SYNOPSIS (Page 1 of 3)

Title of the Study: Study DMP 266-020: A phase III, double-blind, placebo-controlled, multicenter study to determine the effectiveness and tolerability of the combination of DMP 266 and indinavir versus indinavir in HIV-infected patients receiving nucleoside analogue (NRTI) therapy

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Publication(s) (reference): Manion DJ, et. al., Durability of Response of Efavirenz (SUSTIVA™)-Containing Regimens: Report of the Post-Control Period Results of Studies with Efavirenz, 6th Conference on Retroviruses and Opportunistic Infections, Chicago, IL Poster 382; Haas DW, et. al., A Phase III, Double-Blind, Placebo-Controlled, Multicenter Study to Determine the Effectiveness and Tolerability of the Combination of Efavirenz (EFV, SUSTIVA™, DMP 266) and Indinavir (IDV) versus Indinavir in HIV-1 Infected Patients Receiving Nucleoside Analogue (NRTI) Therapy at >36 Weeks [Study DMP 266-020], 38th Interscience Conference on Antimicrobial Agents and Chemotherapy, Abs I-244; Fesse WJ, et al., A Phase III, Double-Blind, Placebo-Controlled, Multicenter Study to Determine the Effectiveness and Tolerability of the Combination of Efavirenz (EFV, SUSTIVA™, DMP 266) and Indinavir (IDV) versus Indinavir in HIV-1 Infected Patients Receiving Nucleoside Analogue (NRTI) Therapy at 24 Weeks [Study DMP266-020]; 12th World AIDS Conference, Abs 22343.

Studied Period: 23 April 1997 to 30 October 1998 (24-week, double-blind period)

Clinical Phase: III

Objectives: The primary objectives were to evaluate the effectiveness and tolerability of efavirenz in combination with indinavir relative to treatment with indinavir alone (placebo plus indinavir) on viral load suppression in HIV-infected patients concomitantly receiving NRTIs. The secondary objectives were to evaluate the effectiveness of efavirenz in combination with indinavir relative to treatment with placebo plus indinavir on other markers of disease in HIV-infected patients concomitantly receiving NRTIs. Also, to characterize the time course of development of resistance to efavirenz in combination with indinavir and to characterize, by genotyping and in vitro susceptibility testing, strains of HIV resistant to this combination.
**SYNOPSIS (Page 2 of 3)**

**Methodology:** This double blind, placebo-controlled, multicenter study assessed the safety and antiretroviral (ARV) activity of efavirenz in combination with indinavir in NRTI-experienced, HIV-infected patients. The primary efficacy measure of ARV activity was based on the percentage of patients below 400 copies/mL at Week 24 based on the Roche Amplicor® Assay. Safety was assessed by the incidence of adverse experiences (AEs), clinical laboratory tests, vital signs, electrocardiogram data, and physical examinations. In addition to the NRTI treatments, patients were randomly allocated to receive 600 mg efavirenz QD plus 1000 mg indinavir q8h; or efavirenz-matching placebo QD plus 800 mg indinavir q8h. Efavirenz was administered in a double-blind, placebo-controlled manner; indinavir was administered blinded only to dose level.

| Number of Patients Planned in Entire Study: | 300 patients | Patients Included in Final Analysis: | 327 patients |

**Diagnosis and Criteria for Inclusion:** Be informed of the nature of the study and provide written informed consent; be 13 to 60 years of age, weigh more than 40 kg, and be post-pubescent; have a confirmed diagnosis of HIV infection; have plasma HIV-RNA levels quantified by reverse transcriptase polymerase chain reaction (RT-PCR) of \( \geq 10,000 \) copies/mL and CD4 counts \( \geq 50 \) cells/mm\(^3\) within 30 days prior to anticipated dosing; non-nucleoside reverse transcriptase inhibitor (NNRTI) and protease inhibitor (PI) naive. Patients were to have received NRTI therapy for at least 8 weeks at some time prior to screening. Pregnant or lactating women were not permitted. All patients were required to use an effective medically-accepted (including barrier) method of contraception during the study.

| Test Product, Dose and Mode of Administration; Lot No.: | Efavirenz (100 mg capsules) and efavirenz-matching placebo were provided by the sponsor. Administration of efavirenz was double-blind and placebo-controlled for 24 weeks. The following drug lots were used: Efavirenz: 961893, 971944, 971956, 971966, 971965, 972053, 972012, 972056, 982080; Efavirenz-matching placebo: 961832, 961845, 971929, 972046, 971985. |

| Reference Therapy, Dose, and Mode of Administration; Lot No.: | Indinavir (200 mg capsules) and indinavir-matching placebo were obtained from Merck Research Laboratories and provided by the sponsor open-labeled in patient kits blinded to dose level. The indinavir lots used were equivalent to the commercially-available product. The following sponsor’s drug lots were used: Indinavir: 961912, 961971, 971989, 972044, 972050, 972058, 972059, 972065, 983004; Indinavir-matching placebo: 961914, 971959. |

| Duration of Treatment: | 24 weeks |

| Criteria for Evaluation: The primary efficacy measure for the study was the percentage of patients with plasma HIV-RNA <400 copies/mL, the lower limit of quantification for the Amplicor® Assay. Secondary analyses include the percentage of patients with plasma HIV-RNA <50 copies/mL using the Ultrasensitive Assay; mean log\(_{10}\) change from baseline for plasma HIV-RNA levels (Amplicor® Assay and Ultrasensitive Assay); and the mean change from baseline in CD4 counts. Results were determined to be statistically significant when the associated test yielded a two-tailed probability of 0.05 or less, except for the intent-to-treat (ITT) analyses of the percent of patients with Amplicor® results <400 copies/mL (p=0.038) or when testing treatment-by-site interactions (p=0.10). Two ITT analyses were performed: ITT: last observation carried forward (LOCF) and ITT: noncompleter=failure (NC=F). Safety was evaluated by the incidence of adverse experiences (AEs), clinical laboratory tests, vital signs, electrocardiogram data, and physical examinations. |

| Study Population: The majority of patients were male (83%). Most of the patients were Caucasian (52%), Black (24%), or Hispanic (21%). The patients ranged in age from 20 to 69 years (mean, 38.5). No statistically significant differences between treatment groups were observed. Mean (SD) baseline log\(_{10}\) plasma HIV-RNA levels were 4.41 (0.58) log\(_{10}\) copies/mL (range 2.63-6.07 log\(_{10}\) copies/mL) and mean (SD) baseline CD4 counts were 328.2 (164.9) cells/mm\(^3\) (range 20-1070 cells/mm\(^3\)). The number of years since first diagnosis of HIV ranged from less than 1 year to 16 years (mean 5.4 years). |

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Efficacy Results: For the primary efficacy measure of percentage of the 327 patients with plasma HIV-RNA levels below the limit of quantification of the Amplicor® Assay (<400 copies/mL) significantly (p≤0.038) more patients in the efavirenz group compared with the control group responded at all timepoints after Week 8 using the observed data and LOCF analyses. At Week 24 (LOCF), 68% of the patients in the efavirenz group (107/157) and 52% of the patients in the control group (89/170) had Amplicor® plasma HIV-RNA levels <400 copies/mL (p-value=0.004). With the NC,F analysis, trends in favor of the efavirenz group were noted at all timepoints, statistical significance between the treatment groups was attained at Week 16 (p≤0.05). Similar favorable results were obtained using the Ultrasensitive Assay, where a significantly greater percentage of patients had plasma HIV-RNA levels <50 copies/mL (below limit of quantification) in the efavirenz group compared with the control group at Weeks 16 and 24 (observed data) and at Week 24 (LOCF analysis). Using the NC,F approach, the statistical superiority of the efavirenz group was noted at Week 24. With regard to the mean change from baseline in log₁₀ transformed plasma HIV-RNA data, greater mean decreases from baseline were observed after Week 8 in the efavirenz group than in the control group. With regard to CD₄ counts, greater mean increases from baseline were noted in the efavirenz group compared with the control group after Week 8, with a significant difference between groups, in favor of efavirenz, at Week 24. No notable differences were noted with regard to the Quality of Life assessments or mean changes in body weight. Twelve AIDS-defining events were reported in the 24-week period.

Pharmacokinetic Results: Plasma samples were obtained from patients for determining population pharmacokinetics of efavirenz and indinavir. These data were not available at the time of this report and will be the subject of a separate report.

Safety Results: No significant differences were observed with regard to the overall incidence of adverse experiences (AEs) between the treatment groups (94% in the efavirenz group compared with 93% in the control group). The most commonly occurring (>15%) new-onset AEs in the efavirenz group were diarrhea, nausea, headache, dizziness, fatigue, and vomiting. The most commonly occurring new-onset AEs in the control group were nausea, diarrhea, headache, and fatigue. Although a greater number of patients in the efavirenz group (47%) than in the control group (24%) reported events of nervous system symptoms, these events were of significantly shorter duration in the efavirenz group than in the control group. The incidence of rash-like events was comparable between treatment groups. No deaths occurred in the 24-week study. Eighteen patients in the efavirenz group discontinued the study due to an AE compared with 9 patients in the control group (p≤0.05). No evidence of clinically meaningful abnormalities due to efavirenz were identified in clinical chemistry or hematology parameters. Increased levels of triglycerides were noted, however these levels and those of other lipid parameters were obtained from patients in a non-fasting state.

Summary-Conclusions: The results of this 24-week study demonstrate significant and clinically important superiority of the efficacy of combination antiretroviral therapy with efavirenz and indinavir compared to indinavir alone in patients also receiving NRTIs. The superior efficacy of efavirenz-containing regimens is readily identified in plasma HIV-RNA levels using multiple analytical approaches. The marked reductions in plasma HIV-RNA levels due to efavirenz are accompanied by notable improvements in CD₄ counts. The effectiveness and favorable safety profile seen in this trial provide substantial support for the use of efavirenz in the treatment of HIV infection.