Clinical Pharmacology Review

NDA	21183 (SE5-020)
Submission Date(s)	March 31, 2008
PDUFA Due Date	September 30, 2008
Brand Name	Videx
Generic Name	Didanosine
Dosage Form	Enteric Coated capsule
Dosage Regimen (Proposed by applicant)	*Adults:* 250 mg once daily for < 60 kg and 400 mg once daily for at least 60 kg adult *Pediatrics:* 200 mg once daily for 20-(b)(4) kg and 250 mg once daily for (b)(4)-60 kg weight group
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Submission Type	Supplemental NDA, Efficacy supplement
Proposed indication	Treatment of HIV infection

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Executive Summary

Recommendation

The Office of Clinical Pharmacology (OCP) reviewed the information submitted under supplemental new drug application NDA 21183 (SE5-020) to support pediatric labeling change and hepatic impairment labeling update. The pediatric labeling changes proposed by sponsor are:

- Dosing recommendations for Videx enteric coated capsules (Videx EC) in children greater than 20 kg.

The office

- agrees with the once daily dose of Videx EC for pediatrics but modified the weight cutoffs. The Videx EC formulation is recommended for patients weighing at least 20 kg (median age of 6 years) who can comfortably swallow the capsule:

Body weight (Kg)	Total Daily Dose
20 to less than 25	200 mg EC capsule once daily
25 to less than 60	250 mg EC capsule once daily

2) agrees with the results of study AI454186 which concludes that there is no effect of hepatic impairment on pharmacokinetics of didanosine.

Phase IV commitment

None

Summary of clinical pharmacology findings

Introduction

The applicant provided two reports to support pediatric labeling change and hepatic impairment labeling update for Videx EC (NDA 21183) [redacted].

- The submission covering pediatric labeling change intended to provide recommendations on
  - [redacted]
  - **Conversion from mg/m to mg/kg dosing in pediatrics**
  - **Videx EC in pediatrics with body weight >20 kg**

[redacted]

Therefore, modeling and simulation report to (a) assess viability of body weight based dosing regimen in comparison to the approved mg/m^2 dosing scheme and (b) to justify the use of Videx EC in pediatrics (>20 kg) were considered relevant

to the Videx EC NDA 21183. The report covers meta-analysis of seven pediatric and two adult clinical trials to build a population PK model and then use a model based simulation approach to determine dosing regimen of Videx EC in pediatrics.

- The hepatic impairment study (AI454186) was designed to evaluate the effect of hepatic impairment on pharmacokinetics of didanosine.

1. Didanosine body weight based dosing recommendations for all formulations and Videx EC dosing in pediatrics from 20-60 kg body weight

Didanosine (ddI) is a nucleoside reverse transcriptase inhibitor that is used for the treatment of HIV in combination with other antiretroviral agents. The current dosing recommendations for Videx formulations in adults and pediatrics are provided in the table below:

	Formulation	
	Powder	EC
Strengths	2g or 4g/bottle	125, 200, 250, 400 mg
	Adults	
<60 kg	125 mg BID	250 mg QD
At least 60 kg	200 mg BID	400 mg QD
	Pediatrics	
2 weeks to 8 months	100 mg/m^2 BID	Not Approved
> 8 months	120 mg/m^2 BID	

The sponsor utilized data from seven pediatric and two adult clinical trials to build a population pharmacokinetic model such that all PK parameters were scaled for weight. Effect of age, gender, formulation, dosing regimen and co-administration of zidovudine was evaluated. The model was finally qualified and utilized to simulate various scenarios investigating:

- **Viability of mg/kg dosing in pediatrics**
- **Exposure of didanosine following administration of Videx EC in pediatrics with body weight >20 kg**

Viability of mg/kg dosing in pediatrics (Evaluated to support dose selection for Videx EC)

The sponsor proposed the following dosing regimen based on model based simulation and using the criteria of matching the simulated exposure in pediatrics with observed exposure in adults:

Sponsor Proposed Dosing:

Body weight (Kg)	Total Daily Dose
20 to less than (b) (4) kg	200 mg
(b) (4) to less than 60 kg	250 mg
At least 60 kg	400 mg

Given the BSA based dosing is already approved in pediatrics, the reviewer compared total daily dose derived from the proposed and approved dosing regimen using the observed weight and BSA data from seven pediatric trials and ACTG 152 study (a randomized, double-blind, controlled study demonstrating efficacy of Videx powder formulation in approximately 400 pediatric patients). Pediatric patients (age ≤ 17 years) weighing less than 60 kg were selected. The sponsor's proposal resulted in lower dosing by 13-20% in 25-30 kg group (**Figure 1**). Similar comparison using data from the ACTG 152 study also showed potential lower dosing with the sponsor's proposal. The maximum dose of Videx EC was capped at total daily dose of 250 mg for (b) (4) 60 kg weight range children based on the maximum approved dose for <60 kg adults.

The proposed Videx EC dosing regimen was modified by reviewer to match the total daily dose based on approved BSA based dosing. The objective was to minimize deviation in total daily dose compared to the BSA based dosing regimen. Didanosine related adverse events include pancreatitis, peripheral neuropathy and optical neuritis. The modified dosing recommendations would on an average produce 4% higher dose compared to the approved BSA based dosing regimen in 25-30 kg weight group (**Figure 2**). It is not possible to give a Videx EC BW based dose which consistently matches the approved BSA based dose to all patients. On the other hand, the sponsor's dosing proposal might lead to on an average 17% lower dose in the same weight group. These lower doses could lead to lack of efficacy or development of resistance.

Reviewer modified dosing:

Body weight (Kg)	Total Daily Dose
20 to less than 25	200 mg
25 to less than 60	250 mg
>60 kg	400 mg

Please see QBR where the rationale to justify the reviewer modified dosing scheme is discussed in detail.

Figure 1: BSA based dosing compared to sponsor's proposed BW based dosing (a) Observed data from ACTG 403 and PACTG 1021 (b) Observed data from ACTG 152. Red, blue and green circles represent patients in 20-25, 25-30 and 30-60 kg weight group, respectively.

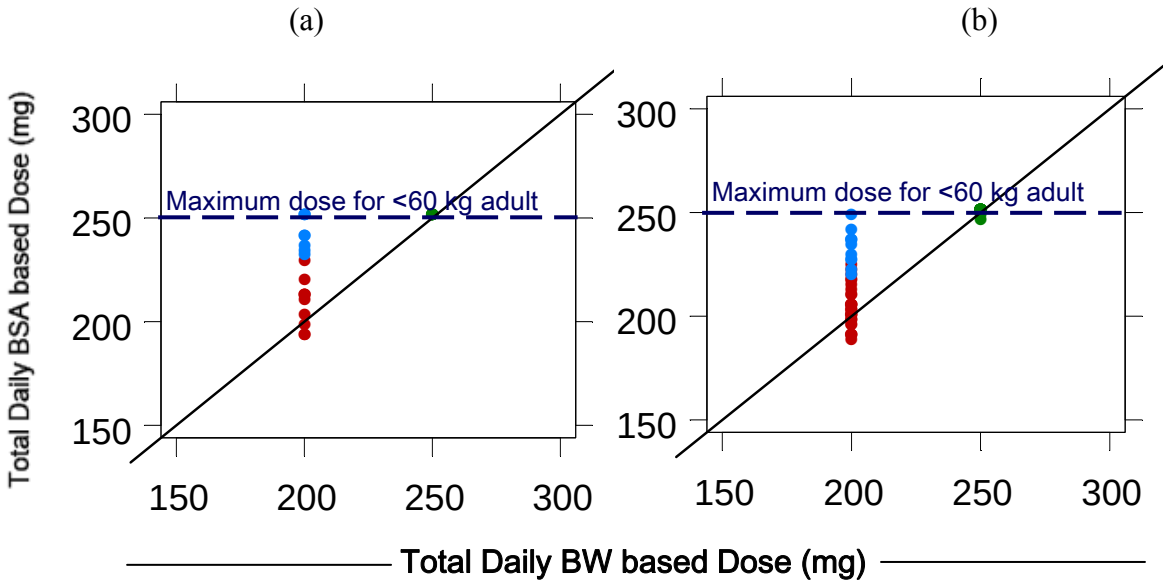
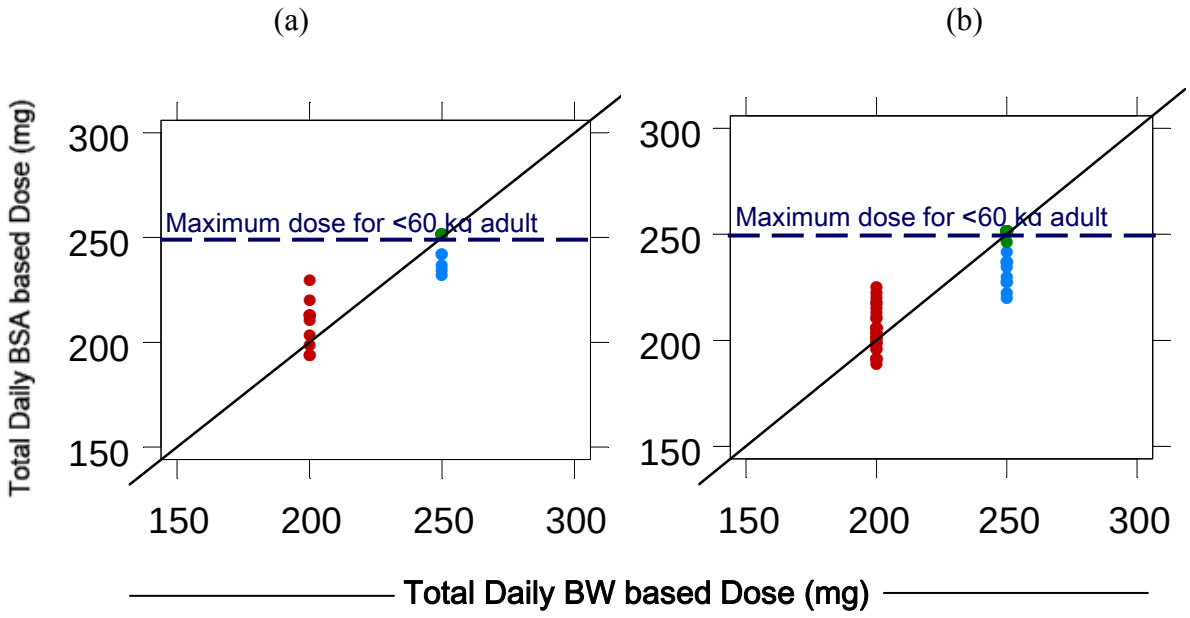


Figure 2: BSA based dosing compared to reviewer's modified BW based dosing (a) Observed data from ACTG 403 and PACTG 1021 (b) Observed data from ACTG 152. Red, blue and green circles represent patients in 20-25, 25-30 and 30-60 kg weight group, respectively.



Exposure of Videx EC in pediatrics with body weight >20 kg

The sponsor simulated various mg/kg doses in different dose groups to match the adult didanosine exposure and to support the following dosing recommendations for Videx EC:

Sponsor proposed dosing:

Body weight (Kg)	Total Daily Dose
20 to less than (b) (4)	200 mg EC capsule once daily
(b) (4) to less than 60	250 mg EC capsule once daily

The sponsor utilized 10th (lower limit) and 90th (upper limit) percentiles of adult AUC values in study AI454157 as a target exposure range (reference). AI454-157 was an open label, single-dose, randomized, two-way crossover study designed to assess the bioequivalence of the chewable/dispersible buffered tablet (approved prior to EC formulation) and the encapsulated enteric-coated bead formulation of didanosine at 400 mg in HIV infected adults. Didanosine was administered under fasting conditions and intensive blood samples were collected over a period of 12 hours post dose for PK assessment. The didanosine concentrations achieved following administration of EC formulation in AI454-157 should be similar to the concentrations in subjects who participated in the pivotal efficacy and safety study that supported approval of Videx EC in adults. The aim of the simulations was to match the AUC achieved by the simulating pediatric dosing regimens to the adult AUC. A pediatric dose for a given body weight group was deemed to be acceptable if ≥ 75% of pediatrics could attain the target AUC. The age-weight distribution was picked from CDC charts such that each age was associated with a median weight.

For evaluating the didanosine exposure following administration of Videx EC in pediatrics, doses were simulated for two weight groups, 20 to **(b) (4)** to <60 kg, with 1000 AUC values generated for each group. According to sponsor's simulation, the target didanosine AUC can be attained at 200 and 250 mg didanosine EC doses in pediatric subjects with BW ranges of 20 to **(b) (4)** to <60 kg, respectively.

The reviewer utilized observed data from studies ACTG 403 and ACTG 1021 and compared exposure (C_{min}, C_{min}/Dose, C_{max}, C_{max}/Dose, AUC, AUC/Dose) in adults receiving Videx EC (400 mg single dose) to exposure in pediatrics (age ≤ 17 years and body weight 20-60 kg) receiving Videx EC capsules matching closely to 240 mg/m^2. The exposure was comparable between adult and pediatrics. To support this empirical evidence, model based simulations were performed using sponsor's population PK model to simulate 1000 replicates for these pediatric subjects (20-60 kg) using dosing scheme proposed by the sponsor and the reviewer modified dosing scheme. Both dosing schemes produced similar results when exposures (AUC and C_{max}, stratified by weight groups) were compared to the target adult reference range. However, reviewer modified dosing scheme is empirically closer when compared to already approved BSA based dosing regimen. Therefore, the reviewer modified dosing regimen was recommended for use in pediatrics presented in the table below.

Reviewer modified dosing

Body weight (Kg)	Total Daily Dose
20 to less than 25	200 mg EC capsule once daily
25 to less than 60	250 mg EC capsule once daily

2. Hepatic impairment study

The primary objective of this study was to compare the pharmacokinetics (PK) of a single 400 mg oral dose of enteric-coated didanosine (ddI-EC) in subjects with hepatic impairment and in healthy control subjects.

24 adult subjects, 12 healthy and 12 hepatic impaired (8 Grade B and 4 Grade C) as defined by Child-Pugh classification were evaluated in this study. Each subject received 400 mg Videx EC and blood samples were collected at prespecified time intervals upto 24 h. Single-dose pharmacokinetic parameters (C_{max}, T_{max}, AUC[INF], AUC[0-T], THALF, CLT/F, Vdss/F) were derived from plasma concentration versus time curve. Didanosine C_{max}, AUC(INF) and AUC(0-T) in subjects with Child-Pugh Class B or C hepatic impairment was 13%, 19% and 21% higher, respectively, compared to healthy subjects. The mean plasma concentration-time profiles of ddI were similar between the healthy and the hepatic impaired subjects although variability appears to be high around C_{max}. Scatterplots of individual didanosine PK parameter overlapped between healthy and hepatic impaired subjects. Moreover, didanosine being a nucleoside reverse transcriptase inhibitor is metabolized by endogenous purine metabolic pathways, and excreted primarily via kidney, hence, hepatic impairment is unlikely to affect its PK profile. However, 90% CI for the ratio of adjusted geometric means were wide and not within 80-125% (the criteria required to show no effect of hepatic impairment as per Guidance for Industry "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling"), which is expected given the small number of subjects and variability in the data. Thus, based on the results of the hepatic impairment study conducted by the sponsor, it would be reasonable to conclude that hepatic impairment does not alter pharmacokinetics of didanosine and hence dose adjustment is not necessary in hepatic impaired individuals.

Question Based Review

A General Attributes of the Drug

(a) What is the proposed therapeutic indication?

Videx in combination with other antiretroviral agents is used for treatment of HIV-1 infection.

(b) What is the proposed dosage and route of administration?

Videx is approved in adults and pediatrics as powder for oral solution and as enteric coated formulation in adults. The data provided in the present submission proposes the use of Videx EC capsules once daily in pediatrics:

Sponsor's proposed dose:

Body weight (Kg)	Total Daily Dose
20 to less than (b) (4)	200 mg EC capsule once daily
(b) (4) to less than 60	250 mg EC capsule once daily

(b) (4)

(c) What efficacy and safety information contribute to the assessment of clinical pharmacology and biopharmaceutics study data?

The present submission does not include new data on the assessment of efficacy or safety. The efficacy and safety is extrapolated from previous adult and pediatric approval.

B General Clinical Pharmacology

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

Not applicable in the current submission

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

A validated LC/MS/MS method was employed for the determination of didanosine in human plasma samples from the hepatic impairment study. Even though, didanosine is not the active moiety, the exposure of didanosine is acceptable as a surrogate for its activity.

(c) What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?

The present submission does not include new data on the assessment of exposure-response for efficacy or safety. The efficacy and safety is extrapolated from previous adult and pediatric approval.

C Intrinsic Factors

Effect of renal impairment on didanosine PK has been established (For details see Videx EC label). Sponsor conducted a study to evaluate the effect of hepatic impairment on the pharmacokinetics of didanosine. The key question to be addressed is:

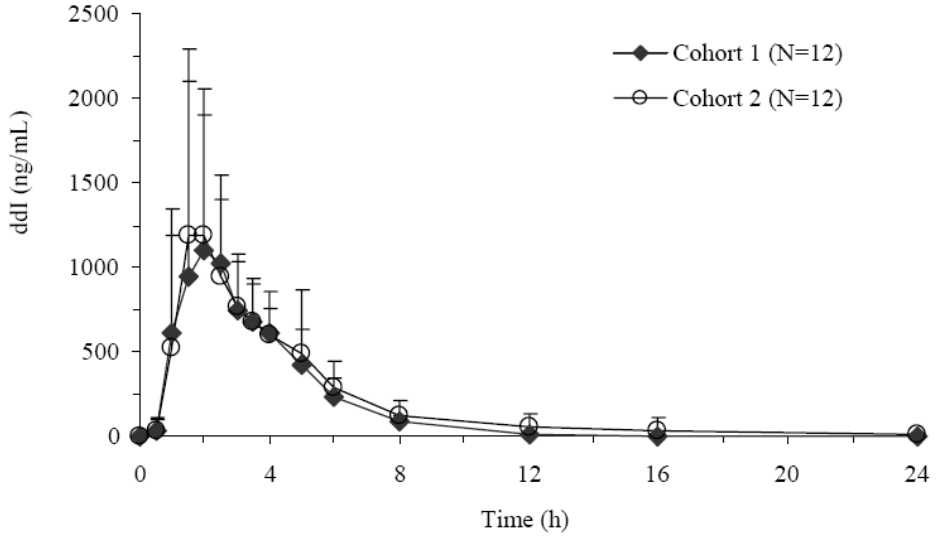
Is there an effect of hepatic impairment on pharmacokinetics of didanosine?

Hepatic impairment doesn't seem to affect the pharmacokinetics of didanosine following administration of Videx EC. The plasma concentration profiles (**Figure 3**) of healthy and hepatic impaired subjects overlapped with each other and the PK parameters were similar between two groups (**Table 1**).

Table 1: Statistical comparison with point estimates and 90% confidence intervals

Pharmacokinetic Parameter	Adjusted Geometric Means		Ratios of Adjusted Geometric Means Point Estimate (90% CI)
	Healthy Subjects (Cohort 1)	Hepatic Impaired Subjects (Cohort 2)	Cohort 2 / Cohort 1
C_{max} (ng/mL)	1141	1284	1.125 (0.696, 1.817)
AUC(INF) (ng•h/mL)	3667	4346	1.185 (0.872, 1.611)
AUC(0-T) (ng•h/mL)	3654	4409	1.207 (0.896, 1.625)

Figure 3: Mean (S.D.) plasma concentration versus time profiles of didanosine in healthy control and hepatic impaired subjects



Cohort 1: Healthy control subjects
Cohort 2: Hepatic impaired subjects, Grade B or C

D Extrinsic Factors

For complete details for extrinsic factors affecting didanosine PK, refer to Videx EC label.

E General Biopharmaceutics

Videx is approved as pediatric powder for oral solution and enteric coated formulation. The characteristics of these formulations are well documented in NDAs 20-154, 20-156, 20-183. The present submission deals with use of Videx EC in pediatrics. The composition of Videx EC capsule is given in **Table 2**.

Table 2: Composition of Videx EC Capsule

Ingredients	**125 mg**	**200 mg**	**250 mg**	**400 mg**
	Amount in g/ capsule			
Uncoated Beads				
Didanosine	(b) (4)			
Sodium Starch Glycolate, NF	(b) (4)			
Carboxymethylcellulose Sodium 12, NF	(b) (4)			
(b) (4)	(b) (4)			
(b) (4)				
Methacrylic Acid Copolymer (b) (4)				
Diethyl Phthalate, NF	(b) (4)			
Sodium Hydroxide, NF 3	(b) (4)			
(b) (4)				
Talc, USP	(b) (4)			
Net Capsule Weight (g)	(b) (4)			
Encapsulation				
White, Opaque, (b) (4) Hard Gelatin Capsule, Size	(b) (4)			
(b) (4)				

F Analytical Method

A Validated LC/MS/MS method (b) (4)) was used to determine concentration of didanosine in human plasma for the hepatic impairment study (AI454186, report-(b) (4) 02a-238).

Table 3: Details of the bioanalytical method.

Criteria	**Observation**	**Comment**
Calibration Range	0.5-500 ng/ml with $R_2 \geq 0.98$	Satisfactory
MRM Transitions	Didanosine:237.2 > 137.3, Internal Standard: (b) (4) (b) (4)	Satisfactory
Accuracy	Within ± 10% at all quality control levels	Satisfactory
Precision	< 10% Deviation at all quality control levels	Satisfactory
Specificity	No Significant interference in any of the samples for	Satisfactory

	drug or internal standard	
Sensitivity	LLOQ = 0.5 ng/ml	Satisfactory
Extraction efficiency	~ 90% for both didanosine and IS	Satisfactory
Stability	Bench top stability in human plasma (22 h), freeze thaw stability upto three freeze thaw cycles, refrigerated extract stability (78 h) and room temperature autoinjector stability (70 h) was established	Satisfactory

G Are the dosing recommendations for Videx EC in pediatric patients acceptable?

Sponsor's Analysis

The key questions pertinent to the present submission were:

1. Can dosing of Videx EC be considered in pediatric subjects >20 kg who can comfortably swallow the capsule?
2. Is body weight dosing a viable option?

   Note: The body weight dosing evaluation supports dose selection for Videx EC. (b) (4)

The details for the sponsor's analysis are present in Modeling and Simulation report (m&sreport).

Objectives:

(1) To characterize the PK of didanosine in HIV-1 infected pediatric and adult subjects following the oral administration with a population PK model

(2) To evaluate subject matters related to dosing didanosine in pediatric subjects by using model-based simulation:
- − Didanosine exposures in neonates
- − Didanosine daily exposures under once-daily (QD) and twice-daily (BID) regimens
- − Oral clearance of didanosine in pediatric patients with and without co-administration of zidovudine (ZDV)
- − Dosing didanosine enteric-coated (EC) capsule formulation (gastro-resistant capsules or Videx ®EC) in pediatric subjects
- − Viability of a body weight adjusted pediatric dosing scheme

Data utilized:

Population pharmacokinetic analysis was performed to estimate the PK parameters of didanosine in pediatric and adult subjects. Pooled plasma concentration-time data from seven (7) pediatric and two (2) adult clinical trials were utilized for model building. Total of 2011 plasma concentration-time data points from 151 subjects were utilized to build the model. The patients were in an age range from neonates (Day 1 after birth) to adults (up to 50 years old) and in a BW range from 2.3 to 111 kg. Brief descriptions of design and dosing conditions of each study are provided in **Table 4**. As highlighted in the table below, data from EC formulation was available from two studies (ACTG-403 and PACTG1021).

Table 4: Summary of Didanosine Data Information

Study (Number of subjects)	Formulation	Dose	Regimen	PK Sampling	LLQ (ng/ml)	Age Range
AI455-094 (n=18)	Solution	120 mg/m2	BID	Up to 6 samples per subject during 0-8 hours post dose	3 *RIA	1-21 days
HIV-NAT007 (n=8)	Solution	100 mg/m2	QD	Up to 5 samples per subject during 0-10 hours post dose	3 RIA	14-28 days
DDI-BR001 (n=22)	Solution	180 mg/m2 90 mg/m2	QD BID	Sampled at 0.5, 1, 3 hours post morning dose	3 RIA	1-11 years
ACTG403 (n=8)	**EC-capsule**	**240 mg/m2**	**QD**	**Up to 6 samples per subject during 0-12 hours post dose**	**3 RIA**	**4-12 years**
PACTG-1021 (n=35)	**Solution EC-capsule**	**240 mg/m2**	**QD**	**Up to 6 samples / subject / formulation during 0-24** hours post dose	**10 LC-MS**	**3-21 years**
AI454-003 (n=16)	Solution	80-180 mg/m2	BID	Up to 8 samples per subject during 0-9 hours post dose	25 LC	0.7-11 years
AI454-005 (n=4)	Solution	80-180 mg/m2	BID	Up to 8 samples per subject during 0-9 hours post dose	25 LC	8-17 years
AI-454-002 (n=10)	Solution	0.8-6 mg/kg	BID	Up to 12 samples per subject during 0-12 hours post dose	25 LC	>18 years
AI454-157 (n=30)	EC-capsule Tablet	400 mg	Single dose	Up to 20 samples per subject per formulation during 0-12 hours post dose	5 RIA	>18 years

*Analytic method: RIA= radioimmunoassay; LC = liquid chromatography, LC-MS = LC with mass spectrum detector

Source: Table 3.3 of Sponsor's Modeling and Simulation Report

Methods:

The PK of didanosine in pediatric and adult subjects were characterized simultaneously by a population PK model, using non-linear mixed effect modeling approach in which PK

parameters were scaled based on body weight (BW). The model was used to evaluate effects of age, gender, dosing schedule, formulations (oral solution, buffered tablets and EC capsules), and co-administration with ZDV on didanosine exposures. Bioavailability of the solution formulation was assessed relative to that of the tablet and EC formulations. The population model was evaluated using predictive check. Model-based simulation was employed to evaluate 1) didanosine exposure in neonates, 2) comparability of daily AUC (area under the concentration ~ time curve) between QD and BID regimens, 3) didanosine EC doses for pediatric subjects, and 4) viability of a BW-based dosing scheme. The daily AUC range of didanosine estimated by non-compartmental analysis (NCA) at a therapeutic 400 mg dose in HIV-1 infected adults was used as a reference (i.e. target range) for these evaluations and a regimen was deemed to be appropriate if more than 75% of patients AUCs lie within the 80% CI of adult target range.

Results:
The PK of oral didanosine in pediatric and adult subjects was described adequately by a first order absorption and one-compartment disposition model. BW was employed as a primary covariate on the absorption rate constant (Ka), the apparent volume of distribution (V/F) and the apparent clearance (CL/F), and was incorporated into the base model. Age was found to be a significant covariate on V/F and CL/F in addition to BW. Furthermore, Ka was formulation-dependent; Ka for the oral solution was approximately 2- and 14-fold higher than respective Ka for the tablet and EC formulations. Effects of gender, dosing schedule and co-administration with ZDV on CL/F were negligible. The extent of bioavailability among the three formulations appeared to be equivalent. The parameter estimates of the final model are presented in **Table 5**.

Table 5: Parameter estimates of the covariate model

Name[a,b] [Units]	Symbol	Estimate[c]	Standard Error (RSE%)[d]	95% Confidence Interval[e]
Fixed Effects				
CL [L/h/70kg]	θ1	172	8.82 (5.13)	155 - 189
V [L/70kg]	θ2	296	16.3 (5.51)	264 - 328
KAEC [h-1]	θ3	0.603	0.0804 (13.3)	0.445 - 0.761
KABT [h-1]	θ4	4.17	0.893 (21.4)	2.42 - 5.92
KAOS [h-1]	θ5	8.62	1.99 (23.1)	4.72 - 12.5
PBWCL	θ6	0.623	0.0310 (4.98)	0.562 - 0.684
PBWV[f]	θ7	1.00		
PBWKA	θ8	0.733	0.128 (17.5)	0.482 - 0.984
bcl	θ9	-0.428	0.0789 (18.4)	-0.583 - 0.273
kcl [yr-1]	θ10	2.84	1.32 (46.5)	0.253 - 5.43
bv	θ11	1.74	0.516 (29.7)	0.729 - 2.75
kv [yr-1]	θ12	21.5	7.81 (36.3)	6.19 - 36.8
Random Effects				
ZCL	ω1,1	0.163 (0.404)	0.0231 (14.2)	0.118 - 0.208
ZV	ω2,2	0.243 (0.493)	0.0445 (18.3)	0.156 - 0.330

ZKA	ω3,3	0.550 (0.742)	0.0885 (16.1)	0.377 - 0.723
ZCL:ZV	ω1,2	0.185 (0.930)	0.0296 (16.0)	0.127 - 0.243
Residual Error				
PERRELISA	σ1,1	0.240 (0.490)	0.00870 (3.62)	0.223 - 0.257
AERRELISA	σ2,2	253 (15.9)	8.79 (3.47)	236 - 270
PERRLC	σ3,3	0.146 (0.382)	0.00837 (5.73)	0.130 - 0.162

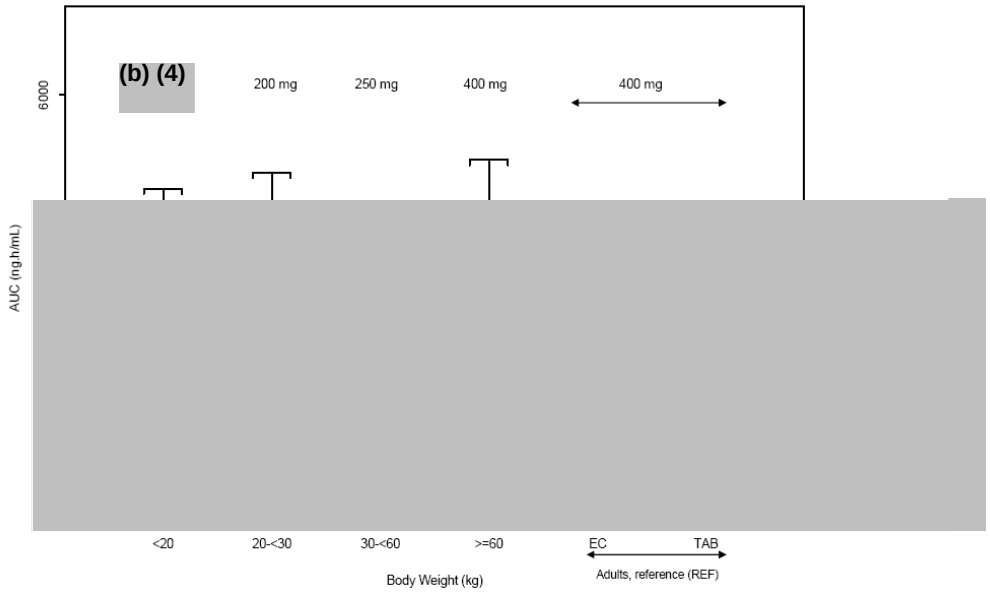
[a] Parameters with fixed values (not estimated) are denoted with a superscript '*f*' after the names, with the fixed value given in the Estimate column
[b] Random Effects and Residual Error parameter names containing a colon (:) denote correlated parameters
[c] Random Effects and Residual Error parameter estimates are shown as *Variance (Standard Deviation)* for diagonal
elements (ωi,i or σi,i) and *Covariance (Correlation)* for off-diagonal elements (ωi,j or σi,j)
[d] RSE% is the relative standard error (Standard Error as a percentage of Estimate)
[e] Confidence intervals of Random Effects and Residual Error parameters are for *Variance* or *Covariance*

Based on model based simulation sponsor proposed a body weight based dosing strategy and suitability of Videx EC in pediatrics >20 kg (**Figure 4** and **Table 6**):

Table 6: Proposed body weight dosing regimen for ddI

Body weight (Kg)	**Total Daily Dose**
[redacted]	[redacted]
20 to less than [redacted]	200 mg
[redacted] to less than 60 kg	250 mg
At least 60 kg	400 mg

Figure 4: Model based simulation depicting the suitability of Videx in pediatrics



Reviewer's Comments

The sponsor followed a reasonable and systematic approach in describing the population pharmacokinetics of didanosine. The model reasonably described the data in hand and was evaluated using predictive check. However, reviewer does not agree with the dosing

regimen proposed by sponsor in (b) (4) 20-60 kg weight band and the details are provided in the following section.

Reviewer's Analysis

Objective:

1. To compare the approved BSA based dosing with proposed BW based dosing.
2. To asses the similarity in didanosine exposures following administration of Videx EC in adults and pediatrics which would indicate similar efficacy:
   a. Empirical evidence: To compare the observed exposures (AUC, C_{max} and C_{min}) achieved in pediatrics who were administered Videx EC (ACTG403 and PACTG1021) with that achieved in adults after Videx EC administration (AI-454-157).
   b. Supportive model based evidence: Simulate the proposed sponsor's dosing scheme and reviewer's modified dosing scheme for administration of Videx EC in >20 kg pediatrics using the observed data.

Methods:

1. To address the first question, the approved BSA based dosing was compared with the proposed BW dosing for pediatrics less than 60 kg weight from the age-WT-BSA data in seven pediatric trials and data from 394 patients in the ACTG 152 study. Study ACTG 152 was a randomized, double-blind, controlled study (conducted 1991-1995) involving 831 patients 3 months to 18 years of age treated for more than 1.5 years with zidovudine (180 mg/m^2 every 6 hours), didanosine (120 mg/m^2 every 12 hours), or zidovudine (120 mg/m^2 every 6 hours) plus didanosine (90 mg/m^2 every 12 hours). Similar comparison was made between the approved BSA based dosing and the reviewer modified BW dosing.
2. To answer the viability of Videx EC in pediatrics, subjects with age <17 years were selected from the studies ACTG403 and PACTG1021. Peak concentrations designated as C_{max} (between time 1.5 and 2.5 h) and trough concentrations (time ≥ 8h) were compared with the corresponding adult values. Since some of the pediatric subjects had rich samples (upto 6 samples in 24 h) computation of AUC was possible using non compartmental analysis and compared with AUCs of adults administered EC in study AI-454157. Finally, both the sponsor's proposed dosing scheme and reviewer's modified dosing scheme were simulated using the sponsor's population PK model to examine the range of exposures (AUC, C_{max}) obtained.

Results and Discussion:

1. **Figure 5** illustrates the proposed BW dosing vs the BSA based dosing (240 mg/m^2) as seen for the observed patients (< 60 kg). There are two issues which are evident from the figure below.

First, is the large deviation in dose for the (b) (4) weight group in which (b) (4) mg/kg regimen is likely to yield lower dose. It was seen that as the deviation could be as high as 30% and might lead to lack of efficacy due to reduced exposure. Similar comparison

using the age-wt-BSA distribution in 144 subjects less than (b) (4) kg from ACTG 152 study also showed that sponsor's proposed dosing scheme is likely to yield lower dose. The histogram in

Figure 6 showing the distribution of the ratio of Sponsor's Body weight based dose to approved BSA based dose. The ratio of less than 1 means that the dose derived based on the proposed BW dosing will yield lower dose than the approved BSA dosing. Thus, an empirical dosing strategy (12 mg/kg in < 10 kg and 10 mg/kg in 10-20 kg pediatrics) based on the observed data was established such that the deviation from the actual BSA dose is minimum in the (b) (4) kg wt group (

Figure 7).

Figure 5: BSA based dosing compared to BW based dosing proposed by sponsor

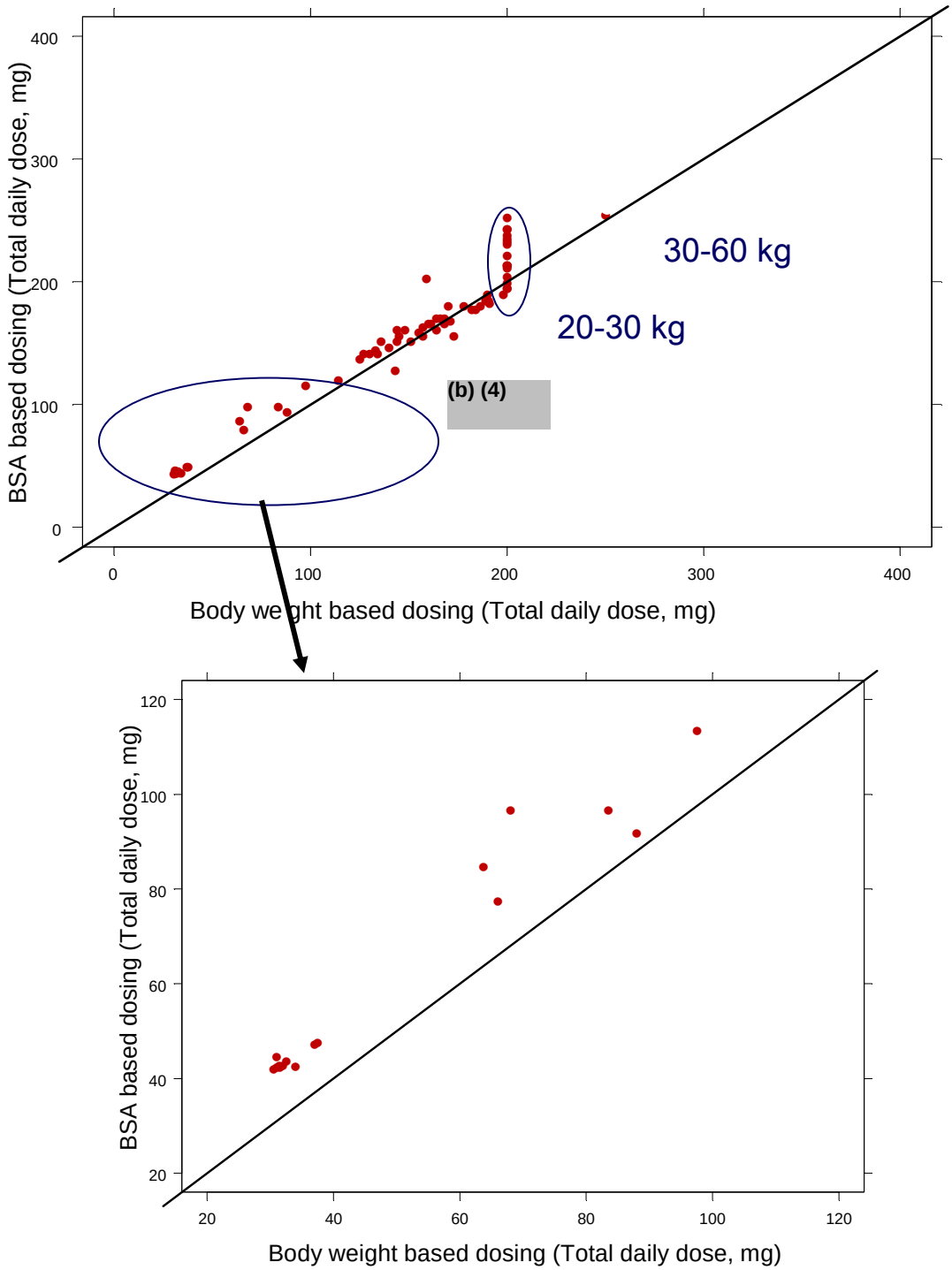
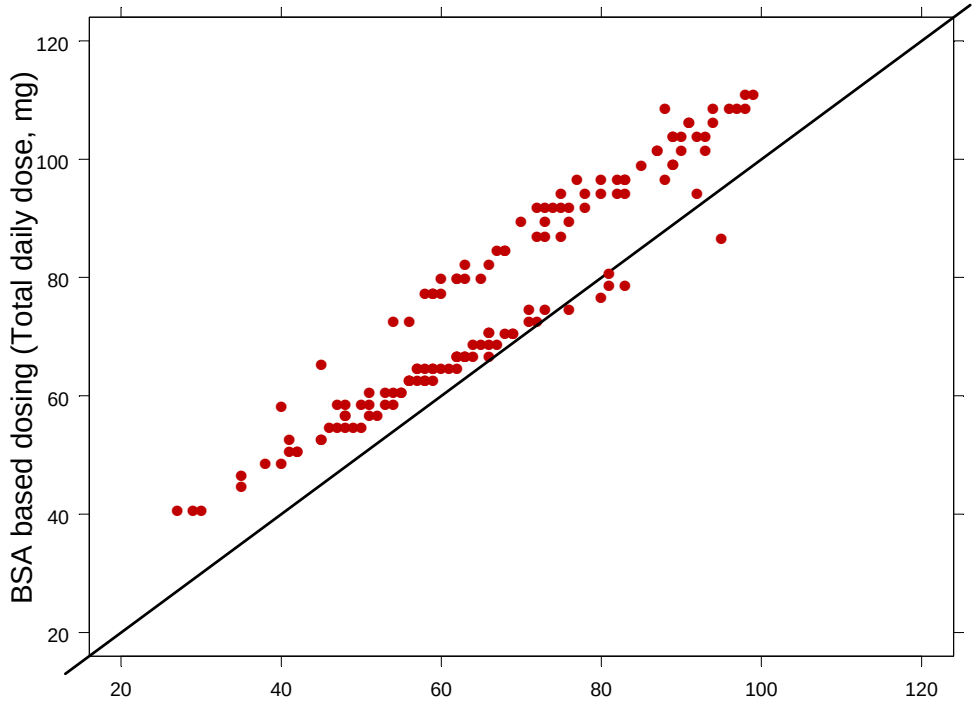


Figure 6: BSA based dosing compared to sponsor's proposed dosing scheme from the ACTG 152 data, showing high probability of lower dosing in (b) (4) group.



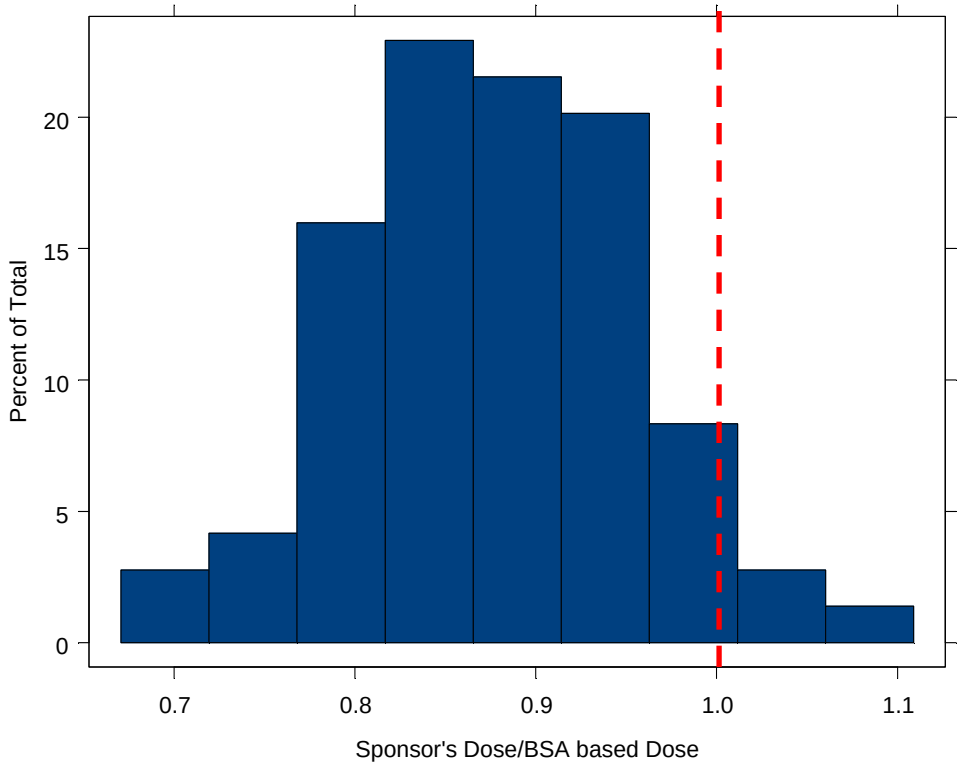
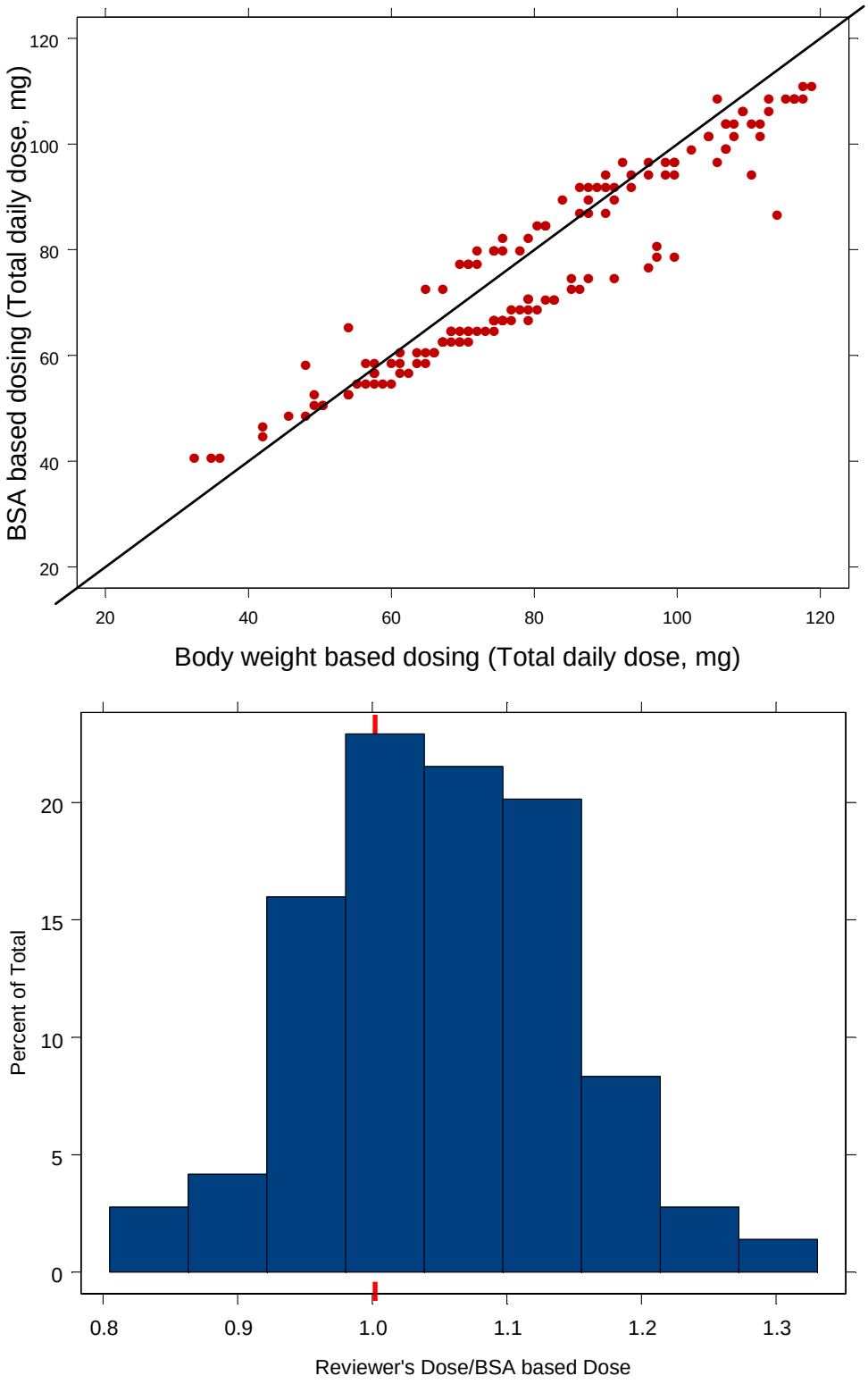


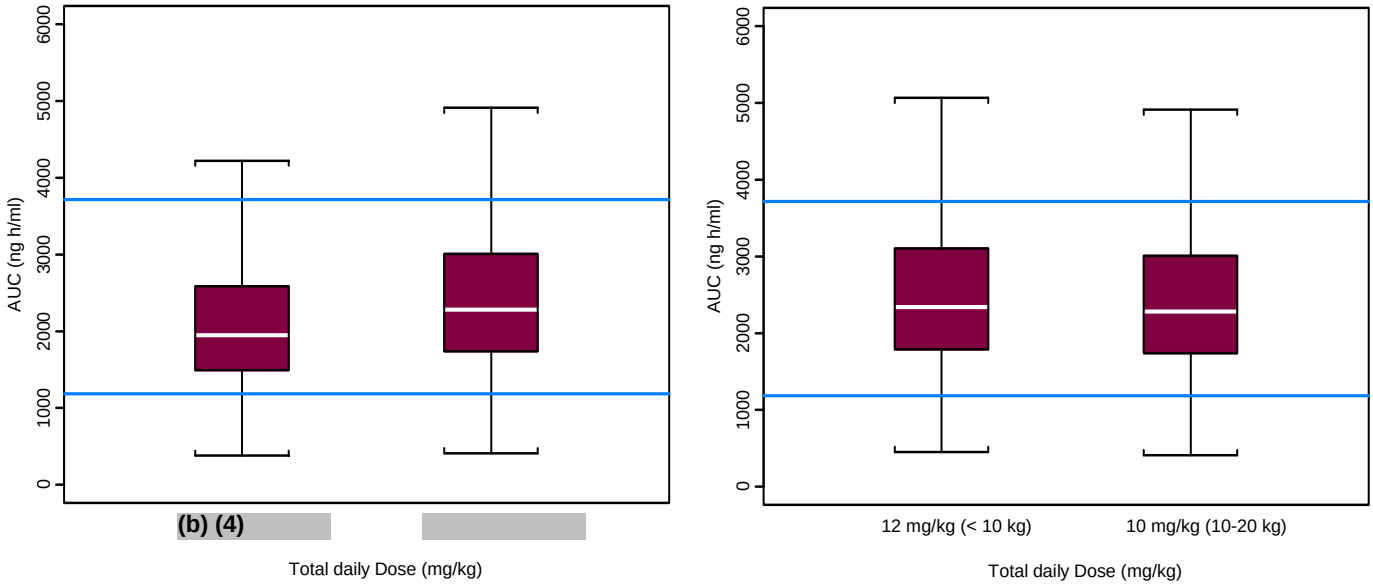
Figure 7: BSA based dosing compared to Reviewer's proposed dosing scheme for <10 kg group from the ACTG 152 data, showing more probability of subjects to have BSA based approved dose.



Simulations based on sponsors population PK model also showed that the AUC achieved by 12 mg/kg and 10 mg/kg were similar and within the target therapeutic range of the adults (**Figure 8**). Sponsor's population PK model was utilized to simulate sponsor's and reviewer's dosing scheme for the <10 and 10-20 kg pediatrics from the studies ACTG 403 and PACTG 1021 (1000 replicates) and AUCs were compared to the observed exposure in adults. It can be seen that even though the distribution of AUCs were shifted above in the <10 kg weight group for the reviewer proposed dosing scheme, they lied within the adult target concentration range.

Figure 8: Evaluation of AUC using Model based simulation of (a) sponsor's and (b) reviewer's dosing scheme for the <10 and 10-20 kg weight group (the blue solid lines are the 10th and 90th percentile of AUC obtained in adults.

(a) (b)



Second, the sponsor dosing scheme also seems to give lower dose in the 20-60 kg weight group by as high as 30% when compared with approved BSA based dosing. **Figure 9** summarizes the current body weight based dosing scheme proposed by sponsor in <60 kg pediatrics.

Figure 9: Schematic representation of the dosing strategy proposed by the sponsor

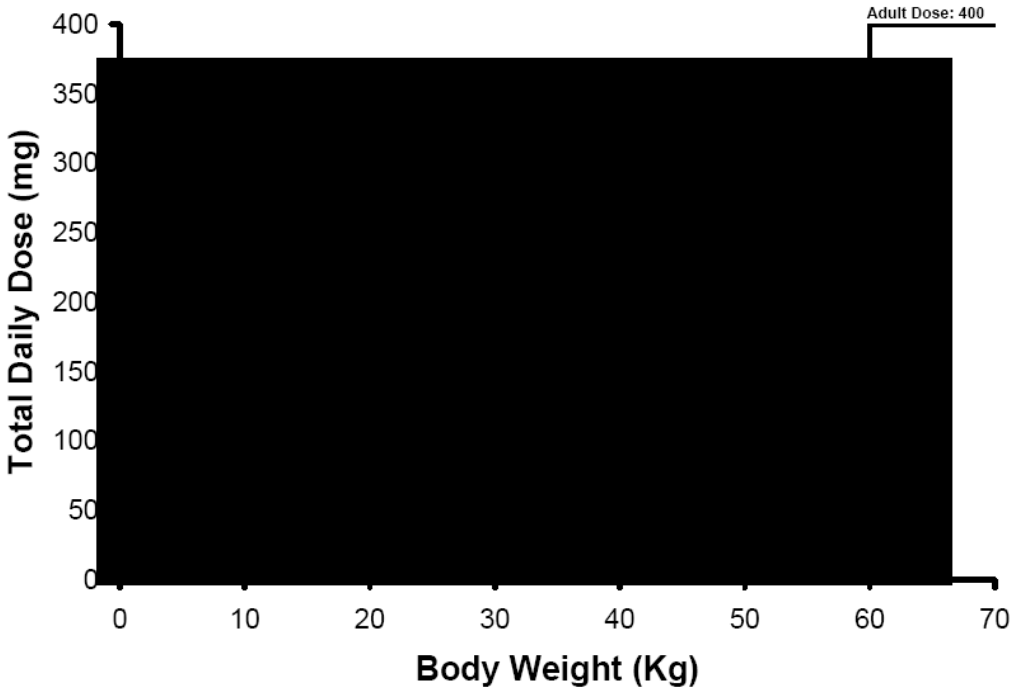
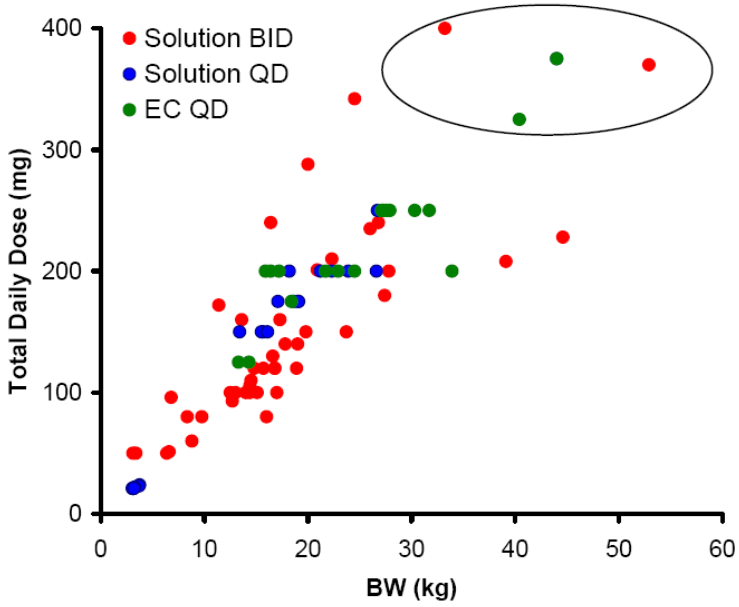


Figure 10: Weight-Total daily dose distribution of pediatrics <60 kg from the seven pediatric trails



It can be seen from the graph above that there is a continuum in dosing until 30 kg such that <20 kg weight range pediatrics receive mg/kg dose and 20-30 kg a total dose of 200 mg (6.7-10 mg/kg). However, a discontinuity is observed in dosing from 30-60 kg such that pediatrics in this weight range are capped at a total daily dose of 250 mg (4.2-8.3 mg/kg) based on the highest dose approved for <60 kg adult. With this upper limit, even though the approved dose is 240 mg/m^2 in pediatrics, a patient weighing 30 kg with a median BSA of 1.12 m^2 will receive a 250 mg dose even when the total dose based on the approved BSA based dose should be 268 mg. For subjects beyond this weight until 60 kg, the dose will be capped at 250 mg total daily and will change to 400mg for >60 kg subjects.

There is no evidence in the clinical trial (ACTG 152) that supports the capping of the pediatric dose at 250 mg (Zidovudine, Didanosine, or both as the initial treatment for symptomatic HIV infected children, New England Journal of Medicine, June 1997, 1704-1712). Moreover, based on a guidance for the use of antiretroviral agents developed by the members of the working group on the antiretroviral therapy and medical management of HIV-infected children ((http://aidsinfo.nih.gov/contentfiles/PediatricGL_SupI.pdf)), 120 mg/m2 twice daily is the standard dose of ddI which appears to be safe and is associated with clinical improvement. There is no mention on the upper limit of 250mg dose for pediatrics in this document also. And, it was seen in trials ACTG 403 and PACTG 1021, doses of VIDEX EC equivalent to 240 mg/m^2 were administered and there were four cases where >250 mg were administered to pediatrics between 30-60 kg (**Figure 10**). However, dose distribution data from ACTG 152 was not available for verification. Thus a modified dosing strategy was evaluated by the reviewer with 325 mg dose for 35-60 kg weight group (**Table 7** and **Figure 11** , **Figure 12**) from pharmacokinetic perspective. The modified dosing scheme is closer to the approved BSA based dosing and maintains the continuum in dosing from two week to 60 kg child.

Table 7: Reviewer modified body weight dosing scheme for ddI to produce continuum in dosing from 20-60 kg pediatrics

Body weight (Kg)	Total Daily Dose
Less than 10 kg	12 mg/kg
10 to less than 20	(b) (4)
20 to less than 25	200 mg
25 to less than 35	250 mg
35 to less than-60	325 mg

The graph below (**Figure 11**) shows a modified version of **Figure 9** with 325 mg dose to be administered to 35- 60 kg pediatrics.

Figure 11: Schematic representation of the dosing strategy evaluated by the reviewer

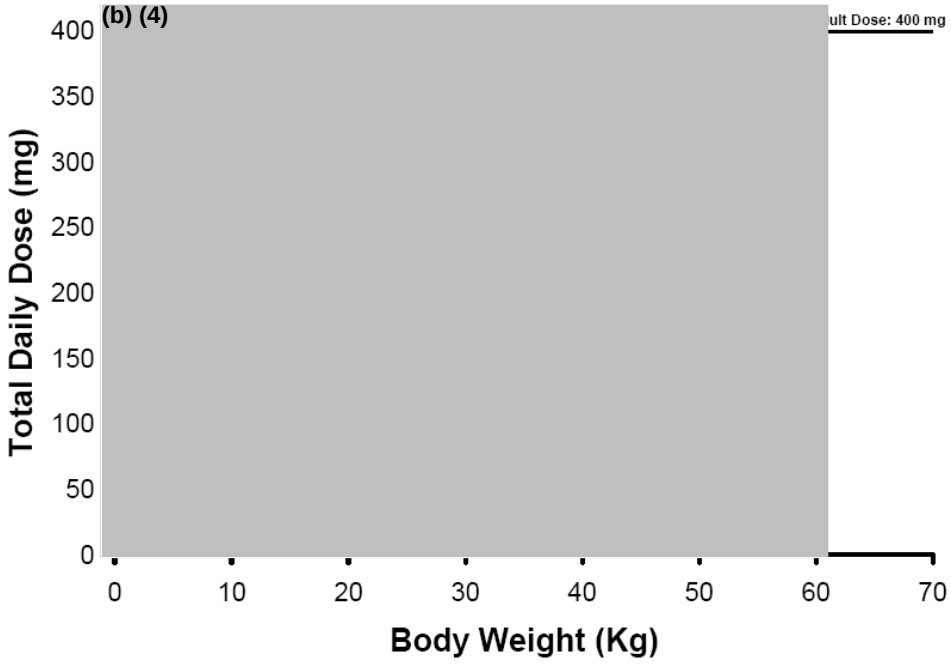
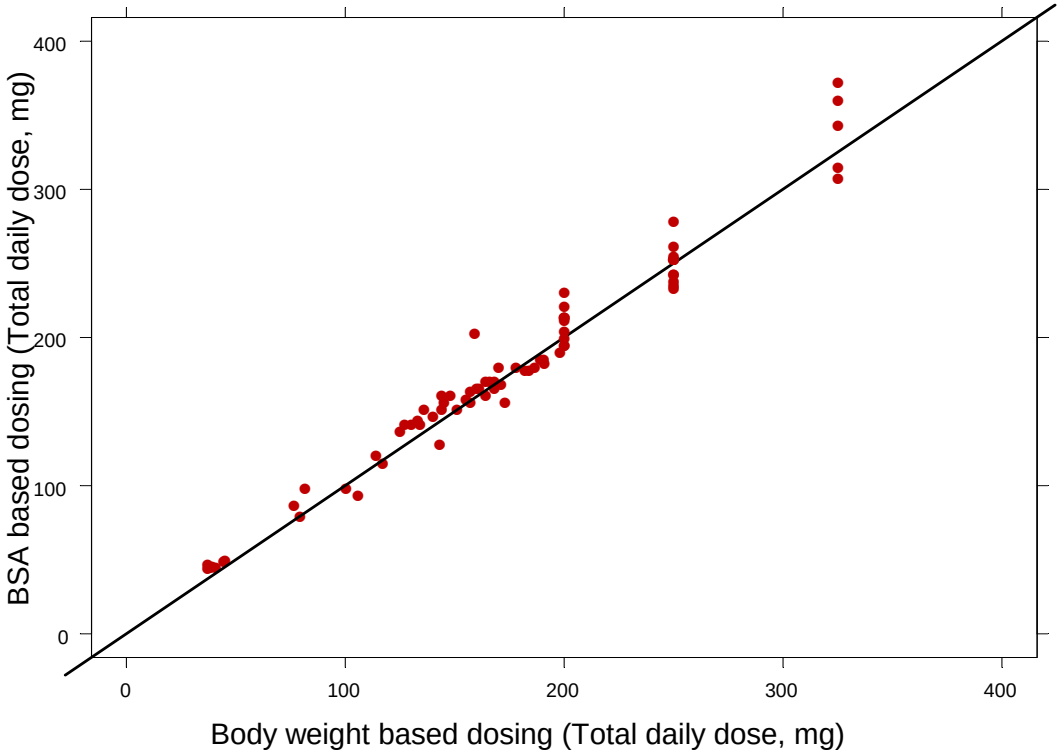
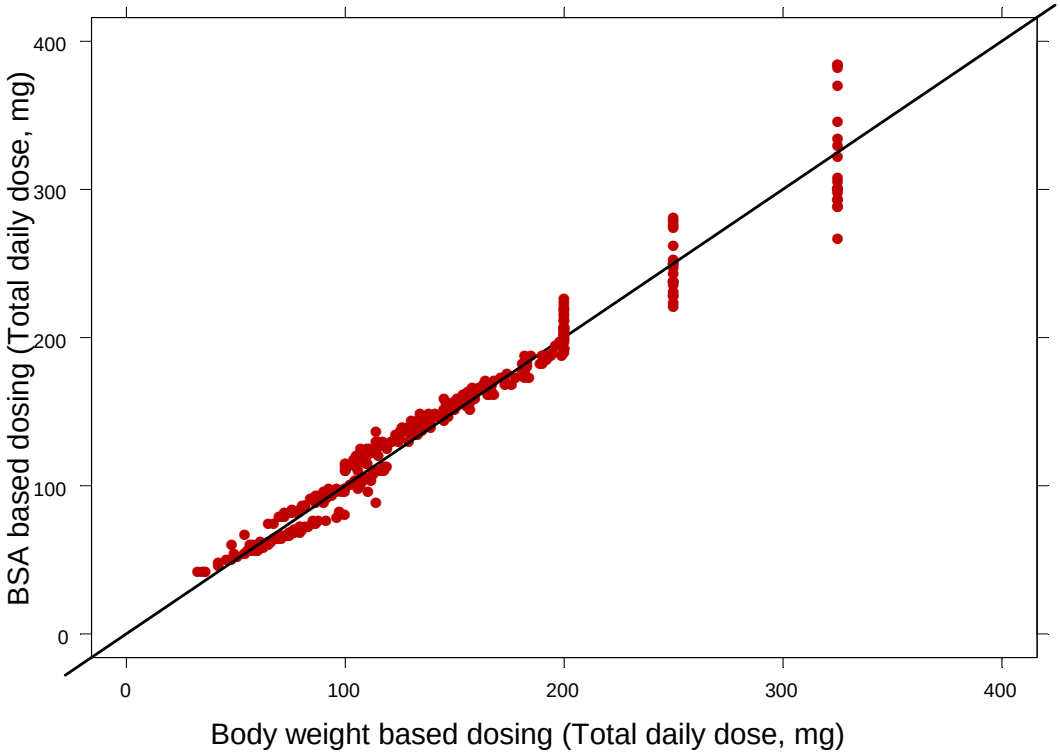


Figure 12: BSA based dosing compared to reviewer modified BW based dosing (a) Observed data from ACTG 403 and PACTG 1021 (b) Observed data from ACTG 152

(a)



(b)



For this strategy to take effect, the approval history of didanosine was important to understand the rationale behind recommending 250 mg dose for <60 kg adults.

Videx (Tablets and Buffered Powder) was first approved in 1991 based on changes in surrogate endpoints in non-randomized phase-I studies. The doses approved were higher than the current recommended doses of Videx and are highlighted below:

Table 8: Doses first approved for Videx powder and buffered tablets in 1991

Patient Weight	Videx Tablets	Videx Buffered Powder
≥ 75 kg	300 mg BID	375 mg BID
50-74	200 mg BID	250 mg BID
35-49	125 mg BID	167 mg BID

Videx buffered powder (adult powder, not the current approved pediatric powder) is 20-25% less bioavailable than tablet and hence the higher corresponding dose. The dosing recommendations were revised based on the results of ACTG116B/117 in 1992 which demonstrated a clinical benefit for adults with advanced HIV infection who switched after prolonged use of zidovudine. ACTG116B/117 was a multicenter, randomized, double blind trial that compared the clinical efficacy and safety of zidovudine with those of didanosine in subjects who had tolerated atleast 16 weeks of zidovudine. Two weight adjusted daily doses of buffered powder formulation were studied:

High dose strategy: **375 mg BID** (250 mg BID mg <60 kg patient)
Low Dose strategy: **250 mg BID** (167 mg BID <60 kg patient)

As per the medical officer review from the action package for ddI approval in 1992 "The results from ACTG 116B/117 demonstrate that patients randomized to low dose ddI had a statistically significant increase in the time to progression of disease, as defined by a new AIDS defining event or death, when compared to patients randomized to continue on ZDV therapy. High dose ddI was not statistically significantly better than ZDV. In addition, low dose ddI was found to be safer and better tolerated than high dose ddI. Most importantly, fewer cases of pancreatitis were seen in the low dose arm and there were no drug related fatalities in the low dose arm. These data clearly demonstrate that there is no additional efficacy benefit associated with administering doses of ddI which exceed 200mg bid of the chewable dispersable tablet. In addition, these data clearly demonstrate that doses which exceed 200 mg bid are less safe. Therefore the recommended dosing schedule has been revised to reflect that which was administered in the low dose ddI arm. The major clinical adverse events associated with ddI therapy during the course of study were pancreatitis and neuropathy. The one-year rates for pancreatitis were 13 percent for ddI high dose and 7 percent ddI at the recommended dose as compared to 3 percent for ZDV (p=0. 001 and p=0. 09 , respectively). There were two episodes of fatal pancreatitis in the ddI high dose arm. The one-year rates of grades 2, 3 or 4 peripheral neuropathy were 14 percent, 13 percent and 14 percent (high dose ddI versus ZDV, p=0. 790 and ddI

at the recommended dose versus ZDV, p=0. 946)" . Thus the dosing recommendations were modified to:

Table 9: Doses modified following results from ACTG116B/117 in 1992

Patient Weight	Videx Tablets	Videx Buffered Powder
≥ 60	200 mg BID	250 mg BID
< 60	125 mg BID	167 mg BID

At this approval, the 250 mg (125 mg BID) cutoff for a <60 kg individual was introduced for didanosine. However, it is important to note that the rate of pancreatitis stratified by weight group were not available which would have provided information about the incidence of pancreatitis in <60 kg adults. And the choice of doses (500 and 334 mg equivalent to 400 and 250 mg tablet) was guided by the availability of buffered powder formulation. The reviewer's modified dosing scheme (Total daily dose of 325 ~162.5 mg BID for <60 kg patient) falls between the low and high dose strategies tested in ACTG 116/117B. Thus, provided the 325 mg total daily dose was never tested earlier, lack of information about the cases of pancreatitis in <60 kg patients from trial ACTG116B/117 might raise concerns about the 325 mg daily dose. Therefore, the dose was capped at 250 mg for < 60 kg patients and final dosing recommendations are as follows:

Table 10: Reviewer modified dosing scheme with 250 mg as the highest total dose recommended considering the results from ACTG116B/117.

Body weight (Kg)	Sponsor's Proposed Total Daily Dose	Reviewer's Modified Total Daily Dose
Less than 10 kg	(b) (4)	12 mg/kg
10 to less than 20		10 mg/kg
(b) (4) to less than 25	200 mg	200 mg
25 to less than (b) (4)	(b) (4)	250 mg
(b) (4) to less than 60	250 mg	

2. To asses the viability of Videx EC in pediatric:
   (a) Peaks, troughs and AUCs appear to overlap among adults and pediatrics administered Videx EC (

Figure 13, **Figure 14** and **Figure 15**). The doses of didanosine used in pediatrics and adults in these clinical trials are given in **Table 4**.

Figure 13: Comparison of (a) peak concentrations (b) and dose normalized peak concentrations of didanosine following administration of Videx EC among adults and pediatrics.

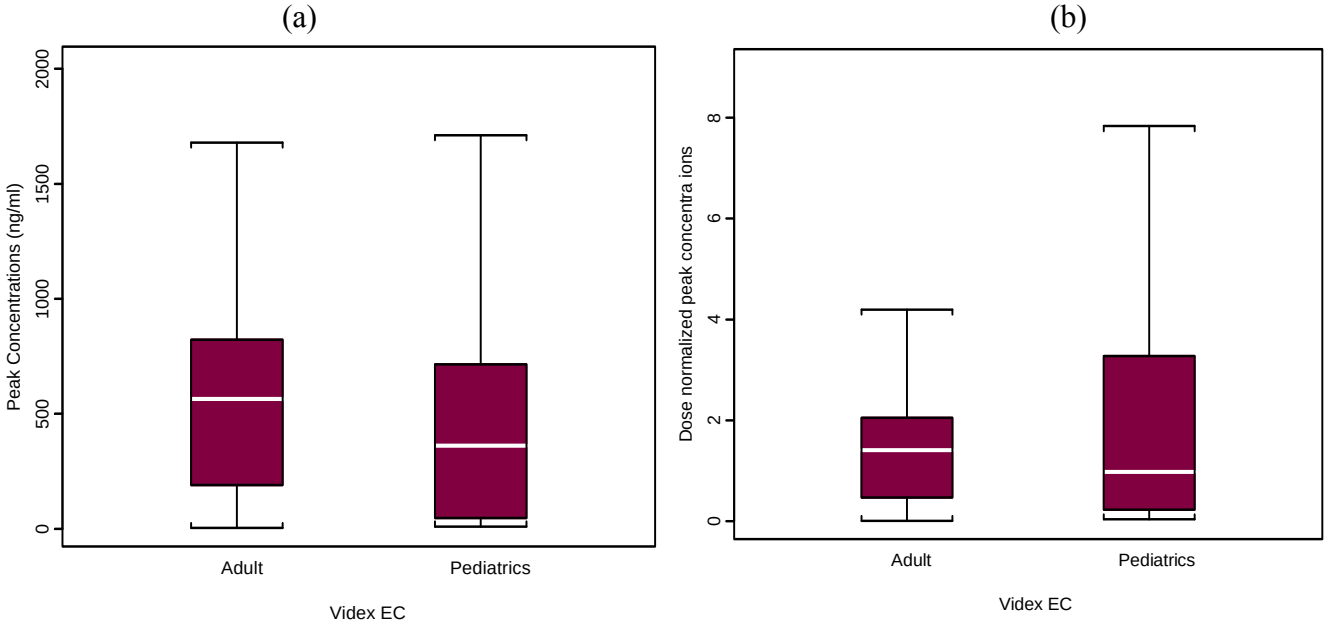


Figure 14: Comparison of (a) trough concentrations and (b) dose normalized trough concentrations of didanosine following administration of Videx EC among adults and pediatrics.

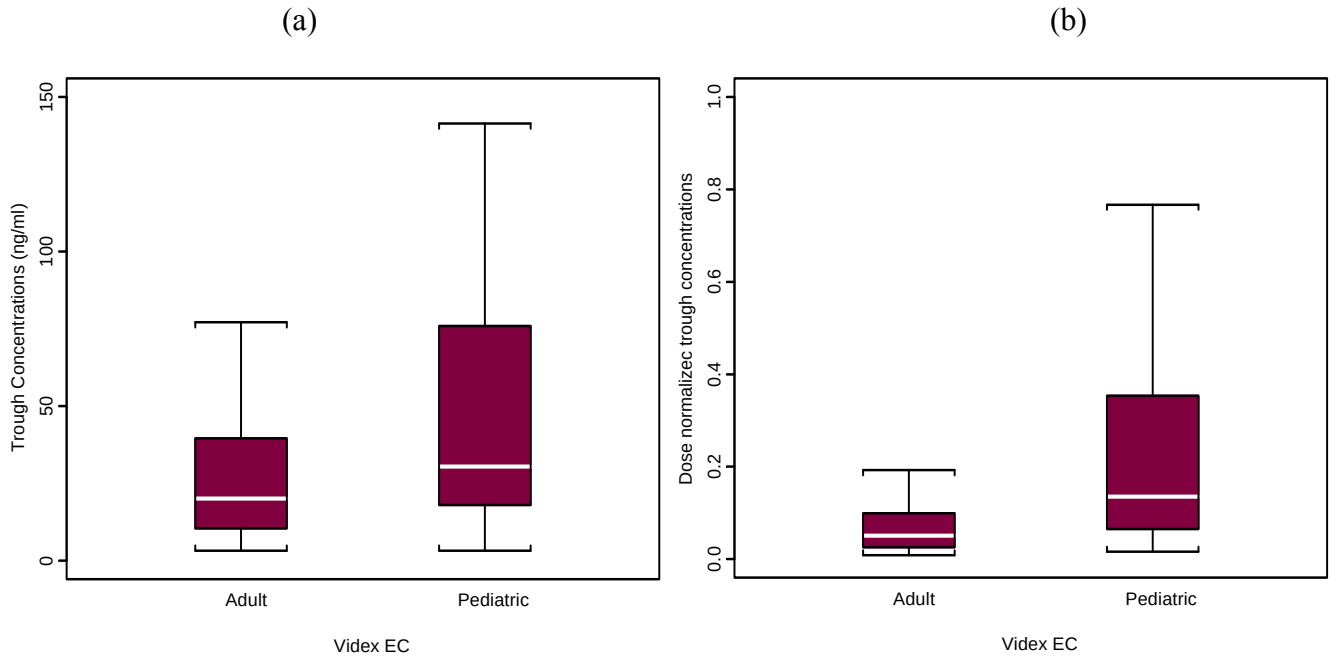
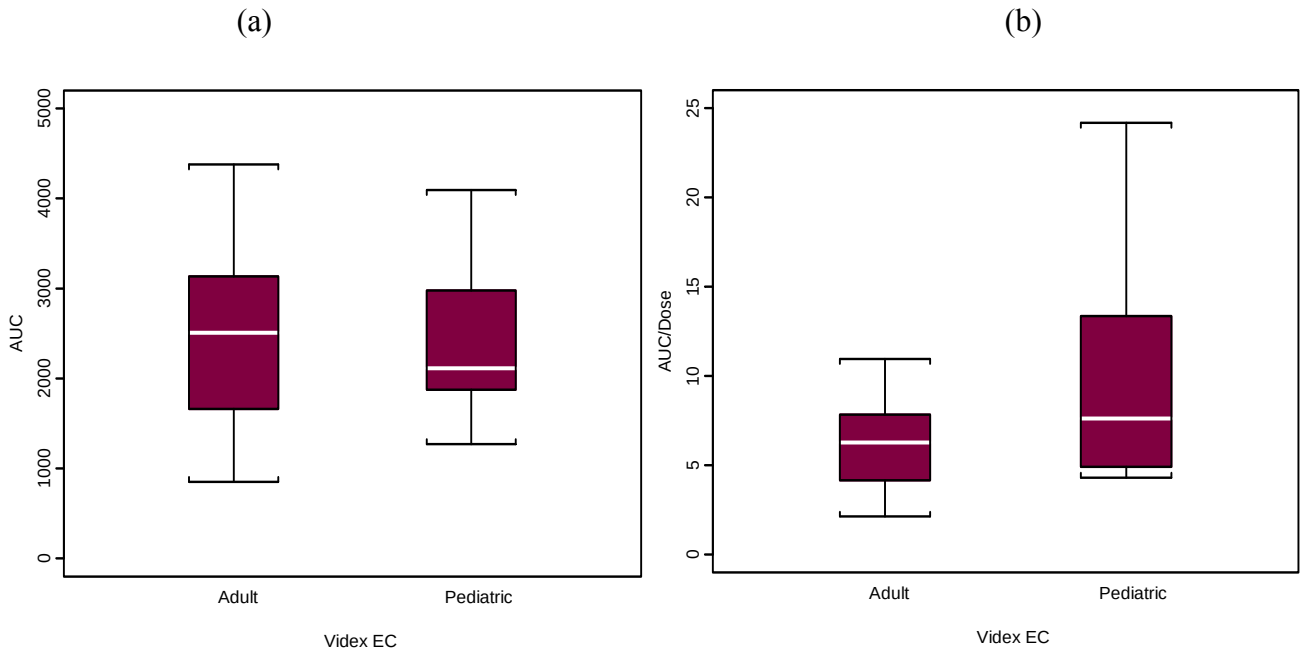


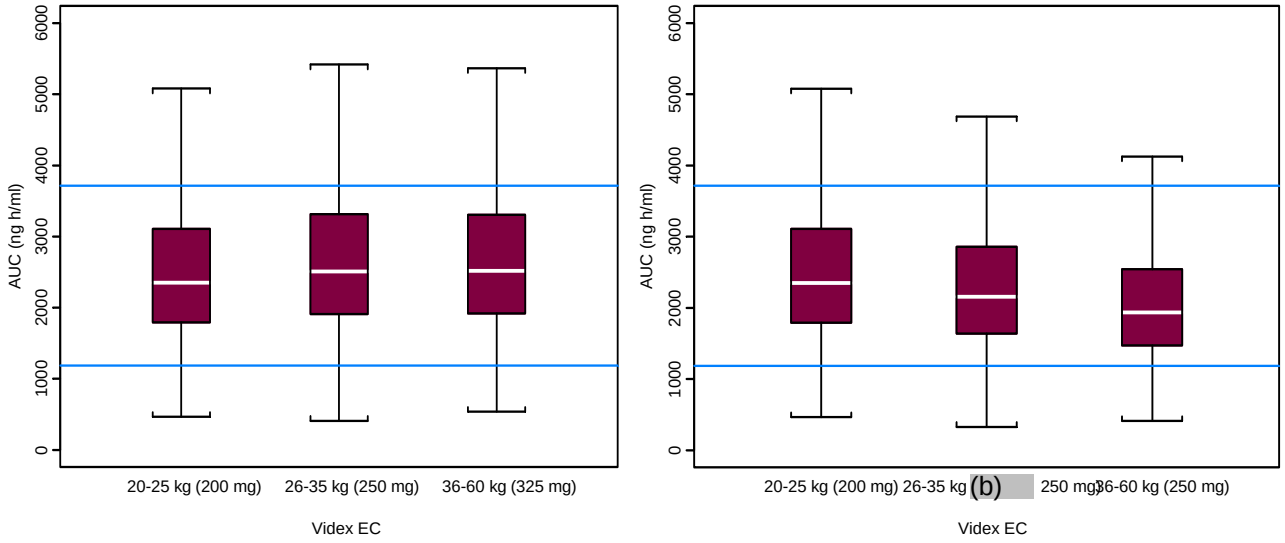
Figure 15: Comparison of (a) AUC and (b) dose normalized AUC of didanosine following administration of Videx EC among adults and pediatrics.



The similarity in exposures in adults and pediatrics gives us an indication that 240 mg/m^2 EC dose employed in studies ACTG 403 and PACTG 1021 might be effective in pediatrics.

(b) The sponsor's and reviewer's dosing scheme (high dose strategy with 325 mg dose for 35-60 kg weight group (**Table 7**) and final dosing recommendations highlighted in **Table 10**) were simulated for the observed data from > 20 kg pediatrics (1000 replicates) and exposures (C_{max} and AUCs) were compared to the observed exposure in adults. Similar results were obtained for both the dosing schemes, however the distribution of AUC and C_{max} for 25-35 and 35-60 weight groups shifted slightly above because higher dose is recommended for these weight groups (**Figure 16** and **Figure 17**). Similar results were obtained when simulations were performed with final dosing recommendations (**Table 10**, **Figure 18** and **Figure 19**). AUC's were also simulated for 20-30 kg weight pediatrics using approved BSA based dosing to compare the exposures with the reviewer proposed dose.

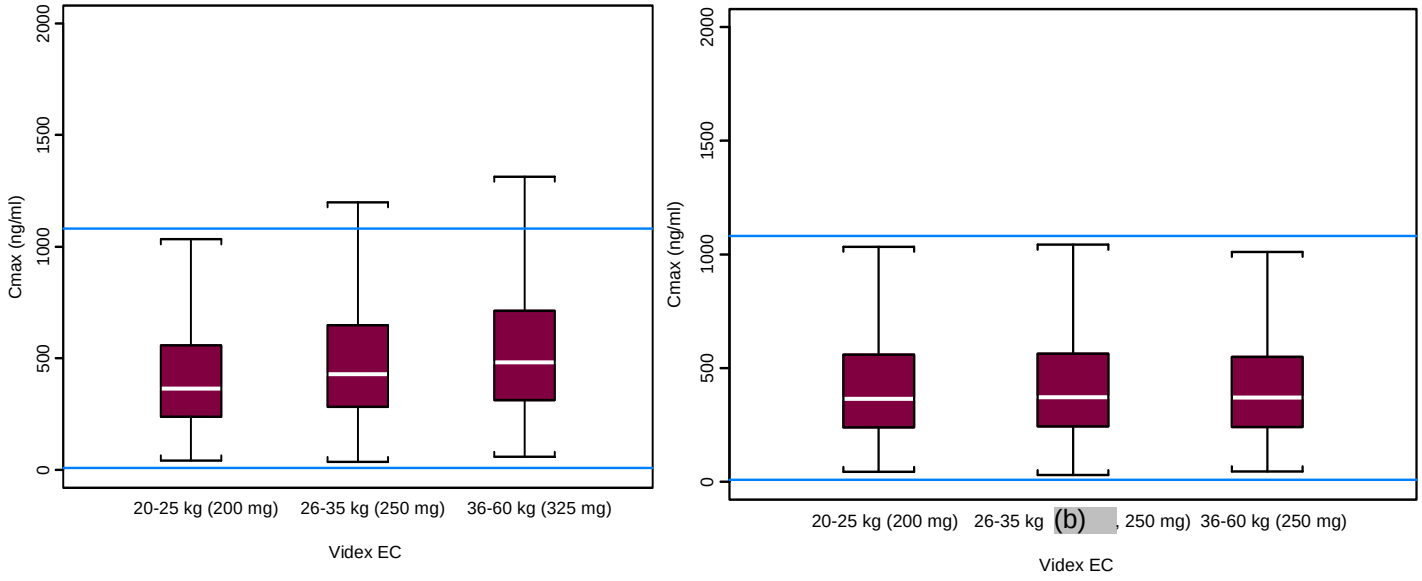
Figure 16: Evaluation of AUC using Model based simulation of reviewer's (high dose strategy with 325 mg dose for 35-60 kg children (**Table 7**)) and sponsor's dosing scheme (the blue solid lines are the 10th and 90th percentile of AUC obtained in adults receiving EC formulation.



Reviewer's modified dosing scheme

Sponsor's proposed dosing scheme

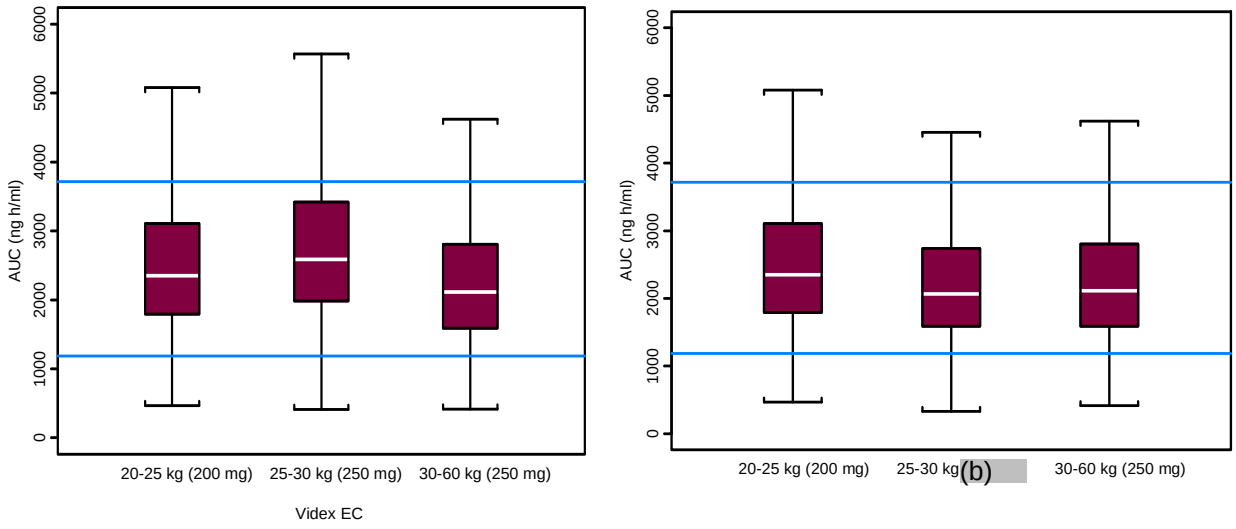
Figure 17: Evaluation of C_{max} using model based simulation of reviewer's (high dose strategy with 325 mg dose for 35-60 kg children (**Table 7**)) and sponsor's dosing scheme (the blue solid lines are the 10th and 90th percentile of C_{max} obtained in adults receiving EC formulation.



Reviewer's modified dosing Scheme

Sponsor's proposed dosing scheme

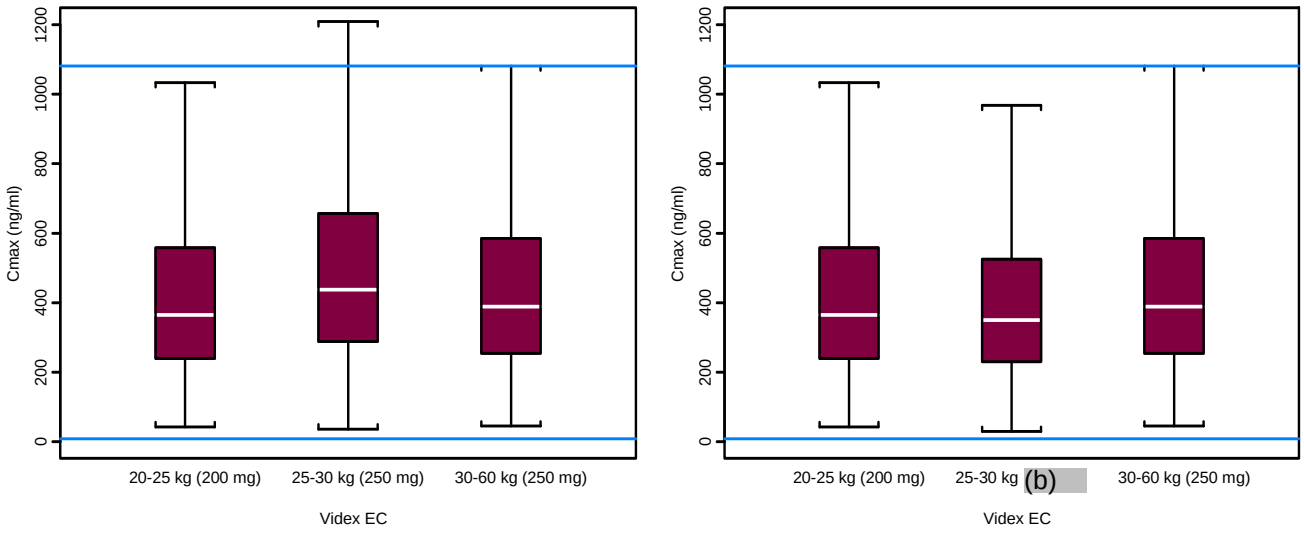
Figure 18: Evaluation of AUC using Model based simulation of reviewer's (low dose strategy with 250 mg dose for 25-60 kg children (**Table 10**)) and sponsor's dosing scheme (the blue solid lines are the 10th and 90th percentile of AUC obtained in adults receiving EC formulation.



Reviewer's modified dosing scheme

Sponsor's proposed dosing scheme

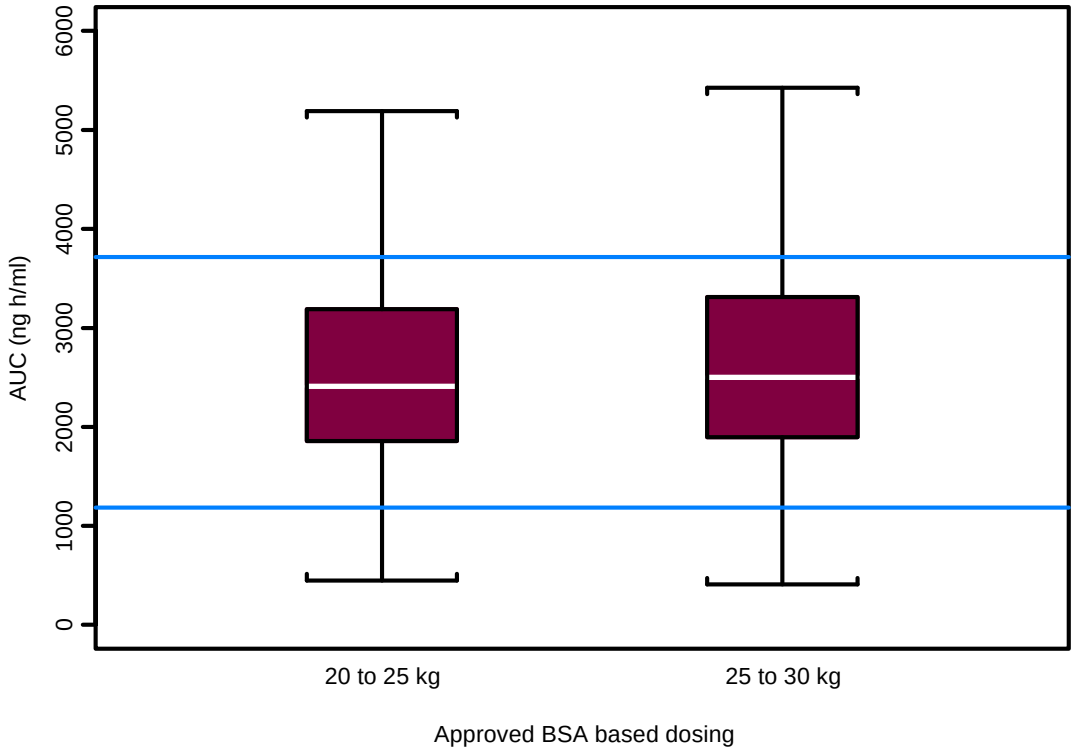
Figure 19: Evaluation of C_{max} using model based simulation of reviewer's (high dose strategy with 250 mg dose for 25-60 kg children (**Table 10**)) and sponsor's dosing scheme (the blue solid lines are the 10th and 90th percentile of C_{max} obtained in adults receiving EC formulation.



Reviewer's modified dosing Scheme

Sponsor's proposed dosing scheme

Figure 20: Evaluation of AUC using model based simulation of approved BSA based dosing regimen (240 mg/m^2 total daily dose in 20-30 weight group (the blue solid lines are the 10th and 90th percentile of AUC obtained in adults receiving EC formulation.

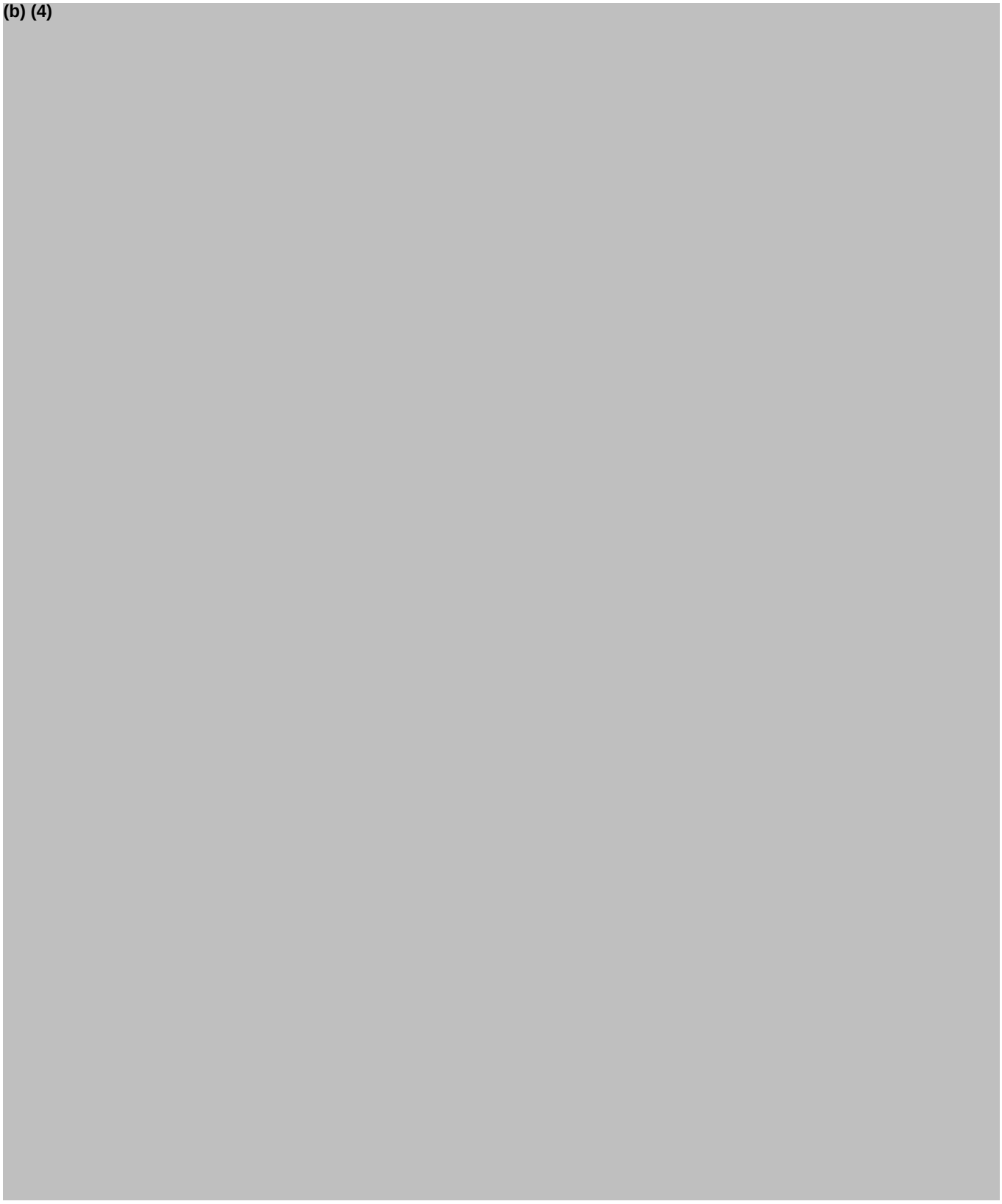


Even though both dosing proposals tested by the reviewer and the sponsor's dosing proposal performed similarly on simulation and exposures were comparable with the BSA based dosing regimen, the dosing recommendations in **Table 10** were recommended because current data do not support a pediatric dose that exceeds the adult dose and they appear to match closely to the already approved BSA based dosing regimen.

Labeling Recommendations

The following are the labeling recommendations relevant to clinical pharmacology for NDA 21183. The ~~red strikeout font~~ is used to show the proposed text to be deleted and underline blue font to show text to be included or comments communicated to the sponsor. The labeling language is mutually agreed by the sponsor and the agency.

(b) (4)



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Appendix

(Individual Study Review: Hepatic impairment study)

Objective:

Primary Objective

The primary objective of this study was to compare the pharmacokinetics of a single 400 mg oral dose of enteric-coated didanosine (ddI-EC) in subjects with hepatic impairment and in healthy control subjects.

Secondary Objective(s)

The secondary objectives were:

- To assess the safety and tolerability of a single oral dose of ddI-EC in subjects with hepatic impairment or in healthy subjects.
- To explore the relationship between the Child-Pugh classification and ddI-EC pharmacokinetic parameters.
- To explore the relationship between the (b) (4) (FibroTest-ActiTest) score and ddI-EC pharmacokinetic parameters.

Study Design:

Twenty-four (24) subjects with or without hepatic impairment were planned to be enrolled in this single dose, non-randomized, open-label study. Twelve (12) subjects with Grade B (n=8) or Grade C (n=4) hepatic impairment as defined by Child-Pugh classification, were enrolled in the hepatic impaired group. Subjects with hepatic impairment were matched (1:1) with healthy control subjects with regard to age (± 5 years), weight (± 15%), smoking status (light [< 10 cigarettes per day], moderate [10-20 cigarettes per day], heavy [> 1 pack per day], and gender. Each matched healthy control subject was not enrolled until the matched hepatic-impaired subject had completed the study. Twelve (12) healthy matching subjects were planned to be enrolled. However, one subject had to be replaced due to improper matching. Therefore, thirteen (13) subjects were enrolled in this cohort. Of note, while safety data was reported for all 25 enrolled subjects, PK data was reported for 24 subjects, excluding the replaced subject. Each subject received a single 400 mg oral dose of ddI-EC in the fasted state. Blood samples for measurement of didanosine concentrations were obtained before and at selected times up to 24 hours after the dose. Clinical evaluation, including physical examination, vital sign measurement and clinical laboratory tests were performed at screening, at baseline on Day -1 (within 24 hours prior to dosing), and prior to study discharge (Day 2). Co-medications which might inhibit or induce enzymes system or may interact with didanosine were prohibited. For complete details on inclusion, exclusion criteria's, refer study report AI454186.

Table 11: Demographic Characteristics

	Healthy Control or Hepatic Impairment Group	
Characteristic	Healthy Controls (Cohort 1) (n=13)	Hepatic Impaired (Cohort 2) (n=12)
Age, years		
Mean	53	54
SD	7	6
Range	45-69	46-66
Gender, n (%)		
Male	9 (69)	8 (67)
Female	4 (31)	4 (33)
Race, n (%)		
White	11 (85)	11 (92)
Black	2 (15)	1 (8)
Ethnicity, n (%)		
Not Hispanic/Latino	5 (38)	10 (83)
Hispanic/Latino	8 (62)	2 (17)
Weight, kg		
Mean	84.5	83.4
SD	10.3	11.1
Range	64.1-102.3	59.6-97.7
Height, cm		
Mean	172.0	171.3
SD	8.6	10.5
Range	159.0-185.5	158.0-188.2
Body Mass Index, kg/m2		
Mean	28.4	28.5
SD	3.1	3.2
Range	21.0-32.9	21.6-32.9

Pharmacokinetic Sample Receipts and Assay Methods:
Validated LC/MS/MS method as described before in QBR was employed for analysis of didanosine in human plasma.

Calculation of Pharmacokinetic Parameters
Plasma concentration versus time data was analyzed by non-compartmental methods using the program Kinetica®. Protocol-specified nominal sampling times were used for PK calculations except when the actual times deviated from nominal times by ≥10%. In those cases, nominal times were changed to actual times. For the purpose of calculating PK parameters, predose concentrations and concentrations prior to the first quantifiable

concentration that were below the lower limit of quantification (LLQ) were treated as "missing" for the calculation of summary statistics. The peak concentrations in plasma, C_{max}, and the times to reach peak concentrations, T_{max}, were recorded directly from experimental observations. The area under the concentration-time curves from time zero to the last quantifiable plasma concentration, AUC(0-T), was calculated by log- and linear-trapezoidal summations. Using no weighting factor, the slopes of the terminal phases of the plasma concentration-time profiles, λ, was determined by log-linear regression of at least three data points which yielded a minimum mean square error. The absolute values of λ were used to estimate the apparent terminal half-lives (T-HALF) by: T-HALF = ln 2/λ. The areas under the concentration-time curve from zero extrapolated to infinite time, AUC(INF), was calculated by log- and linear-trapezoidal summations over the collection period, with the last quantifiable plasma concentration being divided by λ and the product added to the total area.

Analysis of Safety Data
All recorded adverse events were listed and tabulated by primary term, body system, and cohort. Vital signs and clinical laboratory test results were listed and summarized by cohort. Any significant physical examination findings and clinical laboratory results were listed. ECG recordings were evaluated by the investigator and abnormalities, if present, were listed.

Analysis of Pharmacokinetic Data
To assess the effects of hepatic impairment on the pharmacokinetics of didanosine, analyses of variance were performed on log[AUC(INF)] and log(Cmax). The factors in the analyses were cohort, gender, and age. Point estimates and 90% confidence intervals for means, and for differences between means, on the log scale were exponentiated to express the results as geometric means and ratios of geometric means on the original scale. No adjustments were made for multiplicity.
Summary statistics for each of the pharmacokinetic parameters were tabulated by study cohort. Geometric means and CVs were reported for AUC(INF) and C_{max}. Medians, minima, and maxima were reported for T_{max}. Means and standard deviations were reported for all other pharmacokinetic parameters. The relationship between Child-Pugh Score and pharmacokinetic parameters were explored for the hepatic impaired subjects. The association between CLT/F and the Child-Pugh Score were evaluated by regression analysis, with CLT/F as the dependent variable and the Child-Pugh Score as an independent variable. Box plots of CLT/F over severity categories defined by Child-Pugh Scores (healthy, Grade B, Grade C, and Grades B and C) were created. The same analyses were performed to explore the relationship between Vdss/F and the Child-Pugh Score. Similar analyses, including data from all subjects, were performed to explore the relationship between these pharmacokinetic parameters (CLT/F and Vdss/F) and total bilirubin, albumin, prothrombin time, and **(b) (4)** (Fibro-Test™). In addition, CLT/F and Vdss/F were summarized by total bilirubin, albumin, and prothrombin time categories defined in the Child-Pugh classification.

Safety Results:
There were no deaths, serious adverse events (SAEs) or discontinuations due to AEs. AEs occurred in 2 of 12 subjects (16.7%) in the hepatic impaired group and in 1 of 13 subjects (7.7%) in the healthy control group. All AEs were of mild and moderate intensity in the hepatic impaired and healthy control groups, respectively. All AEs reported in the healthy control group were deemed by the Investigator to be unrelated to study medication, while all AEs in the hepatic impaired group were deemed possibly or probably related to study medication.
In total there were 6 AEs. The AEs, (by preferred term) reported in the study were: gastritis, nausea, vomiting (approximately 19 hours post-dose), fatigue, anorexia, and headache; none of which occurred more than once and none were of greater than moderate intensity.

Pharmacokinetic Results:
In general, the mean plasma concentration-time profiles of ddI are similar between the healthy and the hepatic impaired subjects, although variability appears to be high around C_{max} (**Figure 3**). There are also considerable overlaps in the individual subject C_{max}, AUC (INF) between healthy control and hepatic impaired subjects (**Figure 21** and **Figure 22**). The pharmacokinetic parameters and statistical comparison between healthy and hepatic impaired subjects is provided in **Table 12** and **Table 1**.

Table 12: Summary statistics of ddI pharmacokinetic parameters

Pharmacokinetic Parameter	**Healthy Subjects (n = 12)**	**Hepatic Impaired Subjects (n = 12)**
C_{max} (ng/mL) Geometric Mean (CV%)	1144 (72)	1278 (64)
AUC(INF) (ng•h/mL) Geometric Mean (CV%)	3577 (43)	4265[a] (31)
AUC(0-T) (ng•h/mL) Geometric Mean (CV%)	3569 (43)	4331[b] (30)
Tmax (h) Median (Min, Max)	2.0 (1.5, 4.0)	2.25 (1.5, 5.0)
T-HALF (h) Mean (S.D.)	1.89 (0.65)	2.30[a] (1.14)
CLT/F (mL/min) Mean (S.D.)	2116 (1326)	1625[a] (468)
Vdss/F (L) Mean (S.D.)	532 (447)	451[a] (327)

[a] N=11 because terminal phase cannot be determined from Subject AI454186-2-104
[b] Geometric mean (CV%) of AUC(0-T) without Subject AI454186-2-104 is 4233 (31)

Figure 21: Scatterplot of Individual C_{max} vs. Cohort for ddI

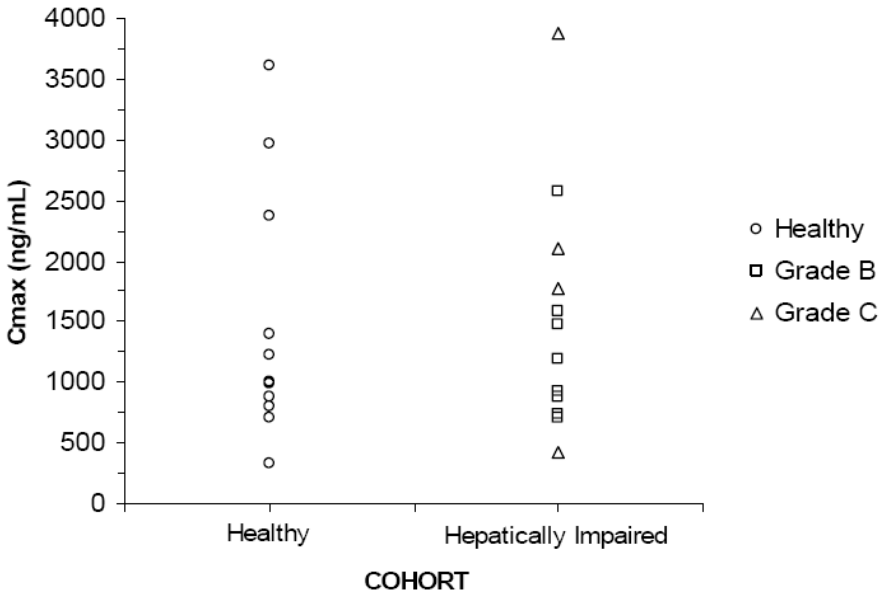
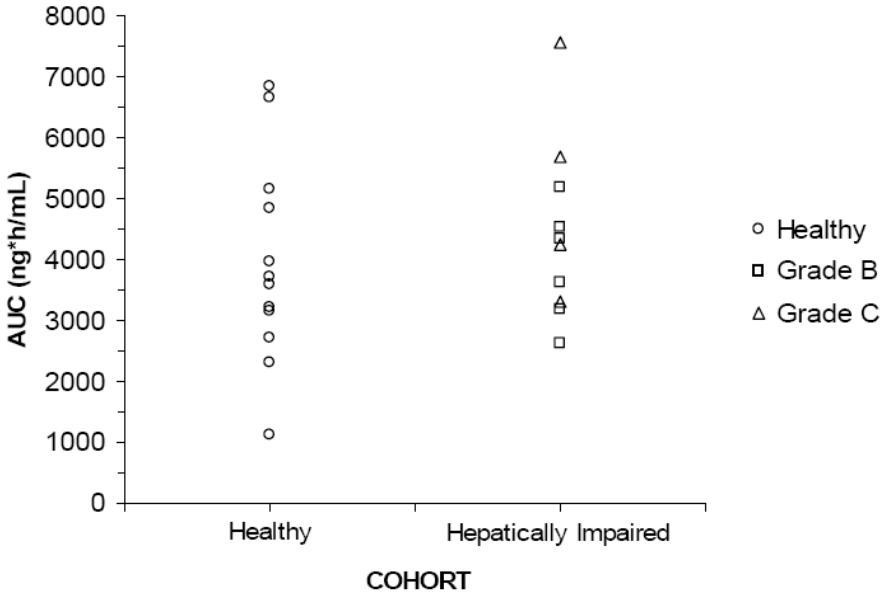


Figure 22: Scatterplot of Individual AUC(INF) vs. Cohort for ddI



Reviewer's Comments

It is reasonable to conclude that there is no effect of hepatic impairment on the PK of didanosine. Didnaosine, being a nucleoside analogue is expected to be eliminated by non-hepatic endogenous purine metabolic pathways and ultimately excreted via kidney. Thus physiologically, hepatic impairment should not alter the PK of didnaosine which can be concluded from the present study. The criteria for having no effect of hepatic impairment as stated in "Guidance for Industry-Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling" is to have a 90% CI of 80-125 for AUC and C_{max}. Even though, the ratio of adjusted geometric means were wide (which can be partly explained by high variability in the data) and not within 80-125% (**Table 1**), point estimate for mean difference in PK parameters was around 20% which could be considered clinically insignificant. Thus, based on the hepatic impairment study conducted by the sponsor, it can be concluded that hepatic impairment does not alter the PK of didanosine.

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/s/

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