The pharmacokinetic and metabolic studies have shown that valganciclovir is a prodrug of ganciclovir which is rapidly absorbed and efficiently hydrolysed in all non-clinical species investigated. The bioavailability of ganciclovir from an oral dose of valganciclovir is increased over that of ganciclovir by almost a factor of 10 in rats and cynomolgus monkeys and is 100% in mice and dogs. Ganciclovir is the only metabolite of valganciclovir and the tissue distribution pattern following i.v. doses of either compound is the same, supporting the premise that valganciclovir is an alternative and more effective means of delivering ganciclovir.

Non-clinical safety studies demonstrated a toxicological profile that is essentially the same as the well-documented toxicity profile of ganciclovir with no additional findings with valganciclovir. The main target organs for both compounds were the reproductive, hematopoietic, renal, intestinal, and adnexal systems.

At the highest exposure achieved for valganciclovir following i.v. doses to mice (10 times greater than the maximum clinical dose of 900 mg b.i.d.), no toxicological findings were recorded other than those expected from exposure to ganciclovir.

Toxicity is induced by ganciclovir exposures equal to or lower than the therapeutic human exposure. However, the therapeutic dose of valganciclovir has been selected to give a ganciclovir AUC comparable to that achieved with current intravenous ganciclovir where the safety profile is well known and manageable in clinical practice.

6. HUMAN PHARMACOKINETICS AND BIOAVAILABILITY

Since valganciclovir is a pro-drug whose main function is to deliver ganciclovir, it is the pharmacokinetics of ganciclovir which are more pertinent to the efficacy and safety of the product. For ease of review a summary of the pharmacokinetics of oral and i.v. ganciclovir is provided followed by the information for valganciclovir.

6.1 Human Pharmacokinetics and Bioavailability Summary for Ganciclovir

This application includes a report reviewing the current state of knowledge regarding the pharmacokinetics of oral and i.v. ganciclovir. This document is intended as supportive information to the human pharmacokinetics and biopharmaceutics summary for valganciclovir.

The data reviewed originates from internal studies used in support of previous submissions for i.v. and oral ganciclovir and from data available as published literature.

6.1.1 Summary of Ganciclovir Pharmacokinetics

6.1.1.1 Absorption

The absolute bioavailability of ganciclovir capsules under fasting conditions ranged from 3 to 13%. At the recommended dose, food increased the steady state AUC by 20%, increased the C_{max} slightly and delayed the time taken to reach peak concentration. The absolute bioavailability of ganciclovir under fed conditions averaged 6% to 9%.

6.1.1.2 Distribution

The steady state volume of distribution of ganciclovir following i.v. administration ranged from 0.54 to 0.87 L/kg. These values were consistent with distribution to total body water given the low binding of ganciclovir to plasma proteins (1 to 2%).

For i.v. ganciclovir, volume of distribution was correlated with body weight, and is therefore dosed on a mg/kg basis. For oral ganciclovir capsules no correlation was seen between AUC and the reciprocal weight over a weight range of 55 to 128 kg.

Ganciclovir has been shown to penetrate the CSF (cerebrospinal fluid). Available data show that ganciclovir concentrations in the CSF range from 24 to 67% of those measured simultaneously in plasma following administration of i.v. ganciclovir.

6.1.1.3 Metabolism

Ganciclovir is not metabolized to any appreciable extent. In patients with normal renal function, more than 90% of administered i.v. ganciclovir was recovered unchanged in the urine. Following oral administration of a single 1000 mg dose of ^{14}C-labelled ganciclovir, 86 ± 3% of the administered dose was recovered in the feces and 5 ± 1% was recovered in the urine. Total metabolite (and/or impurities) revovered in excreta did not account for more than 3.5% of total drug.

6.1.1.4 Elimination

When administered intravenously, ganciclovir exhibits linear pharmacokinetics over the range of 1.6 to 5.0 mg/kg and when administered orally, it exhibits linear kinetics up to a total daily dose of 4 g/day. The major route of ganciclovir elimination is renal excretion of unchanged drug by glomerular filtration and renal tubular secretion. In subjects with normal renal function, systemic clearance ranged from 2.64 ± 0.38 mL/min/kg to 4.52 ± 2.79 mL/min/kg and renal clearance ranged from 2.57 ± 0.69 mL/min/kg to 3.48 ± 0.68 mL/min/kg, corresponding to 90-101% of administered ganciclovir. Half-lives in subjects without renal impairment ranged from 2.73 to 3.98 hours. Following oral administration, longer half-life has been observed, ranging from 2.85 ± 1.86 to 10.5 ± 3.5 hours.

6.1.1.5 Relative exposure

Systemic exposure (AUC_{0-24}) ranged from 19 to 26 µg.h/mL in HIV/CMV+ subjects or AIDS patients following i.v. ganciclovir (5 mg/kg/day). Lower exposure, 13 to 19 µg.h/mL, was seen in the same patient population following oral ganciclovir (3 g/day). Systemic exposure was increased in renal transplant patients by approximately two-fold when compared to HIV/CMV+ subjects but differences in C_{max} were marginal.

6.1.1.6 Special Populations

Renal Impairment

Dose adjustments are required for i.v. ganciclovir and recommended for oral ganciclovir in patients whose creatinine clearance falls below 70 mL/min. The recommended dose adjustments are shown below.

	Intravenous Ganciclovir				Oral Ganciclovir	
	Induction		Maintenance			
Estimated CrCL (mL/min)	Dose i.v. (mg/kg)	Dosing Interval (h)	Dose i.v. (mg/kg)	Dosing Interval (h)	Dose (mg)	Interval (h)
≥ 70	5	12	5	24	1000 (or 500)	t.i.d. (or 6x/day)
50 - 69	2.5	12	2.5	24	1500 (or 500)	q.d. (or t.i.d.)
25 - 49	2.5	24	1.25	24	1000 (or 500)	q.d. (or b.i.d.)
10 - 24	1.25	24	0.625	24	500	q.d.
<10	1.25	t.i.w. after dialysis	0.625	t.i.w. after dialysis	500	t.i.w. after dialysis

Hemodialysis

Ganciclovir is readily removable by hemodialysis. The amount of ganciclovir removed in one dialysis session is about 50%, the actual value depends upon the type and to a lesser extent upon the conditions of dialysis. Intermittent dialysis is associated with clearance values of 42 to 92 mL/min (30 to 66 L/week) while continuous dialysis is associated with lower clearance values of 4.0 to 29.6 mL/min but greater removal of ganciclovir as dialysis is continuous (40 to 298 L/week).

Race and Gender

In Blacks and Hispanics there appeared to be a tendency towards a lower steady state C_{max} and AUC_{0-8} following oral ganciclovir compared to Caucasians. There were no differences in AUC_{0-8}, C_{max} or renal clearance between age and race matched males and females despite a small apparent difference in elimination half-life.

Solid Organ Transplant Recipients vs. HIV

The pharmacokinetics of ganciclovir in solid organ transplant recipients (kidney and liver transplants) have shown an increase of exposure ($AUC_{0\text{-}24}$ of 50 and 60 μg.hr/mL) compared to HIV patients (AUC ranging from 13 to 19 μg.hr/mL) due to the influence of renal dysfunction in transplant patients.

Bone Marrow Transplant Recipients

The pharmacokinetics of oral ganciclovir were studied in adult patients with and without acute gastrointestinal graft versus host disease. The absolute bioavailability was similar between the two patient groups and the 8 hour AUCs at steady-state were also similar. However, the AUCs observed were higher than those previously seen in other populations (HIV patients and solid organ transplant recipients with normal renal function).

Pediatrics

Studies in neonates aged 2 to 49 days and children aged 9 months to 12 years revealed that the pharmacokinetics of i.v. ganciclovir are similar to those in adults.

6.1.2 Exposure Response Relationships

Higher exposures of ganciclovir (represented by AUC) were statistically significantly associated with longer times to progression of CMV retinitis. C_{max} did not add any further predictive value over AUC. Therefore average AUC, and not average C_{max}, is a better predictor of clinical response.

A 4-arm randomized, parallel group study (I*) compared maintenance treatment with daily oral doses of 3 g, 4.5 g and 6 g ganciclovir with 5 mg/kg i.v. ganciclovir in patients with AIDS and CMV retinitis that was stable after at least 4 weeks of i.v. ganciclovir treatment.

Protocol No/ Report No/ Ref	Design	Dose	Subjects
I*	Parallel group study comparing the efficacy of 3 oral and 1 intravenous regimen of ganciclovir in the maintenance treatment of CMV retinitis	A: 3 g/day oral GCV B: 4.5 g/day oral GCV C: 6 g/day oral GCV D: 5 mg/kg/day i.v. GCV	281

The primary endpoint, 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 drawn routinely at Weeks 2 and 6 from all patients for assay of ganciclovir concentration. Additional samples were also collected if renal function deteriorated, a serious adverse event occurred or progression of CMV retinitis was diagnosed.

A previous population pharmacokinetic and pharmacodynamic analysis of this study has shown that increases in ganciclovir area under the plasma

concentration versus time curve $AUC_{0\text{-}24}$ (calculated using the dose to which subjects were randomized) was associated with statistically significant increases in the time to progression (TTP) of CMV retinitis.

An additional retrospective analysis was performed to further define the relationship between individual derived pharmacokinetic parameters with time to progression. This additional analysis included:

- a review of actual treatment details (dose and time) for the population pharmacokinetic analysis
- simultaneous modeling of oral and i.v. data,
- the derivation of exposure parameters: $AUC_{0\text{-}24}$, C_{max} and C_{min}, using treatment information on the day prior to photographic progression of CMV retinitis and individual pharmacokinetic parameters estimated on that day,
- the derivation of exposure parameters: average $AUC_{0\text{-}24}$, C_{max} and C_{min} using the entire dosing history to first photographic progression,
- investigation of the relationship between average $AUC_{0\text{-}24}$, C_{max} and C_{min} and time to first photographic progression.

Pharmacokinetic parameters were derived by applying non-linear mixed effects modeling (NONMEM) to fit the ganciclovir concentration data. The association between time to progression of CMV retinitis and exposure parameters was investigated using the Cox proportional hazards model and the Weibull accelerated failure model.

The results of the Cox regression analysis showed that neither $AUC_{0\text{-}24}$ nor C_{max} estimated on the day prior to first photographic progression offered better predictor value over the other. In contrast, increases in average $AUC_{0\text{-}24}$ were statistically significantly associated with increases in the 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 the time to progression ($p=0.0326$) when fitted in a separate model. However, when average $AUC_{0\text{-}24}$ and average C_{max} were fitted in the same model the association between $AUC_{0\text{-}24}$ 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. Thus these findings indicate that average $AUC_{0\text{-}24}$ is a better predictor of time to progression and average C_{max} does not add any predictive value over average $AUC_{0\text{-}24}$.

6.2 Human Pharmacokinetics and Bioavailability Summary for Valganciclovir

Since valganciclovir is a pro-drug whose main function is to act as a delivery system for ganciclovir, it is the pharmacokinetics of ganciclovir which are more pertinent to the efficacy and safety of the product. The valganciclovir clinical program focuses on:

1. Characterization of the repeat dose pharmacokinetics and dose proportionality of valganciclovir and its antiviral metabolite ganciclovir (Study WP15347).
2. Assessment of the effect of food on the pharmacokinetics of valganciclovir and ganciclovir (Study WP15347).
3. Determination of the absolute bioavailability of ganciclovir from valganciclovir (Studies F* D* G* E* H* & 15376).
4. Demonstration of bioequivalence between the clinical trial formulation and proposed market formulation (Study G*).
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 E*).
6. Investigation of single dose pharmacokinetics of valganciclovir in relation to those of i.v ganciclovir and oral ganciclovir in liver transplant recipients to allow selection of an appropriate dose for use in this patient population (Study H*).

6.2.1 Drug Formulation Development Summary

Solid oral dosage forms (tablets) and an oral solution have been developed for use in the clinical program. The market formulation is a 450 mg tablet (MF450), which is similar in composition to the formulation used in the clincial studies (CT450).

A total of 4 formulations were used in the clinical development program.

Table 12 Formulations Used in Clinical Studies

Formulation Type	Strength	Identifier	Formulation No.
Tablets	450mg	CT450	013
Tablets	450mg	MF450	019
Tablets	875mg	CT875	014
Oral solution	30mg/mL	SOLN	003

The development of the initial tablet formulation (CT450) occurred early in the development program and all the studies except the initial entry into humans study and the bioequivalence study have used this formulation. The same formulation was used in Phase III studies and is similar, but not identical, to the proposed market formulation. The major difference between the market (MF450) and Phase III (CT450) formulation is the addition of a film coat to the market formulation. The proposed commercial tablet formulation is bioequivalent to the formulation used in the primary efficacy/safety studies based on AUC (point estimate 101%, 90% CI 97%, 105%), but not C_{max} (point estimate 114%, 90% CI 101%, 128%).

The tablet formulation CT875 was used in one study only (' D*), which assessed dose proportionality and the effects of food on ganciclovir and valganciclovir pharmacokinetics following dosing with oral valganciclovir.

Dissolution testing was carried out under standardized conditions throughout the formulation development. The data show that all clinical trial dosage forms have similar *in vitro* dissolution characteristics.

6.2.2 Summary of Pharmacokinetics for Valganciclovir

Pharmacokinetic information has been derived in 190 subjects. The population of subjects recruited for the valganciclovir clinical program consisted predominantly of subjects who were HIV/CMV scropositive and HIV positive patients with CMV retinitis. In addition, the compound was studied in renally impaired subjects, liver transplant recipients and healthy volunteers. The subjects in the valganciclovir clinical program who had pharmacokinetic sampling are shown in , categorized by disease group and CMV status.

Table 13 Subjects Included in the Clinical Pharmacology and Therapeutic Valganciclovir Studies Who had Pharmacokinetic Sampling, By Disease Group

	Healthy volunteers	HIV+	HIV+-, CMV+	HIV+/ CMV+ retinitis	Renally Impaired	Liver Tx*	Total
Randomized	12	18	65	160	24	28	307
Evaluable for pk	12	18	58	51	23	28	190

*Liver tx recipients who were either CMV+ and 45-90 days post tx or CMV-ve and had received an organ from a CMV+ donor

Valganciclovir and ganciclovir concentrations have been measured in plasma using HPLC, with fluorescence detection. Model-independent pharmacokinetic parameters have been estimated by standard techniques.

6.2.2.1 Absorption

Valganciclovir is highly effective in delivering ganciclovir to the systemic circulation. Valganciclovir is well absorbed from the gastrointestinal tract and is rapidly and extensively converted by intestinal and hepatic esterases to ganciclovir. Peak plasma concentrations of valganciclovir occurred within 2 hours across all studies, formulations and doses.

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. This figure is consistent across doses and patient populations. A comparison of the rate of appearance

of ganciclovir achieved through dosing valganciclovir relative to that from oral ganciclovir capsules has been performed in two studies: F* in HIV, CMV seropositive subjects, and H* in liver transplant recipients. In both studies, the rate of appearance of ganciclovir following administration of valganciclovir is more rapid than seen with the currently approved oral capsule formulation of ganciclovir.

Valganciclovir when given with food over a dose range of 450 mg to 2625 mg leads to an increase in the extent of exposure of ganciclovir (AUC_{0-24}) by 24-56% (30% at 900 mg). The effect of food on ganciclovir AUC_{0-24} was found to be statistically significant (p= ≤0.001). The mean C_{max} values of ganciclovir were increased when valganciclovir was given after food. The increases seen were smaller than those seen with AUC_{0-24} and were not statistically significant (p= 0.079). Estimates of the effect of food are shown in Table 14.

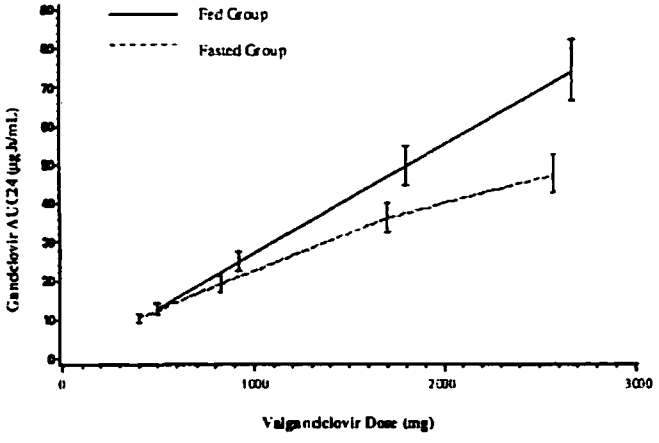
Table 14 Bioavailability of Ganciclovir When Valganciclovir is Dosed After Food Relative to Dosing in the Fasted State (D*)

Parameter	Dose (mg)	Relative Bioavailability	95% Confidence Limits
AUC_{0-24} (μg.h/mL)	450	1.24	[1.07, 1.44]
AUC_{0-24} (μg.h/mL)	875	1.30	[1.12, 1.51]
AUC_{0-24} (μg.h/mL)	1750	1.37	[1.18, 1.59]
AUC_{0-24} (μg.h/mL)	2625	1.56	[1.35, 1.81]
C_{max} (μg/mL)	450	1.06	[0.89, 1.26]
C_{max} (μg/mL)	875	1.14	[0.95, 1.36]
C_{max} (μg/mL)	1750	1.15	[0.96, 1.37]
C_{max} (μg/mL)	2625	1.26	[1.05, 1.50]

Study WV15347 also showed that 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.

Other parameters increased with increasing dose but the increases were not dose proportional. The analysis of the log-transformed and dose adjusted parameters AUC_{0-24} and C_{max} showed significant deviation from dose proportionality (p= <0.001). For the AUC_{0-24} there was a significant interaction between the food group and the dose (p= ≤0.001), indicating that the dose response relationship was different for the two food groups. Due to this significant interaction, the test for dose proportionality was performed separately for the fed and fasted food groups for AUC_{0-24}. While for the fed group no significant deviation from dose proportionality was found (p=0.997), in the fasted group there was significant deviation (p≤ 0.001) such that increases in dose were accompanied by less than proportional increases in AUC_{0-24} or C_{max}. The dose response (split by food group) is shown for AUC_{0-24} in Figure 6 together with the 95% confidence intervals. On the basis of these results, it is recommended that valganciclovir is given with food.

Figure 6 **Dose Proportionality of Ganciclovir AUC_{0-24} Following Administration of Valganciclovir**
(' D*)



6.2.2.2 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 Vss of ganciclovir with valganciclovir dosing appear independent of patient population and are consistent with distribution of ganciclovir in total body water.

No data are available regarding the penetration of valganciclovir into the cerebrospinal fluid (CSF). Published data show that concentrations of ganciclovir in the CSF, following dosing with i.v ganciclovir, range from 24-67% of those measured simultaneously in plasma.

No data are available regarding the intra-ocular penetration of valganciclovir. Based upon published data with i.v. ganciclovir, intra-ocular concentrations of ganciclovir range from 40-88% of those measured simultaneously in plasma. Average intravitreal concentrations in the eye following induction and maintenance dosing with i.v. ganciclovir were 1.15 and 1.00 µg/mL, respectively. The half-life of ganciclovir within the eye is much longer than that seen in plasma with estimates ranging from 13.3 to 18.8 hours.

The protein binding of valganciclovir has not been determined. Binding of ganciclovir to human plasma proteins over ganciclovir concentrations of 0.5 to 51 µg/mL is 1 to 2%.

Data obtained using an *ex vivo* model for placental transfer have shown that ganciclovir crosses the human placenta. The transfer occurred via simple

diffusion and the transfer rate was not saturated over the concentration range studied (1 to 10 µg/mL).

6.2.2.3 Metabolism

In accordance with pre-clinical data, valganciclovir when given orally undergoes rapid and extensive pre-systemic conversion to ganciclovir as suggested by the substantially higher plasma concentrations of ganciclovir compared to valganciclovir. Systemic exposure to valganciclovir is low at all doses with an AUC ratio of valganciclovir to ganciclovir of 0.99% ±0.51% (n=319) and a C_{max} ratio of 3.06 ± 1.49% (n=320). *In vitro* studies using human and animal (dog and mouse) intestinal and hepatic S9 fractions show that valganciclovir is metabolized to ganciclovir with no other metabolites having been identified.

6.2.2.4 Elimination

Valganciclovir is eliminated primarily by metabolism to ganciclovir and the latter is subsequently eliminated renally. 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.

The major route of elimination of ganciclovir is renal clearance of unchanged drug by both glomerular filtration and net active tubular secretion. From the data presented in Table 15 it can be seen that the values obtained for the clearance of ganciclovir range from 1.87 (%CV 35) mL/min/kg to 3.39 (%CV 15) mL/min/kg, whilst values for the renal clearance of ganciclovir range from 1.49 (%CV 38) mL/min/kg to 3.11 (%CV 23) mL/min/kg. The clearance of ganciclovir appears to be slower in liver transplant recipients, but this is accounted for by the lower renal clearance in these subjects. The data from all the above studies were pooled and used to calculate an average value (±SD) of 2.77 ±0.92 mL/min/kg (n=113) for the systemic clearance of ganciclovir with renal clearance of 2.08 ±0.923mL/min/kg (n=71) accounting for 81.5 ±22% of the systemic clearance (n=70). The clearance of ganciclovir has previously been well characterized with average values in subjects with normal renal function for systemic clearance (CL_{iv}) ranging from 2.64 ±0.38 mL/min/kg to 3.86 ±0.59 mL/min/kg and those for renal clearance ranging from 2.57 ±0.69 mL/min/kg to 3.48 ±0.68 mL/min/kg. The values obtained for the elimination of ganciclovir obtained during the development of valganciclovir are thus consistent with previous data.

Table 15 Clearance and Renal Clearance of Ganciclovir (Mean (%CV))

Study No	Patient Population	N	CL_{iv} (mL/min/kg)	CL_R (mL/min/kg)
F*	HIV, CMV seropositive	18	3.39 (15)	nc
G*	HIV seropositive	17	2.77 (23)	nc
E*	Healthy volunteers	8	3.38 (16)	2.88 (20)
	HIV, CMV seropositive	7	3.34 (13)	3.11 (23)
WV15376	HIV seropositive, CMV retinitis	17	2.97 (44)	1.96 (42)
	HIV seropositive, CMV retinitis	18	2.82 (23)	2.14 (44)
H*	Liver Transplant Recipients	28	1.87 (35)	1.49 (38)

6.2.2.5 Accumulation and Dose Proportionality

The multiple dose pharmacokinetics of valganciclovir and ganciclovir were investigated in study D* The study showed that valganciclovir does not accumulate with multiple dosing at doses of 450 to 2625 mg given once daily. Plasma concentrations of valganciclovir could not be quantified in pre-dose samples in all subjects, and were not quantifiable in the majority of subjects by 6 hours at the highest dose. Although the accumulation ratio for the metabolite ganciclovir was not determined, accumulation is not expected based on its half-life of 3.5 to 4.5 hours.

As discussed in Section 6.2.2.1, in study D* , when valganciclovir is given with food, the AUC_{0-24} for ganciclovir is dose proportional over the dose range studied. C_{max} values for ganciclovir and valganciclovir increased with increasing dose but were not dose proportional in both the fed and fasted states.

6.2.2.6 Bioavailability/bioequivalence

The absolute bioavailability of oral ganciclovir capsules was 5 to 7% in the clinical pharmacology studies performed in the valganciclovir development program (Table 16). This is consistent with values of 6 to 9% previously reported for oral ganciclovir.

Table 16 Absolute Bioavailability of Oral Ganciclovir 250 mg Capsules

Study	Dose (g)	Formulation	Nominal/Actual i.v. Dose	Population	F (95% CI)
F*	1	250 mg caps	Actual	HIV CMV+	5.57 (1.81)*
H*	3	250 mg caps	Nominal	Liver Tx	6.3 (5.5 to 7.1)

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

The absolute bioavailability of ganciclovir from orally dosed valganciclovir is much greater (approximately 10 fold) than that seen with the existing ganciclovir capsule formulation, showing that valganciclovir is an effective mechanism for the delivery of ganciclovir to the systemic circulation. The absolute bioavailability of ganciclovir from valganciclovir is approximately 60% and appears to be independent of the patient population studied (Table 17).

Table 17 Absolute Bioavailability of Ganciclovir when Administered as Valganciclovir

Study	Dose mg	Formulation	Nominal/Actual i.v. Dose	Population	F (95% CI)
F*	360	SOLN	Actual	HIV CMV+	60.9 (9.10)* - as in report
H*	450	CT450	Nominal	Liver Tx	60 (56 to 64)
	900	CT450	Nominal	Liver Tx	59 (55 to 63)
E*	900	CT450	Nominal	HIV CMV+	61 (55 to 67)
	900	CT450	Nominal	Healthy volunteers	59 (54 to 64)
G*	900	CT450	Nominal	HIV+	59 (56 to 62)
	900	MF450	Nominal	HIV+	59 (56 to 62)
WV15376	900 (b.i.d.)	CT450	Nominal	HIV+ retinitis	64 (49 to 78)
	900	CT450	Nominal	HIV+ retinitis	59 (42 to 76)

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

The proposed market tablet formulation is bioequivalent to the formulation used in the primary efficacy/safety studies based on AUC (point estimate 101%, 90% CI 97%, 105%), but not C_{max} (point estimate 114%, 90% CI 101%, 128%). However, the dissolution profiles of the two formulations were found to be equivalent. It is unlikely that an increase in C_{max} of this magnitude will lead to safety concerns, given that treatment with i.v ganciclovir (5 mg/kg) is associated with C_{max} values (10 μg/mL) approximately double those observed for the market formulation.

6.2.2.7 Effects of Demography

The findings of a meta-analysis conducted on the data pooled from all the valganciclovir clinical studies are summarized below:

Liver transplant recipients had a substantially reduced systemic and renal clearance in comparison to the other groups examined. This resulted in a higher mean ganciclovir AUC (approximately 40% higher in relation to

HIV+/CMV+ subjects and 20% higher relative to AIDS/CMV retinitis patients) and $t_{1/2}$ (approximately 20% relative to both HIV+/CMV+ and AIDS/CMV retinitis subjects) in liver transplant recipients relative to other subject groups.

The mean AUC of ganciclovir (either as 24h, infinity or pooled) observed in AIDS patients with CMV retinitis was approximately 30% higher compared to asymptomatic HIV+/CMV seropositive subjects. This is most probably related to reduced renal clearance in the retinitis patients, although the contrast between these two populations with respect to renal clearance failed to reach statistical significance by a small margin (ratio of geometric means of renal clearance and 95% CI of 0.618; 0.433 to 0.883, adjusted p-value 0.0637).

There was some evidence of a linear association between body weight (R^2-value ranging between 5.59 – 27.9) and a number of pharmacokinetic parameters, however, in all instances the extent of the variability in the pharmacokinetic parameter in question was not explained by variation in subject weight alone.

In patients with renal impairment there was a trend towards an increase in mean valganciclovir AUC_{last} and C_{max} with increasing degrees of impairment but because of the low overall systemic exposure to valganciclovir, this is unlikely to be clinically significant.

An influence of age was not found irrespective of the analyte or the route considered.

A statistically significant shorter $t_{1/2}$ for ganciclovir after dosing with valganciclovir was found in female relative to male subjects, with a ratio in geometric means of females to males of 0.831 (95% CI 0.733, 0.943; adjusted p=0.0276). However, in the absence of an impact on any of the major pharmacokinetic parameters and in particular on AUC, the clinical relevance of the observed shorter half-life in females is doubtful. This comparison was based on 70 males (84.3%) and 13 females (15.7%); as such the exploration of the effect of gender was limited.

6.2.2.8 Pharmacokinetics in Special Patient Populations

Renal Impairment

The effect of renal impairment on the pharmacokinetics of ganciclovir and valganciclovir was examined in study E* The study was conducted in 44 subjects belonging to the following groups:

Group 1 8 HIV+/CMV+ subjects, with normal renal function (creatinine clearance ≥ 70 mL/min)

Group 2 12 healthy subjects, with normal renal function (creatinine clearance ≥ 70 mL/min)

Group 3 — 6 renally impaired, otherwise healthy subjects, not requiring dialysis with creatinine clearance of 51-70 mL/min

Group 4 — 6 renally impaired, otherwise healthy subjects, not requiring dialysis with creatinine clearance of 21-50 mL/min

Group 5 — 6 renally impaired, otherwise healthy subjects, not requiring dialysis with creatinine clearance of 11-20 mL/min

Group 6 — 6 renally impaired subjects requiring dialysis treatment ≤ 3 times per week, with creatinine clearance of ≤ 10 mL/min

All subjects in Group 1 and 8 subjects from Group 2 were in an open-label, randomized two-way crossover study design. Each subject received a single dose of 900 mg valganciclovir and a single i.v. infusion of 5 mg/kg ganciclovir. This randomized crossover portion of the study was included to evaluate any differences in bioavailability of ganciclovir (when given as oral valganciclovir) in healthy volunteers and HIV+/CMV+ subjects. This would allow any differences in bioavailability between the two populations to be taken into account when designing a dose reduction algorithm for valganciclovir.

For the remaining 4 subjects from Group 2, as well as Groups 3 to 6, this was an open-label, parallel group study. Each subject received a single dose of 900 mg valganciclovir only. These subjects, together with those subjects from Group 2 above formed the population base for investigation of the effects of renal impairment on the pharmacokinetics of valganciclovir and ganciclovir.

The pharmacokinetic parameters for valganciclovir were similar in HIV/CMV+ subjects and healthy volunteers. Systemic exposure to valganciclovir was low in all groups (range of mean AUC_{last} values: 0.173 to 0.858 μg.h/mL) although the average AUC_{last} and C_{max} values did increase slightly with increasing renal impairment. After adjustment for the molecular weights of the two compounds, mean C_{max} values for valganciclovir were between 2% and 4% of those of the metabolite ganciclovir. Mean AUC_{last} values for valganciclovir were less than 1% of those for ganciclovir.

There were no apparent relevant differences in the pharmacokinetics of either i.v. ganciclovir or ganciclovir administered as valganciclovir between HIV/CMV+ subjects and healthy volunteers.

The absolute bioavailability of ganciclovir when administered as valganciclovir was estimated as 59% in healthy volunteers and 61% in HIV/CMV subjects. These values are consistent with those reported in other studies.

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 7 and summarized in Table 18.

Figure 7 **Mean Ganciclovir Plasma Concentrations Following Single Oral Doses of 900 mg Valganciclovir in Subjects With Increasing Renal Impairment (E*)**

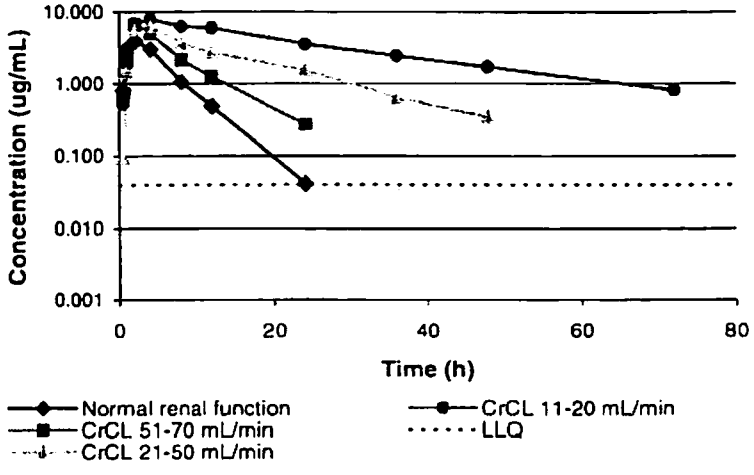


Table 18 **Effect of Renal Impairment on Mean (%CV) Ganciclovir Pharmacokinetic Parameters**

CrCL (mL/min)	AUC_{last} (μg.h/mL)	$AUC_{0-\infty}$ (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}

This 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, the expected mean daily ganciclovir AUC values at steady state were estimated for the different creatinine clearance levels and daily doses of valganciclovir. This relationship was used to derive dose reduction algorithms for the use of valganciclovir as induction and maintenance treatment in renally impaired patients.

Pediatrics and The Elderly

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

6.2.2.9 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 both groups.

Plasma concentrations for ganciclovir obtained after administration of i.v. ganciclovir and oral valganciclovir are presented in Figure 8. The main pharmacokinetic parameters for ganciclovir are summarized in Table 19.

Figure 8 **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)**

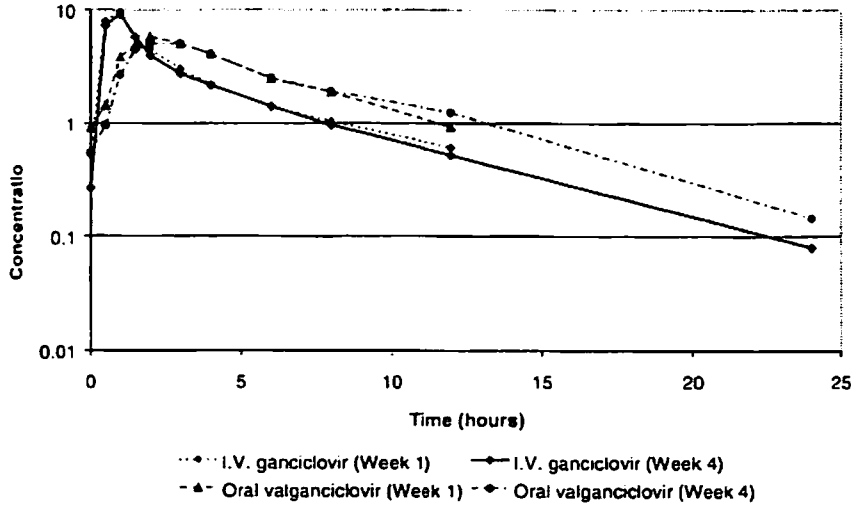


Table 19 Summary of Mean (CV%) Ganciclovir Pharmacokinetic Parameters Following Oral Valganciclovir and i.v. Ganciclovir (WV15376)

	AUC* (μg.h/mL)	C_{max} (μg/mL)	t_{max} (h)	$t_{½}$ (h)	k_{el} (h^{-1})	CL_T (mL/min/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)

*AUC_{0-12} for Week 1, AUC_{0-24} for Week 4

Similar ganciclovir systemic exposures (AUC_{0-12} and AUC_{0-24}) were seen with each treatment group for both weeks, but there was a tendency toward higher exposures following oral valganciclovir when compared to i.v. ganciclovir. 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.

The study was not formally powered to assess comparisons in AUC or in C_{max} between the two randomized treatment groups. The ratio of the AUCs of ganciclovir from oral valganciclovir relative to i.v. ganciclovir was 116% (90% CI; 98-136%) at Week 1 and 109% (90% CI; 91-131%) at Week 4. The confidence intervals are not included in the standard bioequivalence reference region 0.8-1.25, but the 100% value is included, indicating that there is no statistically significant difference (Table 20).

Table 20 Bioequivalence Analysis With Respect to C_{max} and AUC_{last} of Ganciclovir from Oral Valganciclovir and i.v. Ganciclovir at Week 1 and Week 4

Parameter	VGCV Mean	N for VGCV	GCV Mean	N for GCV	Ratio of geometric means (VGCV/GCV)	90% confidence interval for ratio
Week 1						
C_{max} (µg/mL)	6.39	25	9.55	18	0.67	0.55, 0.8
AUC_{0-12} (µg.h/mL)	31.45	25	27.18	18	1.16	0.98, 1.36
Week 4						
C_{max} (µg/mL)	5.59	21	9.45	18	0.59	0.50, 0.70
AUC_{0-24} (µg.h/mL)	32.51	20	29.88	18	1.09	0.91, 1.31

6.2.2.10 Drug Interactions

Valganciclovir is a substrate for the intestinal transporter hpepT1 with a Km of 3-5 mM and at the proposed clinical dose, this pathway is likely to contribute, at least in part, to its mechanism of absorption. Although specific interaction studies in humans have not been conducted, investigations using a rat in-situ model showed that valaciclovir, cyclosporin, omeprazole, nelfinavir, or mycophenolate mofetil had no effect on the permeability of valganciclovir.

As valganciclovir is rapidly converted to ganciclovir, the drug interactions applicable to ganciclovir will also be applicable to valganciclovir. A full description of these can be found in the Human Pharmacokinetics and Bioavailability Summary for Ganciclovir.

6.2.2.11 Comparison with Pharmacokinetics in Animals

The good oral absorption and rapid conversion of valganciclovir to ganciclovir observed in man, is also reflected in the animal species studied, with estimates of ganciclovir bioavailability of 56% in rats to 100% in dogs and mice.

In line with the findings in humans, the systemic exposure (AUC) of valganciclovir relative to ganciclovir is low (1-2% in dogs, 3-4% in mice and 4-8% in rats) and the plasma half-life is short (5 minutes in mice and 28 minutes in dogs).

6.2.3 Conclusions

The principal findings from the valganciclovir program can be summarized as follows:

- Valganciclovir is well absorbed from the gastrointestinal tract and is rapidly and extensively converted to ganciclovir. Systemic exposure to valganciclovir is low at all doses with an AUC ratio of valganciclovir to ganciclovir of approximately 1% and a C_{max} ratio of approximately 3%.
- A consistent estimate for the mean absolute bioavailability of ganciclovir from orally dosed valganciclovir of approximately 60% was obtained across all patient populations studied.
- Both valganciclovir and its metabolite ganciclovir have well defined and predictable pharmacokinetic profiles.
- Once daily dosing with valganciclovir can achieve plasma exposures of ganciclovir comparable with standard regimens of intravenous ganciclovir.
- Dose adjustments are required for patients with impaired renal function.

7. MICROBIOLOGY

7.1 Summary of Non-Clinical Virology for Ganciclovir

A summary of the pharmacodynamic properties of GCV is provided to support the application for approval of the use of valganciclovir against human cytomegalovirus (HCMV) infection in immunocompromised patients.

7.1.1 Summary Statements

Valganciclovir is a valyl ester of ganciclovir (GCV). It is rapidly converted into GCV on absorption. Therefore, the effective antiviral properties of valganciclovir are those of GCV itself. GCV is a nucleoside analogue of guanosine. It requires phosphorylation to its tri–phosphate for activity. In HCMV–infected cells, a viral protein kinase (UL97) carries out the initial mono–phosphorylation, and the tri–phosphate is formed subsequently by cellular enzymes. GCV tri–phosphate (GCV–TP) functions as a competitive inhibitor of the incorporation of dGTP into DNA by HCMV DNA polymerase (UL54) and it may be incorporated into DNA. GCV selectively inhibits the HCMV enzyme by up to 10–fold, despite similarities of structure between HCMV UL54 and cellular DNA polymerase–α. Slow intracellular catabolism of GCV–TP results in a long intracellular half–life (>6-<24h) and prolongs antiviral activity.

GCV is active against all known human herpesviruses, with activity (IC_{50} values) in the range 0.08–14 μM (0.02–3.58 μg/mL) against HCMV. In addition, activity against CMV from several different animal species has been reported.

GCV–mediated inhibition of cellular proliferation is found at higher concentrations (TC_{50} 40 – >1000 μM) in established cell lines. This provides