CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Valcyte 50 mg/ml, powder for oral solution
Roche Nederland B.V., the Netherlands

valganciclovir (as hydrochloride)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This report contains one annex, in which the variation NL/H/0323/001-002/II/054 is discussed.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/0323/002/DC
Registration number in the Netherlands: RVG 34730

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Pharmacotherapeutic group:	nucleosides and nucleotides excl. reverse transcriptase inhibitors
ATC code:	J05AB14
Route of administration:	oral
Therapeutic indication:	induction and maintenance treatment of CMV retinitis in patients with acquired AIDS; prevention of CMV disease in CMV-negative patients who have received a solid organ transplant from a CMV-positive donor
Prescription status:	prescription only
Date of authorisation in NL:	23 September 2008
Concerned Member States:	Decentralised procedure with AT, BE, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, IS, IT, LI, LT, LU, LV, NO, PT, SE, SK, UK
Application type/legal basis:	Directive 2001/83/EC, Article 8(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SmPC), package leaflet and labelling. 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 14-43. A list of abbreviations is given on pages 44-45.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Valcyte 50 mg/ml, powder for oral solution, from Roche Nederland B.V. The date of authorisation was on 23 September 2008 in the Netherlands.

The product is indicated for:

- 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.

A comprehensive description of the indications and posology is given in the SmPC.

Valganciclovir is an L-valyl ester (prodrug) of ganciclovir. After oral administration, valganciclovir is rapidly and extensively metabolised to ganciclovir by intestinal and hepatic esterases. Ganciclovir is a synthetic analogue of 2'-deoxyguanosine and inhibits replication of herpes viruses in vitro and in vivo. Sensitive human viruses include human cytomegalovirus (HCMV), herpes simplex virus-1 and -2 (HSV-1 and HSV-2), human herpes virus -6, -7 and -8 (HHV-6, HHV-7, HHV-8), Epstein-Barr virus (EBV), varicella-zoster virus (VZV) and hepatitis B virus (HBV).

This decentralised procedure concerns an application for a new formulation of Valcyte (valganciclovir), available on the market as 450 mg film-coated tablets. The new formulation is a powder for oral solution, which would be registered for the same indications and provide convenient and suitable dosing regimens for patients with varying degrees of impaired renal function and for those who are unable to swallow tablets. Additionally, the new formulation offers the possibility for once daily dosing compared to intermittent tablet dosing according to the degree of renal function.

The marketing authorisation is granted based on article 8(3) of Directive 2001/83/EC.

This application is a line extension of the 450 mg tablet dossier presented for procedure NL/H/0323/001/DC. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the 450 mg tablet. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of Valcyte 450 mg film-coated tablets.

No additional non-clinical data have been submitted, which is acceptable for this kind of application.

No scientific advice has been given to the MAH with respect to these products.

No paediatric development programme has been submitted at the time of application submission.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is valganciclovir hydrochloride, an established active substance not described in the European or British Pharmacopoeia, nor in the USP (Ph.Eur.*). The drug substance is a white to off-white crystalline powder that is freely soluble in 0.001N Hydrochloric acid and 95% ethanol. The drug substance is a mixture of two stereoisomers.

Manufacture
The routes to valganciclovir are based upon analogous chemical processes for the parent compound, ganciclovir. The manufacturing process and in-process controls have been adequately described.

Control of drug substance
The active substance specification is considered adequate to control the quality. Several HPLC-methods are used. The MAH has provided batch analysis for three final batches, demonstrating compliance with the specification. The MAH committed to develop a validated test method for determination of residual solvents potentially present from the process and amend the drug substance specifications and provide the outcome by June 2008.

Stability of drug substance
Stability data has been obtained during storage at 25°C/60% RH and 40°C/75% RH. The drug substance was packaged in the commercial packaging during the stability testing. Photostability for the drug substance was demonstrated. Based on the stability studies a retest period of 2 years with no additional storage condition could be granted.

** Ph.Eur., USP, BP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU, USA, or UK respectively.*

Medicinal Product

Composition
Valcyte 50 mg/ml contains as active substance 50 mg/ml of valganciclovir hydrochloride and is a granulate with a white to slightly yellow colour. When the powder is dissolved, it forms a clear, colourless to brown solution.

The powder for oral solution is packed in 100 ml amber glass bottles with a child-resistant plastic screw cap, a plastic bottle adapter and a plastic bag containing 2 plastic oral dispensers graduated to 500 mg with graduations of 25 mg. The dispensers can deliver portions in dosage range (2-18 ml) with suitable accuracy. Each bottle contains 12 g of powder for oral solution.

The excipients are: povidone, fumaric acid, sodium benzoate (E211), sodium saccharin, mannitol, maltodextrins (maize), propylene glycol, arabic gum E414 and natural flavouring substances mainly consisting of banana, pineapple and peach flavour.

Pharmaceutical development
In general development of the product is satisfactory performed and explained. The objective was to develop a valganciclovir hydrochloride product suitable for patients with severe renal impairment who need haemodialysis and/or those who cannot swallow tablets. These patients are currently treated with

i.v. ganciclovir, which is not ideal, since i.v. ganciclovir is impractical for long treatment periods and has been associated with catheter-related complications. Development of the new oral solution formulation was initiated to reduce or avoid long-term complications associated with i.v. ganciclovir, by utilizing the flexibility in dosing schedule to a more convenient once-daily oral regimen in patients with different degrees of renal impairment.
The excipients used are common in the manufacture of (granules for) oral solutions, except for the flavouring agent. The MAH has submitted sufficient data regarding the flavouring agent.

Manufacturing process
The granules are formed by wet granulation. The MAH has submitted sufficient information regarding the manufacturing process, which consists of 6 main steps. There are no critical steps in the manufacturing process and no intermediates are used. Batch results on 3 commercial scale batches have been presented. The analytical results provide evidence that the product can be manufactured on a constant basis. The manufacturing process has been sufficiently validated.

Container closure interaction testing and dosing device
Prior to administration, the Valcyte powder for oral solution is constituted in a 120 ml Type I amber glass bottle by adding the necessary amount of purified water followed by shaking the bottle. Then the press-in bottle adapter (PIBA) is placed in the bottle neck. In order to withdraw the solution, the oral dispenser (plastic syringe) is introduced into the hole of the PIBA and the bottle is turned upside down. During this withdrawal process the oral solution is, for a short time, in contact with the surface of the PIBA. After the withdrawal process the bottle is closed with a plastic child-resistant (CR) cap with liner. Extractable evaluation was performed on the PIBA. On the basis of the results it is concluded that the press-in bottle adapter (PIBA), the plastic child-resistant (CR) cap with liner and the plastic oral dispenser are suitable to be used with constituted Valcyte powder for oral solution..
The MAH provided sufficient information on the rationale for supplying the medication dosing device marked in milligram increments with the proposed Valcyte powder for oral solution formulation.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, colour, pH, identification of valganciclovir and sodium benzoate, content of valganciclovir and sodium benzoate, degradation products, water content and microbial quality (not routinely tested i.e. at least 1 batch per year). The analytical procedures have been adequately described. The MAH committed to re-evaluate the limits and identification of unknown impurities and to provide the results.
Batch analysis data have been provided for six batches. Compliance with the release requirements is demonstrated.

Microbial attributes
The applicant has examined the microbiological attributes of 6 batches. All batches fulfilled the requirements of Ph. Eur. 5.1.3. Furthermore, efficacy of antimicrobial preservation for these batches was demonstrated both during storage and in-use.

Stability tests on the finished product
Three batches have been stored at 25°C/60% RH, 30°C/60% RH and 40°C/75% RH during the stability tests. Based on the results of the stability studies the claimed shelf life of 2 years with no additional storage condition was granted. The MAH committed to evaluate the shelf life specification for the assay as soon as the end of the proposed shelf life stability data is available.

Stability testing on reconstituted powder / In-use stability testing on reconstituted drug product
Three months stability studies on the three full-scale primary batches were performed on the bottles containing the reconstituted drug product. The storage conditions include 5ºC, 15ºC and 20ºC/60%RH.
Sampling was based on the worst case use scenario with withdrawing 2 ml per day. Since the product contains 100 ml, it is most likely that the bottle will be empty after 49 days. The reconstituted powder remains stable for three months at 5ºC and up to two months at 25ºC. In-use stability data show that the reconstituted product, when stored at refrigerated conditions (2-8°C) is suitable for use for at least 49 days

from a chemical physical and microbial perspective, which is longer than the maximum useable time (i.e. 45 days) for minimum dosing of the product (2 ml/dose/day; minimum usable volume of 88 ml). No increase in bacteria or fungi count is seen.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non clinical aspects

This product is a line extension of Valcyte 450 mg film-coated tablets which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of valganciclovir released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Valganciclovir is a well-known pro-drug (active substance being ganciclovir) with established efficacy and tolerability.

For this application, the MAH has submitted a bioequivalence study comparing the pharmacokinetic profile of ganciclovir from Valcyte 50 mg/ml oral solution and the commercial Valcyte 450 mg tablet at a dose of 900 mg in kidney transplant recipients. Furthermore, supportive data were provided to substantiate the dose recommendations in patients with varying degrees of renal impairment.

Design
A multiple-centre, open-label, randomized, 3-way crossover bioequivalence study was carried out in 23 eligible subjects (12 male/11 female) with stable first and second kidney transplant. Recipients at risk of developing CMV disease were included. The kidney recipients had been receiving CMV prophylaxis with Valcyte, and had adequate renal (inclusion criteria > 60 ml/min) and haematological function.
Patients received either Valcyte 450 mg film-coated tablets, Valcyte tutti-frutti flavoured oral solution or Valcyte strawberry flavoured oral solution. Except for the flavour, the pharmaceutical constitution of both oral solutions is the same.
Each treatment period consisted of single doses (900 mg) of valganciclovir on two consecutive days. The dose was administered within 15 minutes after completion of breakfast. Blood samples were taken pre-dose and at 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours after administration of the formulation, at day 2, 4 and 6.

Study conditions
The standard dose regimen of valganciclovir for prophylaxis is 900 mg once daily, administered with food. Therefore, a study under fed conditions is acceptable. The periods were separated by two days. This is considered acceptable as patients had a creatinine clearance > 60 ml/min, for which the ganciclovir elimination half-life is about 5.5 hours. No carry over effect is expected.

Analytical/statistical methods
Plasma was analysed for ganciclovir using a validated LC-MS/MS method. For estimation of bioequivalence a three-way ANOVA analysis on the log-transformed AUC and Cmax variables was carried out. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

Samples obtained from 2 subjects were excluded for analysis, as time of blood sample collection could not be verified and as blood samples were taken into tubes containing lithium heparin as anticoagulant, while the analytical method was only validated for plasma obtained with EDTA as anticoagulant.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of ganciclovir under fed conditions.

Treatment N=21	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µxg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
A) Test Tutti-frutti	52.3 ± 10.3	-	6.60 ± 1.8	2.00 (1.00-6.03)	5.67 ± 1.34
B) Test Strawberry	51.0 ± 10.2	-	6.72 ± 1.85	2.00 (0.75-4.00)	5.77 ± 1.50
C) Reference	52.2 ± 10.0	-	6.90 ± 1.49	3.00 (1.00-4.00)	5.71 ± 1.40
***Ratio (90%CI) A vs. C**	1.00 (0.96-1.04)	-	0.95 (0.89-1.01)	-	-
***Ratio (90%CI) A vs. B**	0.98 (0.94-1.01)	-	1.03 (0.96-1.09)	-	-
CV (%)	-	-	-	-	-

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. As could be expected, the median tmax after administration of the solution (median 2 h) was a little earlier compared to that after administration of the tablet (median 3 h). However, this had no effect on C_{max}. Based on the pharmacokinetic parameters of ganciclovir under fed conditions, it can be concluded that Valcyte 50 mg/ml powder for oral solution with tutti-frutti flavour and Valcyte 450 mg film-coated tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance. Also, the tutti-frutti oral solution is bioequivalent with the strawberry oral solution. The strawberry formulation is not compared directly with the tablet formulation. However, considering the similar PK outcomes, it may be assumed that the strawberry formulation is bioequivalent to the tablet, like the tutti-frutti flavour.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Dose recommendations in patients with impaired renal function

In a previously submitted study it was shown that decreasing renal function results in decreased renal and apparent clearance of ganciclovir and a corresponding increase in the terminal half-life and AUC. The relationship established between CrCl and the apparent clearance of ganciclovir (Clpo = 2.33 x CrCl1.13) was therefore used to estimate the expected mean daily ganciclovir AUC values at steady state resulting from different CrCl levels and different daily doses of valganciclovir. The current dosing recommendation for patients with moderate to severe renal impairment (CrCl 10 – 39 mL/min) is based on the availability of only one dose strength of the valganciclovir tablet (450 mg) and comprises doses of valganciclovir tablets either every two days or twice-weekly.

Patients with moderate to severe renal impairment (CrCl 10 – 39 ml/min)
From a previous population PK analysis based on two studies, a 2-compartment model for ganciclovir was developed, which was utilized to simulate ganciclovir exposures ($AUC_{0\text{-}24h}$) for patients with renal impairment. A total of 300 subjects (10 subjects per CrCL value) were simulated using the final population PK parameters and the inter-subject variability. The simulations clearly demonstrate that, on average, the proposed dosing regimen (see Table 2) delivers comparable daily exposures to ganciclovir as the current dosing recommendation, indicating that similar levels of clinical outcome would be expected (Table 3).

Table 2. Current and proposed dose regimens for patients with varying degrees of renal function.

	Current (450 mg tablet)		**Proposed (50 mg/mL oral solution)**	
CrCL (mL/min)	Induction Dose	Maintenance/ Prevention Dose	Induction Dose	Maintenance/ Prevention Dose
≥ 60	900 mg b.i.d.	900 mg o.d.	900 mg b.i.d.	900 mg o.d.
40-59	450 mg b.i.d.	450 mg o.d.	450 mg b.i.d.	450 mg o.d.
25-39	450 mg o.d.	450 mg every 2 days	450 mg o.d.	**225 mg o.d.**
10-24	**450 mg every 2 days**	**450 mg twice weekly**	**225 mg o.d.**	**125 mg o.d.**
< 10	not recommended	not recommended	**200 mg (3 x weekly after dialysis)**	**100 mg (3 x weekly after dialysis)**

Bold text indicates changed dose recommendation

Table 3. Simulated average daily ganciclovir exposure at steady state ($AUC_{0\text{-}24h}$)

$AUC_{0\text{-}24h}$ (µg.h/mL)	**CrCL (mL/min)**			
	10-24		25-39	
	Current dose	**Proposed dose**	**Current dose**	**Proposed dose**
Mean	30.3	29.4	30.1	30.1
SD	9.1	8.9	7.7	7.7
Min	15.4	14.9	16.2	16.2
Max	58.7	57.1	57.5	57.5

This dosing strategy requires that the clinical effectiveness of (val)ganciclovir is driven by the systemic exposure to ganciclovir. Evidence for this was previously obtained from a study comparing three doses of oral ganciclovir to i.v. ganciclovir for the maintenance treatment of cytomegalovirus (CMV) retinitis (see NL/H/323/01). This study demonstrated that $AUC_{0\text{-}24h}$ appeared to be the most relevant PK parameter for predicting clinical response (progression of CMV retinitis). Further evidence for this finding was obtained from a study comparing the efficacy and safety of valganciclovir versus oral ganciclovir for prevention of CMV disease in solid organ transplant, where the development of viremia in high risk solid organ transplant patients during treatment with both valganciclovir and ganciclovir appeared to be related to the systemic exposure to ganciclovir.
The proposed once-daily oral dosing regimens for patients with moderate to severe renal impairment offers a benefit to patients by helping to ensure their compliance (and hence maintain their protection from CMV), together with allowing physicians to tailor the dose to match the specific degree of renal impairment experienced by the patient. Furthermore, as resistance to ganciclovir is most likely to develop in patients not achieving a consistently sufficient exposure to the drug, there should be a reduced likelihood of the development of ganciclovir resistance in these patients. Once-daily dosing in patients with impaired renal function will allow maintenance of more consistent drug levels which should be favourable in helping to prevent development of ganciclovir resistant virus.

Patients with end stage renal impairment (CrCl < 10 ml/min)
Patients with end stage renal impairment (CrCL < 10 mL/min), who need hemodialysis treatment, are currently treated with i.v. ganciclovir (Cymevene; 1.25 mg/kg/day during the induction phase, and 0.625

mg/kg/day during the maintenance phase). Since valganciclovir tablets are only available as a single dose strength of 450 mg, it was not possible to derive a pragmatic and clinically useful dosing regimen using the valganciclovir tablet for this group of patients. The i.v. ganciclovir formulation is impractical for long treatment periods outside of the hospital setting and its use is associated with i.v. infusion-related complications, such as infection and irritation at the injection site. Using the more dose flexible oral solution, dose recommendation can be developed based upon the i.v. ganciclovir dose. Conversion of the i.v. ganciclovir dose to the oral valganciclovir dose is shown in Table 4.

Table 4. Calculation of the oral valganciclovir dose in patients with end stage renal impairment.

Induction dose i.v. ganciclovir:	1.25 mg/kg/day after hemodialysis
Standard body weight	70 kg
Bioavailability of ganciclovir	0.6

Molecular weight : valganciclovir = 354.3 and ganciclovir = 255.2

Therefore, the calculation for the proposed valganciclovir dose is performed in three steps:

1. Convert mg/kg/day dose to a fixed dose: *1.25 x 70 = 87.5 mg*
2. Adjust for bioavailability: *87.5 / 0.6 = 146 mg*
3. Adjust for difference in molecular weight:

   146 x 354.2 / 255.2 = 202.6 mg
4. Round to the nearest appropriate dosing increment: *200 mg*

The final estimate was rounded to the nearest multiple of 25 mg which is the smallest dosing increment recommended with the dosing dispenser provided with the powder for oral solution formulation. This results in the recommended induction and maintenance doses of 200 mg and 100 mg, respectively, of valganciclovir oral solution following hemodialysis, up to 3 times a week.

Risk management plan

Valganciclovir was first approved in 2001, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of valganciclovir can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SmPC. The oral solution dosing recommendations for patients with CrCL of 10 – 39 mL/min deliver the same daily exposure as the current dosing recommendations for the tablets: therefore, no safety concerns are anticipated. As the oral solution dosing recommendation for patients with end stage renal impairment (CrCL < 10 mL/min) is derived from the approved dose of i.v. ganciclovir, no additional safety concerns are anticipated. Routine pharmacovigilance activities are performed to identify actual or potential risks and a detailed European Risk Management Plan is in place for Valcyte including its new formulation powder for oral solution.

Pharmacovigilance

The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. However, a statement of the MAH and the qualified person regarding the means for the notification of adverse events is still missing and should be provided. Also, there was no detailed discussion regarding 'patients with severe uncontrolled diarrhoea, or with evidence of malabsorption'. The MAH should discuss why patients with severe uncontrolled diarrhoea or with evidence of malabsorption are not mentioned in the SmPC as contraindicated as these patients were left out in the clinical trials. The

MAH committed to address the following in upcoming PSURs: close monitoring for reports suggestive of gastrointestinal intolerance; monitoring the safety of usage of Valcyte in off-label indications, especially of usage in the paediatric population; performing surveillance in the group of patients with CrCl < 10 ml/min.

Product information

Readability test

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test, followed by two rounds with 10 participants each. Respondents were chosen from among the general population. The recruited respondents comprised of males and females between the ages of 16 and 60 educated to different levels – those who left education at 16 years of age, those who left at 18, and those who had received further education.

The first twenty questions addressed specific aspects of the leaflet and the final two questions asked respondents to consider the overall layout, readability and ease of understanding of the whole leaflet. The PIL passed the first round of testing and therefore the same PIL was used for the second round, without any modifications. The second round was completed successfully. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Valcyte 50 mg/ml, powder for oral solution has a proven chemical-pharmaceutical quality and is a line extension of Valcyte 450 mg film-coated tablets, which are available on the European market.

Valcyte 50 mg/ml provides convenient and suitable dosing regimens for patients with varying degrees of impaired renal function and for those who are unable to swallow tablets. Additionally, the new formulation offers the possibility for once daily dosing compared to intermittent tablet dosing according to the degree of renal function.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents. Furthermore, supportive data were provided to substantiate the dose recommendations in patients with varying degrees of renal impairment.

MEB agreed on a list of post-approval commitments to be completed by the MAH with regard to quality, pharmacovigilance and future PSURs/RMP (see below).

The SmPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that Valcyte 50 mg/ml, powder for oral solution is a legitimate line extension of Valcyte 450 mg film-coated tablets, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 17 January 2008. Valcyte 50 mg/ml, powder for oral solution is authorised in the Netherlands on 23 September 2008.

A European harmonised birth date has been allocated (29 March 2001) and subsequently the next data lock point for valganciclovir is 30 September 2008. The 10th Periodic Safety Update Report (PSUR) for valganciclovir (Valcyte®) covers the period 1 October 2007 to 30 September 2008. This PSUR covers both the 450 mg film-coated tablets as well as the 50 mg/ml powder for oral solution formulation. The first PSUR will cover the period from January 2008 to September 2008, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 17 January 2013.

The following post-approval commitments have been made during the procedure:

Quality - active substance
- The MAH committed to develop a validated test method for determination of residual solvents potentially present from the process and amend the drug substance specifications and provide the outcome by June 2008.

Quality - medicinal product
- The MAH committed to evaluate the shelf life specification for the assay as soon as the end of the proposed shelf life stability data is available.
- The MAH committed to re-evaluate the limits and identification of unknown impurities and to provide the results.

Pharmacovigilance system
- The MAH committed to provide a statement of both the MAH and the QP regarding the means for the notification of adverse events.
- The MAH committed to provide a detailed discussion regarding ‘patients with severe uncontrolled diarrhoea, or with evidence of malabsorption’.

Future PSURs / RMP

- The MAH committed to address the following in upcoming PSURs: close monitoring for reports suggestive of gastrointestinal intolerance; monitoring the safety of usage of Valcyte in off-label indications, especially of usage in the paediatric population; performing surveillance in the group of patients with CrCl < 10 ml/min.

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
Change in the name of the MAH in Germany.	NL/H/0323/002/IA/028	IA	8-6-2009	22-6-2009	Approval	N
Change of address of MAH in Estonia	NL/H/0323/002/IA/031	IA	23-10-2009	6-11-2009	Approval	N
Batch release in Finland	NL/H/0323/002/IA/032	IA	16-3-2010	15-4-2010	Approval	N
Update of SmPC: Treatment duration in kidney transplant patients at risk	NL/H/0323/002/II/024	II	31-7-2009	4-6-2010	Approval	N
Submission of validation results as post-approval commitment	NL/H/0323/IB/033/G	IB	27-7-2010	26-8-2010	Approval	N
Addition of manufacturing sites for drug intermediate and the drug substance	NL/H/0323/002/II/030	II	24-3-2010	27-11-2010	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
Addition of relevant paediatric information to the product information	NL/H/0323/002/II/029	II	12-7-2010	23-6-2011	Approval	N
Deletion of manufacturing site	NL/H/0323/002/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
Alignment of the package leaflet for Valcyte powder for oral solution with the package leaflet for Valcyte film-coated tablets.	NL/H/0323/002/IB/042	IB	13-9-2011	13-10-2011	Approval	N
Replacement batch release site	NL/H/0323/IA/123/G	IA	27-10-2011	27-10-2011	Non-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
Name change active substance manufacturer	NL/H/0323/002/IA/048	IA	1-8-2012	31-8-2012	Approval	N
Change in PSUR submission date	NL/H/0323/002/IA/052	IA	11-6-2013	11-7-2013	Approval	N
Renewal	NL/H/0323/002/R/001	Renewal	30-8-2012	24-4-2013	Approval	N
Addition of Bulgaria, Croatia, Liechtenstein, Malta, Norway, Poland, Romania and Slovenia	NL/H/0323/002/E/001	Repeat-use	9-9-2013	8-12-2013	Approval	N
Updates to the Product Information to fulfil post-approval commitments	NL/H/0323/002/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/0323/002/II/054	II	3-1-2014	20-6-2014	Approval	Y, See annex I
Change in the name of an excipient	NL/H/0323/002/IA/059	IA	13-8-2014	12-9-2014	Approval	N
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
Extension shelf-life from 2 years to 3 years	NL/H/0323/002/IB/058	IB	21-8-2014	19-10-2014	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	NL/H/0323/	II	15-8-2014	11-3-2015	Approval	N

CDS together with editorial changes to SmPC 4.6 and 5.2	002/II/055					
Change in the address of the marketing authorisation holder in Norway	NL/H/0323/ 002/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

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)

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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 $logK_{ow}$ of -1.96, which is 5 $logK_{ow}$ units below the Phase II Tier A threshold for bioaccumulation testing and 6.5 $logK_{ow}$ 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, $AUC_{0\text{-}24h}$ = 68.1 µg.h/ml and $t_{1/2}$ = 2 hours. The range of the estimated steady state $AUC_{0\text{-}24h}$ 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, randomized, 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 randomized 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/1.73m^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/1.73m2), 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/1.73m^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 randomized of which one dropped out before randomization. Forty-seven were randomized to the active substance (VGCV) and 49 were randomized 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

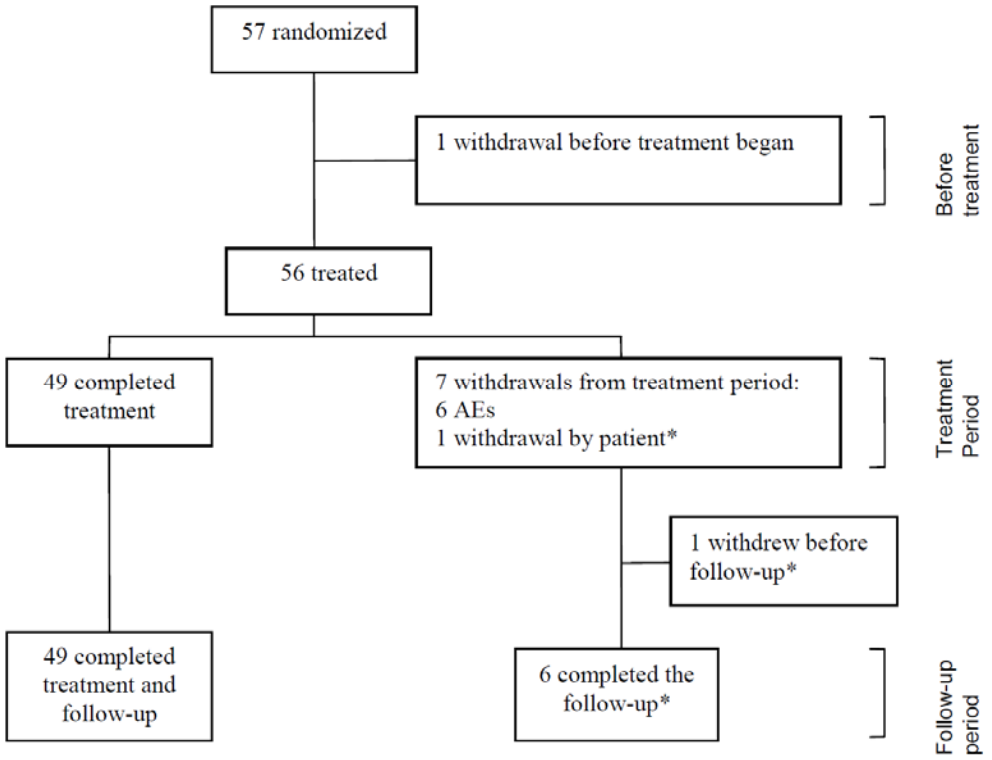
Male or female kidney transplant patients aged 4 months to 16 years who were at risk of developing CMV disease were included in the study if they had adequate haematological and renal function and were able to tolerate oral medication.
Patients were excluded from the study if they had exhibited an allergic 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 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.

[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.

[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.

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.
- 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 specialized 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, randomized 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).

[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.

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 × BSA × 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**Fout! Verwijzingsbron niet gevonden.**.

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 ≥ 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 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

[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

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

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 randomized 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 randomized 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.

[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.

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
Important Potential Risks		
Male infertility	Routine PV Additional PV activity: Study WV25651	SmPC 4.4
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 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.*"

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.

A popPK model has been previously developed for GCV after IV or oral administration or from VGCV in SOT paediatric patients (combining data from studies WP16296, WP16303, and WV16726). This popPK model, after optimalisation, was also used to predict the PK in children < 4 months of age (study NP22523). Goodness-of-fit plots showed that the model fits the data well, which was further supported by the visual predictive check. For the pooled analysis population, it appeared that GCV exposures were higher in the younger children (< 2 years old) as compared to those in the older age groups. However, this is consistent with previously reported estimates of GCV exposure in paediatric SOT patients.

In study NV25409 patients received a once daily dose of VGCV based on a dosing algorithm (7x body surface area x creatinine clearance). This dosing algorithm was already agreed upon during variation II/0029 (which resulted in adding the algorithm to SmPC section 5.1). The maximum paediatric dose was 900 mg daily (equals the maximum adult dosage). Treatment period was 200 days and follow-up was till week 52.

In the phase IV open-label tolerability (safety) study (NV25409) 57 paediatric kidney transplant patients 1 year to 16 years of age were included, although the study should have included patients over 4 months of age. In supportive study WV16726 paediatric SOT patients aged 4 months to 16 years were included. In the PK study (NP22523) 14 paediatric heart transplant patients aged <4 months were included. In order to substantiate the safety in the paediatric population birth to ≤30 days the MAH submitted a randomised placebo controlled phase III study (CASG112) in 109 patients with congenital CMV aged <30 days, which is a non-approved indication in the EU.

In addition the MAH referred to three previously assessed studies in paediatric SOT patients, which were assessed in variation II/0029. To add, in the initial SOT adult efficacy trials PV16000 and NT18435 (MAA application) 12 adolescent patients were included (aged 14 to 18 years; n=4 were 17 years) was conducted in the proposed indication. Based on these paediatric data the use of VGCV in all paediatric patients from birth to 18 years is sufficiently covered. It should be noted that paediatric patients aged >16 years can be treated with the adult dosage. In total 59 paediatric D+/R- patients were included in the studies up-to-now.

In conclusion, the MAH has sufficiently demonstrated that the previously established popPK model is also applicable in paediatric patients. The established paediatric dosing algorithm is adequate.

Although the total number of paediatric patients is limited, the results of the performed studies indicate that the mode of action of VGVC will be equal in the prophylaxis of CMV-disease in paediatric SOT patients and adult SOT patients.
TDM is currently not warranted as the risk of potential underdosing and overdosing is minimized as in the SmPC is advised to regularly check the patients creatinine serum levels, weight and height (SmPC section 4.2) while on prophylaxis and regularly monitor complete blood counts especially in the renal impaired and paediatrics (SmPC section 4.4).

As CMV infection remains a major cause of morbidity and mortality after solid organ transplantation, it is important to prevent a CMV infection. The submitted studies showed a low incidence of CMV. The observed results are in line with the observed results from the adult SOT studies.

The safety data from studies NV25409 and NP22523 showed a similar safety profile as observed in adult SOT patients. The safety data from study CASG112 showed similar frequencies of AEs in paediatric patients aged <30 days as already reported in SOT patients. All reported AEs are already correctly stated in the SmPC. In paediatric heart transplant patients a higher frequency of anaemia has been observed, which may be attributed to blood loss and/or concomitant medications.

The variation was discussed in the Board meeting of January 30, 2014.

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_{0-24h} were very similar across all age groups, including adults. Mean values for AUC_{0-24h} 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_{0-24h} 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_{0-24h} ranges for ganciclovir from these two studies, as well as mean and standard deviation values for AUC_{0-24h}, 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_{0-24h} (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_{0-24h} (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_{0-24h}	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~~

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

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

~~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_{0-12h} was lower compared to the mean AUC_{0-12h} 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)
$AUC_{0-\infty}$ (µg·h/mL)	25.4 ± 4.32	-	-	-
AUC_{0-12h} (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
ASMF	Active Substance Master File
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical classification
AUC	Area under curve
BCF	Bioconcentration factors
BID	Twice daily
BP	British Pharmacopoeia
BPAR	Biopsy-proven acute rejection
BSA	Body Surface Area
CE	Conformité Européenne
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximal concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMR	Carcinogenic, mutagenic, reprotoxic substances
CMS	Concerned member state
CMV	Cytolomegalovirus
CrCIS	Creatinine Clearance calculated using the Schwarz formula
CV	Coefficient of Variation
DCP	Decentralised procedure
D+/R-	Donor positive/Receptor negative
DT50	Degradation time for 50% of a compound
EBV	Epstein-Barr virus
EC	Effective concentration
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
ERA	Environmental Risk Assessment
ESRD	End stage renal disease
EU	European Union
GCP	Good Clinical Practice
GCV	Ganciclovir
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
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
MEB	Medicines Evaluation Board in the Netherlands
MRP	Mutual recognition procedure
NOEC	No Observed Effect Concentration
OECD	The Organisation for Economic Co-operation and Development
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
PBT	Persistence, bioaccumulation, and toxicity

PDCO	Paediatric committee
PEC_{sw}	Predicted Environmental concentration in surface water
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
popPK	Population Pharmacokinetics
POS	Powder for oral solution
PSUR	Periodic Safety Update Report
RCT	Randomised controlled trial
RMS	Reference Member State
SAE	Serious Adverse Events
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SOC	Standard of Care/system organ class
SOT	Solid Organ Transplant
$t_{½}$	Half-life
TDM	Therapeutic drug monitoring
t_{max}	Time for maximum concentration
USP	Pharmacopoeia in the United States
VGCV	Valganciclovir