# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**20-636 /S-017**
**20-933 /S-007**

# STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

| | |
|---|---|
| **IND#:** | 36-026/S-369 |
| **APPLICANT:** | Boehringer-Ingolheim Pharmaceuticals, Inc |
| **NAME OF DRUG:** | Viramune® (Nevirapine) |
| **INDICATION:** | Treatment of HIV Infection |
| **TYPE OF REVIEW:** | Clinical |
| **DOCUMENTS REVIEWED:** | Volumes |
| **MEDICAL INPUT:** | Harry Haverkos, M.D. (HFD-530) |

**STATISTICAL REVIEW AND EVALUATION**

**IND#:** 36-026

1. Background

2. Trial 1090
2.1 Objectives in Trial
2.2 Summary of Study Design
2.3 Patient Accounting and Baseline Characteristics
2.4 Summary of Methods of Assessment
2.4.1 Schedule of Measurements
2.4.2 Assessment of Treatment Effects
2.5 Summary of Statistical Analysis
2.6 Summary of Applicant's Results
2.7 Summary of Applicant's Conclusions

3. Statistical Reviewer's Comments and Analyses on Trial 1090
3.1 Times to Viral Rebound
3.2 Times to CDC Events
3.3 Times to CDC Events and Viral Failure

4. Trial 1229 (INCAS Trial)
4.1 Objectives in Trial
4.2 Summary of Study Design
4.3 Patient Accounting and Baseline Characteristics
4.4 Summary of Methods of Assessment
4.4.1 Schedule of Measurements
4.4.2 Assessment of Treatment Effects
4.5 Summary of Statistical Analysis
4.6 Summary of Applicant's Results
4.7 CD4 Responses
4.8 Summary of Applicant's Conclusions

5. Statistical Reviewer's Comments and Analyses on INCAS Trial

6. Trial 1229 (Atlantic Trial)
6.1 Objectives in Trial
6.2 Summary of Study Design
6.3 Patient Accounting and Baseline Characteristics
6.4 Summary of Methods of Assessment

## 1. Background

The applicant submitted five randomized, controlled clinical trials with Viramune (nevirapine, NVP) for this supplement: trial 1090, the Atlantic trial, the INCAS trial, ACTG 193a, and ACTG 241. The 1090, Atlantic, and INCAS trials were the applicant's planned pivotal trials; the other trials were supportive.

## 2. Trial 1090

### 2.1 Objectives in Trial

The primary objective of this study was to compare the efficacy of NVP therapy at a dose of 200 mg bid to that of placebo when used in combination with 3TC plus other anti-retroviral therapies. The primary efficacy endpoint was time to clinical disease progression. Subsequently, at the recommendation of the DAVDP, the primary efficacy endpoint was changed to time to virologic failure, defined as increase in the HIV RNA levels above limit of quantitation (LOQ). The study population was HIV-1 infected non-nucleoside reverse transcriptase inhibitor (NNRTI) naive patients with CD4 counts <= 200 cells/$mm^3$.

### 2.2 Summary of Study Design

The study was double-blind, double-dummy, randomized, two-arm, parallel, placebo-controlled, multi-center trials conducted in the US, Europe, Australia, Argentina, and South Africa.

Subjects were randomly assigned in a 1:1 ratio to 200 mg bid NVP (preceded by a lead-in dose of 200 mg qd for 2 weeks) or NVP placebo (same schedule). All subjects also received 3TC 150 mg bid plus one other anti-retroviral (ZDV, ddC, ddI, d4T, saquinavir (SQV), indinavir (IDV), or ritonavir (RTV)).

Randomization was stratified by site.

## 2.3 Patient Accounting and Baseline Characteristics

2256 patients were enrolled in trial 1090. Of these, 7 patients never started treatment. Of the 2249 eligible patients who started treatment, 549 discontinued treatment before the end of the study. The subjects were enrolled at 170 centers on five continents. 969 subjects were European, 562 North American, 522 South African, 182 South American, and 14 Australian. The exact distribution of patients and sites by country is given in table 2.3 A.

TABLE 2.3 A
PATIENTS, SITES BY COUNTRY, TRIAL 1090

| Country | Patients | Sites | Country | Patients | Sites |
|---|---|---|---|---|---|
| USA | 481 | 45 | UK | 224 | 10 |
| CANADA | 81 | 13 | SPAIN | 267 | 17 |
| ARGENTINA | 182 | 5 | FRANCE | 171 | 18 |
| AUSTRALIA | 14 | 7 | GERMANY | 129 | 18 |
| S. AFRICA | 522 | 16 | ITALY | 121 | 13 |
| | | | BELGIUM | 52 | 6 |
| | | | NETHERLANDS | 2 | 1 |
| | | | SWEDEN | 3 | 1 |

The distribution of patients by size of the center is given in table 2.3 B.

TABLE 2.3 B
TRIAL 1090, NUMBER OF PATIENTS BY SIZE OF CENTER.

| Pt/Center | Centers | Patients |
|---|---|---|
| 99 | 1 | 99 |
| 82 | 1 | 82 |
| 65 | 1 | 65 |
| 41-60 | 3 | 171 |
| 31-40 | 9 | 312 |
| 21-30 | 17 | 434 |
| 11-20 | 45 | 660 |
| <=10 | 93 | 426 |

In trial 1090, the study population was 79% male with a mean age of 38 years. They were 70% white and 24% black. The mean CD4 count at baseline was 107 cells/$mm^3$; the mean HIV RNA level

was 4.4 logs. 620 subjects tested positive for hepatitis antigens/antibodies out of 2232 tested.

Table 2.3 C summarizes the primary reasons for discontinuation from study and from double blind treatment.

TABLE 2.3 C
PATIENT STATUS, TRIAL 1090

| | NVP | Placebo |
|---|---|---|
| Randomized | 1124 | 1132 |
| In Treated ITT | 1121 | 1128 |
| Discontinued Trial | 255 | 294 |
| Progression, Illness | 44 | 57 |
| Adverse Event | 23 | 12 |
| Lack of Efficacy | 2 | 3 |
| Other | 186 | 222 |

## 2.4 Summary of Methods of Assessment

### 2.4.1 Schedule of Measurements

Patients had CD4 counts taken at weeks 0, 2, 4, monthly to month 8, and every 2 months thereafter to month 20. HIV RNA was measured on almost the same schedule (every 4 months after month 8). Plasma samples were frozen and later assessed by the Roche Ultrasensitive assay. HIV RNA levels were not evaluated during the trial and were not used to make decisions about switching treatment.

### 2.4.2 Assessment of Treatment Effects

The protocol specified primary endpoint was time to disease progression or death. Because protease inhibitors (PI) became widely available during the trial and because the protocol was modified to permit the addition of PI's to assigned therapy, the applicant and the FDA decided that the trial was no longer adequately powered to detect differences in clinical progression. The endpoint was changed prior to unblinding to percent of subjects with virologic failure. Virologic failure was defined as either no confirmed HIV RNA levels below limit of quantitation (BLQ) or confirmed rebound to above limit of quantitation (LOQ) after being BLQ or switch off assigned therapy (including loss to follow-up) or clinical progression or death.

## 2.5 Summary of Statistical Analysis

The planned primary analysis was a stratified Fisher exact test on the percent of subjects without virologic failure at week 48. The stratifying variables were to be prior anti-retroviral therapy (ART) (none, ZDV only, other), HIV disease status (Group A/B or Group C), baseline CD4 count (<25, 25-49, 50-100, >100), and baseline HIV RNA (<5K, 5K-100K, >100K). The strata were not used in randomization but were selected prior to unblinding and prior to actual measurement of stored plasma samples.

## 2.6 Summary of Applicant's Results

### 2.6.1 Trial 1090

The results for trial 1090 are given in table 2.6.1 A. The primary analysis found nevirapine to be superior to placebo with a p-value < .001.

TABLE 2.6.1 A

HIV RNA RESULTS IN TRIAL 1090

| Stratum | NVP | Placebo |
|---|---|---|
| Pooled | 219/1121 = 20% | 30/1128 = 3% |
| Disease History | | |
| Group A/B | 146/611 = 24% | 22/623 = 4% |
| Group C | 73/510 = 14% | 8/505 = 2% |
| Treatment History | | |
| Naive | 49/117 = 42% | 4/131 = 3% |
| ZDV Only | 49/131 = 37% | 5/148 = 3% |
| Other | 121/873 = 14% | 21/849 = 2% |
| Baseline CD4 Count | | |
| <25 | 14/194 = 7% | 2/181 = 1% |
| 25-50 | 15/140 = 11% | 5/139 = 4% |
| 50-100 | 39/269 = 15% | 11/255 = 4% |
| >100 | 151/518 = 29% | 12/553 = 2% |
| Baseline HIV RNA | | |
| <5K | 56/188 = 30% | 15/222 = 7% |
| 5K-100K | 104/565 = 18% | 10/578 = 2% |
| >100K | 59/349 = 17% | 5/311 = 2% |

Table 2.6.1 B shows the breakdown of the failures in each arm by cause.

TABLE 2.6.1 B

REASONS FOR FAILURE IN TRIAL 1090

| | NVP | Placebo |
|---|---|---|
| Enrolled | 1121 | 1128 |
| Success at 48 weeks | 219 = 20% | 30 = 3% |
| Never < 50 copies/mL | 621 = 55% | 926 = 82% |
| Confirmed Rebound | 130 = 12% | 110 = 10% |
| Class C Event | 9 = 1% | 1 < 1% |
| Lost to Follow-up | 52 = 5% | 17 = 2% |
| Added New ART | 54 = 5% | 12 = 1% |
| No Viral Specimens | 36 = 3% | 32 = 3% |

## 2.7 Summary of Applicant's Conclusions

The applicant concluded from trial 1090 that the use of either 200 mg BID Viramune in conjunction with 3TC plus another ART resulted in significant improvement in percent of subjects BLQ at 48 weeks, compared to 3TC plus other ART alone.

## 3. Statistical Reviewer's Comments and Analyses on Trial 1090

This review will discuss the following issues with respect to trial 1090. First, the reviewer will re-analyze the time to viral rebounds, using the standard algorithm employed in other NDA reviews for AIDS drugs. Second, the reviewer will compare the two arms with respect to the clinical progression, which was the original primary endpoint of this trial. Third, the reviewer will discuss the association between viral response and clinical progression. The conclusion of these analyses will be that this trial has shown a statistically significant superiority of nevaripine over placebo in both time to viral rebound and time to clinical progression. Finally, the reviewer will make comparisons of the two arms stratified by a number of covariates, both with respect to viral suppression and with respect to CDC events.

### 3.1 Times to Viral Rebound

The FDA reviewer has recalculated the times to failure (loss of BLQ status) using a somewhat different algorithm than the sponsor. The FDA algorithm is the same one that has been used in other NDA reviews for HIV indications. The sponsor and the FDA reviewer both considered subjects as failures at the earlier of two consecutive visits with HIV RNA > LOQ after a response = decrease of HIV RNA to < LOQ. If the subject never responded, the subject was a failure at time zero. The FDA algorithm differs from the sponsor's algorithm in the following particulars.

1) A subject responds on the earlier of two consecutive visits with HIV RNA BLQ, but not on the first such visit if the next visit has HIV RNA > LOQ.

2) A subject is a failure at the time of disease progression or change of therapy away from original assignment.

3) A subject is a failure at the time of loss to follow-up at the time of last visit with an HIV RNA, regardless of whether the sponsor classifies such subjects as having completed trial. (The sponsor classified as completing the trial 257 nevaripine subjects and 283 placebo subjects who were all actually lost to follow-up.) However, if the last such visit occurs later than

day 46*7, then the subject is considered to have completed the trial and not to be lost to follow-up.

4) A subject lost to follow-up before day 46*7 is considered a failure at that date even if HIV RNA is still BLQ. A subject with HIV RNA BLQ is not censored at that date.

5) If a subject fails because of loss to follow-up, viral load > LOQ at last visit, or two consecutive viral loads > LOQ, then the time of failure is the earliest of time of loss to follow-up, time of viral rebound, and eight weeks after the last observed viral load that was still BLQ. This provision is to compensate for the sporadic nature of HIV RNA measurements.

The use of the standard FDA algorithm resulted in slightly lower success rates on both arms than with the sponsor's algorithm. The difference between the NVP and placebo arms is also slightly smaller. Nonetheless, the NVP arm continues to have statistically significantly superior results to the placebo arm and the overall change in success rate in each arm due to the more stringent definition success is small relative to the difference in rates between the arms. The Kaplan-Meier curves for time to virologic failure using both algorithms on both arms are given in figures 3.1 A and 3.1 B. Figure 3.1 A shows for times until viral rebound from below 400 copies/mL; figure 3.1 B shows times until rebound from below 50 copies/mL.

Figure 3.1 A shows the survival curves when the LOQ = 400 copies/mL for both arms using both the sponsor's algorithm and the standard FDA algorithm. The higher pair of curves are for the nevaripine arm, the lower pair for placebo. One can see that the sponsor's algorithm is slightly more favorable to nevaripine. Nonetheless, the observed difference between the arms is much larger than the difference between the algorithms. Regardless of algorithm, the nevaripine arm is statistically significantly superior with p-value < .0001.

Figure 3.1 B shows the survival curves when the LOQ = 50 copies/mL for both arms for two different algorithms used by the sponsor and the standard FDA algorithm. As the figure shows, the three algorithms are barely distinguishable. The higher triplet of curves is the nevaripine arm. As was the case for LOQ = 400, the nevaripine arm is statistically significantly superior

with p-value < .0001.

Appears This Way
On Original

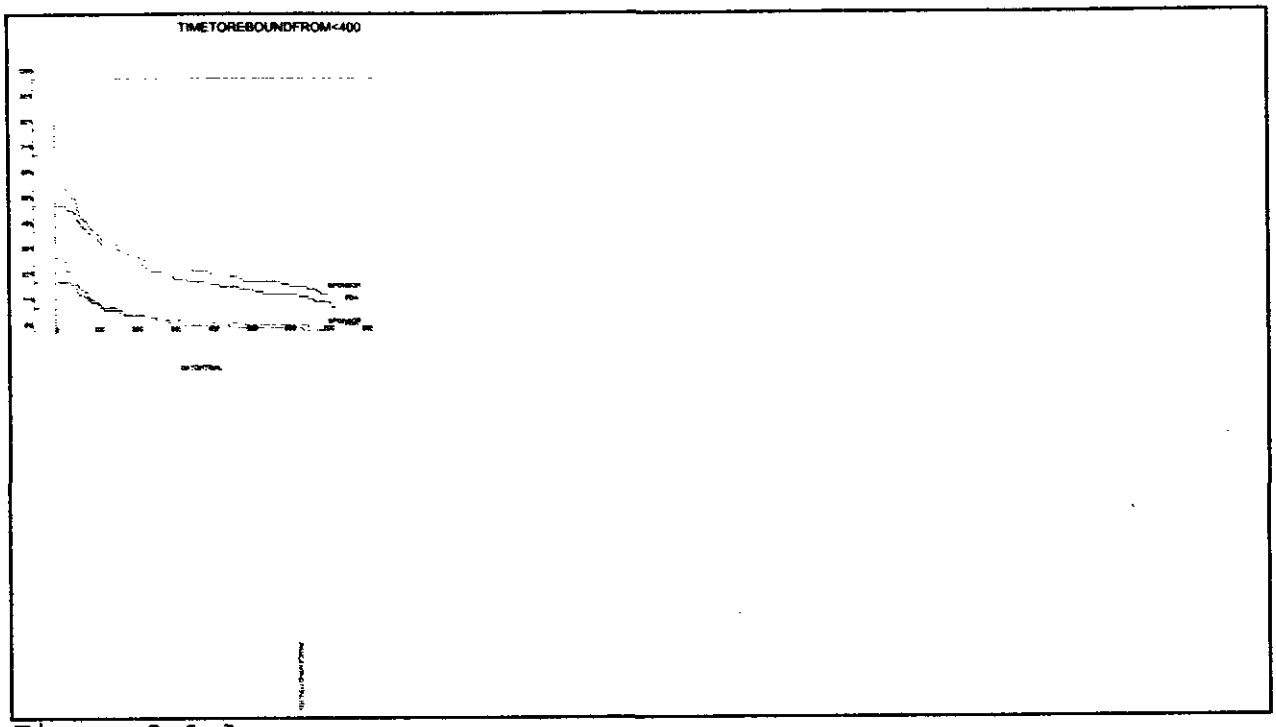


Figure 3.1 A



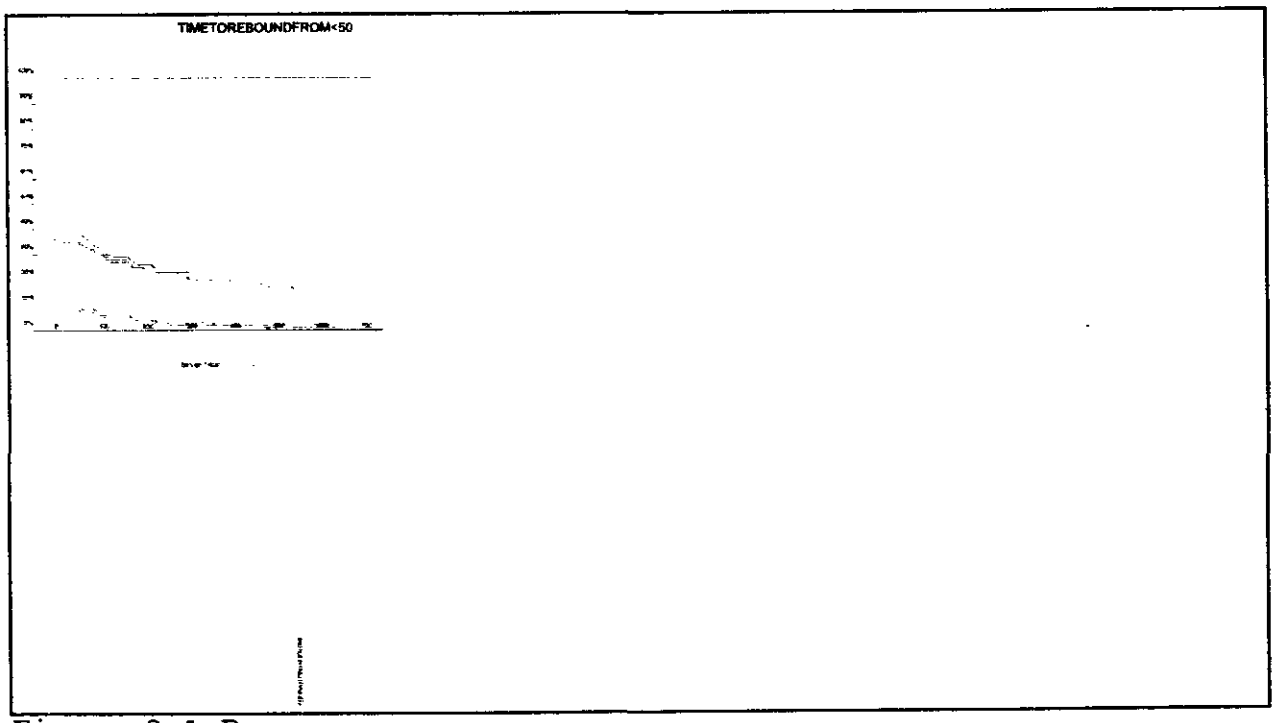


Figure 3.1 B

## 3.2 Times to CDC Events

The primary endpoint in Trial 1090 was originally the clinical endpoint of time to first CDC event. A preliminary analysis of this endpoint suggested that there was no statistically significant difference between the arms and that the trial failed to demonstrate the efficacy of nevaripine. The DAVDP recommended that the data by re-analyzed using time to viral failure. Nonetheless, it would be difficult to argue that a difference in rates of viral failure was clinically meaningful if there was no difference in rates of clinical progression and the common rate of clinical progression was large. The raw rates of clinical progression in the two arms were 154/1121 = 14% on nevaripine and 186/1128 = 16% on placebo. The two-tailed Fisher exact p-value for this difference is .077. Thus, on first examination, the data are suggestive but not convincing of a small difference in the rate of clinical progression.

The FDA reviewer has conducted some further analyses on the clinical progression data. Figures 3.2 A, A' shows the Kaplan-Meier plot for time to first CDC event on the two arms. The first figure censors only on last day observed; the second figure censors on the earlier of change of therapy and last day observed.

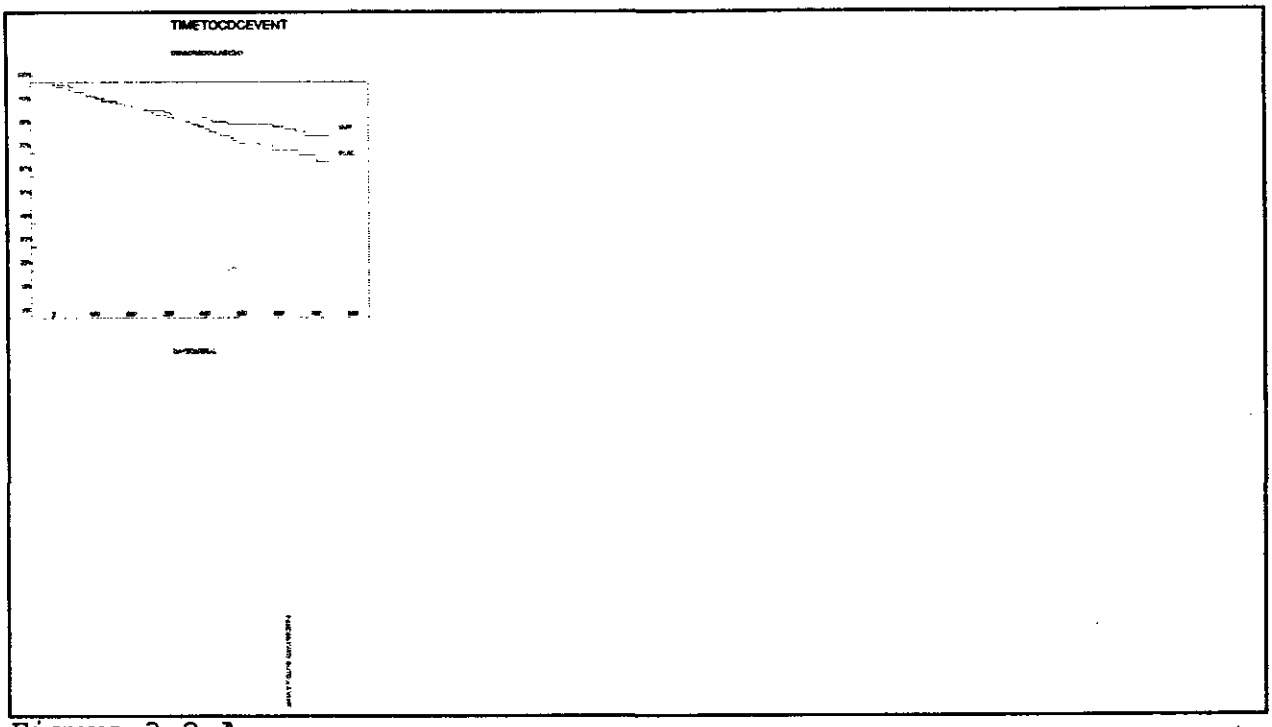


Figure 3.2 A



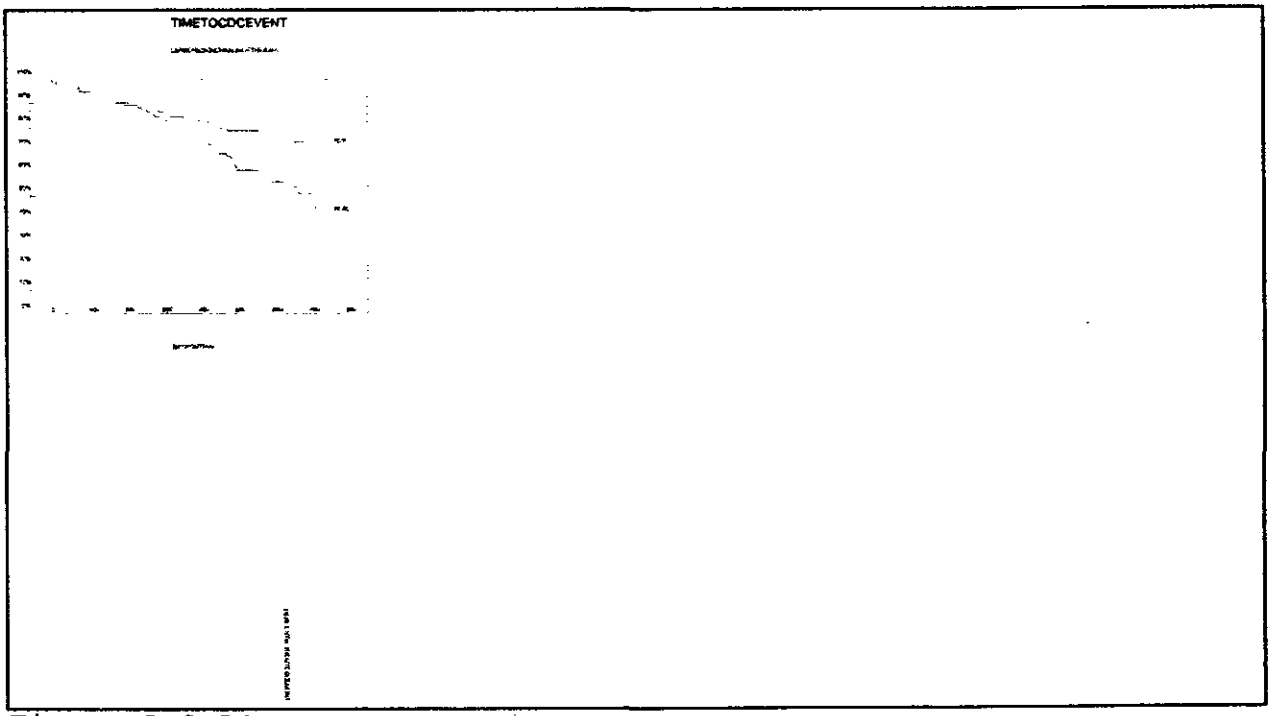


Figure 3.2 A'

One can see that, censoring only on last day, the two survival curves coincide out to about day 300 but by day 700 there is a difference of 77% not progressed on nevaripine versus 66% on placebo. If one censored on the addition of new therapy as well, the difference at day 700 increases to 70% not progressed on nevaripine versus 51% on placebo. Many subjects were lost to follow-up after day 300 so observed disease progressions after day 300 account for larger differences in the estimated final rate at day 700. (This is how a difference of only 2% in percent ever progressed becomes an estimated of 17% is percent progressed by day 700.)

These subjects lost to follow-up are a potential problem with interpreting these data. As one sensitivity analysis, the FDA reviewer has computed new Kaplan-Meier curves, counting the earlier of CDC event and change from assigned therapy as failures. These curves are given below in figure 3.2 B.

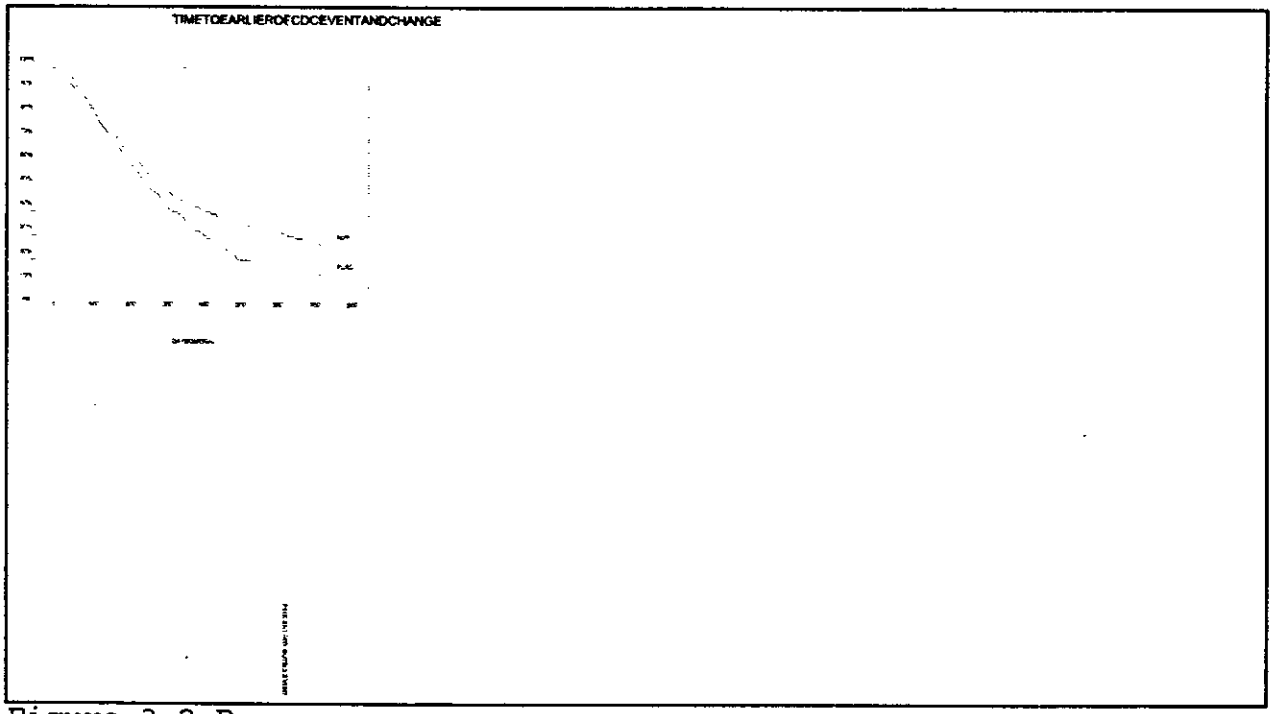


Figure 3.2 B



Here, the curves begin to separate around day 200; by day 350, nevaripine has 44% neither progressed nor changed therapy

versus 38% for placebo. The nevaripine and placebo rates are 37% versus 25% by day 450 and 26% versus 13% by day 700.

A second sensitivity analysis counted the earliest of CDC event, change from assigned therapy, and loss to follow-up as failure. These curves are given in figure 3.2 C.

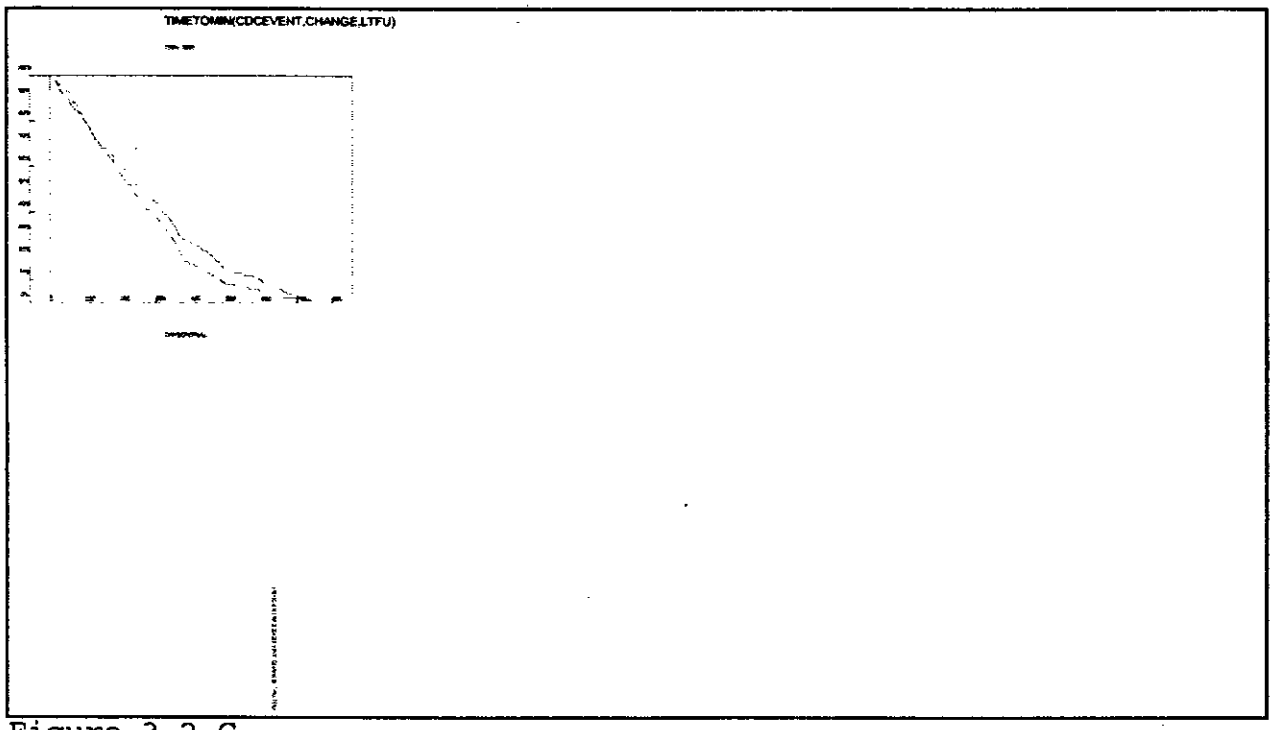


Figure 3.2 C



For these curves, the nevaripine arm has a 45% success rate at day 300 versus 38% for placebo. The difference increases to 27% versus 17% by day 400 and then diminishes steadily as most of the subjects reach the end of their HIV RNA data. All subjects eventually fail in this analysis since the day of last visit is counted as failure here.

The log-rank p-values for these two three to failure are .006 when failure = only CDC events and <.0001 when failure includes change of therapy or both change of therapy and last HIV RNA data.

## 3.3 Times to CDC Events and Viral Failure

The FDA reviewer also conducted analyses relating time to CDC event to viral failure. In these analyses, Kaplan-Meier curves were computed for time to CDC event for each combination of arm and viral success or failure. Subjects who never had confirmed viral load BLQ were considered viral failures from the start of the trial until the day they changed therapy. Subjects who ever had confirmed viral load BLQ were considered viral successes from the start of the trial until the day of confirmed viral rebound or change of therapy. If they experienced a confirmed rebound prior to either CDC event or change in therapy, they were re-entered into the analysis as a second, new subject with time starting at the day of viral rebound. This new subject was still on the same arm but was now a viral failure. Finally, subjects who changed therapy were re-entered as a new subject with time starting at the day of therapy change. These new subjects were on a third arm (Change) and were all counted as viral failures.

The five Kaplan-Meier curves for time to CDC event for Viral Success Placebo, Viral Failure Placebo, Viral Success Nevaripine, Viral Failure Nevaripine, and Viral Failure Changed are shown in figure 3.3 A. One can see that there is only a slight incidence rate of CDC progression on the two viral suppressed arms. Among the viral failures, there is little difference between the placebo, nevaripine, and changed therapy arms. The differences between the arms within each stratum of viral failures or viral successes are not statistically significant. Within each arm, the differences between viral successes and viral failures are statistically significant.

These data suggest that the difference in times to CDC event between nevaripine and placebo observed in figures 3.2 A and B above are due to longer periods of viral suppression for the nevaripine subjects. This also confirms that duration of viral suppression is a valid surrogate marker for clinical progression.

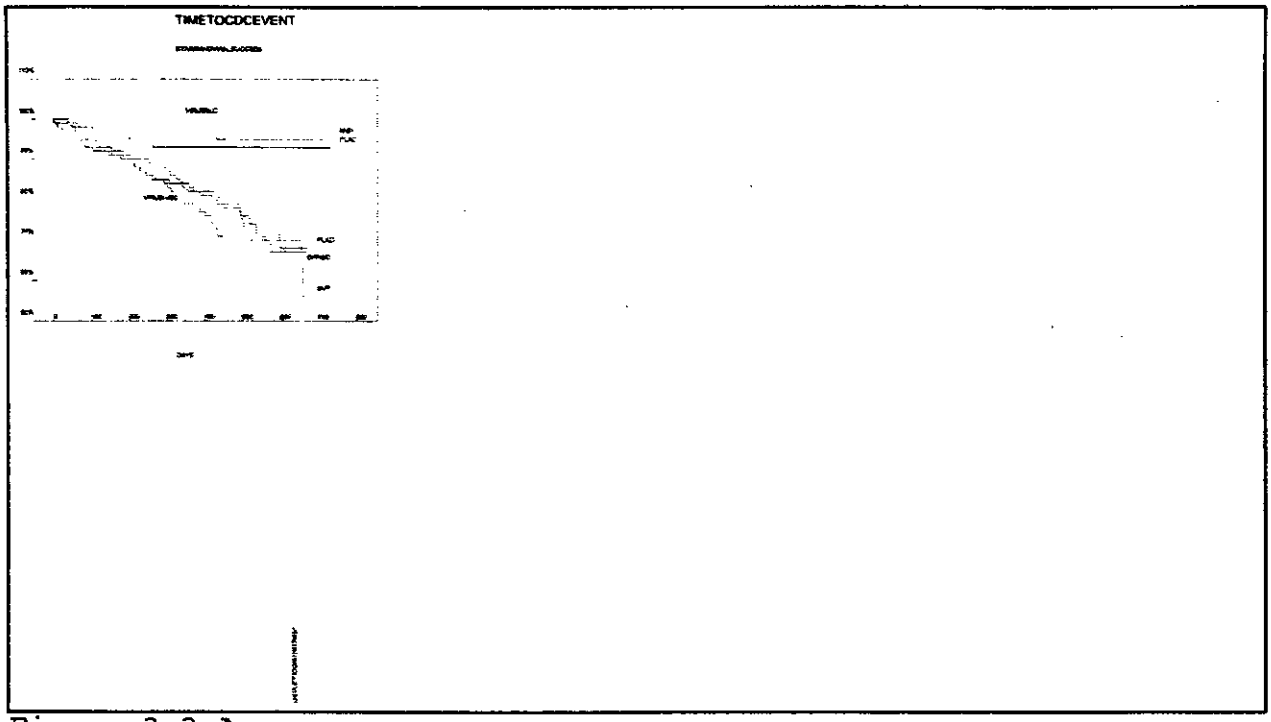


Figure 3.3 A

## 3.4 Viral Suppresssion and CDC Events Stratified by Covariates

Table 3.4 A shows the percent of subjects with viral load still confirmed below 50 copies/mL while on assigned therapy at week 48. This tables also show the 95% lower and upper confidence limits for success on NVP minus on success on Placebo. Lower bounds > 0 favor NVP. The analagous table for viral success at LOQ = 400 copies/mL is given in the appendix.

TABLE 3.4 A
VIRAL SUCCESS RATES AT WEEK 48, TRIAL 1090
LOQ = 50

| | PLACEBO | NVP | NVP-PLAC LOWER | UPPER |
|---|---|---|---|---|
| All | 19/1128 = 2% | 200/1121 = 18% | 14% | 19% |
| PRIOR_TRT | | | | |
| Naive | 0/131 = 0% | 46/117 = 39% | 30% | 48% |
| ZDV | 18/849 = 2% | 108/873 = 12% | 8% | 13% |
| Other | 1/148 = 1% | 46/131 = 35% | 26% | 43% |
| CD4_STRATUM | | | | |
| <25 | 1/181 = 1% | 13/194 = 7% | 2% | 10% |
| 25-50 | 6/139 = 4% | 12/140 = 9% | -1% | 10% |
| 50-100 | 4/255 = 2% | 38/269 = 14% | 8% | 17% |
| >100 | 8/553 = 1% | 137/518 = 26% | 21% | 29% |
| RNA_STRATUM | | | | |
| <5K | 11/222 = 5% | 54/188 = 29% | 17% | 31% |
| 5K-100K | 5/578 = 1% | 91/565 = 16% | 12% | 18% |
| >100K | 2/311 = 1% | 55/349 = 16% | 11% | 19% |
| CDCGROUP | | | | |
| Cat A/B | 15/623 = 2% | 133/611 = 22% | 16% | 23% |
| Cat C | 4/505 = 1% | 67/510 = 13% | 9% | 15% |
| PRIOR_DISEASE | | | | |
| AIDS | 4/498 = 1% | 67/504 = 13% | 9% | 16% |
| No AIDS | 15/630 = 2% | 133/617 = 22% | 16% | 23% |

TABLE 3.4 A (cont)
VIRAL SUCCESS RATES AT WEEK 48, TRIAL 1090
LOQ = 50

| | PLACEBO | NVP | NVP-PLAC LOWER | NVP-PLAC UPPER |
|---|---|---|---|---|
| COUNTRY | | | | |
| USA | 4/246 = 2% | 26/235 = 11% | 5% | 14% |
| Canada | 2/39 = 5% | 3/42 = 7% | -8% | 12% |
| UK | 5/109 = 5% | 29/115 = 25% | 12% | 29% |
| Spain | 5/135 = 4% | 14/132 = 11% | 1% | 13% |
| France | 0/87 = 0% | 13/84 = 15% | 8% | 23% |
| Germany | 0/68 = 0% | 3/61 = 5% | -1% | 10% |
| Italy | 0/61 = 0% | 11/60 = 18% | 9% | 28% |
| Low Countries | 0/26 = 0% | 1/28 = 4% | -3% | 10% |
| Argentina | 2/90 = 2% | 20/92 = 22% | 11% | 28% |
| Australia | 0/5 = 0% | 1/9 = 11% | -9% | 32% |
| S.Africa | 1/260 = 0% | 79/262 = 30% | 24% | 35% |
| CONTINENT | | | | |
| Europe | 10/488 = 2% | 71/480 = 15% | 9% | 16% |
| North America | 6/289 = 2% | 30/286 = 10% | 5% | 12% |
| South Africa | 1/261 = 0% | 79/263 = 30% | 24% | 35% |
| South America | 2/90 = 2% | 20/92 = 22% | 11% | 28% |
| RACE | | | | |
| White | 14/835 = 2% | 140/816 = 17% | 13% | 18% |
| Black | 5/264 = 2% | 52/277 = 19% | 12% | 22% |
| Other | 0/29 = 0% | 8/28 = 29% | 12% | 45% |
| SEX | | | | |
| Male | 14/902 = 2% | 143/879 = 16% | 12% | 17% |
| Female | 5/226 = 2% | 57/242 = 24% | 16% | 27% |
| IV_DRUG_USE | | | | |
| Never Used | 13/921 = 1% | 181/918 = 20% | 16% | 21% |
| Stopped Use | 6/206 = 3% | 19/200 = 10% | 2% | 11% |
| YEARS_SEROPOSITIVE | | | | |
| <=1.5 | 7/392 = 2% | 97/378 = 26% | 19% | 28% |
| 1.6-6.3 | 5/409 = 1% | 67/433 = 15% | 11% | 18% |
| 6.4-15.9 | 7/327 = 2% | 36/310 = 12% | 6% | 13% |
| AGE | | | | |
| 17-33 | 3/337 = 1% | 56/339 = 17% | 12% | 20% |
| 33-41 | 11/447 = 2% | 76/458 = 17% | 10% | 18% |
| 41-72 | 5/344 = 1% | 68/324 = 21% | 15% | 24% |

This table shows the placebo arm had minimal efficacy in all strata while the nevaripine arm had its greatest anti-viral efficacy in the healthier strata: treatment naive, baseline CD4 count > 100, baseline HIV RNA < 5 K copies/mL, CDC disease status A or B, no prior AIDS, <= 1.5 years seropositive, no IV drug use. In these strata, 22%-39% of nevaripine subjects were virally suppressed below 50 copies/mL at the end of one year.

Table 3.4 B shows counts of subjects without CDC events through 96 weeks of follow-up. The first line shows the Kaplan-Meier estimates of progression-free survival. All the lines in the table show rates of no CDC event among subjects with at least 96 weeks of follow-up. The Kaplan-Meier curve treats subjects lost to follow-up as censored and imputes them as successes or failures as the rates in the subjects not lost to follow-up. The other analyses discard subjects lost to follow-up from numerator and denominator. The Kaplan-Meier estimate is more accurate but within subgroups, the Kaplan-Meier estimates of confidence for the difference between the arms becomes incalculable. Therefore, the results discarding subjects lost to follow-up are used. One should note from the first two lines that, although discarding loss to follow-up substantially underestimates the success rate in each arm, the confidence for the extent of NVP superiority are nearly the same.

The pattern is similar to the results found with viral suppression. NVP generally appears superior in all strata with adequate sample size. There is a suggestion that NVP is more beneficial in strata with low baseline HIV RNA, high baseline CD4 count, no prior AIDS, and CDC category A/B at baseline.

Analagous results through week 46 are given in the appendix. The NVP is not so superior in those tables. As mentioned in section 3.2 above, the two arms do not separate significantly with respect to time CDC events until the second year.

TABLE 3.4 B
SUBJECTS WITHOUT CDC EVENTS
96 WEEKS OF FOLLOW-UP

| | | | NVP-PLAC | |
|---|---|---|---|---|
| | PLACEBO | NVP | LOWER | UPPER |
| All | 68% | 78% | 4% | 16% |
| All | 51/237 = 22% | 70/224 = 31% | 2% | 18% |
| PRIOR_TRT | | | | |
| Naive | 0/22 = 0% | 1/13 = 8% | -7% | 22% |
| ZDV | 32/162 = 20% | 53/176 = 30% | 1% | 19% |
| Other | 19/53 = 36% | 16/35 = 46% | -11% | 31% |
| CD4_STRATUM | | | | |
| <25 | 3/74 = 4% | 7/74 = 9% | -3% | 13% |
| 25-50 | 2/42 = 5% | 5/35 = 14% | -4% | 23% |
| 50-100 | 10/45 = 22% | 11/41 = 27% | -14% | 23% |
| >100 | 36/76 = 47% | 47/74 = 64% | 0% | 32% |
| RNA_STRATUM | | | | |
| <5K | 15/31 = 48% | 16/29 = 55% | -18% | 32% |
| 5K-100K | 25/116 = 22% | 39/112 = 35% | 2% | 25% |
| >100K | 11/90 = 12% | 15/81 = 19% | -5% | 17% |
| CDCGROUP | | | | |
| Cat A/B | 35/112 = 31% | 48/111 = 43% | -1% | 25% |
| Cat C | 16/125 = 13% | 22/113 = 19% | -3% | 16% |
| PRIOR_DISEASE | | | | |
| AIDS | 16/123 = 13% | 22/111 = 20% | -3% | 16% |
| No AIDS | 35/114 = 31% | 48/113 = 42% | -1% | 24% |

TABLE 3.4 B (cont)
SUBJECTS WITHOUT CDC EVENTS
96 WEEKS OF FOLLOW-UP

| | | | NVP-PLAC | |
|---|---|---|---|---|
| | PLACEBO | NVP | LOWER | UPPER |
| COUNTRY | | | | |
| USA | 13/56 = 23% | 22/64 = 34% | -5% | 27% |
| Canada | 0/6 = 0% | 1/8 = 13% | -10% | 35% |
| UK | 4/18 = 22% | 8/19 = 42% | -9% | 49% |
| Spain | 1/14 = 7% | 6/18 = 33% | 1% | 52% |
| France | 12/21 = 57% | 17/22 = 77% | -7% | 48% |
| Germany | 4/17 = 24% | 1/7 = 14% | -42% | 24% |
| Italy | 0/6 = 0% | 1/6 = 17% | -13% | 46% |
| Low Countries | 1/6 = 17% | 0/6 = 0% | -46% | 13% |
| Argentina | 0/15 = 0% | 0/15 = 0% | 0% | 0% |
| Australia | 0/1 = 0% | 1/1 = 100% | 100% | 100 |
| S.Africa | 16/77 = 21% | 13/57 = 23% | -12% | 16% |
| CONTINENT | | | | |
| Europe | 22/82 = 27% | 33/79 = 42% | 0% | 29% |
| North America | 13/63 = 21% | 24/73 = 33% | -2% | 27% |
| South Africa | 16/77 = 21% | 13/57 = 23% | -12% | 16% |
| South America | 0/15 = 0% | 0/15 = 0% | 0% | 0% |
| RACE | | | | |
| White | 37/161 = 23% | 58/167 = 35% | 2% | 21% |
| Black | 13/67 = 19% | 11/53 = 21% | -13% | 16% |
| Other | 1/9 = 11% | 1/4 = 25% | -33% | 61% |
| SEX | | | | |
| Male | 40/195 = 21% | 59/185 = 32% | 3% | 20% |
| Female | 11/42 = 26% | 11/39 = 28% | -17% | 21% |
| IV_DRUG_USE | | | | |
| Never Used | 46/205 = 22% | 58/185 = 31% | 0% | 18% |
| Stopped Use | 5/32 = 16% | 12/39 = 31% | -4% | 34% |
| YEARS_SEROPOSITIVE | | | | |
| <=1.5 | 19/87 = 22% | 20/77 = 26% | -9% | 17% |
| 1.6-6.3 | 19/97 = 20% | 29/91 = 32% | -0% | 25% |
| 6.4-15.9 | 13/53 = 25% | 21/56 = 38% | -4% | 30% |
| AGE | | | | |
| 17-33 | 10/63 = 16% | 15/58 = 26% | -4% | 24% |
| 33-41 | 20/102 = 20% | 31/95 = 33% | 1% | 25% |
| 41-72 | 21/72 = 29% | 24/71 = 34% | -11% | 20% |

Finally, table 3.4 C contains a summary of viral suppression results, stratified by number and type of other drugs used at baseline. In the section of the table covering protease inhibitor (PI) use prior to failure, a subject who fails at day zero because their viral load was never below 400 copies is considered to be a pre-failure PI user if they used PI before week 24.

TABLE 3.4 C
VIRAL SUPPRESSION AT < 400

| | PLACEBO | NVP |
|---|---|---|
| DRUGS AT BASELINE | | |
| 1 | 1/20 = 5% | 3/23 = 13% |
| 2 | 12/652 = 2% | 137/600 = 23% |
| 3 | 27/428 = 6% | 90/464 = 19% |
| 4 | 1/23 = 4% | 2/28 = 7% |
| 5 | 0/5 = 0% | 0/6 = 0% |
| PI USE EVER | | |
| NO | 26/446 = 6% | 213/553 = 39% |
| YES | 15/682 = 2% | 19/568 = 3% |
| PI USE BEFORE FAIL | | |
| NO | 28/862 = 3% | 221/920 = 24% |
| YES | 13/266 = 5% | 11/201 = 5% |

## 4. INCAS Trial (1046)

### 4.1 Objectives in Trial

The primary objective of this study was to compare the efficacy of one triple drug regimen and two dual drug regimens. The three regimens compared 1) NVP at a dose of 200 mg bid plus ddI at 250 or 400 mg and ZDV at 600 mg (all bid) to 2) ddI and ZDV alone to 3) NVP and ZDV alone. The primary efficacy endpoint was percent BLQ on the Amplicor assay (LOQ = 400 copies/mL) at 48 weeks. The study population was HIV-1 infected anti-retroviral naive patients with CD4 counts of 200-600 cells/$mm^3$ without AIDS defining illness or active invasive infection or malignancy.

### 4.2 Summary of Study Design

The study was double-blind, randomized, three-arm, parallel, active-controlled, multi-center trials conducted in Europe, Australia, and Canada.

Subjects were randomly assigned in a 1:1:1 ratio to 1) NVP plus ZDV plus ddI, 2) NVP plus ZDV, or 3) ZDV plus ddI. In the various arms the doses of the drugs were NVP at 200 mg bid (preceded by a lead-in dose of 200 mg qd for 2 weeks), ZDV at 600 mg/day and ddI at 200 mg bid (125 mg bid if weight < 60 kg).

### 4.3 Patient Accounting and Baseline Characteristics

153 patients were enrolled in the INCAS trial. Of these, 2 patients never started treatment. 52 patients discontinued treatment before week 52, 27 because of an adverse event. The subjects were enrolled at 29 centers. The exact distribution of patients and sites by country is given in table 4.3 A. One patient among the 151 receiving treatment is unaccounted for in this table.

TABLE 4.3 A
PATIENTS, SITES BY COUNTRY, INCAS TRIAL

| Country | Patients | Sites |
|---|---|---|
| Netherlands | 29 | 9 |
| Italy | 16 | 4 |
| Australia | 36 | 13 |
| Canada | 69 | 3 |

In the INCAS trial 1046, the study population was 93% male with a mean age of 38 years. They were 93% white. The mean CD4 count at baseline was 373 cells/$mm^3$; the mean HIV RNA level was 4.32 logs.

Table 4.3 C summarizes the primary reasons for discontinuation from study and from double blind treatment.

TABLE 4.3 C
PATIENT STATUS, INCAS TRIAL

| | NVP+ddI | ddI | NVP* |
|---|---|---|---|
| Randomized | 51 | 53 | 47 |
| Discontinued Trial | 14 | 18 | 20 |
| Adverse Event | 8 | 7 | 12 |
| Other | 6 | 11 | 8 |

*All arms also get ZDV

## 4.4 Summary of Methods of Assessment

### 4.4.1 Schedule of Measurements

Patients had CD4 counts taken and HIV RNA measured at weeks 0, 2, 4, every 4 weeks to week 52. Follow-up was subsequently extended to week 76. HIV RNA was measured on the Amplicor assay. Specimens with Amplicor measurement < 500 copies/mL were remeasured using the Ultra-Direct assay, which has an LOQ = — copies/mL.

### 4.4.2 Assessment of Treatment Effects

Time to viral failure was defined as the time until two consecutive HIV RNA levels above LOQ following confirmed achievement of levels BLQ. HIV RNA levels for scheduled visits after a subject was lost to follow-up were considered above LOQ. Time to failure was zero if the subject never had two consecutive HIV RNA levels BLQ. Subjects were considered viral successes if their time to viral failure exceeded 52 weeks.

## 4.5 Summary of Statistical Analysis

The primary endpoint was the proportion of viral successes by week 48, computed using the Amplicor assay LOQ of 400 copies/mL.

Secondary analyses included percent of viral successes computed using the Ultra-Direct assay LOQ of 20 copies/mL; Kaplan-Meier curves for time to viral failure; and Cox regressions for time to viral failure including the covariate baseline CD4 count.

## 4.6 Summary of Applicant's Results, INCAS Trial

The results for INCAS trial 1046 are given in table 4.6 A. The primary analysis found that adding nevirapine to ddI+ZDV background gave a statistically significant increase in sustained viral suppression, from 19% to 45% (log rank p-value < .001). It was also found that ddI+ZDV was statistically signicantly superior to nevaripine + ZDV (log-rank p-value < .001).

TABLE 4.6 A
RATES OF SUSTAINED HIV RNA SUPPRESSION
WEEK 48, INCAS TRIAL

| Stratum | NVP+ddI+ZDV | ddI+ZDV | NVP+ZDV |
|---|---|---|---|
| LOQ = 400 | 23/51 = 45% | 10/53 = 19% | 0/47 = 0% |
| LOQ = 20 | 18/51 = 35% | 5/53 = 9% | 0/47 = 0% |

Table 4.6 B shows the breakdown of the failures in each arm by cause.

TABLE 4.6 B
REASONS FOR FAILURE IN INCAS TRIAL

| | NVP+ddI+ZDV | ddI+ZDV | NVP+ZDV |
|---|---|---|---|
| Enrolled | 51 | 53 | 47 |
| Success at 48 weeks | 23 = 45% | 10 = 19% | 0 = 0% |
| Never < 400 copies/mL | 6 = 12% | 20 = 38% | 20 = 43% |
| Confirmed Rebound | 18 = 35% | 20 = 38% | 23 = 49% |
| Class C Event | 1 = 2% | 0 | 0 |
| Lost to Follow-up | 3 = 6% | 1 = 2% | 3 = 6% |
| No Viral Specimens | 0 | 2 = 4% | 1 = 2% |

## 4.7 CD4 Responses

The applicant also compared the three arms with respect to sustained change from baseline CD4 count. This parameter was defined to be the DAVG or area under the curve minus baseline divided by time observed to week 52. Handling of missing data is not described. The results are given in table 4.7 A.

TABLE 4.7 A
DAVG OF CD4 COUNT, WK 52

| Arm | DAVG CD4 Count | P-value |
|---|---|---|
| NVP/ddI/ZDV | 99 | |
| ddI/ZDV | 66 | .07 vs Triple |
| NVP/ZDV | 35 | .09 vs ddI/ZDV |

One can see that with respect to long-term CD4 count, the triple arm was marginally statistically significantly superior to ddI/ZDV but the NVP/ZDV dual therapy was marginally statistically significantly inferior to ddI/ZDV. For both comparisons, the estimated magnitude of the difference was about 30 cells.

## 4.8 HIV Disease Progression

Rates of HIV disease progression as reported by the investigators are given in table 4.8 A. These include some events occurring in subjects who were already classified as viral failures on the basis of viral load. Thus more events are included here than in table 4.6 above.

TABLE 4.8 A
HIV DISEASE PROGRESSION, INCAS TRIAL

| Arm | Number, % Progressed | P-value to ddI/ZDV |
|---|---|---|
| NVP/ddI/ZDV | 6/51 = 12% | .08 |
| ddI/ZDV | 14/53 = 26% | |
| NVP/ZDV | 11/47 = 23% | |

## 4.9 Summary of Applicant's Conclusions

The NVP/ddI/ZDV triple therapy was statistically and clinically significantly superior to the ddI/ZDV dual therapy with respect to percentage of subjects with long term (48 week) sustained viral suppression to BLQ levels. The statistical significance is preserved after adjustment for comparisons with two NVP containing arms. The triple therapy arm was also marginally statistically significantly superior to ddI/ZDV with respect to long term increases in CD4 count and reduction in risk of HIV disease progression.

The NVP/ZDV dual therapy was statistically and clinically significantly inferior to the ddI/ZDV dual therapy with respect to percentage of subjects with long term (48 week) sustained viral suppression to BLQ levels. The dual NVP therapy arm was also marginally statistically significantly inferior to ddI/ZDV with respect to long term increases in CD4 count and approximately equivalent in reduction in risk of HIV disease progression.

## 5. Statistical Reviewer's Comments and Analyses on INCAS Trial:

This review will discuss the following issues with respect to trial 1046. First, the reviewer will re-analyze the time to viral rebounds, using the standard algorithm employed in other NDA reviews for AIDS drugs. This section will confirm that there is a statistically significant superiority of NVP triple therapy to ddI/ZDV, even adjusting for the presence of two opportunities for NVP to be declared effective. It will also be noted that this trial confirms that NVP should not be used with only one NRTI. Second, the reviewer will compare the NVP/ddI/ZDV and ddI/ZDV arms stratified by a number of covariates. It will be shown that no convincing demonstration of treatment-covariate interactions exists in this trial.

### 5.1 Times to Viral Rebound:

The same comments made in section 3.1 above apply to the algorithms used by the applicant and the FDA statistical reviewer in computing times to viral rebound. The results presented here will all use the times as recalculated by the FDA reviewer.

Although the INCAS trial has a small sample size, there is a statistically significant improvement of 26% in Percent BLQ for NVP+zdv+ddi compared to zdv+ddi (97.5% confidence interval = 6.3% to 45.7%). This improvement is statistically significant even with the multiple comparison adjustment resulting from using the two-sided 97.5% interval.

Figures 5.1 A-D show the plots of Kaplan-Meier analyses of these times. Figures 5.1 A and B show the results using LOQ = 400 copies/mL. Figure 5.1 A shows the two Kaplan-Meier curves for the NVP triple therapy and the ddI/ZDV control arm. The NVP triple therapy arm is consistently superior. Figure 5.1 B shows the 95% confidence bands for difference in percent BLQ for ddI/ZDV control minus NVP triple therapy. For the entire time period for which data is available, NVP is, with 95% confidence, at least 10 better than the dual therapy control. One should note that these confidence limit plots are adjusted to give simultaneous confidence of 95% at any given time point for both

comparator arms. They are not adjusted to give simultaneous 95% confidence over all time points. If one is primarily interested in results at one year, the lack of simultaneity over time is not a problem. The confidence band is for the difference between NVP dual therapy and the ddI/ZDV is not given since there is no question that NVP + a single NRTI is ineffective therapy.

Figures 5.1 C and D show the same results for LOQ = —— copies/mL. Again, with 95% confidence, NVP triple therapy is at least 10% better than ddI/ZDV.

Appears This Way
On Original

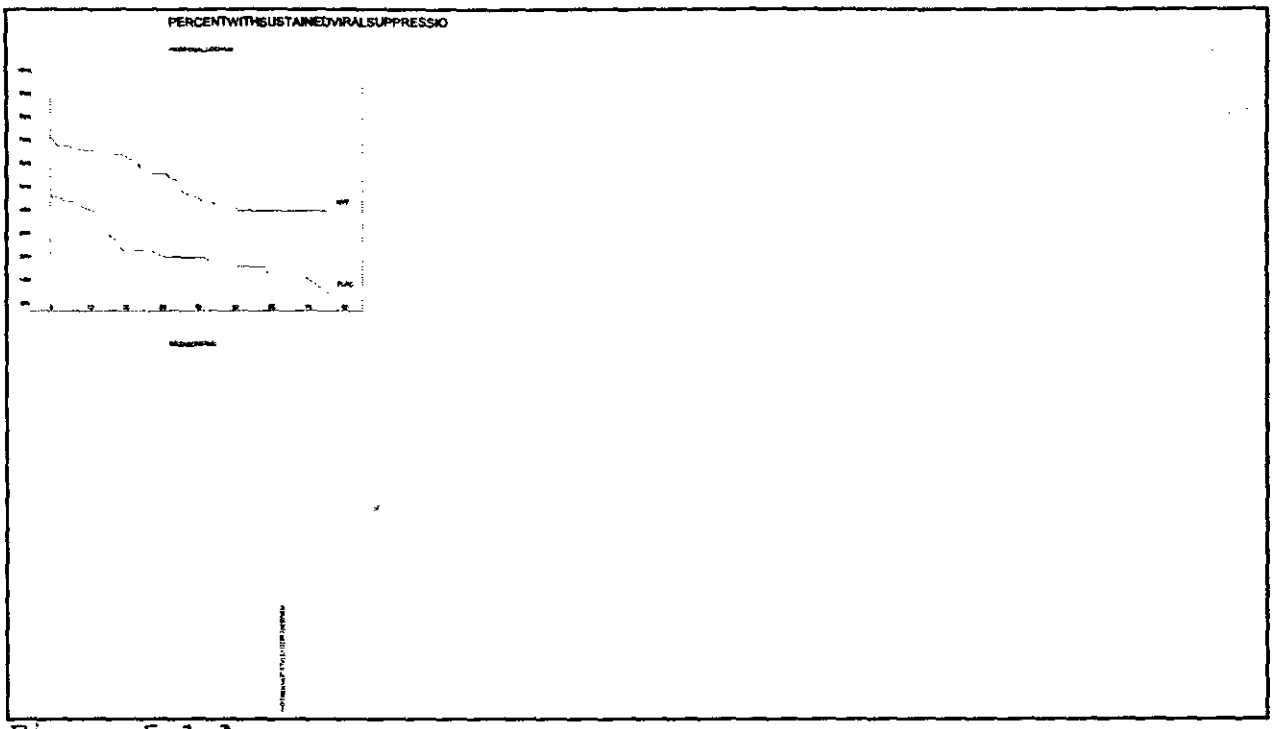


Figure 5.1 A



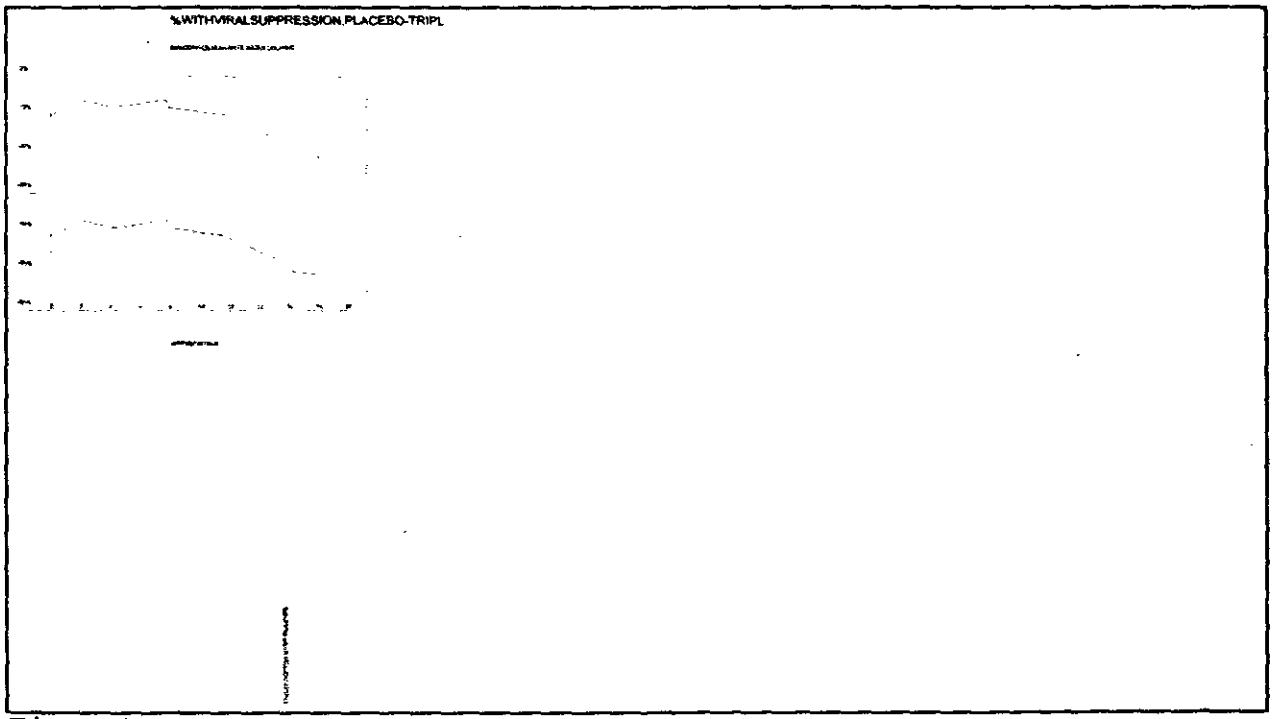


Figure 5.1 B

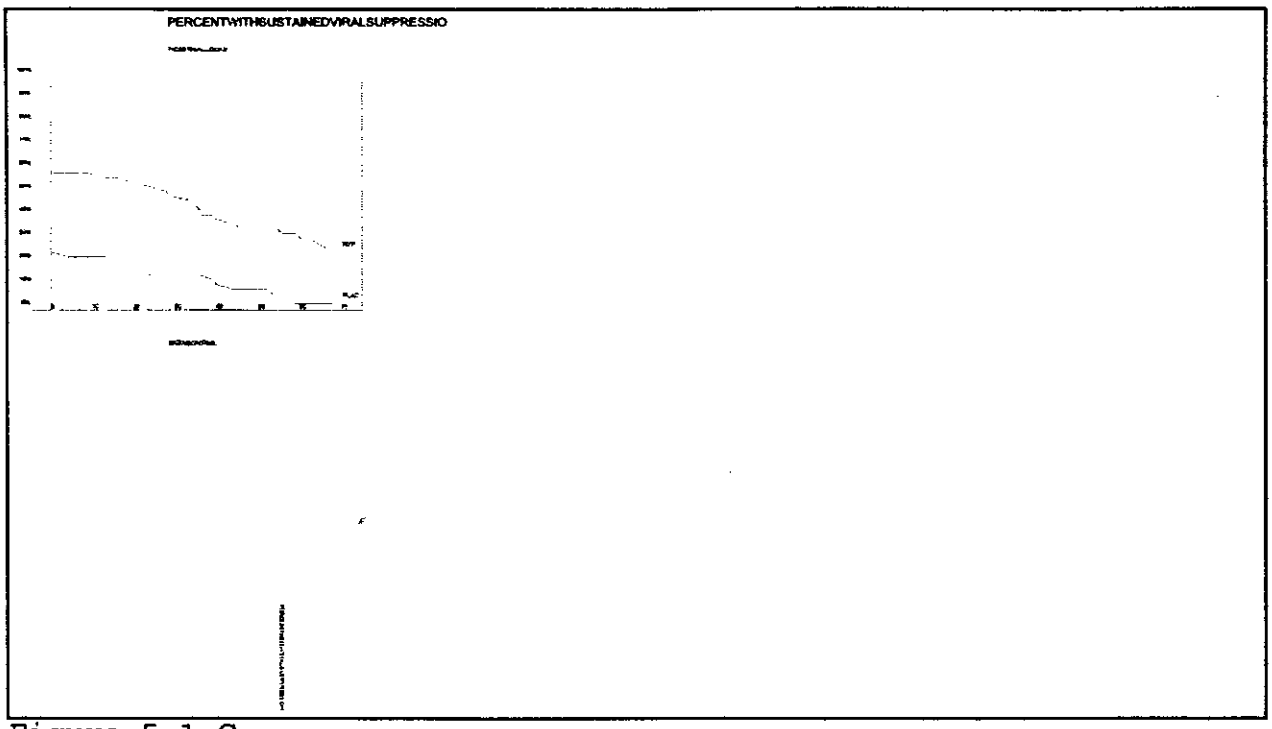


Figure 5.1 C



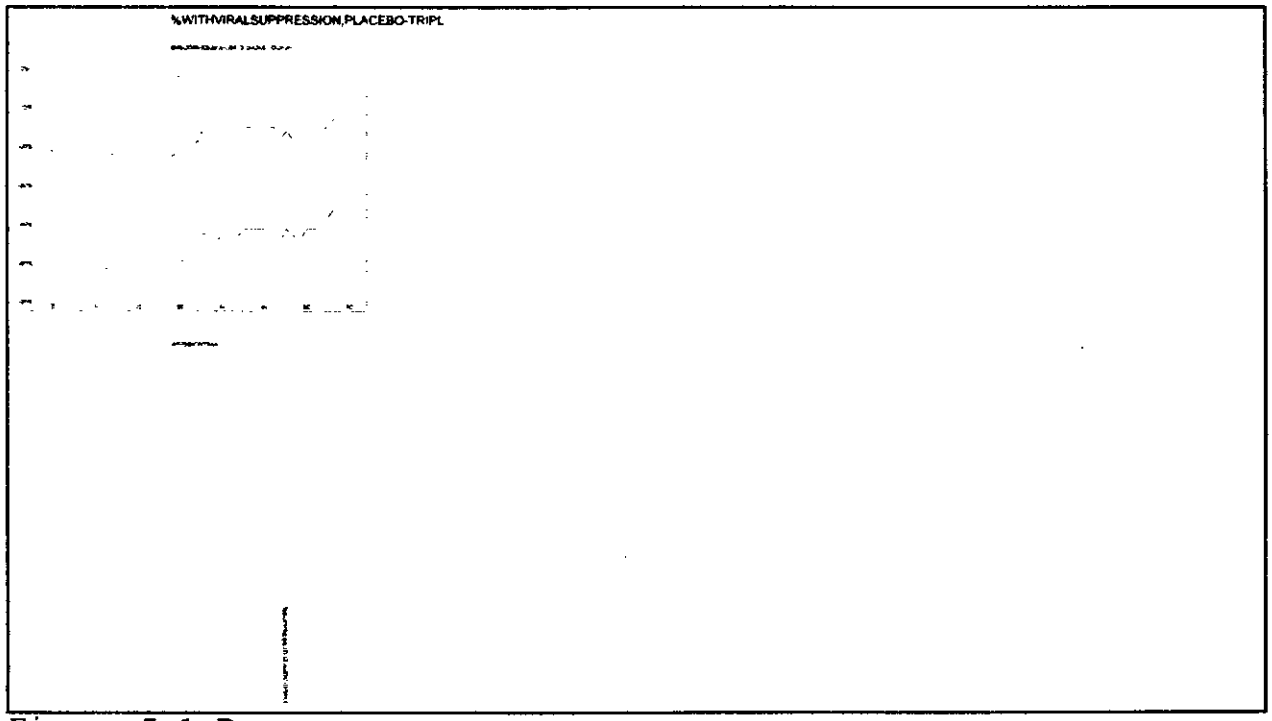


Figure 5.1 D

A summary of these results is that NPV/ddI/ZDV is clearly superior to ddI/ZDV and shows a NVP contribution of at least 6.3% to the two NRTI background. The results from the NVP/ZDV arm (no subjects with viral load < 400) also shows that NVP is inadequate therapy if used only in conjunction with a single NRTI.

## 5.2 Results Stratified by Baseline Covariates

Table 5.2 A shows the percent of subjects with viral load still confirmed below 400 copies/mL while on assigned therapy at week 48. Table 5.2 B shows the percent of subjects with viral load still confirmed below 20 copies/mL while on assigned therapy at week 48.

TABLE 5.2 A

PERCENT WITH SUSTAINED VIRAL SUPPRESSION AT 48 WEEKS

POINT ESTIMATES, 95% LOWER & UPPER BOUNDS

INCAS TRIAL, LOQ = 400

| | DDI/ZDV | | | | NVP/DDI/ZDV | | | |
|---|---|---|---|---|---|---|---|---|
| | Est. | LB | UB | N | Est. | LB | UB | N |
| Pooled | 19% | 10% | 28% | 53 | 43% | 32% | 54% | 51 |
| CD4_STRATUM | | | | | | | | |
| 145-285 | 18% | 0% | 37% | 11 | 54% | 31% | 77% | 13 |
| 290-370 | 25% | 4% | 46% | 12 | 44% | 17% | 72% | 9 |
| 375-455 | 20% | 3% | 37% | 15 | 43% | 22% | 64% | 16 |
| 457-755 | 13% | 0% | 28% | 15 | 31% | 10% | 52% | 13 |
| RNA_STRATUM | | | | | | | | |
| <10K | 27% | 5% | 49% | 11 | 59% | 39% | 78% | 17 |
| 10K-30K | 23% | 4% | 42% | 13 | 47% | 29% | 66% | 19 |
| 30K-70K | 20% | 3% | 37% | 15 | 0% | 0% | 0% | 9 |
| >70K | 7% | 0% | 18% | 14 | 17% | 0% | 42% | 6 |
| COUNTRY | | | | | | | | |
| Australia | 0% | 0% | 0% | 12 | 23% | 4% | 42% | 13 |
| Canada | 15% | 4% | 27% | 26 | 45% | 28% | 63% | 22 |
| Italy | 40% | 4% | 76% | 5 | 33% | 2% | 65% | 6 |
| Dutch | 40% | 15% | 65% | 10 | 70% | 46% | 94% | 10 |
| SEX | | | | | | | | |
| Male | 18% | 9% | 27% | 50 | 44% | 32% | 56% | 47 |
| Female | 33% | 0% | 78% | 3 | 25% | 0% | 61% | 4 |
| IV_DRUG_USE | | | | | | | | |
| Never_Used | 23% | 13% | 34% | 43 | 46% | 34% | 59% | 45 |
| Stopped_Use | 0% | 0% | 0% | 9 | 0% | 0% | 0% | 4 |
| YEARS_SEROPOSITIVE | | | | | | | | |
| 0.0-1.5 | 25% | 12% | 38% | 28 | 31% | 15% | 48% | 22 |
| 1.6-3.3 | 18% | 0% | 37% | 11 | 73% | 51% | 95% | 11 |
| 3.5-10.2 | 7% | 0% | 18% | 14 | 39% | 20% | 58% | 18 |
| AGE | | | | | | | | |
| 22-30 | 11% | 0% | 28% | 9 | 18% | 0% | 37% | 11 |
| 30-39 | 17% | 4% | 29% | 24 | 38% | 20% | 55% | 21 |
| 40-65 | 25% | 9% | 41% | 20 | 63% | 45% | 81% | 19 |

There is inadequate sample size in this trial to find convincing demonstration of treatment-covariate interactions. There are two suggestive patterns. The NVP effect appears to be

larger in subjects with smaller baseline CD4 count but also appears to be larger in subjects with smaller baseline HIV RNA levels. These two apparent effects contradict each other so it is difficult to believe that either one is real. Table 5.2 B shows the results of Mantel-Haenszel tests stratifying by baseline CD4 count and baseline HIV RNA levels. The rates and confidence limits be stratum are given above. Table 5.2 B contains only two p-values for each stratifying covariate. The first is the p-value that tests for superiority of NVP over placebo, stratifying by the baseline covariate. The second is the p-value that tests for stratum homogeneity, i.e. the presence of a treatment-covariate interaction.

TABLE 5.2 B
INCAS TRIAL
SUSTAINED VIRAL SUPPRESSION TO WEEK 48, LOQ = 400
P-VALUES FROM MANTEL-HAENSZEL TESTS

| Covariate | P-value for Treatment Effect | Stratum Homogeneity |
|---|---|---|
| Baseline HIV RNA | .027 | .84 |
| Baseline CD4 Count | .008 | .73 |
| Country | .013 | .49 |
| Gender | .005 | .32 |
| Years Seropositive | .007 | .4 |
| Age | .003 | .78 |

One will notice that the NVP/ddI/ZDV superiority to ddI/ZDV is preserved when stratifying by any of the baseline covariates considered. One will also notice that, largely because of the small sample size, one is unable to detect any treatment covariate interactions.

## 6. Atlantic Trial (1229)

### 6.1 Objectives in Trial

The primary objective of this study was to compare the efficacy of three different triple drug regimens. The three regimens compared NVP at a dose of 400 mg qd to the protease inhibitor Indinavir (IDV) at 800 mg bid and to the NRTI 3TC at 150 mg bid when each was used in combination with two other NRTI's: ddI and d4T. The primary efficacy endpoint was percent BLQ (below limit of quantitation) on the Ultrasensitive assay (LOQ = 50 copies/mL) at 48 weeks. The study population was asymptomatic HIV-1 infected non-nucleoside reverse transcriptase inhibitor (NNRTI) naive patients with CD4 counts > 200 cells/$mm^3$ and HIV RNA >= 500 copies/mL.

### 6.2 Summary of Study Design

The study was open-label, randomized, three-arm, parallel, active-controlled, multi-center trials conducted in the US and Europe.

Subjects were randomly assigned in a 1:1:1 ratio to 400 mg qd NVP (preceded by a lead-in dose of 200 mg qd for 2 weeks), IDV at 800 mg bid, or 3TC at 150 mg bid. All subjects also received ddI (at 250 or 400 mg qd, depending on weight) and d4t (at 30 or 40 mg bid, depending on weight).

### 6.3 Patient Accounting and Baseline Characteristics

289 patients were enrolled in the Atlantic trial. Of these, 15 patients never started treatment. 84 patients discontinued treatment before week 48, 30 because of an adverse event. The subjects were enrolled at 19 centers on two continents. 176 subjects were West European, 33 subjects were East European, and 89 were North American. The exact distribution of patients and sites by country is given in table 6.3 A.

TABLE 6.3 A

PATIENTS, SITES BY COUNTRY, ATLANTIC TRIAL

| Country | Patients | Sites | Country | Patients | Sites |
|---|---|---|---|---|---|
| USA | 81 | 4 | Netherlands | 12 | 3 |
| Canada | 7 | 1 | Belgium | 12 | 1 |
| Spain | 59 | 3 | Italy | 10 | 1 |
| France | 52 | 1 | Portugal | 6 | 1 |
| Poland | 31 | 1 | Hungary | 3 | 1 |
| Germany | 25 | 2 | | | |

The distribution of patients by size of the center is given in table 6.3 B.

TABLE 6.3 B

ATLANTIC TRIAL, NUMBER OF PATIENTS BY SIZE OF CENTER.

| Pt/Center | Centers | Patients |
|---|---|---|
| 52 | 1 | 52 |
| 31-40 | 2 | 68 |
| 21-30 | 3 | 82 |
| 11-20 | 2 | 29 |
| 1-10 | 11 | 67 |

In the Atlantic trial 1229, the study population was 80% male with a mean age of 36 years. The racial composition of the population is not given. The median CD4 count at baseline was 406 cells/$mm^3$; the median HIV RNA level was 4.25 logs. 13% had viral load > 100K copies/mL; 92% had CDC stage A HIV infection.

Table 6.3 C summarizes the primary reasons for discontinuation from study and from double blind treatment.

TABLE 6.3 C

PATIENT STATUS, ATLANTIC TRIAL

| REASON_DISCONTINUED | NVP | IDV | 3TC |
|---|---|---|---|
| Completed | 53 | 54 | 64 |
| Death | 0 | 0 | 1 |
| Lack_of_response | 4 | 2 | 5 |
| Adverse_event | 13 | 18 | 13 |
| Other_hospital | 2 | 0 | 1 |
| Request | 10 | 14 | 11 |
| Lost_to_follow-up | 7 | 12 | 14 |

## 6.4 Summary of Methods of Assessment

### 6.4.1 Schedule of Measurements

Patients had CD4 counts taken at weeks 0, 2, 4, every 4 weeks to week 12, and every 12 weeks to week 48. HIV RNA was measured on almost the same schedule on the Roche Ultrasensitive assay. Follow-up was subsequently extended to week 264.

### 6.4.2 Assessment of Treatment Effects

The primary endpoint was the proportion of viral successes by week 48. Subjects were considered viral failures if a) they had a baseline viral load >= 5K copies/mL which did not decline by 1 log by week 12, b) they had a confirmed viral load above 500 copies/mL after week 24, or c) they did not have sustained viral load below 50 copies/mL = LOQ out to week 48.

## 6.5 Summary of Statistical Analysis

The primary analysis used 95% two-sided confidence intervals for the difference in success rates, using the simple normal approximation to the binomial. A supplemental analysis employed a logistic regression, using sex, region, mode of infection, baseline HIV RNA, and baseline CD4 count as covariates (no convariate-treatment interactions). Two-sided 95% confidence intervals for the odds ratios between treatment arms summarized the results. Times to viral failure were compared by Kaplan-Meier curves.

## 6.6 Summary of Applicant's Results, Atlantic Trial

The number and percentage of subjects with viral load <50 at week 48 for Atlantic trial 1229 are given in table 6.6 A. The numbers and percents reported in the applicant's text (54% for NVP, 55% for IDV, 46% for EPV) are incorrect. The numbers in this table are based on the applicant's own computer files. (In general, the quality of work in this NDA is remarkably low.)

The applicant performed both an ITT analysis, using all subjects, and an ITTI analysis, discarding 15 subjects who never started their assigned drugs. The DAVDP has generally approved of ITTI analyses so only those results are reported here for the stratified analyses. The baseline CD4 and RNA strata in this table correspond to the quartiles of those two variables.

TABLE 6.6 A
HIV RNA <50 AT WK 48 IN ATLANTIC TRIAL

| Stratum | NVP | IDV | 3TC |
|---|---|---|---|
| Pooled ITT | 48/89 = 54% | 56/100 = 56% | 53/109 = 49% |
| Pooled ITTI | 48/85 = 57% | 55/94 = 59% | 50/104 = 48% |
| CD4 Stratum | | | |
| 141-320 | 9/20 = 45% | 10/19 = 53% | 13/29 = 45% |
| 322-405 | 12/23 = 52% | 13/25 = 52% | 12/24 = 50% |
| 406-528 | 10/19 = 53% | 16/23 = 70% | 17/32 = 53% |
| 528-1260 | 17/23 = 74% | 17/27 = 63% | 11/19 = 58% |
| RNA_Stratum | | | |
| 400-8.4 K | 11/18 = 61% | 13/23 = 57% | 20/28 = 71% |
| 8.4-24 K | 13/21 = 62% | 16/25 = 64% | 15/26 = 58% |
| 24-58 K | 18/28 = 64% | 13/22 = 59% | 8/21 = 38% |
| >58 K | 6/18 = 33% | 14/24 = 58% | 10/29 = 34% |

TABLE 6.6 A (cont.)
HIV RNA <50 AT WK 48 IN ATLANTIC TRIAL

| | | | |
|---|---|---|---|
| Transmission Mode | | | |
| MSM | 27/49 = 55% | 31/49 = 63% | 29/60 = 48% |
| Hetero | 14/25 = 56% | 15/26 = 58% | 13/20 = 65% |
| IVD | 6/10 = 60% | 4/11 = 36% | 9/20 = 45% |
| Other | 1/1 = 100% | 6/8 = 75% | 2/4 = 50% |
| Sex | | | |
| Male | 40/68 = 59% | 45/74 = 61% | 43/85 = 51% |
| Female | 8/17 = 47% | 11/20 = 55% | 10/19 = 53% |
| Age | | | |
| 20-32 | 14/30 = 47% | 20/38 = 53% | 13/32 = 41% |
| 33-39 | 22/31 = 71% | 20/31 = 65% | 25/47 = 53% |
| 40-69 | 12/24 = 50% | 16/25 = 64% | 15/25 = 60% |

The 95% confidence intervals for NVP success rate minus control rates are given in table 6.6 B. This table includes both the rates reported in the applicant's text, which are incorrect, and the rates computed from the applicant's own data. This table does not correct two mistakes made by the applicant: the wrong algorithm was used to classify subjects as failures or not and the correct confidence limits to use are 97.5%, not 95%.

TABLE 6.6 B
95% CONFIDENCE LIMITS FOR % BLQ AT WK 48
NEVARIPINE - CONTROL

| LOQ = 50 | NVP-IDV | NVP-EPV |
|---|---|---|
| Sponsor's Text | -17% to 13% | -6% to 22% |
| Sponsor's Data | -18% to 11% | -9% to 20% |
| LOQ = 500 | | |
| Sponsor's Text | -14% to 15% | -14% to 14% |
| Sponsor's Data | -14% to 15% | -15% to 13% |

## 6.7 CD4 Responses

The applicant also compared the three arms with respect to sustained change from baseline CD4 count. This parameter was defined to be the average of values at weeks 24, 36, and 48. Missing data were replaced by last observation carried forward (LOCF). The results are given in table 6.7 A.

TABLE 6.7 A

AVG CHANGE FROM BASELINE CD4 COUNT, WKS 24-48

| Arm | Mean Change in CD4 Count | 95% Confidence Interval |
|---|---|---|
| NVP | 99 | 66 - 131 |
| IDV | 124 | 93 - 155 |
| EPV | 118 | 89 - 147 |

## 6.8 Summary of Applicant's Conclusions

All three arms were effective in suppressing viral load to < 500 copies/mL. The sample sizes are small so that confidence intervals for the differences between the arms are large. Nonetheless, the actual observed differences are small. The CD4 endpoints also support a conclusion of efficacy of all three arms. There were too few cases of clinical progression to draw any conclusions about this endpoint.

## 7. Statistical Reviewer's Comments and Analyses on Atlantic Trial:

This review will discuss the following issues with respect to trial 1229. First, the reviewer will re-analyze the time to viral rebounds, using the standard algorithm employed in other NDA reviews for AIDS drugs. Second, the reviewer will present comparisons of the two arms stratified by a number of covariates. Finally, the reviewer will give an estimate of the improvement NVP would have over a placebo arm, had it been ethical to include one in the trial. The conclusion will be that the trial has too small a sample size to convincingly demonstrate that the 400 mg qd dose of NVP is clinically effective.

### 7.1 Times to Viral Rebound:

The same comments made in section 3.1 above apply to the algorithms used by the applicant and the FDA statistical reviewer in computing times to viral rebound. Figures 7.1 A and B show the results using LOQ = 50 copies/mL. Figure 7.1 A shows the three Kaplan-Meier curves for the NVP, IDV, and 3TC arms. The NVP arm is usually in the middle. Figure 7.1 B shows the two 97.5% confidence bands for difference in percent BLQ. The upper confidence band is for NVP - 3TC. For most of the time period for which data is available, NVP is, with 95% confidence, no more than 10-15% worse than 3TC. The lower confidence band is for NVP - IDV. For most of the time period, NVP is, with 95% confidence, no more than 20% worse than IDV. One should note that these confidence limit plots are adjusted to give simultaneous confidence of 95% at any given time point for both comparator arms. They are not adjusted to give simultaneous 95% confidence over all time points. If one is primarily interested in results at one year, the lack of simultaneity over time is not a problem.

Figures 7.1 C and D show the same results for LOQ = [redacted] copies/mL. Here all three arms are indistinguishable out to 400 days on trial. With confidence of 95% (adjusted for two comparator arms), NVP is no more than 20% worse than either comparator at week 48.

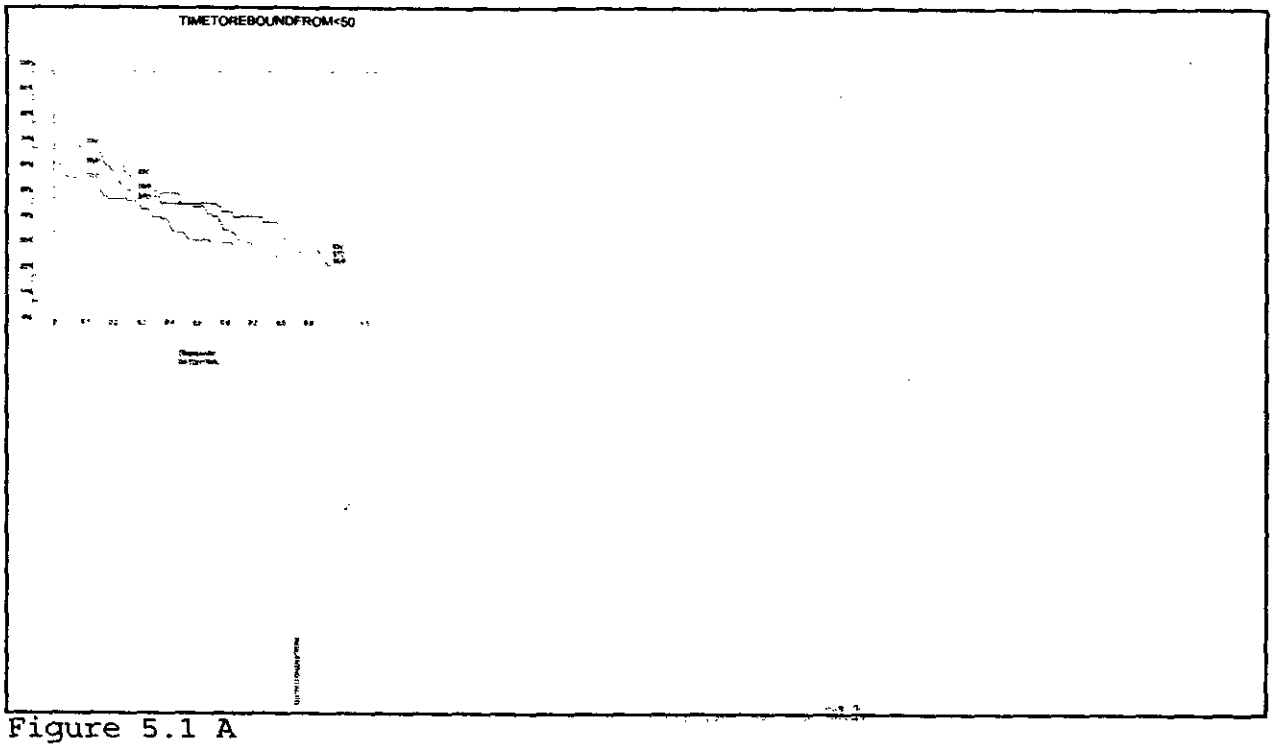


Figure 5.1 A



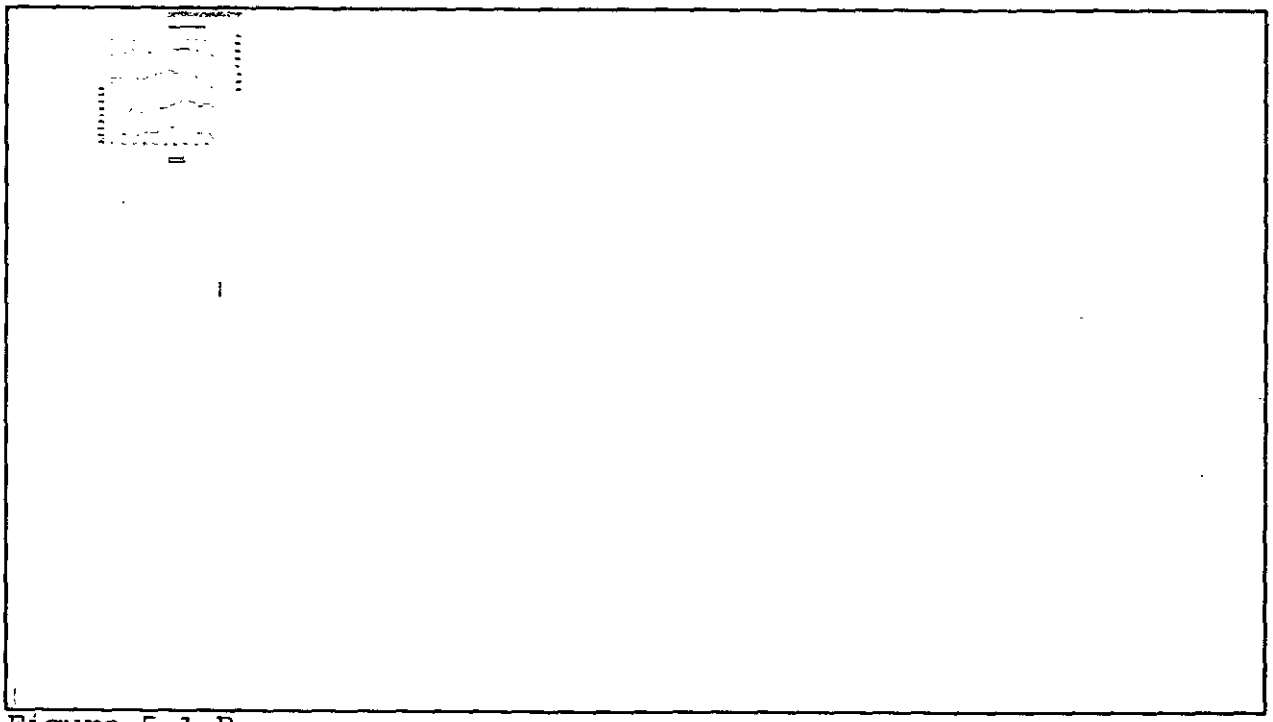

Figure 5.1 B

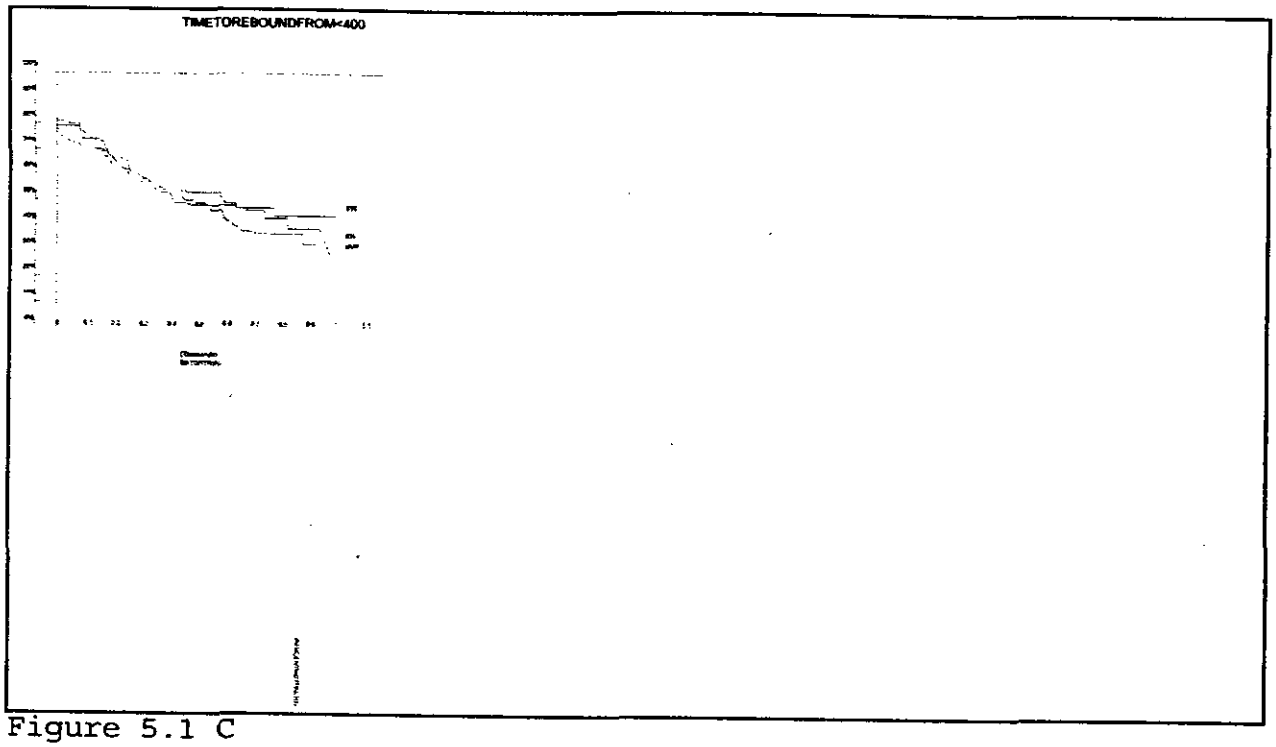


Figure 5.1 C



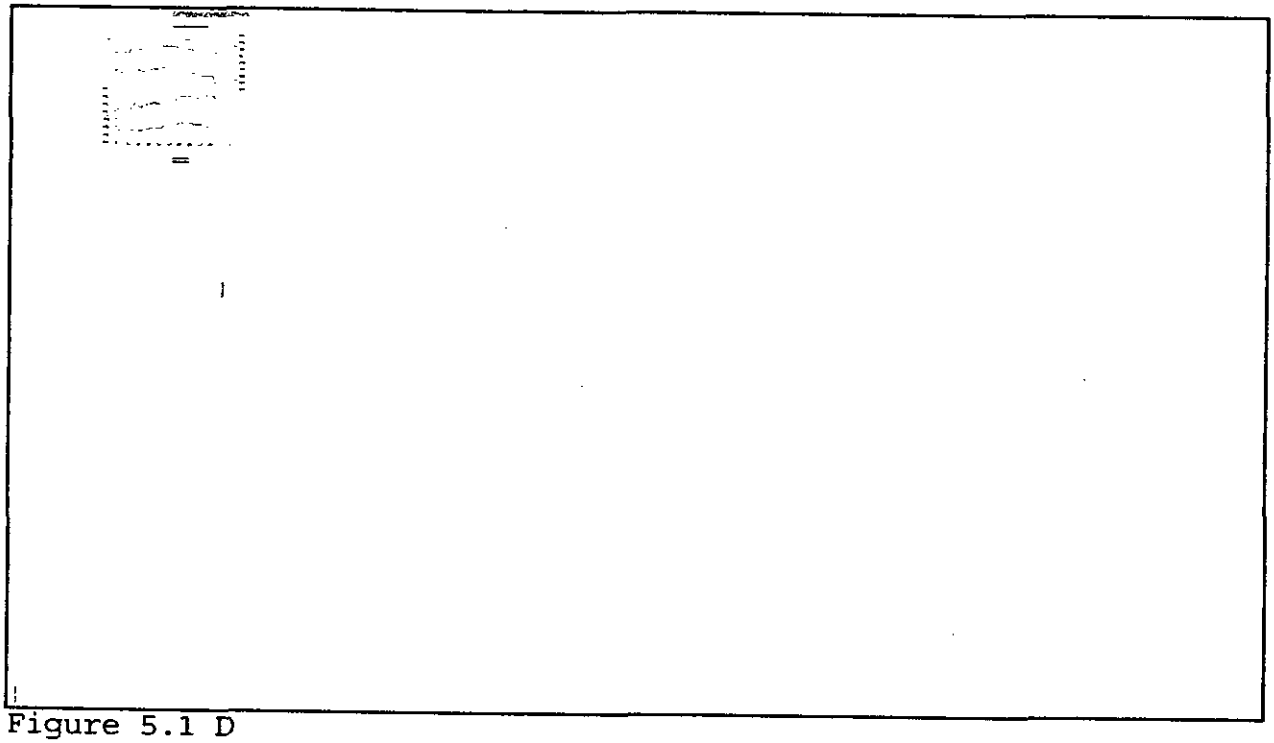

Figure 5.1 D

## 7.2 Results Stratified by Baseline Covariates

Table 7.2 A shows the percent of subjects with viral load still confirmed below 400 copies/mL while on assigned therapy at week 48. Table 7.2 B shows the percent of subjects with viral load still confirmed below 50 copies/mL while on assigned therapy at week 48.

TABLE 7.2 A
VIRAL SUCCESS RATES AT WEEK 48, TRIAL 1229
LOQ = 400

| | NEVARIPINE | INDINAVIR | EPIVIR |
|---|---|---|---|
| Pooled | 51/85 = 60% | 57/94 = 61% | 62/104 = 60% |
| CD4_STRATUM | | | |
| 141-320 | 10/20 = 50% | 11/19 = 58% | 16/29 = 55% |
| 322-405 | 12/23 = 52% | 13/25 = 52% | 15/24 = 63% |
| 406-528 | 11/19 = 58% | 17/23 = 74% | 18/32 = 56% |
| 528-1260 | 18/23 = 78% | 16/27 = 59% | 13/19 = 68% |
| RNA_STRATUM | | | |
| 400-8.4 K | 11/18 = 61% | 13/23 = 57% | 21/28 = 75% |
| 8.4-24 K | 13/21 = 62% | 17/25 = 68% | 15/26 = 58% |
| 24-58 K | 20/28 = 71% | 13/22 = 59% | 11/21 = 52% |
| >58 K | 7/18 = 39% | 14/24 = 58% | 15/29 = 52% |
| TRANSMISSION_MODE | | | |
| MSM | 30/49 = 61% | 32/49 = 65% | 37/60 = 62% |
| Hetero | 15/25 = 60% | 16/26 = 62% | 14/20 = 70% |
| IVD | 5/10 = 50% | 3/11 = 27% | 9/20 = 45% |
| Other | 1/1 = 100% | 6/8 = 75% | 2/4 = 50% |
| SEX | | | |
| Male | 42/68 = 62% | 46/74 = 62% | 52/85 = 61% |
| Female | 9/17 = 53% | 11/20 = 55% | 10/19 = 53% |
| AGE | | | |
| 20-32 | 18/30 = 60% | 20/38 = 53% | 17/32 = 53% |
| 33-39 | 21/31 = 68% | 21/31 = 68% | 30/47 = 64% |
| 40-69 | 12/24 = 50% | 16/25 = 64% | 15/25 = 60% |

TABLE 7.2 A (cont)
VIRAL SUCCESS RATES AT WEEK 48, TRIAL 1229
LOQ = 400

| | NEVARIPINE | INDINAVIR | EPIVIR |
|---|---|---|---|
| COUNTRY | | | |
| USA | 16/25 = 64% | 17/27 = 63% | 16/28 = 57% |
| Canada | 0/1 = 0% | 1/4 = 25% | 0/2 = 0% |
| Iberia | 12/18 = 67% | 13/20 = 65% | 12/25 = 48% |
| France | 8/15 = 53% | 11/18 = 61% | 12/17 = 71% |
| Germany | 5/8 = 63% | 4/6 = 67% | 6/8 = 75% |
| Poland/Hungary | 5/9 = 56% | 4/10 = 40% | 6/11 = 55% |
| Italy | 0/1 = 0% | 3/3 = 100% | 2/4 = 50% |
| Low Countries | 5/8 = 63% | 4/6 = 67% | 8/9 = 89% |
| CONTINENT | | | |
| NAmerica | 16/26 = 62% | 18/30 = 60% | 16/30 = 53% |
| WEurope | 30/50 = 60% | 35/53 = 66% | 40/62 = 65% |
| EEurope | 5/9 = 56% | 4/10 = 40% | 6/11 = 55% |
| STATUS | | | |
| Completed | 40/48 = 83% | 40/45 = 89% | 50/57 = 88% |
| Death/Prog | 0/1 = 0% | 1/1 = 100% | 0/1 = 0% |
| LOE | 1/4 = 25% | 1/2 = 50% | 1/5 = 20% |
| Adverse_Event | 3/15 = 20% | 7/18 = 39% | 4/14 = 29% |
| LTFU | 4/7 = 57% | 3/14 = 21% | 3/16 = 19% |
| Other | 3/10 = 30% | 5/14 = 36% | 4/11 = 36% |

TABLE 7.2 B

VIRAL SUCCESS RATES AT WEEK 48, TRIAL 1229

LOQ = 50

| | NEVARIPINE | INDINAVIR | EPIVIR |
|---|---|---|---|
| Pooled | 45/85 = 53% | 54/94 = 57% | 50/104 = 48% |
| CD4_STRATUM | | | |
| 141-320 | 9/20 = 45% | 9/19 = 47% | 14/29 = 48% |
| 322-405 | 12/23 = 52% | 13/25 = 52% | 10/24 = 42% |
| 406-528 | 10/19 = 53% | 16/23 = 70% | 15/32 = 47% |
| 528-1260 | 14/23 = 61% | 16/27 = 59% | 11/19 = 58% |
| RNA_STRATUM | | | |
| 400-8.4 K | 10/18 = 56% | 12/23 = 52% | 21/28 = 75% |
| 8.4-24 K | 13/21 = 62% | 17/25 = 68% | 15/26 = 58% |
| 24-58 K | 16/28 = 57% | 13/22 = 59% | 6/21 = 29% |
| >58 K | 6/18 = 33% | 12/24 = 50% | 8/29 = 28% |
| TRANSMISSION_MODE | | | |
| MSM | 26/49 = 53% | 30/49 = 61% | 30/60 = 50% |
| Hetero | 13/25 = 52% | 16/26 = 62% | 11/20 = 55% |
| IVD | 5/10 = 50% | 2/11 = 18% | 7/20 = 35% |
| Other | 1/1 = 100% | 6/8 = 75% | 2/4 = 50% |
| SEX | | | |
| Male | 37/68 = 54% | 43/74 = 58% | 42/85 = 49% |
| Female | 8/17 = 47% | 11/20 = 55% | 8/19 = 42% |
| AGE | | | |
| 20-32 | 13/30 = 43% | 19/38 = 50% | 12/32 = 38% |
| 33-39 | 21/31 = 68% | 19/31 = 61% | 25/47 = 53% |
| 40-69 | 11/24 = 46% | 16/25 = 64% | 13/25 = 52% |

TABLE 7.2 B (cont.)
VIRAL SUCCESS RATES AT WEEK 48, TRIAL 1229
LOQ = 50

| | NEVARIPINE | INDINAVIR | EPIVIR |
|---|---|---|---|
| COUNTRY | | | |
| USA | 14/25 = 56% | 17/27 = 63% | 15/28 = 54% |
| Canada | 0/1 = 0% | 1/4 = 25% | 0/2 = 0% |
| Iberia | 11/18 = 61% | 11/20 = 55% | 8/25 = 32% |
| France | 6/15 = 40% | 11/18 = 61% | 10/17 = 59% |
| Germany | 4/8 = 50% | 4/6 = 67% | 4/8 = 50% |
| Poland/Hungary | 5/9 = 56% | 3/10 = 30% | 5/11 = 45% |
| Italy | 0/1 = 0% | 3/3 = 100% | 1/4 = 25% |
| Low Countries | 5/8 = 63% | 4/6 = 67% | 7/9 = 78% |
| CONTINENT | | | |
| NAmerica | 14/26 = 54% | 18/30 = 60% | 15/30 = 50% |
| WEurope | 26/50 = 52% | 33/53 = 62% | 30/62 = 48% |
| EEurope | 5/9 = 56% | 3/10 = 30% | 5/11 = 45% |
| STATUS | | | |
| Completed | 35/48 = 73% | 38/45 = 84% | 42/57 = 74% |
| Death/Prog | 0/1 = 0% | 1/1 = 100% | 0/1 = 0% |
| LOE | 1/4 = 25% | 1/2 = 50% | 0/5 = 0% |
| Adverse_Event | 3/15 = 20% | 6/18 = 33% | 3/14 = 21% |
| LTFU | 3/7 = 43% | 3/14 = 21% | 2/16 = 13% |
| Other | 3/10 = 30% | 5/14 = 36% | 3/11 = 27% |

There are no obvious patterns in these data. Unlike the 1090 trial, these data don't even give an unambiguous impression that subjects with worse CD4 counts or HIV RNA levels at baseline do worse on all three arms. There are also no obvious treatment covariate interactions.

## 7.3 Estimated Differences between NVP and Placebo

Table 7.3 A shows the 97.5% confidence intervals for percent BLQ on NVP minus the comparable percent on each of the two control arms. The subjects were randomized by site so these analyses use a Mantel-Haenszel pooling by site. These results are the corrected versions of the confidence intervals reported by the applicant in table 4.6 B. The applicant is correct in that this trial is under-powered for a proper non-inferiority trial. Therefore, the FDA reviewer has also included as the

final column of table 7.3 A, the level of the two-sided confidence interval at which NVP would be concluded no more than 10% worse than the control arm. This is the analogue of p-value for non-inferiority trials: the closer the level is to 97.5%, the stronger the evidence for non-inferiority.

TABLE 7.3 A
97.5% CONFIDENCE INTERVALS FOR % BLQ AT WK 48
NEVARIPINE - CONTROL

| | | | LEVEL OF -10% vs | |
|---|---|---|---|---|
| LOQ = 50 | NVP-IDV | NVP-EPV | IDV | EPV |
| Pooled Data | -21% to 12% | -12% to 21% | 54% | 96% |
| Stratified by Site | -25% to 9% | -16% to 17% | 17% | 85% |
| LOQ = 400 | | | | |
| Pooled Data | -17% to 16% | -16% to 16% | 80% | 85% |
| Stratified by Site | -21% to 12% | -19% to 13% | 56% | 65% |

In general, properly adjusting results for the fact that subjects were randomized within each site, widens the confidence intervals and decreases the confidence that NVP is no more than 10% worse than the control. The data do not confirm but reasonably suggest that all three arms are comparable with respect to percent of subjects with viral load sustained below 400 copies for a year; NVP is likely to be inferior to IDV and possibly superior to EPV with respect to percent of subjects with viral load below 50 copies.

One can also attempt to use estimates of the IDV effect to get additional evidence in support of NVP efficacy. This analysis proceeds in two steps. First, one uses the data from the Atlantic trial to estimate the difference between IDV and NVP. Second, one uses historic control data comparing IDV to placebo to estimate the difference between IDV and placebo. The resulting estimates can be added to give the estimated difference between NVP and placebo.

The Atlantic trial provides a direct estimate of the effect of NVP+ddI+d4t minus the effect of IDV+ddI+d4t. The data from trials Merck 028 and ACTG 320 in the IDV NDA give direct estimates of the effect of IDV+zdv minus the effect of zdv and of the effect of IDV+zdv+3tc minus the effect of zdv+3tc. One can

interpret these three quantities as estimates of
1) Effect of NVP+background - Effect of IDV+background and two estimates of 2) Effect of IDV+backgroung - Effect of background. Therefore, estimate 1) minus a weighted average of the other two estimates is an estimate of 3) Effect of NVP+background - Effect of background.

One must notice two sources of uncertainty in this equation. First, background changes from ddI+d4t to zdv to zdv+3tc, depending on which trial the data come from. Second, the clinical quantity on which treatment effect are computed changes from Percent < 400 at week 48 to Percent < 500 at week 48 to Percent < 500 at week 40, depending on the trial from which the data come.

These uncertainties cannot be simply expressed as statistical standard errors. The FDA statistical reviewer attempted to conduct sensitivity analyses for the possible effects of this additional uncertainty by using the following final estimates for the difference between the effects of NVP + background and Plac + background.

NVP - PLAC = (NVP - IDV) + A*(IDV - PLAC)

Here the two quantities in parentheses on the right come from the Atlantic trial and the IDV NDA, respectively. The factor A is a discount factor by which one may reduce the estimated benefit due to IDV to allow for differences in the background therapy, differences in the LOQ, and differences in the week observed among the trials.

The standard error of this quantity is estimated by the square root of the sum of the square of SEE(NVP-IDV) and the square of B*SEE(IDP-PLAC). Here B is an additional factor on which one inflates the standard error from the IDV NDA to adjust for the differences among the trials.

In table 7.3 B, the statistical reviewer gives the 95% two-sided lower confidence bound for NVP effect =
Percent BLQ on NVP + background - Percent BLQ on background, using the data from the Atlantic study and from the two trials in the IDV NDA, Merck 028 and ACTG 320.

TABLE 7.3 B
95% LOWER BOUNDS FOR NVP EFFECT

| Effect | Trial(s) | Wk | Est | SEE | Lower Bound |
|---|---|---|---|---|---|
| NVP+ddI+d4t - IDV+ddI+d4t | Atlantic | 48 | -1% | 7.3% | |
| IDV+zdv - zdv | Merck 028 | 48 | 18% | 2.6% | |
| IDV+zdv+3tc - zdv+3tc | ACTG 320 | 40 | 15% | 4.0% | |
| IDV+backgr - backgr | Both above | 48 | 17% | 2.2% | |
| NVP+backgr - backgr | Atl+Both IDV | 40/48 | 16% | 7.6% | 1.0% |
| | | 40/48 | 12% | 7.9% | -3.7%* |

* Historic controls discounted as described in table 7.3 C.

Table 7.3 C shows the results of discounting the estimated NVP-Placebo effect by 0, 10%, and 25% (multiplying the estimated effect of 16% by factors A = 1, .9. or .75) and of inflating the estimated standard errors by 0, 10%, 21% or 33.1% (multiplying the estimated standard errors of 7.6% by factors B = 1, 1.1, 1.221, or 1.331. These provide a feel for the robustness of the naive pooled estimate that says the 95% lower bound for NVP-Plac is still 1.0%. Depending on how much one believes that the two Merck trials gave estimates the Indinavir effect that do not generalize to the population in the INCAS trial, one gets estiamtes of NVP-Placebo lower bound ranging from +1% to -3.7% at confidence level 95% and ranging for -1.1% to -5.9% at confidence 97.5%.

TABLE 7.3 C
TRIAL 1229
SENSITIVITY ANALYSES ON NVP-PLACEBO EFFECT

| Discount Factors | | NVP-PLAC | | Lower Bounds | |
|---|---|---|---|---|---|
| A | B | Estimate | SEE | 95% | 97.5% |
| 1 | 1 | 16.0% | 7.6% | 1.0% | -1.1% |
| 0.9 | 1 | 14.3% | 7.6% | -0.7% | -2.8% |
| 0.75 | 1 | 11.8% | 7.6% | -3.2% | -5.4% |
| 1 | 1.1 | 16.0% | 7.7% | 0.9% | -1.3% |
| 0.9 | 1.1 | 14.3% | 7.7% | -0.8% | -3.0% |
| 0.75 | 1.1 | 11.8% | 7.7% | -3.4% | -5.5% |
| 1 | 1.21 | 16.0% | 7.8% | 0.7% | -1.4% |
| 0.9 | 1.21 | 14.3% | 7.8% | -1.0% | -3.1% |
| 0.75 | 1.21 | 11.8% | 7.8% | -3.5% | -5.7% |
| 1 | 1.331 | 16.0% | 7.9% | 0.5% | -1.7% |
| 0.9 | 1.331 | 14.3% | 7.9% | -1.2% | -3.4% |
| 0.75 | 1.331 | 11.8% | 7.9% | -3.7% | -5.9% |

On the whole, one gets the impression that unless one believes that the two indinavir NDA trials could be pooled with trial 1229 without adjustment for differences in populations and endpoints, one must conclude that there is still doubt as to whether the 400 mg qd dose of NVP is truly more effective than placebo.

5. Statistical Reviewer's Summary

Nevaripine at 200 mg bid has been shown to be an effective treatment for HIV-1 infections when added to at least two other effective anti-retrovirals. Trial 1090 provides convincing evidence that nevaripine plus background regimens of two or more drugs reduced the occurence of class C CDC events. There was no difference in the rates of events in the first year of the study but by the end of two years the regimens with nevaripine had incidence rates estimated to be 11% to 19% lower than the regimens without nevaripine. The precise estimate of the difference depends on how subjects adding additional drugs are handled in the analysis.

In addition, nevaripine showed higher rates of viral suppression sustained out to 48 weeks: 18% versus 2% on the placebo containing regimens. For the most part, these regimens were older and less likely to contain protease inhibitors than contemporary regimens. This would suggest that nevaripine added to a larger HAART regimen than was common in this trial would give 18% sustained suppression. Whether it would increase suppression by 16% cannot be determined from these data.

Finally, this trial also showed that subjects with sustained viral suppression were at neglible risk of CDC events compared to subjects without such suppression so the improved rate of suppression is associated with the improved rate of progression.

In a second trial, nevaripine also showed a statistically significant increase in sustained viral suppression compared to placebo when added to a background of ddI and ZDV. The nevaripine arm had a suppression rate of 54% compared to a background rate of 28%.

In this same trial, a third arm with nevaripine double therapy showed 0% suppression. Nevaripine should not be used with fewer than two additional effective anti-retrovirals.

In a third trial, at 400 mg qd rather than 200 mg bid, nevaripine had results that were comparable to indinavir or to

3TC when one of them was added to a background regimen. This trial was small and confidence intervals were too wide to support a firm conclusion that nevaripine was no less than 10% worse than indinavir or 3TC. The trial is suggestive but would be inadequate to support a change of dose application.

Thomas Hammerstrom, Ph.D.
Mathematical Statistician

Concur: Dr. Soon

cc:
Archival IND #36-026/S-369
HFD-530
HFD-530/Dr. Birnkrant
HFD-530/Dr. Haverkos
HFD-530/Mr. Byrd
HFD-530/Dr. Murray
HFD-725/Dr. Hammerstrom
HFD-700/Dr. Anello
HFD-725/Dr. Huque
HFD-725/Ms. Robinette

APPENDIX

TABLE APPEENDIX A
VIRAL SUCCESS RATES AT WEEK 48, TRIAL 1090
LOQ = 400

| | PLACEBO | NVP | NVP-PLAC LOWER | NVP-PLAC UPPER |
|---|---|---|---|---|
| | 41/1128 = 4% | 232/1121 = 21% | 14% | 20% |
| STATUS | | | | |
| AE | 0/12 = 0% | 0/23 = 0% | 0% | 0% |
| Completed | 41/545 = 8% | 227/609 = 37% | 25% | 34% |
| LOE | 0/3 = 0% | 0/2 = 0% | 0% | 0% |
| LTFU | 0/392 = 0% | 4/353 = 1% | 0% | 2% |
| Other | 0/119 = 0% | 1/90 = 1% | -1% | 3% |
| Prog | 0/57 = 0% | 0/44 = 0% | 0% | 0% |
| PRIOR_TRT | | | | |
| Naive | 2/131 = 2% | 51/117 = 44% | 33% | 51% |
| ZDV | 36/849 = 4% | 132/873 = 15% | 8% | 14% |
| Other | 3/148 = 2% | 49/131 = 37% | 27% | 44% |
| CD4_STRATUM | | | | |
| <25 | 3/181 = 2% | 16/194 = 8% | 2% | 11% |
| 25-50 | 7/139 = 5% | 14/140 = 10% | -1% | 11% |
| 50-100 | 8/255 = 3% | 43/269 = 16% | 8% | 18% |
| >100 | 23/553 = 4% | 159/518 = 31% | 22% | 31% |
| RNA_STRATUM | | | | |
| <5K | 28/222 = 13% | 65/188 = 35% | 14% | 30% |
| 5K-100K | 9/578 = 2% | 104/565 = 18% | 13% | 20% |
| >100K | 3/311 = 1% | 63/349 = 18% | 13% | 21% |
| CDCGROUP | | | | |
| Cat A/B | 26/623 = 4% | 156/611 = 26% | 18% | 25% |
| Cat C | 15/505 = 3% | 76/510 = 15% | 9% | 15% |
| PRIOR_DISEASE | | | | |
| AIDS | 14/498 = 3% | 76/504 = 15% | 9% | 16% |
| No AIDS | 27/630 = 4% | 156/617 = 25% | 17% | 25% |

TABLE APPENDIX A (CONT)
VIRAL SUCCESS RATES AT WEEK 48, TRIAL 1090
LOQ = 400

| | PLACEBO | NVP | NVP-PLAC LOWER | NVP-PLAC UPPER |
|---|---|---|---|---|
| COUNTRY | 9/246 = 4% | 35/235 = 15% | 6% | 16% |
| USA | 2/39 = 5% | 4/42 = 10% | -7% | 16% |
| Canada | 9/109 = 8% | 30/115 = 26% | 8% | 27% |
| UK | 9/135 = 7% | 17/132 = 13% | -1% | 13% |
| Spain | 1/87 = 1% | 16/84 = 19% | 9% | 27% |
| France | 1/68 = 1% | 4/61 = 7% | -2% | 12% |
| Germany | 4/61 = 7% | 12/60 = 20% | 2% | 25% |
| Italy | 0/26 = 0% | 1/28 = 4% | -3% | 10% |
| Low Countries | 2/90 = 2% | 23/92 = 25% | 13% | 32% |
| Argentina | 0/5 = 0% | 1/9 = 11% | -9% | 32% |
| Australia | 4/260 = 2% | 89/262 = 34% | 27% | 38% |
| S.Africa | | | | |
| CONTINENT | 24/488 = 5% | 80/480 = 17% | 8% | 16% |
| Europe | 11/289 = 4% | 40/286 = 14% | 6% | 15% |
| North America | 4/261 = 2% | 89/263 = 34% | 26% | 38% |
| South Africa | 2/90 = 2% | 23/92 = 25% | 13% | 32% |
| South America | | | | |
| RACE | 31/835 = 4% | 163/816 = 20% | 13% | 19% |
| White | 10/264 = 4% | 61/277 = 22% | 13% | 24% |
| Black | 0/29 = 0% | 8/28 = 29% | 12% | 45% |
| Other | | | | |
| SEX | 27/902 = 3% | 170/879 = 19% | 14% | 19% |
| Male | 14/226 = 6% | 62/242 = 26% | 13% | 26% |
| Female | | | | |
| IV_DRUG_USE | 28/921 = 3% | 205/918 = 22% | 16% | 22% |
| Never Used | 13/206 = 6% | 27/200 = 14% | 1% | 13% |
| Stopped Use | ITIVE | | | |
| YEARS_SEROPOSITI | 15/392 = 4% | 106/378 = 28% | 19% | 29% |
| <=1.5 | 12/409 = 3% | 80/433 = 18% | 12% | 20% |
| 1.6-6.3 | 14/327 = 4% | 46/310 = 15% | 6% | 15% |
| 6.4-15.9 | | | | |
| AGE | 10/337 = 3% | 68/339 = 20% | 12% | 22% |
| 17-33 | 21/447 = 5% | 89/458 = 19% | 11% | 19% |
| 33-41 | 10/344 = 3% | 75/324 = 23% | 15% | 25% |
| 41-72 | | | | |

Percents Observed to 46 weeks without CDC event
Kaplan-Meier Estimates treatint loss to follow-up as censored

TABLE APPENDIX B
PERCENTS WITHOUT CDC EVENTS
TO WEEK 46

| | PLACEBO | NVP | NVP-PLAC LOWER | UPPER |
|---|---|---|---|---|
| KAPLAN-MEIER ESTIMATES OF 1 YEAR SURVIVAL | | | | |
| | 84% | 86% | -1% | 5% |
| _LTFU_BEFORE_46_WEEKS_DISCARDED | | | | |
| | 535/721 = 74% | 607/761 = 80% | 1% | 10% |
| STATUS | | | | |
| AE | 0/11 = 0% | 0/20 = 0% | | |
| Completed | 498/545 = 91% | 577/609 = 95% | 0% | 6% |
| LOE | 0/1 = 0% | 1/2 = 50% | | |
| LTFU | 22/63 = 35% | 18/60 = 30% | -21% | 12% |
| Other | 15/46 = 33% | 11/27 = 41% | -15% | 31% |
| Prog | 0/55 = 0% | 0/43 = 0% | | |
| PRIOR_TRT | | | | |
| Naive | 74/96 = 77% | 80/92 = 87% | -1% | 21% |
| ZDV | 380/510 = 75% | 439/562 = 78% | -1% | 9% |
| Other | 81/115 = 70% | 88/107 = 82% | 1% | 23% |
| CD4_STRATUM | | | | |
| <25 | 57/128 = 45% | 67/134 = 50% | -7% | 18% |
| 25-50 | 54/94 = 57% | 56/86 = 65% | -7% | 22% |
| 50-100 | 113/148 = 76% | 140/170 = 82% | -3% | 15% |
| >100 | 311/351 = 89% | 344/371 = 93% | -0% | 8% |
| RNA_STRATUM | | | | |
| <5K | 134/150 = 89% | 119/132 = 90% | -6% | 8% |
| 5K-100K | 271/362 = 75% | 324/397 = 82% | 1% | 13% |
| >100K | 128/207 = 62% | 163/229 = 71% | 0% | 18% |
| CDCGROUP | | | | |
| Cat A/B | 339/416 = 81% | 360/423 = 85% | -1% | 9% |
| Cat C | 196/305 = 64% | 247/338 = 73% | 2% | 16% |
| PRIOR_DISEASE | | | | |
| AIDS | 191/298 = 64% | 246/335 = 73% | 2% | 17% |
| No AIDS | 344/423 = 81% | 361/426 = 85% | -2% | 8% |

TABLE APPENDIX B (cont)
PERCENTS WITHOUT CDC EVENTS
TO WEEK 46

| | PLACEBO | NVP | NVP-PLAC LOWER | NVP-PLAC UPPER |
|---|---|---|---|---|
| COUNTRY | | | | |
| USA | 99/142 = 70% | 104/146 = 71% | -9% | 12% |
| Canada | 12/18 = 67% | 17/24 = 71% | -24% | 33% |
| UK | 48/62 = 77% | 66/77 = 86% | -5% | 21% |
| Spain | 68/81 = 84% | 80/92 = 87% | -8% | 14% |
| France | 42/51 = 82% | 53/58 = 91% | -4% | 22% |
| Germany | 18/31 = 58% | 20/26 = 77% | -5% | 43% |
| Italy | 28/34 = 82% | 31/36 = 86% | -13% | 21% |
| Low Countries | 9/14 = 64% | 7/13 = 54% | -47% | 26% |
| Argentina | 58/73 = 79% | 55/70 = 79% | -14% | 12% |
| Australia | 4/5 = 80% | 6/6 = 100% | -15% | 55% |
| S.Africa | 148/209 = 71% | 168/212 = 79% | 0% | 17% |
| CONTINENT | | | | |
| Europe | 214/274 = 78% | 256/302 = 85% | 0% | 13% |
| North America | 114/164 = 70% | 127/176 = 72% | -7% | 12% |
| South Africa | 149/210 = 71% | 169/213 = 79% | 0% | 17% |
| South America | 58/73 = 79% | 55/70 = 79% | -14% | 12% |
| RACE | | | | |
| White | 398/522 = 76% | 442/551 = 80% | -1% | 9% |
| Black | 130/184 = 71% | 151/193 = 78% | -1% | 16% |
| Other | 7/15 = 47% | 14/17 = 82% | 5% | 67% |
| SEX | | | | |
| Male | 422/577 = 73% | 473/599 = 79% | 1% | 11% |
| Female | 113/144 = 78% | 134/162 = 83% | -5% | 13% |
| IV_DRUG_USE | | | | |
| Never Used | 438/597 = 73% | 505/632 = 80% | 2% | 11% |
| Stopped Use | 97/124 = 78% | 101/128 = 79% | -9% | 11% |
| YEARS_SEROPOSITIVE | | | | |
| <=1.5 | 201/269 = 75% | 218/275 = 79% | -3% | 12% |
| 1.6-6.3 | 191/269 = 71% | 227/289 = 79% | 0% | 15% |
| 6.4-15.9 | 143/183 = 78% | 162/197 = 82% | -4% | 12% |
| AGE | | | | |
| 17-33 | 165/218 = 76% | 189/232 = 81% | -2% | 13% |
| 33-41 | 203/285 = 71% | 243/307 = 79% | 1% | 15% |
| 41-72 | 167/218 = 77% | 175/222 = 79% | -6% | 10% |

Figure Appendix 1 shows the results of 95% confidence limits for the difference in log(-log(survival)) as estimated from the Kaplan-Meier curves for time to first CDC event. The Cox test for applicability of proportional hazards regression to these data accepts the constant hazard ratio if a horizontal line will fit between the upper and lower confidence limits. One can see that the upper limit is initially below zero, the lower limit is above zero after about day 300. Thus NVP has slightly risk than placebo for the first few months but has clearly lower risk beyond the first year. This graph supports NVP superiority but also clearly shows that any statements based on a proportional hazards regression will be misleading.