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Two-Year Analysis of Stavudine Extended-Release/Prolonged Release Capsules (XR/PRC) as Compared to Stavudine Immediate-Release (IR): Efficacy and Safety

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ABSTRACT

Background: Stavudine (d4T) XR/PRC provides equivalent 24 hour exposure to d4T IR, but has 1/2 the peak and 2-3 fold higher trough plasma levels. Week (wk) 48 efficacy and safety data demonstrated comparability, but the differing pharmacokinetics could result in clinically relevant differences in outcomes with longer dosing.

Methods: This analysis integrates results from two randomized, double-blind (through 1 year), studies of treatment-naive patients comparing XR/PRC versus IR, each with lamivudine (3TC) and efavirenz (EFV). At 1 year, subjects could elect to rollover into a common long-term dosing study. Efficacy is not censored for successful 1 year completers who did not rollover. Safety data are cumulative from start of therapy through on-going dosing as of March 2003.

Results: Median baseline values: HIV RNA 4.8 $\log_{10}$ c/mL and CD4 277 cells/mm^3. Median time on treatment: 115 wks. The most common regimen-related adverse events (AE) were dizziness, peripheral neurologic symptoms (PNS)* and rash.

	XR/PRC N=466		IR N=468	
WK 104 POOLED EFFICACY	**N**	**%**	**N**	**%**
Intention to Treat (ITT): HIV RNA <400 c/mL	298	**64**	280	**60**
ITT HIV RNA <50 c/mL	218	**47**	184	**39**
Mean ΔCD_4 (cells/mm^3)	+297		+279	
SELECTED SAFETY				
PNS* - Grades (GR) 1 - 4, Related (R)	85	**18**	110	**24**
PNS* - GR 2 - 4, R	17	**4**	38	**8**
Discontinuation (DC) due to PNS*	6	**1**	12	**3**
Lipodystrophy (LD = lipoatrophy and/or lipohypertrophy) GR 1 - 4, R	52	**11**	69	**15**
LD - GR 2 - 4, R	15	**3**	24	**5**
DC due to LD	4	**<1**	9	**2**

* PNS includes numbness, paresthesias, or pain in distal extremities.

Conclusion: Overall two-year efficacy and safety for Stavudine XR/PRC are comparable to IR, with trends which favor XR for safety events of interest.

BACKGROUND/INTRODUCTION

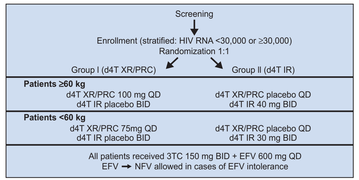
Stavudine XR/PRC (extended release/prolonged release capsules) was designed to enhance convenience to patients with once daily dosing while providing an overall drug exposure comparable to that of conventional stavudine IR (immediate release). The continuous release of drug throughout the gastrointestinal tract results in lower peak levels (approximately 1/2 that of IR) and higher trough levels (2-3 times higher than IR). Week 48 efficacy and safety data from two clinical trials have demonstrated non-inferior efficacy and comparable safety between the two stavudine formulations.

Both the efficacy and safety of Nucleoside Reverse Transcriptase Inhibitors (NRTIs) are believed to be mediated through the PK of the active triphosphate form. There are limited data available regarding intracellular stavudine triphosphate dynamics in samples from patients under treatment with stavudine.[i,ii] These limited data are consistent with previous *in vitro* information suggesting that stavudine enters and leaves cells rapidly by non-facilitated diffusion.[iii] Although the intracellular PK relationships between XR/PRC and IR remain to be explored, it is expected that the lower plasma peak and higher plasma trough of XR/PRC will persist qualitatively in clinical samples. Thus, differing pharmacokinetics (PK) could result in clinically relevant differences in outcomes with longer dosing. One safety parameter of particular importance is peripheral neuropathy, since it is the only dose-related clinical toxicity[iv] that has been identified. This analysis provides two-year efficacy follow-up for both trials and long-term (maximum duration 178 weeks) integrated safety follow-up.

METHODS

STUDY DESIGN

- Studies 096 and 099 were multinational, randomized, double-blind, placebo-controlled studies in treatment naïve HIV-infected. Study 096, initiated October 1999, was powered for non-inferiority of XR/PRC versus IR with respect to the change in HIV RNA from baseline through 48 weeks; treated subjects totaled 150 (74 XR/PRC; 76 IR). Study 099 was initiated in July 2000 and was powered for non-inferiority of XR/PRC versus IR with a total of 784 treated subjects (392 XR/PRC; 392 IR). The primary endpoint was the proportion of subjects having an HIV RNA below 400 c/mL at 48 weeks.
- After the completion of these one-year studies, patients from both were eligible to roll over onto a long-term, follow-up protocol (study 110) which remains on-going. On 110, subjects continue open-label dosing with their original XR/PRC versus IR formulation of stavudine. Both study cohorts enrolled antiretroviral-naive subjects, either with HIV RNA >5000 c/mL (study 096) or > 2000 c/mL (study 099), and having a CD4 count ≥100 cells/μL(c/μL) without acute opportunistic infections at enrollment.[v]



EFFICACY ANALYSIS:

- **Intention To Treat - ITT:** The primary analyses presented here use the denominator of all-treated subjects and provide a cross-sectional assessment of HIV RNA values at a single timepoint (i.e., the specified analysis week). In these ITT analyses, non-completers are considered to be failures (NC=F). With respect to the 110 experience, these analyses are not censored for successful 1 year completers who did not rollover onto the long-term study. Pooled results are provided in the abstract above; results by study cohorts (096/110 and 099/110) are provided in the RESULTS section below.
- **Observed Cases - OC:** In addition, Week 104 response rates are provided for an observed cases (OC) analysis. This uses the same cross-sectional criteria to assess HIV RNA response as in the ITT analysis, but the denominator includes only those observed cases for whom a value is available at the selected analysis timepoint (e.g., Week 104).

SAFETY ANALYSES:

- Safety data from studies 096, 099 and 110 were integrated into a single, cumulative database. All on-study data are presented for the pooled population.
- Peripheral Neuropathy (Peripheral Neurologic Symptoms or PNS) was prospectively assessed at each study visit with both a targeted physical exam and symptom review.
- Among spontaneously reported adverse events, the following were considered of specific interest: pancreatitis, symptomatic hyperlactatemia (SHL) or lactic acidosis syndrome (LAS).
- Criteria for 'lipodystrophy' were not prospectively defined in the protocols, and these events were not objectively confirmed. Events reported under this term were queried and the Investigator was asked to classify the event as 'lipohypertrophy', 'lipoatrophy' or both. The term 'lipohypertrophy' includes reports of increased abdominal girth, buffalo hump, and breast enlargement in women. The term 'lipoatrophy' includes events of facial, extremity, or subcutaneous fat loss or wasting. Reports of 'gynecomastia' refer specifically to breast enlargement in males.

RESULTS

Table 1: Baseline Characteristics

Selected Demographic and Baseline HIV Characteristics	Treatment Regimen Pooled XR/PRC N=466	Treatment Regimen Pooled IR N=468
Median Age (yrs)	33	33
Female Gender (%)	31%	29%
Race (%):		
White	48%	46%
Hispanic/Latino	20%	23%
Black	23%	18%
Asian/Pacific Islander	8%	8%
Other	3%	4%
HIV RNA:		
Median (log 10 c/mL)	4.79	4.76
% ≥100,000 c/mL	39%	37%
CD4 (cells/mm^3)		
Mean (SE)	320 (8)	323 (9)
Median	294	269
% Meeting AIDS Criteria		
CD4 <200 c/mL	26%	30%
Clinical Diagnosis	4%	3%

Table 2: Subject Disposition

	Pooled Subjects Treatment Regimen XR/PRC N	Pooled Subjects Treatment Regimen IR N
Randomized	474	478
Never Treated	8 (2%)	10 (2%)
Treated	**466 (98%)**	**468 (98%)**
DC Prior to Week 48	56 (12%)	75 (16%)
Completed Original Protocol	**402 (85%)**	**377 (79%)**
Enrolled on 110	**389 (82%)**	**358 (75%)**
DC 110 Prior to Week 104	38 (8%)	38 (8%)
Continuing on 110 at Week 104	**351 (74%)**	**320 (67%)**
Cumulative Discontinuations (DC) through Datalock	**120 (25%)**	**148 (31%)**
DC due to AE	32 (7%)	43 (9%)
DC - Treatment Failure	7 (1%)	4 (<1%)
DC - Other (lost to follow-up, pregnancy etc)	81 (17%)	101 (21%)

EFFICACY:

- Pooled results from both study cohorts through 104 weeks of dosing are presented in the Abstract.
- Efficacy results by originating study are presented in Figures 1-4. Successful 1 year completers who did not rollover onto 110 are not censored in these analyses.

Figure 1: ITT Response - AI455-099, Week 104

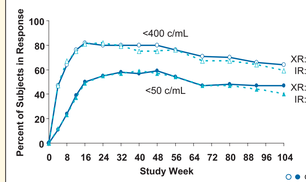


Figure 2: OC Response - AI455-099, Week 104

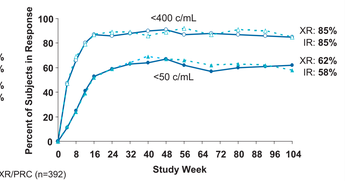


Figure 3: ITT Response - AI455-096, Week 104

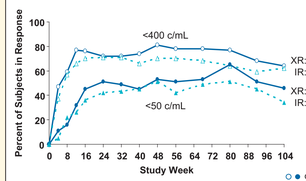
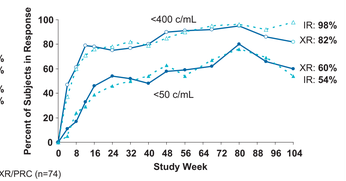


Figure 4: OC Response - AI455-096, Week 104



SAFETY:

Exposure:

- Median follow-up for the pooled treatment groups is 116 weeks for XR/PRC and 114 weeks for IR (153 and 146 weeks respectively for the 096/110 cohort; 115 and 111 weeks respectively for the 099/110 cohort).

Overall Safety:

- The most common adverse events related to study regimen and of moderate to severe intensity (Grades 2-4) were comparable between the two treatment groups.
- There have been a total of 9 deaths on this study, 5 on XR/PRC and 4 on IR.

Table 3: Moderate to Severe Treatment-Related Adverse Events

Safety Event:	Pooled XR/PRC (N = 466)	Pooled IR (N = 468)
AEs - Grade 2 - 4, Related (≥3% in either study arm)		
Dizziness	28 (6%)	24 (5%)
Rash	28 (6%)	22 (5%)
PNS	17 (4%)	38 (8%)
Headache	17 (4%)	7 (1%)
Insomnia	17 (4%)	7 (1%)
Abnormal Dream	16 (3%)	10 (2%)
Fatigue	15 (3%)	4 (<1%)
Diarrhea	13 (3%)	10 (2%)
Lipodystophy	12 (3%)	20 (4%)
Nausea	12 (3%)	8 (2%)

Table 4: Laboratory Abnormalities, Grade 3-4

Laboratory Abnormalities, Grade 3-4 (≥3% in either study arm)	Pooled XR/PRC (N = 466)	Pooled IR (N = 468)
Neutrophils	31 (7%)	27 (6%)
AST	11 (2%)	13 (3%)
ALT	15 (3%)	18 (4%)
Lipase	24 (5%)	19 (4%)
Triglyceride (Fasting)	23 (5%)	33 (8%)

EVENTS OF INTEREST:

Table 5: Peripheral Neuropathy

Event:	Pooled XR/PRC (N = 466)	Pooled IR (N = 468)
PNS, related (grades 1-4)*	85 (18%)	110 (24%)
PNS, related (grades 2-4)**	17 (4%)	38 (8%)
DC due to PNS	6 (1%)	12 (3%)
Dose Reduction (DR) due to PNS	5 (1%)	13 (3%)
Treatment Alteration (either DC or DR) due to PNS	11 (2%)	22 (5%)

* PNS includes numbness, paresthesias, or pain in distal extremities.
** p = 0.005

Table 6: Lipodystrophy and Gynecomastia

Event (any grade):	Pooled 096/099/110 XR/PRC (N = 466)	Pooled 096/099/110 IR (N = 468)
Any Lipodystrophy*	52 (11%)	73 (16%)
Lipohypertrophy[1]	16 (3%)	9 (2%)
Lipoatrophy[2]	28 (6%)	50 (11%)
Mixed	8 (2%)	14 (3%)
Any Lipoatrophy**	36 (8%)	64 (14%)
Gynecomastia (male)[3]	14 (3%)	11 (2%)

* Any lipodystrophy: p = 0.05
** Any lipoatrophy: p = 0.004
1. 'lipohypertrophy' includes reports of increased abdominal girth, buffalo hump, and breast enlargement in women.
2. 'lipoatrophy' includes events of facial, extremity, or subcutaneous fat loss or wasting.
3. 'gynecomastia' refers specifically to breast enlargement in males.

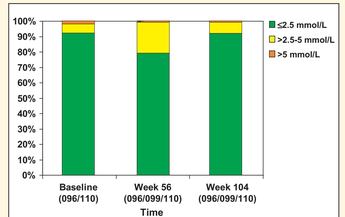
Table 7: Other Events

Events of SHL/LAS; Pancreatitis	N Events*	Pooled XR/PRC (N = 466)	Pooled IR (N = 468)
All:		4 (<1%)	8 (2%)
SHL	7	2 (<1%)	5 (1%)
LAS	2	1 (<1%)	1 (<1%)
Pancreatitis	5	1 (<1%)	4 (<1%)

* some subjects may have had >1 event

- For cases of SHL/LAS, the median time to presentation of symptoms was 44 weeks (range 34 - 57 weeks). No additional events have been reported through the datalock for this analysis, suggesting that in naive patients there may be a window of highest risk for this event between 9-14 months after initiating treatment with antiretrovirals.

Figure 5: Pooled Lactate Distribution (%)



- The concept of a 'window of risk' for lactate-related events is supported by the lactate distribution data that show a maximum upward shift at Week 56, followed by a progressive return to a normal distribution over the second year of dosing.

CONCLUSIONS

- The treatment regimen of stavudine (XR/PRC vs IR), 3TC and EFV was well tolerated, with 74% of those randomized to XR/PRC and 67% of those randomized to IR continuing on-study at 104 weeks.
- The overall efficacy and safety profiles of stavudine XR/PRC are comparable to those of stavudine IR.
- Events of PNS consistently occur at lower rates on XR/PRC, and this trend has significance for grade 2-4 events that are judged by the investigator to be related to study therapy
- Overall, there were fewer events of lipodystrophy in the XR/PRC treatment group and lipodystrophy events (isolated lipoatrophy + mixed lipoatrophy/ lipohypertrophy) are significantly less frequent in the XR/PRC treatment group.
- Clinical events of special interest (SHL/LAS; pancreatitis) occurred at low and comparable rates in both treatment groups, and each occurred in ≤1% of subjects. The absolute number of events was consistently lower for XR/PRC.
- The time distribution for clinical events of SHL/LAS and the shifts in lactate distribution over time both support the concept that there may be a window of highest risk for lactate-related events that occurs between 9-14 months after starting antiretrovirals in naive patients.
- Stavudine XR/PRC may be used to construct fully once-daily regimens that may improve patient adherence and may thereby result in better long-term clinical outcomes.

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