

Name of Sponsor/Company: Bristol-Myers Squibb	Individual Study Table Referring to the Dossier	<i>(For National Authority Use Only)</i>
Name of Finished Product:		
Name of Active Ingredient:		

SYNOPSIS

Clinical Study Report DMP266049/AI266049

TITLE OF STUDY: A Phase IV, Open-Label, Randomized, Multicenter Study to Determine the Safety and Duration of Viral Suppression of Continued Therapy with One or Two Protease Inhibitors + Two Nucleoside Analogue Reverse Transcriptase Inhibitor Regimen Versus Substitution Therapy with Efavirenz + the Same Two Nucleoside Analogue Reverse Transcriptase Inhibitors in HIV-Infected Patients

INVESTIGATORS AND STUDY CENTERS: This study was conducted at 89 sites in the United States and Canada. A list of investigators and their affiliations is provided in Appendix A.2 of this report.

PUBLICATIONS: Becker *et al.*, 8th Conference on Retroviruses and Opportunistic Infections, Oral Presentation, Chicago, IL, February 2001; Becker *et al.*, 5th International Congress on Drug Therapy in HIV Infection, Glasgow, UK, Poster Presentation, October 2000; Rachlis *et al.*, 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, Canada, Oral Presentation, September 2000; Rachlis *et al.*, 1st IAS Conference on HIV Pathogenesis and Treatment, Buenos Aires, Argentina, Poster Presentation, July 2001

STUDY PERIOD: Date first subject enrolled: 08-Feb-1999

Date last subject completed: 13-Dec-2000

CLINICAL PHASE: IV

OBJECTIVES:

Primary: 1) To compare the duration of HIV-RNA suppression of a continued protease inhibitor(s) (PI) + two nucleoside analogue reverse transcriptase inhibitor (NRTI) regimen to an efavirenz substitution regimen in subjects who have achieved plasma HIV - RNA levels below the limit of quantification (< 50 copies/mL) using the Roche Ultrasensitive assay, 2) To evaluate the safety and tolerability of the continuation and substitution regimens

Secondary: To compare the effect of the treatment regimens on CD₄ counts

METHODOLOGY:

This was a 48-week, open-label, randomized, multicenter efficacy and safety study. In the original protocol, subjects were randomly allocated to one of the two following treatment regimens in a 1:1 ratio:

- Continued therapy with current PI(s) + two NRTI or two PI + two NRTI regimen (Treatment A)
- Efavirenz (600 mg orally once daily [QD]) + continued therapy with two NRTIs (Treatment B)

After Amendment 1, subjects were randomized in a 1:2 ratio in favor of the efavirenz substitution regimen.

For Treatment A, the NRTIs and PI(s) remained the same as those administered prior to study entry and were the subject's first effective HIV PI-containing regimen. For Treatment B, subjects randomized to efavirenz and the continued therapy with two NRTIs remained on their current regimen including PI(s) for a 7-day overlap period after starting efavirenz. If the PI was indinavir, the dose was increased to 1000 mg every 8 hours (q8h) for the 7-day period because of an interaction with efavirenz. These subjects then discontinued the PI and continued with the same two NRTIs and efavirenz for the remainder of the study. The NRTI and PI doses were those recommended in the current package insert. Subjects had to be naive to efavirenz and all other NNRTIs.

Efficacy assessments included plasma HIV-RNA levels, CD₄ counts, MOS-HIV health survey, and body weight. Safety assessments included physical examination measurements, vital signs, clinical laboratory tests (including lipid profiles), anthropomorphic measurements, and monitoring of adverse experiences (AEs).

NUMBER OF SUBJECTS:

Total Planned: 300

Total Enrolled: 346

Total Completed: 275

226 subjects were randomized to the efavirenz + two NRTIs group and 120 subjects were randomized to the PI + two NRTIs group. Fifteen subjects in the PI + two NRTIs group and 10 subjects in the efavirenz + two NRTIs group were randomized but not dosed.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

To be enrolled in the study, a subject had to be at least 13 years of age, of either gender, weigh at least 40 kg, have a documented diagnosis of HIV infection, and have two consecutive plasma HIV-RNA levels below quantifiable limits (< 50 copies/mL quantified by the Roche Ultrasensitive Assay) while on their first antiretroviral regimen of a PI + two NRTIs or two PIs + two NRTIs

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:

Test Product: 200 mg efavirenz capsules;

Lot Nos.: 983046, 993186, 982080, and 993082; and commercial efavirenz per Administrative Revision #2 (01-Jun-1999);

Dose and Mode of Administration: 600 mg (3x200 mg capsules) oral dose QD.

Concomitant Therapy: NRTIs and PIs approved for use in the country where the study was being conducted.

Dose and Mode of Administration: NRTI and PI doses were given as recommended in the most current package insert; however, if the PI to be given concomitantly with efavirenz was indinavir, the dose had to be 1000 mg q8h during the 7-day overlap period due to an interaction with efavirenz.

DURATION OF TREATMENT:

48 weeks.

CRITERIA FOR EVALUATION:

The primary effectiveness measure was the time-to-treatment failure with failure defined as two consecutive plasma HIV - RNA levels ≥ 50 copies/mL quantified by an ultrasensitive assay, discontinuation from study for any reason, or any new-onset AIDS-defining event except a CD₄ count < 200 cell/mm³. Time-to-virologic failure, where only virologic rebound was considered failure, was performed as a complementary analysis. Secondary measures of efficacy included change from baseline in CD₄ counts and body weight. Safety was assessed by evaluation of signs and symptoms of AEs, laboratory parameters (serum chemistry, hematology, lipid profiles and urinalysis), physical examinations, anthropomorphic measurements and vital signs. Subjects were to have consumed $\geq 80\%$ of study medication over the course of 1 month.

STATISTICAL METHODS:

The log rank test was used to assess differences among treatments. Kaplan-Meier estimates for time-to-treatment failure and time-to-virologic failure were prepared. Mean change from baseline for safety and study population data was assessed within each treatment group for statistical significance using a paired t-test. A one-way ANOVA model was used to assess differences among the three treatment groups. Treatment compliance was calculated for the percent of subjects who consumed at least 80% of study medication and summarized by visit. The adherence questionnaires were analyzed for the number of doses missed and the percent of compliance based on the questionnaire.

STUDY POPULATION RESULTS: Most of the subjects were White (72%) or Black (19%). The mean (\pm SD) age was 41 years and ranged from 22 to 70 years. At baseline, the overall mean CD₄ cell count was 575 cell/mm³. The number of subjects with HIV-RNA levels < 50 copies/mL was 331 (96%). The mean duration of prior PI treatment was 678 days (range 17 to 1447 days).

EFFICACY RESULTS:

Fifteen (12.5%) subjects in the PI + two NRTIs group and 10 (4.4%) in the efavirenz + two NRTIs group were randomized but not dosed. Additionally, 7 (14.3%) subjects in the PI + two NRTIs group and 8 (3.5%) in the efavirenz + two NRTIs group withdrew consent after starting therapy. Both of these differences were statistically significant, $p = 0.0083$ and $p = 0.0007$, respectively. In the analysis of time-to-treatment failure, patients who refused dosing or who withdrew consent were considered failures. Consequently in this open-label trial, the interpretation of the time-to event analyses is limited due to this differential in censoring.

For the primary measure of efficacy, the log-rank test for the time-to-treatment failure analysis showed that the efavirenz + two NRTIs group had an overall higher "survival rate" than the PI + two NRTIs group in both the analysis for all randomized subjects ($p = 0.0003$) and the analysis excluding subjects who were randomized but not dosed ($p = 0.0092$). The time-to-virologic failure analysis, included as a complementary analysis to the primary analysis, showed that the efavirenz + two NRTIs group maintained virologic success in a statistically significantly greater number of subjects compared to the PI + two NRTIs group ($p = 0.0242$).

For the secondary measures of efficacy, mean CD₄ cell counts increased similarly in both the efavirenz-substitution group and the PI-continuation group overall; however, statistically significantly greater increases from baseline were noted for the PI + two NRTIs arm over the efavirenz + two NRTIs arm at Week 32. The quality of life for subjects in both treatment groups remained high throughout the study with no differences between groups. Mean change in body weight showed minimal mean decreases from baseline (≤ 5.3 kg) within the treatment groups.

SAFETY RESULTS:

The most frequently occurring AEs in greater than 15% of the subjects in the efavirenz + two NRTIs group were dreaming abnormal, influenza-like symptoms, headache, diarrhea, and fatigue, upper respiratory tract infection, pain, and dizziness. The most frequently occurring AEs in greater than 15% of the subjects in the PI + two NRTIs group were influenza-like symptoms, upper respiratory tract infection, diarrhea, and pain. Statistically significantly more AEs were experienced by the efavirenz + two NRTIs group (91.2%) than in the PI + two NRTIs group (80.0%). No clinical laboratory results were reported as AEs by the investigator for greater than 5% of the subjects in the either group. There was no statistical difference between the percentages of subjects in the two treatment groups who discontinued because of an AE (4.42% of subjects in the efavirenz + two NRTIs group and 3.33% in the PI + two NRTIs group).

There was one death in this study (cardiac arrest; considered unrelated to study treatment). Treatment-related serious AEs were reported infrequently in this study. Treatment-related Serious AEs (SAEs) were reported for four subjects in the efavirenz + two NRTIs treatment group that included bilateral leg cramps disorder, allergic reaction, pancreatitis, homicidal ideations, and suicidal ideations. No evidence of clinically meaningful abnormalities due to efavirenz was identified in serum chemistry or hematology parameters.

CONCLUSIONS:

In a select patient population of subjects willing to be randomized to a switch from a PI-containing regimen which has conferred maximal viral suppression and which has been tolerated, substituting efavirenz for the PI resulted in a statistically significantly longer time-to-treatment failure and time-to-virologic failure than maintaining the PI + two NRTIs regimen.

In this open-label study, much of this benefit may be due to the different pattern of discontinuation seen between the test regimens.

Despite the addition of a new agent only in those subjects randomized to the efavirenz + two NRTIs regimen, the efavirenz group tolerated their regimen to a similar extent as the PI + two NRTIs group in terms of subjects with study discontinuations because of AEs, SAEs, or Grade 3 or 4 AEs.

DATE OF REPORT: 01-Aug-2002