

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: Sustiva [®] /Stocrin [®]		
Name of Active Ingredient: efavirenz		

SYNOPSIS

Clinical Study Report AI266006

TITLE OF STUDY: A Phase III, Multicenter, Randomized, Open-Label Study To Compare Antiretroviral Activity and Tolerability of Three Different Combination Regimens (Efavirenz + Indinavir, Efavirenz + Zidovudine + Lamivudine, Indinavir + Zidovudine + Lamivudine) In HIV-Infected Patients

INVESTIGATORS: 110

STUDY CENTER: 88 sites total; 61 in North America, 27 in Europe

PUBLICATIONS: Staszewski S *et al.* 12th World AIDS Conference, Geneva, Switzerland; 28 June-3 July 1998. Abstract 22336. Morales-Ramirez J *et al.* 38th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego; 24-27 September 1998. Abstract I-103. Manion DJ *et al.* 36th Annual Meeting of the Infectious Diseases Society of America, Denver; 12-15 November 1998. Abstract 447 Sa. Staszewski S *et al.* AIDS (November 1998) Vol. 12, Supp [4] pp. OP51. Abstract OP51. Tashima K *et al.* *JID*. 1999; 180:862-864. Staszewski S *et al.* *N Engl J Med*. 1999; 341(25):1865-73. Manion DJ *et al.* 6th Conference on Retroviruses and Opportunistic Infections, Chicago; 31 January-4 February 1999. Abstract 383. Tashima K *et al.* 6th Conference on Retroviruses and Opportunistic Infections, Chicago; 4 February 1999. Abstract LB16. Williams G *et al.* *Can J Infect Dis*. March/April 1999; 10(suppl B):28B. Abstract B229. Staszewski S. *International Journal of Clinical Practice*. June 1999; (Suppl 103):10-15. Tashima K *et al.* 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco; 26-29 September 1999; 39:503. Abstract I1304. Staszewski S *et al.* 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco; 26-29 September 1999; 39:472. Abstract 507. Williams G *et al.* 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco; 26-29 September 1999; 39:736. Abstract 457. Tashima K *et al.* 37th Annual Meet Infect Dis Soc Am; Philadelphia; November 1999. Abstract 366. Tashima K *et al.* *Clin Microbiol Infect*. 2000;6(Suppl. 1):139. Abstract WeP252. Bacheler LT *et al.* 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto; 17-20 September 2000; 40:311. Abstract I-1278. Baker D, Bacheler L. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto; 17-20 September 2000;40:328. Abstract 1545. Moyle GJ *et al.* 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto; 17-20 September 2000 40:283. Abstract 547. Ruiz NM *et al.* 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto; 17-20 September 2000; 40:279. Abstract 479. Plosker GL *et al.* *Pharmacoeconomics*. 2001; 19(4):421-36. Levy R *et al.* 8th Conf Retroviruses Opportunistic Infect. Chicago; February 2001. Abstract 325. Arribas J *et al.* 11th ECCMID, Istanbul, Turkey; 1-4 April 2001. Abstract. Tashima K *et al.* 1st International Aids Society Conference on Pathogenesis and Treatment; Buenos Aires, 8-11 July 2001. Abstract 810. Johnson M *et al.* 8th European Conference on Clinical Aspects and Treatment of HIV Infection. Athens, Greece; 28-31 October 2001. Abstract 314. Lupo LJ *et al.* 6th International Congress on Drug Therapy in HIV. Glasgow, Scotland; 17-21 November 2002. Abstract P61. Tashima KT *et al.* *HIV Clin Trials*. 2003; 4(1):29-36. Tashima KT *et*

al. 10th Conference on Retroviruses and Opportunistic Infections; Boston; 10-14 February 2003; Abstract 737. Tashima K *et al.* 9th European Conference of Clinical Microbiology and Infectious Diseases; Berlin, Germany; March 1999. Abstract PO552.

STUDY PERIOD: Date first subject enrolled: 28-Jan-1997

Date last subject completed: 27-Mar-2002

CLINICAL PHASE: III

OBJECTIVES:

The objectives of this study as defined in the protocol and subsequent amendments were

- To compare the antiretroviral activity (both magnitude and duration), as measured by plasma HIV-RNA levels and CD4 cell counts, and safety profile of the following regimens:
 - Efavirenz (EFV) + indinavir (IDV) vs. IDV + zidovudine (ZDV) + lamivudine (3TC) (double vs. triple therapy [primary comparison])
 - EFV + ZDV + 3TC vs. IDV + ZDV + 3TC (triple vs. triple therapy)
 - EFV + IDV vs. EFV + ZDV + 3TC (double vs. triple therapy)
- To characterize the incidence of resistance to EFV and IDV, ZDV, and 3TC, and to characterize the development of resistance by genotypic analysis of plasma virus
- To compare the long-term duration of HIV-RNA suppression between
 - EFV + IDV and IDV + ZDV + 3TC
 - EFV + ZDV + 3TC and IDV + ZDV + 3TC

The primary efficacy analysis in the initial part of the trial consisted of an evaluation of the proportion of subjects with HIV RNA < 400 c/mL at 24 weeks. These data have been previously summarized in an interim analysis report.

Primary Objective of the Final Clinical Study Report

- To compare the durability of virologic suppression of the following regimens by assessing the proportion of subjects in response (HIV RNA < 400 c/mL) at Week 168:
 - EFV + ZDV + 3TC vs. IDV + ZDV + 3TC
 - EFV + IDV vs. IDV + ZDV + 3TC

Secondary Objectives of the Final Clinical Study Report

- To compare the magnitude and duration of CD4 count changes on the three treatment regimens (two comparisons described above)
- To compare the safety profile of the treatment regimens (two comparisons described above)
- To compare the long-term duration of HIV-RNA suppression and response to treatment based on Time to Loss of Virologic Response (TLOVR), Time to Treatment Failure (TTF) and Virologic Response - Observed Cases (VR-OC) definitions (two comparisons described above)

METHODOLOGY:

AI266006 was originally designed as a 24-week, multicenter, open-label, comparative effectiveness and safety study involving 330 qualified subjects who were randomly allocated (1:1:1) to receive one of three treatment regimens: EFV + IDV, EFV + ZDV + 3TC, or IDV + ZDV + 3TC. The protocol was subsequently amended nine times; major changes included: (1) increase in sample size to 1200 subjects and an increase in the treatment observation period in order to report time-to-treatment failure; the study was ultimately extended until the last subject enrolled had completed 168 weeks on study, (2) addition of analysis of HIV RNA levels by the Amplicor[®] Monitor Ultrasensitive method (lower limit of quantification (LOQ) 50 c/mL), (3) modification of EFV and IDV doses in the EFV + IDV arm (see dose section below). Study visits occurred at Weeks 2 and 4, then every 4 weeks until Week 60. Beyond Week 60, study visits occurred quarterly. At the study visits, subjects were provided study medication, had blood drawn for HIV-RNA levels and CD4 cell counts, and were evaluated for safety.

NUMBER OF SUBJECTS:

1200 planned; 1266 randomized: 429 subjects to receive EFV + IDV, 422 to receive EFV + ZDV + 3TC, 415 to receive IDV + ZDV + 3TC.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

All subjects in this study were to be HIV-infected with measurable viral loads above 10,000 c/mL. Subjects were required to have CD4 cell counts ≥ 50 cells/mm³ on one occasion within 30 days of initial dosing. Subjects were to be naïve to protease inhibitor (PI), 3TC, and non-nucleoside reverse transcriptase inhibitor (NNRTI) treatment and between the ages of 13 and 60 years, inclusive (between the ages of 18 and 60 years for European sites). Pregnant or lactating females were excluded, and all subjects were required to use effective (including barrier) contraception (oral contraceptives were not to be used as the sole method of birth control).

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, LOT NUMBERS: EFV 600 (3 x 200 or 6 x 100) mg administered orally (PO) once daily (QD). Approximately 30 subjects randomized to the EFV + IDV arm initially received 400 mg of EFV QD, which was subsequently increased to 600 mg QD. See batch numbers below.

EFV 100 mg	EFV 200 mg
961844, 961904, 971928, 971943, 971944, 971957, 971975, 971976, 972001, 972002, 972003, 972004, 972029	971977, 972011, 972012, 972014, 972016, 972017, 972018, 972019, 972053, 972055, 972056, 982080, 983035, 983036, 983041, 983042, 983044, 983045, 993079, 993081, 993082, 993114, 993185, 993186, 993150, 003245, 003248, 003317

CONCOMITANT ANTIRETROVIRAL THERAPY, DOSE AND MODE OF ADMINISTRATION, ZDV (3 x 100) mg PO every 12 hours (q12h), 3TC 150 mg PO q12h. Subsequently, use of the fixed dose oral ZDV-3TC combination (Combivir[®]), containing the same doses of ZDV and 3TC, was allowed. IDV 800 (4 x 200) mg PO every 8 hours (q8h) was administered in the IDV + ZDV + 3TC arm. Approximately 30 subjects randomized to the EFV + IDV arm initially received IDV 1200 (6 x 200) mg PO QD, which was subsequently lowered to 1000 mg (5 x 200 mg) QD on the basis of pharmacokinetic data derived from Study DMP 266-003. See batch numbers in the following table.

IDV ^a	ZDV ^a	3TC ^a	Combivir ^{®a}
961836, 961847, 961911, 961912, 961913, 971930, 971958, 971989, 972044, 972050, 972058, 972059, 972065, 983004, 983024, 983039, 993114, 993088, 993147, 993148, 993182, 003212, 003231, 003258, 003259, 013354, 013393	961827, 961861, 961901, 961902, 961916, 972029, 972060, 972063, 982077, 982092, 983022, 983026, 983057, 983069, 993091, 993130, 993195, 003265	961860, 961897, 961915, 972028, 972061, 972064, 982078, 982091, 983023, 983027, 983059, 993092, 993125, 993196, 003255	993143, 993144, 993180, 003211, 003232, 003254

^a From Sponsor drug lots

DURATION OF TREATMENT:

All medications were to be administered until the last subject enrolled completed at least 168 weeks on-study. The longest time that a subject was on study was 264 weeks.

CRITERIA FOR EVALUATION:

Efficacy: The primary efficacy objective comparing the durability of virologic suppression and response to treatment was realized by performing three principal efficacy analyses: Comparison of proportion of subjects in response at Week 168 using TLOVR, TTF and pure virologic (VR-OC) definitions of response (suppression defined as viral load < 400 c/mL in each analysis). The primary efficacy analysis consisted of a comparison of the proportions of subjects in response (viral load < 400 c/mL) at Week 168 using the TLOVR definition of response (EFV + ZDV + 3TC vs. IDV + ZDV + 3TC and EFV + IDV vs. IDV + ZDV + 3TC). Other analyses of efficacy were supportive. Week 168 was selected for the primary efficacy comparison because the protocol specified the study would be terminated after the last subject had been followed for 168 weeks. In addition, subjects in all treatment arms had reached the median time to treatment failure by 168 weeks, thus satisfying a commitment to the US Food and Drug administration (US FDA) that the sponsor submit efficacy data from AI266006 until subjects in each treatment arm reach the median time to failure.

Safety: Safety analyses were conducted on treated subjects (except serious adverse event [SAE] analyses, which were conducted on randomized subjects). The following were summarized by treatment regimen: on-study clinical adverse events (AEs), treatment-related AEs, deaths, analyses of nervous system symptoms and psychiatric symptoms, summaries of new-onset events by time period on-study, SAEs, AEs leading to discontinuation of study therapy, and liver enzyme abnormalities among subjects co-infected with hepatitis B and C.

STATISTICAL METHODS:

This study had 90% power to compare durability of HIV RNA suppression between EFV + ZDV + 3TC or EFV + IDV vs. IDV + ZDV + 3TC (control) for the primary endpoint of the proportion of subjects responding to treatment with HIV RNA < 400 c/mL. In study planning, the power calculations assumed treatments would be considered equivalent (non-inferior) if there was less than a 12% difference in the

percentage of subjects with HIV-RNA still suppressed below 400 c/mL. For the purposes of evaluation of the primary long-term efficacy variable, proportion responding (< 400 c/mL) according to the TLOVR definition of success at Week 168, EFV + ZDV + 3TC and EFV + IDV would be determined to be non-inferior to IDV + ZDV + 3TC if the 97.5% confidence interval for the difference estimates for proportions < 400 c/mL had a lower limit greater than -12%. If non-inferiority was established, then a test for superiority was conducted at an alpha level of 0.025. Because the test of superiority was only conducted if the test for non-inferiority was successful, significance level was not adjusted for the first test. The primary analysis uses the FDA-defined sustained virologic suppression algorithm TLOVR to determine response. TLOVR employed a response definition of a minimum of two consecutive HIV RNA measurements $< LOQ$ maintained through end of study without intervening confirmed rebounds or treatment discontinuations. If the last measurement on-study was $> LOQ$, the subject was considered a failure for that visit. Deaths, loss to follow-up, and changes in antiretroviral therapy also counted as failure in the TLOVR algorithm. Subjects who were in response but elected not to continue in the voluntary extension phases of the study were censored on the date of their last on-treatment HIV RNA measurement. TTF was defined as loss of HIV RNA suppression (confirmed RNA ≥ 400 c/mL), development of a CDC Class C AIDS-defining event, treatment discontinuation or start of alternative HIV treatment after having two consecutive HIV RNA determinations $< LOQ$, or failure to virologically suppress or failure to receive study medication after randomization up to the reported visit week. The VR-OC definition classified subjects who remained on treatment according to a single HIV RNA measurement, either $< LOQ$ or $\geq LOQ$ closest to the scheduled visit and within a predefined visit window. Only those subjects who remained on treatment at the time of their visit week were included. Subjects with HIV RNA $\geq LOQ$ were considered failures. Subjects who remained on treatment and were missing a measurement were classified as responders only if their immediately previous and subsequent viral loads met the VR-OC criteria for response. Treatment comparisons were computed for Week 168, except for time to analyses, which use all available data. Secondary efficacy endpoints were the proportion of subjects with HIV RNA < 50 c/mL (TLOVR definition of response); time to failure (TTF; TLOVR) through the end of study; VR-OC (LOQ 50 c/mL and LOQ 400 c/mL) and the magnitude and durability of changes in HIV RNA levels and CD4+ cell counts from baseline through Week 168. Efficacy analyses included all randomized subjects. The 97.5% CIs were computed using a normal approximation. The Time-Averaged Differences (TAD) between treatment arms in the change from baseline HIV RNA and CD4 cell count through Week 168 were computed with 97.5% CIs. Time to treatment failure for LOQ = 400 c/mL was compared using hazard ratios and 97.5% CI from Cox proportional hazards models.

RESULTS:

Subject Disposition and Demographics at Baseline - N (%)

	EFV+IDV	EFV+ZDV+3TC	IDV+ZDV+3TC
Randomized	429	422	415
Treated	415 (97)	412 (98)	401 (97)
Never Treated	14 (3)	10 (2)	14 (3)
Completed	160 (37)	196 (46)	127 (31)
Discontinued Prior to Week 48 Visit	130 (30)	97 (23)	154 (37)
Failed to return/Lost to follow-up	40 (9)	40 (9)	32 (8)
Adverse event	33 (8)	33 (8)	74 (18)
Protocol violation	22 (5)	11 (3)	25 (6)
Subject withdrew consent	10 (2)	7 (2)	12 (3)
Treatment failure/lack of efficacy	18 (4)	5 (1)	8 (2)
Other	7 (2)	1 (<1)	3 (<1)
Discontinued at Week 48 or later and prior to Week 168 visit	103 (24)	85 (20)	100 (24)
Failed to return/Lost to follow-up	28 (7)	23 (5)	16 (4)
Adverse event	14 (3)	14 (3)	26 (6)
Protocol violation	7 (2)	13 (3)	12 (3)
Subject withdrew consent	18 (4)	13 (3)	24 (6)
Treatment failure/lack of efficacy	30 (7)	12 (3)	18 (4)
Other	6 (1)	10 (2)	4 (<1)
Age - Median (Range)	35 (18 - 73)	36 (19 - 81)	35 (19 - 68)
Gender (% Male)	86	82	80
Race (% White, % Black, % Hispanic)	60, 20, 17	60, 21, 17	62, 19, 16
HIV RNA Level (log ₁₀ c/mL): median (min, max)	4.8 (2.5 - 6.5)	4.8 (3.2 - 6.5)	4.7 (3.4 - 7.0)
CD4 cell counts (cells/mm ³): median (min, max)	320.0 (2 - 1169)	314.5 (26 - 1234)	331.0 (18 - 1198)
NRTIs prior to study (%)	16	18	13

(Note: Week 48 visit: Study Day 332; Week 168 visit: Study Day 1134)

- Premature discontinuations were more common on the IDV + ZDV + 3TC regimen in this open label study. There were more discontinuations for AEs in this group.
- Baseline demographics were consistent among the treatment regimens. Most subjects were antiretroviral naïve.

EFFICACY RESULTS:

Efficacy Results at Week 168 - Responders/Evaluable (%)

	EFV+IDV	EFV+ZDV+3TC	IDV+ZDV+3TC
TLOVR ^a Response Rate (LOQ 400 c/mL)	171/429 (40)	203/422 (48)	123/415 (30)
TLOVR ^a Response Rate (LOQ 50 c/mL)	134/429 (31)	180/422 (43)	96/415 (23)
TTF ^b Response Rate (LOQ 400 c/mL)	161/429 (38)	190/422 (45)	114/415 (27)
TTF ^b Response Rate (LOQ 50 c/mL)	128/429 (30)	169/422 (40)	89/415 (21)
VR-OC (LOQ 400 c/mL) at Week 168	172/181 (95)	216/228 (95)	127/140 (91)
VR-OC (LOQ 50 c/mL) at Week 168	158/181 (87)	207/228 (91)	113/140 (81)
HIV RNA level (log ₁₀ c/mL) median change from baseline	-3.08	-3.09	-2.96
CD4 cell counts (cells/mm ³) median change from baseline	300	292	292

^a Proportion responding using the TLOVR definition of response

^b Proportion responding using the TTF definition of response

- Virologic suppression conferred by EFV + ZDV + 3TC is durable at 168 weeks of follow-up. In the primary efficacy analysis (proportion in response at Week 168 using TLOVR definition of response with viral suppression defined as viral load < 400 c/mL), response rates in the three treatment groups were 48% (EFV + ZDV + 3TC), 40% (EFV + IDV), and 30% (IDV + ZDV + 3TC). At 168 weeks, the percentage of subjects who had failed virologically in the TLOVR analysis (rebound or never suppressed) were 12% (EFV + ZDV + 3TC), 19% (EFV + IDV), and 17% (IDV + ZDV + 3TC).
- In this randomized, open label study, the higher response rate in the EFV + ZDV + 3TC arm compared with the IDV control arm that was evident at the 48-week interim analysis persisted at extended follow-up.
- There was a slightly higher rate of discontinuation for lack of effect/treatment failure in the EFV + IDV group.
- CD4 cell count increases continued over time in all groups.

SAFETY RESULTS:

Deaths, AEs, and Laboratory Abnormalities N (%)			
	EFV+IDV N = 415	EFV+ZDV+3TC N = 412	IDV+ZDV+3TC N = 401
Median follow-up	102 weeks	180 weeks	76 weeks
Deaths (Deaths/1000 Subject-Years of Follow-up)	5 (5.1)	8 (7.0)	3 (3.6)
AEs Leading to Discontinuations	50 (12)	52 (13)	104 (26)
Serious AEs	79 (19)	94 (23)	67 (17)
Selected Grade 3/4 Laboratory Abnormalities			
- White Blood Cells	1 (0)	4 (1)	6 (1)
- Neutrophils	11 (3)	41 (10)	21 (5)
- Platelets	0 (0)	2 (0)	1 (0)
- Hemoglobin	0 (0)	6 (1)	4 (0)
- Bilirubin	5 (1)	3 (1)	59 (15)
- AST	25 (6)	20 (5)	19 (5)
- ALT	35 (8)	21 (5)	21 (5)
- GGT	28 (7)	34 (8)	13 (3)
- Alkaline Phosphatase	0 (0)	2 (0)	0 (0)
- Amylase	18 (4)	15 (4)	5 (1)

- No new unexpected late-onset safety signal was appreciable among long-term recipients of EFV.
- Sixteen deaths were reported. There were five deaths in the EFV + IDV group and eight deaths in the EFV + ZDV + 3TC group, all of which were considered unlikely to be related to treatment except for one death from unspecified causes for which a relationship to study therapy was not provided. Three deaths were reported for subjects treated with IDV + ZDV + 3TC, one of which was considered possibly related to study therapy. The significance of these mortality figures is unknown, given the higher dropout rate in the control group.
- A higher percentage of subjects in the IDV + ZDV + 3TC group (26%) discontinued study treatment as a result of an AE.
- No SAE captured in the CRF (clinical) database affected more than 2% of randomized subjects with the exception of drug abuse, which was experienced by 2-3% of subjects in each treatment group.
- In general, AEs tended to be mild to moderate in severity in all groups. Grade 3/4 AEs occurred in 39%, 42%, and 48% of subjects in the EFV + IDV, EFV + ZDV + 3TC, and IDV + ZDV + 3TC groups, respectively. Treatment-related Grade 3/4 AEs occurred among 22%, 24% and 34% of EFV + IDV, EFV + ZDV + 3TC, and IDV + ZDV + 3TC recipients, respectively.
- Seventy-two percent of subjects in the IDV + ZDV + 3TC group developed one or more treatment-related AEs of at least Grade 2 severity, versus 66% and 62% of subjects treated with EFV + IDV and EFV + ZDV + 3TC, respectively. Treatment-related AEs of at least Grade 2 severity for which the frequency in either of the EFV-containing groups exceeded that in the IDV + ZDV + 3TC group by ≥ 5% included: dizziness (9% in each of the EFV groups vs. 2% in the IDV + ZDV + 3TC group), headache (EFV + IDV: 5%, EFV + ZDV + 3TC: 8%, IDV + ZDV + 3TC: 3%), insomnia (7% in each of the EFV groups and 2% in the IDV + ZDV + 3TC group), concentration impaired (EFV + IDV: 3%,

EFV + ZDV + 3TC: 5%, IDV + ZDV + 3TC: 2 subjects rounded to zero percent), and maculopapular rash (EFV + IDV: 11%, EFV + ZDV + 3TC: 9%, IDV + ZDV + 3TC: 4%). Treatment related AEs of at least Grade 2 severity for which the frequency in the IDV + ZDV + 3TC group exceeded the frequency in either of the EFV groups by 5% include pain, nausea, vomiting, hyperbilirubinemia, renal calculus, and renal pain. These between-group differences are consistent with the known safety profiles of the study drugs.

- Analyses of AEs (all grades) by time-frame on-study showed that neurologic AEs and maculopapular rash were seen early after the initiation of EFV-based regimens. The incidence of each of these events during latter phases of the study (> 24 weeks) was roughly comparable to that seen in the control arm. Conversely, the incidence of nausea remained higher in the control group up to 48 weeks on study and the incidence of bilirubinemia and renal calculus formation in the control group remained higher than that seen among EFV recipients at extended follow-up.
- When all psychiatric AEs on-study were evaluated using a definition for psychiatric symptoms consisting of a constellation of predetermined World Health Organization Adverse Reaction Term (WHOART) codes (aggressive reaction, Grade 3/4 depression, depression psychotic, manic reaction, paranoid reaction, psychosis, suicide attempt, depression aggravated, and psychosis manic-depressive) one or more psychiatric system symptoms was reported in 5% of subjects who received EFV + IDV and by 8% of subjects who received EFV + ZDV + 3TC. The incidence of these events was lower in the IDV + ZDV + 3TC group (3%).
- New onset Grade 3/4 transaminase abnormalities occurred with similar frequency (5% to 8%) among the study groups. An increased frequency of transaminase abnormalities was observed among subjects treated with both EFV and IDV. Alkaline phosphatase and GGT abnormalities were approximately twice as common among EFV recipients compared with subjects in the IDV control group, while bilirubin abnormalities were more frequent in the control group.
- There were 137 subjects treated with EFV and 84 treated with IDV + ZDV + 3TC who were seropositive for hepatitis B (surface antigen positive) and/or C (hepatitis C antibody positive). After a median duration of therapy of 68 weeks (EFV groups) and 56 weeks (IDV + ZDV + 3TC), an analysis of mean change from baseline in liver enzymes revealed mild-to-moderate increases in transaminases in the EFV groups compared with the IDV + ZDV + 3TC group. The transaminase elevations were generally mild in the EFV + ZDV + 3TC group. By comparison, mean changes from baseline in transaminase values were more consistently positive in the EFV + IDV group. New-onset (new or grade worse than baseline) Grade 3/4 (> 5 X ULN) transaminase abnormalities were more frequent among hepatitis co-infected recipients of EFV (AST 13%; ALT 20%) versus co-infected recipients of IDV + ZDV + 3TC (AST 7%; ALT 7%). New-onset Grade 3/4 GGT abnormalities occurred in 18% of co-infected EFV-treated subjects versus 4% of co-infected IDV + ZDV + 3TC treated subjects. The higher risk of Grade 3/4 liver enzyme abnormalities among co-infected recipients of EFV did not translate into frequent discontinuations from the study for hepatic or biliary AEs.
- Use of non-fasting blood samples did not allow reliable interpretation of triglycerides and LDL data. Increases in HDL cholesterol were more marked at approximately Week 96 in the EFV arms, whereas combined use of EFV and IDV, each of which appeared to be associated with comparable increases in total cholesterol (TC) when given alone, resulted in an apparent additive effect on TC at this timepoint. Attrition and selection bias may have affected these and other laboratory analyses at late study timepoints.
- Notably, the rates of hyperbilirubinemia and renal calculus formation in the EFV + IDV arm were lower than that seen in the IDV + ZDV + 3TC arm. This may be explained by lower IDV clearance related to EFV-induced augmentation of hepatic enzyme metabolism.

OVERALL CONCLUSIONS:

- EFV + ZDV + 3TC provides potent and durable virologic suppression through 168 weeks of therapy and is well tolerated.
- Between-group differences in response rates in this open-label study, favoring EFV + ZDV + 3TC over IDV + ZDV + 3TC, endure at over 3 years of follow-up.
- All three regimens produced continued decreases in HIV RNA levels with continued therapy among those subjects who remained on-study. The overall and LOCF TAD estimates showed statistically significant differences in favor of EFV + ZDV + 3TC over IDV + ZDV + 3TC.
- For all three treatment regimens, CD4 cell counts continued to rise with continued therapy with mean increases of approximately 300 cells/mm³.
- In this open-label study, more subjects discontinued the study prematurely in the IDV + ZDV + 3TC arm than in the EFV treatment arms, primarily as a result of AEs.
- No new unexpected late-onset safety signal was appreciable among long-term recipients of EFV. EFV + ZDV + 3TC was better tolerated than the IDV-containing control regimen.

DATE: 12-Jul-2004