CLINICAL PHARMACOLOGY REVIEW

Application Number	IND 106,153 PIND (b) (4) NDA 18,603
Link to EDR	\\Cdsesub4\nonectd\IND (b) (4) \6189802 \\Cdsesub4\nonectd\IND106153\6150678
Submission Date	9/2/2016 (IND 106,153) 10/12/2018 (NDA 18,603)
Submission Type	*Pediatric efficacy supplement under BPCA's off-patent process*
Brand Name	ZOVIRAX
Generic Name	Acyclovir
Dosage Form and Strength	Powder for IV administration (50 mg/mL after reconstitution)
Route of Administration	IV infusion
Proposed Indication	Treatment of herpes simplex virus (HSV) infection
Applicant	Dr. Brian Smith at Duke University /NIH
OCP Review Team	*Su-Young Choi, Pharm.D., Ph.D* *Jeffry Florian, Ph.D* *Shirley Seo, Ph.D*

The applicant is different from the sponsor of NDA 18,603 (ZOVIRAX). In this review, unless otherwise noted, the "applicant" refers to Dr. Brian smith.

1. Executive Summary

This application (IND 106,153) was submitted to support changes in dosing regimens of intravenous (IV) acyclovir for the treatment of neonatal infection through BPCA off-patent labeling change process. The current approved dosing regimen of acyclovir for neonatal HSV infection is 10 mg/kg every 8 hours for 10 days. However, a higher dose and longer duration (20 mg/kg every 8 hours for 21 days) is commonly used in clinical practice based on a publication (Kimberlin et al, 2001, referred to as the Kimberlin trial in this review) where superiority of the high dose/longer duration regimen to the FDA approved dosing regimen was observed.

To support the labeling changes, the following clinical study reports have been submitted from the applicant under IND 106,653. In addition, clinical study report and datasets for the Kimberlin trial were also submitted by NIH under PIND (b) (4) Therefore, a total of three clinical study reports have been submitted to support the changes in acyclovir dosing regimens.

- An open-label study to describe the pharmacokinetics of acyclovir in premature infants (ACY01) under IND 106,653
- Safety and efficacy of high-dose acyclovir in infants with HSV or suspected HSV (ACY02 – although it is titled as safety and efficacy, no efficacy data were included) under IND 106,653

- Safety and efficacy of high-dose intravenous acyclovir in the management of neonatal herpes simplex virus infection (referred as the Kimberlin trial throughout the review) under PIND (b) (4)

The applicant proposed the following dosing regimens for the treatment of neonatal HSV infection.

- (b) (4)
- 20 mg/kg q8h in infants (b) (4) weeks PMA
- 20 mg/kg q12h in infants (b) (4) weeks PMA

Upon review, FDA concluded that the following dosing regimens are recommended for the treatment of neonatal HSV infection.

- 20 mg/kg q8h in infants ≥ 34 weeks PMA
- 20 mg/kg q12h in infants < 34 weeks PMA

1.2 OCP recommendation

The Office of Clinical Pharmacology (OCP) recommends the approval of 20 mg/kg every 8 hours for 21 days for the treatment of neonatal HSV infection in infants greater than or equal to 34 weeks post-menstrual age and 20 mg/kg every 12 hours for 21 days in infants less than 34 weeks post-menstrual age.

1.3 Labeling recommendations

The Office of Clinical Pharmacology recommends the following labeling changes. Note that the current ZOVIRAX and generic drugs' USPI do not follow the Physician Labeling Rule (PLR) format and the review team decided not to update the format at this time.

CLINICAL PHARMACOLOGY SECTION
Special Populations: Pediatrics

- Acyclovir pharmacokinetic (PK) data in neonates aged from Birth to 3 Months stratified by post-menstrual age is summarized.

DOSAGE AND ADMINISTRATION SECTION
Neonatal Herpes Simplex Virus Infection

- PMA of at Least 34 Weeks: 20 mg/kg infused at a constant rate over 1 hour, every 8 hours for 21 days.
- PMA of Less than 34 Weeks: 20 mg/kg infused at a constant rate over 1 hour, every 12 hours for 21 days.
- General statement "*In neonates with ongoing medical conditions affecting their renal function beyond the effect of prematurity, the doses recommended should be used with caution*" is added for consistency in USPI

Reviewer's comments:
On June 20, 2018, the Agency requested GSK implement labeling changes and submit a Supplement – Changes Being Effected (CBE-0) in response to Section 409i of the Public Health Service Act (42 U.S.C. 284m) which authorizes the Food and Drug Administration (FDA) to require holders of approved applications to make labeling changes based upon information that becomes available from pediatric studies conducted pursuant to this law. GSK subsequently submitted an efficacy supplement/response on

October 12, 2018 (SDN293, NDA 18603) to this request with an alternative dosing regimen based on creatinine clearance regardless of PMA. The review team sent a list of issues related to the proposed target exposures of acyclovir and the use of creatinine clearance-based dosing regimens in neonates to GSK (FDA letter dated 12/4/2018, NDA 18603). Upon further discussion with the FDA, GSK agreed to accept the FDA's current recommendation as is (b) (4) .

2. Summary of Clinical Pharmacology Review

2.1 Overview of the Product and Regulatory Background

The BPCA requires that the NIH identify and study therapeutic areas for which there is a critical need for pediatric trial information and labeling information. NICHD prioritized acyclovir as a drug that needed further study in pediatric populations with HSV infections in its 2005 Federal Register notice.

Acyclovir is a nucleoside analog antiviral drug approved for various types of herpes simplex virus (HSV) infections including neonatal HSV infection. The current approved dosing regimen of acyclovir for neonatal HSV infection is 10 mg/kg every 8 hours for 10 days. This dosing regimen was approved based on a clinical trial where comparable efficacy was demonstrated between acyclovir (30 mg/kg/day) and vidarabine (30 mg/kg/day) in 202 infants infected with neonatal herpes simplex virus (ZOVIRAX USPI, Whitley et al, 1991). However, following the publication by Kimberlin et al in 2001, the approved dosing regimen is no longer used in clinical practice. In the Kimberlin trial, a higher dose and longer duration of acyclovir administration (20 mg/kg q8hr for 21 days) was associated with a better clinical outcome (lower mortality) as compared to 15 mg/kg q8hr for 21 days or the currently approved dose (10 mg/kg q8h for 10 days). Based on this publication, 20 mg/kg q8hr for 21 days (or dosing regimens similar to this) are typically used in clinical practice.

Due to this discrepancy between the approved dosing regimen and the dosing regimens routinely used in clinical practice, acyclovir use for neonatal HSV infection was selected as one of the therapeutic areas for which there is a critical need for pediatric trial information and labeling information by the National Institute of Child Health and Human Development (NICHD). The NICHD awarded a contract to the applicant (Dr. Brian Smith et. al, Duke University) and a clinical trial to determine pharmacokinetics of acyclovir in infants was conducted.

FDA has extensively discussed the path forward for updating the acyclovir dosing regimen in the label. FDA concluded that pharmacokinetic data conducted by the applicant alone are not sufficient and efficacy data will be needed to support the use of high dose acyclovir for the treatment of neonatal HSV infection. With collaborative efforts between FDA and NIH, clinical study report and datasets from the Kimberlin trial have been submitted to support a labeling change of acyclovir under a different IND (IND (b) (4)

2.2. Approved indication and general clinical pharmacology characteristics of acyclovir

Acyclovir is a nucleoside analog antiviral active against herpesvirus. The IV formulation of acyclovir is approved for the following indications.

Table 1. IV acyclovir indications

Herpes Simplex Infections – mucosal and cutaneous HSV-1 and HSV-2 infections in immunocompromised patients	
• Adults and adolescents • Pediatrics (under 12 years of age)	• 5 mg/kg infused over 1hr at a constant rate, q8h for 7d • 10 mg/kg infused over 1hr at a constant rate, q8h for 7d
Severe initial clinical episode of herpes genitalis	
• Adult and adolescents	• 5 mg/kg infused over 1hr at a constant rate, q8h for 5d
Herpes simplex encephalitis	
• Adults and adolescents • Pediatrics (3 mo to 12 years old)	• 10 mg/kg infused over 1hr at a constant rate, q8h for 10d • 20 mg/kg infused over 1hr at a constant rate, q8h for 10d
Neonatal herpes simplex virus infections (all types- mucosal, cutaneous, disseminated, or CNS)	
• Birth to 3 mo	• 10 mg/kg infused at a constant rate over 1 hour, every 8 hours for 10 days. In neonatal herpes simplex infections, doses of 15 mg/kg or 20 mg/kg (infused at a constant rate over 1 hour every 8 hours) have been used; the safety and efficacy of these doses are not known.
Varicella zoster infections in immunocompromised patients	
• Adults and adolescents • Pediatrics (under 12 years old)	• 10 mg/kg infused over 1hr at a constant rate, q8h for 7d • 20 mg/kg infused over 1hr at a constant rate, q8h for 7d

Pharmacokinetic characteristics

Absorption

- Following the IV administration in adult patients with normal renal function, proportionality between the dose and plasma levels was seen doses from 2.5 mg/kg up to 15 mg/kg.

Distribution

- Plasma protein binding: low (9-33%)
- Concentrations in the cerebrospinal fluid: ~ 50% of plasma values

Metabolism/Elimination

- Renal excretion of unchanged drug is the major route of elimination, accounting for 62-95% of the dose.
- Half life in adults with normal renal function: approximately 2.5 hours

Table 2. Pharmacokinetic parameters in infants and adults

Adult	Dosage	N	Cmax (µg/mL)	Ctrough(µg/mL)	reference
	5 mg/kg every 8 hours	8	9.8 (range:5.5-13.8)	0.7 (range:0.2-1.0)	Zovirax Label
	10 mg/kg every 8 hours	7	22.9 (range:14.1-44.1)	1.9 (range:0.5-2.9)	Zovirax Label
Pediatric	Acyclovir pharmacokinetics were determined in 16 pediatric patients with normal renal function ranging in age from 3 months to 16 years at doses of approximately 10 mg/kg and 20 mg/kg every 8 hours. Concentrations achieved at these regimens are similar to those in adults receiving 5 mg/kg and 10 mg/kg every 8 hours, respectively. (No Cmax, Ctrough available in the label)				Zovirax Label
Neonates	5 mg/kg every 8 hours	4	6.04 ± 1.17 (range: 3.6-8.9)	0.98 ± 0.72 (range: 0.45-2.3)	Zovirax IV review (5/22/98)

	10 mg/kg every 8 hours	4	13.9 ± 2.4 (range: 11.3-18.9)	2.2 ± 1.0 (range: 1.15-3.04)	
	15 mg/kg every 8 hours	4	20.4 ± 4.2 (range:15.6-33.2)	3.0 ± 2.8 (range:1.3-19.4)	

2.3. Overview of clinical trials submitted to support the proposed changes

1. Kimberlin Trial ([redacted]) (b) (4)

Title: Safety and efficacy of high-dose intravenous acyclovir in the management of neonatal herpes simplex virus infection

Design: The study was an open-label evaluation of intravenous acyclovir for the treatment of neonatal HSV infection. The first 16 patients enrolled received intermediate-dose acyclovir (45 mg/kg/day), and the next 72 patients received high-dose acyclovir (60 mg/kg/day). Acyclovir was administered in 3 divided daily doses for 21 days. Neonates were assessed prospectively throughout treatment and at scheduled follow-up visits for the first 4 years of life. Data were compared with the previous trial in which patients received the FDA-approved acyclovir dose (30 mg/kg/day) for 10 days.

Results: The survival rate for the patients with disseminated HSV disease treated with high-dose acyclovir was significantly higher as compared to patients dosed with intermediate-dose acyclovir or the FDA approved dose of acyclovir. When the missing data were treated as the patient surviving, the 6-month mortality rates for the high-dose, the intermediate dose, and the FDA approved dose were 27%, 57%, and 61%, respectively. The high dose showed a similar level of benefit over the other doses in terms of mortality at other time points (12 and 24 months) and when the missing data were treated as a patient death. For patients with CNS disease, however, survival rates were similar for the high-dose (HD) and standard-dose (SD) groups. No significant or new safety issues were identified.

2. ACY01 (IND [redacted] (b) (4))

Title: An open-label study to describe the pharmacokinetics of acyclovir in premature infants

Design: The safety and PK of IV acyclovir in preterm and term infants with suspected systemic infections was evaluated. Thirteen participants were enrolled under version 1.0 of the protocol (BSA based dosing regimen, 500 mg/m2 IV q8h) and nineteen participants were enrolled under version 2.0 of the protocol as described below. Sparse samples were collected around the first dose and at steady-state and population pharmacokinetic analysis was performed.

Table 3. Dosing regimen of ACY01

Version 1.0 Group	Gestational Age	Postnatal Age	Dosage
1	23-29 weeks	< 14 days	500 mg/m^2 IV q8h
2	30-42 weeks	< 14 days	500 mg/m^2 IV q8h
3	23-29 weeks	14-60 days	500 mg/m^2 IV q8h
4	30-42 weeks	14-60 days	500 mg/m^2 IV q8h

Version ≥2.0 Group	Gestational Age	Postnatal Age	Dosage
1	23-29 weeks	< 14 days	10 mg/kg IV q12h
2	23-29 weeks	14-44 days	20 mg/kg IV q12h
3	30-34 weeks	<45 days	20 mg/kg IV q8h

Results:
Acyclovir population PK was characterized by a one compartment model. PMA was identified as the most significant age covariate [compared to post-natal age (PNA) or gestational age (GA)] for acyclovir CL. The final population pharmacokinetic model is CL (L/h/kg) = 0.305 * (PMA/31.3)$^{3\,02}$ and V (L/kg) = 2.8.

3. ACY02 (IND)
Title: Safety and efficacy of high-dose acyclovir in infants with HSV or suspected HSV

Study design:
All infants with confirmed or suspected HSV in the Pediatrix Medical Group PMG administrative database, discharged between 2002 and 2012, who received acyclovir per standard of care, were identified to evaluate the safety of acyclovir treatment. Medical records provided by Duke University Medical Center, Children's Hospital of Orange County, University of North Carolina and Cincinnati Children's Hospital were also used to evaluate the safety of intravenous HD acyclovir (60 mg/kg/day).

Results:
The median mean daily study dose per kg of participant dosing weight was 58.8 mg/kg (20.1 - 431.4). Rash was the most common diagnostic AE reported (37%). Elevated liver enzymes were the most commonly reported laboratory AEs. No efficacy analysis was performed. Refer to Clinical reviewer's assessments. Efficacy was not evaluated.

3. Clinical Pharmacology Review Questions

a. What is the pivotal evidence for effectiveness of a high dose acyclovir for the treatment of neonatal HSV infection? And to what extent does the available clinical pharmacology information provide pivotal or supportive effectiveness?

The benefit of a higher dose and longer duration (20 mg/kg q8h for 21 days) to the approved dose (10 mg/kg q8h for 10 days) for the neonatal HSV infection was demonstrated in the Kimberlin trial. The study was an open-label evaluation of IV acyclovir doses at 15 mg/kg q8h for 21 days (n=16) and 20

mg/kg q8h for 21 days (n=72) in neonates with HSV infection. The survival rate for the patients with disseminated HSV disease treated with high-dose acyclovir was significantly higher as compared to patients dosed with intermediate-dose acyclovir or the FDA approved dose of acyclovir. When the missing data were treated as the patient surviving, the 6-month mortality rates for the high-dose, the intermediate dose, and the FDA approved dose were 27%, 57%, and 61%, respectively. The high dose showed a similar level of benefit over the other doses in terms of mortality at other time points (12 and 24 months) and when the missing data were treated as a patient death.

Although there are several critical issues associated with the Kimberlin trial's study design and data (non-randomized, open-label, historical-controlled trial with a significant amount of missing data after the 6 months follow up period), FDA concluded that the trial provides reasonable evidence that a higher dose and longer duration of acyclovir is associated with a better clinical outcome compared to the approved dose and agreed to update the label. Refer to the clinical/biostat review for detailed information.

It should be noted that full extrapolation of efficacy (solely matching acyclovir exposures to those associated with efficacy in adults or older pediatric patients) was not deemed an acceptable approach for this application due to the different disease progression of HSV infection in neonates. However, pharmacokinetic data submitted by the applicant are utilized to derive a dosing regimen for preterm neonates. See section d.

b. Is the proposed dosing regimen appropriate?

No, we disagree with the applicant's proposed dosing regimen, (b) (4)

Applicant's proposed dosing regimens for the treatment of neonatal HSV infection are as follows.

- (b) (4)
- 20 mg/kg q8h in infants (b) (4) weeks PMA
- 20 mg/kg q12h in infants (b) (4) weeks PMA

(b) (4)

However, the OCP review team has concluded that the proposed doses are not acceptable. The applicant-defined target concentration is not a validated marker for efficacy. A defnitive quantitative relationship between the in vitro susceptibility of herpes viruses to antivirals and the clinical response to therapy has not been established. Therefore, dosing recommendations based (b) (4) is not acceptable. Second, there is no exposure-response relationship data supporting doses (b) (4)

(b) (4)

In summary, OCP recommends the dose evaluated in the Kimberlin trial, 20 mg/kg q8h for 21 days for the treatment of neonatal HSV infection for approval. This message has been conveyed to the applicant , and the applicant submitted the following labeling proposal on the 12th of April. This will be discussed in Section d in detail.

- 20 mg/kg every 12 hours in infants (b) (4) weeks PMA
- 20 mg/kg every 8 hours in infants (b) (4) weeks PMA

c. What is the pharmacokinetics of acyclovir in neonates?

In ACY01, the pharmacokinetics of acyclovir was determined in 28 neonates (81 samples) who received various doses of acyclovir due to suspected neonatal HSV infection. The doses administered in neonates ranged from 20 mg/kg/day to 178 mg/kg/day and the median (range) gestational age and PMA were 30.1 weeks (23-40 weeks) and 31.3 weeks (25 to 41 weeks), respectively.

Acyclovir population PK was characterized by a one compartment model. PMA was identified as the most significant age covariate [compared to post-natal age (PNA) or gestational age (GA)] for acyclovir CL. The final population pharmacokinetic model is CL (L/h/kg) = 0.305 * $(PMA/31.3)^{3.02}$ and V (L/kg) = 2.8.

Table 4. Individual empirical Bayesian post-hoc parameter estimates for acyclovir

PMA	N	CL (L/h/kg)	V (L/kg)	$t_{1/2}$ (h)	$Cmax_{ss}$ (mg/L)	$C50_{ss}$ (mg/L)	$Cmin_{ss}$ (mg/L)
<30	13	0.211 (0.095-0.310)	2.88 (0.646-5.30)	10.2 (4.73-13.2)	10.3 (4.59-110)	7.12 (3.38-65.7)	3.92 (2.38-39.3)
30 - <36	9	0.449 (0.302-0.812)	4.49 (1.87-10.85)	6.55 (4.28-9.26)	8.83 (5.44-29.8)	6.80 (3.72-16.9)	5.10 (2.54-9.62)
36 - 41	6	0.589 (0.126-0.769)	2.55 (0.293-4.09)	3.00 (1.61-3.69)	12.4 (10.8-86.1)	5.82 (5.23-22.0)	2.90 (2.19-7.46)
Overall	28	0.278 (0.095-0.812)	3.34 (0.293-10.85)	7.07 (1.61-13.2)	11.1 (4.59-110)	6.33 (3.38-65.7)	4.15 (2.19-39.3)

Data are median (range).

d. What is OCP's recommended dosing regimen for premature neonates?

The efficacy and safety of acyclovir was evaluated in full term or near-full term neonates in the Kimberlin trial. The median gestational age of the patients was 39 weeks and only 11% of patients were less than the gestational age of 34 weeks. The minimum age for the enrollment was 32 weeks. Therefore, the safety and efficacy of high dose acyclovir was mostly evaluated in full term neonates in the Kimberlin trial. As renal function is not fully maturated in premature neonates, a reduction in dose and/or an increase in the dosing interval should be considered for preterm neonates.

Using data from ACY01, OCP determined doses in premature neonates that produce exposures comparable to those observed in full term neonates receiving 20 mg/kg q8h. Various cutoff PMA values and dose adjustment (either dose reduction or duration increase) were explored including the proposed dose by the applicant (PMA cutoff at (b) (4) weeks). OCP concluded that 20 mg/kg q12 hour for neonates with PMA less than 34 weeks is predicted to produce exposures comparable to 20 mg/kg q8h in neonates

with PMA > 34 weeks. The predicted Cmax values are all below the reported concentrations (50 µg/mL) associated with toxicity in case reports.

Table 5. Simulated acyclovir exposures for the review team's proposed dosing regimen. Demographics and pharmacokinetic parameters from the simulations are shown for each group (26 to <34 weeks, 34 to 42 weeks).

Parameter	PMA Group	
	26 to <34 Weeks 20 mg/kg q12 hr	**34 to 42 Weeks 20 mg/kg q8hr**
GM AUC (mg/L/hr)	159.1	109.6
[IQR]	[107.5; 234.6]	[74.5; 160.9]
Geometric CV	62%	62%
SD	118.4	80.8
GM Cmax (mg/L)	10.7	8.4
[IQR]	[6.7; 16.7]	[5.2; 13.2]
Geometric CV	75%	79%
SD	10.7	8.9
GM Ctrough (mg/L)	3.6	1.9
[IQR]	[2.5; 5.2]	[1.3; 2.8]
Geometric CV	56%	55%
SD	2.3	1.2
Mean age (PMA)	29.5	38.0
Mean weight (kg)	1.20	2.75
Clearance (L/hr/kg)	0.297	0.644
Volume (L/kg)	3.97	4.06

4. POPULATION PHARMACOKINETIC ANALYSES

4.1 Applicant's Population PK Analysis of acyclovir

A population PK model was developed based on data from preterm and term infants in study NICHD-2011-ACY01. The objectives of this analysis were:

1) Characterize the PK of IV acyclovir in premature and term infants 23-42 weeks gestational age (GA) and <61 days postnatal age (PNA)
2) Identify covariates that impact acyclovir exposures in this population
3) Identify percentage of pediatrics who achieved surrogate pharmacodynamics targets of steady-state plasma acyclovir peak ($Cmax_{ss}$), concentration at 50% of the dosing interval ($C50_{ss}$), and trough concentration ($Cmin_{SS}$) ≥3 mg/L and ≥1 mg/L

4.1.1 Study Pharmacokinetic Data

Pediatric data from NICHD-2011-ACY01 under two separate dosing paradigms was included in this analysis. Version 1.0 was a single-center, open-label, PK study that enrolled 13 infants 23–42 weeks GA and <61 days PNA with suspected infection. Version ≥2.0 was a multi-center, open-label, PK study that enrolled 19 infants 23–34 weeks GA and <45 days PNA with suspected infection. Study dosing was as shown below in Table 4.1-1. All doses were administered as 1-hour infusions.

Table 4.1-1: Preterm and term infant dosing for NICHD-2011-ACY01

Protocol Version	Number of Subjects	GA (weeks)	PNA (days)	Dose
Version 1.0	1	23-29	<14	500 mg/m2 IV q8h
	1	30-42	<14	
	3	23-29	14-60	
	8[a]	30-42	14-60	
Version ≥2.0	9[b]	23-29	<14	10 mg/kg IV q12h
	4	23-29	14-44	20 mg/kg IV q12h
	6[a]	30-34	<45	20 mg/kg IV q8h

[a]Number of subjects are 7 and 5, respectively, are removing those without PK samples
[b]Number of subjects are 7 after removing two subjects with only a single sample
Source: Adapted from applicant's 16.4.1.1_ACY01-PK-Report-Main-Narrative.pdf, pg 11, Table 1

In Version 1.0, PK samples were planned to be collected after the first dose at three times (0-5 minutes, 2-4 hours, and 6-8 hours after the end of the infusion) and four times steady state (prior to dosing and 0-5 minutes, 2-4 hours, and 6-8 hours after the end of the infusion). In Version ≥2.0, PK samples were planned to be collected after the first dose (0-15 minutes after end of infusion and within 30 minutes prior to administration of the second dose), at steady state (30 minutes prior to dosing, 0-15 minutes and 2-3 hours after end of infusion, and within 30 minutes of the next dose), and following the last dose (15-18 hours after drug administration).

In all, there was PK data available from 28 of the 32 subjects. A total of 81 of the original 92 plasma samples were available for the analysis. The reason for excluding data from 4 of the subjects was: i) two infants did not contribute any PK samples (GA/PNA of 37/1 and 34/6,

respectively); and ii) two infants contributed only a single sample which were outlying high values and were not included in the final analysis (GA/PNA of 24/3 and 24/3, respectively). The reason for excluding the 11 samples were: i) single sample from a subject as stated previously; and ii) samples suspected to be drawn during the infusion or flush. Demographics for the 28 subjects included in the analysis are shown below in Table 4.1-2.

Table 4.1-2: Subject demographics for preterm and term infants included in the population PK analysis

Variable	Total (%) or Median (Range)
Gestational age (weeks)	30.5 (23-40)
Postnatal age (days)	3.5 (1-30)
Postmenstrual age (weeks)	31.3 (25-41)
Birth weight (grams)	1295 (510-4840)
Weight (grams)	1370 (578-5720)
Female	15 (54%)
White	16 (57%)
Serum creatinine (mg/dL)	0.9 (0.3-1.8)
Vasopressin use	1 (4%)
Dopamine use	4 (14%)
Epinephrine use	7 (25%)

Values for GA, PNA, PMA, and weight are at the time of first PK sample collection.

Source: Applicant's 16.4.1.1_ACY01-PK-Report-Main-Narrative.pdf, pg 15, Table 2

4.1.2 Model Development and Evaluation

The concentration-time data were modeled and simulated using NONMEM version 7 (b) (4) , interfaced with Pirana version 4.0 (http://www.pirana-software.com/) and WINGS for NONMEM version 7 (Auckland, NZ). Diagnostic plots were executed in Xpose version 4 (http://xpose.sourceforge.net/) and Stata version 11 (StataCorp, College Station, TX). The bootstrap was performed using WINGS for NONMEM. Excel (Microsoft, Redmond, WA) and STATA were used to generate PK tables, figures, and listings.

One and 2-compartment structural models and proportional and proportional plus additive residual error models were explored. Random effects on structural model parameters were considered supported by the data if shrinkage was <30%. Weight with an exponent of 1 was included *a priori* as a covariate for V and CL in the base model. Standard PK models and equations incorporated into NONMEM, ADVAN1, and TRANS2 subroutines were used in this analysis. Individual estimates of elimination rate constant (Ke), $t_{1/2}$, $Cmax_{ss}$, $C50_{ss}$, and $Cmin_{ss}$ at steady state were calculated from the individual empirical Bayesian estimates of CL and V.

Diagnostic plots included the following: observed concentration versus predicted concentration and versus individual predicted concentration; weighted residuals and conditional weighted residuals versus predicted concentration and versus time after dose; conditional weighted residuals histogram; and observed versus predicted and individual predicted concentrations by patient. Diagnostic plots and objective function value (OFV) were used to assess goodness of fit of the base model.

Covariates were investigated for their influence on PK parameters (e.g., CL and V). Continuous covariates evaluated were PNA, GA, PMA, and SCR; categorical covariates included race, ethnicity, sex, and use of concomitant vasopressin, dopamine, and epinephrine. Missing covariate values were imputed using the closest value available for that subject using either a carry-forward approach or back-fill approach depending on which date was closest. If there was a tie in the number of days from the prior and next available value, then the prior available value was used (i.e., carried forward).

Individual subject ETAs (η), defined as the deviation from the typical population parameter values, were plotted against covariates to graphically assess relationships between variability in PK parameters and covariates. Covariates with a discernible graphical relationship to ETA CL and ETA V were evaluated for inclusion in the final model. The threshold for significance of a single covariate was reduction of the objective function by more than 3.84 ($p<0.05$).

The robustness and stability of the final PK model was assessed by nonparametric bootstrap. One thousand replicates of the final model were generated to assess precision of the PK parameters and agreement between final model and bootstrap parameter estimates. A VPC was conducted to provide visual comparison between distributions of 1000 simulated datasets from the final model overlaid with observed acyclovir concentrations. The threshold for good agreement between simulated and observed data was <15% of observed concentrations falling outside the 90% prediction interval.

4.1.3 Simulations

The Pediatrix Medical Group database contains information from infants discharged from 322 U.S. neonatal intensive care units managed by the Pediatrix Medical Group from 1997–2011. A random sample of 1000 infants was obtained from the Pediatrix database to inform covariate distributions (GA, PNA, PMA, and SCR) for simulations.

Steady-state concentration ≥3 mg/L was chosen as the surrogate PD target for acyclovir. PK measures for evaluation included $Cmax_{ss}$, $C50_{ss}$, and $Cmin_{ss}$ at steady state. Dosing regimens were proposed and evaluated based on achieving the PD and safety targets; namely, maximizing the fraction of infants with concentrations ≥3 mg/L and minimizing the fraction of infants with concentrations ≥50 and 70 mg/L, respectively.

4.1.4 Modeling Results

Base model: A 1-compartment model was selected (ADVAN1 TRANS2), as a 2-compartment model did not significantly improve goodness of fit. A proportional residual error model was selected over a proportional plus additive model as the latter did not significantly improve goodness of fit. As a plot of ETA CL vs. ETA V suggested correlation, covariance between these parameters was estimated. Random effects were supported on CL and V with shrinkage <20%.

Final model: Weight with an exponent of 1 was included *a priori* as a covariate for V and CL in the base and final model. An exponent of 1 was used in the base and final model despite modest improvement in goodness of fit with an estimated exponent ($\Delta OFV = -9.38$) because 1) the relationship of weight to CL is likely dataset-dependent and 2) to aid in interpretability by clinicians. Plots of PMA, PNA, GA, and SCR were suggestive of a relationship with ETA CL;

no covariates were suggestive of a relationship with ETA V other than weight. PMA was identified as the most significant age covariate for acyclovir CL. SCR was the only significant non-age covariate for CL. Addition of SCR to the PMA model did not significantly reduce the OFV. Thus, the final model only includes weight and PMA as covariates for CL and weight as the only covariate for V. The final model and bootstrap PK parameters are summarized in Table 4.1-3. The final model has high inter-subject variability in CL and V (52% and 85%, respectively), suggesting highly variable PK. This is likely due to the limited data set, sparse sampling from patients, and rapid pediatric development (e.g., renal maturation) over the treatment duration.

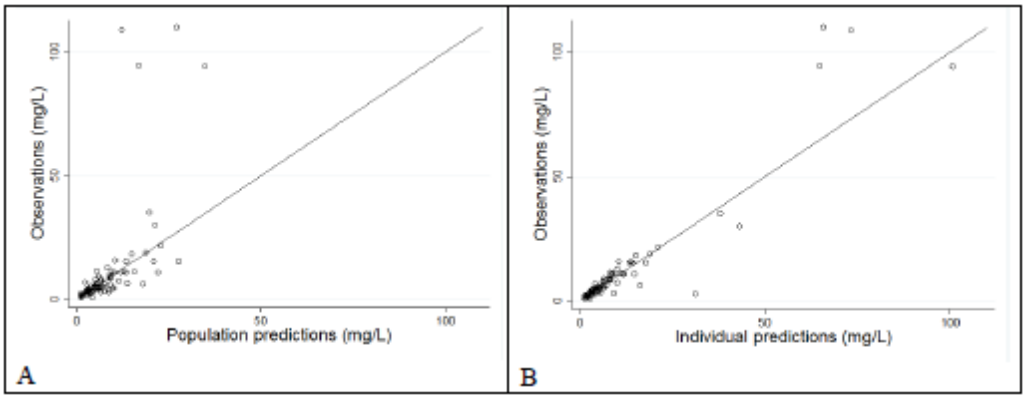
Table 4.1-3: Final model and bootstrap PK parameters for the acyclovir population PK analysis

			Bootstrap CI		
Parameter	**Point Estimate**	**%RSE**	**2.5%**	**Median**	**97.5%**
CL (L/h/kg)	0.305	13.9	0.237	0.307	0.379
V (L/kg)	2.8	14.8	1.82	2.80	3.67
CL, PMA	3.02	11.5	2.39	3.02	4.18
Inter-individual variability (CV%)					
CL	52.8	36.2	35.6	53.2	84.4
V	85.0	51.5	4.89	81.3	140
CL vs. V correlation coefficient	0.98	45.7	0.62	1.00	1.02
Residual variability (CV%)	34.5	35.0	21.1	32.0	43.4

Source: Applicant's 16.4.1.1_ACY01-PK-Report-Main-Narrative.pdf, pg 21, Table 5

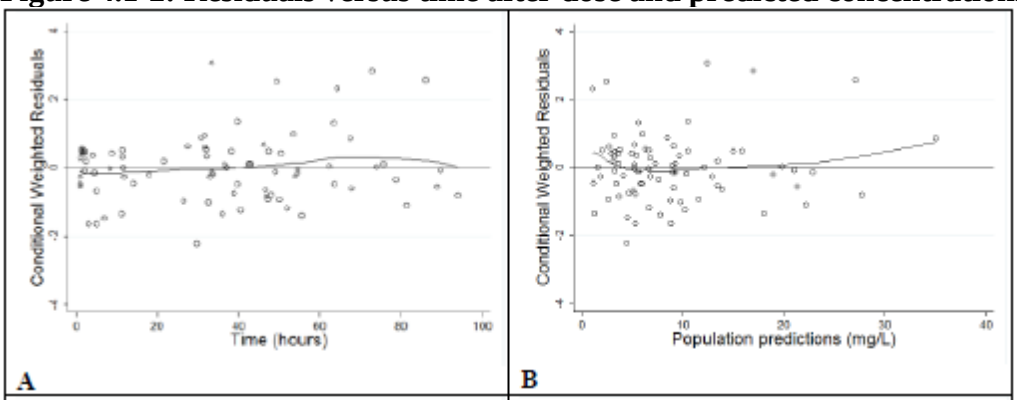
Diagnostic plots are shown in Figure 4.1-1 and 4.1-2 below. Residuals were randomly scattered around zero, and no trends were observed with increasing time or concentration. A summary of individual empirical Bayesian post-hoc parameter estimates for the preterm and term infants is shown below in Table 4.1-4.

Figure 4.1-1: Observed versus predicted (A) and observed versus predicted concentration for the final model



Source: Applicant's 16.4.1.1_ACY01-PK-Report-Main-Narrative.pdf, pg 18, Figure 3

Figure 4.1-2: Residuals versus time after dose and predicted concentrations



Source: Adapted from applicant's 16.4.1.1_ACY01-PK-Report-Main-Narrative.pdf, pg 19, Figure 4

Table 4.1-4: Acyclovir EBEs by post-menstrual age (PMA) category and overall

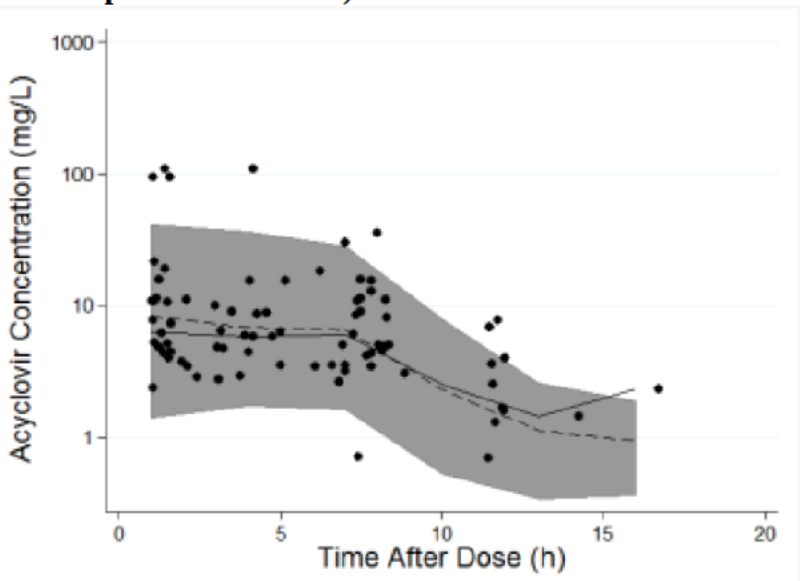
PMA	N	CL (L/h/kg)	V (L/kg)	$t_{1/2}$ (h)	$Cmax_{ss}$ (mg/L)	$C50_{ss}$ (mg/L)	$Cmin_{ss}$ (mg/L)
<30	13	0.211 (0.095-0.310)	2.88 (0.646-5.30)	10.2 (4.73-13.2)	10.3 (4.59-110)	7.12 (3.38-65.7)	3.92 (2.38-39.3)
30 - <36	9	0.449 (0.302-0.812)	4.49 (1.87-10.85)	6.55 (4.28-9.26)	8.83 (5.44-29.8)	6.80 (3.72-16.9)	5.10 (2.54-9.62)
36 - 41	6	0.589 (0.126-0.769)	2.55 (0.293-4.09)	3.00 (1.61-3.69)	12.4 (10.8-86.1)	5.82 (5.23-22.0)	2.90 (2.19-7.46)
Overall	28	0.278 (0.095-0.812)	3.34 (0.293-10.85)	7.07 (1.61-13.2)	11.1 (4.59-110)	6.33 (3.38-65.7)	4.15 (2.19-39.3)

Data are median (range)

Source: Applicant's 16.4.1.1_ACY01-PK-Report-Main-Narrative.pdf, pg 20, Table 4

The VPC indicates good agreement between observed and model-simulated concentrations. Of observed concentrations, 7.4% (6/81) were outside the 90% prediction interval (Figure 3). The estimated and observed median acyclovir concentrations were similar over time.

Figure 4.1-3: Visual predictive check of acyclovir concentrations versus time (circles: observed; shaded: 90% prediction interval; solid black line: observed median; dashed black line: predicted median)



Source: Adapted from applicant's 16.4.1.1_ACY01-PK-Report-Main-Narrative.pdf, pg 22, Figure 6

A PMA-based dosing regimen was developed to account for developmental changes in acyclovir disposition, to avoid cumbersome body surface area calculations, and to provide simplicity in clinical application:

- 20 mg/kg q12 hours in infants PMA <30 weeks
- 20 mg/kg q8 hours in infants PMA 30 to <36 weeks
- 20 mg/kg q6 hours in infants PMA ≥36–41 weeks

The final PK model was used to perform Monte Carlo simulations in 1000 randomly selected infants from the Pediatrix database. The PMA-based dosing regimen was then compared to regimens found in commonly used pediatric handbooks. The proposed dosing regimen predicts 94% and 100% of infants would have $C50_{ss} \geq 3$ mg/L, respectively (Table 4.1-5).

Table 4.1-5: PD target attainment rate for the proposed acyclovir dosing regimen and regimens in commonly used pediatric handbooks

				% Subjects ≥3 mg/L		
Source	Dose	GA (weeks)	PMA (weeks)	Cmax,ss	C50,ss	Cmin,ss
Proposed	20 mg/kg q12h	any	<30	100	97	89
	20 mg/kg q8h	any	30 - <36	98	94	75
						(b) (4)
Redbook and Lexicomp	20 mg/kg q8h	any	<30	100	100	100
	20 mg/kg q8h	any	30 - <36	98	94	74
	20 mg/kg q8h	any	36 - 41	94	70	10
	20 mg/kg q8h	*any*	*≤41*	*97*	*85*	*53*

	20 mg/kg q12h	<34	NA	96	90	55
Harriet Lane	20 mg/kg q8h	≥34	NA	95	77	22
	20 mg/kg q12h	<37	<34	96	83	37
Neofax	20 mg/kg q8h	Any	≥34	97	89	55

Source: Applicant's 16.4.1.1_ACY01-PK-Report-Main-Narrative.pdf, pg 23-4, Table 7-8

Reviewer's Comments: The reviewer evaluated the population PK provided by the Applicant and could recreate the analysis. The reviewer agrees with the selected compartmental structure and the identified covariates (body weight and PMA). The reviewer considers the developed model appropriate to describe acyclovir exposure in neonates of PMA 24 to 40 weeks, which encompasses the data used in the model development. The model may be less reliable for pre-mature neonates of less than 24 weeks PMA given uncertainties in renal maturation in such patients, additional complications in such patients, and as no data was available from such subjects. The model may be more reliable for predicting exposure in neonates older than PMA of 40 weeks given what is known regarding renal maturation following birth.

The Applicant has condensed PNA and GA into a single covariate (PMA) in the provided analysis. This covariate selection had the lowest objective function value and permits simplified dosing (i.e., dosing based on body weight and PMA instead of body weight, PNA, and GA). The reviewer concurs with dosing based PMA on body weight patient factors as proposed by the Applicant.

The Applicant has included body weight a priori as a covariate in the model based on the population. This covariate was included as an allometric scaling relationship with the exponent fixed to 1. Analyses conducted by the Applicant and recreated by the reviewer identify that an improvement in the objective function is attainable by estimating the exponent on clearance. However, this results in relatively minor changes in model parameters (<5-10%). Given the limited amount of information in the dataset, sparseness of information per subject, variability in the obtained samples, and as parameter values do not substantially change by estimating the exponent, the reviewer agrees with the Applicant's model where the exponent on clearance was fixed to 1.

The Applicant has provided pharmacodynamic analyses comparing the percentage of patients who would achieve a selected metric (≥ 3 mg/L) *for the proposed dosing regimen and other dosing regimens in pediatric handbooks. However, this pharmacodynamic measure has not been validated and the review team does not agree with the Applicant's utilization of it to inform dosing. Instead, analyses were conducted by the review team to determine doses in premature neonates that will produce exposures comparable to those observed in full term neonates using NICHD-2011-ACY01acyclovir PK trial.*

The Applicant originally proposed a three-tiered dosing regimen for neonates as follows:

- *20 mg/kg q12 hours in infants PMA* (b) (4) *weeks*
- *20 mg/kg q8 hours in infants PMA* (b) (4) *weeks*
- (b) (4)

Based on feedback from the review team at a March 15, 2017 teleconference, the Applicant simplified the dosing regimen, replacing the (b) (4) dosing option with q8h dosing. The final proposed regimen by the Applicant is:

- *20 mg/kg q12 hours in infants PMA (b) (4) weeks*
- *20 mg/kg q8 hours in infants PMA (b) (4) weeks*

The clinical pharmacology review team concurs with simplifying the regimen to two dosing tiers instead of three. However, the clinical pharmacology review team proposes a PMA cutoff of 34 weeks instead of (b) (4) weeks for switching from 20 mg/kg q12h to 20 mg/kg q8h. The rationale behind this change in the cutoff value is that similar age cutoffs are used for dosing of other drugs in neonates and that it represents a distinction between (b) (4) . The dosing in neonates between PMA (b) (4) to 34 weeks are the only differences between the regimen proposed by the Applicant and that proposed by the clinical pharmacology review team.

Of note, exposures would be higher in neonates with PMA (b) (4) weeks with all the proposed regimens. This was considered acceptable as safety concerns with acyclovir use is relatively minor and given the population, indication, and uncertainty in exposure, it was preferable to have to exposures higher than needed rather than to potentially under-dose. Simulated exposures for the proposed dosing (Applicant and review team) is described in additional detail in Section 4.2 as the proposed dosing scenario was not explicitly evaluated by the Applicant and as the review team has proposed alternative dosing in a subset of patients.

4.2 Reviewer's Population PK Analysis and Simulations

The reviewer utilized the applicants developed population PK model for neonates administered acyclovir to generate exposure measures versus PMA for the Applicant's proposed two-tiered dosing regimen based on an age cut-off of (b) (4) weeks PMA.

4.2.1 Study Pharmacokinetic Data, Model, and Simulation Dataset

The reviewer utilized the same materials provided by the Applicant (population PK model and demographics from the Pediatrix database), which are described above in Section 4.1. The reviewer used analytical expressions for a one-compartment model with linear kinetics and an intravenous infusion over 1-hour to calculate AUC (steady state over 24-hours), steady state C_{max}, and steady state C_{trough} for the Applicant's proposed dosing algorithm. At least 2500 patients were simulated for PMA increments between 26 to 42 weeks. Summaries of pharmacokinetic parameters were calculated based on geometric mean, 25th percentile, and 75th percentile for the following age groups: i) 26 to < 30 weeks; ii) 30 to <34 weeks; iii) 34 to <38 weeks; and iv 38 to 42 weeks. Graphical displays for all pharmacokinetic parameters were generated using the *ggplot* package in R (version 3.3.3).

4.2.2 Simulation Results

A summary of exposures in neonates of PMA 26 to <30 weeks, 30 to <34 weeks, 34 to <38 weeks, and 38 to 42 weeks for the review team's proposed acyclovir regimen is shown in Table 4.2-1. With the proposed dosing, AUC, C_{max}, and C_{trough} are all higher in neonates of PMA (b) (4) weeks compared to the exposures in neonates of PMA (b) (4) weeks. Exposures in neonates 30 to <34 weeks were simulated for both the review team's and Applicant's proposed dosing regimen

to illustrate how the different proposals would impact exposures in this age group (Table 4.2-2). Finally, the trend in exposures for the proposed dosing, as well as the differences in the two proposed dosing regimens with respect to PMA as a continuous measure, is illustrated in Figure 4.2-1.

With the Applicant's proposed dosing the exposure in neonates of PMA 30 to 34 weeks is comparable to exposures in neonates of PMA 26 to <30 weeks and exceeds AUC exposures in neonates of PMA 38 to 42 weeks and 34 to <38 weeks by 2.1-fold and 1.4-fold, respectively. In contrast, with the review team's proposed dosing in neonates of PMA 30 to <34 weeks the AUC, C_{max}, and C_{trough} are all between the simulated exposures in neonates of PMA 34 to 42 weeks. The review team considers this regimen to be more appropriate as it results in comparable exposures across the neonates of PMA 30 to 42 weeks. It is acknowledged that with the proposed regimen exposures in neonates of PMA (b) (4) weeks would be (b) (4) fold higher than that in other neonate age groups. This could be addressed with a third dosing tier. However, the higher exposures were considered acceptable for this population given the relatively minor safety concerns with acyclovir, uncertainty in exposure for this neonatal age group, and in the interest of having a parsimonious dosing regimen.

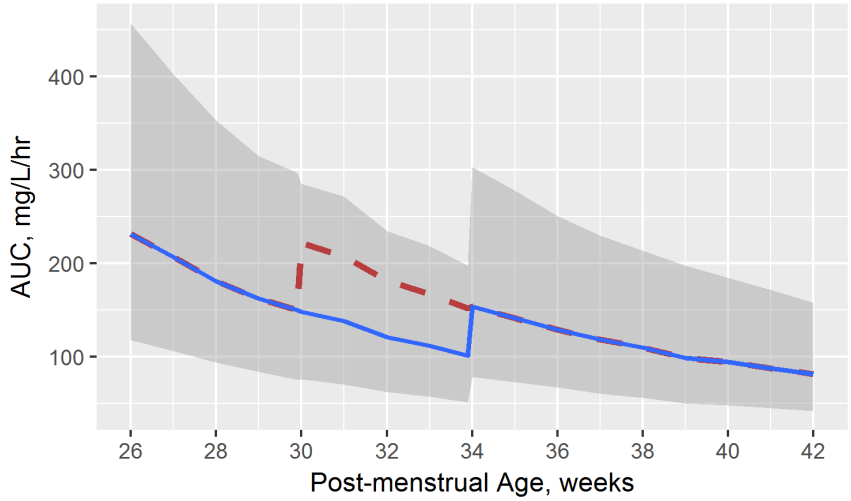
Table 4.2-1: Simulated acyclovir exposures for the review team's proposed dosing regimen. Demographics and pharmacokinetic parameters from the simulations are shown for each group (26 to <30 weeks, 30 to <34 weeks, 34 to <38 weeks, and 38 to 42 weeks). Note: GM = geometric mean

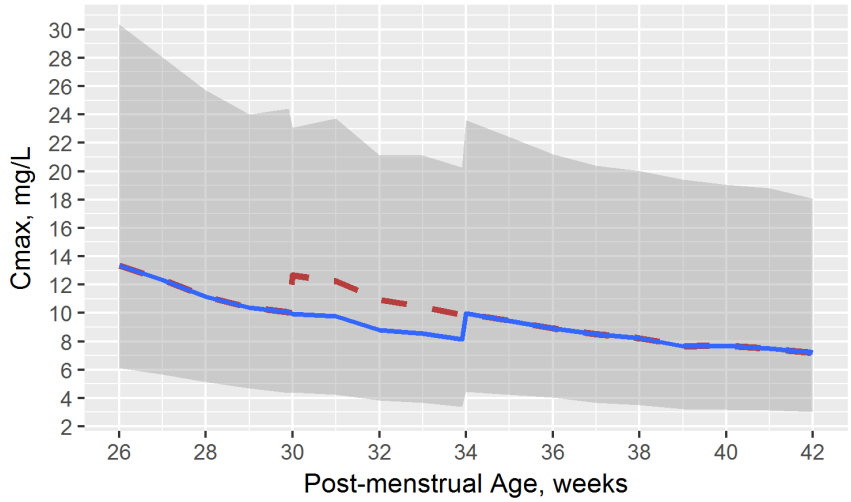
	PMA Group			
Parameter	26 to <30	30 to <34	34 to <38	38 to 42
GM AUC (mg/L/hr)	194.3	129.2	136.3	92.5
[IQR]	[134.1; 282.7]	[89.6; 186.3]	[94.5; 196.0]	[64.0; 133.4]
GM Cmax (mg/L)	12.0	9.4	9.5	7.6
[IQR]	[7.7; 18.5]	[5.9; 14.8]	[6.0; 14.7]	[4.7; 12.2]
GM Ctrough (mg/L)	5.0	2.6	2.9	1.4
[IQR]	[3.8; 6.7]	[2.0; 3.3]	[2.2; 3.7]	[1.1; 1.8]
Mean age (PMA)	27.5	31.5	35.5	40.1
Mean weight (kg)	0.96	1.44	2.31	3.11
Clearance (L/hr/kg)	0.240	0.359	0.509	0.750
Volume (L/kg)	4.1	4.0	4.0	4.1

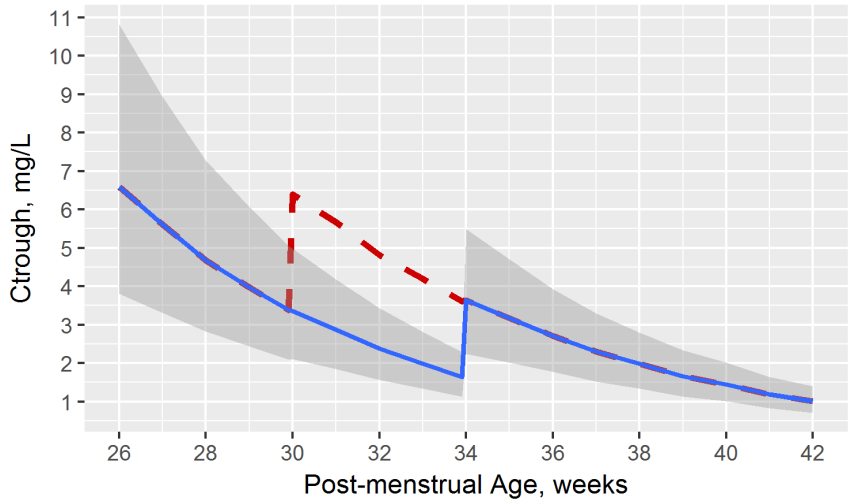
Table 4.2-2: Simulated acyclovir exposures for the Applicant's and review team's proposed dosing regimen in neonates 30 to <34 weeks PMA. Demographics and pharmacokinetic parameters from the simulations are shown for each group.

	Age group: 30 to <34 weeks	
Parameter	*Dose: 20 mg/kg q8 hours*	*Dose: 20 mg/kg q12 hours*
Geometric mean AUC (mg/L/hr)	193.9	129.2
[Interquartile range]	[134.5; 279.5]	[89.6; 186.3]
Geometric mean Cmax (mg/L)	11.7	9.4
[Interquartile range]	[7.6; 17.9]	[5.9; 14.8]
Geometric mean Ctrough (mg/L)	5.1	2.6
[Interquartile range]	[3.9; 6.9]	[2.0; 3.3]
Mean age (PMA)	31.5	31.5
Mean weight (kg)	1.44	1.44
Clearance (L/hr/kg)	0.359	0.359
Volume of Distribution (L/kg)	4.0	4.0

Figure 4.2-1: Simulated acyclovir AUC (top), C_{max} (middle), and C_{trough} (bottom) versus PMA for the clinical pharmacology review team's (median – blue solid line; 90% prediction interval – shaded region) and the Applicant's (median – red dashed) proposed dosing in neonates







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