Public Assessment Report

Scientific discussion

Valcyte 450 mg film-coated tablets (valganciclovir)

NL/H/0323/001/MR

Date: 16 January 2002
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This module reflects the scientific discussion for the approval of Valcyte 450 mg film-coated tablets. The procedure was finalised at 5 March 2002. For information on changes after this date please refer to the module 'Update'. In annex I variation NL/H/0323/001-002/II/054 is discussed: the extension of the CMV prevention indication to include paediatric SOT patients.
See pages 26-53. A list of abbreviations is given on page 54.
This report starts with a summary in English and Dutch .

COLLEGE TER BEOORDELING VAN GENEESMIDDELEN - MEDICINES EVALUATION BOARD

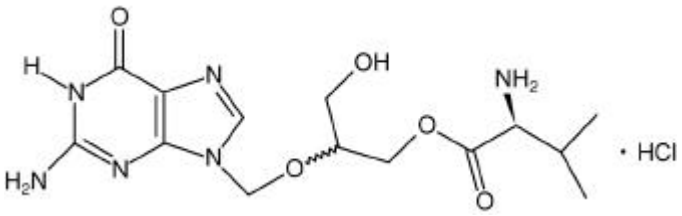
PUBLIC ASSESSMENT REPORT

Valcyte 450 mg film-coated tablets, film-coated tablets RVG 25992

International Non-proprietary Name (INN) Valganciclovir

Report version: 1st NPAR, original Date: 2002-01-16

GENERAL INFORMATION

Active substance:	Valganciclovir hydrochloride 496.3 mg/tablet, equivalent to 450 mg valganciclovir
Structural formula	
Pharmacotherapeutic group:	anti-viral agents
ATC code:	J05A Bxx
Pharmaceutical dosage form	film-coated tablet
Route of administration:	oral
Therapeutic indication:	treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS).
Prescription information:	prescription only
Marketing Authorisation Holder:	ROCHE NEDERLAND Mijdrecht
Date of first application (national):	2000-10-26
Application type/legal basis:	Directive 65/65/EEC, Article 4.8
Date of authorisation:	2001-09-20

ABSTRACT

On September 20, 2001, the Medicines Evaluation Board in the Netherlands issued a marketing authorisation for the medicinal product, Valcyte 450 mg film-coated tablets, containing valganciclovir hydrochloride.

On 5 March 2002 a mutual recognition procedure for this product was approved. The Netherlands acted as reference member state in this procedure, while the concerned member states were Austria, Belgium, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Norway, Portugal, Spain, Sweden and the United Kingdom.

The approved indication is the treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS).

Valcyte is given orally, the recommended induction dose is 900 mg (two 450 mg tablets) twice a day for 21 days. Following induction treatment the recommended maintenance treatment is 900 mg (two 450 mg tablets) once daily.

Detailed conditions for the use of this product are described in the Summary of Product Characteristics (SPC, part IB1 of the dossier) which is adhered to this Public Assessment Report.

Valcyte is presented as pink, film-coated, convex oval tablets and has a shelf life of 3 years. Conventional animal studies have shown ganciclovir to be mutagenic, carcinogenic and teratogenic at subtherapeutic exposures. Therefore, tablets must not be crushed and skin contact with accidentally damaged tablets must be avoided.

The active substance of Valcyte, valganciclovir hydrochloride, is an L-valyl ester (prodrug) of ganciclovir, which after oral administration is rapidly and extensively metabolised to ganciclovir by intestinal and hepatic esterases. The bioavailibility of ganciclovir from Valcyte is 10-fold higher than from ganciclovir capsules. Ganciclovir is a synthetic analogue of 2'-deoxyguanosine, which inhibits replication of herpes viruses in vitro and in vivo. The virostatic activity of ganciclovir is due to inhibition of viral DNA synthesis.

Clinical trials investigated the efficacy and safety of Valcyte in the treatment of CMV retinitis in patients with AIDS. In comparison with intravenous ganciclovir, essentially similar results in efficacy and safety between both groups were attained. The most frequently (>10%) reported adverse events for valganciclovir during induction therapy are diarrhoea, neutropenia, pyrexia and oral candidiasis. Under maintenance therapy, nausea, and anaemia extend this set.

In patients with impaired renal function, a dosage adjustment is required according to creatinine clearance. In patients with severe neutropenia (neutrophil count < 500 cells/µl), thrombocytopenia (platelet count < 25000 cells/µl) or anaemia (haemoglobin < 8 g/dl or 5mmol/l) therapy with Valcyte should not be initiated.

The Medicines Evaluation Board, on the basis of the quality, efficacy and safety data submitted, considered that Valcyte can be consistently produced with sufficient quality, and efficacy for the therapeutic indication, as well as safety, has been adequately shown.

SAMENVATTING

Op 20 september 2001 heeft het College ter beoordeling van geneesmiddelen Valcyte 450 mg filmomhulde tabletten geregistreerd. Dit geneesmiddel bevat per tablet 450 mg valganciclovir, aanwezig als hydrochloride.

De goedgekeurde indicatie is de behandeling van cytomegalovirus (CMV)-retinitis bij patiënten met het "acquired immunodeficiency syndrome" (AIDS).

Valcyte wordt oraal toegediend, de aanbevolen dosering voor inductiebehandeling is 900 mg, oftewel twee tabletten tweemaal per dag gedurende 21 dagen. Op de inductiebehandeling volgt de onderhoudsbehandeling met twee tabletten éénmaal per dag.

De gedétailleerde voorwaarden voor het gebruik van het geneesmiddel staan beschreven in de Samenvatting van de kenmerken van het product (deel IB1 van het registratiedossier). Deel IB1 is bij dit rapport gevoegd.

Valcyte tabletten zijn roze, filmomhulde, ovale tabletten die drie jaar kunnen worden bewaard.
In gebruikelijke dierstudies blijkt ganciclovir mutageen, carcinogeen en teratogeen te zijn. Daarom mogen de tabletten niet worden gebroken of fijngemaakt en moet contact met de huid met per ongeluk beschadigde tabletten worden vermeden.

Het werkzame bestanddeel van Valcyte, valganciclovir hydrochloride is een L-valyl ester (prodrug) van ganciclovir. Na orale toediening wordt de ester snel en vrijwel volledig gemetaboliseerd tot ganciclovir door esterases in de lever. De biobeschikbaarheid van ganciclovir uit Valcyte is tien keer hoger dan uit capsules met ganciclovir. .
Ganclovir is een synthetisch analogon van 2'-deoxyguanosine, dat de replicatie van herpes virussen in vitro en in vivo remt. De virusremmende werking van ganciclovir is toe te schrijven aan remming van de synthese van virus-DNA.

De werkzaamheid en veiligheid van Valcyte bij de behandeling van CMV-retinitis bij patiënten met AIDS zijn klinisch onderzocht. De resultaten van de behandelingen met valganciclovir enerzijds en ganciclovir anderzijds zijn vergelijkbaar. De meest voorkomende (>10%) bijwerkingen van valganciclovir bij de inductiebehandeling zijn diarree, neutropenie, pyrexie en orale candidiasis. Bij de onderhoudsbehandeling treden ook misselijkheid en anemie op.

Bij patiënten met een verminderde nierfunctie is aanpassing van de dosering nodig op geleide van de creatinineklaring. De behandeling moet niet worden begonnen bij een ernstige neutropenie (minder dan 500 neutrofielen per µl), trombocytopenie (minder dan 25000 trombocyten per µl) of anemie (hemoglobinegehalte < 8g/dl of 5 mmol/l).

Het College ter beoordeling van geneesmiddelen heeft op basis van de overgelegde gegevens geconstateerd dat Valcyte met constante, voldoende kwaliteit kan worden geproduceerd. De werkzaamheid en veiligheid bij de gestelde indicatie zijn voldoende bewezen.

INTRODUCTION

Valcyte is an anti-viral drug, containing 450 mg valganciclovir (VAL) per film-coated tablet, developed for the treatment of cytomegalovirus (CMV) retinitis in patients with the acquired immunodeficiency syndrome (AIDS). VAL is the L-valyl ester (prodrug) of ganciclovir (GAN), a nucleoside analogue licensed for the treatment of human CMV infection (Cymevene). After oral administration and absorption, VAL is rapidly metabolised to GAN, and therefore much of the clinical development of VAL was built upon the experience with GAN.

CMV retinitis is an important opportunistic infection in patients with AIDS. Untreated CMV retinitis often leads to loss of vision. CMV retinitis manifests as a chorioretinitis that begins as a focus of infection that spreads and destroys retinal tissue. The destruction of retinal tissue is irreversible, and in the involved area there is total loss of vision. The lesions spread by outward movement of the lesion edge. Sometimes a new lesion appears in a previously healthy area of retina, and multiple discrete lesions may occur in the same eye. The goal of therapy for CMV retinitis is to delay or prevent progression into healthy retinal tissue.

The clinical trial program for VAL was seriously hampered by the introduction of highly active antiretroviral therapy (HAART) for AIDS in 1995, which reduced the incidence of new CMV retinitis to 20% or less of the pre-HAART numbers.

The use of HAART has resulted in patients with CMV retinitis at two ends of a broad spectrum of disease:

- One population has responded to HAART with a CD4+ - lymphocyte count >100/μL and few, if any, active opportunistic infections. They have predominantly inactive and healed retinitis.
- The second population consists of patients with newly diagnosed CMV retinitis, who have continued to be severely immunocompromised in spite of HAART, with a low CD4+ count (< 100/μL), a high HIV viral load, and multiple opportunistic infections. These patients, even though on HAART, are not responding to the anti-HIV therapy. These patients have CMV retinitis characterised by relatively short progression times and frequent progression of retinitis.

The dose for induction treatment with VAL is 900 mg twice daily for 21 days, and the dose for maintenance treatment is 900 mg once daily. There is an algorithm for downward dose adjustments in the case of impaired renal function. For patients on haemodialysis, intravenous GAN is recommended for use in accordance with the dose-reduction algorithm.

Position amongst current therapy options

The induction treatment of CMV retinitis involves intravenous (iv.) administration of one of three currently approved antiviral drugs, GAN 5 mg/kg twice daily, foscarnet, or cidofovir. There is also an intraocular treatment available with GAN implant, but CMV infection is systemic and this local formulation treats only the involved eye. When CMV retinitis is diagnosed, induction treatment is given. Upon treatment, in most patients the haemorrhage and retinal oedema will begin to resolve and progression of the lesion edges will stop. What remains after healing is non-functional scarred retinal tissue. If therapy is stopped, and if the patient remains immunocompromised, in 2 to 6 weeks the disease exacerbates. Re-initiation of induction treatment is indicated. To avoid this progression - healing- progression pattern, maintenance treatment with either intravenous GAN at 5 mg/kg once daily, or with a capsule formulation of GAN, is initiated to reduce the risk of progression of the disease. Although oral GAN has low oral bioavailability (about 6%) the maintenance treatment dose of 3000 mg/day

delays progression of retinitis. The success of maintenance treatment is quantified by measuring the time from the start of therapy to the next progression of the retinitis.

VAL was developed to provide the following benefits over current treatments:

- To provide a therapeutic alternative to intravenous induction and maintenance treatment of CMV retinitis.
- To avoid risks associated with long-term intravenous access required for intravenous treatment of retinitis.
- To offer a simple oral regimen that could improve compliance during maintenance treatment of retinitis.

CHEMICAL-PHARMACEUTICAL ASPECTS

Appearance and composition

Valcyte film-coated tablets 450 mg are pink, convex oval tablets. Each tablet contains 496.3 mg valganciclovir hydrochloride, the equivalent of 450 mg valganciclovir. The tablet core consists of the following excipients: povidone, crospovidone, microcrystalline cellulose and stearic acid powder.

Coating ingredients are:
Hypromellose, titanium dioxide, polyethylene glycol, red iron oxide and polysorbate.

Packaging type and material

The tablets are packed in a square container-closure system of 90 ml white high density polyethylene, with a child resistant closure. The child-resistant closure has an outer shell of white polypropylene, an inner shell of natural polypropylene and an induction seal liner. Cotton is used as padding material.

Active substance

Valganciclovir is an L-valyl ester of ganciclovir that exists as a mixture of diastereomers. Valganciclovir hydrochloride is not described in the Ph.Eur. It is a white to off-white crystalline powder with the molecular formula $C_{14}H_{22}N_6O_5.HCl$. The molecular weight is 390.83. Valganciclovir is a polar hydrophilic compound with a solubility of 70 mg/ml in water at 25°C at a pH of 7.0 and an n-octanol/water partition coefficient of 0.0095 at pH 7.0. The pKa for valganciclovir is 7.6.The quality of valganciclovir is checked by specifications for appearance, identification, water content, residue on ignition, heavy metals, residual solvents (isopropyl alcohol), organic impurities, enantiomeric impurities, diasteriomer ratio, assay and particle size.

Other ingredients

All excipients comply with their Ph.Eur. monograph, except for red iron oxide which complies with directive 94/36/EEC. All excipients can be considered TSE safe.

Product development and finished product

Development pharmaceutics

The shape of the tablet has been chosen to improve the ease of swallowing. The tablet contains a coating layer for safety reasons since the active substance is considered teratogenic and carcinogenic, the film coating prevents fragmentation of the tablet core. For the same reason, a handling instruction is given in the product information not to crush the tablets and to avoid skin contact with accidentally damaged tablets. Excipients are usual for immediate release tablets, their amounts have been chosen to obtain tablets with a certain dissolution profile.

Manufacture

The tablets are made by a granulation process. These tablet cores are film coated. The process is documented and sufficiently validated with respect to the content uniformity of the tablets.

Specifications of the medicinal product

The quality of the final product is checked with respect to the following parameters.
Appearance and sizes of the tablets;
Identity of the active substance (UV and HPLC);
Identity of titanium dioxide and iron oxide (colour reaction);
Assay of the active substances and related substances (HPLC);
Dissolution specification;
Uniformity of mass;
Microbial quality.

All methods are sufficiently described and validated. The specifications for the finished product are suitable with respect to both quality and safety. Batch analysis results of various batches show that the product meets the specifications set.

Stability of the medicinal product and shelf-life

The registered shelf life is 3 years (without specific storage conditions) in HDPE bottles.
All stability studies were conducted sufficiently in accordance to the ICH/CPMP-Guidelines.
The end-of-shelf-life specifications for the finished product are adequate with respect to both quality and safety.

PRECLINICAL PHARMACOLOGICAL AND TOXICOLOGICAL ASPECTS

The data submitted with the registration dossier for Valcyte is based on the studies of the ganciclovir dossier, supplemented with new valganciclovir studies. The toxicity profile of valganciclovir was compared to that of ganciclovir. As valganciclovir is rapidly absorbed and converted to ganciclovir after oral administration, the toxic effects will predominantly result from the exposure to ganciclovir.

Pharmacodynamics

Pharmacodynamic studies are predominantly carried out with ganciclovir since valganciclovir is the valyl ester of ganciclovir. After oral administration, valganciclovir is rapidly absorbed and converted into ganciclovir. Ganciclovir is a nucleoside analogue of guanosine. Ganciclovir is activated by three phosphorylation steps to generate ganciclovir-triphosphate (GCV-TP). It is first phosphorylated by a viral protein kinase followed by two cellular kinases.

GCV-TP selectively inhibits viral DNA polymerase and acts as a competitive inhibitor of the incorporation of deoxyguanosine triphosphate into DNA by HCMV and HSV-1 DNA polymerase. The virological properties of valganciclovir are identical to those of ganciclovir.

There were no clinically relevant effects detected with valganciclovir in safety pharmacology tests on renal, intestinal, autonomic nervous or cardio-respiratory systems and on gross behaviour. Drug interactions associated with ganciclovir can be expected for valganciclovir also. Therefore, drug interaction studies only focussed on the effect of ganciclovir. Studies on the interaction with more recently used drugs to treat HIV infections were also included in the dossier.

Pharmacokinetics

Absorption, distribution, biotransformation and excretion

Absorption of valganciclovir in mice, rats, dogs and monkeys is high as compared to ganciclovir. Valganciclovir is absorbed via a combination of passive and active transport. Distribution of intravenously administered radiolabelled valganciclovir and ganciclovir in rats was quick, showing tissue exposure exceeding that in whole blood, and low exposure of the central nervous system. Both compounds showed similar distribution patterns.

The highest exposure was found in the kidneys, pancreas, Harderian gland and liver. Elimination from tissues was fast.

No distribution data in pregnant animals were provided. Literature data indicate that ganciclovir passes the *ex vivo* human placenta in significant quantities.

Valganciclovir was hydrolysed very quickly by intestinal and liver S9 homogenates. In addition, it slowly hydrolyses at a pH of about 7. After oral administration of valganciclovir, the predominant systemically circulating compound is ganciclovir. Exposure to the prodrug is low, due to a quick first-pass metabolism (with high capacity) in intestinal wall and liver.

Ganciclovir is the major metabolite which is excreted (>90%) unchanged via the kidneys, and therefore, excretion in bile was not examined. There was no evidence of enterohepatic recirculation.

Toxicology

Single/repeated dose toxicity

After single dose administration valganciclovir and ganciclovir revealed similar toxicity profiles in mice and dogs.

Studies in the mouse, rat and dog with valganciclovir demonstrated the reproductive, haematopoietic, renal and gastrointestinal systems to be the target organs for toxicity.

The male reproductive system was the most frequently affected target organ. Lesions seen were testicular epithelial cell atrophy, oligospermia, and changes in accessory sex organs at sub-therapeutic exposure levels, i.e. there is no safety margin for these effects. Female reproductive changes were confined to uterine, ovarian and clitoral atrophy.

Reproduction studies

Ganciclovir was shown to be teratogenic and embryotoxic in reproduction studies. These data can be extrapolated to valganciclovir, reproduction studies with valganciclovir were not undertaken.

Mutagenic potential

Valganciclovir was positive in an in vitro mouse lymphoma assay (with/without metabolic activation) and in an in vivo rat micronucleus study, indicating that valganciclovir possess mutagenic and clastogenic potential. Ganciclovir showed the same mutagenic potential as valganciclovir.

Carcinogenic potential

In mice ganciclovir induced multiple tumours in organs having human counterparts at exposures levels of ganciclovir comparable and below those achieved in humans treated with valganciclovir. Based on these findings, carcinogenicity studies with valganciclovir were not undertaken. Both ganciclovir and valganciclovir can be regarded as carcinogenic.

Other toxicological aspects

Valganciclovir induced intestinal mucosal and/or crypt degeneration in mice and dogs.
A range of reversible haematopoietic changes was induced which included lymphoreticular gland atrophy, leukopenia (particularly neutropenia), anaemia, thrombocytopenia and bone marrow hypocellularity. Small changes in blood clotting parameters were observed after valganciclovir administration in rats and not in mice and dogs. These changes could be attributed to the active component ganciclovir. Clinical experience with ganciclovir has not revealed any problems with blood clotting parameters.

Renal toxicity was recorded in mice as tubular basophilia, pelvic dilatation and necrosis with associated changes in clinical pathology. Some renal effects were observed in dogs at 50 mg/kg resulting in an AUC-level of ± 170 μg.h/ml.

CLINICAL ASPECTS

The following abbreviations appear in this chapter

ANC	Absolute neutrophil count
GAN	Ganciclovir
HAART	Highly active antiretroviral therapy
VAL	Valganciclovir

Overview of clinical studies

The clinical program for VAL was not typical for a new chemical entity. Because VAL is a prodrug of GAN, use of existing GAN data was appropriate. Seven clinical trials of VAL were included in the application: five clinical pharmacokinetic studies and two therapeutic studies evaluating efficacy and safety. The characteristics of the submitted studies are summarised in the following table.

Study	Design	Diagnosis, inclusion criteria	Criteria for evaluation	Drug, dose, duration	Number
1	Single centre, OL, R, Single dose, 3-way x-over	HIV+, CMV+ subjects with no history of CMV disease , no AIDS def. illness, CD4 count ≥ 100 cells/µl, adequate baseline hematologic & renal function	PK: standard PK, incl. abs.bioav. AUC, C_{max},T_{max}, Safety: adverse events, laboratory	360mg VAL solution; 1000mg oral GAN; 5mg/kg GAN iv. Single doses under fasting condition on days 1, 8 and 15	18 (15M,3F) 22-51 years
2	Single centre, OL, R, single dose 3-way x-over	HIV+ male subjects, Cr.Cl >70ml/min, CD4 count ≥ 100 cells/µl	PK: AUC_{0-24}, c_{max}, T_{max}, k_{el}, $t_{1/2}$, CL, F,AUC_{∞} Safety: adverse events, laboratory, vital signs	VAL 900mg (clin.trial) VAL (marketing) IV GAN 5mg/kg	18 (18M,0F) 22-53 years
3	7 centre, OL, R, single dose 4-way x-over	Liver transplant recipients with CrCl>50ml/min; CMV+ 45-90 days post Tx or CMV-, with CMV- donor, 21-90 post Tx	PK: AUC_{0-24}, C_{max}, T_{max}, k_{el}, $t_{1/2}$, CL_{po}, CL_{iv}, CL_r AUC_{∞} Safety: adverse events, laboratory, vital signs	VAL 450mg VAL 900mg Oral GAN 3000mg Iv GAN 5mg/kg	28 (21M, 7F) 20-60 years
4	2 centre, Groups 1 & 2 Germany OL,R,2-way x-over, single dose Groups 2UK, 3-6 OL, R, parallel single dose	Gr1: HIV+, CMV+, CrCl ≥ 70 ml/min Gr 2: healthy, CrCL ≥ 70 ml/min Renal impairment: Gr 3: mild CrCL 51-70 ml/min Gr4: moderate CrCL 21-50 ml/min Gr 5: severe CrCL 11-20ml/min Gr 6: haemodialysis: CrCL ≤ 10ml/min	PK: c_{max}, T_{max}, k_{el}, $t_{1/2}$, CL_{po}, CL_{iv},(normal ren.function) CL_r , CL_d, FR, k_d (hemo-dialysis) AUC_{∞} Safety: adverse events, laboratory, vital signs	groups 1+2 Germany VAL 900 mg Iv GAN 5mg/kg Wash-out ≥ 6 days Groups, 2UK, 3-6 VAL 900 mg	44 (35M, 9F) 22-73 yeas
5	2-centre, OL, 2 group parallel 4-way x-over	HIV+, CMV+volunteers, CD4 ≥ 100 cells/µl	PK: AUC_{0-24}, C_{max}, T_{max}, lag time and $t_{1/2}$ Safety: adverse events, laboratory, vital signs	VAL: 3 days 450mg, 875mg, 1750mg and 2625 mg dd 4-way x-over. Group A fasted Group B following food	39 (37M, 2F) 20-47years
6	Multi centre (42), OL,R, parallel	HIV+ patients > 13 years, newly diagnosed CMV retinitis; absolute neutrophil count ≥ 750 cells/µl, platelet count ≥ 75,000/µl, CrCl >70ml/min	Efficacy: proportion with progression of CMV retinitis by wk 4; satisfactory induction by wk 4-6 PD: reduction in CMV viral load by CMV-PCR PK: AUC_{ss}, C_{max} Safety: adverse events, laboratory, vital signs	Pts 1:1 randomised to VAL 900mg bid 3 wks + 900mg od 1 wk or IV GAN 5mg/kg bid 3 wks+5mg/kg od 1 wk. After wk 4: all pts VAL 900mg o.d. with re-induction with VAL 900mg bid in case of progression	160 (145M,15F) 21-61 years
7	Multi centre (43), OL, uncontrolled	HIV+, ≥ 13 years, with CMV retinitis following ≥ 4 wks anti-CMV treatment	Safety: adverse events, laboratory, vital signs Efficacy: unmasked ophthalmologic assessment of time to progression of CMV retinitis, development of contralateral retinitis, deterioration of visual acuity, develop. of extra-ocular CMV disease.	All patients VAL : Induction 900mg bid for 3 weeks Maintenance VAL 900mg o.d. Re-induction with VAL 900mg bid permitted upon CMV progression	212 (193M,19F) 22-61 years

CI = confidence interval; CrCl= creatinin clearance, GAN + ganciclovir, i.v =intravenous, o. d. + once daily, OL = open label; PCR= polymerase chain reaction, R = randomised; x-over = crossover; t.i.d. 3 times a day, VAL= valganciclovir, Tx = transplantation

VAL is a prodrug of GAN. After absorption in the gut wall, VAL is hydrolysed to GAN. The pharmacodynamics and pharmacokinetics of GAN are well known. The absolute bioavailability of GAN from valganciclovir tablets is 10 times higher than from GAN capsules. The most important issue with respect to the pharmacokinetics is the extent of exposure to GAN after oral administration of VAL. GAN is normally administered intravenously or orally. For an effective dose of VAL, exposure to GAN should be comparable with intravenous or orally administered GAN. The marketing authorisation holder submitted five studies that compared the pharmacokinetics of GAN after administration of VAL with the pharmacokinetics following intravenous and oral administration of GAN.

Absorption

Absolute bioavailability
The pharmacokinetics of VAL and GAN were estimated after intravenous administration of 5 mg/kg GAN and oral administration of 1000 mg GAN or 360 mg VAL. The bioavailability of GAN after administration of VAL was 10 times higher than after oral administration of GAN. The maximum concentrations of GAN after administration of VAL were reached after approximately one hour, indicating rapid conversion of VAL to GAN. The variability in the pharmacokinetic characteristics was comparable after oral administration of both compounds.
The bioavailability of VAL after repeated oral dosing was not changed. Absorption takes place in the upper part of GI-tract and as diarrhoea is mainly associated with the lower part, it is unlikely to affect the bioavailibility of VAL.

Dose proportionality and influence of food

The dose proportionality, especially of the absorption, was investigated in 32 HIV- and CMV-seropositive subjects in a 2-group, open label design. Each group received 4 doses of VAL once daily for 3 consecutive days with washout periods of 4 days in a 4-way crossover design: 450 mg, 875 mg, 1750 mg and 2625 mg. One group received all doses in fasted state, 1 hour before food. The second group received all doses following food.

Food consistently increased the absorption of VAL, but not in a statistically significant way. The exposure of GAN after administration of VAL with food is increased by 25 to 50% depending on the dose. The pharmacokinetics of GAN can be considered linear after administration of VAL in the dosing range 450 mg to 2625 mg when taken with food. The product was administered with food in all subsequent clinical studies.

The pharmacokinetic parameters of GAN were also determined in liver transplant recipients in an open label, four-way crossover study with 28 patients. From the results of this study it was concluded that 1 g oral GAN 3X/day is comparable with respect to the extent of absorption with 450 mg VAL once daily. 900 mg VAL orally is comparable with 5 mg/kg

80% of ganciclovir is excreted unchanged in urine. Probenecid and other substances affecting tubular excretion influence renal excretion.

Interactions

No special interaction studies with respect to the administration of VAL were submitted. As the pharmacokinetics of VAL were determined by the well known pharmacokinetics of GAN and the formation of GAN from VAL is very rapid, no special interaction studies are deemed to be necessary.

Special patient groups

The pharmacokinetics of GAN in HIV+, CMV+ subjects was compared with healthy volunteers. In this study, the influence of renal impairment and dialysis on the pharmacokinetics of GAN was also investigated. Eight healthy volunteers and eight HIV+, -CMV+ patients received, in a two-way crossover design, 900 mg VAL orally or 5 mg/kg GAN intravenously. Parallel to these patients, four groups of six patients with renal impairment received 900 mg VAL orally. One group had a creatinine clearance of 51-70 ml/min; one group 21-50 ml/min and one group 11-20 ml/min. The last group of subjects, with creatinine clearance ≤ 10 ml/min, received dialysis treatment ≤ 3 times per week.

The results of this study demonstrated that the pharmacokinetics are not different between healthy volunteers and HIV+, CMV+ patients and that 5 mg/kg iv. GAN results in a comparable exposure as 900 mg VAL orally. Also, it was demonstrated that increasing degrees of renal impairment results in an increasing half-life of GAN. C_{max} was affected to a much lesser extent, with maximum concentrations becoming higher and occurring later, with increasing renal impairment. Using the relationship established between creatinine clearance and the apparent clearance for GAN (Cl_{po}), the expected mean daily GAN AUC values at steady state were estimated for different creatinine clearance levels and different daily doses of VAL. With these data, an algorithm for dose adjustment of VAL in patients with renal impairment was generated. In this model, daily exposure to GAN would be 50 µg.h/ml for patients with a creatinine clearance of 10 ml/min following 450 mg VAL taken twice weekly. For a patient with a creatinine clearance of 50 ml/min and a dose of 450 mg VAL once daily an AUC of 30 µg.h/ml will be achieved.

Population Pharmacokinetics

A population pharmacokinetic analysis was performed with pharmacokinetic data from GAN studies. In this analysis, 182 patients received oral GAN and 40 patients received iv GAN. Sparse blood samples were obtained for each subject at weeks 2 and 6 of the study. In order to define the pharmacokinetic model, a further 15 patients who had received iv GAN with intensive blood sampling in a previous study were included. Population pharmacokinetic parameters were derived with NONMEM (non-linear mixed effects modelling). The data were fitted to a two-compartment model with first-order elimination. Association of time to progression of CMV retinitis with C_{max} and $AUC_{0\text{-}24h}$ were investigated using the Cox proportional hazard model and the Weibull accelerated failure time model. In addition, serum concentrations obtained at the time of renal impairment and adverse events were tabulated. According to this analysis, increases in AUC were significantly associated with increases in time to progression of CMV disease, and AUC was a better predictor than C_{max}. Pharmacokinetic data obtained from subjects with renal impairment and at the time of adverse event were too limited to be conclusive.

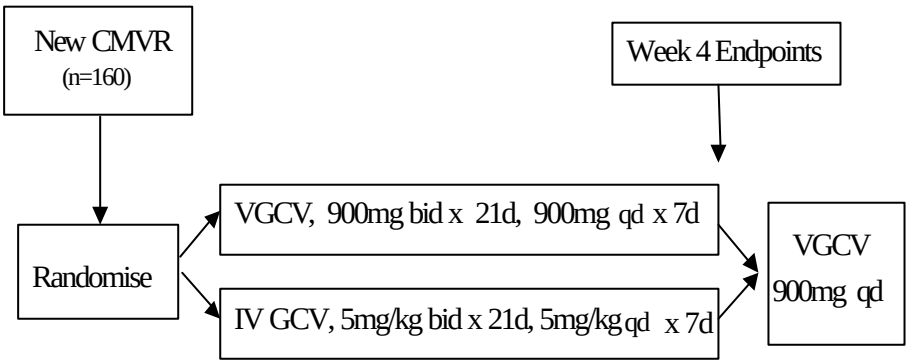
pharmacokinetics
The absolute bioavailability of GAN after oral administration of VAL is about 60%, being 10 times higher than after oral administration of GAN. The conversion of VAL to GAN is fast resulting in a maximum concentration of GAN after administration of VAL in 1-2 hours. Food increases the absorption of VAL by approximately 30%. In clinical studies, VAL was administered with food in accordance with the SPC. HIV+, CMV+ patients showed comparable pharmacokinetics of GAN as healthy subjects. However, renal impairment affects the pharmacokinetics and exposure is related to the creatinine clearance.

Clinical Efficacy

The clinical trial program of VAL was seriously hampered by the introduction of highly active anti-retroviral therapy (HAART) for AIDS in 1995, which reduced the incidence of new CMV retinitis and made the conduct of CMV retinitis trials difficult. Two clinical trials (study 6 and 7) were performed to evaluate the efficacy and safety of VAL in AIDS patients with CMV retinitis.

Study 6
Study 6 was conducted to evaluate the efficacy and safety of VAL induction treatment in patients with newly diagnosed retinitis. This was an open label, parallel designed trial (see figure below).

Schematic of Study 6



Baseline characteristics
The population consisted of patients with newly diagnosed CMV retinitis, continued severe immunocompromise in spite of HAART, a low CD4 count (< 100/ µL), a high HIV viral load, and multiple opportunistic infections. These patients have CMV retinitis characterised by relatively short progression times and frequent progressions of retinitis. Approximately 60% of patients were receiving treatment with an HIV protease inhibitor (PI) drug at study entry, and of these patients, the majority had received PI therapy for more than 3 months prior to study entry. Of the remaining 40%, half had never received treatment with a PI, and half had received PI therapy but were not receiving PIs at the start of the study.

Randomisation achieved a good balance at baseline between the two groups except for two factors - visual acuity and CMV virology. Patients in the VAL arm had more frequently impaired vision in the best eye (7%) and severely impaired vision in the worst eye (15%) than did patients in the iv. GAN arm (1% and 4%, respectively). Patients in the iv. GAN treatment arm were more often CMV culture positive, 65% versus 46%, and more often

week 4. This clinical endpoint was not previously used as a primary endpoint, although several prior studies conducted with intravenous GAN had used this endpoint as a secondary measure. In prior studies, this endpoint consistently showed that untreated, newly diagnosed CMV retinitis will progress within 14 to 28 days in most patients. Induction treatment with an active anti-CMV drug will prevent this progression in the majority of patients.
Patients received 3 weeks of twice-daily induction dosing followed by maintenance level dosing between week 3 and 4. Week 4 was selected for the assessment of the efficacy of induction therapy because the clinical status of the eye generally lags behind therapy by approximately 1 week.

The results of the primary endpoint based upon the blinded assessment of retinal photographs showed that seven patients (7/73) in each treatment group had progression. The proportion of progressors at week 4 was 0.100 vs. 0.099 for the intravenous GAN and VAL groups, respectively. The lower boundary of the 90% CI (confidence interval) (-0.082) was well above the predefined equivalence value (-0.250). The scoring of progression at week 4 by the ophthalmologists conducting the eye evaluations, who were unblinded to study drug assignment, gave different results. Progression was scored in only one patient in the iv. GAN arm vs. 12 patients in VAL arm. The difference in proportions was -0.150 (90% CI -0.226 to -0.075), (see table below). The discordance between ophthalmologic and photographic assessments is well described in the literature, even when the ophthalmologist is masked to treatment. Photographs are considered the “gold standard” for clinical trials; use of photographic assessments allows comparison across studies.

Progression at week 4 - Study 6

Outcome Measure	**iv. GAN/ VAL**	**VAL/VAL**
No. of patients	73	73
Photographic progression/ evaluable patients	7/70	7/71
Proportion progressed	0.100	0.099
Difference (D_p) (90% CI)	0.001 (-0.082, +0.085)	
Difference (D_p) (95% CI)	(-0.097, +0.100)	
Ophthalmologic progression/ evaluable patients	1/72	12/73
Proportion progressed	0.014	0.164
Difference (D_p) (90% CI)	-0.150 (-0.226, -0.075)	
Comparison of methods		
Progressors according to both methods at same visit	-	2 (3%)
Progressors first detected photographically	7 (10%)	5 (7%)
Progressors first detected ophtalmologically	1 (1%)	10 (14%)
Not yet progressed by either method	62 (85%)	55 (75%)

The most important secondary endpoint was the proportion of patients with satisfactory response to induction treatment at week 4, defined as no progression, no increase in lesion activity, and a reduction in retinitis border activity. Time from start of treatment to progression of CMV retinitis was also measured.

This secondary efficacy measure also showed comparability between the two treatments for those patients for whom an analysis of satisfactory induction was possible; 77% of patients

on intravenous. GAN and 72% on VAL had a satisfactory response by week 4; at week 6 these proportion were 63% and 70% respectively. Scoring of lesion activity by the ophthalmologists showed that retinitis failed to become inactive in 19 patients (26%) in the iv. GAN arm compared to 27 patients (37%) in the VAL arm.

At baseline a higher proportion of patients in the GAN group were culture (urine, semen or blood) positive compared to the VAL group. For the majority of patients urine was the source sample used for CMV culture assessment. CMV shedding decreased from 46% to 7% in the VAL group and from 65% to 6% in the GAN group (see table below).

Change in CMV culture status between baseline and week 4 - Study 6

	iv. GAN/ VAL n=80	VAL/VAL, n=80
Baseline		
Positive	46 (65%)	33 (46%)
Negative	25 (35%)	38 (54%)
Not known	9	9
Week 4		
Positive	4 (6%)	4 (7%)
Negative	60 (94%)	54 (93%)
Not known	16	22

Median time to photographically documented progression was 125 days in the arm originally randomised to intravenous GAN (42 progressors) and 160 days in the arm originally randomised to VAL (41 progressors). Median time to first progression as scored by the ophthalmologist was 337 days for the intravenous GAN arm and 196 days for the VAL arm.

The median time to withdrawal from the study was 376 in the VAL group compared to 419 days in the GAN group.

Second induction therapy

In 19/42 (45%) patients initially randomised to GAN/VAL a second progression occurred, in the patients initially randomised to VAL/VAL this percentage was 39% (16/41). Patients who experienced progression of CMV retinitis received a re-induction therapy with 900 mg VAL twice daily. Following photographic confirmation of progression, the first set of photos within ± 5 days of the start of reinduction therapy were used as the “new baseline” photographs for the assessment of second progression. Time-to-second- progression data were submitted, however, they should be interpreted with care, since a reliable baseline date for new progression could be calculated in only eight patients.

Antiviral efficacy in prior ganciclovir trials

In an effort to place the results of study six in context with prior GAN studies, the results were compared with data from four studies of newly diagnosed CMV retinitis conducted between 1987 and 1998. These four studies were considered to have designs that allow a valid comparison with study 6; used similar endpoints and except for one included a no-treatment control group. As shown in the table below, the results for VAL and iv. GAN in study 6 appeared to be close to the ranges for iv GAN treatment in prior studies.

The median times to progression in prior studies of GAN, before the widespread use of HAART, ranged from 49 to 70 days.

Study A	**1987 (pre-HAART)**				
IV. GAN		23	57%	57%	49
no Treatment		17	0%	6%	25
Study B	**1990 (pre-HAART)**				
IV. GAN		13	NE[b]	75%	50
delayed treat.		22	NE	14%	14
Study C	**1993 (pre-HAART)**				
IV. GAN		161 (57[a])	NE	89%	70[c]
Study D	**1998 (post-HAART)**				
I.O. Fomivirsen		18	72%	75%	72
delayed treat.		10	0%	<50% [d]	14
Study 6	**1999 (post-HAART)**				
oral VAL		73	76%	90%	160
IV. GAN		73	78%	90%	125[e]

[a] Number of patients included in time to progression estimate.
[b] NE; not evaluated
[c] Time from start of induction treatment to progression is estimated as sum of the time from start of maintenance treatment to progression plus 21day duration of induction treatment.
[d] Estimated based upon median time to progression of 14 days.
[e] This treatment group received iv. GAN for the first 4 weeks of study, then received VAL maintenance treatment of 900 mg once daily.

The table below supports the conclusion that the antiviral effects of iv. GAN and VAL in study 6 were comparable to those seen in study C.

CMV virology results from a prior CMV retinitis treatment trial compared to results in Study 6 patients with newly diagnosed CMV retinitis

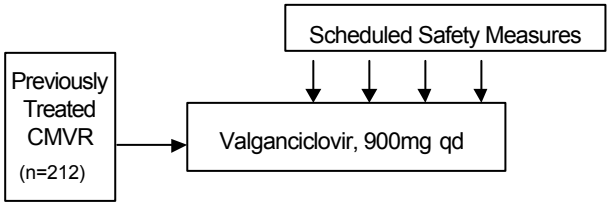
Study	iv. GAN		VAL	
	Baseline	End Induction	Baseline	End Induction
Study C	28/46 (61)*	5/37 (14)	NA	NA
Study 6	46/71 (65)	4/64 (6)	33/71 (46)	4/58 (7)

* number of culture positive patients / all patients with culture (%)

Study 7

Study 7 was initiated to evaluate the safety of VAL in AIDS patients with CMV retinitis. This was a single arm, open-label study designed to maximise patient enrolment by recruiting those with previously treated CMV retinitis. 212 Patients entered the trial. The study design is shown in the following figure.

Schematic of Study 7 (Safety assessments at baseline, week 2, and then every 4 weeks.)



All safety assessments and laboratory data were collected at baseline, week 2 and then at monthly visits, and for 30 days after study termination. The efficacy endpoints included the

The epidemiological information available shows that new CMV retinitis presently occurs with an incidence of about one-fifth the rate before the widespread use of HAART. Additionally, even in the occurring cases of CMV retinitis, the natural history of the disease may be altered. This fact limited both the size and the design of the clinical trials of VAL. In the end two clinical studies were done, including a total of 370 (safety evaluable) patients. In study 6, the efficacy of VAL 900 mg twice daily was shown in comparison to intravenous GAN 5mg/kg bid in induction treatment. For maintenance treatment oral GAN is recommended in a daily dose of 3 g divided over 3 or 6 doses and intravenous GAN is recommended at a daily dose of 5 mg/kg over 1 hour infusion. Considering the pharmacokinetics of iv GAN and oral VAL, a daily dose of 900 mg VAL would result in more or less similar systemic exposure for both formulations for the maintenance treatment. The second VAL clinical trial was a safety study (study 7) that was open non-comparative, to maximise the number of patients exposed to the drug for the longest duration, i.e. maintenance therapy.

Clinical safety

Like many nucleoside analogue drugs GAN has a narrow therapeutic margin. Several populations of mammalian germinal cells are particularly sensitive to the inhibition of cell replication by ganciclovir, including haemopoietic progenitors, spermatogonia, and gastrointestinal epithelium germinal layers. The clinical use of GAN, and therefore of VAL, must take into consideration this characteristic.

The VAL safety data are mainly from the two clinical trials. These data indicate that VAL has a safety profile not markedly different from that of intravenous GAN.

Adverse events reported in study 6 in the two treatment groups during the first 4 weeks are listed in the table below. Although the differences were marginal, diarrhoea was more common in the VAL group and nausea was more common in the iv. GAN group. In addition, there was more than twice as much use of antibiotics during the induction treatment period in the intravenous GAN arm as in the VAL arm. There were no differences between the treatment groups for any haematology measure during the induction treatment phase. Approximately 6% of patients had an absolute neutrophil count (ANC) < 500/ µl, and about 5% had a haemoglobin < 8 g/dl during the induction period. The most frequently reported adverse events for valganciclovir during induction therapy were diarrhoea, neutropenia, pyrexia and oral candidiasis.

There were no notable differences between the adverse events observed in study 6 and prior iv. GAN induction treatment groups, with the exception of oral candidiasis. It is unclear what aetiology could cause this difference, but it was a consistent finding in study 6.

All adverse events reported during induction treatment, by decreasing frequency (overall incidence >2%)

	Study 6 - induction	
Adverse event	**GAN/VAL**	**VAL/VAL**
	%	**%**
Diarrhoea NOS	10	19
Neutropenia	13	14
Pyrexia	13	14
Nausea	14	9
Oral candidiasis	6	14
Vomiting NOS	11	9
Anaemia NOS	8	9
Dermatitis NOS	8	6
Headache NOS	5	9
Fatigue	5	8
Cough	5	6
Abdominal pain	5	4
Pruritus	5	4
Retinal detachment	6	3
Taste disturbance	6	3
Appetite decreased	3	5
Paraesthesia	6	1
Influenza	3	4
Injection site infection	4	3
Leucopenia NOS	5	1
Venous phlebitis and thrombophlebitis	6	-
Vitreous floaters	4	3
Weakness	3	4
Constipation	3	3
Depression NOS	1	4
Injection site inflammation	5	-
Insomnia	3	3
Pneumocystis carinii pneumonia	4	1

Adverse events reported during maintenance treatment in study 6 and 7 are summarised and compared in the table below, which also includes comparative treatment groups from prior GAN studies. This table shows data pooled from studies conducted over a period of more than 10 years, and the contents may reflect differences in study conduct, data collection and analysis methods, differences in concomitant medication, and other factors. Care should thus be taken in interpretation of this information.

The adverse events appearing more frequently in the combined VAL maintenance treatment group relative to intravenous and/or oral GAN in prior studies include dermatitis, insomnia, retinal detachment, oral candidiasis, cataracts, lipodystrophy, hypersensitivity reaction, and macular oedema. These are not adverse events traditionally linked with GAN treatment. A causal relation was not suggested, because of the considerable variation in the frequencies of these events among the treatment groups, suggesting these differences are study specific. Moreover, all of these events, except perhaps for insomnia, are clinical findings that can be attributed to the underlying disease of CMV retinitis and advanced HIV infection.

Three adverse events, which were likely to be VAL related, were diarrhoea, neutropenia, and anaemia. Diarrhoea was equally prevalent in the VAL and oral GAN groups and more frequent than in the iv. GAN and placebo groups, suggesting a relationship of diarrhoea to both oral formulations. In study 6 anaemia (haemoglobin < 8.0 g/dl, 5 mmol/l) was more common in patients originally treated with VAL induction treatment than in the iv. GAN group during maintenance treatment (29% vs. 16%, respectively). Neutropenia, anaemia and pyrexia were less frequent overall in the patients in study 7 compared to study 6.

Adverse events reported during VAL and GAN maintenance treatment, by decreasing frequency (overall incidence (≥ 4%)

Adverse Event	VGCV	IV GCV	oral GCV 3 grams	oral GCV 4.5 grams	oral GCV 6 grams	Placebo
			(Prior studies)			
	N = 370	N = 412	N = 536	N = 180	N = 206	N = 119
	%	%	%	%	%	%
Pyrexia	*23.8*	*35.9*	*34.9*	*31.7*	*30.6*	*35.3*
Diarrhoea	*34.1*	*26.5*	*31.2*	*36.1*	*29.6*	*24.4*
Neutropenia	*20.5*	*25.7*	*22.6*	*22.8*	*28.2*	*11.8*
Nausea	*21.6*	*19.4*	*24.6*	*23.9*	*23.8*	*21.8*
Fatigue	*18.1*	*18.2*	*16.6*	*23.9*	*12.1*	*22.7*
Anaemia	*20.0*	*19.7*	*17.2*	*9.4*	*17.5*	*16.8*
Headache	*15.9*	*18.7*	*16.0*	*17.8*	*13.6*	*16.0*
Cough	*14.6*	*16.0*	*14.7*	*15.6*	*11.2*	*15.1*
Vomiting	*16.8*	*12.4*	*12.9*	*19.4*	*16.0*	*12.6*
Oral candidiasis	***17.3***	*6.3*	*9.3*	*8.3*	*22.3*	*12.6*
Dyspnoea	*8.4*	*10.7*	*9.9*	*16.1*	*9.2*	*10.9*
Dermatitis	***16.5***	*5.8*	*8.4*	*15.6*	*7.3*	*9.2*
Abdominal pain	*11.9*	*9.0*	*9.5*	*12.8*	*9.2*	*7.6*
Sinusitis	*9.5*	*6.3*	*3.9*	*9.4*	*9.7*	*13.4*
Appetite decreased	*7.0*	*6.3*	*6.5*	*11.7*	*6.8*	*8.4*
Candida	*3.8*	*10.4*	*6.2*	*11.1*	*6.3*	*4.2*
Insomnia	*13.2*	*5.1*	*4.7*	*6.1*	*6.3*	*7.6*
Pneumonia	*6.5*	*7.3*	*2.2*	*17.8*	*4.4*	*15.1*
Night sweats	*6.5*	*8.3*	*6.9*	*5.6*	*3.4*	*8.4*
Weight decrease	*9.2*	*6.1*	*5.2*	*6.7*	*5.3*	*7.6*
Depression	*7.8*	*5.6*	*5.6*	*8.9*	*4.9*	*7.6*

			(Prior studies)			
	N = 370	N = 412	N = 536	N = 180	N = 206	N = 119
	%	%	%	%	%	%
Peripheral neuropathy	*7.0*	*5.6*	*4.7*	*8.9*	*5.3*	*13.4*
P. carinii pneumonia	*4.6*	*7.3*	*6.3*	*8.3*	*8.7*	*2.5*
Thrombocytopenia	*5.1*	*6.6*	*6.9*	*5.6*	*4.9*	*5.0*
Retinal detachment	***11.9***	*2.4*	*3.0*	*8.9*	*5.3*	*5.0*
Dizziness (excl. vertigo)	*8.6*	*4.4*	*4.1*	*7.8*	*3.4*	*5.0*
Rigors	*2.4*	*7.8*	*6.0*	*4.4*	*2.9*	*8.4*
Weakness	*2.7*	*4.9*	*5.8*	*7.8*	*5.3*	*7.6*
M. Avium complex	*2.7*	*4.9*	*5.0*	*6.7*	*9.2*	*4.2*

Serious adverse events

During the randomised treatment phase in study 6, there were 29 serious adverse events in 19 patients (24%) in the iv. GAN treatment group and 13 serious events in 8 patients (10%) in the VAL group. The most common serious adverse events were infections and infestations (experienced by 11 patients in the GAN group, 1 patient in the VAL group).

Five patients in the 2 studies developed persistent, severe pancytopenia during treatment and the blood cell counts did not show evidence of recovery. All of these patients died while still pancytopenic although the deaths were not attributed to the cytopenia in all cases. Categorising the pancytopenia cases from among other patients with serious haematologic abnormalities was based on clinical judgement. One patient in study 6 developed pancytopenia with severe, persistent thrombocytopenia and then had epistaxis. This patient died due to haemorrhage. This patient was receiving full dose VAL maintenance treatment despite having renal impairment that required a dose reduction. Four patients in study 7 had pancytopenia that developed between 1 and 8 months on study. One was receiving concomitant hydroxyurea; other patients also had contributory factors. In spite of discontinuation of study drug, cytopenia persisted in these patients. One patient had confirmed bone marrow myelodysplasia. The overall frequency of severe pancytopenia in patients treated with VAL was similar to that reported as adverse events in prior iv. and oral GAN studies, which ranged from 0.5% to 1.7%.

Deaths

In study 6, 24 patients (30%) in the GAN group and 14 patients (18%) in the VAL group died during the study period; in study 7, 21 patients (10%) died during the study period.

The fatality rate (deaths per patient-year) for the maintenance phase was 0.220 in study 6 and 0.072 in study 7. The fatality rate for both VAL studies combined was 0.133, which compares favourably to the fatality rates in prior studies of iv. GAN (0.470) and 3 g qd oral GAN (0.502). It is likely that much of the reduction in mortality can be attributed to the introduction of HAART. In study 6 32/38 deaths occurred ≤30 days after the last medication. One death (hypovolaemic shock) was considered related. In 3 patients in study 7 the cause of death was considered related to treatment with VAL (one death due to P.carinii pneumonia, one due to multi-organ failure and one due to pulmonary sepsis resulting from life-threatening neutropenia).

Virology and Ganciclovir Resistance

Viral resistance was evaluated in study 6 by both genotyping (sequencing of plasma and restriction enzyme digest of blood leukocytes) and phenotyping methods. A total of 14/148 patients (9%) carried one or more mutations associated with resistance, 6 in the iv. GAN

It cannot be excluded that a somewhat higher exposure to ganciclovir with the VAL dosage has been responsible for the observed higher rate of, e.g., haematological toxicity and oral candidiasis. These observed differences between VAL and GAN are not so concerning that they have hampered licensing. The company made a commitment to gain additional safety data from ongoing trials and post marketing experience after registration. These safety data will be evaluated, and may lead to a dose adjustment if necessary.

Conclusion on safety

Like many nucleoside analogue drugs GAN has a narrow therapeutic margin. Several populations of mammalian germinal cells are particularly sensitive to the inhibition of cell replication by ganciclovir, including haemopoietic progenitors, spermatogonia, and gastrointestinal epithelium germinal layers. The clinical use of GAN, and therefore of VAL, must take into consideration this characteristic.

The safety profile of induction treatment with VAL at 900 mg twice daily in study 6 was clinically essentially similar to that of induction treatment with intravenous GAN at 5 mg/kg. twice daily. More diarrhoea and oral candidiasis appeared in the VAL treated patients. With intravenous GAN, more nausea, injection site infections and antibiotic use occurred.

The most frequently (>10%) reported adverse events for valganciclovir during induction therapy were diarrhoea, neutropenia, pyrexia and oral candidiasis. Under maintenance therapy, the most frequently reported adverse reactions were diarrhoea, pyrexia, nausea, neutropenia, and anaemia.

However, there was a modest increase in anaemia in the VAL group compared to the intravenous GAN group in study 6. This same trend was also observed in an analysis of time to anaemia. There were five cases of severe, persistent and irreversible pancytopenia reported among the 370 patients treated with VAL in the two studies. All five patients died, and four deaths were related to infection or haemorrhage, although only one death was scored as probably related to the study drug. It is suggested that concomitant treatment with hydroxyurea or failure to adjust the dose of VAL to account for renal impairment may have contributed to several of these adverse events.

OVERALL CONCLUSION ON QUALITY, EFFICACY, SAFETY AND BENEFIT/RISK ASSESSMENT

Quality

The chemical pharmaceutical documentation concerning the manufacturing, the quality of the raw materials and the finished product, and the stability of the product are sufficient with respect to the European regulatory rules

Preclinical pharmacology and toxicology

A range of studies have been undertaken which show that valganciclovir shares the same safety pharmacology and toxicity profile as ganciclovir. The safety pharmacology studies showed that no clinically relevant extra safety findings were induced. Conventional animal studies have shown ganciclovir to be mutagenic, carcinogenic and teratogenic at subtherapeutic exposures.

Clinical aspects and benefit risk assessment

The safety and efficacy profiles of intravenous ganciclovir have been well established over approximately 12 years of licensed clinical use. Since oral valganciclovir is rapidly and extensively hydrolysed to ganciclovir, the biological activities of valganciclovir were to some extent inferred from ganciclovir pharmacokinetic and clinical data.

It appears that oral valganciclovir 900 mg bid is therapeutically equivalent to iv ganciclovir 5mg/kg bid in the induction treatment of newly diagnosed CMV retinitis in AIDS patients. Also maintenance therapy with VAL appears successful.

It cannot be excluded that a somewhat higher exposure to ganciclovir with the valganciclovir dosage was responsible for the observed higher rate of, e.g., haematological toxicities and oral candidiasis. Overall, the safety profile of oral valganciclovir is more or less similar to the safety profile of ganciclovir.

PUBLISHED CLINICAL STUDIES

Boivin G., Gilbert C., Gaudreau A., Greenfield I., Sudlow R., and Roberts N. Rate of emergence of cytomegalovirus (CMV) mutations in leukocytes of patients with Acquired Immunodeficiency Syndrome who are receiving valganciclovir as induction and maintenance therapy for CMV retinitis. The Journal of Infectious Diseases, 2001; 184; 1598-602.

Pescovitz M. et al. Valganciclovir results in improved oral absorption of ganciclovir in liver transplant recipients. Antimicrobial agents and chemotherapy, Oct. 2000, p. 2811-2815.

Curran M. and Noble S. Valganciclovir. Drugs 2001; 61(8); 1145-1150.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Revision of section 5.1 of the SmPC	NL/H/0323/ 001/W/001	II	4-12-2002	9-5-2003	Approval	N
Addition of the indication prevention of CMV disease in CMV-negative patients who have received a solid organ transplant from a CMV-positive donor.	NL/H/0323/ 001/W/002	II	4-12-2002	9-5-2003	Approval	N
Change of the manufacturing site(s) for part or all of the manufacturing process of the medicinal product	NL/H/0323/ 001/V/003	IB	24-9-2003	24-10-2003	Approval	N
Change in the name and/or address of the marketing authorisation holder	NL/H/0323/ 001/IA/004	IA	16-3-2004	30-3-2004	Approval	N
Tightening of specification limits of the finished product	NL/H/0323/ 001/IB/005	IB	23-3-2004	22-4-2004	Approval	N
Tightening of specification limits of a starting material/intermediate	NL/H/0323/ 001/IB/006	IB	23-3-2004	22-4-2004	Approval	N
Addition of Cyprus, Czech republic, Estonia, Hungary, Latvia, Lithuania, and Slovakia	NL/H/032/0 01/E/001	Repeat-Use	22-12-2004	22-3-2005	Approval	N
Change in batch size of the finished product	NL/H/0323/ 001/IB/008	IB	22-8-2005	27-9-2005	Approval	N
Minor change to an approved test procedure of the finished product	NL/H/0323/ 001/IA/007	IA	27-9-2005	11-10-2005	Approval	N
Replacement or addition of a manufacturer responsible for batch release, not including batch control/testing	NL/H/0323/ 001/IA/009	IA	16-3-2006	16-3-2006	Non-approval	N
Change in the address of the MAH in the United Kindom and Ireland	NL/H/0323/ 001/IA/012	IA	22-3-2006	5-4-2006	Approval	N
Change in the name and address of the MAH in Lithuania	NL/H/0323/ 001/IA/013	IA	22-3-2006	5-4-2006	Approval	N
Change in the name of the MAH in Latvia	NL/H/0323/ 001/IA/014	IA	22-3-2006	5-4-2006	Approval	N
Change in the name of the MAH in Estonia	NL/H/0323/ 001/IA/015	IA	22-3-2006	5-4-2006	Approval	N
Replacement or addition of a manufacturer responsible for batch release, not including batch control/testing	NL/H/0323/ 001/IA/010	IA	13-7-2006	13-7-2006	Approval	N
Submission of a new or updated TSE Ph. Eur. Certificate of Suitability for an excipient	NL/H/0323/ 001/IA/016	IA	3-7-2006	17-7-2006	Approval	N
Addition of secondary packaging site	NL/H/0323/ 001/IA/017	IA	19-1-2007	2-2-2007	Approval	N
Submission of a new or updated TSE Ph. Eur. Certificate of Suitability for an excipient	NL/H/0323/ 001/IA/018	IA	8-3-2007	22-3-2007	Approval	N
Change in the name and/or address of a manufacturer of the finished product	NL/H/0323/ 001/IA/019	IA	13-3-2007	27-3-2007	Approval	N
Change in the name of the MAH	NL/H/0323/ 001/IA/020	IA	26-3-2007	9-4-2007	Approval	N
Renewal	NL/H/0323/ 001/R/001	Renewal	24-7-2006	12-4-2007	Approval	N
Addition of PhVig system to the dossier	NL/H/0323/ 001/II/021	II	16-11-2008	17-12-2008	Approval	N
Addition of Bulgaria, Poland, and Romania	NL/H/0323/ 001/E/002	Repeat-Use	17-11-2008	31-12-2008	Approval	N
Addition of batch release site	NL/H/0323/ 001/IA/022	IA	2-4-2009	16-4-2009	Approval	N
Change in the address of the MAH in Estonia and Finland	NL/H/0323/ 001/IA/025	IA	29-5-2009	12-6-2009	Approval	N
Addition batch release sites	NL/H/0323/ 001/IA/026	IA	8-6-2009	22-6-2009	Approval	N
Change in source of an excipient or reagent from a TSE risk to a	NL/H/0323/ 001/IA/027	IA	8-6-2009	22-6-2009	Approval	N

vegetal						
Addition of readability test to the dossier	NL/H/0323/ 001/II/023	II	7-5-2009	2-7-2009	Non-approval	N
Batch release in Finland	NL/H/0323/ 001/IA/032	IA	16-3-2010	15-4-2010	Approval	N
New dosing regimen for the prevention of CMS disease	NL/H/0323/ 001/II/024	II	31-7-2009	4-6-2010	Approval	N
Addition of manufacturing sites for drug intermediate and the drug substance	NL/H/0323/ 001/II/030	II	24-3-2010	27-11-2010	Approval	N
Change in the name and/or address of the MAH	NL/H/0323/IA/034/G	IA	26-11-2010	26-12-2010	Approval	N
Replacement or addition of a manufacturer responsible for batch release, not including batch control/testing	NL/H/0323/IA/035/G	IA	26-11-2010	26-12-2010	Approval	N
Change in batch release site for Finland	NL/H/0323/IA/037/G	IA	17-3-2011	15-4-2011	Non-approval	N
Update of the patient information leaflet	NL/H/0323/ 001/IB/036	IB	15-2-2011	26-5-2011	Approval	N
Addition of relevant paediatric information to the product information	NL/H/0323/ 001/II/029	II	12-7-2010	23-6-2011	Approval	N
Deletion of manufacturing site	NL/H/0323/ 001/IA/039	IA	15-6-2011	15-7-2011	Approval	N
Change batch release manufacturer for IE, CY and EL only.	NL/H/0323/IA/038/G	IA	24-6-2011	8-8-2011	Approval	N
Change in batch release site for Finland	NL/H/0323/IA/040/G	IA	27-7-2011	26-8-2011	Approval	N
Replacement batch release site	NL/H/0323/IA/123/G	IA	27-10-2011	27-10-2011	Non-approval	N
Update section 4.8 of the SmPC	NL/H/0323/ 001/IB/041	IB	7-10-2011	7-11-2011	Approval	N
Address change MAH	NL/H/0323/IA/043/G	IA	16-11-2011	16-12-2011	Approval	N
Implementation of a new version of the DDPS	NL/H/0323/IA/045/G	IA	17-12-2011	16-1-2012	Approval	N
Replacement batch release sites	NL/H/0323/IA/046/G	IA	4-1-2012	3-2-2012	Approval	N
Addition of a new specification parameter with its corresponding test	NL/H/0323/ 001/IA/047	IA	5-4-2012	7-5-2012	Approval	N
Name change active substance manufacturer	NL/H/0323/ 001/IA/048	IA	1-8-2012	31-8-2012	Approval	N
Update RMP	NL/H/0323/ 001/IB/049	IB	23-11-2012	27-2-2013	Approval	N
Introduction PSMF	NL/H/0323/ 001/IA/051	IA	15-2-2013	17-3-2013	Approval	N
Update of product information to comply with QRD template	NL/H/0323/ 001/IB/050	IB	27-3-2013	20-6-2013	Approval	N
Change in PSUR submission date	NL/H/0323/ 001/IA/052	IA	11-6-2013	11-7-2013	Approval	N
Addition of Croatia, Liechtenstein, Malta, and Slovenia	NL/H/0323/ 001/E/003	Repeat-use	9-9-2013	8-12-2013	Approval	N
Renewal	NL/H/0323/ 001/R/002	Renewal	23-8-2013	9-12-2013	Approval	N
Updates to the Product Information to fulfil post-approval commitments	NL/H/0323/ 001/II/053	II	3-1-2014	20-6-2014	Approval	N
Addition of a paediatric indication and consequential updates to SmPC section 4.2, 4.8 and section 5	NL/H/0323/ 001/II/054	II	3-1-2014	20-6-2014	Approval	Y, See annex I
Addition of a secondary packaging site, replacement of a site for microbial testing	NL/H/0323/IA/056/G	IA	21-8-2014	20-9-2014	Approval	N
Introduction PSMF	NL/H/0323/IA/060/G	IA	23-12-2014	22-1-2015	Approval	N
Update SmPC 5.1 to be in line with CDS together with editorial changes to SmPC 4.6 and 5.2	NL/H/0323/ 001/II/055	II	15-8-2014	11-3-2015	Approval	N
Change in the address of the marketing authorisation holder in Norway	NL/H/0323/ 001/IA/061	IA	23-2-2015	25-3-2015	Approval	N

Introduction PSMF	NL/H/0323/ IA/062/G	IA	4-8-2015	3-9-2015	Approval	N
Change in the address of the marketing authorisation holder in Italy	NL/H/0323/ 001/IA/064	IA	5-12-2016	3-1-2017	Approval	N
Change in the address of the marketing authorisation holder in the Czech Republic	NL/H/0323/ 001/IA/066	IA	13-2-2017	1-3-2017	Approval	N

ANNEX I – Type II variation for expansion of the indication 'prevention of CMV disease in patients who have received a solid organ transplant from a CMV-positive donor' to include children (aged from birth to 18 years) (NL/H/0323/001-002/II/054)

Table of contents

I. RECOMMENDATION

Based on the review of the data on safety and efficacy, the type II variation for Valcyte for expansion of the indication *Prevention of CMV disease in adults who have received a solid organ transplant from a CMV-positive donor* with *and children (aged from birth to 18 years)* is considered approvable.

This conclusion was agreed by the RMS and concerned member states. Therefore the variation was concluded with a positive outcome on 20 June 2014.

II. EXECUTIVE SUMMARY

The MAH submitted a type II variation in which the addition of an indication for Valcyte for CMV prophylaxis in paediatric solid organ transplant patients was proposed, supported by data from clinical studies:

The full indication (before the variation) was:

- for the induction and maintenance treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS).
- prevention of CMV disease in CMV-negative patients who have received a solid organ transplant from a CMV-positive donor.

The indication prevention of CMV disease is expanded to:

For the prevention of CMV disease in CMV-negative adults and children (aged from birth to 18 years) who have received a solid organ transplant from a CMV-positive donor.

Valcyte is an antiviral medicine. The active substance is valganciclovir (VGCV).
It has been approved in all European member states. There are two presentations of Valcyte: film-coated tablets and powder for oral solution. Valcyte 450 mg film-coated tablets is registered via the mutual recognition procedure (MRP) NL/H/0323/001/MR. It is registered in the Netherlands since 2001. Valcyte 50 mg/ml, powder for oral solution (POS) is registered via the decentralised procedure (DCP) NL/H/0323/002/DC since 2007.

Valcyte has an approved Paediatric Investigation Plan (PIP) (P/0220/2013) for the indication 'Prevention of CMV disease in CMV-negative patients who have received a solid organ transplant from a CMV-positive donor'. Two paediatric clinical studies (NV25409 and NP22523) have been completed as clinical measures for the PIP. The final clinical study reports for these two studies were submitted to the Paediatric Committee (PDCO) within a PIP Compliance Check which was approved at PDCO on 11 October 2013.

The clinical documentation in support of this type II variation consisted of three studies. Study NV25409 was a phase IV, open-label tolerability study in 57 kidney transplant patients between 4 months and 16 years of age. Study NP22523 was a phase I, open-label pharmacokinetics study in 14 heart transplant subjects under 4 months of age. Besides these two studies required by the PIP, the additional study CASG112 was performed. Study CASG112 was a phase III, double-blind, placebo controlled study in 109 infants with congenital CMV disease younger than 30 days.
The results of the studies are briefly discussed in this annex.

III. SCIENTIFIC DISCUSSION

III.1 Quality aspects

The MAH considered that no quality aspects were applicable for this variation. However, one of the concerned member states (CMS) requested a sample of the dosing syringe of Valcyte POS in order to verify that the dispenser is appropriate for dosing children. Instead of supplying a sample the MAH submitted the results of a dosing accuracy study, which the CMS agreed with.
The POS formulation is supplied together with a Conformité Européenne (CE) marked plastic oral dispenser (syringe) with press-in bottle adapter. The oral dispensers are graduated to 500 mg with graduations of 25 mg.

The results of the dosing accuracy study fulfil the requirements of the Ph.Eur.2.9.27 monograph on uniformity of mass of delivered doses from multi-dose containers. These findings sufficiently confirm the dosing accuracy of the dispenser at the lowest foreseen dosing level of 1 ml.

III.2 Non-clinical aspects

III.2.1 Non-clinical safety studies

Non-clinical safety studies were carried out to support the original Marketing Authorisation Application (MAA) for Valcyte. No additional non-clinical investigations were submitted to support the use of VGCV for the requested paediatric indications. This is justified for the following reasons:

1. The safety and tolerability data of VGCV has already been established in humans. These findings are valid for paediatric age groups as well as for adults. As VGCV is a pro-drug of ganciclovir (GCV), this data is augmented by even more clinical safety data for GCV.

2. The toxicity of VGCV seen in pre-clinical safety studies was the same as that seen with GCV and was induced at GCV exposure levels comparable to, or lower than, the therapeutic exposure in humans.
The relevant findings were already highlighted in the Summary of Product Characteristics (SmPC) for VGCV. It was already established that a sound benefit/risk assessment should be made on an individual basis for all patients regardless of age.

3. The overall safety profile (i.e. adverse drug reactions) in paediatric patients observed in the clinical studies was of a similar nature as in adults. These data were considered more relevant to the paediatric safety profile of VGCV than those that would be provided by additional non-clinical studies.

Considering the known toxicity of VGCV, and the already existing experience in children, the view of the MAH that additional non-clinical studies will not significantly contribute to paediatric safety was endorsed, provided that the paediatric clinical studies would not reveal unexpected effects which should be investigated further in non-clinical studies. This was not the case.

III.2.2 Environmental Risk Assessment

An environmental risk assessment (ERA) for VGCV was submitted within the original application for Valcyte in 1999. According to the 2006 EMA Guideline on the ERA of Human Medicinal Products (EMEA/CHMP/SWP/4447/00; 01.06.2006), a full ERA is required for new MAAs or for Type II variations if there is an increase in the environmental exposure, e.g., through a significant increase in use resulting from an extension of indication to another patient group. It is estimated that the inclusion of paediatric organ transplants will increase the patient population with 7.6%, which warrants an ERA.

As the MAH indicates in the ERA, VGCV is a prodrug. It is the L-valyl ester of GCV, to which it is rapidly converted by intestinal and hepatic esterases. No other significant metabolites have been observed and GCV is excreted by a renal pathway. The molecule relevant to the ERA is therefore GCV. Exposure modelling based on VGCV doses are therefore corrected by the ratio of the molecular weights of GCV and VGCV, which is 0.720.

III.2.2.1 Phase I

High and low concentrations of GCV were tested in parallel at three target pHs each (pH 5, 7, and 9) using the Organisation for Economic Co-operation and Development (OECD) 107 (shake flask) guideline. The K_{ow} value of each of the GCV concentrations and pH levels was determined. This procedure resulted in an average K_{ow} of 0.011, which translates to a $\log K_{ow}$ of -1.96, which is 5 $\log K_{ow}$ units below the Phase II Tier A threshold for bioaccumulation testing and 6.5 $\log K_{ow}$ units below the Phase I threshold for persistence, bioaccumulation, and toxicity (PBT) assessment. Therefore there was no need for a PBT-assessment.
The following formula was used to calculate $PEC_{surfacewater}$ (PEC_{sw}):

$$PEC_{SW} = \frac{DOSEai \cdot F_{pen}}{WASTEW_{inhab} \cdot DILUTION}$$

Using data on the number of solid organ transplants and the prevalence of CMV retinitis in paediatric patients in the EU the F_{pen} was estimated to be 0.00000648 patients/inhabitant. Calculating with the maximum dose of 900 mg/patient/day the PEC_{sw} was calculated to be 12.10 ng/L.
This value exceeds the action limit of 0.01 µg/L. In addition, this substance is classified as CMR category 1 and may affect the reproduction of vertebrate or lower animals at concentrations lower than 0.01 µg/L. Therefore a Phase II ERA is warranted and a tailored risk assessment strategy should be followed that addresses the products specific mechanism of action. The environmental endpoints are shown in Table 1.

Table 1: Environmental endpoints

Substance (INN/Invented Name): ganciclovir					
CAS-number (if available): 82410-32-0					
PBT screening		Result			Conclusion
Bioaccumulation potential – log K_{ow}	Not provided	-			-
PBT-assessment					
Parameter	Result relevant for conclusion				Conclusion
Bioaccumulation	log K_{ow}	Not provided			B/not B
	BCF	L/kg			B/not B
Persistence	DT50 or ready biodegradability	Not provided			P/not P
Toxicity	NOEC or CMR	CMR			T/not T
PBT-statement	No PBT statement could be made because of absence of data.				
Phase I					
Calculation	Value	Unit			Conclusion
$PEC_{surfacewater}$, refined (e.g. prevalence, literature)	16.8	ng/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)		CMR			(Y)
Phase II Physical-chemical properties and fate					
Study type	Test protocol	Results			Remarks
Adsorption-Desorption	OECD 106 or OPPTS 835.1110	Not provided			List all values
Ready Biodegradability Test	OECD 301	Not provided			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	Not provided			Not required if readily biodegradable
Phase IIa Effect studies					
Study type	Test protocol	Endpoint	value	Unit	Remarks
Algae, Growth Inhibition Test	OECD 201	NOEC		µg/L	Not provided
Daphnia sp. Reproduction Test	OECD 211	NOEC		µg/L	Not provided
Fish, Early Life Stage Toxicity Test	OECD 210	NOEC		µg/L	Not provided
Activated Sludge, Respiration Inhibition Test	OECD 209	EC		µg/L	Not provided
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF		L/kg	Not provided
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$			Not provided
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect		mg/kg	Not provided
Terrestrial Plants, Growth Test	OECD 208	NOEC		mg/kg	Not provided
Earthworm, Acute Toxicity Tests	OECD 207	NOEC		mg/kg	Not provided
Collembola, Reproduction Test	ISO 11267	NOEC		mg/kg	Not provided

Sediment dwelling organism	OECD 218/219	NOEC		mg/kg	Not provided

The MAH committed to submit the updated ERA, including clear information on the excreted fractions of unchanged parent and metabolites for the prodrug and the active substance. The member states agreed to accept this post-approval commitment, as fulfillment of the studies takes some time.

III.3 Clinical aspects

III.3.1 Overview

In total the MAH has submitted three paediatric studies for valganciclovir (VGCV) supporting this type II variation. The two developmental studies NV25409 and NP22523 are in the proposed paediatric indication: prevention of CMV disease in children (aged from birth to 18 years) who have received a solid organ transplant (SOT) from a CMV-positive donor. The age of the paediatric patients was between 4 months and 16 years of age and < 4 months of age, respectively. The third study (CASG112) provides supportive safety data in the very young patient population (≤30 days) with congenital CMV disease, which is not an approved indication. These three paediatric studies are first submitted within this variation.

Table 2 provides a summary of the three newly submitted paediatric
studies. As the patient population, formulations and treatment exposure differed across the studies, results were not integrated. This approach is acceptable.

Table 2: Overview of New Studies of Valganciclovir in Paediatric Populations

Study No.	Study Design	Population	No. of Patients Enrolled	Dose, Route, and Regimen	Study Duration (Exposure and Follow-up)
NV25409	Phase IV, Open-Label	Prevention of CMV disease in pediatric kidney transplant patients aged between 4 months and ≤ 16 years.	57	VGCV POS or FCT, dose (mg) = 7 × BSA × CrCLS	up to 200 days prophylaxis with follow-up until Week 52
NP22523	Phase I, Open-Label	Prevention of CMV disease in neonatal and infant heart transplant patients < 4 months of age.	14	VGCV POS, dose (mg) = 7 × BSA × CrCLS	2 days prophylaxis with 7 days follow-up
CASG112	Phase III, Randomized, Placebo controlled	Treatment of symptomatic congenital CMV infection in neonates and infants ≤ 30 days of age.	109	VGCV POS, 16 mg/kg/dose BID	6 months treatment with 2 years follow-up

BID = Twice a Day; BSA = Body Surface Area; CrCLS = creatinine clearance calculated using a modified Schwartz equation; FCT = film-coated tablet; OD = Once Daily; POS = Powder for Oral Solution; VGCV = valganciclovir.

Because of the inherent concern, especially among treating physicians, that children tend to shed virus at higher viral loads and for longer (as laid down in the PIP requirements), all CMV serostatus types were included. Inclusion was not restricted to the donor positive/receptor negative (D+/R–) population only, which is the currently approved adult indication and the population which is at highest risk. It is agreed that the serostatus of the patients would not influence the safety profile of VGCV.

The MAH also referred to two previously submitted studies in adults, PV16000 and NT18435, as these also included a limited number of paediatric patients (adolescent subset; n=12; aged 14 – 18 years). This data is used to bridge the gap between the newly submitted studies in 16-18 years old patients, and provide further supporting safety information.

III.3.2 Clinical pharmacology

III.3.2.1 Study NP22523

Study NP22523 was a Phase I, multi-centre, non-comparative, open-label pharmacokinetic and safety study investigating VGCV therapy in paediatric heart transplant patients <4 months of age. Fourteen patients were included in the report submitted to support this variation, fulfilling the requirements laid out in the PIP.

The objective of this study was to perform a population pharmacokinetics (popPK) analysis in order to construct a dosing algorithm for VGCV in children younger than 4 months of age.
A dosing algorithm for VGCV was previously established for the paediatric population (infants aged ≥ 4 months, children and adolescents) in variation NL/H/0323/001-002/II/029. With this variation it was approved to include this algorithm (dose (mg) =7 x BSA x CrCl) in section 5.1 of the SmPC, but not in section 4.2, as no sufficient data was available to justify a dosage recommendation.

The formula was shown to deliver similar exposures of GCV from VGCV to children of all age groups older than 4 months as those exposures which were found to be safe and effective in adults. The algorithm for VGCV dosing has not been assessed previously in children younger than 4 months of age.

Study NP22523 aimed to address this lack of pharmacokinetics (PK) data in very young children by determining the PK profile of GCV from VGCV POS in fourteen children younger than 4 months of age following two doses as determined by the dosing algorithm already established in older children. The study was limited to paediatric patients younger than 4 months of age who had received a heart transplant and considered to be at risk of CMV disease, who were therefore receiving prophylaxis with intravenous (IV) GCV or VGCV POS as part of their routine post-transplant standard of care (SOC).

Twelve of the fourteen included patients were between the ages of 6 weeks and 4 months and 2 patients were aged between birth and 6 weeks. Most patients (11 out of 14) were white and the number of males and females was similar (8 and 6, respectively). Patients had the following CMV serology status: D+/R+ (50%), D−/R+ (29%) or D+/R− (21%).

III.3.2.1.1 Methods

The 14 patients enrolled were at risk of developing CMV disease and were already receiving, or due to receive, CMV preventative therapy with either GCV or VGCV POS. Patients already receiving CMV prophylaxis had their existing prophylaxis regimen interrupted for 2 days in order to participate in the study. During the study, patients received two doses of VGCV POS (one dose per day). Dosing was determined using the algorithm as described in the SmPC: dose (mg) = 7×BSA× CrCLS (where BSA = body surface area, CrClS = creatinine clearance calculated using the Schwarz formula, with a maximum of 150 ml/min/1.73m^2 for creatinine clearance).

Blood samples for the measurement of GCV and VGCV were collected for popPK analysis on dosing day 2 at the following intervals: pre-dose (within 1 hour prior to VGCV administration) and at 1-3 hours, 3-7 hours (at least 1 hour after the previous blood draw), 7-12 hours (at least 2 hours after the previous blood draw) and 24 (+/- 1) hours after VGCV administration.

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable. Internal sample re-analysis data showed good reproducibility.

III.3.2.1.2 Results

After administration of VGCV to heart transplant patients aged younger than 4 months, the mean values of estimated PK parameters for GCV were: total body clearance = 1.25 l/h, relative bioavailability = 64%, C_{max} = 10.5 µg/ml, AUC_{0-24h} = 68.1 µg.h/ml and $t_{1/2}$ = 2 hours. The range of the estimated steady state AUC_{0-24h} was 34−124 µg.h/ml. The PK parameters are shown in Table 3.

Using these data, two formulas were used to establish a clearance model for continuous and categorical covariates.
The model has been described in sufficient detail and fits the data well, with good individual predictions. The goodness of fit plots did not exhibit any patterns indicating a prediction bias.

Table 3: Summary of model-estimated GCV steady-state AUC_{0-24h} and C_{max} for different age groups in study NP22523

PK Parameter	Age Group		
	<6 weeks	6 weeks–4 months	Combined
AUC_{0-24h} (µg•h/mL) [a]	n=3	n=15	n=18
Mean	64.7	68.8	68.1
Median	57.3	67.4	64.6
CV	22.1	30.7	29.0
Range	—	—	34–124
C_{max} (µg/mL)	n=2	n=12	n=14
Mean	8.33	10.8	10.5
Median	8.33	11.0	10.7
CV	10.8	32.4	31.9

AUC_{0-24h} = area under the plasma concentration-time curve between dosing intervals (pre-dose to 24 hours); C_{max} = maximum observed plasma concentration; CL = clearance; CrCLS = creatinine clearance calculated using a modified Schwartz equation; CV = coefficient of variation; F1 = relative bioavailability; GCV = ganciclovir; n = number of observations; PK = pharmacokinetics.

[a] All the doses administered to patients on Day 2 were used for the calculation of AUC_{0-24h} (n = 12, mean = 70 µg•h/mL, CV = 31.4). In addition, the oral doses received as standard of care from 3 patients and one Day 1 dose that was different than the patient's Day 2 dose as a result of CrCLS change were also included in the AUC calculation (AUC_{0-24h} = Dose × F1/CL).

GCV plasma concentration data in paediatric heart transplant patients (n=14) obtained in this study were used to refine the previously assessed popPK model developed using data from the studies WP16296 (n = 25), WP16303 (n = 18), and WV16726 (n = 62). This model was developed to characterise the pharmacokinetics of GCV after IV or oral administration of VGCV in SOT paediatric patients. A total of 985 measured plasma concentrations of GCV from 119 patients were included in the analysis. An additional 10 samples from 6 patients were excluded because of uncertain sample collection or dose time information. The model included CrCIS and height as covariates.

VGCV dosing is based on AUC values. The variability observed for GCV AUC_{0-24h} across dose groups was moderate. No trend was observed in AUC values obtained from children of about 20 – 120 days old. It appeared that younger children experienced higher GCV exposures than those in the older age groups, which is consistent with previously reported estimates of GCV exposure in paediatric SOT patients. Specifically, it appeared that the infants younger than 4 months in study NP22523 experienced exposures approximately 23% higher than the youngest group studied in previous clinical trials.

The model predicted AUC of 68.1 µg.h/ml was just higher than the targeted AUC_{0-24h} range of 40-60 µg.h/ml, which has previously been shown to provide efficacy in adults.

The relationship between GCV AUC and age within the current study is analysed. Although the data in the patients < 6 weeks is limited, there appears to be no meaningful difference in the exposures when compared with the patients aged ≥ 6 weeks to 4 months.

As previously established for the older age groups, body size and creatinine clearance are both significant covariates of the pharmacokinetics of VGCV. Body weight and CrCLS were used as covariates in the paediatric dosing algorithm. The addition of Study NP22523 data to the historical paediatric SOT patient PK database did not change the findings of the model previously described.

Additionally, the estimated exposure data in children < 4 months of age were reasonable in line with those in other transplant patient groups (see Table 4).

Table 4: Summary of model-estimated mean (±SD) pharmacokinetics of GCV in patients by transplant group and age (study WV16726 and NP22523)

Transplant Subgroup	PK Parameter	Age Group			
		<4 months (n=14)	4 months to ≤2 years (n=6)	>2 to <12 years (n=2) [a]	≥ 12 years (n=4)
		NP22523		WV16726	
Kidney (N=33)	AUC_{0-24h} (µg•h/mL)	—	65.2 (16.6)	55.0 (11.9)	50.0 (11.6)
	C_{max} (µg/mL)	—	10.0 (0.04)	8.74 (2.49)	7.85 (2.10)
	$t_{1/2}$ (h)	—	3.10 (0.59)	4.40 (1.41)	5.67 (1.06)
Liver (N=17)	AUC_{0-24h} (µg•h/mL)	—	69.4 (35.4)	58.4 (6.18)	35.6 (2.76)
	C_{max} (µg/mL)	—	11.7 (3.59)	9.35 (2.33)	5.55 (1.34)
	$t_{1/2}$ (h)	—	2.72 (1.32)	3.61 (0.80)	4.50 (0.25)
Heart (N=26)	AUC_{0-24h} (µg•h/mL)	68.1(19.8) [b]	56.3 (23.2)	60.0 (19.3)	61.2 (26.0)
	C_{max} (µg/mL)	10.5 (3.35)	8.22 (2.44)	12.5 (1.02)	9.50 (3.34)
	$t_{1/2}$ (h)	2.00 (0.19)	3.60 (1.73)	2.62 (0.65)	5.05 (0.70)

AUC_{0-24h} = area under the plasma concentration-time curve between dosing intervals (pre-dose to 24 hours); C_{max} = maximum observed plasma concentration; GCV = ganciclovir; N = number of observations; PK = pharmacokinetics; SD = standard deviation; $t_{1/2}$ = half-life.

[a] There was 1 patient who received both a kidney and liver transplant. The PK profile for this patient has not been included in this table as it is not possible to determine whether the effects observed are from the kidney/liver transplant or neither.

[b] n = 18 observations: 3 patients contributed more than one value per patient.

The MAH submitted the final report after all paediatric patients <6 weeks (4 in total) were evaluated. Since the submission of the variation dossier, an additional 3 patients were enrolled into Study NP22523, bringing the total enrolment to 17 patients. Sixteen of these patients provided blood samples for PK assessment and are included in an updated final study report.
Analysis of the PK data obtained from Study NP22523 has demonstrated that the exposure of GCV following administration of VGCV in the <6 weeks age group and the 6 weeks to < 4 months age group is similar. GCV exposures were also similar when comparing across the paediatric age groups in Studies NP22523 (<4 months of age) and WV16726 (4 months to 16 years of age) using the same dosing algorithm. Based on these results the MAH sufficiently demonstrated that the current paediatric dosing algorithm for VGCV in transplant patients >4 months of age can be extended to paediatric transplant patients <4 months of age.

III.3.2.2 Study CASG112

This study was a phase III, randomised, placebo-controlled, blinded investigation of 6 weeks versus 6 months of oral VGCV therapy in infants ≤ 30 days of age with symptomatic congenital CMV infection.
The primary purpose of this study was to estimate GCV PK parameters from a larger sample size than previously studied, and to use these data to assess adherence to the regimen over the first 6 weeks and 6 months of oral VGCV therapy.

III.3.2.2.1 Methods

All subjects received open label VGCV for the first 6 weeks. At the end of the open label period, subjects were randomised to continuing therapy with either the active substance (VGCV) or placebo.
The dose of oral VGCV was 16 mg/kg/dose twice daily (BID) as oral solution, which had been identified previously as the dose that achieved efficacy.
If the calculated renal function was normal (creatinine clearance ≥ 20 ml/min/1.73 m^2), the full dose of study medication was administered at the same intervals (VGCV/placebo 16 mg/kg/dose BID). If renal function was moderately impaired (creatinine clearance 10-19 mL/min/1.73 m2), then the full dose of study medication was administered at decreased intervals (VGCV/placebo 16 mg/kg/dose administered once daily). If renal function was severely impaired (creatinine clearance < 10 mL/min/1.73 m^2), study medication was discontinued.
A single sample (0.2 ml) of whole blood was obtained at each visit up to and including week 6 (weeks 1-6, no clinic visit is scheduled for week 5), and again at week 8, week 10, week 12, and months 4, 5, and 6. Up to 11 samples were collected over the first 6 months of the study.

III.3.2.2.2 Results

A total of 109 subjects (aged <30 days) were enrolled over a three year period and 97 were randomised of which one dropped out before randomization. Forty-seven were randomised to the active substance (VGCV) and 49 were randomised to placebo. In both groups, 41 subjects completed the 6 month trial period.
The average AUC_{0-12} and associated SD value are 20.85 ± 5.4 µg·hr/mL, with minimum and maximum values of 3.51 and 47.0 µg.hr/mL, respectively. Fifty values fall within the target range of 20–55 µg·hr/mL, while the other 50% of cases had an AUC_{0-12} below the target range (N = 100).

The PK results from Study CASG112 were provided within the variation dossier to support the safety evaluation only. Patients in this study received VGCV using a different dosing algorithm than in the other studies, and it is known that the pharmacokinetics of GCV in the indication of congenital CMV infection are different from those in patients following SOT.
The systemic drug exposure of GCV in Study CASG112 is similar to previous study findings in congenital CMV. The average AUC_{0-12} value is within the target range of range of 20–55 µg·hr/mL, indicating the appropriateness of this particular dosing algorithm for treating paediatric patients that did not receive SOT with symptomatic congenital CMV.
Based on these data section 5.2 of the SmPC was updated. The data are too limited to allow conclusions regarding efficacy or posology recommendations for paediatric patients with congenital CMV infection in the SmPC.

III.3.3 Clinical efficacy

III.3.3.1 Study NV25409

Study NV25409 was a phase IV, multi-center, open label, single arm, non-comparative safety study to describe the tolerability of up to 200 days of VGCV prophylaxis (POS and film-coated tablet formulations) in paediatric kidney transplant patients (4 months to ≤16 years, although the youngest subjects included were aged 1 year), with off-treatment follow-up until week 52 post-transplant.
The primary objective of this study was to describe the tolerability profile of up to 200 days VGCV prophylaxis, with as secondary objectives to describe the incidence of CMV infection (viremia) and disease (CMV syndrome or tissue invasive CMV disease) within the first 52 weeks post-transplant.

Since a placebo-controlled trial or active-comparator study has not been feasible for this product in this patient population, the paediatric program, as agreed with the PDCO and other health authorities,

has focused on targeting a range of AUC exposures through PK assessments and the development of an appropriate dosing algorithm to achieve this AUC range.

39.3% of the paediatric subjects fell in the highest risk population (serostatus D+/R-; (i.e. 22 patients; n=2, ≤2 years; n=3, 2-12 years; n=13, ≥12 years). In addition, data of 25 paediatric patients with serostatus D+/R- obtained in WP16726 were included in the analysis. Therewith a total of 47 paediatric patients with serostatus D+/R- were included.

Efficacy has been proven in the high-risk (D+/R–) adult population. Based on the VGCV mechanism of action (i.e. a direct acting antiviral) extrapolation of efficacy from the adult population to children is appropriate.
Because of this, the target population for the prophylaxis indication should mirror that of the adult target population if the safety profile remains consistent and benefit-risk remains positive.
With respect to viral shedding differences between adults and children, there is evidence to suggest that in congenitally infected infants and healthy children, viral shedding of CMV can continue for several months if not years, compared with seroconverted adults, who shed virus for several months but which usually ceases within about half a year.

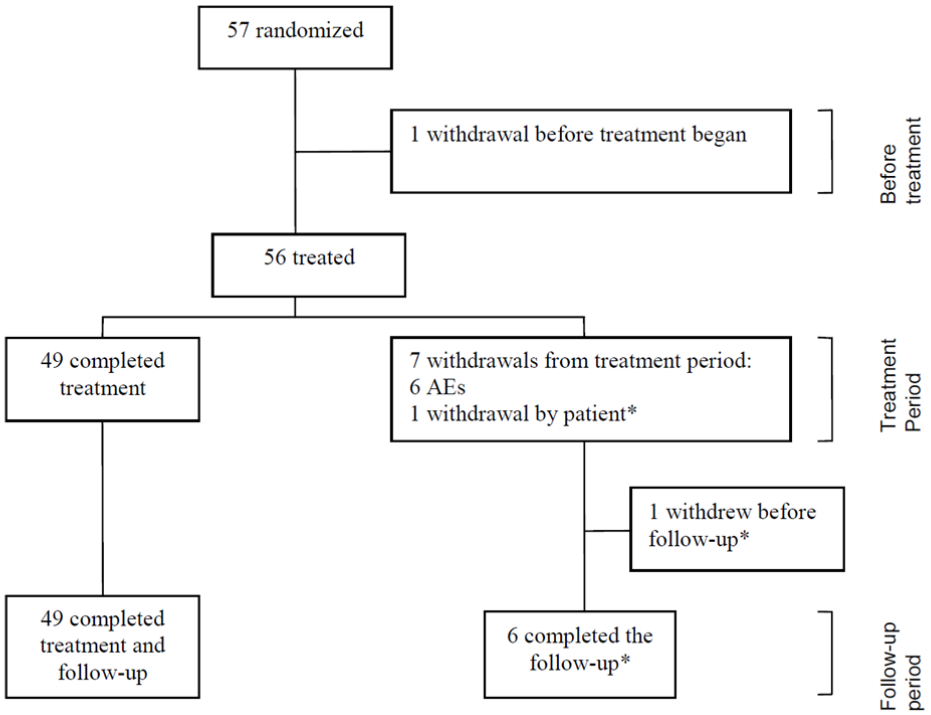
III.3.3.1.1 Methods

Male or female kidney transplant patients aged 4 months to 16 years who were at risk of developing CMV disease were included in the study if they had adequate haematological and renal function and were able to tolerate oral medication.
Patients were excluded from the study if they had exhibited an allergic or other significant adverse reaction to acyclovir, valacyclovir or GCV in the past; had severe, uncontrolled diarrhea (more than 5 watery stools per day); had liver enzyme elevation of more than 5 times the upper limit of normal for aspartate aminotransferase (AST) or alanine aminotransferase (ALT); required the use of any protocol prohibited concomitant medications; or were pregnant or lactating.

Patients received VGCV as POS or film-coated tablet once daily conform the previously established dosing algorithm, starting within 10 days of transplant.
The dose, up to a maximum of the 900 mg adult dose, was recalculated at each study visit. If required, a dose adjustment was made.

Studied parameters were incidence of CMV disease, incidence of CMV infection (viremia), viral load and resistance, biopsy proven acute rejection, and patient and graft survival.
The study design and patient disposition are shown in figure 1.

Figure 1: Patient disposition in study NV25409



III.3.3.1.2 Results

A total of 57 patients were enrolled. Fifty-six patients were dosed with VGCV (ITT population): 6 patients (11%) in the ≤ 2 years age group, 18 patients (32%) in the >2 to <12 years age group and 32 patients (57%) in the ≥12 years age group. There were more males than females (55% vs. 45%, respectively). The most common races of patients were white (29 patients [52%]) and hispanic or latino (31 patients [55%]). The primary reasons for transplant varied, with no one form of end-stage renal disease (ESRD) predominating. For the majority of patients (54/56) it was their first kidney transplant, of which approximately half were living donor transplants. Most patients had a CMV serology status of D+/R+ (45%) or D+/R- (39%). Forty-nine patients completed the treatment phase.

A total of 37 patients (66.1% of the patients) received the maximum study drug duration for more than 190 days. Five patients (8.9%) received treatment for less than the per protocol cut-off of 150 days (all data incorporates any dose interruptions).
All patients in the ≤2 years age group received VGCV POS throughout the study; 61.1% patients in the >2 to <12 years group received only VGCV POS and 38.9% patients received both VGCV POS and film-coated tablets over the course of the study. In the ≥12 years age group, 6.3% of patients received VGCV POS only, 40.6% patients received only film-coated tablets and 53.1% received both POS and film-coated tablets over the course of the study. Overall the average daily dose was 677 mg. As expected, the average daily dose was highest in the ≥12 years age group (780 mg) and lowest in the ≤2 years age group (463 mg). The average daily dose in the >2 to <12 years age group was 563 mg.

The dosage regimen resulted in comparable exposures between age groups and between organ transplant types. Mean C_{max} values ranged from 5.5 -12.5 mg/l. The mean observed exposure ranged from 35.6 to 69.4 mg.h/ml, which is in the order of the therapeutic range in adults of 40 – 60 mg.h/l.

None of the paediatric patients had CMV disease.
Overall 10 patients had quantifiable levels of viral DNA (lower limit of quantification (LLOQ) ≥ 150 copies/ml). Two patients (9.1%, both D+/R-) had low levels of CMV during the study period. One of the patients had a significant dose adjustment and interruption of study drug treatment due to neutropenia prior to this positive sample at week 24. The second patient had low levels of CMV viremia and did not receive additional treatment. The latter patient had undetectable levels of CMV at the end of the follow-up period. Eight patients (n=4, D+/R-; n= 4, D+/R+) had quantifiable CMV DNA in the follow-up period following completion of study drug. Six patients did not receive any treatment for their CMV viremia, and the events subsequently resolved.

Two patients were treated for CMV viremia in their follow-up period with VGCV. Both patients were considered CMV negative after treatment.

Two patients (D-/R+ and D+/R-) who did not experience any CMV-related symptoms or have any positive CMV samples received secondary VGCV prophylaxis during the follow-up period. One patient experiencing anaemia and neutropenia during the treatment phase discontinued treatment, and the second patient experienced an acute rejection at the end of the treatment period.

Thirteen patients had a biopsy for a suspected rejection; of which six (10.7%) had a confirmed Biopsy-proven Acute Rejection (BPAR); one patient in the ≤2 years age group, one in the >2 to <12 years age group and four in the ≥12 years age group. Most patients experienced one rejection episode. The rate of BPAR episodes was low and of mild to moderate intensity. Patients were treated and the rejection resolved, however data on 2 patients were lost due to refusal of treatment and diagnosed at the end of follow-up. One of the six patients had a CMV infection prior to the rejection episode in the follow-up period.

Dose modifications were expected during the study due to changes in the patient's renal function, calculated according to the dosing algorithm. Excluding per protocol dose modifications, about 50% of patients had at least one dose modification.

The incidence (9.1%) of CMV disease shows a similar trend as what has been observed in adults: the incidence of CMV disease at 12 months post-transplant was 17.8% and consistent with the incidence in literature (at 6 months 15% of the D+/R- liver transplant patients given oral ganciclovir developed CMV[1]).
The incidence of CMV disease in D+/R- patients in the follow-up period is 18.1%, a similar incidence was observed in adult patients 12 months post transplant.

Although viral loads were only collected monthly in this study, the data show that while on prophylaxis, breakthrough viremia does not occur. This is different to adults where some viral

[1] Gane *et al.*, Randomised trial of efficacy and safety of oral ganciclovir in the prevention of cytomegalovirus disease in liver-transplant recipients. The Oral Ganciclovir International Transplantation Study Group [corrected] Lancet. 1997 Dec 13;350(9093):1729-33.

breakthrough was observed. This difference could be related to better compliance and closer patient physician care in the vulnerable paediatric population. However, it is well understood that in the post prophylaxis period CMV can begin to replicate again and that it may be dependent on the level of a patient's immune constitution. Some viral shedding did occur in the paediatric studies of the MAH during the post prophylaxis period in both D+/R- and D+/R+ patients, but this was more sporadic and at much lower viral loads than has been seen in the adult setting. It is possible to infer, based on the data generated in the paediatric population, that not only the highest risk D+/R- patients are likely to benefit most but also the D+/R+ patients. However, the D+/R+ population have not been studied in adults or children with respect to prophylaxis and therefore the MAH does not know the suitable duration of prophylaxis to recommend, or even if prophylaxis is appropriate (alternative being pre emptive therapy) in order to provide the greatest benefit for D+/R+ patients.
The current adult prophylaxis indication is considered the appropriate target indication for prophylaxis in children from an efficacy perspective (i.e., high risk paediatric patients with serostatus D+/R-) based on the current understanding of the data.

III.3.3.2 Therapeutic drug monitoring (TDM)

Considering the variability in pharmacokinetics, it is likely that several patients will have AUC-values below the target value of 40 µg.h/ml. Considering the severeness of the disease this may result in underdosing of (paediatric) patients. Hence the MAH was requested to discuss the need for therapeutic drug monitoring (TDM). The RMS advised the MAH to discuss a possible association between Cmax and adverse events, discuss the recently published articles by Villeneuve[2] and Asberg[3] and to address the consequences for the adequacy of the current paediatric dose recommendations. In addition, the MAH was asked to discuss which measurements should be taken to reduce the risk of both over- and underdosing in paediatric patients and the place of TDM in this matter. Where appropriate the MAH was requested to update the SmPC.

TDM is the practice of routine measurement of a drug in the blood in order to maintain constant drug concentrations. It is unnecessary for the majority of drugs, but can be useful for monitoring drugs with narrow therapeutic windows, drugs with extensive PK variability, or for drugs that have a clear concentration-effect relationship. VGCV does not fall into any of these categories.
The proposed dosing strategy is for prophylaxis, thereby maintaining suppression of viral replication while a patient is at highest risk of reactivation of virus from the donor organ, or of infection via a different source when the patient is most highly immunosuppressed after organ transplant. The MAH agrees that established disease can be serious, particularly disease with organ involvement (tissue invasive CMV), but this is treated with IV GCV, as accepted within global consensus guidelines for CMV in solid organ transplant.
TDM in relation to GCV or VGCV has been the subject of two peer reviewed articles in the past 10 years[4] [5]. Both come to a conclusion similar to that of the MAH: TDM is not likely to afford additional benefit in this patient population and therefore is not justifiable for the following reasons:

- Doses are already managed by way of the dosing algorithm on the key parameters that affect the pharmacokinetics of the drug, based on the correlation between systemic exposure to GCV and antiviral activity. The proposed SmPC highlights that these parameters should be measured on a regular basis and adjustments need to be made in order to ensure that patients remain on a suitable dosage.
- No formal therapeutic window for VGCV or GCV has been established, because the dosing range in which it is effective but not toxic is not well defined. No clear correlation has been established for GCV between Cmax or Cmin concentrations and either efficacy or toxicity of the drug.

[2] Villeneuve D, Brothers A, Harvey E, et al. Valganciclovir dosing using area under the curve calculations in pediatric solid organ transplant recipients. Pediatr Transplant 2013;17:80-5.
[3] Asberg A, Bjerre A, Neely M. New algorithm for valganciclovir dosing in pediatric solid organ transplant recipients. Pediatr Transplant 2014;18:103-11.
[4] Scott JC, Partovi N, Ensom MH. Ganciclovir in solid organ transplant recipients: is there a role for clinical pharmacokinetic monitoring? Ther Drug Monit 2004;26:68-77.
[5] Perrottet N, Decosterd LA, Meylan P, et al. Valganciclovir in adult solid organ transplant recipients: pharmacokinetic and pharmacodynamic characteristics and clinical interpretation of plasma concentration measurements. Clin Pharmacokinet 2009;48:399-418.

- The doses resulting in an overall average exposure range of 40–60 μg.h/mL proved to be effective in the majority of paediatric SOT patients, as cases of CMV disease were extremely rare (1 possible event of CMV syndrome and no events of tissue invasive disease). In those patients where CMV virus was measurable and who were therefore at risk of CMV disease, CMV DNA analysis showed that the viral load was very low (much lower than would require treatment. This does not necessarily mean that all individual patient AUC values must be within this range; this would only be the case if a one-to-one correlation existed between an individual's clinical response and a single AUC value, forming the basis of TDM. Such is not the case for GCV. The MAH has demonstrated that the overall AUC value of GCV adheres to the 40– limit reasonably well in paediatric solid organ transplant patients < 4 months–16 years of age using the current dosing algorithm.
- TDM is not considered necessary in order to prevent overdosing. In patients where dosing resulted in an exposure > 60 μg.h/mL, no causal relationship between GCV exposure and the frequency of adverse events in general, and the frequency of anaemia in particular, could be established. Application of the dose modifications as described in section 4.2 and 4.4 of the SmPC proved effective to manage any occurring blood and lymphatic system disorder.
- To perform TDM properly, serial blood samples have to be collected within a 24-hour period, which may exacerbate any anaemia already present in this population. Such intensive blood sampling would be very difficult to achieve routinely, even in a hospital setting, because local measurement of GCV levels would be difficult in all but specialised institutions. Most samples would therefore need to be sent to a suitable laboratory, possibly outside of that country, with suitably sensitive and reproducible assays, and with a fast enough response time to get results back to the hospital within a clinically meaningful timeframe.

Based on this argumentation, it was agreed that TDM for VGCV is not required.

III.3.3.3 Paediatric efficacy data from other studies

Paediatric efficacy data were also derived from the previously submitted studies WP16303, WV16726, and WP16296, which were assessed in variation NL/H/0323/001/II/029.

The open label, randomised study WV16726 included 63 paediatric patients (4 months to 16 years, of which 25 had a D+/R- serostatus) scheduled for SOT (kidney, heart, liver). Patients received up to 100 days post transplant VGCV in line with the approved paediatric dosing algorithm.
No CMV tissue disease or CMV syndrome was observed in this paediatric population during the 6 months period post transplantation. However, two out of the 25 D+/R- patients developed CMV viremia (i.e. presence of virus without developing other signs or symptoms).
In the adult comparative study the incidence of CMV syndrome with tissue invasive disease was 12.1% in the VGCV arm (n=239) compared with 15.2% in the oral GCV arm (n=125) during the first 6 months after transplantation.

Furthermore additional data were obtained from the previously submitted two studies in adults (PV16000 and NT18435). A total of 12 patients aged ≤18 years were enrolled into studies PV16000 (9 patients; 4 kidney, 4 liver and 1 heart transplant) and NT18435 (3 patients; all kidney transplant). Of these, 1 received oral GCV for up to 100 days (one other was randomised but never received GCV study drug), 9 received VGCV for up to 100 days and 1 received VGCV for up to 200 days. Patient age ranged from 14 to 18 years (four patients were aged 17 years), with 50% male patients. The BSA range was 1.02 to 2.01, and patient dosing was according to approved adult dosing recommendations. The most frequently reported AE was of the system organ class (SOC) blood and lymphatic disorders.
No new data on patients 16 to 18 years were submitted.
Based on this study it was concluded that the recommended dosage for patients between 16 and 18 years must be the same as the recommended dose for adults.

III.3.3.4 Final Dose Recommendation

Given the studies discussed above, the MAH considered the paediatric dosing algorithm of $7 \times \text{BSA} \times \text{CrCL}$ (BSA = body surface area; CrCL = creatinine clearance) to be appropriate to ensure the safety and efficacy of VGCV in paediatric SOT patients. This is agreed by the member states.

III.3.4 Clinical safety

The safety results of each of the three studies NV25409, NP22523, and CASG112 are described below, followed by a discussion of the risk assessment. Treatment (indication), dose of study drug, formulation and duration of treatment differed for each newly submitted study.

Table 1 provides a summary of the planned dosing regimen, and the number of patients who received the full course of treatment by study.

Table 1: Summary of the Planned Dosing Regimen and the Number of Patients who Received the Full Course of Treatment by Study.

Study Number (N [a])	Drug	Formulation	Dose and Frequency	Treatment Duration (Exposure)	Number who Received the Full Course of Treatment
NV25409 (56)	VGCV	POS or FCTs	dose (mg) = 7 × BSA (m^2) × CrCLS (mL/min/1.73 m^2) OD	up to 200 days	49
NP22523 (14)	VGCV	POS	dose (mg) = 7 × BSA (m^2) × CrCLS (mL/min/1.73 m^2) OD	2 days	14
CASG112 (97)	VGCV	POS	16 mg/kg/dose BID	up to 6 months	86

BID = twice a day; BSA = body surface area; CrCLS = creatinine clearance calculated using a modified Schwartz equation; FCT=film coated tablet; OD = once daily; POS = powder for oral solution; VGCV = valganciclovir.

[a] Number of patients randomized.

III.3.4.1 Study NV25409

For study objectives, methods and general results refer to section III.3.3.1.

III.3.4.1.1 Safety related results

The most commonly affected SOCs during the study (200 days treatment and follow-up until week 52) were infections and infestations (78.6%), blood and lymphatic system disorders (57.1%), gastrointestinal disorders (53.6%), renal and urinary disorders (48.2%), metabolism and nutrition disorders (44.6%) and nervous system disorders (44.6%).

Adverse events were classed by the investigator as probably, possibly, or remotely related, or unrelated to study drug. Of the AEs that occurred on-treatment, twice as many (54 vs. 27) were considered by the investigator to be unrelated to study medication than those considered related to

study medication. The proportion of patients who had AEs considered by the investigator to be related to study medication was higher in the older age groups (20 out of 32 [62.5%] in the ≥ 12 years age group) than in the > 2 to < 12 years age group (7 out of 18 [38.9%]). There were none considered related in the youngest age group. Overall, the most common related AEs were leukopenia (12 patients [21.4%]), neutropenia (11 patients [19.6%]), and anaemia (4 patients [7.1%]).

The most common reason for dose modification was due to an AE (22 patients (39.3%]; 40 AEs). Only 2 patients (33.3%) in the youngest age group had a dose modification, both due to AEs.
The majority of AEs leading to dose modification/interruption were blood and lymphatic disorders, predominantly leukopenia (9 patients [16.1%]) and neutropenia (7 patients [12.5%]). The proportion of patients who had these events was higher from days 1 to 100 than from days 101 to 228 (6 patients [10.7%] vs. 3 patients [5.4%] for each AE). Most of the other AEs that led to dose modification were isolated (i.e., only one patient required a dose modification due to that event).

A summary of all adverse events that occurred in each study period (1-100 days, 101-200 days and total on treatment period) in more than >10% of the total population is given by MeDRA preferred term and study period in table 5.

Table 5: All Adverse Events with a >10% Incidence by MeDRA preferred term and Study Period (Safety Population)

MedDRA Preferred Term	1-100 Days (N=56)	101-228 Days (N=56)	Total (N=56)
Total number of patients with at least one adverse event	55 (98.2%)	51 (91.1%)	56 (100.0%)
Total number of events	322	205	527
URINARY TRACT INFECTION	13 (23.2%)	11 (19.6%)	19 (33.9%)
UPPER RESPIRATORY TRACT INFECTION	12 (21.4%)	11 (19.6%)	19 (33.9%)
DIARRHOEA	14 (25.0%)	8 (14.3%)	18 (32.1%)
LEUKOPENIA	9 (16.1%)	7 (12.5%)	14 (25.0%)
NEUTROPENIA	11 (19.6%)	6 (10.7%)	13 (23.2%)
HEADACHE	8 (14.3%)	6 (10.7%)	12 (21.4%)
TREMOR	8 (14.3%)	3 (5.4%)	10 (17.9%)
ABDOMINAL PAIN	6 (10.7%)	4 (7.1%)	10 (17.9%)
BLOOD CREATININE INCREASED	8 (14.3%)	3 (5.4%)	9 (16.1%)
DYSURIA	9 (16.1%)	1 (1.8%)	10 (17.9%)
PYREXIA	4 (7.1%)	7 (12.5%)	9 (16.1%)
HYPERTENSION	7 (12.5%)	3 (5.4%)	9 (16.1%)
ANAEMIA	8 (14.3%)	1 (1.8%)	9 (16.1%)
ESCHERICHIA URINARY TRACT INFECTION	4 (7.1%)	6 (10.7%)	7 (12.5%)
VOMITING	5 (8.9%)	2 (3.6%)	7 (12.5%)
HAEMATURIA	6 (10.7%)	-	6 (10.7%)

Nearly all patients (98.2%) experienced at least one AE during the first 100 days and 91.1% experienced at least one AE between day 101 and 228.
The following events were reported in more patients from days 1-100 than from days 101-228: diarrhea (25.0% vs. 14.3%), neutropenia (19.6% vs. 10.7%), tremor (14.3% vs. 5.4%), blood creatinine increased (14.3% vs. 5.4%), dysuria (16.1% vs. 1.8%), hypertension (12.5% vs. 5.4%), anaemia (14.3% vs. 1.8%), vomiting (8.9% vs. 3.6%), and haematuria (10.7% vs. 0%).

The incidence of gastrointestinal disorder AEs was slightly higher from days 1-100 (5.4%) than from days 101-228 where no related AE was reported. The higher incidence of related gastrointestinal disorders from days 1-100 vs. days 101-228 was due to 2 AEs of vomiting, all other AEs were reported as single occurrence. There were no major differences in any of the other system organ classes or AEs.

The intensity of all AEs that occurred during the study was similar to that seen on treatment, but there were some additional events. Adverse events which were severe in intensity (25 out of 56) were most commonly isolated events, with the exception of neutropenia (6 patients [10.7%]), gastroenteritis (3 patients [5.4%]), increased blood creatinine (3 patients [5.4%]), leukopenia (3 patients [5.4%]), urinary tract infection (3 patients [5.4%]), viral upper respiratory tract infection (3 patients [5.4%]), headache (2 patients [3.6%]), increased weight (2 patients [3.6%]) and pyelonephritis (2 patients [3.6%]).

Comparing the severity of AEs reported on treatment with AEs throughout the whole study, the overall intensity of AEs on treatment was broadly similar throughout the whole study (ratio of mild to moderate AEs was 6:5 in the two younger age groups (≤ 2 years and > 2 to < 12 years) and 3:2 in the ≥ 12 years age group. The proportion of severe AEs throughout the whole study was higher in the younger patients: 50.0%, 55.6% and 37.5% in the ≤ 2 years, > 2 to < 12 years and ≥ 12 years age groups, respectively.

A total of 106 serious adverse events (SAEs) in 41 patients were reported throughout the entire study period (5 patients [83.3%] in the ≤ 2 years age group, 14 [77.8%] in the > 2 to < 12 years age group and 22 [68.8%] in the ≥ 12 years age group). The most common types of SAEs were reported from the SOC infections and infestations (27 patients [48.2%]), blood and lymphatic disorders (9 patients [16.1%]) and renal and urinary disorders (7 patients [12.5%]). The most common SAEs were urinary tract infection (7 patients [12.5%]), escherichia urinary tract infection (5 patients [8.9%]), neutropenia (5 patients [8.9%]) and increased blood creatinine (5 patients [8.9%]).

A total of 83 SAEs were reported by 37 patients (66.1%) while on treatment. As with SAEs for the whole study, the most common types of SAEs were infections and infestations (23 patients [41.1%]) and blood and lymphatic disorders (9 patients [16.1%]). The most common SAEs were urinary tract infection (7 patients [12.5%]), Escherichia urinary tract infection (5 patients [8.9%]) and neutropenia (5 patients [8.9%]). The majority of SAEs were considered by the investigator to be unrelated to VGCV with a total of 14 related SAEs in nine patients on treatment.

The reported AEs were already stated in section 4.8 of the SmPC.

III.3.4.1.1.1 Haematological Adverse Events

In study NV25409 n=32 patients (57.1%) had a total of 55 haematological AEs (including non-serious and serious adverse events), of which only one of these events occurred off-treatment. Three of the events occurred in the ≤2 year age group, seventeen in the > 2 to < 12 years age group and 35 in the ≥ 12 years age group. The most common were leukopenia (14 patients [25.0%]), neutropenia (13 patients [23.2%]) and anaemia (10 patients [17.9%]), with only one event of neutropenia not resolved by the end of the study. The most common serious haematological AE was neutropenia (5 events) followed by leukopenia (2 events), pancytopenia (2 events), anaemia (1 event) and bicytopenia (1 event) observed.

Haematologic AEs are a common side effect associated with VGCV treatment. All haematological AEs are already stated in section 4.8 of the SmPC.

III.3.4.2 Study NP22523

For study objectives, methods and general results refer to section III.3.2.1.

III.3.4.2.1 Safety related results

In study NP22523 only 14 paediatric patients were included. Hence no firm conclusions regarding the safety can be drawn.

A summary of AEs that occurred during study NP22523 is provided by frequency in Table 6.

Table 6: Summary of Adverse Events in Study NP22523.

Adverse Event	Birth to < 6 Weeks N = 2 No. (%)	6 Weeks to < 4 Months N = 12 No. (%)	Total N = 14 No. (%)
ANAEMIA	1	3 (25)	4 (29)
VOMITING	-	2 (17)	2 (14)
DEHYDRATION	-	1 (8)	1 (7)
DIARRHOEA	-	1 (8)	1 (7)
FLATULENCE	-	1 (8)	1 (7)
HAEMATOCHEZIA	-	1 (8)	1 (7)
HYPERKALAEMIA	-	1 (8)	1 (7)
METABOLIC ACIDOSIS	-	1 (8)	1 (7)
POSTOPERATIVE WOUND INFECTION	-	1 (8)	1 (7)
RESPIRATORY TRACT INFECTION	-	1 (8)	1 (7)
TACHYPNOEA	-	1 (8)	1 (7)
THROMBOCYTOSIS	-	1 (8)	1 (7)
URINARY TRACT INFECTION	-	1 (8)	1 (7)
VENTRICULAR TACHYCARDIA	-	1 (8)	1 (7)

Of the 14 patients included in the safety population, seven (50%) presented at least one AE. Overall, 16 AEs were reported: 5 AEs (in 3 patients, all in the 6 weeks to <4 months age group) occurred during the prophylaxis period (study days 1 and 2), and 11 AEs (in 6 patients) occurred during the follow-up period (study days 3 to 9).

Due to the small sample size no firm safety conclusion can be drawn. Adverse events associated with blood and lymphatic disorders (5 patients [36%]), gastrointestinal disorders (3 patients [21%]), and metabolism and nutrition disorders (3 patients [21%]) were among the most frequently reported by patients receiving VGCV. Anaemia was the most common AE, experienced by 4 patients (29%).

One of these patients was in the $<$ 6 weeks age group and 3 were in the $\geq$ 6 weeks and $<$ 4 months age group. Three anaemia AEs occurred during follow-up, and a single case of anaemia occurred on-treatment. Vomiting was experienced by 2 patients (14%). One case concerned worsening of pre-existing anaemia. All these events were reported as mild or moderate in intensity and none were serious. One event of anaemia was reported on day 2, 2 events were reported on day 3, and 1 event was reported on day 6. All the events resolved either on the day of diagnosis or within 7 days after treatment with blood or red cells transfusions.

The remaining AEs were experienced by one patient each. There was only one possibly related AE, which occurred on-treatment, all other AEs (on or off-treatment) were considered not related to VGCV by the investigator. The possibly related AE was a single case of anaemia in one patient in the 6 weeks to <4 months age group.

III.3.4.2.2 Overall haematological safety

Anaemia was reported with a higher incidence (4/17 patients in final study report, 24%) in the heart transplanted patients compared to the kidney transplanted patients (16.1%) in study NV25409.
In study NP22523 all patients experiencing anaemia presented with low haemoglobin and low haematocrit levels at screening, probably related to the intensive surgery (i.e., heart transplantation) that patients had undergone before enrolment in the study. Recovery from anaemia-related blood loss may require 2–3 weeks, during which time the haemoglobin concentration will be seen to rise[6]. Heart

[6] Harrison's Principles of Internal Medicine, 18e [resource in the Internet]. 2012 [cited 11 March 2014]. Available from: http://accessmedicine.mhmedical.com/content.aspx?bookid=331&sectionid=40726784&jumpsectionID=40732013

transplant surgery may have led to higher blood loss with subsequently lower haemoglobin and haematocrit levels, compared with patients who have undergone kidney transplant surgery, as in Study NV25409, and may account for differences in rates of anaemia seen between these populations. Worsening of haemoglobin and haematocrit levels in patients during the first few days of Study NP22523 may be attributed to blood samples collected on days 2 and 3 as part of the study procedures for PK assessments. Although the volume of blood sampled in this study can be considered low (2.5 mL in total) it may be significant in these weak and very young patients with pre-existing low haemoglobin and haematocrit values and relatively low overall blood volume. No blood samples for PK analysis were taken in Study NV25409, therefore there was no consequent impact on haemoglobin and haematocrit levels. It should be also noted that in Study NP22523, the mean values of haemoglobin and haematocrit, which include values from all patients, remained stable from screening to day 9, with a slight decrease on day 3 in patients < 6 weeks of age. The decrease in this age group can be attributed to the effect of blood draws on these parameters in 1 patient who was reported with anaemia on day 3. This explanation for the observed differences is considered plausible.

As haematologic AEs are a common side effect associated with VGCV treatment the reported laboratory values can be expected.

Based on the PK estimates in study NP22523 it was observed that the average AUC was 68.1 µg.h/ml. This is above the overall average AUC range of 40-60 µg.h/ml of GCV in adults, achieved at the approved VGCV standard adult dose of 900 mg, or at doses adjusted according to the SmPC for renal function. Furthermore, exposure to VGCV in these patients was approximately 23% higher compared to paediatric patients in other studies. Six out of the 10 patients who presented an AUC above 60 µg.h/mL presented at least 1 adverse event, while of the 6 patients who presented an AUC below 60 µg.h/mL, 1 presented an adverse event (low AUC at 36.3 µg.h/mL), so based on these data, it might be concluded that an increased frequency of adverse events is associated with the higher exposure to GCV. However, as a result of the limited number of patients included in this study, there is an uncertainty whether the adverse event frequencies will be higher in this patient population in general, or if it is the result of the concomitant medications or other factors like underlying disease. For this reason, a detailed review was conducted of all adverse events reported in patients with an AUC above 60 µg.h/mL, to assess whether these adverse events might have a causal relationship with VGCV or are explained by concomitant medications or underlying diseases. Based on this assessment, it is concluded that indeed AEs were not related to VGCV but related to underlying diseases, concomitant medications, and/or study procedures.
It should also be noted that the AUC range of 40-60 µg.h/ml is not an exactly defined or 'target' therapeutic range or therapeutic window for an individual patient. If a GCV AUC strays out of this range it does not result in immediate toxicity (myelotoxicity).
The study is still ongoing so more data will become available. The MAH committed to provide these when available.

In adults, overdose was reported associated with haematological toxicity, hepatotoxicity, renal toxicity, gastrointestinal toxicity and neurotoxicity. Two patients in study NP22523 reported gastrointestinal disorders (vomiting and diarrhea), which are also known adverse events at normal dose. Besides anaemia, no other events associated with the known overdose toxicity in adults were reported in this study. In addition, no clear correlation has been established between peak or trough concentrations and either efficacy or toxicity of the drug[7]. Therefore, on the basis of the data from Study NP22523, no causal relationship between VGCV exposure and the frequency of AEs in general and the frequency of anaemia in particular could be established.

III.3.4.3 Study CASG112

For study objectives, methods and general results refer to section III.3.2.2

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[7] Scott JC, Partovi N, Ensom MH. Ganciclovir in solid organ transplant recipients: is there a role for clinical pharmacokinetic monitoring? Ther Drug Monit 2004;26:68-77.

III.3.4.3.1 Safety related results

Six hundred and seventy-five (675) AEs were reported in 96 patients during the study: 246 AEs during the open-label portion of the study, and 432 AEs during the blinded portion of the study (213 AEs reported in VGCV-treated patients, and 216 AEs reported in placebo-treated patients). By intensity, a similar distribution of AEs was observed during the initial 6 weeks of open-label VGCV treatment compared to the 6 months of blinded VGCV treatment (69.9% versus 67.1% were grade 1, 26.4% versus 28.6% were grade 2, and 3.7% versus 3.8% were grade 3, respectively).

Of the reported AEs, 98 (14.5%) were considered related to the study drug of which 9 AEs were ACTG grade 3, and one AE was grade 4. In randomised patients, the most frequently reported related AEs were neutropenia (42 AEs [12 in active, 30 in placebo]), anaemia (12 AEs [3 in active, 9 in placebo]), liver function test abnormal (9 AEs [3 in active, 6 in placebo]), and diarrhea (7 AEs [1 in active, 6 in placebo]).

Among the 96 randomised patients, a total of 46 SAEs were reported in 29 patients (19 SAEs in 10 VGCV-treated patients, and 27 SAEs in 19 placebo-treated patients). The most frequently reported SAEs were neutropenia (26.1%), respiratory syncytial virus (10.9%), anaemia (8.7%), and bronchiolitis (8.7%). All other SAEs occurred at a frequency of ≤4.7%.
No subjects were discontinued from the study or had a dose reduction due to a SAE.

SAEs were considered related to the use of the study drug for 2 VGCV-treated patients (3 SAEs) and for 10 placebo-treated patients (11 SAEs). The related SAEs were either neutropenia (11 patients [2 VGCV; 9 placebo]) or anaemia (3 patients [1 VGCV; 2 placebo]). The majority of the related SAEs were life-threatening; one case of both neutropenia and anaemia was severe in intensity.

Within study CASG112 the most reported AEs were neutropenia, anaemia, liver function test abnormal and diarrhea, which seems consistent with the AEs observed in SOT patients. The most frequently reported SAEs were neutropenia, respiratory syncytial virus, anaemia and bronchiolitis.

III.3.4.4 Overall safety conclusions

The most frequently reported on-treatment AEs in study NV25409 were: upper respiratory tract infection, urinary tract infection, diarrhea, leukopenia, neutropenia and headache.

In study NP22523 only 14 paediatric patients were included. Hence no firm conclusions regarding the safety can be drawn.

Within study CASG112 the most reported AEs were neutropenia, anaemia, liver function test abnormal and diarrhea, which seems consistent with the AEs observed in SOT patients. The most frequently reported SAEs were neutropenia, respiratory syncytial virus, anaemia and bronchiolitis.

Haematologic AEs are a common side effect associated with VGCV. In paediatric heart transplant patients a higher frequency of anaemia has been observed, which may be attributed to blood loss and/or concomitant medications.

All reported AEs from these studies are already stated in SmPC section 4.8. Therefore no changes are proposed by the RMS.

No deaths were reported in studies NV25409 and CASG112. In study NP22523 there was one death reported following the patient's completion of the study, which occurred approximately 3 weeks after the end of study follow-up. This patient had a post-operative wound infection that resulted in death 1 month after receiving study medication, and approximately 3 weeks after completing the study (the death was considered unrelated to study medication by the Investigator).

III.3.4.5 Post-marketing safety data

Post-marketing safety data retrieved in the paediatric population has been compared with post-marketing safety data retrieved from the adult population. In the paediatric population, 383 AEs (of which 292 were SAEs) have been reported in 218 patients.

Although VGCV was not approved in paediatric patients in the EU, it does have a paediatric indication in the USA for patients aged 4 months of age and older; therefore, these data reflect approved use in the US as well as off-label use.

Within the paediatric population, the 383 AEs were reported across the following age groups:
• Neonatal patients (birth to < 1 month): 32 AEs (of which 29 were SAEs)
• Infant age group (≥ 1 month to< 2 years): 115 AEs (of which 99 were SAEs)
• Child age group (≥ 2 years to< 12 years): 143 AEs (of which 96 were SAEs)
• Adolescent age group (≥ 12 years to < 18 years): 93 AEs (of which 68 were SAEs).

The frequency and pattern of AE reporting by SOC was similar between the paediatric and adult populations, and was consistent with the known safety profile of VGCV. By SOC, the most frequently reported AEs in the paediatric population were blood and lymphatic disorders (24%), infections and infestations (17.2%), investigations (14.4%), and gastrointestinal disorders (8.6%). Similarly, in the adult population, the most frequently reported AEs were blood and lymphatic disorders (19.7%), infections and infestations (17.6%), investigations (11.7%), general disorders (8.8%), and gastrointestinal disorders (8.1%).
The reported AEs are in line with the known safety profile for VGCV and already stated in the SmPC.

III.3.4.6 Risk Management plan

The MAH provided an updated risk management plan (RMP), with amendments regarding the indication for children.

In section 3 (brief overview of development) and section 12 (recent study reports with implications for safety concerns) the completed studies NP22523 (n=14) and NV25409 (n=57) in paediatric SOT patients were added. In addition, clinical safety data from study CASG112 in paediatric patients (n=109) with symptomatic congenital CMV disease was added to the RMP. The overall safety profile was consistent with the known safety profile of VGCV.

In section 10.2 (potential for paediatric off-label use) of the RMP the MAH states that this proposal for indication for children would remove the risk associated with off-label use of VGCV in the paediatric population.

As the safety profile of VGCV is considered to be well established, routine pharmacovigilance practices and routine risk minimization activities are considered adequate. No changes in the safety specifications, pharmacovigilance plan and risk minimization were necessary.
As the number of paediatric patients with the approved indication which received the dose algorithm as mentioned in the SmPC is limited, the MAH was asked to include this safety concern as missing information in the RMP.
The MAH was of the opinion that the clinical trial safety data in patients ≥ 4 months of age (165 patients), as well as the post-marketing safety data (since launch in the United States in 2010, approximately 401 paediatric patients have been exposed to Valcyte POS), is now substantial and therefore does not qualify as missing information to be included in the RMP. The safety data from all of the paediatric studies, as well as post-marketing data collected up to the present date, do not show a different safety profile for VGCV in the paediatric population, as compared with the adult population. However, as the number of paediatric patients < 4 months of age who have received paediatric dosing as detailed in the SmPC is limited, it was agreed to closely monitor adverse events in patients < 4 months of age and to include this safety concern as missing information in the RMP. All adverse events, including anaemia, will be monitored in this age group.

Two measures to limit high GCV exposure in paediatric patients are included in SmPC section 4.2: (a) if the calculated Schwartz creatinine clearance exceeds 150 mL/min/1.73m^2, apply a maximum creatinine clearance value of 150 mL/min/1.73m^2; and (b) if the calculated dose exceeds 900 mg, a maximum dose of 900 mg should be administered. In addition, based on the PK results of Study NP22523, the MAH has added clarifications in the SmPC for the k value of the proposed dosing

algorithm for patients < 2 years ("For appropriate sub-populations a lowering of k value may also be necessary") which should be applied to patients with low birth weight and therefore should limit high GCV exposure in this population. For these reasons, the MAH is not considering the addition of overdose as a safety concern in the RMP. Information on overdose in general is presented in the dedicated section of the RMP. This is agreed.

The summary of the RMP is provided in Table 7.

Table 7: Summary of the Risk Management Plan

Safety concern	Pharmacovigilance	Risk Minimisation
Important Identified Risks		
Haematopoietic cytopenias and associated infections and hemorrhages	Routine PV	SmPC 4.4
Hypersensitivity	Routine PV	SmPC 4.3
Identified interactions: seizures associated with co-administration with Imipenem-cilastatin	Routine PV	SmPC 4.4
Male infertility	Routine PV	SmPC 4.4
	Additional PV activity: Study WV25651	
Important Potential Risks		
Adverse pregnancy outcomes	Routine PV	SmPC 4.4 and 4.6
Carcinogenicity	Routine PV	SmPC 4.4
Potential for overdose in renal impaired patients	Routine PV	SmPC 4.4
Potential interactions with other drugs that cause myelosuppresion	Routine PV	SmPC 4.4
Potential interaction with drugs which are excreted through the kidneys	Routine PV	SmPC 4.4
Missing Information		
Patients with severe uncontrolled diarrhea or with evidence of malabsorption	Routine PV	Risk mitigation through labeling

IV. UPDATED DISCUSSION, OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Quality

This variation has no impact on the quality of the product. The MAH has sufficiently demonstrated that the dosing scheme as proposed in the SmPC is possible with the syringe of Valcyte POS.

Non-clinical aspects

Considering the known toxicity of VGCV, and the already existing experience in children, the view of the MAH that additional non-clinical studies will not significantly contribute to paediatric safety, is endorsed. The paediatric clinical studies did not reveal unexpected effects which should be investigated further in non-clinical studies.

The documentation provided for the ERA is incomplete. A post-approval commitment has been made by the MAH to conduct the Phase II Tier A tests with the active metabolite GCV according to OECD guidelines under good laboratory practices (GLP) quality assurance.

Clinical aspects

The MAH submitted three new paediatric studies (NV25409, NP22523 and CASG112). Based on these studies the MAH proposes to expand the indication: "*for the prevention of CMV disease in CMV-negative patients who have received a solid organ transplant from a CMV-positive donor.*" to "*for*

Overall, based on the results presented, the RMS and concerned member states take the view that the expansion of the CMV prophylaxis indication to include children is approvable. Refer to section V below for the approved indication and further changes to the product information).

The benefit-risk for Valcyte FCT and POS remains unchanged. The variation procedure was finalised with a positive outcome on 20 June 2014.

V. CHANGES IN PRODUCT INFORMATION

The revised paragraphs of the SmPC and package leaflet are outlined below, new text underlined, deleted text strikethrough.

SmPC

Section 4.1: Therapeutic indications

Valcyte is indicated for the induction and maintenance treatment of cytomegalovirus (CMV) retinitis in adult patients with acquired immunodeficiency syndrome (AIDS).
Valcyte is indicated for the prevention of CMV disease in CMV-negative ~~patients~~ adults and children (aged from birth to 18 years) who have received a solid organ transplant from a CMV-positive donor.

Section 4.2: Posology and method of administration:

Paediatric population
The safety and efficacy of Valcyte in the treatment of CMV retinitis have not been established in adequate and well-controlled clinical studies in paediatric patients.

(…)
Paediatric population
The safety and efficacy of Valcyte in the treatment of CMV retinitis have not been established in adequate and well-controlled clinical studies in paediatric patients.
Under 'Prevention of CMV disease in solid organ transplantation:
Paediatric population
In paediatric solid organ transplant patients, aged from birth, who are at risk of developing CMV disease, the recommended once daily dose of Valcyte is based on body surface area (BSA) and creatinine clearance (CrCl) derived from Schwartz formula (CrCLS), and is calculated using the equation below:
Paediatric Dose (mg) = 7 x BSA x CrCLS (see Mosteller BSA formula and Schwartz Creatinine Clearance formula below).
If the calculated Schwartz creatinine clearance exceeds 150 mL/min/1.73m^2, then a maximum value of 150 mL/min/1.73m^2 should be used in the equation:

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

$$Schwartz\ Creatinine\ Clearance\,(ml/min/1.73m^2) = \frac{k\ x\ Height\,(cm)}{Serum\ Creatinine\,(mg/dl)}$$

where k = 0.45* for patients aged < 2 years, 0.55 for boys aged 2 to < 13 years and girls aged 2 to 16 years, and 0.7 for boys aged 13 to 16 years. Refer to adult dosing for patients older than 16 years of age.
The k values provided are based on the Jaffe method of measuring serum creatinine and may require correction when enzymatic methods are used.

*For appropriate sub-populations a lowering of k value may also be necessary (e.g. in paediatric patients with low birth weight).

For paediatric kidney transplant patients, the recommended once daily mg dose (7 x BSA x CrCLS) should start within 10 days post-transplantation and continue until 200 days post-transplantation.

For paediatric patients who have received a solid organ transplant other than kidney, the recommended once daily mg dose (7x BSA x CrCLS) should start within 10 days post-transplantation and continue until 100 days post-transplantation.
All calculated doses should be rounded to the nearest 25 mg increment for the actual deliverable dose. If the calculated dose exceeds 900 mg, a maximum dose of 900 mg should be administered. The oral solution is the preferred formulation since it provides the ability to administer a dose calculated according to the formula above; however, Valcyte film-coated tablets may be used if the calculated doses are within 10% of available tablet doses, and the patient is able to swallow tablets. For example, if the calculated dose is between 405 mg and 495 mg, one 450 mg tablet may be taken.
It is recommended to monitor serum creatinine levels regularly and consider changes in height and body weight and adapt the dose as appropriate during the prophylaxis period.

~~The safety and efficacy of Valcyte in paediatric patients have not been established in adequate and well controlled clinical studies. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made~~. Dosing of paediatric SOT patients is individualized based on a patient's renal function, together with body length and weight.

For paediatric patients who are unable to swallow Valcyte film-coated tablets, Valcyte powder for oral solution can be administered.

Section 4.4: Special warnings and precautions for use

It is recommended that complete blood counts and platelet counts should be monitored regularly during therapy. Increased haematological monitoring may be warranted in patients with renal impairment and paediatrics, at a minimum each time the patient attends the transplant clinic.

Section 4.8: Undesirable effects

The overall safety profile of Valcyte did not change with the extension of prophylaxis up to 200 days in adult kidney transplant patients at high risk of CMV disease (D+/R-). Leucopenia was reported with a slightly higher incidence in the 200 days arm while the incidence of neutropenia, anaemia and thrombocytopenia were similar in both arms.

~~There are very limited paediatric data on the exposure to valganciclovir (see also sections 5.1 and 5.2). The following table provides a summary of all adverse events which occurred in more than 10% (very common) of the total paediatric population on treatment:~~

~~**Body System**~~	~~**Very Common Adverse Events Reported in Clinical Trials**~~
~~Blood and lymphatic system disorders~~	~~Anemia, neutropenia~~
~~Vascular disorders~~	~~Hypertension~~
~~Respiratory, thoracic and mediastinal disorders~~	~~Upper respiratory tract infection~~
~~Gastrointestinal disorders~~	~~Diarrhoea, nausea , vomiting, constipation~~
~~General disorders and administration site conditions~~	~~Pyrexia , transplant rejection~~

Valcyte has been studied in 179 paediatric solid organ transplant patients who were at risk of developing CMV disease (aged 3 weeks to 16 years) and in 133 neonates with symptomatic congenital CMV disease (aged 2 to 31 days), with duration of ganciclovir exposure ranging from 2 to 200 days.

The most frequently reported adverse reactions on treatment in paediatric clinical trials were diarrhea, nausea, neutropenia, leucopenia and anaemia.
In solid organ transplant patients, the overall safety profile was similar in paediatric patients as compared to adults. However, the rates of certain adverse events, such as upper respiratory tract infection, pyrexia, abdominal pain and dysuria, which may be characteristic of the paediatric population, were reported in higher incidence in paediatrics than in adults. Neutropenia was also

reported with slightly higher incidence in the two studies conducted in paediatric solid organ transplant patients as compared to adults, but there was no correlation between neutropenia and infectious adverse events in the paediatric population.
In kidney transplant paediatric patients, prolongation of valganciclovir exposure up to 200 days was not associated with an overall increase in the incidence of adverse events. The incidence of severe neutropenia (ANC < 500/µL) was higher in paediatric kidney patients treated until Day 200 as compared to paediatric patients treated until Day 100 and as compared to adult kidney transplant patients treated until Day 100 or Day 200 (see section 4.4).
Only limited data are available in neonates or infants with symptomatic congenital CMV infection treated with Valcyte, however the safety appears to be consistent with the known safety profile of valganciclovir/ganciclovir.

Section 5.1: Pharmacodynamic properties

Treatment of CMV retinitis:
The European Medicines Agency has waived the obligation to perform studies with Valcyte in all subsets of the paediatric population in the treatment of infection due to CMV in immuno-compromised patients (see section 4.2 for information on paediatric use).

(…)

Prevention of CMV disease in transplantation
A phase II pharmacokinetic and safety study in paediatric solid organ transplant recipients (aged 4 months to 16 years, n = 63) receiving valganciclovir once daily for up to 100 days according to the paediatric dosing algorithm (see section 4.2) produced exposures similar to that in adults (see section 5.2). Follow up after treatment was 12 weeks. CMV D/R serology status at baseline was D+/R- in 40%, D+/R+ in 38%, D-/R+ in 19% and D-/R- in 3% of the cases. Presence of CMV virus was reported in 7 patients. The observed adverse drug reactions were of similar nature as those in adults (see section 4.8). ~~These data are too limited to allow conclusions regarding efficacy or posology recommendations for paediatric patients.~~

A phase IV tolerability study in paediatric kidney transplant recipients (aged 1 to 16 years, n=57) receiving valganciclovir once daily for up to 200 days according to the dosing algorithm (see section 4.2) resulted in a low incidence of CMV. Follow up after treatment was 24 weeks. CMV D/R serology status at baseline was D+/R+ in 45%, D+/R- in 39%, D-/R+ in 7%, D-/R- in 7% and ND/R+ in 2% of the cases. CMV viremia was reported in 3 patients and a case of CMV syndrome was suspected in one patient but not confirmed by CMV PCR by the central laboratory. The observed adverse drug reactions were of similar nature to those in adults (see section 4.8).

These data support the extrapolation of efficacy data from adults to children and provide posology recommendations for paediatric patients.

A phase I pharmacokinetic and safety study in heart transplant patients (aged 3 weeks to 125 days, n=14) who received a single daily dose of valganciclovir according to the paediatric dosing algorithm (see section 4.2) on 2 consecutive days produced exposures similar to those in adults (see section 5.2). Follow up after treatment was 7 days. The safety profile was consistent with other paediatric and adult studies, although patient numbers and valganciclovir exposure were limited in this study.

Congenital CMV
The efficacy and safety of ganciclovir and/or valganciclovir was studied in neonates and infants with congenital symptomatic CMV infection in two studies.

In the first study, the pharmacokinetics and safety of a single dose of valganciclovir (dose range 14-16-20 mg/kg/dose) was studied in 24 neonates (aged 8 to 34 days) with symptomatic congenital CMV disease (see section 5.2). The neonates received 6 weeks of antiviral treatment, whereas 19 of the 24 patients received up to 4 weeks of treatment with oral valganciclovir, in the remaining 2 weeks they received i.v. ganciclovir. The 5 remaining patients received i.v. ganciclovir for the most time of the study period. In the second study the efficacy and safety of six weeks versus six months of valganciclovir treatment was studied in 109 infants aged 2 to 30 days with symptomatic congenital CMV disease. All infants received oral valganciclovir at a dose of 16 mg/kg b.i.d. for 6 weeks. After 6

weeks of treatment the infants were randomized 1:1 to continue treatment with valganciclovir at the same dose or receive a matched placebo to complete 6 months of treatment.

Section 5.2: Pharmacokinetic properties

Paediatric population

(…)In a phase I pharmacokinetic and safety study in paediatric heart transplant recipients (aged 3 weeks to 125 days, n = 14), valganciclovir was given once daily for two study days. Population pharmacokinetics estimated that mean bioavailability was 64%.

A comparison of the results from these two studies and the pharmacokinetic results from the adult population shows that ranges of $AUC_{0\text{-}24h}$ were very similar across all age groups, including adults. Mean values for $AUC_{0\text{-}24h}$ and C_{max} were also similar across the paediatric age groups < 12 years old, although there was a trend of decreasing mean values for $AUC_{0\text{-}24h}$ and C_{max} across the entire paediatric age range, which appeared to correlate with increasing age. This trend was more apparent for mean values of clearance and half-life ($t_{1/2}$); however this is to be expected as clearance is influenced by changes in weight, height and renal function associated with patient growth, as indicated by population pharmacokinetic modelling.

The following table summarizes the model-estimated $AUC_{0\text{-}24h}$ ranges for ganciclovir from these two studies, as well as mean and standard deviation values for $AUC_{0\text{-}24h}$, C_{max}, CL and t ½ for the relevant paediatric age groups compared to adult data:

~~PK Parameter~~	~~Adults*~~	~~Paediatrics~~			
	~~≥ 18 years (n=160)~~	~~≤ 2 years (n=17)~~	~~> 2 - < 12 years (n=21)~~	~~≥ 12 years (n=25)~~
~~$AUC_{0\text{-}24h}$ (µg·h/ml)~~	~~46.3 ± 15.2~~	~~64.3 ± 29.2~~	~~59.2 ± 15.1~~	~~50.3 ± 15.0~~
~~C_{max} (µg/ml)~~	~~5.3 ± 1.5~~	~~10.3 ± 3.3~~	~~9.4 ± 2.7~~	~~8.0 ± 2.4~~
~~Clearance (l/h)~~	~~12.7 ± 4.5~~	~~2.5 ± 2.4~~	~~4.5 ± 2.9~~	~~6.4 ± 2.9~~
~~$t_{1/2}$ (h)~~	~~6.5 ± 1.4~~	~~3.1 ±1.4~~	~~4.1 ± 1.3~~	~~5.5 ± 1.1~~

PK Parameter	Adults*	**Paediatrics**			
	≥ 18 years (n=160)	**< 4 months (n = 14)**	4 months - ≤ 2 years (n=17)	> 2 - < 12 years (n=21)	≥ 12 years – 16 years (n=25)
$AUC_{0\text{-}24h}$ (µg·h/ml)	46.3 ± 15.2	68.1 ± 19.8	64.3 ± 29.2	59.2 ± 15.1	50.3 ± 15.0
Range of $AUC_{0\text{-}24h}$	15.4 – 116.1	34 - 124	34 - 152	36 - 108	22 - 93
C_{max} (µg/ml)	5.3 ± 1.5	10.5 ± 3.36	10.3 ± 3.3	9.4 ± 2.7	8.0 ± 2.4
Clearance (l/h)	12.7 ± 4.5	1.25 ± 0.473	2.5 ± 2.4	4.5 ± 2.9	6.4 ± 2.9
$t_{1/2}$ (h)	6.5 ± 1.4	1.97 ± 0.185	3.1 ±1.4	4.1 ± 1.3	5.5 ± 1.1

* Extracted from study report PV 16000

The once daily dose of Valcyte in both of the studies described above was based on body surface area (BSA) and creatinine clearance (CrCl) derived from a modified Schwartz formula, and was calculated using the dosing algorithm presented in section 4.2.

~~Paediatric Dose (mg) = 7 x BSA x CrCl (calculated using the modified Schwartz formula)~~
~~where~~

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

~~$Schwartz\ Creatinine\ Clearance\ (ml/\min/1.73m^2) = \frac{k\ x\ Height\ (cm)}{Serum\ Creatinine\ (mg/dl)}$~~

~~where k = 0.45 for patients aged < 2 years, 0.55 for boys aged 2 to < 13 years and girls aged 2 to 16 years, and 0.7 for boys aged 13 to 16 years.~~

~~The dose should not exceed the adult 900 mg dose. In addition, if the calculated Schwartz creatinine clearance exceeds 150 ml/min/1.73m^2, then a maximum value of 150 ml/min/1.73m^2 should be used in the equation. It should be noted that the paediatric dosage algorithm was developed based on pharmacokinetic data only and has not been verified in efficacy and safety studies (see 5.1).~~

Ganciclovir pharmacokinetics following valganciclovir administration were also evaluated in two studies in neonates and infants with symptomatic congenital CMV disease. In the first study 24 neonates aged 8 to 34 days received 6 mg/kg intravenous ganciclovir twice daily. Patients were then treated with oral valganciclovir, where the dose of valganciclovir powder for oral solution ranged from 14 mg/kg to 20 mg/kg twice daily; total treatment duration was 6 weeks. A dose of 16 mg/kg twice daily of valganciclovir powder for oral solution provided comparable ganciclovir exposure as 6 mg/kg intravenous ganciclovir twice daily in neonates, and also achieved ganciclovir exposure similar to the effective adult 5 mg/kg intravenous dose.

In the second study, 109 neonates aged 2 to 30 days received 16 mg/kg valganciclovir powder for oral solution twice daily for 6 weeks and subsequently 96 out of 109 enrolled patients were randomized to continue receiving valganciclovir or placebo for 6 months. However, the mean $AUC_{0\text{-}12h}$ was lower compared to the mean $AUC_{0\text{-}12h}$ values from the first study. The following table shows the mean values of AUC, C_{max}, and $t_{½}$ including standard deviations compared with adult data:

~~PK Parameter~~	~~Adults~~	~~Neonates~~	
	~~5 mg/kg GAN Single dose (n=8)~~	~~6 mg/kg GAN Twice daily (n=19)~~	~~16 mg/kg VAL Twice daily (n=19)~~
~~AUC0-∞ (mg.h/l)~~	~~25.4 ± 4.32~~	~~-~~	~~-~~
~~AUC_{12h} (mg.h/l)~~	~~-~~	~~38.2 5 ± 42.7~~	~~30.1 ± 15.1~~
~~C_{max} (µg/ml)~~	~~9.03 ± 1.26~~	~~12.9 ± 21.5~~	~~5.44 ± 4.04~~
~~$t_{1/2}$ (h)~~	~~3.32 ± 0.47~~	~~2.52 ± 0.55~~	~~2.98 ± 1.26~~

PK Parameter	Adults	Paediatrics (neonates and infants)		
	5 mg/kg GAN Single dose (n=8)	6 mg/kg GAN Twice daily (n=19)	16 mg/kg VAL Twice daily (n=19)	16 mg/kg VAL Twice daily (n = 100)
$AUC_{0\text{-}\infty}$ (µg·h/mL)	25.4 ± 4.32	-	-	-
$AUC_{0\text{-}12h}$ (µg·h/mL)	-	38.2 ± 42.7	30.1 ± 15.1	20.85 ± 5.40
C_{max} (µg/ml)	9.03 ± 1.26	12.9 ± 21.5	5.44 ± 4. 04	-
$t_{1/2}$ (h)	3.32 ± 0.47	2.52 ± 0. 55	2.98 ± 1. 26	2.98 ± 1.12

GAN = Ganciclovir, i.v. VAL = Valganciclovir, oral

These data are too limited to allow conclusions regarding efficacy or posology recommendations for paediatric patients with congenital CMV infection.

Package leaflet

Section 1:

Valcyte is used:

- for the treatment of CMV-infections of the retina of the eye in adult patients with acquired immunodeficiency syndrome (AIDS). CMV-infection of the retina of the eye can cause vision problems and even blindness.

- to prevent CMV-infections in adults and children who are not infected with CMV and who have received an organ transplant from somebody who was infected by CMV.

Section 2:

~~Children and adolescents~~
~~Present studies do not sufficiently show how the medicine works in children.~~

Section 3:

Use in children and adolescents:
Prevention of CMV disease in transplant patients
Children should start to take this medicine within 10 days of their transplant. The dose given will vary depending on the size of the child and should be taken ONCE daily. Your doctor will decide the most appropriate dose based on your child's height, weight and renal function. You should continue with this dose for up to 100 days. If your child has received a kidney transplant, your doctor may advise you to take the dose for 200 days.

For children who are unable to swallow Valcyte film-coated tables, Valcyte powder for oral solution can be used.

Section 4:
Additional side effects in children and adolescents
The side effects reported in children and adolescents are similar to the side effects reported for adults.

List of abbreviations

ACTG	AIDS Clinical Trial Group
AIDS	Acquired immunodeficiency syndrome
AE	Adverse event
ALT	alanineaminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	Area under curve
BCF	Bioconcentration factors
BID	Twice daily
BPAR	Biopsy-proven acute rejection
BSA	Body Surface Area
CE	Conformité Européenne
C_{max}	Maximal concentration
CMR	Carcinogenic, mutagenic, reprotoxic substances
CMS	Concerned member state
CMV	Cytolomegalovirus
CrClS	Creatinine Clearance calculated using the Schwarz formula
DCP	Decentralised procedure
D+/R-	Donor positive/Receptor negative
DT50	Degradation time for 50% of a compound
EBV	Epstein-Barr virus
EC	Effective concentration
ERA	Environmental Risk Assessment
ESRD	End stage renal disease
GAN	Ganciclovir
GCV	Ganciclovir
GCV-TP	ganciclovir-triphosphate
HAART	highly active antiretroviral therapy
INN	International Nonproprietary Name
ITT	Intention to treat
IV	Intravenous
K_{ow}	Octanol-Water Partition Coefficient
LLOQ	Lower limit of quantification
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MRP	Mutual recognition procedure
NOEC	No Observed Effect Concentration
NONMEM	non-linear mixed effects modelling
OECD	The Organisation for Economic Co-operation and Development
PBT	Persistence, bioaccumulation, and toxicity
PDCO	Paediatric committee
PEC_{sw}	Predicted Environmental concentration in surface water
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
popPK	Population Pharmacokinetics
POS	Powder for oral solution
RCT	Randomised controlled trial
RMS	Reference Member State
SAE	Serious Adverse Events
S(m)PC	Summary of Product Characteristics
SOC	Standard of Care/system organ class
SOT	Solid Organ Transplant
TDM	Therapeutic drug monitoring
VAL	Valganciclovir
VGCV	Valganciclovir