ARTICLE

Pediatric Dosing of Ganciclovir and Valganciclovir: How Model-Based Simulations Can Prevent Underexposure and Potential Treatment Failure

Karin Jorga[1], Bruno Reigner[2,*], Clarisse Chavanne[2], Giuseppe Alvaro[3] and Nicolas Frey[2]

Intravenous ganciclovir and oral valganciclovir are effective in the prevention and treatment of pediatric cytomegalovirus (CMV) infection but various dosing regimens are used in medical practice. Population pharmacokinetic (PopPK) model-based simulations were used to propose a new ganciclovir pediatric dosing algorithm for regulatory review and to evaluate the approved valganciclovir pediatric dosing algorithm against published dosing recommendations derived from quantitative approaches. Oral valganciclovir (mg = 7 × body surface area (BSA) × creatinine clearance according to the Schwarz formula (CrCLS) daily) and i.v. ganciclovir (mg = 3 × BSA × CrCLS daily) are effective in reaching ganciclovir target exposure for the prevention of CMV (area under the concentration-time curve $(AUC)_{0-24}$ 40–60 µg · hour/mL) in most pediatric patients across the full pediatric age range. In contrast, ganciclovir and valganciclovir dosing based on body weight, as commonly used in medical practice, leads to underexposure, particularly in younger pediatric patients. This example shows that model-based dosing algorithms built on clinical pharmacology and implemented using good modeling practice can prevent underexposure and reduce the risk of treatment failure in pediatric patients.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ The pediatric dosing of oral valganciclovir (pro-drug of ganciclovir) based on BSA/CrCLS provides adequate exposure for the prevention of CMV in pediatric patients across all ages. In the absence of pediatric data, i.v. ganciclovir is commonly dosed in pediatric patients as milligrams/kilograms.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ We derived a pediatric dosing algorithm for i.v. ganciclovir and explored the performance of alternative pediatric dosing recommendations for oral valganciclovir.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ The clinical practice of dosing i.v. ganciclovir and oral valganciclovir as milligrams/kilograms leads to underexposure in pediatric patients, whereas dosing based on BSA/CrCLS provides adequate exposure for the prevention of CMV in pediatric patients across all ages.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?
☑ Based on this work, a pediatric posology for i.v. ganciclovir has been added to the prescribing information to avoid underdosing and potential treatment failure.

Today, the value of pharmacometrics to support pediatric dosing algorithms is widely accepted, as model-based approaches can bridge between adult and pediatric patients and simulations can be used to fine-tune the pediatric dosing algorithms across all age groups. We have recently published our model-based approach combining population pharmacokinetic (PopPK) and physiologically based pharmacokinetic (PBPK) to support the pediatric dosing algorithm for valganciclovir in the prevention of human cytomegalovirus (CMV) infection.[1] The current article builds on this work and illustrates how we applied our validated PopPK model[2–5] in simulation mode to address two critical clinical questions.

First, we evaluated the approved pediatric valganciclovir dosing algorithm, which is based on creatinine clearance according to the Schwartz formula (CrCLS)[6–8] and on patient body surface area (BSA) vs. other pediatric dosing algorithms published in the literature.[9,10] These alternative algorithms were also derived using quantitative approaches and concluded that pediatric doses based

on body weight (BW) or BW and glomerular filtration rate (GFR) would be more appropriate than dosing by BSA and CrCLS.

Second, we addressed a regulatory request for a pediatric dose recommendation for i.v. ganciclovir, the active metabolite of oral valganciclovir. Ganciclovir in adults is dosed on a milligram/kilogram basis, and pediatric patients in medical practice are commonly treated with the same dose, in the absence of an appropriate guidance.

We show in this article that model-based simulations using a verified model built on good science can demonstrate that the commonly proposed BW-based dosing of valganciclovir and ganciclovir leads to underexposure of ganciclovir in pediatric patients. This could potentially cause treatment failure particularly in very young patients. The work presented was submitted for regulatory review in Europe and is the basis for the inclusion of a new pediatric posology based on BSA/CrCLS in the prescribing information for ganciclovir in Europe.

Ganciclovir (Cymevene; Roche Products, Welwyn Garden City, UK), and the pro-drug of ganciclovir, valganciclovir (Valcyte, Roche Products, Welwyn Garden City, UK) are both established as effective agents in the prevention and treatment of CMV infection in adult patients.[11] Patients who develop CMV disease should receive treatment to prevent the morbidity and mortality that could otherwise ensue.[12–14] CMV prevention is recommended in patients with drug-induced immunosuppression following organ transplantation or cancer chemotherapy.[15–17] The ganciclovir adult dose for treatment of CMV is 5 mg/kg given as 1-hour i.v. infusion, every 12 hours for 14–21 days followed by once daily (q.d.) i.v. infusions of 5 mg/kg as maintenance therapy. For prevention of CMV in adult patients, ganciclovir is given as 1-hour i.v. infusion of 5 mg/kg every 24 hours or as oral valganciclovir at 900 mg q.d.

Clinical efficacy data of ganciclovir and valganciclovir are limited in pediatric patients, and although consensus exists that i.v. ganciclovir and oral valganciclovir are effective in prevention and treatment of pediatric CMV infection,[18,19] the appropriate pediatric dosing strategy is a topic of broad debate.[9,10,20]

For valganciclovir, a pediatric dosing algorithm for the prevention of CMV has been derived.[1]

$$Dose(mg) = 7 \times BSA \times CrCLS$$

BSA is calculated according to Mosteller's equation[21] and a maximum CrCLS value of 150 mL/minute/1.73 m^2 is assumed. The pediatric dose should not exceed the adult dose of 900 mg. This algorithm targets a plasma concentration vs. area under the time curve over 24 hours (AUC$_{0–24}$) of 40–60 µg · hour/mL[2] and takes into account that ganciclovir is eliminated almost exclusively by renal excretion.[22]

For i.v. ganciclovir, no specific studies were conducted and pediatric patients are usually treated on a BW basis according to the adult dose of 5 mg/kg q.d. for prevention and 5 mg/kg twice daily (b.i.d.) for 14–21 days followed by 5 mg/kg q.d. for treatment of CMV infection.

The inconsistency of pediatric dosing of i.v. ganciclovir based on BW and oral valganciclovir based on BSA/CrCLS is unsatisfactory. The pediatric dosing algorithm for valganciclovir is based on the understanding that renal clearance is a key driver for the pharmacokinetics (PK) of ganciclovir, particularly in pediatric patients, and clinical studies have validated the appropriateness of this posology.[1,3,5] Early valganciclovir studies have shown that BSA dosing alone leads to low levels in infants and young children[4] and several articles have reported subtherapeutic exposures in pediatric patients after administration of 5 mg/kg i.v. ganciclovir for treatment (b.i.d.) or prevention (q.d.) of CMV.[23–26] Nevertheless, recent publications have challenged the valganciclovir pediatric dosing algorithm based on BSA/CrCLS, and simulations have suggested that a simple BW-based dosing regimen of 14–16 mg/kg valganciclovir b.i.d.[9] or an alternative algorithm using BW and GFR based on the Cockcroft–Gault equation[10] would be more appropriate to achieve therapeutic concentrations of ganciclovir.

We have conducted a structured exploration using our validated pediatric PopPK model and applied a verified simulation methodology used previously to address various questions from various health authorities regarding the dosing of valganciclovir in pediatric patients.[1]

For valganciclovir, we simulated the ganciclovir AUC$_{0–24}$ when valganciclovir was given as recommended in the package insert (dose in mg = 7 × BSA × CrCLS) or according to the regimens proposed by Asberg *et al.*[10] and Villeneuve *et al.*[9] For ganciclovir, we simulated ganciclovir AUC$_{0–24}$ when i.v. ganciclovir was given in line with the adult dose (5 mg/kg) or according to a dosing regimen based on BSA/CrCLS (dose in mg = 3 × BSA × CrCLS), which we derived from the valganciclovir pediatric dosing algorithm. To compare the algorithms, we used the established target range of AUC$_{0–24}$ of 40–60 µg · hour/mL for the prevention of CMV disease. For treatment of CMV disease, no therapeutic exposure target range is defined, but a range of AUC$_{0–12}$ of 40–60 µg · hour/mL, which equals AUC$_{0–24}$ of 80–120 µg · hour/mL has been suggested.[9,10] This exposure range is in line with the average AUC$_{0–24}$ achieved after the recommended dose of 5 mg/kg i.v. ganciclovir b.i.d. in adults (100 µg · hour/mL)[27] and, therefore, AUC$_{0–24}$ of 80–120 µg · hour/mL was applied as a reference range for treatment of CMV. Furthermore, an analysis of the relationship between exposure and safety was performed to compare the safety of ganciclovir at AUC$_{0–24}$ of 80–120 µg · hour/mL with the safety at the established pediatric exposure range of 40–60 µg · hour/mL.

METHODS
Software
Model development and population simulations were performed in NONMEM version 7.1.0 (ICON, Dublin, Ireland).

Pediatric valganciclovir/ganciclovir PopPK model
The model describing ganciclovir PK is two-compartment with first-order formation from oral valganciclovir, lag time, and relative bioavailability of ganciclovir from valganciclovir.[1] The model was built on a database composed of 948 ganciclovir plasma concentrations from 119 patients aged from 1 month to 17 years old. The population parameters were well estimated, and the goodness-of-fit plots did not show any systematic

Table 1 Demographic distribution (min–max) of the pediatric dataset used for simulations of ganciclovir AUC_{0-24} in pediatric patients aged from birth to 16 years (1,473 data records)

	< 4 months (*n* = 781)	≥ 4 months to ≤ 2 years (*n* = 384)	> 2 to < 6 years (*n* = 86)	≥ 6 to < 12 years (*n* = 96)	≥ 12 to ≤ 16 years (*n* = 126)
Age (years)	0.01–0.33	0.33–2.00	2.08–5.92	6.25–11.83	12.00–16.00
BSA (m^2)	0.15–0.37	0.26–0.56	0.43–0.80	0.65–1.22	0.75–1.83
Creatinine (mg/dL)	0.10–24.0	0.08–76.0	0.10–231.0	0.30–610.0	0.30–535.0
Creatinine clearance (mL/minute/1.73 m^2)	24.3–281.7	21.7–371.3	6.0–489.5	7.5–234.7	9.0–247.5
Height (cm)	41.0–65.5	54.5–82.0	80.0–118.0	104.0–142.0	112.0–170.0
Weight (kg)	1.80–8.30	4.30–13.90	8.1–20.0	14.7–44.0	18.2–71.0

AUC_{0-24}, area under the concentration–time curve over 24 hours; BSA, body surface area.

bias.[1] The model was qualified for simulations using visual predictive check plots.

Estimated CrCLS was identified as a significant covariate for ganciclovir clearance. BW, using allometric scaling, was also a significant covariate for clearance and volume of distribution of ganciclovir.

Simulation methods

For the simulations, a dataset of 1,473 patient records representing typical combinations of body size and renal function for the pediatric CMV population was used. The demographic data were obtained from four studies (as previously described[1]) and cover the full range of demographic characteristics across the pediatric age range (**Table 1**).

For the simulations, ganciclovir or valganciclovir doses for each individual demographic patient record were calculated according to the algorithms described below. A single Monte Carlo simulation was conducted with the ganciclovir/valganciclovir PopPK model to generate model parameters for each individual data record and compute individual steady-state AUC_{0-24} values based on ganciclovir or valganciclovir dose, BW, and CrCLS.

Dosing algorithms

Valganciclovir dose according to the prescribing information (7 × BSA × CrCLS). BSA and CrCLS values were used to compute individual valganciclovir doses for each individual covariate dataset according to valganciclovir dose (mg) = 7 × BSA × CrCLS, with 150 mL/minute/1.73 m^2 as maximum value for CrCLS.

Valganciclovir dose according to Villeneuve *et al.*[9] BW and CrCLS values were used to compute individual valganciclovir doses for each individual covariate dataset according to Villeneuve *et al.*[9] For pediatric patients with CrCLS ≥ 60 mL/minute/1.73 m^2, the valganciclovir dose was 14–16 mg/kg/day; for pediatric patients with CrCLS of 40–59 mL/minute/1.73 m^2, the dose was 7–8 mg/kg/day; for pediatric patients with CrCLS of 25–39 mL/minute/1.73 m^2, the dose was 7–8 mg/kg every other day; and for pediatric patients with CrCLS of 10–24 mL/minute/1.73 m^2, the dose was 7–8 mg/kg twice weekly.

Valganciclovir dose according to Asberg *et al.*[10] BW and GFR values according to Cockcroft–Gault were used to compute individual valganciclovir doses for each individual covariate dataset by applying the proposed algorithm valganciclovir dose (mg) = BW × (0.07 × GFR+*k*), where *k* = 5 for GFR ≤ 30 mL/minute, *k* = 10 for GFR > 30 mL/minute and BW > 30 kg, and *k* = 15 for GFR > 30 mL/minute and BW ≤ 30 kg.

Ganciclovir dose according to BW. BW and GFR values according to Cockcroft–Gault were used to compute individual ganciclovir doses (1-hour infusion) for each individual covariate dataset according to the posology for adults. For pediatric patients with GFR ≥ 70 mL/minute, the dose was 5 mg/kg b.i.d. (treatment) or q.d. (prevention); for pediatric patients with GFR of 50–69 mL/minute, the dose was 2.5 mg/kg b.i.d. (treatment) or q.d. (prevention); for pediatric patients with GFR of 25–49 mL/minute, the dose was 2.5 mg/kg q.d. (treatment) and 1.25 mg/kg q.d. (prevention); and for pediatric patients with GFR of 10–24 mL/minute, the dose was 1.25 mg/kg q.d. (treatment).

Ganciclovir dose according to BSA and renal function. The ganciclovir dosing algorithm based on BSA/CrCLS was derived from the approved valganciclovir pediatric dosing algorithm by adjusting for the difference in molecular weight (MW) of ganciclovir vs. valganciclovir and the oral bioavailability of ganciclovir after oral valganciclovir dosing.

$MW_{ganciclovir}/MW_{valganciclovir}$ = 255.23/354.362 = 0.72
$Bioavailability_{valganciclovir}$ = 0.59
Ganciclovir dose (mg) = (0.72 × 0.59 × 7) × BSA × CrCLS

Ganciclovir dose (mg) = 3 × BSA × CrCLS. For the simulations, BSA and CrCLS values were used to compute individual ganciclovir doses for each individual covariate dataset by applying the pediatric dose algorithm ganciclovir dose (mg) = 3 × BSA × CrCLS, with 150 mL/minute/1.73 m^2 as maximum value for CrCLS.

Relationship between systemic exposure and safety

The exposure/safety relationship was explored in pediatric and adult solid organ transplant patients using data from randomized clinical trials in prevention of CMV (at least 2 weeks of treatment). The database contained data from 78 pediatric patients (aged 4 months to 16 years) and 120 adult patients (17 years

Table 2 Simulated steady-state AUC_{0-24} for ganciclovir in pediatric patients dosed using various valganciclovir and ganciclovir dosing regimens for the prevention of CMV infection (1,473 data records); target AUC_{0-24} range is 40–60 μg · hour/mL

	Oral valganciclovir dosing			i.v. ganciclovir dosing		
	mg = 7 × BSA × CrCLS	Villeneuve[9]	Asberg[10]	5 mg/kg q.d.	5 mg/kg b.i.d.	mg = 3 × BSA × CrCLS
Age 0–16 years (*n* = 1,473), AUC_{0-24} (median)	53.2	21.5	20.6	18.2	36.4	55.4
< 40 μg · hour/mL, *n* (%)	324 (22)	1,357 (92)	1,289 (88)	1,439 (98)	876 (59)	191 (13)
40–60 μg · hour/mL, *n* (%)	627 (43)	101 (6.9)	146 (9.9)	32 (2.2)	457 (31)	741 (50)
> 60 μg · hour/mL, *n* (%)	522 (35)	12 (< 1)	38 (2.6)	2 (< 1)	140 (10)	541 (37)
Age < 4 months (*n* = 781), AUC_{0-24} (median)	54.5	20.0	13.6	17.4	34.8	55.6
< 40 μg · hour/mL, *n* (%)	148 (19)	751 (96)	764 (98)	777 (99)	529 (68)	89 (11)
40–60 μg · hour/mL, *n* (%)	343 (44)	28 (3.6)	15 (1.9)	4 (< 1)	218 (28)	398 (51)
> 60 μg · hour/mL, *n* (%)	290 (37)	2 (< 1)	2 (< 1)	0	34 (4.4)	294 (38)
Age ≥ 4 months ≤ 2 years (*n* = 384), AUC_{0-24} (median)	55.2	20.5	24.0	16.9	33.7	56.9
< 40 μg · hour/mL, *n* (%)	65 (17)	364 (96)	342 (89)	382 (99)	255 (66)	38 (10)
40–60 μg · hour/mL, *n* (%)	168 (44)	19 (4.9)	37 (9.6)	2 (< 1)	116 (30)	195 (51)
> 60 μg · hour/mL, *n* (%)	151 (39)	1 (< 1)	5 (1.3)	0	13 (3.4)	151 (39)
Age > 2 years to < 6 years (*n* = 86), AUC_{0-24} (median)	50.4	24.4	31.3	19.6	39.3	54.4
< 40 μg · hour/mL, *n* (%)	21 (24)	78 (91)	71 (83)	86 (100)	46 (53)	13 (15)
40–60 μg · hour/mL, *n* (%)	38 (44)	8 (9.3)	14 (16)	0	32 (37)	44 (51)
> 60 μg · hour/mL, *n* (%)	27 (31)	0	1 (1.2)	0	8 (9.3)	29 (34)
Age ≥ 6 years to < 12 years (*n* = 96), AUC_{0-24} (median)	48.3	28.5	40.7	24.7	49.5	51.3
< 40 μg · hour/mL, *n* (%)	30 (31)	75 (78)	47 (49)	83 (86)	29 (30)	23 (24)
40–60 μg · hour/mL, *n* (%)	38 (40)	15 (16)	37 (39)	12 (13)	36 (38)	41 (43)
> 60 μg · hour/mL, *n* (%)	28 (29)	6 (6.3)	12 (1.3)	1 (< 1)	31 (33)	32 (33)
Age ≥ 12 years to ≤ 16 years (*n* = 126), AUC_{0-24} (median)	41.7	30.7	38.0	28.2	56.3	51.4
< 40 μg · hour/mL, *n* (%)	60 (48)	89 (71)	65 (52)	111 (88)	17 (13)	28 (22)
40–60 μg · hour/mL, *n* (%)	40 (32)	31 (25)	43 (34)	14 (11)	55 (44)	63 (50)
> 60 μg · hour/mL, *n* (%)	26 (21)	6 (4.8)	18 (14)	1 (< 1)	54 (43)	35 (28)

AUC_{0-24}, area under the concentration–time curve over 24 hours; BSA, body surface area; CMV, cytomegalovirus; CrCLS, creatinine clearance according to the Schwarz formula.
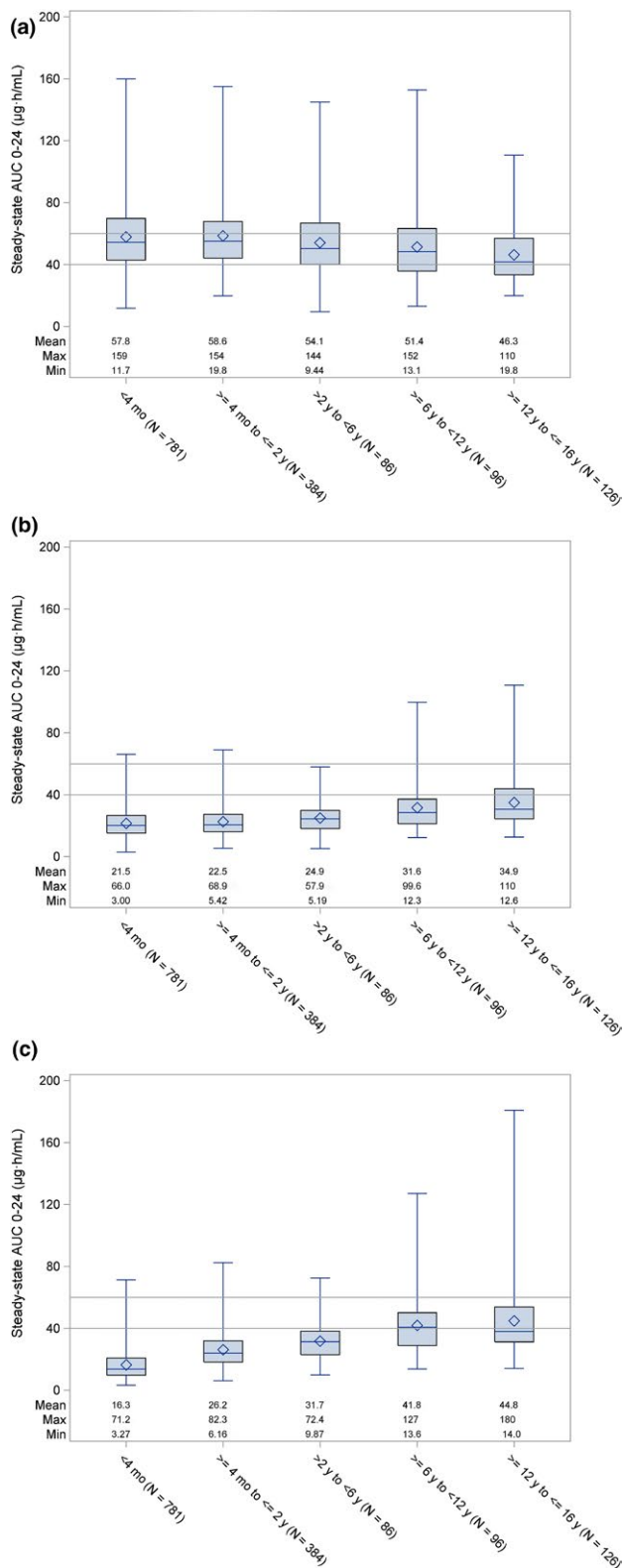
and older) treated for CMV prevention following solid organ transplantation. Adverse events that occurred after CMV infection were not considered, to avoid confounders (e.g., leukopenia is known to be a sign of CMV infection). The evaluation focused on the occurrence of cytopenia (leukopenia, lymphocytopenia, neutropenia, and anemia) based on the prevalence with valganciclovir/ganciclovir treatment. The laboratory parameters were graded according to AIDS Clinical Trials Group (ACTG) classifications. Individual AUC_{0-24} values were calculated with the PopPK model using *post hoc* empirical Bayesian estimation based on the population parameters and the patient's observed ganciclovir concentrations. The average exposure at time of event was calculated taking the dosing history of the patient into account. The correlation analyses between individual ganciclovir AUC_{0-24} and the occurrence of safety adverse events (yes/no) were performed by logistic regression, as described previously.[2,28]

RESULTS

Valganciclovir dosing algorithms for the prevention of CMV disease

The simulated median AUC_{0-24} values, together with the fraction of patients within, below, and above the target range of 40–60 μg · hour/mL for each age group after dosing with valganciclovir are summarized in **Table 2**. The simulations project that dosing by BSA/CrCLS achieves a median AUC_{0-24} of 53.2 μg · hour/mL across the entire pediatric age range (range across age groups: 41.7–55.2 μg · hour/mL; **Figure 1a**). For all age groups combined, 43% of AUC_{0-24} values are within the target range; 22% are below, and 35% are above. These simulations are consistent with the observed data from clinical trials in which this algorithm was applied (**Table 3**).

The BW-based algorithm proposed by Villeneuve *et al.*[9] results in a median AUC_{0-24} of 21.5 μg · hour/mL (range across age groups: 20.0–30.7 μg · hour/mL). Only 6.9% of patients are projected to reach the target range with this algorithm and the majority of patients (92%) have predicted

(a)

	<4 mo (N = 781)	≥4 mo to <2 y (N = 384)	>2 y to <6 y (N = 86)	≥6 y to <12 y (N = 96)	≥12 y to <=16 y (N = 126)
Mean	57.8	58.6	54.1	51.4	46.3
Max	159	154	144	152	110
Min	11.7	19.8	9.44	13.1	19.8

(b)

	<4 mo (N = 781)	≥4 mo to <2 y (N = 384)	>2 y to <6 y (N = 86)	≥6 y to <12 y (N = 96)	≥12 y to <=16 y (N = 126)
Mean	21.5	22.5	24.9	31.6	34.9
Max	66.0	68.9	57.9	99.6	110
Min	3.00	5.42	5.19	12.3	12.6

(c)

	<4 mo (N = 781)	≥4 mo to <2 y (N = 384)	>2 y to <6 y (N = 86)	≥6 y to <12 y (N = 96)	≥12 y to <=16 y (N = 126)
Mean	16.3	26.2	31.7	41.8	44.8
Max	71.2	82.3	72.4	127	180
Min	3.27	6.16	9.87	13.6	14.0

Figure 1 Simulated ganciclovir AUC_{0-24} by age group for an oral valganciclovir dose of (**a**) $7 \times BSA \times CrCLS$ and according to (**b**) Villeneuve et al.[9] and (**c**) Asberg et al.[10]. Note: The graph represents mean (diamond), median (line), and minimum and maximum values for each cohort. The lines at 40 and 60 µg · hour/mL represent the target exposure. AUC_{0-24}, area under the concentration-time curve over 24 hours; BSA, body surface area; CrCLS, creatinine clearance according to the Schwarz formula.

(96% in < 4 months and in 4 months to 2 years) than in older pediatric patients (71% in 12–16 years).

The algorithm proposed by Asberg et al.[10] is based on BW and GFR and achieves considerably lower exposure levels than the algorithms based on BSA and CrCLS. The median AUC_{0-24} across the entire dataset is 20.6 µg · hour/mL with 88% of patients having levels below 40 µg · hour/mL. For this algorithm, there is also a trend toward lower exposure in younger pediatric patients compared with older pediatric patients. In patients younger than 2 years, < 10% achieve the target AUC_{0-24} range, whereas in patients aged 6–12 years and 12–16 years, 39% and 34% achieve the target AUC_{0-24} range, respectively (**Figure 1c**).

Intravenous ganciclovir dosing algorithms for the prevention of CMV disease

The i.v. ganciclovir dosing regimens of 5 mg/kg q.d. or b.i.d. are projected to achieve ganciclovir exposures in the lower range, particularly in younger pediatric patients (**Figure 2a,b**). The median AUC_{0-24} after 5 mg/kg is 18.2 µg · hour/mL and 36.4 µg · hour/mL for q.d. and b.i.d., respectively (**Table 2**). With q.d. dosing, the majority of patients (98%) do not achieve the target range. With b.i.d. dosing, 31% of pediatric patients have AUC_{0-24} values between 40 and 60 µg · hour/mL, with a higher proportion of younger pediatric patients below the target range (68% and 66% in pediatric patients < 4 months and between 4 months and 2 years, respectively) compared with older pediatric patients (13% in the range of 12–16 years).

The i.v. ganciclovir dosing regimen based on BSA/CrCLS performs very similarly to the respective valganciclovir regimen (**Table 2**). The simulations project a median AUC_{0-24} of 55.4 µg · hour/mL (range across age groups: 51.4– 56.9 µg · hour/mL; **Figure 2c**). Overall, 50% of AUC_{0-24} values are within the target range; 13% are below and 37% are above.

Intravenous ganciclovir dosing algorithms for treatment of CMV disease

The i.v. ganciclovir dosing regimen of 5 mg/kg b.i.d. fails to achieve the reference AUC_{0-24} range in all pediatric age groups (**Table 4**). The median AUC_{0-24} is 36.4 µg · hour/mL and only very few children and adolescents aged 6 years and older are projected to reach ganciclovir exposures, compared with adults, at the approved ganciclovir dose (range 80–120 µg · hour/mL). Increasing the dose to 5 mg/kg given 4 times q.d. achieves an average AUC_{0-24} of 72.7 µg · hour/mL and brings 31% of patients within the reference exposure range. In contrast, applying the i.v. ganciclovir dosing regimen based on BSA/

exposures below 40 µg · hour/mL. A clear trend to increasing exposure with increasing age is observed with BW-based dosing (**Figure 1b**), with a larger fraction of patients of AUC_{0-24} below 40 µg · hour/mL in younger pediatric patients

Table 3 Observed ganciclovir AUC_{0-24} (µg · hour/mL) for patients treated with a valganciclovir dose (mg) of 7 × BSA × CrCLS[3,21]

	< 4 months	≥ 4 months to ≤ 2 years	> 2 to < 6 years	≥ 6 to < 12 years	≥ 12 to ≤ 16 years	All patients
No. patients	14	17	8	12	25	76
No. AUC_{0-24} estimates[a]	19	101	29	56	59	264
Median	61.4	59.5	54.9	53.1	49.0	55.1
Minimum	33.8	33.3	40.7	30.9	24.2	24.2
Maximum	123.2	107.1	82.0	93.6	96.6	123.2
P5	33.8	38.4	42.7	38.2	29.1	36.6
P95	123.2	89.7	80.1	77.6	79.8	83.2
Patients AUC_{0-24} < 40 µg · hour/mL	1 (7%)	1 (6%)	—	—	8 (32%)	10 (13%)
Patients AUC_{0-24} 40–60 µg · hour/mL	5 (36%)	8 (47%)	5 (62%)	9 (75%)	12 (48%)	39 (51%)
Patients AUC_{0-24} > 60 µg · hour/mL	8 (57%)	8 (47%)	3 (38%)	3 (25%)	5 (20%)	27 (36%)

AUC_{0-24}, area under the concentration-time curve over 24 hours; BSA, body surface area; CrCLS, creatinine clearance according to the Schwarz formula; P5, 5th percentile; P95, 95th percentile.
[a]Some patients provided more than one set of pharmacokinetic samples (observations) for the estimation.

CrCLS, increasing the dose in mg = 3 × BSA × CrCLS to b.i.d. performs well and the projected AUC_{0-24} of 110.8 µg · hour/mL across the entire pediatric age range with median values between 102.7 and 113.7 µg · hour/mL for the various age groups is close to the observed levels in adults treated with ganciclovir at 5 mg/kg b.i.d. (AUC_{0-24} ~100 µg · hour/mL).[27]

Relationship between exposure and safety

Figure 3 illustrates the probability of leukopenia, lymphopenia, neutropenia, and anemia in pediatric patients (green) and adult patients (blue) separately. The incidence of leukopenia (white blood cell count $\leq 2.5 \times 10^9$ cells/L) in pediatric patients (5/73) was low and seemed independent of ganciclovir exposure. In adult patients, the occurrence was higher and a small tendency to increasing probability of leukopenia with increasing ganciclovir exposure was observed. Across the combined population (pediatric and adult patients) the probability of leukopenia in the ganciclovir exposure range (AUC_{0-24}) of 40–60 µg · hour/mL was about 10%. The probability increased by approximately threefold for the exposure range of 80–120 µg · hour/mL, but the uncertainty of the estimate is relatively large due to the limited amount of data above 80 µg · hour/mL.

The incidence of lymphopenia (lymphocyte count $\leq 1.0 \times 10^9$ cells/L) was lower in pediatric patients (27%) compared with adults (67%) and although an increase in incidence with increasing ganciclovir exposure was observed in adults, the relationship seemed to be reversed in pediatric patients. The reason for this difference is unknown, but it was mainly driven by data from pediatric study patients who received a liver transplant. In liver transplant patients, lower exposures to ganciclovir and a higher incidence of lymphopenia were observed, which could create a bias when pooling the data across all organ transplant patients.
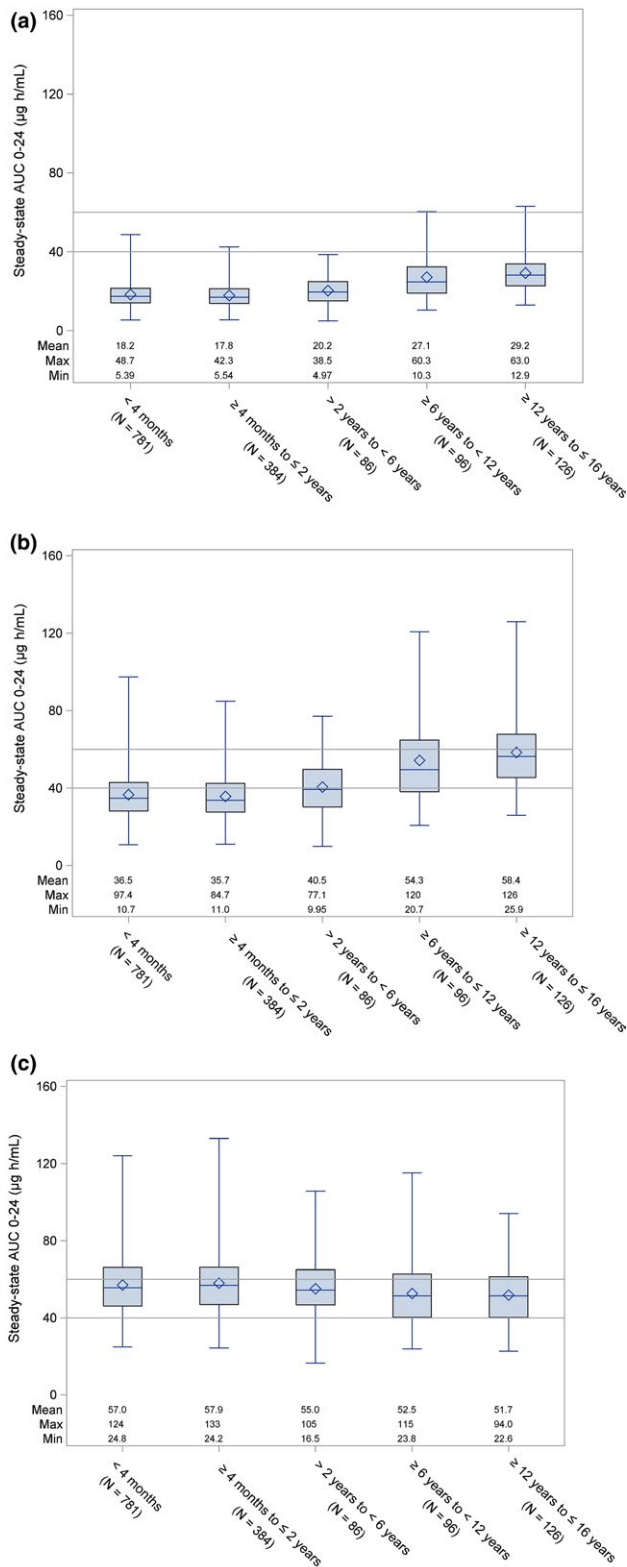
The incidence of neutropenia and anemia in pediatric and adult patients was low and the increase of probability of occurrence with ganciclovir exposure seemed similar.

The combined analysis predicts an increase in neutropenia from about 10% to 20% and for anemia from about 5% to 15% when comparing the ganciclovir exposure ranges of 40–60 µg · hour/mL with 80–120 µg · hour/mL.

DISCUSSION

The objective of our study was to explore various pediatric dosing algorithms for i.v. ganciclovir and oral valganciclovir using a validated pediatric PopPK model in simulation mode to propose a pediatric dosing algorithm for i.v. ganciclovir for health authority review, as well as to assess whether dosing regimens currently used in medical practice or proposed in the literature can achieve the ganciclovir target exposure in all pediatric age groups from birth to 16 years.

For valganciclovir used in prevention of CMV infection, a pediatric dosing algorithm based on BSA and CrCLS (mg = 7 × BSA × CrCLS) has been developed and is approved in Europe, the United States, and other countries for the prevention of CMV in patients up to 16 years. Nevertheless, Villeneuve et al.[9] reported that, according to their investigation, a simple BW-based dosing approach for valganciclovir gives a higher probability for therapeutic AUCs compared with the manufacturer-recommended BSA/CrCLS dosing in pediatric transplant patients aged 6 months to 3 years with normal renal function. Our work cannot confirm this hypothesis. We used a validated PopPK model and demographic data from a wide range of pediatric patients to simulate ganciclovir exposure levels (AUC_{0-24}) using the valganciclovir BSA/CrCLS-based algorithm and the valganciclovir BW-based dosing proposed by Villeneuve et al.[9] Although the simulations for the BSA/CrCLS-based algorithm were consistent with the data from the clinical studies, the Villeneuve dosing approach is projected to lead to considerable underdosing in pediatric patients of all ages. Over 90% of pediatric patients below 6 years of age would not reach the therapeutic target

(a)

	< 4 months (N = 781)	≥ 4 months to ≤ 2 years (N = 384)	> 2 years to < 6 years (N = 86)	≥ 6 years to < 12 years (N = 96)	≥ 12 years to ≤ 16 years (N = 126)
Mean	18.2	17.8	20.2	27.1	29.2
Max	48.7	42.3	38.5	60.3	63.0
Min	5.39	5.54	4.97	10.3	12.9

(b)

	< 4 months (N = 781)	≥ 4 months to ≤ 2 years (N = 384)	> 2 years to < 6 years (N = 86)	≥ 6 years to < 12 years (N = 96)	≥ 12 years to ≤ 16 years (N = 126)
Mean	36.5	35.7	40.5	54.3	58.4
Max	97.4	84.7	77.1	120	126
Min	10.7	11.0	9.95	20.7	25.9

(c)

	< 4 months (N = 781)	≥ 4 months to ≤ 2 years (N = 384)	> 2 years to < 6 years (N = 86)	≥ 6 years to < 12 years (N = 96)	≥ 12 years to ≤ 16 years (N = 126)
Mean	57.0	57.9	55.0	52.5	51.7
Max	124	133	105	115	94.0
Min	24.8	24.2	16.5	23.8	22.6

Figure 2 Simulated ganciclovir AUC_{0-24} by age group for an i.v. ganciclovir dose of (**a**) 5 mg/kg q.d., (**b**) 5 mg/kg b.i.d., and (**c**) according to 3 × BSA × CrCLS. Note: The graph represents mean (diamond), median (line), and minimum and maximum values for each cohort. The lines at 40 and 60 µg · hour/mL represent the target exposure. AUC_{0-24}, area under the concentration-time curve over 24 hours; BSA, body surface area; CrCLS, creatinine clearance according to the Schwarz formula.

was also used to establish the original ganciclovir AUC_{0-24} target range of 40–60 µg · hour/mL in adults.[2] The PopPK models used are essentially the same and the AUC values can be compared directly. In contrast, calculation of ganciclovir AUC_{0-24} in the Villeneuve et al.[9] study was based on very few measured ganciclovir concentrations (2–4 samples) and a simple AUC calculation using the trapezoidal method. Although the study shows that the BSA/CrCLS dosing algorithm leads to higher valganciclovir doses in pediatric patients compared with BW-based dosing, the extrapolated ganciclovir AUC_{0-24} values are generally higher, leading to the assumption that the BSA/CrCLS-based dosing algorithm results in supratherapeutic drug levels. This is not consistent with the data observed in clinical studies (**Table 3**) and we, therefore, assume that the method to derive the ganciclovir AUC values for comparison with the therapeutic target range of 40–60 µg · hour/mL in the Villeneuve et al.[9] study is suboptimal.

In another study, Asberg et al.[10] proposed an alternative valganciclovir pediatric dosing algorithm using BW and GFR and concluded that this new algorithm outperforms the valganciclovir BSA/CrCLS-based algorithm. Because Asberg et al.[10] used the same patient dataset and a comparable method (PopPK model) to that used in our study, we expected that the alternative valganciclovir pediatric dosing approach based on BW and GFR would behave relatively similarly to the BSA/CrCLS dosing algorithm, as both methods correct for body size and renal function. However, our simulations projected much lower ganciclovir exposures for the Asberg algorithm compared with BSA/CrCLS dosing, particularly in younger patients, and discovered that, in the Asberg et al.[10] publication, the simulated ganciclovir AUC_{0-24} values were inconsistent with the observed values from the dataset used to derive the model. For example, the projected average ganciclovir AUC_{0-24} when applying the Asberg model for pediatric patients aged 6 months (0.5 years) was close to 120 µg · hour/mL with the BSA/CrCLS algorithm; whereas the observed values in pediatric patients dosed with this algorithm and included in this model development were centered around 60 µg · hour/mL for patients up to 4 months and around 55 µg · hour/mL for patients between 4 months and 2 years old. We are, therefore, unsure about the methods applied in the Asberg et al.[10] study. According to our work, which is based on simulations using a validated PopPK model, the BSA/CrCLS algorithm achieves therapeutic plasma levels in a considerably higher proportion of patients compared with the dosing strategy proposed by Asberg et al.[10] (**Table 3**).

For i.v. ganciclovir, no approved pediatric dosing algorithm exists, and our most important finding is that applying the adult dose of 5 mg/kg q.d. in prevention of CMV and

exposure, if dosed according to Villeneuve et al.[9] with valganciclovir 14–16 mg/kg q.d. One fundamental difference in our work is that we used the same methodology to calculate ganciclovir AUC_{0-24} estimates in pediatric patients as

Table 4 Simulated steady-state AUC_{0-24} for ganciclovir in pediatric patients dosed using various ganciclovir dosing regimens for the prevention and treatment of CMV infection (1,473 data records); target AUC_{0-24} range is 80–120 µg · hour/mL

	i.v. ganciclovir dosing		
	5 mg/kg b.i.d.	5 mg/kg 4 times q.d.	mg = 3 × BSA × CrCLS b.i.d.
Age 0–16 years (*n* = 1,473), AUC_{0-24} (median)	36.4	72.7	110.8
< 80 µg · hour/mL, *n* (%)	1,439 (98)	878 (59)	191 (13)
80–120 µg · hour/mL, *n* (%)	32 (2.2)	457 (31)	741 (50)
> 120 µg · hour/mL, *n* (%)	2 (< 1)	140 (10)	541 (37)
Age < 4 months (*n* = 781), AUC_{0-24} (median)	34.8	69.5	111.2
< 80 µg · hour/mL, *n* (%)	777 (99)	529 (68)	89 (11)
80–120 µg · hour/mL, *n* (%)	4 (< 1)	218 (28)	398 (51)
> 120 µg · hour/mL, *n* (%)	0	34 (4)	294 (38)
Age ≥ 4 months ≤ 2 years (*n* = 384), AUC_{0-24} (median)	33.7	67.4	113.7
< 80 µg · hour/mL, *n* (%)	382 (99)	255 (66)	38 (10)
80–120 µg · hour/mL, *n* (%)	2 (< 1)	116 (30)	195 (51)
> 120 µg · hour/mL, *n* (%)	0	13 (3)	151 (39)
Age > 2 years to < 6 years (*n* = 86), AUC_{0-24} (median)	39.3	78.6	108.7
< 80 µg · hour/mL, *n* (%)	86 (100)	46 (53)	13 (15)
80–120 µg · hour/mL, *n* (%)	0	32 (37)	44 (51)
> 80 µg · hour/mL, *n* (%)	0	8 (9)	29 (34)
Age ≥ 6 years to < 12 years (*n* = 96), AUC_{0-24} (median)	49.5	99.0	102.7
< 80 µg · hour/mL, *n* (%)	83 (86)	29 (30)	23 (24)
80–120 µg · hour/mL, *n* (%)	12 (13)	36 (38)	41 (43)
> 120 µg · hour/mL, *n* (%)	1 (< 1)	31 (32)	32 (33)
Age ≥ 12 years to ≤ 16 years (*n* = 126), AUC_{0-24} (median)	56.3	112.7	102.8
< 80 µg · hour/mL, *n* (%)	111 (88)	17 (13)	28 (22)
80–120 µg · hour/mL, *n* (%)	14 (11)	55 (44)	63 (50)
> 120 µg · hour/mL, *n* (%)	1 (< 1)	54 (43)	35 (28)

AUC_{0-24}, area under the concentration–time curve over 24 hours; BSA, body surface area; CMV, cytomegalovirus; CrCLS, creatinine clearance according to the Schwarz formula; i.v., intravenous.

5 mg/kg b.i.d. in treatment of CMV—in line with international guidelines[18,19]—leads to considerable underexposure in pediatric patients. When using ganciclovir as universal prophylaxis to prevent CMV, there is an established AUC_{0-24} target range of 40–60 µg · hour/mL, which was also used to develop the pediatric dosing algorithm of valganciclovir. Our simulations demonstrate that i.v. ganciclovir at the adult dose of 5 mg/kg q.d. fails to reach the target exposure for the prevention of CMV disease in each pediatric age group from birth to 16 years. Predicted mean ganciclovir exposure in the pediatric population based on ganciclovir dosing using a dosing algorithm based on renal function and BSA (dose in mg = 3 × BSA × CrCLS) achieves the target AUC_{0-24} for the prevention of CMV in most patients across all age groups from birth to 16 years. These levels of exposure are also achieved with the valganciclovir pediatric dosing algorithm and so the safety data available for valganciclovir in pediatric patients from birth provide reassurance regarding dosing pediatric patients with i.v. ganciclovir (dose in mg = 3 × BSA × CrCLS) for the prevention of CMV.

There is no established ganciclovir target AUC_{0-24} for treatment of CMV disease, and valganciclovir is not authorized in this indication. Because adult treatment doses of i.v. ganciclovir are double those for the prevention of CMV, we used an AUC_{0-24} range of 80–120 µg · hour/mL as reference. These levels could rarely be reached in pediatric patients using the adult 5 mg/kg b.i.d. dosing. Although i.v. ganciclovir given at a dose in mg = 3 × BSA × CrCLS b.i.d. would be able to reach these exposure levels in the majority of pediatric patients of all ages, the safety of such an exposure has not been established in this population. Our exposure/safety analysis has shown that the relationship among leukopenia, anemia, neutropenia, and ganciclovir exposure shows a modest increase in adverse event rates with increasing AUC_{0-24} levels above 60 µg · hour/mL. However, a precise prediction of the safety of ganciclovir in pediatric patients at an AUC_{0-24} range of 80–120 µg · hour/mL is not possible due to the limited data available at AUC_{0-24} above 80 µg · hour/mL.
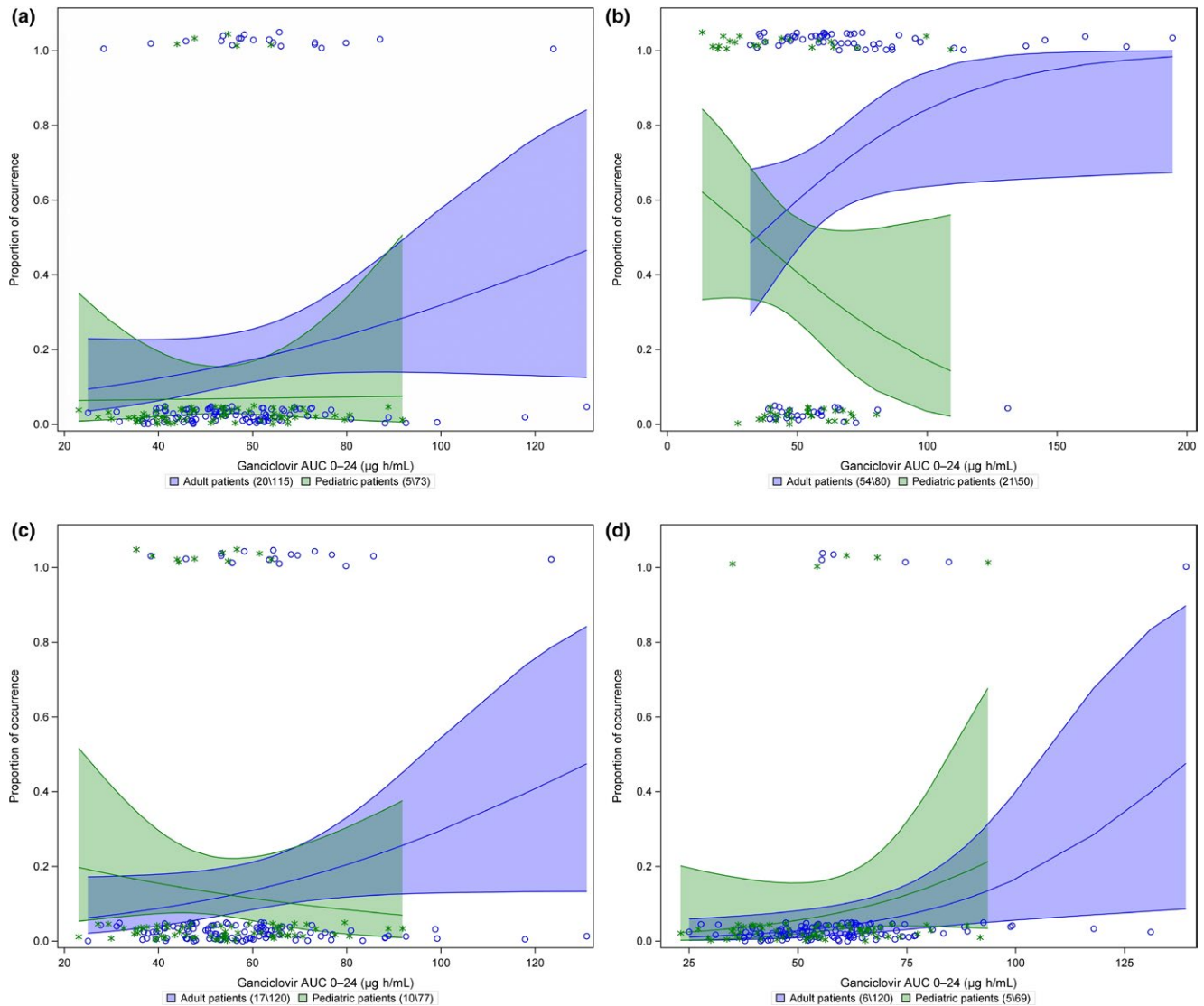
In conclusion, model-based simulations have confirmed that BW-based dosing of ganciclovir and valganciclovir leads to underexposure, particularly in younger pediatric patients. Therapeutic target concentrations of ganciclovir are best achieved when ganciclovir or valganciclovir are dosed by BSA/CrCLS in pediatric patients. Valganciclovir given as dose in mg = 7 × BSA × CrCLS q.d. or i.v. ganciclovir given as dose in mg = 3 × BSA × CrCLS q.d. are equally effective in reaching therapeutic target levels for the prevention of CMV (AUC_{0-24} 40–60 µg · hour/mL) in the majority of pediatric patients. The new pediatric dosing algorithm for ganciclovir, which is solely derived with quantitative methods and supported by PK and safety information from valganciclovir, has been reviewed by the European Medicines Agency (EMA) and has been added to the ganciclovir prescribing information.

Figure 3 Predicted probability of (**a**) leukopenia (white blood cells ≤ 2.5 × 10⁹ cells/L), (**b**) lymphopenia (lymphocyte count ≤ 1.0 × 10⁹ cells/L), (**c**) neutropenia (neutrophil count ≤ 1.0 × 10⁹ cells/L), and (**d**) anemia (hemoglobin < 80 g/L) vs. ganciclovir AUC_{0-24} in pediatric and adult patients. Green stars and blue circles are observed responses in pediatric and adult patients, respectively (vertically jittered for better visualization). The line in the middle of the shaded area shows the logistic regression line and the shaded area represents the 90% confidence intervals of the regression line. AUC_{0-24}, area under the concentration-time curve over 24 hours.

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