as a hemoglobin level of < 8.0 g/dL) during study WV15376. There were insufficient numbers of events to calculate a median time to first incidence of anemia, however, from a graphical presentation of the results (Appendix 18) it appears that the incidence of anemia was higher in the valganciclovir group during the long term extension phase. Risk assessment calculations for time to anemia show a higher risk of anemia (hemoglobin < 8.0 g/dL) amongst those patients originally randomized to valganciclovir, however there is considerable overlap in the confidence limits for the survival estimates for both treatment arms. If this does reflect a true difference, the explanation is unclear, as all patients received valganciclovir after week 4.



Table 11 Minimum ANC, Hemoglobin and Platelet Levels and Maximum Serum Creatinine Values Reported During Study WV15376

	ae03L24, L25, L26 and L27 Ro 107-9070		WV15376		FINAL DATA	
Laboratory Parameter Values During Treatment (Safety Population)						
	GCV/VGCV N=79		VGCV/VGCV N=79		All Patients N=158	
ANC (cells/uL)						
< 500	20	(25.3%)	18	(22.8%)	38	(24.1%)
500 to < 750	22	(27.8%)	16	(20.3%)	38	(24.1%)
750 to < 1000	15	(19.0%)	19	(24.1%)	34	(21.5%)
>= 1000	22	(27.8%)	26	(32.9%)	48	(30.4%)
Hemoglobin (g/dl)						
< 6.5	6	(7.6%)	10	(12.7%)	16	(10.1%)
6.5 to < 8.0	7	(8.9%)	13	(16.5%)	20	(12.7%)
8.0 to < 9.5	24	(30.4%)	13	(16.5%)	37	(23.4%)
>= 9.5	42	(53.2%)	43	(54.4%)	85	(53.8%)
Platelets (cells/uL)						
< 25000	4	(5.1%)	2	(2.5%)	6	(3.8%)
25000 to < 50000	4	(5.1%)	6	(7.6%)	10	(6.3%)
50000 to < 100000	21	(26.6%)	13	(16.5%)	34	(21.5%)
>= 100000	50	(63.3%)	58	(73.4%)	108	(68.4%)
Creatinine (mg/dL)						
<= 1.5	71	(89.9%)	74	(93.7%)	145	(91.8%)
> 1.5 to 2.5	6	(7.6%)	4	(5.1%)	10	(6.3%)
> 2.5	2	(2.5%)	1	(1.3%)	3	(1.9%)

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9.2.6 Adverse Events Reported During Valganciclovir Studies WV15376 and WV15705

This section summarizes the pooled adverse event and laboratory data from valganciclovir studies WV15376 and WV15705. The analysis includes all adverse event data from study start to the common clinical cut-off of 30 September 1999, and includes data from the initial four week randomized treatment period in study WV15376.

The most common adverse event was diarrhea, reported by 38% of patients during the studies (Table 12). Other frequent gastrointestinal events included nausea (25%), vomiting (20%) and abdominal pain (13%). The opportunistic infection, oral candidiasis, was reported in 20% of patients. Other common infections included sinusitis (10%) and nasopharyngitis (10%). Disorders of the blood and lymphatic system were also common with 24% and 22% of patients experiencing neutropenia and anemia, respectively. Frequently reported general disorders included pyrexia (26%) and fatigue (20%). The most common neurological disorders were headache (18%) and insomnia (14%). Dermatitis, cough and retinal detachment were reported in 18%, 16% and 13% of patients, respectively. The majority (2808/3381, 83%) of adverse events reported were considered by the investigator to be of mild or moderate intensity, and unrelated to study treatment (2888/3555; 81%).

Table 12 Adverse Events Reported During Valganciclovir Therapeutic Studies, by Decreasing Frequency (Incidence ≥ 10%)

Summary of Adverse Events With an Incidence Rate of at Least 10 % by Trial Treatment
 All Adverse Events
 Protocol(s): WV15376 WV15705
 Analysis: SAFETY Center: ALL CENTERS
 SUMMARY OF ALL AEs BY FREQUENCY (ALL)
 Adverse Event Onset between Study Day 1, Clock Time 00:00 and Study Day 9999, Clock Time 23:59

Adverse Event	VGCV	
	N =	(%)
DIARRHOEA NOS	139	(38)
PYREXIA	97	(26)
NAUSEA	92	(25)
NEUTROPENIA	89	(24)
ANAEMIA NOS	81	(22)
ORAL CANDIDIASIS	74	(20)
VOMITING NOS	74	(20)
FATIGUE	73	(20)
HEADACHE NOS	68	(18)
DERMATITIS NOS	66	(18)
COUGH	60	(16)
INSOMNIA	51	(14)
RETINAL DETACHMENT	49	(13)
ABDOMINAL PAIN NOS	48	(13)
SINUSITIS NOS	37	(10)
NASOPHARYNGITIS	36	(10)

Percentages are based on N. Percentages not calculated if N < 10.
 Multiple occurrences of the same adverse event in one individual counted only once.
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9.2.7 Laboratory Data Reported During Valganciclovir Studies WV15376 and WV15705

The most common marked laboratory shift (defined as a shift from ACTG Grade 0 to Grade 3 or 4, or from ACTG Grade 1 to Grade 4) that occurred during the valganciclovir therapeutic studies was a reduction in the absolute neutrophil count (ANC), experienced by a total of 81 patients (22%) (Table 13). Marked reductions in the level of hemoglobin were observed in 48 patients (13%), and of platelets in 20 patients (6%). Other marked shifts included elevations in the enzymes AST (SGOT) (15 patients), ALT (SGPT) (19 patients), GGT (25 patients) and alkaline phosphatase (6 patients).

Table 13 Marked Shifts From Baseline in Key Laboratory Parameters During Valganciclovir Therapeutic Studies in AIDS Patients

Laboratory Parameter		Valganciclovir 900 mg (n = 370)
Hemoglobin	Low	48 (13%)
Platelets	Low	20 (6%)
ANC	Low	81 (22%)
AST (SGOT)	High	15 (4%)
Alkaline Phosphatase	High	6 (2%)
ALT (SGPT)	High	19 (5%)
GGT	High	25 (7%)
BUN	High	0
Creatinine	High	1 (< 1%)

Note: percentages in table refer to number of patients exhibiting event out of the number of patients for whom a parameter measurement was available, and not total patient number.

The minimum absolute neutrophil count (ANC), minimum hemoglobin level, minimum platelet count and maximum serum creatinine level recorded for each patient during the valganciclovir therapeutic studies are summarized in Table 14.

Fifty percent of patients had a minimum ANC value no lower than 1000 cells/ μ L during the studies, with the remaining patients being equally divided between the ranges 750 to 1000 cells/ μ L, 500 to 750 cells/ μ L, and < 500 cells/ μ L. Overall, 16% of patients experienced Grade 4 neutropenia (ANC < 500 cells/ μ L).

A minimum hemoglobin value \geq 9.5 g/dL was recorded for 257 of the 370 patients (70%). Seventeen percent of patients had a hemoglobin value < 8.0 g/dL, and 25 patients (7%) experienced a Grade 4 hemoglobin level of < 6.5 g/dL.

For the majority of patients, the minimum platelet count was greater than 50,000 / μ L, and serum creatinine levels did not exceed 1.5 mg/dL.

Most patients who experienced clinically significant cytopenias during treatment with valganciclovir had recovery of cell counts following interruption of study drug. However, there were 5 patients with severe cytopenia involving one or more cell lines (4 in study WV15705 and 1 in study WV15376) who died without documented recovery of peripheral blood cell counts. In only one case did the investigator assess the death as related to study drug.

Table 14 Minimum ANC, Hemoglobin and Platelet Levels and Maximum Serum Creatinine Values During Valganciclovir Therapeutic Studies in AIDS Patients

Minimum ANC, Minimum Hemoglobin, Minimum Platelet
and Maximum Serum Creatinine Values During Treatment
- All from WV15376 & WV15705

	VGCV N=370
Minimum ANC (cells/ μ L)	
< 500	60 (16.2%)
500 to < 750	62 (16.8%)
750 to < 1000	63 (17.0%)
\geq 1000	185 (50.0%)
Minimum Hemoglobin (g/dL)	
< 6.5	25 (6.8%)
6.5 to < 8.0	37 (10.0%)
8.0 to < 9.5	51 (13.8%)
\geq 9.5	257 (69.5%)
Minimum Platelets (cells/ μ L)	
Unevaluable	1
< 25000	10 (2.7%)
25000 to < 50000	18 (4.9%)
50000 to < 100000	77 (20.9%)
\geq 100000	264 (71.5%)
Maximum Serum Creatinine (mg/dL)	
\leq 1.5	324 (87.6%)
> 1.5 to 2.5	40 (10.8%)
> 2.5	6 (1.6%)

Note: percentages refer to number of patients exhibiting event out of number of patients for whom a parameter measurement was available and not total patient number

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9.2.8 Deaths, Serious Adverse Events and Premature Withdrawals due to Adverse Events Reported During Valganciclovir Studies WV15376 and WV15705

Deaths reported for patients participating in the valganciclovir therapeutic studies in AIDS patients, or which came to the attention of the investigator within 30 days after each patient's cessation of study drug, up to the clinical cut-off of 30 September 1999, are summarized by cause of death in Appendix 19. One female patient developed fatal bone marrow depression (medullary aplasia) after dosing that was at least 10-fold greater than recommended for the patient's degree of renal impairment. The cause of death was severe thrombocytopenia and hemorrhage.

The most frequently reported serious adverse events were neutropenia, pyrexia and anemia (6% incidence), followed by *Pneumocystis carinii* pneumonia and non specified pneumonia (5%). The most common serious adverse events considered by the investigator to be related to study treatment were neutropenia (6%), anemia (5%) and pancytopenia (2%).

Forty patients (11%) withdrew prematurely from the valganciclovir studies due to clinical adverse events. The main adverse events leading to withdrawal were anemia,

neutropenia, leukopenia, thrombocytopenia and pancytopenia (15 patients, 4%), gastrointestinal disorders including: diarrhea, vomiting, nausea, abdominal pain and gastric hemorrhage (6 patients, 2%), and infections and infestations, notably pneumonia, PCP and HIV infection (7 patients, 2%).

9.2.9 Adverse Events Reported During Valganciclovir Maintenance Treatment, Comparison With Prior Ganciclovir Studies

In this section, the safety results reported in the two valganciclovir therapeutic trials are compared to safety results from prior ganciclovir studies of i.v. and oral ganciclovir maintenance treatment. It should be noted that the valganciclovir and ganciclovir studies were conducted several years apart, with differing patient populations, and different durations of treatment exposure. The comparisons below should be considered with these caveats in mind.

Appendix 20 compares pooled adverse event data reported during valganciclovir maintenance treatment (studies WV15376 and WV15705 combined) to pooled adverse event data reported during i.v. and oral ganciclovir maintenance treatment, and oral placebo plus ganciclovir implant data. All adverse event data from study WV15705 are pooled with maintenance adverse event data from WV15376 (excluding the first 4 weeks of adverse events reported in study WV15376).

The most frequently reported adverse events during maintenance treatment for all treatment groups, including placebo + implant, were pyrexia, diarrhea, neutropenia, nausea, fatigue, anemia, headache, cough and vomiting (Appendix 20). The adverse events reported more frequently in the combined valganciclovir maintenance treatment group relative to i.v. and oral ganciclovir were oral candidiasis, dermatitis, insomnia and retinal detachment. However, oral candidiasis and dermatitis were reported with a similar frequency in the oral ganciclovir 6 g and 4.5 g groups, respectively. Diarrhea was reported with a greater frequency in the valganciclovir patients compared to i.v. ganciclovir, but with a similar frequency to oral ganciclovir. Neutropenia was reported with similar frequency in the valganciclovir group compared to all ganciclovir groups. There were also no notable differences in the frequency of anemia among the valganciclovir and ganciclovir groups in this analysis. Pancytopenia (reported as an adverse event, not based upon laboratory data) was reported in 2% of valganciclovir treated patients and in 1 to 2% of those receiving ganciclovir.

9.2.10 Laboratory Data Reported During Valganciclovir Maintenance Treatment, Comparison With Prior Ganciclovir Studies

The proportion of patients with Grade 4 neutropenia (ANC < 500 cells/ μ L) or Grade 3/4 anemia (hemoglobin < 8.0 g/dL), based on minimum ANC and hemoglobin levels recorded during treatment, was similar for the valganciclovir and prior i.v. ganciclovir treatment groups (~20%). The proportion of patients exhibiting Grade 4 anemia (hemoglobin < 6.5 g/dL) was higher for the valganciclovir patients (7%) than in the oral and placebo groups from prior studies (1-3%) (Appendix 21).

9.2.11 Special Safety Considerations

No new toxicities or clinical observations were observed during treatment with valganciclovir that have not been observed during treatment with i.v. or oral ganciclovir. Valaciclovir, a valyl ester prodrug of aciclovir, when given at high doses to immunocompromised patients, has been associated with a serious clinical syndrome recognized as hemolytic uremic syndrome / thrombotic thrombocytopenia purpura (HUS/TTP), a complex pathology characterized by a consumptive coagulopathy. No signs or symptoms of HUS/TTP were observed in any patient during the valganciclovir therapeutic studies, although all investigators were alerted to observe carefully for this possible complication. HUS/TTP causes schistocytosis of circulating erythrocytes. Red blood cell morphology was assessed as part of the routine laboratory testing in both studies. Five patients each had a single report of schistocytosis, however all 5 patients had no other clinical manifestations of HUS/TTP at any time during the studies.

10. DATA FROM 4 MONTH SAFETY UPDATE

Safety information from the completed clinical pharmacology studies and the ongoing studies in AIDS patients, up to a clinical cut-off of 30 September 1999 were presented in the original NDA submission. The 4 month safety update provides an expanded summary of the safety of valganciclovir in AIDS patients (studies WV15376 and WV15705), up to a clinical cut-off of 30 April 2000.

There were no differences between the two cut-off dates, in terms of the types of adverse events reported. There were minor increases in the frequencies of the most common adverse events (Appendix 22), and laboratory abnormalities (neutropenia, anemia and thrombocytopenia)(Appendix 23), consistent with the extended safety reporting period in this patient population. The increase in the drug exposure, in terms of mean days of drug treatment, increased by approximately 34% (mean/median duration of exposure: 429 and 493 days, respectively), and the total number of adverse events increased by 23% between the two cut-off dates.

The overall safety profile of valganciclovir is consistent with that reported in the original NDA submission, and is similar to that reported for systemic ganciclovir. Continued usage of valganciclovir by this patient population did not lead to any major changes in either the type or the incidence of adverse events or laboratory abnormalities. There were no indications of any late or delayed toxicities that appeared with the additional dosing and follow-up. The conclusions derived from this patient population at the time of the original safety cut-off therefore remain valid at the update clinical cut-off date.

11. BENEFIT/RISK SUMMARY

Based upon masked assessment of retinal photographs, orally administered valganciclovir induction treatment of newly diagnosed CMV retinitis is associated with a progression rate which is the same as that of i.v. ganciclovir induction treatment. The 95% confidence interval for the difference in the proportion of patients with progression is: (-0.097, 0.100). In addition, oral valganciclovir induction treatment is comparable to i.v. ganciclovir in terms of achieving a satisfactory response to induction treatment (proportion of patients with satisfactory induction : 0.72 versus 0.77, respectively).

Patients with newly diagnosed CMV retinitis taking oral valganciclovir maintenance treatment following valganciclovir induction therapy were found to have a median time to progression of CMV retinitis of 160 days. This is considerably longer than has been seen historically with i.v. or oral ganciclovir maintenance treatment and is at least partially due to the effects of HAART.

Valganciclovir induction treatment causes a clinical antiviral response similar to i.v. ganciclovir as measured by both CMV culture and plasma CMV DNA PCR. The reduction in viremia persists during maintenance therapy.

A simplified valganciclovir dose regimen (two tablets once daily) will provide for greater convenience and improved adherence to long-term maintenance treatment compared to other anti-CMV drugs. It is expected that valganciclovir will significantly improve quality of life for patients with CMV retinitis.

All of the drugs approved for the treatment of CMV retinitis have narrow therapeutic margins and carry known risks and toxicities. For each drug these risks must be balanced with the benefits of treatment in order to establish the clinical usefulness of each therapy. Adverse events and laboratory abnormalities seen with oral valganciclovir and i.v. ganciclovir during induction treatment in study WV15376 were directly compared. The risks associated with valganciclovir maintenance treatment were assessed using data from both valganciclovir clinical studies and from prior experience with ganciclovir.

Induction treatment with valganciclovir results in fewer adverse events related to i.v. access than i.v. ganciclovir, including fewer i.v. injection site adverse events. In addition, serious adverse events during the first 4 weeks of treatment were reduced by at least 50% (24% of patients in the i.v. ganciclovir group compared to 10% of patients in the valganciclovir group).

Compared to i.v. ganciclovir induction treatment however, valganciclovir is associated with an increased frequency of diarrhea (16% versus 10%), and oral candidiasis (11% versus 6%). However, these are not of sufficient severity to require dose interruption. During valganciclovir maintenance treatment the frequency of reversible grade 3 or 4 cytopenia is about the same as with i.v. ganciclovir: neutropenia (ANC < 500/ μ L), 15%; anemia (hemoglobin < 8.0 g/dL), 16%; thrombocytopenia (< 25,000/ μ L), 3%.

Persistent or irreversible pancytopenia occurs occasionally in patients taking i.v. and oral ganciclovir. Pancytopenia is also observed with valganciclovir treatment. The overall

frequency of persistent pancytopenia in the valganciclovir studies was 1-2%, not dissimilar from ganciclovir [5].

Errors in prescribing, dispensing, or dose administration are potential risks of treatment with valganciclovir. There is a risk of overdose when patients are switching from oral ganciclovir to valganciclovir maintenance treatment (12 or 6 capsules versus 2 tablets per day, respectively). In the worst scenario this would result in a six-fold valganciclovir overdose, which taken for several days could result in life-threatening hematologic toxicity. In addition, given the convenience of oral administration, it will be easier for physicians to extend the 21 day induction treatment period, which may also result in additional toxicity. Precautionary measures in the form of patient, pharmacist and physician education, label warnings and special notations on the final consumer container are planned.

Ganciclovir is excreted primarily via the kidneys, and ganciclovir blood levels are sensitive to changes in renal clearance. For a variety of reasons patients receiving valganciclovir may have a decreased creatinine clearance (< 60 mL/min) which requires a reduction in dose. Failure to detect the reduction in creatinine clearance or failure to reduce the dose will cause a relative overdose with potentially serious consequences.

Following dosing with valganciclovir, the maximum systemic exposure of a patient to the parent compound valganciclovir is about 1-2% that of the ganciclovir exposure. Although the safety profile of valganciclovir is consistent with the known adverse event profile of ganciclovir, as with any new drug there is a risk that one or more uncommon, drug-related toxicities associated with the valyl ester modification could be observed as larger numbers of patients are dosed.

Because the active moiety of valganciclovir is ganciclovir, with valganciclovir treatment there is the risk of carcinogenesis, mutagenesis, teratogenesis, or decreased spermatogenesis.

12. CONCLUSION

Valganciclovir, an oral prodrug of ganciclovir with high bioavailability provides an effective and convenient treatment for CMV retinitis. The safety profile is comparable to that of ganciclovir, with the significant benefit of reduced morbidity associated with i.v. ganciclovir administration.

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Appendix 1 Preclinical Characteristics of Valganciclovir

Antiviral Activity and Mechanism of Action

Ganciclovir is an acyclic nucleoside analogue of 2'-deoxyguanosine that inhibits replication of herpes viruses *in vitro* and *in vivo*. Ganciclovir must be phosphorylated in order to exert its antiviral activity. Ganciclovir is specifically phosphorylated to its mono-phosphate in human CMV-infected cells by the CMV-encoded kinase, UL97. Cellular enzymes then complete formation of the active metabolite, ganciclovir tri-phosphate (GCV-TP). This tri-phosphate acts as a competitive inhibitor of the viral DNA polymerase (UL54) and shows potent antiviral activity against a range of different laboratory strains and clinical isolates of human CMV, with activity (IC₅₀ values) in the range of 0.08 to 14 μM (0.02 – 3.58 $\mu\text{g}/\text{mL}$). The catabolism of the tri-phosphate to ganciclovir di-phosphate is slow (between 6 and 24 hours), leading to prolonged intracellular antiviral activity despite somewhat faster plasma clearance of ganciclovir. This depot effect is consistent with the PK/PD relationship correlating systemic exposure (as measured by AUC) with therapeutic response.

The position of the valyl ester on valganciclovir is thought to preclude it being a substrate for the viral kinase, inhibiting the initial phosphorylation of the alcohol which is needed for antiviral activity of nucleoside analogues. This together with the rapid conversion of valganciclovir to ganciclovir on absorption, has led to the belief that the anti-viral activity of valganciclovir is that of the ganciclovir formed and not of the low levels of valganciclovir present [6].

Preclinical Pharmacokinetics, Mechanism of Absorption and Conversion to Ganciclovir

A cross-species comparison of the pharmacokinetics and metabolism of valganciclovir has been carried out to determine the suitability of this compound as a pro-drug for delivering ganciclovir with a higher oral bioavailability. The species that were studied (mouse, rat, dog and cynomolgus monkey), were chosen on the basis of previous knowledge of the fate of ganciclovir so that comparisons could be made.

All of the studies for the development of valganciclovir have used a similar analytical method. Valganciclovir hydrolyses relatively slowly in plasma despite its rapid hydrolysis in both intestine and liver to ganciclovir. Samples could be stored, without measurable degradation, for periods up to 1 month at -20°C before being transferred to -70°C storage. These storage periods are suitable for all the species (mouse, rat, dog and man) investigated during this development program [7]. Since ganciclovir is stable for up to 20 months at -20°C , its stability was not a concern.

Appendix 1 Preclinical Characteristics of Valganciclovir (Cont.)

The bioavailability of oral ganciclovir is limited in man (~6%), rat and cynomolgus monkey (7-10%), but good in mice (45%) and dogs (97%), whereas valganciclovir is rapidly absorbed and extensively hydrolyzed delivering good bioavailability of ganciclovir in all species tested, 50% in cynomolgus monkeys, 56% in rats, 60% in man and 100% in dogs and mice. Since ganciclovir is the only metabolite of valganciclovir and ganciclovir is excreted almost wholly unchanged via the kidney, these figures also represent the absorption of valganciclovir.

In vitro studies show that valganciclovir is a substrate for the human intestinal transporter hpepT1 with a K_m of 3 – 5 mM [8]. *In situ* studies in rats show that both trans and paracellular pathways are also available, and at the proposed clinical dose, it is likely that active transport contributes, at least in part, to its absorption. Specific absorption interaction studies have not been conducted in humans. Studies using a rat *in situ* model showed that valaciclovir (also an hpepT1 substrate), cyclosporin, omeprazole, nelfinavir and mycophenolate mofetil had no effect on the permeability of valganciclovir.

The exposure of valganciclovir is low in all species studied (1-2% in dogs, 2-4% in mice) which is consistent with its rapid and efficient hydrolysis to ganciclovir measured in *in vitro* studies in man, dog and mouse intestinal and hepatic S9. In man the intestinal K_m is the same as the intestinal concentration expected from the proposed oral dose, therefore other substrates for the same enzymes are unlikely to compete with this pathway. In the liver, the K_m is an order of magnitude higher than the expected concentration, making competing interactions very unlikely.

The capacity of this enzyme system to metabolize valganciclovir is large. The intrinsic clearance calculated from these enzyme kinetics in both the intestine and the liver suggest that the intestine is responsible for the metabolism of 85% of the absorbed dose, leaving 15% of the absorbed valganciclovir reaching the liver. From similar calculations, 89% of this portion of the dose is metabolized in the liver, leaving a systemic bioavailability of valganciclovir of approximately 1%. This is in close agreement with the low exposure seen in man (~1% of the AUC of ganciclovir). As the liver is responsible for metabolizing only 15% of the absorbed dose, it was assumed that an *in vivo* hepatic impairment study was unnecessary.

These *in vitro* findings are consistent with the results from the *in vivo* non-clinical pharmacokinetic and toxicokinetic studies, where high doses were administered, limited only by the toxicity of ganciclovir. At doses giving AUCs of both compounds 3-6 times higher than expected in man, there was no evidence for saturable absorption or of reduced clearance for valganciclovir. In the more varied patient population, it is expected that the absorption and clearance of valganciclovir will be linear.

Appendix 1 Preclinical Characteristics of Valganciclovir (Cont.)

The distribution pattern of intravenous doses of radiolabeled material following administration to rats is essentially the same for valganciclovir as for ganciclovir. The dose is distributed to all well-perfused organs and tissues in agreement with valganciclovir's measured distribution volume, 0.3 L/kg in dogs and 0.45 L/kg in cynomolgus monkeys, which equates to extra-cellular fluid. The dose is rapidly excreted, predominantly via the kidney where this organ is exposed to 5-fold higher concentrations than any other tissue.

Preclinical Toxicology

The duration of valganciclovir multiple dose toxicology studies was 3 months for the rat and dog, and 6 months for the mouse, with a full interim report at 3 months for direct comparison [9]. The toxicokinetic data for ganciclovir have been compared following oral and i.v. doses of valganciclovir and ganciclovir.

As the first pass metabolism of valganciclovir is very high, only low exposures are achieved following oral doses. In order to increase this exposure and thus improve the chance of detecting any valganciclovir specific toxicities, intravenous doses of valganciclovir were studied. This was performed in a two week study in the mouse where the limiting toxicity of ganciclovir allowed the maximum intravenous dose. This increased the AUC of valganciclovir relative to that of ganciclovir to 80%.

In all studies, the safety profile of valganciclovir is consistent with that of ganciclovir at comparable levels of exposure, with no valganciclovir specific toxicities detected at any dose level in any study. At the lowest i.v. dose of valganciclovir, the AUC of valganciclovir was ten times the maximum anticipated in man, which suggests a safety margin for valganciclovir of at least 10-fold.

Valganciclovir is rapidly and extensively converted to ganciclovir, and the systemic exposure of ganciclovir was the main determining factor in inducing toxicity, such that the same target organs were affected with both valganciclovir and ganciclovir, namely: the reproductive system, hematopoietic, renal, intestinal and adnexal systems, the degree of effect being related to the exposure of ganciclovir achieved. In the clinic, these adverse results correspond to anemia, leukopenia, thrombocytopenia, nephrotoxicity and intestinal disturbances. The chronic toxicity, reprotoxicity and carcinogenicity studies undertaken for ganciclovir were not repeated with valganciclovir as similar results were expected.



Appendix 2 Overview of Valganciclovir Clinical Studies

Clinical Pharmacology Studies										
Protocol No (Report No.)	Center/ Location	Status	Study Design	Drug	Dosage	Formulation	Duration of Treatment	No of Subjects Enrolled	Sex (M/F)	Age range (years)
GANS 2661 (P-180043)	1 Center US	Complete	Open label, randomized, 3-way crossover study in HIV+, CMV+ subjects	VGCV	360 mg p.o.	30 mg/mL (free base) aqueous soln. ganciclovir sodium infusion	Single dose separated by 7 days	18	15/3	22-51
				GCV	5 mg/kg i.v.					
				GCV	1000 mg p.o.					
WP15347 (W-144073)	2 Centers US	Complete	Open label, 2 group (with and without food), randomized, 4-way crossover study in HIV+, CMV+ subjects	VGCV	450 mg p.o.	450 mg tablets	Multiple dose, once daily for 3 days	39	37/2	20-47
					875 mg p.o.	875 mg tablets				
					1750 mg p.o.	2 × 875 mg tablets				
					2625 mg p.o.	3 × 875 mg tablets				
WP15511 (W-144128)	2 Centers UK, Germany	Complete	Open label, parallel group, randomized, 2-way crossover study in healthy, HIV+,CMV+ and renally impaired subjects	VGCV	900 mg p.o.	2 × 450 mg tablets	Single dose separated by 6 days	44	35/9	22-73
				GCV	5 mg/kg i.v.	ganciclovir sodium infusion				



Appendix 2 Overview of Valganciclovir Clinical Studies (Cont.)

Clinical Pharmacology Studies										
Protocol No (Report No)	Center/ Location	Status	Study Design	Drug	Dosage	Formulation	Duration of Treatment	No of Subjects Enrolled	Sex (M/F)	Age range (years)
WP15509 (W-144111)	1 Center UK	Complete	Open label, randomized, 3-way crossover study in HIV+ subjects	VGCV	900 mg p.o.	2 × 450 mg tablets clinical trial formulation	Single dose separated by 5-7 days	18	18/0	22-53
				VGCV	900 mg p.o.	2 × 450 mg tablets market formulation				
				GCV	5 mg/kg i.v.	ganciclovir sodium infusion				

Appendix 2 Overview of Valganciclovir Clinical Studies (Cont.)

Therapeutic Studies in AIDS Patients

Protocol No (Report No)	Center/ Location	Status	Study Design	Drug /Dosage	Formulation	Duration of Treatment	No of Patients Enrolled	Sex (M/F)	Age range (years)
WV15376 (W-144125)	42 Centers International	Ongoing; Clinical data cut-off 30 Sept.1999	Open label, randomized, parallel group study in HIV+ patients with newly diagnosed CMV retinitis	<u>Induction:</u> GCV 5 mg/kg i.v., b.i.d for 3 weeks, then 5 mg/kg i.v. o.d. for 1 week VGCV 900 mg p.o., b.i.d. for 3 weeks, then 900 mg p.o., o.d for 1 week <u>Maintenance:</u> VGCV 900 mg p.o., o.d.	Ganciclovir sodium infusion 2 × 450 mg tablets	2 days to 30 mths (up to clinical cut-off)	160	145/15	21-61
WV15705 (W-144126)	43 Centers International	Ongoing; Clinical data cut-off 30 Sept. 1999	Open label, single arm study in patients with AIDS and previously treated CMV retinitis	<u>Maintenance:</u> VGCV 900 mg p.o., o.d. <u>Induction (as required to treat active retinitis):</u> VGCV 900 mg p.o., b.i.d. for 3 weeks,	2 × 450 mg tablets	12 days to 17 mths (up to clinical cut-off)	212	193/19	22-61



Appendix 2 Overview of Valganciclovir Clinical Studies (Cont.)

Solid Organ Transplant Studies

Protocol No (Report No)	Center/ Location	Status	Study Design	Drug Dosage	Formulation	Duration of Treatment	No of Subjects Enrolled	Sex (M/F)	Age range (years)
WP15711 (W-144127)	7 Centers USA, UK	Complete	Open label, randomized, 4-way crossover study in liver transplant recipients	GCV 3000 mg p.o. as 3 divided doses of 1000 mg p.o.	4 × 250 mg capsules	Single dose separated by 3-7 days	28	21/7	20-60
				VGCV 450 mg p.o. VGCV 900 mg p.o.	1 × 450 mg tablets 2 × 450 mg tablets				
				GCV 5 mg/kg i.v.	ganciclovir sodium infusion				
PV16000	50-60 Centers International	Ongoing	Randomized, double-blind, double dummy, 2-arm, parallel, active-comparator controlled study in high-risk heart, kidney and liver transplant recipients	VGCV 900 mg p.o., o.d. GCV 3000 mg p.o. (1000 mg t.i.d.)	2 × 450 mg tablets 4 × 250 mg capsules	90 days	~372 planned; 232 enrolled as of 9 Jan 2001	NK	NK

NK = not known at this time



Appendix 3 Valganciclovir Solid Organ Transplant Study PV16000

Study PV16000 is an ongoing, randomized, double-blind, double-dummy, 2-arm, parallel, controlled study to determine the comparative efficacy and safety of valganciclovir relative to oral ganciclovir for the prevention of CMV disease in high risk (D+/R-) heart, liver, kidney, and kidney-pancreas allograft recipients. Patients receive either oral valganciclovir 900 mg o.d. or oral ganciclovir 1000 mg t.i.d. as soon as they are able to tolerate oral medication (but no later than 10 days post-transplant) through 100 days post transplant, with a 2:1 valganciclovir : ganciclovir randomization. There are currently 232 patients enrolled in the study, and 150 patients have reached day 100 post transplantation.

The primary efficacy endpoint in study PV16000 is CMV disease defined as either:

1. **CMV syndrome:** clinical evidence of systemic CMV infection as manifested by (a) a positive CMV blood culture or antigenemia assay and (b) otherwise unexplained fever of $\geq 38^{\circ}\text{C}$ for ≥ 2 days and one or more of the following: malaise, leukopenia (WBC $< 4,000$ on 2 successive measurements), atypical lymphocytosis, thrombocytopenia (platelet count $< 100,000$) or elevation of hepatic transaminases (ALT, AST) to at least $2 \times \text{ULN}$ (non-liver transplant recipient) or
2. **Tissue-invasive CMV disease:** (a) evidence of localized CMV infection (CMV inclusion cells or in situ detection of CMV antigen or DNA by immunostain or hybridization, respectively) in a biopsy or other appropriate specimen (e.g., cerebrospinal fluid, bronchoalveolar lavage) and (b) relevant symptoms or signs of organ dysfunction (specified in the protocol). If the affected organ is the allograft, acute rejection must be excluded as a possible cause for the patient's clinical findings.

Considerations in selecting the primary endpoint of symptomatic CMV infection, with or without evidence of specific organ involvement were (1) the opinion of experts in the field of transplant infectious disease, (2) current clinical practice and (3) the likely incidence and nature of CMV disease in a population receiving antiviral prophylaxis.

Safety assessments include adverse events and laboratory parameters during and for 14 days following treatment with study drug, and patient survival at 6 and 12 months post transplant.

Appendix 4 Evidence of an Exposure Response Relationship for Ganciclovir (Study GANS 2226)

Study GANS 2226 was a 4-arm randomized, parallel group study comparing the efficacy of three different doses of oral ganciclovir (3 g, 4.5 g and 6 g/day) with that of i.v. ganciclovir (5 mg/kg/day) as maintenance treatment for CMV retinitis. A total of 281 patients with AIDS and CMV retinitis participated in this study. All patients enrolled had received at least 4 weeks of prior i.v. ganciclovir treatment, and had stable CMV retinitis. The primary endpoint in this study, the time to first photographic progression of CMV retinitis, was assessed by masked reading of fundus photographs, which were taken every 2 weeks. A single blood sample was taken routinely from all patients at weeks 2 and 6 for assay of ganciclovir concentration.

An analysis was performed to define the relationship between individual pharmacokinetic parameters and time to progression of CMV retinitis [4]. Using actual individual dosing history information and final model estimates for each subject, simulated plasma profiles from the time of randomization to the time of first photographic progression were obtained, via use of the standard population pharmacokinetic software package, NONMEM. Pharmacokinetic parameters of interest, namely AUC, C_{\max} and C_{\min} were estimated using the mean of the corresponding daily values.

Increases in average AUC_{0-24} were associated with statistically significant increases in time to progression of CMV retinitis when fitted by the Cox regression model ($p=0.0002$). The average C_{\max} was also statistically significantly associated with time to progression ($p=0.0326$) when fitted in a separate model. However, when average AUC_{0-24} and average C_{\max} were fitted in the same model, the association between AUC_{0-24} and time to progression of CMV retinitis was highly statistically significant ($p=0.0019$), while C_{\max} was not ($p=0.6022$). Similar results were found with the Weibull model. The association between average C_{\min} and time to first photographic progression did not reach statistical significance when fitted in either a separate Cox ($p=0.1854$) or Weibull model ($p=0.2819$). Thus, these findings indicate that average AUC_{0-24} is a better correlate with time to progression, and that average C_{\max} does not add predictive value over average AUC_{0-24} (see Figure below).

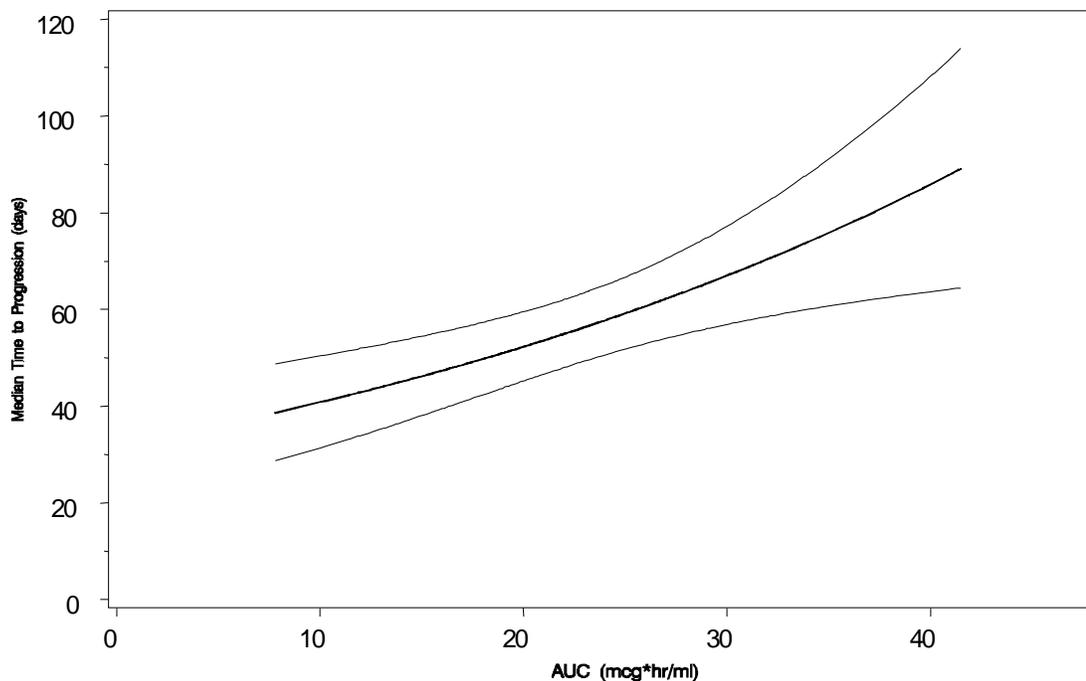
These results support an exposure response relationship for ganciclovir in the treatment of CMV retinitis. Efficacy is correlated with overall ganciclovir exposure, as measured by average AUC_{0-24} , and not with the short duration peaks or troughs in plasma ganciclovir concentrations. This pattern is consistent with the intracellular pharmacodynamics of GCV triphosphate.



Appendix 4 Evidence of an Exposure Response Relationship for Ganciclovir (Study GANS 2226) (Cont.)

Estimated Median Time to First Photographic Progression of CMV Retinitis Versus Estimated Average Ganciclovir AUC₀₋₂₄ (Study GANS 2226)

Estimated Median Time (with 95% CI) to CMV Retinitis Progression vs. Estimated Average Exposure (AUC)
All Oral and IV Efficacy Subjects





Appendix 5 Absolute Bioavailability of Ganciclovir when Administered as Valganciclovir

Study	Dose (mg)	Nominal/Actual i.v. Dose	Population	F (95% CI)
GANS2661	360	Actual	HIV CMV+	60.9 (9.10)*
WP15711	450	Nominal	Liver transplant	60 (56 to 64)
	900	Nominal	Liver transplant	59 (55 to 63)
WP15511	900	Nominal	HIV CMV+	61 (55 to 67)
	900	Nominal	Healthy volunteers	59 (54 to 64)
WP 15509	900	Nominal	HIV+	59 (56 to 62)
	900	Nominal	HIV+	59 (56 to 62)
WV15376	900 (b.i.d.)	Nominal	HIV+ with retinitis	69 (49 to 78)
	900	Nominal	HIV+ with retinitis	59 (42 to 76)

* value shown is the standard deviation, CI for bioavailability was not calculated for this study

Appendix 6 Effect of Renal Impairment on Mean (%CV) Ganciclovir Pharmacokinetic Parameters

CrCL (mL/min)	AUC _{last} (μg.h/mL)	AUC _{0-∞} (μg.h/mL)	C _{max} (μg/mL)	T _{max} (h)	t _{1/2p} (h)	CL _{po} (mL/min)	CL _R (mL/min)
>70 (Group 2G)	27.1 (26)	27.8 (25)	5.56 (29)	2.0	3.46 (19)	413 (28)	209 (21)
51-70 (Group 3)	49.5 (45)	50.5 (46)	6.88 (37)	2.0	4.85 (28)	249 (40)	145 (41)
21-50 (Group 4)	91.9 (48)	99.7 (55)	7.08 (23)	3.0	10.2 (43)	136 (48)	67.1 (40)
11-20 (Group 5)	223 (21)	252 (25)	8.54 (14)	3.0	21.8 (24)	45 (25)	21.4 (38)

Mean values in table refer to arithmetic mean.

Median values presented for T_{max}



Appendix 7 Inclusion and Exclusion Criteria for Studies WV15376 and WV15705

INCLUSION CRITERIA	WV15376	WV15705
Seropositive for HIV	✓	✓
<u>Sex</u> Male	✓	✓
Female	✓	✓
Newly diagnosed, untreated CMV retinitis which can be confirmed photographically	✓	
CMV retinitis diagnosed by experienced ophthalmologist	✓	✓
Age ≥ 13 years	✓	✓
Absolute neutrophil count (ANC) ≥ 750 cells/μL	✓	✓
Platelet count ≥ 75,000/μL ≥ 25,000/μL	✓	✓
Estimated creatinine clearance > 70 mL/min > 50 mL/min	✓	✓
Minimum of 4 weeks prior CMV treatment with either ganciclovir / foscarnet / cidofovir / intraocular ganciclovir implant. Investigational anti-CMV compounds acceptable if approved by a Roche Clinical Scientist		✓
Intraocular implant permissible in either or both eyes, provided active CMV retinitis in one eye		✓



Appendix 7 Inclusion and Exclusion Criteria for Studies WV15376 and WV15705 (Cont.)

EXCLUSION CRITERIA	WV15376	WV15705
History of CMV retinitis	✓	
Active extraocular CMV disease		✓
Severe, uncontrolled diarrhea or evidence of malabsorption	✓	✓
Karnofsky score of < 70% < 60%	✓	✓
Condition precluding use of indwelling i.v. catheter for at least 1 month	✓	
Systemic anti-CMV therapy of > 3 weeks duration (total) at any time, or any systemic anti-CMV therapy within 3 months of randomization	✓	
Simultaneous participation in another study	✓	✓
Therapy with an investigational drug within 30 days of study entry	✓	
Use of prohibited concomitant medications acyclovir at doses > 800 mg/day valacyclovir famciclovir foscarnet cidofovir CMV hyperimmune globulin probenecid investigational agents except as approved by a Roche Clinical Scientist	✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓	✓ ✓ ✓ ✓ ✓
Ocular media opacities (corneal, aqueous, lens or vitreous) preventing ophthalmologic retinal assessment or fundus photography	✓	✓
Condition involving affected eye likely to require surgical intervention within 4 weeks of study entry (e.g. retinal detachment)	✓	
Enrolled in or eligible for enrollment in study WV15376		✓



Appendix 8 Summary of Demographic Data – Study WV15376 (ITT Population)

Summary of Demographic Data by Trial Treatment

Protocol(s): WV15376

Analysis: INTENT-TO-TREAT Center: ALL CENTERS

SUMMARY OF DEMOGRAPHIC DATA BY TREATMENTS (ITT POPULATION)

	GCV/VGCV N = 80	VGCV/VGCV N = 80
Sex		
MALE	73 (91%)	72 (90%)
FEMALE	7 (9%)	8 (10%)
n	80	80
Race		
CAUCASIAN	42 (53%)	43 (54%)
BLACK	9 (11%)	9 (11%)
ORIENTAL	1 (1%)	1 (1%)
OTHER	28 (35%)	27 (34%)
n	80	80
Age		
Mean	37.7	39.6
SD	7.28	7.62
SEM	0.81	0.85
Median	36.5	39.0
Min-Max	23 - 57	21 - 61
n	80	80
Weight in kg		
Mean	66.20	64.78
SD	11.805	12.171
SEM	1.320	1.361
Median	63.65	63.75
Min-Max	46.8 - 107.0	39.0 - 95.5
n	80	80
Height in cm		
Mean	174.315	173.457
SD	9.3124	8.9823
SEM	1.0544	1.0106
Median	175.260	172.720
Min-Max	152.40 - 190.00	149.86 - 200.66
n	78	79
Karnofsky PS		
N	80.0	80.0
Mean	85.9	82.6
Median	90.0	80.0
Standard deviation	10.3	10.1
Minimum	60.0	60.0
Maximum	100.0	100.0
Creatinine Clearance		
N	67.0	67.0
Mean	119.7	119.5
Median	115.0	119.0
Standard deviation	27.7	32.3
Minimum	67.8	63.0
Maximum	208.8	212.0
CD4 Count		
N	74.0	75.0
Mean	53.6	58.0
Median	26.0	20.0
Standard deviation	67.6	80.8
Minimum	2.0	2.0
Maximum	365.0	390.0

n represents number of patients contributing to summary statistics. Percentages are based on n (number of valid values). Percentages not calculated if n < 10. Where <X was recorded for CD4 count, X has been used in the calculation. Units : CD4 count (cells/uL) and CRCL (mL/min).

DML1.pdrd 13JAN2000:12:50:24 (1 of 1)

Program : \$PROD/cdp01269/i15376b/Tkwei.sas / Output : TkweiT102.pdrd. 14JAN2000 12:00 Page 1 of 1

Appendix 9 Assessment of the Possible Influence of HAART During the Randomized Phase of Study WV15376

Exploratory subgroup analyses found no notable treatment group difference in the proportion of patients who progressed by week 4 according to use of HIV protease inhibitors (PI) at baseline, duration of PI use at baseline, or receipt of new PI therapy during the first 4 weeks of the study. In addition, the possible influence of HAART has been addressed by evaluating changes in three related parameters during the first 4 weeks of the study (analyses were based on the standard population):

- Antiretroviral medication use
- CD4 lymphocyte counts
- HIV viral load

Changes in Antiretroviral Medications:

Although the protocol specified that patients should be on a stable antiretroviral regimen during the randomized phase of the study, a number of patients initiated or stopped one or more antiretroviral agents during this time period. The number of patients who made such changes was comparable between the two treatment groups: 21% (15/73) of patients randomized to i.v. ganciclovir induction and 19% (14/73) of patients randomized to valganciclovir induction started a new antiretroviral medication, while 8% and 12%, respectively, stopped taking an antiretroviral agent. Eleven patients in the ganciclovir treatment group and 9 patients in the valganciclovir group began taking an HIV protease inhibitor during the first 4 weeks of the study.

Changes in CD4 Lymphocyte Count:

A total of 50 patients in each group (68% of the standard population) had a CD4 count at screening and at least one additional post-screening CD4 count during the first 4 weeks of the study. The change in CD4 count for these patients is summarized below. Among the 50 patients in each group with CD4 count change data, the majority of patients experienced either no change or a decrease in CD4 count during the randomized phase. Among those patients who had a CD4 count increase, most counts increased by less than 10 cells/ μ L.

Change in CD4 Counts from Screening up to Week 4 in Study WV15376

Summary of change in patients CD4 counts from Screening up to Week 4 for study WV15376
by Treatment group - Standard population

	GCV/VGCV	VGCV/VGCV
N	50	50
Decrease	27 (54%)	25 (50%)
No change	7 (14%)	6 (12%)
0 < Increase < 10	8 (16%)	11 (22%)
10 <= Increase < 25	3 (6%)	4 (8%)
25 <= Increase < 50	2 (4%)	2 (4%)
Increase >= 50	3 (6%)	2 (4%)

Program : \$PROD/cdp01269/cd4_376.sas
Output : \$PROD/cdp01269/reports/cd4_376006.s18
14NOV2000 11:40 Page 1 of 1



Appendix 9 Assessment of the Possible Influence of HAART During the Randomized Phase of Study WV15376 (Cont.)

Changes in HIV Viral Load:

The table below summarizes the HIV load at screening for the standard population, expressed as genome copies/mL and log values. The mean and median HIV loads were comparable between treatment groups. There was a similar distribution of HIV loads, and the majority of patients in both treatment groups (GCV 66%, VGCV 64%) had a screening HIV load greater than 4 logs.

At week 4, mean and median HIV loads remained comparable between treatment groups (see table Summary of HIV Load at Week 4). Compared to screening values, the mean HIV loads in both groups had decreased slightly (-0.10 log for the GCV group, -0.05 log for the VGCV group), as had the median HIV load in the GCV group (-0.07 log). The median HIV load value for the VGCV group had increased slightly compared to screening (+0.14 log). These are small changes that would not be expected to be clinically meaningful. There was a similar distribution of HIV loads within the treatment groups, and the majority of patients in both treatment groups had a week 4 HIV load greater than 4 logs.

Summary of HIV Load at Screening

HivscrT90 + hivscrT91 Ro 107-9070 WV15376 FINAL DATA

Summary of Log HIV load at Screening

	GCV/VGCV N = 73	VGCV/VGCV N = 73
Absolute HIV load at Screening		
N	61	59
Mean	216849	214261
SD	263285	271923
Median	75000	72326
Range	50 to 750000	50 to 750000
Log HIV load at Screening		
No HIV load data at Screening	12 (16%)	14 (19%)
Screening HIV load <=2 logs	6 (8%)	3 (4%)
2 < Screening HIV load <=3 logs	6 (8%)	4 (5%)
3 < Screening HIV load <=4 logs	1 (1%)	5 (7%)
4 < Screening HIV load <=5 logs	21 (29%)	24 (33%)
Screening HIV load > 5 logs	27 (37%)	23 (32%)

Program : /hivscr.sas / Output : \$PROD/cdp01269/i15376b/reports/hivscrT91.s17
Page 1 of 1

Appendix 9 Assessment of the Possible Influence of HAART During the Randomized Phase of Study WV15376 (Cont.)

Summary of HIV Load at Week 4

Hivwk4T90 + hivwk4T91 Ro 107-9070 WV15376 FINAL DATA

Summary of Log HIV load at Week 4

	GCV/VGCV N = 73	VGCV/VGCV N = 73
Absolute HIV load at Week 4		
N	62	61
Mean	174499	189195
SD	241410	236437
Median	64383	100885
Range	50 to 750000	50 to 750000
Log HIV load at Week 4		
No HIV load data at Week 4	11 (15%)	12 (16%)
Week 4 HIV load <=2 logs	8 (11%)	3 (4%)
2 < Week 4 HIV load <=3 logs	6 (8%)	7 (10%)
3 < Week 4 HIV load <=4 logs	4 (5%)	5 (7%)
4 < Week 4 HIV load <=5 logs	18 (25%)	15 (21%)
Week 4 HIV load > 5 logs	26 (36%)	31 (42%)

Program : /hivwk4.sas / Output : \$PROD/cdp01269/i15376b/reports/hivwk4T91.s17
Page 1 of 1

An analysis of the distribution of changes in log HIV load between screening and week 4 is summarized in the table below. Most HIV viral load changes were within the range of -1.0 log to +1.0 log. A higher proportion of ganciclovir treated patients compared to valganciclovir treated patients experienced a decrease in HIV viral load, notably in the range of 0.5 to 1.0 log. Similarly, a greater proportion of valganciclovir patients experienced an increase in HIV viral load. Among the valganciclovir patients, 4% (3/73) experienced a 1-2 log increase in HIV load, while no ganciclovir patients experienced this degree of increase.

Summary of Changes in Log HIV from Screening to Week 4

-tchgehivT93 Ro 107-9070 WV15376 FINAL DATA

Summary of Change in Log HIV Load from Screening to Week 4

Change in log HIV [screen to week 4]	GCV/VGCV N = 73	VGCV/VGCV N = 73
Change not calculable	18 (25%)	17 (23%)
Change in HIV load < -2 logs	2 (3%)	1 (1%)
-2 < Change in HIV load <= -1.5 logs	1 (1%)	1 (1%)
-1.5 < Change in HIV load <= -1 logs	2 (3%)	2 (3%)
-1 < Change in HIV load < -0.5 logs	11 (15%)	5 (7%)
-0.5 < Change in HIV load < 0 logs	15 (21%)	17 (23%)
No change in HIV load	4 (5%)	5 (7%)
0 < Change in HIV load <= 0.5 logs	15 (21%)	14 (19%)
0.5 < Change in HIV load <= 1 logs	5 (7%)	8 (11%)
1 < Change in HIV load <= 1.5 logs	.	2 (3%)
1.5 < Change in HIV load <= 2 logs	.	1 (1%)

Program : /tchgehiv.sas / Output : \$PROD/cdp01269/i15376b/reports/tchgehivT93.s17
age 1 of 1

Appendix 9 Assessment of the Possible Influence of HAART During the Randomized Phase of Study WV15376 (Cont.)

A review of CD4 count and HIV viral load changes during the first 4 weeks for the 7 patients on each treatment arm who progressed during the randomized phase of the study revealed no discernible pattern to the changes.

Overall, any impact of HAART during the randomized phase of the study is thus generally small, and does not influence the primary comparison of oral valganciclovir and i.v. ganciclovir induction therapy. The noted imbalance between groups in the proportion of patients with HIV load increases versus decreases does not favor the valganciclovir group.



Appendix 10 Satisfactory Response to Induction Therapy by Week 4 Based on Photographic Assessment (Standard Population)

satstrt95T23 Ro 107-9070

WV15376

FINAL DATA

Analysis of Satisfactory Induction of Therapy at Week 4 - 95% Confidence Intervals (Standard Population)

	GCV/VGCV N = 73	VGCV/VGCV N = 73
SUMMARY OF INDUCTION THERAPY AT WEEK 4		
UNSATISFACTORY	14 (19%)	18 (25%)
SATISFACTORY	47 (64%)	46 (63%)
UNEVALUABLE	12 (16%)	9 (12%)
SECONDARY EFFICACY ANALYSIS AT WEEK 4		
SATISFACTORY INDUCTION PROPORTION	0.770	0.719
UNSATISFACTORY INDUCTION PROPORTION	0.230	0.281
DIFFERENCE IN SATISFACTORY INDUCTION PROPORTIONS		-0.052
95% CONFIDENCE INTERVAL		(-0.204, 0.101)
FOR PATIENTS WITH SATISFACTORY INDUCTION:		
RETINITIS ACTIVE AT WEEK 4		
NO	32 (68%)	35 (76%)
YES	15 (32%)	11 (24%)
BORDER PROPORTION ACTIVE >=5% AT WEEK 4		
NO	33 (70%)	37 (80%)
YES	14 (30%)	9 (20%)
FAILURE TO DECREASE ACTIVITY >=3 STEPS FROM BASELINE TO WEEK 4		
NO	35 (74%)	34 (74%)
YES	12 (26%)	12 (26%)
ALL OF THE ABOVE(1)		
YES	30 (64%)	32 (70%)
NO	17 (36%)	14 (30%)

Unevaluable - Data is either missing or response is cannot grade

Unevaluable patients are excluded from the calculations for the efficacy analysis

(1) patients with no active retinitis, less than 5% border activity and >=3 steps decrease in activity

Program : \$PROD/cdp01269/wv15376/satstrt95.sas / Output : \$PROD/cdp01269/i15376b/reports/satstrt95T23.s17
22MAR2000 16:03

Page 1 of 1



Appendix 11 Change in Visual Acuity Between Baseline and Weeks 2, 4 and 6

Baseline

Ro 107-9070 WV15376 FINAL DATA
Summary of Baseline Visual Acuity from Ophthalmology Examination Data, expressed as Best and Worst Eye (Standard Population)

Corrected Visual Acuity	GCV/VGCV N = 73	VGCV/VGCV N = 73
BEST EYE		
NORMAL	72 (99%)	68 (93%)
IMPAIRED	1 (1%)	5 (7%)
SEVERELY IMPAIRED	0 (0%)	0 (0%)
UNEVALUABLE	0 (0%)	0 (0%)
WORST EYE		
NORMAL	65 (89%)	56 (77%)
IMPAIRED	5 (7%)	6 (8%)
SEVERELY IMPAIRED	3 (4%)	11 (15%)
UNEVALUABLE	0 (0%)	0 (0%)

If there was no baseline visit then the screening visit was used instead.

Program : \$PROD/cdp01269/i15376b/bcvas.sas / Output : bcvasT05.s17
14JAN2000 12:00 Page 1 of 1

Weeks 2, 4 and 6

Ro 107-9070 WV15376 FINAL DATA
Summary of Visual Acuity from Ophthalmology Examination at Weeks 2, 4 and 6 (Standard Population)

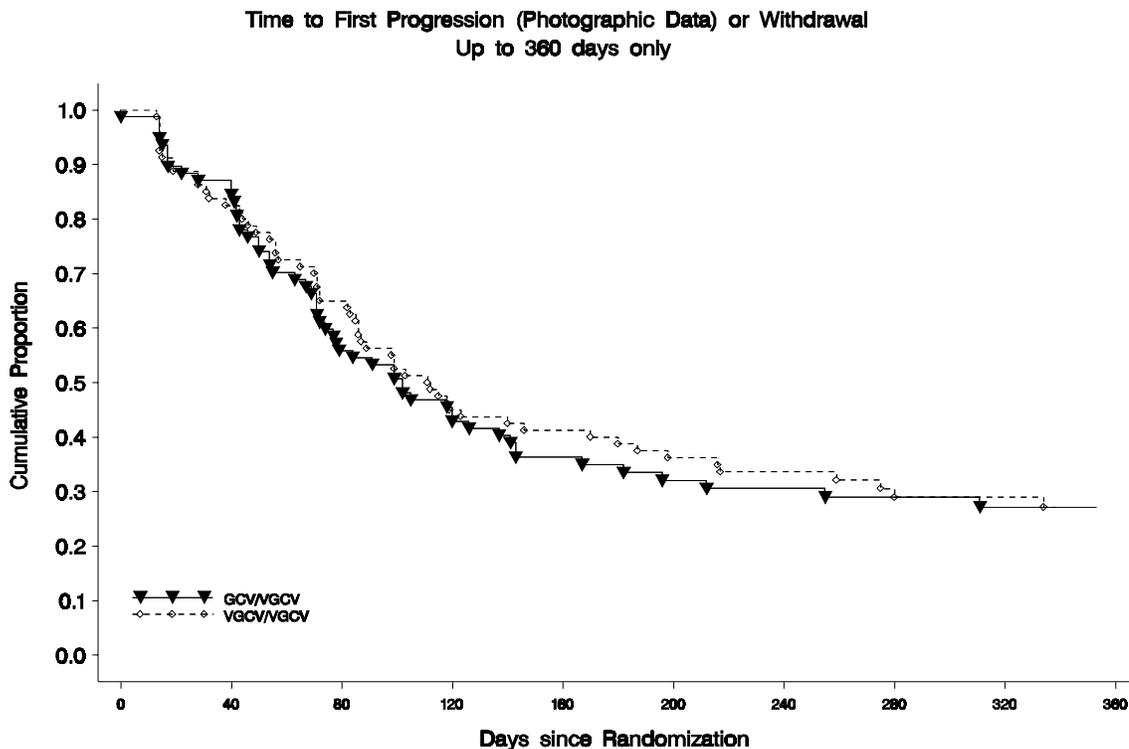
	GCV/VGCV N = 73	VGCV/VGCV N = 73
Deterioration from baseline to week 2		
IMPROVEMENT	2 (3%)	2 (3%)
NO DETERIORATION	64 (88%)	56 (77%)
DETERIORATION	1 (1%)	9 (12%)
UNEVALUABLE	6 (8%)	6 (8%)
Deterioration from baseline to week 4		
IMPROVEMENT	3 (4%)	7 (10%)
NO DETERIORATION	61 (84%)	54 (74%)
DETERIORATION	3 (4%)	8 (11%)
UNEVALUABLE	6 (8%)	4 (5%)
Deterioration from baseline to week 6		
IMPROVEMENT	3 (4%)	5 (7%)
NO DETERIORATION	57 (78%)	49 (67%)
DETERIORATION	4 (5%)	7 (10%)
UNEVALUABLE	9 (12%)	12 (16%)

For those patients who did not have a baseline value for visual acuity their screening visit has been used instead

Program : \$PROD/cdp01269/i15376b/cva21s.sas / Output : cva21sT29/cva41sT37/cva61sT72.pdrd
14JAN2000 12:00

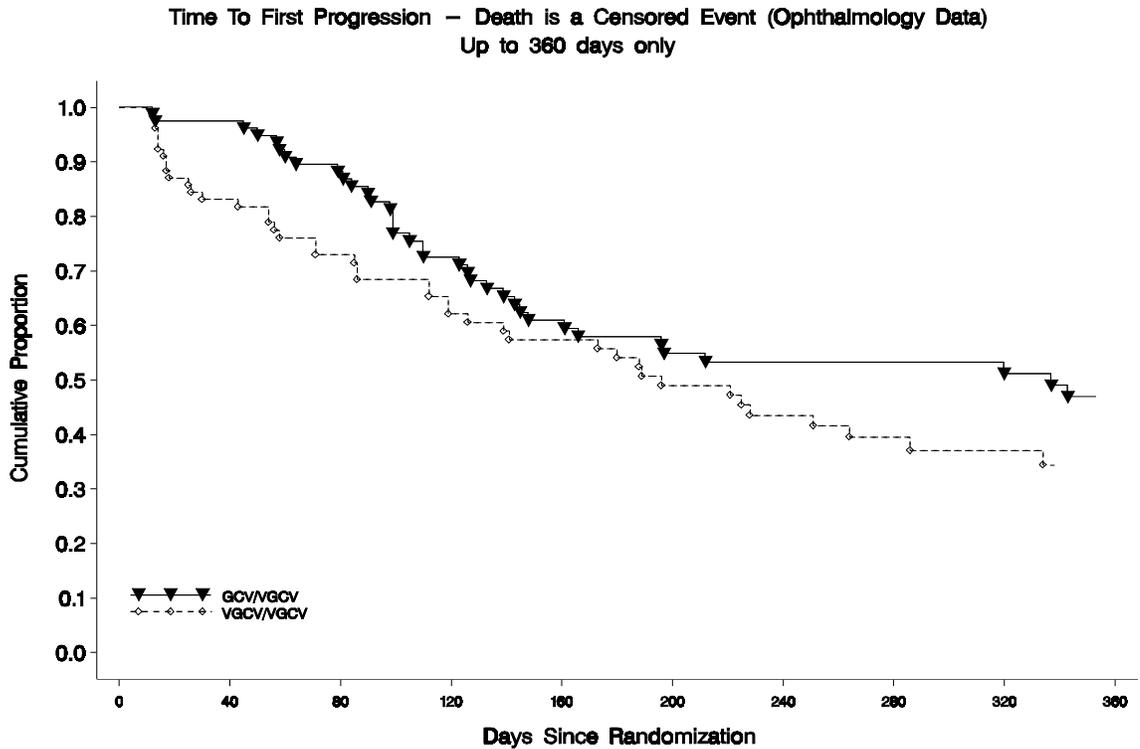


Appendix 12 Time to First Progression of CMV Retinitis up to Study Day 360 Where Death is a Censored Event (Based on Photographic Assessment; ITT Population), or Withdrawal



Ro 107-9070 WY1078 FINAL DATA
Pages: 6/PRODC/0128/1007/9070/Appendix12 / Output: 04/04/01

Appendix 13 Time to First Progression of CMV Retinitis up to Study Day 360 Where Death is a Censored Event, Based on Ophthalmological Assessment (ITT Population)

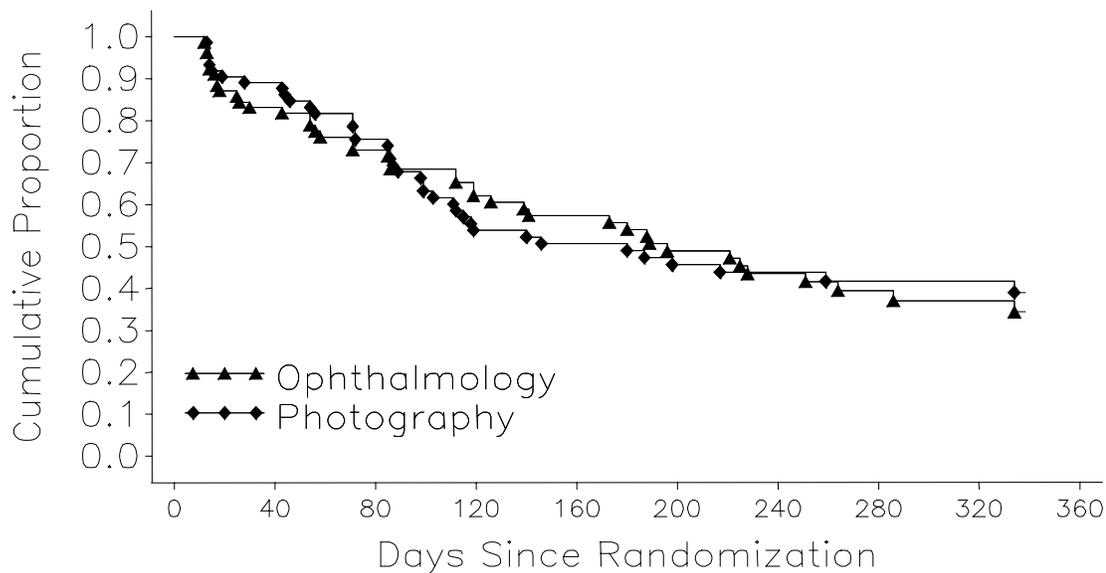


No 107-9070 WY10798 FINAL DCR
Program : @PR001colp01281110798agept1.asa / Output : agept1282
14/04/2010 10:20



Appendix 14 Time to First Progression Where Death is a Censored Event – Valganciclovir (Ophthalmologic vs Photographic Data, ITT Population)

Time To First Progression – Valganciclovir (Ophthalmology + Photographic Data)
Up to 360 days only

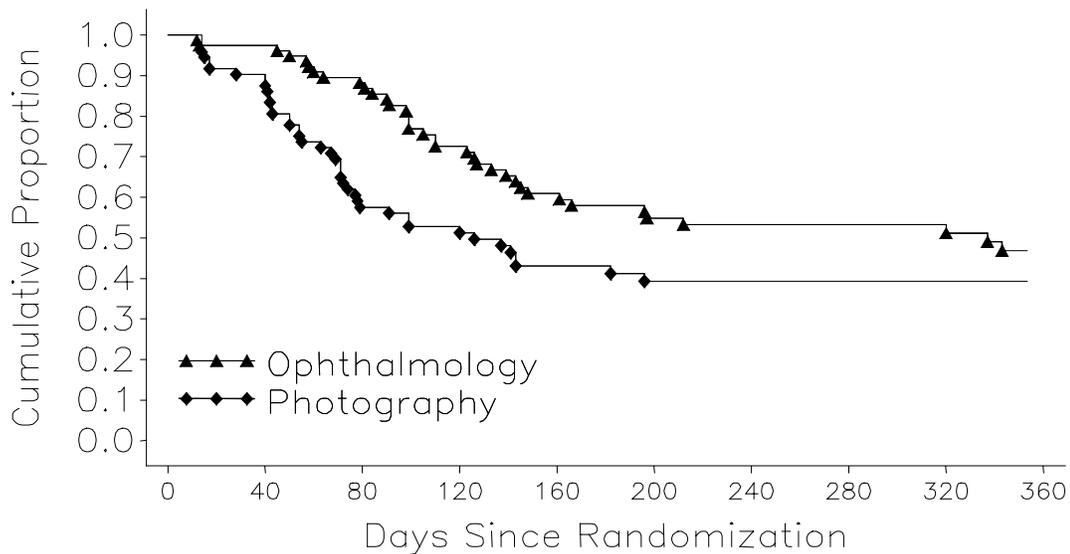


Ro 107-9070 - W19576 - Final Data
Program: S42M/cas1210/1376/symms2.ans / Output: symms202



Appendix 15 Time to First Progression Where Death is a Censored Event – Ganciclovir (Ophthalmologic vs Photographic Data, ITT Population)

Time To First Progression – Ganciclovir (Ophthalmology + Photographic Data)
Up to 360 days only



Ro 107-9070 WV10378 FINAL DATA
Program 1: S:\DVC\9901269\1163768\990901_309 / Output 1: 990901.C1



**Appendix 16 Summary of Quantitative CMV PCR Data (CMV Viral Load)
Obtained in CMV PCR Positive Patients**

Summary of Quantitative PCR for Patients Who Have a Positive Qual. Plasma Result (RMS) at Screening (ITT Population)

Visit		GCV/VGCV N = 39	VGCV/VGCV N = 31
Screening	N	38	31
	Mean	3.5	3.6
	SD	0.8	0.7
	Median	3.4	3.6
	Range	2.5 to 5.5	2.6 to 4.8
Week 4	N	28	14
	Mean	2.6	2.6
	SD	0.1	0.1
	Median	2.6	2.6
	Range	2.6 to 3.2	2.6 to 2.8

The level of quantification (400) has been used where the Quantitative PCR result was below the level of quantification. The quantitative PCR results have all been converted to log base 10.
Program : /plasma.sas / Output : \$PROD/cdp01269/i15376b/reports/plasmaT05.s17



Appendix 17 Summary of Demographic Data – Study WV15705 (All Patients)

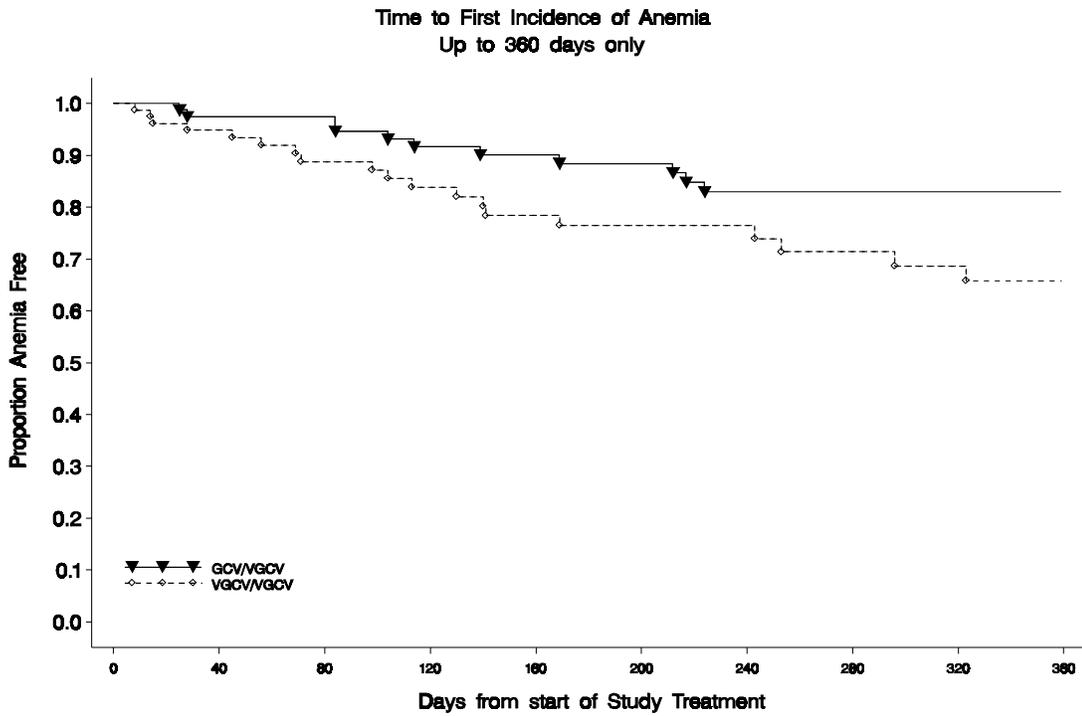
Summary of Demographic Data by Trial Treatment
Protocol(s): WV15705
Analysis: SAFETY Center: ALL CENTERS

	VALGANCICLOVIR N = 212
Sex	
MALE	193 (91%)
FEMALE	19 (9%)
n	212
Race	
CAUCASIAN	167 (79%)
BLACK	15 (7%)
ORIENTAL	2 (1%)
OTHER	28 (13%)
n	212
Age	
Mean	40.9
SD	7.38
SEM	0.51
Median	40.0
Min-Max	22 - 61
n	212
Weight in kg	
Mean	70.22
SD	10.714
SEM	0.736
Median	69.05
Min-Max	46.5 - 104.0
n	212
Height in cm	
Mean	175.476
SD	7.8227
SEM	0.5411
Median	175.260
Min-Max	155.00 - 198.12
n	209
Karnofsky score	
Mean	88.7
SD	10.16
SEM	0.70
Median	90.0
Min-Max	60 - 100
n	212
Creatinine Clearance	
N	208.0
Mean	108.2
Median	105.0
Standard deviation	32.5
Minimum	46.0
Maximum	250.0
CD4 Count	
N	201.0
Mean	170.8
Median	140.0
Standard deviation	157.0
Minimum	3.0
Maximum	998.0

n represents number of patients contributing to summary statistics. Percentages are based on n (number of valid values). Percentages not calculated if n < 10. Where <X was recorded for CD4 count, X has been used in the calculation. Units : CD4 count (cells/uL) and CRCL (mL/min)
Program : \$PROD/cdp01269/i15705b/oTkw.sas / Output : oTkwCT102.pdrd. 25JAN2000 4:10 Page 1 of 1
DML1 19JAN2000:16:04:43 (1 of 1)



Appendix 18 Kaplan-Meier Plot of Time to First Incidence of Anemia (Hemoglobin < 8.0 g/dL) in Study WV15376



Ro 107-9070 WV15376 Final Draft
Project : 01/10/2008/2008/2008 / Output : 0801_8
14/10/2008 12:28



Appendix 19 Summary of Causes of Patient Deaths During Valganciclovir Therapeutic Studies

Summary of Deaths by Trial Treatment
 Protocol(s): WV15376 WV15705
 Analysis: SAFETY Center: ALL CENTERS
 SUMMARY OF PATIENTS DEATHS BY TREATMENT (ALL)

Cause of Death	VGCV	
	N = 370	No. (%)
Total No. of Deaths	46	(12)
CARDIAC ARREST	4	(1)
HIV INFECTION CDC GROUP IV SUBGROUP C1	4	(1)
PNEUMOCYSTIS CARINII PNEUMONIA	4	(1)
CARDIO-RESPIRATORY ARREST	3	(1)
LYMPHOMA NOS	3	(1)
HIV INFECTION CDC GROUP IV SUBGROUP E	2	(1)
HYPOVOLAEMIC SHOCK	2	(1)
PNEUMONIA NOS	2	(1)
RESPIRATORY ARREST (EXC NEONATAL)	2	(1)
RESPIRATORY FAILURE (EXC NEONATAL)	2	(1)
SUICIDE (ACCOMPLISHED)	2	(1)
ADULT RESPIRATORY DISTRESS SYNDROME	1	(<1)
BRONCHOPULMONARY ASPERGILLOSIS	1	(<1)
CARDIOMYOPATHY SECONDARY NOS	1	(<1)
CEREBRAL HAEMORRHAGE	1	(<1)
CORONARY ARTERY DISEASE NOS	1	(<1)
DEATH	1	(<1)
HIV INFECTION CDC GROUP IV SUBGROUP A	1	(<1)
HIV INFECTION NOS	1	(<1)
LUNG CANCER NOS	1	(<1)
MULTI-ORGAN FAILURE	1	(<1)
PNEUMONITIS NOS	1	(<1)
SEPSIS NOS	1	(<1)
SEPSIS SECONDARY	1	(<1)
SEPTICAEMIA NOS	1	(<1)
TOXOPLASMOSIS	1	(<1)
VIRAEMIA NOS	1	(<1)

Percentages are based on N. Percentages not calculated if N < 10.
 DD11 23MAR2000:15:48:46 (1 of 1)



Appendix 20 Adverse Events Reported During Valganciclovir Maintenance Treatment, by Decreasing Frequency (Overall Incidence (≥ 4%), Using Data From Previous Ganciclovir Studies for Comparison)

Summary of Adverse Events With an Incidence Rate of at Least 4 % by Trial Treatment - All Adverse Events
 Protocol(s): S0034 S0041 S1653 S1697 S1774 S2226 S2304 WV15376 WV15705
 Analysis: SAFETY Center: ALL CENTERS
 SUMMARY OF ALL AEs BY FREQUENCY
 Adverse Event Onset between Study Day 1, Clock Time 00:00 and Study Day 9999, Clock Time 23:59

Adverse Event	VGCV	IV GCV	PO GCV 3G	PO GCV 4.5G	PO GCV 6G	Placebo
	N = 370 No. (%)	(prior studies) N = 412 No. (%)	(prior studies) N = 536 No. (%)	(prior studies) N = 180 No. (%)	(prior studies) N = 206 No. (%)	(prior studies)* N = 119 No. (%)
PYREXIA	88 (23.8)	148 (35.9)	187 (34.9)	57 (31.7)	63 (30.6)	42 (35.3)
DIARRHOEA NOS	126 (34.1)	109 (26.5)	167 (31.2)	65 (36.1)	61 (29.6)	29 (24.4)
NEUTROPENIA	76 (20.5)	106 (25.7)	121 (22.6)	41 (22.8)	58 (28.2)	14 (11.8)
NAUSEA	80 (21.6)	80 (19.4)	132 (24.6)	43 (23.9)	49 (23.8)	26 (21.8)
FATIGUE	67 (18.1)	75 (18.2)	89 (16.6)	43 (23.9)	25 (12.1)	27 (22.7)
ANAEMIA NOS	74 (20.0)	81 (19.7)	92 (17.2)	17 (9.4)	36 (17.5)	20 (16.8)
HEADACHE NOS	59 (15.9)	77 (18.7)	86 (16.0)	32 (17.8)	28 (13.6)	19 (16.0)
COUGH	54 (14.6)	66 (16.0)	79 (14.7)	28 (15.6)	23 (11.2)	18 (15.1)
VOMITING NOS	62 (16.8)	51 (12.4)	69 (12.9)	35 (19.4)	33 (16.0)	15 (12.6)
ORAL CANDIDIASIS	64 (17.3)	26 (6.3)	50 (9.3)	15 (8.3)	46 (22.3)	15 (12.6)
DYSPNOEA	31 (8.4)	44 (10.7)	53 (9.9)	29 (16.1)	19 (9.2)	13 (10.9)
DERMATITIS NOS	61 (16.5)	24 (5.8)	45 (8.4)	28 (15.6)	15 (7.3)	11 (9.2)
ABDOMINAL PAIN NOS	44 (11.9)	37 (9.0)	51 (9.5)	23 (12.8)	19 (9.2)	9 (7.6)
SINUSITIS NOS	35 (9.5)	26 (6.3)	21 (3.9)	17 (9.4)	20 (9.7)	16 (13.4)
APPETITE DECREASED	26 (7.0)	26 (6.3)	35 (6.5)	21 (11.7)	14 (6.8)	10 (8.4)
CANDIDA NOS	14 (3.8)	43 (10.4)	33 (6.2)	20 (11.1)	13 (6.3)	5 (4.2)
INSOMNIA	49 (13.2)	21 (5.1)	25 (4.7)	11 (6.1)	13 (6.3)	9 (7.6)
PNEUMONIA NOS	24 (6.5)	30 (7.3)	12 (2.2)	32 (17.8)	9 (4.4)	18 (15.1)
NIGHT SWEATS	24 (6.5)	34 (8.3)	37 (6.9)	10 (5.6)	7 (3.4)	10 (8.4)
WEIGHT DECREASE	34 (9.2)	25 (6.1)	28 (5.2)	12 (6.7)	11 (5.3)	9 (7.6)
DEPRESSION NOS	29 (7.8)	23 (5.6)	30 (5.6)	16 (8.9)	10 (4.9)	9 (7.6)
PERIPHERAL NEUROPATHY NOS	26 (7.0)	23 (5.6)	25 (4.7)	16 (8.9)	11 (5.3)	16 (13.4)
PNEUMOCYSTIS CARINII PNEUMONIA	17 (4.6)	30 (7.3)	34 (6.3)	15 (8.3)	18 (8.7)	3 (2.5)
THROMBOCYTOPENIA	19 (5.1)	27 (6.6)	37 (6.9)	10 (5.6)	10 (4.9)	6 (5.0)
RETINAL DETACHMENT	44 (11.9)	10 (2.4)	16 (3.0)	16 (8.9)	11 (5.3)	6 (5.0)
DIZZINESS (EXC VERTIGO)	32 (8.6)	18 (4.4)	22 (4.1)	14 (7.8)	7 (3.4)	6 (5.0)
RIGORS	9 (2.4)	32 (7.8)	32 (6.0)	8 (4.4)	6 (2.9)	10 (8.4)
WEAKNESS	10 (2.7)	20 (4.9)	31 (5.8)	14 (7.8)	11 (5.3)	9 (7.6)
MYCOBACTERIUM AVIUM COMPLEX	10 (2.7)	20 (4.9)	27 (5.0)	12 (6.7)	19 (9.2)	5 (4.2)

Percentages are based on N. Percentages not calculated if N < 10.
 Multiple occurrences of the same adverse event in one individual counted only once.
 * Oral placebo + ganciclovir intravitreal implant group from study 2304.
 AE13 18JUL2000:20:17:02

(pdrd)



Appendix 21 Minimum ANC, Hemoglobin and Platelet Levels, and Maximum Serum Creatinine Values During Valganciclovir Maintenance Treatment, Using Data From Previous Ganciclovir Studies for Comparison

ae203b24, b25, b26 and b27 Laboratory Values During Treatment - Maintenance from all protocols

	VGCV N=370	IV GCV (prior studies) N=412	PO GCV 3g (prior studies) N=536	PO GCV 4.5g (prior studies) N=180	PO GCV 6g (prior studies) N=206	Placebo (prior studies)* N=119
ANC (cells/ul)						
Unevaluable	7	312	535	64	203	11
< 500	55 (15.2%)	16 (16.0%)		31 (26.7%)		12 (11.1%)
500 to < 750	54 (14.9%)	9 (9.0%)		17 (14.7%)	1 (33.3%)	18 (16.7%)
750 to < 1000	59 (16.3%)	25 (25.0%)		20 (17.2%)		19 (17.6%)
>= 1000	195 (53.7%)	50 (50.0%)	1 (100%)	48 (41.4%)	2 (66.7%)	59 (54.6%)
Hemoglobin (g/dl)						
Unevaluable	7	84	18	6	5	10
< 6.5	25 (6.9%)	10 (3.0%)	7 (1.4%)	5 (2.9%)	3 (1.5%)	1 (0.9%)
6.5 to < 8.0	34 (9.4%)	53 (16.2%)	48 (9.3%)	15 (8.6%)	13 (6.5%)	11 (10.1%)
8.0 to < 9.5	39 (10.7%)	88 (26.8%)	120 (23.2%)	40 (23.0%)	47 (23.4%)	25 (22.9%)
>= 9.5	265 (73.0%)	177 (54.0%)	343 (66.2%)	114 (65.5%)	138 (68.7%)	72 (66.1%)
Platelets (cells/mm3)						
Unevaluable	9	118	104	24	49	11
< 25000	10 (2.8%)	8 (2.7%)	6 (1.4%)	3 (1.9%)	3 (1.9%)	1 (0.9%)
25000 to < 50000	17 (4.7%)	19 (6.5%)	36 (8.3%)	8 (5.1%)	11 (7.0%)	3 (2.8%)
50000 to < 100000	73 (20.2%)	68 (23.1%)	98 (22.7%)	40 (25.6%)	39 (24.8%)	16 (14.8%)
>= 100000	261 (72.3%)	199 (67.7%)	292 (67.6%)	105 (67.3%)	104 (66.2%)	88 (81.5%)
Creatinine (mg/dl)						
Unevaluable	7	88	23	9	11	13
<= 1.5	318 (87.6%)	282 (87.0%)	452 (88.1%)	146 (85.4%)	174 (89.2%)	90 (84.9%)
> 1.5 to 2.5	39 (10.7%)	38 (11.7%)	54 (10.5%)	24 (14.0%)	17 (8.7%)	15 (14.2%)
> 2.5	6 (1.7%)	4 (1.2%)	7 (1.4%)	1 (0.6%)	4 (2.1%)	1 (0.9%)

Note: percentages refer to number of patients exhibiting event out of number of patients for whom a parameter measurement was available and not total patient number

* Oral placebo + ganciclovir intravitreal implant group from study 2304.

Program : \$PROD/cdp01269/ae203.sas / Output : \$PROD/cdp01269/reports/ae203b24.sl8
29AUG2000 13:13 (pdrd)



Appendix 22 Updated Adverse Events Reported During Valganciclovir Studies WV15376 and WV15705, by Decreasing Frequency (Updated Incidence ≥ 10%)

Safety Update	NDA (Integrated Summary of Safety, Table 17)																																																																																												
<p>Summary of Adverse Events With an Incidence Rate of at Least 10 % by Trial Treatment All Adverse Events Protocol(s): WV15376 WV15705 Analysis: SAFETY Center: ALL CENTERS SUMMARY OF ALL AEs BY FREQUENCY (ALL) Adverse Event Onset between Study Day 1, Time 00:00 and Study Day 9999, Time 23:59</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: left;">Adverse Event</th> <th style="text-align: center;">VGCV N = 370 No. (%)</th> </tr> </thead> <tbody> <tr><td>DIARRHOEA NOS</td><td style="text-align: center;">150 (41)</td></tr> <tr><td>PYREXIA</td><td style="text-align: center;">115 (31)</td></tr> <tr><td>NAUSEA</td><td style="text-align: center;">110 (30)</td></tr> <tr><td>NEUTROPENIA</td><td style="text-align: center;">99 (27)</td></tr> <tr><td>ANAEMIA NOS</td><td style="text-align: center;">95 (26)</td></tr> <tr><td>ORAL CANDIDIASIS</td><td style="text-align: center;">87 (24)</td></tr> <tr><td>DERMATITIS NOS</td><td style="text-align: center;">81 (22)</td></tr> <tr><td>HEADACHE NOS</td><td style="text-align: center;">80 (22)</td></tr> <tr><td>FATIGUE</td><td style="text-align: center;">78 (21)</td></tr> <tr><td>VOMITING NOS</td><td style="text-align: center;">78 (21)</td></tr> <tr><td>COUGH</td><td style="text-align: center;">70 (19)</td></tr> <tr><td>INSOMNIA</td><td style="text-align: center;">58 (16)</td></tr> <tr><td>ABDOMINAL PAIN NOS</td><td style="text-align: center;">57 (15)</td></tr> <tr><td>INFLUENZA</td><td style="text-align: center;">57 (15)</td></tr> <tr><td>RETINAL DETACHMENT</td><td style="text-align: center;">56 (15)</td></tr> <tr><td>NASOPHARYNGITIS</td><td style="text-align: center;">44 (12)</td></tr> <tr><td>SINUSITIS NOS</td><td style="text-align: center;">43 (12)</td></tr> <tr><td>UPPER RESPIRATORY TRACT INFECTION NOS</td><td style="text-align: center;">43 (12)</td></tr> <tr><td>DEPRESSION NOS</td><td style="text-align: center;">41 (11)</td></tr> <tr><td>BRONCHITIS NOS</td><td style="text-align: center;">40 (11)</td></tr> <tr><td>DIZZINESS (EXC VERTIGO)</td><td style="text-align: center;">39 (11)</td></tr> <tr><td>WEIGHT DECREASE</td><td style="text-align: center;">39 (11)</td></tr> </tbody> </table> <p>Percentages are based on N. Percentages not calculated if N < 10. Multiple occurrences of the same adverse event in one individual counted only once. 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Appendix 23 Minimum ANC, Hemoglobin and Platelet Levels and Maximum Serum Creatinine Values During Valganciclovir Studies WV15376 and WV15705

valganciclovir (Ro 107-9070)



FDA Advisory Committee Briefing Document

FDA Advisory Committee Briefing Document - 91

Safety Update	NDA (Integrated Summary of Safety, Table 31)
cg_ae203d24,25,26,27 Laboratory Values During Treatment - All from wv15376 & wv15705	ae203d24,25,26,27 Laboratory Values During Treatment - All from wv15376 & wv15705
VGCV N=370	VGCV N=370
ANC (cells/ul)	ANC (cells/ul)
< 500 69 (18.6%)	< 500 60 (16.2%)
500 to < 750 63 (17.0%)	500 to < 750 62 (16.8%)
750 to < 1000 63 (17.0%)	750 to < 1000 63 (17.0%)
>= 1000 175 (47.3%)	>= 1000 185 (50.0%)
Hemoglobin (g/dL)	Hemoglobin (g/dL)
< 6.5 26 (7.0%)	< 6.5 25 (6.8%)
6.5 to < 8.0 48 (13.0%)	6.5 to < 8.0 37 (10.0%)
8.0 to < 9.5 58 (15.7%)	8.0 to < 9.5 51 (13.8%)
>= 9.5 238 (64.3%)	>= 9.5 257 (69.5%)
Platelets (cells/mm3)	Platelets (cells/mm3)
Unevaluable 1	Unevaluable 1
< 25000 13 (3.5%)	< 25000 10 (2.7%)
25000 to < 50000 22 (6.0%)	25000 to < 50000 18 (4.9%)
50000 to < 100000 80 (21.7%)	50000 to < 100000 77 (20.9%)
>= 100000 254 (68.8%)	>= 100000 264 (71.5%)
Creatinine (mg/dL)	Creatinine (mg/dL)
<= 1.5 317 (85.7%)	<= 1.5 324 (87.6%)
> 1.5 to 2.5 43 (11.6%)	> 1.5 to 2.5 40 (10.8%)
> 2.5 10 (2.7%)	> 2.5 6 (1.6%)
Note: percentages refer to number of patients exhibiting event out of number of patients for whom a parameter measurement was available and not total patient number	Note: percentages refer to number of patients exhibiting event out of number of patients for whom a parameter measurement was available and not total patient number
Program : \$PROD/cdp01269/cg_ae203.sas / Output : \$PROD/cdp01269/reports/cg_ae203d24,25,26,27.s18 05OCT2000 15:06 pdrd	Program : \$HOME/cdp01269/ae203.sas / Output : \$HOME/cdp01269/reports/ae203d24,25,26,27.s18 10MAY2000 16:13 pdrd