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APPLICATION NUMBER

NDA 21-453

Medical Review(s)

NDA 21-453

Medical Review
NDA 21-453

Date submitted: December 10, 2001
Date Received: December 16, 2001
Date Assigned: March 25, 2002
Date Completed: December 30, 2002

Applicant: Bristol-Myers Squibb Pharmaceuticals
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660

Drug: Generic: stavudine extended release
Trade: Zerit XRTM
Chemical: 2',3'-didehydro-3'-deoxythymidine

Drug class: antiviral agent

Route of administration: oral

Dosage form: 100 mg, 75 mg, 50 mg, and 37.5 mg capsules

Proposed Indication: treatment of HIV infection

Related IND's: 30-486

Related NDA's: 20-412, 20-413

Medical Reviewer: Kendall Marcus, M.D.

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Executive Summary

1 Recommendations

1.1 Recommendations on Approvability

Based on review of the data submitted by Bristol-Myers Squibb in support of NDA 21-453, it is recommended that this application for the extended release formulation of stavudine for the treatment of HIV-1 infection, in combination with other antiretroviral agents, be approved.

Approval of this application will allow patients access to an antiretroviral agent that needs to be taken only once daily and has a minimal pill burden (one pill each day). For selected patients, this may positively impact treatment compliance, and as a result, treatment success. Data submitted in support of this NDA demonstrate that the safety and efficacy of the extended release formulation of stavudine is similar to the immediate release formulation in studies of up to 48 weeks duration.

A newly described adverse event of motor weakness associated with antiretroviral therapy was identified during the conduct of studies to support this NDA, however, this adverse event does not appear to be unique to stavudine. Additionally, it has not been determined whether this adverse event results from a class effect of nucleoside analogue reverse transcriptase inhibitors, or whether it is unrelated to antiretroviral therapy. At this time, no causal link has been identified and it has not been determined whether similar cases have a single etiology.

1.2 Recommendations on Postmarketing Studies

The applicant has agreed to complete the following phase IV commitments:

- Elucidate the complete metabolic fate of stavudine in humans. This was a Phase IV commitment for the original stavudine NDA. Final report due: 4Q 2005.
- Conduct and submit the results of studies or simulations in patients with impaired renal function based on the known pharmacokinetic information of both stavudine immediate and extended release formulations, if Zerit XR[®] is to be used in this population. Final report due: 2Q 2003.
- Assess genotypes and phenotypes of pre-therapy and post-therapy HIV-1 isolates from a large number of patients failing stavudine therapy. Final report due: 4Q 2004.
- Evaluate the cross-resistance of stavudine resistant HIV-1 isolates to all approved NRTIs, and the efficacy of d4T against HIV-1 isolates resistant to all approved NRTIs. Final report due: 4Q 2004.
- Determine the *in vitro* combination activity relationships of stavudine with all approved NRTIs and determine the effect of ribavirin on anti-HIV-1 activity of stavudine *in vitro*. Final report due: 2Q 2003.

2 Summary of Clinical Findings

2.1 Overview of Clinical Program

Proposed Trade name:	Zerit XR™
Generic name:	stavudine extended release formulation (d4T ER)
Formulation:	37.5 mg, 50 mg, 75 mg, and 100 mg capsules
Dosage:	100 mg once daily for patients \geq 60 kg 75 mg once daily for patients $<$ 60 kg
Indication:	Zerit XR, in combination with other antiretroviral agents, is indicated for the treatment of HIV-1 infection.

The submitted application contained a number of small single and multiple-dose pharmacokinetic and safety studies conducted in healthy volunteers and HIV-infected patients, and data derived from two clinical trials conducted in HIV-infected patients. Safety data is available from 613 subjects who received the extended release formulation of stavudine for periods ranging from 1 day to greater than 100 weeks.

Clinical study AI455-096 was a blinded, double-dummy, randomized 1:1 comparison of d4T ER (100 mg QD) and the immediate release formulation of stavudine (d4T IR, 40 mg BID), each in combination with open label lamivudine (3TC) and efavirenz (EFV) in antiretroviral naïve HIV-infected subjects. A total of 150 subjects were treated in this study.

Clinical study AI455-099 was identical in design to study 096, with the exception of two minor differences in enrollment criteria. A total of 783 subjects were treated in this study.

Clinical study AI455-110 was a rollover study in which patients who had successfully completed enrollment in 096 or 099 were allowed to continue on their originally assigned treatment, but in open-label fashion after data lock for the previous study. The primary purpose of this study was to accumulate long term safety data.

2.2 Efficacy Summary

While the AUC and the C_{max} of the extended release formulation are lower than that of the immediate release formulation in pharmacokinetic studies of HIV-infected subjects, the C_{min} is several-fold higher. In order to determine if the difference between the two formulations is clinically relevant, the sponsor conducted the pilot study AI455-096 (096) followed by the larger registrational study AI455-099 (099).

Analyses of the primary efficacy outcome of study 099, the proportion of patients with week 48 HIV RNA below the limit of quantitation (LOQ) of 400 copies/mL, demonstrated similarity of the d4T ER and d4T IR containing regimens. The data were examined in three ways.

The first was Virologic Response – Treated Subjects. The Virologic Response - Treated (VR-T) analysis classified subjects who remained on treatment as responders according to a single HIV RNA measurement < LOQ closest to the scheduled 48 week visit and within a predefined visit window. Subjects who discontinued on or prior to the scheduled visit with no HIV RNA measurement in the visit window were considered failures in this analysis. The denominator was based on all treated subjects.

A second analysis of Virologic Response - Completers (VR-C) was based on observed cases and excluded subjects who discontinued prior to week 48. Response and failure were based solely on HIV RNA < LOQ, and the denominator excluded subjects who discontinued prior to the Week 48 visit. Visit-by-visit analyses of VR-C were defined similarly with the denominator for each visit excluding subjects who discontinued prior to that visit.

The third analysis, Treatment Response Without Prior Failure (TRWPF), included treated subjects in the denominator and utilized the definitions of response and failure from the FDA guidance to define the numerator. For any visit, subjects with the following events before or at the visit were regarded as failures for that visit:

- Death;
- Disease progression (newly diagnosed CDC Class C AIDS event);
- Discontinuation of the treatment;
- Lost to follow-up;
- Have not achieved confirmed < LOQ status or achieved confirmed < LOQ status but rebounded (two consecutive > LOQ c/mL or one > LOQ c/mL if last available visit).

Other subjects were regarded as responders. Therefore, responders were those who had achieved confirmed viral load < LOQ before the visit of interest but had not become a virologic failure yet based on the above criteria.

NOTE: *On March 3, 2002 the Division sent a facsimile to the applicant requesting that efficacy data be evaluated using the Division's new Time to Loss of Virologic Response (TLOVR) algorithm. The applicant provided the Division with a response on May 30, 2002. Please see the statistical review of this NDA for an assessment of the applicants response: the TLOVR analysis also supported the conclusion of similarity of the two formulations of stavudine. Please note that product labeling reflects the TLOVR analysis.*

In study 099, the proportion of responders in the VR-T analysis at 48 weeks was 80 percent of ER subjects and 75 percent of IR subjects. In the VR-C analysis, 91 percent of ER subjects and 89 percent of IR subjects were considered responders. In the TRWPF analysis, 78 percent of ER subjects and 73 percent of IR subjects were considered responders. No statistically significant differences were observed between the ER and IR treatment arms across any of these analyses. In addition, similarity of antiviral activity was maintained for the more stringent endpoint of < LOQ of 50 copies/mL. This data is summarized below.

Proportion HIV RNA <LOQ	Efficacy and Treatment Outcome		XR - IR Difference Estimate (95% CI)
	d4T ER 3TC+EFV N = 392 Week 48 Responders/Evaluable N (%)	d4T IR 3TC+EFV N = 391 Week 48 Responders/Evaluable N (%)	
LOQ = 400 c/mL			
Virologic Response			
VR-T	312/392 (80)	294/391 (75)	4.4 (-1.5, 10.3)
VR-C	312/343 (91)	294/332 (89)	2.3 (-2.2, 6.9)
TRWPF	306/392 (78)	286/391 (73)	4.9 (-1.1, 10.9)
LOQ = 50 c/mL			
Virologic Response			
VR-T	231/392 (59)	223/391 (57)	1.9 (-5.0, 8.8)
VR-C	231/343 (67)	223/332 (67)	0.0 (-7.0, 7.0)
TRWPF	213/392 (54)	217/391 (55)	-1.2 (-8.1, 5.8)

During review of these trials it was discovered that HIV RNA samples were not being handled uniformly at all investigative sites; some specimens were being shipped at room temperature to central labs for processing, some were being shipped frozen, and others were being processed locally. At different study sites, investigators found that significant discrepancies existed in results obtained from paired samples that were being processed both locally and by central labs. Steps were then taken by the applicant to standardize all sample handling to conform to current Roche Amplicor assay specifications, however, this standardization was not completed prior to week 24 of study 099.

Due to the above mentioned problems with sample handling, the applicant was asked to provide sensitivity analyses examining the effect of sample handling on study results. The applicant's response to this request was considered a major amendment to the NDA; as a result of this the review clock was extended by three months.

Multiple analyses examining the effect of sample handling on results were also conducted by the statistical review team to support the conclusion of similarity of the two formulations of stavudine. These analyses are outlined in detail in the statistical review of this NDA. Alternative analyses on the primary endpoint stratified by specimen shipment handling supported similar treatment effects between the d4T ER and the d4T IR regimen.

In summary, data from registrational trial 099 support the hypothesis that the extended release and the immediate release formulations of stavudine have similar antiviral activity.

2.3 Safety Summary

The applicant provided safety data from 392 patients who received an average of 48 weeks of stavudine ER in study 099/110, 74 patients who received an average of 96 weeks of stavudine ER in study 096/110, 23 subjects who received treatment in study 049 for an unspecified period of time, and 124 subjects participating in pharmacokinetic studies who received stavudine ER for 1-9 days. This data was determined to be sufficient to demonstrate that the safety profile of stavudine ER is similar to the profile of stavudine IR. The reported adverse events that could be attributed to stavudine were similar in type and frequency between the two treatment arms and consistent with the known adverse event profile of the drug; specifically, the incidence and severity of peripheral neuropathy, pancreatitis, hepatitis, and symptomatic hyperlactatemia/lactic acidosis syndrome (SHL/LAS) were comparable across treatments.

A newly described clinical syndrome associated with nucleoside analogue therapy became apparent during the conduct of these trials. Motor weakness resembling Guillaine-Barre syndrome was reported in two subjects receiving stavudine ER and one subject receiving stavudine IR in study 099 and in two subjects receiving stavudine IR in Bristol-Myers Squibb sponsored trials unrelated to this NDA. In all cases, the motor weakness appeared to occur in association with lactic acidosis syndrome, although lactic acidosis was not confirmed in every case. Causality of the motor weakness has not been established. Additional cases associated with stavudine use and cases occurring in patients not receiving stavudine were identified through a search of the Adverse Event Reporting System (AERS) database.

As this syndrome appears to occur predominantly in the setting of SHL/LAS, the incidence can be expected to be similar to the incidence of SHL/LAS. Based on retrospective and longitudinal cohort studies recently reported in the literature, the incidence of SHL/LAS in patients receiving stavudine in combination with other antiretroviral agents appears to be increased relative to the incidence with nucleoside analogue combinations not including stavudine. Changes were recently made to the stavudine IR label to include motor weakness as a potential sign associated with SHL/LAS and to reflect the increased incidence of SHL/LAS that has been reported with stavudine use relative to other nucleoside analogues. These changes are also included in the stavudine ER label.

2.4 Dosing, Regimen, and Administration

Zerit XRTM will be indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents. Patients weighing ≥ 60 kg will receive 100 mg once daily as an oral capsule. Patients weighing < 60 kg will receive 75 mg once daily as an oral capsule.

2.5 Drug-Drug Interactions

As the metabolism and elimination pathway of stavudine are not altered by the extended release formulation, drug interactions are not expected to differ substantially from those of the immediate release formulation. Three pharmacokinetic drug interaction studies of the immediate release formulation of stavudine were performed with indinavir, lamivudine and didanosine to determine if any clinically relevant interactions could be identified. These three studies showed no significant alterations in the pharmacokinetic parameters of any of the drugs studied.

It is currently recommended that the immediate release formulation of stavudine not be co-administered with zidovudine due to competitive inhibition of intracellular phosphorylation of both drugs. This concern also exists for the extended release formulation of stavudine, and will be reflected in product labeling.

In vitro data indicate that the phosphorylation of stavudine is inhibited at relevant concentrations by doxorubicin and ribavirin; therefore, product labeling will recommend that coadministration of stavudine with either doxorubicin or ribavirin be undertaken with caution.

No other drug interactions are expected for the extended release formulation of stavudine based on metabolism, elimination and protein binding.

2.6 Special Populations

The current application does not add to the currently available information regarding populations with renal or hepatic impairment, pediatric patients, geriatric patients or for the use of stavudine in pregnancy.

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). Examination of pharmacokinetic data, by gender, from studies that investigated the 100 mg ER formulation revealed no clinically relevant differences between male and female subjects.

Three patterns were observed in the various sub-population analyses of proportion of subjects with HIV RNA below the LOQ (either 400 c/mL or 50 c/mL) for studies 096 and 099 combined;

- 1) Women tended to respond at a higher rate than men. This trend remained after adjustment for weight.
- 2) Black/mixed and "other" racial groups tended to respond at higher rates than whites.
- 3) Subjects from the "Rest of the World (ROW)" and Europe consistently had higher response rates than those from North America. When adjusted for gender and race, region was not a significant predictor of viral suppression.

It is postulated by the applicant that the observed gender and racial differences can be accounted for by differences in compliance, as no significant pharmacokinetic differences were found for gender or race in stavudine IR studies. It may also be due to other factors that are currently unrecognized.

Clinical Review

1 Introduction and Background

1.2 Established and Proposed Trade Name of Drug, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Stavudine, a nucleoside analogue of thymidine, is phosphorylated by cellular kinases to the active metabolite stavudine triphosphate. Stavudine triphosphate inhibits the activity of HIV-1 reverse transcriptase (RT) by competing with the natural substrate thymidine triphosphate ($K_i = 0.0083$ to $0.032 \mu\text{M}$) and by causing DNA chain termination following its incorporation into viral DNA. Stavudine triphosphate inhibits cellular DNA polymerases β and γ and markedly reduces the synthesis of mitochondrial DNA.

This application is for the extended release formulation of stavudine, which has the proposed trade name of Zerit XRTM. The sponsor submitted this application to support the indication for Zerit XRTM for the treatment of HIV-1 infection in combination with other antiretroviral agents. The proposed dose is one 100 mg capsule once daily for patients weighing 60 kg or more and one 75 mg capsule for patients weighing less than 60 kg. The drug should be administered in combination with other antiretroviral agents as part of highly active antiretroviral therapy (HAART).

1.3 State of Armamentarium for Indication

There are currently sixteen drugs approved for the treatment of HIV infection. Despite the advances made in the treatment of HIV disease with the advent of HAART and the marked decrease in mortality due to HIV disease observed in the USA over the past 6 years, treatment success remains limited by acute and chronic toxicities of antiretroviral agents, increasing drug resistance due to high rates of treatment failure, and due to issues related to compliance.

With regard to compliance, it has been found that missing from at least one out of four doses of medication to as few as one out of twenty doses may result in reduced efficacy of a treatment regimen. Compliance in turn can be influenced by side effects, the dosing schedule of a regimen, food restrictions, and the number of pills (pill burden) that a patient must take each day.

Simplifying treatment regimens so that they need to be taken only once a day has been postulated by some physicians caring for HIV infected patients to be a reasonable approach to improve compliance. In addition, it is thought that a once daily regimen will

also facilitate the administration of directly observed therapy (DOT), a treatment strategy that has resulted in improved outcomes and decreased transmission rates for tuberculosis.

One concern, however, is that missing the dose of a once daily medication may put patients at greater risk of developing drug resistance as compared to the risk associated with missing a single dose of a twice daily medication. Subjects on once daily regimens may experience failure rates that are higher than those experienced by subjects receiving regimens that are dosed more frequently. To date, there has been no evidence substantiating that once daily regimens lead to greater compliance than other regimens.

1.4 Important Milestones in Product Development

NDA 20-412 for the immediate release formulation of stavudine was submitted on December 28, 1993 and was approved on June 24, 1994. On August 30, 1999, IND 32,486 was amended to add the extended release formulation for once daily dosing. Because the extended and immediate release formulations were not bioequivalent, the applicant was advised that clinical data would be necessary to ensure that the differences in the AUC, C_{max} and C_{min} would not impact safety or efficacy.

On October 11, 1999, the applicant initiated AI455-096 (096), the pilot clinical study for the ER development program. AI455-096 was a blinded, double-dummy, randomized 1:1 comparison of d4T ER (100 mg QD) and the immediate release formulation of stavudine (d4T IR, 40 mg BID), each in combination with open label lamivudine (3TC) and efavirenz (EFV) in antiretroviral naïve HIV-infected subjects. This study was designed to provide preliminary efficacy data in a small patient population ($N_{\text{treated}} = 150$) and was powered to assess the change from baseline in log₁₀ HIV RNA expressed as the Time-Averaged Difference from baseline through 48 weeks of therapy.

On July 24, 2000, the applicant initiated AI455-099 (099), the pivotal registrational study. Clinical study 099 was identical in design to study 096, with the exception of two minor differences in enrollment criteria. A total of 783 subjects were treated in this study. This study was powered for a primary endpoint of proportion of subjects with HIV RNA < 400 c/mL at 48.

Clinical study AI455-110 was a rollover study in which patients who had successfully completed enrollment in 096 or 099 were allowed to continue on their originally assigned treatment, but in open-label fashion after data lock for the previous study. The primary purpose of this study was to accumulate long term safety data.

The applicant and the Division met on July 20, 2001 to discuss the suitability of the stavudine ER development program to support submission of an NDA. The Division requested that the applicant provide preliminary 24 week data from study 099 for review prior to the submission of the NDA. Following this meeting it was agreed that the NDA could be filed with 24 week data from study 099 and that 48 week data could be submitted as a clinical update no later than halfway through the review clock of the NDA. NDA 21-453 for stavudine ER was submitted on December 10, 2001.

1.5 Important Issues with Pharmacologically Related Agents

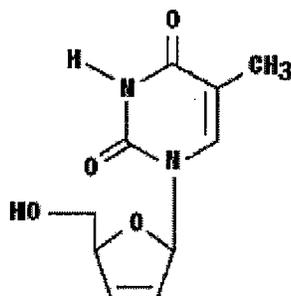
Acute and chronic toxicities associated with NRTI administration include hepatitis, pancreatitis, peripheral neuropathy, symptomatic hyperlactatemia/lactic acidosis syndrome, hyperlipidemia, fat redistribution and impaired glucose tolerance/diabetes. The extended release formulation of stavudine appears to have a similar adverse event profile as the currently marketed NRTIs.

2 Significant Findings from Chemistry, Animal Pharmacology/Toxicology, and Microbiology

2.1 Chemistry

Please see Dr. Ko-yu Lo's review for a detailed review of the chemistry, manufacturing, and controls of Zerit XRTM.

The chemical name for stavudine is 2',3'-didehydro-3'-deoxythymidine. Stavudine has the following structural formula:



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.

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 beads contain stavudine and the following inactive ingredients: distilled acetylated monoglycerides, ethylcellulose aqueous dispersion, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and talc. The capsule shells contain gelatin, iron oxide colorant, silicon dioxide, sodium lauryl sulfate, and titanium dioxide. The capsules are printed with edible inks.

2.2 Pharmacology/Toxicology

Nonclinical pharmacology and toxicology data were summarized in the original NDA submissions for stavudine (NDA 20-412 and NDA 20-413). There are no new nonclinical pharmacology and toxicology data pertinent to this NDA. Please see Dr. Bigger's review for further information.

2.3 Microbiology

No new information regarding the microbiology of stavudine was submitted with this NDA. Please see Dr. Lalji Mishra's review for further information.

3 Human Pharmacokinetics and Pharmacodynamics

3.1 Pharmacokinetics

Please see Dr. Jenny Zheng's review for a detailed review of the pharmacokinetics and pharmacodynamics of Zerit XRTM.

When compared to the stavudine immediate release formulation (stavudine IR - marketed formulation), the ER capsule formulation releases the drug more slowly and throughout the GI tract, resulting in the slow and prolonged absorption of the drug and generation of an extended release plasma concentration time profile.

Food interaction studies were performed in healthy volunteers to determine if any clinically relevant food interactions occur with administration of the extended release formulation. No clinically relevant differences were identified when stavudine ER was administered in the fasted state, with a high fat or light meal, or with yogurt or applesauce; as a result, it will be recommended that stavudine ER 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 (about 2 tablespoons) of yogurt or applesauce. Patients should be cautioned not to crush the beads while chewing or swallowing.

In pharmacokinetic studies of stavudine ER in HIV-infected patients, the following has been observed:

- No significant accumulation of stavudine occurs after repeated administration of the ER capsule every 24 hours.
- The mean C_{max} value for the ER formulation (100 mg once daily) is 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 is about 30% 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 several fold higher C_{min} compared to IR formulation.

- There is 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 is approximately 14%-49% lower when compared to healthy subjects.

The applicant proposed dosing regimens for patients with impaired renal function based on data extrapolated from the immediate release formulation; however, the extrapolation may not be appropriate and will not be included in product labeling.

3.2 Pharmacodynamics

Based on comparable efficacy and safety profiles between the evaluated regimens containing the IR formulation (40 mg BID for patients with body weight (BW) \geq 60 kg and 30 mg BID for patients with BW < 60 kg) and the evaluated regimens containing the ER formulation (100 mg QD for patients with BW \geq 60 kg and 75 mg QD for patients with BW < 60 kg), and the pharmacokinetic characteristics of stavudine ER formulation, the following dosing regimens are recommended for patients with normal renal function:

- 100 mg once daily for patients \geq 60 kg
- 75 mg once daily for patients < 60 kg

4 Description of Clinical Data and Sources

4.1 Sources of Clinical Data

This NDA contains data from 4 clinical trials conducted with the extended release formulation of stavudine. Of these trials, study AI455-099 was the pivotal study for this application.

AI455-096, the pilot study for the ER development program, was designed to provide preliminary efficacy data in a small patient population ($N_{\text{treated}} = 150$) and was powered to assess the change from baseline in log₁₀ HIV RNA expressed as the Time-Averaged Difference (TAD) from baseline through 48 weeks of therapy. Secondary outcome measures included proportion of subjects with HIV RNA below the limit of quantitation (LOQ) (using cutoffs of LOQ = 400 c/mL and LOQ = 50 c/mL), and changes in CD4 cell count.

AI455-099 is the pivotal registrational study and was powered for a primary endpoint of proportion of subjects with HIV RNA < 400 c/mL at 48 weeks ($N_{\text{treated}} = 783$). Secondary outcome measures included proportion of subjects with HIV RNA < 50 c/mL, the change from baseline in log₁₀ HIV RNA expressed as the TAD through 48 weeks of therapy, and changes in CD4 cell count.

Safety data from two supportive studies was also submitted. Study AI455-110 is an open-label rollover protocol for subjects from studies 096 and 099; subjects were allowed to

continue on their originally assigned treatment in open-label fashion following data base lock for the previous study. Study AI424-049 is an open-label once daily HAART regimen for subjects with good virologic control on their prior HAART regimen.

4.3 Postmarketing Experience

Zerit XRTM has been marketed in Europe for two months. There is currently no information available regarding postmarketing experience with Zerit XRTM.

4.4 Literature Review

Zerit XRTM has been marketed in Europe for the past two months; therefore, no literature review was conducted for assessment of safety and efficacy.

5 Clinical Review Methods

5.1 Overview of Materials Consulted in Review

This NDA was received in electronic format on December 11, 2001. A clinical update was received in electronic format on May 30, 2002. The following modules/items were included in this NDA and were reviewed for the clinical section of this review: Labeling, Investigators and Study Sites, Clinical Overview, Clinical Summary, Clinical Study Reports 096, 099, 110 and 049, Case Report Tabulations, and Case Report Forms.

The following items from the update received on May 30, 2002 were reviewed: Proposed Labeling, Integrated Safety Summary, Clinical Study Reports for 099, 110 and 049, Pediatric Development Plan, Assessment of Genotypic and Phenotypic Profiles, Analysis of Subjects with Diarrhea, Case Report Forms, and Case Report Tabulations.

In addition, submissions received on the following dates were also reviewed:

July 11, 2002 (4)	October 22, 2002
August 13, 2002	October 25, 2002
August 16, 2002	November 25, 2002
September 23, 2002	December 4, 2002
September 24, 2002	December 6, 2002
	December 12, 2002

5.2 Were Trials Conducted in Accordance with Accepted Ethical Standards

All study protocols were written to conform to accepted ethical standards and were reviewed and approved by Institutional Review Boards overseeing each investigative site prior to enrollment of subjects.

5.3 Evaluation of Financial Disclosure

The applicant requested that all investigators and subinvestigators from studies 070, 073, 095, 096, 099, 103, 107, 108, 109, 110, and 114 disclose proprietary interest or significant equity as defined in the regulations.

One investigator and four subinvestigators failed to complete the financial disclosure form. The investigator for site [] that enrolled - subjects failed to submit financial disclosure information; as of Dec 4, 2001 and despite multiple requests he had not submitted this information. One subinvestigator for site [] failed to complete the financial disclosure information for study [] but had provided the appropriate documentation for study [] stating that he had no disclosable interests. Two subinvestigators who failed to provide information were removed from the 1572 forms prior to the sites randomizing any subjects.

Three investigators had disclosable financial information. Dr. [] reported holdings of BMS common stock worth about \$50,000; he is the principal investigator at site [] that enrolled - subjects. - subjects are now participating in the - study. Dr. [] is the principal investigator at site [] He is also a sub-investigator at site [] He reported receipt of honoraria from BMS several times over the past 2 years for giving presentations sponsored by BMS. As an investigator, [] enrolled - subjects, - of whom are now participating in the - study. Dr. [] was also a subinvestigator at a site that enrolled - subjects, all of whom are now participating in the - study. And finally, Dr. [] disclosed holdings of BMS common stock worth more than \$50,000. Dr. [] was a sub-investigator for site [] He was not responsible for recruiting subjects or adverse event evaluations.

In summary, due to the small numbers of subjects enrolled by investigators with financial interests in BMS, it was determined that participation by these investigators in pharmacokinetic and clinical studies of stavudine ER would not impact safety or efficacy findings of any of these studies.

6 Integrated Review of Efficacy

6.1 Brief Statement of Conclusions

While the AUC and the C_{max} of the extended release formulation are lower than that of the immediate release formulation in pharmacokinetic studies of HIV-infected subjects, the C_{min} is about five-fold higher. In order to determine if the difference between the two formulations is clinically relevant, the sponsor conducted pilot study AI455-096 (096) followed by the larger registrational study AI455-099 (099). These trials demonstrated that Zerit XRTM has antiviral activity that is similar to the currently marketed immediate release formulation over 48 weeks of dosing.

During review of these trials it was discovered that HIV RNA samples were not being handled uniformly at all investigative sites; some specimens were being shipped at room temperature to central labs for processing, some were being shipped frozen, and others were being processed locally. At different study sites, investigators found that significant discrepancies existed in results obtained from paired samples that were being processed both locally and by central labs. Steps were then taken by the applicant to standardize all sample handling to conform to current Roche Amplicor assay specifications; however, this standardization was not completed prior to week 24 of study 099.

Due to the above mentioned problems with sample handling, multiple analyses examining the effect of sample handling on results were conducted by the statistical review team to support/validate the conclusion of similarity of the two formulations of stavudine. These analyses are outlined in detail in the statistical review of this NDA.

6.2 Detailed Review of Trials by Indication

6.2.1 Clinical Trial AI455-096

“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”

6.2.1.1 Study Design and Subject Population

This study was a pilot blinded, double-dummy, randomized 1:1 comparison of d4T ER (100 mg QD) and d4T IR (40 mg BID), each in combination with open label lamivudine (3TC) and efavirenz (EFV) in antiretroviral naïve HIV-infected subjects. Subjects with plasma HIV RNA $\geq 5,000$ c/mL and CD4 cell counts ≥ 100 cells/mm (≥ 75 cells/mm if no prior AIDS-defining event) were enrolled in the trial. Randomization was stratified by HIV RNA ($< 30,000$ copies/mL; $\geq 30,000$ copies/mL).

6.2.1.2 Endpoints

The primary protocol-defined endpoint for response was the comparison between groups of the change in viral load (plasma HIV RNA) expressed as the Time-Averaged Difference (TAD) (\log_{10}) from baseline through 48 weeks of therapy. Secondary endpoints included the proportion of subjects with HIV RNA < 400 copies/mL at 48 weeks, < 50 copies/mL at 48 weeks, and changes in CD4 cell counts over 48 weeks.

6.2.1.3 Analysis Plan

This study was powered (90%) to demonstrate similarity of antiviral activity within 0.5 \log_{10} between the d4T ER and d4T IR regimens for the primary endpoint of magnitude in reduction of HIV RNA from baseline, using TAD. All efficacy analyses were based on treated subjects. The TAD between d4T ER and d4T IR (TAD [ER-IR]) in change from baseline \log_{10} plasma HIV RNA over 48 weeks of therapy, stratified by the HIV RNA level obtained prior to randomization ($< 30,000$ c/mL, $\geq 30,000$ c/mL), were computed along with a 95% confidence interval. Three secondary analyses provided an estimate of, and 95% confidence interval for, the differences between the two treatment regimens in the proportion of subjects with HIV RNA < 400 c/mL and < 50 c/mL at week 48 using

three methods for defining response and evaluability. The proportions were computed within HIV RNA strata and combined using a weighted average with weights proportional to the size of the strata.

6.2.1.4 Study Population and Patient Disposition

A total of 155 subjects were randomized; 150 subjects received treatment. Five randomized subjects never started therapy, one in the d4T ER treatment regimen and four in the d4T IR treatment regimen.

Subject demographics were similar for all groups and are summarized in the following table. Subjects were predominantly male (75%) and Caucasian (70%), with a median age of 35 years. Seventy-one percent of subjects were enrolled at North American sites and the remainder were enrolled from South American sites.

Characteristic	Baseline Characteristics	
	Treatment Regimen	
	d4T ER 3TC/EFV N = 74	d4T IR 3TC/EFV N = 76
Age (years):		
Mean (SE)	34.6 (1.1)	35.9 (1.0)
Median	33.5	34
Range	20 - 69	22 - 67.0
Gender: N (%)		
Male	54 (73)	58 (76)
Female	20 (27)	18 (24)
Race: N (%)		
White	55 (74)	50 (66)
Black ^a	14 (19)	14 (18)
Hispanic/Latino	5 (7)	10 (13)
American/Alaskan Native	--	1 (1)
Asian/Pacific Islander	--	1 (1)
Region: N (%)		
North America	50 (68)	56 (74)
South America	24 (32)	20 (26)
IV Drug Use: N (%)	11 (15)	8 (11)
AIDS: N (%)	4 (5)	4 (5)
Weight (kg):		
Mean (SE) ^b	70.8 (2.0)	71 (1.8)
Median	68.0	69.2
Range	35.0 - 113.9	37.0 - 118.8

Baseline viral loads were similar between groups, however, the mean and median CD4 cell counts were significantly lower in the IR than in the ER group. In addition, more subjects in the IR than in the ER group had viral loads > 30,000 copies/mL (54% vs. 47%).

Baseline HIV RNA Level and CD4 Cell Count
Number of Subjects (%)
Treatment Regimen

	d4T ER 3TC/EFV N = 74	d4T IR 3TC/EFV N = 76
HIV RNA Level (log₁₀ c/mL):		
Mean (SE)	4.63 (0.09)	4.70 (0.07)
Median	4.69	4.63
Range	2.3 - 5.9	2.9 - 5.9
HIV RNA Level Distribution^a: N (%)		
< 30,000	28 (38)	24 (32)
≥ 30,000	46 (62)	52 (68)
Mean (SE)	359 (23.0)	314 (22.2)
Median	354	260
Range	75 - 953	63 - 962
< 200	18 (24)	25 (33)
200 - < 350	18 (24)	27 (36)
350 - < 500	22 (30)	14 (18)
≥ 500	16 (22)	10 (13)

Of those treated, twenty-one subjects (14%) discontinued prior to Week 48, 7 in the d4T ER regimen and 14 in the d4T IR regimen. Five treated subjects (3%) discontinued after Week 48 (2 in the d4T ER regimen and 3 in the d4T IR regimen). More subjects in the d4T IR treatment group discontinued due to adverse events and noncompliance/lost to follow-up than in the d4T ER treatment group.

Patient Disposition

	Number of Subjects (%)	
	d4T ER 3TC/EFV N = 75	d4T IR 3TC/EFV N = 80
Randomized	75 (100)	80 (100)
Never treated	1 (1)	4 (5)
Treated	74 (99)	76 (95)
Premature discontinuation prior to Week 48	7 (9)	14(18)
Disease progression	2 (3)	2 (3)
Subject withdrew	2 (3)	1 (1)
Adverse event	1 (1)	5 (6)
Non-compliance	1 (1)	4 (5)
Lost to follow-up	1 (1)	2 (3)
Discontinued after Week 48	67 (89)	62 (78)
Adverse event	1 (1)	2 (3)
Pregnancy	1 (1)	1 (1)
Completed treatment	65 (87)	59 (74)

6.2.1.5 Protocol Violations

Four randomized subjects had a violation of protocol eligibility requirements. All were assigned to the IR treatment group; one never received study drug. There were two subjects with CD4 cell counts < 100 cells/mm³ (but both had > 75 cells/mm³) and a previous AIDS-defining event (one disseminated histoplasmosis and one *Pneumocystis carinii* pneumonia. These enrollment violations occurred without the knowledge of the BMS medical monitor; once recognized, it was agreed to permit both subjects to continue on study. One subject was taking anti-tuberculosis medications including rifampin at the time of randomization. Rifampin was contraindicated by the study protocol. However, at the time that BMS personnel became aware of this violation, updated recommendations suggesting that it is reasonable to co-administer rifampin and efavirenz had been published by the Centers for Disease Control. This subject was permitted to continue on the study.

A total of 31 subjects had protocol deviations, and these were evenly distributed between the treatment groups (15 ER; 16 IR). Four protocol deviations occurred in four subjects (3 d4T ER; 1 d4T IR) who received study treatment different from what was assigned. One of these subjects was transiently incarcerated during the course of the study and received open-label, marketed d4T during this period. The other three drug assignment errors were made by on-site personnel in the selection of drug supplies. These three assignment errors generated incorrect dosing (IR instead of ER) for periods of 28, 39 and 86 days. Relative to the total dosing periods of these subjects (443, 464, 358 days respectively), these errors are believed by the applicant to have minimal clinical significance.

Two subjects received doses not appropriate for weight. Both subjects (one each in ER and IR) were > 60 kg and received the < 60 kg dose. In addition, one site ran out of study supply and dispensed commercial IR supplies of d4T to seven subjects (4 ER; 3 IR) for a median period of 9 days (range 3 - 18). Other deviations included seven subjects with > 14 days between screening and randomization (all < 28 days) and 14 subjects with > 3 days between randomization and first dose (11 < 7 days; 3 < 21 days). None of these deviations were judged by the applicant to have affected the validity of the study.

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Protocol Deviations - Randomized Subjects		
Number of Subjects (%)		
Type of Deviation	Treatment Regimen	
	d4T ER 3TC/EFV N = 75	d4T IR 3TC/EFV N = 80
Subjects with at least one deviation.	15 (20)	16 (20)
Treatment received different from assigned.	3 (4)	1 (1)
Treatment dose not appropriate for weight.	1 (1)	1 (1)
Subject took commercial supply.	4 (5)	3 (4)
Number of days between screening and randomization > 14.	4 (5)	3 (4)
Number of days between randomization and start of therapy > 3.	4 (5)	10 (13)

6.2.1.6 Efficacy Endpoint Outcomes

The primary efficacy measure was the magnitude of viral suppression measured as the change in plasma HIV RNA from baseline through week 48 expressed in log₁₀. By week 12, both groups had achieved median decreases greater than 2.4 log₁₀. This reduction in viral load was sustained through week 48 in both treatment groups, with a median decrease of 2.9 log₁₀ in the ER group and 2.7 log₁₀ in the IR group. The overall magnitude and pattern of response was similar between the two treatment groups at all time points.

Time-Averaged Difference in HIV RNA Change from Baseline Through Week 48

Change from Baseline HIV RNA Level (log₁₀ c/mL)

d4T ER - d4T IR

Time-Averaged Difference Through Week 48

Estimate	Estimate 95% CI
Overall	-0.01 (-0.21, 0.18)
Last obs carried forward	-0.07 (-0.26, 0.13)

The similarity of the d4T ER regimen relative to the d4T IR regimen is further supported by the three analyses of the proportion of subjects with HIV RNA < 400 copies/mL at week 48. Response rates at week 48 ranged from 66% to 88% depending on the analysis. The difference of the means of the two treatment arms had a lower 95% CI bound (%) above -12%, which meets the pre-specified non-inferiority level for all three analyses

and supports the conclusion of similarity of the two regimens. Efficacy results are summarized below.

Analysis	Proportions in Response at Week 48 (LOQ = 400 c/mL)		
	Treatment Regimen		Difference Estimate (95% CI)
	d4T ER 3TC/EFV Responders/Evaluable (%)	d4T IR 3TC/EFV Responders/Evaluable (%)	
Virologic Response			
-Treated (VR-T)	58/74 (78)	51/76 (67)	11.3 (-3.0, 25.6)
-Completers (VR-C)	58/66 (88)	51/62 (82)	5.6 (-6.7, 17.9)
Treatment Response Without Prior Failure (TRWPF)	52/74 (70)	50/76 (66)	3.8 (-11.0, 18.7)

The following table of Treatment Outcomes at week 48 for LOQ = 400 c/mL is based on the TRWPF analysis and provides a classification of reasons for failure. The higher response rate in the ER regimen is related to the lower discontinuation rate for adverse events and other reasons. The slightly higher rates of virologic failure in the ER group reflects a higher number of subjects with viral rebound (10 subjects for ER; 5 for IR).

Treatment Outcomes (TRWPF) at Week 48 (LOQ = 400 c/mL)

	Number of Subjects (%)	
	Treatment Regimen	
	d4T ER 3TC/EFV N = 74	d4T IR 3TC/EFV N = 76
Responder	52 (70)	50 (66)
Virologic Failure	14 (19)	11 (14)
Disease Progression	3 (4)	3 (4)
Discontinued Due to Adverse Events	1 (1)	5 (7)
Discontinued Due to Other Reasons	4 (5)	7 (9)

The following are tables of proportions in response and treatment outcomes (TRWPF) at week 48 for LOQ ≤ 50 c/mL. The higher response rate in the ER regimen for treated subjects is related to the lower discontinuation rate for adverse events and other reasons. Again, there is a higher rate of virologic failure in the ER group, but in this analysis the difference between groups is accounted for by a higher number of subjects who fail to

achieve a confirmed response in the ER group versus the IR group (26 [35%] for ER versus 21 [28%] for IR).

Treatment Outcomes (TRWPF) at Week 48 (LOQ = 50 c/mL)
Number of Subjects (%)

	Treatment Regimen	
	d4T ER 3TC/EFV N = 74	d4T IR 3TC/EFV N = 76
Responder	30 (41)	29 (38)
Virologic Failure	39 (53)	33 (43)
Disease Progression	2 (3)	3 (4)
Discontinued Due to Adverse Events	1 (1)	5 (7)
Discontinued Due to Other Reasons	2 (3)	6 (8)

Both the d4T ER and d4T IR treatment regimens were associated with a substantial increase in CD4 cell counts over 48 weeks: the mean increase was 232 c/mm³ for ER and 195 c/mm³ for IR. The two regimens were comparable with respect to the magnitude and rate of the CD4 cell count increase. The Time-Averaged Difference TAD estimate (ER - IR) for changes in CD4 cell counts through Week 48 was 29.8 (95% CI 0.7, 59.0) favoring the d4T ER treatment group. These results should be interpreted in the context of the higher baseline CD4 cell count in the ER group.

Time-Averaged Difference in CD4 Cell Counts Change from Baseline Through Week 48

Change from Baseline CD4 Cell Count (cells/mL)
d4T ER/3TC/EFV - d4T IR/3TC/EFV

	Time-Averaged Difference Through Week 48
Estimate	Estimate (95% CI)
Overall	29.8 (0.7, 59.0)
Last observation carried forward	33.0 (4.0, 62.0)

6.2.2 Clinical Trial AI 455-099

"The Safety and Antiviral Efficacy of Stavudine Extended Release Formulation as Compared to Stavudine Immediate Release Formulation, Each as Part of Potent Antiretroviral Combination Therapy"

6.2.2.1 Study Design and Patient Population

This registrational study is a double-blind, double-dummy, randomized 1:1 comparison of d4T ER and d4T IR in combination with lamivudine (3TC) and efavirenz (EFV) in antiretroviral naïve HIV-infected subjects. Eligible subjects were ARV therapy naïve patients with plasma HIV RNA > 2,000 c/mL and CD4 count > 100 cells/mm³ (> 75 cells/mm³ if no prior AIDS-defining event). Randomization was stratified by screening HIV viral load of < 30,000 c/mL or ≥ 30,000 c/mL.

6.2.2.2 Endpoints

The primary protocol-defined endpoint for response was the comparison between groups of the proportion of subjects with HIV RNA < 400 c/mL at 24 weeks of therapy, with a confirmatory analysis at week 48. Secondary endpoints included the proportion of subjects with HIV RNA < 50 c/mL at weeks 24 and 48.

6.2.2.3 Analysis Plan

The study was designed with a target sample size of 730 treated subjects equally allocated between d4T ER and d4T IR (365 per group) to provide at least 90% power to demonstrate that the antiviral activity of d4T ER was similar to d4T IR, each in combination with 3TC/EFV.

The data were examined in three ways. The first was Virologic Response – Treated subjects. Virologic Response - Treated subjects (VR-T) classified subjects who remained on treatment as responders according to a single HIV RNA measurement < LOQ (400 c/mL for primary efficacy analysis and 50 c/mL for the secondary analysis) closest to the scheduled visit and within a predefined visit window. The denominator was based on all treated subjects. Subjects with HIV RNA < LOQ and those who discontinued on or prior to the scheduled visit with no HIV RNA measurement in the visit window were considered failures in this analysis. The comparisons of treatment regimens was based on the week 48 visit. Subjects who remained on treatment and were missing their week 48 measurement were classified as responders only if their previous and subsequent measurements were < LOQ. Visit-by-visit analyses of VR-T were defined similarly.

A second analysis of Virologic - Completers (VR-C) was based on observed cases and excluded subjects who discontinued prior to week 48. LOQ was 400 c/mL for the primary analysis and 50 c/mL for the secondary analysis. Response and failure were based solely on HIV RNA < LOQ or = LOQ, and the denominator excluded subjects who discontinued prior to the week 48 visit. Visit-by-visit analyses of VR-C were defined similarly with the denominator for each visit excluding subjects who discontinued prior to that visit.

The analysis for Treatment Response Without Prior Failure (TRWPF) included treated subjects in the denominator, and utilized the definitions of response and failure from the FDA guidance to define the numerator:

For any visit, subjects with the following events before or at the visit were regarded as failures for that visit:

- Death;
- Disease progression (newly diagnosed CDC Class C AIDS event);
- Discontinuation of the treatment;
- Lost to follow-up;
- Have not achieved confirmed < LOQ (400 c/mL for primary analysis and 50 c/mL for secondary analysis) status or achieved confirmed < LOQ status but rebounded (two consecutive > LOQ c/mL or one > LOQ c/mL if last available visit).

Other subjects were regarded as responders. Therefore, responders were those who had achieved confirmed viral load < LOQ before the visit of interest but had not experienced virologic failure yet.

NOTE: *On March 3, 2002 the Division sent a facsimile to the applicant requesting that efficacy data be evaluated using the Division's new Time to Loss of Virologic Response (TLOVR) algorithm. The applicant provided the Division with a response on May 30, 2002. Please see the statistical review of this NDA for an assessment of the applicants response.*

The TLOVR analysis included treated subjects in the denominator and utilized definitions of response and failure from the FDA's new guidance. For each visit, a subject with the following events prior to or at that visit will be considered as a non-responder or failure for that visit if any of the follow occur:

- Never treated
- Death
- Permanent discontinuation of the study
- Introducing a new drug to the regimen
- Loss to follow-up
- Have not achieved confirmed <LOQ status or achieved confirmed <LOQ status but rebounded (i.e., two consecutive \geq LOQ copies/mL or one \geq LOQ copies/mL for the last available visit).

From the above definitions for a non-responder or failure, a subject who is not a non-responder or failure will be regarded as a responder. In other words, responders are those who had achieved viral load < LOQ that is confirmed later, prior to, or at the visit of interest, but had not yet lost the virologic response defined by the TLOVR algorithm.

6.2.2.4 Study Population and Patient Disposition

The study enrolled 1030 and randomized 797 subjects; 783 subjects received treatment. Fourteen randomized subjects never started therapy, 7 in the d4T ER regimen and 7 in the d4T IR regimen. Of those treated, 108 subjects (14%) discontinued prior to week 48, 49 (12%) on the d4T ER regimen and 59 (15%) on the d4T IR regimen. Similar numbers of subjects in the d4T ER treatment group discontinued due to adverse events and noncompliance/lost to follow-up as in the d4T IR treatment group.

	Subject Disposition (Randomization to Completion of Study)	
	Number of Subjects (%)	
	Treatment Regimen	
	d4T ER 3TC/EFV N = 399	d4T IR 3TC/EFV N = 398
Randomized	399 (100)	398 (100)
Never treated	7 (2)	7 (2)
Treated	392 (98)	391 (98)
Discontinued on or before Week 48 assessment	49 (12)	59 (15)
Adverse event	15 (4)	16 (4)
Lost to follow-up	11 (3)	19 (5)
Subject withdrew	6 (2)	9 (2)
Pregnancy	5 (1)	8 (2)
Protocol violation while on study	4 (1)	3 (< 1)
Death	3 (< 1)	2 (< 1)

The study population was predominantly male (69%), with a median age of 33 years. Non-white racial groups comprised 57% of the population. The majority of subjects (34%) were from North America, 23% from Europe, 20% from South America, 15% from Africa, and 9% from Asia. In general, there was equal distribution of populations between treatment regimens. The baseline characteristics of study subjects between treatment arms are summarized below:

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Characteristic	Baseline Characteristics	
	Number of Subjects Treatment Regimen	
	d4T ER 3TC/EFV N = 392	d4T IR 3TC/EFV N = 391
Age (years):		
Mean (SE)	34.4 (0.4)	34.2 (0.5)
Median	33	33
Range	18 - 69	18 - 68
Gender: N (%)		
Male	267 (68)	273 (70)
Female	125 (32)	118 (30)
Race: N (%)		
White	168 (43)	163 (42)
Black ^a	99 (25)	91 (23)
Hispanic/Latino	86 (22)	98 (25)
American/Alaskan Native	2 (1)	-
Asian/Pacific Islander	36 (9)	38 (10)
Hispanic/Native American	1 (< 1)	--
Canadian Native	--	1 (< 1)
Region: N (%)		
North America	135 (34)	133 (34)
Europe	87 (22)	90 (23)
South America	80 (20)	75 (19)
Africa	57 (15)	58 (15)
Asia	33 (8)	35 (9)

Subjects in this trial generally had only modest immune-compromise based on CD4 cell counts, with almost no difference between treatment groups for HIV RNA levels. The baseline mean CD4 cell count was higher in the d4T IR treatment group, however, the median count was higher in the d4T ER treatment group (median 285 and mean 313 cells/mm³ for d4T ER; versus median 272 and mean 324 cells/mm³ for d4T IR), but this difference was not significant.

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	Baseline HIV RNA Level and CD4 Cell Count	
	Number of Subjects	
	Treatment Regimen	
	d4T ER 3TC/EFV	d4T IR 3TC/EFV
	N = 392	N = 391
HIV RNA Level (log₁₀ c/mL):		
Mean (SE)	4.79 (0.03)	4.75 (0.03)
Median	4.80	4.80
Range	2.8 - 6.8	2.6 - 6.4
HIV RNA Level Distribution: N (%)		
< 30,000	114 (29)	113 (29)
≥ 30,000	278 (71)	278 (71)
CD4 Cell Count (cells/mm³):		
Mean (SE)	313 (9)	324 (10)
Median	285	272
Range	62 - 1044	61 - 1215
CD4 Cell Count Distribution: N (%)		
< 200	105 (27)	116 (30)
200 - < 350	143 (36)	134 (34)
350 - < 500	93 (24)	70 (18)
≥ 500	51 (13)	70 (18)
Missing	--	(< 1)

6.2.2.5 Protocol Violations

After randomization, one hundred and three subjects had at least one protocol deviation. Only 14 of these deviations were considered potentially important by the applicant. Thirteen of these deviations consisted of subjects (7 ER; 6 IR) who received study treatment different from that assigned by the central drug assignment phone system. These were site-dispensing errors. The longest duration of dosing with drug that was different from that assigned was 85 days. In addition, one ER subject enrolled in a concurrent antiretroviral treatment trial at Week 44. The other trial provided interleukin 2 therapy (IL2); the subject had completed study 099 and had enrolled in study 110 when BMS became aware of this deviation. She was discontinued from study 110 at BMS request. Neither her Week 48 CD4 or HIV RNA values differed significantly from her pre-IL-2 week 40 values (HIV RNA < 50 c/mL at both times; CD4 325 and 357 cells/mm³ at weeks 40 and 48 respectively). All of the protocol deviations are summarized below.

Protocol Deviations - Randomized Subjects
Number of Subjects (%)
Treatment Regimen

Type of Deviation	Treatment Regimen	
	d4T ER 3TC/EFV N = 399	d4T IR 3TC/EFV N = 398
All subjects with at least one deviation	50 (13)	53 (14)
Number of days between randomization and start of therapy > 3	23 (6)	21 (5)
Treatment received different from assigned	7 (2)	6 (2)
Number of days between screening and randomization > 21	10 (3)	12 (3)
Treatment dose not appropriate for weight	6 (2)	9 (2)
Co-administration of contraindicated medications	4 (1)	4 (1)
Subject took commercial supply	--	1 (<1%)

6.2.2.6 Efficacy Endpoint Outcomes

The similarity of the d4T ER regimen relative to the d4T IR regimen was supported by the three analyses of the proportion of subjects with HIV RNA < 400 c/mL at week 48. Response rates ranged from 78% to 91% for ER and 73% to 89% for IR depending on the analysis. For each of the three analyses the difference of the means of the two treatment arms had a lower 95% CI bound (%) above -12% which meets the pre-specified non-inferiority level. This supports the conclusion of similarity of the two regimens.

Proportion HIV RNA < LOQ	Efficacy and Treatment Outcome		Difference Est. (95% CI)
	d4T ER 3TC+EFV N = 392	d4T IR 3TC+EFV N = 391	
Week 48 Responders/Evaluable N (%)			
LOQ = 400 c/mL			
Virologic Response			
VR-T	312/392 (80)	294/391 (75)	4.4 (-1.5, 10.3)
VR-C	312/343 (91)	294/332 (89)	2.3 (-2.2, 6.9)
TRWPF	306/392 (78)	286/391 (73)	4.9 (-1.1, 10.9)

The following table of treatment outcomes at week 48 is based on the TRWPF analysis and provides a classification of reasons for failure. There were no notable differences between the treatment groups with reference to reason for failure. Virologic failure (10% ER, 11% IR) and discontinuation for reasons other than an AE (7% ER, 10% IR) were the most frequent reasons for failure in both treatment groups

	Treatment Outcomes (TRWPF) at Week 48	
	(LOQ = 400 c/mL)	
	Number of Subjects (%)	
	Treatment Regimen	
	d4T ER/3TC/EFV	d4T IR/3TC/EFV
	N = 392	N = 391
Responder	306 (78)	286 (73)
Virologic failure	38 (10)	43 (11)
Rebound	20 (5)	25 (6)
No Response	18 (5)	18 (5)
Death or disease progression	7 (2)	5 (1)
Discontinued due to adverse events	14 (4)	17 (4)
Discontinued due to other reasons	27 (7)	40 (10)

NOTE: On March 3, 2002 the Division sent a facsimile to the applicant requesting that efficacy data be evaluated using the Division's new Time to Loss of Virologic Response (TLOVR) algorithm. The applicant provided the Division with a response on May 30, 2002. Please see the statistical review of this NDA for an assessment of the applicants response: the TLOVR analysis supported the conclusion of similarity of the two formulations of stavudine. Please note that product labeling reflects the TLOVR analysis.

The similarity of the d4T ER regimen relative to the d4T IR regimen is further supported by three efficacy analyses of the secondary endpoint of proportions of subjects with HIV RNA < 50 c/mL at week 48. Response rates ranged from 54% to 67% depending on the analysis. For each of the three analyses, the lower confidence limit of the difference estimate is less than the pre-specified boundary of -12%, supporting the conclusion that the two regimens are similar in efficacy.

Results at Week 48 (LOQ = 50 c/mL)			
Responders/Evaluable (%)			
Analysis (LOQ = 50 c/mL)	Treatment Regimen		Difference Estimate (95% CI)
	d4T ER 3TC/EFV	d4T IR 3TC/EFV	
Virologic Response			
Treated subjects (VR-T)	231/392 (59)	223/391 (57)	1.9 (-5.0, 8.8)
Completers (VR-C)	231/343 (67)	223/332 (67)	0.0 (-7.0, 7.0)
Treatment Response Without Prior Failure (TRWPF)	213/392 (54)	217/391 (55)	-1.2 (-8.1, 5.8)

The following table of treatment outcomes at week 48 for LOQ < 50 copies/ml is based on the TRWPF analysis and provides a classification of failure reasons. In this analysis, there is a comparable rate of virologic failure in the ER and IR treatment groups.

Treatment Outcomes (TRWPF) at Week 48 (LOQ = 50 c/mL)			
Number of Subjects (%)			
	Treatment Regimen		
	d4T ER 3TC/EFV N = 392	d4T IR 3TC/EFV N = 391	
Responder	213 (54)	217 (55)	
Virologic failure	134 (34)	123 (31)	
Rebound	39 (10)	37 (9)	
No Response	95 (24)	86 (22)	
Discontinued due to adverse events	13 (3)	14 (4)	
Discontinued due to other reasons	25 (6)	34 (9)	

Both treatment regimens were associated with a substantial increase in CD4 cell counts over 48 weeks: the mean increase was 202 c/mm³ for d4T ER and 182 c/mm³ for d4T IR. The two regimens were comparable with respect to the magnitude and rate of the CD4 cell count increase. The TAD estimate (ER - IR) for changes in CD4 cell counts through Week 48 was 7.2 (95% CI -7.8, 22.2).

6.2.2.7 Efficacy Endpoint Outcomes by Specimen Handling

During the review of studies 096 and 099 it was discovered that HIV RNA samples were not being handled uniformly at all investigative sites; some specimens were being shipped at room temperature to central labs for processing, some were being shipped frozen, and others were being processed locally. At different study sites, investigators found that significant discrepancies existed in results obtained from paired samples that were being processed both locally and by central labs. Steps were then taken by the applicant to standardize all sample handling to conform to current Roche Amplicor assay

specifications, however, this standardization was not completed prior to week 24 of study 099.

Due to the above mentioned problems with sample handling, the applicant was asked to provide sensitivity analyses examining the effect of sample handling on study results. The applicant's response to this request was considered a major amendment to the NDA; as a result of this the review clock was extended by three months.

Multiple analyses examining the effect of sample handling on results were also conducted by the statistical review team to support the conclusion of similarity of the two formulations of stavudine. These analyses are outlined in detail in the statistical review of this NDA. Alternative analyses on the primary endpoint stratified by specimen shipment handling supported similar treatment effects between the d4T ER and the d4T IR regimens in study 099.

7 Integrated Review of Safety

7.1 Brief Statement of Findings

The higher trough concentration and lower C_{max} of the ER formulation does not appear to change the recognized safety and tolerability profile of stavudine. Adverse events and laboratory findings in both groups were comparable between the two formulations. Adverse events believed to be related to the administration of stavudine occurred with equal frequency between treatment arms and appeared to occur at a frequency similar to that reported in other clinical trials.

Studies 096 and 099 support the claim that d4T ER is similar to d4T IR with regard to safety when used in a standard HAART regimen for the treatment of antiretroviral-naïve, HIV-infected subjects over a period of 48 weeks

7.2 Material Utilized in this Review

This NDA was received in electronic format on December 11, 2001. A clinical update was received in electronic format on May 31, 2002. The following modules/items were included in this NDA and were reviewed for the clinical section of this review; Labeling, Investigators and Study Sites, Clinical Overview, Clinical Summary, Clinical Study Reports 096, 099, 110 and 049, Case Report Tabulations, and Case Report Forms.

The following items from the update received on May 30, 2002 were reviewed: Proposed Labeling, Integrated Safety Summary, Clinical Study Reports for 099, 110 and 049, Pediatric Development Plan, Assessment of Genotypic and Phenotypic Profiles, , Analysis of Subjects with Diarrhea, Case Report Forms, and Case Report Tabulations.

7.3 Description of Patient Exposure

The evaluation of clinical safety for the extended release formulation of stavudine is based on data derived from three studies: 096, 099, and 110. The three trials provide information related to stavudine use (ER or IR) in a combination HAART regimen with the same co-administered drugs: 3TC and EFV. Studies 096 and 099 provide safety data for two distinct cohorts of patients during the first year of dosing in previously treatment-naïve subjects; enrollment in study 096 was limited to North and South American countries, while enrollment in 099 was global and included subjects from North and South American, European, African, and Asian countries.

Median treatment exposure on the two primary studies is 53 weeks for 096 and 56 weeks on 099. The median exposure for the integrated population over all three studies is 56 weeks. The exposure of the smaller 096/110 cohort has a median time on treatment of 100 weeks for the ER treatment group and 99 weeks for the IR group. Thus, for events in which the cumulative risk increases over time, the two studies sometimes demonstrate substantially different adverse event rates.

The mean daily doses of stavudine differed by subject weight and by ER versus IR regimen. The mean daily dose of stavudine ER in the pooled population was 98 mg for those weighing ≥ 60 kg and 76 mg for those weighing < 60 kg. The mean daily dose of d4T IR was 78 mg for those weighing ≥ 60 kg and 61 mg for those weighing < 60 kg.

7.4 Safety Findings from Clinical Studies

The safety data collected during the conduct of these trials does not identify new adverse events related to stavudine use with the exception of motor weakness resembling Guillain-Barre syndrome; however, causality of this adverse event has not been determined. Comparisons between the two treatment groups does provide information regarding the relative rates of events related to nucleoside analogue use between the two formulations of stavudine. Special safety issues for stavudine focus on hepatic dysfunction, pancreatitis, symptomatic hyperlactatemia/lactic acidosis syndrome (SHL/LAS), peripheral neuropathy, lipid abnormalities and lipodystrophy/fat redistribution syndromes.

In the pooled dataset adverse events that were judged by the on-site medical staff as related to the study drug regimen were evenly balanced between the the two treatment groups. Clinical adverse events of any grade were reported frequently: 86% of all ER subjects and 87% of all IR subjects reported at least one adverse event of any grade, with this rate being slightly higher in the more mature 096/110 cohort. The reported rates for Grade 3 - 4 events were 11% for each treatment group in cohort 099/110 and 23% for the ER and 21% for the IR in cohort 096/110.

Serious Adverse Events

The definition of serious adverse events (SAE) in studies with stavudine ER included events that: were fatal or life threatening; resulted in permanent disability; required or prolonged hospitalization; involved cancer, congenital anomaly, or overdose; or any other event which an investigator believed was medically important to report as an SAE.

Overall, SAEs occurred in 9% of the pooled population and with comparable rates for the ER (47; 10%) and IR (43; 9%) treatment groups. In the 096/110 cohort, more ER subjects had SAEs than IR subjects (17; 23% ER vs 10; 13% IR). However, there was no pattern to suggest a particular toxicity related to the formulation. In the 099/110 cohort overall SAEs were balanced (30; 8% ER; and 33; 8% IR).

SAE event clusters in which there was a difference of three or more subjects between the ER and IR treatment groups included the following: events more common in the ER treated group were vomiting (3; <1% ER and 0 IR) and pneumonia (5; 1% ER and 2; < 1% IR). Events occurring with a greater incidence in the IR treated group were pancreatitis (1; < 1% ER and 4; < 1% IR), cholelithiasis (0 ER and 3; < 1% IR), peripheral neurologic symptoms (PNS) (0 ER and 3; < 1% IR), and abortion (0 ER and 4; < 1% IR). No single event occurred at a rate greater than 1% in the pooled population.

There were a total of 21 clinical events in 17 subjects (7 ER, 10 IR) of sufficient severity to constitute an SAE or result in discontinuation of study drug that could possibly be related to mitochondrial toxicity. These events were classified as hepatic toxicity, pancreatitis, symptomatic hyperlactatemia, and lactic acidosis syndrome; this does not include discontinuations due to peripheral neuropathy. Four of these events were attributed by investigators to causes other than study drug; three hepatitis cases were attributed to active hepatitis B and one case of pancreatitis was attributed to gallstones. These events will be discussed in further detail within each adverse event category.

Discontinuations due to an adverse event of peripheral neuropathy (PN) occurred in 3 (< 1%) ER subjects and in 9 (2%) IR subjects; however, this adverse event was not handled in a uniform manner by investigators and subjects.

Discontinuations Due to Adverse Events

Overall, discontinuations due to adverse events were balanced between treatment arms. There were 22 (5% of treated subjects) discontinuations in the ER treatment arms and 31(7% of treated subjects) in the IR treatment arms. The three most frequent body systems involved were the nervous system, the digestive system, and the metabolic/nutritional system.

In general, the discontinuations/deaths due to NRTI associated adverse events were roughly balanced between treatment groups, although more patients discontinued due to peripheral nervous system symptoms in the IR group than in the ER group: 9 (2%) IR versus 3 (< 1%) ER.

A total of 9 subjects experienced a total of 13 lactic acidosis related events; 6 in the IR group and 3 in the ER group. A total of 5 subjects in the IR group discontinued treatment due to SHL. One IR subject with SHL was treated with vitamins B1 and B2 and experienced resolution of symptoms without discontinuation of therapy. One subject in the ER group discontinued due to SHL and two subjects in the ER group died due to complications related to lactic acidosis syndrome and ascending motor weakness.

A total of 6 subjects (3 in each treatment group) experienced elevations in LFTs or progression of clinical liver disease that resulted in death (1 subject in ER) or discontinuation of study drug. All 6 subjects had underlying hepatitis B or C, and one of the six had elevated transaminases secondary to lactic acidosis.

AIDS Defining Events

On-study CDC Class C AIDS-defining clinical events occurred at comparable rates in the two treatment groups: 10 (2%) ER and 8 (2%) IR.

Peripheral Neuropathy

Peripheral neuropathy (PN) is a well-described complication in HIV-infected patients; it can be due both to underlying disease and to drug-related toxicity, particularly in association with NRTI use. The incidence rate for PN of all grades in the ER development program is 17% for ER and 19% for IR. PN of moderate to severe intensity (Grades 2 - 4) that was judged by investigators to be related to study drug occurred in 3% of subjects in the ER treatment group and 5% in the IR group. Dose reductions due to PN occurred in 2 (< 1%) ER subjects versus 10 (2%) IR subjects.

Discontinuations due to an AE of PN occurred in 3 (< 1%) ER subjects and in 9 (2%) IR subjects; however, this adverse event was not handled uniformly by investigators and subjects. Three subjects tried dose reduction prior to discontinuation of therapy, while the remainder chose to discontinue medication without an attempt at dose reduction or discontinued due to lack of improvement of symptoms with treatment interruption. Three subjects chose to discontinue treatment despite improvement of PN with treatment interruption/dose reduction.

The recently described syndrome of motor weakness which has occurred most often in temporal association with LAS was identified in three subjects (2 ER; 1 IR) from the stavudine development program. The two subjects in the ER treatment arm died due to complications related to motor weakness and LAS.

While the overall incidence of peripheral neuropathy appears to be balanced between treatment groups, there does appear to be a small numerical difference favoring the extended release formulation of stavudine in terms of the incidence of peripheral neuropathy of sufficient severity to require dose reduction/discontinuation; however, the low incidence of these events and the lack of uniform handling of events by subjects and investigators makes it difficult to reach any conclusions.

Lipodystrophy

Lipodystrophy (LD) events were spontaneously reported in 16 (3%) of ER subjects and 22 (5%) of IR subjects. The protocol did not specify any prospective criteria for events that should be reported as lipodystrophy, and the majority of events were not described in sufficient detail to characterize as either lipohypertrophy, lipoatrophy, or both. Events occurred in 22 (3%) men and in 16 (6%) women.

Serial waist and hip measurements were collected on all three studies within the ER development program, and waist-to-hip ratios were calculated from these measurements. These measurements can be used to provide information on changes in fat distribution (lipodystrophy) on treatment and to identify those patients with potentially increased risk for cardiovascular disease. The absolute value of the cutoff associated with increased risk varies from article to article (general range 0.8 - 0.9 for women; 0.9 - 1.0 in men), but for the purposes of this analysis the applicant chose the following cutoffs as reflecting a higher cardiovascular risk: > 0.95 for men and > 0.85 for women. In both cohorts 096/110 and 099/110, the proportion of subjects having a ratio greater than these cutoffs did not change substantially for men over the first 48 weeks of dosing, whereas there was a modest but consistent increase for women (absolute increase in the 8 - 30% range, depending on the study group and cohort). These data represent an exploratory investigation.

Pancreatitis

Pancreatitis is a recognized adverse event of ARV therapy known to occur in association with stavudine therapy. The rate of pancreatitis with stavudine monotherapy or stavudine-containing dual nucleoside therapy appears to be < 1%, with a slightly higher rate (0.75 - 1.6%) when used in HAART. In studies 096/110 and 099/110, pancreatitis occurred at a rate of < 1% overall: 1 (< 1%) on ER and 4 (1%) on IR. None of the cases were fatal. Laboratory evaluation demonstrated that lipase elevations of any grade occurred in 14 % of subjects in each treatment group who had a normal value at baseline, and in a similar proportion for all subjects (16% ER; 15% IR). Grade 3 - 4 abnormalities occurred in 4% of ER subjects versus 3% IR.

Hepatic Dysfunction

Stavudine is recognized to be associated with transaminase elevations and liver dysfunction, and these findings would be expected regardless of formulation. In the current pooled database 39% of subjects who started treatment with a normal baseline ALT developed some elevation of any grade, regardless of formulation (39% ER vs 38% IR). Of these, 3% were Grade 3 - 4 elevations. For all subjects regardless of baseline ALT status, the rates for an elevated ALT of any grade are 43% for ER and 42% for IR, with 3% in both groups being Grades 3 - 4. There are no data available as to what proportion of these study subjects had active co-infection with hepatitis B or C. For any elevation of ALT, the rates in the cohort that had longer dosing (096/110 cohort) were somewhat higher than for the pooled population.

These data are consistent with the rates previously reported for d4T containing HAART regimens. The clinical event rate for subjects having an AE related to hepatic dysfunction (other than due to infectious hepatitis) was < 1% in this dataset. A total of 6 subjects (3 in each treatment group) experienced elevations in LFTs or progression of clinical liver disease that resulted in an SAE, death, or discontinuation of study drug. All 6 subjects had underlying hepatitis B or C, and one of the six had elevated transaminases lactate-associated hepatic disease.

Lactic Acidosis Syndrome and Symptomatic Hyperlactatemia

Lactic acidosis syndrome (LAS) and symptomatic hyperlactatemia (SHL) constitute a clinical syndrome that has been clearly linked to nucleoside analogue treatment; the risk for developing this syndrome appears to be increased with stavudine use. In the stavudine ER development program, nine subjects (3 ER; 6 IR) experienced a total of 13 lactate-associated events (5 ER; 8 IR); according to the applicant this corresponds to an incidence of 8.8 cases/1000 patient years.

The nine cases occurring in this development program included two deaths that were associated with severe motor weakness, one with confirmed hepatic steatosis on post-mortem biopsy; one with LAS. The other seven cases included one case of LAS that occurred with a simultaneous acute pancreatitis and six cases of SHL. Of the six SHL cases, one was associated with pancreatitis; another was associated with the evolution of non-fatal motor weakness; and one was treated over a period of several months with nutritional supplementation (Vitamins B1 and B2). In this case interruption of study drug was successfully avoided, and symptoms eventually resolved with a decrease in lactate level to within normal range. The remaining three cases represented uncomplicated SHL that led to discontinuation of study drug with resolution of symptoms.

Of the nine subjects having events related to lactate disorders and described above, seven were female and two were male. The mean age was 33 years (range 28 - 39), and the median time to presentation of symptoms was 44 weeks of dosing (range 34 - 57). Of these nine subjects, two were normal weight (BMI < 25), 4 were overweight (BMI ≥ 25 and < 30) and three were obese (BMS ≥ 30). Previous analyses of LAS/SHL cases from BMS sponsored clinical trials have correlated these events with female gender and obesity.

Deaths

In total, eight deaths occurred among all subjects in the stavudine ER registrational program. Of the eight deaths, three appeared to be unrelated either to the underlying HIV disease or to study treatment, one on ER and two on IR. These include two murders and a death due to metastatic breast cancer in an IR subject that occurred greater than 6 months after discontinuation of study treatment (study therapy was stopped when the subject presented with recurrence of breast cancer).

Two deaths appeared to be related to opportunistic infection and/or to the underlying HIV status of these subjects, and both occurred in subjects receiving the IR formulation: one subject died on day 85 on study of a complicated, recurrent pneumonia which had first presented on day 43 of treatment: a second died on day 75 on study of recurrent central nervous system (CNS) toxoplasmosis which had first been identified on day 11 of treatment. Both events occurred within the first 3 months of study treatment. Both subjects had a relatively high HIV RNA at baseline (127,000 - 197,000 c/mL for one subject; 1.9 - 2.9 million for the other subject) and both had CD4 values < 150 c/mm³ at baseline. Both subjects responded well to therapy with significant decreases in viral load and increases in CD4 cell counts. These data suggest that some component of the

inflammatory response which accompanied both complications may have been related to immune reconstitution.

Finally, three deaths occurred that are consistent with treatment-related toxicity. Although all three occurred in subjects taking stavudine ER, the small number of events makes it difficult to assess whether this observation is clinically significant. One death from hepatic failure occurred in a subject who entered the study with normal baseline transaminases and total bilirubin (Grade 1 alkaline phosphatase), but who had had compensated cirrhosis diagnosed one to two months prior to entry into the study at the time of a cholecystectomy. This subject was subsequently found to be hepatitis B surface antigen positive, although HBV DNA was negative. It is possible that study and other medications, superimposed on his underlying hepatic disease, contributed to the complications resulting in death.

The second likely treatment-related death occurred in a young, otherwise healthy woman, and appeared to represent complications of therapy that are likely attributable to mitochondrial toxicity. This subject died after a month-long illness that included gastrointestinal symptoms leading to but not resolving with a cholecystectomy (gallbladder pathology consistent with cholecystitis), followed by a complicated course involving neuromuscular weakness, ophthalmologic changes, and signs and symptoms consistent with lactic acidosis. A follow-up post-mortem liver biopsy confirmed severe hepatic steatosis.

The third treatment-related death also occurred in a young, otherwise healthy woman and also appeared to represent complications of therapy attributable to mitochondrial toxicity. This subject developed symptomatic hyperlactatemia (SHL) with nausea and vomiting after approximately 59 weeks on therapy. Despite discontinuation of study drug, her illness progressed to include both refractory acidosis and a progressive, ascending motor weakness evolving to paralysis.

Clinical Laboratory Evaluations

The proportion of subjects having a laboratory abnormality reported as an AE was comparable between the two treatment groups: 11% of ER subjects versus 12% of IR subjects. The most frequent laboratory AEs were neutropenia, increased ALT, hypertriglyceridemia, increased AST, and anemia. None occurred in greater than 2% of subjects, and the frequencies were comparable between treatment groups. Of the 105 individuals involved, about half (53) had Grade 3 - 4 events which were evenly distributed between treatment groups (29 ER; 24 IR). Grade 3 - 4 events were predominantly neutropenia and anemia.

Hematology

Of hematologic laboratory assessments, white blood cell (WBC) and neutrophil abnormalities were reported most frequently, in up to one quarter of all subjects. The rates were comparable between the study groups: abnormal WBC were reported in 27% of ER and 29% of IR subjects; abnormal neutrophils were reported in 21% of ER and

22% of IR subjects. Grade 3 - 4 abnormalities were infrequent, with abnormal neutrophils (5% each treatment group) reported more frequently than other cell lines.

Liver Function Tests

Elevations of transaminases were frequent and occurred in approximately 40% of all subjects (range 35 - 43%). Incidence rates were higher in the longer 096/110 study (43% - 53%) than in the 099/110 study (33% - 42%) but were comparable between treatment groups. Most on-study increases were to Grade 2; Grade 3 - 4 events occurred in only 3% of subjects overall. Subjects with an abnormal baseline transaminase value had a higher rate of developing Grade 2 - 4 abnormalities while on-study than did those with a normal baseline transaminase value. Elevations in bilirubin were unusual and infrequently accompanied other hepatic abnormalities, and occurred in only 2% of all subjects. Bilirubin abnormalities occurred equally between treatment groups. An elevated alkaline phosphatase occurred in 18% of ER and 13% of IR subjects. The difference is driven by an imbalance between treatment groups in 096 (35% ER; 21% IR, $p = \text{NS}$) which was not confirmed in 099 (15% ER and 12% IR). Grade 3 - 4 events were infrequent ($< 1\%$).

Glucose and Lipids

Abnormalities in fasting glucose and triglycerides occurred on-study with comparable frequency in both treatment regimens. Any hyperglycemia occurred in 8% of ER and 13% of IR subjects, but Grade 3 - 4 events occurred in $< 1\%$ of both groups. At week 48 the mean fasting glucose demonstrated a marginal increase over baseline which was comparable between the two groups: 6.8 mg/dL or 7% for ER and 8.7 mg/dL or 9% for IR. Between weeks 48 and 72 there appears to be no consistent further upward trend for glucose.

Elevated triglycerides occurred in approximately one third of all subjects (30% ER; 31% IR); only 3% of ER and 4% of IR subjects had events of Grade 3 - 4 severity. At week 48, the mean fasting triglyceride value had increased relative to baseline by 67 mg/dL (41%) in the ER group versus 59 mg/dL (41%) in the IR group. Only 7 individuals (4 ER, 3 IR) had week 48 values greater than 750 mg/dL as compared to one subject (IR) at baseline.

At week 48, mean total and HDL cholesterol had increased, and the changes for the ER group were comparable to those for the IR group. The mean total cholesterol increased 27% (absolute increase 44 mg/dL) in each treatment group. The mean HDL cholesterol increased 24% in each treatment group (absolute increases of 9 mg/dL for ER, 10 mg/dL for IR). Although the proportion of subjects having an LDL ≥ 160 mg/dL approximately triples from baseline (5% ER; 3% IR) to Week 48 (17% ER; 19% IR), those with a protective HDL value (≥ 60 mg/dL) also triples, from 5% to 16% in the ER group and from 4% to 19% in the IR group. Thus, the proportion of subjects having a total:HDL cholesterol ratio > 5 at Week 48 increases only marginally over the proportion at baseline: 23% increases to 30% on ER; 27% increases to 31% on IR. Subjects with a fasting LDL:HDL cholesterol ratio > 5 ranges from 0 - 4% in both treatment groups through Week 72.

The 48-week increase in total and HDL cholesterol in this study (27% and 24%, respectively, in both formulations) is consistent with the 20% and 25% increases, respectively, reported in the EFV package insert for HIV-infected patients treated with EFV, AZT and 3TC. Some investigators have demonstrated that although switching the PI component of HAART to EFV in those with clinical lipodystrophy produces a statistically significant decrease in triglycerides, the triglycerides do not return to baseline.

Lactate Levels – Exploratory Investigation

In the 096/110 cohort, both ER and IR treatment groups demonstrate an increase from baseline in mean and median lactates at 48 weeks, although both values in each group remain within the normal range. The mean lactate increased from 1.4 mmol/L to 2.0 mmol/L for the ER treatment group and from 1.3 mmol/L to 1.8 mmol/L for the IR treatment group. The median lactate increased from 1.2 mmol/L to 1.4 mmol/L for the ER treatment group and from 1.1 mmol/L to 1.7 mmol/L for the IR treatment group. By week 96, the mean and median values for both treatment groups had decreased (1.6 and 1.5 mmol/L, respectively, for both ER and IR). Data from the 099/110 cohort, though limited by the absence of baseline values, demonstrate mean and median 48-week lactate values that are comparable to those observed in the 096/110 cohort: ER 1.8 and 1.7 mmol/L, respectively; and IR 1.9 and 1.6 mmol/L, respectively.

Although the numbers of observations are small, the proportions of subjects with moderate elevations in lactate appears to have returned to baseline by week 96.

7.5 Miscellaneous Studies

Safety data from one non-BMS study was submitted with this NDA. This study is being conducted at the [] and carries the BMS designation AI424049. This is the only non-registrational study using stavudine ER for which subjects have received dosing prior to the cutoff date for the analysis for NDA submission.

The study is titled, “A Phase II, 48 Week, Uncontrolled, Open-Label Study to Evaluate the Safety and Efficacy of Once-a-day Antiretroviral Regimen to Treat HIV-1 Infection Including BMS-232632, Lamivudine and Extended Release Stavudine” It is a Phase II observational, randomized open-label trial which is designed to assess the safety and efficacy of a simplified, once-daily regimen in subjects who have previously achieved rigorous antiviral control after the initiation of therapy during primary infection. The previous regimens required two or three times daily dosing; all subjects switch onto the same simplified regimen, which consists of stavudine ER, 3TC and atazanavir (ATV) all given once-daily. In addition, subjects are randomized to an enhanced adherence intervention versus routine adherence supervision. The primary objective is maintenance of viral suppression as measured by HIV RNA.

At the time of database lock, 23 subjects had been enrolled into this study. There have been no deaths and no discontinuations due to adverse events or any other reason on

AI424049. One SAE has been reported, and involved leucopenia and granulocytopenia leading to interruption of study therapy in a 50-year-old male who had been on study for 8 weeks (following three years of another regimen). Study medications were held for 28 days; since restarting study medications there has been no recurrence of neutropenia.

There have been 41 adverse events reported on this study. Severity was reported as mild in 37 of these events and moderate in the remaining four events. The two most frequent events were upper respiratory infection (8), and fatigue (5), with all others occurring once or twice each. The body system most frequently involved was the digestive system (14 events: adominal bloating, heartburn, flatulence, epigastric discomfort, abdominal cramps, constipation, esophagel reflux, loose stool, peptic ulcer disease, decreased appetite, gastroenteritis, nausea), followed by body system as a whole (9 events: fatigue, headache and lower extremity edema) and respiratory system (9 events: pneumonia and upper respiratory infection).

7.6 Literature Review for Safety

Zerit XR™ has been marketed in Europe for the past two months; therefore, no literature review was conducted for assessment of safety.

7.7 Postmarketing Surveillance

Zerit XR™ has been marketed in Europe for two months. There is currently no information available regarding postmarketing experience with Zerit XR™.

7.8 Safety Update

The safety review contains all safety data available for this NDA and contains information from a safety and efficacy update submitted to this NDA on May 30, 2002. The safety update was integrated into the primary analysis of this NDA.

7.9 Drug Withdrawal, Abuse, and Overdose Experience

This medication has no potential for withdrawal or abuse. No data is available on overdosage of stavudine ER as no subject participating in studies 096, 099 or 110 was documented as having ingested more than the recommended daily dosage.

Experience with adults treated with the immediate release formulation at 12 to 24 times the recommended daily dosage revealed no acute toxicity. Complications of chronic overdosage include peripheral neuropathy and hepatic toxicity. Stavudine can be removed by hemodialysis; the mean \pm SD hemodialysis clearance of stavudine is 120 ± 18 mL/min. Whether stavudine is eliminated by peritoneal dialysis has not been studied.

7.10 Adequacy of Safety Testing

The studies submitted for this NDA appear to be adequate to determine the safety of the extended release formulation of stavudine relative to the immediate release formulation. It is difficult to determine from the size of these studies if the more serious but infrequent complications of stavudine therapy such as lactic acid syndrome and pancreatitis will be more common with the ER formulation, however, these trials provide no evidence to suggest that they will occur more frequently.

7.11 Postmarketing Studies

The applicant agreed to complete the following phase IV commitments:

- Elucidate the complete metabolic fate of stavudine in humans. This was a Phase IV commitment for the original stavudine NDA. Final report due: 4Q 2005.
- Conduct and submit the results of studies or simulations in patients with impaired renal function based on the known pharmacokinetic information of both stavudine immediate and extended release formulations, if Zerit XR[®] is to be used in this population. Final report due: 2Q 2003.
- Assess genotypes and phenotypes of pre-therapy and post-therapy HIV-1 isolates from a large number of patients failing stavudine therapy. Final report due: 4Q 2004.
- Evaluate the cross-resistance of stavudine resistant HIV-1 isolates to all approved NRTIs, and the efficacy of d4T against HIV-1 isolates resistant to all approved NRTIs. Final report due: 4Q 2004.
- Determine the *in vitro* combination activity relationships of stavudine with all approved NRTIs and determine the effect of ribavirin on anti-HIV-1 activity of stavudine *in vitro*. Final report due: 2Q 2003.

8 Use in Special Populations

8.1 Efficacy and Safety Analyses of Effects of Gender, Race, and Ethnicity

Efficacy Analysis

Analyses of baseline disease characteristics by gender among those subjects who received treatment with stavudine ER, demonstrated that:

- 1) Males had a higher median baseline HIV RNA than females (4.85 vs 4.62 log₁₀ c/mL, respectively).
- 2) A greater number of males compared to females had baseline HIV RNA \geq 30,000 c/mL (72% vs 63%, respectively).
- 3) CD4 cell counts were comparable between males (median 293 c/mm³) and females (median 295 c/mm³).
- 4) The distribution of CD4 cell counts was comparable between males and females.

According to the applicant, the observation that despite comparable CD4 cell counts men had higher viral loads than women (difference of 0.23 log₁₀ c/mL) is consistent with the

magnitude of differences noted in other studies of those with established HIV infection: 0.25 log₁₀ c/mL in the ALIVE cohort and 0.28 log₁₀ c/mL in ACTG 175.

For their analyses of subpopulations, the applicant chose to consolidate racial groups in order to have categories of reasonable size, with Hispanics and Asians consolidated into "Other" (White, N = 223; Black/Mixed, N = 113; and Other, N = 130). Analyses of baseline disease characteristics by race among those subjects who received treatment with stavudine ER, demonstrate that,

- 1) Black/Mixed and White racial groups both had a slightly higher median HIV RNA (4.84 log₁₀ and 4.81 log₁₀ c/mL, respectively) than the racial group classified as Other (4.75 log₁₀ c/mL).
- 2) Whites had a higher percentage with HIV RNA > 30,000 c/mL (73%) than Black/Mixed (68%) or Other (65%).
- 3) Median CD4 cell counts were higher in Whites (304/mm³) than in Other (279/ mm³), and were lowest in Black/Mixed (264/ mm³).
- 4) The distribution of subjects by CD4 cell count shows a lower proportion with CD4 < 200 mm³ for Other (22% vs 27% and 30% for White and Black/Mixed respectively) and a lower proportion with CD4 > 500/mm³ for Black/Mixed (9% vs 16% and 17% for White and Other, respectively).

Sub-population analyses of the principal efficacy parameters for those subjects treated with stavudine ER were performed based on the criteria of gender (male; female), race (White; Black/Mixed; Other), and geographic region (Europe; North America; Rest of World [ROW]). The largest sub-population analyzed is males (N = 321) versus females (N = 145), and the smallest is subjects from Europe (N = 87) versus North America (N = 185) and ROW (N = 194).

The difference in duration of the studies at the time of this analysis (48 weeks for AI455-096 versus 24 weeks for AI455-099) limited the information available. All efficacy analyses for the pooled data are carried through week 24 only.

Three consistent patterns emerged in the various sub-population analyses of proportion of subjects with HIV RNA below the LOQ (either 400 c/mL or 50 c/mL);

- 1) Women tend to respond at higher rates than men.
- 2) The black/mixed and "other" racial groups consistently respond at higher rates than whites; the race-related difference is more pronounced when the measure of virologic success is < 50 c/mL level.
- 3) Subjects from ROW and Europe consistently have higher response rates than those from North America.

Due to the recruitment patterns for these studies, the demographic factors of gender, race and region may be confounded. In addition, the observation in the AI455-096 population PK analysis that ER subjects with a weight ≥ 60 kg appear to have a marginally lower

drug exposure than those on IR, further analysis of clinical outcome by weight category was performed.

To address these factors and their potential interactions, a stepwise linear regression model for HIV RNA at 24 weeks with baseline HIV RNA as a covariate was applied to the stavudine ER group and selected male gender (versus female) and white race (versus non-white) as significant predictors of less viral suppression. When this model was applied to the pooled study population with variables for weight (≥ 60 kg versus < 60 kg), treatment (ER versus IR) and treatment interaction terms (treatment by male sex; treatment by white race; treatment by weight), none of these interaction terms was significant. The conclusions from these analyses performed by the applicant and based on these studies, were:

- 1) Gender and race are significant predictors of viral suppression in these studies at 24 weeks.
- 2) There is no evidence that weight predicts viral suppression.
- 3) When gender and race are accounted for, region is not a significant predictor of viral suppression.

Safety Analysis

The only toxicity related to stavudine administration for which intrinsic factors have been found to possibly play a role is the frequency or severity of lactic acid syndrome (LAS). Although the incidence of LAS in these studies is too low to convincingly demonstrate these associations, the literature and other safety assessments suggest that LAS shows an association with female gender, pregnancy, and obesity. The three cases that meet criteria for lactic acidosis syndrome from this patient database are all female (none pregnant), with a mean body mass index (BMI) at the visit closest to the event of 33.7 (all > 25 , consistent with "overweight"; 2 of 3 > 30 , consistent with "obese").

8.2 Pediatric Program

At the pre-NDA meeting held on July 20, 2001, Bristol-Myers Squibb Company was granted a pediatric deferral of the pediatric study requirements for the NDA for Zerit XRTM Extended Release Capsules. This requirement was deferred until after approval of the extended release formulation for the treatment of HIV infection in adults.

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8.3 Data Available or Needed in Other Populations

Renal Impairment

No studies were performed to examine the rate of elimination of stavudine after administration of stavudine ER to patients with renal impairment. As a result, no recommendations will be made in product labeling for dosing of stavudine ER in patients with creatinine clearance ≤ 50 mL/min. The label has the following recommendation when treating patients with renal impairment; "Please consult the complete prescribing information for ZERIT (stavudine) Capsules and ZERIT for Oral Solution for dosage and administration of stavudine to patients with creatinine clearance ≤ 50 mL/min."

Hepatic Impairment

No alterations in stavudine pharmacokinetics were observed in five non-HIV infected patients with hepatic impairment secondary to cirrhosis following the administration of 40 mg of the immediate release formulation. Since the metabolism characteristics of stavudine is not expected to be altered by the ER formulation, the pharmacokinetics of stavudine from the ER formulation should be unaltered in patients with hepatic impairment. No dose reduction of Zerit XRTM is being recommended for patients with hepatic impairment.

Pregnancy

This product received a pregnancy category C rating. Reproduction studies have been performed in rats and rabbits with exposures up to 399 and 183 times that seen at a clinical dosage of 1 mg/kg/day and have revealed no evidence of teratogenicity. The incidence of a common skeletal variation and early rat neonatal mortality was increased at 399 times the level of human exposure. A slight implantation loss was noted at 216 times the human exposure. A study in rats showed that stavudine is transferred to the fetus through the placenta. The concentration in fetal tissue was approximately one-half the concentration in maternal plasma.

There are no adequate and well-controlled studies of stavudine in pregnant women. Zerit XRTM is being recommended for use in pregnancy only if the potential benefit clearly outweighs the risk.

Stavudine in combination with didanosine should be used with caution in pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk. This recommendation is based on reports of lactic acidosis, including fatal cases, in pregnant women receiving this combination of the immediate release formulation of stavudine and didanosine.

Geriatrics

A total of 5 subjects aged 65 and over were enrolled in clinical studies of the extended release formulation of stavudine; it is not possible to determine whether they respond

differently than younger subjects. Stavudine is known to be substantially excreted by the kidneys. Because elderly patients are more likely to have decreased renal function, it may be useful to assess the renal function of elderly patients prior to initiation of stavudine ER.

9 Conclusions, Recommendations, and Labeling

9.1 Conclusions Regarding Safety and Efficacy

Data available from registrational study 099, pilot study 096, and rollover study 110 support the conclusion of similarity of the safety and efficacy of the extended and immediate release formulations of stavudine.

9.2 Recommendations on Approvability

Based on review of the data submitted by Bristol-Myers Squibb in support of NDA 21-453, it is recommended that this application for the extended release formulation of stavudine for the treatment of HIV-1 infection, in combination with other antiretroviral agents, be approved.

9.3 Labeling

Two significant revisions were made to the initial labeling proposal submitted by the applicant. The first was elimination of dosage reduction recommendations for patients with renal impairment due to a lack of data regarding the pharmacokinetics of the extended release formulation of stavudine in this population.

The second major revision was the addition of a recommendation for physicians to consider switching patients requiring treatment interruption for peripheral neuropathy to an alternate regimen as opposed to attempting dose reduction. If this is not suitable, however, dose reduction of the extended release formulation is an acceptable management strategy. This recommendation is being made due to the lack of sufficient numbers of subjects undergoing dose reduction in clinical trials to determine if response rates of patients receiving reduced doses of stavudine are similar to response rates of subjects receiving standard doses.

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Kendall Marcus
1/6/03 02:03:45 PM
MEDICAL OFFICER

Stanka Kukich
1/10/03 12:28:36 PM
MEDICAL OFFICER

Debra Birnkrant
1/10/03 12:42:40 PM
MEDICAL OFFICER

Team Leader's Memorandum

NDA: 21-453

Drug and Indication: Zerit®XR (stavudine) extended-release capsules for the treatment of HIV-1 infection in combination with other antiretroviral agents

Dose: 100 mg once daily for patients \geq 60 kg and 75 mg for patients < 60 kg

Date of Submission: December 10, 2001

Date of MO Review: December 30, 2002

Date of Memorandum: December 23, 2002

Bristol-Myers Squibb Company has submitted a New Drug Application (NDA) requesting approval for Zerit® XR (stavudine) extended release capsules, a new formulation of stavudine, for the treatment of HIV-1 infection in adults as part of a combination regimen. This is in addition to the already approved Zerit® immediate release capsules and Zerit® for oral solution. Stavudine is a synthetic thymidine analog and effects HIV replication primarily by competitive inhibition of the HIV reverse transcriptase activity. In adult patients, the recommended dose of Zerit® immediate release formulation (IR) is 40 mg twice daily for patients \geq 60 kg or 30 mg twice daily for patients <60 kg. This new extended release formulation (XR) will allow for once daily dosing of stavudine.

Because the plasma half-life of stavudine is short (1.56 hours in HIV infected subjects), prolonged gastrointestinal release and absorption are necessary for once daily dosing. For that reason a new formulation was developed. Stavudine extended release capsules contain [] beads supplying 37.5 mg, 50 mg, 75 mg, and 100 mg of stavudine. The final core bead formulation contains — stavudine, [] microcrystalline cellulose, — lactose, and — magnesium stearate.

The primary support for a new dosing recommendation came from one principal trial of 56-week duration, one smaller supportive clinical study, and several pharmacokinetic trials. The objectives of these trials were to show that the antiviral effect of the once daily Zerit® extended release formulation was similar to that of the already approved twice daily Zerit® immediate release formulation when used as a part of antiretroviral regimen in HIV-infected treatment-naïve subjects.

The initial dose selection was based on the results of pharmacokinetic modeling and simulations. It was predicted that the 100 mg of stavudine extended release formulation

(higher than the currently recommended dose of 80 mg/day for immediate release formulation), would compensate for lower absorption from the colon and maintain the average steady state concentration above 100 ng/mL for 24 hours. Based on these conclusions the bioavailability and food effect studies were conducted.

The total daily exposure for the stavudine extended release formulation in HIV-infected subjects was approximately 14%-49% lower than in healthy subjects.

A single and multiple dose pharmacokinetic studies of stavudine were conducted in 32 HIV-infected adults who were enrolled in AI455-096 and AI455-103 trials. The mean C_{max} value for the XR formulation was about 50% lower and the C_{min} was 5-fold higher compared with the IR formulation. The total daily stavudine exposure achieved following administration of 100 mg once daily of the extended release formulation was about 30% lower compared with 40 mg twice daily of the immediate release formulation.

During the review process the applicant submitted a safety update and the 48-week HIV RNA results from the pivotal AI455-099 study. This was a multicenter, double-blind, international trial that included 71 centers. Seven hundred and ninety seven HIV-infected antiretroviral naïve subjects were randomized to receive stavudine extended release 100 mg or 75 mg once daily (based on weight) or the stavudine immediate release formulation 40 mg or 30 mg twice daily in combination with lamivudine 150 mg twice daily and efavirez 600 mg once daily. Randomization was stratified by baseline HIV viral load of <30,000 or ≥30,000 copies/mL. The treatment response at week-48 was evaluated by calculating the proportion of patients with plasma HIV-1 RNA levels below 400 copies/mL (Roch Amplicor HIV-1 Monitor™ assays Version 1.0 and 1.5), and below 50 copies/mL (Amplicor HIV-1 Monitor™ ultrasensitive assay), and increases in CD4 cell count from baseline.

Approximately eight weeks prior to the action due date, in the datasets for HIV RNA viral load, multiple values for viral load measurement for a single patient at a single time point were discovered. After discussion with the applicant it was clear that for both studies AI455-096 and AI455-099, specimens were stored and transported to the central laboratory in an ambient state via overnight priority express courier for arrival within 24 hours. For study 096, sites were instructed to keep back up frozen samples for each sample shipped to the central laboratory, however, this was not required for the larger 099 study. After it was discovered that samples processed in the ambient state had higher HIV RNA values, all centers in 099 study were instructed to transport all specimens to the central laboratory in the frozen state. However, 21 sites did not switch to the frozen shipment procedures. In study 099, for the week 24 and 48 analyses of HIV RNA viral load, the majority of specimens were stored and transported frozen and according to Roche Amplicor HIV RNA assay specifications. When 667 paired specimens of ambient and frozen shipment of $\left[\begin{array}{c} \text{ } \\ \text{ } \end{array} \right]^1$ tubes were compared with regard to HIV RNA viral load (study 096), the ambient data showed a small positive bias compared to the frozen specimens. The mean difference was 0.33 log₁₀.

In addition, specimens for HIV RNA testing were collected in the [Tubes [] and were centrifuged for periods varying between [] minutes. The range of centrifugation time and force was broader than that specified in the Roche Amplicor assay specifications. It is not completely clear whether these deviations in processing of plasma samples had any significant effect on the variability of viral load measurements.

Detailed discussion of stavudine safety and efficacy is provided in the medical and statistical review of this new drug application. I am in agreement with the conclusions of the primary reviewers that this application should be approved. Because of the problems with specimen handling, multiple sensitivity analyses of the HIV RNA measurements were performed excluding either ambient, local or the frozen samples. It appears that no matter how HIV RNA data were analyzed the confidence intervals for the difference between the stavudine extended release and immediate release regimens fall within an acceptable range.

In study 099, the week 48 treatment effect of the once daily extended release formulation of stavudine appears to be similar to the already approved stavudine twice daily formulation when the time to loss of virologic response was calculated using HIV RNA results based on the specimens transported according to the Roche assay specifications. According to the applicant's analysis, 78% (307/392) of patients who received stavudine extended release and 77 % (301/391) of patients who received stavudine immediate release formulation had HIV RNA <400 copies/mL at week-48. Estimated difference between the treatment arms was 1.3 and the confidence interval for the difference was (-4.5, 7.2). For the LOQ of ≤ 50 copies/mL, 55% (215/392) of patients who received stavudine extended release and 57 % (223/391) of patients who received stavudine immediate release formulation had HIV RNA below the level of quantification at week-48. Estimated difference between the treatment arms was -2.2 and the confidence interval for the difference was (-9.1, 4.7).

The second smaller trial was a 48-week, randomized, double-blind study that compared stavudine extended release 100 mg once daily to stavudine immediate release in combination with lamivudine and efavirenz in 150 treatment naïve HIV-infected patients. The primary endpoint of this trial was the change in \log_{10} HIV RNA from baseline calculated as the time-averaged difference through week 48. The results of this pilot trial were consistent with the safety and efficacy of once daily stavudine demonstrated in the larger pivotal trial.

The safety profiles of the two regimens appears to be similar and the safety information that was provided in this supplemental NDA did not alter the overall understanding of the stavudine safety profile. The once daily stavudine treatment may provide the advantage of a lower pill burden and convenience of once daily dosing, and therefore, may improve compliance with antiretroviral therapy. However, it should be emphasized that strict compliance with once daily regimen is important because if a daily dose is missed it may lead to prolonged periods of lower stavudine exposure and possibly promote emergence of resistance.

Because of the problems with HIV RNA specimen handling, on September 23, 2002, the applicant submitted additional information regarding the specimen processing and shipment to the central laboratory. This major amendment included the new statistical analyses of Time to Loss of Virologic Response using HIV RNA measurements from the specimens either shipped frozen, in ambient state, processed in a local laboratory, or were processed according to the instructions, and also the corresponding HIV RNA datasets were submitted. Therefore, the review time of this application was extended under CFR 314.60 for an additional 90 days.

The labeling discussions were focused on Microbiology, Clinical Pharmacology, Indication and Usage, Precautions, and Adverse Reactions Sections of the Package Insert for Zerit XR. A need for a separate labeling for Zerit XR in addition to the already existing product information for Zerit Capsules and Zerit for Oral Solution was also included in the labeling discussions.

The following are the phase 4 commitments for the stavudine extended release capsules, NDA 21-453:

1. Please elucidate the complete metabolic fate of stavudine in humans. This was a Phase IV commitment for the original stavudine NDA. Final report due: 4Q 2005.
2. Please conduct and submit the results of studies or simulations in patients with impaired renal function based on the known pharmacokinetic information of both stavudine immediate and extended release formulations, if Zerit XR is desired to be used in this population. Final report due: 2Q 2003.
3. Please continue to assess genotypes and phenotypes of pre-therapy and post-therapy HIV-1 isolates from a large number of patients failing stavudine therapy. Final report due: 4Q 2004.
4. Please evaluate the cross-resistance of stavudine resistant HIV-1 isolates to all approved NRTIs, and the efficacy of stavudine against HIV-1 resistant isolates to all approved NRTIs. Final report due: 4Q 2004.
5. Please determine the in vitro combination activity relationships of stavudine with all approved NRTIs and determine the effect of ribavirin on anti-HIV-1 activity of stavudine in vitro. Final report due: 2Q 2003.

NDA 21-453

Stanka Kukich, M.D.
Medical Team Leader, DAVDP

Concurrence:
HFD-530/D.Div.Director/JMurray

cc:NDA 21-453
HFD-530/MO/KMarcus

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/s/

Stanka Kukich
1/23/03 10:55:10 AM
MEDICAL OFFICER

Jeffrey Murray
2/7/03 04:17:00 PM
MEDICAL OFFICER