2. BACKGROUND AND SCIENTIFIC RATIONALE FOR DEVELOPMENT OF VALGANCICLOVIR

Human cytomegalovirus (CMV) is a herpes virus recognized to be an important pathogen in immunocompromised individuals, notably those with advanced human immunodeficiency virus infection (HIV+) and those who have been actively immunosuppressed to receive or maintain organ transplants. Ganciclovir (9-(1,3-dihydroxy-2-propoxymethyl) guanine) was the first antiviral drug approved for the treatment of human CMV infection and disease, and was among the early drugs approved for the treatment of opportunistic infections in patients with acquired immunodeficiency syndrome (AIDS). The safety and efficacy of ganciclovir has been well characterized for the treatment of CMV retinitis in AIDS patients.

CMV retinitis is an ocular manifestation of a systemic viral infection, appearing as a retinal locus of infection that enlarges and destroys retinal tissue. On indirect ophthalmoscopy, CMV retinitis is characterized by edema of the involved area, often with perivascular cuffing and varying degrees of hemorrhage. The destruction of retinal tissue results in 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.

Ganciclovir is available as a lyophilized powder for intravenous (i.v.) infusion, or as capsules for oral administration. Intravenous ganciclovir is generally available for the treatment of CMV retinitis in immunocompromised patients, and for the prevention of CMV disease in transplant patients at risk of CMV disease. Oral ganciclovir is available as an alternative to the i.v. formulation for maintenance treatment of CMV retinitis in patients with AIDS, whose retinitis has been stabilized by prior anti-cytomegalovirus therapy. Oral ganciclovir is also efficacious in the prevention of CMV disease in solid organ transplant recipients, and in individuals with advanced HIV infection at risk of developing CMV disease.

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 implant. Systemic ganciclovir treatment starts with induction treatment at 5mg/kg b.i.d. for 14 to 21 days. The great majority of patients will respond with a decrease in hemorrhage and edema, and no further lesion enlargement. This is 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, the lesion eventually becomes inflamed, hemorrhagic, and a progression

occurs. A repeat cycle of induction treatment is effective, but with each progression, additional retinal tissue is destroyed.

The goal of maintenance treatment is to prevent or delay progression following a satisfactory response to induction treatment. The success of maintenance treatment is measured by the time from the start of therapy to the next progression of retinitis. Standards have evolved for the definition of CMV retinitis progression and for measuring the *time to progression.* Maintenance treatment with i.v. ganciclovir at 5 mg/kg once daily or oral ganciclovir at 1000 mg t.i.d. is initiated at the completion of an induction cycle.

Valganciclovir (Ro 107-9070) is a valyl ester prodrug of ganciclovir that is rapidly hydrolysed to ganciclovir following ingestion. Conversion to ganciclovir occurs primarily during pre-systemic absorption, with only 1-2% of absorbed valganciclovir appearing as valganciclovir in the plasma, the remainder being found as ganciclovir. The absolute bioavailability of valganciclovir is approximately 60%, a 10-fold improvement over the approximate 6% bioavailability of the current oral ganciclovir formulation.

In addition, a dose of 900 mg of valganciclovir (two 450-mg film-coated tablets) taken twice a day after food achieves ganciclovir exposure (measured as plasma AUC) comparable to that of the standard i.v. ganciclovir induction dose of 5 mg/kg b.i.d; and 900 mg of valganciclovir once a day achieves ganciclovir exposure comparable to that of the standard i.v. ganciclovir maintenance dose of 5 mg/kg once daily. A pharmacokinetic (PK) / pharmacodynamic (PD) relationship derived from previous preclinical and clinical studies with both i.v. and oral ganciclovir relationship shows that the area under the plasma concentration time curve (AUC), a measure of systemic ganciclovir exposure, is the driving pharmacokinetic parameter for clinical efficacy.

Therefore, the pharmacokinetic profile and improved oral bioavailability of ganciclovir from valganciclovir provides the potential for:

- A therapeutic alternative to i.v. ganciclovir induction and maintenance treatment of CMV retinitis
- Avoidance of risks associated with long-term intravenous access required for i.v. ganciclovir
- A simple oral regimen that could improve adherence to long-term maintenance treatment

Concurrent with the early clinical development of valganciclovir, the introduction of highly active anti-retroviral therapy (HAART) for the treatment of HIV infection was accompanied by a marked reduction in the global incidence of HIV-related opportunistic infections, particularly CMV retinitis. This had a significant impact on the valganciclovir development program. Because the use of HAART changed the epidemiology and clinical

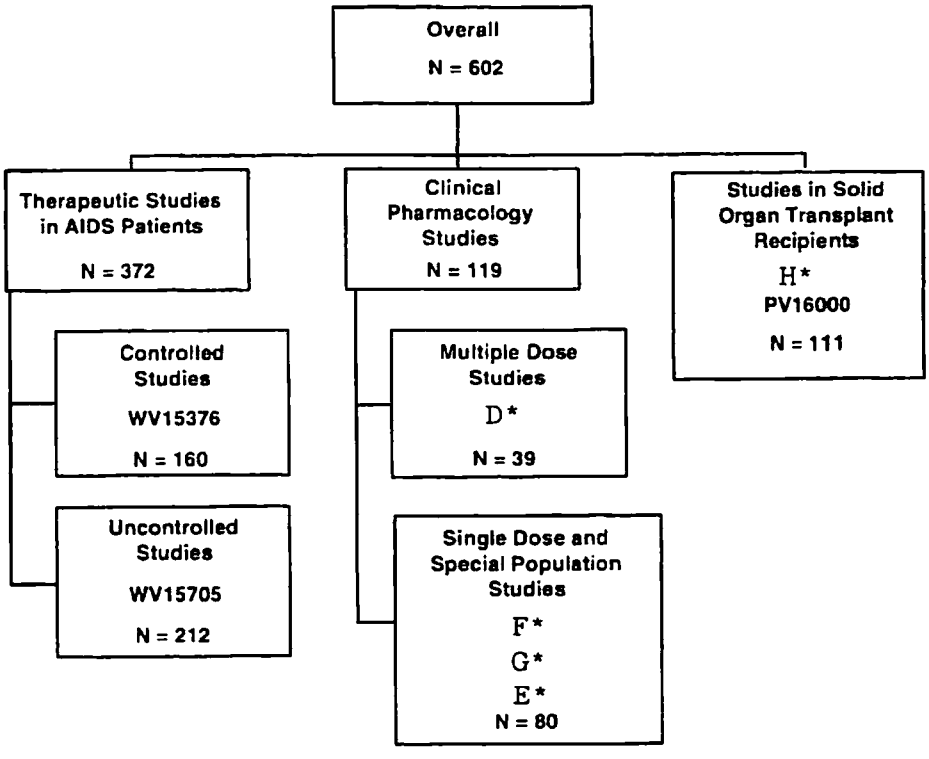
course of HIV-related CMV retinitis, this sponsor, among others, encountered great difficulty in attempting to conduct large comparative studies.

Therefore, the valganciclovir 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, as well as pharmacokinetic and pharmacodynamic data. In addition, because valganciclovir is rapidly and extensively converted to ganciclovir, and provides ganciclovir blood levels comparable to i.v. ganciclovir, the valganciclovir clinical program builds upon the efficacy and safety data previously generated with ganciclovir. Relevant non-clinical and clinical data from previous ganciclovir studies are also included in this submission for ease of review and for comparative purposes.

2.1 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 schematically in Figure 1, and in Table 7. Although this application only seeks approval for valganciclovir in the treatment of CMV retinitis, note that this submission also includes preliminary safety data from an ongoing prophylaxis study in solid organ transplant recipients to further describe the safety profile of valganciclovir.

Figure 1 Overview of the Clinical Program



☐ Supportive information

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Table 7 Detailed Overview of Valganciclovir Clinical Studies

Detailed Overview of Valganciclovir Clinical Studies

Clinical Pharmacology Studies										
Protocol No (Report No.) [ref]	Center/ Location	Status	Study Design	Drug	Dosage	Formulation	Duration of Treatment	No of Subjects Enrolled	Sex (M/F)	Age range (years)
F*	1 center US	Complete	Open label, randomized, 3-way crossover study in HIV+, CMV+ subjects	VGCV GCV GCV	360 mg p.o. 5 mg/kg i.v. 1000 mg p.o.	30 mg/ml (free base) aqueous soln. F79070-003 ganciclovir sodium infusion F21592-027 250 mg capsules F21592-049	Single dose separated by 7 days	18	15/3	22-51
D*	2 center US	Complete	Open label, 2 group (with and without food), randomized, 4-way crossover study in HIV+, CMV+ subjects	VGCV	450 mg p.o. 875 mg p.o. 1750 mg p.o. 2625 mg p.o.	450 mg tablets F79070 013 875 mg tablets F79070-013 2 x 875 mg tablets 3 x 875 mg tablets	Multiple dose, once daily for 3 days	39	37/2	20-47
E*	2 center UK, Germany	Complete	Open label, parallel group, randomized, 2-way crossover study in healthy, HIV+,CMV+ and renally impaired subjects	VGCV GCV	900 mg p.o. 5 mg/kg i.v.	2 x 450 mg tablets F79070-013 ganciclovir sodium infusion	Single dose separated by 6 days	44	35/9	22-73

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Table 7 Detailed Overview of Valganciclovir Clinical Studies (Cont.)

Clinical Pharmacology Studies										
Protocol No (Report No) [ref]	**Center/ Location**	**Status**	**Study Design**	**Drug**	**Dosage**	**Formulation**	**Duration of Treatment**	**No of Subjects Enrolled**	**Sex (M/F)**	**Age range (years)**
G*	1 center UK	Complete	Open label, randomized, 3-way crossover study in HIV+ subjects	VGCV	900 mg p.o.	2 x 450 mg tablets clinical trial formulation I-79070-013	Single dose separated by 5-7 days	18	18/0	22-53
				VGCV	900 mg p.o.	2 x 450 mg tablets market formulation I-79070-019				
				GCV	5 mg/kg i.v.	ganciclovir sodium infusion				

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Table 7 Detailed Overview of Valganciclovir Clinical Studies (Cont.)

Therapeutic Studies in AIDS Patients									
Protocol No (Report No) [ref]	**Center/ Location**	**Status**	**Study Design**	**Drug /Dosage**	**Formulation**	**Duration of Treatment**	**No of Patients Enrolled**	**Sex (M/F)**	**Age range (years)**
WV15376	42 Centers International	Ongoing;	Open label, randomized, parallel group study in HIV+ patients with newly diagnosed CMV retinitis	Induction: 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 Maintenance: VGCV 900 mg p.o., o.d.	Ganciclovir sodium infusion F21592-087 2 x 450 mg tablets F79070-013	2 days to 30 mths (up to clinical cut-off)	160	145/15	21-61
WV15705	43 Centers International	Ongoing;	Open label, single arm study in patients with AIDS and CMV retinitis	Induction: VGCV 900 mg p.o., b.i.d. for 3 weeks, when required to treat active retinitis Maintenance: VGCV 900 mg p.o., o.d.	2 x 450 mg tablets F79070-013 and F79070-019	12 days to 17 mths (up to clinical cut-off)	212	193/19	22-61

Table 7 Detailed Overview of Valganciclovir Clinical Studies (Cont.)

Solid Organ Transplant Studies									
Protocol No (Report No) [ref]	Center/ Location	Status	Study Design	Drug Dosage	Formulation	Duration of Treatment	No of Subjects Enrolled	Sex (M/F)	Age range (years)
H*	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. VGCV 450 mg p.o. VGCV 900 mg p.o. GCV 5 mg/kg i.v.	4 x 250 mg capsules 1 x 450 mg tablets 2 x 450 mg tablets F79070-013 ganciclovir sodium infusion	Single dose separated by 3-7 days	28	21/7	20-60
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 x 450 mg tablets F79070-020 4 x 250 mg capsules	90 days	~372 planned; 83 enrolled as of 28* July 2000	NK	NK

NK = not known at this time

* : 新薬承認情報提供時に置き換えた

2.1.1 Valganciclovir Clinical Pharmacology Studies

A total of 147 patients/subjects participated in five phase I/II clinical pharmacology studies conducted to describe the pharmacokinetic properties of valganciclovir.

2.1.1.1 Study F*

This was an open label, randomized, three-way crossover study to investigate the fasting, single-dose pharmacokinetics and absolute and relative bioavailability of valganciclovir (in ganciclovir equivalents) administered orally (p.o.) as compared with intravenous (i.v.) and oral ganciclovir in HIV- and CMV- seropositive subjects. Over three consecutive weeks, subjects received a 5 mg/kg i.v.ganciclovir infusion, 1000 mg oral ganciclovir and 360 mg oral valganciclovir in random order, with a 7-day washout period between each dose.

2.1.1.2 Study D*

This was an open-label, two group design, randomized, four-way crossover study to investigate the steady state pharmacokinetics of four different doses of valganciclovir following multiple oral dosing (with and without food), in HIV-, CMV- seropositive subjects. The two groups of subjects (fasted and fed) received each of the four doses 450 mg, 875 mg, 1750 mg and 2625 mg valganciclovir, once daily over 3 days, with a washout phase of 4 days between each treatment period.

2.1.1.3 Study E*

This was an open-label, combined parallel group and randomized two-way crossover study to investigate the effect of renal impairment on the pharmacokinetics of valganciclovir and ganciclovir following oral administration of valganciclovir. Additional objectives were to provide a dosing algorithm for use of valganciclovir in renally impaired patients, to investigate the effects of hemodialysis on the pharmacokinetics of ganciclovir (from valganciclovir), and to compare the absolute bioavailability of ganciclovir from valganciclovir in healthy and HIV- seropositive subjects. Two groups of healthy and HIV-, CMV- seropositive subjects, respectively, received single doses of valganciclovir 900 mg and i.v. ganciclovir 5 mg/kg in a randomized manner, with a 6-day washout period between each treatment. Five groups of otherwise healthy subjects with varying degrees of renal impairment, each received a single dose of valganciclovir 900 mg.

2.1.1.4 Study G*

This was an open-label, randomized, three-way crossover study in HIV+ subjects to demonstrate the bioequivalence, and establish the absolute bioavailability of ganciclovir following single oral doses of clinical trial and market formulations of valganciclovir tablets. Over 3 consecutive weeks, subjects were randomly allocated to receive single oral doses (900 mg) of the

clinical trial and market formulations of valganciclovir tablets, and a single 5 mg/kg intravenous infusion of ganciclovir, with a 5 to 7 day washout period between each treatment.

2.1.1.5 Study H*

This was an open-label, randomized, four-way crossover study in liver transplant recipients. The objective of the study was to determine a dose of valganciclovir given once daily which would provide a ganciclovir exposure, measured as area under the plasma concentration time curve, bracketed by the exposure provided by i.v. ganciclovir given at 5 mg/kg/day and oral ganciclovir given at 3000 mg/day. Each subject received single doses of 3000 mg oral ganciclovir (as 3 divided doses; 1000 mg t.i.d.), 450 mg oral valganciclovir, 900 mg oral valganciclovir and 5 mg/kg i.v. ganciclovir in a random, crossover fashion, with a 3 to 7 day washout period between each treatment.

2.1.2 Valganciclovir Therapeutic Studies in AIDS Patients

A total of 160 patients participated in the controlled, open-label, randomized efficacy and safety study WV15376, and 212 patients participated in the non-comparative open-label safety study WV15705. Both studies are ongoing, and this application summarizes data from 30 months of study conduct in the case of study WV15376 and 17 months of study conduct for WV15705, including data up to a clinical cut-off date of

2.1.2.1 Study WV15376

The primary purpose of this ongoing, multicenter, international, randomized, open label, parallel group study was to investigate the efficacy of valganciclovir compared to i.v. ganciclovir when used as induction therapy in subjects with newly diagnosed CMV retinitis. Additional objectives of this study were to investigate the safety profile of valganciclovir in this indication, to assess the effects of induction and maintenance level dosing of valganciclovir on CMV viral load, as measured by CMV culture and PCR, and to assess the pharmacokinetics of ganciclovir following administration of valganciclovir in the target population.

Patients with AIDS and newly diagnosed CMV retinitis were randomized to receive therapy with either 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. Masked reading of fundus photographs was used to determine the response of retinitis to treatment. Those patients who completed the 4 weeks of randomized therapy were offered the opportunity to receive continuing therapy with oral valganciclovir 900 mg o.d. in an extension of the study designed to provide long term safety and efficacy information.

2.1.2.2 Study WV15705

This is an ongoing, multicenter, international, open-label, non-comparative study, to evaluate the safety and tolerability of valganciclovir when given as treatment for CMV retinitis. The study also includes the collection of uncontrolled efficacy data, comprising ophthalmology assessments.

Patients with AIDS and previously treated CMV retinitis were enrolled. Patients with quiescent CMV retinitis at study entry received a maintenance dose of 900 mg once daily. For patients with active CMV retinitis, treatment could be initiated at 900 mg b.i.d. for 21 days and continued with the maintenance dose of 900 mg once daily. Patients who had progression of CMV retinitis during the trial could receive multiple cycles of induction and maintenance therapy, according to best medical judgment.

2.1.3 Valganciclovir Solid Organ Transplant Study PV16000

This is an ongoing, multicenter, international, 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 day 100 post transplant, with a 2:1 valganciclovir: ganciclovir randomization. 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.

The first patient was enrolled in study PV16000 on 3 April, 2000, and as of 28 July 2000, a total of 83 patients are currently participating in the study. Preliminary safety data from this study, comprising serious adverse events reported up to 28 July 2000 are presented in The Integrated Summary of Safety Information for Valganciclovir.

3. FOREIGN MARKETING HISTORY

Applications for the use of valganciclovir for the treatment of CMV retinitis are planned for submission globally. To date, approval for the treatment of CMV retinitis with valganciclovir has not been obtained in any market.

4. CHEMISTRY, MANUFACTURING AND CONTROL

4.1 Drug Substance Summary