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RESEARCH**

APPLICATION NUMBER:

21-226/S-003

21-251/S-004

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

Medical Division: Division of Antiviral Drug Products (HFD-530)

Biometrics Division: Division of Biometrics III (HFD-725)

NEW DRUG APPLICATION (NDA), SERIAL NUMBER:	21-226, SE8-003 and 21-251, SE8-004
NAME OF DRUG:	KALETRA™ (lopinavir 133.3mg/ritonavir 33.3 mg) capsules KALETRA™ (lopinavir 80/ritonavir 20 mg/mL) oral solution
DOSE	KALETRA™ 400/100 mg BID (adults) KALETRA™ 300/75 mg/m ² BID (pediatric)
INDICATION(S):	Treatment of HIV Infection
APPLICANT:	Abbott Laboratories
DOCUMENTS REVIEWED:	Submissions dated March 19, 2001 and July 12, 2001
STATISTICAL REVIEWER:	Rafia Bhore, Ph.D. (HFD-725)
STATISTICAL TEAM LEADER:	Greg Soon, Ph.D. (HFD-725)
BIOMETRICS DIVISION DIRECTOR:	Mohammad Huque, Ph.D. (HFD-725)
CLINICAL REVIEWERS:	Kimberly Struble, PharmD. (HFD-530) Linda Lewis, M.D. (HFD-530)
PROJECT MANAGER:	Sean Belouin, R.Ph. (HFD-530)

EXECUTIVE SUMMARY

KALETRA™ (lopinavir/ritonavir) is a co-formulation of two Protease Inhibitors—lopinavir (LPV) and ritonavir (RTV)—and is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients age six months and older.

KALETRA™ was granted accelerated approval by the FDA on September 15, 2000. KALETRA™ (lopinavir/ritonavir) is available as 133.3/33.3 mg oral soft gel capsules and as 80/20 mg/mL oral solution. The currently approved adult dose for KALETRA is 400/100 mg BID and for pediatric patients, the finally chosen dose is KALETRA 300/75 mg/m² BID, based on Study 940 contained one of the two NDAs being reviewed here.

The submission, NDA 21-226, SE8-003, is an efficacy labeling supplement consisting of 48-week clinical data on a Phase III study, M98-863, and a Phase II study, M98-957. The submission, NDA 21-251, SE8-004, is a labeling supplement consisting of 48-week clinical data on a Pediatric study, M98-940. Since it is the Division's (Division of Antiviral Drug Products / FDA) intent to combine the label updates for adults and pediatrics into a single label, the two submissions are being reviewed together.

The focus of this statistical review was the 48-week efficacy data for the adult Phase III study, M98-863, and 48-week efficacy data for the pediatric study, M98-940.

Based on all the available data through Week 48 in Studies 863 and 940 we conclude the following.

1. Study 863 demonstrated that a statistically significantly higher proportion of patients treated in the KALETRA+d4T+3TC arm (75%) maintained their viral load <400 copies/mL through Week 48 as compared to those patients treated with nelfinavir+d4T+3TC (62%). Also, there were significantly lower virologic failures (≥ 400 copies/mL) in the KALETRA arm through Week 48 as compared to the nelfinavir arm. Mean changes from baseline in CD4+ cell count were similar in both treatment groups.
2. In Study 863, the treatment effect size for the proportion of patients maintaining viral load <400 copies/mL through Week 48 and with viral load <50 copies/mL at Week 48 increases with baseline HIV-1 RNA levels. The superiority of KALETRA over nelfinavir was mainly seen in patients with baseline viral load $\geq 30,000$ copies/mL. Below this threshold of baseline viral load, KALETRA was similar to nelfinavir.
3. In Study 863, the treatment effect size for the proportion of patients maintaining viral load <400 copies/mL through Week 48 decreases with baseline CD4 counts. After adjusting for the baseline viral load, the treatment effect sizes were similar across baseline CD4+ cell counts, suggesting that baseline CD4 did not modify the treatment effects after taking baseline HIV-1 RNA into consideration.

4. Additionally, in Study 863, the superiority of KALETRA over nelfinavir was seen in subgroups of male and female patients as well as in younger (≤ 35 years age) and older (≥ 35 years age) patients. This superiority was also seen in Caucasian patients (some of whom were Hispanics). However, in Black patients, the proportion of responders were similar in both, KALETRA and nelfinavir arms.
5. In Study 940, there was a numerically higher, but statistically not superior response in the antiretroviral naïve patients compared to the experienced patients with respect to the proportion of patients who maintained their viral load < 400 copies/mL through Week 48. There were statistically significant increases from baseline in CD4+ cell counts at each study visit for all pediatric patients.

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STATISTICAL REVIEW AND EVALUATION

1. Introduction and Background

KALETRA™ (lopinavir/ritonavir) is a co-formulation of two Protease Inhibitors, lopinavir (LPV) and ritonavir (RTV) and is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients age six months and older.

KALETRA™ was granted accelerated approval by the FDA on September 15, 2000. KALETRA™ (lopinavir/ritonavir) is available as 133.3/33.3 mg oral soft gel capsules and as 80/20 mg/mL oral solution. The currently approved adult dose for KALETRA is 400/100 mg BID and for pediatric patients the finally chosen dose is KALETRA 300/75 mg/m² BID.

The submission, NDA 21-226, SE8-003, is an efficacy labeling supplement consisting of 48-week clinical data on a Phase III study, M98-863, and a Phase II study, M98-957. The submission, NDA 21-251, SE8-004, is a labeling supplement consisting of 48-week clinical data on a Pediatric study, M98-940. Since it is the Division's (Division of Antiviral Drug Products / FDA) intent to combine the label updates for adults and pediatrics into a single label, the two submissions are being reviewed together.

The focus of this statistical review will be the 48-week efficacy data for the adult Phase III study, M98-863, and for the pediatric study, M98-940.

2. Study Designs and Data Analyzed

2.1 Study M98-863 — 48-Week Data (Phase III Study in Antiretroviral-Naïve Patients)

Title: "A Randomized, Double-Blind, Phase III study of ABT-378/Ritonavir Plus Stavudine and Lamivudine vs. Nelfinavir Plus Stavudine and Lamivudine in Antiretroviral-Naïve HIV-Infected Subjects".

The summary is based on the revised protocol incorporating Administrative Letters No. 1, 2, 3.1 and Amendment No. 1. The revision date is November 4, 1999.

The planned sample size was 660 patients. Patients were to be centrally randomized 1:1 into two treatment groups:

- A. KALETRA 400/100 mg BID + nelfinavir Placebo TID + Stavudine 30mg or 40 mg (based on weight) BID + Lamivudine 150 mg BID
- B. KALETRA Placebo + nelfinavir 750 mg TID + Stavudine BID 30mg or 40

mg (based on weight) + Lamivudine 150 mg BID

The CD4 cell counts and viral loads were to be assessed at Week 4, 8, 12, 16, 24, 32, 40, 48 and every 12 weeks thereafter until the end of the study.

Key inclusion/exclusion criteria:

1. HIV RNA level > 400 copies/mL by the Roche Amplicor Assay,
2. >12 years old,
3. Never taken stavudine and lamivudine. No more than 14 days on any other antiretroviral therapy.

The primary outcome measure was the proportion of subjects with plasma HIV-1 RNA level below 400 copies/mL using the Roche Amplicor Assay at Week 24, and time until loss of virologic response through Week 48. Proportion below 50 copies/mL using the Roche Ultrasensitive Assay was one of the secondary endpoint.

Comparison of the proportions was to be conducted by the Pearson Chi-square test, and the 95% confidence interval for the difference of proportions was to be calculated by normal approximation. Comparison of the time to loss of virologic response and the calculation of the 95% confidence interval for the hazard ratio was to be by Cox proportional hazard model. At Week 24, if the Kaletra arm was no more than 10% worse than the Nelfinavir arm, then the two treatments was to be regarded as equivalent. Further, if the difference in proportions was statistically significant at level 0.05, then Kaletra arm was to be considered superior. The decision rule was not specified at Week 48.

All randomized subjects with at least one post-baseline measurement were to be used for the primary analysis.

2.2 Study M98-940 — 48-Week Data (Pediatric Study)

Title: "An Open-Label Phase I/II Study of ABT-378/Ritonavir in Combination with Reverse Transcriptase Inhibitors in HIV-Infected Children".

Objective: To determine an adult equivalent dose of KALETRA in HIV-infected children based on the pharmacokinetics and tolerability of KALETRA in combination with reverse transcriptase inhibitors (RTIs or nucleoside analogs), and to assess the safety and antiviral activity of KALETRA in combination with nucleoside analogs.

Note that KALETRA (lopinavir/ritonavir) is also referred to as ABT-378/ritonavir.

The summary is based on the revised protocol incorporating Administrative Letters No. 1, 2, and 3, and Amendment No. 1, 2 and 3. The revision date of the

protocol is May 16, 2000.

The planned sample size of Protocol 940 was 100 patients. Patients were to be stratified according to the following factors prior to randomization:

- age at enrollment (i.e., 3 months to 2 years and 2 years to 12 years) and
- prior antiretroviral experience (i.e., naïve or treatment-experienced).

Then patients were to be equally randomized (1:1) into one of the two *open-label* arms:

Group 1: ABT-378/ritonavir at a dose of 230/57.5 mg/m² Q12H (n=50)

Group 2: ABT-378/ritonavir at a dose of 300/75 mg/m² Q12H (n=50)

Reverse transcriptase inhibitor therapy will be initiated at the same time as ABT-378/ritonavir. Patients would continue to receive ABT-378/ritonavir until it becomes commercially available or clinical development is discontinued.

Note: The first pediatric dose of 230/57.5 mg/m² Q12H was chosen because it is an estimate of the adult equivalent pediatric dosage based on body surface area conversion (assuming an average adult body surface area of 1.73 m²). The second pediatric dose of 300/75 mg/m² was also chosen which is a 30% increase over the body surface area based on adult equivalent dose. The adult dose of KALETRA is 400mg/100mg BID.

Following the completion of study enrollment and an analysis of safety/tolerability, efficacy, and pharmacokinetic data through Day 22 (Week 3), all patients will be switched to either 230/57.5 mg/m² or 300/75 mg/m². The dose selection will be one that meets all of the following criteria:

- a) <20% of patients experience a Grade 3 or higher adverse event or laboratory abnormality;
- b) >75% of patients experience at least a 0.5 log reduction in viral load in the first three weeks of dosing; and
- c) the central values for AUC and C_{min} are within 80% and 130% of the average adult exposure.

Note: Following Administrative Letter No. 2, dated November 15, 1999, the dosing of KALETRA was changed from Q12H (every 12 hours) to BID (twice daily) dosing throughout the study. Also, based on the pharmacokinetics, safety/tolerability and efficacy data, KALETRA 300/75 mg/m² was chosen as the final dose to which patients were switched after Day 22 (Week 3).

Key inclusion/exclusion criteria:

- 1) Age between 3 months and 12 years (inclusive).

- 2) HIV RNA >400 copies/mL by Roche Amplicor assay.
- 3) Must be NNRTI-naïve.

The CD4 and viral loads were to be assessed at Screening, Day 1, Week 3, 8, 12, 16, 20, 24, 32, 40 and 48, and every 12 weeks thereafter until the end of study or discontinuation.

The efficacy will be characterized for all patients enrolled in this study and have at least one post-baseline measurement for a given efficacy parameter. All efficacy variables will be summarized after combining data from both randomized groups and regardless of their age at enrollment.

Mean change from baseline in viral load and CD4/CD8 cell counts will be summarized at each study visit for all patients. Patients will be then stratified according to age at enrollment (3 months to 2 years, and 2 to 12 years) and potential age differences will be assessed using one-way ANOVA with age as the only effect. The time-normalized area under the curve minus baseline (AUCMB) will also be computed through Weeks 16, 24, and 48 for viral load and CD4/CD8 cell counts. The proportion of patients with viral load <400 copies/mL will be summarized for each study visit for all patients regardless of their age at enrollment. Then patients will be stratified according to their age (3 months to 2 years, and 2 to 12 years) and potential age differences will be assessed using Fisher's exact test. The duration of virologic response will be characterized through Weeks 24 and 48 for all patients regardless of their age at enrollment and will be summarized over time using a Kaplan-Meier procedure.

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3. Applicant's Results and Conclusions

3.1 Demographics and Baseline Characteristics

Study 863 was a Phase III study in antiretroviral naïve adult patients (n=653, ITT population) whereas Study 940 was a Pediatric study in antiretroviral naïve and experienced children (n=100, ITT population). Table 1 shows the demographics and baseline characteristics of patients in the two studies.

In Study 863 the age of the patients ranged from 19 years to 84 years with the mean age being 38 years and the majority of the patients being male (80%) and Caucasian (69%). The mean baseline viral load of patients in Study 863 was 4.9 HIV RNA log₁₀ copies/mL (approximately 80,000 copies/mL) and the mean baseline CD4+ cell count was 259 cells/mm³.

In Study 940, the age of the pediatric patients ranged from 0.5 years to 12.6 years. There were 14 patients under 2 years of age and 86 patients ≥2 years old. The number of antiretroviral naïve (n=44) and experienced (n=56) were almost equal. The number of male (n=43) and female (n=57) patients were also similar. Majority of the pediatric patients (57%) were of Black origin and majority of the pediatric patients had acquired HIV through vertical transmission. The mean baseline viral load of patients in Study 940 was 4.7 HIV RNA log₁₀ copies/mL (approximately 50,000 copies/mL) and their mean baseline CD4+ cell count was 1226 cells/mm³.

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Table 1: Demographics and Baseline Characteristics by Study (Intent-to-Treat Population)

Characteristic		Study	
		863 N=653	940 N=100
Age (Years)	Mean	37.8	5.25
	Range	19 to 84	0.5 to 12.6
Age Subgroups (Years)	<2 years		14%
	≥2 years		86%
Antiretroviral Experience Groups	Naïve	100%	44%
	Experienced		56%
Weight (kg)	Mean	73.9	18
Gender	Male	80%	43%
	Female	20%	57%
Race	Caucasian	69%	14%
	Hispanic ¹	13%	29%
	Black	26%	57%
	Asian/Pacific Islander	3%	
	Native American/Alaskan Native	1%	
	Mixed Race / Other	1%	
Route of HIV Transmission²	Homosexual/Bisexual contact	56%	
	Heterosexual contact	33%	
	Injectable drug use	8%	
	Hemophilia-associated injections	<1%	
	Vertical Transmission		96%
	Transfusion	2%	1%
	Unknown/Other	18%	3%
Baseline HIV RNA(log₁₀ copies/mL)	Mean (Range)	4.9	4.7
Baseline plasma HIV-1 RNA	_____	12%	
	_____	25%	
	_____	15%	
	_____	24%	
	_____	13%	
	_____	12%	
Baseline CD4+ (cells/mm³)	Mean	259	838
Baseline CD4+ cell count	<50 cells/mm ³	19%	
	≥50–200 cells/mm ³	26%	
	≥200–350 cells/mm ³	26%	
	≥350 cells/mm ³	30%	

¹ In Study 863, 13% of the 69% Caucasians were also Hispanics, while in Study 940 Caucasian and Hispanic were separate categories of race.

² Percentages for route of HIV transmission may not add to 100%, because patient could have acquired HIV through more than one way.

Source: Table 14.1_4.1, 14.1_8.1, and 14.1_9.1 of Protocol 863 Clinical Study Report.
 Tables 14.1_4.1, 14.1_4.2, 14.1_8.1, 14.1_9.1.1, 14.1_9.1.2, 14.1_9.1.3 of Protocol 940 Study Report.

4. Statistical Reviewer's Findings

In both studies, Protocol 863 and 940, plasma HIV-1 RNA was measured by the *standard assay*, namely, the Roche Amplicor HIV-1 Monitor Test (Standard, LOD=400 copies/mL) at screening, pre-baseline, baseline (Day 1), Weeks 4, 8, 12, 16, 20, 24 and every 8 weeks thereafter. After Week 24, the Roche Ultrasensitive assay (Ultrasensitive, LOD=50 copies/mL) was also used for those patients who were suppressed (viral load <400 copies/mL using the standard assay).

The standard assay will be used for the primary efficacy analysis and will be the focus of this review. The results of the ultrasensitive assay at Week 48 (a snapshot) will also be presented. In addition, CD4 results will also be discussed.

Subgroup efficacy analyses based on the baseline characteristics—such as baseline viral load and baseline CD4—and the demographics, such as age, gender and race are also discussed.

4.1 Plasma HIV-1 RNA with Standard Assay (LOD=400 copies/mL) and Ultrasensitive Assay (LOD=50 copies/mL)

The primary efficacy endpoint for Study 863 and Study 940 for the 48-week data was the durability of the antiviral response, defined as the *time to loss of virologic response* through Week 48.

Although the applicant had proposed an algorithm for computing the *time to loss of virologic response* through Week 48 in the protocol, the following algorithm as defined by the Division of Antiviral Drug Products (DAVDP)/FDA, was used to perform the final efficacy analyses and present the results in the KALETRA label. This algorithm has been used to determine the “success” status of patients 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 FDA algorithm will appear in the updated version of 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 patient is suppressed virologically without discontinuing therapy, then the patient 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 DAVDP/FDA)

For NDAs with 48 week virologic data, one analysis for computing time to virologic failure may be assessed using the following algorithm.

1. 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. Data should not be interpolated for visits or time points with missing data.
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.

For open-label studies, algorithms that incorporate other ways of handling missing data or treatment discontinuations may be used for additional sensitivity analyses. For example, sponsors should perform analyses that treat nonprotocol-specified treatment discontinuations as failures in the study arm and as censored at the time of discontinuation in the control arm and as exploring sensitivity of the results to potential biases related to an open-label design.

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

a. Study 863

Table 2 shows the proportion of patients who were virologically suppressed (<400 copies/mL) through Week 48 in Study 863.

Table 2:
 Proportion of Patients with HIV-1 RNA <400 copies/mL through Week 48
 (Study 863)†

	Study 863	
	Treatment Group	
	KALETRA+d4T+3TC N=326	nelfinavir+d4T+3TC N=327
Number (%) of successes (plasma HIV-1 RNA <400 copies/mL)	246 (75%)	204 (62%)
p-value or treatment difference (95% CI)	<0.001‡ 13% (6%, 20%)	
Percentages calculated are based on the number of randomized subjects in each group. Results are based on the Standard Assay.		
† Scenario: Time to loss-of-virologic response-algorithm.		
‡ P-value comparing treatment groups is based on Pearson's chi-square test.		

Source: FDA Statistical Reviewer's analysis

Failures were due to virologic failure (viral load ≥400 copies/mL) or due to discontinuation of randomized treatment. Table 3 shows the status of these subjects at Week 48 in Study 863.

Table 3: Efficacy Outcomes of Randomized Treatment Through Week 48 (Study 863)

Outcome	KALETRA+d4T+3TC (N=326)	Nelfinavir+d4T+3TC (N=327)
	n (%)	n (%)
Responder¹	246 (75%)	204 (62%)
Virologic Failure²	28 (9%)	81 (25%)
Rebound	22 (7%)	50 (15%)
Never suppressed through Week 48	6 (2%)	31 (9%)
Death	5 (2%)	2 (1%)
Discontinued due to adverse events	14 (4%)	13 (4%)
Discontinued due to other reasons³	33 (10%)	27 (8%)
Consent withdrawn (Personal reasons)	7 (2%)	6 (2%)
Loss to follow	12 (4%)	15 (5%)
Non-compliance	8 (2%)	5 (2%)
Protocol violation (Required prohibited medication)	1 (<1%)	0 (0%)
Other	5 (2%)	1 (<1%)
Total	326 (100%)	327 (100%)

* Corresponds to rates at Week 48 in Source: FDA Statistical Reviewer's analysis.
Figure 1.
 1 Patients achieved and maintained confirmed HIV RNA <400 copies/mL through Week 48.
 2 Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Week 48.
 3 Includes loss to follow-up, patient's withdrawal, non-compliance, protocol violation and other reasons.

Source: FDA Statistical Reviewer's analysis.

In Study 863, the proportion of patients with HIV-1 RNA <400 copies/mL in the KALETRA arm (75%) was statistically significantly higher than that in the nelfinavir arm (62%). Also, the proportion of patients with HIV-1 RNA ≥400 copies/mL in the KALETRA arm (9%) was significantly lower than that in the nelfinavir arm (25%). The remaining failures were due to discontinuations of randomized treatment and death. The discontinuations were similar in both treatment arms. The efficacy outcome was attributed to death in 7 patients (5 in KALETRA arm and 2 in nelfinavir arm). Additionally, one patient died in the KALETRA arm who had a virologic rebound first. The efficacy outcome of this patient was attributed to rebound. per the *time to loss-of-virologic response* algorithm.

Table 4 shows the proportion of patients with HIV-1 RNA <50 copies/mL at Week 48. These results are a snapshot at Week 48, since the Ultrasensitive Assay was used only after Week 24 when patients had a viral load <400 copies/mL with the Standard Assay. Therefore the time to loss-of-virologic response algorithm could not be used.

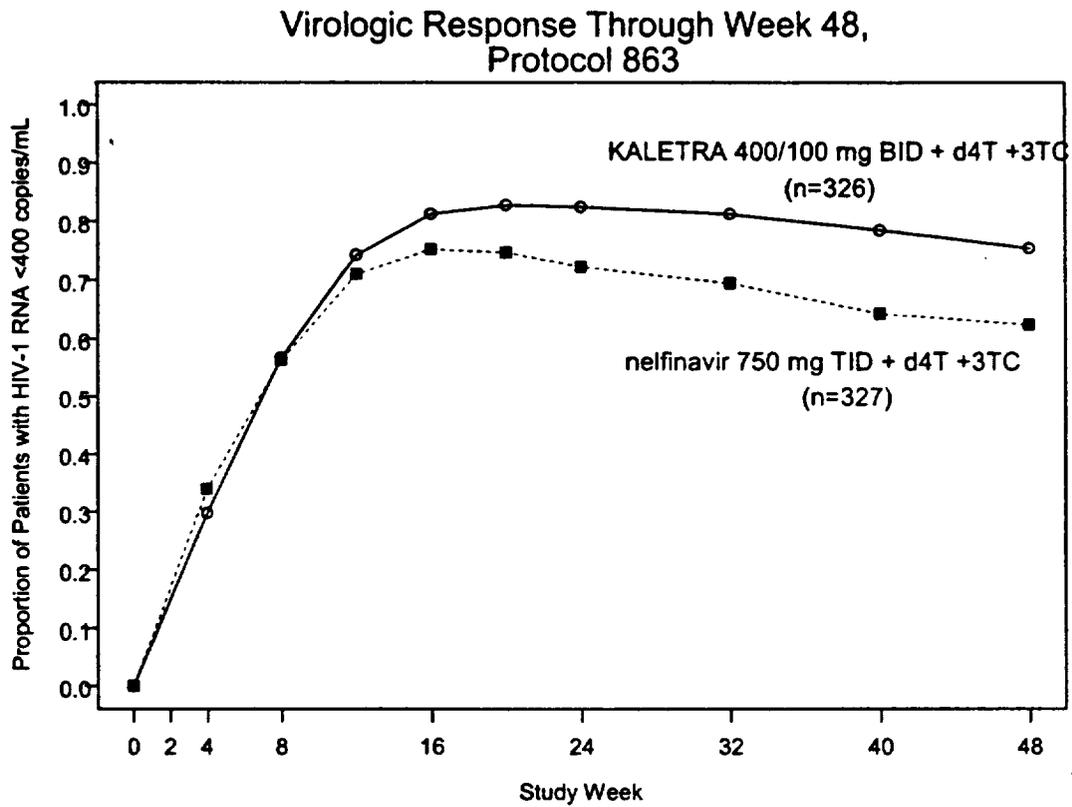
Table 4:
 Proportion of Patients with HIV-1 RNA <50 copies/mL at Week 48
 (Study 863)†

	Study 863	
	Treatment Group	
	KALETRA+d4T+3TC N=326	nelfinavir+d4T+3TC N=327
Number (%) of successes (plasma HIV-1 RNA <400 copies/mL)	218 (67%)	169 (52%)
p-value or treatment difference (95% CI)	<0.001‡ 15% (8%, 23%)	
Percentages calculated are based on the number of randomized subjects in each group. Results are based on the Ultrasensitive Assay. † Scenario: Snapshot at Week 48. ‡ P-value comparing treatment groups is based on Pearson's chi-square test.		

Source: FDA Statistical Reviewer's analysis.

The proportion of patients with HIV-1 RNA <50 copies/mL was statistically significantly higher in the KALETRA arm (67%) as compared to the nelfinavir arm (52%).

Figure 1 shows the proportion of successes (<400 copies/mL) at each time point through Week 48 for the KALETRA and nelfinavir arms.



Source: FDA Statistical Reviewer's analysis.

Figure 1: Proportion of Patients with HIV-1 RNA <400 copies/mL Through Week 48 (Study 863)

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b. Study 940

Table 5 shows the proportion of responders, i.e., patients who were virologically suppressed (<400 copies/mL) through Week 48, in Study 940. This table also shows the status of the non-responders.

Table 5:
Efficacy Outcomes of Treatment Through Week 48 (Study 940)

Outcome	Antiretroviral Naïve (N=44)	Antiretroviral Experienced (N=56)
	n (%)	n (%)
Responder¹	35 (80%)	40 (71%)
Virologic Failure²	8 (18%)	15 (27%)
Rebound	5 (11%)	5 (9%)
Never suppressed through Week 48	3 (7%)	10 (18%)
Death	0 (0%)	0 (0%)
Discontinued due to adverse events	1 (2%)	1 (2%)
Discontinued due to other reasons³	0 (0%)	0 (0%)
Consent withdrawn	0 (0%)	0 (0%)
Loss to follow	0 (0%)	0 (0%)
Non-compliance	0 (0%)	0 (0%)
Protocol violation	0 (0%)	0 (0%)
Other	0 (0%)	0 (0%)
Total	44 (100%)	56 (100%)

1 Patients achieved and maintained confirmed HIV RNA <400 copies/mL through Week 48.
 2 Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Week 48.
 3 Includes loss to follow-up, patient's withdrawal, non-compliance, protocol violation and other reasons.

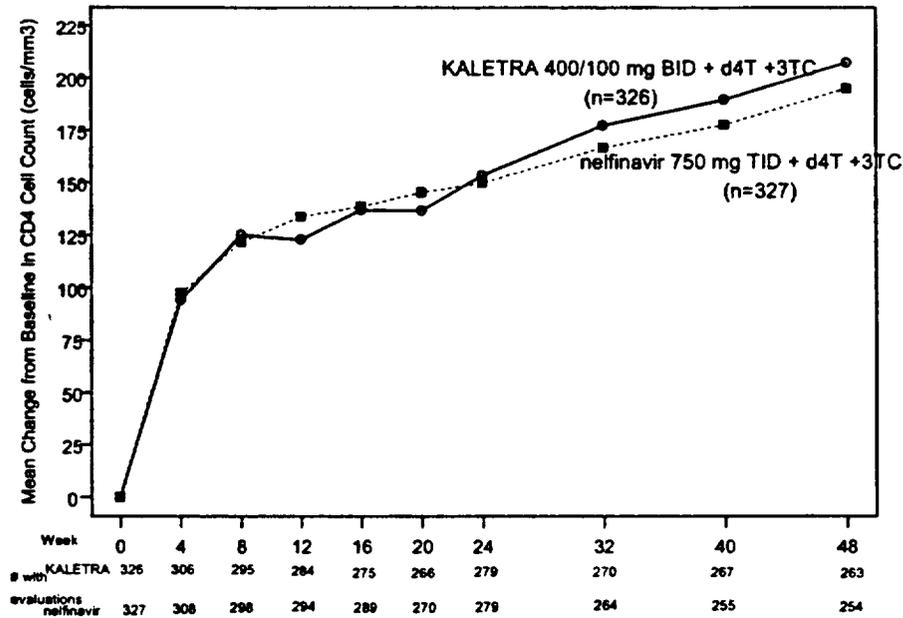
Source: FDA Statistical Reviewer's analysis.

Although the proportion of responders in the antiretroviral naïve pediatric patients (80%) was numerically higher than that in the antiretroviral experienced pediatric patients (71%), this difference was not statistically significant.

4.2 CD4+ Cell Count

Figure 2 and Figure 3 show the trend in the mean change from baseline in CD4+ cell counts (cells/mm³) in Study 863 and 940, respectively. The increase in CD4+ cell counts were similar in both, KALETRA and nelfinavir arms through all the visits in Study 863. As shown in Figure 3, there were significant increases in CD4+ cell counts for ARV naïve, PI naïve and PI experienced pediatric patients in Study 940 at all visits.

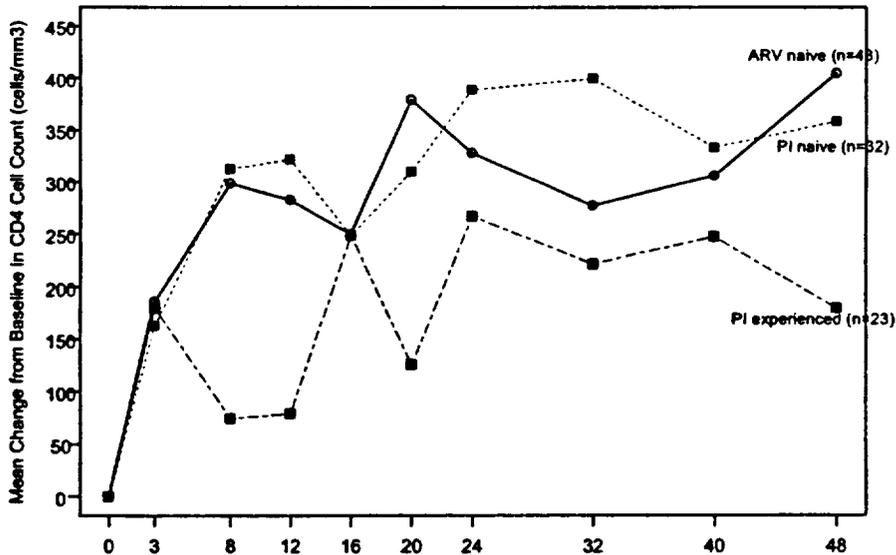
Mean Change from Baseline in CD4+ Cell Count, Protocol 863



Source: FDA Statistical Reviewer's analysis.

Figure 2: Mean Change from Baseline in CD4+ Cell Count Through Week 48 (Study 863)

Mean Change from Baseline in CD4+ Cell Count, KALETRA Protocol 940



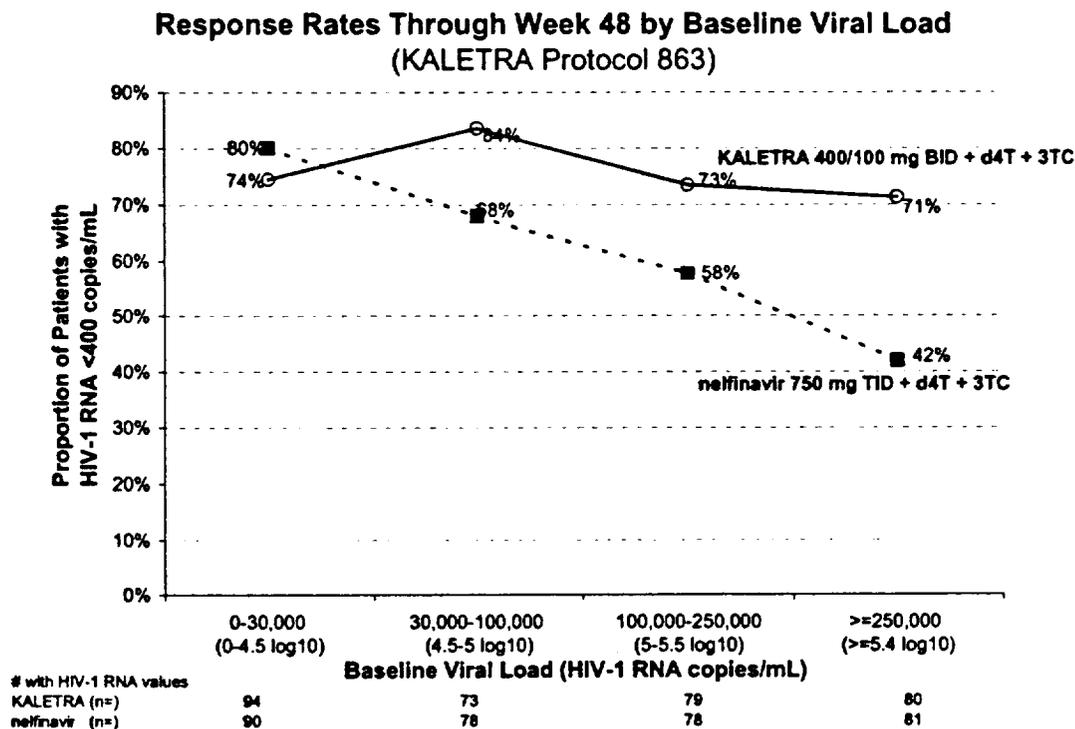
Source: FDA Statistical Reviewer's analysis.

Figure 3: Mean Change from Baseline in CD4+ Cell Count Through Week 48 (Study 940)

5. Findings in Special/Subgroup Populations

5.1 Subgroup Analyses by Baseline Viral Load and Baseline CD4+ Cell Count

Figure 4 shows the proportion of patients who were virologically suppressed (i.e., maintained viral load <400 copies/mL) by baseline viral load for Study 863. The baseline viral load was split into categories such as 0-30,000 copies/mL (0-4.5 log₁₀ HIV RNA copies/mL) and then split with increments of about 0.5 log₁₀ copies/mL thereafter. These categories were chosen because they represented the approximate quartiles of the distribution for baseline viral load.

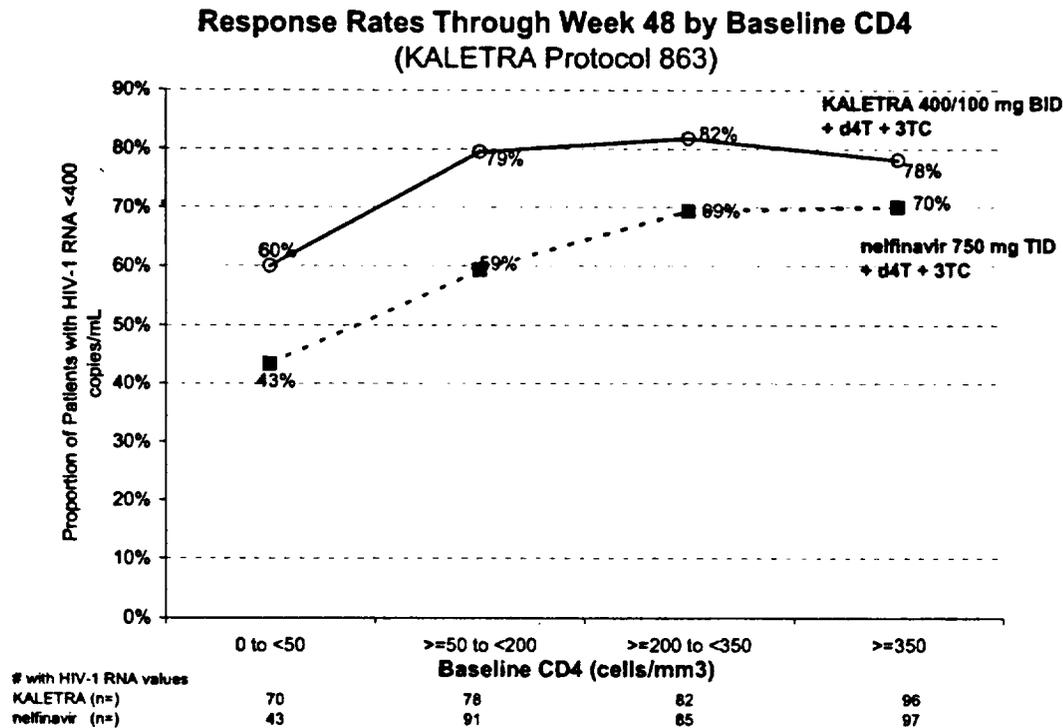


Source: FDA Statistical Reviewer's analysis

Figure 4: Proportion of Patients with HIV-1 RNA <400 copies/mL Through Week 48, by Baseline Viral Load (Study 863)

When the baseline viral load of patients is below approximately 30,000 copies/mL, KALETRA does not show superiority over nelfinavir. However, as the baseline viral load increases, the treatment effect size (difference in response rates) between KALETRA and nelfinavir is larger.

Similarly, Figure 5 shows the response rates by baseline CD4+ cell count.



Source: FDA Statistical Reviewer's analysis.

Figure 5: Proportion of Patients with HIV-1 RNA <400 copies/mL Through Week 48, by Baseline CD4+ Cell Count (Study 863)

The proportion of patients who were virologically suppressed in Study 863 through Week 48, in the KALETRA arm were numerically higher than that in the nelfinavir arm in patients whose baseline CD4+ cell counts were lower than 200 cells/mm³. However, when the baseline CD4+ cell counts were greater than 200 cells/mm³, the treatment difference in proportion of successes, between KALETRA and nelfinavir reduced.

Furthermore, additional subgroup analyses were done to test for statistical interaction between baseline viral load and baseline CD4 cell count. The purpose of this analysis is to examine whether baseline CD4 cell count or baseline viral load modifies the superiority of KALETRA over nelfinavir.

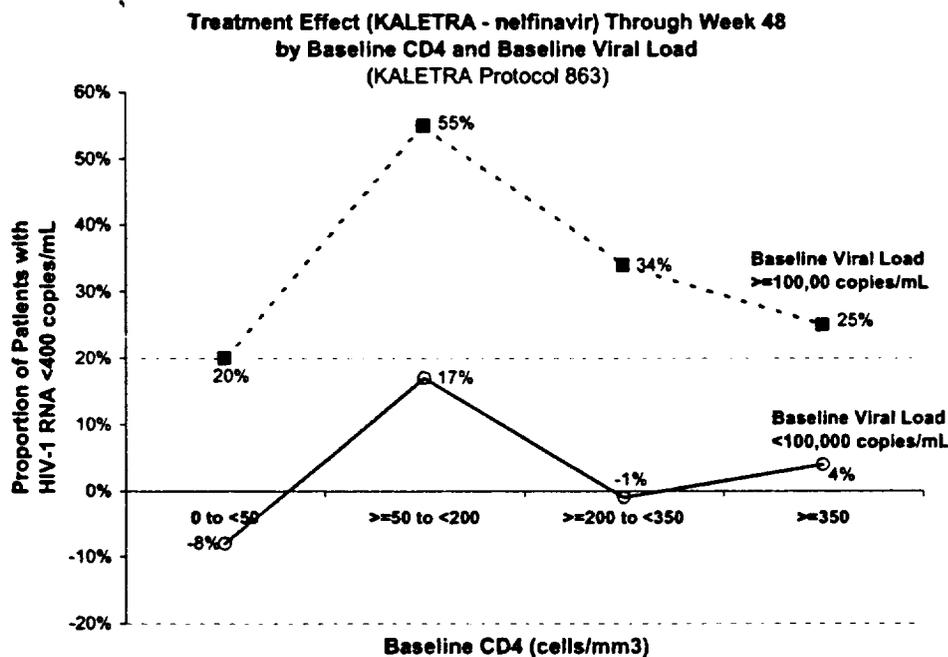
Table 6:
Proportion of Patients with HIV-1 RNA <400 copies/mL Through Week 48—
Baseline Viral Load by Baseline CD4 by Treatment Group Interaction
(Study 863)

Baseline CD4 cell count (cells/mm ³)	Baseline Viral Load					
	<100,000 HIV-1 RNA copies/mL			≥100,000 HIV-1 RNA copies/mL		
	KALETRA+ d4T+3TC	nelfinavir+ d4T+3TC	Treatment Effect (Kaletra – NFV)	KALETRA+ d4T+3TC	nelfinavir+ d4T+3TC	Treatment Effect (Kaletra – NFV)
0–50	10/15 (67%)	6/8 (75%)	-8%	32/55 (58%)	17/45 (38%)	20%
50–200	19/23 (83%)	23/35 (66%)	17%	43/55 (78%)	31/56 (55%)	55%
200–350	43/56 (77%)	38/49 (78%)	-1%	24/26 (92%)	21/36 (58%)	34%
≥350	59/73 (81%)	58/75 (77%)	4%	16/23 (70%)	10/22 (45%)	25%
Interaction Terms†			p-value†			
Viral Load by CD4 cell count			0.6064			
Treatment Group by Viral Load			0.0185*			
Treatment Group by CD4			0.6551			
Treatment Group by Viral Load by CD4			0.5372			
† P-values are based on a logistic regression model for response rates with treatment group, baseline CD4 and baseline viral load as main effects, and baseline viral load by baseline CD4, treatment group by viral load, treatment group by CD4 and treatment group by viral load by CD4 as interaction terms.						
* Interaction term is statistically significant at 0.10 level of significance since p-value is <0.10.						

Source: FDA Statistical Reviewer's analysis.

For the subgroup analyses that would test the interaction effect, a logistic regression model was fit for the proportion of patients who maintained HIV-1 RNA level <400 copies/mL through Week 48 using treatment group, baseline CD4 and baseline viral load as main effects, as well as two-way and three-way interactions of these 3 terms. For the purpose of illustration, Table 6 shows the treatment effects for various categories of baseline CD4 cell count after adjusting for the baseline viral load (<100,000 copies/mL versus ≥100,000 copies/mL) and vice versa. The cut-off of 100,000 HIV-1 RNA copies/mL was chosen for this illustration because this is approximately the median baseline viral load for patients in Study 863.

As shown in Table 6, the three-way interaction of *Treatment Group by Viral Load by CD4* is not statistically significant (p -value=0.5372). This is illustrated by the fact that for each category of baseline CD4 cell count, the differences in treatment effect across the two categories of baseline viral load are not significantly different (i.e., $20\% - (-8\%) = 28\%$, $55\% - 17\% = 38\%$, $34\% - (-1\%) = 35\%$, $25\% - 4\% = 21\%$ are not statistically significantly different). Also as shown below, in Figure 6, the fact that the two curves are parallel indicates that there is no evidence of a three-way interaction.



Source: FDA Statistical Reviewer's analysis.

Figure 6: Treatment Group by Baseline Viral Load by Baseline CD4 Interaction (Study 863)

After ruling out the highest-order interaction, that is the three-way interaction of *Treatment Group by Viral Load by CD4*, we next examine the two-way interaction terms.

After adjusting for the baseline CD4 cell counts, the treatment effects at the two baseline viral load categories were statistically significantly different (p -value=0.0185 < 0.10 nominal level of significance). This *Treatment Group by Viral Load* interaction—after adjusting for the baseline CD4—can also be seen by the higher treatment effects of 20%, 55%, 34%, and 25% when baseline viral load is higher ($\geq 100,000$ copies/mL) and by the relatively lower treatment effects of

-8%, 17%, -1%, and 4% when baseline viral load is lower (<100,000 copies/mL). The *Treatment Group by Viral Load* interaction is also illustrated in Figure 4 by fact that the curves for Treatment Group by Baseline Viral Load cross each other and are not parallel. The unadjusted (unadjusted for baseline CD4) treatment difference as calculated from numbers in Table 6 was 22% (KALETRA 72% vs nelfinavir 50%) when baseline viral load was $\geq 100,000$ copies/mL and a lower treatment difference of only 3% (KALETRA 78% vs nelfinavir 75%) was seen when baseline viral load was <100,000 copies/mL.

Finally, consider the *Treatment Group by CD4* interaction effect. The p-value for *Treatment Group by CD4* interaction was 0.6551 which was not statistically significant. Therefore there is no evidence that baseline CD4 cell counts modify the treatment effect of KALETRA versus nelfinavir.

Statistical Reviewer's Note:

In conclusion, there was evidence that the Baseline Viral Load modifies the treatment effect of KALETRA versus nelfinavir, after adjusting for Baseline CD4 cell counts. The superiority of KALETRA over nelfinavir was clear in "sicker" patients with higher baseline viral loads ($\geq 100,000$ copies/mL), but when the baseline viral loads were lower (<100,000 copies/mL), KALETRA was similar to nelfinavir. Also, there was not enough evidence to conclude that Baseline CD4 modifies the treatment effect of KALETRA versus nelfinavir.

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5.2 Subgroup Analyses by Age, Gender, Race/Ethnic Origin

Table 7, Figure 7, and Table 8 show subgroups analyses (response rates) for KALETRA and nelfinavir by gender, age and race respectively, for Study 863. Recall that the median age of patients in Study 863 was about 38 years. Therefore, the age groups were split around ≤ 35 years and > 35 years.

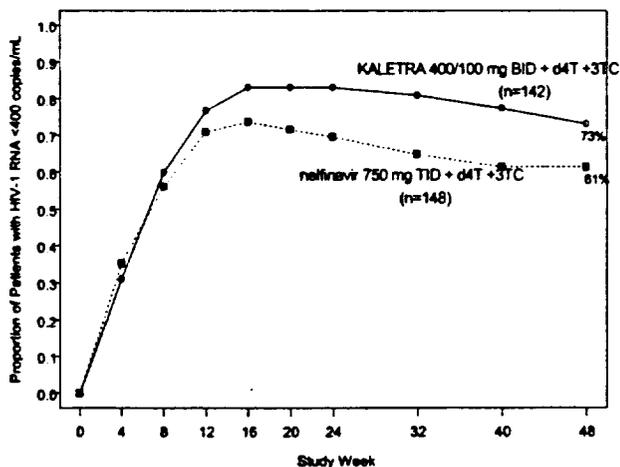
Table 7:
 Proportion of Patients with HIV-1 RNA < 400 copies/mL through Week 48 by Gender (Study 863)[†]

	KALETRA+d4T+3TC (N=326)	nelfinavir+d4T+3TC (N=327)
Males	200/260 (77%)	169/264 (64%)
Females	46/66 (70%)	35/63 (56%)

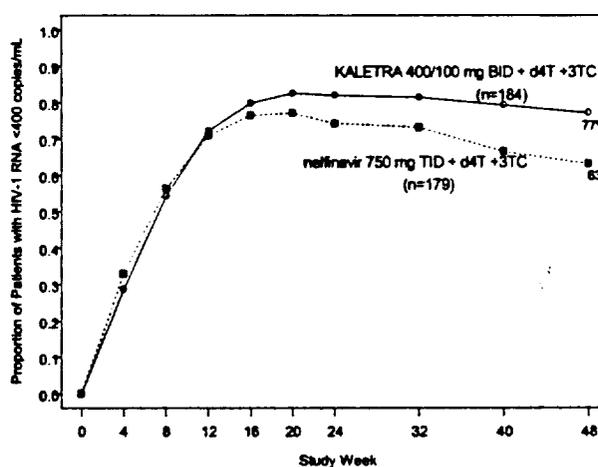
[†] Based on time to loss of virologic response algorithm.

Source: FDA Statistical Reviewer's analysis.

Virologic Response Through Week 48, Protocol 863, AGE ≤ 35



Virologic Response Through Week 48, Protocol 863, AGE > 35



Source: FDA Statistical Reviewer's analysis.

Figure 7: Proportion of Patients with HIV-1 RNA < 400 copies/mL Through Week 48, by Age (Study 863)

For males and females, as well as for patients in either age groups (≤ 35 years or > 35 years), the proportion of responders were higher in the KALETRA arm than in the nelfinavir arm. See Table 7 and Figure 7.

Table 8:
 Proportion of Patients with HIV-1 RNA <400 copies/mL
 through Week 48 by Race (Study 863)†

	KALETRA+d4T+3TC (N=326)	nelfinavir+d4T+3TC (N=327)
Caucasian	180/227 (79%)	137/223 (61%)
Black	57/88 (65%)	53/87 (61%)
Asian/Pacific Islander	6/8 (75%)	10/12 (83%)
Native American /Alaskan Native	3/3 (100%)	2/3 (67%)
Missing	NA	2/2 (100%)
NA=Not applicable.		
† Based on time to loss of virologic response algorithm.		

Source: FDA Statistical Reviewer's analysis.

Similarly, a superiority of KALETRA over nelfinavir was seen in Caucasian patients. Recall that from Table 1, 69% of patients were Caucasian, of which 13% were Hispanics. However, KALETRA did not show superiority over nelfinavir in Black patients who were the largest minority among adult patients. The other minorities were much smaller in numbers to make any definitive conclusions. Statistical testing for the homogeneity of treatment effects between the Caucasian vs. non-Caucasian yielded a two-sided p-value of 0.048, suggesting that the apparent different effect sizes in Caucasian and non-Caucasian may be real.

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6. Conclusions and Recommendations

Based on all the available data through Week 48 in Studies 863 and 940 we conclude the following.

1. Study 863 demonstrated that a statistically significantly higher proportion of patients treated in the KALETRA+d4T+3TC arm (75%) maintained their viral load <400 copies/mL through Week 48 as compared to those patients treated with nelfinavir+d4T+3TC (62%). Also, there were significantly lower virologic failures (≥ 400 copies/mL) in the KALETRA arm through Week 48 as compared to the nelfinavir arm. Mean changes from baseline in CD4+ cell count were similar in both treatment groups.
2. In Study 863, the treatment effect size for the proportion of patients maintaining viral load <400 copies/mL through Week 48 and with viral load <50 copies/mL at Week 48 increases with baseline HIV-1 RNA levels. The superiority of KALETRA over nelfinavir was mainly seen in patients with baseline viral load $\geq 30,000$ copies/mL. Below this threshold of baseline viral load, KALETRA was similar to nelfinavir.
3. In Study 863, the treatment effect size for the proportion of patients maintaining viral load <400 copies/mL through Week 48 decreases with baseline CD4 counts. After adjusting for the baseline viral load, the treatment effect sizes were similar across baseline CD4+ cell counts, suggesting that baseline CD4 did not modify the treatment effects after taking baseline HIV-1 RNA into consideration.
4. Additionally, in Study 863, the superiority of KALETRA over nelfinavir was seen in subgroups of male and female patients as well as in younger (≤ 35 years age) and older (≥ 35 years age) patients. This superiority was also seen in Caucasian patients (some of whom were Hispanics). However, in Black patients, the proportion of responders were similar in both, KALETRA and nelfinavir arms.
5. In Study 940, there was a numerically higher, but statistically not superior response in the antiretroviral naïve patients compared to the experienced patients with respect to the proportion of patients who maintained their viral load <400 copies/mL through Week 48. There were statistically significant increases from baseline in CD4+ cell counts at each study visit for all pediatric patients.

Rafia Bhore, Ph.D.

Mathematical Statistician

concur: Greg Soon, Ph.D.
Statistics Team Leader

cc:

HFD-530/MedDivDir/Dr. D. Birnkrant
HFD-530/MedDepDivDir/Dr. J. Murray
HFD-530/ActgMOTL/Dr. J. Murray
HFD-530/MO/Dr. K. Struble
HFD-530/MO/Dr. L. Lewis
HFD-530/PM/Mr. S. Belouin
HFD-530/StatReviewer/Dr. R. Bhole
HFD-725/StatTL/Dr. G. Soon
HFD-725/StatDivDir/Dr. M. Huque
HFD-700/OBDepDir/Dr. C. Anello

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Rafia Bhore
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Greg Soon
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