

Pharmacokinetics and Safety of Famciclovir in Children with Herpes Simplex or Varicella-Zoster Virus Infection[∇]

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Two multicenter, open-label, single-arm, two-phase studies evaluated single-dose pharmacokinetics and single- and multiple-dose safety of a pediatric oral famciclovir formulation (prodrug of penciclovir) in children aged 1 to 12 years with suspicion or evidence of herpes simplex virus (HSV) or varicella-zoster virus (VZV) infection. Pooled pharmacokinetic data were generated after single doses in 51 participants (~12.5 mg/kg of body weight [BW] for children weighing <40 kg and 500 mg for children weighing ≥40 kg). The average systemic exposure to penciclovir was similar (6- to 12-year-olds) or slightly lower (1- to <6-year-olds) than that in adults receiving a 500-mg dose of famciclovir (historical data). The apparent clearance of penciclovir increased with BW in a nonlinear manner, proportional to BW^{0.696}. An eight-step weight-based dosing regimen was developed to optimize exposure in smaller children and was used in the 7-day multiple-dose safety phases of both studies, which enrolled 100 patients with confirmed/suspected viral infections. Twenty-six of 47 (55.3%) HSV-infected patients who received famciclovir twice a day and 24 of 53 (45.3%) VZV-infected patients who received famciclovir three times a day experienced at least one adverse event. Most adverse events were gastrointestinal in nature. Exploratory analysis following 7-day famciclovir dosing regimen showed resolution of symptoms in most children with active HSV (19/21 [90.5%]) or VZV disease (49/53 [92.5%]). Famciclovir formulation (sprinkle capsules in OraSweet) was acceptable to participants/caregivers. In summary, we present a weight-adjusted dosing schedule for children that achieves systemic exposures similar to those for adults given the 500-mg dose.

Intravenous and high-dose oral acyclovir has been the gold standard for many children requiring treatment and/or prevention of herpes simplex virus (HSV) and varicella-zoster virus (VZV) infections (3, 14, 15, 25). However, intravenous acyclovir requires hospitalization, and oral acyclovir has limited bioavailability, necessitating frequent dosing, and may not provide maximum therapeutic benefit especially in immunocompromised hosts requiring higher plasma drug levels (22). It is therefore desirable to identify more pharmacokinetically appealing therapies for children with conditions caused by HSV or VZV infections. Alternative therapies for treating herpesvirus infections have become available over the last decade, including valacyclovir and famciclovir (5, 18), but only acyclovir is currently approved for pediatric use in many countries.

Penciclovir, a nucleoside analogue, possesses potent *in vitro* antiviral activity against HSV types 1 and 2 and VZV (21). Famciclovir, the oral prodrug of penciclovir, is currently approved for the treatment of herpes zoster and herpes labialis, treatment or suppression of genital herpes in immunocompetent adult patients, and treatment of HSV infections and herpes zoster in immunocompromised adults. Although pharma-

cokinetic and safety data for famciclovir have been reported for adults (7, 11, 12, 18), there has been limited pharmacokinetic information in children. Because effective treatment requires attaining a therapeutic target concentration, determination of famciclovir's pharmacokinetic profile in pediatric patients is essential.

This paper describes the findings of two studies in children, ages 1 to 12 years, with confirmed or suspected HSV or VZV infection treated with a new oral pediatric formulation of famciclovir (i.e., "sprinkle" hard gelatin capsules containing famciclovir mixed with OraSweet). The initial section of this paper describes the pharmacokinetic and safety data following a single famciclovir dose. The subsequent section summarizes the multiple-dose regimen phase in order to evaluate the safety and exploratory efficacy after administration of famciclovir for 7 days.

MATERIALS AND METHODS

Study overview and design. Two multicountry, multicenter, open-label, single-arm studies were conducted. The two studies were identical in design, differing only in the viral infection being treated and dose frequency in the multiple-dose phase. The studies consisted of two phases (a single-dose phase and a multiple-dose phase). Pharmacokinetic data following single-dose administration (the first phase) were evaluated and used to define the multiple-dose famciclovir regimen. The second phase of each study evaluated the safety/tolerability of the famciclovir pediatric formulation and its efficacy in treating active HSV or VZV disease. The single-dose pharmacokinetic and safety/tolerability data from the two stud-

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ies were pooled. Multiple-dose safety data from each of the studies are presented separately, as the famciclovir daily dosage regimens for HSV- and VZV-infected patients differ.

Approval of the study protocols and consent forms was obtained from each investigator's independent ethics committee or institutional review board, and all study activities were conducted in accordance with good clinical practice and the Declaration of Helsinki. Written informed consent was provided by the parent/legal guardian; assent was obtained from the participant, if appropriate.

Study population. For each phase of the study, participants were enrolled and stratified by age (cohort 1, 1 to <2 years; cohort 2, 2 to <6 years; and cohort 3, 6 to \leq 12 years).

The primary inclusion criteria included clinical or laboratory evidence suggestive of HSV or VZV infection. Participants with latent or suspected HSV infection were allowed entry into the study if they were candidates for antiviral therapy.

Key exclusion criteria included an inability to swallow medication; history of any condition that could affect drug absorption, distribution, metabolism, or excretion; hepatic abnormalities (aspartate aminotransferase or alanine transaminase level greater than three times the upper limit of normal [ULN] or total bilirubin level greater than twice the ULN) or renal abnormalities (serum creatinine level greater than the ULN); absolute white blood cell count of $<4,000/\text{mm}^3$; platelet count of $<50,000/\text{mm}^3$; hemoglobin level of $<7 \text{ gm/dl}$; or a significant blood volume loss ($>3\%$ of calculated blood volume) in the previous 30 days. Children with a body weight (BW) of $<9 \text{ kg}$ were excluded from the multiple-dose phase of each study. Probenecid was prohibited due to its effects on renal physiology and because it might elevate plasma levels of penciclovir.

Study and concomitant medications. Famciclovir was provided as 25-mg and 100-mg sprinkle capsules. The contents of the appropriate number of capsules were mixed with 5 ml of OraSweet just prior to dosing and administered within 30 min. In the single-dose phase, the participant's intake of food and beverages was restricted, and famciclovir dosing was supervised by study site personnel. For participants aged 1 to <2 years, administration of up to 90 ml (3 oz) of one of the following was permitted up to 1 h prior to dosing: breast milk, formula, or a suitable milk substitute. Normal feeding was allowed 1 h postdose. For participants aged 2 to \leq 12 years, the intake of foods and beverages was prohibited from 2 h predose until 2 h postdose. In the multiple-dose phase of the studies, study medication could be taken without regard to food or beverage consumption. For both phases of the study, unrestricted intake of water was allowed.

Single-dose phase. A dose of 12.5 mg of famciclovir/kg of BW was targeted (i.e., the dose closest to 12.5 mg/kg using 25-mg and 100-mg sprinkle capsules was given) with a maximum dose of 500 mg for participants weighing $\geq 40 \text{ kg}$. The weight-adjusted dose of 12.5-mg/kg dose was chosen based on a priori population pharmacokinetic modeling using adult and limited pediatric data and simulation approaches aiming to obtain similar systemic exposure to penciclovir in children as that obtained after a single dose of 500 mg of famciclovir in adults.

A minimum 12-h washout period prior to study medication administration was recommended for participants receiving oral, intravenous, or topical antihyperp therapy. However, when medical need dictated, concomitant use of other antiviral medications was allowed.

Multiple-dose phase. Patients with known or suspected HSV infection were dosed twice daily (b.i.d.), and those with presumed VZV infection were dosed three times daily (t.i.d.) for 7 days. Based on the pharmacokinetic results of the single-dose phase, the linear dosing scheme (12.5 mg/kg) was revised. Accordingly, an eight-step dosage schedule based on weight was designed to simplify dosing and at the same time provide systemic exposures in pediatric patients similar to those in a 70-kg adult treated with the standard famciclovir dose of 500 mg, which has been demonstrated to be safe and effective in adults. The maximum single dose was 500 mg for children weighing $\geq 40 \text{ kg}$.

Pharmacokinetic evaluation. Blood (1 ml) was collected predose and 1, 2, 3, 4, and 5 h after administration of famciclovir using tubes containing EDTA as the anticoagulant. Plasma was separated using centrifugation and stored at -20°C until analysis. Penciclovir and 6-deoxypenciclovir (an inactive metabolite of famciclovir and the precursor of the active metabolite penciclovir [7, 18]) concentrations in plasma were determined by liquid chromatography/tandem mass spectrometry. The limit of quantification was 0.15 $\mu\text{g/ml}$ for both compounds.

Safety/tolerability and acceptability evaluation. In the single-dose phase, participants were evaluated for safety/tolerability at 8 and 24 h after dosing and with a follow-up telephone call 7 days postdose. In the multiple-dose phase, patients had safety assessments via phone calls on days 2 and 5, a clinic visit for physical examination and laboratory assessment on day 8 (12 to 24 h after the last dose), and a follow-up telephone call 7 days after the last dose (day 15). Clinical laboratory (e.g., hematology, clinical chemistry) tests were performed for all

patients at screening and on day 8 after completion of therapy; some patients also had evaluations on days 2 to 5 and day 15 if a clinic visit occurred.

Safety assessments consisted of monitoring and recording all adverse events (AEs), serious AEs, physical examination, and vital sign measurements. For the multiple-dose phase of each study, end-of-treatment laboratory tests (routine hematology and clinical chemistry) were obtained, and toxicity shifts from baseline to posttreatment were recorded.

Patients rated the acceptability of the famciclovir pediatric formulation taken after the single dose and the first, second, and last doses of the multiple-dose regimen. The taste of the famciclovir pediatric formulation was evaluated immediately after swallowing the study medication and then 2 to 5 min later using a modified, five-point facial hedonic scale (1, 16). Patients of ≥ 5 years of age were asked to complete the questionnaire themselves, while parents/legal guardians completed the questionnaire for patients 1 to <5 years of age and for older patients if necessary. In addition to the hedonic scale, caregivers also provided a study medication acceptability response (i.e., how well the child accepted the medication) for each patient.

Exploratory efficacy evaluation. For the multiple-dose phase of each study, patients were assessed by the investigator at baseline for the presence of HSV or VZV infection-related symptoms, lesions, and presence/absence of disease complications. The severity of active disease, if present, was graded by the investigator as mild, moderate, or severe. At each patient's completion of the study, the investigator assessed whether disease had resolved, improved, remained similar, or worsened compared to baseline.

Pharmacokinetic analysis. Plasma drug concentration-time data were used to calculate the following pharmacokinetic parameters of penciclovir: C_{max} (maximum concentration), T_{max} (time to C_{max}), $\text{AUC}_{0-T_{\text{last}}}$ (area under the plasma drug concentration-time curve from time zero to the time of the last quantifiable concentration [C_{last}]), $\text{AUC}_{0-\infty}$ (AUC from time zero to infinity), $t_{1/2}$ (apparent terminal elimination half-life), and CL/F (apparent oral clearance). Calculations were performed in WinNonlin (Pharsight Corporation, Mountain View, CA) using noncompartmental methods. $\text{AUC}_{0-T_{\text{last}}}$ was calculated by the linear trapezoidal rule as follows: $\text{AUC}_{0-\infty} = \text{AUC}_{0-T_{\text{last}}} + C_{\text{last}}/\lambda_z$, where λ_z is the apparent elimination rate constant estimated by linear regression analysis of the terminal portion of the log-linear plasma drug concentration-time curve; $t_{1/2} = \ln 2/\lambda_z$; and $\text{CL/F} = \text{dose of famciclovir} \times 0.7884/\text{AUC}_{0-\infty}$, where 0.7884 is the ratio of the molecular weight of penciclovir (253.3 g/mol) to famciclovir (321.3 g/mol). The relationship between CL/F and BW was evaluated by fitting an empirical power model ($\text{CL/F} = A \times \text{BW}^B$) to the data.

Assuming dose proportionality of systemic exposure (12), exposure parameters (C_{max} , $\text{AUC}_{0-T_{\text{last}}}$, and $\text{AUC}_{0-\infty}$) of penciclovir were predicted for the "optimized" doses to be given in the multiple-dose phase by multiplying the parameters obtained in the single-dose phase with the ratios of "optimized" dose to the dose given in the single-dose phase.

Sample size and statistical methods. For the single-dose pharmacokinetic phase, 26 participants per study were planned (i.e., HSV- and VZV-infected participants) with a sample size of 6 to 12 participants per cohort (depending on age group) based on common practices for pharmacokinetic studies in pediatric participants. Simulation analyses predicted that a sample size of 26 participants for the single-dose phase would allow apparent clearance of penciclovir to be predicted with a precision of approximately 20%. For the multiple-dose safety phase, the sample size consisted of approximately 50 patients in each of the HSV- and VZV-infected cohorts (100 total) based on the assumption that if a specific AE was not observed in 50 patients, one could exclude an incidence of $>6\%$ for this event (based on the 95% confidence interval for the rate).

Descriptive summaries of demographics, medical history, pharmacokinetics, safety, and efficacy data, as well as medication acceptability were provided. Safety and efficacy data were analyzed by PRA International, using SAS 9.1.3. No inferential analyses were performed.

RESULTS

Participants. The single-dose pharmacokinetic and safety phase of the pooled studies enrolled 51 participants aged 1 to 12 years (25 HSV-infected and 26 VZV-infected participants; Table 1). All participants completed this phase and comprised both the pharmacokinetic and safety (intent-to-treat) populations. The multiple-dose safety phase of both studies enrolled 100 patients with confirmed or suspected viral infections (47 HSV-infected and 53 VZV-infected patients; Table 2); 1 HSV-

TABLE 1. Demographic and baseline characteristics by age group for pooled single-dose phase (safety and pharmacokinetic population)

Characteristic	No. of participants (%) or parameter value (range)			
	Cohort 1 (1 to <2 yr) (n = 10)	Cohort 2 (2 to <6 yr) (n = 24)	Cohort 3 (6 to ≤12 yr) (n = 17)	Total (all cohorts) (n = 51)
HSV infection	4 (40.0)	13 (54.2)	8 (47.1)	25 (49.0)
VZV infection	6 (60.0)	11 (45.8)	9 (52.9)	26 (51.0)
Immunocompromised	0 (0)	1 (4.2)	2 (11.8)	3 (5.9)
Male	5 (50.0)	9 (37.5)	10 (58.8)	24 (47.1)
Age, yr [median (range)]	1.0	3.5 (2–5)	10.0 (6–11)	4.0 (1–11)
Race				
Caucasian	2 (20.0)	7 (29.2)	4 (23.5)	13 (25.5)
Black	2 (20.0)	9 (37.5)	4 (23.5)	15 (29.4)
Other	6 (60.0)	8 (33.3)	9 (52.9)	23 (45.1)
Ethnicity				
Hispanic/Latino	4 (40.0)	13 (54.2)	6 (35.3)	23 (45.1)
Other	6 (60.0)	9 (37.5)	11 (64.7)	26 (51.0)
Missing	0 (0)	2 (8.3)	0 (0)	2 (3.9)
Wt, kg [median (range)]	10.1 (7.0–13.8)	17.1 (12.0–25.0)	33.2 (17.0–61.7)	17.4 (7.0–61.7)

infected patient and 5 VZV-infected patients did not complete the study (3 protocol deviations, 2 adverse events, and 1 patient lost to follow-up). All 100 patients took study medication and comprised the safety population. Active clinical disease was reported for 21 HSV-infected patients at enrollment (all mucocutaneous disease) versus 26 with a past history of clinical disease (i.e., latent infection). Laboratory confirmation of HSV

was documented for 22 of 47 patients (10 with active infection versus 12 with latent infection) as follows: PCR, 6 patients; viral culture, 6 patients; and serology, 10 patients. For VZV-infected patients, all 53 had clinically active disease (all chicken pox; none had herpes zoster); 7 had laboratory confirmation (5 by PCR and 2 by culture). In the single-dose phase, three HSV-infected and four VZV-infected participants took con-

TABLE 2. Demographic and baseline characteristics by age group for multiple-dose phase (safety population)^a

Group and characteristic	No. of patients (%) or parameter value (range)			
	Cohort 1 (1 to <2 yr)	Cohort 2 (2 to <6 yr)	Cohort 3 (6 to ≤12 yr)	Total (all cohorts)
HSV-infected group				
Active disease	11 (84.6)	5 (31.3)	5 (27.8)	21 (44.7)
Mild	4 (30.8)	2 (12.5)	4 (22.2)	10 (21.3)
Moderate	7 (53.8)	3 (18.8)	1 (5.6)	11 (23.4)
Immunocompromised	1 (7.7)	0 (0)	1 (5.6)	2 (4.3)
Male	6 (46.2)	6 (37.5)	11 (61.1)	23 (48.9)
Age, yr [median (range)]	1.0	4.0 (2–5)	10.0 (6–12)	4.0 (1–12)
Race				
Caucasian	3 (23.1)	9 (56.3)	9 (50.0)	21 (44.7)
Black	2 (15.4)	4 (25.0)	4 (22.2)	10 (21.3)
Other	8 (61.5)	3 (18.8)	5 (27.8)	16 (34.0)
Ethnicity				
Hispanic/Latino	9 (69.2)	4 (25.0)	3 (16.7)	16 (34.0)
Other	4 (30.8)	12 (75.0)	15 (83.3)	31 (66.0)
Wt, kg [median (range)]	11.3 (9.6–13.0)	16.3 (10.1–21.8)	31.2 (18.6–75.1)	17.4 (9.6–75.1)
Receiving concomitant acyclovir therapy	1 (7.7)	1 (6.3)	1 (5.6)	3 (6.4)
VZV-infected group				
Active disease	18 (100)	19 (100)	16 (100)	53 (100)
Mild	4 (22.2)	5 (26.3)	1 (6.3)	10 (18.9)
Moderate	12 (66.7)	9 (47.4)	12 (75.0)	33 (62.3)
Severe	2 (11.1)	5 (26.3)	3 (18.8)	10 (18.9)
Immunocompromised	0 (0)	0 (0)	0 (0)	0 (0)
Male	8 (44.4)	14 (73.7)	5 (31.3)	27 (50.9)
Age, yr [median (range)]	1.0	4.0 (2–5)	8.5 (7–11)	3.0 (1–11)
Race				
Caucasian	11 (61.1)	11 (57.9)	10 (62.5)	32 (60.4)
Other	7 (38.9)	8 (42.1)	6 (37.5)	21 (39.6)
Hispanic/Latino ethnicity	18 (100)	19 (100)	16 (100)	53 (100)
Wt, kg [median (range)]	11.0 (9.0–13.0)	16.0 (11.5–19.8)	31.7 (20.3–47.8)	15.7 (9.0–47.8)
Receiving concomitant acyclovir therapy	0	0	1 (6.3)	1 (1.9)

^a The number of patients in the various cohorts for the HSV-infected and VZV-infected groups were as follows: for the HSV-infected group, cohort 1 (n = 13), cohort 2 (n = 16), cohort 3 (n = 18), and total (n = 47); for the VZV-infected group, cohort 1 (n = 18), cohort 2 (n = 19), cohort 3 (n = 16), and total (n = 53).

TABLE 3. Pharmacokinetic parameters of penciclovir in pediatric participants (pooled single-dose phase) compared with historical data in healthy adult volunteers after a single dose of famciclovir

Pharmacokinetic parameter	Value [mean \pm SD (range)] ^a for pharmacokinetic parameter for:			
	Cohort 1 (1 to <2 yr) (n = 10)	Cohort 2 (2 to <6 yr) (n = 24)	Cohort 3 (6 to \leq 12 yr) (n = 17)	Adults (healthy volunteers) ^b (n = 24)
T_{\max} (h) ^c	1.08 (1.00–1.50)	1.07 (0.93–4.03)	1.00 (1.00–2.07)	0.75 (0.50–1.50)
C_{\max} (μ g/ml)	3.06 \pm 1.06 (1.42–5.08)	2.78 \pm 0.93 ^d (0.42–4.86)	3.41 \pm 0.96 (1.52–5.41)	3.45 \pm 0.82 (1.88–5.82)
$AUC_{0-7\text{last}}$ (μ g/ml \cdot h)	6.52 \pm 2.39 (3.02–11.97)	6.31 \pm 1.84 ^d (1.63–11.85)	7.98 \pm 1.64 (4.72–11.41)	8.54 \pm (1.70 (5.80–11.40)
$AUC_{0-\infty}$ (μ g/ml \cdot h)	7.16 \pm 2.75 (3.43–13.74)	7.23 \pm 1.90 ^{d,e} (3.19–13.20)	9.33 \pm 1.84 (6.49–13.65)	8.94 \pm 1.69 (6.31–11.84)
$t_{1/2}$ (h) ^f	1.20 \pm 0.16 (1.01–1.53)	1.28 \pm 0.21 ^d (0.83–1.70)	1.62 \pm 0.26 (1.16–2.11)	1.89 \pm 0.28 (1.27–2.39)
CL/F (liter/h)	16.7 \pm 6.8 (5.7–28.8)	24.6 \pm 4.3 ^d (17.0–33.3)	34.7 \pm 11.6 (16.6–60.8)	45.7 \pm 9.0 (33.3–62.5)
BW-adjusted dose (mg/kg)	13.0 \pm 0.8 (12.0–14.3)	12.8 \pm 1.3 (7.3–13.7)	12.2 \pm 1.3 (8.1–13.2)	6.7 \pm 0.8 (5.8–8.7)

^a Each value is the mean \pm standard deviation (range) unless specified otherwise.

^b Data from study in healthy volunteers who fasted (mean age, 34 \pm 7 years; mean BW, 75.6 \pm 7.9 kg) following a single oral dose of famciclovir 500 mg (data on file at Novartis).

^c T_{\max} values reported as median (range).

^d Mean \pm SD without the one participant who received an incorrect dose (125 mg instead of 225 mg): C_{\max} (n = 23), 2.83 \pm 0.91 μ g/ml; $AUC_{0-7\text{last}}$ (n = 23), 6.46 \pm 1.73 μ g/ml \cdot h; $AUC_{0-\infty}$ (n = 19), 7.44 \pm 1.69 μ g/ml \cdot h.

^e n = 20.

^f Half-life.

comitant acyclovir after the start of study medication, as did four patients (three HSV-infected patients and one VZV-infected patient) in the multiple-dose phase.

Single-dose pharmacokinetics. Data from 51 participants (25 HSV-infected and 26 VZV-infected participants) were available for the pooled pharmacokinetic analysis (10 in cohort 1 [1- to <2-year age group], 24 in cohort 2 [2- to <6-year age group], and 17 in cohort 3 [6- to 12-year age group]). The mean famciclovir dose administered to cohorts 1, 2, and 3 was 13.0 mg/kg, 12.8 mg/kg, and 12.2 mg/kg, respectively (Table 3); the mean dose across all 51 participants was 12.6 mg/kg.

Mean plasma drug concentration-versus-time profiles of penciclovir and 6-deoxypenciclovir for the three age groups are presented in Fig. 1. Concentrations of 6-deoxypenciclovir were consistently lower than those of penciclovir and were measurable only up to 1 or 2 h postdose in most children. For all three age groups, the mean C_{\max} of penciclovir occurred approximately 1 h postdose. Penciclovir pharmacokinetic parameters for the pooled single-dose phase are summarized in Table 3 and compared to historical data for adult healthy volunteers given a single 500-mg dose of famciclovir. The BW-adjusted dose of famciclovir in the three age groups of children (mean of 12.2 to 13.0 mg/kg) was about two times higher than the adult dose (6.7 mg/kg). With these doses, the mean exposure metrics C_{\max} , $AUC_{0-7\text{last}}$, and $AUC_{0-\infty}$ of penciclovir in the children were similar (6- to 12-year age cohort) or slightly below (1- to <2-year and 2- to <6-year age cohorts) those observed in adults administered 500 mg.

One participant in the 2- to <6-year age group received an incorrect dose (i.e., was given 125 mg but should have received 225 mg). Thus, the dose-related parameters C_{\max} , $AUC_{0-7\text{last}}$, and $AUC_{0-\infty}$ in this age group (cohort 2) were also summarized after exclusion of this subject (see footnote *d* in Table 3). These mean values are slightly higher than the means for all participants of this age group, reflecting that systemic exposure to penciclovir was comparatively low in the underdosed participant.

The relationship between $AUC_{0-\infty}$ of penciclovir and BW in children is shown in the upper panel of Fig. 2. With the linear

dosing algorithm of 12.5 mg/kg used in the single-dose phase, exposure in terms of $AUC_{0-\infty}$ appeared to be lower in about half of the smaller children in the 1- to <2-year and 2- to <6-year age groups compared to the larger children in the 6-

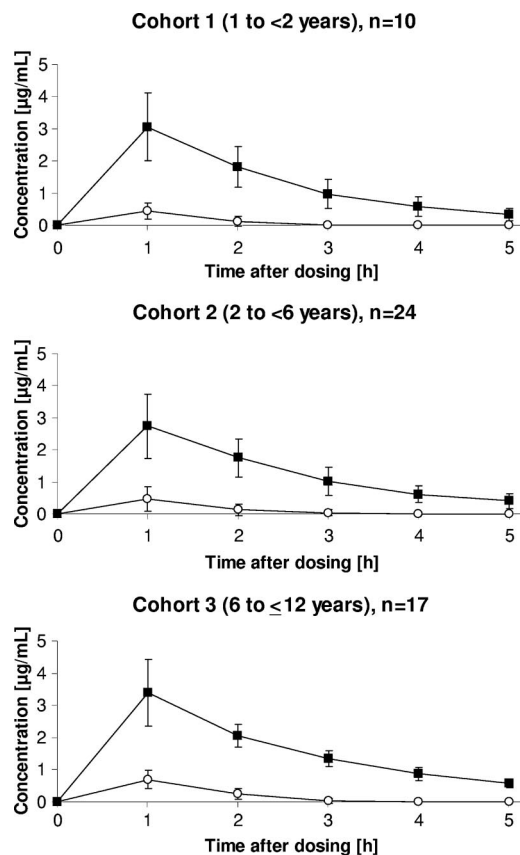


FIG. 1. Plasma drug concentration-time profiles of penciclovir and 6-deoxypenciclovir after a single oral famciclovir dose administered to children stratified by age. Values are means \pm standard deviations (error bars). Symbols: ■, penciclovir; ○, 6-deoxypenciclovir.

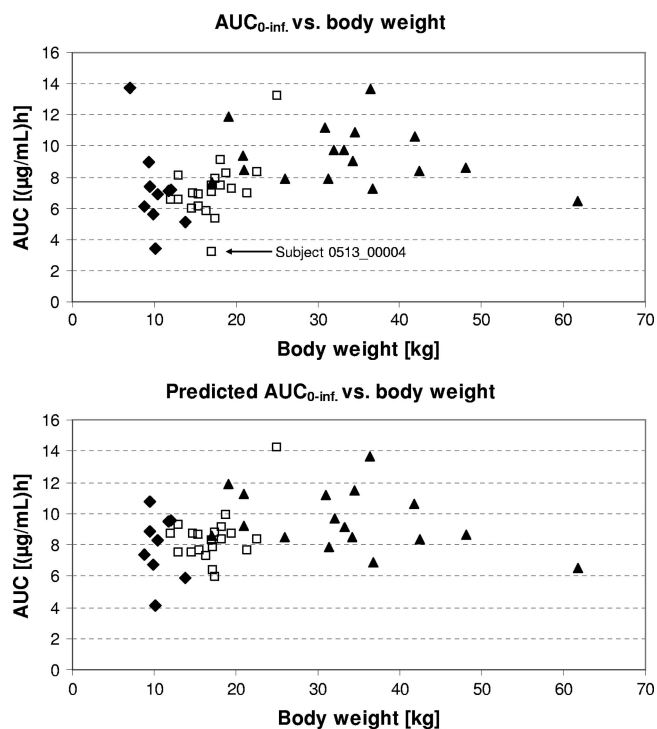


FIG. 2. Relationship between $AUC_{0-\infty}$ of penciclovir and body weight. (Upper) Observed $AUC_{0-\infty}$ ($AUC_{0-inf.}$) after a single oral famciclovir dose. Participant 0513-00004 received an incorrect dose (i.e., 125 mg instead of the scheduled dose of 225 mg). (Lower) $AUC_{0-\infty}$ predicted for the optimized doses according to the dosing scheme used in the second phase of both studies. Symbols: \blacklozenge , cohort 1 (1 to <2 year olds); \square , cohort 2 (2 to <6 year olds); \blacktriangle , cohort 3 (6 to ≤ 12 year olds).

to ≤ 12 -year age group. The participant in the 2- to <6-year age group who received a lower dose than planned defines the lower limit of the $AUC_{0-\infty}$ range. Clearance of penciclovir also increased with age and BW. The relationship between CL/F (liter/h) of penciclovir and BW (kg) is shown in Fig. 3, together with the fit of an empirical power model to the data. The fitted model is as follows: $CL/F = 3.162 \times BW^{0.696}$. Elimination half-life was shorter in younger children (1- to <6-year-old children), approximately 1.2 h, and increased in the 6- to ≤ 12 -year-old children (1.6 h), approaching the values observed for healthy adult volunteers (1.9 h).

Single-dose safety/tolerability and acceptability. Three participants (all in the HSV-infected group) reported at least one AE: two in the 2- to <6-year age group and one in the 6- to ≤ 12 -year age group. The AEs included one headache, one upper abdominal pain, one furuncle, and one rash. None of the AEs were considered to be drug related by the investigator. There were no discontinuations for safety reasons.

Most children liked the taste of the famciclovir formulation administered, with acceptance more favorable 2 to 5 min after swallowing the study medication compared to immediately after swallowing. Overall, the caregivers considered famciclovir pediatric formulation to be well or very well accepted in the majority of children (34 of 51 [67%]). However, the caregivers reported that 15.7% (8 of 51) of participants disliked the taste of the medication.

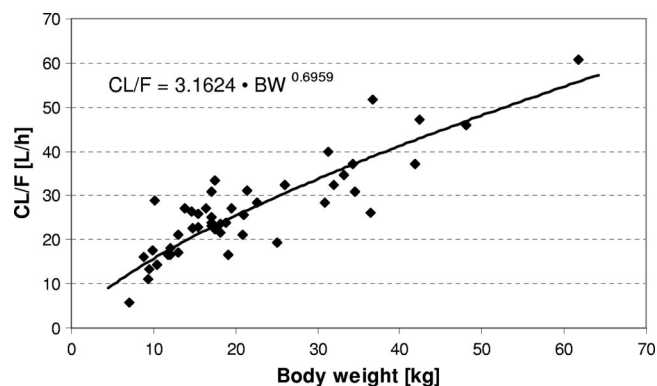


FIG. 3. Relationship between CL/F of penciclovir and body weight. The line shows the fit of an empirical power model ($CL/F = A \times BW^B$) to the data; the equation of the fitted model is given.

Predicted exposure pharmacokinetics following optimized doses. The pharmacokinetic data from the single-dose phase were used to derive a simplified eight-step weight-based dosing scheme that would address the observed trend for lower exposures in children below 6 years of age when using a linear dosing scheme (12.5 mg/kg) and provide all children with exposures similar to those of an adult given 500 mg of famciclovir. “Predicted” exposure parameters for all participants completing the single-dose phase were calculated assuming that these participants would have received the “optimized” doses based on the simplified eight-step dosing scheme. The lower panel of Fig. 2 shows the predicted individual $AUC_{0-\infty}$ values plotted against BW. These calculations revealed that the average exposure increased slightly in the younger children (1- to <2-year and 2- to <6-year age groups) (Table 4) compared to the exposure observed with the linear dosing scheme (Table 3). Little change was seen for the 6- to ≤ 12 -year-old children (Table 4).

Multiple-dose safety/tolerability and acceptability. Because patients with HSV and VZV infections were treated with different daily dose regimens of famciclovir (i.e., b.i.d. versus t.i.d.), the risk of AEs may differ for the two populations of children. For HSV-infected children, the mean BW-adjusted daily dose of famciclovir was 30.9 mg/kg for 1- to <2-year-olds, 27.6 mg/kg for 2- to <6-year-olds, and 23.5 mg/kg for 6- to ≤ 12 -year-olds with an overall mean exposure of 7.3 days. Adherence to the study medication was excellent; 97.7% of patients took all 14 prescribed doses. For VZV-infected children, the mean BW-adjusted daily dose of famciclovir was 40.8 mg/kg for 1- to <2-year-olds, 40.6 mg/kg for 2- to <6-year-olds, and 35.5 mg/kg for 6- to ≤ 12 -year-olds with an overall mean exposure of 7.3 days; 81.1% of patients took all 21 prescribed doses.

Twenty-six of 47 (55.3%) HSV-infected patients receiving the twice-daily famciclovir regimen experienced at least one AE. The most frequent AEs were vomiting (five patients [10.6%]), diarrhea and headache (each occurring in four patients [8.5%]), and nausea (three patients [6.4%]) (Table 5). All headache AEs occurred in the 6- to ≤ 12 -year age group. AEs that were considered drug related by the investigator occurred in ≤ 2 patients for any type of AE and age group and included nausea, flatulence, vomiting, clumsiness, and pruritus.

TABLE 4. "Predicted" exposure parameters for penciclovir by age group for pooled single-dose phase following optimized famciclovir doses based on eight-step dosing scheme

Pharmacokinetic parameter	Value [mean ± SD (range)] for pharmacokinetic parameter for:		
	Cohort 1 (1 to <2 yr) (n = 9 ^a)	Cohort 2 (2 to <6 yr) (n = 24)	Cohort 3 (6 to ≤12 yr) (n = 17)
C _{max} (µg/ml)	3.48 ± 1.06 (1.70–5.36)	3.28 ± 1.00 (0.48–5.23)	3.48 ± 0.97 (1.52–5.41)
AUC _{0–T_{last}} (µg/ml · h)	7.26 ± 1.98 (3.62–10.14)	7.40 ± 1.80 (1.86–7.40)	8.15 ± 1.73 (4.72–11.41)
AUC _{0–∞} (µg/ml · h)	7.90 ± 2.09 (4.12–10.79)	8.44 ± 1.66 ^b (5.92–14.22)	9.52 ± 1.90 (6.49–13.65)

^a Because dosing scheme for phase 2 of each study excluded participants with a body weight (BW) of <9 kg, no exposure parameters were predicted for one participant (BW of 7.0 kg) enrolled in the single-dose phase.
^b n = 20.

A total of 24 of 53 (45.3%) VZV-infected patients given the t.i.d. famciclovir regimen experienced an AE. The most common AEs were diarrhea (6 patients [11.3%]), vomiting (5 patients [9.4%]), and pyrexia (4 patients [7.5%]) (Table 5). All vomiting AEs were reported for the 1- to <2-year age group. The most frequent drug-related AEs were diarrhea and vomiting. There were no deaths or serious AEs. In children with HSV, there were no discontinuations due to AEs. Two VZV-infected patients (9- and 11-year-old males) discontinued study medication due to treatment-related abdominal pain of moderate severity on day 7. Both events persisted for 4 days.

There were no meaningful changes from baseline in vital signs. For both patient groups, there were no clinically relevant changes in hematology or chemistry parameters (values ≥ grade 2 toxicity). No patient had a shift from normal baseline values to grade 2 toxicity or higher after initiation of study drug for any hematology or chemistry parameter, with the exception of one HSV-infected patient whose normal serum sodium value at baseline shifted to grade 2 toxicity after initiation of study drug (decreased from 137 to 134 mmol/liter).

The majority of HSV-infected patients (or their caregivers) rated the taste of the famciclovir formulation as neutral (i.e.,

neither good nor bad): 53.2% at day 1 after the first dose in the clinic, 61.7% at day 1 after the first dose at home, and 63.8% at day 8 after the last dose at home. Most of the VZV-infected children rated the taste of the formulation as neutral, well liked, or very well liked: 69.8% at day 1 after the first dose in the clinic, 56.6% at day 1 after the first dose at home, and 69.8% at day 8 after the last dose at home. For both HSV-infected and VZV-infected patient populations combined, the taste of the formulation was more pleasant or liked 2 to 5 min after swallowing the study medication than immediately after swallowing. Overall, caregivers indicated that nearly half the children infected with either HSV or VZV considered famciclovir pediatric formulation to be well or very well accepted.

Exploratory efficacy with multiple dosing. Twenty-one patients had active HSV disease at baseline. Following a 7-day famciclovir b.i.d. regimen, symptoms were resolved in the majority of children (19/21 [90.5%]). In two patients whose symptoms did not resolve (one in the 1- to <2-year age group and one in the 2- to <6-year age group), the disease was mild and reportedly improved. Fifty-three patients had active VZV disease at baseline. Following a 7-day famciclovir t.i.d. regimen, symptoms were resolved in the majority of patients (49/53

TABLE 5. Number of patients with adverse events occurring in ≥3% of patients in multiple-dose phase (safety population)^a

Group and AE	No. (%) of patients with AE in:			
	Cohort 1 (1 to <2 yr)	Cohort 2 (2 to <6 yr)	Cohort 3 (6 to ≤12 yr)	Total (all cohorts)
HSV-infected group				
At least one AE	6 (42.2)	8 (50.0)	12 (66.7)	26 (55.3)
Vomiting	2 (15.4)	1 (6.3)	2 (11.1)	5 (10.6)
Diarrhea	1 (7.7)	1 (6.3)	2 (11.1)	4 (8.5)
Headache	0 (0.0)	0 (0.0)	4 (22.2)	4 (8.5)
Nausea	1 (7.7)	0 (0.0)	2 (11.1)	3 (6.4)
Cough	1 (7.7)	1 (6.3)	1 (5.6)	3 (6.4)
Abdominal pain (upper)	0 (0.0)	1 (6.3)	1 (5.6)	2 (4.3)
Pyrexia	2 (15.4)	0 (0.0)	0 (0.0)	2 (4.3)
VZV-infected group				
At least one AE	7 (38.9)	10 (52.6)	7 (43.8)	24 (45.3)
Diarrhea	2 (11.1)	1 (5.3)	3 (18.8)	6 (11.3)
Vomiting	5 (27.8)	0 (0.0)	0 (0.0)	5 (9.4)
Pyrexia	2 (11.1)	1 (5.3)	1 (6.3)	4 (7.5)
Abdominal pain	0 (0.0)	0 (0.0)	2 (12.5)	2 (3.8)
Nausea	0 (0.0)	1 (5.3)	1 (6.3)	2 (3.8)
Cellulitis	0 (0.0)	1 (5.3)	1 (6.3)	2 (3.8)
Headache	0 (0.0)	0 (0.0)	2 (12.5)	2 (3.8)
Pruritus	1 (5.6)	0 (0.0)	1 (6.3)	2 (3.8)

^a AEs are reported as treatment-emergent events (include all events regardless of drug relatedness). The number of patients in the various cohorts for the HSV-infected and VZV-infected groups were as follows: for the HSV-infected group, cohort 1 (n = 13), cohort 2 (n = 16), cohort 3 (n = 18), and total (n = 47); for VZV-infected group, cohort 1 (n = 18), cohort 2 (n = 19), cohort 3 (n = 16), and total (n = 53).

[92.5%]) and improved in two patients. Only one patient (in the 1- to <2-year age group) had a disease status at the end of therapy that was similar to that at baseline. One additional patient (in the 2- to <6-year age group) developed a VZV-related complication (i.e., impetigo).

DISCUSSION

Although clinical experience with famciclovir in children is limited, the relatively high intracellular concentrations of penciclovir (active drug) combined with its less frequent dosing regimens (b.i.d. or t.i.d.) for HSV/VZV treatment and prophylaxis may provide clinicians and patients with an alternative therapy and allow immunocompetent children to be treated at home (18). Accordingly, the effects of age and weight on the pharmacokinetics of the prodrug famciclovir in children required further assessment in order to ensure adequate penciclovir concentrations for effective treatment of herpesvirus infections. Prior to initiation of the current studies, a population modeling approach was used to characterize the pharmacokinetics of penciclovir and to derive a dosage algorithm for children based on available adult and limited pediatric data. The aim of the dosage algorithm was to ensure that drug exposure in children corresponded to the exposure in adults following a single 500-mg dose of famciclovir, while mitigating the risk that the smallest children would be overdosed. For this reason, dose was scaled on a mg/kg (linear) basis for children with a BW of <40 kg (i.e., 12.5 mg/kg). A dose of 500 mg was to be given to children with a BW of ≥ 40 kg. This dosing algorithm was used in the single-dose pharmacokinetic profiling of the new oral formulation of famciclovir (sprinkle capsules) in children with HSV or VZV.

In the first phase of our study, model-independent comparisons of the systemic exposure metrics (C_{\max} and AUC) of penciclovir in the pediatric population with the adult exposure for a dose of 500 mg famciclovir (historical data) confirmed that the dosage algorithm was successful in attaining exposures that generally did not exceed those observed in adults. Taking $AUC_{0-\infty}$ as the most reliable measure of the extent of exposure and bioavailability of penciclovir, 43 of the 47 individual values in all age groups did not exceed the range seen in a previous adult study (6.31 to 11.84 $\mu\text{g}/\text{ml} \cdot \text{h}$) (data on file at Novartis), and the highest value (13.74 $\mu\text{g}/\text{ml} \cdot \text{h}$) was only 16% above the upper limit of the adult range. Of note, the participant showing the highest exposure was the smallest participant in the current study (weight, 7 kg; <5th percentile for age). Although no AEs were reported for this participant, it was decided to exclude children with a BW of <9 kg from the multiple-dose phase of the study.

The average $AUC_{0-\infty}$ in the 6- to ≤ 12 -year age group (9.33 $\mu\text{g}/\text{ml} \cdot \text{h}$) differed by only 4% from that observed in adults (8.94 $\mu\text{g}/\text{ml} \cdot \text{h}$). However, a trend was apparent in the pediatric data with exposure decreasing with BW in the participants of less than 6 years of age. The mean $AUC_{0-\infty}$ values for both the 1- to <2-year and 2- to <6-year age groups were about 20% lower than in adults.

The analysis of the relationship between the apparent clearance of penciclovir (CL/F) and BW using an empirical power model ($\text{CL}/\text{F} = A \times \text{BW}^B$) gives a BW exponent of 0.696. This is close to 0.75, the typical allometric scaling factor used for

TABLE 6. Theoretical doses of famciclovir to achieve the target exposure in children and optimized doses according to the eight-step dosing scheme used in the multiple-dose phase

BW (kg)	Theoretical dose ^a (mg)	Dose (mg) according to the eight-step dosing scheme
9–11	165–190	150
12–14	202–225	200
15–19	236–278	250
20–24	288–327	300
25–29	337–374	350
30–34	382–417	400
35–39	426–459	450
≥ 40	≥ 467	500

^a Theoretical dose = $3.162 \times \text{BW}^{0.696} \times (\text{AUC}_{0-\infty}/0.7884)$, where $\text{AUC}_{0-\infty}$ defines the target exposure seen in adults after a single 500-mg dose of famciclovir ($\text{AUC}_{0-\infty} = 8.94 \mu\text{g}/\text{ml} \cdot \text{h}$).

scaling clearance-related processes in biology (4, 24). Thus, clearance of penciclovir increased with BW in a nonlinear manner, and the observed trend for decreasing exposure in younger children was to be expected, given the linear dosing algorithm used in this single-dose phase. Subsequent pharmacokinetic analyses and modeling of the single-dose data addressed the underexposure in children with a lower BW and derived an optimized eight-step dosing regimen aiming to slightly increase exposure in younger and smaller children while simplifying the dosing scheme (50-mg steps instead of 25-mg steps). It is noteworthy that predictions of exposure after optimized doses (Table 4), according to the simplified eight-step dosing scheme, showed that average exposure increased slightly in children 1 to <6 years old but was similar for children 6 to ≤ 12 years old. Exposure in individual participants is also predicted to be more homogenous following the optimized doses compared with the exposure obtained in the single-dose phase. These observations provided support for the proposed eight-step multiple-dose regimen, which was utilized in the second phase of the studies.

The derived relationship between CL/F and BW ($\text{CL}/\text{F} = 3.162 \times \text{BW}^{0.696}$) can be used to calculate the dose for a given BW, which should result in the target exposure of 8.94 $\mu\text{g}/\text{ml} \cdot \text{h}$, the mean $\text{AUC}_{0-\infty}$ in adults. Since CL/F is the ratio of dose \times 0.7884 divided by $\text{AUC}_{0-\infty}$, the dose to achieve the target exposure is as follows: dose (mg) = $3.162 \times \text{BW}^{0.696} \times (8.94/0.7884)$. Accordingly, “theoretical” doses for children with BWs between 9 and 40 kg were estimated and compared with the doses of the optimized eight-step dosing scheme (Table 6). Apart from the lowest weight group, the optimized doses are in good agreement with the theoretical doses. For children with BWs between 9 and 11 kg, the optimized dose of 150 mg may still result—on average—in a somewhat lower exposure (as predicted for the 1- to <2-year age group), but this is taken into account to mitigate the risk of overdosing these smaller children.

One participant in the 2- to <6-year age group showed an exceptionally low exposure to penciclovir compared with the other participants in this cohort. The flat concentration-time profile did not allow a full pharmacokinetic evaluation for this participant (i.e., $\text{AUC}_{0-\infty}$ could not be calculated). C_{\max} of penciclovir (0.42 $\mu\text{g}/\text{ml}$), observed at 4 h postdose, was only 15% of the average C_{\max} in this age group. There was no

indication that the formation of penciclovir was affected in this participant. This should have resulted in an increase of the concentration of 6-deoxypenciclovir, the precursor of penciclovir. However, the opposite was seen, with no 6-deoxypenciclovir detected in any sample. Thus, the most likely explanation for the unusual concentration-time profile of penciclovir is an incomplete and delayed absorption of famciclovir in this participant.

In studies of adults, famciclovir was rapidly absorbed and extensively metabolized to the active metabolite, penciclovir (7, 11, 18). The absolute bioavailability of penciclovir from oral famciclovir was 77% compared with intravenous administration of penciclovir (7). 6-Deoxypenciclovir is an intermediate metabolite in the conversion of famciclovir to penciclovir and results from bis-deacetylation of the prodrug. Generally, little or no unchanged famciclovir was detected in plasma, and plasma concentrations of 6-deoxypenciclovir were typically at least threefold less than that of penciclovir and detectable only for a short time period after dosing (12). The latter observation was also seen in our pediatric studies (Fig. 1), indicating that the formation of penciclovir is similar in children and adults. Our analysis showed that BW is the most important covariate for penciclovir exposure in children between 1 and 12 years. This analysis reveals that absorption, biotransformation, and clearance processes of famciclovir/penciclovir appear to be similar in children and adults.

Few oral antiviral options are available for the treatment of herpesvirus infections in children. Famciclovir has several attractive attributes, including an improved pharmacokinetic profile compared with the standard agent, acyclovir, which has been reported to have a low and variable oral bioavailability (approximately 10 to 30%) (6, 8). Valacyclovir, the oral prodrug of acyclovir, has a more favorable pharmacokinetic profile than acyclovir does (10, 23). Yet, unlike the administration of the crushed valacyclovir tablet in standard syrup, which is often associated with an unpleasant taste (9), the taste of the famciclovir pediatric formulation used herein (sprinkle capsules in OraSweet) was liked by most participants. The famciclovir oral formulation was well tolerated in children, with gastrointestinal adverse events reported most commonly, thereby supporting observations in clinical trials with adults (2, 13, 17, 19, 20). Thus, the new pediatric oral formulation of famciclovir for children may be a valuable therapeutic option in clinical practice.

Our exploratory efficacy findings following famciclovir therapy in children with clinical evidence of HSV (i.e., mucocutaneous infections) or VZV (i.e., severe chickenpox) infections suggest that the symptoms were resolved or improved in 90.5% and 92.5% of patients, respectively. There was no dissemination or worsening of disease. Although there was no placebo control in these studies to define a true treatment effect, these results are in line with those observed in adults with other conditions caused by HSV (e.g., genital herpes, herpes labialis) or VZV (e.g., shingles) who received famciclovir therapy (2, 13, 17, 19, 20).

There are certain limitations for the interpretation of the results. Like most prospective studies of pediatric pharmacokinetics, the sample size was relatively small. Because children below 6 years of age are likely to experience some variability in exposure to famciclovir, careful monitoring for lack of disease

progression or untoward effects is recommended. As with any phase I/II study, the safety, tolerability, and acceptability of the new oral famciclovir formulation will need to be confirmed on wider usage. Finally, it must be emphasized that the efficacy results reported for famciclovir in children infected with HSV and VZV are exploratory, as there was no inferential analysis or placebo control. These findings will require validation when more experience is gained, in both immunocompetent and immunocompromised patients.

In summary, we derived from single-dose pharmacokinetic data a safe and well-tolerated eight-step dosage regimen for a new oral famciclovir formulation for administration to children (1 to 12 years old) requiring antiviral therapy. Famciclovir is a potential alternative to acyclovir therapy in pediatric patients because of the higher and more consistent bioavailability and the less frequent dosing than that needed for acyclovir.

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