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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-453

**Clinical Pharmacology and Biopharmaceutics
Review**

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
REVIEW**

NDA: 21453	Submission Date(s): 12/10/2001
Brand Name	Zerit [®] XR
Generic Name	Stavudine
Reviewer	Jenny H. Zheng
Team Leader	Kellie Reynolds
OCPB Division	DPE III
ORM division	DAVDP
Applicant	Bristol-Myers Squibb Company
Relevant IND(s)	32486
Submission Type; Code	Standard (S)
Formulation; Strength(s)	Extended Release Capsules 37.5, 50, 75, and 100 mg
Indication	Treatment of HIV-1 infection

1 Executive Summary

1.1 Recommendation

Stavudine, a Nucleoside Reverse Transcriptase Inhibitor (NRTI), is approved for the treatment of HIV-1 infection. The current marketed formulations are immediate release (IR) capsules and a powder for oral solution. The applicant submitted this NDA for approval of an extended-release formulation of stavudine for the treatment of HIV-1 infection.

The Clinical Pharmacology and Biopharmaceutics information provided by the applicant in NDA 21-453 is acceptable, except for the in vitro-in vivo correlation (IVIVC), dissolution specification, and dosing regimens for renal impaired subjects proposed by the applicant.

In order to establish IVIVC, we recommend that:

- External validation needs to be performed. Although a Level A IVIVC model based on the mean convolution approach with non-linear time scaling and in vitro dissolution data at pH 1.2 passed internal validation, other approaches all failed the internal validation.
- An IVIVC model based on individual assessment needs to be established. A mean convolution method is not acceptable.

According to the FDA "Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations" guidance, when setting dissolution specifications without an IVIVC, the recommended range at any dissolution time point specification is $\pm 10\%$ deviation from the mean dissolution profile obtained from the clinical/bioavailability lots, and does not exceed 25% range. In addition, a minimum of

three time points is recommended to set the specifications, and these time points should cover the early, middle, and late stages of the dissolution profile. Therefore, we recommend dissolution specifications be set as [] at 2 hours, [] at 8 hours and [] at 16 hours using Stage 2 testing. The stability data support this specification.

The effects of renal dysfunction on the pharmacokinetics of the extended-release capsule have not been investigated. Data from two studies with an immediate-release formulation of stavudine indicated that the apparent oral clearance of stavudine decreased and the terminal elimination half-life increased as creatinine clearance decreased. The applicant proposed to extrapolate the results from the IR formulation to the ER formulation. Patients with creatinine clearance of 26-50 mL/min will be given half dose (50 mg QD for patients ≥60kg and 37.5 mg QD for patients < 60 kg). Patients with creatinine clearance of 10-25 mL/min or patients under hemodialysis will be given half dose with a doubled interval (50 mg every 48 hour for patients ≥60kg and 37.5 mg every 48 hour for patients < 60 kg). However, the extrapolation may not be applicable in the renal impaired subjects, because elimination of stavudine ER in subjects with normal renal function is an absorption rate limited process. The magnitude of decrease in apparent oral clearance of stavudine in the renal impaired subjects for ER product may not be the same as those observed after administration of IR product. We suggest that the applicant either conduct studies or simulations for renal impaired subjects based on the known pharmacokinetic information of both stavudine IR and ER. Without this information, stavudine ER can not be approved for renal impaired patients.

1.2 Phase IV Commitment

1. Please elucidate the complete metabolic fate of stavudine in humans. This was a Phase IV commitment for the original stavudine NDA, and we have not received any information regarding the plan for the study.
2. Please conduct studies or simulations for renal impaired subjects based on the known pharmacokinetic information of both stavudine IR and ER, if stavudine ER is desired to be used in renal impaired subjects.

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3 Summary of CPB Findings

Stavudine, a Nucleoside Reverse Transcriptase Inhibitor (NRTI), is approved for the treatment of HIV-1 infection. The current marketed formulations are immediate release (IR) capsules in strengths of 15, 20, 30, and 40 mg of stavudine per capsule, and a powder for oral solution in bottles with 1 mg of stavudine per mL of constituted solution. The recommended starting dose for IR capsules in adults is 30 mg twice daily (BID) for human immunodeficiency virus (HIV) infected adult patients < 60 kg, and 40 mg BID for patients ≥60 kg. To enhance compliance, sustain stavudine plasma levels, and improve patient convenience by reducing pill burden with triple-drug highly active antiretroviral therapy (HAART) regimens, Bristol-Myers Squibb developed an extended or prolonged release formulation of stavudine (ER capsule), which could be administered once daily. The pharmacokinetics of stavudine ER capsules were studied in healthy subjects and HIV-infected patients.

In healthy subjects, the stavudine ER formulation has the following characteristics:

- AUC increased proportionally with dose in the oral dose range of 37.5 to 100 mg.
- There is no food effect on stavudine ER formulation. Therefore, stavudine ER formulation can be given without regard to food.

In HIV-infected patients, the stavudine ER formulation has the following characteristics:

- No significant accumulation of stavudine was observed after repeated administration of the ER capsule every 24 hours.
- The mean C_{max} value for the ER formulation (100 mg once daily) was approximately 50% lower than C_{max} for the IR formulation (40 mg twice daily), and the total daily exposure of stavudine from the ER formulation was about 31% lower compared to total daily exposure for the IR formulation, despite the greater dose relative to the IR formulation.
- ER formulation has 50% lower concentration fluctuation and 5-fold higher C_{min} compared to IR formulation.
- There was high inter-subject variability in the estimate of terminal half-life.
- The time to reach C_{max} (T_{max}) is approximately 3-4 hours for the ER capsule compared with approximately 1 hour for the IR capsule.
- The total daily exposure for the ER formulation in HIV-infected patients was approximately 14%-49% lower when compared to healthy subjects.

Based on comparable efficacy and safety profiles between the approved regimens with IR formulation (40 mg BID for patients with BW ≥ 60 kg and 30 mg for patients with BW < 60 kg) and the evaluated regimens with ER formulation (100 mg QD for patients with BW ≥ 60 kg and 75 mg for patients with BW < 60 kg), and the pharmacokinetic characteristics of stavudine ER formulation, the following dosing regimens are recommended by the applicant for patients with normal renal functions:

100 mg once daily for patients ≥60 kg.

75 mg once daily for patients <60 kg.

Stavudine ER formulation can be taken with or without food. For patients who have difficulty swallowing intact capsules, the capsule can be carefully opened and the contents mixed with a small amount of yogurt or applesauce. Patients should be cautioned not to crush the beads while chewing or swallowing. The proposed regimens are acceptable.

The applicant also proposed the following dosing regimens for patients with impaired renal function:

[

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4 QBR

4.1 General Attributes

4.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

ZERIT XR (stavudine) Capsules, containing extended-release beads, are supplied for oral administration in strengths of 37.5 mg, 50 mg, 75 mg, and 100 mg of stavudine. The following table summarizes the components of ZERIT XR (stavudine) capsules.

Component	Reference	Function	Quantity per unit dose (mg)			
			37.5 mg	50 mg	75 mg	100 mg
Stavudine		└	37.5 ^A	50.0 ^A	75.0 ^A	100.0 ^A
Lactose Monohydrate	NF					
Microcrystalline Cellulose	NF					
Magnesium Stearate	NF					
Hydroxypropyl Methylcellulose	USP					
	USP					
Ethylcellulose Aqueous Dispersion	NF					
Distilled Acetylated Monoglycerides ^(D)	FCC ^E					
Purified Water	USP					
Total Capsule Fill Weight (mg)						
Red, [redacted] and Yellow, [redacted] Size #4 Capsule						
Orange, [redacted] Size #4 Capsule						
Red, [redacted] Size #4 Capsule						
Rich Yellow, [redacted] Size #3 Capsule						└

A

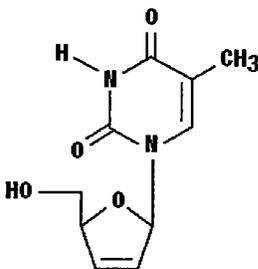
B

C

D

There are two FDA approved dosage forms of stavudine: Zerit ® (stavudine) Capsules (immediate release formulation) and Zerit ® (stavudine) for Oral Solution.

The chemical name for stavudine is 2',3'-dideoxy-3'-deoxythymidine.



Stavudine is a white to off-white crystalline solid with the molecular formula $C_{10}H_{12}N_2O_4$ and a molecular weight of 224.2. The solubility of stavudine at 23° C is approximately 83 mg/mL in water and 30 mg/mL in propylene glycol. The n-octanol/water partition coefficient of stavudine at 23° C is 0.144.

4.1.2 What is the proposed mechanism of drug action and therapeutic indication?

Stavudine, a nucleoside analogue of thymidine, inhibits the replication of HIV in human cells *in vitro*. Stavudine is phosphorylated by cellular kinases to the active metabolite stavudine triphosphate. Stavudine triphosphate is an obligate chain terminator, inhibiting the activity of HIV reverse transcriptase by competing with the natural substrate thymidine triphosphate ($K_i = 0.0083$ to $0.032 \mu\text{M}$) and causing DNA chain termination following its incorporation during viral DNA replication. Stavudine triphosphate inhibits cellular DNA polymerase gamma and markedly reduces the synthesis of mitochondrial DNA.

4.1.3 What is the proposed dosage and route of administration?

The proposed daily dose of ZERIT XR (stavudine ER formulation) in adults is based on body weight and is administered once-daily orally with or without food:

- 100 mg once daily for patients ≥ 60 kg.
- 75 mg once daily for patients < 60 kg.

The dose was selected based on the similar efficacy and safety of stavudine ER formulation 100 mg (75 mg for < 60 kg) once daily compared to approved dosing regimens for immediate release formulation (IR) 40 mg (30 mg for < 60 kg) twice daily.

4.1.4 What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology and biopharmaceutics study data?

Since stavudine has an established record in the therapy of both treatment-naïve and treatment-experienced HIV-infected patients with IR formulation, the objective of the development program was to make the comparison of clinical efficacy between the two formulations, ER and IR. Two randomized, controlled, double-blind, multinational clinical trials in treatment-naïve HIV-infected subjects (AI455-096 and AI455-099) were conducted, both with a single-substitution design matching ER to IR stavudine, in combination with lamivudine (3TC) and efavirenz (EFV). Although ER may provide lower stavudine AUC and C_{max} compared to IR, both studies showed comparable efficacy and

safety profiles between formulations, when stavudine was administered with 3TC and EFV.

4.2 General Clinical Pharmacology

4.2.1 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

AUC increased proportionally with dose in the oral dose range of 37.5 to 100 mg. However, for C_{max}, the lower limit of the 90% CI for the ratio of the test to reference treatments slightly fell below the pre-defined limits (0.8-1.25) for 50 mg and 37.5 mg doses. The deviation from dose proportionality is small. For NRTIs, it is presumed that total exposure has a greater impact than C_{max} on efficacy.

4.2.2 Do PK parameters change with time following chronic dosing?

No significant accumulation of stavudine was observed after repeated administration of the extended-release capsule every 24 hours.

4.2.3 How does the PK of stavudine ER in healthy volunteers compare to that in patients?

The following table (Table 4.2.3) summarizes geometric means (%CV) of AUC and C_{max} of stavudine ER and IR in healthy subjects and in HIV+ patients.

Table 4.2.3

Study	Content	Subject:	n	Dosage/condition	AUC (0-24) (ng.h/mL) Geo. Mean (%CV)	C _{max} (ng/mL) Geo. Mean (%CV)	
107	IVIVC (single dose)	Healthy	26	ER (100 mg)	3226*(20)	321 (21)	
				IR (40 mg BID)	3990 ^a (20)	1906 (32)	
108	Dose proportionality	Healthy	25	100 mg ER	2366 (21)	304 (40)	
				75 mg ER	1949 (20)	240 (24)	
				50 mg ER	1147 (26)	134 (38)	
				37.5 mg ER	912 (25)	102 (37)	
109	Food effect	Healthy	24	Fasting (100 mg)	2714 (16)	286 (11)	
				Light meal (100 mg)	2528 (20)	254 (25)	
				Yogurt (100 mg)	2936 (16)	325 (38)	
				Applesauce (100 mg)	2800 (16)	294 (19)	
114	Food effect	Healthy	23	IR (40 mg BID)	3567 (13)	692 (29)	
				ER (100 mg) Fasting	3131 (16)	338 (14)	
				ER (100 mg) High fat meal	3392 (16)	362 (34)	
103	Single/multiple dose PK	HIV+	15	ER (100 mg) Day 1	2045 (31)	239 (122)	
				ER (100 mg) Day 7	1975 (29)	234 (26)	
				ER (100 mg) Day 9	1890 (31)	212 (26)	
96 ^c	Pivotal Clinical study	HIV+	10	IR Day 1	2418 (17)	523 (22)	
				8	IR Day 14	2533 (18)	520 (27)
				6	ER Day 1	1835 (35)	187 (34)
				5	ER Day 14	1747 (40)	237 (30)
IR	Original NDA (Phase I)	HIV+			1246-2500 ^b	603-1532 ^b	

^a AUC(INF)

^b Arithmetic mean

^c The data presented here is from full PK substudy. Additional population PK analyses were conducted in this study, and was determined to be not acceptable.

The data show a trend towards lower exposures in HIV-infected patients. The total daily exposure or AUC for the ER formulation was approximately 14%-49% lower when compared to healthy subjects.

4.2.4 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

There was a high inter-subject variability in the estimate of terminal half-life. The variability could be due to the concentrations for last few time points being close to the detection limit or due to the existence of two phases of absorption. There was less than 10% intra-subject variability in AUC and C_{max} .

4.3 Intrinsic Factors

4.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics? What dosage regimen adjustments, if any, are recommended for each of these subgroups?

The effect of gender, race, renal dysfunction, and hepatic dysfunction were studied with an IR formulation of stavudine, and were not studied with an ER formulation. Each individual factor is discussed in the following sections. Dose adjustment will be discussed for patients with peripheral neuropathy.

4.3.1.1 *Gender*

The effects of gender on the pharmacokinetics of the extended-release capsule have not been investigated. For the immediate-release capsule, a population pharmacokinetic analysis of data collected during a controlled clinical study in HIV-infected patients showed no clinically important differences between males (n=291) and females (n=27).

4.3.1.2 *Race*

The effects of race on the pharmacokinetics of the extended-release capsule have not been investigated. For the immediate-release capsule, a population pharmacokinetic analysis of data collected during a controlled clinical study in HIV-infected patients showed no clinically important differences between races (n=233 Caucasian, 29 African-American, 41 Hispanic, 1 Asian, and 4 other).

4.3.1.3 *Renal dysfunction*

The effects of renal dysfunction on the pharmacokinetics of the extended-release capsule have not been investigated. Data from two studies with an immediate-release formulation of stavudine indicated that the apparent oral clearance of stavudine decreased and the terminal elimination half-life increased as creatinine clearance decreased.

Table 4.3.1.3: Mean \pm SD Pharmacokinetic Parameter Values of Stavudine^a in Adults with Varying Degrees of Renal Function

	Creatinine Clearance			Hemodialysis Patients ^b n = 11
	>50 mL/min n = 10	26-50 mL/min n = 5	9-25 mL/min n = 5	
Creatinine clearance (mL/min)	104 \pm 28	41 \pm 5	17 \pm 3	NA
Apparent oral clearance (mL/min)	335 \pm 57	191 \pm 39	116 \pm 25	105 \pm 17
Renal clearance (mL/min)	167 \pm 65	73 \pm 18	17 \pm 3	NA
T _{1/2} (h)	1.7 \pm 0.4	3.5 \pm 2.5	4.6 \pm 0.9	5.4 \pm 1.4

^a Single 40-mg oral dose of the immediate-release formulation.

^b Determined while patients were off dialysis.

T_{1/2} = terminal elimination half-life.

NA = not applicable.

C_{max} and T_{max} were not significantly altered by renal insufficiency. The mean \pm SD hemodialysis clearance value of stavudine was 120 \pm 18 mL/min (n=12); the mean \pm SD percentage of the stavudine dose recovered in the dialysate, timed to occur between 2 and 6 hours post-dose, was 31 \pm 5%. Based on these observations, stavudine IR is reduced to half dose (20 mg BID for patients \geq 60kg and 15 mg BID for patients < 60 kg) in patients with creatinine clearance of 26-50 mL/min, and reduced to half dose with a doubled interval (20 mg QD for patients \geq 60kg and 15 mg QD for patients < 60 kg) in patients with creatinine clearance of 10-25 mL/min or patients under hemodialysis. The applicant proposed to extrapolate this recommendation to stavudine ER as shown in the following table.

However, the extrapolation may not be applicable in the renal impaired subjects, because elimination of stavudine ER in subjects with normal renal function is an absorption rate limited process. The magnitude of decrease in apparent oral clearance of stavudine in the renal impaired subjects for ER product may not be the same as that observed after administration of IR product. We suggest that the applicant either conduct studies or simulations for renal impaired subjects based on the known pharmacokinetic information of both stavudine IR and ER.

4.3.1.4 Hepatic dysfunction

The effects of Hepatic dysfunction on the pharmacokinetics of the extended-release capsule have not been investigated. For the immediate-release capsule, stavudine

pharmacokinetics were not altered in five non-HIV-infected patients with hepatic impairment secondary to cirrhosis (Child-Pugh classification B or C).

4.3.1.5 *Peripheral neuropathy*

Patients should be monitored for the development of peripheral neuropathy, which is usually manifested by numbness, tingling, or pain in the feet or hands. If these symptoms develop during treatment, stavudine therapy should be interrupted. Symptoms may resolve if therapy is withdrawn promptly. In some cases, symptoms may worsen temporarily following discontinuation of therapy. If symptoms resolve completely, patients may tolerate resumption of treatment at one-half the recommended dose, as indicated in the label for the IR formulation. If neuropathy recurs, permanent discontinuation of ZERIT XR should be considered.

4.3.1.6 *Diarrhea*

Theoretically, diarrhea may have a higher impact on PK and efficacy of stavudine ER as compared to stavudine IR, due to longer duration of ER formulation in GI tract as compared to IR formulation. However, statistic analysis done by statistic reviewer does not show any diarrhea impact on efficacy for both ER and IR formulation.

4.4 Extrinsic Factors

4.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

Zidovudine may competitively inhibit the intracellular phosphorylation of stavudine. Therefore, use of zidovudine in combination with ZERIT XR is not recommended. Based on *in vitro* data, the phosphorylation of stavudine has also been shown to be inhibited at relevant concentrations by doxorubicin. The clinical significance of this finding is unknown.

Renal elimination accounted for about 40% of the overall clearance regardless of the route of administration. The metabolic fate of stavudine has not been elucidated in humans. Stavudine does not inhibit the major cytochrome P450 isoforms CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4; therefore, it is unlikely that clinically significant drug interactions will occur with drugs metabolized through these pathways. Drug-drug interaction studies of an immediate-release formulation of ZERIT with didanosine, lamivudine, and nelfinavir showed no clinically significant pharmacokinetic interactions. The results of these studies may be expected to apply to stavudine XR.

Because stavudine is not protein-bound, it is not expected to affect the pharmacokinetics of protein-bound drugs.

4.5 General Biopharmaceutics

4.5.1 What is the in vivo relationship of the ER formulation compared to IR formulation in terms of comparative exposure?

The ER formulation tends to have lower C_{max} and AUC as compared to the IR formulation (Table 4.2.3). However, ER formulation has less concentration fluctuation and a higher C_{min} compared to IR formulation. The efficacy analysis in two pivotal studies showed that ER formulation has a comparable efficacy profile compared to IR formulation.

4.5.2 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Studies AI455-109 and AI455-114 showed that there was no food effect on the exposure of stavudine. Thus, Stavudine ER can be give with or without food.

PK parameter	Study	Contrast	Ratios of Geo. Means Pt. Estimate (90% C.I.)
C _{max}	AI455-109	Light meal (373 kcal)/Fasting	0.89 (0.82, 0.96)
	AI455-109	Yogurt (26.4 kcal)/Fasting	1.14 (1.05, 1.23)
	AI455-109	Applesauce (32.5 kcal)/Fasting	1.03 (0.95, 1.11)
	AI455-114	Heavy meal (945 kcal)/Fasting	1.06 (0.94, 1.21)
AUC (0-24 h)	AI455-109	Light meal (373 kcal)/Fasting	0.93 (0.88, 0.98)
	AI455-109	Yogurt (26.4 kcal)/Fasting	1.08 (1.03, 1.14)
	AI455-109	Applesauce (32.5 kcal)/Fasting	1.03 (0.98, 1.09)
	AI455-114	Heavy meal (945 kcal)/Fasting	1.08 (1.03, 1.14)

4.5.3 How do the dissolution conditions and specifications assure in vivo performance and quality of the product?

The sponsor tried to develop an in vitro-in vivo correlation (IVIVC) for the stavudine extended release formulations. However, IVIVC is not acceptable due to:

- External validation was not performed. Although a Level A IVIVC model based on the mean convolution approach with non-linear time scaling and in vitro dissolution data at pH 1.2 passed internal validation, other approaches (mean deconvolution, individual convolution, or compartmental modeling with linear or non-linear time scaling, and mean convolution with linear time scaling) all failed the internal validation.
- The mean convolution method is not acceptable.

We recommend a better dissolution method be developed to establish linear IVIVC.

The applicant also developed a dissolution method as follows for quality control.

Dosage form: capsule
Strength(s): 100 mg, 75 mg, 50 mg, and 37.5 mg
Apparatus type: Basket
Rotation speed: 100 rpm
Media: 0.1M phosphate buffer pH 6.8

Volume: 1000 ml

Temperature: 37°C ± 0.5°C

Sampling time points: 1, 2, 4, 8, 12, 16, and 24 hours

Analytical method: HPLC

Dissolution specification: 1 hour, [] 4 hours, [] and 24 hours, []

According to the FDA "Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations" guidance, when setting dissolution specifications without an IVVC, the recommended range at any dissolution time point specification is ± 10% deviation from the mean dissolution profile obtained from the clinical/bioavailability lots. Deviations from the ± 10% range can be accepted, but the range cannot exceed 25%. In addition, a minimum of three time points is recommended to set the specifications, and these time points should cover the early, middle, and late stages of the dissolution profile. Therefore, we recommend dissolution specifications be set as [] at 2 hours, [] at 8 hours and [] at 16 hours using Stage 2 testing. The stability data support this specification.

4.5.4 What is the basis of the approval for all the strengths of stavudine ER?

Dose proportionality studies showed that AUC increased proportionally with dose in the oral dose range of 37.5 to 100 mg for stavudine ER and in the oral dose range of 5 mg to 40 mg for stavudine IR. For stavudine ER, capsules at different strengths vary only in the amount of ER beadlets included in the capsules, and there is no suggestion of PK non-dose proportionality. All four strengths 37.5, 50, 75, and 100 mg ER capsules have been used in Clinical studies 096 and 099. Statistic analysis done by statistic reviewer showed that patients with body weights < 60 kg who were administered 75 mg stavudine ER once daily have similar efficacy compared to patients with body weights ≥ 60 kg who were administered 100 mg stavudine ER once daily. Therefore, the approval for all the strengths of stavudine ER may be granted.

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4.6 Analytical

4.6.1 What bioanalytical methods are used to assess concentrations?

The following table summarizes the *in vitro* analytical methods used for the determination of plasma stavudine concentrations in each study.

Studies	Methods	MQL ^a (ng/ml)	Linear range (ng/ml)	Between Run Precision (%CV)	Between Run Bias (% nominal)	QC samples (ng/mL)	Validation sample for stability and conditions
AI455-107	LC/MS/MS ^b	0.5	0.5-1000 ($r^2 \geq 0.9886$)	0 to 3.9	-1.3 to 1.7	1.5, 600, 800, and 2000	Stable at room temperature for
AI455-108	LC/MS/MS ^b	0.5	0.5-1000 ($r^2 \geq 0.990$)	3.7 to 5.8	-3.5 to 0.6	1.4, 350, and 800	Stable at -20°C for
AI455-109	LC/MS/MS ^b	0.5	0.5-1000 ($r^2 \geq 0.985$) ^c	0 to 4.6	-5.5 to 53.2	1.4, 350, 800, and 5000	
AI455-114	LC/MS/MS ^b	0.5	0.5-1000 ($r^2 \geq 0.993$)	5.4 to 15.2	-5.5 to 3.7	1.4, 350, 800, and 5000	
AI455-103	LC/MS/MS ^b	0.5	0.5-1000 ($r^2 \geq 0.9998$)	0.4 to 2.4	-3.2 to 1.4	1.4, 350, 800, and 8000	
AI455-96	LC/MS/MS ^b	0.5	0.5-1000 ($r^2 \geq 0.9997$)	0 to 1.1	0.7 to 1.5	1.5, 400, and 800	

^a minimum quantitative level

^b high performance liquid chromatography/tandem mass spectrometry

^c Eleven runs with $r^2 \geq 0.995$ but one run with $r^2 = 0.879$

The acceptance criteria established by the applicant for analysis of stavudine specified that (1) the predicted concentrations of at least three-fourths of the standards shall be within $\pm 15\%$ ($\pm 20\%$ for the lowest standard) of their individual nominal concentrations; (2) at least one replicate of the lowest concentration in the standard curve shall be within $\pm 20\%$ of the nominal concentration for that level to qualify as the lower limit of quantification (LLQ); otherwise, the next level is subjected to same test and the LLQ raised accordingly; and (3) the predicted concentrations of two-thirds of all quality control (QC) samples shall be within $\pm 15\%$ of their individual nominal concentrations. In addition, at least one QC sample at each concentration must be within $\pm 15\%$ of its nominal concentration value. These criteria are wider than the criteria defined in "Bioanalytical Method Validation" Guidance, where the predicted concentrations at each concentration level shall be within $\pm 15\%$ of their individual nominal concentrations (except for LLQ, where it should not exceed 20%) and should not exceed 15% of the coefficient of variation (CV) (except for the LLOQ, where it should not exceed 20% of the CV). All studies met FDA criteria except Study AI455-109, where more variability was observed for QC 1.4 ng/ml, although the between-run variability and the within-run variability for analytical QCs were no greater than 4.6% C.V., and deviations from the nominal concentrations were no more than $\pm 5.5\%$ for other QCs. The large within run C.V. for QC 1.4 ng/ml (187.8%) and deviation from nominal concentration (53.2%) calculated in the ANOVA, is the result of 4 runs (out of 15 runs) that had within-run precision of greater than 33% C.V. and mean deviations from nominal concentrations of greater than 30%. One sample in QC 1.4 ng/ml in Run 2 was determined to be 27.18 ng/ml, which also contribute to the great variability. Although one of the three QC's (1.4 ng/ml) in Study AI455-109 has high % Dev value, analysis of QC samples in other studies shows that the analytical data are reasonably accurate and precise. Also, the low

concentrations do not contribute significantly to the total exposure. In addition, for all subjects, plasma samples from all four arms (fasted, light meal, mixed with yogurt, and mixed with applesauce) were assayed together in a given analytical run. Therefore, this analysis problem may not affect the overall conclusions.

5 Labeling Recommendations

The following labeling changes are recommended:

- In “Clinical Pharmacology/Pharmacokinetics in Adults/Absorption” section, please replace the information [] with information for HIV-infected patients.
- In Table 1, please recheck the information for Zerit XR 100 mg QD. There were only 5 patients from the ER arm whose pharmacokinetics were evaluated on Day 14. Please do not use the results from the population PK analysis.
- In “Clinical Pharmacology/Pharmacokinetics in Adults/Effect of Food on Oral Absorption” and “Dosage and Administration/Adults” sections, please indicate the amount of yogurt or applesauce (i.e. 2 tablespoons).
- In “Clinical Pharmacology/Pharmacokinetics in Adults/Effect of Food on Oral Absorption” section, please delete “ [] .
- In table 2, for urinary recovery of stavudine, please indicate the period of time urine was collected.
- In table 2, for ratio of CSF to plasma concentration, please indicate the time when the value was evaluated.
- In “Clinical Pharmacology/Pharmacokinetics in Adults/metabolism” section, please delete the sentence []
- In “Clinical Pharmacology/Special Populations/Renal Impairment” section, please delete the whole paragraph and Table 3. Reword the paragraph as:
“The effects of renal dysfunction on the pharmacokinetics of the extended-release capsule have not been investigated. Data from two studies with an immediate-release formulation of stavudine indicated that the apparent oral clearance of stavudine decreased and the terminal elimination half-life increased as creatinine clearance decreased. The applicability of the results from the immediate release formulation to the extended release formulation needs to be further investigated.
[]
- Please delete Tables 4 and 5. Include the information in text (one sentence), because no significant interactions were observed.
- Please delete the last paragraph on Page 9 of the label. Complete metabolic fate of stavudine has not been evaluated.

Jenny H. Zheng, Ph.D.
Reviewer, Pharmacokinetics
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Concurrence:

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cc: HFD-530 /NDA 21453
/MO/KMarcus
CSO/SLynche
HFD-880 /JHZheng
HFD-880 /TL/KReynolds

6 Appendix

6.1 Individual Study Reviews

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Gamma Scintigraphic Evaluation of the Intestinal Absorption of Stavudine in Healthy Male Volunteers (AI455-070, Item 6, Volume 1)

Objectives: To evaluate the bioavailability of stavudine, in powder form, released directly into the proximal small intestine, distal small intestine, or ileocecal/ascending colon, relative to the marketed immediate release formulation ingested orally.

Subjects: 8 healthy male subjects were enrolled.

Study design: This was a single center, open-label, randomized, four-way crossover study. Each subject was randomized to one of the following 4 sequences:

Sequence	Period 1	Period 2	Period 3	Period 4
1	Treatment 1	Treatment 2	Treatment 3	Treatment 4
2	Treatment 4	Treatment 3	Treatment 2	Treatment 1
3	Treatment 2	Treatment 4	Treatment 1	Treatment 3
4	Treatment 3	Treatment 1	Treatment 4	Treatment 2

Treatment 1: A 40 mg dose of stavudine as a 1 x 40 mg Zerit® capsule

Treatment 2: A 40 mg dose of stavudine as a powder in a remote drug delivery capsule to be activated for release in the proximal small intestine

Treatment 3: A 40 mg dose of stavudine as a powder in a remote drug delivery capsule to be activated for release in the distal small intestine

Treatment 4: A 40 mg dose of stavudine as a powder in a remote drug delivery capsule to be activated for release in the ileocecal/ascending colon

Stavudine was given orally after an overnight fast of at least 10 hours, and food was not permitted for 4-hours postdose. Treatments were separated by at least one week.

Formulation: 40 mg Zerit® capsules for Treatment 1. For Treatments 2, 3, and 4, 40 mg stavudine powder (Lot Number 2MAN114) and ^{99m}technetium diethylenetriaminepentaacetic acid (^{99m}TcDTPA) were filled in [] remote drug delivery capsules. ^{99m}TcDTPA is a water-soluble radioactive marker that is used to provide visual confirmation of in vivo release of stavudine at the point of activation.

Sample Assay Methods: Plasma concentrations of stavudine were determined using a validated high performance liquid chromatography/tandem mass spectrometry (LC/MS/MS) method.

PK analysis: The following table shows the geometric mean pharmacokinetic parameters for each treatment, and compares parameters for treatments 2-4 to those for treatment 1 (point estimate and 90% CI).

Parameter	Treatment ^a	Geometric Mean	Treatment Comparison	Ratio of Geometric Means Point Estimate (90% C.I.)
C _{MAX} (ng/mL)	1	716.12		
	2	725.10	2 vs. 1	1.013 (0.654, 1.568)
	3	507.78	3 vs. 1	0.709 (0.413, 1.217)
	4	70.50	4 vs. 1	0.098 (0.026, 0.268)
AUC(INF) (ng•hr/mL)	1	1657.97		
	2	1764.56	2 vs. 1	1.064 (0.871, 1.300)
	3	1566.66	3 vs. 1	0.945 (0.736, 1.177)
	4	-- ^b	4 vs. 1	-- ^b
AUC(0-T) ^c (ng•hr/mL)	1	1612.22		
	2	1706.32	2 vs. 1	1.058 (0.855, 1.310)
	3	1500.49	3 vs. 1	0.931 (0.736, 1.177)
	4	446.56	4 vs. 1	0.277 (0.061, 1.251)

^aStavudine capsule (1) or stavudine powder released in the proximal intestine (2), distal intestine (3), or ileocecal/ascending colon (4); ^bValue not reported since a log-linear terminal phase could not be characterized; ^cT = 10 hr

Based on the point estimates for AUC(0-T), the extent of stavudine absorption when released directly into the proximal or distal small intestine was not appreciably different from that observed following oral administration of stavudine immediate release formulation. When the drug was released directly in the colon, the extent of absorption was lower than from the immediate release formulation. The applicant indicated that the lower absorption from the colon maybe related to low motility and a limited amount of fluid available in this region of the gut. Based on this study, the applicant was willing to develop an extended release formulation due to no exclusive absorption window of stavudine in the small intestine.

Conclusion:

Stavudine is absorbed from all regions of the gastrointestinal tract but the exposure following colonic administration is significantly lower than the exposure following administration into the small intestine. Based on this study, the applicant decided to go forward with development of an extended release formulation.

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Effect of a High Fat Meal on the Bioavailability of Stavudine from Two Extended Release Prototype Formulations in Healthy Volunteers (AI455-095, Item 6, Volume 5)

Objectives: To assess the effect of a high fat meal on the bioavailability of stavudine in healthy subjects following oral administration of a 100 mg dose of stavudine as an extended release (ER) tablet or ER beadlet prototype formulation.

Subjects: 16 men or women, 18 to 50 years of age, were enrolled into the study.

Study design: This was an open-label, single dose, randomized, four-way crossover study in healthy subjects. Each subject was randomized to one of the following 4 sequences:

Sequence	Period 1	Period 2	Period 3	Period 4
1	Treatment A	Treatment B	Treatment C	Treatment D
2	Treatment D	Treatment C	Treatment B	Treatment A
3	Treatment B	Treatment D	Treatment A	Treatment C
4	Treatment C	Treatment A	Treatment D	Treatment B

Treatment A: A single 100 mg oral dose of stavudine as an ER tablet prototype formulation after a 10 h overnight fast

Treatment B: A single 100 mg oral dose of stavudine as an ER tablet prototype formulation within 5 min after completion of a high fat meal

Treatment C: A single 100 mg oral dose of stavudine as ER beadlets in a capsule prototype formulation after a 10 h overnight fast

Treatment D: A single 100 mg oral dose of stavudine as an ER beadlets in a capsule prototype formulation within 5 min after completion of a high fat meal

Treatments were separated by at least 3 days.

The following table shows the contents of high fat meal administered to subjects in Treatments B and D.

Food Item	Calories	Fat (g)	Carbohydrates (g)	Protein (g)
2 eggs fried in butter	203	16.2	1.2	12.2
2 slices white bread toasted	128	1.8	23.4	4.2
1 teaspoonful butter	36	4.1	trace	0
1 tablespoon jelly	55	trace	14.1	trace
2 strips bacon	70	6.2	0.2	3.2
4 oz hash brown potatoes	72	0.1	16.4	1.8
8 oz whole milk	157	8.9	11.4	8
Total	721	37.3	66.7	29.4
% Total Calories	100	47	37	16

Formulation: 100 mg ER tablet prototype formulation (batch number N98111) and 100 mg ER beadlets in a capsule prototype formulation (batch number N98123).

Sample Assay Methods: Plasma concentrations were quantified by a validated liquid chromatography/mass spectrometry (LC/MS/MS) analytical method.

PK analysis: Serial blood samples were collected for 24 hr post-dose. The following table shows the arithmetic mean (SD) pharmacokinetic parameters for stavudine.

Treatment ^a (N=16)	C _{MAX} (ng/mL)	T _{MAX} ^b (h)	AUC(0-T) ^c (ng•h/mL)	AUC(INF) (ng•h/mL)	T-HALF (h)	T-LAG ^b (h)
A	421 (90.2)	2.50 (1.00, 3.50)	2680 (445)	2809 (476)	5.95 (2.65)	0.50 (0.50, 0.50)
B	448 (81.7)	3.50 (2.00, 5.00)	3150 (788)	3232 (812)	5.17 (2.40)	0.50 (0.50, 0.50)
C	259 (63.4)	3.50 (2.50, 5.00)	1969 (287)	2862 (858)	20.6 (15.6)	0.50 (0.50, 1.00)
D	364 (117)	5.50 (4.00, 8.00)	2650 (580)	3100 (744)	12.5 (15.8)	0.75 (0.50, 1.00)

^a(A) Stavudine ER tablet after fasting, (B) stavudine ER tablet after a high fat meal, (C) stavudine ER beadlets capsule formulation after fasting, and (D) stavudine ER beadlets capsule formulation after a high fat meal; ^bMedian (minimum, maximum) value; ^cAUC(0-T) equals AUC from 0 to 24 h

The following table shows stavudine geometric mean ratios and 90% confidence intervals for C_{max} and AUC(0-24).

Parameter	Treatment ^a (N = 16)	Geometric Mean	Treatment Comparison	Ratios of Geometric Means Point Estimate (90% C.I.)
C _{MAX} (ng/mL)	A	412		
	B	442	B vs. A	1.073 (0.940, 1.225)
	C	253		
	D	347	D vs. C	1.372 (1.201, 1.567)
AUC(0-T) (ng•h/mL)	A	2642		
	B	3071	B vs. A	1.162 (1.049, 1.288)
	C	1950		
	D	2593	D vs. C	1.330 (1.200, 1.473)

^a(A) Stavudine ER tablet after fasting, (B) stavudine ER tablet after a high fat meal, (C) stavudine ER beadlets capsule formulation after fasting, and (D) stavudine ER beadlets capsule formulation after a high fat meal

The data show that for the ER tablet formulation, stavudine pharmacokinetics were marginally affected by a high fat meal. For the ER beadlets in a capsule formulation, exposures were about 35% higher in the fed state.

Conclusion: Administration of high fat meal increased the C_{max} and AUC of the ER prototype tablet by 7% and 16% respectively, and of the ER prototype beadlets formulation by 37% and 33%, respectively. These results suggest that a high fat meal may increase the bioavailability of the prototype ER formulations.

Bioavailability of Three Extended Release Clinical Prototype Formulations of Stavudine,
Relative to the 40 mg Commercial Capsule, in Healthy Subjects
(AI455-073, Item 6, Volume 3)

Objectives: To evaluate the bioavailability of stavudine from three extended release clinical prototype formulations, relative to the commercial capsule formulation ingested orally.

Subjects: A total of 17 subjects (men or women) were enrolled and randomized to the study, but only 16 subjects completed all four periods. One subject discontinued after the first period of treatment and was replaced.

Study design: This was a single center, open-label, randomized, four-way crossover study. On four occasions separated by at least three days, each subject received one of the following treatments after an overnight fast of at least 10h:

Treatment A: 40 mg Zerit® instant release (IR) capsule given twice (12 h apart)

Treatment B: A single 100 mg dose of stavudine as an extended release (ER) tablet prototype formulation

Treatment C: A single 100 mg dose of stavudine as an extended release gelucire capsule prototype formulation

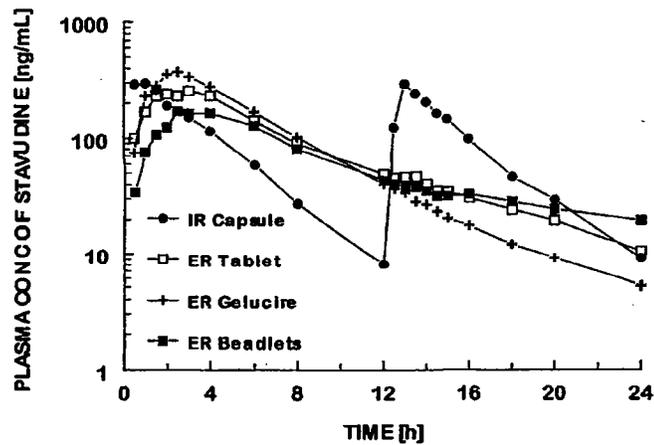
Treatment D: A single 100 mg dose of stavudine as extended release beadlets in a capsule prototype formulation

Treatment A was administered in the morning and evening, while Treatments B, C, and D were given in the morning. Food was not permitted for 4 hr post-dose (for morning dose only). The evening dose of the instant release capsule was administered 1 h prior to dinner.

Formulation: 40 mg Zerit® capsules (Batch # MEH66), 100 mg extended release (ER) tablet prototype formulation (Batch # N98111), 100 mg extended release gelucire capsule prototype formulation (Batch # N98115), 100 mg extended release beadlets in a capsule prototype formulation (Batch # N98123)

Sample Assay Methods: Plasma concentrations were determined by a validated LC/MS/MS analytical method.

PK analysis: Serial blood samples were collected at selected times over a 24-h period. The pharmacokinetic parameters were determined by non-compartmental pharmacokinetic analysis. The following figure shows the mean plasma concentration versus time profiles of stavudine



The following table shows the mean (SD) pharmacokinetic parameters for stavudine:

Treatment ^a (N = 16)	C _{MAX} (ng/mL)	T _{MAX} ^b (h)	AUC(0-T) ^c (ng·h/mL)	AUC(INF) (ng·h/mL)	T-HALF (h)
A	378.39 (100.87)	0.75 (0.50, 2.00)	2126.18 (275.48)	2144.93 (285.95)	2.37 (0.57)
B	285.30 (62.38)	3.00 (1.00, 4.00)	1993.02 (421.47)	2092.44 (471.45)	5.71 (2.76)
C	409.08 (73.45)	2.50 (1.50, 4.00)	2244.43 (327.41)	2284.52 (329.35)	4.65 (1.96)
D	200.45 (74.07)	3.50 (2.50, 6.00)	1550.00 (318.48)	2070.11 (689.47)	15.37 (14.10)

^aStavudine instant release capsule (A), stavudine extended release tablet (B), stavudine extended release gelucire capsule formulation (C), and stavudine extended release beadlets capsule formulation (D);
^bMedian (minimum, maximum) value; ^cAUC(0-T) equals AUC from 0 to 24 h

The point estimates and 90% confidence intervals (CI) for stavudine are given below:

Parameter	Treatment ^a (N = 16)	Geometric Mean	Treatment Comparison	Ratios of Geometric Means
C _{MAX} (ng/mL)	A	366.1		
	B	279.3	B vs A	0.76 (0.66, 0.88)
	C	402.5	C vs A	1.10 (0.96, 1.26)
	D	190.9	D vs A	0.52 (0.45, 0.60)
AUC(0-T) (ng·h/mL)	A	2108.5		
	B	1952.0	B vs A	0.93 (0.86, 1.00)
	C	2222.8	C vs A	1.05 (0.98, 1.14)
	D	1521.5	D vs A	0.72 (0.67, 0.78)
AUC(INF) ^b (ng·h/mL)	A	2126.09		0.96
	B	2044.26	B vs A	1.06
	C	2263.54	C vs A	0.93
	D	1977.73	D vs A	

^aStavudine instant release capsule (A), stavudine extended release tablet (B), stavudine extended release gelucire capsule formulation (C), and stavudine extended release beadlets capsule formulation (D)
^bnot evaluated based on 90% CI – values provided for comparison sake

Since the elimination phase of stavudine from the extended release beadlets formulation was not adequately characterized, AUC(0-T) instead of AUC(INF) was employed for the

statistical comparison. The results show that the beadlet capsule formulation produced the longest half-life, and thus the highest trough concentration compared to the IR and other two formulations. In addition, the beadlet capsule formulation has the lowest C_{max}. Therefore, the sponsor decided to choose beadlet capsule formulations for further development.

Conclusion: The beadlet capsule formulation produced the longest half-life and thus the highest trough concentration, compared to the IR and other two formulations. In addition, the beadlet capsule formulation has the lowest C_{max}. Therefore, the sponsor decided to choose beadlet capsule formulations for further development.

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Study Of Bioavailability of Stavudine from Three Extended Release Encapsulated Bead Formulations (Slow, Intermediate, And Fast Release Rates) Relative to the 40 mg Commercial Capsule in Healthy Subjects (A1455-107, Item 6, Volumes 6 & 7)

Objectives:

1. To assess the bioavailability and pharmacokinetics of stavudine after administration of three extended release (ER) encapsulated bead formulations (1 x 100 mg) relative to the immediate release (IR) commercial capsule (2 x 40 mg) in healthy subjects.
2. To define a possible IVIVC model for stavudine (d4T) extended release encapsulated bead formulation.

Subjects: A total of 28 subjects (men or women) were enrolled, 26 completed treatment, and 2 discontinued from the study.

Study design: This was an open-label, randomized, four-period, four-treatment, study balanced for first order crossover effects in healthy subjects under fasting conditions. Enrolled subjects received one of the following four treatments in each period according to a randomization schedule:

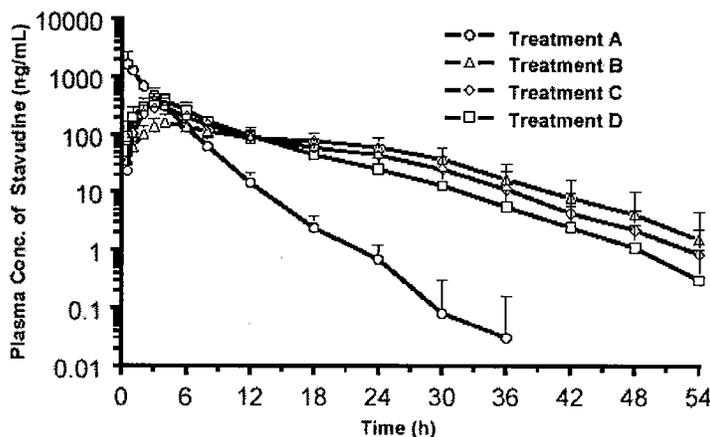
- Treatment A: 40 mg stavudine (40 mg Zerit® commercial capsules) BID
Treatment B: 100 mg stavudine (1 x 100 mg slow release ER bead in capsule)
Treatment C: 100 mg stavudine (1 x 100 mg intermediate release ER bead in capsule)
Treatment D: 100 mg stavudine (1 x 100 mg fast release ER bead in capsule)

There was at least a 7-day washout period between each dose. For each treatment period, subjects were confined to the clinical facility until 54 hours post-dose. Blood samples were collected for pharmacokinetic analysis up to 54 hours post-dose.

Formulation: Stavudine 100 mg ER formulations, with slow (Batch No.: N00212), intermediate (Batch No.: N99089, to-be-marketed formulation), and fast (Batch No.: N00194)] release profiles.

Sample Assay Methods: Plasma samples for stavudine were analyzed at Bristol-Myers Squibb Saint-Nazaire, France, by a validated high performance liquid chromatography/tandem mass spectrometry (LC/MS/MS) method.

PK analysis: The mean plasma concentration-time profiles are shown in the following figure.



The following two tables summarize stavudine pharmacokinetic parameters and statistical analysis.

Pharmacokinetic Parameter	Treatment A (n = 26)	Treatment C (n = 26)	Treatment B (n = 25)	Treatment D (n = 26)
C _{max} (ng/mL)				
Geometric Mean (CV%)	1906 (32)	321 (21)	171 (26)	409 (26)
AUC(INF) (ng•h/mL)				
Geometric Mean (CV%)	3990 (16)	3226 (20)	2829 (25)	3509 (20)
T _{max} (h)				
Median (min, max)	0.5 C	4.0	4.0	3.5 J
T _{1/2} (h)				
Mean (SD)	2.93 (1.28)	5.14 (2.09)	4.70 (2.04)	4.40 (1.74)

Pharmacokinetic Parameter	Treatment	Geometric* Mean	Contrast	Ratios of Geo. Means Pt. Estimate (90% C.I.)
C _{max} (ng/mL)	A	1902	C vs. A	0.1678 (0.1509, 0.1865)
	C	319	B vs. A	0.0893 (0.0802, 0.0994)
	B	169	D vs. A	0.2150 (0.1934, 0.2390)
	D	409	B vs. C	0.5321 (0.4779, 0.5924)
			D vs. C	1.2813 (1.1526, 1.4243)
AUC(INF) (ng•h/mL)	A	3965	C vs. A	0.8102 (0.7587, 0.8652)
	C	3213	B vs. A	0.7054 (0.6599, 0.7540)
	B	2793	D vs. A	0.8800 (0.8240, 0.9397)
	D	3489	B vs. C	0.8706 (0.8144, 0.9306)
			D vs. C	1.0861 (1.0170, 1.1598)

*Adjusted geometric mean or least square mean

With respect to the bioequivalence of the fast and slow release ER formulations, relative to the intermediate release ER formulation, the C_{max} for both the slow and fast release ER formulation failed to satisfy the bioequivalence criterion. However, the AUC(INF) for the slow release ER and fast release ER formulations were comparable to the intermediate release rate ER formulation. The intermediate release ER formulation (to-be-marketed formulation) had lower AUC compared to the IR formulation, although there was a higher dose contained in the ER formulation relative to the IR formulation.

Conclusion:

1. The C_{max} values of stavudine for the slow, intermediate (to-be-marketed formulation) and fast release rate 100 mg ER formulations were reduced by 91%, 83%, and 79%, respectively, and AUC(INF) values were reduced by 29%, 19%, and 12%, respectively, compared to the 40 mg BID IR formulation.
2. The slow and fast release rate ER formulation were comparable to the intermediate release rate ER formulation with respect to AUC(INF) but not C_{max}.
3. The intermediate release ER formulation (to-be-marketed formulation) had lower AUC compared to the IR formulation, although in the ER formulation contains a higher dose relative to the IR formulation.

Development of In Vitro - In Vivo Correlation for the Stavudine Extended Release Formulations (AI455-107, Item 6, Volumes 7)

In vivo pharmacokinetic data for the fast, intermediate, and slow extended release (ER) capsule formulations of stavudine from Study AI455-107 and in vitro dissolution data at pH 6.8 (n=12), 4.5 (n=6), and 1.2 (n=12) were used to establish a Level A in vitro-in vivo correlation (IVIVC). Several approaches (mean convolution, mean deconvolution, individual convolution, or compartmental modeling with linear or non-linear time scaling) were tested to develop a Level A IVIVC model.

In Vitro Dissolution:

The following tables show the individual dissolution data for the stavudine ER formulations at pH 6.8, 4.5, and 1.2. A pH 6.8 medium was selected for dissolution testing for quality control, because it minimizes the potential for acid hydrolysis of stavudine to thymine and no significant differences existed between the pH 1.2 and pH 6.8 dissolution profiles.

Stavudine ER (Fast Batch) Lot: N00194: pH 6.8

Percent Labeled Dissolved

Vessel	Tablet Weight (mg)	Time (hours)						
		1	2	4	8	12	16	24
1	277							
2	271							
3	288							
4	285							
5	260							
6	283							
7	274							
8	279							
9	273							
10	289							
11	280							
12	268							
Mean	-	19	35	59	82	92	97	99
%RSD	-	9.86	7.85	6.81	5.46	5.78	4.75	4.93

Stavudine ER (Fast Batch) Lot: N00194: pH 4.5

Percent Labeled Dissolved

Vessels	Tablet Weight (mg)	Time (hours)						
		1	2	4	8	12	16	24
1	267.3							
2	285.7							
3	280.6							
4	268.8							
5	272.3							
6	284.5							
Mean	-	18	32	53	77	89	95	100
%RSD	-	8.25	5.76	5.12	4.67	4.47	4.07	4.06

Stavudine ER (Fast Batch) Lot: N00194: pH 1.2

Percent Labeled Dissolved

Vessels	Tablet Weight (mg)	Time (hours)						
		1	2	4	8	12	16	24
1	270.9							
2	283.3							
3	278.2							
4	286.6							
5	285.2							
6	285.4							
7	280.4							
8	276.6							
9	286.2							
10	276.8							
11	274.7							
12	285.3							
Mean	-	19	35	56	80	92	98	102
%RSD	-	13.13	9.23	7.44	5.58	4.94	4.92	4.83

Stavudine ER (Intermediate Batch) Lot: N99089: pH 6.8

Percent Labeled Dissolved

Vessels	Tablet Weight (mg)	Time (hours)						
		1	2	4	8	12	16	24
1	271							
2	270							
3	268							
4	264							
5	265							
6	264							
7	273							
8	276							
9	270							
10	264							
11	273							
12	273							
Mean	-	9	19	35	63	80	90	95
%RSD	-	20.16	15.22	10.06	5.43	4.19	3.28	2.32

Stavudine ER (Intermediate Batch) Lot: N99089: pH 4.5

Percent Labeled Dissolved

Vessel s	Tablet Weight (mg)	Time (hours)						
		1	2	4	8	12	16	24
1	276	[
2	277.3							
3	272.9							
4	282.5							
5	275.7							
6	275.3							
Mean	-	9	18	35	64	82	92	96
%RSD	-	16.22	14.50	10.24	5.70	4.11	3.37	2.79

Stavudine ER (Intermediate Batch) Lot: N99089: pH 1.2

Percent Labeled Dissolved

Vessel s	Tablet Weight (mg)	Time (hours)						
		1	2	4	8	12	16	24
1	2675	[
2	270.9							
3	281.3							
4	273.5							
5	268.4							
6	269							
7	262.4							
8	269.1							
9	276.8							
10	269.9							
11	271.3							
12	277.3							
Mean	-	9	19	37	63	80	90	96
%RSD	-	17.85	14.03	10.26	6.00	5.92	5.53	3.46

Stavudine ER (Slow Batch) Lot: N00212: pH 6.8

Percent Labeled Dissolved

Vessel s	Tablet Weight (mg)	Time (hours)							
		1	2	4	8	12	16	24	36
1	287								
2	280								
3	285								
4	280								
5	279								
6	290								
7	274								
8	279								
9	273								
10	289								
11	280								
12	268								
Mean	-	7	13	28	52	71	82	91	92
%RSD	-	10.50	10.82	9.08	6.43	4.22	3.70	2.72	3.47

Stavudine ER (Slow Batch) Lot: N00212: pH 4.5

Percent Labeled Dissolved

Vessel s	Tablet Weight (mg)	Time (hours)							
		1	2	4	8	12	16	24	36
1	283.3								
2	278								
3	279								
4	285.6								
5	282.5								
6	286.9								
Mean	-	7	13	26	50	68	81	94	99
%RSD	-	5.97	6.45	6.90	4.26	3.64	3.02	2.27	1.64

Stavudine ER (Slow Batch) Lot: N00212: pH 1.2

Percent Labeled Dissolved

Vessel s	Tablet Weight (mg)	Time (hours)							
		1	2	4	8	12	16	24	36
1	279.3								
2	282.5								
3	278.9								
4	279.6								
5	280.7								
6	277.8								
7	279.6								
8	281.2								
9	280.2								
10	280.2								
11	285.1								
12	276.8								
Mean	-	5	10	21	44	64	78	94	99
%RSD	-	29.04	17.49	9.37	5.07	3.81	3.19	2.39	1.45

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IVIVC:

From the mean concentration-time in vivo data obtained after dosing of the stavudine (d4T) immediate release (IR) formulation in pharmacokinetic study AI455-107, impulse response parameter estimates were determined. Using the mean concentration-time profile from in vivo data for the three extended release (ER) formulations, in vivo release profiles were obtained using the deconvolution approach. Deconvolution involved estimation of the in vivo release or absorption rate (X'_{vivo}) via nonlinear regression using a model that describes the relationship between X'_{vivo} and the resulting plasma concentrations (c) according to the convolution integral equation

$$c(t) = \int_0^t c_{\delta}(t-u) x'_{vivo}(u) du. \quad (1)$$

Here, $C_{\delta}(t)$ is the unit impulse response function defined by the concentration time course following the unit IR dose, t is time, u is the variable of integration, and du is the derivative of u . The concentration-time course following the IR dose $c_{IR}(t)$ was described by the product of the IR dose (D_{IR}) and the unit impulse response, i.e.,

$$c_{IR}(t) = D_{IR} c_{\delta}(t). \quad (2)$$

In vivo release or absorption rate (X'_{vivo}) was the time derivative of the amount of the drug released or absorbed in vivo (X_{vivo}). The mean in vivo and in vitro release profiles were compared and used for exploratory analysis of a Level A IVIVC model.

Mean Convolution Approach with Linear Time Scaling

A potential Level A IVIVC model was constructed using a convolution-based approach. The modeling strategy involved selecting a model for the relationship between the mean in vitro release (X_{vitro} or X'_{vitro}) and the mean in vivo input (X_{vivo} or X'_{vivo}), substituting that model for X'_{vivo} in equation (1), and simultaneously fitting the entire expression to the plasma concentrations from the various ER formulations. A linear IVIVC model was used based on equation (1), where

$$x_{vivo}(t) = \begin{cases} 0, & t < 0. \\ a_1 + a_2 x_{vitro}(-b_1 + b_2 t), & t \geq 0. \end{cases} \quad (3)$$

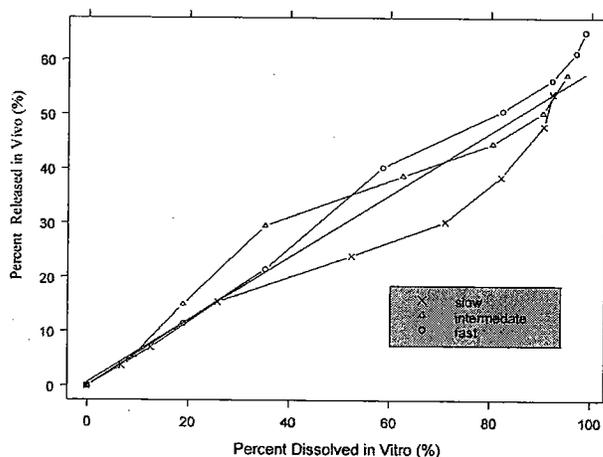
While a_1 is the intercept of the relationship between in vitro and in vivo profiles, a_2 is the slope and b_1 and b_2 are the time-shift and time-scale parameters.

The overall model for the concentrations following ER dosing was given by:

$$c_{ER}(t) = a_1 c_{\delta}(t) + \int_0^t c_{\delta}(t-u) a_2 x'_{vitro}(-b_1 + b_2 u) du. \quad (4)$$

The IVIVC model parameters were estimated using in vitro dissolution data at pH 6.8.

The following figure shows the mean in vivo release as a function of in vitro dissolution.



The model failed to predict C_{max} of the ER formulations, with the mean absolute percent prediction error of 20.5%.

Individual Convolution Approach with Linear Time Scaling

An individual Level A IVIVC model was constructed using a convolution-based approach. For each subject, an individual model was developed as described in Mean Convolution Approach with Linear Time Scaling section. Then the results were summarized over all subjects. The IVIVC model parameters were estimated using in vitro dissolution data at pH 6.8. The model also failed to predict C_{max} of the ER formulations, with the mean absolute percent prediction error of 20.4%.

Mean Deconvolution Approach with Linear Time Scaling

A potential Level A IVIVC model was also constructed using a deconvolution-based approach. The mean-based deconvolution approach involved modeling of the mean IR and ER profiles to reconstruct the mean in vivo release amount. The result of the analysis was the mean in vivo release profiles for the various stavudine ER treatments. Mathematical Level A IVIVC models relating in vitro dissolution obtained from the current dissolution test system with in vivo release was developed by a two-stage procedure:

- Estimate the parameters of mean $C_d(t)$ function by fitting the polyexponential approximations to the mean plasma concentrations obtained from dosing of the IR formulation in each pharmacokinetic study, and estimate the mean in vivo release functions using deconvolution of equation (1).
- Estimate the IVIVC model parameters by fitting the in vivo release and in vitro dissolution data to the model shown in equation (3)

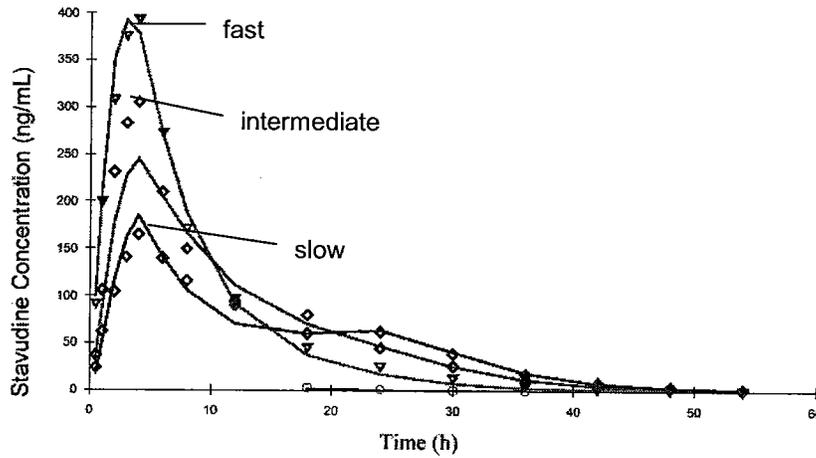
The model also failed to predict C_{max} of the ER formulations, with the mean absolute percent prediction error of 21.8%.

Compartmental Modeling Approach with Linear Time Scaling

The two-compartment linear model with first-order absorption was developed to describe the immediate release (IR) data. The estimated parameters from the IR model were fixed in the model for the ER formulation. The models were fitted to the concentration-time data for the extended release formulations.

The fit of the compartmental model is illustrated in the following figure. It shows that the

C_{max} of the formulation with the intermediate release rate is significantly under-predicted. No formal validation of the compartmental model was performed.



Mean Convolution Approach with Non-Linear Time Scaling

Mean convolution IVIVC Level A model was developed using the interpolated in vitro data with non-linear time scaling. The in vitro time t was scaled as

$$t_1 = t/K_1;$$

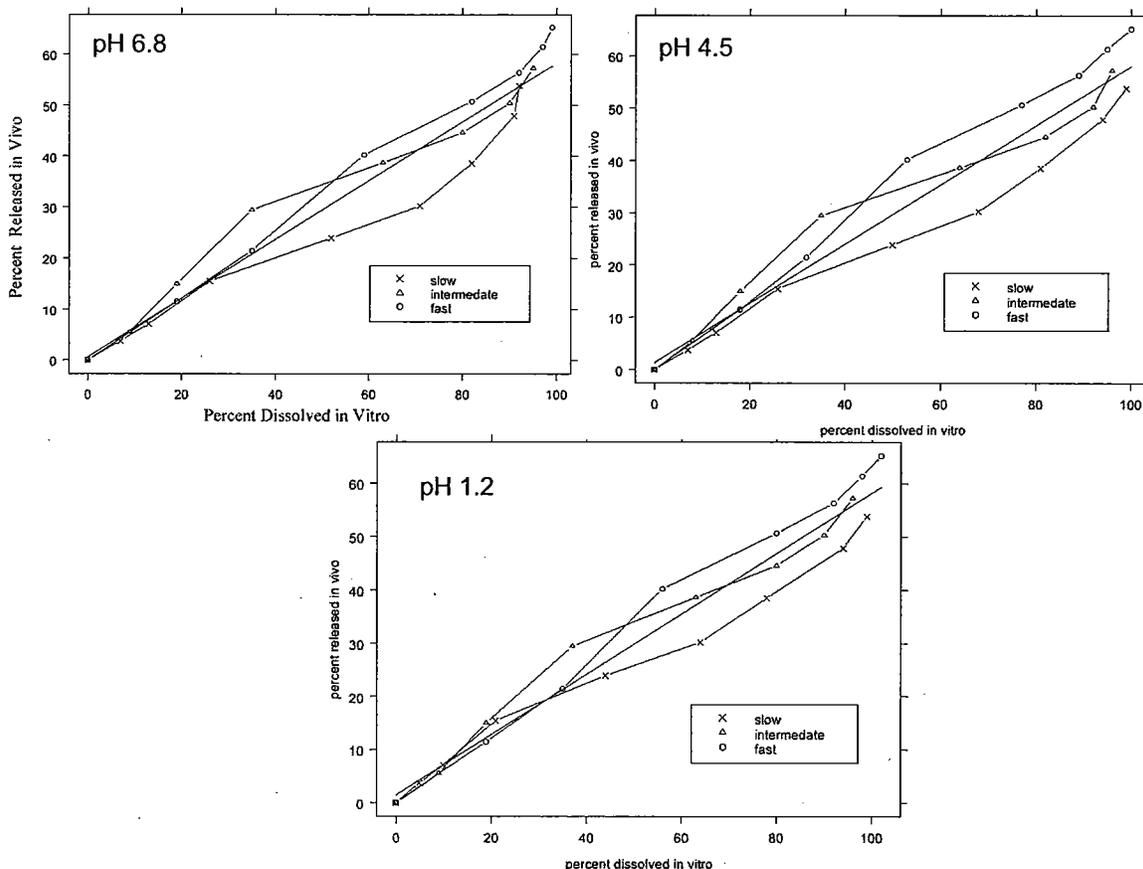
$$t_2 = t_1 \quad \text{if } t_1 \leq t_c ;$$

$$t_2 = t_c + (t_1 - t_c)/K_2 \quad \text{if } t_1 > t_c .$$

Here t_c is the cutoff time and K_1 and K_2 are the rate factors.

The following figures show the mean in vivo release as a function of in vitro dissolution at pH 6.8, 4.5 and 1.2.

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The following table shows the absolute percent prediction error ($|\%PE|$) for C_{max} and AUC using in vitro dissolution data from three in vitro dissolution media (pH 6.8, 4.5 and 1.2).

Formulation	$\%PE$ for C _{max}			$\%PE$ for AUC		
	pH 6.8	pH 4.5	pH 1.2	pH 6.8	pH 4.5	pH 1.2
Slow	5.1	15.4	4.8	8.9	7.4	8.9
intermediate	22	13.9	8.5	0.8	7.5	6.7
Fast	0.4	1.55	6.5	5.2	11.7	9.1
Mean	9.0	10.3	6.6	5.0	8.9	8.2

The results show that a Level A IVIVC model based on the mean convolution approach with non-linear time scaling and in vitro dissolution data at pH 1.2 was the best among all considered models. The applicant indicated since the MAPPE for C_{max} and AUC were below 10% and PEs for each formulation were below 15%, according to the Committee for Proprietary Medicinal Products (CPMP) and the Food and Drug Administration (FDA) Guidances, validation of the IVIVC model using external predictability was not necessary. After consultation with Dr. Patrick Marroum who led the IVIVC Guidance Working Group, we conclude that:

- External validation is needed to establish IVIVC. If a real IVIVC exists, all IVIVC approaches should lead to the same conclusion.
- The mean convolution method is not acceptable.
- A better dissolution method may be developed to establish linear IVIVC.

Relative Bioavailability of Stavudine from the Extended Release Formulation after
Coadministration with Food (Light Meal, Yogurt, or Applesauce) in Healthy Subjects
(A1455-109, Item 6, Volume 8)

Objectives: To assess the impact of the coadministration of a light meal, yogurt, or applesauce on the bioavailability of stavudine from the extended release (ER) formulation in healthy subjects.

Subjects: A total of 28 healthy subjects (men or women) were enrolled in the study and 24 subjects completed the study. Two subjects did not receive their treatment correctly, one subject did not complete the study, and one subject dropped out because of upper respiratory infection.

Study design: This was an open-label, randomized, four-way crossover study. Subjects were randomized to receive the following four treatments, with at least a 5-day washout period between each treatment, in one of four randomly assigned treatment sequences:

Treatment A: 100 mg of stavudine ER bead formulation under fasting conditions.

Treatment B: 100 mg of stavudine ER bead formulation within 5 minutes of a light meal (373 calories).

Treatment C: 100 mg of stavudine ER bead formulation, with the contents of the capsule opened and mixed with 2 tablespoons of plain yogurt (26.4 calories).

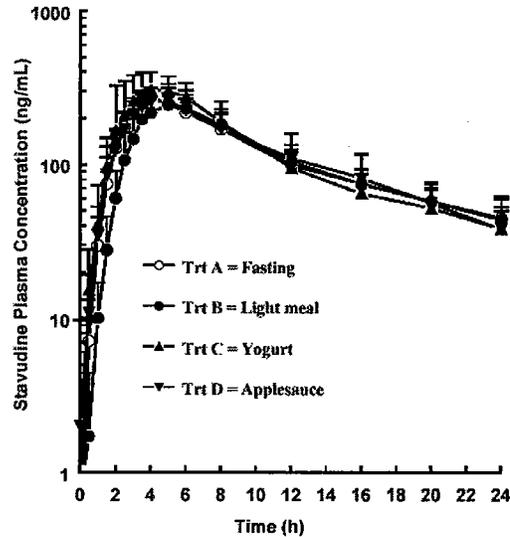
Treatment D: 100 mg of stavudine ER bead formulation, with the contents of the capsule opened and mixed with 2 tablespoons of applesauce (32.5 calories).

For treatments A and B, the capsules were swallowed intact with 180 mL of tap water. For Treatments C and D, the capsule contents and yogurt (26.4 calories) or applesauce (32.5 calories) were gently mixed in a disposable plastic cup and the contents consumed. Subjects were instructed not to chew the bead formulation. The disposable plastic cup was rinsed with 60 mL of tap water at room temperature, which was swallowed by the subjects after ingestion of the drug-food mixture. The subjects receiving Treatment C and D drank 120 mL of tap water at room temperature.

Formulation: Stavudine 100 mg ER Beadlet commercial formulation, Batch # M0050.

Sample Assay Methods: Plasma samples for stavudine were analyzed at λ by a validated high performance liquid chromatography/tandem mass spectrometry (LC/MS/MS) method.

PK analysis: Blood samples were collected for 24 hours post-dose to determine stavudine concentrations. The following figure shows the mean (SD) plasma concentration-time profiles of stavudine. The pharmacokinetic parameters of stavudine and statistics are summarized in the following two tables.

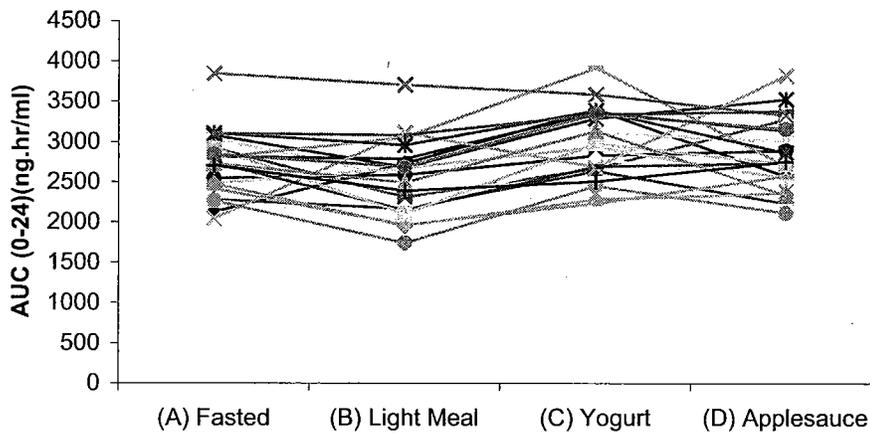
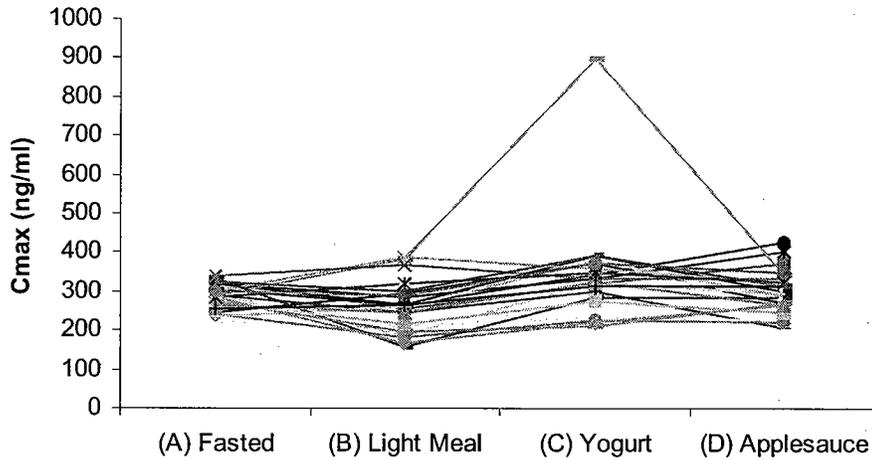


Pharmacokinetic Parameter	Fasting	Light Meal	Yogurt	Applesauce
C _{max} (ng/mL)				
Geometric Mean	285.8	253.6	325.0	293.6
(C.V.%)	(11)	(25)	(38)	(19)
TAUC(0-T) (ng•h/mL)				
Geometric Mean	2714.5	2528.4	2936.1	2799.6
(C.V.%)	(16)	(20)	(16)	(16)
T _{max} (h)				
Median	4.0	5.0	5.0	4.0
(min, max)	[-]

Pharmacokinetic Parameter	Geometric		Contrast	Ratios of Geo. Means Pt. Estimate (90% C.I.)
	Treatment	Mean		
C _{max} (ng/mL)	A	285.8		
	B	253.6	B vs. A	0.8874 (0.8200, 0.9605)
	C	325.0	C vs. A	1.1373 (1.0508, 1.2309)
	D	293.6	D vs. A	1.0274 (0.9493, 1.1119)
TAUC(0-T) (ng•h/mL)	A	2714.5		
	B	2528.4	B vs. A	0.9315 (0.8850, 0.9804)
	C	2936.1	C vs. A	1.0816 (1.0276, 1.1384)
	D	2799.6	D vs. A	1.0314 (0.9799, 1.0855)

The results indicate that food did not have an effect on the pharmacokinetics of stavudine. The lack of food effect is consistent across subjects as shown in the following

stick plots. The 90% C.I. for the ratios of the geometric means for C_{max} and total daily AUC (TAUC) for a light meal, yogurt, or applesauce treatment, relative to fasted conditions, were entirely contained within the pre-specified interval of 0.8 to 1.25.



Conclusion: Light meal, yogurt, or applesauce had no effect on C_{max} and AUC values for the ER formulation, relative to the fasted condition. These results indicate that the ER formulation of stavudine can be administered fasted, with a light meal, or the capsule contents can be mixed with a small amount of yogurt or applesauce.

Relative Bioavailability of Stavudine from the Extended Release Formulation After
Coadministration With A High Fat Meal In Healthy Volunteers
(A1455-114, Item 6, Volume 10)

Objectives:

1. To assess the impact of the coadministration of a high fat meal on the bioavailability of stavudine from the extended release (ER) formulation in healthy subjects.
2. To determine the single dose bioavailability of stavudine from the ER bead formulation relative to the currently marketed immediate release (IR) formulation.

Subjects: A total of 24 subjects (men or women) were enrolled in the study and 23 subjects completed the study. One subject did not complete the study.

Study design: This was an open-label, randomized, three-way crossover study with balanced carryover effects in healthy subjects. Subjects were randomized to one of six sequences of the following treatments, with at least a 5-day washout period between each treatment:

Treatment A: 40 mg of stavudine IR formulation every 12 hours under fasting conditions.

Treatment B: 100 mg of stavudine ER bead formulation under fasting conditions.

Treatment C: 100 mg of stavudine ER bead formulation within 5 minutes of a high fat meal.

Food Item	Calories ^a (kcal)	Fat ^a (g)	Carbohydrates ^a (g)	Protein ^a (g)
2 eggs fried in butter	184	13.8	1.2	12.4
2 slices white bread toasted	134	1.8	24.8	4.1
1 tablespoon butter	102	11.5	trace	0.1
1 tablespoon jelly	52	Trace	13.5	0.1
2 strips bacon	72	6.2	trace	3.8
4 ounces hash brown potatoes	244	12.4	31.5	3.6
8 ounces whole milk	157	8.9	11.4	8.0
Total	945	54.6	82.4	32.1
Calories		487 kcal	330 kcal	128 kcal
% of Total Calories		51.5%	34.9%	13.6%

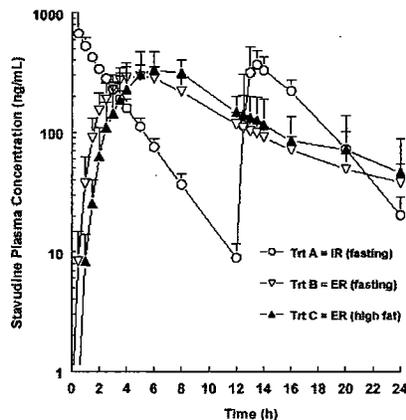
The following table shows a standard high fat meal used in Treatment C.

Each subject was given 180 mL of tap water at room temperature immediately following each dose. Blood samples were collected for pharmacokinetic analysis up to 24 hours post-dose for the ER formulation. Pharmacokinetic sampling for the IR dose began after administration of the first dose and continued for 12 hours after administration of the second dose.

Formulation: Stavudine 100 mg ER Beadlet commercial formulation, Batch # M0050.

Sample Assay Methods: Plasma samples for stavudine were analyzed by a validated high performance liquid chromatography/tandem mass spectrometry (LC/MS/MS) method.

PK analysis: Blood samples were collected for 24 hours post-dose to determine stavudine concentrations. The following figure shows the mean (SD) plasma concentration-time profiles of stavudine.



The pharmacokinetic parameters of stavudine and statistics are summarized in the following two tables.

Pharmacokinetic Parameter	40 mg Stavudine BID	Stavudine ER Fasted	Stavudine ER Fed
C _{max} (ng/mL)			
Geometric Mean	692.4	338.4	361.6
(C.V.%)	(29)	(14)	(34)
TAUC(0-T) (ng•h/mL)			
Geometric Mean	3567.1	3131.4	3392.0
(C.V.%)	(13)	(16)	(16)
T _{max} (h)			
Median	0.50	4.0	6.0
(min, max)	[]

Pharmacokinetic Parameter	Treatment	Adjusted Geometric Mean	Contrast	Ratios of Adjusted Geometric Means Point Estimate (90% C.I.)
C _{max} (ng/mL)	A	694.2		
	B	339.5	B vs. A	0.4891 (0.4308, 0.5551)
	C	361.0	C vs. B	1.0632 (0.9367, 1.2069)
TAUC(0-T) (ng•h/mL)	A	3572.1		
	B	3139.0	B vs. A	0.8788 (0.8350, 0.9248)
	C	3387.7	C vs. B	1.0792 (1.0255, 1.1358)

The results indicate that a high fat meal did not have an effect on the pharmacokinetics of stavudine. The 90% C.I.s for the ratios of the geometric means for C_{max} and total daily AUC (TAUC) for administration with a high fat meal, relative to fasted conditions,

were entirely contained within the pre-specified interval of 0.8 to 1.25. Additionally, the AUC for the ER formulation was comparable to the exposure observed with the IR formulation under fasted conditions, uncorrected for dose.

Conclusion: Relative to the fasted treatment, a high fat meal had no effect on the C_{max} and AUC values for the ER formulation. This indicates that the ER formulation of stavudine may be administered with or without a high fat meal. The total daily exposure (AUC) for the ER formulation was equivalent to the IR formulation under fasted conditions, uncorrected for dose.

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Single-Dose, Dose Proportionality Study of Stavudine in Healthy Subjects Following Oral Administration of Stavudine Extended Release Formulation (A1455-108, Item 6, Volume 12)

Objectives: To assess the dose proportionality in the pharmacokinetics of stavudine from the extended release bead formulation.

Subjects: A total of 28 subjects (men or women) were enrolled in the study and 25 subjects completed the study. Three subjects dropped out due to personal reasons.

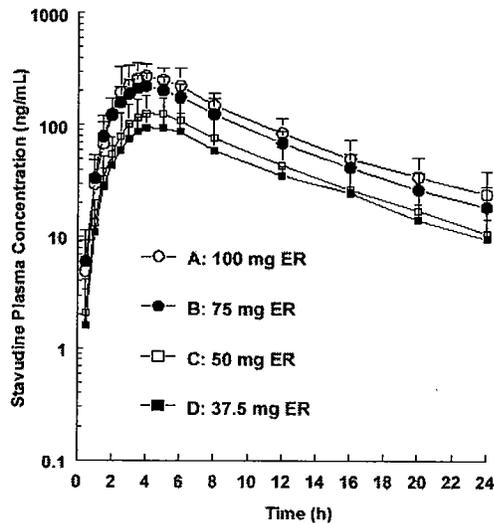
Study design: This was an open-label, single dose, randomized, four-way crossover study in healthy subjects. Subjects were randomized to receive the following four treatments under fasting conditions, with at least a 5-day washout period between each treatment, in one of four randomly assigned treatment sequences:

- Treatment A: 100 mg of stavudine ER bead formulation.
- Treatment B: 75 mg of stavudine ER bead formulation.
- Treatment C: 50 mg of stavudine ER bead formulation.
- Treatment D: 37.5 mg of stavudine ER bead formulation.

Formulation: Commercial stavudine ER 100 mg (batch number M00050), 75 mg (batch number M00052), 50 mg (batch number N00245) and 37.5 mg (batch number N00246) capsules.

Sample Assay Methods: Plasma samples for stavudine were analyzed by a validated LC/MS/MS method.

PK analysis: Blood samples were collected for 24 hours post-dose to determine stavudine concentrations. The following figure shows the mean (SD) plasma concentration-time profiles of stavudine.



The following table summarizes stavudine PK parameters.

Pharmacokinetic Parameter	Treatment A	Treatment B	Treatment C	Treatment D
Dose Normalized ^a				
C _{max} (ng/mL)				
Geometric Mean	3.0	3.2	2.7	2.7
(C.V.%)	(40)	(24)	(38)	(37)
Non-Scaled				
C _{max} (ng/mL)				
Geometric Mean	304	240	134	102
(C.V.%)	(40)	(24)	(38)	(37)
Dose Normalized ^a				
TAUC(0-T) (ng•h/mL)				
Geometric Mean	23.7	26.0	22.9	24.3
(C.V.%)	(21)	(20)	(26)	(25)
Non-Scaled				
TAUC(0-T) (ng•h/mL)				
Geometric Mean	2366	1949	1147	912
(C.V.%)	(21)	(20)	(26)	(25)

The following table shows the statistical analysis of dose normalized (1 mg stavudine) C_{max} and Total daily AUC (TAUC(0-T)) for stavudine.

Pharmacokinetic Parameter	Adjusted Treatment	Geometric Mean	Contrast	Ratios of Geometric Means Point Estimate (90% C.I.)
C _{max} (ng/mL)	A	3.037		
	B	3.192	B vs. A	1.0512 (0.9356, 1.1811)
	C	2.666	C vs. A	0.8778 (0.7813, 0.9863)
	D	2.683	D vs. A	0.8834 (0.7862, 0.9926)
TAUC(0-T) (ng•h/mL)	A	23.623		
	B	25.988	B vs. A	1.1001 (1.0222, 1.1839)
	C	22.884	C vs. A	0.9687 (0.9001, 1.0425)
	D	24.148	D vs. A	1.0222 (0.9499, 1.1001)

Treatment A: 100 mg Stavudine ER

Treatment B: 75 mg Stavudine ER

Treatment C: 50 mg Stavudine ER

Treatment D: 37.5 mg Stavudine ER

a Dose normalized to 1 mg

For TAUC(0-T), the 90% confidence intervals for the ratios of the geometric means for all test to reference comparisons fell within the prescribed limits (0.8-1.25). However, for C_{max}, the lower limit of the 90% CI for the ratio of the test to reference treatments slightly fell below the pre-defined limits (0.8-1.25) for 50 mg and 37.5 mg doses. The deviation from dose proportionality is small. For NRTIs, it is presumed that total exposure has a greater impact than C_{max} on efficacy.

Conclusion: The extended release formulation for stavudine was dose proportional in the dose range of 37.5 mg to 100 mg with respect to AUC; the non-dose proportionality of C_{max} is not clinically significant.

Single and Multiple Dose Pharmacokinetics of Stavudine from an Extended Release Encapsulated Beadlet Formulation in Asymptomatic HIV Infected Subjects
(A1455-103, Item 6, Volume 14)

Objectives:

1. To assess the pharmacokinetics of stavudine after a single and multiple (QD X 9 days) oral doses of a 100 mg extended release (ER) encapsulated beadlets formulation
2. To evaluate the intra-subject variability in the pharmacokinetics of stavudine after multiple doses of a 100 mg extended release (ER) encapsulated beadlets formulation.

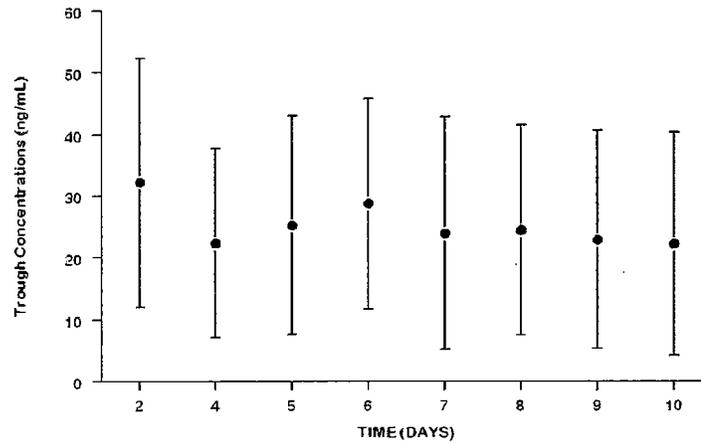
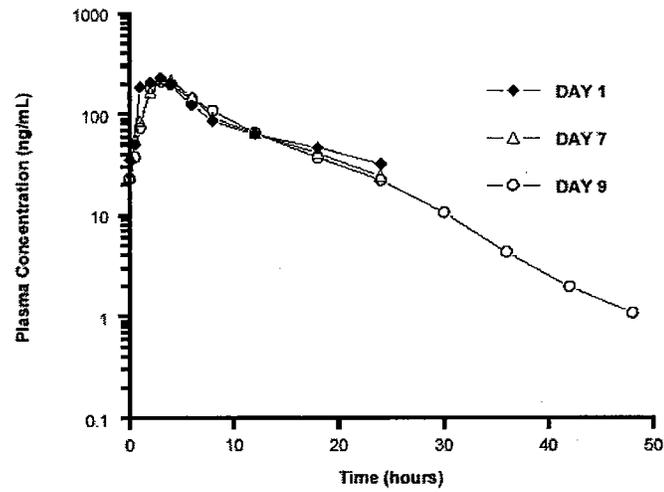
Subjects: A total of 16 subjects (men or women) were enrolled in the study, but only 15 subjects completed the study. One subject discontinued after Day 7 for personal reasons. All subjects have bodyweight at least 60 kg. Subjects who were on stavudine therapy in combination with other anti-HIV agents were restricted from taking their regular stavudine medication from Day -1 until discharge. However, subjects who were on therapy with other anti-HIV agents, with the exception of zidovudine, were allowed to take their regular medication during the study. The use of zidovudine was not permitted from Day -1 until study discharge.

Study design: This was a single center, open-label, multiple dose study in asymptomatic HIV infected subjects. Subjects received a single daily dose of 100 mg of an extended release encapsulated beadlet formulation on Days 1 through 9, in the morning following an overnight fast of 8 hours. Each treatment was administered with approximately 240 mL of water, followed by a mouth check. Food was not permitted for 2 hr post-dose. Water was allowed *ad libitum* during the fasting period and at other times. All subjects had a similar diet at any given lunch, afternoon snack, or dinner. Subjects were confined to the test facility for 11 days and 11 nights.

Formulation: 100 mg stavudine extended release encapsulated beadlets commercial formulation with batch number N99089.

Sample Assay Methods: Plasma concentrations were determined by a validated LC/MS/MS analytical method. All plasma samples were analyzed in a total of 5 analytical runs, which met the acceptance criteria established for sample analysis. The standard curves were quadratic over the concentration range of 0.5-1000 ng/mL. The mean predicted concentrations of the analytical QCs were within $\pm 3.2\%$ of their nominal values; between-run and within-run variabilities were within 2.4 % CV and 3.4 % CV, respectively. The standard curve and QC data indicated that the plasma assay method was acceptable.

PK analysis: Serial blood samples were collected at selected times over a 24-h period on Days 1, 7, and 9; additional samples were collected at 30, 36, 42, and 48 hours post-dose following the Day 9 dose. In addition, samples for trough levels were collected on Days 4, 5, and 6. The following figures show profiles of mean plasma concentration vs. time and mean (SD) plot of the trough concentrations (C_{min}). The C_{min} of stavudine was 24.48 ± 16.96 ng/ml on Day 7 and 22.28 ± 18.09 ng/ml. The data show that there is no stavudine accumulation after multiple once daily doses.

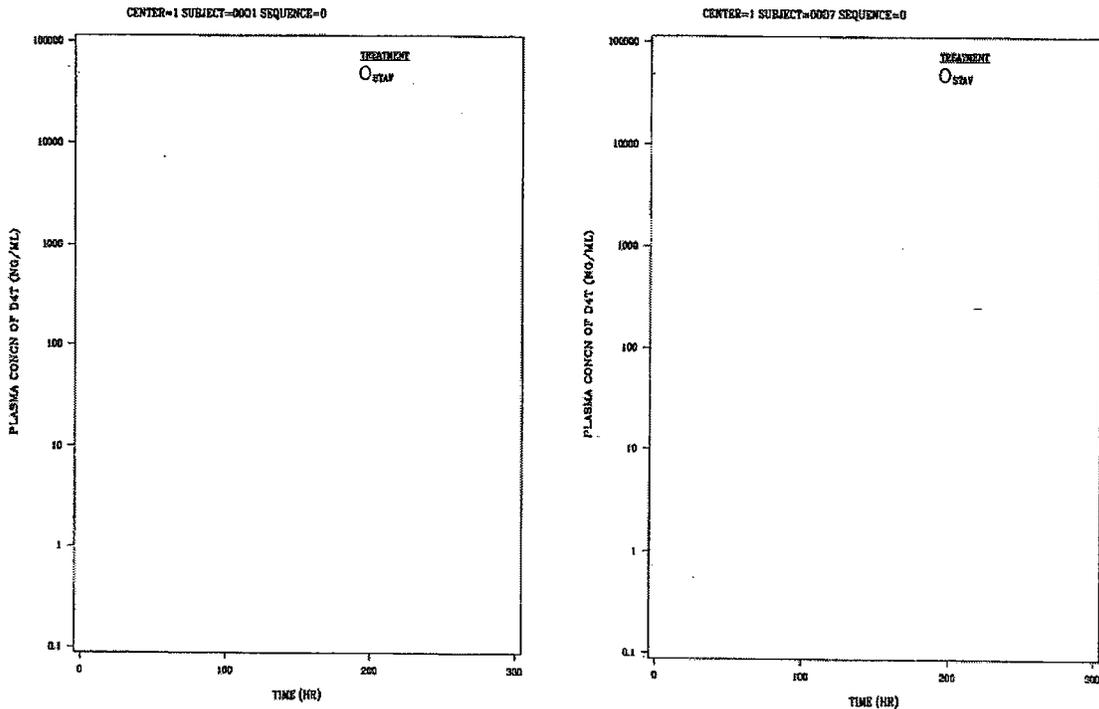


The following table shows statistics for stavudine pharmacokinetic parameters.

Pharmacokinetic Parameter	Day 1	Day 7	Day 9
C_{max} (ng/mL)			
Geometric Mean	238.6	234.0	212.1
(C.V.%)	(122.12)	(25.8)	(26.5)
AUC(TAU) (ng•h/mL)			
Geometric Mean	2045.3	1975.0	1890.4
(C.V.%)	(31.3)	(28.9)	(31.2)
T-HALF (h)			
Mean	-	-	18.1 ^a
(S.D.)	-	-	(47.5)
T_{max} (h)			
Median	3.0	4.0	3.0

^a The mean T-half value was 4.0 ± 1.8 h upon exclusion of Subjects 1 and 7, who had T-half values at 32.0 and 187.6 h, respectively, which were felt to be aberrantly high.

As shown in the above table, the mean T-half value was 4 hours upon exclusion of Subjects 1 and 7. The following figures show the plasma concentration vs. time profile for Subjects 1 and 7. The figures show that the concentrations for last few time points are close to the detection limit, and therefore the estimated T-half values may not be accurate. The real T-half values for these two subjects may be much shorter than estimated. Another possibility is there are two phases of absorption. The estimate of 4 hours is consistent with the previous estimate (5 hours) in healthy subjects in Study AI455-107, and is higher than ~2 hour half-life observed for stavudine, following oral administration of the IR formulation. The relatively longer half-life observed for the ER formulation is probably due to a slower absorption rate rather than a slower elimination rate. The data also show that there is no stavudine accumulation after multiple once daily doses.



Fluctuation Index, defined as $(C_{max}-C_{min})/C_{ss,avg}$, is determined to be 2.51 ± 0.76 after multiple dose administration of 100 mg of stavudine ER formulation.

Estimates of the intra-subject variability of C_{max} and $AUC(TAU)$ from the analysis of variance are summarized in the following table:

Pharmacokinetic Parameter	Standard Deviation on Log Scale	Coefficient of Variation
C _{max} (ng/mL)	0.097	9.7%
AUC(TAU) (ng•h/mL)	0.083	8.3%

Discussion: The exposures in asymptomatic HIV infected subjects are relatively low compared to that in healthy subject after 100 mg QD of stavudine ER. C_{max} of stavudine ER in this study was 212-238 ng/ml, as compared to 253-361 ng/ml in healthy subjects (Study AI455-107, 108, 109, and 114). AUC₀₋₂₄ was 1890-2045 ng•h/ml, as compared to 2366–3392 ng•h/ml in healthy subjects (Study AI455-107, 108, 109, and 114). The average body weights are comparable among all of these studies.

Conclusion:

1. There was no stavudine accumulation after multiple once daily doses.
2. There was less than 10% intra-subject variability in AUC and C_{max}.
3. There was high inter-subject variability in terminal half-life in patients.
4. The terminal half-life for the ER formulation is relatively longer than the value observed for the immediate release (IR) formulations (~2 hours), which is probably due to a slower absorption rate rather than a slower elimination rate.
5. The exposures in asymptomatic HIV infected subjects are relatively low compared to that in healthy subject after 100 mg QD of stavudine ER.

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Evaluation of the Safety and Antiviral Activity of Stavudine Extended Release Formulation as Compared to Stavudine Immediate Release Formulation, Each as Part of Potent Antiretroviral Combination Therapy (AI455-96, Item 6, Volume 14)

Objectives: The overall objective of this Phase II/III study was to compare the antiviral activity, pharmacokinetic parameters and safety of the stavudine extended release formulation (d4T ER) given once daily relative to the immediate release formulation (d4T IR) given twice daily, in combination with lamivudine (3TC) BID and efavirenz (EFV) QD through 48 weeks of dosing.

Subjects: The study enrolled 217 and randomized 155 subjects. One hundred fifty (150) subjects received treatment. A total of 16 subjects participated in the pharmacokinetic substudy. For the single dose administration (Day 1), 6 and 10 subjects participated in the ER and IR arms of the study, respectively. At steady state (Day 14), 5 and 8 subjects participated in the ER and IR arms of the study, respectively. Subjects who participated in the PK substudy all weigh at least 60 kg.

Study design: The study was a blinded, double-dummy, randomized 1:1 comparison of d4T ER (100 mg QD) and d4T IR (40 mg BID) in combination with 3TC and EFV in antiretroviral naïve HIV-infected subjects. The 3TC and EFV were administered open label. Randomization was stratified by screening HIV viral load of < 30,000 c/mL or ≥30,000 c/mL.

Treatment Group I (A): d4T ER 100 mg QD + d4T IR placebo BID + 3TC 150 mg BID + EFV 600 mg QD

Treatment Group II (B): d4T ER placebo QD + d4T IR 40 mg BID + 3TC 150 mg BID + EFV 600 mg QD

Subjects ≥60 kg at baseline received d4T ER 100 mg QD or d4T IR 40 mg BID, and 3TC 150 mg BID; Subjects < 60 kg received d4T ER 75 mg QD or d4T IR 30 mg BID, and 3TC 150 mg BID. All the subjects received 600 mg EFV once daily. Substitution of Nelfinavir (NFV) for EFV was permissible for a subject experiencing a ≥ grade 2 adverse event. Subjects were monitored for the development of peripheral neuropathy. If symptoms of Grade 2 or higher peripheral neuropathy developed while the subject was on treatment, d4T (ER or IR) treatment was interrupted. If symptoms resolved to Grade 1 or baseline, the subject was to resume treatment at one-half the original dose. The d4T ER 100 mg dose was reduced to 50 mg. The d4T ER 75 mg dose was reduced to 37.5 mg. The d4T IR 40 mg dose was reduced to 20 mg and the d4T IR 30 mg dose was reduced to 15 mg. The subjects could resume treatment at full dose if, in the opinion of the investigator, it was medically appropriate to do so. Antiviral response was analyzed at 12 and 48 weeks. Treatment continued until the last treated subject completed 48 weeks of therapy.

The pharmacokinetic substudy was conducted at selected sites. This includes determination of full plasma concentration-time profiles on Day 1 (single-dose) and Day 14 (steady-state). Plasma samples were also collected for population pharmacokinetic analysis.

Formulation: The following table summarized batch numbers of study drugs. All marketed study drugs were obtained by the investigators through commercial suppliers.

Product Description	Batch Numbers	Expiration Date
d4T 15 mg capsule, IR	C96082	30-Apr-2001
d4T 20 mg capsule, IR	C96083	30-Apr-2001
d4T 30 mg capsule, IR	N98074	30-Jun-2002
	C99029	31-Mar-2002
d4T 40 mg capsule, IR	N98081	30-Jun-2001
	C00163	30-Jun-2002
Placebo 30 mg capsule, IR	N96046	31-Oct-2001
	N00018	31-Jan-2004
Placebo 40 mg capsule, IR	N96048	31-Oct-2001
	N00019	31-Jan-2004
Placebo capsule ER	N99059	31-May-2003
Placebo capsule, ER	N99077	30-Jun-2003
Placebo 20 mg capsule, IR	N96047	31-Oct-2001
Placebo 15 mg capsule, IR	N96041	31-Oct-2001
d4T ER 37.5 mg capsule	N99123	31-Jul-2001
d4T ER 50 mg capsule	N99124	31-Jul-2001
d4T ER 75 mg capsule	N99089	31-Jul-2002
	N00047	31-Jan-2002
d4T ER 100 mg capsule	N00048	31-Jan-2002
	N99092	31-Jul-2001

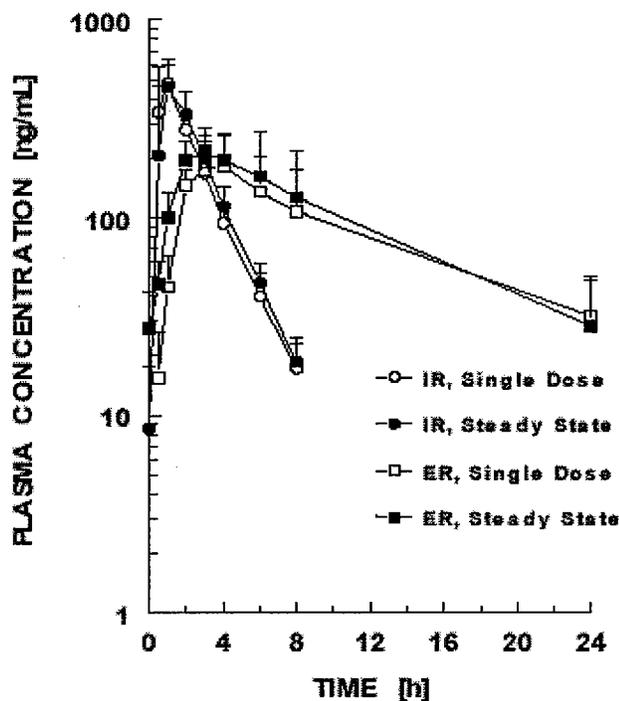
Stavudine extended release encapsulated bead formulation (100 mg) and stavudine immediate release capsule (Zerit[®], 40 mg) were used in PK substudy.

Sample Assay Methods: Plasma concentrations were determined by a validated LC/MS/MS analytical method. The standard curves were quadratic over the concentration range of 0.5-1000 ng/mL. The coefficient of determination of the standard curves was ≥ 0.9997 . The mean predicted concentrations of the analytical QCs were within 1.5% of their nominal values; between-run and within-run variabilities were within 1.1% CV and 4.2% CV, respectively. The standard curve and QC data indicated that the plasma assay method was acceptable.

PK analysis:

Full PK profiles:

Mean (SD) plots of plasma concentration versus time for the ER and IR formulations are shown in the following figure. The following table lists geometric mean (%CV) of stavudine pharmacokinetic parameters following Stavudine ER and IR administration.



Formulation	Study Day	Cmax (ng/ml) (%CV)	Cmin (ng/ml) (%CV)	Tmax (h) ^a (min,max)	AUC(0-24) (ng·h/ml) (%CV)	T1/2 (h) ^b (%CV)	A.I. ^c (%CV)	F.I. ^d (%CV)
ER	Day 1 Single Dose (N = 6)	187.27 (33.78)	-	3.5 []	1834.72 (34.82)	16.23 (17.62)	-	-
	Day 14 Steady State (N = 4 or 5) ^h	237.47 (30.99)	23.87 (53.33)	3.0 []	1746.94 (40.14)	10.30 (7.75)	1.08 (26.92)	2.36 (43.16)
IR	Day 1 Single Dose (N = 10)	522.63 (21.82)	-	1.0 []	2418.83 (17.24)	1.56 (0.23)	-	-
	Day 14 Steady State (N = 8)	520.19 (27.34)	4.23 (99.77)	1.0 []	2533.01 (17.68)	1.51 (0.12)	1.03 (24.16)	4.85 (23.93)

^a Median

^b Terminal half-life in a dosing interval of 24 hours for stavudine ER formulation, and 12 hours for IR formulation

^c Accumulation indices

^d Fluctuation Indices

^h n=5 for Cmax and Tmax, n=4 for the other PK parameters

The data showed that accumulation index on Day 14 was approximately 1 for both stavudine ER and IR, suggesting a lack of accumulation of stavudine following multiple dosing of both formulations. In a dosing interval of 24 (ER) and 12 (IR) hours, the apparent elimination half-life for the ER formulation was relatively longer (single dose, 16 h; steady state, 10 h) when compared to the half-life for the IR formulation (single dose,

1.56 h; steady state, 1.51 h). There was high inter-subject variability in half-life estimate, which was seen in Study AI455-103. Mean C_{max} value for the ER formulation was approximately 50% lower than the IR formulation, and the total daily exposure of stavudine from the ER formulation was about 31% lower compared to the IR formulation, despite the greater dose relative to the IR formulation. This is in contrast to the findings in healthy volunteers, where the AUC values for the two formulations were approximately equivalent. The observed difference in exposure may be partially due to the differences in study design (AI455-096 versus AI455-114). Study AI455-096 was a parallel design study conducted in HIV-infected patients; whereas, Study AI455-114 was a crossover design study in healthy volunteers.

There was a trend towards lower exposures in HIV-infected patients compared to healthy volunteers; the total daily exposure (AUC) for the ER formulation was approximately 24%-47% lower when compared to healthy subjects. The variability in C_{max} and AUC for the IR formulation was similar between healthy subjects (29% and 13%, respectively; n = 23, AI455-114) and HIV-infected patients (22% and 17%, respectively; n = 8; AI455-096). Variability in C_{max} and AUC for the ER formulation was also similar between the two populations (healthy subjects: 25% and 22%, respectively; n = 100; patients: 27% and 32%, respectively, n = 19).

Population PK/PD analysis:

A population PK/PD analysis was performed using NONMEM on data from 142 (69 ER and 73 IR) subjects. Datasets for population pharmacokinetic analysis require a time-ordered sequence of dosing and observation events for each subject; however, in retrospect, the case report forms (CRFs) were not adequately designed to collect all necessary dosing information for population pharmacokinetic analysis. The applicant thus imputed certain dosing information. The total number of concentrations that were directly dependent upon an imputed time-of-last-dose was 148 (41%; for 58 of 69 patients) for the ER formulation and 36 (9%; for 10 of 73 patients) for the IR formulation. We communicated with the applicant during the pre-NDA meeting that imputed dosing information is not acceptable. Therefore, population PK analysis is not acceptable.

The individual empirical Bayesian estimates of the pharmacokinetic model parameters were used to simulate patient-specific concentration-time profiles. The simulated concentrations were used to compute estimates of individual subject AUC_{0-24hr}, C_{max}, and C_{min} values. These estimated PK parameters were used to establish PK/PD relationships. Since population PK analysis is not acceptable, the resulting PK/PD analysis is not acceptable either.

Conclusion:

1. The total daily exposure for the ER formulation in HIV-infected patients was approximately 24%-47% lower when compared to healthy subjects.
2. The mean C_{max} value for the ER formulation was approximately 50% lower than the C_{max} for the IR formulation, and the total daily exposure of stavudine from the ER formulation was about 31% lower compared to the exposure for the IR formulation, despite the greater dose relative to the IR formulation.

3. The fluctuation index for the ER formulation was about 50% lower compared to the value for the IR formulation.
4. The mean Cmin value for the ER formulation was approximately 5-fold higher than the Cmin for the IR formulation
5. There was high inter-subject variability in the estimate of terminal half-life in patients.

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Dissolution (Item 4, Volume 1-2)

The to-be marketed formulation was used in PK studies AI455-103, 107, 108, 109, and 114, and pivotal clinical trials AI455-96 and 99. The following table summarizes batches used in these studies. Non-to-be marketed formulations used in Study AI455-107 (IVIVC study) are not included in the list.

Study #	Batches
AI455-103	N99089 (100 mg)
AI455-107	N99089 (100 mg)
AI455-108	M00050 (100 mg), M00052 (75 mg), N00245 (50 mg), N00246 (37.5 mg)
AI455-109	M00050 (100 mg)
AI455-114	M00050 (100 mg)
AI455-96	N99123 (37.5 mg), N99124 (50 mg), N99089 (75 mg), N00047 (75 mg), N00048 (100 mg), N99092 (100 mg)
AI455-99	N99123 (37.5 mg), N00050 (50 mg), M00052 (75 mg), N00047 (75 mg), M00050 (100 mg), N00048 (100 mg)

In the batch number, the prefix before number indicates the manufacture site. N stands for New Brunswick, and M stands for Moreton, England.

The **applicant proposed** the following dissolution method for the to-be-marketed formulation:

Dosage form: capsule

Strength(s): 100 mg, 75 mg, 50 mg, 37.5 mg

Apparatus type: Basket

Rotation speed: 100 rpm

Media: 0.1M phosphate buffer pH 6.8

Volume: 1000 ml

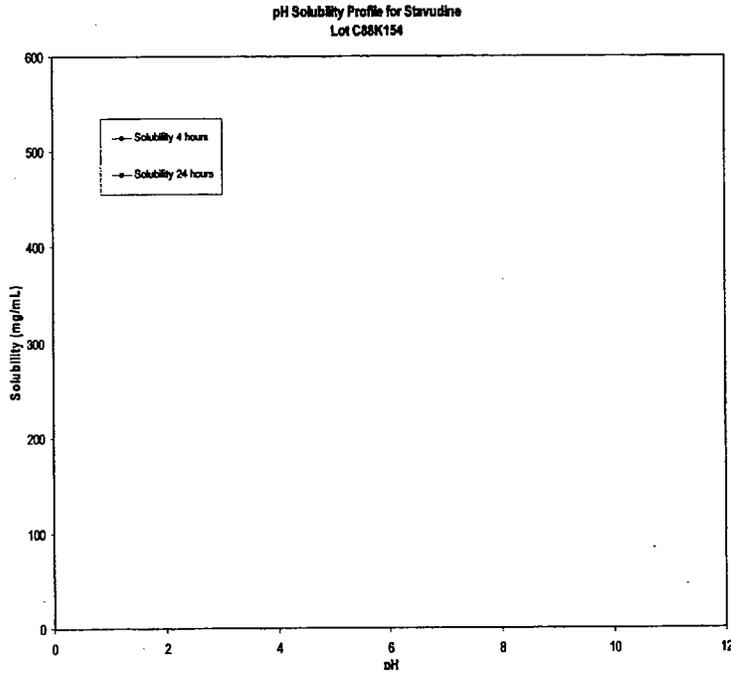
Temperature: 37°C ± 0.5°C

Sampling time point: 1, 2, 4, 8, 12, 16, and 24 hours

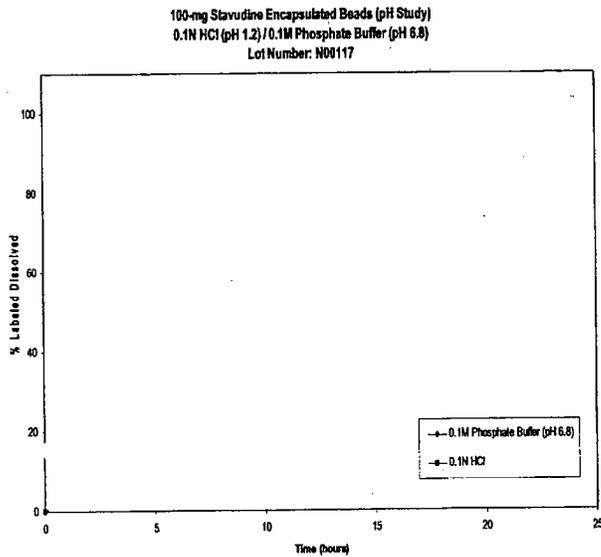
Analytical method: HPLC

Dissolution specification: 1 hour, 4 hours, and 24 hours

A study was conducted to determine the effects of dissolution methods and media pH on the dissolution characteristics of the stavudine extended release capsule product proposed for registration. Both clinical and stability lots were used in the development of dissolution method. Bead formulations with different coating levels were evaluated to demonstrate that the method discriminates between different coating levels. The solubility of the stavudine drug substance remains constant throughout the pH range of 1.20 to 8.54, but increased markedly at pH 9.98, as shown in the following figure.



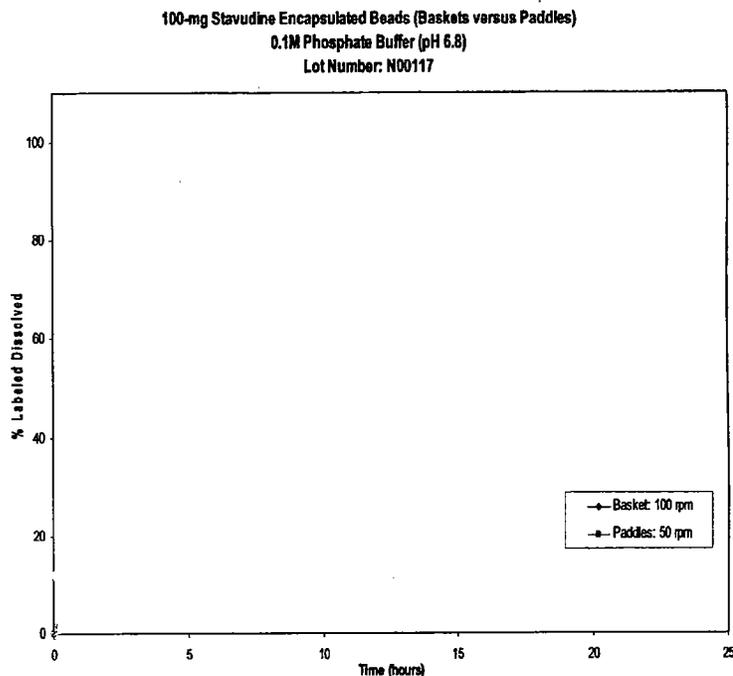
The result is consistent with its pK_a of 10.0. Therefore, we anticipate that the dissolution profile would not be impacted by media pH changes. The following figure show dissolution profiles for media 0.1N hydrochloric acid (pH 1.2) and pH 6.8, phosphate buffer using baskets at 100 rpm.



The dissolution profile for the extended release formulation was comparable and complete, irrespective of pH, with comparable variation. The applicant selected a media pH 6.8 for dissolution testing, because it minimizes the potential for acid hydrolysis of

stavudine to thymine and no significant differences existed between the pH 1.2 and pH 6.8 dissolution profiles, which is acceptable.

The following figure shows the dissolution profile for clinical batch N00117, using paddles at 50 rpm and baskets at 100 rpm, pH 6.8.

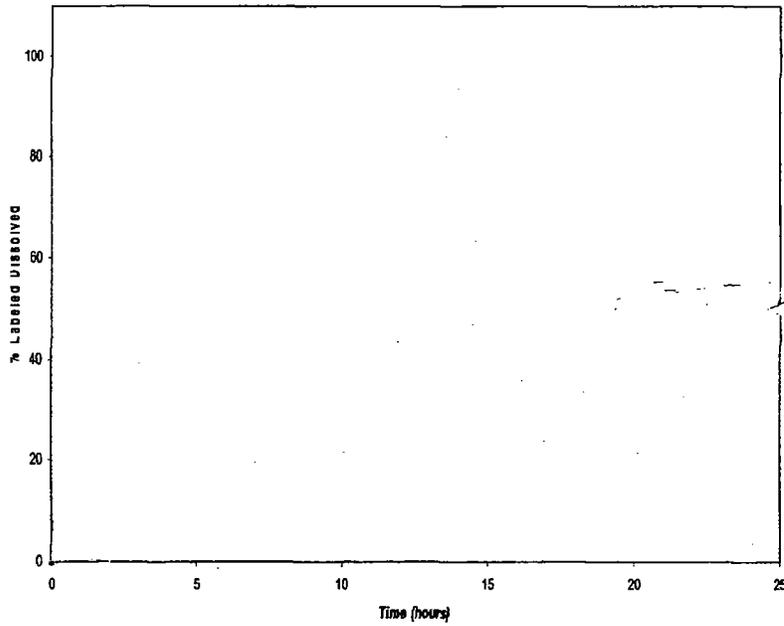


Due to the ease of operation, opportunity for automation, and comparable dissolution profiles for the two methods, the basket method was selected over the paddle method, which is acceptable.

The following figure shows the dissolution profile in pH 6.8 medium for a stability lot (Lot 45743-099) at different storage conditions. The data demonstrates that the dissolution method is capable of identifying changes in the drug release rate caused by storage at elevated humidity and temperature.

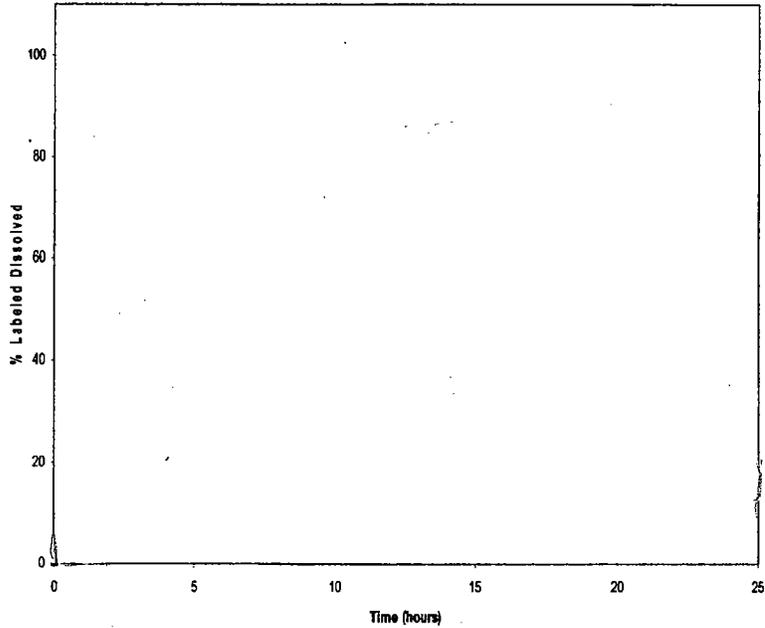
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100-mg Stavudine Encapsulated Beads (Stability Study)
Lot #: 2200001516
0.1M Phosphate Buffer (pH 6.8)



The following figure shows the dissolution profiles in pH 6.8 media for products with different levels of coating. The dissolution profiles show that this method will differentiate between coating levels. Therefore, the selected dissolution method is acceptable.

100-mg Stavudine Encapsulated Beads (Coating Level Study)
0.1M Phosphate Buffer (pH 6.8)
Lot #: N00109



The following tables show individual dissolution data for the stavudine extended release formulation used in clinical and pharmacokinetic trials.

(1) Batch N00246 (37.5 mg capsules)

Vessel/Time	1 hr	2 hr	4 hr	8 hr	12 hr	16 hr	24 hr
Vessel 1	┌						
Vessel 2							
Vessel 3							
Vessel 4							
Vessel 5							
Vessel 6							┐
Average	6	17	40	74	90	94	95

(2) Batch N99123 (37.5 mg capsules)

Vessel/Time	1 hr	2 hr	4 hr	8 hr	12 hr	16 hr	24 hr
Vessel 1	┌						
Vessel 2							
Vessel 3							
Vessel 4							
Vessel 5							
Vessel 6							┐
Average	5	12	27	54	75	87	94

(3) Batch N00245 (50 mg capsules)

Vessel/Time	1 hr	2 hr	4 hr	8 hr	12 hr	16 hr	24 hr
Vessel 1	┌						
Vessel 2							
Vessel 3							
Vessel 4							
Vessel 5							
Vessel 6							┐
Average	6	19	39	72	90	96	98

(4) Batch N00246 (50 mg capsules)

Vessel/Time	1 hr	2 hr	4 hr	8 hr	12 hr	16 hr	24 hr
Vessel 1	┌						
Vessel 2							
Vessel 3							
Vessel 4							
Vessel 5							
Vessel 6							┐
Average	6	17	40	74	90	94	95

(5) Batch N00050 (50 mg capsules)

Vessel/Time	1 hr	2 hr	4 hr	8 hr	12 hr	16 hr	24 hr
Vessel 1	┌						
Vessel 2							
Vessel 3							
Vessel 4							
Vessel 5							
Vessel 6							┐
Average	6	16	40	75	92	99	103

(6) Batch N99124 (50 mg capsules)

Vessel/Time	1 hr	2 hr	4 hr	8 hr	12 hr	16 hr	24 hr
Vessel 1							
Vessel 2	┌						
Vessel 3							
Vessel 4							
Vessel 5							
Vessel 6							┐
Average	5	12	26	54	76	88	96

(7) Batch M00052 (75 mg capsules)

Vessel/Time	1 hr	2 hr	4 hr	8 hr	12 hr	16 hr	24 hr
Vessel 1	┌						
Vessel 2							
Vessel 3							
Vessel 4							
Vessel 5							
Vessel 6							┐
Average	7	18	39	76	93	99	101

(8) Batch N00047 (75 mg capsules)

Vessel/Time	1 hr	2 hr	4 hr	8 hr	12 hr	16 hr	24 hr
Vessel 1	┌						
Vessel 2							
Vessel 3							
Vessel 4							
Vessel 5							
Vessel 6							┐
Average	6	18	42	76	92	98	102

(9) Batch N00048 (100 mg capsules)

Vessel/Time	1 hr	2 hr	4 hr	8 hr	12 hr	16 hr	24 hr
Vessel 1	┌						
Vessel 2							
Vessel 3							
Vessel 4							
Vessel 5							
Vessel 6							┐
Average	7	19	45	81	96	102	104

(8) Batch N99092 (100 mg capsules)

Vessel/Time	1 hr	2 hr	4 hr	8 hr	12 hr	16 hr	24 hr
Vessel 1	┌						
Vessel 2							
Vessel 3							
Vessel 4							
Vessel 5							
Vessel 6							
Average	7	17	37	70	87	95	98

(10) Batch M00050 (100 mg capsules)

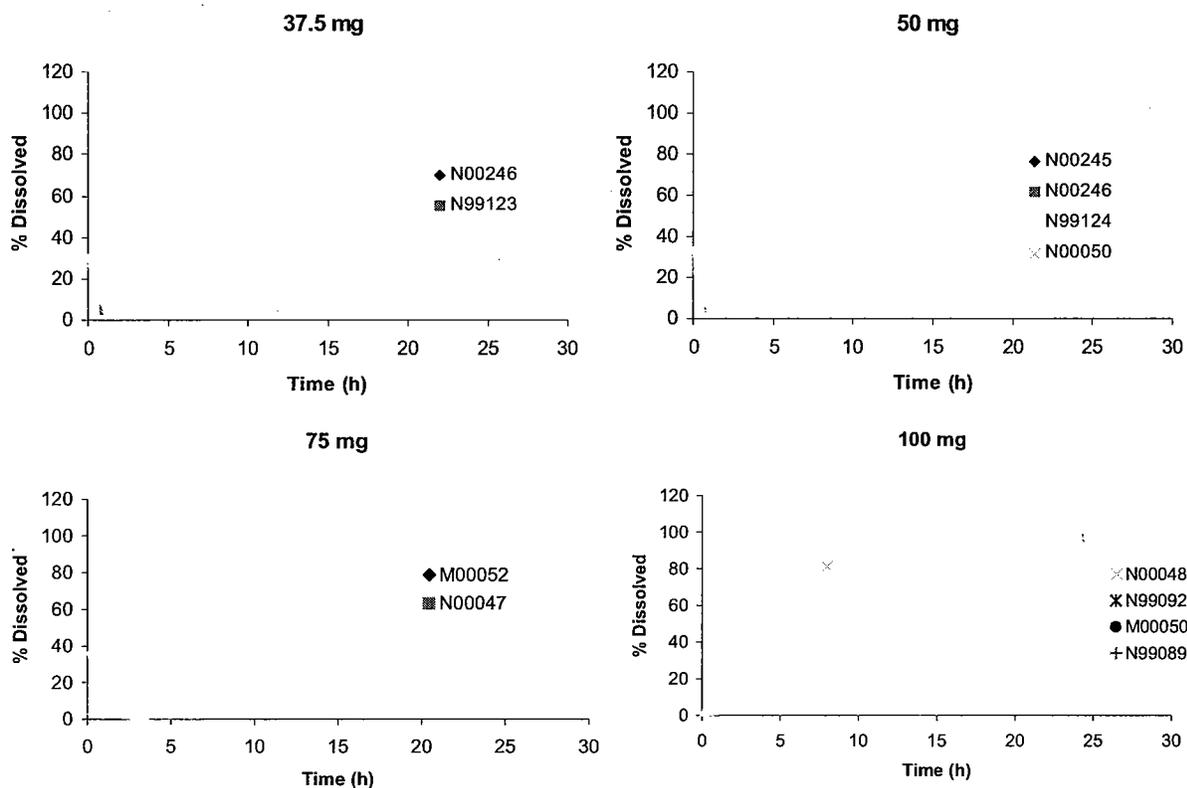
Vessel/Time	1 hr	2 hr	4 hr	8 hr	12 hr	16 hr	24 hr
Vessel 1	┌						
Vessel 2							
Vessel 3							
Vessel 4							
Vessel 5							
Vessel 6							
Average	6	17	38	74	91	97	98

(11) Batch N99089* (100 mg capsules)

Vessel/Time	1 hr	2 hr	4 hr	8 hr	12 hr	16 hr	24 hr
Vessel 1	┌						
Vessel 2							
Vessel 3							
Vessel 4							
Vessel 5							
Vessel 6							
Vessel 7							
Vessel 8							
Vessel 9							
Vessel 10							
Vessel 11							
Vessel 12		--	--				
Average	9	19	35	63	80	90	95

*Batch used in the IVIVC study

The following figures show individual dissolution profiles for extended-release formulations in different strengths.



The following table shows mean (range: $\pm 10\%$) dissolution data for all strengths.

Time (h)	1	2	4	8	12	16	24
% dissolution mean (range: $\pm 10\%$)	6	15	33	64	85	94	98

The applicant proposed the dissolution specification as follows: [] at 1 hour, [] at 4 hours; and [] at 24 hours. According to the FDA "Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations" guidance, when setting dissolution specifications without an IVIVC, "the recommended range at any dissolution time point specification is $\pm 10\%$ deviation from the mean dissolution profile obtained from the clinical/bioavailability lots". However, reasonable deviations from the $\pm 10\%$ range can be accepted provided that the range at any time point does not exceed 25%. In addition, a minimum of three time points is recommended to set the specifications, and these time points should cover the early, middle, and late stages of the dissolution profile. Therefore, we recommend dissolution specifications be set at 2 hours, 8 hours and 16 hours. At 8 hours, the average dissolution data in each bio/clinical lot is in the range of [], which exceeds the 25% range. After examining the dissolution profiles of bio/clinical and stability lots, we noticed that dissolution data from Lots N99123 and N99124 are relatively lower compared to all other lots. These two

lots were manufactured from the same beadlet lot. The Chemistry reviewer examined these two lots, and did not notice any manufacture deviation from other clinical lots. However, all other bio/clinical and stability lots have 8-hour dissolution data toward the higher margin, we set the dissolution specification as [] Overall, we recommend dissolution specifications set as [] at 2 hours, [] at 8 hours and [] at 16 hours using Stage 2 dissolution testing. The stability data support this specification.

Conclusion: We recommend dissolution specification be set as [] at 2 hours, [] at 8 hours and [] at 16 hours using Stage 2 dissolution testing.

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6.2 NDA Filing and Review Form

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form				
<u>General Information About the Submission</u>				
	Information		Information	
NDA Number	N21453	Brand Name	Zerit® XR	
OCPB Division (I, II, III)	III	Generic Name	Stavudine XR	
Medical Division	530	Drug Class	NRTI	
OCPB Reviewer	Jenny H. Zheng	Indication(s)	HIV-1 infection	
OCPB Team Leader	Kellie Reynolds	Dosage Form	Extended Release Capsules	
Date of Submission	Dec 10	Dosing Regimen	100 mg QD for patients ≥ 60 kg 75 mg QD for patients < 60 kg	
Estimated Due Date of OCPB Review	September	Route of Administration	Oral	
PDUFA Due Date	Oct 10	Sponsor	Bristol-Myers Squibb	
Division Due Date		Priority Classification	Standard?	
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	1		Study A1455-107
multiple dose:				
Patients-				
single dose:	x	2		Studies A1455-096 + 103
multiple dose:	x	2		Studies A1455-096 + 103
Dose proportionality -				
fasting / non-fasting single dose:	x	1		Study A1455-108
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				

hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	x	1		Study AI455-096
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	x	3		Studies AI455-073 + 070 + 107
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	x	3		Studies AI455-095 + 109 + 114
Dissolution:	x			
(IVIVC):	x	1		Study AI455-107
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		11		

Filability and QBR comments		
	"X" if yes	Comments
Application filable?	x	Reasons if the application <u>is not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?	x	Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-453, HFD-850(P. Lee), HFD-860 (M. Mehta), HFD-530(S. Lynche), HFD-880(K. Reynolds, J. Lazor, A. Selen), CDR

6.3 Proposed labeling

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/s/

Jenny H. Zheng
12/4/02 02:00:38 PM
BIOPHARMACEUTICS

Kellie Reynolds
12/4/02 02:56:19 PM
BIOPHARMACEUTICS