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Stavudine Extended/Prolonged Release (XR/PRC*) *vs* Stavudine Immediate Release (IR) in Combination with Lamivudine and Efavirenz: 48 Week Efficacy and Safety

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ABSTRACT

Background: A multinational, randomized, double-blind, placebo-controlled study evaluated the antiviral activity, safety and tolerability of once-daily d4T extended/prolonged release capsules (XR/PRC) compared to the current twice-daily formulation of d4T immediate release (IR), when used in a HAART regimen in treatment-naïve HIV-infected subjects. **Methods:** Adult subjects with CD4 ≥100 cells/µL (≥ 75 cells/µL if no prior AIDS event) and HIV RNA ≥ 2,000 copies/mL (c/mL) were randomized to either d4T XR/PRC or d4T IR, each in combination with 3TC + EFV (standard doses). The study had 90% power to demonstrate non-inferiority based on the primary outcome of proportion with HIV RNA < 400 c/mL at 48 weeks (wks). **Results:** Of 797 randomized subjects, 783 began treatment. Median baseline HIV RNA and CD4 were 4.8 log10 c/mL and 277 cells/µL, respectively. All subjects had 48 wks of follow-up (median 56 wks). Two virologic response (VR) analyses for LOQ <400 c/mL demonstrate similarity: VR-Treated (VR-T, an ITT analysis for all treated subjects), XR/PRC 80% vs IR 75% ([XR/PRC-IR], 4.4, 95%CI -1.5, 10.3); VR-Completers (VR-C; an On-Treatment analysis), 91% XR/PRC vs 89% IR. Analyses for LOQ <50 c/mL also support similarity: VR-T, XR/PRC 59% vs IR 57%; VR-C, XR/PRC 67% vs IR 67%. Mean increases in CD4 were: XR/PRC +202 vs IR +182 c/mL. At 48 wks, 4% of subjects discontinued therapy in each group due to an adverse event (AE). Grade 3/4 clinical AEs occurred in 43 (11%) of XR/PRC and 41 (10%) of IR subjects. Events of hepatotoxicity, pancreatitis, or symptomatic hyperlactacidemia/lactic acidosis syndrome occurred in a total of 3 (<1%) XR/PRC vs 7 (1.5%) IR subjects. Grade 2-4 peripheral neurologic symptoms related to treatment occurred in 3% of XR/PRC and 5% of IR subjects. **Conclusion:** d4T XR/PRC is well tolerated and exhibits an antiviral and immunologic profile similar to that of d4T IR when used in a HAART regimen for treatment-naïve patients. d4T XR/PRC is an option when designing once daily regimens.

INTRODUCTION

Stavudine (d4T) is currently approved as an immediate release formulation (d4T IR), dosed 40 mg BID for patients ≥60 kg and 30 mg BID for those <60 kg body weight. An extended-release encapsulated bead formulation of d4T (d4T XR/PRC*) that can be dosed once-daily was developed to simplify HIV treatment and improve patient adherence to therapy. The 100 mg QD dose was selected based on modeling and simulations that predicted comparable daily exposure (AUC) to the 40 mg IR BID. The difference in total daily dose is due to lower absorption of d4T from the colon; IR releases all drug in the upper GI tract whereas XR/PRC releases drug continuously throughout the entire GI tract. Data from Phase I PK studies have confirmed the dose-equivalence between XR/PRC 100 mg QD and IR 40 mg BID and that XR/PRC can be taken without regard to food intake (see poster TuPeB4555; additional PK data is presented in poster TuPeB4554). Previously presented data from the final analysis of a 48-week Phase II/III clinical trial comparing d4T XR/PRC and d4T IR when used in combination with lamivudine (3TC) and efavirenz (EFV) have shown similar virologic and immunologic responses as well as comparable safety and tolerability (BMS 096)[1]. This study, BMS 099, is a similarly designed Phase III trial to evaluate the antiviral activity, safety, and tolerability of d4T XR/PRC compared to d4T IR when used in combination with 3TC and EFV in antiretroviral naive adults. Data presented here are from the 48-week analysis.

OBJECTIVES

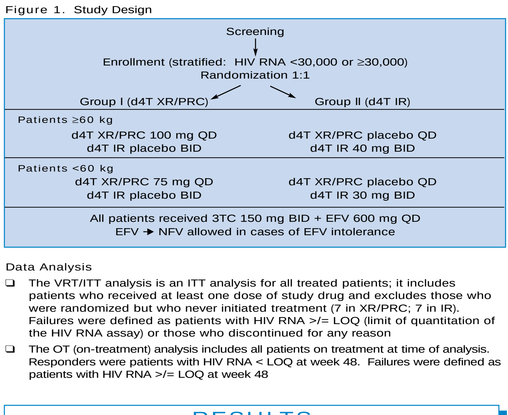
Compare the following outcomes between d4T XR/PRC and d4T IR treatment groups through 48 weeks:

- Primary outcome:
  - Proportion of patients with HIV RNA <400 copies/mL @ week 48
- Secondary outcomes:
  - Proportion of patients with HIV RNA <50 copies/mL @ week 48
  - Magnitude and durability of HIV RNA and CD4+ cell changes from baseline through week 48
  - Safety/tolerability

METHODS

- Phase III multinational, prospective, randomized, double-blind, double-dummy study
- Inclusion criteria
  - HIV RNA ≥2000 copies/mL
  - CD4+ ≥100 cells/mm³ (≥75 if no prior AIDS-defining event)
  - Antiretroviral-naive (≤30 days of any NRTI, NNRTI, or PI)
- Patients with primary (acute) HIV infection or a newly diagnosed HIV-related opportunistic infection or condition were excluded
- This study was designed to provide at least 90% power to demonstrate similar antiviral activity (proportion of patients with HIV RNA <400 copies/mL at 48 weeks) between the d4T XR/PRC and d4T IR-containing regimens
  - Treatment regimens were considered similar if the lower limit of the 95% confidence interval (CI) of the difference in proportions (XR/PRC-IR) was greater than -12%

Figure 1. Study Design



Data Analysis

- The VRT/ITT analysis is an ITT analysis for all treated patients; it includes patients who received at least one dose of study drug and excludes those who were randomized but who never initiated treatment (7 in XR/PRC; 7 in IR). Failures were defined as patients with HIV RNA >/= LOQ (limit of quantitation of the HIV RNA assay) or those who discontinued for any reason
- The OT (on-treatment) analysis includes all patients on treatment at time of analysis. Responders were patients with HIV RNA < LOQ at week 48. Failures were defined as patients with HIV RNA >/= LOQ at week 48

RESULTS

- 797 patients were randomized; 783 initiated therapy at 71 sites worldwide
- The baseline characteristics were well matched between the two treatment groups as shown in Table 1

Table 1. Baseline Characteristics

	d4T XR/PRC *n* = 392	d4T IR *n* = 391
Age, median years	33	33
Gender, *n* (%)		
Male	267 (68)	273 (70)
Female	125 (32)	118 (30)
Race, *n* (%)		
White	168 (43)	163 (42)
Black	91 (23)	75 (19)
Hispanic/Latino	86 (22)	98 (25)
Asian/Pacific Islander	36 (9)	38 (10)
Other*	11 (3)	17 (4)
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)
HIV RNA, $\log_{10}$ copies/mL		
Median	4.8	4.8
Range	2.8–5.9	2.6–5.9
CD4, cells/mm³		
Median	285	272
Range	65–1044	61–1215

*Mostly mixed/biracial subjects.

RESULTS (continued)

Table 2. Patient Disposition From Randomization to Week 48

	Patients, *n* (%)	
	d4T XR/PRC *n* = 399	d4T IR *n* = 398
Randomized	399 (100)	398 (100)
Never treated	7 (2)	7 (2)
Initiated treatment	392 (98)	391 (98)
Discontinued on or before week 48	49 (12)	59 (15)
Adverse event	15 (4)	16 (4)
Lost to follow-up	11 (3)	19 (5)
Other*	7 (2)	5 (1)
Patient withdrew	6 (2)	9 (2)
Pregnancy†	5 (1)	8 (2)
Death‡	3 (<1)	2 (<1)
Treatment failure	2 (<1)	—
Total treated patients completing week 48	343 (86)	332 (83)

*Other includes noncompliance, administration decision, and protocol violation.
†Refers to the % of total patients randomized, not % female patients randomized.
‡One additional IR death (metastatic breast cancer) was not a reason for study discontinuation; therefore does not appear in this table.

- 23 patients (16 XR/PRC; 7 IR) switched the EFV component of the regimen to NFV

Figure 2. Proportion of Patients With HIV-1 RNA < LOQ at Week 48

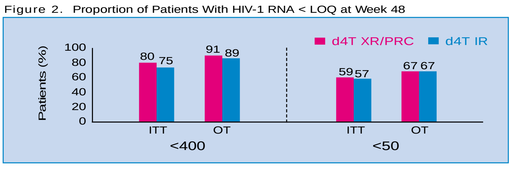
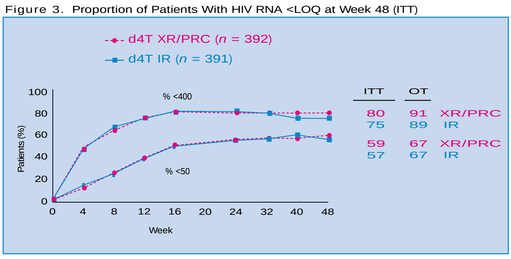


Figure 3. Proportion of Patients With HIV RNA <LOQ at Week 48 (ITT)



- The difference estimates (XR/PRC-IR) for the 2 analyses at both LOQ=400 and LOQ=50 all met the prescribed criteria (lower limit greater than -12%) demonstrating similarity between XR/PRC and IR regimens

Figure 4. HIV RNA: Mean Change From Baseline to Week 48

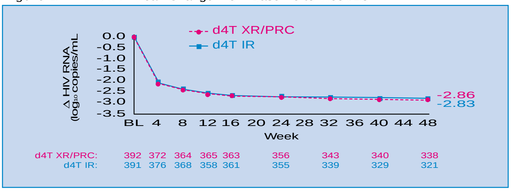


Figure 5. CD4 Count: Mean Change From Baseline to Week 48

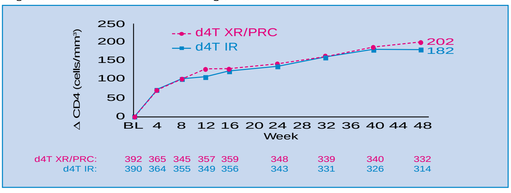


Table 3. Clinical Adverse Events and Laboratory Abnormalities (median time on study = 56 weeks)

Clinical Adverse Events Related to Study Regimen, All Treated Patients (Grade 2-4 events occurring in at least 3% of patients)	d4T XR/PRC/3TC/EFV *n* = 392 Number (%)	d4T IR/3TC/EFV *n* = 391 Number (%)
Any adverse event Grade 2-4	116 (30)	113 (29)
Dizziness	25 (6)	18 (5)
Rash	24 (6)	17 (4)
Abnormal dream	13 (3)	8 (2)
Headache	12 (3)	6 (2)
Insomnia	11 (3)	4 (1)
Fatigue	11 (3)	4 (1)
Peripheral neurologic symptoms	10 (3)	18 (5)

Laboratory Abnormalities (Grade 3-4), All Patients With Laboratory Values Available	d4T XR/PRC/3TC/EFV *n* = 383 Number (%)	d4T IR/3TC/EFV *n* = 387 Number (%)
Hemoglobin	2 (<1)	—
Neutrophils	20 (5)	19 (5)
Platelets	3 (<1)	4 (1)
AST/SGOT	7 (2)	8 (2)
ALT/SGPT	11 (3)	11 (3)
Bilirubin	1 (<1)	—
Lipase	13 (3)	9 (2)

- Over a median follow-up of 56 weeks the following safety observations were made:
  - Pancreatitis occurred in 0 XR/PRC subjects and in 3 IR subjects
  - Lactic acidosis syndrome (LAS) or symptomatic hyperlactemia (SHL) occurred in 2 XR/PRC subjects and 6 IR subjects
  - Lipodystrophy was reported in only 3% of XR/PRC subjects and 4% of IR subjects

DISCUSSION/CONCLUSIONS

- Stavudine XR/PRC 100 mg dosed once daily (75 mg QD for those <60 kg) provides comparable daily drug exposure (AUC) to 40 mg IR dosed twice daily (30 mg BID for those <60 kg). This AUC equivalence translates into similar clinical efficacy and comparable safety as measured by:
  - Proportion of patients achieving HIV RNA <400 or <50 copies/mL
  - HIV RNA mean change from baseline
  - CD4+ cell mean change from baseline
  - Overall rates of clinical adverse events and laboratory abnormalities
- Stavudine was well tolerated through week 48, with only 4% of patients in each arm discontinuing due to adverse events
- Although not achieving statistical significance, medically important events of peripheral neurologic symptoms, pancreatitis, and LAS/SHL occurred in fewer XR/PRC subjects than IR subjects (Table 3)
- 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.

References

[1]Montaner, 8th Eur. Conf. Clin. Aspects Treat. HIV Infect. Abstract LB/O4, 2001.

Acknowledgements

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*Refers to stavudine extended release capsules/prolonged release capsule.