OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	19-910 SE2 033 (Dosing in pediatric patients)
Submission Date:	March 21, 2008
Brand Name:	RETROVIR
Generic Name:	Zidovudine
Reviewers:	Shirley K. Lu, Ph.D. Pravin Jadhav, Ph.D.
Team Leaders:	Kellie S. Reynolds, Pharm.D. Jogarao V. Gobburu, Ph.D.
OCP Division:	Division of Clinical Pharmacology 4
OND Division:	Division of Antiviral Products
Sponsor:	GlaxoSmithKline
Formulation/Strength(s):	Syrup, 50 mg/5 mL
Current Pediatric Dosing Regimen:	For pediatric patients 6 weeks to 12 years of age: 160 mg/m^2 every 8 hours (480 mg/m^2/day up to a maximum of 200 mg every 8 hours)
Proposed Pediatric Dosing Regimens:	For pediatric patients 6 weeks to (b) (4) years of age, the doses are calculated according to the following weight bands: 4 kg to ≤9 kg: 12 mg/kg BID ≥9 kg to <30 kg: 9 mg/kg BID ≥30 kg: 300 mg BID

Table of Contents

1 Executive Summary

Zidovudine (ZDV, Retrovir®) is a nucleoside analogue reverse transcriptase inhibitor that is used in the treatment of HIV infection in combination with other antiretroviral drugs and for the prevention of maternal-fetal transmission of HIV. Retrovir is currently indicated for use in pediatric patients at a dosing regimen of 160 mg/m^2 every 8 hours for patients 6 weeks to 12 years of age in combination with other antiretroviral drugs. The sponsor is seeking a change in the pediatric dosing regimen from a BSA-based regimen to a weight-based one and also to change the frequency of dosing from three times daily to twice daily. The sponsor's proposed dosing regimen is as follows: 4 to <9 kg→12 mg/kg BID; ≥9 to <30 kg→9 mg/kg BID; ≥30 kg→300 mg BID.

The sponsor has not conducted any new studies in support of this supplement. The scientific rationale for the change in recommended dosing has come from historical pediatric and adult data, simulated pediatric data, and literature evidence. In order to obtain regulatory approval for the change in recommended dosing regimen, the data need to provide evidence that the consequences of switching from BSA-based to weight-based dosing and from TID to BID dosing will not significantly affect the efficacy or safety of ZDV in pediatric patients.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the information submitted in this efficacy supplement and agrees that it supports the proposed dosing changes. The dosing information to be included in the label is as follows:

Weight	***Total Daily Dose***	***Regimen***	
		BID	*TID*
4 to <9 kg	*24 mg/kg/day*	*12 mg/kg*	*8 mg/kg*
9 to <30 kg	*18 mg/kg/day*	*9 mg/kg*	*6 mg/kg*
≥30 kg	*600 mg/day*	*300 mg*	*200 mg*

Alternatively, dosing for RETROVIR can be based on body surface area (BSA) for each child. The recommended oral dose of RETROVIR is 480 mg/m^2/day in divided doses (240 mg/m^2 twice daily or 160 mg/m^2 three times daily). In some cases the dose calculated by mg/kg will not be the same as that calculated by BSA.

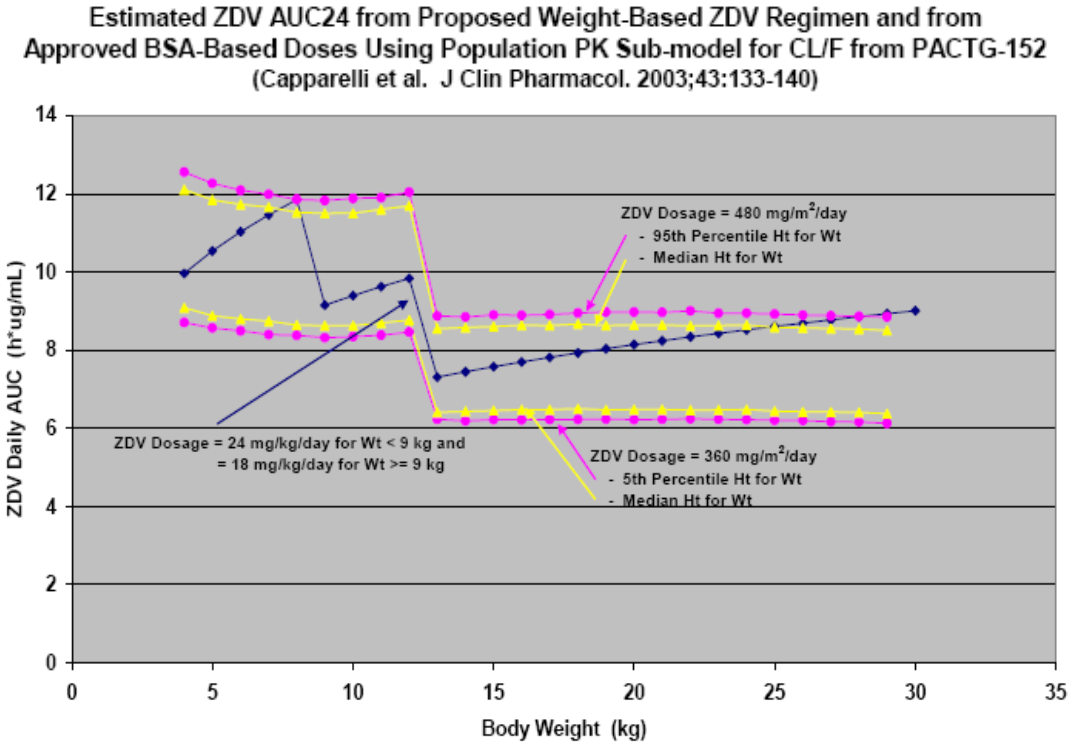
Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Zidovudine is approved for the following indications in adults and pediatric patients:

Indication	Patient Population	Dosing Regimen
For the treatment of HIV infection (in combination with other antiretroviral agents)	Adults (and pediatric patients >12 y.o.a.)	600 mg per day in divided doses (in combination with other antiretroviral agents)
For the treatment of HIV infection (in combination with other antiretroviral agents)	Pediatric patients (6 weeks to 12 y.o.a.)	**160 mg/m^2 every 8 hours** (480 mg/m^2/day up to a maximum of 200 mg every 8 hours)
Prevention of maternal-fetal HIV transmission	Pregnant women (>14 weeks of pregnancy)	100 mg orally 5 times per day until the start of labor. During labor and delivery, I.V. Retrovir should be administered at 2 mg/kg (total b.w.) over 1 hour followed by I.V. infusion of 1 mg/kg/hour (total b.w.) until clamping of the umbilical cord.
Prevention of maternal-fetal HIV transmission	Neonates	2 mg/kg orally every 6 hours starting within 12 hours after birth and continuing through 6 weeks of age. (Neonates unable to receive oral dosing may be administered Retrovir I.V. at 1.5 mg/kg infused over 30 minutes, every 6 hours.)

The sponsor's proposed pediatric dosing regimen includes switching from a BSA-based dosing regimen to a weight-based dosing regimen and from 3X daily dosing to twice daily dosing. From a review of the sponsor's simulated pharmacokinetic (PK) data, the proposed weight breakpoints appear reasonable and meet the goal of minimizing the potential for underdosing and viral resistance and also avoiding an excessively high exposure that could lead to toxicity. The main concern with switching from three times daily dosing to twice daily dosing is the possibility of a change in *in vivo* ZDV disposition that would affect the efficacy of ZDV in pediatric patients.

The figure below represents sponsor-provided simulated exposures for their proposed dosing regimen and how it compares with simulated exposures obtained from the reanalysis of PK data in study PACTG152. The pink lines represent exposures for the 95th percentile for height and weight and the yellow lines represent exposures for the 5th percentile. The upper two lines reflect exposures resulting from the U.S. recommended total daily dose of 480 mg/m^2 (160 mg/m^2 TID) while the bottom two lines reflect exposures resulting from the European Union's (E.U.) recommended total daily dose of 360 mg/m^2 (120 mg/m^2 TID). The simulated exposures for the proposed dosing show that there is a potential for patients to have lower exposures than the U.S. dosing recommendations, but would not fall below the predicted exposures from the E.U.'s recommended dosing. Although the E.U. approved dose is not being used as a primary comparison for the proposed dose, the E.U. dosing regimen has been used effectively in previously reviewed pediatric studies as a background regimen. In addition, no weight range would be predicted to have exposures fall below mean historical adult exposures (see Figure 4, section 2.3.6).



In adults, the change in dosing recommendations from q4h dosing to BID dosing was made based on a 48-week, randomized efficacy and safety study (N=320) that confirmed the lack of a difference in efficacy or safety between the two treatment regimens. In pediatrics, the lower predicted exposures at certain weights are supported by efficacy data in studies using lower doses (E.U. dose) that were shown to be effective. In further support, literature data show similarities in historical adult and pediatric clearance along with a lack of a difference in the ZDV phosphorylation process between adults and pediatrics. The totality of these data indicates that there is unlikely to be a significant difference in efficacy or safety upon switching to a weight-based, twice daily regimen.

To accommodate healthcare providers who prefer the current BSA-based dosing regimen, an alternative BSA-based BID dose will be included in the label. A higher Cmax would be anticipated for BSA-based doses divided as 240mg/m^2 BID rather than 160 mg/m^2 TID. However, these differences in Cmax are not expected to be significantly different from Cmax exposures resulting from the proposed dosing regimen. Thus, the safety discussion in this review also supports the mg/m^2 BID dosing regimen.

2 Question based review (QBR)

2.1 General Attributes of the Drug

2.1.1 What are the highlights/properties of the drug product formulation as they relate to the clinical pharmacology review?

There are no changes to the drug substance or formulation of the drug product for this supplement since the only changes being made are to the dosing recommendations. The tablet, capsule, and oral syrup formulations provide equivalent AUC exposures. However, Cmax was higher for both the tablet and syrup formulations when compared with the capsule.

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

The mechanism of action for zidovudine has been well-established. Briefly, ZDV is an HIV nucleoside reverse transcriptase inhibitor that is sequentially phosphorylated intracellularly to the active triphosphate form (ZDV-TP). However, due to saturation of the conversion process from the mono- to diphosphate forms, pooling occurs at the monophosphate level. When the diphosphate form does convert to the ZDV-TP, the active ZDV-TP has a much longer half-life than parent ZDV. ZDV is indicated for the treatment of HIV infection and prevention of maternal-fetal transmission of HIV.

2.1.3 What are the basic pharmacokinetic properties of zidovudine?

The pharmacokinetics of ZDV are dose-independent at oral dosing regimens between 2 mg/kg q8h and 10 mg/kg q4h. Due to first-pass metabolism, the bioavailability of ZDV is approximately 68% and remains constant between oral doses of 250 and 1250 mg. The volume of distribution following oral administration is 1.6 ± 0.6 L/kg and peak plasma concentrations are reached approximately 0.5-1.5 hours following an oral dose. Peak plasma levels of ZDV increase proportionately with dose between doses of 2 mg/kg q8h and 10 mg/kg q4h. Plasma clearance of ZDV is rapid with an elimination half-life of 1.1 hours. ZDV is primarily metabolized by hepatic glucuronidation and its metabolite, GZDV (glucuronidated ZDV), is eliminated via the kidney. Approximately 74% of an oral dose is recovered as GZDV in urine.

In pediatric patients who are infected with HIV, ZDV pharmacokinetics are similar to HIV-infected adults. However, infants under the age of 2 weeks old have a sizable delay in ZDV elimination and prolonged half-life. These differences can be attributed to an immature glucuronidation process and/or variable gastrointestinal absorption in very young infants. Some researchers have suggested that the maturation process is essentially complete by the end of the first 2 weeks of life, while others have suggested the process continues through the first 2 years of life. A study conducted by the sponsor in support of the indication for the prevention of maternal-fetal HIV transmission shows that the clearance of IV ZDV in infants increases dramatically until 14-28 days of age (study ACTG049). After 28 days, infants begin to have near-adult levels of clearance on a per kg weight basis.

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

The route of administration (oral) will remain the same. The proposed dosages for each weight group are presented below.

Weight (kg)	Dosage Regimen Using RETROVIR Syrup		Total Daily Dose (mg)
	AM Dose	PM Dose	
4 to <9	12mg/kg	12mg/kg	96 to 192
≥9 to <30	9mg/kg	9mg/kg	162 to 522
≥30	300mg	300mg	600

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?

No new clinical studies were conducted in support of this supplement. Observed and simulated pharmacokinetic data from two historical pediatric studies (PACTG 152 and P53-04) were used to support the sponsor's proposed dosing changes.

Study PACTG 152 was an efficacy study comparing ZDV, didanosine (ddI), and ZDV+ddI in symptomatic HIV-infected infants and children ages 3 months through 18 years (mean age: 45.2 months; mean b.w.: 15.5 kg). ZDV alone was administered at 180 mg/m^2 every 6 hours, while in combination with ddI, ZDV was administered at 120 mg/m^2 every 6 hours. A total of 394 subjects had sparse ZDV plasma concentration data available for population PK analysis.

Study P53-054 was an efficacy study evaluating IV and oral PK of ZDV in pediatric HIV-infected patients ages 6 months to 13 years (mean age: 4.4 years; mean b.w.: 15.8 kg) with AIDS or AIDS-related complex. Initially, patients received 8 weeks of IV ZDV as 1-hour infusions every 6 hours at a dose of either 80 mg/m^2 or 160 mg/m^2. This regimen was followed by 4 weeks of oral solution dosing at either 120 or 240 mg/m^2 every 6 hours. A later protocol amendment allowed for an intermediate level dose of 120 mg/m^2 IV and 80 mg/m^2 orally. Blood samples were collected prior to dosing and through 6 hours post-dose following the first IV and oral doses. Standard PK parameter estimates were calculated for a total of 28 subjects (out of 36 enrolled). PK data from these two historical studies were reanalyzed and the sponsor's population PK modeling utilized data from study PACTG 152.

2.3 Review Issues

2.3.1 Is the sponsor's proposal to switch from ZDV mg/m2 to mg/kg based dosing reasonable?

The sponsor's proposal is reasonable. Other body weight cut-offs were also explored and do not offer additional advantage over the proposed body weight cut-offs (See section 2.3.4).

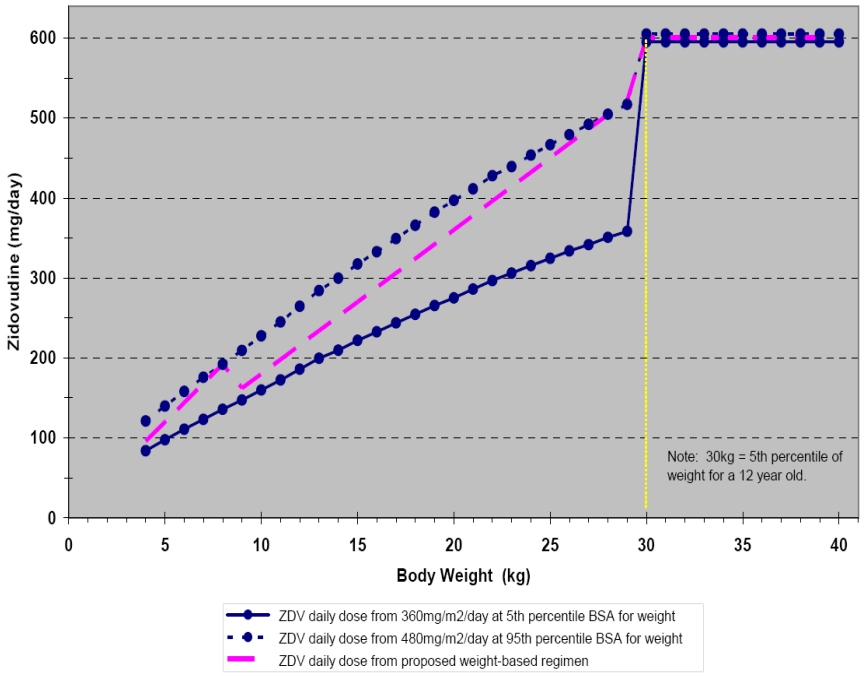
Body weight	ZDV regimen
4 to < 9 kg	24 mg/kg/day (8 mg/kg TID)
≥9 to < 30 kg	18 mg/kg/day (6 mg/kg TID)
≥30 kg	200 mg TID (approved dose for ≥12 years of age)

2.3.2 What are the differences among the dosing recommendations (current U.S. BSA-based, and proposed body weight based) for total daily dose delivered to a given patient?

According to the sponsor, the weight breakpoints for the proposed dose changes (i.e., specifically 9 and 30 kg) were chosen to provide a milligram total daily dose that is closer to the BSA based dosing approved in the US while minimizing the number of breakpoints. The primary goals were to avoid significant underdosing in order to minimize the risk for development of viral resistance and to avoid excessive doses that may be associated with toxicity. Using the 5th and 95th percentile of BSA for a given body weight and two (USA and EU) dosing recommendations, the sponsor justified that daily dose of ZDV (from the proposed body weight based dosing) fall within the currently approved BSA based dosing range (Figure 1; Upper Panel). The currently approved daily dose of ZDV in the United States (480 mg/m^2) and European Union (360 mg/m^2) are different. The reason for differences in two dosing recommendations is unknown. Both regimens are frequently used in the current clinical practice.

The sponsor's proposal was evaluated using BSA and body weight data from 388 patients (body weight 4-92.8 Kg) in PACTG Study 152. For every patient the dose was calculated using three dosing recommendations (Figure 1; Lower Panel). On average, a daily dose from the proposed body weight based dosing was lower (~10%) than from the currently approved BSA based dosing (480 mg/m^2) in the US (Figure 2; Upper panel). The dose, however, on average was higher (~20%) than from the currently approved BSA based dosing (360 mg/m^2) in the EU (Figure 2; Lower panel).

Figure 1: ZDV Total Daily Dose (mg) vs. Body Weight from the proposed weight-based dosing and from USA and EU approved product labeling (Upper panel: The sponsor's justification from the using BSA and body weight data from the CDC growth charts; Lower panel: Reviewer's analysis using BSA and body weight data from PACTG Study 152)



Source: Sponsor's Figure 2 from Clinical-Overview.pdf- Page 10 of 50

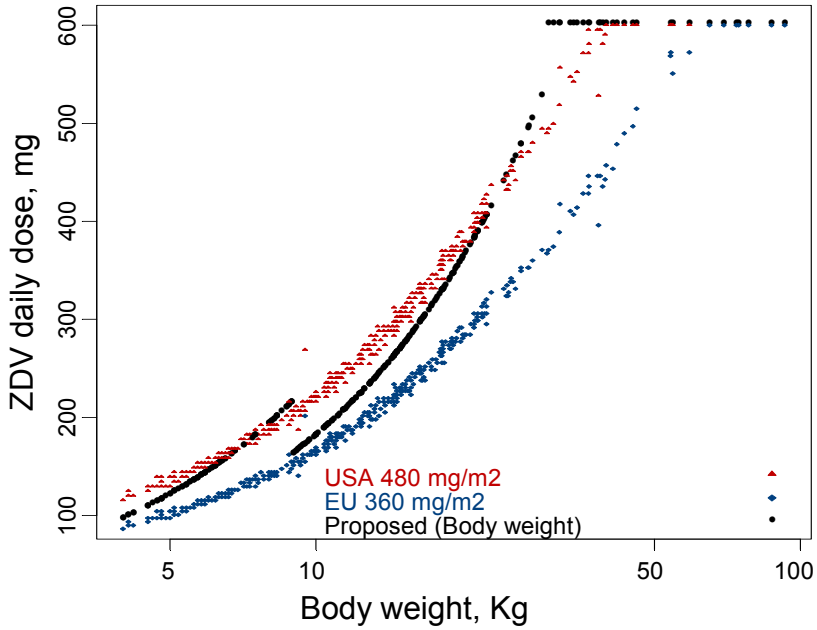
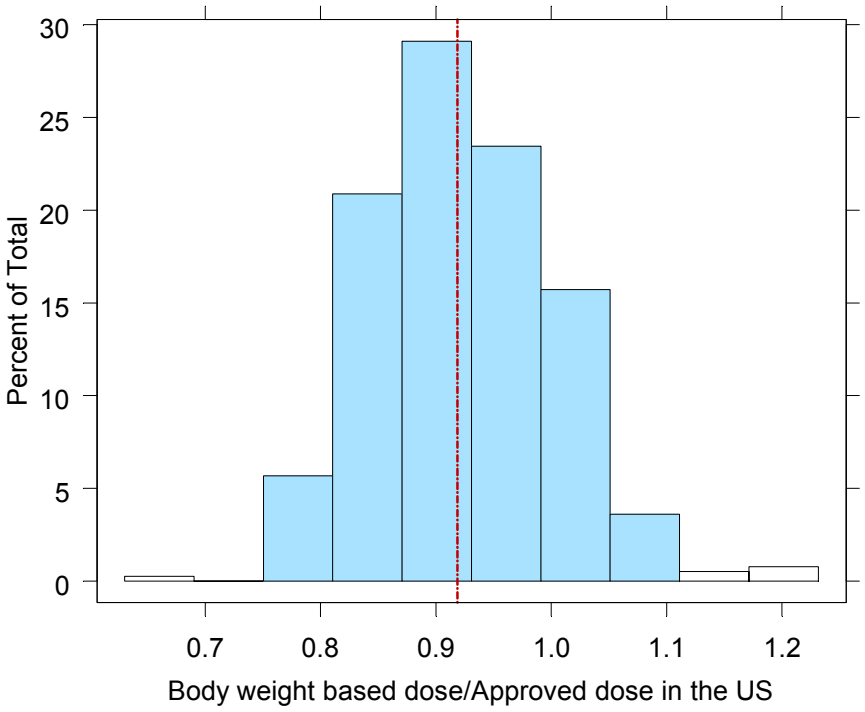
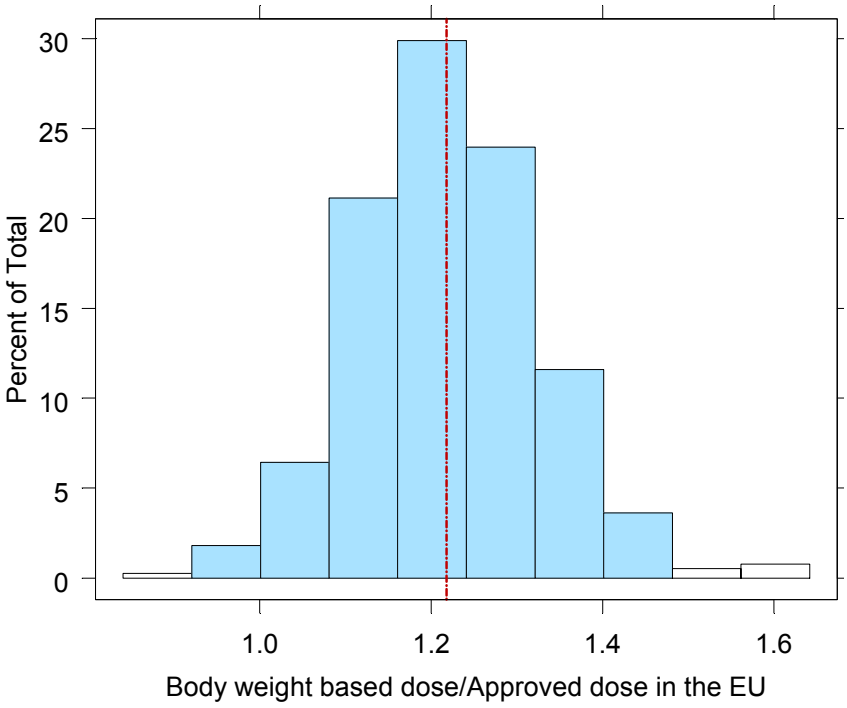


Figure 2: The ratios of total daily dose for 388 pediatric patients (PACTG Study 152) derived from the proposed body weight based dosing and dose approved in the US and EU, respectively. The dotted line represents the median quantity.





2.3.3 Is the popPK model used by the sponsor appropriate?

The model described data reasonably. However, at lower ZDV concentrations (<500 ug/L) the model predictions are higher compared to observed data. The bias in predictions is primarily due to variability in ZDV pharmacokinetics. This could be due to several sources that cannot be easily captured in large clinical trials. The large inter-individual and inter-occasion variability in ZDV pharmacokinetics is documented in literature. The sponsored simulated ZDV exposures (daily AUC, Cmax) from both approved mg/m2 TID and proposed mg/kg BID dose regimens were weight-based clearance values from the population PK analysis of PACTG 152 [Capparelli, 2003]. ZDV exposures from the proposed mg/kg dose given TID were also simulated for comparison to the BID dosing.

PACTG 152 examined the use of ZDV 180 mg/m2 every six hours, didanosine (ddI) 120 mg/m2 every 12 hours, or the combination at reduced doses of both ZDV (120mg/m2 q6h) and ddI (90mg/m2 q12h). Patients ranged from 3 months to 18 years of age, with a mean (± SD) age of 45.2 (± 45.0) months and body weight of 15.5 ± (12.4) kg. A total of 394 HIV infected pediatric patients had ZDV plasma concentration data available from sparse sampling for population PK analysis. The final clearance model is described below:

$$CL/F\,(L/h/kg) = \left[(4.37 + 0.475 \bullet WK0 + 0.754 \bullet CHILD) \bullet WT^{-1/4}\right] \bullet \exp(\eta 1)$$

where WT is body weight in kg; WK0 =1 if first dose or =0 if after first dose; CHILD = 1 if age > 2 years and = 0 if age ≤ 2years; the interindividual variability in CL/F was 30%. The modeling results are summarized in the appendix of this review.

2.3.4 Are there other weight cut-offs that could be used to deliver a daily dose closer to the mg/m^2 dosing regimen?

As agreed at the pre-NDA meeting, the sponsor investigated other weight cut-offs (Table 1) using similar approach as described above.

Table 1: Scenarios with various breakpoints and mg/kg dose

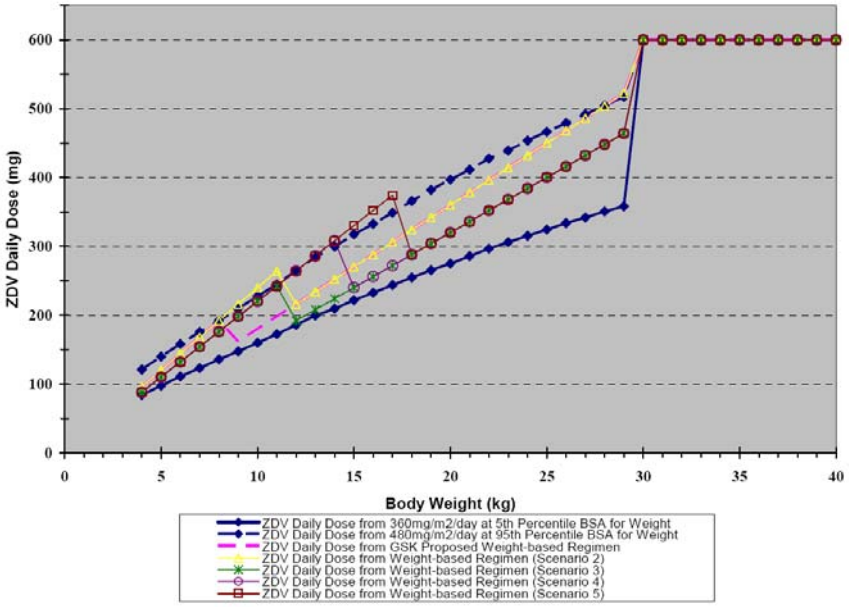
Scenario	Weight Breakpoints	Weight Range (kg)	Dose
1	**9kg and 30kg**	4 to <9	24 mg/kg/day
		9 to <30	18 mg/kg/day
		≥ 30	600 mg/day
2	**12kg and 30kg**	4 to <12	24 mg/kg/day
		12 to <30	18 mg/kg/day
		≥ 30	600 mg/day
3	**12kg and 30kg**	4 to <12	22 mg/kg/day
		12 to <30	16 mg/kg/day
		≥ 30	600 mg/day

4	**15kg and 30kg**	4 to <15	22 mg/kg/day
		15 to <30	16 mg/kg/day
		≥ 30	600 mg/day
5	**18kg and 30kg**	4 to <18	22 mg/kg/day
		18 to <30	16 mg/kg/day
		≥ 30	600 mg/day

The total daily mg dose resulting from these scenarios relative to the range of daily doses from approved mg/m^2 regimens are shown in Figure 3. According to the sponsor, compared to the proposed weight cut-offs and dose regimen, other scenarios for different weight breakpoints and dose regimens (Scenario 2, 4, and 5) generate ZDV total daily mg doses exceeding the upper end of the range based on the approved mg/m^2 dosing. While ZDV total daily doses from Scenario 3 fall within the range based on the approved mg/m2 dosing, there is a larger dose reduction (from 242 mg to 192 mg) at the first weight breakpoint (12 kg) than what is seen with the proposed regimen (from 192 mg to 162 mg) at the first weight breakpoint (9 kg). Therefore, the proposed weight-based regimen based on 9-and 30-kg breakpoints is considered more appropriate than these other scenarios.

In general, all of the scenarios including the proposed scenario lead to lower doses compared to the BSA based dosing the US. The derived dose irrespective of the scenario (with further minor adjustments to scenarios 2, 4 and 5) falls between the US and EU BSA based dosing recommendation. All of the above cut-offs are empirical and any given scenario does not offer any special advantage over any other scenarios.

Figure 3: ZDV total daily dose (mg) vs. body weight from the sponsor's proposed weight based dosing, various weight cut-off scenarios, and from the current US and EU approved BSA based dosing.



Source: Sponsor's Figure 3 from Clinical-Overview.pdf- Page 16 of 50

2.3.5 What is the highest deviation for a total daily dose for the proposed weight based dosing from the BSA based dosing?

If the approved E.U. and U.S. BSA-based dosing were considered as lower and upper threshold of acceptable ZDV doses, the current proposal would lead to doses between those boundaries with few instances of higher or lower dosing. The biggest difference was seen at the weight cut-off points.

In the 388 patients from PACTG152, the highest deviation leads to a ~22% higher exposure. In other words, 600 mg for a 30-Kg patient with BSA 1.02 m^2 from the body weight based dosing was 22% higher than 490 mg from the BSA based dosing approved in the U.S.

On the other hand, in the 388 patients from PACTG152, the highest deviation leading to under exposure was ~15%. In other words, 171 mg for a 9.5 Kg patient with BSA 0.56 m^2 from the body weight based dosing was 15% lower than 202 mg from the BSA based dosing approved in the E.U. For the same patient, the dose was 269 mg (36% lower) from the BSA based dosing in the US. As shown in Figure 1 (Lower panel), the BSA of 0.5 m^2 for a 9.5 Kg was outlier observation compared to overall population.

Data were further analyzed by excluding the outlier patient observation. In 387 patients from the PACTG Study 152, no patients receive doses lower than E.U. recommended dosing. And the highest deviation from the U.S. dose was 22% (171 mg from the body weight based dosing versus 211 mg the BSA based dosing in the U.S.)

- **If a patient receives a 22% higher dose from the proposed body weight based dosing compared to dose from the currently approved regimen(s), are safety data available at such high exposures?**

  Yes, safety data are available for a dose that would likely result in a ~50% higher exposure (720 mg/m^2/day). Assuming linear PK, a 50% higher dose would result in approximately 50% higher exposures. Analysis of these data support approval of a dose that is 22% higher than the current approved dose. Please refer to the medical officer's review for further details on safety information.

- **If a patient receives a 22% lower dose from the proposed body weight based dosing compared to dose from the currently approved regimen(s), are efficacy data available at such low exposures?**

  Yes, lower doses than the U.S. dose are known to be effective. The E.U. dose (360 mg/m^2/day) has been used as the background regimen in several clinical studies in pediatric patients. Specifically, this dose was used in the study that supported approval of the pediatric use of abacavir and showed similar efficacy to historical studies. Please refer to the medical officer's review for further details on efficacy information.

In summary, pediatric patients will receive a daily dose similar to or lower than the currently approved dose in the US, but most pediatric patients will receive a daily dose higher than the EU recommendations.

2.3.6 What are the relevant points in the approval history of Retrovir?

In September 1996, a twice daily dosing regimen for Retrovir capsules was approved in adults previously. The new regimen is given as two 300-mg doses during the day instead of the approved 100-mg dose given every 4 hours (originally approved as 200 mg given every 4 hours). A randomized double-blind efficacy and safety study was conducted in support of this change. The study included 158 patients in the 100-mg q4h arm and 162 patients in the 300-mg q12h arm. At the time the study was conducted (1990-1992), viral load measurements had not yet been developed as one of the clinical standards for measuring efficacy. Thus, CD4 cell counts were used as a surrogate endpoint. After 48 weeks of treatment, there were no differences in CD4 counts between the two arms. Additionally, no differences in safety data with respect to incidence of new opportunistic infections, neoplasms, and deaths were found. The incidence of adverse events was similar between the two treatments, with hematologic toxicity being the most common adverse event observed in both groups. Thus, in adults, the BID dosing regimen provided similar efficacy (CD4 counts) and safety profiles as the q4h dosing. The following table shows the progression of Retrovir approved dosing. As additional data have been collected from studies conducted in the U.S. and abroad, the trend in dosing is towards a lower dose as well as a lower frequency of dosing.

Table 2 Progression of approved Retrovir dosing

ADULTS

NDA	Dosage form & strength	Date approved or changed	Regimen
19-655	Capsule, 100 mg	Approved March 19, 1987	200 mg q4h around the clock ↓ 100 mg q4h monotherapy;
		August 8, 1994	200 mg q8h in combination w/ zalcitabine; Approved for use in preventing vertical transmission
		October 4, 1996 (to present)	600 mg per day in divided doses in combination w/ other ARTs
19-910	Oral syrup, 50 mg/5 mL	Approved September 28, 1989	4 teaspoonfuls (20 mL) syrup q4h around the clock ↓ 2 teaspoonfuls (10 mL) syrup q4h;
		August 8, 1994	Approved for use in preventing vertical transmission
		October 4, 1996 (to present)	Removed from D&A section for adults
19-951	IV Injection 10 mg/mL	Approved February 2, 1990	1 mg/kg infused over 1 hour administered q4h around the clock (6 mg/kg daily)
		CURRENT	1 mg/kg infused over 1 hour administered 5-6 times daily (5-6 mg/kg daily)
20-518	Tablet, 300 mg	Approved October 4, 1996 (to present)	600 mg per day in divided doses in combination w/ other ARTs

PEDIATRICS

19-910	Oral syrup, 50 mg/5 mL	Approved for <u>pediatric use</u> May, 1990	3 mos. – 12 y.o.a.: 180 mg/m^2 q6h (720 mg/m^2 per day), not to exceed 200 mg q6h
		CURRENT	6 wks. – 12 y.o.a.: 160 mg/m^2 q8h (480 mg/m^2 per day) not to exceed 200 mg q8h

2.3.7 Is the sponsor's proposal to change ZDV dosing from three times daily to twice daily regimen in pediatric patients reasonable?

The sponsor's dosing proposal is reasonable.

Body weight	ZDV regimen
4 to < 9 kg	24 mg/kg/day (12 mg/kg BID)
≥9 to < 30 kg	18 mg/kg/day (9 mg/kg BID)
≥30 kg	300mg BID (approved dose for ≥12 years of age)

Since a daily dose of Retrovir in adults can be administered twice daily or three times daily, the same strategy could be used for pediatrics. The safety and efficacy of twice daily dosing in adults has been established. The safety and efficacy of twice daily ZDV dosing in pediatric patients has been studied in combination with lamivudine both with and without abacavir (study CNAA3006). In that study, ZDV was administered as 180 mg/m^2 twice daily in treatment-experienced patients ages 0.6 to 13 years of age for 48 weeks. The BID dosing was generally well-tolerated and safe. The efficacy of the triple combination regimen (ZDV+3TC+ABC) was greater than the dual combination regimen (ZDV+3TC), however, the efficacy of the twice daily dual combination regimen was consistent with previous experience in treatment-experienced pediatric patients.

The pharmacokinetic consequence of dosing ZDV three times vs. two times daily has never been directly compared in a clinical study in pediatric subjects. In the absence of this empirical data, the safety and effectiveness of twice daily dosing in pediatrics would need to be validated using existing historical PK data from adults and children and PK simulations. Data from studies PACTG152 and P53-04 (as described in section 2.2.1 of this review) were used to produce the box plots for figures 4 and 5. Since the two studies did not actually investigate weight-based or TID/BID dosing, the sponsor ran PK simulations using reanalyzed data from PACTG152. The reanalyzed data from PACTG152 were used as the primary comparison as the Monte Carlo simulations tended to be an overestimation.

Figure 4 shows that the simulated daily AUC exposures resulting from BID dosing are not expected to be significantly different from exposures resulting from TID dosing. In addition, the predicted AUC exposures using reanalyzed PK data from PACTG152 are not significantly different from the historical dose-adjusted pediatric exposures in children weighing between 9 and 30 kg. Although exposures in the 4 to <9kg group is predicted to be approximately 30% higher than historical pediatric data, when compared to only the exposures (at the actual dose administered) from pediatrics weighing 4 to <9kg, the predicted exposure is only 19% higher. Predicted Cmax exposures are expected to be higher in BID dosing regimens as compared with TID regimens (as shown in Figure 5). These higher Cmax values are supported by safety data from previous pediatric studies (please see the medical officer's review for further details on safety).

Figure 4 **Box plots of daily ZDV AUC exposures from simulations representing proposed weight-based and BID dosing**

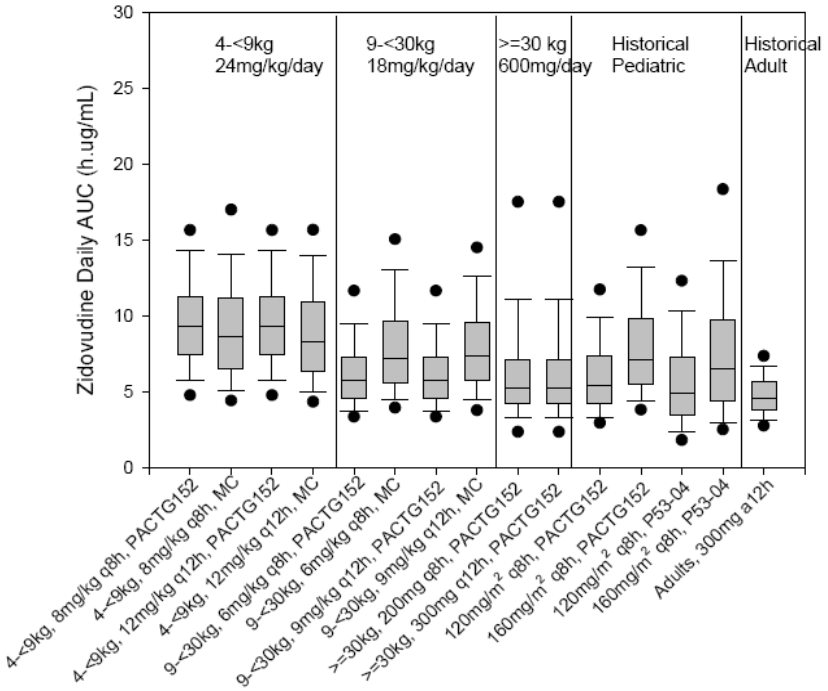
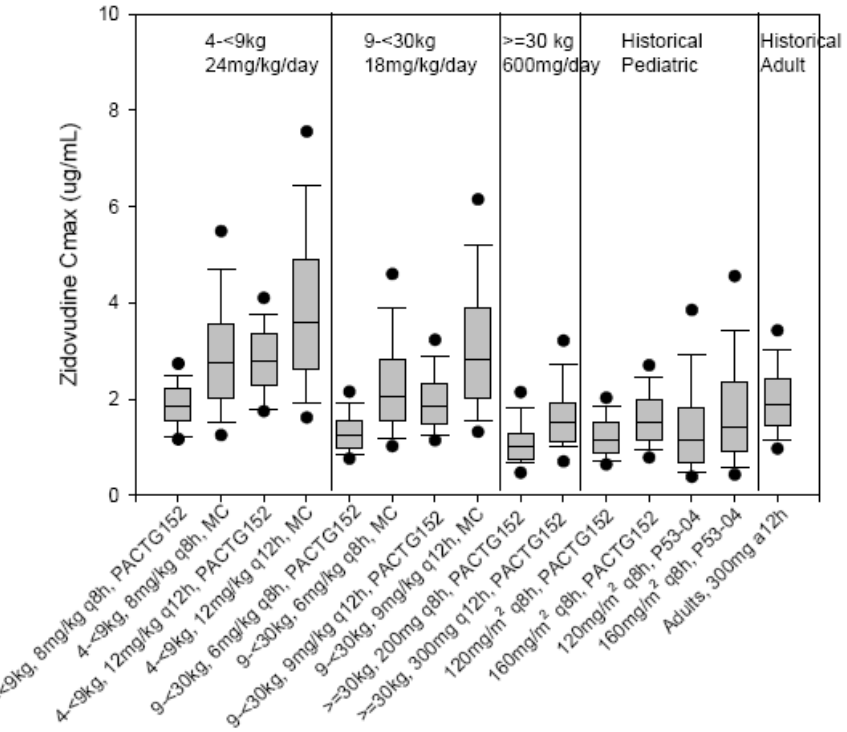


Figure 5 **Box plots of daily ZDV Cmax exposures from simulations representing proposed weight-based and BID dosing**



Note: Box represents median, 25th, and 75th percentiles, bars represent 10th and 90th percentiles, dots represent 5th and 95th percentiles. MC= Monte Carlo Simulation; PACTG152 – Simulations based predictions from post hoc parameters.

- **Does the clearance in adults or pediatrics change if the ZDV dosing regimen is changed from three times daily to twice daily?**

It is known that plasma concentrations of ZDV increase proportionally with dose and the efficacy of the BID regimen in adults has been demonstrated. Therefore, if the oral clearance is constant between TID and BID dosing in adults and is similar to clearance in pediatrics, one would not expect a significant change in ZDV disposition between TID and BID dosing in pediatrics.

Several studies have reported clearances in adults using both the TID and BID dosing regimens. In instances where adult clearance values were originally presented as L/h in the publication, the value is weight-normalized here based on an average 70-kg adult. Collier (1993) found that following administration of Retrovir capsules alone at 200 mg TID, the average adult ZDV clearance was 2.23 L/h/kg (N=15). In a study of the pharmacokinetics of saquinavir, ZDV, and zalcitabine combination therapy (Vanhove et al, 1997), ZDV administered to adults in combination with zalcitabine resulted in an oral ZDV clearance of 3.47 L/h/kg (N=73). When ZDV was administered as BID doses in combination with abacavir and lamivudine in adults (Cremieux et al, 2001), the average oral clearance of ZDV was 3.02 L/h/kg (N=24). Thus, in adults, the apparent oral clearance of ZDV ranges from 2.23 to 3.47 L/h/kg across TID and BID dosing regimens.

In pediatric patients, data on BID dosing are limited. Only the Bergshoeff (2004) study examined the pharmacokinetics of BID dosing in pediatrics (retrospectively). The apparent oral clearance was approximately 79.5 L/h*m^2 (or 3.36 L/h/kg when normalized for reported median weight and age) for the subjects studied (N=6). In the same retrospective study, oral clearance for TID dosing was found to be 2.68 L/h/kg. The pharmacokinetics of TID dosing has been directly evaluated in PACTG 338 (Fletcher et al, 2004). ZDV administered to pediatric patients at a dose of 160 mg/m^2 three times daily resulted in an average oral clearance of 3.89 L/h/kg (N=7). As can be seen in table 6, there are no significant differences in clearance in historical adult data between TID and BID dosing. In addition, no differences exist between adult clearances and pediatric clearances. Thus, a change in clearance in pediatrics would not be expected when switching from TID dosing to BID dosing.

Table 6 Summary of ZDV clearance data from literature

Source	Adults or Peds?	N	Regimen (TID or BID)	Part of combination therapy?	Weight-normalized oral clearance* (L/h/kg)
Collier et al, 1997	Adults	15	TID	N	2.23
Vanhove et al, 1997	Adults	73	TID	Y-zalcitabine	3.47
Cremieux et al, 2001	Adults	24	BID	Y-abacavir & lamivudine	3.02
Fletcher et al, 2004	Peds	7	TID	Y-lamivudine & ritonavir	3.89
Bergshoeff et al, 2004	Peds	6	TID	N	2.68
		6	BID	N	3.36

*Cl/F is normalized to an average 70-kg adult for the adult studies. In the case of the pediatric studies, the CL/F is normalized to the mean (or median) weight reported in the article.

- **Are the observed exposures from a twice daily regimen in adults comparable to a three times daily regimen in adults?**

When the tablet dosage form of Retrovir was approved in 1996, the recommended dosing regimen was 600 mg per day in divided doses. This regimen provided the option of twice daily dosing in adults using the approved 300-mg tablet. Both twice daily and three times daily dosing have been studied and routinely administered to adults. Since the total daily dose remains the same, a similar total daily exposure would be expected between the two regimens. The following table summarizes historical studies which confirm this assumption.

Table 4 Summary of adult ZDV exposure data from literature

Source	N	Regimen (TID or BID)	Part of combination therapy?	Daily AUC exposure (µg*h/mL)
Collier et al, 1997	6	TID	N	3.69
	9	TID	N	4.68
Vanhove et al, 1997	73	TID	Y-zalcitabine	3.06
McDowell et al, 2000	20	TID	Y-abacavir	3.12
	6	BID	Y-abacavir	3.42
Cremieux et al, 2001	12	BID	Y-abacavir & lamivudine	2.92

- **Are the observed exposures from a twice daily regimen in pediatrics comparable to a three times daily regimen in pediatrics?**

Published reports on experience with BID dosing in pediatrics is extremely limited. There is only one retrospective study that has examined ZDV plasma concentrations from TID vs. BID dosing in pediatric patients receiving ZDV as part of a triple combination therapy (Bergshoeff et al, 2004). The ZDV

portion was initially administered in a TID regimen as 120 mg/m^2 every 8h (approved EU dose) and then was switched to a BID regimen administered as 180 mg/m^2 every 12h. Data from a total of six HIV-infected children (age range: 2.5-13.4 years, median: 7.8 years) were analyzed. AUC_{0-24} and Cmax exposures were not significantly different between the two treatments (table 5). Clearance and half-life estimates were also similar between patients receiving twice daily ZDV versus three times daily. However, the daily exposures were higher than historical exposures in adults resulting from a dose of 300 mg every 12h. This difference in exposures is likely a result of similar clearances between pediatric patients and adult patients but a higher per kg b.w. pediatric dose. For an average 9-year old child, a daily dose of 360 mg/m^2 translates to approximately 11.9 mg/kg/day assuming a mean BSA of 1.04 m^2 and an average weight of 29 kg; whereas in adults, the daily dose of 600 mg translates to approximately 8.6 mg/kg/day, assuming an average weight of 70 kg.

Table 5 ZDV pharmacokinetic parameter estimates in pediatric patients given a TID vs. BID regimen

Pharmacokinetic parameter	Children using zidovudine 120 mg/m^2 every 8 h in current study (GM + 90% CI) $n = 6$	Children using zidovudine 180 mg/m^2 every 12 h in current study (GM + 90% CI) $n = 6$
AUC_{0-24} (mg/L·h)	5.24 (3.73–7.35)	4.72 (3.50–6.36)
C_{max} (mg/L)	0.96 (0.55–1.70)	1.04 (0.69–1.57)
C_{min} (mg/L) (median)	<0.017	<0.017
CL/F·m^2 (L/h·m^2)	63.3 (46.6–85.8)	79.5 (60.3–104.8)
$t_{1/2}$ (h)	1.31 (0.99–1.72)	1.15 (0.90–1.47)

(source: Bergshoeff et al, 2004)

- **Does the phosphorylation process in pediatrics change if ZDV regimen is changed to twice daily from three times daily?**

The intracellular phosphorylation process is essential to the antiretroviral function of ZDV. ZDV must be sequentially phosphorylated to the active triphosphate (TP) form in order to impart its full pharmacological action. Pooling occurs at the level of the ZDV mono-phosphate intermediate. This step is rate-limiting and thus allows for continued phosphorylation to the active moiety although plasma concentrations of ZDV are low. This maintenance effect of ZDV-TP contributes to its long intracellular half-life.

Direct measurement and comparison of ZDV-TP levels between TID and BID dosing has not been studied in pediatric patients <12 years of age. However, if the phosphorylation process is similar between pediatrics and adults, and adults have demonstrated efficacy at both the TID and BID dosing regimens, then a difference in phosphorylation affecting ZDV efficacy would not be expected in pediatric patients who change regimens. In one early report investigating levels of the overall concentration of phosphorylated ZDV in pediatric patients (a sum of the mono-, di-, and tri-phosphate forms), the phosphorylated ZDV concentration range is similar between pediatric patients and adults: 0-5.38 vs. 0.33-3.54 pmol/10^6 cells, respectively (Wintermeyer et al, 1997).

2.4 Conclusions

The simulation model employed by the sponsor is not fully reliable due to the high variability in ZDV pharmacokinetics and it relies on the assumption that the pharmacokinetic parameters do not change from TID vs. BID administration. However, the latter assumption is supported by empirical data. The comparison of TID and BID dosing using simulations demonstrates acceptable exposures after BID vs. TID administration. Overall, the empirical data and modeling support the dosing recommendations.

Historical PK data from several studies show that TID and BID dosing of Retrovir resulted in similar exposures in adults. Although limited data is available in pediatric patients, one small retrospective study showed that ZDV exposures were not significantly different between a TID and BID regimen in pediatrics. Reported clearance values are also similar between adults and pediatric patients irrespective of the dosing regimen. Mechanistically, the *in vivo* phosphorylation process is likely to be similar between adults and pediatric patients. Since TID and BID dosing have both been proved to be effective in adults, it is unlikely that the change from TID to BID dosing will affect the efficacy of ZDV in pediatric patients. The totality of the PK data and simulations along with the mechanistic properties of ZDV are supportive of a switch in dosing from BSA-based to weight-based dosing and from a TID to BID regimen in pediatric patients.

4 Page(s) Withheld

X Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio-

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Shirley Lu
9/17/2008 12:17:09 PM
BIOPHARMACEUTICS

Pravin Jadhav
9/17/2008 12:27:50 PM
BIOPHARMACEUTICS

Jogarao Gobburu
9/17/2008 12:33:35 PM
BIOPHARMACEUTICS

Kellie Reynolds
9/17/2008 02:00:01 PM
BIOPHARMACEUTICS