# CENTER FOR DRUG EVALUATION AND RESEARCH

**Application Number** 21-007
21-039

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## STATISTICAL REVIEW(S)

# Statistical Review and Evaluation

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| **NDA#:** | 21007 |
| **APPLICANT:** | Glaxo Wellcome Inc. |
| **NAME OF DRUG:** | AGENERASE™ (amprenavir, 141W94) Capsules |
| **INDICATION:** | Treatment of HIV infection |
| **DOCUMENTS REVIEWED:** | Original submission dated 10/15/98: Vol. 10.1, 10.7-10.19<br>24 Week Update for PROAB3006 dated 12/22/98<br>24 Week Update dated 10/28/98: Vol. 1 – 3<br>Pre-submission: Vol. 8.25 – 8.34<br>Pre-submission dated 9/28/98: Vol. 7.1<br>Pre-submission dated 8/31/98: Vol. 5.9 – 5.14 |
| **Clinical Reviewer:** | HFD-530: John Martin, M.D. |

## A: Background

Amprenavir (APV) is an inhibitor of HIV-1 aspartyl protease. FDA designated this drug as a "fast track" drug product on 3/18/98.

This NDA contains two pivotal, randomized, multicenter, controlled trials to support the accelerated approval of the proposed indication for the treatment of HIV infection. Results of eight Phase II trials were also submitted to support the effectiveness of this application. Only the two pivotal trials will be reviewed here.

### Protocols

PROAB3001

Title: "A Phase III Trial to Evaluate the Safety and Antiviral Efficacy of 141W94 in Combination with RETROVIR and EPIVIR compared to RETROVIR and EPIVIR Alone in Patients with HIV Infection"

This is a randomized, double-blind, placebo-controlled, multicenter study conducted in the US and Europe in anti-retroviral naïve HIV-infected subjects 18 years of age or older who had no previous or current diagnosis of AIDS (1993 CDC Classification Category C). Two hundred thirty subjects were to be enrolled into the study to yield a total of 82 treatment failures. Subjects were to be equally randomized to the following two treatment groups stratified by screening HIV-1 RNA level (≥10,000-30,000, >30,000-100,000, or >100,000 copies/mL) using a centralized randomization code on a BID schedule:

APV (1200mg) + ZDV (300mg) + 3TC (150mg)
PLA (1200mg) + ZDV (300mg) + 3TC (150mg)

Subjects were to receive 48 weeks of randomized treatment unless they met the switching criteria as follows:

- Two consecutive viral load measurements (within 3 weeks of one another) ≥400 copies/mL at Week 16 or thereafter.
- Progression to a confirmed CDC Class C (AIDS defining) event after 4 weeks on study.

Subjects who met switching criteria could continue the randomized therapy, and/or switch to open-label amprenavir, and/or add abacavir (ABC), and/or change nucleoside reverse transcriptase inhibitors (NRTIs), and/or add another approved HIV protease inhibitor except Ritonavir, and/or change to any other approved protease inhibitor. Treatments received before switching were kept blinded.

Primary efficacy analysis will be to assess the durability of the viral load response over 48 weeks based on time to event, defined as time to first confirmed viral load rebound (≥400 copies/mL) or permanent discontinuation of randomized therapy or progression to a CDC Class C event or death. Early anti-viral efficacy will be assessed at Week 16 based on proportion of patients with HIV RNA < 400 copies/mL who did not progress to a CDC Class C event or death. Change in CD4+ cells and $\log_{10}$ HIV-1 RNA levels as measured by AAUCMBs will also be evaluated. Real-time viral load measurements will be performed every 8 weeks. Plasma HIV-1 RNA were to be measured by Roche Amplicor HIV-1 Monitor test.

Primary efficacy analyses were to be based on the intent-to-treat population that includes all subjects randomized. Week 16 analysis of the primary endpoint was to be based on Cochran-Mantel-Haenzel test stratified by randomization strata. Time-to-event analysis as defined earlier was to be based on a permutation-based log-rank test, stratified by the randomization strata. The distribution of time-to-event will be estimated by Kaplan-Meier product limit method.

The protocol was finalized on February 26, 1998 (Amendment 2).

PROAB3006

Title: "A Phase III Trial to Compare the Safety and Antiviral Efficacy of 141W94 and Indinavir in Combination with Standard Nucleoside Reverse Transcriptase Inhibitor (NRTI) Therapy in NRTI Experienced, Protease Inhibitor (PI) Naïve HIV-1 Infected Patients".

This is a randomized, open-label, placebo-controlled, multicenter study conducted in the US and Europe in NRTI-experienced, protease inhibitor naïve HIV-infected subjects 18 years of age or older who had no active AIDS defining opportunistic infection or disease. Four hundred sixty subjects with a screening viral load of ≥ 400 copies/mL were to be equally randomized to the two treatment arms by using a centralized randomization code with stratification by viral load (≥400 - 10,000; >10,000 - 100,000; or >100,000 HIV RNA copies/mL) and by whether they plan to change at least one NRTI at entry. The two treatment arms are:

141W94 1200 mg BID + NRTI (≥230 subjects)
Indinavir (IND) 800 mg every 8 hours + NRTI (≥230 subjects)

Primary efficacy analysis will be the durability of the viral load response over 48 weeks based on the proportions of patients with viral load < 400 copies/mL who did not progress to a CDC Class C event or death after Week 4. Early anti-viral efficacy will be assessed similarly at Week 16. Change in CD4+ cells and $\log_{10}$ HIV-1 RNA levels as measured by AAUCMBs will also be evaluated. Real-time viral load measurements will be performed every 8 weeks.

At Week 8, the patient will have the option to switch treatment if their viral load is > 0.7 log above the screening value with confirmation. The criteria for determining treatment-switching beginning from Week 16 and every 8 weeks thereafter will be ≥400 copies/mL with confirmation. CDC Class C events and toxicity requiring permanent discontinuation of randomized therapy may also trigger change of medication.

Sample size was determined assuming a success rate of 70% at Week 48 and 80% power to detect < 12% in the difference of proportions for assessing equivalence of the treatment groups at the 5% level of significance.

Statistical analysis will be based on all patients randomized. Patients who permanently discontinued randomized study medication and patients with a first or new CDC Class C event will be considered failures.

The equivalence of the success rates will be assessed using 95% confidence intervals about the differences in proportions, controlling for the randomization strata. Time-to-detectable virus will be compared using Kaplan-Meier curves. AAUCMBs will be compared between treatment groups using Van Elteran's test, controlling for randomization strata. This comparison will be confirmed with non-parametric ANCOVA with covariates of stratification groups and baseline surrogate marker measurements. The 95% confidence interval for the treatment differences in AAUCMB will be calculated with parametric methods.

**B. Results of the Applicant's Analyses**

**Baseline Characteristics**

The two pivotal studies differed in entry criteria and population studied. The following table describes some of the baseline variables by study.

## Baseline Characteristics by Study

| Baseline Characteristics | | 3001 N=232 | 3006 N=504 |
|---|---|---|---|
| Median Age (years) | | 36 | 37 |
| Median Weight (kg) | | 77 | 74 |
| Gender | Male | 89% | 80% |
| | Female | 11% | 20% |
| Ethnic Origin | White | 75% | 72% |
| | Black | 11% | 19% |
| | Hispanic | 12% | 7% |
| | Other | 3% | 2% |
| Route of Transmission | Homosexual/bisexual Contact | 74% | 60% |
| | Heterosexual contact | 18% | 29% |
| | Injectable drug use | 3% | 9% |
| | Other | 6% | 2% |
| | Missing | 5% | 0% |
| Hepatitis B Test Result | Negative | 84% | 88% |
| | Positive Confirmed | 5% | 7% |
| | Missing | 13% | 5% |
| Hepatitis C Test Result | Negative | 82% | 77% |
| | Reactive | 6% | 18% |
| | Missing | 12% | 5% |
| CDC Classification | A: Asymptomatic or lymphadenopathy | 75% | 62% |
| | B: Symptomatic, not AIDS | 18% | 26% |
| | C: AIDS | 2% | 10% |
| | Missing | 4% | 3% |
| Baseline Median | Plasma HIV-1 RNA ($log_{10}$ copies/mL) | 4.67 | 3.93 |
| | CD4+ cell count (cells/$mm^3$) | 416 | 399 |
| Baseline HIV-1 RNA | <400 copies/mL | 0% | 2% |
| | 400-<10,000 copies/mL | 4% | 52% |
| | ≥10,000-30,000 copies/mL | 32% | 37% |
| | >30,000-100,000 copies/mL | 38% | |
| | >100,000 copies/mL | 23% | 8% |
| | Missing | 3% | 1% |
| Baseline CD4+ cell count | <50 cells/$mm^3$ | 0% | 2% |
| | 50-200 cells/$mm^3$ | 1% | 11% |
| | >200-500 cells/$mm^3$ | 63% | 57% |
| | >500 cells/$mm^3$ | 34% | 29% |
| | Missing | 3% | 2% |

Based on tables on pages 65 and 66, and Tables 12 and 15 of Study Report 5.9 for Study 3001.
Based on tables on pages 74 and 75, and Tables 11 and 14 of Study Report 8.24 for Study 3006.

Subjects in the two studies were similar in baseline age, weight, gender, ethic origin and hepatitis B test results. They differed in route of transmission, hepatitis C test results, CDC Classification, HIV-1 RNA level and CD4 count.

- A higher proportion of subjects acquired the disease through homosexual relationships in Study 3001 (74%) than in Study 3006 (60%).
- A lower proportion of subjects had reactive hepatitis C testing results (6%) in Study 3001 than in Study 3006 (18%).
- The disease was in a less advanced stage in Study 3001 than was in Study 3006 according to CDC Classification and CD4 counts; but subjects were more ill in the Study 3001 according to HIV-1 RNA levels.

**Subject Accountability**

The following table presents the disposition of subjects.

**Subject Status and Reason Discontinued by Treatment Group and Study**

| | 3001 | | | | 3006 | | | |
|---|---|---|---|---|---|---|---|---|
| Week | 16[a] | | 24[b] | | 16[b] | | 24[c] | |
| Analysis Cutoff Date | 03/13/98 | | 07/01/98 | | 06/25/98 | | 08/31/98 | |
| Treatment | APV | PLA | APV | PLA | APV | IND | APV | IND |
| Total Randomized | 116 | 116 | 116 | 116 | 254 | 250 | 254 | 250 |
| No. Treated | 112 | 109 | 112 | 109 | 245 | 241 | 245 | 241 |
| No. discontinued randomized treatment | 33 | 11 | 57 | 96 | 73 | 36 | 84 | 54 |
| Adverse Event | 17 | 3 | 18 | 3 | 39 | 14 | 42 | 22 |
| Consent Withdrawn | 5 | 3 | 7 | 7 | 9 | 6 | 8 | 6 |
| Lost to Follow-up | 7 | 3 | 7 | 3 | 8 | 7 | 9 | 10 |
| Met Protocol Defined Switch Criteria | 0 | 0 | 21 | 81 | 10 | 4 | 14 | 9 |
| Protocol Violation | 0 | 0 | 0 | 0 | 1 | 0 | 3 | 1 |
| Other | 4 | 2 | 4 | 2 | 6 | 4 | 8 | 6 |

[a] Discontinuations occurred by the end of 16 weeks treatment.
[b] Discontinuations occurred before the cutoff date.
[c] Discontinuations occurred by the end of 24 weeks treatment.
Based on tables on pages 61 of Vol. 5.9, page 70 of Vol. 8.24, page 21 of Vol. 1, page 19 of Vol 2 of the 24 weeks update and Table 7 of 12/22/98 update.

In both studies, more subjects discontinued the study medication due to adverse events in the regimen containing amprenavir than in the control arms.

## Efficacy Endpoints

The tables below display the results for HIV RNA viral load and CD4+ counts. In the analysis of viral load, a subject with viral load below 400 copies/mL was regarded as a "Success". Subjects who discontinued the randomized treatment earlier were regarded as failures while missing values were imputed with the value of the next visit if available or the previous visit. Even though the protocols and their amendments specified that the primary analysis population is all subjects randomized, the actual analyses submitted were mainly based on subjects randomized who took at least one dose of study medication.

**Proportion of Subjects below 400 copies/mL by Treatment and Study**

With Missing Imputed and Failures Carried Forward

| | 3001 | | | | 3006 | | | |
|---|---|---|---|---|---|---|---|---|
| Week | 16 | | 24 | | 16 | | 24 | |
| Treatment | APV | PLA | APV | PLA | APV | IND | APV | IND |
| Total Randomized | 116 | 116 | 116 | 116 | 254 | 250 | 254 | 250 |
| No. Treated | 112 | 109 | 112 | 109 | 245 | 241 | 245 | 241 |
| Overall (N) | 66 | 19 | 61 | 12 | 128 | 159 | 105 | 138 |
| Overall (%) | 59 | 17 | 54 | 11 | 52 | 66 | 43 | 57 |
| p-value or 95% CI | <0.001[a] | | NA | | (-22%, -5%) | | NA | |

[a] Results of Cochran-Mantel-Haenszel test controlling for randomization stratum.

Based on tables on pages 69 of Vol. 5.9, page 80 of Vol. 8.24, page 23 of Vol. 1 and page 23 of Vol 2 of the 24 weeks update, and the 24-week update for 3006 submitted on 12/22/98.

The applicant concluded superiority of amprenavir vs. placebo based on Study 3001. No comparative statement was made for Study 3006.

The table below summarizes CD4+ cell count over the course of the study. Increases were seen for all treatment arms and no statistical comparison was presented. Subjects with missing values were excluded.

**Summary of Median CD4+ Change from Baseline over Time**

| | 3001* | | | | 3006** | | | |
|---|---|---|---|---|---|---|---|---|
| | APV | | PLA | | APV | | IND | |
| Treatment Week | N | Cells/mm$^3$ | N | Cells/mm$^3$ | N | Cells/mm$^3$ | N | Cells/mm$^3$ |
| Baseline | 109 | 448 | 106 | 405 | 253 | 390 | 242 | 412 |
| Week 2 | 101 | +24 | 100 | +37 | 225 | +11 | 224 | +24 |
| Week 4 | 100 | +37 | 101 | +60 | 218 | +16 | 229 | +31 |
| Week 8 | 91 | +51 | 98 | +73 | 218 | +25 | 223 | +30 |
| Week 12 | 81 | +63 | 95 | +93 | 213 | +23 | 219 | +40 |
| Week 16 | 75 | +55 | 89 | +49 | 194 | +27 | 201 | +46 |
| Week 20 | 73 | +72 | 89 | +56 | 166 | +37 | 178 | +66 |
| Week 24 - | 72 | +113 | 82 | +69 | 169 | +42 | 177 | +88 |

* Based on tables on page 27 of Vol. 1. Measurements for both the randomized and open-label phase were used.
** Based on Table 3 of the 12/22/98 update. Only measurements while on the randomized treatment were used.

**Subgroup Analysis**

The subgroup analysis by age, gender and race were conducted for selected populations with descriptive statistics. No statistical conclusion was drawn. The reviewer will conduct further analysis later.

**C. Statistical Reviewer's Comments**

The protocol-specified analysis population was the intent-to-treat population including all the subjects randomized. The applicant's submitted analysis excluded subjects who did not take any study medication. In the reviewer's analysis the protocol-specified population will be used. Since the number of subjects who were randomized but did not take any study medication were similar between treatment groups in both studies, the analysis results based on the two populations are nearly identical.

Week 16 data was planned to be used for this submission. Based upon an FDA request, Week 24 data were made available and will be described in the following.

In handling missing viral load values, the protocol-specified method and the actual method submitted were different. However, both methods used neighboring values for imputation. In the reviewer analysis, missing will be regarded as a separate category and will be treated as failures in evaluating virological response rates. Sensitivity analysis will be conducted to assess the impact of the missing values for Study 3006.

Study 3006 was stratified by the screening viral load and the plan on changing NRTIs at entry. However, 13% of the subjects did not follow through on their initial plan. Analyses were also

conducted based on the actual NRTI change at entry instead of the planned change. No meaningful differences were found for the two analyses and only analyses based on the original planned NRTI change is reported.

CD4 comparisons for both studies will be based on all available data, with analysis for the measurements while on the randomized treatments as supportive.

**D. Statistical Reviewer's Analyses**

Plasma HIV-1 RNA was measured by the Roche Amplicor HIV-1 Monitor Test (Primers 1.0, standard. LOD = 400 copies/mL) and Roche Amplicor HIV-1 Monitor Test (Primers 1.0, ultrasensitive. LOD = – copies/mL). The standard assay was used for the primary analysis and will be the focus of this review. With the recent approval of the ultrasensitive assay by the Center for Biologics Evaluation and Research (CBER) of FDA, the ultrasensitive assay is also of interest and will be briefly discussed in the review. In addition, CD4 results will be discussed.

**D.1 HIV-1 RNA with Standard Assay**

Recall that the primary endpoint is the proportion of subjects who had HIV RNA level < 400 copies/mL without discontinuing the randomized therapy or progressing to a new CDC Class C event or death. Since not all visits occurred as scheduled and sometimes there were multiple evaluations for a given visit, the following algorithm was used to determine the status at any given visit.

1. All randomized subjects were included.
2. Only viral load measurements while on the randomized treatment were used.
3. Any measurement that occurred during the specified time window was regarded as a measurement for that visit. For example, all the measurements during study days [156, 183] were regarded as Week 24 measurements. The table below lists the windows for each visit. The windows include the "From" and "To" days.

| Week | 1 | 2 | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 52 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| From | 2 | 12 | 23 | 44 | 72 | 100 | 128 | 155 | 184 | 212 | 240 | 268 | 296 | 324 | 352 |
| To | 11 | 22 | 43 | 71 | 99 | 127 | 155 | 183 | 211 | 239 | 267 | 295 | 323 | 351 | 379 |

4. For any visit, the worst case during that visit was used.
5. Any new CDC Class C event (relative to baseline HIV-1 associated conditions) that occurred before or at the visit while on the randomized therapy was identified, even if it occurred during the first 4 weeks.
6. If discontinuation occurred at or before the last window day, the subject was classified as discontinued. For example, subjects who discontinued before or at day 183 were regarded as discontinued for the Week 24 analysis.
7. Only on treatment HIV RNA < 400 copies/mL without progression to a new CDC Class C event were regarded as success for the calculation of response rates.

Based on this algorithm, the Week 24 virological responses for the two studies are summarized below.

Study 3001

**Week 24 HIV-1 RNA Status with Missing Regarded as Failures**

| | < 400 copies/mL | Difference and 95% CI** | p-value* |
|---|---|---|---|
| APV (N=116) | 62 (53.4%) | 42.2% (31.8%, 52.7%) | <0.001 |
| PLA (N=116) | 13 (11.2%) | | |

* Stratified Cochran-Mantel-Haenszel test.

** Randomization stratum adjusted difference with continuity correction. Weight for a stratum with $n_1$ and $n_2$ subjects in the two arms is proportional to $n_1*n_2/(n_1+n_2)$.

Failures could be due to viral load ≥ 400 copies/mL, or a new CDC Class C event or discontinuation of the randomized treatment. The disposition of these subjects is summarized below.

**Week 24 Status of Subjects Who Were Regarded as Failures**

| | APV (N=116) | PLA (N=116) |
|---|---|---|
| **Progressed to a new CDC Class C event** | 0 | 0 |
| **On Treatment Week 24 HIV-1 RNA** | | |
| Missing | 0 (0.0%) | 1 (0.9%) |
| ≥ 400 copies/mL | 6 (5.2%) | 18 (15.5%) |
| **Discontinued the randomized therapy by Week 24 due to** | | |
| Adverse events | 17 (14.1%) | 4 (3.3%) |
| Virological rebound | 9 (7.4%) | 54 (44.6%) |
| Before taking any study medication | 4 (3.4%) | 7 (6.0%) |
| Consent withdrawn, Lost to follow-up, Protocol Violation, Other | 18 (15.5%) | 19 (16.4%) |

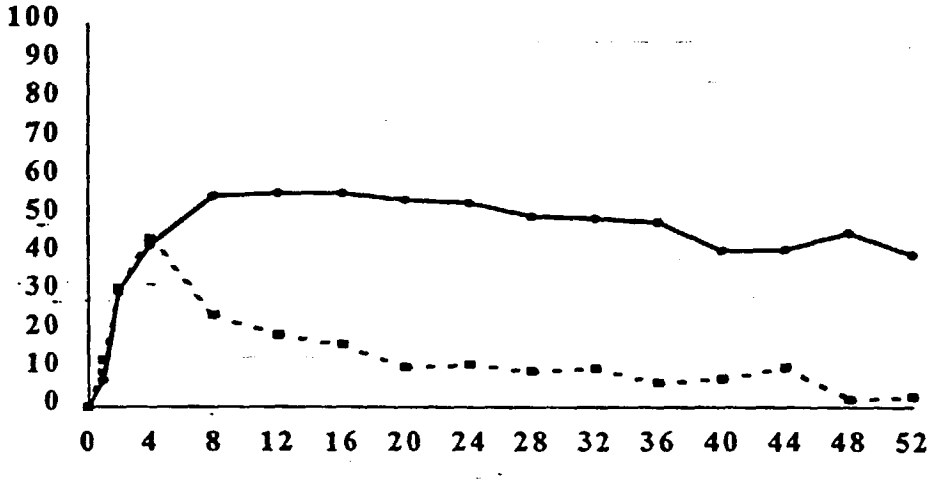
Failures in the placebo arm were mostly due to HIV RNA ≥ 400 copies/mL at Week 24 or discontinuations caused by prior viral rebound, while failures in the amprenavir arm were mostly due to discontinuations caused by adverse events. Overall, the amprenavir arm showed a higher response rate at Week 24 than the placebo arm.

By the cutoff date for the 24 weeks analysis, about 1/3 of subjects already completed 52 weeks of the trial. Response rates over time are plotted below.

# Percent HIV RNA <400 for Study 3001

## All Randomized Subject

**Discontinuations, New CDC Class C Event and Missing Regarded as Failures**




| Sample size | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PLA | 116 | 116 | 116 | 116 | 116 | 116 | 116 | 116 | 107 | 92 | 80 | 58 | 48 | 37 |
| | APV | 116 | 116 | 116 | 116 | 116 | 116 | 116 | 116 | 111 | 93 | 78 | 63 | 46 | 35 |

• APV (N=116) ■ PLA (N=116)

It appears that the treatment difference was maintained over time once past Week 16 or 20. However, the response rate for the placebo-containing arm appears to be decreasing sharply immediately after Week 4 and then declines steadily, while the rate started to decline slowly after Week 8 for the amprenavir-containing arm.

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The response rates are described below.

**Week 24 HIV-1 RNA Status with Missing Regarded as Failures**

| | < 400 copies/mL | Difference and 95% CI** | p-value* |
|---|---|---|---|
| APV (N=254) | 108 (42.5%) | -10.8% (-19.3%, -2.3%) | 0.014 |
| IND (N=250) | 133 (53.2%) | | |

* Stratified Cochran-Mantel-Haenszel test.

** Randomization stratum adjusted difference with continuity correction. Weight for a stratum with $n_1$ and $n_2$ subjects in the two arms is proportional to $n_1*n_2/(n_1+n_2)$.

The table below lists the detailed status of subjects who were regarded as failures in the analysis above.

**Week 24 Status of Subjects Who Were Regarded as Failures**

| | APV (N=254) | IND (N=250) |
|---|---|---|
| **Progressed to a new CDC Class C event** | 1 (0.4%) | 4 (1.6%) |
| **On Treatment Week 24 HIV-1 RNA** | | |
| Missing | 11 (4.3%) | 17 (6.8%) |
| ≥ 400 copies/mL | 45 (17.7%) | 40 (16.0%) |
| **Discontinued the randomized therapy by Week 24 due to** | | |
| Adverse events | 41 (16.1%) | 19 (7.6%) |
| Early virological rebound | 12 (4.7%) | 6 (2.4%) |
| Before taking any study medication | 9 (3.5%) | 9 (3.6%) |
| Consent withdrawn, Lost to follow-up, Protocol Violation, Other | 27 (10.6%) | 22 (8.6%) |

The 10.7% difference in failure rates between amprenavir and indinavir arms is comprised of the differences in discontinuations due to adverse events (8.5%), lack of efficacy (HIV RNA ≥ 400 copies/mL or CDC Class C event or discontinuation due to early virological failures, 2.8%), missing values (-2.5%) and others (2.0%).

For Study 3001, there was only one missing Week 24 value and the observed treatment difference was large, therefore the interpretation of this missing value has little impact on the analysis outcome. In contrast, there were more missing values in Study 3006 and the observed treatment difference was relatively small, therefore how these values were handled will have a significant impact on the analysis outcome. Since there were more missing values in the indinavir arm than there were in the amprenavir arm at Week 24, it is likely that both the response rates and the treatment difference have been affected by regarding missing values as failures. To investigate this problem three sensitivity analyses will be conducted below.

The first analysis will exclude subjects with missing Week 24 HIV RNA. This implicitly assumes that the response rates among these subjects were similar to those subjects with non-

missing HIV RNA in each arm.

The other two analyses utilize Week 20 values. The Week 20 and 24 virological status are cross-tabulated below.

**Joint Virological Status at Weeks 20 and 24 by Treatment**

| APV | | | Week 24 | | | | |
|---|---|---|---|---|---|---|---|
| | | | On Treatment w/o CDC Class C | | | Others** | Total |
| | | | <400 | ≥400 | Missing | | |
| Week 20 | On Treatment w/o CDC Class C | <400 | 91 | 10 | 6 | 1 | 108 |
| | | ≥400 | 13 | 32 | 3 | 6 | 54 |
| | | Missing | 4 | 3 | 2* | 1 | 10 |
| | Others** | | 0 | 0 | 0 | 82 | 82 |
| | Total | | 108 | 45 | 11 | 90 | 254 |

| IND | | | Week 24 | | | | |
|---|---|---|---|---|---|---|---|
| | | | On Treatment w/o CDC Class C | | | Others** | Total |
| | | | <400 | ≥400 | Missing | | |
| Week 20 | On Treatment w/o CDC Class C | <400 | 123 | 7 | 12 | 3 | 145 |
| | | ≥400 | 7 | 28 | 4 | 7 | 46 |
| | | Missing | 3 | 5 | 1* | 2 | 11 |
| | Others** | | 0 | 0 | 0 | 48 | 48 |
| | Total | | 133 | 40 | 17 | 60 | 250 |

* The last available HIV RNA values were ≥400 copies/mL

** Discontinued the randomized treatment or had a new CDC Class C event

To see if Week 24 values could be reasonably replaced by the Week 20 values, subjects with both Weeks 20 and 24 on treatment HIV RNA values were examined. Among the 91+10+123+7=231 subjects with on treatment HIV RNA < 400 copies/mL at Week 20, 91+123=214 (93%) maintained their status at Week 24. Among 80 subjects with on treatment HIV RNA ≥ 400 copies/mL at Week 20, 60 (75%) of them maintained their status at Week 24. It appears that Week 20 predicts Week 24 reasonably well for subjects who had both Weeks 20 and 24 measurements. Assuming that this relationship holds for the subjects with missing values at Week 24, it would be reasonable to replace Week 24 values with Week 20 or earlier values. This is the second sensitivity analysis.

The second analysis above assumes that the Week 24 values could be almost fully predicted by Week 20 values. In the third analysis, instead of making assumptions on the missing data, we modify the endpoint. As mentioned earlier in the algorithm, the virological status at Week 24 was determined by the worst HIV RNA value in the window [156, 183] days. The new endpoint will be defined as the worst value in the combined Week 20 and Week 24 window [128, 183] days. With this approach, there will be only 3 subjects, 2 in the amprenavir arm and the other in the indinavir arm, with missing HIV RNA values and they will be regarded as failures in the analysis.

Because only slightly over half of the subjects completed 28 weeks of trial, Week 28 HIV RNA values were not used for filling the Week 24 missing values.

The results of these three sensitivity analyses, together with the original approach of treating missing as failures, are summarized in the following table.

**Sensitivity Analyses for Virological Endpoint at Week 24**

| | Missing As Failures | | Missing Excluded | | Imputed by Week 20 | | New Endpoint | |
|---|---|---|---|---|---|---|---|---|
| | APV | IND | APV | IND | APV | IND | APV | IND |
| N | 254 | 250 | 243 | 233 | 254 | 250 | 254 | 250 |
| Success | 108 | 133 | 108 | 133 | 114 | 145 | 101 | 138 |
| Rate (%) | 42.5 | 53.2 | 44.4 | 57.1 | 44.9 | 58.0 | 39.8 | 55.2 |
| Diff (%)** | -10.8 | | -12.4 | | -13.2 | | -15.6 | |
| 95% CI (%)** | -19.3, -2.3 | | -21.1, -3.6 | | -21.7, -4.8 | | -24.0, -7.1 | |
| p-value* | 0.014 | | 0.006 | | 0.003 | | 0.001 | |

* Stratified Cochran-Mantel-Haenszel test.

** Randomization stratum adjusted difference with continuity correction. Weight for a stratum with $n_1$ and $n_2$ subjects in the two arms is proportional to $n_1*n_2/(n_1+n_2)$.

The four analyses above showed that the treatment difference between the two treatments could be as large as 24% in favor of indinavir. This shows that amprenavir has not been shown to be equivalent to indinavir. In addition, it appears that subjects treated with indinavir were less likely to discontinue the randomized treatment before Week 24, experiencing a new CDC Class C event, or have viral load ≥ 400 copies/mL at Week 24.

Since the difference in the discontinuation due to AE accounted for a large portion of the observed treatment difference, further analysis will be conducted in the Section E for subjects who could tolerate the drugs.

The response rates over time corresponding to the first two analyses in the table were plotted on the next page. Missing values were regarded as failures in the first while they were excluded in the second.

Note that less than one third of subjects had evaluations beyond Week 28, therefore the tails of the curves were more variable and should be viewed with caution. There was no suggestion that the two curves would converge. As noted earlier for Study 3001, the response rates started to decline after Week 8 for the amprenavir arm, while the decline appears to start after Week 12 for the indinavir arm.

## Percent HIV RNA <400 for Study 3006

### All Randomized Subject

**Discontinuations, New CDC Class C Event and Missing Regarded as Failures**

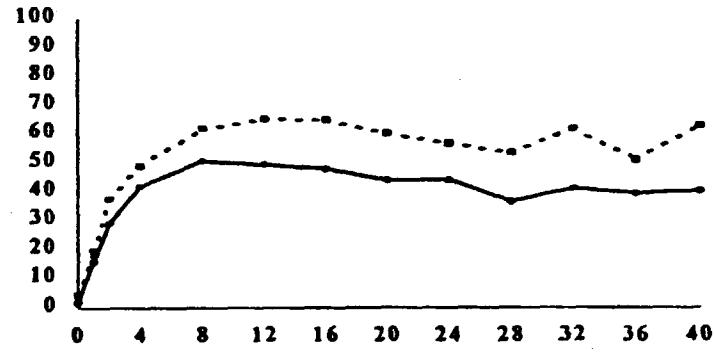

| Sample size | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | IDV | 254 | 254 | 254 | 254 | 254 | 254 | 254 | 144 | 79 | 56 | 29 |
| | APV | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 132 | 75 | 51 | 21 |

• APV (N=254) ■ IND (N=250)

## Percent HIV RNA <400 for Study 3006

### On Treatment Missing Excluded

**Discontinuations and New CDC Class C Event Regarded as Failures**




| Sample size | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | IDV | 253 | 245 | 250 | 252 | 238 | 244 | 243 | 122 | 70 | 53 | 27 |
| | APV | 248 | 243 | 244 | 243 | 232 | 239 | 233 | 108 | 66 | 43 | 19 |

• APV (N=254) ■ IND (N=250)

## D.2 HIV-1 RNA with Ultrasensitive Assay

The plasma HIV-1 RNA levels of the ultrasensitive assay were available at Week 16 and 24 only for subjects whose plasma levels were not detectable with the standard assay. This limits the interpretability of the results. The response rates at Week 16 and 24 are described below for the two studies.

**Virological Response Rates at Weeks 16 and 24 with Ultrasensitive Assay**

Study 3001

| | APV (N=116) | | | PLA (N=116) | | |
|---|---|---|---|---|---|---|
| | Success* | Failure** | Missing*** | Success* | Failure** | Missing*** |
| Week 16 | 44.8 | 50 | 5.2 | 9.5 | 87.1 | 3.4 |
| Week 24 | 46.6 | 50 | 3.4 | 4.3 | 92.2 | 3.4 |

Study 3006

| | APV (N=254) | | | IND (N=250) | | |
|---|---|---|---|---|---|---|
| | Success* | Failure** | Missing*** | Success* | Failure** | Missing*** |
| Week 16 | 31.5 | 60.6 | 7.9 | 42.8 | 49.6 | 7.6 |
| Week 24 | 28.7 | 65.0 | 6.3 | 44.0 | 48.0 | 8.0 |

* On treatment HIV-1 RNA < — copies/mL without experiencing any new CDC Class C event.

** On treatment HIV-1 RNA > — copies/mL or have had a new CDC Class C event or have discontinued the randomized treatment earlier.

*** On treatment but no evaluation of plasma HIV-1 RNA level.

The treatment differences shown here are similar to the ones based on the standard assay with the results slightly less favorable for amprenavir.

## D.3 CD4

For Study 3001, the applicant's table for CD4 change used CD4 measurements while on the randomized or open-label treatment. For Study 3006, the applicant provided only the table based on the randomized phase in its 12/22/98 update. The table below calculates the changes based on all the data collected, including those during the follow-up.

**Summary of Median CD4+ Change from Baseline over Time**

All Measurements Included

| | 3001 | | | | 3006 | | | |
|---|---|---|---|---|---|---|---|---|
| | APV | | PLA | | APV | | IND | |
| Treatment Week | N | Cells/mm$^3$ | N | Cells/mm$^3$ | N | Cells/mm$^3$ | N | Cells/mm$^3$ |
| Baseline | 113 | 435 | 113 | 409 | 253 | 390 | 243 | 414 |
| Week 2 | 105 | +27 | 101 | +37 | 225 | +9 | 223 | +23 |
| Week 4 | 103 | +37 | 102 | +56 | 218 | +14 | 227 | +31 |
| Week 8 | 99 | +54 | 100 | +72 | 218 | +24 | 223 | +29 |
| Week 12 | 92 | +58 | 99 | +88 | 213 | +19 | 219 | +37 |
| Week 16 | 85 | +51 | 91 | +50 | 194 | +27 | 201 | +41 |
| Week 20 | 79 | +71 | 92 | +55 | 166 | +37 | 178 | +62 |
| Week 24 | 77 | +82 | 86 | +67 | 190 | +42 | 177 | +83 |
| Week 28 | 68 | +90 | 83 | +83 | 118 | +60 | 177 | +90 |
| Week 32 | 63 | +101 | 74 | +103 | 60 | +30 | 177 | +84 |
| Week 36 | 50 | +107 | 63 | +70 | 44 | +28 | 177 | +97 |
| Week 40 | 40 | +86 | 48 | +76 | 27 | +76 | 177 | +75 |

The statistical analysis of CD4 below is based on the average Area Under Curve Minus Baseline (AUCMB), which is a measure of the average change. The results are summarized below.

**AUCMB for CD4**

| | 3001 | | 3006 | |
|---|---|---|---|---|
| | APV | PLA | APV | IND |
| Mean | 40.7 | 45.2 | 33.2 | 46.4 |
| p-value* | 0.7100 | | 0.003 | |

* Cochran-Mantel-Haenszel Test stratified by randomization stratification variables.

It appears that the CD4 change in Study 3001 is not statistically significantly different. However, for Study 3006, indinavir treatment appears to lead to significantly more increase in CD4 than amprenavir treatment. Note that the CD4 were not available for a substantial number of subjects (30% in 3001 and 27% in 3006 at Week 24) in both studies due to withdrawals or missing clinical visits. Therefore, the results should be viewed cautiously.

Alternatively, analysis was also conducted with only measurements while on the randomized treatment.

**Summary of Median CD4+ Change from Baseline over Time**

Randomized Phase

| | 3001 | | | | 3006 | | | |
|---|---|---|---|---|---|---|---|---|
| | APV | | PLA | | APV | | IND | |
| Treatment Week | N | Cells/mm$^3$ | N | Cells/mm$^3$ | N | Cells/mm$^3$ | N | Cells/mm$^3$ |
| Baseline | 113 | 435 | 113 | 409 | 253 | 390 | 243 | 414 |
| Week 2 | 101 | +24 | 100 | +37 | 216 | +11 | 222 | +24 |
| Week 4 | 100 | +37 | 100 | +56 | 205 | +16 | 223 | +31 |
| Week 8 | 91 | +51 | 98 | +73 | 199 | +25 | 213 | +30 |
| Week 12 | 81 | +63 | 95 | +93 | 188 | +23 | 205 | +40 |
| Week 16 | 76 | +54 | 89 | +49 | 160 | +27 | 184 | +46 |
| Week 20 | 72 | +72 | 86 | +51 | 138 | +37 | 166 | +66 |
| Week 24 | 64 | +114 | 35 | +49 | 154 | +42 | 176 | +88 |

The results of the AUCMB:

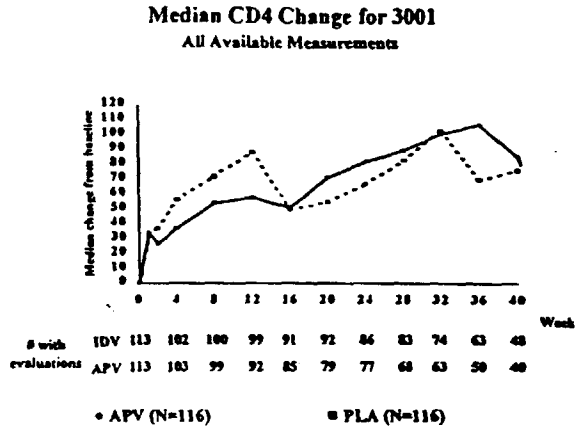
**AUCMB for CD4**

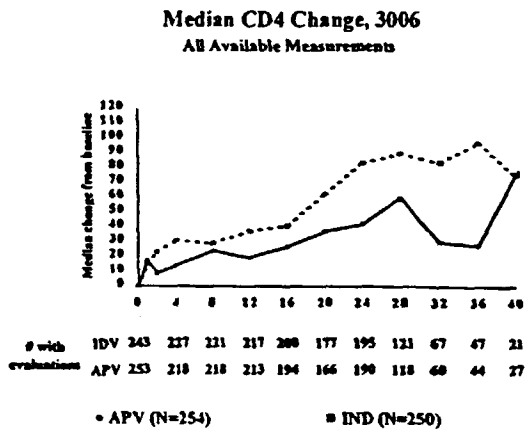
| | 3001 | | 3006 | |
|---|---|---|---|---|
| | APV | PLA | APV | IND |
| Mean | 38.8 | 26.5 | 17.8 | 40.7 |
| p-value* | 0.256 | | <0.001 | |

* Cochran-Mantel-Haenszel Test stratified by randomization stratification variables.

Again, the AUCMB for the CD4 based on all available data in the randomized phase before cutoff date were not significantly different between the amprenavir and placebo treatment for Study 3001, but they were significantly different in Study 3006 in favor of indinavir. These conclusions agree with the previous conclusions based on all collected data.

The median CD4 changes were plotted in the two plots below. The number of subjects with data is listed at the bottom of the graph. In both graphs the solid line represents the amprenavir arm while the dashed line represents the control arm.






## D.4 Subgroup Analysis

The subgroup analysis will be performed for Week 24 virological response, which was defined as having viral load < 400 copies/mL and still on the randomized therapy at Week 24 and without experiencing any new CDC Class C event.

Randomization Stratum

For Study 3001, the randomization was stratified by the screening viral load. The response rates in each subgroup were summarized below.

**Week 24 Response by Screening Viral Load**

| | 10,000 – 30,000 (N=37/arm) | 30,000 – 100,000 (N=55/arm) | >100,000 (N=24/arm) |
|---|---|---|---|
| APV | 70.3% | 47.3% | 37.5% |
| PLA | 27.0% | 5.5% | 0% |

The response rates were lower for subjects with higher screening viral load ($p < 0.001$). However, the homogeneity of treatment differences across the subgroups was not rejected ($p=0.25$).

For Study 3006, the randomization was stratified by the screening viral load and by whether they plan to change at least one NRTI at entry. Again, the response rate was lower for subjects with higher screening viral load ($p < 0.001$) for both amprenavir and indinavir arms. However, the response rates were nearly identical in each treatment arm for both those who planned to change at least one NRTI and those who planned not to change. The homogeneity of treatment differences across the subgroups was not rejected ($p=0.954$).

Gender, Age, Ethnic origin

**Week 24 Response by Gender**

| | 3001 | |
|---|---|---|
| | Male (N) | Female (N) |
| APV | 58.3% (103) | 7.7% (13) |
| PLA | 11.7% (103) | 7.7% (13) |

| | 3006 | |
|---|---|---|
| | Male | Female |
| APV | 47.6% (206) | 25.0% (48) |
| IND | 61.2% (196) | 31.5% (54) |

Females tend to have lower response rate than males ($p < 0.001$ for both 3001 and 3006). However, the similarity of treatment differences for males and females was not rejected ($p>0.5$ for both studies).

There was no difference in treatment effects for white vs. non-white comparisons.

The response rate appears to increase with age ($p=0.006$). Again, there is no treatment interaction with age ($p=0.8$).

**E. Exploratory Analysis**

Study 3006 was designed to demonstrate the equivalence of amprenavir and indinavir. Based on the analysis of proportion of subjects who achieved viral load < 400 copies/mL while still on the randomized therapy at Week 24, the indinavir appeared to be more efficacious than amprenavir and the treatment difference could be over 20% based on the upper bound of the 95% confidence interval for the treatment difference. However, it was also noted that the majority of the treatment difference was due to the differential rates in discontinuations due to adverse events. Therefore, the interpretation of how discontinuation due to adverse events related to the Week 24 failure will have a significant impact on the efficacy conclusion.

This section attempts to answer the following question: if discontinuations due to adverse events were regarded as not related to Week 24 efficacy, what would be the treatment difference between the two regimens?

This can be tentatively addressed by examining only subjects who did not discontinue due to adverse events. Discontinuations due to virological rebound or other reasons were regarded as treatment failures. With this interpretation and different ways of handling missing values discussed in the Section D.1., the analysis can be similarly summarized in the following table.

**Sensitivity Analyses for Virological Endpoint**

Discontinuations before or at Week 24 due to AEs excluded

| | Missing As Failures | | Missing Excluded | | Imputed by Week 20 | | New Endpoint | |
|---|---|---|---|---|---|---|---|---|
| | APV | IND | APV | IND | APV | IND | APV | IND |
| N | 213 | 231 | 202 | 214 | 213 | 231 | 213 | 231 |
| Success | 108 | 133 | 108 | 133 | 114 | 145 | 101 | 138 |
| Rate (%) | 50.7 | 57.6 | 53.5 | 62.1 | 53.5 | 62.8 | 47.4 | 59.7 |
| Diff (%)** | -7.2 | | -8.5 | | -9.6 | | -12.7 | |
| 95% CI (%)** | -16.3, 1.9 | | -17.8, 0.7 | | -18.6, -0.7 | | -21.7, -3.7 | |
| p-value* | 0.126 | | 0.074 | | 0.037 | | 0.007 | |

* Stratified Cochran-Mantel-Haenszel test.

** Randomization stratum adjusted difference with continuity correction. Weight for a stratum with $n_1$ and $n_2$ subjects in the two arms is proportional to $n_1 * n_2/(n_1+n_2)$.

It appears that even when discontinuations due to adverse events were regarded as not related to the virological response, the treatment difference could be as large as 22% in favor of indinavir. In addition, there was marginal evidence that the indinavir arm has a significantly higher response rate at Week 24 than the amprenavir arm.

**F. Overall Assessment**

Based on the available data up to Week 24 cutoff date,

1. 3001 demonstrated that a higher proportion of amprenavir + 3TC + ZDV treated subjects remained on the randomized treatment without experiencing any new CDC Class C event and achieved viral load < 400 copies/mL at Week 24 than subjects treated with 3TC + ZDV. The CD4 changes over time were similar for the two groups.

2. 3006 demonstrated that the amprenavir is not equivalent to indinavir. Based on the 95% confidence interval, the treatment difference could be 19% or larger in favor of indinavir (missing= failure analysis). The upper bound indicates the difference is likely to be at least 2% in favor of indinavir.

   This treatment difference was caused by both more frequent discontinuations due to AE and more frequent virological failures in the amprenavir arm. For subjects who did not discontinue due to adverse events, the equivalence was not demonstrated and the treatment difference was marginally significant in favor of indinavir.

   Based on available CD4 data (27% missing at Week 24), the CD4 changes over time were significantly different in favor of indinavir.