OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	20-487, [redacted] (Dosing in pediatric patients)
Submission Date:	December 10, 2007
Brand Name:	VALTREX
Generic Name:	Valacyclovir Hydrochloride
Reviewer:	Shirley K. Lu, Ph.D.
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OCP Division:	Division of Clinical Pharmacology 4
OND Division:	DAVP
Sponsor:	GlaxoSmithKline
Submission Type; Code:	505 (b)(1); 1P
Formulation/Strength(s):	Extemporaneous Oral Suspension, 25 mg/mL and 50 mg/mL

Indications and Accompanying Dosing Regimens: (Approved in Adults)		
	Herpes Zoster	1 g TID for 7 days
	Genital Herpes:	
	Initial episode	1 g BID for 10 days
	Recurrent episodes	500 mg BID for 3 days
	Suppressive therapy (immunocompetent)	1 g QD
	Suppressive therapy (alternative dose in immunocompetent adults with ≤9 recurrences/year)	500 mg QD
	Suppressive therapy in HIV (CD4 count ≥100 cells/mm^3)	500 mg BID
	Reduction of transmission for source partner	500 mg QD
	Herpes Labialis (cold sores)	2 g BID for 1 day

(b) (4) [redacted]

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1. Executive Summary

Valacyclovir (VACV, Valtrex®) is the L-valyl ester pro-drug of acyclovir (Zovirax). VACV is approved in adults for the treatment of herpes zoster, genital herpes (initial episodes, recurrent episodes, suppressive therapy, and reduction of transmission), and herpes labialis. VACV is currently approved for use in patients ≥12 years of age for the treatment of herpes labialis.

The sponsor has conducted three studies (HS210914, HS210915, and HS210916) in pediatric subjects to evaluate the pharmacokinetics and safety of a new extemporaneous oral suspension formulation. The overall purpose of these studies was to characterize acyclovir pharmacokinetics after administration of VACV to support dosing for treatment of relevant indications in pediatric patients. In order to obtain regulatory approval of these indications, the proposed doses should achieve acyclovir systemic exposures comparable to historical adult and pediatric exposures following administration of approved doses of either VACV or acyclovir (ACV, Zovirax®) and demonstrate adequate safety at the proposed dose level for the proposed duration of treatment.

A single (b) (4) supplement was originally submitted on December 10, 2007 and included requests (b) (4) for chickenpox in children ages 1-12 years old. (b) (4) S-014 includes the request for the chickenpox indication. This review will consist of an evaluation of the results of two studies (HS210914 and HS210915) that are relevant to the recurrent genital herpes indication request. A review of study HS210916 will be included in the review of S-014. The PDUFA due date for S-014 was extended by 3 months due to the submission of a major amendment on May 2, 2008 that included pharmacokinetic rationale to support dosing in adolescents (ages 12-18).

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the information submitted in this (b) (4) supplement and provides the following comments (b) (4)

- **Recurrent Genital Herpes:** The pediatric exposures from study HS210915 did not match the historical adult exposures for VACV given at 500 mg twice daily for the treatment of recurrent genital herpes, although it did match historical acyclovir exposures in adults treated with acyclovir given at 200 mg 5 times daily for the treatment of initial and intermittent therapy of genital herpes. (b) (4)

1.2 Phase IV Commitments

Not applicable to this supplement.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Valacyclovir is approved for the following indications in adults with accompanying dosing regimens:

Indication	Valacyclovir Dose
Herpes Zoster	1 g TID for 7 days
Genital Herpes:	
Initial episode	1 g BID for 10 days
Recurrent episodes	500 mg BID for 3 days
Suppressive therapy (immunocompetent)	1 g QD
Suppressive therapy (alternative dose in immunocompetent adults with ≤9 recurrences/year)	500 mg QD
Suppressive therapy in HIV (CD4 count ≥100 cells/mm^3)	500 mg BID
Reduction of transmission for source partner	500 mg QD
Herpes Labialis* (cold sores)	2 g BID for 1 day

*Note: the indication for herpes labialis was approved after the issuance of the pediatric written request.

The three studies listed below were submitted in order to fulfill the pediatric written request (sent by the DAVP in a written request in 2001 and later amended in 2002) (b) (4) . However, this review (b) (4) will include a review of only the first two studies.

Study #1 (HS210914): A single-dose pharmacokinetic and safety study in infants and children age one month to less than six years who have a current herpes virus infection or who may have a potential future recurrence, or who are at risk for development of a herpes virus infection.

Study #2 (HS210915): A single-dose pharmacokinetic, multiple-dose safety study in immunocompetent and/or immunocompromised infants and children age 1-12 years who have HSV infections.

Study #3 (HS210916): A single-dose pharmacokinetic, multiple-dose safety study in immunocompetent and/or immunocompromised infants and children age 1-12 years who have varicella zoster virus (VZV) infections.

The major findings from the first two studies are summarized below:

Study HS210914 was an open-label, single dose, PK and safety study of a 25 mg/kg dose of VACV oral suspension in infants and children ages 1 month to <6 years old. The major PK findings are presented in the table below.

Mean (±SD) Plasma Acyclovir Pharmacokinetic Parameter Estimates Following Single-Dose Administration of 25 mg/kg Valacyclovir Oral Suspension to Pediatric Patients

Acyclovir PK Parameter	25 mg/kg Suspension in Pediatric Subjects						1 g Solid Dose in Adults[a] (N=15)	
	Cohort 1 2 to <6 yr (N=12)	Cohort 2 1 to <2 yr (N=9)	Cohort 3 6 mo to <1 yr (N=7)	Cohort 4 3 to <6 mo (N=9)	Cohort 5 1 to <3 mo (N=9)	Overall: 1 mo to <6 yrs (N=46)	Actual Adult PK Sampling Schedule	Estimates Using Peds PK Sampling Schedule
AUC(0-∞) (μg•h/mL)								
Mean (CV%)	19.9 (13)	15.3[1] (34)	14.1[2] (25)	17.7 (37)	27.6 (25)	19.5[3] (35)	18.8 (24)	17.2 (18)
Geometric Mean (95% CI)	19.8 (18.2-21.5)	14.5[1] (10.3-20.4)	13.7[2] (10.6-17.7)	16.0 (10.5-24.5)	26.9 (22.2-32.5)	18.2[3] (16.1-20.6)	N/A	N/A
Cmax (μg/mL)								
Mean (CV%)	6.52 (19)	4.67 (44)	4.94 (21)	5.17 (43)	7.02 (22)	5.75 (32)	5.20 (37)	4.72 (29)
Geometric Mean (95% CI)	6.40 (5.63-7.28)	4.14 (2.67-6.43)	4.86 (4.03-5.86)	4.67 (3.13-6.97)	6.88 (5.85-8.08)	5.38 (4.76-6.07)	N/A	N/A
t½ (h)								
Mean (CV%)	1.45 (14)	1.33[1] (7)	1.25[2] (12)	1.79 (41)	2.03 (23)	1.60[3] (31)	2.77 (13)	2.11 (21)
Geometric Mean (95% CI)	1.44 (1.32-1.57)	1.33[1] (1.24-1.42)	1.24[2] (1.09-1.41)	1.69 (1.31-2.19)	1.99 (1.69-2.34)	1.54[3] (1.42-1.67)	N/A	N/A
tmax (h)								
Median (Range)	1.00 (0.50-2.00)	2.00 (1.00-4.02)	2.00 (1.08-2.30)	2.00 (0.98-2.08)	2.03 (0.97-2.25)	2.00 (0.50-4.02)	2.0 (0.75-2.50)	2.0 (1.00-2.00)
Mean (CV%)	1.21 (41)	1.93 (48)	1.81 (27)	1.58 (34)	1.87 (22)	1.64 (39)	1.82 (32)	1.67 (29)
CL/F/kg (mL/min/kg)								
Mean (CV%)	14.9 (13)	21.2[1] (38)	21.9[2] (24)	21.6 (85)	11.0 (25)	17.5[3] (57)	9.0 (21)	11.6 (31)
Geometric Mean (95% CI)	14.8 (13.6-16.0)	20.0[1] (14.3-28.1)	21.3[2] (16.4-27.7)	18.0 (11.8-27.5)	10.7 (8.84-13.0)	15.9[3] (14.1-18.0)	N/A	N/A

Source Data: Table 11.5 and Table 11.6; [a] [Weller, 1993]
[1]N=7; [2]N=6; [3]N=43

The main conclusions from this study were:

- Following a single dose of 25 mg/kg VACV oral suspension, AUC and Cmax exposures in the youngest cohort were appreciably higher than historical adult acyclovir exposures following a dose of VACV 1 g QD. All other age groups (from 3 months to <6 years old) had comparable exposures to the adult dose of 1 g.
- The dose for this study was selected based on the dose being studied in two efficacy studies at the NIH in 2002 (300 mg/m^2). However, these studies did not provide efficacy data to support this dose. Thus, in the absence of efficacy and multiple-dose safety data, this dose is not recommended for approval for any pediatric indication.

Study HS210915 was an open-label, multiple-dose, PK and safety study of 10 mg/kg of VACV oral suspension in children ages 1 year to <12 years old. The major PK findings are presented in the table below.

Mean (±SD) Plasma Acyclovir Pharmacokinetic Parameter Estimates Following First-Dose Administration of 10 mg/kg Valacyclovir Oral Suspension to Pediatric Patients vs. 500 mg Valacyclovir Single Dose to Adults

Dose (mg/kg)	Parameter	Age			
		1 - <2 yr	2 - <6 yr	6 - <12 yr	Adult 500 mg VACV solid dose*
10	N	6	12	8	15
	AUC (mcg•hr/mL)	6.63 (1.79)	5.72 (1.72)	8.84 (1.50)	10.3 (1.85)
	C_{max} (mcg/mL)	2.49 (0.74)	2.05 (0.47)	3.08 (0.46)	3.07 (0.89)

*Historical estimates using pediatric pharmacokinetic sampling schedule

The main conclusions from this study were:

- In the age groups that were <6 years old, most subjects had lower exposures than the mean historical exposures resulting from ACV given 200 mg 5 times daily in adults. However, pediatric subjects that were older than 6 years of age exceeded these adult exposures.
- The projected mean daily acyclovir AUC and Cmax exposures across all age groups were lower than the targeted adult historical exposures from the approved VACV dose of 500 mg BID for the treatment of recurrent genital herpes.
- The relevance of this indication in the pediatric patient population may be limited.

2 Question based review (QBR)

2.1 General Attributes of the Drug

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to the clinical pharmacology and biopharmaceutics review?

Valacyclovir hydrochloride (Valtrex, VACV) is the hydrochloride salt of the L-valine ester pro-drug of acyclovir, a synthetic nucleoside analogue that is active against herpes simplex virus types 1 and 2 and varicella zoster virus. Each Valtrex caplet contains valacyclovir HCl equivalent to either 500 mg or 1 g valacyclovir free base. VACV is rapidly converted to acyclovir via first-pass intestinal and/or hepatic metabolism. Due to higher acyclovir bioavailability following oral administration of VACV (54.5% ± 9.1%) as compared with acyclovir administration (10-20%), VACV can achieve higher plasma concentrations of acyclovir with less frequent dosing.

Valacyclovir hydrochloride is a white to off-white powder with the molecular formula $C_{13}H_{20}N_6O_4$•HCl and a molecular weight of 360.80. The maximum solubility in water at 25°C is 174 mg/mL. The proposed final formulation of the extemporaneously prepared oral suspension of VACV is listed below. Detailed instructions on how to prepare the extemporaneous formulation will be included in the final labeling.

Composition of prepared VACV oral suspension

Ingredient	Formula Quantity per 100 mL	
	Valaciclovir Oral Suspension 25 mg/mL	Valaciclovir Oral Suspension 50 mg/mL
VALTREX CAPLETS 500mg	5 caplets	10 caplets
Cherry Flavor (b) (4) (b) (4) (b) (4)		
Suspension Structured Vehicle USNF	To 100mL	To 100mL

(b) (4)

Composition of 500 mg VACV caplets

Component	Quantity (mg/Caplet)	Reasonable Variation (mg)	Function
Core Valacyclovir Hydrochloride[1] Microcrystalline Cellulose, NF Crospovidone, NF (b) (4) Magnesium Stearate, NF/EP Silicon Dioxide Colloidal, NF	(b) (4)		
(b) (4)			
Approximate Coated Caplet Weight[6]	710.22	(b) (4)	-

2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

Valacyclovir hydrochloride is rapidly converted to acyclovir which has demonstrated antiviral activity against herpes simplex virus types 1 (HSV-1) and 2 (HSV-2) and varicella-zoster virus (VZV) both *in vitro* and *in vivo*. The following indications and dose regimens are approved in adults:

Indication	Valacyclovir Dose
Herpes Zoster	1 g TID for 7 days
Genital Herpes:	
Initial episode	1 g BID for 10 days
Recurrent episodes	500 mg BID for 3 days
Suppressive therapy (immunocompetent)	1 g QD
Suppressive therapy (alternative dose in immunocompetent adults with ≤9 recurrences/year)	500 mg QD
Suppressive therapy in HIV (CD4 count ≥100 cells/mm^3)	500 mg BID
Reduction of transmission for source partner	500 mg QD
Herpes Labialis	2 g BID for 1 day

2.1.3. What are the proposed dosage(s) and route(s) of administration?

(b) (4)

[redacted]

2.2 General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The three studies that the sponsor conducted were designed to fulfill the pediatric written request. The intent of the request was to gain PK and safety information from the administration of valacyclovir to pediatric patients between ages 1 month to 12 years old with either active HSV or VZV infections or who were at risk of developing HSV infections. To meet these objectives, the sponsor conducted the following studies:

Study #1 (HS210914): A single-dose pharmacokinetic and safety study in infants and children age one month to less than six years who have a current herpes virus infection or who may have a potential future recurrence, or who are at risk for development of a herpes virus infection.

Study #2 (HS210915): A single-dose pharmacokinetic, multiple-dose safety study in immunocompetent and/or immunocompromised infants and children age 1-12 years who have HSV infections.

Study #3 (HS210916):: A single-dose pharmacokinetic, multiple-dose safety study in immunocompetent and/or immunocompromised infants and children age 1-12 years who have varicella zoster virus (VZV) infections.

2.2.2. What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics [PD]) and how are they measured in clinical pharmacology and clinical studies?

Clinical and micobiological responses would be appropriate endpoints for measurement for herpes virus indications. However, response endpoints were not evaluated in these pediatric studies as the overall goal was to match systemic exposures to those seen in historical adult populations given approved VACV and ACV doses and to assess the safety of the proposed pediatric doses.

2.2.3. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, the sponsor has appropriately measured acyclovir levels in plasma as the primary moiety for PK evaluation. Plasma concentrations of VACV are low and transient, as it is rapidly converted to the active form, acyclovir. VACV typically becomes non-quantifiable by 3 hours post-administration. The long-term stability of VACV and ACV is an issue that is still pending the sponsor's response. The results will be included in the review of supplement S-014.

2.2.4. Exposure-Response

2.2.4.1. What are the characteristics of exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

Sufficient data are not available for determining exposure-response relationships for efficacy with VACV. The clinical endpoint is different for each herpes virus indication.

2.2.4.2. What are the characteristics of exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

No data are available for exposure-response relationships for safety with VACV.

2.2.4.3. Does valacyclovir prolong QT or QTc interval?

Not applicable to this submission.

2.2.4.4. Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The doses selected by the sponsor reflect what is known about adult exposures at approved doses and the intrinsic PK characteristics of children. The pediatric dose given in study HS210915 provided lower exposures than the respective targeted, historical adult exposures. The sponsor explained that this most likely occurred due to the use of an equation that was given in an older version of a textbook that under-calculated pediatric doses by 40%.

2.2.5. What are the PK characteristics of valacyclovir?

VACV is rapidly absorbed in the GI tract and extensively converted to acyclovir. The average oral bioavailability of acyclovir following administration of VACV is 54.5% as compared with 10-20% following administration of ACV. The following table shows the mean acyclovir AUC and Cmax exposures in healthy adults receiving doses between 100 mg and 1,000 mg of VACV (values are taken from the text of the current label). AUC and Cmax exposures do not increase proportionally with dose between the 250 and 1000 mg doses.

Mean (±SD) Plasma Acyclovir Pharmacokinetic Parameters Following Administration of VALTREX to Healthy Adult Volunteers

	Single-Dose Administration (N = 8)		Multiple-Dose Administration* (N = 24, 8 per treatment arm)	
Dose	C_{max} (±SD) (mcg/mL)	AUC (±SD) (hr•mcg/mL)	C_{max} (±SD) (mcg/mL)	AUC (±SD) (hr•mcg/mL)
100 mg	0.83 (±0.14)	2.28 (±0.40)	ND	ND
250 mg	2.15 (±0.50)	5.76 (±0.60)	2.11 (±0.33)	5.66 (±1.09)
500 mg	3.28 (±0.83)	11.59 (±1.79)	3.69 (±0.87)	9.88 (±2.01)
750 mg	4.17 (±1.14)	14.11 (±3.54)	ND	ND
1,000 mg	5.65 (±2.37)	19.52 (±6.04)	4.96 (±0.64)	15.70 (±2.27)

*Administered 4 times daily for 11 days.
ND = not done.

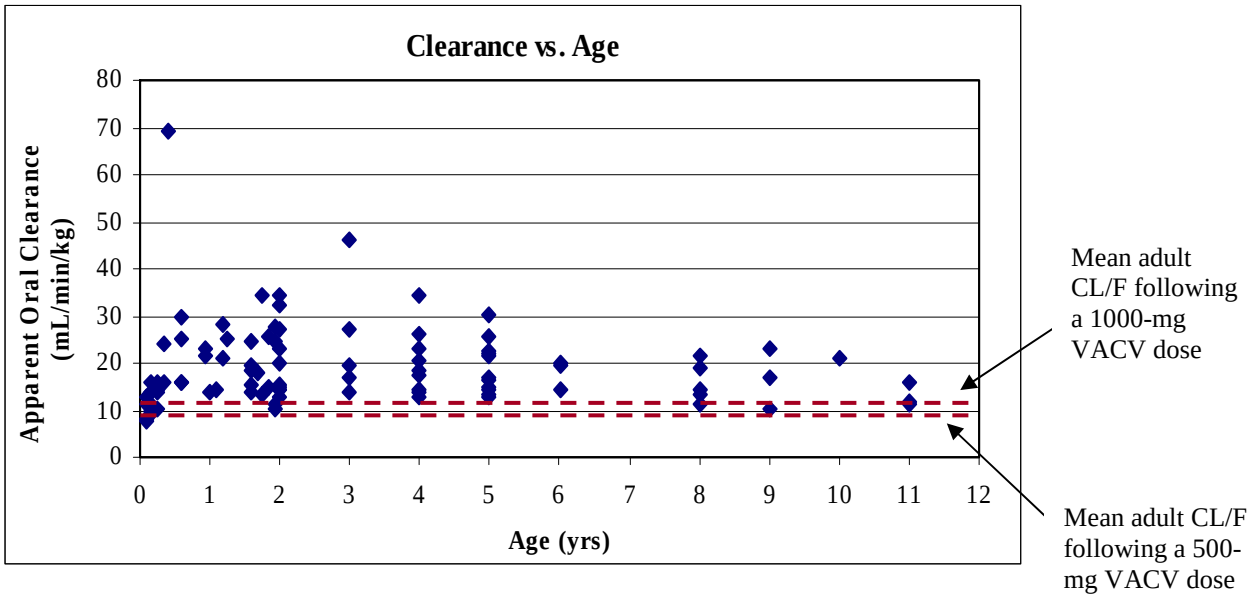
2.3 Intrinsic Factors

2.3.1. Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

Pediatric Patients: Children generally have higher clearance rates than adults owing to age-related differences in renal function. Thus, on a per weight basis, pediatric patients would require a higher dose in order to match adult systemic

acyclovir exposures. The age groups between 3 months old and 6 years old tended to have higher clearances than the 1-3 month old infants and the oldest age group (6-12 years old). Clearance in the oldest age group approached adult clearance levels. The following graph depicts the relationship between clearance and age for the pediatric patients for all three studies.

Apparent Oral Clearance for All Age Groups Across All Three Studies



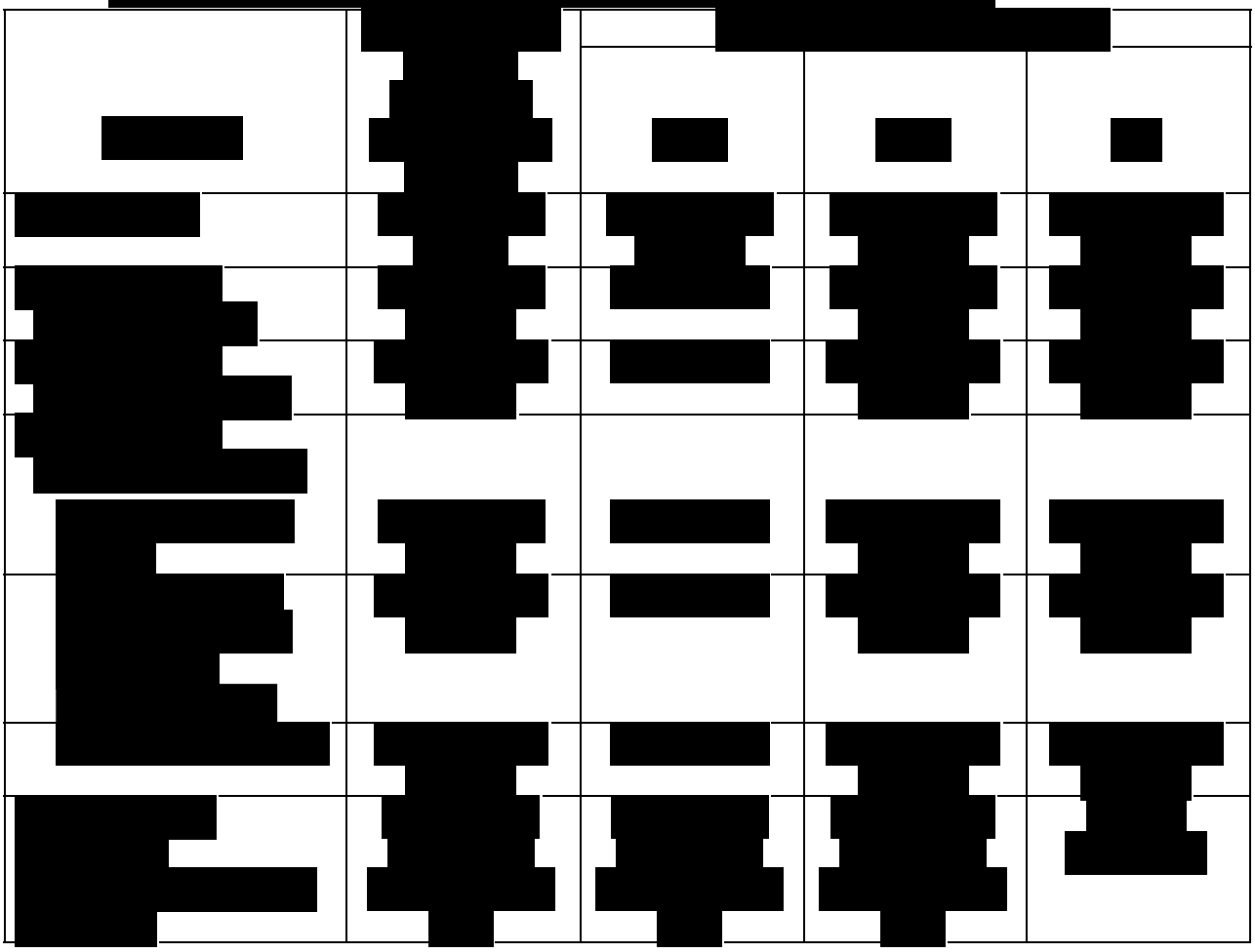
The following information is taken from the Valtrex label:

Geriatrics: Acyclovir plasma concentrations are higher in geriatric patients compared to younger adults, in part due to age-related changes in renal function. Dosage reduction may be required in geriatric patients with underlying renal impairment.

Adults with Impaired Renal Function: The half-life and total body clearance of acyclovir are dependent on renal function. A dosage adjustment is recommended for patients with reduced renal function.

According to the Valtrex label, precipitation of acyclovir in renal tubules may occur when the solubility (2.5 mg/mL) is exceeded in the intratubular fluid. Thus, not reducing the dose for patients with existing renal insufficiency may result in further renal toxicity or renal failure. The following dosage adjustment table for adults with renal impairment is contained within the Dosage and Administration section of the label.

(b) (4) [redacted]



2.4 Extrinsic Factors

2.4.1. What extrinsic factors influence dose-exposure and/or –response, and what is the impact of any differences in exposure on response?

Effect of food: Please see section 2.5.3 for the effect of food on bioavailability.

Effect of drug interactions: Acyclovir Cmax and AUC following a single dose of VACV (1 g) increased by 8% and 32%, respectively, after a single dose of cimetidine (800 mg) or by 22% and 49%, respectively, after probenecid (1 g), or by 30% and 78%, respectively, after a combination of cimetidine and probenecid. This effect is primarily due to a reduction in renal clearance of acyclovir. However, no dose adjustment is necessary when giving these drugs in combination with VACV in patients with normal renal function.

2.5 General Biopharmaceutics

2.5.1. Based on the biopharmaceutics classification system (BCS) principles, in what

class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

The information that is available from its solubility, permeability, and dissolution characteristics is inconclusive but would most likely indicate that valacyclovir is a BCS class III drug (low permeability, high solubility), although a BCS class I classification is not precluded.

Solubility: The solubility of valacyclovir in water is 174 mg/mL. At the highest dose strength, the BCS volume would be 5.75 mL (1000 mg ÷ 174 mg/mL). Solubilities in other pH media are not reported in the label or original OCPB review.

Permeability: The absolute bioavailability of VACV after oral administration is ~54%. However, this does not preclude VACV from being classified as BCS class 1 since bioavailability does not solely depict the extent of intestinal absorption, which is the main criteria for the "high permeability" designation.

Dissolution: Dissolution of VACV is pH-dependent. The sponsor's testing of the pure drug substance revealed that the dissolution rate was [redacted] in 0.1 N HCl than in water. Three batches of 500 mg VACV caplets of the same formulation were used in the BE study (conducted as part of the original NDA submission). The dissolution rates between the three batches were highly variable, ranging from [redacted] dissolved in water in 30 mins. and from [redacted] dissolved in 0.1 N HCl in 30 mins. The final specification was: NLT [redacted] (Q) dissolved in 45 minutes in 0.1 N HCl.

2.5.2. What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial formulation?

The bioavailability of the caplet formulation of VACV is ~54.5%, but the bioavailability of the oral suspension has not been investigated. However, information on the relative bioavailability of the oral suspension formulation to the caplet would not be critical if the exposure levels are comparable between the oral suspension in children and caplets in adults.

2.5.2.1. What data support or do not support a waiver of *in vivo* BE data?

Not applicable

2.5.2.2. What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90 % CI using equivalence limits of 80-125 %?

Not applicable.

2.5.3. What is the effect of food on the bioavailability (BA) of acyclovir from the

dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The bioavailability of acyclovir from the administration of VACV caplets is not altered by administration with food in adults. However, the Tmax for acyclovir increased by 77% following a high-fat meal. Since the clinical significance of the delayed Tmax is not known, the label states that VACV may be given without regard to meals. The effect of food on the bioavailability of the oral suspension has not been studied.

2.6 Analytical Section

2.6.1. How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Acyclovir and valacyclovir are extracted from plasma samples using a (b) (4) [redacted]. The samples are then reconstituted and analyzed using HPLC/MS/MS.

2.6.2. Which metabolites have been selected for analysis and why?

Metabolites were not measured in these studies.

2.6.3. For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Total concentrations of acyclovir and valacyclovir were measured.

2.6.4 What bioanalytical methods are used to assess concentrations?

Acyclovir and valacyclovir are extracted from plasma samples using a (b) (4) [redacted] procedure. The samples are then reconstituted and analyzed using HPLC/MS/MS. The lower limit of quantitation for both analytes is 10 ng/mL using a 50-µL aliquot of human plasma.

Note: The long-term stability of VACV and ACV is an issue that is still pending the sponsor's response. The results will be included in the review of supplement S-014.

3. Labeling Recommendations

Labeling sections pertaining to pediatric dosing for the chickenpox indication and information summarizing the results of all three studies have been agreed upon with the sponsor. (b) (4) [redacted] The PDUFA due date for S-014 was extended by 3 months due to the submission of a major amendment on May 2, 2008 that included pharmacokinetic rationale to support dosing in adolescents (ages 12-18).

4. Appendices

4.1 Individual Study Review

Study HS210914

"An open-label, single-dose, multicenter, pharmacokinetic, safety, and tolerability study of valacyclovir oral suspension in infants and children."

1. Objectives

- Primary objective:
  - To assess the pharmacokinetics of ACV after a single dose of VACV oral suspension (25 mg/kg) to infants and children who might receive immediate or potential future benefit from valacyclovir therapy.
- Secondary objectives:
  - To evaluate the safety and tolerability of a single 25 mg/kg dose of valacyclovir oral suspension to infants and children
  - To assess the PK of VACV after a single 25 mg/kg dose of VACV oral suspension.

2. Study Design

The study was a multicenter, open-label, single-dose study that was designed to include 36-40 evaluable infants and children. Five cohorts were planned and included infants and children aged 1 month to 6 years old, divided by age. The five cohorts (and recommended target enrollment numbers from FDA) were:

Cohort 1: age 2 to <6 years (N = 12);
Cohort 2: age 1 to <2 years (N = 6);
Cohort 3: age 6 months to <1 year (N = 6);
Cohort 4: age 3 to <6 months (N = 6 to 8);
Cohort 5: age 1 to <3 months (N = 6 to 8).

The study started with cohort 1 and proceeded forward with enrollment only after initial safety and pharmacokinetic data from subjects 2 years of age or older were evaluated. Of the total 57 subjects that were enrolled in the study, PK data were evaluable for 12/12 subjects in cohort 1, 9/9 subjects in cohort 2, 7/10 subjects in cohort 3, 9/12 subjects in cohort 4, and 9/14 subjects in cohort 5. Enrollment for each cohort met the FDA-recommended target numbers for enrollment from the pediatric written request.

3. Rationale for Dose Selection

The sponsor chose to target the exposures for the adult dose indicated for suppression of recurrent genital herpes episodes (1 g once daily). Since renal clearance in children (>3 months old) is generally higher than clearance in adults, an equation from Rowland and

Tozer (1980) was used to estimate an appropriate pediatric dose for drugs that are predominantly cleared by the kidney. The equation is:

$$\text{Pediatric Dose (mg)} = (\text{Child's weight/Adult weight})^{0.7} * \text{Adult Dose (mg)}$$

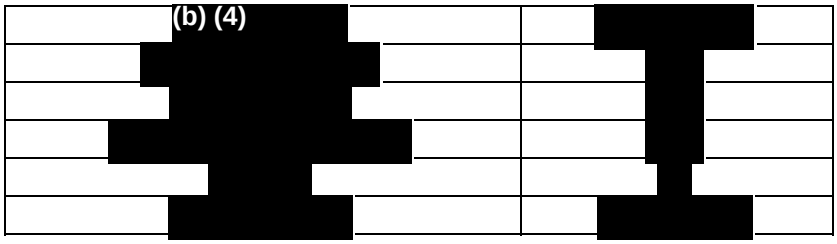
For an average 70 kg adult, 1000 mg of VACV corresponds to a dose of 14.3 mg/kg. Infants and children enrolled in this study were expected to weigh between 4 and 20 kg, which corresponds to doses ranging from 21 to 34 mg/kg. Thus, the average dose was 25 mg/kg (the dose chosen for the study). The higher mg/kg dose for the children and infants as compared with the adult dose is reflective of the higher renal clearance expected for children.

In addition, the dose evaluated in this study was selected to approximate the dose used in concurrent efficacy studies. At the time of initiation of this study, there were two ongoing NIH trials evaluating the efficacy of a 300 mg/m^2 oral suspension dose following IV acyclovir for the treatment of neonatal HSV infections. With a typical body surface area of 0.25 to 0.4 m^2 for infants ages 1 to 7 months, the infants in the NIH studies received between 225 mg and 360 mg of oral acyclovir per day. Due to a 10-20% bioavailability of oral acyclovir, the systemically available acyclovir totaled 45 mg/day (range: 23-72 mg/day). A dose of 25 mg/kg/day of VACV oral suspension for the infants in this study (4-8 kg weight) with an average 43% bioavailability (range 33-52%) would correlate to approximately 65 mg/day (range 33-104 mg/day). Thus the range of bioavailable acyclovir would provide a comparable range to the NIH studies. However, these studies were not completed and thus did not provide useful efficacy information.

4. Drug Used in the Trial

An extemporaneous oral suspension formulation was used for this study as well as studies HS210915 and HS210916. VACV oral suspension was prepared by crushing 500-mg Valtrex caplets and suspending the resultant powder in the suspension structured vehicle USNF. The following table (table 1) shows the components and composition of the vehicle.

Table 1 Components of suspension vehicle



VACV oral suspension in 25 mg/mL and 50 mg/mL strengths was prepared in lots of 100 mL using a mortar and pestle to grind Valtrex caplets into a fine powder and adding aliquots of vehicle. Cherry flavor (b) (4) was added to the last aliquot of vehicle that was added to the VACV. Table 2 shows the composition of the resultant suspension.

Table 2 Composition of final oral suspension dosed to patients

Ingredient	Formula Quantity per 100 mL	
	Valaciclovir Oral Suspension 25 mg/mL	Valaciclovir Oral Suspension 50 mg/mL
VALTREX CAPLETS 500mg	5 caplets	10 caplets
Cherry Flavor (b) (4) (b) (4)		
Suspension Structured Vehicle USNF	To 100mL	To 100mL

5. Sample Collection, Bioanalysis, PK Assessments, and Statistical Analysis

Sample Collection

Blood samples (1 mL each) were collected on Day 1 at pre-dose (within 15 minutes of dosing), 0.5, 1, 2, 4, and 6 hours post-dose. The subjects remained in the clinic facility for the duration of the blood collection period.

Bioanalysis

The bioanalytical portion of the study was conducted at (b) (4) Sample analysis began on 3/26/03 and ended on 3/8/07 as samples were continuously being received from GSK. ACV and VACV along with their respective internal standards were extracted from samples using (b) (4). Samples were quantitated using HPLC/MS/MS. The LLOQ for ACV and VACV is 10 ng/mL using a 50-µL aliquot of serum.

The calibration standard concentration levels were 10, 20, 50, 100, 200, 400, 600, 800, and 1000 ng/mL for both ACV and VACV. The QC sample concentrations were 30, 400, and 800 ng/mL for both analytes. Dilution validation samples were prepared at a 1:10 and 1:100 dilution.

The interday precision (%CV) for each ACV QC was 7.5 (low), 5.1 (med), and 5.5 (high). The interday accuracy (%bias) for each ACV QC was 0.7 (low), 1.6 (med), and 1.3 (high). The interday precision (%CV) for each VACV QC was 5.8 (low), 5.5 (med), and 5.0 (high). The interday accuracy (%bias) for each VACV QC was 4.0 (low), 4.0 (med), and 5.2 (high).

Due to stability issues with valacyclovir stored at -20^{o} C, all study samples and QC samples were moved to -70^{o} C on 1/7/04. The long-term storage stability data was submitted in an amendment to this supplement. The issues pertaining to the long-term storage stability of VACV will be addressed in the review of S-014, as complete data from the sponsor were still pending at the time of completion of this review.

Pharmacokinetic Assessments

PK analyses were conducted using a non-compartmental model using WinNonlin Professional Edition Version 4.1. Actual elapsed times from dosing were used to estimate

individual PK parameters for evaluable subjects. In addition, when calculating oral clearance (and other related parameters), the actual individual dose administered was used instead of the nominal dose.

Reviewer's comment:
-An accurate calculation of K_{el} for most subjects was possible with the sparse pediatric sampling scheme since Tmax is relatively short (~2 hours). Therefore, there were three available data points in the elimination phase that could be used to calculate the elimination rate constant for most subjects.

Statistical Analysis

Statistical analysis was not needed for this study as the intent was only to characterize acyclovir/valacyclovir PK and safety in children of various ages.

6. Results

The data for 46 (43 full PK data, 3 partial PK data) out of the 57 subjects enrolled were included in the PK analysis for acyclovir. Of the eleven excluded subjects, four had incomplete sampling which precluded PK parameter estimation. Seven subjects had pre-dose acyclovir concentrations that were >5% of Cmax values or had measurable VACV concentrations (>5% of Cmax), thus their data were excluded. The sponsor states that these subjects did not report receiving VACV or ACV prior to the start of the study. No other reasons were found for the quantifiable pre-dose drug concentrations detected in plasma.

One additional subject had pre-dose ACV levels that were 8.7% of Cmax, but had been receiving IV acyclovir (~20 mg/kg TID) for treatment of neonatal herpes. The protocol for this study states that subjects receiving systemic ACV prior to the start of the study can be included if there is a washout period of at least 6 hours from the time of the last systemic ACV dose to VACV administration in this study. The last dose for this subject was administered 10 hours prior to receiving the VACV study dose. Thus, this subject was included in the study and the sponsor used the method of reverse superposition to estimate ACV plasma concentrations derived from the single dose of VACV used in the study. A summary of the subject demographics is listed in Table 3.

Table 3 Summary of Demographic Characteristics

Demographics	Valaciclovir 25 mg/kg Single-Dose Oral Suspension					
	Total Population N=57	Cohort 1 2-<6 yr n=12	Cohort 2 1-<2 yr n=9	Cohort 3 6mo-<1yr n=10	Cohort 4 3-<6 mo n=12	Cohort 5 1-<3mo n=14
Mean Age, months (SD)	15.6 (19.3)	48.6 (15.0)	18.2 (4.2)	7.9 (1.9)	3.6 (0.8)	1.6 (0.5)
Sex, n (%)						
Females	25 (44)	7 (58)	3 (33)	5 (50)	4 (33)	6 (43)
Males	32 (56)	5 (42)	6 (67)	5 (50)	8 (67)	8 (57)
Race, n (%)						
Black/African American	24 (42)	2 (17)	3 (33)	2 (20)	7 (58)	10 (71)
White	23 (40)	10 (83)	6 (67)	1 (10)	4 (33)	2 (14)
Other	10 (18)	0	0	7 (70)	1 (8)	2 (14)
Ethnicity, n (%)						
Hispanic or Latino	15 (26)	4 (33)	0	6 (60)	2 (17)	3 (21)
Not Hispanic /Latino	42 (74)	8 (67)	9 (100)	4 (40)	10 (83)	11 (79)
Mean Height[a], cm (SD)	73.4 (18.4)	103.3 (12.2)	80.4 (4.5)	67.7 (3.9)	61.5 (4.8)	57.6 (3.8)
Mean Weight[a], kg (SD)	10.0 (6.2)	19.6 (7.0)	10.7 (1.3)	8.3 (1.2)	6.4 (0.9)	5.5 (1.3)

a. Measured at Screening visit

Plasma VACV levels were low across all age groups (as shown in Table 4). However, the plasma VACV levels for cohort 5 (1 to <3 months) were higher than the levels in the other older cohorts. These elevated plasma levels resulted in approximately 2.5-fold greater AUC exposure and 2-fold greater Cmax exposure over the oldest age group (2-6 y.o.). In addition to having higher exposures, circulating levels of VACV tended to stay above the limit of quantitation longer (~6 hours or longer), whereas most VACV plasma concentrations in the other cohorts were below the limit of quantitation after the four-hour sampling timepoint (Figure 1). The higher levels of VACV plasma concentrations in the youngest age group may reflect a lag in the development of hepatic and/or intestinal metabolism that is necessary for the conversion of VACV into ACV.

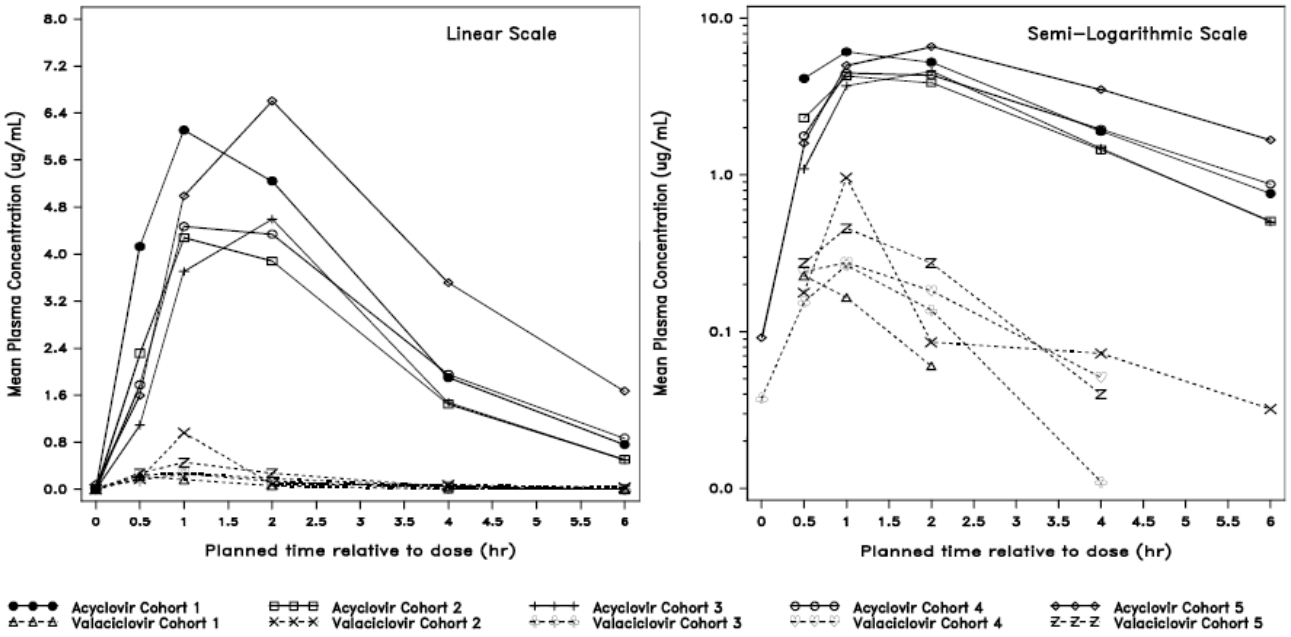
Table 4 Valacyclovir PK Parameter Estimates Following a Single 25 mg/kg Dose

Valaciclovir PK Parameter	Cohort 1 2 to <6 yr (N=11)	Cohort 2 1 to <2 yr (N=7)	Cohort 3 6 mo to <1 yr (N=5)	Cohort 4 3 to <6 mo (N=8)	Cohort 5 1 to <3 mo (N=9)	Overall: 1 mo to <6 yr (N=40)
AUC(0-∞) (μg•h/mL)						
Mean (CV%)	0.357[1] (22)	0.221[2] (59)	0.457[2] (15)	0.505[3] (44)	0.901[4] (32)	0.528[5] (57)
Geometric Mean (95% CI)	0.349[1] (0.289-0.421)	0.198[2] (0.049-0.796)	0.453[2] (0.306-0.672)	0.459[3] (0.241-0.874)	0.869[4] (0.671-1.13)	0.454[5] (0.361-0.572)
Cmax (μg/mL)						
Mean (CV%)	0.266 (57)	0.176 (94)	0.253 (32)	0.287 (57)	0.522 (36)	0.311 (62)
Geometric Mean (95% CI)	0.224 (0.145-0.346)	0.129 (0.060-0.275)	0.242 (0.160-0.366)	0.241 (0.139-0.419)	0.496 (0.384-0.640)	0.249 (0.198-0.313)
t½ (h)						
Mean (CV%)	0.743[1] (36)	1.06[2] (26)	0.707[2] (4)	1.04[3] (60)	0.835[4] (18)	0.857[5] (39)
Geometric Mean (95% CI)	0.700[1] (0.512-0.958)	1.04[2] (0.510-2.11)	0.706[2] (0.640-0.780)	0.911[3] (0.458-1.81)	0.820[4] (0.671-1.00)	0.805[5] (0.698-0.929)
tmax (h)						
Median (Range)	0.50 (0.50-2.00)	1.00 (0.50-1.97)	1.08 (1.03-2.30)	1.01 (0.50-2.08)	1.03 (0.68-1.98)	1.00 (0.50-2.30)
Mean (CV%)	0.773 (60)	1.03 (46)	1.32 (41)	1.09 (59)	1.09 (32)	1.02 (49)

Source Data: Table 11.8 and Table 11.9

[1]N=8; [2]N=3; [3]N=5; [4]N=7; [5]N=26

Figure 1 Mean Acyclovir and Valacyclovir Plasma Concentrations



Acyclovir exposures in children receiving a 25 mg/kg dose are compared to exposures in adults given a 1 g dose (table 5). The adult historical data used for comparison purposes are taken from the Weller study (Weller, 1993). In that study, the actual adult PK sampling schedule was more intensive, with collection times at 0.25, 0.5, 0.75, 1, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, and 24 hours post-dose. The PK parameters reflect sampling after single-dose administration (day 1 of 11). The sponsor has included estimates of PK parameters using the pediatric PK sampling schedule to provide a more accurate comparison.

Table 5 Acyclovir PK Parameter Estimates Following a Single 25 mg/kg Dose

Acyclovir PK Parameter	25 mg/kg Suspension in Pediatric Subjects						1 g Solid Dose in Adults[a] (N=15)	
	Cohort 1 2 to <6 yr (N=12)	Cohort 2 1 to <2 yr (N=9)	Cohort 3 6 mo to <1 yr (N=7)	Cohort 4 3 to <6 mo (N=9)	Cohort 5 1 to <3 mo (N=9)	Overall: 1 mo to <6 yrs (N=46)	Actual Adult PK Sampling Schedule	Estimates Using Peds PK Sampling Schedule
AUC(0-∞) (μg•h/mL)								
Mean (CV%)	19.9 (13)	15.3[1] (34)	14.1[2] (25)	17.7 (37)	27.6 (25)	19.5[3] (35)	18.8 (24)	17.2 (18)
Geometric Mean (95% CI)	19.8 (18.2-21.5)	14.5[1] (10.3-20.4)	13.7[2] (10.6-17.7)	16.0 (10.5-24.5)	26.9 (22.2-32.5)	18.2[3] (16.1-20.6)	N/A	N/A
Cmax (μg/mL)								
Mean (CV%)	6.52 (19)	4.67 (44)	4.94 (21)	5.17 (43)	7.02 (22)	5.75 (32)	5.20 (37)	4.72 (29)
Geometric Mean (95% CI)	6.40 (5.63-7.28)	4.14 (2.67-6.43)	4.86 (4.03-5.86)	4.67 (3.13-6.97)	6.88 (5.85-8.08)	5.38 (4.76-6.07)	N/A	N/A
t½ (h)								
Mean (CV%)	1.45 (14)	1.33[1] (7)	1.25[2] (12)	1.79 (41)	2.03 (23)	1.60[3] (31)	2.77 (13)	2.11 (21)
Geometric Mean (95% CI)	1.44 (1.32-1.57)	1.33[1] (1.24-1.42)	1.24[2] (1.09-1.41)	1.69 (1.31-2.19)	1.99 (1.69-2.34)	1.54[3] (1.42-1.67)	N/A	N/A
tmax (h)								
Median (Range)	1.00 (0.50-2.00)	2.00 (1.00-4.02)	2.00 (1.08-2.30)	2.00 (0.98-2.08)	2.03 (0.97-2.25)	2.00 (0.50-4.02)	2.0 (0.75-2.50)	2.0 (1.00-2.00)
Mean (CV%)	1.21 (41)	1.93 (48)	1.81 (27)	1.58 (34)	1.87 (22)	1.64 (39)	1.82 (32)	1.67 (29)
CL/F/kg (mL/min/kg)								
Mean (CV%)	14.9 (13)	21.2[1] (38)	21.9[2] (24)	21.6 (85)	11.0 (25)	17.5[3] (57)	9.0 (21)	11.6 (31)
Geometric Mean (95% CI)	14.8 (13.6-16.0)	20.0[1] (14.3-28.1)	21.3[2] (16.4-27.7)	18.0 (11.8-27.5)	10.7 (8.84-13.0)	15.9[3] (14.1-18.0)	N/A	N/A

Source Data: Table 11.5 and Table 11.6; [a] [Weller, 1993]
[1]N=7; [2]N=6; [3]N=43

The data for the adult 1-g dose was used as a historical comparison. Valtrex® 1 g QD and Zovirax® (acyclovir) 400 mg BID are both approved for chronic suppressive therapy of recurrent genital herpes in adults. A regimen of Valtrex 500 mg QD is approved for adults with a history of less than 10 recurrences per year in the absence of suppressive therapy.

As compared with mean historical ACV exposures in adults, infants less than 6 months old had much higher exposures than all three regimens in adults, while exposures in children between the ages of 6 months and 2 years old were bracketed by the adult daily ACV exposures resulting from VACV 500 mg QD and VACV 1 g QD dosing (Figure 2). Infants ages 1 to <3 months had appreciably higher AUC (+60%) and Cmax (+49%) exposures likely due to under-developed renal function leading to reduced weight-normalized clearance (Figure 3).

Figure 2 **Comparison of Projected Daily ACV AUC Exposures Following a Single 25 mg/kg dose of Oral VACV in Children to Mean Historical Exposures**

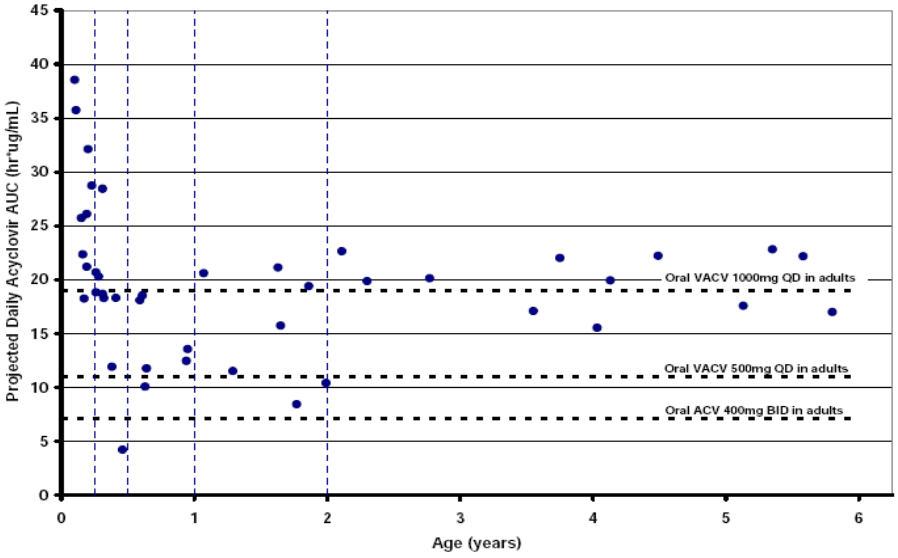
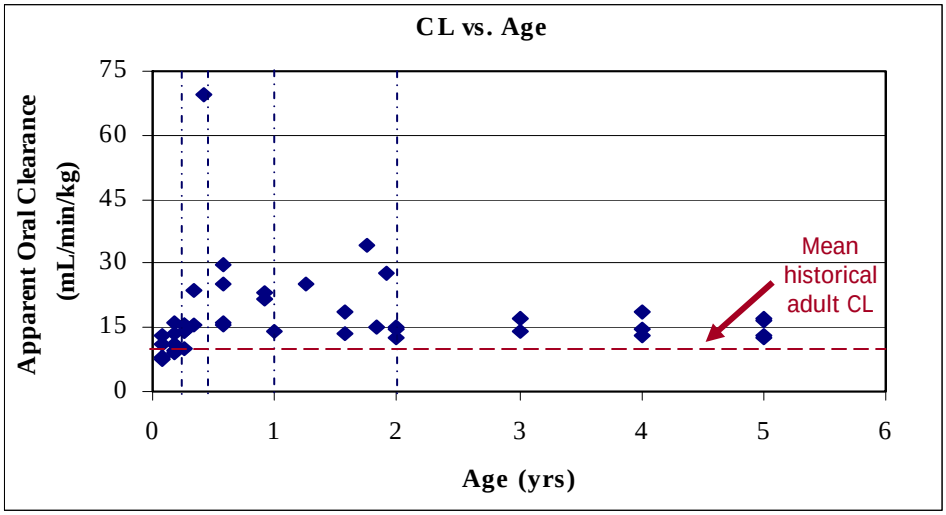


Figure 3 **Weight-Normalized Oral Clearance for Each Age Group Following a Single 25 mg/kg dose of VACV**



7. Conclusion

As a result of lower clearance (per kg) in the youngest age group, infants ages 1 to <3 months old had much higher exposures. Thus, this age group would require a lower dose to match adult exposures. AUC and Cmax acyclovir exposures for the 2-6 year old age group were comparable to historical PK data in adults given a single 1 g VACV dose using the pediatric sampling schedule estimates. However, there is no efficacy data to support this dose in children and there is no multiple-dose safety data to support dosing at this dose level.

(b) (4) [redacted]

Study HS210915

"An open-label, multiple-dose, multicenter, pharmacokinetic, safety, and tolerability study of valacyclovir oral suspension in infants and children with HSV infection."

1. Objectives

- Primary objective:
  - To assess the pharmacokinetics of ACV after the first dose administration of VACV oral suspension (10 mg/kg) to herpes simplex virus (HSV)-infected infants and children.
- Secondary objectives:
  - To evaluate the safety and tolerability of valacyclovir oral suspension, 10 mg/kg administered twice daily (BID) for three days, to HSV-infected infants and children.
  - To assess the PK of VACV after the first dose administration of valacyclovir oral suspension (10 mg/kg) to HSV-infected infants and children.

2. Study Design

The study was a multicenter, open-label, multiple-dose study designed to include 26 evaluable HSV-infected infants and children that were to be dosed BID for 3-5 days. Three cohorts were planned and included children aged 1 year to <12 years old. The three cohorts were:

Cohort 1: Eight children aged 6 years to <12 years.

Cohort 2: Twelve children aged 2 years to <6 years.

Cohort 3: Six infants aged 1 year to <2 years.

Seven subjects were enrolled for cohort 1 (6 included in PK evaluation), 13 subjects for cohort 2 (12 included in PK evaluation), and 8 subjects were enrolled for cohort 3 (8 subjects included in PK evaluation), for a total of 28 subjects enrolled (26 evaluable). Enrollment for each cohort met the FDA-recommended target numbers for enrollment from the pediatric written request.

3. Rationale for Dose Selection

For this study, the sponsor chose to match the exposures of a target dose of 500 mg BID in adults. Valtrex is approved to treat recurrent genital herpes episodes in adults at a regimen of 500 mg BID for 3 to 5 days. The sponsor predicted that 10 mg/kg BID in children would provide comparable systemic exposures to 500 mg BID in adults.

Since renal clearance in children (>3 months old) is generally higher than clearance in adults, an equation from Rowland and Tozer (1980) was used to estimate an appropriate pediatric dose for drugs that are predominantly cleared by the kidney. The equation is:

Pediatric Dose (mg) = (Child's weight/Adult weight)$^{0.7}$ * Adult Dose (mg)

For an average 70 kg adult, 500 mg of VACV corresponds to a dose of 7.1 mg/kg. Infants and children enrolled in this study were expected to weigh between 10 and 40 kg, which corresponds to doses ranging from 8.4 to 12.8 mg/kg. Thus, the average dose was 10 mg/kg (the dose chosen for the study). The higher mg/kg dose for the children and infants as compared with the adult dose is reflective of the higher renal clearance expected for this age group.

4. Drug Used in the Trial

An extemporaneous oral suspension formulation was used for this study as well as studies HS210914 and HS210916. VACV oral suspension was prepared by crushing 500-mg Valtrex caplets and suspending the resultant powder in the suspension structured vehicle USNF. Refer to table 1 for the components and composition of the vehicle.

VACV oral suspension in 25 mg/mL and 50 mg/mL strengths was prepared in lots of 100 mL using a mortar and pestle to grind Valtrex caplets into a fine powder and adding aliquots of vehicle. Cherry flavor (b) (4) was added to the last aliquot of vehicle that is added to the VACV. Refer to table 2 for the composition of the resultant suspension.

5. Sample Collection, Bioanalysis, PK Assessments, and Statistical Analysis

Sample Collection

Blood samples (1 mL each) were collected on Day 1 at pre-dose (within 15 minutes of dosing), 0.5, 1, 2, 4, and 6 hours post-dose. The subjects remained in the clinic facility for the duration of the blood collection period.

Bioanalysis

The bioanalytical portion of the study was conducted at (b) (4) Sample analysis began on 3/26/03 and ended on 7/29/04 as samples were continuously being received from GSK. ACV and VACV along with their respective internal standards were extracted from samples using (b) (4). Samples were quantitated using HPLC/MS/MS. The LLOQ for ACV and VACV is 10 ng/mL using a 50-µL aliquot of serum.

The calibration standard concentration levels were 10, 20, 50, 100, 200, 400, 600, 800, and 1000 ng/mL for both ACV and VACV. The QC sample concentrations were 30, 400, and 800 ng/mL for both analytes. Dilution validation samples were prepared at a 1:10 and 1:100 dilution.

The mean interday precision (%CV) for each ACV QC was 6.9 (low), 4.9 (med), and 5.0 (high). The mean interday accuracy (%bias) for each ACV QC was 2.7 (low), 3.3 (med), and 2.9 (high). The interday precision (%CV) for each VACV QC was 4.3 (low), 4.8 (med), and 4.6 (high). The interday accuracy (%bias) for each VACV QC was 3.3 (low), 2.1 (med), and 3.5 (high).

Due to stability issues with valacyclovir stored at -20^{o} C, all study samples and QC samples were moved to -70^{o} C on 1/7/04. The long-term storage stability data was submitted in an amendment to this supplement. The issues pertaining to the long-term storage stability of VACV will be addressed in the review of S-014, as complete data from the sponsor were still pending at the time of completion of this review.

Pharmacokinetic Assessments

PK analyses were conducted using a non-compartmental model using WinNonlin Professional Edition Version 4.1. Actual elapsed times from dosing were used to estimate individual PK parameters for evaluable subjects. In addition, when calculating oral clearance (and other related parameters), the actual individual dose administered was used instead of the nominal dose.

Reviewer's comment:
-An accurate calculation of K_{el} for most subjects was possible with the sparse pediatric sampling scheme since Tmax is relatively short (~2 hours). Therefore, there were three available data points in the elimination phase that could be used to calculate the elimination rate constant for most subjects.

Statistical Analysis

Statistical analysis was not needed for this study as the intent was only to characterize acyclovir/valacyclovir PK and safety in children of various ages.

6. Results

Each subject in this study was dosed with 10 mg/kg BID for 3 to 5 days. PK sampling was performed following the administration of the first dose of VACV on day 1. A total of 28 subjects were enrolled, with 27 of them completing the study and 26 subjects included in the PK analysis. One subject's family withdrew the subject from the study prior to completion. Another subject was excluded from PK analysis due to quantifiable pre-dose concentrations of 530.6 ng/mL and 946.8 ng/mL for acyclovir and valacyclovir, respectively. Since these values represented concentrations that were greater than 5% of that subject's respective Cmax values, this subject was excluded from the PK analysis population. A summary of the subject demographics is listed in Table 6.

Table 6 Summary of Demographic Characteristics

	Valaciclovir 10 mg/kg BID for 3 to 5 days			
Demographics	Total Population N=28	Cohort 1 Age 6-<12 yrs N=8	Cohort 2 Age 2-<6 yrs N=13	Cohort 3 Age 1-<2 yrs N=7
Age, months				
Mean	61.1	123.3	45.6	19.0
SD	43.5	17.0	14.6	2.6
Sex, n (%)				
Females	17 (61)	4 (50)	9 (69)	4 (57)
Males	11 (39)	4 (50)	4 (31)	3 (43)
Race, n (%)				
Black/African-American	6 (21)	0	2 (15)	4 (57)
White	15 (54)	8 (100)	5 (38)	2 (29)
Other	7 (25)	0	6 (46)	1 (14)
Ethnicity, n (%)				
Hispanic/Latino	1 (4)	0	1 (8)	0
Not Hispanic/Latino	27 (96)	8 (100)	12 (92)	7 (100)
Height[a], cm				
Mean	105.9	142.5	95.8	82.7
SD	25.7	8.2	9.8	8.0
Weight[a], kg				
Mean	19.8	35.5	14.8	11.1
SD	11.0	5.0	4.3	1.6

a. Measured at Screening.

As shown by the PK parameters in Table 7, VACV levels were low compared to acyclovir. Most subjects' VACV plasma concentrations dipped below the limit of quantitation after approximately 2 hours post-dose. Acyclovir exposures in children receiving a 10 mg/kg dose of the oral suspension are compared to exposures in adults given a 500 mg solid oral dose of VACV (Table 8). The sponsor has included estimates of adult PK parameters using the pediatric PK sampling schedule to provide a more accurate comparison.

Table 7 Valacyclovir PK Parameter Estimates Following a Single 10 mg/kg Dose

Valaciclovir PK Parameter	Age 6 to <12 yrs (N=8)	Age 2 to <6 yrs (N=12)	Age 1 to <2 yrs (N=6)	Overall, Age 1 to <12 yrs (N=26)
Cmax (μg/mL)				
Geometric Mean (95% CI)	0.088 (0.065, 0.120)	0.093 (0.068, 0.129)	0.143 (0.105, 0.194)	0.101 (0.084, 0.121)
tmax (h)				
Median (Range)	0.50 (0.50-2.00)	0.63 (0.50-2.00)	0.58 (0.47-0.87)	0.58 (0.47-2.00)

Table 8 Acyclovir PK Parameter Estimates Following a Single 10 mg/kg Dose

Acyclovir PK Parameter	10 mg/kg Suspension in Pediatric Subjects (N=26)				500 mg Solid Dose in Adults[c] (N=15)	
	Age 6 to <12 yrs (N=8)	Age 2 to <6 yrs (N=12[a])	Age 1 to <2 yrs (N=6)	Overall: Age 1 to <12 yrs (N=26[b])	Actual Adult PK Sampling Schedule	Estimates using Peds PK Sampling
AUC(0-∞) (µg•h/mL)						
Mean (CV%)	8.84 (17)	5.72 (30)	6.63 (27)	6.94 (31)	11.1 (16)	10.3 (18)
Geometric Mean (95% CI)	8.72 (7.55 – 10.1)	5.48 (4.46 – 6.74)	6.44 (4.89 – 8.48)	6.61 (5.79 – 7.55)	NA	NA
Cmax (µg/mL)						
Mean (CV%)	3.08 (15)	2.05 (23)	2.49 (37)	2.47 (30)	3.37 (28)	3.07 (29)
Geometric Mean (95% CI)	3.05 (2.65 – 3.51)	2.00 (1.73 – 2.32)	2.35 (1.58 – 3.49)	2.37 (2.09 – 2.68)	NA	NA
t½ (h)						
Mean (CV%)	1.58 (19)	1.65 (45)	1.39 (22)	1.57 (34)	2.90 (13)	2.09 (29)
Geometric Mean (95% CI)	1.56 (1.34 – 1.82)	1.53 (1.19 – 1.97)	1.37 (1.08 – 1.73)	1.50 (1.33 – 1.69)	NA	NA
tmax (h)						
Median (Range)	1.00 (0.50-2.00)	1.00 (0.50-2.00)	0.96 (0.58-2.07)	1.00 (0.50-2.07)	1.0 (0.75-2.5)	1.0 (0.5-2.0)
Mean (CV%)	1.19 (45)	1.15 (47)	1.19 (57)	1.17 (47)	1.4 (38)	1.4 (40)
CL/F/kg (mL/min/kg)						
Mean (CV%)	13.5 (17)	21.9 (31)	18.8 (23)	18.5 (34)	7.33 (18)	9.52 (23)
Geometric Mean (95% CI)	13.3 (11.5 – 15.3)	21.0 (17.2 – 25.7)	18.4 (14.4 – 23.5)	17.6 (15.4 – 20.0)	NA	NA

NA=not available

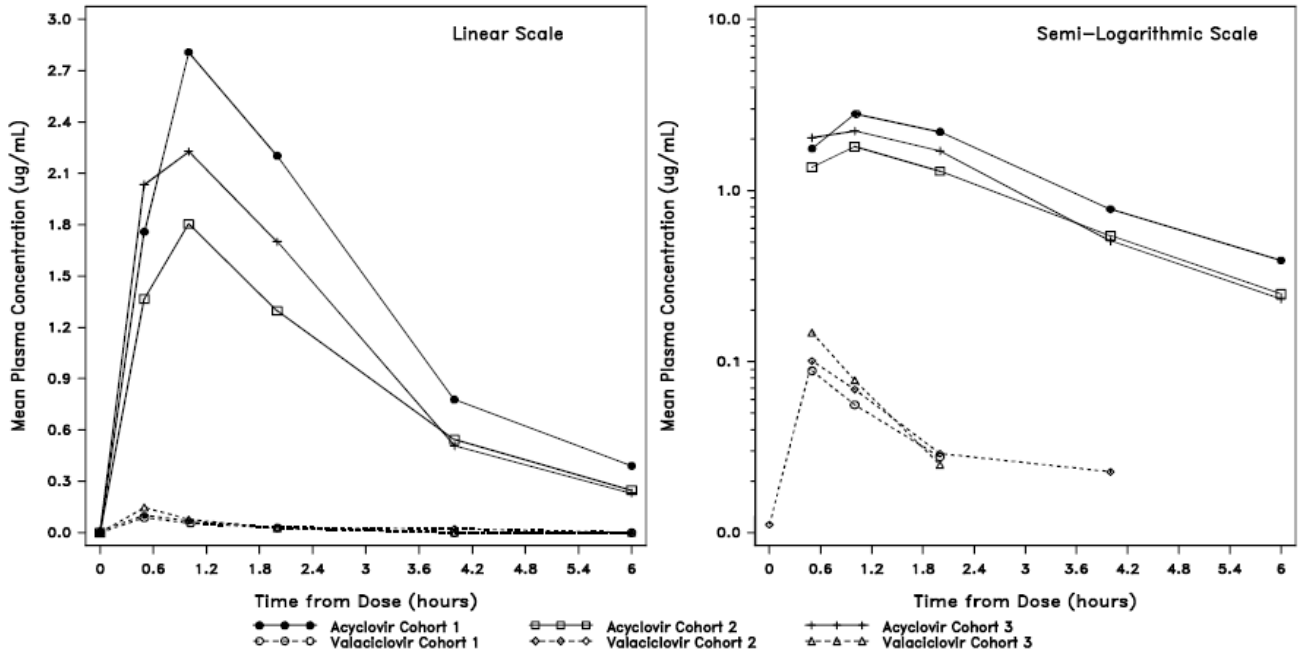
a. N=12 for Cmax and tmax; N=11 for AUC(0-∞), t½, and CL/F/kg.

b. N=26 for Cmax and tmax; N=25 for AUC(0-∞), t½, and CL/F/kg.

c. GSK Document ID Number THRS/93/0015/01; GSK Document ID Number THRS/93/0021/02; Weller, 1993.

Data Source: Table 11.5 and Table 11.6.

Figure 4 Mean Acyclovir and Valacyclovir Plasma Concentrations

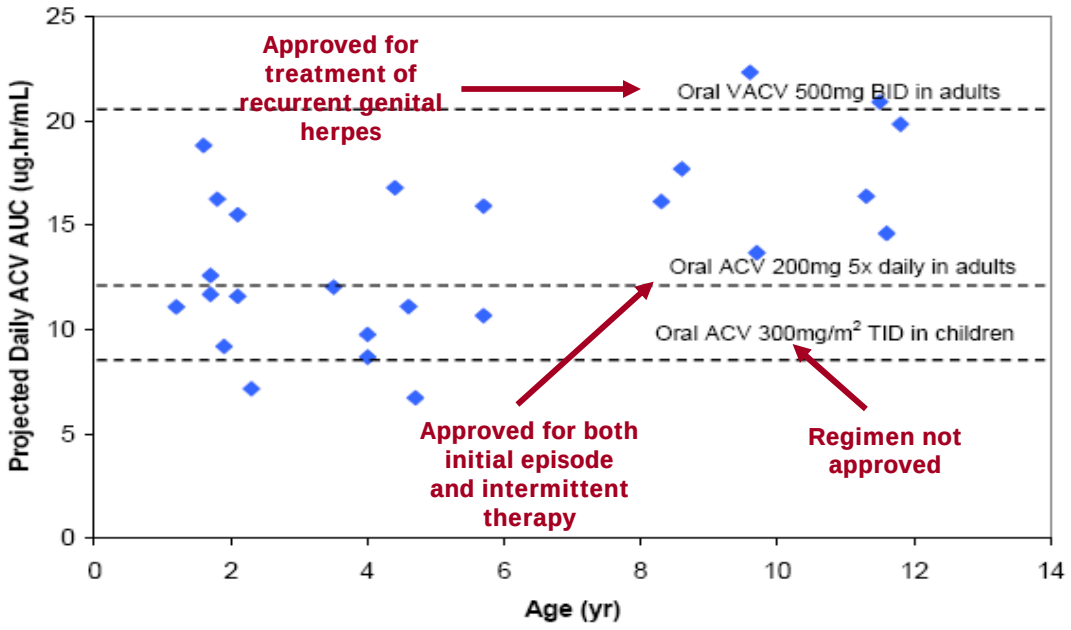


Mean acyclovir exposures across all three pediatric age groups receiving a single 10 mg/kg dose were significantly lower than the targeted historical adult exposures resulting from a single 500 mg dose (33% lower for AUC_{inf} and 20% lower for Cmax). The 6 to <12 year age group had higher AUC_{inf} and Cmax exposures that approached adult levels with a corresponding lower renal clearance than the other two groups, suggesting age-related

differences in renal function. Although the age-related differences in exposures could also be attributed to variable bioavailability of the formulation between different age groups, this explanation is unlikely to be a contributing factor since there was a lack of a clear correlation between age and peak valacyclovir levels.

When compared with historical adult daily exposure data of ACV (VACV given at 500 mg BID), most pediatric subjects' projected daily acyclovir AUC exposures did not achieve equivalent levels (Figure 5). The projected total daily AUC exposures for this study were calculated by multiplying the single-dose AUC_{inf} by 2, for twice daily dosing. The resulting values for each individual subject are represented as dots on the graph in Figure 5. The dotted lines represent mean historical AUC of the dose and population described in text on the figure. Most subjects in this study did achieve comparable or higher projected ACV daily exposures compared to adults given 200 mg ACV 5 times daily (approved for the treatment of initial and suppressive therapy of genital herpes in adults) as well as children given ACV suspension (Zovirax®) at 300 mg/m^2 TID (used anecdotally to treat HSV infection in children). However, the 300 mg/m^2 TID dose is not an approved regimen.

Figure 5 Comparison of Projected Daily ACV AUC Exposures following a single 10 mg/kg dose of Oral VACV in Children to Mean Historical Exposures



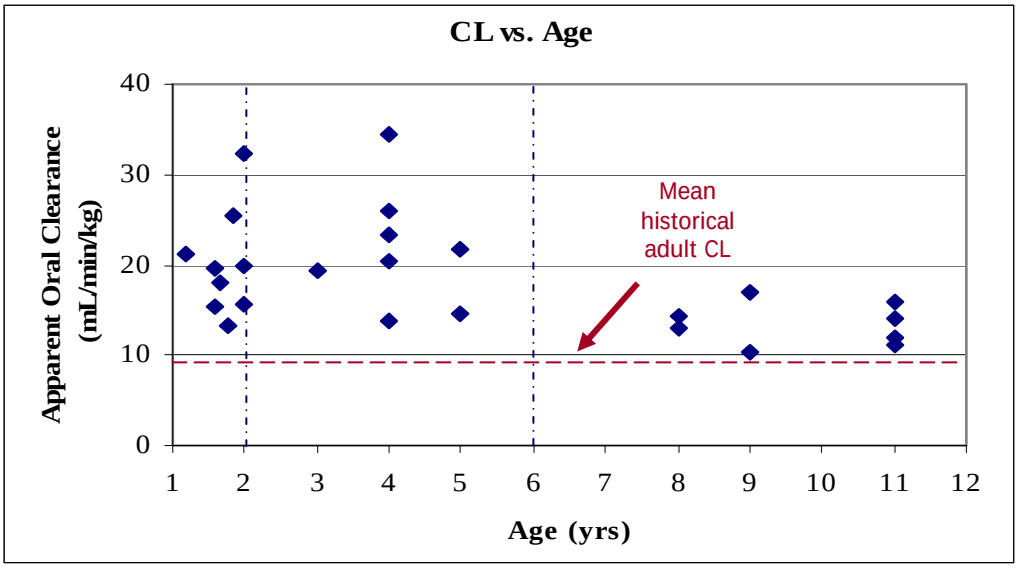
-Oral VACV 500 mg BID for 3 days in adults is approved for the treatment of recurrent genital herpes.
-Oral ACV 200 mg 5 times daily in adults is approved for both initial episode and intermittent therapy.
-Oral ACV 300 mg/m^2 TID in children is not an approved use.

7. Safety Assessments

No subject experienced serious adverse events or death in this study. No subject experienced an adverse event leading to discontinuation of the study treatment or the study itself. Nine subjects experienced a total of 21 adverse events. The investigator deemed 6 of

these events as being related to the study drug. The most frequently noted adverse events were diarrhea (2 events; 7% of total study population) and dehydration (2 events; 7% of total study population). Safety data are available for a mean duration of 3.9 days of treatment. For a more detailed analysis, please refer to the medical officer's review.

Figure 6 Weight-Normalized Oral Clearance for Each Pediatric Subject Following a Single 10 mg/kg dose of VACV



8. Conclusion

Figure 6 shows that acyclovir clearance (per kg basis) is age-dependent. The older pediatric subjects (>6 years old) had lower weight-normalized clearances and thus correspondingly higher acyclovir exposures. As the age of the pediatric patients increased, the clearance decreased, approaching adult levels.

The projected mean daily acyclovir AUC and Cmax exposures across all age groups did not meet the targeted adult historical exposures from the approved VACV dose of 500 mg BID for the treatment of recurrent genital herpes. Mean exposures for all age groups were above the historical pediatric exposures from oral ACV, 300 mg/m^2. However, this dose is not approved for any indication. Although the mean exposures obtained in this study across all ages were higher than the ACV 200 mg 5 times daily regimen (for the treatment of initial and intermittent genital herpes) in adults, this indication would have very limited relevance in pediatric patients of this age range.

In addition, sufficient data are not available to support VACV for the treatment of recurrent genital herpes in the 1 to <12 year age group because clinical information on recurrent genital herpes in young children is limited. Subjects in this study did not have genital herpes. Please refer to the medical officer's review for further details.

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