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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-972/S-001

Medical/Statistical Review(s)

DRAFT

DA 20-972
S-001

Joint Medical and Statistical Review

Date Submitted: May 26, 1999
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Applicant: DuPont Pharmaceutical Company
Maple Run Grove Road
Wilmington, DE 19880

Drug:
Chemical: (S)6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4- (trifluoromethyl)-2H-3,1-benzpxazin-2-one
Generic: Efavirenz
Trade: SUSTIVA ™

Route: Oral

Dosage Form: 50 mg, 100 mg, and 200 mg capsules

Proposed Indication: Treatment of HIV-1 infection in combination with other antiretroviral agents

Related INDs: 49,465 and 56,836

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1. Resume

The applicant has requested traditional approval for Sustiva ™ (efavirenz capsules), a non-nucleoside reverse transcriptase inhibitor (NNRTI) for the treatment of HIV-1 infection, when used in combination with other antiretroviral agents. This indication is based on surrogate endpoint analyses of plasma HIV RNA levels in controlled studies through 48 weeks in duration.

In support of the request for traditional approval, the applicant has submitted the 48-week surrogate endpoint and safety data from two adequate and well-controlled trials. In addition, the applicant has submitted updated 24-week surrogate endpoint and safety data from an additional adequate and well-controlled trial, and safety experience from an expanded access program and five additional phase 2/3 studies.

The principal controlled studies, DMP 266-006, and ACTG 364, provide adequate evidence that efavirenz in combination with other antiretroviral agents has an effect on surrogate endpoints over 48 weeks that are reasonably likely to be associated with clinical benefit. The primary efficacy measure was time to treatment failure.

Study DMP 266-006 is an ongoing, open-label, randomized trial that compared efavirenz (EFV)/ zidovudine (ZDV)/lamivudine (3TC) or efavirenz/indinavir (IDV) to indinavir/zidovudine/lamivudine in 1,266 HIV-infected patients who were naïve to efavirenz, lamivudine, other non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors. Sixty-eight percent of patients in the EFV/ZDV/3TC arm and 55% of patients in the EFV/IDV arm compared to 49% of patients in the IDV/ZDV/3TC arm achieved HIV RNA < 400 copies/ml at week 48 of treatment. More patients in the IDV/ZDV/3TC arm discontinued study treatment due to adverse events compared to the other two treatment arms. It appears that part of the observed treatment effect may be due to early discontinuations in the control arm. However, efavirenz- containing arms certainly demonstrated efficacy comparable to the control arm. There was no significant difference in the mean CD4 cell counts among the treatment arms; the overall mean increase was 176 cells/mm^3 at 48 weeks.

ACTG 364 was a 48-week double-blind, placebo-controlled trial that enrolled 196 NRTI-experienced patients who had completed two prior ACTG studies. One treatment group received EFV in combination with nelfinavir (NFV) and two nucleoside reverse transcriptase inhibitors (NRTIs), another received EFV and two NRTIs, and the third group received NFV and two NRTIs. Seventy-two percent of patients in the EFV/IDV/2NRTIs arm and 62% of patients in the EFV/2NRTIs arm compared to 42% in the NFV/2NRTIs arm achieved HIV RNA < 500 copies/ml at week 48 of treatment. There was no significant difference in the mean CD4 cell counts among the treatment arms; the overall increase was approximately 105 cells/mm^3 at 48 weeks.

A supportive trial, Study DMP 266-020, was a 24-week randomized, double-blind, placebo-controlled trial that compared EFV/IDV/NRTIs to placebo/IDV/NRTIs in 327 HIV infected patients who were NRTI-experienced, but NNRTI, and protease inhibitor

(PI) treatment-naïve. Physicians were allowed to add up to two NRTIs of their choice to the treatment regimen of EFV/IDV or placebo/IDV. Fifty-nine percent of patients who received EFV/IDV/NRTIs compared to 51% of patients who received IDV/NRTIs achieved HIV RNA < 400 copies/ml at 24 weeks of treatment. Although the results were not statistically significant using HIV RNA < 400 copies/ml as a cutoff, the results were significant using the Ultrasensitive HIV-1 RNA Monitor™ assay and 50 copies/ml as a cutoff. The study does provide supportive evidence of efficacy. There was no significant difference in the mean CD4 cell count between treatment arms; the overall mean increase was 155 cells/mm^3 at 24 weeks.

A total of 10,142 patients were enrolled in the nine studies presented in the NDA. A total of 9,469 patients received efavirenz at various doses; and 1,196 received efavirenz at a dose of 600 mg qd as part of a controlled trial.

The following table lists the number of patients enrolled in each of the nine studies.

Table 1. List of studies and number of patients

Study	Patients enrolled	Received EFV at any dose	Randomized to EFV 600 mg qd in controlled trial
DMP 266-006*	1,266	851	851
ACTG 364*	196	129	129
DMP 266-020*	327	154	154
DMP 266-003	201	201	---
DMP 266-004*	93	85	28
DMP 266-005*	137	127	34
DMP 266-021	18	18	---
DMP 266-024	62	62	---
DMP 903 (Expanded Access)	7,842	7,842	---

* Controlled trial

The most concerning adverse events associated with efavirenz therapy were nervous system symptoms, psychiatric adverse events and skin rash. Fifty-three percent of patients receiving efavirenz reported nervous system and psychiatric symptoms compared to 25% in control groups. These symptoms included, but were not limited to, dizziness, impaired concentration, somnolence, abnormal dreams and insomnia. In about 3% of patients in clinical trials, nervous system and/or psychiatric symptoms were serious and included severe depression, suicidal ideation/attempts, and aggressive behavior. Patients with a history of a pre-existing psychiatric disorder or substance abuse were more likely to develop these serious nervous system and psychiatric adverse events. In clinical trials, 2.1% of patients discontinued efavirenz therapy because of nervous system symptoms or psychiatric events compared to 1.1% in control arms. Overall, these symptoms usually began during the first or second day of therapy and generally resolved after the first 2-4 weeks of treatment.

Skin rash was reported by 26% of adult patients treated with 600 mg qd of efavirenz compared to 18% of patients in the control groups. In clinical trials, one patient developed erythema multiforme and another patient developed Stevens-Johnson syndrome.

The data in this application support the conclusion that efavirenz in combination with other antiretroviral agents is indicated for the treatment of HIV-infection.

2. Regulatory history

The first IND for DMP 266, also known as efavirenz, was submitted by DuPont Merck Pharmaceutical Company on December 21, 1995. A discussion of the results of phase 1 and 2 trials was conducted with FDA on December 9, 1996. The applicant met with the Division of Antiviral Drug Products Advisory Committee in closed session on July 9, 1997 to discuss adequacy of overall drug development. The applicant returned to FDA for an End-of-Phase 2 meeting on December 1, 1997 and a Pre-NDA meeting on December 17, 1997. A rolling submission of the results of phase 1 and 2 studies was initiated in March 1998. Fast Track designation was assigned to the IND on May 29, 1998. On June 11, 1998, the NDA package for accelerated approval was submitted and was approved on September 17, 1998. On May 26, 1999, the NDA package for traditional approval was submitted.

3. Summary of NDA clinical section

The clinical section of this application includes the study reports of three phase 3 clinical trials, and safety reports of five additional trials in adults and an expanded access program.

In the three phase 3 studies, data are presented on 1,784 HIV-infected patients who entered clinical trials that compared patients on efavirenz-containing regimens with those on other antiretroviral combinations. A total of 1,138 patients were randomized to efavirenz-containing therapies in those studies.

A. DMP 266-006 is an ongoing, open-label, randomized trial that compared efavirenz 600 mg qd + zidovudine 300 mg bid + lamivudine 150 mg bid or efavirenz 600 mg qd + indinavir 1000 mg q8h to indinavir 800 mg q8h + zidovudine 300 mg bid + lamivudine 150 mg bid in HIV-infected patients. Twelve hundred sixty six patients who were naïve to efavirenz, lamivudine, other non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors were enrolled and followed through week 48.

B. ACTG 364 was a randomized, double blind, placebo-controlled 48-week study in NRTI-experienced patients who had completed two prior ACTG studies. One hundred ninety-six patients were randomized to receive NRTIs in combination with efavirenz 600 mg qd, or nelfinavir 750 mg tid, or efavirenz + nelfinavir. Upon entry into the study, all patients were assigned a new open label NRTI regimen, which was dependent on their previous NRTI treatment experience.

C. DMP 266-020 was a randomized, double-blind, placebo-controlled 24-week study in NRTI-experienced, protease inhibitor and NNRTI-naïve patients and compared efavirenz 600 mg qd + indinavir 1000 mg q8h + NRTIs with indinavir 800 mg q8h + NRTIs. Sixty-eight percent of the 327 patients changed their NRTI regimen at study entry.

In addition to the three phase 3 studies, the sponsor provided the safety results of six additional studies. Three studies were double-blind, placebo-controlled phase 2 studies employing efavirenz at doses of 200, 400, or 600 mg qd (Studies DMP 266-003, DMP 266-004, and DMP 266-005). Two phase 2, open-label studies evaluating efavirenz in combination with indinavir or nelfinavir were conducted (DMP 266-021 and DMP 266-024). An open-label expanded access program provided efavirenz for 7,842 patients 13 years and older and with advanced HIV disease (DMP 266-903).

4. Phase 3 clinical trials

The review of the application included an evaluation of the analyses presented by the applicant and construction of safety and efficacy tables from the electronic database on all patients in the principal studies. This review also included an examination of case report forms and patient narratives for patients with serious nervous system symptoms and selected patients with other adverse events.

In the two principal studies (Study 006 and ACTG 364), the response was measured as the time to treatment failure. This analysis allows for inclusion of data beyond 48 weeks as Kaplan-Meier estimates by accounting for patients who are still virologic responders at 48 weeks or longer but have not yet reached 112 weeks in Study 006 or 72 weeks in ACTG 364. Plasma HIV RNA levels were quantified using the Amplicor HIV-1 RNA Monitor™ (assay limit 400 copies/ml in study 006 and 500 copies/ml in ACTG 364). Patients were considered to have reached this endpoint if they 1) failed to achieve initial suppression of virus to below the assay limit 2) dropped out of the study, 3) switched antiretroviral therapy, 4) achieved levels below the assay limit but subsequently had a confirmed rise to the assay limit or above it, or 5) had a CDC Category C event. The inclusion of CDC Category C events as failures is different from the standard definition of failures in non-completers equals failure (NC=F) analyses.

Secondary efficacy analyses describes the proportion of patients with plasma HIV-RNA (Amplicor HIV-1 RNA Monitor™ assay) levels less than 400 copies/ml (for studies DMP 266-006 and DMP 266-020) or 500 copies/ml (for ACTG 364). The efficacy data were also presented by the applicant describing the proportion of patients with plasma HIV-RNA (Ultrasensitive HIV-1 RNA Monitor™ assay) levels less than 50 copies/ml. Mean change in CD4 cell counts from baseline also will be presented.

Several addenda were submitted during the review process. A response to questions regarding nervous system and serious psychiatric adverse events was submitted on September 13, 1999. The original submission for study 006 reported 614/1266 (48%) patients who had completed 48 weeks of therapy. An efficacy update for Study 006 was submitted on November 8, 1999 which provided Kaplan-Meier estimates for studies

ACTG 364 and Study 006. The results of Study 006 were updated to reflect that all 1266 patients had either reached a failure endpoint or were virologic responders through 48 weeks. On December 10, 1999 the applicant submitted a revised outcome tables for studies ACTG 364 and Study 006 based on modified rules for attribution of failure endpoints agreed upon by the reviewers and the applicant. On December 16, 1999 the sponsor provided further discussion of the Kaplan-Meier plots for inclusion in the label.

Statistical Analysis: Kaplan-Meier Estimates

Since this is the first application where efficacy results will be summarized using a Kaplan-Meier (KM) analysis, it is worthwhile to discuss how the KM analysis differs from the "raw" success rates in a proportion analysis. Consider the following example, with one treatment arm and two time points.

	Start	Week 24	Week 48
Success	100	60	36
Failed	0	40	54
Censored	0	0	10
Proportion	100%	60%	40% (4/10 censored imputed success)
KM	100%	60%	43% (7/10 censored imputed success)

Proportion Success
Censored are removed from numerator and denominator, so the success rate is 36/(36+54)=36/90=40%. This is equivalent to assuming that the 10 censored outcomes are similar to the 90 observed week 48 outcomes, that is, 4 of 10 are successes and 6 of 10 are failures: (36+4)/(36+4+54+6)=40/100=40%.

Kaplan-Meier
Of the 60 patient who were success at week 24, 36 are successes, 14 failures, and 10 censored. These 10 censored are assumed to similar to the 50 non-censored patients on study past 24 weeks, in contrast to the proportion analysis where the 10 censored are assumed to be similar to the other 90 patients. Therefore, the calculation is 36/(36+14)=36/50≈70%. So the 10 censored patients are assumed to be 7 success and 3 failures. Thus, the KM success rate is (36+7)/(36+7+54+3)=43/100=43%.

The key distinction is that the KM rate uses the partial knowledge about the censored patients: that they were successes at week 24. Therefore, they are more like the 50 other successes at week 24 for which we have 48 week data, rather than being similar to all 90 patients with 48 week data. While the overall difference in this example is only 3%, the imputed success rates are quite different: 40% versus 70%.

The proportion analysis, in the presence of censoring, is not a valid method. However, that does not mean the KM analysis is always valid. The KM analysis has two main assumptions:
1. Patients enrolled early are similar to patients enrolled late

2. Censoring is independent of efficacy
Point number 1 is likely to be reasonable except when the enrollment period is long compared to the follow-up period, combined with a situation where there are changes in the clinical treatment setting over that period. An example is if the protocol were amended halfway through a treatment naive trial to allow for enrollment of advanced patients. Point number 2 is valid when patients are censored "administratively", e.g., due to a fixed date for database closure. Point 2 is rarely valid in other circumstances, e.g., loss-to-follow-up. These assumptions appear to be valid for studies 006 and ACTG 364.

A. Clinical trial DMP 266-006

Title: "A phase III multicenter, randomized, open-label study to compare antiretroviral activity and tolerability of three different combination regimens (DMP266 + indinavir, DMP266 + zidovudine + lamivudine, indinavir + zidovudine + lamivudine) in HIV-infected patients"

Design: This open-label, randomized study was designed to evaluate safety and efficacy of EFV in combination with ZDV+3TC compared to indinavir + ZDV + 3TC and secondarily EFV + IDV to IDV + ZDV + 3TC. This is an ongoing study that enrolled 1266 patients and is being conducted at 82 clinical sites in the USA, Canada, Germany, France, Italy, Spain, Switzerland, and the United Kingdom. In order to evaluate long term durability of response, the sample size was increased to 1200 patients and the study was extended so that each patient would participate in the study until the last patient completed 60 weeks of therapy. The first patient was enrolled on January 28, 1997. The report includes clinical data gathered through October 30, 1998.

The study was designed as an open label study. For this study to be conducted in a blinded manner would have required each patient to take 29 pills per day. The sponsor felt the risks of non-compliance with such a regimen outweighed the benefits of a blinded study.

HIV-infected patients with CD4 cell counts > 50 cells/ml, HIV-RNA levels >10,000 copies/ml, and with no prior exposure to EFV, 3TC, NNRTI or PI were randomized to:

Treatment 1: 600 mg EFV qhs + 300 mg ZDV bid + 150 mg 3TC bid
Treatment 2: 600 mg EFV qhs + 1000mg IDV q8h in a fasted state
Treatment 3: 300 mg ZDV bid + 150 mg 3TC bid + 800 mg IDV q8h

Endpoints: The primary endpoint was the time to treatment failure (TTF) using the Amplicor HIV-1 RNA Monitor™ assay. Selected secondary measures included the proportion of patients with plasma HIV-RNA below quantifiable levels and changes in CD4 counts.

Study Population: Twelve hundred sixty-six patients were randomized. Overall, 83% were male, 60% White, 20% Black, 17% Hispanic, 61% were homosexual males, mean age of 36.5 years, age range 18-81 years, known HIV-positive status for a mean of 3.1

years, mean baseline CD4 cell count of 341 cells/mm^3, and mean baseline HIV-RNA level of 4.78 log $_{10}$ copies/ml. There were no significant differences between study arms for gender, age, race, height, weight, years of HIV positivity, baseline CD4 cell counts or baseline HIV-RNA levels. All patients in the study were HIV-infected with measurable viral loads above 10,000 copies/ml and were EFV, 3TC, NNRTI, and PI-naïve at study entry. One hundred eighty-seven (15%) patients had some prior exposure to NRTIs; 171 had prior experience with ZDV. There was no statistically significant difference in NRTI exposure rates between study arms.

Disposition of subjects: Of 1,266 randomized patents, 362 (29%) discontinued therapy prematurely; 122 (10%) due to adverse events, 88 due to loss to follow-up, 49 due to protocol violation, 38 were randomized but not dosed, 28 withdrew consent, 28 for lack of effect, and 9 for reasons not specified. A significant increase in discontinuations attributed to adverse events was noted in the comparitor arm (IDV+ZDV+3TC); commonly due to nausea and/or other gastrointestinal (48/74) or urinary symptom complaints, i.e., nephrolithiaisis (11/74).

The following table depicts premature discontinuations. The protocol allows discontinuations for a variety of reasons, if deemed appropriate by the sponsor or investigator, including experiencing a Grade 4 AE or repeated Grade 3 AE, and, if in the investigator's opinion, it was not in the patient's best interest to continue.

The following table depicts the reasons for premature discontinuations.

Table 2. Premature Discontinuations

Reason for discontinuation	EFV + ZDV + 3TC N=422	EFV + IDV N=429	IDV + ZDV + 3TC N=415
Adverse event	27*	27*	68
Protocol violation	9	20	20
Withdrew consent	6	8	11
Failed to return	31	33	24
Lack of effect/ Rx failure	5	16	7
Other	2	5	2
Did not continue in extension	0	2	1
Randomized but not dosed	10	14	14
Total	90 (21%)*	125 (29%)	147 (35%)

Data Source: Figure 4.1, [6/48]

* Statistically significant difference from control group, $p < 0.05$.

It is difficult to assess the clinical significance of the AEs for which some discontinuations occurred. In the control arm, 29 patients discontinued treatment for Grade 1 (mild) or Grade 2 (moderate) gastrointestinal events. Nausea was the most common gastrointestinal adverse event reported. Due to its subjective nature, it

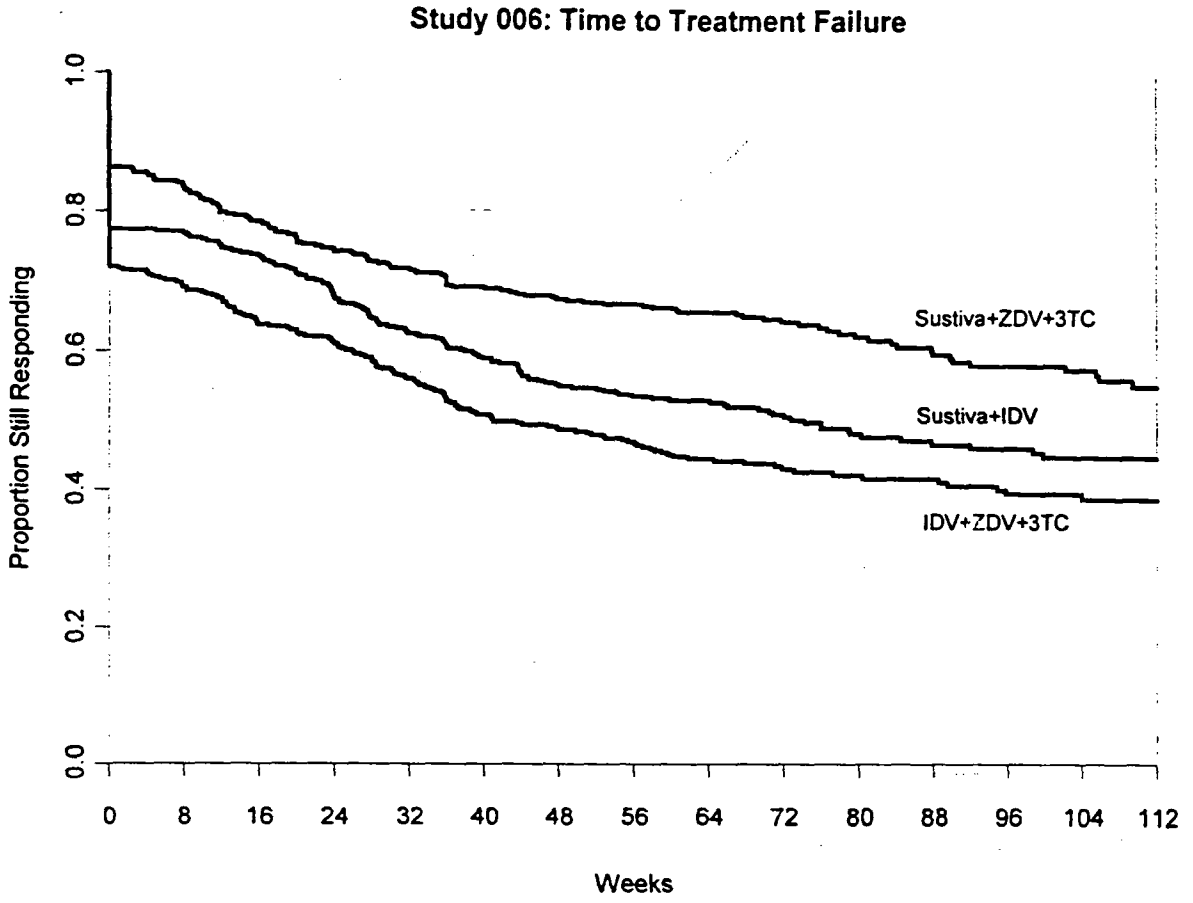
represents an adverse event that may be difficult to quantify. In an open-label study, some patients may have discontinued therapy for other reasons.

Efficacy Results

The primary endpoint was the **time to treatment failure** (TTF). Patients were considered to have reached this endpoint if they 1) failed to achieve initial suppression of virus to below 400 copies/ml 2) dropped out of the study, 3) switched antiretroviral therapy, 4) achieved below 400 copies/ml but subsequently had a confirmed rise to 400 copies /ml or above it, or 5) had a CDC Category C event[1]. Results of this analysis are shown as Kaplan-Meier estimates in Figure 1.

[1] These analyses are based on the database that includes *Herpes simplex* as a CDC event. These events, however, are not felt to be indicative of AIDS and are not included as failures in the analyses for the final label. Since the exclusion of these events does not substantively impact the results, the numbers in this review reflect those found in the database.

Figure1



The following table, Table 3, shows the success rates at various time points. The relative efficacy of the three arms is relatively constant throughout. The table includes analyses of the 48 week results using both the proportion analysis and the KM analysis. Since there is no censoring prior to 48 weeks, the point estimates are the same in both analyses. Hypothesis testing gives slightly different p-values, as might be expected since the survival analysis (log rank test) uses the entire curve and the proportion analysis (chi square) uses only the 48 week values. Week 112 results are similar to week 48. At week 112, only the KM analysis is valid. The table also shows the median duration of response. This may prove to be a very informative measure of treatment efficacy in future studies.

This analysis allows for inclusion of data beyond 48 weeks as Kaplan-Meier estimates by accounting for patients who are still virologic responders at 48 weeks or longer but have not yet reached a treatment outcome at later time points. All 1266 patients had either reached a failure endpoint or were a virologic success at week 48. Nine hundred ninety patients (78%) had either reached a failure endpoint or were a virologic success at week 72; the remaining 276 patients were virologic successes at the last time point tested but had not yet reached 72 weeks on study treatment. At 96 weeks, 72% had reached a

treatment outcome; at 112 weeks, 60% had reached an outcome. Beyond 112 weeks, the Kaplan-Meier estimates were less meaningful. The success rates of patients at various time points are shown in the following table.

Table 3. Study 006 Success Rates

	EFV + ZDV + 3TC	EFV + IDV	IDV + ZDV + 3TC
Randomized	422	429	415
Success at Week 24	74%	68%	61%
Success at Week 48	68%	55%	49%
Δ* (95% CI)	19% (12%, 25%)	6.3% (-.4%, 13%)	---
Chi square p-value	<.001	.066	---
KM Δ (95% CI)	19% (12%, 25%)	6.3% (-.3%, 13%)	---
Logrank p-value	<.001	.041	---
Success at Week 72	64%	51%	43%
Success at Week 96	58%	46%	40%
Success at Week 112	55%	45%	39%
KM Δ (95% CI)	16% (8%, 24%)	6% (-1.5%, 13.5%)	---
Logrank p-value	<.001	.029	---
Median Response	>112 weeks	74 weeks	44 weeks

* Difference in success rates

Table 4 gives a more detailed breakdown of the reasons for treatment failure through week 48.

Table 4. Study 006 Week 48 Results

	EFV + ZDV + 3TC	EFV + IDV	IDV + ZDV + 3TC
Randomized	422	429	415
Week 48 Success	286 (68%)	237 (55%)	203 (49%)
Week 48 Failure	136 (32%)	192 (45%)	212 (51%)
First Failure Condition Met			
No Initial Response	38 (9%)	77 (18%)	87 (21%)
Virologic Failure	19 (5%)	47 (11%)	31 (7%)
Discontinued Med	59 (14%)	58 (14%)	81 (20%)
AIDS-defining Event	20 (5%)	10 (2%)	13 (3%)

There are some serious caveats to keep in mind when interpreting the table above, because these categories are not really exclusive. The percentages given correspond to the first reason for treatment failure. Thus, for example, a subject who has a virologic rebound and subsequently discontinues study medication will be counted as a virologic rebound for the purposes of this tabulation. The complex interplay between safety and efficacy for HIV studies means that, for example, a more easily tolerated drug may show more virologic failures, simply because there would be fewer patients in the other arm at risk for such events. It is a problem similar to that from HIV clinical event studies, with a combined endpoint of AIDS/death. Reporting the rate of AIDS on its own is known to be misleading, since patients who die would in effect be censored out of the calculation.

The KM figure representing the combined endpoint and the associated success rates and hypothesis tests may be the most appropriate manner to report results from studies of this type. More detailed breakdowns can be used for some assurance that the results are not being driven by substantial imbalances in the reasons for failure, or if they are, what the cause of such imbalances may be.

Overall, this study provides strong evidence of the efficacy of efavirenz. The trial was designed to 1) show equivalence of efavirenz to indinavir (when both are combined with ZDV+3TC) and 2) show equivalence of EFV to ZDV+3TC (when both are combined with indinavir). The study met both of these objectives, as shown by the lower confidence intervals (+12% for comparison one and -.4% for comparison 2 at 48 weeks). In addition, this study showed that EFV + ZDV + 3TC was superior to IDV + ZDV + 3TC; however, the magnitude of the difference may be overstated given the increased number of discontinuations in the control arm resulting from mild to moderate gastrointestinal events in an open label study. Differences between the arms appeared early on and were maintained throughout the course of the study. The comparison of EFV + IDV to IDV + ZDV + 3TC did not quite meet statistical significance (p=.041 at week 48, p=.029 at week 112; critical p is .025). Compared to control, EFV +IDV appeared to prolong the TTF by approximately 6 months, and EFV + ZDV + 3TC appeared to prolong the duration of response by at least 1 year.

CD4 cell counts

At 48 weeks of therapy, there was no significant difference in the mean CD4 cell count among treatment groups; the mean overall increase in CD4 cell counts was 176 cells/mm^3.

Subset analyses

The proportions of subjects considered treatment responders by Kaplan Meier estimates (TTF analysis) at approximately one year of study are listed in the following table.

Table 5. TTF analysis, Kaplan-Meier estimates (%) at time interval days 351-378, by gender and race/ethnicity

Subset	EFV + ZDV + 3TC	EFV + IDV	IDV + ZDV + 3TC
Female	N=75 50%	N=57 43%	N=79 35%
Male	N=342 71%	N=345 55%	N=325 49%
Hispanic	N=70 51%	N=70 60%	N=64 39%
Black	N=90 58%	N=81 48%	N=76 42%
White	N=246 76%	N=240 53%	N=251 53%

Data Source: Tables D.2.1 – D2.5 (Appendix D) [11/92-106]

Although the study was not powered to compare groups by race and gender, results favoring efavirenz-containing regimens over the control arm were maintained for females, Caucasians, African-Americans, and Hispanics. In general, males did better than females and whites did better than Blacks in all treatment arms, although the studies were not powered for those comparisons.

The following table list the results of study 266-006 with patients stratified by baseline HIV-RNA levels.

Table 6. Intent-to-treat: NC=F analysis at week 48 stratified by baseline HIV-RNA

Baseline HIV-RNA	EFV + ZDV + 3TC	EFV+IDV	IDV + ZDV + 3TC
< 100,000 copies/ml	N=281 68%	N=264 61%	N=277 52%
≥ 100,000 copies/ml	N=133 68%	N=161 47%	N=135 44%

Data Source: Table 5.6, [6/82] and November 1999 efficacy updates

Although the study was not powered to compare groups by baseline HIV RNA levels, results favoring efavirenz-containing regimens over the control arm were maintained for patients with baseline HIV RNA levels above 100,000 copies/ml.

Evaluation of Safety

There were five deaths in the study, three in the EFV + IDV arm (pulmonary Kaposi's sarcoma, myocardial infarction, and one of unknown cause 10 weeks after discontinuing study) and one each in the EFV + ZDV + 3TC arm (myocardial infarction) and IDV + ZDV + 3TC arm (unknown cause).

There were 52 patients who developed potential AIDS-defining events during the study, 11 in the EFV + IDV arm, 22 in the EFV + ZDV + 3TC arm, and 19 in the IDV + ZDV + 3TC arm. The more frequent of those potential AIDS-defining events are listed in the following table.

Table 7. Potential AIDS-defining events by treatment group

Potential AIDS-Defining Event	EFV+ZDV+3TC N=412	EFV+IDV N=415	IDV+ZDV+3TC N=401
Herpes simplex	14	5	13
Sarcoma	0	3	2
Fungal infection	2	0	1
Lymphoma	2	0	0
PCP	0	2	0

Data Source: Table 10.23 [6/335-8]

The most frequently reported potential AIDS-defining event was herpes simplex infection. It is not clear in the initial submission whether these events represent serious

enough infections to be classified as CDC class C events or simply represented recurrent *herpes labialis* or *herpes genitalis*. In the final analysis, the sponsor determined that none of the herpes simplex events represented true CDC Category C AIDS-defining events.

Serious adverse events were reported in 49/415 (12%) patients in the efavirenz-indinavir arm, 49/412 (12%) in the efavirenz/ZDV/3TC arm, and 43/401 (11%) in the indinavir/ZDV/3TC arm, as shown in the following table.

Table 8. Serious adverse events reported by the sponsor

Serious Adverse Events	EFV+ZDV+3TC N=412	EFV+IDV N=415	IDV+ZDV+3TC N=401
Drug abuse	9	5	10
GU pain/stones	4	3	7
Malignancy	3	0	4
Pneumonia	4	5	2
Depression	2	2	2
N/V/D	0	1	2
Anemia	3	3	1
Suicide attempt	1	3	0
Convulsion	1	1	0
Myocardial infarction	1	1	0
Rash	1	1	0
Hallucination	0	0	0
Aggressive behavior	0	0	0
Leg abscess	2	2	0
Rectal abscess	0	0	0
Pancreatitis	1	1	0

Data Source: Table 10.39 [7/535-55]

Of the 29 serious adverse events in 24 patients listed as drug abuse, represented as drug overdose, a specific drug was reported in 23 events: efavirenz (11), indinavir (5), alcohol (3), heroin (1), zidovudine (1), lamivudine (1), and indinavir, zidovudine, and lamivudine (1). Many of these events involving efavirenz or indinavir resulted from accidental ingestion or administrative errors.

The review team requested a re-analysis of nervous system and psychiatric adverse events employing another definition of serious adverse events. The applicant was asked to redefine "serious adverse events" to include any adverse event (of any grade) designated as delusions (hallucinations, psychosis), inappropriate behaviors (aggression), aggravated or severe depression, suicide attempt, or seizures (convulsions) as important medical events. The applicant submitted the re-analysis of nervous system and psychiatric adverse events on September 13, 1999. The following table lists serious nervous system/psychiatric adverse events reported after re-analysis.

Table 9. Serious nervous system/psychiatric adverse events reported after reanalysis

Serious adverse event	EFV+ZDV+3TC N=412	EFV+IDV N=415	IDV+ZDV+3TC N=401
Hallucinations	3	5	0
Seizures/Convulsion	2	5	1
Aggravated Depression	2	3	2
Severe depression	4	0	2
Suicide Ideation/attempt	3	2	0
Psychosis, manic depressive	0	1	3
Aggressive behavior	0	3	1
Paranoid reaction	0	2	0

Data Source: 9/13/99 submission and JMP data sets.

Using data presented from re-analysis, patients treated with 400 or 600 mg of efavirenz daily were compared to the control arm. By the 24th week of treatment, when most of the patients were still receiving the randomized treatment regimen, 3.3% of the efavirenz-treated patients experienced at least one serious nervous system or psychiatric adverse event versus 0.7% of the patients from the control arm.

In general, differences in rates of specific serious nervous system/psychiatric adverse events between efavirenz-treated patients and controls were not significant. Temporal relationships of such events to initiation of therapy were not apparent. In addition, confounding variables, such as prior history such events or intervening factors associated with such events, were identified for patients in both treated and control arms.

For one patient, two suicide attempts were reported; he had a past medical history of suicide attempts, convulsions, possible head injuries, depression, adjustment disorder, and narcissistic personality disorder. Five months after beginning efavirenz he reported an overdose of sleeping pills after a domestic disturbance with his partner; gastric lavage did not recover pills. Eleven days later he was hospitalized after lacerating his wrists. Four patients reported suicidal ideation 1-4 months after starting efavirenz. One patient had a history of previous suicide attempts, polysubstance abuse and major depressive disorder; one had a history of depression and was an active substance abuser, one was an active heroin abuser, and another had a history of depression.

Hallucinations appear to be associated with efavirenz therapy. Eight patients, all in the efavirenz treatment arm reported hallucinations. In five of the eight patients, hallucinations appeared within the first week efavirenz therapy. In four of those 5 patients, hallucinations were described as "moderate" – symptoms that may interfere with daily activities (grade 2). Hallucinations resolved within a few days on continued therapy (2 patients), dose reduction (1 patient), dose interruption (1 patient), or discontinuation (1 patient). Three other patients reported hallucinations at later times on efavirenz therapy (2 – 4 months). Hallucinations were persistent for one patient, lasted 3 months for

another patient, and were recurrent in the third patient. All three patients gave a significant psychiatric history (depression and drug abuse, opiate abuse, or schizophrenia).

Three patients treated with efavirenz developed aggressive behavior; one patient had a history of aggressive behavior associated with alcohol abuse. Another patient with narcissistic personality and adjustment disorder was acting out a conflict with a sexual partner. The third patient developed aggressive behavior that was considered mild and did not require treatment.

In conclusion, it appears that efavirenz treated patients had higher rates of serious nervous system and psychiatric events than controls. However, other than for hallucinations, it is difficult to attribute other specific serious psychiatric events to efavirenz due to the lack of a temporal relationship to initiating therapy and the presence of confounding variables.

Similar percentages (95%) of patients in all groups reported new-onset AEs. The most frequent new-onset adverse events, independent of clinician determination of causality, are listed in the following table.

Table 10. New onset adverse events

Adverse experience	EFV + IDV (N=415)	EFV + ZDV + 3TC (N=412)	IDV+ZDV+3TC (N=401)
Nausea*	29%	34%	55%
Rash*	34	28	17
Headache	24	27	25
Fatigue	20	25	29
Diarrhea	30	24	21
Dizziness*	28	30	7
Vomiting*	14	17	27
Flu-like symptoms	21	19	17
Insomnia*	19	17	10
Dyspepsia	13	17	14
Pain	12	14	18
Coughing	12	11	11
Depression	10	13	9
Concentration impaired*	7	10	1
Dreaming abnormal*	6	7	0
Nervousness*	6	6	1

Rash includes maculopapular, localized, generalized, and erythematous rashes.
* Statistical differences noted between EFV-containing arms and control, $p < 0.05$.
Data Source: Table 7.1, [6/99-100]

Laboratory abnormalities

Adverse events due to laboratory abnormalities were reported among all three treatment arms. Hyperbilirubinemia and hematuria were reported more frequently among patients in the control arm; anemia in the zidovudine containing arms. The results of laboratory abnormalities are shown in following two tables.

Table 11. Laboratory abnormalities (≥ 3% in any arm)

Lab abnormality	EFV + ZDV + 3TC (N=412)	EFV + IDV (N=415)	IDV + ZDV + 3TC (N=401)
Granulocytopenia	30 (7%)	14 (3%)	18 (4%)
Bilirubinemia*	1 (0)	2 (0)	51 (13)
SGPT increased	13 (3)	17 (4)	11 (3)
SGOT increased	13 (3)	13 (3)	13 (3)
Hypercholesterolemia*	11 (3)	22 (5)	5 (1)
Hypertriglyceridemia	13 (3)	15 (4)	9 (2)
Gamma-GT increased*	19 (5)	12 (3)	6 (1)
Anemia	16 (4)	1 (0)	17 (4)
Hematuria	7 (2)	5 (1)	19 (5)
Amylase increased*	9 (2)	13 (3)	3 (1)

Data source Table 7.1 [6/100]

* Statistically significant differences noted between EFV-containing arms and control ($p<0.05$)

Table 12. Results - Lipid testing

Characteristic	EFV + ZDV + 3TC	EFV + IDV	IDV + ZDV + 3TC
No. with baseline testing	216	216	198
No. tested during treatment	373	375	334
Number tested at both times	215	215	196
Baseline cholesterol (mean)	163.5	167.9	160.3
Cholesterol during treatment (mean)	193.4	219.3	186.8
Difference in Cholesterol (mean)	+ 24.3	+ 51.4	+ 22.0
Baseline triglycerides (mean)	156.2	156.9	151.5
Triglycerides during treatment (mean)	203.0	213.7	179.3
Difference in triglycerides (mean)	+ 24.6	+ 48.2	+ 16.7

Data Source: [7/588-90]

Safety summary

Nervous system symptoms, such as dizziness, headache, insomnia, depression, impaired concentration, abnormal dreams, described as "altered sensorium" experiences, were common with approximately 53% of EFV-treated patients experiencing at least one such nervous system symptom on EFV compared to 21% in the comparison arm (IDV+ZDV+3TC). Nervous system experiences usually start within the first day of efavirenz therapy and resolve in the majority of patients within 3 weeks.

Serious and potentially life-threatening nervous system and/or psychiatric adverse events have been reported for patients treated with efavirenz. These events included severe acute depression (0.4%), suicide ideation/attempts (0.6%), seizures (1%), and aggressive behaviors (0.4%).

Rash was more commonly reported in each of the efavirenz-containing arms than in the IDV +ZDV + 3TC arm (28% vs. 16%). Two hundred twenty-eight of 827 patients receiving efavirenz developed rash; over 96% of the rashes were Grade 1 or 2. One patient developed a Grade 4 rash on day 6 of EFV + IDV treatment. The median time to onset of rash in the efavirenz-containing arms was 10-12 days and median number of days with > Grade 1 rash was 15-17 days.

Gastrointestinal adverse events, including nausea, vomiting, and diarrhea were reported more frequently in the IDV + ZDV + 3TC arm in addition to nephrolithiasis and hyperbilirubinemia. The discontinuation rate was significantly higher in this arm and the difference was primarily the result of 48 discontinuations due to GI AEs, predominantly nausea, and 11 discontinuations due to urinary tract adverse events, predominantly nephrolithiasis.

Approximately one percent of patients treated with efavirenz discontinued therapy due to increased liver function tests. Gamma GT levels increased at a significantly greater rate among efavirenz-treated patients (4%) compared to controls (1%). Hyperbilirubinemia was reported more commonly for control patients (13%) than efavirenz-treated patients (0%). Otherwise no differences in liver function testing were noted between treatment arms.

Cholesterol levels were reported to be elevated during efavirenz treatment (3%) more frequently than the control arm (1%). The effects of efavirenz on cholesterol levels were not well characterized since samples were commonly taken from non-fasting patients.

Summary Conclusions of Study DMP 266-006:

The results of study DMP 266-006 support efavirenz as safe and effective therapy in combination with other antiretroviral agents for the treatment of HIV-1 infection. With a total of 1266 subjects included in the analysis, the time to treatment failure was longer for both the efavirenz-containing arms compared to the control arm.

The differences were statistically significant. The median time to treatment failure was 44 weeks for the control arm, 74 weeks for the EFV+IDV arm and not yet reached after 112 weeks of follow-up for the EFV+ZDV+3TC arm.

Although the studies were not powered to compare groups by race and gender, results favoring efavirenz-containing regimens over the control arm were maintained for females, males, Caucasians, African-Americans, and Hispanics.

All three groups experienced significant increases in CD4 cell counts compared to baseline (overall mean increase of 176 cells/mm^3); however, no differences among treatment groups were noted.

Nervous system symptoms were noted in approximately half of patients treated with efavirenz, usually presenting on the first or second day of therapy and resolving during the first 2-3 weeks of therapy. Serious nervous system adverse events, including hallucinations (1%), suicide attempts (0.6%), aggressive behavior (0.4%) and paranoid reactions (0.2%) were noted in the efavirenz-treated arms. Rash was reported by about 30% patients treated with efavirenz, generally presented during the second week of therapy and resolved during the ensuing 2-3 weeks of therapy. Elevated liver enzymes were observed in all three arms of the study, at rates of approximately 3 percent in each group. Elevations in cholesterol and triglycerides were noted in all three treatment arms; however, these lipid studies were not conducted in a systematic fashion and did not use fasting blood levels for analysis.

B. ACTG 364

Title: "Comparison of the virologic efficacy of nelfinavir and/or DMP 266 in combination with one or two new nucleoside analogs in nucleoside experienced subjects: A rollover to ACTG 302/303"

Design: Study ACTG 364 was designed as a follow-up trial for those patients in previous ACTG studies of nucleoside reverse transcriptase inhibitors (NRTIs) given as monotherapy or in two drug combinations. This was a randomized, double-blind, partially placebo-controlled, multicenter study designed to evaluate the safety and efficacy of EFV + NFV +2NRTIs compared to NFV + 2NRTIs and of EFV + 2NRTIs compared to NFV +2NRTIs. The primary assessment of efficacy was based on the time to treatment failure. A secondary analysis measures the proportion of patients achieving HIV-RNA levels less than 500 copies/ml (Roche Amplicor ^{TM} assay) at 48 weeks of therapy. HIV-infected subjects who had participated in ACTG 302/303 and had no prior exposure to any protease inhibitor or NNRTIs were randomized to:

Treatment 1: EFV 600 mg qd + NFV 750 mg tid + 2NRTIs
Treatment 2: EFV 600 mg qd + NFV placebo + 2NRTIs
Treatment 3: EFV 600 mg placebo + NFV 750 mg tid + 2 NRTIs

NRTIs were open-label and selected to ensure that each patient received at least one new NRTI. The three possible NRTI regimens were:

Didanosine (ddI) 200 mg bid + stavudine (d4T) 40 mg bid
Lamivudine (3TC) 150 mg bid + d4T 40 mg bid
DdI 200 mg bid + 3TC 150 mg bid

Note: Didanosine 125 mg bid for patients weighing less than 60 kg; stavudine 30 mg bid for patients weighing less than 60 kg.

The NRTI combinations employed among treatment arms are listed in the following table.

Table 13. Frequency of selected NRTI combinations among treatment arms at baseline

NRTIs	EFV+NFV+2NRTs (N=65)	EFV+2 NRTIs (N=65)	NFV+2NRTIs (N=66)
DdI + d4T	34	34	34
3TC + d4T	27	27	29
DdI + 3TC	3	4	3

Note: One patient randomized but not dosed, and NRTIs not listed in analysis
Data Source: Tables 10.13, 10.16 [18/167 and 170]

Endpoints: The primary endpoint was the time to treatment failure (TTF) using the Amplicor HIV-1 RNA Monitor™ assay. Patients were considered to have reached this endpoint if they 1) failed to achieve initial suppression of virus to below 500 copies/ml, 2) dropped out of the study, 3) switched antiretroviral therapy, 4) achieved below 500 copies/ml but subsequently had a confirmed rise to 500 copies/ml or above it, or 5) had a CDC Category C event.

Selected secondary measures included the proportion of patients with plasma HIV-RNA below quantifiable levels and changes in CD4 counts.

Study Population: One hundred ninety-six patients were randomized. Overall, 88% were male, 74% Caucasian, 14% African-American, 9% Hispanic, mean age of 41 years, mean baseline CD4 cell count of 388 cells/mm^3, and mean baseline HIV-RNA level of 3.91 $\log_{10}$ copies/ml (app. 8,128). No significant differences between study arms for gender, race, baseline CD4 cell count or baseline HIV-RNA plasma levels were noted. Seven patients had HIV-RNA plasma levels less than 500 copies/ml at baseline (3 in the nelfinavir arm, and 2 each in the efavirenz-containing arms). Patients were NNRTI, and PI-naïve at study entry. All patients had prior exposure to NRTIs. The 196 patients enrolled and treated in ACTG 364 received the following NRTIs: Didanosine + stavudine (102 patients), lamivudine + stavudine (83), and lamivudine + didanosine (10). One patient was randomized but did not receive study medications.

Disposition of subjects: Of the 196 randomized patients, 67 (34%) discontinued therapy prematurely. Over 70% of the discontinuations were the results of virologic failures and are shown in the following table:

Table 14. Premature discontinuations by treatment group.

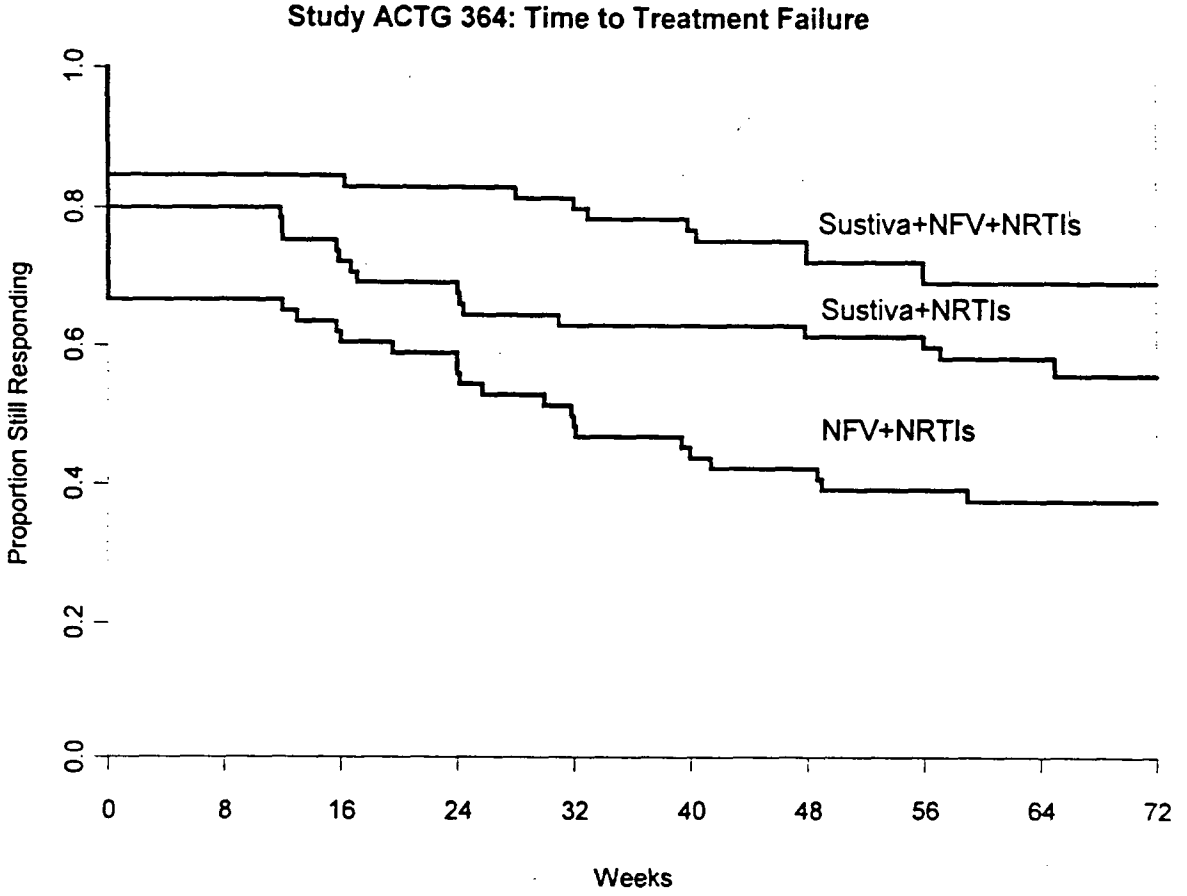
Reason for discontinuation	EFV+NFV+2NRTIs (N=65)	EFV + 2 NRTIs (N=65)	NFV + 2NRTIs (N=66)
Virologic failure	6	15	27
Death	1	1	1
Adverse event/ toxicity	4	1	2
Requested discontinuation	3	1	0
Protocol violation/ non-compliance	2	0	1
Randomized but not dosed	1	0	0

Data Source: Figure 4.1 [18/36]

Efficacy Results – Statistical analysis

Time to treatment failure results are shown in Figure 2.

Figure 2



The stairstep look of the KM curve is a natural consequence of the virologic testing schedule. Virologic failures by definition can only occur every 4 weeks, when such testing is done. Dropouts and a less strict adherence to the test schedule can smooth out the curve by introducing failures in between the 4 week time points. In Study 364, there were fewer patients than in Study 006. Further, the dropout rate was substantially lower. These two points explain why the curve in ACTG 364 is more "jagged" than the curve in Study 006.

This analysis allows for inclusion of data beyond 48 weeks as Kaplan-Meier estimates by accounting for patients who are still virologic responders at 48 weeks or longer but have not yet reached a treatment outcome at later time points. All 196 patients had either reached a failure endpoint or were a virologic success at week 48. One hundred forty six (75%) had either reached a failure endpoint or were a virologic success at week 72; the remaining 50 patients were virologic successes at the last time point tested but had not yet reached 72 weeks on study treatment. Beyond 72 weeks, the Kaplan-Meier estimates were less meaningful.

The following table shows the success rates at various time points.

Table 15. Study 364 Success Rates

	EFV + NFV + NRTIs	EFV + NRTIs	NFV + NRTIs
Randomized	65	65	66
Success at Week 24	83%	68%	56%
Success at Week 48	72%	62%	42%
Δ* (95% CI)	30% (14%, 46%)	19% (2%, 36%)	---
Chi square p-value	<.001	.026	---
KM Δ (95% CI)	30% (14%, 46%)	19% (2%, 36%)	---
Logrank p-value	<.001	.036	---
Success at Week 72	64%	56%	38%
KM Δ (95% CI)	26% (9%, 43%)	18% (1%, 35%)	---
Logrank p-value	<.001	.029	---
Median Response	>72 weeks	>72 weeks	32 weeks

* Difference in success rates

The study was designed to test both for superiority of efavirenz versus placebo (combined with NFV + NRTIs) and for equivalence of EFV versus NFV (combined with NRTIs). Both objectives were met. The EFV versus placebo comparison showed a significant advantage for efavirenz (p<.001). The EFV versus NFV comparison indicated efavirenz was at least as effective as NFV (lower bound on 95% CI = +1%). The comparison did not quite meet statistical significance (p=.036 at Week 48, p=.029 at Week 72, critical p=.025 after Bonferoni adjustment). The median duration of response was at least 40 weeks greater in both efavirenz arms compared with the NFV control arm.

CD4 cell counts

The following table contains the results of CD4 cell counts among the treatment arms:

Table 16. CD4 cell count results, Last observation carried forward analysis – week 48

	EFV+NFV+2NRTIs	EFV + 2NRTIs	NFV+2NRTIs
Total randomized	65	65	66
Mean change CD4 cell count from baseline	107 cells/ml	114 cells/ml	94 cells/ml

Data Source: Table 5.5 [18/69]

Subset analyses

The studies were not powered to compare groups by race and gender. The proportions of subjects with plasma HIV-RNA levels < 500 copies/ml at 48 weeks are listed in the following table:

Table 17. The proportion of patients with HIV RNA < 500 copies/ml at week 48 (ITT, NC=F analysis) by gender and race

Subset	EFV+NFV+2NRTIs	EFV + 2NRTIs	NFV + 2NRTIs
Female	N=6 67%	N=12 58%	N=6 0%
Male	N=38 71%	N=53 55%	N=60 32%
White	N=51 73%	N=46 61%	N=48 29%
Other than White	N=13 62%	N=19 42%	N=18 28%

Tables 10.35, 10.36, 10.37, 10.38 [18/217-220]

Although the studies were not powered to compare groups by race and gender, results favoring efavirenz-containing regimens over the control arm were maintained for females, males, Caucasians, and races other than White.

The following table list the results of ACTG 364 with patients stratified by baseline HIV-RNA levels.

Table 18. Intent-to-treat: NC=F analysis at week 48 stratified by baseline HIV-RNA

Baseline HIV-RNA	EFV+NFV+2NRTIs	EFV + 2NRTIs	NFV + 2NRTIs
< 30,000 copies/ml	N=50 72%	N=46 65%	N=50 44%
≥ 30,000 copies/ml	N=13 54%	N=19 37%	N=16 19%

Baseline HIV-RNA > 30,000 copies/ml represents the upper quartile.
Data Source: Analysis by Statistical Reviewer using November 1999 efficacy updates

Although the study was not powered to compare groups by baseline HIV RNA levels, results favoring efavirenz-containing regimens over the control arm were maintained for patients with baseline HIV RNA levels above 30,000 copies/ml.

Evaluation of Safety

Although 196 patients were randomized, one patient randomized to EFV+NFV+2NRTIs did not receive medication and is not included in the safety analysis.

There were three deaths in the study, one in each arm: EFV/ddI/d4T (pancreatitis on day 194); EFV/NFV/ddI/d4T (post-op GI bleed on day 370); and NFV/ddI/d4T (respiratory arrest on day 281).

One AIDS defining event was reported during the study. A patient treated with EFV/NFV/ddI/d4T developed symptoms on day 22 leading to a diagnosis of lymphoma.

Serious adverse events are listed in the following table:

Table 19. Listing of serious adverse events reported by ACTG

Serious Adverse Event	EFV+NFV+2NRTIs (11 patients)	EFV+2NRTIs (6 patients)	NFV+2NRTIs (12 patients)
Hypertriglyceridemia	3	2	3
Increased LFTs	2	2	3
Rash	2	0	1
Pancreatitis	0	2	1
Depression	0	0	2
Malignancy	2	1	2
Other	2	0	1

Patients may have more than one event listed.
Data Source: Table 7.13 [18/127-32]

Two episodes of pancreatitis in a patient on EFV+2NRTIs eventually resulted in death on day 194. The second episode of pancreatitis in that patient occurred after study treatment discontinued and attributed to cholelithiasis.

There were seven patients who discontinued treatment due to adverse events, one in the EFV arm, four in the EFV+NFV arm and two in the nelfinavir arm. The AEs leading to discontinuations are listed below:
EFV – increased liver function tests at day 176
EFV+NFV – peripheral neuropathy at day 84
EFV+NFV – increased triglycerides at day 407
EFV+NFV – intolerable nightmares at day 335
EFV+NFV - sixteen pound weight loss at day 87
NFV (ddI/d4T) – pancreatitis at day 314
NFV – chronic HBV infection at day 148

ACTG trials report only Grade 2 or higher AEs. There were 21 patients (32%) with Grade 2, 3, or 4 AEs in the EFV arm, 27 (42%) in the EFV+NFV arm, and 29 (44%) in the NFV arm.

The following table contains new onset Grade 2 or higher adverse event data reported independent of causality:

Table 20. New onset Grade 2 or higher adverse events by treatment arm

Adverse event	EFV+NFV+2NRTIs N=64	EFV + 2NRTIs N=65	NFV+2NRTIs N=66
Ache/pain/discomfort	8 (13%)	4 (6%)	11 (17%)
Rash*	7 (11)	5 (8)	10 (15)
Diarrhea/loose stools	9 (14)	2 (3)	6 (9)
Dizzy/lightheaded/fainting	1 (2)	4 (6)	4 (6)
Other nervous system symptoms†	9 (14)	3 (5)	13 (20)

Table 7.1[18/74-76]
* Rash includes erythema, redness, inflammation, macules, papules, pruritus, blisters, ulcers, lesions, allergic rash, urticaria, welts, and hives.
† Other nervous system symptoms include numbness, paresthesias, tingling, headache, depression, neurologic dysfunction, agitation, hyperactive, dreams, insomnia, inappropriate behavior, coordination abnormal, and mental status changes.

The review team requested a re-analysis of nervous system and psychiatric adverse events employing another definition of serious adverse events (see page 15). The sponsor submitted the re-analysis of nervous system and psychiatric adverse events on September 13, 1999. Three patients were reported with severe depression, one was treated with EFV and two in control group. No other serious nervous system or psychiatric adverse events were reported.

The following table lists new onset Grade 2 or higher laboratory abnormalities:

Table 21. Laboratory abnormalities - numbers of patients with a Grade 2 or higher new onset clinical laboratory measure

Lab Abnormality	EFV+NFV+2NRTIs N=64	EFV+2NRTIs N=65	NFV+2NRTIs N=66
Triglycerides	10	7	12
CPK elevation	8	7	13
AST elevation	4	5	5
ALT elevation	2	7	3
GGT elevation	3	1	4
Amylase	0	5	3
Glucose	3	1	2

Table 7.14[18/134]

No statistically significant differences were seen among treatment arms related to laboratory abnormalities.

Safety summary

The ACTG safety reporting system varies significantly from the applicant's reporting system used in DMP 266-006 and DMP 266-020, in that the ACTG reports only Grade 2 or higher adverse events. Using these criteria of reporting, fewer adverse events were reported in all arms of the study than those reported in the DuPont-sponsored studies. Nervous system symptoms and rash were noted in all three arms of the trial. Diarrhea was reported more commonly in the EFV+NFV+2NRTIs arm. No differences in laboratory abnormalities were reported between groups.

Summary Conclusions of ACTG 364:

ACTG 364 was designed to compare 48 week treatment with four drug therapy to triple therapy, i.e., EFV + NFV + 2NRTIs versus NFV + 2 NRTIs. A second analysis

compared EFV + 2NRTIs with NFV + 2NRTIs. Patients were NRTI-experienced and had completed two prior ACTG studies.

The results of study ACTG 364 support efavirenz as safe and effective therapy in combination with other antiretroviral agents in achieving viral suppression through 48 weeks. The EFV+NFV+2NRTI-arm was superior to the control arm, NFV+2NRTIs, in the time to treatment failure analysis; the EFV+2NRTI-arm did at least as well as the control arm, although the results did not quite reach statistical significance when tested for superiority. The median time to treatment failure was 32 weeks for the control arm, and not yet reached after 72 weeks of follow-up for each of the efavirenz-containing arms.

Both efavirenz-containing arms were superior to the control arm measured by the proportion of patients below the HIV-RNA assay limit at 48 weeks. All three groups experienced significant increases in CD4 cell counts compared to baseline (overall mean increase of 105 cells/mm^3); however, no differences among treatment groups were noted.

Nervous system symptoms, presenting as dizziness, lightheadedness and/or fainting, were reported in all study arms. No differences in rash were reported in ACTG between treatment arms. One patient developed severe depression while on efavirenz therapy during the study; no other serious nervous system or psychiatric adverse events, such as, suicide ideation/attempt or aggressive behaviors were reported.

C. DMP266-020

Title: "A phase 3, double-blind, placebo-controlled multicenter study to determine the effectiveness and tolerability of the combination of efavirenz and indinavir versus indinavir in HIV-infected patients receiving nucleoside analogue (NRTI) therapy"

Design: This randomized, double-blind, placebo-controlled trial was conducted at 43 sites in the United States, Canada, and Puerto Rico. The study was extended past the 24-week double blind portion to include an additional 36 week open-label treatment period. The objective of the study was to compare efficacy and safety of:

Treatment 1: Efavirenz (600mg qd) + indinavir (1000mg q8h) + 1 or 2 NRTIs
Treatment 2: Indinavir (800mg q8h)+ 1 or 2 NRTIs

The study population was NRTI-experienced (at least 8 weeks), but PI and NNRTI naïve, had baseline CD4 cell counts > 50 cells/ml, and HIV-RNA levels > 10,000 copies/ml before randomization. Patients' physicians were permitted to change the NRTI regimen on day 0. Sixty eight percent of 327 patients changed NRTIs on day 0. The study was extended beyond the 24-week double-blind portion to include an additional 36-week open-label treatment period.

Endpoints: The primary endpoint was the proportion of patients achieving HIV-RNA suppression below the limit of detection (400 copies/ml on AMPLICOR™ Monitor assay) at 24 weeks of therapy. Comparison of mean change in CD4 cell counts from baseline was the secondary endpoint.

Statistical analysis: The statistical analysis was based on the intention-to-treat principle with noncompleter=failure criteria to account for missing data.

Study population: Three hundred thirty patients were randomized; 327 are included in these analyses. The study groups appear well balanced with regard to demographics and HIV-related characteristics (including equal rates of change of NRTIs at day 0). The mean baseline plasma HIV-RNA level was 25,700 copies/ml and mean baseline CD4 cell count was 328 cells/mm^3. Overall, 83% of the participants were male, and 52% were white. The mean age was 38.5 years, range 20-69 years.

All patients received some NRTI therapy prior to entry. Overall, 89% of the subjects had prior exposure to zidovudine, 76% to lamivudine, 34% stavudine, 29% didanosine, and 24% dideoxycytidine. The mean duration of prior exposure was 1080 days for the efavirenz arm and 1001 days for the control arm. The only statistically significant difference between groups was a longer duration of exposure to dideoxycytidine was observed for the efavirenz group (mean 114 days) compared to the control arm (mean 77 days). For two-thirds of patients, NRTIs were changed at baseline; the remainder continued NRTI therapies. Eighty-nine percent of patients were treated with two NRTIs. The NRTI regimens most frequently used were 3TC + d4T (39%), ZDV+3TC (24%), and didanosine + stavudine (19%). Thirty-two patients (10%) were treated with single NRTI therapy and 5 patients (2%) with triple NRTI therapy. [From Table 4.6 - 4.8, 21/58-61]

Disposition of subjects: Overall, 72% of subjects completed 24 weeks of study. The reasons for premature discontinuations are shown in the following table.

Table 22. Patient discontinuations

Reason for discontinuation	EFV+IDV+NRTIs N=157	IDV+NRTIs N=170
Adverse event*	18	8
Withdrew consent	10	15
Loss to follow-up	10	8
Protocol violation	7	9
Virologic failure	0	1
Other	2	2
Total	47 (30%)	43 (25%)

*Statistical difference between groups
Source: Table 4.1 [21/44] and Table 7.7 [21/107-10].

There were no statistically significant differences between groups regarding patients discontinuing therapy. Of the 26 discontinuations due to AEs, 18 patients were randomized to the efavirenz arm and eight to placebo. Of those, four patients in the EFV

arm discontinued therapy due to nervous system symptoms, 3 in the placebo group. Four patients in the EFV arm discontinued therapy due to new onset of rash; one patient discontinued due to rash in the placebo group.

Efficacy Results

Efficacy results based on proportion of patients with HIV RNA < 400 copies/ml at week 24 (non-completer = failure analysis) can be found in the following table:

Table 23. HIV-RNA plasma levels at 24 weeks by treatment arm

	EFV+IDV+NRTIs N=157	IDV+NRTIs N=170
< 400 copies/ml	93 (59%)	86 (51%)
< 50 copies/ml	77 (49%)	63 (37%)

Source: Tables 5.4 and 5.5 [21/71-2]

The EFV containing arm does not show a statistically significant difference from control arm based on proportion of patients with HIV-RNA levels < 400 copies/ml measured by the Amplicor HIV-1 RNA Monitor™ assay (p=0.12). However, these results are statistically significant when comparing the proportions < 50 copies/ml by the Ultrasensitive HIV-1 RNA Monitor™ assay (p=0.034). The results do provide supportive evidence that efavirenz has antiretroviral activity when combined with other antiretroviral agents including a protease inhibitor and NRTIs.

Subset analyses

The proportions of subjects considered treatment successes (< 400 copies/ml by Amplicor HIV-1 RNA Monitor™ assay, non-completer = failure analysis) at week 24 are listed in the following table:

Table 24. Subset efficacy analyses

Subset	EFV + IDV + NRTIs	IDV + NRTIs
NRTI changed at baseline	N = 107 65%	N=117 56%
No NRTI change at baseline	N=47 49%	N=51 39%
Baseline HIV-RNA < 100,00 copies/ml	N=127 61%	N=140 51%
Baseline HIV-RNA ≥ 100,000 copies/ml	N=28 50%	N=28 50%
Concomitant 3TC + d4T	N=56 57%	N=65 60%
Concomitant ZDV+ 3TC	N=40 55%	N=37 46%
Concomitant ddI + d4T	N=29 76%	N=31 52%

Source: Table 5.7 [21/76]

The studies were not powered to compare groups for various subsets, including specific NRTI combinations or baseline viral load. There were no consistent findings on subset analysis when comparing the efavirenz-containing regimen versus the control arm. Subset analyses for race and gender were not reported.

CD4 cell counts

There was no difference in mean change CD4 cell counts from baseline between the two treatment arms. The overall mean increase in CD4 cell counts from baseline was 155 cells/ml for the 231 patients (104 on efavirenz, 127 on placebo) evaluated at 24 weeks.

Evaluation of Safety

There were no deaths during the first 24 weeks of study medication, however, one patient treated with efavirenz and indinavir was diagnosed with non-Hodgkin's lymphoma at approximately 10 months on study and died three months later.

There were 12 patients who developed AIDS-defining events during the study; four in the efavirenz arm and seven in the control arm and are listed in the following table.

Table 25. AIDS-defining events reported by treatment arm.

AIDS-defining event	EFV + IDV + NRTIs N=154	IDV + NRTI N=168
Herpes simplex	2	6
Lymphoma	1	1
Retinitis	1	0

Source: Text [21/85-6]

Serious adverse events were reported in 13/157 (8.3%) patients in the efavirenz-containing arm and 20/170 (11.8%) in the control arm, as shown in the following table.

Table 26. Listing of serious adverse events reported by the sponsor

Serious Adverse Event	EFV + IDV + NRTIs N=154	IDV + NRTIs N=168
Drug Abuse	2	5
Rash	2	1
Renal calculus	0	2
Gastrointestinal	1	2
Bacterial infection	2	1
Viral infection	0	3
Seizures	0	1
Depression	0	1
Lymphoma	1	1
Anemia	1	0
Granulocytopenia	0	1

Increased LFTs	1	1
Other	3	1

Data Source: Table 7.8 [21/115-9]

The review team requested a re-analysis of nervous system and psychiatric adverse events employing another definition of serious adverse events (see page 15). The sponsor submitted the re-analysis of nervous system and psychiatric adverse events on September 13, 1999. The following table lists serious nervous system and psychiatric events reported after re-analysis.

Table 27. Serious Nervous system/Psychiatric adverse events after re-analysis

Serious adverse event	EFV+IDV+2NRTIs N=154	IDV+2NRTIs N=168
Aggravated depression	4	1
Hallucinations	3	0
Suicide ideation/attempt	0	2
Seizure/Convulsion	0	2
Paranoid reaction	0	1

Note: Two patients randomized to control arm switched to efavirenz before suicide attempt (#30102) and paranoid reaction (#32103).
Data Source: 9/13/99 submission and JMP data sets.

Similar percentages of patients in both groups reported at least one new-onset AEs; 94% for EFV + IDV + NRTIs, and 93% for IDV + NRTIs. The most frequent new-onset adverse events, independent of clinician determination of causality, are listed in the following table.

Table 28. New-onset Adverse Events, independent of clinician determination of causality

Adverse experience	EFV + IDV + NRTIs N=154	IDV + NRTIs N=168
Nausea	44%	40%
Diarrhea*	49	33
Rash	36	36
Headache	33	34
Fatigue	24	27
Dizziness*	31	14
Vomiting	23	20
Pain	20	22
Upper respiratory tract infection	20	21
Anorexia*	18	8
Pharyngitis*	7	20
Paresthesia*	15	4
Somnolence	10	10
Bilirubinemia*	1	12

Renal calculus	1	7

Table 7.1 [21/89-90]
* Statistical difference between treatment arms, $p < 0.05$.

Laboratory abnormalities are shown in the following table.

Table 29. Laboratory abnormalities (> 3% in any arm)

Laboratory abnormality (%)	EFV + IDV +NRTIs N=154	IDV +NRTIs N=168
Creatinine PK increase	7%	5%
Hyperbilirubinemia*	1	7
Gamma GT increase	5	1
Hypertriglyceridemia	5	1

Table 7.1 [21/90]
*Significant difference between treatments, $p < 0.05$

Safety summary
Nervous system AEs were quite common with approximately 47% of patients experiencing at least one nervous system symptom on EFV compared to 24% on the comparison arm. These symptoms usually started on the first or second day of therapy, continued for a median time of 13 days, and included dizziness, headaches, feeling drugged, feeling "spacey" or jittery, insomnia, and disorientation. Efavirenz was discontinued for five patients and was interrupted for three additional patients because of nervous system symptoms.

Serious and potentially life-threatening nervous system and/or psychiatric adverse events have been reported for patients treated with efavirenz and controls. Four patients treated with efavirenz reported severe depression (2.6%). No suicide ideation/attempts, seizures, or aggressive behaviors were reported among patients in DMP 266-020 initiated on efavirenz therapy.

Rash was reported in 20-25% of patients in both arms and started at various times after initiation of efavirenz, the median time to onset was 15 days. The median duration was 18 days. Efavirenz was discontinued for four patients and was interrupted in five additional patients because of rash.

Summary Conclusions of Study DMP 266-020:

Study 020 was designed to compare the safety and efficacy of efavirenz in combination with indinavir + nucleoside RT inhibitors versus indinavir + nucleoside RT inhibitors for 24 weeks. The study was well-balanced for baseline demographic, virologic and immunologic characteristics. Overall, 72 % of subjects completed 24 weeks of therapy.

Patients were NRTI experienced, and were allowed to continue on their regimen of NRTIs or change to new NRTIs at the onset of the study and at the discretion of the

primary physician. No statistically significant differences between treatment arms were observed in types or duration of prior antiretroviral medications received. Patients were on a wide variety of single, double, and triple combination NRTIs in addition to efavirenz/placebo and indinavir. For two-thirds of patients, NRTIs were changed at baseline; the remaining patients continued NRTI therapies.
The results from study 020 suggest that efavirenz has antiretroviral activity when used in combination with other antiretroviral therapies for the treatment of HIV-1 infection. Although the EFV containing arm (EFV + IDV + NRTIs) yields a larger proportion of completers with HIV-RNA levels below 400 copies per ml (59% vs. 51% in the IDV + NRTIs arm), this difference was not statistically significant. When the proportions are compared using HIV-RNA levels below 50 copies per ml measured by the Ultrasensitive HIV-1 RNA Monitor™ assay, the results are statistically significant in favor of the efavirenz arm. The data are clinically relevant and provide support for the use of efavirenz in the treatment of HIV-1 infection. There was no significant difference in the mean CD4 cell count between treatment arms. The overall mean increase from baseline among the 231/327 subjects who completed 24 weeks of therapy was 155 cells/mm^3.

Nervous system symptoms were reported by 47% of patients treated with efavirenz and 24% controls; rash was reported by 24% of patients treated with efavirenz and 20% controls. These adverse events generally resolved over the ensuing one to three weeks of therapy. There was no differences in reports of serious nervous system and psychiatric adverse events between treatment arms.

5. Additional studies submitted for safety analyses

D. DMP 266-003

Title: "A double-blind, placebo-controlled study to assess the safety, tolerability, and antiretroviral activity of efavirenz alone and in combination with open-label indinavir in HIV-infected patients"

Design: This was a double-blind, placebo-controlled study designed to assess safety, tolerability, and efficacy of efavirenz 200 mg qd in combination with indinavir (800 mg or 100 mg q8h) versus indinavir monotherapy in HIV-infected adults. The study was not completed as planned due to data that supported use of combination therapies. Several amendments were submitted to alter treatment regimens and additional cohorts of patients were recruited. After 36 weeks of therapy, patients were treated with efavirenz 600 mg qd, indinavir 1000 mg q8h, and stavudine 40 mg bid.

Study population: Two hundred one patients were enrolled in the study as of the cutoff date of October 30, 1998; 87% were male, 76% were Caucasian. The mean age was 38.4 years (range: 20-65 years). One hundred twenty five patients (62%) remain active in the study. One hundred fifty three (76%) received at least 48 weeks of efavirenz therapy.

Evaluation of Safety
Two patients died during the study. One patient died of an apparent homicide (gunshot wound to the head on day 195) and one of Hodgkin's lymphoma on day 308.

Thirty-eight patients had serious AEs: 26 patients receiving efavirenz and indinavir, and 12 patients who were assigned indinavir alone. Six of the 12 patients assigned to indinavir alone developed serious AEs after addition of efavirenz. Three serious nervous system AE among efavirenz-treated patients were reported; one suicide attempt occurred on day 195 and another on day 128, and psychosis developed on day 358 in another patient.

The adverse event profile was similar to that seen in the three principal studies. Nervous system symptoms were reported for approximately half (77/153) the efavirenz-treated subjects, and were most commonly described as dizziness, insomnia, abnormal dreaming, and agitation. Rash was reported for 74/153 (48%) of efavirenz-treated subjects, with maculo-papular and erythematous rash most frequently reported.

E. DMP 266-004

Title: "A double-blind, placebo-controlled study to assess the safety, tolerability, and antiretroviral activity of DMP 266 in combination with open-label zidovudine and lamivudine in NRTI-experienced HIV-infected patients"

Design: This was a phase 2, placebo-controlled, double-blind study of efavirenz in combination with open-label zidovudine and lamivudine for 16 weeks in asymptomatic or mildly symptomatic HIV infected patients. The study was divided into three cohorts. In cohort 1, ten patients were randomized to 400 mg EFV qd; five patients received placebo. In cohort 2, ten patients were randomized to 600 mg EFV qd; five patients received placebo. In cohort 3, 18 patients were randomized to 600 mg EFV qd, 22 to 400 mg EFV qd, and 23 to placebo (subjects in cohorts 1 and 2 could be extended into cohort 3). All patients completing 16 weeks of therapy were offered EFV 600 mg qd open-label. A total of 85 subjects who received efavirenz are included in the safety analysis, 32 randomized to 400 mg EFV qd, 28 randomized to 600 mg qd, and 25 randomized to placebo. Enrollment stopped in April 1997 as the results from other studies suggested that treatment with 2 NRTIs alone was not adequate therapy. The study was conducted at 15 sites in the USA.

Study population: Ninety-three patients were randomized in the three cohorts. A total of 85 received efavirenz at some time during the study. Of those 85 subjects, 79% were male, 59% were Caucasian, and the mean age was 38.5 years (range: 21-67 years. Forty-four (52%) of the patients were still active on EFV therapy at time of data cutoff: March 31, 1999. Seventy-four (87%) were exposed to EFV at least 24 weeks; 62 (73%) at least 48 weeks.

Evaluation of Safety
There were no deaths during the study.

Nine patients were reported with serious AEs: two assigned to 400 mg EFV, one assigned to 600 mg EFV, and six assigned to placebo. All but one of the serious AEs assigned to placebo occurred after switch to 600 mg EFV. One serious nervous system AE was reported; a patient treated with placebo developed depression, aggressive behavior, and suicide attempt at study day 20.

The adverse event profile was similar to that seen in the three principal studies. Nervous system symptoms were reported for approximately half of the subjects assigned to the 600 mg EFV treatment arm; rash was reported for 15 percent of subjects. The most common reported adverse events were upper respiratory tract infection, depression, rash, dizziness, diarrhea, nausea, pharygitis, rhinitis, and flu-like symptoms.

F. DMP 266-005

Title: "A phase 2, double-blind, placebo-controlled, dose-ranging study to assess the antiretroviral activity and safety of efavirenz in combination with open-label zidovudine (ZDV) and lamivudine (3TC) in HIV-infected patients"

Design: This was a placebo-controlled, randomized, double-blind, dose-ranging study conducted at 14 U.S. sites. HIV-infected patients who were asymptomatic, or mildly symptomatic, and antiretroviral-naïve, were randomized to four treatment arms:

200 mg EFV + ZDV + 3TC,
400 mg EFV + ZDV + 3TC,
600 mg EFV + ZDV + 3TC,
placebo + ZDV + 3TC.

Study medications were blinded through 16 weeks of therapy. After 16 weeks of therapy, all patients were offered open-label EFV 600 mg qd.

Study population: One hundred and thirty seven patients were randomized; 127 received efavirenz during the study and constitute the population evaluated for safety. Of those 127 subjects, 87% were male, 65% were Caucasian, and the mean age was 36.5 years (range 23-71 years). Eighty (63%) remained active on EFV therapy at time of data cutoff: October 30, 1998. Ninety-one patients were exposed to efavirenz at least 48 weeks.

Evaluation of Safety

One patient died during the study, a 36 year old male died on day 205 of sepsis and malignant lymphoma.

Sixteen patients were reported with serious AEs: three assigned to 200 mg EFV (including one with cerebrovascular disease with aphasia, and one myocardial infarction), five assigned to 400 mg EFV, and five assigned to 600 mg EFV (including the death

mentioned above, and one with severe depression). Three serous AEs were reported among patients assigned to placebo (one with pancreatitis diagnosed on day 10, and one with severe depression after switch to 600 mg EFV).

The adverse event profile was similar to that seen in the three principal studies. Nervous system symptoms were reported over half the subjects assigned to the 600 mg EFV treatment arm; rash was reported for about 25 percent of subjects. The most common reported adverse events were nausea, fatigue, dizziness, headache, diarrhea, and flu-like symptoms.

G. DMP 266-021

Title: "A phase 2, open-label study to assess the pharmacokinetic profile of efavirenz dosed at bedtime in combination with indinavir in HIV-infected patients"

Design: This was a single-arm, open-label, multicenter study in which patients were enrolled and treated with 600 mg qhs and indinavir 1000 mg q8h.

Study population: Eighteen patients were enrolled; 15 (83%) were male, 9 (50%) were African-American, and the mean age was 38 years (range 21-59 years). Sixteen (of the patients were exposed to EFV for at least 24 weeks, three for at least 48 weeks.

Evaluation of safety:
No deaths were reported. Six patients experienced serious adverse events, all resulting in hospitalizations. Two of the patients reported depression as a component of the serious AE, one of the patients attempted suicide twice (on days 275 and 289). The most frequently reported new onset AEs were nausea, headache, rash, diarrhea, and fatigue.

H. DMP 266-024

Title: "A phase 2, open-label, multicenter study to characterize the effectiveness, safety, and pharmacokinetics of nelfinavir in combination with efavirenz in retroviral therapy naïve or nucleoside analogue experienced HIV-infected patients"

Design: This was a single-arm, open-label, multicenter study conducted in 32 NRTI-naïve and 30 NRTI-experienced patients to characterize decreases in plasma HIV-RNA levels, increases in CD4 cell counts, and safety of efavirenz in combination with nelfinavir. Patients received EFV 600 mg qhs and NFV 750 mg q8h for 48 weeks.

Study population: Sixty-two patients were enrolled; 94% were male, 68% were Caucasian, and the mean age was 36.6 years (range 17-68 years). Fifty-six (90%) were exposed to EFV for at least 24 weeks, 46 (74%) for at least 48 weeks.

Evaluation of Safety
No deaths were reported. Eleven patients developed serious AEs; one patient reported severe depression on day 269 and a suicide attempt on day 408. The other ten serious

AEs were thrombophlebitis, headache, drug abuse, chest pain, dementia, meningitis, nail disorder, infectious hepatitis, renal calculus, and pneumonia. The most frequent new-onset AEs were diarrhea (67%), nervous system symptoms (53%), and rash (32%). The most frequently reported nervous system symptoms were amnesia, dizziness, and somnolence.

I. DMP 266-903

Title: "Efavirenz (Sustiva ™) Expanded Access Program"

This was an open-label program to provide efavirenz HIV-infected patients with advanced disease. Patients had to be 13 years of age or older, and failing therapy or intolerant of their current antiretroviral therapy and have a CD4 cell count less than 400 cells/mm^3. All patients received additional antiretroviral therapy, including at least one other agent to which they had never been exposed, and were not allowed to use any other NNRTIs.

Data on 7,842 patients were presented and represent data through October 31, 1998. Demographics of patients: Patients enrolled were male (89%), Caucasian (68%), African-American (18%), and Hispanic (12%). The mean age was 40 years (range: 13-94 years). Six hundred forty-four patients (8%) were exposed to study drug for at least 24 weeks.

Evaluation of Safety

As of December 31, 1998 there were 142 deaths in the study; 84 (59%) attributed to progression of HIV/AIDS defining event. Other reported causes of death included suicide (3 – days 45, 46, and 132), pancreatitis (4- three concomitantly treated with ddI), myocardial infarction (3), liver failure (4) and one due to a motor vehicle accident.

One thousand fifty eight (13.5%) of patients reported at least one new-onset Grade 3 or 4 adverse event. One hundred ninety seven new onset Grade 3 and 4 nervous system symptoms were reported and the most common are listed in the following table.

Table 30. New onset Grade 3 or 4 nervous system symptoms

Adverse event	Patients N=7842
Dizziness	73
Insomnia	29
Confusion	29
Depersonalization	15
Hallucination	14
Somnolence	11
Agitation	10

There were 6 patients with suicide attempts, 3 successful suicides, and 2 hospitalizations because of homicidal ideation.

New onset Grade 3 or 4 rash was reported for 213 patients. One report of Stevens Johnson syndrome and three of erythema multiforme were received.

COMMENT: Safety data from the Expanded Access Program is reflective of the adverse event profile in the three principal clinical trials in this NDA. Nervous system symptoms and rash were the most common Grade 3 or 4 AEs reported.

6. Summary of consultation provided by Division of Drug Risk Evaluation II

Due to a large number of spontaneous reports of serious psychiatric events that were received following accelerated approval of efavirenz in September 1998, a review of serious psychiatric adverse events was conducted by the Division of Drug Risk Evaluation II. Results of the review were reported to the Division of Antiviral Drug Products on June 25, 1999.

A search of the AERS database was done using the SOC term, "psychiatric disorders" for efavirenz reports received through 5/13/99. In addition, a manual review of the first two periodic reports received by the FDA, covering 9/17/98 to 3/16/99, was done. One additional probable suicide, received on 5/17/99 was also included.

A total of 113 reports of psychiatric adverse events attributed to efavirenz were received. The following table includes a listing of the 137 psychiatric events reported.

Table 31. Psychiatric adverse events attributed to efavirenz

Adverse event	Number
Sleep disorder	47
Depression	42
Anxiety	25
Suicide ideation/attempt/complete	21
Psychosis/Hallucination	14
Aggressiveness/Homocidal ideation	9

Source: Boxwell D, DDRE consultation, June 25, 1999

Overall, there were 104 domestic reports, 9 from foreign countries; 93 males, 13 females, 7 unknown sex; mean age was 40.5 years (range 25-66 years). The mean onset of adverse events was 36 days (range 2 hours to 20 months). These events resulted in 3 deaths, 2 life-threatening events, and 23 hospitalizations. Evavirenz was discontinued for 19% of these events, continued for 60%, and continuation status unknown for 12%.

The suicide ideation/attempt/completed and aggressiveness/homocidal ideation adverse events warrant further discussion. Of the 21 subjects with depression and suicidal ideation, 7 attempted suicide; of which two were successful. Nineteen were male, 2 female; mean age was 39 years (range 28-55). The mean onset of suicidal ideation was 100 days (range 1 dose – 20 months). Two patients died, 2 were considered life-threatening, 11 were hospitalized, and the outcome of 6 was unknown. Efavirenz was discontinued for 10 (48%), continued for 9 (43%) and unknown course for 2.

Agressiveness/homocidal ideation was reported for 9 patients; of which one resulted in death of the subject (attributed to cerebral edema). Another of the events was considered life-threatening, five resulted in hospitalization, and for 2 the outcome was not reported. All nine patients were male, mean age 35 years (range 29-40 years). The mean onset of symptoms was 84 days (range 2 hours to 9 months). Efavirenz was discontinued for 4, continued for 4, and unknown course for one.

It is difficult to calculate the relative risk of the serious psychiatric events relative to other antiretroviral agents through uncontrolled reports. In addition, HIV-AIDS is a disease in which depression, suicide and other psychiatric events have been reported. However, there appear to be a large number of reports of serious psychiatric adverse events associated with the use of efavirenz and reported in the short time of drug marketing.

7. Additional safety analysis focusing on serious nervous system and/or psychiatric adverse events

The review team requested a re-analysis of nervous system and psychiatric adverse events employing another definition of serious adverse events. The reviewers asked the sponsor to redefine "serious adverse events" to include any adverse event (of any grade) designated as delusions (hallucinations, psychosis), inappropriate behaviors (aggression), aggravated or severe depression, suicide attempt, or seizures (convulsions) as important medical events. The sponsor submitted the re-analysis of nervous system and psychiatric adverse events on September 13, 1999.

In controlled trials (Studies DMP-006, -020, -004, and -005), the frequency of specific serious nervous system symptoms among patients who received efavirenz or control regimens, respectively, were: severe depression (0.9%, 0.5%), suicidal ideation/attempts (0.5%, 0.3%), aggressive behavior (0.3%, 0.3%), paranoid reactions (0.2%, 0.2%) and manic reactions (0.1%, 0%).

The following tables lists serious nervous system events for those treated with efavirenz 600 mg daily versus controls from studies 004, 005, 006, 020 and ACTG 364 and by history of psychiatric disorder.

Table 32. Serious nervous system/psychiatric adverse events reported for patients with a prior history of psychiatric disorder

Adverse event	Efavirenz treatment N=306	Control N=208
Aggravated depression	12 (4.2%)	3 (1.4%)
Hallucinations	8 (2.6%)	0
Suicide ideation/attempts	5 (1.6%)	1 (0.5%)
Seizures	4 (1.3%)	1 (0.6%)
Severe depression	3 (1.0%)	2 (1.0%)
Aggressive reaction	3 (1.0%)	1 (0.5%)
Paranoid reaction	2 (0.7%)	1 (0.5%)

Psychosis - Manic depressive	0	2 (1.0%)
Manic reaction	1 (0.3%)	0

Source: September 13, 1999 submission (patient 006-92203 added to Table 11, p. 37)

Table 33. Serious nervous system/psychiatric adverse events reported for patients with no prior psychiatric history

Adverse event	Efavirenz treatment N=702	Control N=427
Seizures	4 (0.6%)	1 (0.2%)
Hallucinations	4 (0.6%)	0
Severe depression	4 (0.6%)	0
Suicide ideation/attempts	0	1 (0.2%)
Aggressive reaction	0	1 (0.2%)

No reports of aggravated depression, manic reactions, paranoid reactions, or psychosis – manic depression were received.
Source: September 13, 1999 submission (Table 11)

Patients with a prior history of psychiatric disorders in both efavirenz-treated and control arms had a greater risk (relative risk = 4.2) for these serious nervous system/psychiatric adverse experiences. The frequency of each of the above events among efavirenz-treated patients with a prior psychiatric history ranged from 0.3% (manic reaction) to 4.2% (aggravated depression). The presence of efavirenz in a treatment regimen significantly predicted the presence of such an event (RR = 2.1). The risk of having a serious nervous system/psychiatric event was increased for women in both efavirenz-treated and control arms (RR=1.6), but the difference was not statistically significant.

By the 24th week of treatment 3.4% of the patients treated with 400 or 600 mg of efavirenz daily in studies 006 and 020 experienced at least one serious NS adverse events vs. 1.2% patients from the control arm. The time-to-event analyses found the occurrence of the first serious nervous system or psychiatric adverse events significantly different in the two treatment arms.

In conclusion, it appears that efavirenz treated patients had higher rates of serious nervous system and psychiatric events than controls. However, other than for hallucinations, statistically significant differences were not noted for the other specific serious psychiatric events.

8. Summary of safety

There are several safety concerns when using efavirenz in combination with other antiretroviral agents in the treatment of HIV-1 infection.

Nervous system adverse events were reported by 53% of patients in the principal trials treated with efavirenz in combination with other antiretroviral agents, but symptoms were generally of mild or moderate severity. These symptoms included dizziness, headache,

insomnia, depression, concentration impairment, agitation, abnormal dreaming, somnolence, and hallucinations. These symptoms generally began during the first few days of efavirenz therapy and resolved with or without continuing therapy within 2-4 weeks. Dosing at bedtime improved the tolerability of these symptoms.

A subset of patients reported serious nervous system or psychiatric symptoms that included severe depression, delusions, and inappropriate behaviors, including suicide attempts and aggressive behavior. These serious psychiatric symptoms occurred predominantly, but not exclusively, in patients with a history of mental illness or substance abuse. These symptoms began at various times after starting therapy and were more likely to result in hospitalization and discontinuation of efavirenz therapy than those nervous system symptoms described above. Patients who experience serious psychiatric symptoms should contact their doctor immediately because discontinuation of efavirenz may be required.

All patients receiving treatment with efavirenz should be alerted to the potential for additive central nervous system effects if efavirenz is used concomitantly with alcohol or psychoactive drugs. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machinery.

Mild to moderate skin rashes were been reported in 27% adult patients in the principal trials treated with efavirenz compared with 17% of patients in the control group. Severe rashes with blistering, desquamation, or ulceration occurred in about 1% of patients on efavirenz. In clinical trials, one patient developed erythema multiforme and another Stevens-Johnson syndrome. Efavirenz should be discontinued for patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever.

In clinical trials, liver enzyme elevations greater than five times the upper limit of normal were noted at similar rates of 3% in efavirenz-treated and control patients. In 156 patients treated with efavirenz 600 mg qd and seropositive for hepatitis B and/or hepatitis C virus, 7% developed AST levels, 8% developed ALT levels, and 10% developed GGT levels greater than five times upper limit of normal.

Analysis of serum lipids, cholesterol and triglyceride levels were monitored in Study DMP-006, but were not collected in a systematic fashion, and were not taken from patients following an overnight fast. Elevations in cholesterol and triglycerides were noted in all three treatment arms. The clinical significance of these findings is unknown.

9. Reviewer's assessment of safety and efficacy of efavirenz

In support of the safety and efficacy of efavirenz in combination with other antiretroviral agents in adults, the applicant has submitted the results of two adequate and well-controlled trials of 48 weeks duration and a phase 3 trial of 24 weeks duration. The sponsor has also provided safety experience from five phase 2 clinical trials and an expanded access program.

Two pivotal phase 3 studies through 48 weeks for all patients, with longer follow-up for a substantial number of participants, were submitted for review. The fact that these two studies, in different patient populations and using different protease inhibitor containing comparison regimens, showed such similar results is convincing evidence of long term efficacy of efavirenz. Further, the studies provide evidence that efavirenz may have superior efficacy to protease inhibitors when used in the conditions of the two studies.

Although the studies were not powered to compare groups by race and gender, results favoring efavirenz-containing regimens over control regimens were maintained for males and females and for three racial/ethnic groups, i.e., Caucasians, African-Americans, and Hispanics. There were no studies involving pediatric patients included in the NDA package.

The most concerning adverse events associated with efavirenz were nervous system symptoms, psychiatric adverse events, and rash. Nervous system adverse events were reported by 53% of patients in the principal trials treated with efavirenz in combination with other antiretroviral agents, but symptoms were generally of mild or moderate severity. These symptoms included dizziness, headache, insomnia, depression, concentration impairment, agitation, abnormal dreaming, somnolence, and hallucinations. These symptoms generally began during the first few days of efavirenz therapy and resolved with or without continuing therapy within 2-4 weeks. Dosing at bedtime improved the tolerability of these symptoms.

A subset of patients reported serious psychiatric symptoms that included severe depression, delusions, and inappropriate behaviors, including suicide attempts and aggressive behavior. These serious psychiatric symptoms occurred predominantly, but not exclusively, among patients with a history of mental illness or substance abuse. These adverse experiences began at various times after starting therapy and were more likely to result in hospitalization and discontinuation of efavirenz therapy than those nervous system symptoms described above. Patients who experience these serious psychiatric symptoms should contact their doctor immediately because discontinuation of efavirenz may be required.

All patients receiving treatment with efavirenz should be alerted to the potential for additive central nervous system effects if efavirenz is used concomitantly with alcohol or psychoactive drugs. Patients should be instructed that if they experience any nervous system symptoms they should avoid potentially hazardous tasks such as driving or operating machinery.

Mild to moderate skin rashes have been reported for patients on efavirenz. Severe rashes with blistering, desquamation, or ulceration occurred in about 1% of patients on efavirenz. Rare reports of erythema multiforme and Stevens-Johnson syndrome have been reported. Efavirenz should be discontinued for patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever.

Labeling discussions were focused on:

- Provision of safety information regarding nervous system and psychiatric adverse events in the Warnings section of the package insert.
- Presentation of efficacy data as time-to-treatment failure analyses presented both as proportions of patients with HIV-RNA below assay limit and as Kaplan-Meier estimates. The proportion of patient with HIV-RNA below the assay limit has been the Division standard for presentation of efficacy results and appears to be easy to understand for most practicing physicians. Kaplan-Meier estimates may be more difficult to understand, but provide more accurate projections of results for longer periods of time in studies with variable follow-up times among participants.
- Presentation of HIV-RNA data for both the Amplicor and Ultrasensitive HIV-1 RNA Monitor™ assays.
- Presentation of resistance data with some interpretation of results.
- Overall incidence of serious nervous system and psychiatric adverse events in the clinical trials.
- Post-Marketing safety data.

The following phase 4 commitments are proposed:

1. Pediatric Patient Population – To continue with the development of a pediatric program, with emphasis on developing a liquid formulation along with obtaining safety, tolerability, pharmacokinetic and antiviral activity data. Additionally, we refer to our Pediatric Written Request letter.
2. Resistance data – To continue to study and define the resistance profile of efavirenz at the 600 mg dose and correlated resistance with plasma viral RNA.
3. Methadone interaction – To conduct a drug interaction study of efavirenz with methadone.
4. Carcinogenicity studies – To complete the ongoing carcinogenicity studies with efavirenz and submit the data in a timely fashion.
5. Nervous system and psychiatric adverse events –To review clinical trial data and evaluate the association between potential risk factors and development of nervous system and psychiatric adverse events.
6. Lipid profile studies – the applicant will investigate lipid metabolic pathways through in vitro studies. The applicant also agrees to continue monitoring fat distribution, changes in lipid profiles and lipid disorders in ongoing and future clinical trials.
7. Efficacy – the applicant will continue to submit efficacy data from 006 until at least all treatment arms reach the median TTF and present such median results for inclusion in the label.
8. Use as salvage therapy – To evaluate the safety, tolerability, and efficacy of efavirenz-containing regimens in patients who have failed non-efavirenz containing regimens.

10. Recommendations for regulatory action

The recommendation of approval for this application is based on surrogate endpoints, i.e., analyses of plasma HIV-RNA levels and CD4 cell counts, in controlled trials through 48 weeks in duration. The final label is provided in an appendix.

/S/ /S/ /S/

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Concurrences:
HFD-530/Div Dir/Jolson /S/ 2/9/00
HFD-530/SMO/Kukich
HFD-725/Stats/Aras /S/ 2/9/00

CC: HFD-530/NDA 20-972
HFD-530/Div file
HFD-530/CSO/Kelly
HFD-530/Pharm/Wu
HFD-530/Micro/Mishra
HFD-530/Chem/Boring
HFD-530/Biopharm/Sekar
HFD-725/Stats/Araa
HFD-725/Stats/Elashoff
HFD-725/Stats/Breazna
HFD-725/Stats/Huque
HFD-530/MO/Cvetkovich
HFD-530/MO/Haverkos