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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-007/SE7-006
21-039/SE7-006

Statistical Review(s)

STATISTICAL REVIEW AND EVALUATION

NDA#:	21-007, SE7-006
APPLICANT:	Glaxo Wellcome Inc.
NAME OF DRUG:	AGENERASE™ (amprenavir, APV, 141W94) Capsules
INDICATION:	Treatment of HIV infection
DOCUMENTS REVIEWED:	Submission dated : July 13, 2000
CLINICAL REVIEWER:	HFD-530: Russell Fleischer, PA-C, MPH
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STATISTICAL REVIEW AND EVALUATION

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STATISTICAL REVIEW AND EVALUATION

A. Background

AGENERASE™ (amprenavir, APV, 141W94) is an inhibitor of HIV-1 aspartyl protease. FDA designated this drug as a "fast track" drug product on March 18, 1998 and both the formulations, Agenerase Capsules (NDA 21-007) and Agenerase Oral Solution (NDA 21-039), were granted accelerated approval on April 15, 1999 for treatment of HIV infection.

This is a review of the supplemental NDA 21-007, SE7-006, which seeks *traditional approval* of amprenavir capsules for the treatment of HIV infection. The efficacy results in this submission are based on 48 week efficacy data from two Phase III, pivotal, randomized, multicenter, controlled clinical trials (Protocols PROAB3001 and PROAB3006). The accelerated approval of amprenavir and regulatory decisions were based on efficacy and safety data for 24 weeks submitted in the original NDA.

Results of 14 Phase I studies and 3 Phase I/II studies evaluating amprenavir's pharmacology were presented in the original NDA. In addition, longer-term safety and efficacy data through 48 weeks is submitted in this sNDA for 5 Phase II trials conducted in various patient populations to support the efficacy of amprenavir. Only the two pivotal, Phase III trials—Study 3001 and 3006—will be reviewed here.

B. Study Designs

1. Protocol PROAB3001—Placebo-Control Study

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." (Study Period: first subject screened February 25, 1997–last subject completed 48 weeks on October 14, 1998)

This is a Phase III, randomized, double-blind, placebo-controlled, multicenter (23 centers) two-arm superiority trial designed to compare the antiviral activity of the triple combination therapy of [Amprenavir (APV) + RETROVIR(zidovudine, ZDV, AZT) + EPIVIR(lamivudine, 3TC)] versus the double combination therapy of [Amprenavir placebo (PLA) + RETROVIR(AZT) + EPIVIR(3TC)].

Population

The study was conducted in the United States (13 centers) and Europe (10 centers) in *anti-retroviral naïve* subjects ≥18 years (≥13 years in some countries based on local laws) who had no previous or current clinical diagnosis of AIDS. Subjects were to have viral load ≥10,000 plasma HIV-1 RNA copies/mL and CD4+ lymphocyte cell count ≥200

cells/mm^3 within 14 days of study entry.

Sample Size

Sample size of 230 subjects (115 per arm) was determined assuming a success rate at Week 48 of 50% in the APV (test) group and 25% in the Placebo (control) group, accrual time of 16 weeks, and a drop-out rate of 20% over the course of the study would give 85% power to detect a difference in the expected proportions at a two-sided 0.05 level of significance. Success rate is defined as proportion of subjects maintaining viral load <400 copies/mL and not progressing to CDC Class C event or death. This sample size was designed to capture at least 82 events in 48 weeks, otherwise the study period would be extended until 82 events are realized.

Randomization

Approximately 230 subjects were to be randomized to one of the 2 blinded treatment regimen.

Group 1 (Test): APV (1200 mg BID) + AZT (300 mg BID) + 3TC (150 mg BID)

Group 2 (Control): Placebo (1200 mg BID) + AZT (300 mg BID) + 3TC (150 mg BID)

Subjects were to be equally randomized to the 2 groups using a centralized randomization code and stratified by their screening viral load (≥10,000–30,000, >30,000–100,000, or >100,000 plasma HIV-1 RNA copies/mL).

Switching

Subjects were to continue on their randomized treatment (and blinded on both therapy and viral load data for 16 weeks) until the last subject completes 48 weeks (or 96 weeks following Protocol Amendment 3) unless they met a protocol-defined switch criterion defined as

- two consecutive (within 3 weeks of one another) plasma HIV-1 RNA level of ≥400 copies/mL at Week 16 or thereafter, or
- progression to a CDC Class C event after 4 weeks on the study.

Subjects whose confirmatory viral load is <400 copies/mL will not be eligible to switch therapy and will remain on their randomized therapy.

Subjects who met the switching criteria were eligible for the following options: 1) continue randomized therapy, and/or 2) switch to open-label APV, and/or 3) add abacavir (ABC 300 mg BID), and/or 4) change nucleoside reverse transcriptase inhibitor(s) (NRTI[s]), and/or 5) add another approved HIV protease inhibitor (except NORVIR [ritonavir] since no drug interaction data available), and/or 6) change to any

other approved HIV protease inhibitor (including NORVIR [ritonavir]).

After the last subject completes 48 weeks, subjects will be given the option to enter the extension phase of the study and receive open-label therapy until the last subject completes 96 weeks.

Efficacy Analysis

The primary efficacy analysis (as originally defined in the protocol) will be to assess the durability of the viral load response over 48 weeks based on *time to event*, defined as the time to first confirmed viral load rebound (≥400 copies/mL) and/or permanent discontinuation of randomized therapy and/or progression to a CDC Class C event or death.

Plasma HIV-1 RNA will be measured by a *standard assay*—Roche Amplicor HIV-1 Monitor Test (Primers 1.0, standard, LOD=400 copies/mL)—at screening, pre-entry (pre-baseline), baseline (Day 1), Weeks 1, 2, 4 and every 4 weeks thereafter. In addition, in those subjects with viral load <400 plasma HIV-1 RNA copies/mL at Weeks 16, 32, 40, and 48, a more *sensitive assay*—the Roche Amplicor Ultrasensitive Test (Primers 1.0, Ultrasensitive, LOD=50 copies/mL)—was used to measure their viral load at those specific timepoints. The *standard assay* measurements will be used for the primary efficacy analysis.

Changes in CD4+ cells and $\log_{10}$ HIV RNA levels as measured by Average Area Under the Curve Minus Baseline (AAUCMB) will also be evaluated for the 48-week analysis.

The primary population for efficacy analysis will be the *intent-to-treat population* (*ITT*) which includes all randomized subjects.

For the 48-week primary efficacy analysis, the two treatment groups will also be compared with respect to *proportion of subjects with HIV RNA levels <400 copies/mL* using Cochran-Mantel-Haenzel test stratified by the randomization strata.

The distribution of *time to event* will be estimated using the Kaplan–Meier product limit survival method. Differences between the two regimens will be assessed using a permutation based stratified log rank test, stratified by randomization strata. The risk ratio will be estimated using Cox's regression stratified by randomization strata.

The AAUCMBs will be compared between regimens using extended Mantel–Haenszel methodology using the actual values as tables scores controlling for randomization strata.

The protocol was finalized on September 21, 1998 (Amendment 3) and the data cut off date used was November 25, 1998

2. Protocol PROAB3006—Active-Control Study

Title: "A Phase III Trial to Compare the Safety and Antiviral Efficacy of 141W94 with Indinavir in Combination with Nucleoside Reverse Transcriptase Inhibitor (NRTI) Therapy in NRTI Experienced, Protease Inhibitor (PI) Naïve HIV-1 Infected Patients." (Study start date: September 15, 1997 ; Data cut off date: April 1, 1999).

This study was a randomized, open-label, multicenter, comparative trial designed to compare the safety and antiviral efficacy of Amprenavir versus Indinavir in combination with NRTIs.

Population

The study was conducted in the 78 centers in United States (33), Canada (11), Australia (6) and Europe (28) in *NRTI-experienced, protease inhibitor naïve* HIV-1 infected subjects. The subjects were ≥18 years (or ≥16 years of age in some countries) with screening plasma viral load ≥ 400 copies HIV-1 RNA/mL (based on Roche Amplicor HIV-1 Monitor Test [primers 1.0, standard, LOD=400 copies/mL]) but had no AIDS defining opportunistic infection or disease.

Sample Size

Sample size of 460 subjects (230 per arm) was determined assuming a success rate (defined by the primary endpoint) of 70% (in the control group receiving IDV+NRTI) at Week 48 and 80% power to detect <12% (i.e., $\delta = 12\%$) in the difference of proportions for assessing equivalence of the two treatment groups at the 5% level of significance (i.e., $\alpha = 0.05$). Treatment with Amprenavir (APV) was to be considered non-inferior to Indinavir (IDV) if the 95% confidence interval around the difference in proportions between IDV and APV did not include values ≥12%.

Randomization

Approximately 460 subjects were to be equally randomized to one of the following two treatment arms.

Group 1 (Test): Amprenavir (APV) 1200 mg every 12 hours + background NRTI therapy

Group 2 (Control): Indinavir (IDV) 800 mg every 8 hours + background NRTI therapy

Subjects were randomized using a centralized randomization code and stratified according to their screening viral load (≥400-10,000 copies/mL; >10,000-100,000 copies/mL; or >100,000 copies/mL) and according to whether they planned to change at least one background NRTI. Table 1 shows the dosing regimen for the two treatment groups.

Table 1:

Treatment Assignment (Open-label), Protocol PROAB3006

Treatment Group	Drug	Dose Interval	Total Daily Dose	Number of Capsules
1 (Test)	APV (1200 mg every 12 hrs) + NRTI therapy	8x150 mg every 12 hours	2400 mg	16
2 (Control)	IDV (800 mg every 8 hrs) + NRTI therapy	2x400 mg every 8 hours or 4x200 mg every 8 hours	2400 mg	6 or 12

Switching

Subject were to continue on their randomized treatment regimen until the last subject completed 48 weeks of randomized treatment unless they met the protocol defined switch criteria. The subjects were allowed to change therapy (change either one concurrent NRTI therapy or alternate protease inhibitor [any licensed HIV protease inhibitor or open-label APV] or both) if they met any of the following switch criteria:

- Viral load (confirmed by repeat viral load measurement obtained ≥1 week and ≤3 weeks from the date of Week 8 sample) has not decreased by ≥0.7 $\log_{10}$ HIV RNA copies/mL from the baseline.
- Viral load ≥400 HIV RNA copies/mL (confirmed by repeat viral load measurement obtained ≥1 week and ≤3 weeks from the date of the original sample) at Week 16 and every 8 weeks thereafter.
- Progression to a new CDC Class C event anytime after 4 weeks of randomized therapy.
- Toxicity, which will require permanent discontinuation of randomized therapy.

Efficacy Analysis

The primary efficacy endpoint is the durability of the viral load response over 48 weeks of treatment based on the *proportion of subjects with viral load < 400 copies HIV-1 RNA/mL who did not progress to a CDC Class C event or death.*

Changes in plasma viral load were measured using the *standard assay*—namely, the Roche Amplicor HIV-1 Monitor Test (Primers v1.0, standard, LOD=400 copies/mL and below)—at the time points: screening, pre-baseline, baseline, Weeks 1, 2, 4, and every 4 weeks thereafter until the last subject enrolled reached Week 48, and at the follow-up (4,

8, and 12 weeks after withdrawal from study). In addition, a more sensitive assay—the Roche Amplicor Ultrasensitive Test (Primers 1.0, Ultrasensitive, LOD=50 copies/mL)—was used to measure plasma HIV-1 RNA viral load at specific timepoints (Weeks 16, 24, 32, 40 and 48) in those subjects with plasma viral load < 400 copies/mL at those timepoints. The standard assay measurements were used for primary efficacy analysis.

Anti-HIV-1 activity will also be evaluated by estimating the Average Area Under the Curve Minus Baseline (AAUCMB) for the CD4 results and the $\log_{10}$ HIV-1 RNA levels.

For the 48-week analysis, additional secondary endpoints included:

- Time to event (defined as the first date of detectable virus [≥400 copies HIV RNA/mL] following a minimum of 8 weeks of treatment). (For patients who never achieve a viral load <400 copies HIV RNA/mL, the event time will be assigned to 0. For patients who maintain a viral load <400 copies HIV RNA/mL for the duration of the study, the event time will be censored at the date of the last viral load assessment.);
- Proportion of subjects with progression or death (clinical endpoint defined as the progression from baseline HIV-1 disease status to the occurrence of the first new event as follows: CDC category A to C or death; CDC category B to C or death; CDC category C to new C event or death); and
- Measured values and changes from last value on study drug of plasma HIV-1 RNA levels post-change of therapy for subjects who changed randomized therapy.

Statistical analysis will be based on the intent-to-treat population which includes all randomized patients. Patients who prematurely discontinue randomized therapy and patients with first or new CDC class C events (if occurs after 4 weeks on study) will be considered as failures.

The equivalence of the success rates (primary endpoint) will be assessed using 95% confidence intervals about the difference in proportions, controlling for randomization strata. The AAUCMB for the CD4 results and the $\log_{10}$ HIV-1 RNA levels will be calculated using the trapezoidal rule divided by the time on study minus the baseline marker value. Secondary assessments of durability will include graphical comparisons of Kaplan–Meier "time to event" curves, where event is defined by the first date of detectable virus (≥400 copies HIV RNA/mL) following a minimum of 8 weeks of treatment.

The protocol was finalized on December 16, 1998 and the data cut off date used was April 1, 1999.

C. Applicant's Results

1. Demographics and Baseline Characteristics

Protocol 3001 and 3006 differed in terms of the entry criteria and the population studied (antiretroviral naïve subjects in 3001 versus protease-inhibitor naïve, but NRTI-experienced subjects in 3006). Table 2 compares the demographics and baseline characteristics of the subjects in the 2 studies.

As shown in subjects in Table 2, the two studies were similar in terms of demographics such as age, weight, gender, race and in terms of baseline Hepatitis B test results. They differed in terms of route of HIV transmission, Hepatitis C test results, CDC Classification, baseline plasma HIV-1 viral load, and CD4+ cell counts.

- A higher percentage of subjects acquired the disease through homosexual contact in Study 3001 (72%) than in Study 3006 (54%), whereas a lower percentage of subjects in Study 3001 acquired HIV through injectable drug use (3%) than in Study 3006 (13%).
- A lower percentage of subjects had reactive Hepatitis C test results in Study 3001 (6%) than in Study 3006 (18%).
- The disease was in a less advanced stage in Study 3001 than in Study 3006 in terms of CDC classification (higher percentage of CDC class B and C events in Study 3006) and CD4+ cell counts (higher percentage of subjects with lower CD4 cell counts); but more subjects in Study 3001 (who were therapy naïve) had higher baseline HIV viral load.

Table 2: Demographics and Baseline Characteristics by Study (Intent-to-Treat Population)

Characteristic		Study 3001 N=232	Study 3006 N=504
Age (Years)	Median	35	37
	Range	17 to 62	20 to 71
Weight (kg)	Median	76.1	73.6
Gender	Male	89%	80%
	Female	11%	20%
Race	White	75%	72%
	Black	11%	19%
	Hispanic	12%	7%
	Asian	<1%	<1%
	Other	2%	<1%
Route of HIV Transmission	Homosexual contact	72%	54%
	Heterosexual contact	18%	29%
	Injectable drug use	3%	13%
	Hemophilia-associated injections	—	<1%
	Occupational Exposure	<1%	<1%
	Transfusion	2%	2%
	Other	4%	2%
Hepatitis B Test Result	Negative	84%	88%
	Positive confirmed	5%	8%
	Missing	11%	5%
Hepatitis C Test Result	Negative	82%	77%
	Reactive	6%	18%
	Missing	12%	5%
CDC Classification	A: Asymptomatic or Lymphadenopathy	79%	62%
	B: Symptomatic, not AIDS	19%	26%
	C: AIDS	2%	10%
	Missing	—	3%
Baseline HIV RNA (log_{10} copies/mL)	Median (Range)	4.67	3.93
Baseline plasma HIV-1 RNA	<400 copies/mL	—	2%
	400–<10,000 copies/mL	4%	53%
	≥10,000–30,000 copies/mL	32%	
	>30,000–100,000 copies/mL	40%	37%
	>100,000 copies/mL	23%	8%
CD4+ cell count (cells/mm^3)	Baseline Median	424	404
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	35%	30%

Source: Tables 10, 11 and Supporting Tables 12–13, 15 of PROAB3001 Study Report.
Tables 8, 9, and Supporting Tables 16, 17, and 19 of PROAB3006 Study Report.

2. Subject Accounting

Table 3 shows the disposition of subjects through 48 weeks of treatment for the 2 pivotal studies.

Table 3:

Subject Accounting by Treatment Group and Study Through Week 48

Number of Subjects	Study 3001 N=232		Study 3006 N=504	
	Treatment Group		Treatment Group	
	Amprenavir	Placebo	Amprenavir	Indinavir
Total Randomized	116 (100%)	116 (100%)	254 (100%)	250 (100%)
Randomized but not treated	4 (3%)	7 (6%)	9 (4%)	9 (4%)
Treated	112 (97%)	109 (94%)	245 (96%)	241 (96%)
Completed study through Week 48	54 (47%)	12 (10%)	135 (53%)	158 (63%)
Discontinued study prior to Week 48	58 (50%)	97 (84%)	110 (43%)	83 (33%)
due to AE	18 (16%)	5 (4%)	45 (18%)	37 (15%)
due to consent withdrawn	9 (8%)	6 (5%)	10 (4%)	7 (3%)
due to loss to follow	8 (7%)	3 (3%)	15 (6%)	12 (5%)
due to protocol-defined switch criteria	14 (12%)	79 (68%)	23 (9%)	13 (5%)
due to protocol violation	1 (1%)	0 (0%)	3 (1%)	2 (1%)
due to other reasons	8 (7%)	4 (3%)	14 (6%)	12 (5%)

Percentages in table are calculated based on the total number of randomized subjects in each group.

Number of study centers = 23 in Study 3001 and 78 in Study 3006.

Source: Table 2 and Supporting Table 5 for Study 3001. Table 2 and Supporting Table 7 for Study 3006.

In Protocol 3001, a high percentage of subjects (68%) in the placebo arm (receiving dual therapy of AZT+3TC) discontinued due to protocol-defined switch criteria, which was virologic failure at Week 16 or thereafter and/or progression to AIDS. Majority of these discontinuations occurred after Week 16 and prior to Week 24 in the study (Source: Table 4 of Study Report for 3001). These patients were eligible to receive an add-on therapy of protease inhibitor and/or change therapies.

In Protocol 3006, there were fewer subjects in the Amprenavir arm who completed the study (53% vs 63%) and more subjects who discontinued the study (43% vs 33%) than in the Indinavir arm.

3. Efficacy Endpoints

In both studies, the intent-to-treat (ITT) population—consisting of all subjects randomized to treatment—was the primary population for efficacy analyses. The primary efficacy endpoint in both studies was the durability of antiviral activity of the drugs over 48 weeks, defined as the *proportion of subjects with plasma HIV-1 RNA <400 copies/mL* for Study 3006 and for Study 3001 defined as the *time to loss of virologic response* .

The primary efficacy results are shown in Table 4. These results are based on an "*Failures Carried Forward*" algorithm that uses data actually collected (including confirmatory values of viral load) where missing values are treated as failures and premature discontinuations, CDC Class C events, and death are carried forward as failures.

The applicant concluded superiority of Amprenavir over Placebo in terms of durability of antiviral response based on Study 3001. However, based on Study 3006, the applicant failed to show that Amprenavir was equivalent to Indinavir in terms of durability of antiviral response. The 95% confidence interval on treatment difference between APV and IDV showed that APV could be up to 24% worse than IDV.

Table 4:

Proportion of Subjects with Plasma HIV-1 RNA <400 copies/mL at Week 48 by Treatment and Study (ITT Population)
(Scenario: Missing = Failures and Failures Carried Forward)

	Study 3001 N=232		Study 3006 N=504	
	Treatment Group		Treatment Group	
	APV n=116	PLA n=116	APV n=254	IDV n=250
Number (%) of successes	48 (41%)	4 (3%)	76 (30%)	115 (46%)
p-value†	<0.001			
treatment difference (95% CI)‡			-16% (-24%, -8%)	

Percentages calculated are based on the number of randomized subjects in each group.

† Results of Cochran Mantel-Haenszel test controlling for randomization strata.

‡ 95% CI (adjusting for randomization strata) of the difference (APV-IDV) using Mantel-Haenszel weights.

Source: Table on page 45 of Study Report and Table 23 of Vol. 5 for Study 3001. Table on page 82 of Study Report and Table 16 of Vol. 22.

Table 5 shows the efficacy outcomes (i.e., success or failure) at Week 48 including reasons for treatment failure.

Table 5:

Efficacy Outcomes of Randomized Treatment Through Week 48
by Treatment and Study (ITT Population)
(Scenario: Missing = Failure and Failures Carried Forward)

Outcome	Study 3001		Study 3006	
	Treatment Group		Treatment Group	
	Amprenavir N=116	Placebo N=116	Amprenavir N=254	Indinavir N=250
	n %	n %	n %	n %
Treatment success:				
HIV RNA <400 copies/mL	48 (41)	4 (3)	76 (30)	115 (46)
Treatment failure:				
HIV RNA ≥400 copies/mL	5 (4)	8 (7)	44 (17)	33 (13)
Met virological switch criteria	13 (11)	79 (68)	23 (9)	13 (5)
CDC Class C event	1 (<1)	0	2 (<1)	4 (2)
Discontinued due to AE	18 (16)	5 (4)	44 (17)	37 (15)
Discontd due to other reasons				
Consent withdrawn	9 (8)	6 (5)	10 (4)	7 (3)
Lost to follow-up	8 (7)	3 (3)	15 (6)	12 (5)
Protocol violation	1 (<1)	0	3 (1)	2 (<1)
Other	8 (7)	4 (3)	14 (6)	11 (4)
Never Treated	4 (3)	7 (6)	9 (4)	9 (4)
Missing HIV RNA sample	1 (<1)	0	14 (6)	7 (3)
Percentages calculated are based on the number of subjects randomized in each group.				

Source: Table on p.46 of Study Report and Table 24 of vol. 5 for Study 3001. Table on p.83 of Study Report and Table 17 of vol. 22 for Study 3006.

In Study 3001, a higher proportion of subjects in the Placebo arm (75%) experienced treatment failure due to virological failure (viral load ≥400 copies/mL, switched therapy) and clinical events (confirmed CDC Class C event) than in the APV arm (15%). In Study 3006, a higher proportion of subjects in the APV arm (26%) experienced treatment failure due to virological failure (viral load ≥400 copies/mL, switched therapy) and clinical events (confirmed CDC Class C event) than in the IDV arm (20%).

Table 6 below summarizes the median change CD4+ cell count over the course of the study. Increases were seen in all treatment groups in both studies. In Study 3001, there was no apparent difference in the median changes in CD4+ cell count compared to baseline in both, the Amprenavir (APV+AZT+3TC) and Placebo (PLA+AZT+3TC) arm. However, in Study 3006, the median increases in CD4+ cell counts were notably larger after Week 2 in subjects randomized to IDV arm as compared to APV arm.

Table 6:

Summary of Median CD4+ Cell Count Changes from Baseline over Time ‡
(ITT Population)

	Study 3001				Study 3006			
	Treatment Group				Treatment Group			
	Amprenavir		Placebo		Amprenavir		Indinavir	
Treatment Week	n	Cells/mm^3	n	Cells/mm^3	n	Cells/mm^3	n	Cells/mm^3
Baseline Median	116	442	116	410	254	389	250	414
Week 1	106	+32	103	+28	170	+17	168	+15
Week 2	105	+27	102	+35	225	+9	225	+23
Week 4	104	+37	104	+56	218	+12	229	+27
Week 16	86	+52	93	+50	198	+27	206	+41
Week 24	78	+87	88	+63	193	+42	202	+83
Week 48	67	+128	71	+125	156	+97	181	+144
Week 64	34	+143	45	+139	45	+88	49	+141

n = Number of subjects remaining at each week.

+ sign in the table indicates median increase in CD4+ cell count compared to baseline.

‡ Analysis cut-off date for Study 3001 was November 25, 1998 and for Study 3006 was April 1, 1999.

Source: Table on p.60 of Study Report 3001 and Tables 10 and 42 of vol. 5.
Table on p.67 of Study Report 3006 and Tables 8 and 32 of vol. 22.

4. Subgroup Analyses

Subgroup analyses were conducted in both studies by race, gender and country in terms of descriptive statistics. No analyses were conducted for age, since the subjects in both studies were adults.

In both studies, the proportions of subjects with plasma HIV-1 RNA <400 copies/mL at Week 48, in both treatment groups were lower in black subjects compared to those of white subjects, and lower in female subjects compared with male subjects. No differences were seen between sites in Study 3001 and between countries in Study 3006.

D. Statistical Reviewer's Analyses

In both studies, PROAB3001 and PROAB3006, plasma HIV-1 RNA was measured by the *standard assay*, namely, Roche Amplicor HIV-1 Monitor Test (Primers 1.0, standard, LOD=400 copies/mL), at screening, pre-entry (pre-baseline), baseline (Day 1), Weeks 1, 2, 4, 8 and every 4 weeks thereafter. An *ultrasensitive assay* was also used in these studies in those subjects who were suppressed (viral load <400 copies/mL with standard assay) at Weeks 16, 32, 40, and 48.

The standard assay was used for the primary efficacy analysis and will be focus of this review. In addition, CD4 results will also be discussed. Since the ultrasensitive assay was not done on all subjects and not through out the course of the study, these results will not be reviewed.

1. Plasma HIV-1 RNA with Standard Assay

As mentioned before, the primary efficacy endpoint for both studies (3001 and 3006) was the durability of the antiviral response, defined as the *proportion of subjects with plasma HIV-1 RNA <400 copies/mL who did not progress to a CDC Class C event or death* in Study 3006 and in Study 3001 defined as the *time to loss of virologic response.*

The following algorithm defined by the FDA was used to determine the "success" status of subjects at any visit and to compute the time to event (i.e., loss-of-virologic response), because not all visits occur as scheduled and sometimes there are multiple evaluations for a given visit. The algorithm is given in the draft Guidance for Industry (Clinical considerations for Accelerated and Traditional Approval of Antiretroviral Drugs Using Plasma HIV RNA Measurements) dated August 1999.

According to this algorithm, if a subject is suppressed virologically without discontinuing therapy, then the subject is classified as a success regardless of whether a CDC Class C event occurred or not. In this algorithm failures are carried forward.

Time to Loss-of-Virologic-Response Algorithm (defined by FDA)

For NDAs with 48-week virologic data, one analysis computing time to virologic failure, is done using the following algorithm.

1. For 2 and 3 below, discard all visits with no data. In what follows, visit means visit with an observed viral load. All available visits, including off-schedule visits and post Week 48 visits, should be used for the calculation.
2. Subjects who never achieved confirmed HIV RNA levels below the assay limit (on two consecutive visits) before any of the following events will be considered to have failed at time 0.
   a) Death
   b) Discontinuation or switching of study medications. Temporary discontinuation or dose reduction of study medications may be ignored. Discontinuation or dose

reduction of background therapies in blinded studies can be ignored. The handling of other changes in background therapies should be pre-specified in the protocol and discussed with the division.

c) Last available visit

3. For all subjects who have confirmed HIV RNA levels below an assay limit, the time to failure is the earliest of the choices below, with modification specified in 4:
   a) Time of the event as described in 2b
   b) Time of loss to follow-up
   c) Time of confirmed levels above an assay limit. Confirmed is define as two consecutive levels greater than an assay limit or one visit greater than an assay limit followed by loss to follow-up.
   d) Time of death
4. If the time to virologic failure defined above is immediately preceded by a single missing scheduled visit or multiple consecutive missing scheduled visits, then the time of virologic failure is replaced by the time of the first such missing visit.

Based on the algorithm above, the Week 48 virological responses and status of subjects are summarized for both studies.

a. Study 3001

Table 7 shows the proportion of patients who were virologically suppressed (<400 copies/mL) through Week 48 in Study 3001. The proportions are identical to the Applicant's results.

Table 7:

Proportion of Patients with HIV-1 RNA <400 copies/mL at Week 48 †

	Study 3001	
	Treatment Group	
	APV+ZDV+3TC N=116	PLA+ZDV+3TC N=116
Number (%) of successes (plasma HIV-1 RNA <400 copies/mL)	48 (41%)	4 (3%)
p-value or treatment difference (95% CI)	<0.001‡	

Percentages calculated are based on the number of randomized subjects in each group.
† Scenario: Time to loss-of-virologic response-algorithm
‡ Results of permutation based log-rank test.

Failures were due to virologic failure (viral load ≥400 copies/mL), or due to discontinuation of randomized treatment. Table 8 shows the status of these subjects at Week 48 in Study 3001.

Table 8:

Efficacy Outcomes of Subjects Through Week 48
Study 3001

Outcome	AGENERASE (N=116)		Placebo (N=116)	
	n	%	n	%
HIV RNA <400 copies/mL	**48**	**(41%)**	**4**	**(3%)**
HIV RNA ≥400 copies/mL	**21**	**(18%)**	**92**	**(79%)**
Rebound	11	(9%)	31	(27%)
Switch	10	(9%)	61	(53%)
Discontinued due to adverse events	**18**	**(16%)**	**5**	**(4%)**
Discontinued due to other reasons	**25**	**(22%)**	**8**	**(7%)**
Consent withdrawn	8	(7%)	4	(3%)
Loss to follow	8	(7%)	2	(2%)
Protocol violation	1	(1%)	0	(0%)
Other	8	(7%)	2	(2%)
Never treated	4	(3%)	7	(6%)
Total	**116**	**(100%)**	**116**	**(100%)**

In Study 3001, majority of the failures (79%) in the Placebo arm (randomized to the dual therapy of ZDV+3TC) were due to virologic failure (viral load ≥400 copies/mL) which was either viral rebound (27%) or switches (53%). Recall, that in Protocol PROAB3001, subjects were blinded to therapy only until Week 16. At Week 16, the viral load of patients was tested and if they had two consecutive viral loads above 400 copies/mL, the patients were given a choice to switch to open-label Amprenavir or other therapies. All of patients (10 in APV arm and 61 in Placebo arm) who switched therapies were never suppressed at the time of switching therapy.

In the Amprenavir arm, failures were due to HIV RNA ≥400 copies/mL (18%) or adverse events (16%) or discontinuation due to other reasons (22%).

As confirmed in Figure 1 below, most of the patients randomized to the Placebo arm switched therapies after Week 16 . After Week 4, the proportion of patients suppressed on dual therapy (i.e., Placebo arm) continued to decline, whereas the rate of patients suppressed on the triple therapy (i.e., Amprenavir arm) declined slowly after Week 20. It appears that the treatment difference between Amprenavir and Placebo was maintained over time after Week 24. This is intuitive because most of the switches of therapy in the Placebo arm occurred between Week 16 and Week 24.

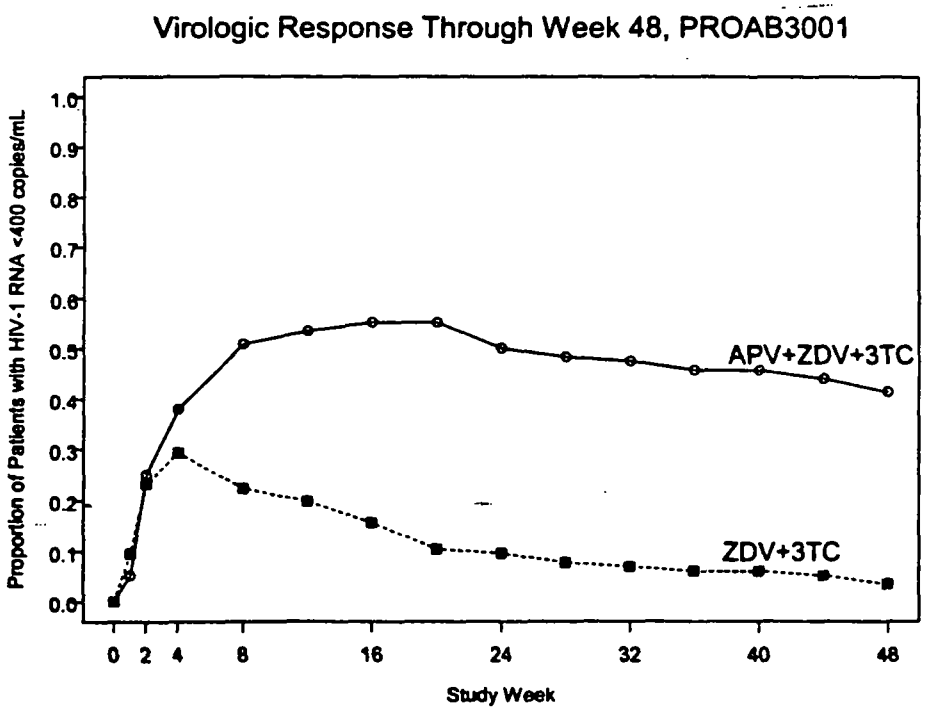

Figure 1: Proportion of Patients with HIV-1 RNA <400 copies/mL Through Week 48 (Protocol PROAB3001)

b. Study 3006

Table 9 shows the proportion of patients who were virologically suppressed (<400 copies/mL) through Week 48 in Study 3006.

Table 9:

Proportion of Patients with HIV-1 RNA <400 copies/mL at Week 48†
Study 3006

	Treatment Group	
	APV+NRTI therapy N=254	IDV+NRTI therapy N=250
Number (%) of successes (plasma HIV-1 RNA <400 copies/mL)	76 (30%)	122 (49%)
p-value	0.001 ‡*	
Treatment difference (95% CI)	-19% (-27%, -10%) §	

Percentages calculated are based on the number of randomized subjects in each group.
† Scenario: Time to loss-of-virologic response-algorithm
‡ Results of stratified Cochran Mantel-Haenszel test.
§ Adjusted for randomization strata and based on Mantel-Haenszel weights
* P-value=0.001 is statistically significant at 0.05 level.

Table 10 shows the status of subjects at Week 48 in Study 3006.

Table 10:

Efficacy Outcomes of Subjects Through Week 48
Study 3006

Outcome	AGENERASE (N=254)		Indinavir (N=250)	
	n	%	n	%
HIV RNA <400 copies/mL	**76**	**(30%)**	**122**	**(49%)**
HIV RNA ≥400 copies/mL	**96**	**(38%)**	**64**	**(26%)**
Rebound	64	(25%)	48	(19%)
Never suppressed	11	(4%)	4	(2%)
Switch	21	(8%)	12	(5%)
Discontinued due to adverse events	**41**	**(16%)**	**31**	**(12%)**
Discontinued due to other reasons	**41**	**(16%)**	**33**	**(13%)**
Consent withdrawn	8	(3%)	6	(2%)
Loss to follow	15	(6%)	9	(4%)
Protocol violation	1	(<1%)	0	(0%)
Pregnancy	1	(<1%)	3	(1%)
Non-compliance	4	(2%)	4	(2%)
Other	3	(1%)	2	(1%)
Never treated	9	(4%)	9	(4%)
Total	**254**	**(100%)**	**250**	**(100%)**

In the Amprenavir arm, the virologic failure rate (proportion with viral load ≥400 copies/mL) was 12% higher than that in the Indinavir arm (38% APV vs 26% IDV). Amprenavir was also worse than Indinavir with respect to the proportion of patients who remained suppressed through Week 48, i.e., proportion of patients with HIV-1 RNA <400 copies/mL (30% APV vs 49% IDV; treatment difference = -19%). The rates of discontinuations due to adverse events (16% APV vs 12% IDV) and other reasons (16% APV vs 13% IDV) were generally similar in both arms.

Figure 2 shows a graphical comparison of the primary efficacy measure—proportion of patients with HIV-1 RNA <400 copies/mL—between subjects randomized to receive APV+NRTI therapy versus IDV+NRTI therapy through Week 72.

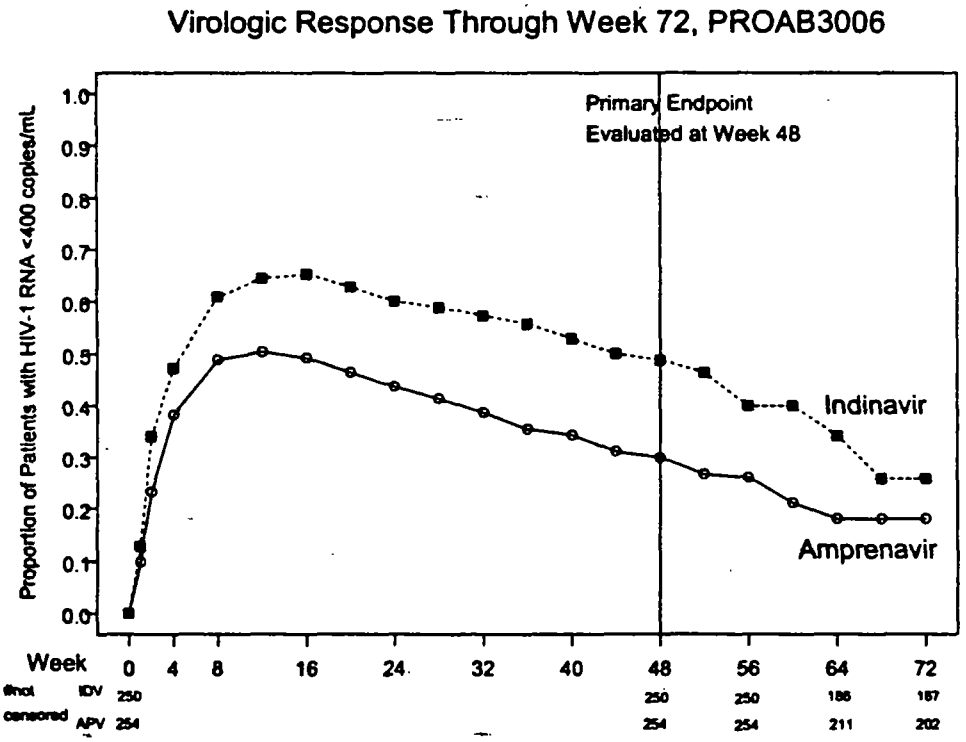

Figure 2: Proportion of Patients with HIV-1 RNA <400 copies/mL Through Week 72 (Protocol PROAB3006)

The Amprenavir arm reached its peak response rate sooner than the Indinavir arm (APV at Week 12 vs IDV at Week 16). The proportion of patients suppressed on Indinavir were higher than those on Amprenavir. After Week 16 through Week 48, the treatment difference between Amprenavir and Indinavir was maintained. The primary endpoint was

to be evaluated at Week 48, but the study continued until the last patient enrolled had completed 48 weeks of therapy, due to which some patients had data beyond Week 48. Data was available through Week 72 (data cut off at April 1, 1999), but the number of subjects that were not censored after Week 48 (i.e., had failed or were followed after Week 48) decreased.

2. CD4+ Cell Count

The median C4+ cell count changes from baseline were summarized for both studies in Table 6. These are also plotted in Figure 4 for Study 3001 and Figure 4 for Study 3006. The number of subjects with evaluations at each time point are also plotted at the bottom of the graph. In both graphs, the solid line with circles represents the Amprenavir arm while the dashed line with squares represents the control arm.

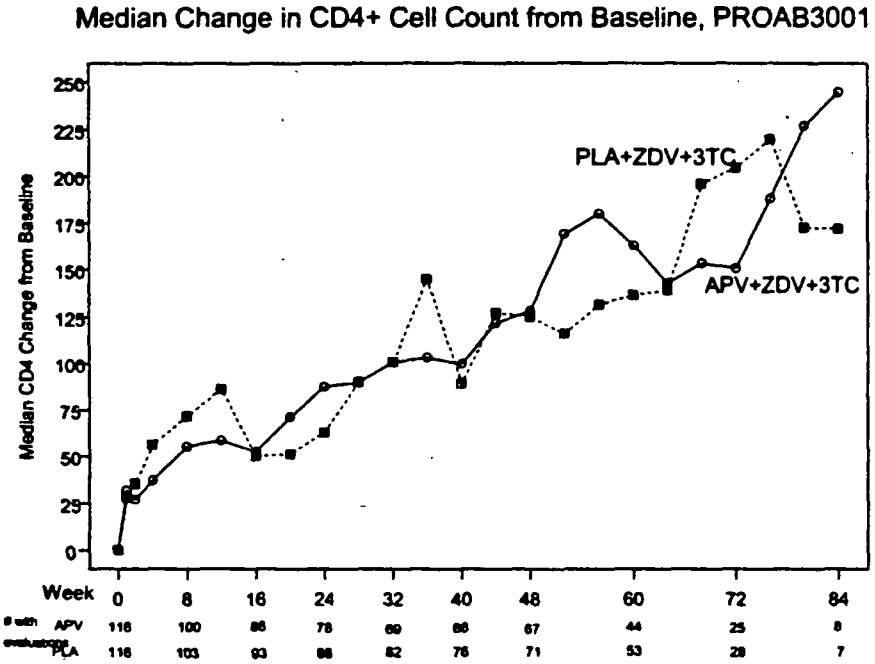

Figure 3: Median CD4+ Cell Count Change from Baseline —All Data Through Nov 25, 1998

In Study 3001, recall that subjects in the placebo arm were allowed to switch from placebo to open-label APV containing regimen or other protease-inhibitor containing regimens. CD4+ cell count increases were seen in both arms over time.

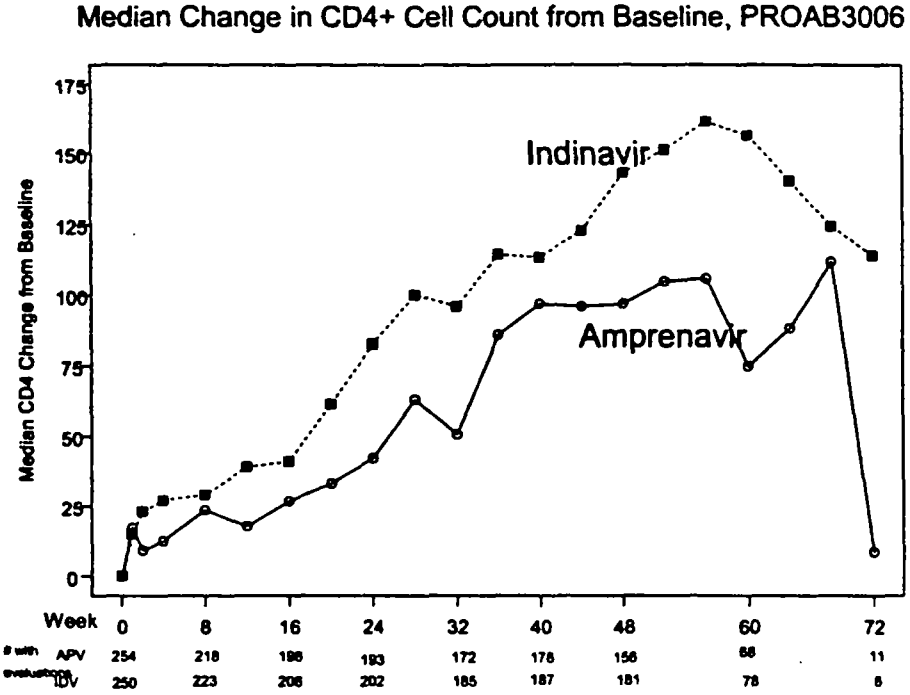

Figure 4: Median CD4+ Cell Count Change from Baseline —All Data Through April 1, 1999

In Study 3006, CD4+ cell count increases from baseline were consistently higher in the Indinavir arm as compared to the Amprenavir arm throughout the course of the study.

3. Subgroup Analyses

a. Randomization Strata

For Study 3001, the randomization was stratified by the screening viral load. The response rates were calculated using the FDA-defined Time to Loss-of-Virologic Response and are summarized below in Table 11.

Table 11:
Proportion of Patients with HIV-1 RNA <400 copies/mL Through Week 48, PROAB3001 by Randomization Strata

	≥10,00-30,000 (N=37/arm)	>30,000-100,00 (N=55/arm)	>100,000 (N=24/arm)
APV+ZDV+3TC	54%	40%	25%
PLA+ZDV+3TC	8%	2%	0%

Subjects with low screening viral load were more likely to be virologically suppressed through Week 48 than those with high screening viral load in both treatment groups. The treatment difference is also larger with lower viral load. This could be due to the fact that the response rate in the Placebo arm is low even for the stratum with the lowest screening viral load.

For Study 3006, the randomization strata were screening viral load and whether the subject planned to change at least one NRTI at entry.

Table 12:

Proportion of Patients with HIV-1 RNA <400 copies/mL Through Week 48 by Randomization Strata, PROAB3006

	≥400-10,000 copies/mL		>10,000-100,000 copies/mL		>100,000 copies/mL	
APV	56/140	(40%)	17/94	(18%)	4/20	(20%)
IDV	77/137	(56%)	41/93	(44%)	4/20	(20%)
Treatment difference (APV–IDV)	-16%		-26%		0%	
95% confidence interval †	(-28%, -5%)		(-39%, -13%)		(-25%, 25%)	

	Planned Change in NRTI		No Planned Change in NRTI	
APV	62/207	(30%)	15/47	(32%)
IDV	98/203	(48%)	24/47	(51%)
Treatment difference (APV–IDV)	-18%		-19%	
95% confidence interval †	(-28%, -9%)		(-39%, 0%)	

† CI calculated using Bristol method (Ref: Clinical Equivalence: Issues in Closeness, 1996)

The largest treatment difference (in terms of responders) between Amprenavir and Indinavir was seen in patients with viral load between 10,000 and 100,000 copies/mL. Amprenavir could be as much as 39% worse than Indinavir in this group of patients (see Table 12). In patients with very high viral load (>100,000 copies/mL), the total number of patients in both arms was small (20/arm) to be able to detect any difference between APV and IDV. We also note that there is substantial overlap in the three confidence intervals related to baseline viral load, indicating that the seemingly different treatment effect in the three viral load strata could occur by chance alone.

With respect to the second strata of whether or not subject planned to change NRTI at entry, the Amprenavir arm remained inferior to the Indinavir arm.

b. Gender, Age, Ethnic Origin

As shown in Table 13, females generally had lower response rates in both studies than males. Note that in both studies, however, the number of females enrolled was much less than the number of males (11% in Study 3001 and 20% in Study 3006). The response rates in the IDV arm were higher than those for APV in both males and females.

Table 13:

Proportion of Patients with HIV-1 RNA <400 copies/mL at Week 48 by Gender †

	Study 3001		Study 3006	
	APV	PLA	APV	IDV
	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Male	48/103 (47)	4/103 (4)	65/206 (32)	99/196 (51)
Female	0/13 (0)	0/13 (0)	11/48 (23)	16/54 (30)

† Based on time to loss of virologic response algorithm.

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

Finally, subgroup analyses by age are shown graphically for the placebo-control study, Study 3001, in Figure 5 and for the active-control study, Study 3006, in Figure 6. Recall that the median age of patients in Study 3001 was 35 years and in Study 3006 was 37 years (see Table 2). In Figure 5 and Figure 6, the response rates are shown for two age groups (<=35 years and >35 years).

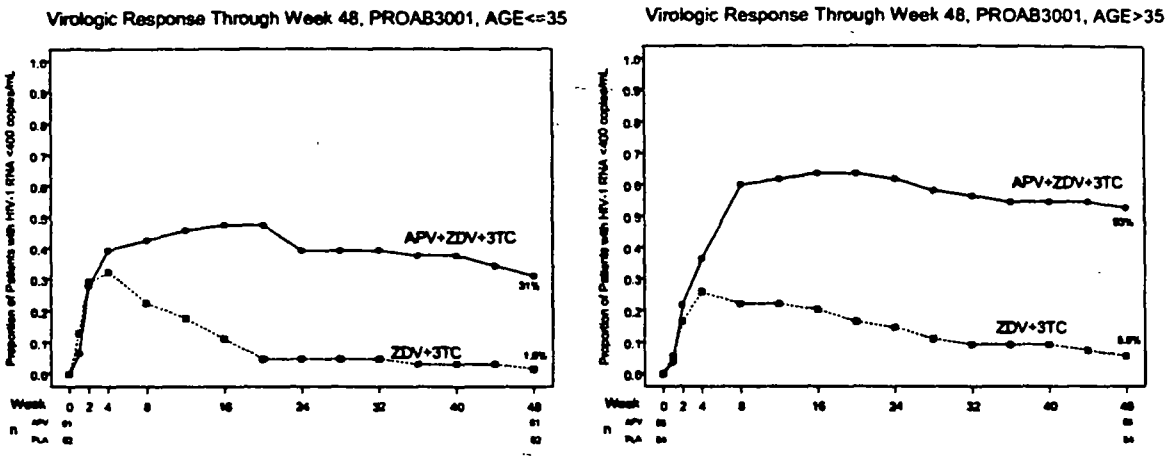

Figure 5: Proportion of Patients with HIV-1 RNA <400 copies/mL Through Week 48 by Age (Protocol PROAB3001)

The treatment difference between the APV group (i.e., APV+ZDV+3TC) and Placebo group (i.e., ZDV+3TC) was smaller for age ≤35 years (treatment difference = 29.4% [31%, APV vs 1.6%, PLA]) than that for age >35 years (treatment difference = 47.5% [53%, APV vs 5.5%, PLA]).

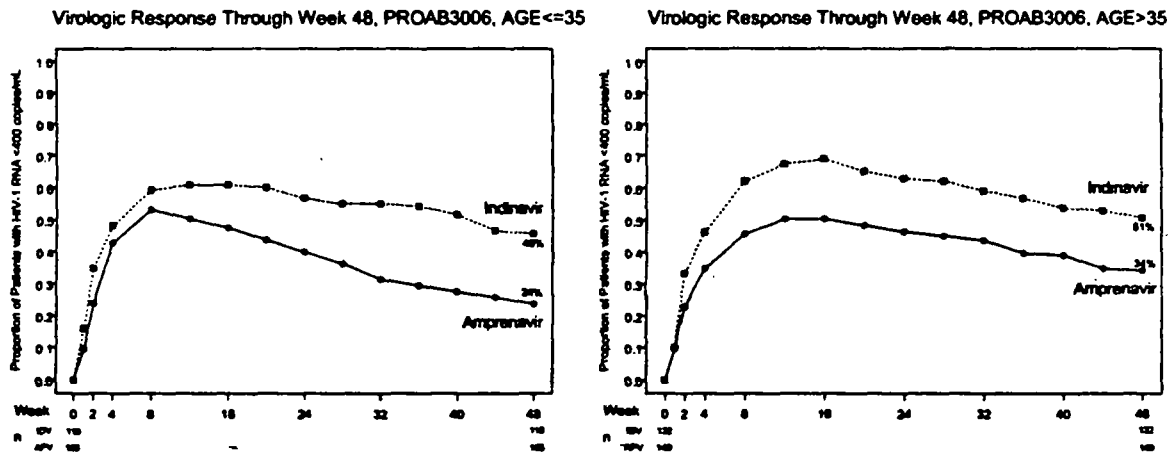

Figure 6: Proportion of Patients with HIV-1 RNA <400 copies/mL Through Week 48 by Age (Protocol PROAB3006)

The treatment difference between APV and IDV was similar in both age groups (treatment difference = -22% [24%, APV vs 46%, IDV] for age <=35 years and treatment difference = -17% [34%, APV vs 51%, IDV] for age >35 years).

E. Statistical Reviewer's Summary

Based on all the available data (through Week 48 and beyond) in Studies PROAB3001 (placebo-controlled) and PROAB3006 (active-controlled) we conclude the following.

1. Study PROAB3001 demonstrated that a higher proportion of patients treated with the triple combination therapy of Amprenavir+ZDV+3TC remained on the randomized treatment and maintained their viral load <400 plasma HIV-1 RNA copies/mL through 48 weeks than patients treated with the dual combination of ZDV+3TC. Changes in CD4+ cell counts were similar for the two groups.
2. Study PROAB3006 demonstrated that the proportion of patients treated with Amprenavir+NRTI therapy who remained on the randomized treatment and maintained their viral load below 400 plasma HIV-1 RNA copies/mL was statistically significantly lower than those treated with Indinavir+NRTI therapy. Therefore, Amprenavir (APV) is inferior to Indinavir (IDV). The observed treatment difference was –19% (APV – IDV) in favor of Indinavir. Based on the 95% confidence interval, the actual treatment difference was at least -10% in favor of Indinavir, and this difference could be as high as –27%.
3. In Study PROAB3006, the median CD4+ cell count changes from baseline were significantly in favor of Indinavir through the entire course of the study.
4. In Study PROAB3006, the proportion of discontinuations by Week 48 (due to adverse events or other reasons) were generally similar between APV and IDV groups, but the APV group had a higher proportion of virologic failures due to viral rebound, switching of therapy and patients never being suppressed.

/S/

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