# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-226**

**21-251**

## STATISTICAL REVIEW(S)

# Statistical Review and Evaluation

| | |
|---|---|
| **NDA#:** | 21226 |
| **APPLICANT:** | Abbott Labarotories |
| **NAME OF DRUG:** | Lopinavir |
| **INDICATION:** | Anti-HIV |
| **DOCUMENTS REVIEWED:** | Submission Dated 6/1/2000 |
| **Clinical Reviewer:** | HFD-530: Kim Struble, R.Ph. |

## A: Introduction

Kaletra (lopinavir/ritonavir) is a co-formulation of lopinavir (LPV) and ritonavir (RTV). LPV is a protease inhibitor (PI). The submission consists of one phase III pivotal trial (Study M98-863), supported by two phase II long term trials (Study M97-720 and 765), two short term Phase II trials (M98-957, M98-940 pediatric), and an ongoing phase III trial (M98-888) with 24 weeks of data available close to the end of the review process.

## B: Study Design

**Study M98-863**
Protocol: "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 + Nefinivir Placebo TID + Stavudine 30mg or 40 mg (based on weight) BID + Lamivudine 150 mg BID
B. Kaletra Placebo + Nefinivir 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.

**Study M97-720**

This is a Phase I/II, randomized, multi-center study of Kaletra in combination with d4T and 3TC in 2 groups (Groups I and II) of HIV-infected, antiretroviral-naive male and female subjects. The study consisted of a double-blind study period and an open-label study period (currently ongoing at the time of this report).

Approximately 32 subjects in Group I were to be equally randomized to Kaletra 200 mg/100 mg every 12 hours (Q12H) or Kaletra 400 mg/100 mg Q12H. Study drug administration for subjects enrolled in Group I began on Study Day 1 with Kaletra; study drug dosing was directly observed for at least one of the daily dosings for Study Days 1-14. Follow-up visits were planned for Study Day 16 and Day 21 (Week 3), and standard doses of d4T and 3TC were added to each Group I subject's Kaletra regimen beginning on Day 22. Subsequent follow-up visits for subjects in Group I were scheduled for Day 28 (Week 4), biweekly until Week 12 (Month 3), monthly until Week 24 (Month 6), and every 3 months thereafter for the duration of the study.

After a safety review of 4 weeks of dosing by the first 16 subjects in Group I, a second cohort of approximately 70 subjects were to be enrolled as Group II. Group II subjects were to be equally randomized to Kaletra 400 mg/100 mg Q12H or Kaletra 400 mg/200 mg Q12H. Subjects also received standard doses of d4T and 3TC beginning on Day 1. Subjects were scheduled to return to clinic on Day 14, Day 28 (Week 4), monthly until Week 24 (Month 6) and every 3 months thereafter for the duration of the study.

Subjects received Kaletra in a dose-blinded fashion until Institutional Review Board (RB) approval of Amendment No. 5 (which occurred after Week 48 for all study subjects), at which time all ongoing trial subjects received open-label Kaletra 400 mg/100 mg Q12H. Study subjects continued to take d4T and 3TC at standard labeled doses. Study visits during the open-label period continued according to the established schedule.

**Study M97-765**

Study M97-765 is a Phase I/II, dose blinded, randomized, multi-center study of 2 doses of Kaletra in combination with 2 NRTIs (at least 1 of which the subject had not received before) and nevirapine in PI-experienced, NNRTI-naive, HIV-infected adults. Approximately 70 subjects with plasma HIV levels of 1000 to 100,000 copies/mL while on their pre-study PI-based regimen were to be enrolled into the study. Subjects were stratified based on their screening HIV RNA level and then randomized in a balanced fashion to receive Kaletra 400 mg/100 mg Q12H or Kaletra 400 mg/200 mg Q12H. The PI in their existing regimen was discontinued on Study Day -1. Subjects were required to return to the clinic prior to their first dose of Kaletra (Study Day 1). For Study Days 1-14, subjects received their assigned Kaletra regimen in combination with the NRTIs that they had been taking in their pre-study regimen. Subjects returned to the clinic on Study Days 7 and 14. On Study Day 15, each subject's NRTI regimen was changed to a new regimen that included at least 1 NRTI that the subject had not previously received. Nevirapine was also added to each subject's regimen beginning on Study Day 15. The nevirapine dose was 200 mg QD for the first 14 days, followed by 200 mg nevirapine BID.

**Study M98-888**

Study M98-888 is a Phase III, open-label, randomized, positive-controlled, multi-center, multi-country study to compare Kaletra in combination with nevirapine and 2 NRTIs versus Investigator Selected PI (ISPI) (s) in combination with nevirapine and 2 NRTIs in antiretroviral-experienced HIV-infected subjects. Approximately 300 NNRTI-naive subjects at least 12 years of age with plasma HIV RNA levels >=1000 copies/mL and <=500,000 copies/mL while treated with a regimen consisting of a single PI and 2 NRTIs that had not been changed for at least 12 weeks were randomly assigned to either the ISPI(s) regimen (as shown in the table below) or to Kaletra 400 mg/100mg BID. In addition, all subjects received nevirapine and 2 NRTIs selected by the investigator according to protocol-defined guidelines.

**Possible Investigator-Selected Protease Inhibitor Regimens (Study M98-888)**

| **Single Protease Inhibitor Regimen:** | **Dose:** |
|---|---|
| Indinavir (IDV) | 1000mg BID |
| Nelfinavir (NFV) | 750 mg TID |
| Ritonavir (RTV) | 600mg BID |
| Saquinavir (SQV) | 1200 mg TID |
| **Dual Protease Inhibitor Regimen:** | **Dose:** |
| RTV/SQV | 400 mg RTV/400 mg SQV BID |
| RTV/IDV | 400 mg RTV/400 mg IDV BID |
| RTV/SQV | 1250 mg NFV/1200 mg SQV BID or<br>750 mg NFV/800 mg SQV TID |

**Study M98-957**

Study M98-957 is a Phase I/II, randomized, open-label, multiple-dose, parallel-group, pharmacokinetic interaction study conducted in multiple centers in Europe and the United States. Approximately 50 HIV-infected subjects experienced with multiple PIs who were NNRTI-naive

were to be randomly assigned in a balanced fashion to 1 of 2 treatment groups. Subjects assigned to Group A received Kaletra 400 mg/100 mg BID. Subjects assigned to Group B also received 400 mg/100 mg BID from Day 1 through Day 13; from Day 14 onward, these subjects received Kaletra 533 mg/133 mg BID. Subjects in both treatment groups also received efavirenz 600 mg QD plus NRTIs that were selected by the investigator. Subjects were required to return to the clinic prior to their first dose of Kaletra. Subsequent visits were scheduled at Week 2, Week 4, Week 8, then monthly until Week 24, every 2 months until Week 48, and every 3 months thereafter for the duration of the study.



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**C: Applicant's Results**

**Proportions <400 for ITT population at Week 24**

| | Study | Treatment Arms | | p-value |
|---|---|---|---|---|
| Anti-retroviral Naive | M98-863 | KALETRA (400/100) | Nelfinavir | 0.015 |
| | | 259/326 (79%) | 233/327 (71%) | |
| | M97-720 Group 1 | KALETRA 400/100 | KALETRA 200/100 | 1 |
| | | 14/16 (88%) | 14/16 (88%) | |
| | M97-720 Group 2 | KALETRA 400/100 | KALETRA 400/200 | 0.674 |
| | | 31/35 (89%) | 31/33 (94%) | |
| Anti-retroviral Experienced | M97-765 | KALETRA 400/100 | KALETRA 400/200 | 0.398 |
| | | 26/36 (72%) | 28/34 (82%) | |
| | M98-957 | KALETRA 400/100 | KALETRA 533/133 | 0.358 |
| | | 20/29 (69%) | 23/28 (82%) | |
| | M98-940 | KALETRA 230/57.5 | KALETRA 300/75 | 0.924 |
| | | 36/49 (74%) | 37/51 (73%) | |
| | M98-888 | KALETRA 400/100 | Investigator Selected PI(s) | 0.093 |
| | | 19/26 (73%) | 12/24 (50%) | |

* Based on Table 2.8.5.1a on Page 70 of Vol. 2

In Anti-retroviral naïve subjects, Study M98-863 showed that Kaletra (400/100) is superior to Nelfinavir in achieving HIV RNA <400 copies/mL at Week 24. Study M97-720 showed a numerically higher response rate for the Kaletra. In anti-retroviral experienced subjects, Kaletra appears to induce a lower but consistent response rates at Week 24 across studies.

**Mean change of CD4 from baseline to Week 24 and its standard error**

| | Study | Treatment Arms (mean change (se)) | | p-value |
|---|---|---|---|---|
| Anti-retroviral Naive | M98-863 | KALETRA (400/100) | Nelfinavir | 0.726 |
| | | 154 (7.4) | 150 (7.4) | |
| | M97-720 Group 1 | KALETRA 400/100 | KALETRA 200/100 | NA |
| | | NA | NA | |
| | M97-720 Group 2 | KALETRA 400/100 | KALETRA 400/200 | NA |
| | | NA | NA | |
| Anti-retroviral Experienced | M97-765 | KALETRA 400/100 | KALETRA 400/200 | NA |
| | | NA | NA | |
| | M98-957 | KALETRA 400/100 | KALETRA 533/133 | 0.840 |
| | | 48 (24.2) | 48 (24.2) | |
| | M98-940 | KALETRA 230/57.5 | KALETRA 300/75 | 0.241 |
| | | 0.20 (0.04)* | 0.15 (0.04)* | |
| | M98-888 | KALETRA 400/100 | Investigator Selected PI(s) | 0.259 |
| | | 82 (23.9) | 40 (27.8) | |

* On $Log_{10}$ scale

* Based on Table 2.8.5.1c on Page 72 of Vol. 2

CD4 changes are not statistically significantly different between Kaletra (400/100) and Nelfinavir (Study M98-863), between Kaletra 400/100 and Kaletra 533/133 (Study M98-957), between Kaletra 230/57.5 and Kaletra 300/75 (Study M98-940), between Kaletra (400/100) and investigator selected PI(s) (Study M98-888). Note the sample sizes for Studies M97-765, M98-957, M98-940 and M98-888 are relatively small so the statistical non-significance does not lead to conclusion of similarity, which requires a narrow confidence interval around 0.

**D: Reviewer's Analyses**

**Study M98-863**

Disposition

Six hundred eighty-six (686) subjects were randomized equally to the 2 treatment groups; 33 subjects were never dosed and were excluded from all analyses. Thus, 653 subjects were randomized and treated; 326 subjects received Kaletra and 327 subjects received Nelfinavir. Since the study is double-blinded, we can safely exclude subjects who did not initiate the study drugs from the intent-to-treat population.

HIV RNA level <400 (50) copies/mL

The reviewer calculated the proportions below 400 copies/mL and proportions below 50 copies/mL using the worst case in the measurement window for each visit with missing or discontinuation regarded as failures. The window for Week 24 is from day 155 to day 196. The results for proportions below 400 is identical to the applicant's results, while the number of subjects below 50 copies/mL are 1 less than the applicant's result in each arm because the applicant used the measurement closest of day 168 for Week 24 measurement.

The table below summarizes the results for proportions below 400 copies/mL and reasons for failures.

Week 24 HIV RNA Status Using Roche Standard Assay

| Status (%) | KALETRA N=326 | NFV N=327 |
|---|---|---|
| Observed <400 | 259 (79.45%) | 233 (71.25%) |
| Observed >=400 | 25 (7.67%) | 53 (16.21%) |
| Missing | 6 (1.84%) | 8 (2.45%) |
| Discontinued | 36 (11.04%) | 33 (10.09%) |
| Death | 2 (0.61%) | 2 (0.61%) |
| Virologic Failure | 0 (0%) | 5 (1.53%) |
| Lost to FU | 9 (2.76%) | 11 (3.36%) |
| AE | 8 (2.45%) | 8 (2.45%) |
| Non-compliant | 5 (1.53%) | 3 (0.92%) |
| Personal Reasons | 4 (1.23%) | 2 (0.61%) |
| Prohibit Medication | 1 (0.31%) | 0 (0%) |
| Other | 7 (2.15%) | 2 (0.61%) |

The first column indicates the Week 24 HIV RNA status, the second and the third column shows the number and percent of subjects in each treatment arm with those status. When missing values and discontinuations are regarded as failures the proportions below 400 copies/mL is 79% for the Kaletra arm and 71% for the Nelfinavir arm. This difference is statistically significant with p-

value 0.015 (z-test or Chi-square test) favoring Kaletra. The 95% confidence interval for the treatment difference is (1.61%, 14.77%).

The category "missing" in the table above includes subjects who did not have Week 24 measurement but were not known to have discontinued the study medication or lost to follow up. Note that the missing rates of 1.84% and 2.45% are relatively small, and the results should be stable regardless how these missing values are handled. In fact, in the worst case where all missing values in the Kaletra arm are regarded as failures but all missing values in the Nelfinavir arm are regarded as HIV RNA below 400 copies/mL, the p-value for the treatment difference is 0.082 favoring Kaletra, and the 95% confidence interval is (-0.73%, 12.23%).

The rates and reasons for discontinuation were similar between the two arms.

Similarly, results for proportions below 50 copies/mL using Roche Ultrasensitive assay is displayed below:

Week 24 HIV RNA Status Using Roche Ultrasensitive Assay

| Status | KALETRA | NFV |
|---|---|---|
| | 326 | 327 |
| Observed <50* | 210 (64.42%) | 196 (59.94%) |
| Observed >=50 | 74 (22.70%) | 90 (27.52%) |
| Missing | 6 (1.84%) | 8 (2.45%) |
| Discontinued | 36 (11.04%) | 33 (10.09%) |
| Death | 2 (0.61%) | 2 (0.61%) |
| Virologic Failure | 0 (0%) | 5 (1.53%) |
| Lost to FU | 9 (2.76%) | 11 (3.36%) |
| AE | 8 (2.45%) | 8 (2.45%) |
| Non-compliant | 5 (1.53%) | 3 (0.92%) |
| Personal Reasons | 4 (1.23%) | 2 (0.61%) |
| Prohibit Medication | 1 (0.31%) | 0 (0%) |
| Other | 7 (2.15%) | 2 (0.61%) |

* one less than applicant results in each arm.

The p-value for the difference in proportions <50 copies/mL is 0.238 (z-test) with 95% confidence interval (-3.0%, 11.9%), indicating that the Kaletra arm is at worst 3% lower than the nelfinavir arm in achieving HIV RNA < 50 copies/mL when missing values and discontinuations are regarded as failures. Even in the worst case senario where all missing values in the Kaletra arm are regarded as failures but all missing values in the Nelfinavir arm are regarded as HIV RNA below 400 copies/mL, the 95% confidence interval for the treatment difference is (-5.36%, 9.42%), indicating that Kaletra is no more than 5.36% worse than Nelfinavir.

Using the same rules, the results at other visits are also examined and listed below.

Percent with plasma HIV RNA <400 and 50 copies/mL over time

| Week | <400 | | <50 | |
|---|---|---|---|---|
| | KALETRA | NFV | KALETRA | NFV |
| 4 | 34.0 | 37.6 | NA | NA |
| 8 | 60.1 | 60.2 | NA | NA |
| 12 | 77.9 | 72.5 | NA | NA |
| 16 | 81.0 | 75.8 | NA | NA |
| 20 | 81.9 | 71.3 | NA | NA |
| 24 | 79.4 | 71.3 | 64.4 | 59.9 |

The table indicates that over time, the numerical difference for porportions below 400 copies/mL between the two arms increases in favor of Kaletra. The ultrasensitive assay was not used for visits other than Week 24.

Subjects using version 1.5 assay

22 subjects had their HIV RNA measured by 1.5 assay. Due to the possible difference in the 1.0 and 1.5 assay in terms of virus being detected, a separate analysis is done.

Week 24 Percents < 400 copies/mL

| Population | Kaletra | NFV | 95% CI | p-value |
|---|---|---|---|---|
| Using 1.0 Assay | 251/316 (79.43) | 229/315 (72.70) | 0.09, 13.37 | 0.047 |
| Using 1.5 Assay | 8/10 (80.00) | 4/12 (33.33) | 10.25, 83.08 | 0.012 |
| All | 259/326 (79.45) | 233/327 (71.25) | 1.61, 14.77 | 0.015 |

Even though the Kaletra arm showed superiority to NFV among the 22 subjects using 1.5 version of assay at Week 24, results at Weeks 12, 16, and 20 are closer (20% difference instead of 47%).

The percents below 50 copies/mL is summarized below. None of the subjects measured with ultrasensitive assay 1.5 achieved below 50 copies/mL status.

Week 24 Percents < 50 copies/mL

| Population | Kaletra | NFV | 95% CI | p-value |
|---|---|---|---|---|
| Using 1.0 Assay | 210/316 (66.46) | 196/315 (62.22) | -3.23, 11.70 | 0.267 |
| Using 1.5 Assay | 0/10 (0.00) | 0/12 (0.00) | NA | NA |
| All | 210/326 (64.42) | 196/327 (59.94) | -2.95, 11.91 | 0.238 |

CD4

CD4 over time are similar between the two arms. The mean increases of CD4 cell counts at Week 24 were 154.5 (Kaletra) vs. 147.3(NFV) with p-value=0.575 (z-test) for the difference.

Overall, the Kaletra arm appears to be better than or similar to the nelfinavir arm in achieving HIV RNA beow 400 copies/mL or 50 copies/mL. The CD4 changes were similar between the two arms.

Subgroup Analyses

Baseline HIV RNA, baseline CD4, gender, age, and race were examined for their influence on treatment responses and treatment differences in proportions of subjects with HIV RNA below 400 copies/mL and 50 copies/mL. Gender and race do not appear to have significant influence while age, baseline HIV RNA and baseline CD4 may have. Detailed analysis for age, baseline HIV RNA and baseline CD4 are provided below.

**Age** was dichotomized according to its median (37 years old). The response rates in each subgroup is displayed below:

Proportions below 400 copies/mL by Age and Treatment

| | Kaletra | Nelfinavir | p-value for the diff. |
|---|---|---|---|
| ≤37 years old | 144/185 (77.8%) | 117/176 (66.5%) | 0.015 |
| >37 years old | 115/141 (81.6%) | 116/151 (76.8%) | 0.317 |
| p-value for the diff. | 0.405 | 0.036 | 0.320 |

Proportions below 50 copies/mL by Age and Treatment

| | Kaletra | Nelfinavir | p-value for the diff. |
|---|---|---|---|
| ≤37 years old | 120/185 (64.9%) | 99/176 (56.3%) | 0.093 |
| >37 years old | 90/141 (63.8%) | 97/151 (64.2%) | 0.942 |
| p-value for the diff. | 0.847 | 0.139 | 0.236 |

It appears that the favorable treatment differences for Kaletra are primarily derived from subjects ≤ 37 years old, largely because subjects ≤37 years old have a lower response rate than subjects >37 years old in the nelfinavir arm. However, test of the homogeneity of the treatment effects across the two age stratums yields p-values of 0.320 and 0.236 for the proportions <400 copies/mL and proportions <50 copies/mL, respectively, suggesting that there are not sufficient statistical evidences for the age by treatment interaction.

**Baseline HIV RNA** is examined in several ways: by dichotomizing roughly according to the median, by dividing it into 4 groups roughly according to quartiles, and examined as a continuous variable. These analyses are necessary in view of its potential labeling implication, and also, like age and baseline CD4, the analysis for its influence on the outcome was not pre-specified.

We start the analysis using 4 subgroups defined by baseline HIV RNA.

Proportion <400 copies/mL by baseline HIV RNA and Treatment

| Baseline HIV RNA | Kaletra | NFV | Diff (%) | p-value & 95% CI |
|---|---|---|---|---|
| <=25,000 | 58/72 (80.6%) | 66/77 (85.7%) | -5.2 | 0.400 (-17.2, 6.9) |
| (25,000, 100,000] | 69/84 (82.1%) | 62/85 (72.9%) | 9.2 | 0.149 (-3.3, 21.7) |
| (100,000, 250,000] | 70/88 (79.5%) | 59/75 (78.7%) | 0.9 | 0.891 (-11.7, 13.4) |
| >250,000 | 60/80 (75.0%) | 42/86 (48.8%) | 26.2 | 0.0003 (12.0, 40.4) |
| Missing | 2/2 (100%) | 4/4 (100%) | 0 | NA |

We see that the response rate tends to be lower with higher baseline viral load (p-value =0.001 with CMH test), but the nelfinavir arm dropped more rapidly than the Kaletra arm. Further, treatment difference tends to be larger with higher baseline viral (p-value for interaction using Breslow-Day test is 0.029).

Since the power of interaction test is affected by the number of categories used. We will use 100,000 as cutpoint to define two categories. The results are as follows:

Proportion <400 copies/mL by baseline HIV RNA and Treatment

| Baseline HIV RNA | KALETRA | NFV | Diff (%) | p-value & 95% CI |
|---|---|---|---|---|
| <=100,000 | 127/156 (81.4%) | 128/162 (79.0%) | 2.4 | 0.591 (-6.4, 11.1) |
| >100,000 | 130/168 (77.4%) | 101/161 (62.7%) | 14.7 | 0.003 (4.9, 24.4) |
| Missing | 2/2 (100%) | 4/4 (100%) | 0 | NA |

Again, the response rate is lower with higher baseline viral load. The p-value for interaction is now 0.135, still suggesting that treatment differences are different in the two subgroups defined by baseline HIV RNA level.

Analysis using proportions <50 copies/mL yields similar results. However, the drop in response rate in the Kaletra arm as baseline HIV RNA level increases is steeper than in the previous two tables. Suggesting that even though the Kaletra arm maintained a somewhat similar proportions <400 copies/mL, but not for proportions below 50 copies/mL.

Proportion <50 copies/mL by baseline HIV RNA and Treatment

| Baseline HIV RNA | Kaletra | NFV | Diff (%) | p-value & 95% CI |
|---|---|---|---|---|
| <=25,000 | 52/72 (72.2%) | 61/77 (79.2%) | -7.0 | 0.319 (-20.8, 6.8) |
| (25,000, 100,000] | 61/84 (72.6%) | 60/85 (70.6%) | 2.0 | 0.770 (-11.6, 15.6) |
| (100,000, 250,000] | 52/88 (59.1%) | 46/75 (61.3%) | -2.2 | 0.771 (-17.3, 12.8) |
| >250,000 | 43/80 (53.8%) | 26/86 (30.2%) | 23.5 | 0.0016 (8.9, 38.1) |
| Missing | 2/2 (100%) | 3/4 (75%) | 0 | NA |

1. Response rate tends to be lower with higher baseline viral load (p-value =0.001 with CMH test)
2. Treatment difference tends to be larger with higher baseline viral load (p-value for interaction using Breslow-Day test is 0.027).

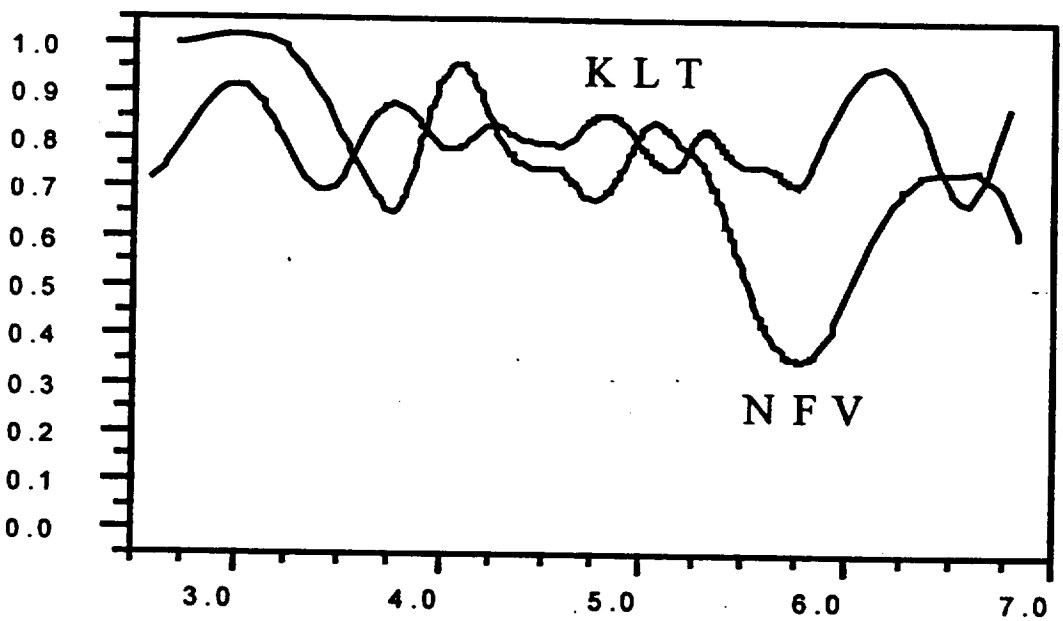
Proportion <50 copies/mL by baseline HIV RNA and Treatment

| Baseline HIV RNA | Kaletra | NFV | Diff (%) | p-value & 95% CI |
|---|---|---|---|---|
| <=100,000 | 113/156 (72.4%) | 121/162 (74.7%) | -2.3 | 0.648 (-12.0, 7.4) |
| >100,000 | 95/168 (56.5%) | 72/161 (44.7%) | 11.8 | 0.031 (1.1, 22.6) |
| Missing | 2/2 (100%) | 3/4 (75%) | 0 | NA |

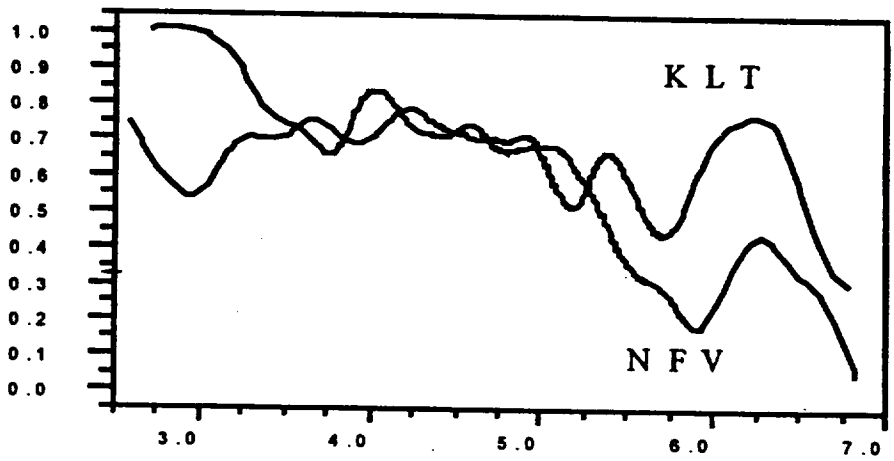
The p-value for interaction is 0.080.

Graphically examine the relationship between the response rate and baseline HIV RNA supports the conclusions above. The graphs below show how the response rates (computed by a weighted local average) change as baseline HIV RNA level increases (on a Log10 scale). Note the two ends should be ignored as they represent only a few cases.

Proportions <400 copies/mL Over Log10 baseline HIV RNA level



Proportions <50 copies/mL Over Log10 Baseline HIV RNA Level




**Baseline CD4** is correlated to the baseline HIV RNA with correlation coefficient 0.65. Therefore the role of baseline CD4 in predicting outcome is similar to baseline HIV RNA. The table below shows the response rates of the two treatment arms in subgroups defined by baseline CD4 (>250 vs. ≤250) and baseline HIV RNA.

Percents <400 for KALETRA vs. NFV at Week 24*

| | | Baseline HIV RNA | | |
|---|---|---|---|---|
| | | <100,000 copies/mL | >=100,000 copies/mL | All |
| CD4 | >250 cells | 83 vs. 81 | 78 vs. 72 | 82 vs. 78 |
| | <=250 cells | 78 vs. 78 | 77 vs. 62 | 78 vs. 68 |
| | All | 82 vs. 80 | 77 vs. 65 | 79 vs. 72 |

* Excluding subjects without baseline CD4 or HIV RNA

For example, among subjects with baseline CD4>250 cells/mm$^3$ and baseline HIV RNA level <100,000 copies/mL, 83% in Kaletra arm vs. 81% in Nelfinavir arm achieved proportions <400 copies/mL at Week 24. The last column shows the response rates in the two categories defined by baseline cd4. We see the pattern is similar to the two subgroups defined by baseline HIV RNA.

After eliminating the effects of baseline HIV RNA, the effect of baseline CD4 to the outcome is no longer significant (p-value=0.24).

**Study M97-720**

This trial was initially blinded, then changed to open-label treatment at Amendment 5. All subjects had been randomized for at least 48 weeks by the time of the change. The background therapies include d4T and 3TC.

The trial consists of two stages. At the first stage 32 subjects were randomized to Kaletra 200/100 and 400/100, at stage II 70 subjects were randomized to Kaletra 400/100 and 400/200. The results of the two Kaletra 400/100 arms were combined in the analysis below.

The applicant's analysis used proportions below 400 copies/mL as the primary endpoint. A slightly different endpoint which regards virologic relapsers and CDC Class C events as failures, in addition to viral load >400 copies/mL, has traditionally been used by FDA for longer-term studies and will also be examined here. The table below shows the results of the two analyses. Similar analyses are also included for proportions <50 copies/mL.

Percent of Responder at Week 48 and Week 72

| | N | Assay[1] | Week 48[2] | Week 72[2] | Week 72 Applicant[3] |
|---|---|---|---|---|---|
| 400/100 | 51 | <400 | 82% | 75% | 80% |
| | | <50 | 78% | 71% | 78% |
| 200/100 | 16 | <400 | 100% | 81% | |
| 400/200 | 33 | <400 | 79% | 70% | |

[1] <400 represents Roche Amplicor assay which has a lower detection limit of 400 copies/mL.
[2] By FDA algorithm where virologic failures and CDC class C events were regarded as failures.
[3] Applicant's planned analysis using only viral load at Week 72.

The numbers in the columns "Week 48" and "Week 72" are based on the new algorithms, and early virologic failures and CDC Class C events were carried forward as failures. The last column, "Week 72 Applicant" is based on the proportions below 400 or 50 copies/mL at Week 72 ignoring the virologic history or CDC Class C events.

First note that the response rates for the Kaletra 400/100 arm at Week 48 and 72 are similar to the results from study M98-863 at Week 24, even with the more conservative definition. Further, at Week 48 the response rate of 82% for Kaletra 400/100 vs. 100% for Kaletra 200/100 yielded a p-value of 0.078 (Fisher's Exact test), suggesting possibility that Kaletra 200/100 may be comparable or better than Kaletra 400/100. However, Week 72 results do not support this conclusion.

Overall this trial shows numerically comparable efficacy results to Study M98-863.

**Study M97-765**

This double-blind trial compares Kaletra 400/100 vs. 400/200 in PI experienced, NNRTI naïve subjects. The background treatments are nevirapine plus 2 NRTIs.

This trial is analyzed similarly to Study M97-720.

Percent of Responder at Week 48 and Week 72

| | N | Assay | Week 48 | Week 72 | Week 72 Applicant |
|---|---|---|---|---|---|
| 400/100 | 36 | <400 | 61% | 58% | 75% |
| 400/200 | 34 | <400 | 71% | 62% | |

Again, columns "Week 48" and "Week 72" are based on the new algorithms for responder while the last column is the proportions below 400 at Week 72.

In Kaletra 400/100 arm, six subjects were virologic relapsers but stayed in the trial with Week 72 viral load <400 copies/mL. Therefore the applicant's result (75%) and the reviewer's result (58%) differ at Week 72. The comparisons between the two arms are not statistically significant at either Week 48 or Week 72.

**Study M98-957**

This open-label trial compares Kaletra 400/100 vs. Kaletra 533/133 in NNRTI naïve but multiple PI experienced subjects. At Week 24 the proportions of subjects with HIV RNA <400 copies/mL are 69% out of 29 subjects in Kaletra 400/100 arm vs. 82% out of 28 subjects in the 533/133 arm. The difference is not statistically significant.

**Study M98-940**

This open-label study compares Kaletra 230/57.5 and 300/75 in HIV-infected children. At Week 24 the proportions of subjects with HIV RNA <400 copies/mL are 74% out of 49 subjects in Kaletra 233/57.5 arm vs. 73% out of 51 subjects in the 300/75 arm.

The study contains both anti-retroviral naïve (44) and anti-retroviral experienced subjects (56), the response rates are 82% vs. 66% with p-value 0.112. These numbers are consistent with the rates observed in Study M98-863 for naïve subjects and the rates in Study M98-888 for experienced subjects.

**Study M98-888**

This open-label phase III trial compares Kaletra 400/100 with the investigator selected PI(s) in anti-retroviral experienced subjects. Complete Week 24 data were updated on July 27, 2000. The results are summarized in the table below.

Proportion of subjects with Plasma HIV RNA < 400 copies/mL at Week 24
Missing as Failures

| Kaletra | ISPI(s) | p-value |
|---|---|---|
| 43/59 (73%) | 31/59 (53%) | 0.022 |

The treatment difference is statistically significant favoring Kaletra.

There were 19 (32%) subjects who discontinued the study medication or lost to follow-up in the ISPI(s) arm vs. only 8 (14%) subjects in the Kaletra arm. The reasons were not listed in the submission.

CD4 changes from baseline to Week 24 are similar between the two arms. The mean changes were 64 cells/mm$^3$ for the Kaletra arm and 68 cells/mm$^3$ for the ISPI(s) arm. The p-value for the difference is 0.883



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**E: Statistical Reviewer's Overall Assessment**

Study M98-863 demonstrated that Kaletra 400/100 is likely to be superior to Nelfinavir when administered together with d4T and 3TC in anti-retroviral naïve subjects in achieving plasma HIV RNA below 400 copies/mL at Week 24. The proportions of subjects achieving plasma HIV RNA below 50 copies/mL is not statistically significantly different between the two arms but Kaletra arm is at most 5% worse than Nelfinavir arm based on the 95% confidence interval of the worst-case analysis. All discontinuations are regarded as failures in the above analyses. Study M97-720 demonstrated a response rate consistent with Study M98-863.

Study M98-888 demonstrated (without reviewer verification) that Kaletra 400/100 is likely to be superior to investigator selected PI(s) when administered together with nevirapine and two NRTIs in anti-retroviral experienced subjects in achieving plasma HIV RNA below 400 copies/mL at Week 24. Studies M97-765, M98-957 showed comparable response rates.

In addition, based on Study M98-863, there is evidence that the treatment difference between Kaletra and Nelfinavir increases as baseline HIV RNA level increases, primarily due to faster decline of response rate in the Nelfinavir arm.

Greg Soon, Ph.D.
Mathematical Statistician 10/6/00

/S/

/S/ 10/6/00

Concur: Mo Huque, Ph.D.
Division Director, DBIII

cc:
HFD-530
HFD-530/MedDivDir/HJolson (via TeamLinks)
HFD-530/MedTL/JMurray
HFD-530/MO/KStruble
HFD-530/PM/SLynche
HFD-725/Stat/GSoon
HFD-725/StatDivDir/MHuque
HFD-725/StatSec/DRobinette

This review contains 18 pages.