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*APPLICATION NUMBER:*

**21-226/S-003**

**21-251/S-004**

**MEDICAL REVIEW**

**Medical Review**  
**NDA 21-226 SE8-003**  
**Lopinavir/Ritonavir for the Treatment of HIV-1 Infection**

**Date Submitted:** March 19, 2001  
**Date Completed:** February 5, 2001

**Applicant:** Abbott Laboratories  
100 Abbott Park Road  
D-491, AP6B-1Sw  
Abbott Park, Illinois 60064-6108

**Drug:** Lopinavir/ritonavir

**Trade name:** KALETRA

**Formulation:** 133/33 mg capsules

**Dosage:** 400/100 mg BID

**Indication:** KALETRA is indicated in combination with other antiretroviral agents for the treatment of HIV infection.

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### Executive Summary

This executive summary contains the Recommendations and the Summary of Clinical Findings for NDA 21-226, KALETRA (lopinavir/ritonavir) for the treatment of HIV-1 Infection. This supplemental application includes additional follow-up on two studies (study 863 and 957) included in the original NDA application. Submission of 48 week data from study 863 partially fulfills the requirements for traditional approval for which two well controlled studies of at least 48 weeks in duration are required. Results from the second 48 week, phase 3 study will be submitted in this calendar year.

#### A. Recommendation on Approvability

Based on the data submitted by Abbott Laboratories, it is recommended that this supplemental application receive an approval action. Results from 2 clinical trials in adults submitted in this sNDA clearly demonstrate a favorable safety and efficacy profile for both treatment naïve and treatment experienced patients following 48 weeks of treatment with lopinavir/ritonavir containing regimens.

#### B. Recommendation on Phase 4 Studies

In the 48-week analyses of data from study 863, the applicant found that Caucasians had a higher treatment response (HIV RNA < 400 copies/mL) than individuals classified as black, 81% vs. 63%, respectively. The higher response rate appeared to be a result of a higher discontinuation rate among blacks for reasons other than adverse events. However, sometimes this "other" category includes patients who may have discontinued drug for intolerability occurring with less severity than what the protocol specifies as requiring drug discontinuation. Upon review of all adverse events of all severity, lopinavir/ritonavir did not appear to be less well tolerated by blacks and than whites. In fact, diarrhea and other gastrointestinal events, which are the more common adverse events associated with lopinavir/ritonavir, occurred somewhat more frequently in white patients. Therefore with the currently available data, it is difficult to conclude whether there a real race related difference in the safety or efficacy of lopinavir/ritonavir. Differences observed in study 863 with respect to treatment response may have been influenced by some other confounding factor.

Given that the issue regarding a potential race effect is unresolved, the Division has asked the applicant to investigate the relative safety and efficacy of lopinavir/ritonavir in Caucasians compared to non-Caucasians (blacks in particular). This could be accomplished, at the time of traditional approval, by conducting analyses of all of Abbott's clinical trial data including ongoing study 888 (the second study for traditional approval).

#### Risk Communication

Wording in the Precautions section of the label regarding the use of lopinavir/ritonavir in patients with hepatic impairment has been strengthened.

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**SUMMARY OF CLINICAL FINDINGS****A. Overview of Clinical Program**

**Trade Name:** KALETRA  
**Class:** Protease Inhibitor  
**Formulation:** Capsules  
**Dosage:** 400/100 mg BID

**Number of important trials:** Two studies, M98-863 and M98-957 were submitted with this efficacy supplement.

**Number of patients enrolled in these trials:** Six hundred and fifty-three patients were included in study M98-863 and 57 patients were included in study M98-957

**Indications studied:** Treatment of HIV infection

**B. Efficacy Summary**

This sNDA provides additional follow-up on efficacy results from a phase 3 comparative 48 week trial in treatment naïve patients and efficacy results from a phase two dose study evaluating two doses of lopinavir/ritonavir in PI experienced patients. In both studies the efficacy of lopinavir/ritonavir was maintained throughout 48 weeks.

In study 863, a greater proportion of patients in the lopinavir/ritonavir group compared to the nelfinavir group achieved HIV RNA levels < 400 and < 50 copies/mL. These results were confirmed to be statistically significant. Notably, response rates for lopinavir/ritonavir were similar across patient subgroups (baseline HIV RNA > 100,000 copies/mL and CD4 < 50 cells); whereas for nelfinavir the 48 week virologic response was lower for subgroups with higher baseline HIV RNA (HIV RNA > 100,000 copies/mL) or lower baseline CD4 counts (CD4 < 50 cells). The efficacy results suggest that lopinavir/ritonavir may be a preferred treatment for antiretroviral naïve patients, particularly those with high baseline HIV RNA levels and/or low CD4 cell counts

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## C. Safety Summary

### 1. Common adverse events and laboratory abnormalities

The adverse event and laboratory abnormality profile seen in the original NDA was consistent with that observed in this sNDA. No new safety concerns were seen with continued dosing of lopinavir/ritonavir through week 48.

Treatment with lopinavir/ritonavir appears to be well tolerated over 48 weeks. In study 863 the most common types of adverse events (all causality, all severity) were diarrhea (62%), nausea (30%), pharyngitis (22%), and asthenia (22%). Rates of discontinuation of randomized therapy due to adverse events were 5.8% in lopinavir/ritonavir group compared to 4.9% in the nelfinavir group. Generally grade 3 and 4 laboratory abnormalities were similar between lopinavir/ritonavir and nelfinavir with few exceptions. Greater proportions of patients in the nelfinavir group (4.1%) developed a grade 3 or 4 increase in AST compared to the lopinavir/ritonavir group (2.2%). A greater proportion of patients in the lopinavir/ritonavir group (9%) developed a grade 3 or 4 increase in total cholesterol compared to the nelfinavir group (5%). A greater proportion of patients in the lopinavir/ritonavir group (9.3%) developed triglycerides > 750 mg/dL compared to patients in the nelfinavir group (1.3%). Discontinuations due to laboratory abnormalities were infrequent. Through week 48, two patients and no patients discontinued from the lopinavir/ritonavir and nelfinavir groups respectively due to laboratory abnormalities.

In study 957, the most common adverse events of any severity and relationship to study drug reported were related predominantly to the CNS system, digestive system and the body as a whole, specifically, diarrhea (39%), dizziness (30%), asthenia (23%), flu syndrome (23%), pain (23%) and abnormal dreams (19%). Only six new events that were considered related to study drug occurred between weeks 24-48. The most common laboratory abnormalities were hypercholesterolemia and hypertriglyceridemia. No patients discontinued study for a laboratory abnormality.

### 2. Recommended Warnings

The updated safety data submitted did not trigger any concerns warranting new statements in the Warnings section of the label.

### 3. Unresolved safety issues

As with all protease inhibitors, lopinavir/ritonavir has been associated with metabolic abnormalities, particularly elevation of lipids including triglycerides and LDL cholesterol. Consequently, the resulting unfavorable effect on lipids may potentially confer increased cardiovascular risks. A pharmaceutical collaboration of eight members is currently funding studies to evaluate potential long-term cardiovascular risks of antiretroviral therapies including PIs.

## Dosing

No new information was submitted with this sNDA with respect to dosing.

## D. Special Populations

### 1. Gender/Ethnic/Racial Analysis

In study 863, the proportion of patients with HIV RNA < 400 copies/mL was assessed by gender and race. The applicant reports that the proportion of patients with HIV RNA < 400 copies/mL was similar between males (76%) and females (71%). A significant difference was observed for Caucasian and Black patients who received lopinavir/ritonavir. The proportion of Caucasian patients who achieved HIV RNA < 400 copies/mL at week 48 was 81% compared to 60% for Black patients. The applicant states that this difference may be due to observed differences in

premature discontinuations due reasons other than adverse events. A statistically significant greater proportion of Black subjects (19%) compared to Caucasian patients (7%) prematurely discontinued study therapy for "other reasons". Race differences in treatment response for the nelfinavir arm were not apparent.

No statistically significant differences in mean CD4 cell counts were observed between patients in subgroups defined by gender or race

Overall the safety profile of lopinavir/ritonavir did not differ according to gender or race. All causality and all severity adverse events were similar in Caucasian and Black patients

At this time it is not clear whether the race differences in response to lopinavir/ritonavir is related to virologic efficacy, tolerability, or some other confounding factor such as baseline disease severity or adherence. Further investigation using a larger pooled study data base may prove to be helpful in this regard.

#### **Other Special Populations**

No new pharmacokinetic information on patients with renal or hepatic insufficiency was submitted in this sNDA; however; the clinical trial database and postmarketing reports were searched for adverse events relating to renal or hepatic failure. There were several cases of hepatitis, transaminase elevation and hepatic decompensation, including fatalities, among patients receiving lopinavir/ritonavir in these reports. A causal relationship was difficult to determine because the vast majority occurred in patients with baseline disease, chronic viral hepatitis and/or cirrhosis. In addition, the interpretation of many of these cases was confounded by the presence of other concomitant medications known to be associated with liver toxicity.

#### **2. Status of pediatric studies and pediatric plan**

Please refer to the review of NDA 21-251 S004 prepared by Dr. Linda Lewis. Supplement 004 contains the updated efficacy and safety data from study M98-940 in antiretroviral naïve and experienced pediatric patients. Also included in S004 was information relating baseline genotype/phenotype to virologic outcome and data on the development of resistance over 48 weeks.

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## Clinical Review

### 1. Background and Introduction

Kaletra (lopinavir/ritonavir) is a protease inhibitor (PI) active against HIV-1. It has been studied for use in the treatment of HIV infection in adult and pediatric patients over the last several years. The initial NDA for Kaletra was granted accelerated approval on September 15, 2000, based on results of 5 phase 2 and 3 studies ranging from 24 – 72 weeks in duration. A brief summary of all clinical trials submitted in original NDA is presented in the table below.

Study Number	Patient Population (N)	Doses Studied/Control Arm	Design	Duration
<b>Phase 2</b>				
M97-720	Naïve (N=100)	200/100 + d4T + 3TC 400/100 + d4T + 3TC 400/200 + d4T + 3TC	Randomized, Open-Label, Dose Ranging	72 weeks
M97-765	Experienced (N=70)	400/100 + NVP + RTIs 400/200 + NVP + RTIs	Blinded, Randomized, Dose Ranging	72 weeks
M98-957	Experienced (N=57)	400/100 + EFV + RTIs 533/133 + EFV + RTIs	Randomized, Open-label	24 weeks
<b>Phase 3</b>				
M98-863	Naïve (N=686)	400/100 + d4T + 3TC Nelfinavir + d4T + 3TC	Randomized, Double-Blind	24 weeks
M98-888	Experienced (N=300) Interim results on 118	400/100 + NVP + RTIs PI Choice + NVP + RTIs	Randomized, Open-label	Interim data on 24 weeks

This sNDA contains 48 week clinical study reports for studies M98-863 and M98-957. Data from the sNDA submission provided information that allowed revisions of the label including 48 week efficacy and safety results from study M98-863 and 48 week clinical virology and safety data from study M98-957. The 48 week data from study M98-863 fulfills one of the two required studies for traditional approval. However, traditional approval will not be granted until the 48 week results from study M98-888 are submitted for review to the Division.

### 2. Relevant Reviews from Other Disciplines

No new chemistry and manufacturing data, pharmacotoxicology data or pharmacokinetic data were submitted with this sNDA. Please refer to the original NDA reviews for background information.

The 48 week clinical virology data from study M98-957 was submitted with this sNDA. Please refer to Dr. O'Rear's review and section 7.2 for further details.

### 3. Description of Data Sources

#### 2.1 Primary Data

This NDA contains clinical data from 2 trials conducted with KALETRA. The clinical submission consists of 119 volumes of study documents and electronic datasets, Case Report Tabulations and Case Report Forms. Clinical efficacy and safety data from the 2 studies were provided in SAS transport file format on CD-ROM.

### 4 Marketing and Post-marketing experience

Kaletra has been approved in the following countries, Argentina, Australia, Austria, Bahrain, Belgium, Brazil, Canada, Chile, Columbia, Costa Rica, Curacao, Denmark,

Dominican Republic, Ecuador, El Salvador, Estonia, Finland, France, Germany, Greece, Guatemala, Honduras, Hong Kong, Hungary, India, Ireland, Israel, Italy, Japan, Korea, Kuwait, Luxemburg, Mexico, Netherlands, Nicaragua, Norway, Panama, Peru, Portugal, Puerto Rico, Romania, Singapore, Spain, Sweden, Switzerland, Taiwan, Thailand, Trinidad & Tobago, Turkey, Uganda, UK, Uruguay, and Venezuela.

#### 5. Review Methods

The medical review is based on the evaluation of NDA Section 8, which includes study reports for two clinical trials and the Integrated Summary of Efficacy and Safety. The applicant's safety and efficacy analyses were confirmed by independent FDA analyses of the data. Dr. Rahia Bhore (Biometrics reviewer) performed the efficacy analyses for the primary and selected secondary endpoints.

For this review the study design, patient demographics, adverse events, laboratory data, efficacy and virology results were reviewed in detail for studies, M98-863 and M98-957. JMP Statistical Discovery software was used to evaluate the efficacy, virology and safety data. In this review, tables that were derived from the applicant's presentation of the data are cited in the table footnotes while those that are derived from reviewer-generated results are not referenced.

DSI audits were not requested for this application. DSI audits were made for the original NDA for study M98-863. Only minor violations were noted at that time and did not appear to affect the quality of the data submitted.

#### Financial disclosure

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## 6 Review of Efficacy in Antiretroviral Naïve Patients

### 6.1 Clinical Trial M98-863

"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"

#### 6.1.1. Study Design

This was a randomized, double-blind, multi-country study in 686 antiretroviral naïve patients with HIV RNA levels > 400 copies/mL. Patients were randomized to one of two blinded treatment arms.

Group 1: 400 mg lopinavir/100 mg ritonavir BID + nelfinavir placebo + stavudine 40 mg BID + lamivudine 150 mg BID

Group 2: Nelfinavir 750 mg TID + Lopinavir/ritonavir placebo + stavudine 40 mg BID + lamivudine 150 mg BID

All patients received open label stavudine and lamivudine. After FDA approval of the twice daily dosing regimen for nelfinavir, patients were given the option to dose nelfinavir or its matching placebo at 1250 mg BID or remain at 750 mg TID.

Adverse events, physical exam, laboratory monitoring for toxicity, and immunologic and virologic assessments of efficacy were performed at regular intervals.

Adverse Events and laboratory abnormalities were assessed by the standardized ACTG Toxicity Grading Table.

#### 6.1.2 Analysis Plan

For this submission the primary efficacy endpoint was the time until loss of virologic response through week 48.

Secondary efficacy endpoints included the proportion of patients with plasma HIV RNA levels < 400 and < 50 copies/mL at each visit and change from baseline and time weighted change from baseline (DAVG) for HIV RNA levels and CD<sub>4</sub> cell counts.

The primary safety endpoint was the incidence of patients with grade 3 or greater adverse events and laboratory abnormalities. The secondary safety endpoints were the proportion of patients who discontinued study drug due to adverse events, time to first study drug dose modification and time to study drug discontinuation and changes in weight and Karnofsky performance status. All patients who received at least 1 dose of study drug were assessed for safety. Treatment-emergent events were compared between arms using COSTART terms

#### 6.1.3. Study Population and Patient Disposition

Patients with who were greater than 12 years of age and had HIV RNA > 400 copies/mL, no evidence of acute illness, had not been treated for an active OI within 30 days of screening and did not require and agreed not to take any medications that are contraindicated with protease inhibitors for the duration of the study were included in the study.

Patients with a history of active substance abuse or psychiatric illness that could preclude compliance with protocol or had the following laboratory abnormalities were excluded from the study; hemoglobin < 8.0 mg/dL, absolute neutrophil count < 750 cells/mm<sup>3</sup>, platelet count < 20,000, ALT/AST > 3x ULN, creatinine > 1.5 X ULN. Patients who were pregnant or lactating, received an investigational drug(s) within 30 days prior to study dosing or any antiretroviral within 30 days prior to screening and received > 14 days of any antiretroviral therapy were excluded from the study.

A total of 686 patients were randomized to this study. Six hundred and fifty three patients received at least one dose of ABT-378/ritonavir or nelfinavir.

Baseline demographics are displayed in Table 6.1.3.A. The baseline demographic characteristics were similar for both treatment groups. The two treatment groups were similar with respect to gender, race, age, baseline mean HIV RNA levels, or baseline mean CD<sub>4</sub> cell counts. Patients were predominantly male (80%) and Caucasian (69%). The mean age was 37.8 years (19-84) with a mean HIV RNA of 4.9 log<sub>10</sub> copies/mL and mean CD<sub>4</sub> cell count of 258 cells/mm<sup>3</sup>.

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Table 6.1.3.A. Demographic and Baseline Data

	Lopinavir/ Ritonavir	Nelfinavir
Number of Patients	326	327
Mean age, Yrs	38.4	37.3
Gender		
Male	260 (80%)	264 (81%)
Female	66 (20%)	63 (19%)
Race:		
Caucasian	226 (69%)	222 (68%)
Black	87 (27%)	86 (26%)
Asian/Pacific Islander	8 (2%)	12 (4%)
Native American/Alaskan Native	3 (<1%)	3 (<1%)
Mixed Race	2 (<1%)	2 (<1%)
Missing	0	2 (<1%)
Baseline mean plasma HIV RNA (PCR), log <sub>10</sub> copies/mL	4.89	4.92
Baseline median CD4 cell count (cells/mm <sup>3</sup> )	260	257

Source: volume 1/119: page 152 Table 11.2a; page 154 Table 11.2b

A total of 56 and 77 patients prematurely discontinued study drug from the lopinavir/ritonavir and nelfinavir groups, respectively. Table 6.1.3.B. summarizes the premature discontinuations. The applicant reports that a statistically significant difference was noted between the treatment groups with respect to proportion of patients who withdrew due to virologic failure; two patients in the lopinavir/ritonavir group (0.6%) and 30 (9.2%) in the nelfinavir group. It is important to note that the protocol did not mandate that patients discontinue due to virologic failure. This finding raises some question regarding the adequacy of the blinding of this study. The applicant encapsulated nelfinavir tablets for the study. Three patients in the nelfinavir group opened the blinded nelfinavir capsules and therefore the blind was broken for these patients. It is unclear if additional patients were able to determine if they were receiving nelfinavir/placebo.

Based on a review of selected patient records it appears that some patients returned approximately one third of the dispensed nelfinavir/placebo. This could be a reflection of poor adherence to the mid day dose. Clearly the blinding was not optimal because some patients were able to break the blind. However, since the applicant was not able to obtain placebo for nelfinavir, over-encapsulating was a reasonable alternative. Given that the endpoint is objective, confirmed laboratory values, this does not raise serious problems with the validity of the overall study conclusions.

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**Table 6.1.3.B. Summary of Primary Reasons for Premature Discontinuation**

	ABT-378/ritonavir	Nelfinavir	P-value <sup>a</sup>
Total Subjects Discontinued <sup>b</sup>	56 (17.2%)	77 (23.5%)	0.052
Adverse event/HIV-related event <sup>c</sup>	16 (4.9%) <sup>d</sup>	14 (4.3%)	0.713
Lost to follow-up	13 (4.0%)	16 (4.9%)	0.705
Other	9 (2.8%)	3 (0.9%)	0.089
Personal reasons	5 (1.5%)	7 (2.1%)	0.772
Subject died	5 (1.5%)	3 (0.9%)	0.505
Subject noncompliant	7 (2.1%)	6 (1.8%)	0.788
Subject required prohibited medication	1 (0.3%)	0 (0.0%)	0.499
Virologic failure <sup>e</sup>	2 (0.6%)	30 (9.2%)	<0.001***

\*\*\* Indicates statistical significance at the 0.001 level.

a P-values computed using Fisher's exact test.

b Subjects could have indicated more than one primary reason for discontinuation.

c Regardless of relationship to study medication.

d Includes one subject who discontinued due to an HIV-related event with onset >30 days after the last dose of study drug.

e The protocol did not require subjects to discontinue for virologic failure.

Source: Vol 1/119 page 147 Table 10.1a

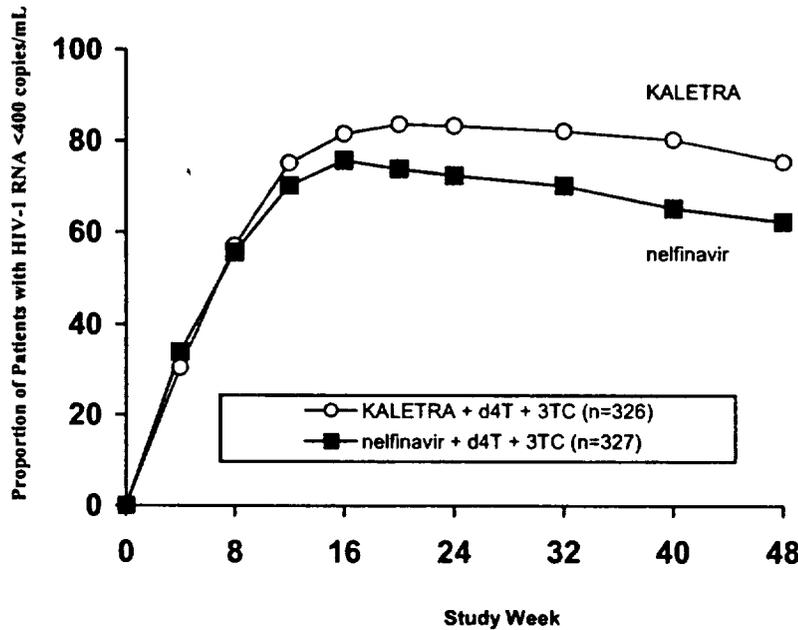
#### 6.1.4. Review of Efficacy:

Please refer to Dr. Bhore's statistical review for a comprehensive analysis of the final efficacy results. The methods of the statistical analysis used are detailed in Dr. Bhore's review. In brief, the Division of Antiviral Drug Products time to loss of virologic response algorithm for the intent to treat population was used for the primary analysis. For NDAs with 48 week virologic data, analyses comparing time to virologic failure is 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.

Proportion of patients with HIV RNA levels < 400 copies/mL and < 50 copies/mL were also evaluated through week 48. The proportion sustaining HIV RNA below 400 copies is shown in the figure and table below. Through 48 weeks of therapy, there was a statistically significantly higher proportion of patients in the KALETRA arm compared to the nelfinavir arm with HIV RNA <400 copies/mL (75% vs. 62%, respectively) and HIV RNA <50 copies/mL (67% vs. 52%, respectively).

**Virologic Response Through Week 48, Study 863\*†**



\* Roche AMPLICOR HIV-1 MONITOR Assay.

† Discontinuations and missing data were considered as HIV-1 RNA ≥400 copies/mL.

**Table 6.1.4.A Outcomes of Randomized Treatment Through Week 48 (Study 863)**

Outcome	KALETRA+d4T+3TC (N=326)	Nelfinavir+d4T+3TC (N=327)
Responder* <sup>1</sup>	75%	62%
Virologic failure <sup>2</sup>	9%	25%
Rebound	7%	15%
Never suppressed through Week 48	2%	9%
Death	2%	1%
Discontinued due to adverse event	4%	4%
Discontinued for other reasons <sup>3</sup>	10%	8%

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

In addition, treatment responses by baseline HIV RNA level subgroups were also evaluated. Results from these analyses are presented in the Table below. Similar HIV RNA responses were observed in both treatment groups for patients with baseline HIV RNA < 30,000 copies/mL. A greater proportion of Kaletra treated patients with baseline HIV RNA  $\geq$  30,000 copies/ml achieved < 400 and < 50 copies compared to patients in the nelfinavir group.

#### Proportion of Responders Through Week 48 by Baseline Viral Load

Baseline Viral Load (HIV-1 RNA copies/mL)	KALETRA +d4T+3TC			Nelfinavir +d4T+3TC		
	<400 copies/mL <sup>1</sup>	<50 copies/mL <sup>2</sup>	n	<400 copies/mL <sup>1</sup>	<50 copies/mL <sup>2</sup>	n
<30,000	74%	71%	82	79%	72%	87
$\geq$ 30,000 to <100,000	81%	73%	79	67%	54%	79
$\geq$ 100,000 to <250,000	75%	64%	83	60%	47%	72
$\geq$ 250,000	72%	60%	82	44%	33%	89

<sup>1</sup> Patients achieved and maintained confirmed HIV RNA <400 copies/mL through Week 48.

<sup>2</sup> Patients achieved HIV RNA <50 copies/mL at Week 48.

CD4 cell count responses were similar for both treatment groups. Through 48 weeks of therapy, the mean increase from baseline in CD4 cell count was 207 cells/mm<sup>3</sup> for the KALETRA arm and 195 cells/mm<sup>3</sup> for the nelfinavir arm.

## 6.2 Clinical Virology:

The applicant evaluated the development of resistance in this study by analyzing the genotype and phenotype of viral isolates from patients who had at least one HIV RNA value  $\geq$  400 copies/mL at week 24, 32, 40 or 48. Genotype and phenotype testing were performed by

The criteria for performing baseline genotype differed for the two treatment arms. For patients randomized to lopinavir/ritonavir, baseline genotype was attempted for every subject for whom a rebound sample was available. This was done to enable a complete analysis of any viral evolution during treatment with lopinavir/ritonavir. For patients randomized to nelfinavir, baseline genotype was attempted retrospectively only for those subjects for whom documented primary resistance to nelfinavir (see definition below) was present at rebound. The purpose for the baseline samples from these subjects was to confirm that evidence of resistance was not present prior to therapy. Genotype was determined by population sequencing and was compared to the pNL4-3 laboratory strain of HIV-1.

Genotypic resistance to nelfinavir was defined as the presence of either the D30N and/or L90M mutation. Genotypic resistance to lopinavir was broadly defined as the presence of any primary mutation in the Pr gene associated with PI resistance or a mutation at any other amino acid in the HIV Pr active site at positions, 8, 30, 32, 46, 47, 48, 50, 82, 84 and 90. Secondary mutations were defined as the presence of any of the following mutations; L10F/I/R/V, K20M/R, L24I, L33F, M36I/V, M46I/L, I54I/T/V, A71I/L/T, G73A/S/T, V77I or N88D.

Phenotype was determined for all approved antiretroviral agents for patients in the lopinavir/ritonavir group. Phenotype was not determined for patients randomized to nelfinavir.

### Genotype/Phenotype Results:

The FDA analysis confirms that presented by the applicant in virology report 8. The FDA analysis utilized data contained in statistical table 3.6: listing of genotype data, and statistical table 3.8:

listing of HIV RNA values for subjects with genotype data. Table 6.2.A. summarizes the genotype results.

**Table 6.2.A. Genotype Results**

	Lopinavir/ritonavir	Nelfinavir
# enrolled	326	327
# with HIV RNA $\geq$ 400	58 (18%)	102 (31%)
Genotype available	37/58 (64%)	76/102 (75%)
Baseline and rebound genotype available	33/37 (89%)	26/76 (34%)
# genotypic resistance to randomized treatment	0/37	24/76 (32%)
# with secondary PI mutation(s) at rebound	5	13

**Development of Primary PI Mutations:**

Fifty-eight patients in the lopinavir/ritonavir group and 102 patients in the nelfinavir group had at least one HIV RNA value  $>$  400 copies/mL. The applicant was able to amplify samples from 37 and 76 patients in the lopinavir/ritonavir and nelfinavir groups, respectively, for genotype. Baseline and rebound samples were available for 33 patients in the lopinavir/ritonavir group and 26 patients in the nelfinavir group.

No patients in the lopinavir/ritonavir group displayed genotypic resistance to lopinavir/ritonavir, specifically, the emergence of primary PI mutations was not observed in these patients. The lack of emergence of primary PI mutations was confirmed by genotypic analysis of 33/37 baseline samples. In each case primary PI mutations were absent at baseline and at the time of virologic rebound. In contrast, evidence of genotypic resistance to nelfinavir was observed in 32% (24/76) of patients treated with nelfinavir. Nineteen patients developed with D30N mutation and 7 patients developed with L90M mutation. One patient developed both the D30N and L90M mutations. The emergence of the D30N and L90M mutations during nelfinavir treatment was confirmed by genotypic analysis of the 24/26 baseline samples. Samples were retrospectively analyzed only for those subjects for whom documented primary resistance to nelfinavir was present at rebound. In each case the D30N or L90M mutation was absent at baseline.

**Development of Secondary PI mutations:**

As mentioned above, baseline and rebound viral isolates were available for 33 patients in the lopinavir ritonavir group. An analysis of the development of secondary mutations was also conducted. Secondary mutations were defined as any of the following: L10F/I/R/V, K201M/R, L24I, L33F, M36I/V, M46I/L, I54L/T/V, A71I/L/V/T, G73A/S/T, V77I or N88D. The results of these analyses are described below.

Five patients in the lopinavir/ritonavir group developed a secondary PI mutation. Three patients developed a M36M/I mutation, one patient developed a L10F mutation and one developed the A71T mutation. Of note, 13/33 patients had at least one of these 3 mutations present at baseline. These mutations present at baseline did not effect the phenotypic susceptibility to lopinavir, therefore it does not appear that these mutations adversely affected response rates.

In contrast more patients in the nelfinavir group developed a secondary PI mutation. Thirteen nelfinavir treated patients developed one or more secondary PI mutations in addition to either the D30N or L90M mutation. Six patients developed an A71T/V mutation, five developed a M36I/M mutation, four developed a M46I/V mutation and two developed a L10F/I/V mutation. The remaining three patients developed a V77I, G73S or N88D mutation. Baseline genotype was only available for those patients who developed a D30N or L90M mutation, therefore it is not

known how many patients had secondary PI mutations at baseline. Of the 26 patients with a baseline and rebound sample, 17 had a secondary PI mutation at baseline. Phenotypic results were not available for the nelfinavir group so it is not known if these mutations effected the phenotypic susceptibility to nelfinavir.

***Development of Other Changes in PR gene:***

Ten patients (30%) in the lopinavir/ritonavir group developed changes in the PR gene other than primary or secondary PI mutations. The following mutations were identified in these patients: I13V (3), L72 I/V (2), H69H/Y, K70T, L19L/V, D60D/E, I62I/V, R57K and N37N/S. The clinical significance of the development of these mutations is unknown at this time. More data is needed to assess whether any of these mutations confer loss of virologic response.

***Development of NRTI Mutations – M184V:***

The applicant also evaluated the number of patients who developed a M184V mutation at virologic rebound. The applicant cites a significant difference in the incidence of 3TC resistance between the lopinavir/ritonavir group (15/37, 41%) and the nelfinavir group (62/76, 82%). Interestingly, all patients who developed either the D30N or L90M mutation also developed the M184V mutation. Although these findings are interesting, they should be viewed with caution. Baseline genotype was not available for 52 (68%) patients in the nelfinavir group, therefore it is not known if the M184V mutation observed during viral rebound was present at baseline. A comparison between the two groups should only be made after baseline genotype is available for all nelfinavir treated patients who developed a M184V mutation.

***Phenotypic Results:***

Phenotypic samples at the time of virologic rebound were available for 36/37 patients in the lopinavir group. No evidence of phenotypic resistance to lopinavir was detected. All samples displayed < 2.5 fold reduced susceptibility to lopinavir, as well as to all other PIs tested, compared to the standard wild-type control virus. Phenotypic data for patients in the nelfinavir group were not collected.

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## Conclusions:

Overall no patients in the lopinavir/ritonavir group developed genotypic or phenotypic resistance to lopinavir, whereas 32% of patients in the nelfinavir group developed genotypic resistance to nelfinavir. Also fewer patients in the lopinavir/ritonavir group compared to patients in the nelfinavir group developed a new secondary PI mutation. The differences in the development of resistance between lopinavir/ritonavir and nelfinavir may be explained by plasma concentrations. One of the objectives of the phase 1 and 2 development of lopinavir was to maximize lopinavir exposures, such that there would be a substantial ratio between plasma concentrations and in vitro inhibitory concentrations. Mean  $C_{min}$  values for lopinavir/ritonavir 400/100 mg BID are approximately 70 fold above the mean  $EC_{50}$  in the presence of human serum. Whereas for nelfinavir, the mean  $C_{min}$  values is approximately 5 fold above the mean  $EC_{50}$ . Therefore the differences in the  $C_{min}$  to  $EC_{50}$  ratios may account for the observed differences in the development of resistance mutations. Longer-term data is needed to assess the development of resistance in antiretroviral naïve patients receiving lopinavir/ritonavir containing regimens.

### 6.3 Review of Safety in Antiretroviral naïve Patients

In general, the FDA analysis of the safety data confirmed the applicant's findings. There were only minor differences between the two analyses, which did not affect the overall results and conclusions.

A total of 653 patients were included in the safety analysis. Data from patients who discontinued drugs due to adverse events were reviewed to identify possible risk factors associated with adverse events. All serious adverse events were reviewed individually.

The median duration of study drug exposure was 378 days for both treatment groups. The applicant states that over 77% of the patients in each treatment group received study drug for greater than 48 weeks.

#### 6.3.1 Overview of Adverse Events

Overall 96% of patients experienced at least one adverse event (all causality/all severity) during the 48 weeks of the study. The most common adverse events of any severity and relationship to study drug reported in the lopinavir/ritonavir group were diarrhea (62%), nausea (30%), pharyngitis (22%), and asthenia (22%). The most common adverse events reported in the nelfinavir group were diarrhea (64%), pharyngitis (27%), nausea (24%) and rash (20%). For either dose group the common adverse events were predominately gastrointestinal events such as diarrhea, and nausea. In the original NDA (data through week 24), a greater proportion of patients in the lopinavir/ritonavir group experienced vomiting, taste perversion, eczema, neuropathy and UTIs compared to patients in the nelfinavir group. With the exception of urinary tract infections (UTIs), these events were also seen with extended dosing through week 48. Through week 48, a greater proportion of patients in the lopinavir/ritonavir group compared to the nelfinavir group experienced the following treatment-emergent adverse events; vomiting (18% vs 12%), taste perversion (5% vs 1%), eczema (6% vs 2%), neuropathy (3% vs 0.3%). In this sNDA (safety data through week 48), the following events were also observed in a greater proportion of patients in the lopinavir/ritonavir group compared to the nelfinavir group; asthenia (22% vs 15%), ear disorder (3% vs 1%), and convulsion and skin ulcer (2% vs 0% each). In addition, a greater proportion of patients in the nelfinavir group compared to the lopinavir/ritonavir group experienced urticaria (2% vs 0%).

Table 6.3.1.A. summarizes treatment-emergent events (at least moderate severity) that are of probable, possible or of unknown relationship to lopinavir/ritonavir or nelfinavir and with an incidence of greater than 2 percent. With the exception of dyspepsia, the incidence of these events were similar between treatment groups and did not appear to increase significantly with extended dosing through week 48.

**Table 6.3.1.A. Treatment-emergent events that are of probable, or possible relationship to study drug and occurring in > 2 percent of patients**

Body System	Weeks 0-24		Weeks 0-48	
	Lopinavir/ritonavir (n=326)	Nelfinavir (N=327)	Lopinavir/ritonavir (n=326)	Nelfinavir (N=327)
<b>Body As A Whole</b>				
Abdominal pain	10 (3.1%)	8 (2.4%)	13 (4%)	10 (3.1%)
Asthenia	11 (3.4%)	9 (2.8%)	13 (4%)	11(3.4%)
Headache	8 (2.5%)	6 (1.8%)	8 (2.5%)	6 (1.8%)
<b>Digestive</b>				
Diarrhea	45 (13.8%)	47 (14.4%)	51 (15.6%)	56 (17.1%)
Dyspepsia			7 (2.1%)	1 (0.3%)
Nausea	21 (6.4%)	13 (4%)	22 (6.7%)	15 (4.6%)
Vomiting	7 (2.1%)	8 (2.4%)	8 (2.5%)	8 (2.4%)

### 6.3.2. New AIDS-defining events:

Table 6.3.2.A lists the patients who experienced a new AIDS defining event during the study. A patient was considered to have experienced a new AIDS defining event (as defined by the 1993 CDC classification system) if the event was not present at baseline or noted in the medical history and occurred after at least 7 days of receiving study drug. Six patients in the lopinavir/ritonavir group and seven patients in the nelfinavir group experienced a new AIDS defining event. The majority of these events were noted in the original NDA. One patient in each treatment group experienced a new AIDS defining event after week 24 (events noted in bold type). Four patients in each arm achieved HIV RNA < 400 copies/mL at week 48 despite developing a new AIDS defining.

**Table 6.3.2.A. List of New AIDS Defining Events Through Week 48**

Patient #	Event	RX day	HIV RNA at week 48	CD4 Cell Count at week 48
<b>Lopinavir/ritonavir</b>				
3123	Cryptosporidiosis	15	< 400	271
<b>3227</b>	<b>Lymphoma, Burkitt's</b>	<b>307, 331</b>	<b>&lt; 400</b>	<b>216</b>
3321	KS	113	Premature DC	Premature DC
3390	KS	14	< 400	146
3574	MAI	71	<400	228
3609	MAI	29	1730	412
<b>Nelfinavir</b>				
3183	MAI	41	Premature DC	Premature DC
3364	Lymphoma	15, 20,22,37, 42,63	Premature DC	Premature DC
<b>3370</b>	<b>KS</b>	<b>218</b>	<b>&lt; 400</b>	<b>261</b>
3459	Lymphoma	20	Premature DC	Premature DC
3463	Lymphoma	140, 164	<400	166
3640	CMV ret	50	<400	165
3641	CMV ret	42	<400	246

### 6.3.3. Other Events of Interest:

#### 6.3.3.1. Hepatic Events:

##### Hepatitis:

In the original NDA, one case of hepatitis was reported in the lopinavir/ritonavir group. Patient #3191 developed hepatitis after receiving lopinavir/ritonavir for approximately 5 months. The patient also had hepatitis C at baseline. The patient reported anorexia and fatigue, however the study drug was never interrupted for this event. The investigator felt that this event was related to hepatitis C infection. It is unclear if this case of hepatitis was also related to lopinavir/ritonavir. The patient had ALT values that were < 2 times the upper limit of normal during treatment. Bilirubin levels peaked at 2.2 mg/dL at a time when the ALT was 67 U/L.

In this sNDA, two additional cases of hepatitis were reported (patients # 3201 and #3685). Both cases were related to hepatitis A and not related to treatment with lopinavir/ritonavir.

One case of moderate hepatitis was reported in the nelfinavir group (patient # 3608). This event was considered not related to nelfinavir use.

#### 6.3.3.2. Pancreatitis:

Four cases of pancreatitis in the lopinavir/ritonavir were reported in the original NDA. No new cases of pancreatitis following an additional 6 months of lopinavir/ritonavir dosing were reported in this sNDA. This finding is encouraging given the concern that patients who develop triglyceride values > 1000 mg/dL, a known laboratory abnormality for the ritonavir component of this product, may be at increased risk for pancreatitis. In the original NDA it was noted that patients with a history of pancreatitis might be at increased risk for recurrence during lopinavir/ritonavir treatment. Therefore, evaluation of cases of pancreatitis during planned and ongoing studies and during post marketing is still essential.

Brief summaries of the cases of pancreatitis are provided below.

- Patient 3430 developed pancreatitis approximately 5 months after receiving ABT-378/ritonavir. His past medical history is unremarkable. Pancreatitis was diagnosed based on an elevated amylase level (249 U/L). However, at baseline his amylase was 241 U/L and remained elevated. Study drug was not interrupted for this event. The patient's peak triglyceride level during treatment with ABT-378/ritonavir was 328 mg/dL. It is unclear if this event was a case of pancreatitis.
- Patient 3651 please refer Deaths (section 6.3.6) for further details
- Patient 3191 please refer Deaths (section 6.3.6) for further details
- Patient 3401 noted mild back pain on study visit 40. His amylase was 730 u/L and pancreatic amylase was 683 u/L. Three days later the patient was hospitalized due to severe epigastric pain and evaluation of pancreatitis. A NG tube was placed and the patient was "pain free." While in the hospital the patient was placed on amphotericin for cryptococcal skin lesions. Several days later his amylase returned to normal. The next day, the patient's pain reoccurred and his amylase increased. The patient was subsequently discharged 13 days after initial hospitalization. At discharge his amylase was 189 u/L. A relationship of this event to lopinavir/ritonavir can not be ruled out, however the patient was also receiving stavudine and lamivudine and Bactrim for 40 weeks.

#### 6.3.3.3 Metabolic Complications:

##### **Body Fat Composition Changes:**

A total of 7 patients in the lopinavir/ritonavir group and 4 patients in the nelfinavir group reported body fat composition changes during the first 24 weeks of the study. Most of these events were considered related to study drug by the investigator. Following 48 weeks of treatment with

lopinavir/ritonavir or nelfinavir, a total of 16 patients in the lopinavir/ritonavir group and 18 patients in the nelfinavir group reported body fat composition changes that were considered related to study drug by the investigator. For the patients randomized to the lopinavir/ritonavir group, the body fat composition changes appeared approximately after 6.5 months of treatment (range 13 days to 1 year). A listing of the body fat composition changes can be found in Table 6.3.3.3.A

**Table 6.3.3.3.A. Summary of Body Fat Composition Changes in Lopinavir/Ritonavir Group Through Week 48**

Description of Event	Number of Patients/ (%)*
Gynecomastia	2 (0.6%)
Lipoma	2 (0.6%)
Increase in abdominal girth	9 (2.8%)
Peripheral Wasting with or without gluteal wasting	4 (1.2%)
Lipodystrophy: symptoms not reported	3 (0.9%)
Buffalo Hump	1 (0.3%)

\* More than one event may have been reported for each patient

Based on publications in the literature, conference abstracts and postmarketing reports, it is difficult to determine if fat redistribution is related to any particular antiretroviral drug or drug class. Therefore, the Division feels that all approved antiretrovirals should now include information on fat redistribution in the package insert and patient package insert. The Kaletra label already includes information on fat redistribution in the PRECAUTIONS section, however changes were made to this section to include facial wasting in the description.

#### **New-onset diabetes:**

One patient in the lopinavir/ritonavir group developed new onset diabetes after approximately 9 months of treatment. On February 9, 2000, the subject was reported to have an elevated blood glucose of 485 mg/dL. Fasting glucose levels repeated on February 14 and February 23, 2000 were reported as 385 mg/dL and 366 mg/dL, respectively. The subject was started on an unspecified glucose-lowering agent. The investigator opinion of the event of new-onset diabetes mellitus was that it was possibly related to study drug with an alternative etiology of a history of gestational diabetes and family history of diabetes mellitus.

Three cases of new onset diabetes were observed in the nelfinavir group. Two cases were considered not related to nelfinavir use.

#### **Bone Events:**

Recent reports in the literature have suggested that HIV-infected patients receiving protease inhibitor regimens may develop osteopenia and osteoporosis at higher rates than HIV negative controls or HIV infected patients receiving no treatment or non-PI regimens. However, the clinical significance of the reported loss of bone mineral in HIV infected patients is unknown. Therefore, FDA is interested in assessing clinical fracture rates in patients receiving both PI and non PI containing regimens. To better understand these issues and to explore the frequency of fractures in other studies of antiretrovirals, FDA conducted a retrospective analysis of 13 trials to evaluate fracture rates in patients receiving PI vs Non PI containing regimens. Commercial phase 3 studies submitted to the Division between 1999 and 2001 were chosen for the analyses. Trials included in the analyses were the principal studies that were used to support accelerated and traditional approval or a dosing change. All 13 trials in this analysis enrolled antiretroviral naïve patients or patients with limited NRTI experience. All studies were designed to have a minimum of 48 weeks of follow up in at least 1 treatment arm. Data collected included: number of patients with clinical fractures in each treatment group; time to fracture; CD4, HIV RNA level and weight at baseline and at time of fracture; steroid use; and other risk factors. Overall in this meta-

analysis of 13 studies, 2% of patients (202/10166) developed a clinical fracture. The proportion of patients who developed a fracture in the PI and Non PI group was 1.7% (97/5565) and 2.3% (105/4601), respectively. The mean time to fracture event was 296 days. The majority of fractures were a result of trauma/accidental injury.

The proportion of patients who experienced a fracture in study 863 was consistent with that seen in the meta-analysis described above. Overall the proportion of patients who developed a fracture was 2.3%. The mean time to fracture was 208 days. However, it is important to note that the incidence of fractures was higher in the lopinavir/ritonavir group compared to the nelfinavir group. The significance of this difference is unknown. Ten patients in the lopinavir/ritonavir group and five patients in the nelfinavir group developed a fracture. All fractures were a result of accidental injury/trauma. No known risk factors were noted except for a fracture in a 49 year old woman with a history of menopause and a compression fracture in a 46 year old male with a history of vertebral fractures and osteopenia. Longer-term safety data are needed to assess the development of metabolic complications, including bone effects in patients receiving antiretroviral therapy. In efforts to better understand these issues, the applicant is conducting a phase IV long term safety surveillance study of subjects enrolled in this trial. Information on all fractures, regardless of causality, is being collected.

#### **6.3.4 Drug Discontinuations Due to Adverse Events:**

Discontinuations due to adverse events were similar for both treatment groups. Twenty patients (6%) in the lopinavir/ritonavir group and 17 patients (5%) in the nelfinavir group prematurely discontinued study due to an adverse event. Drug related adverse events leading to discontinuation occurred in 3.4% of the lopinavir/ritonavir treated patients and 3.7% of the nelfinavir treated patients. Gastrointestinal events were the common reason for discontinuation in the lopinavir/ritonavir group.

#### **6.3.5 Serious and Life-threatening Adverse Events**

More patients in the lopinavir/ritonavir group compared to the nelfinavir group developed serious adverse events. A total of 76 serious adverse events were reported in 41 (12.6%) patients receiving lopinavir/ritonavir for up to 48 weeks. A total of 44 events were reported in 20 (6.1%) patients receiving nelfinavir for up to 48 weeks. From study week 24 through study week 48, the proportion of patients developing a serious adverse event was similar for both groups; 12 patients in the lopinavir/ritonavir group and 10 patients in the nelfinavir group. There was a wide variety of serious adverse events noted in both groups. No discernable pattern was noted, however there was a larger number of cases of convulsion in the lopinavir/ritonavir arm compared to nelfinavir. Also a larger number of cases of GI events was observed in the nelfinavir group compared to the lopinavir/ritonavir group.

Table 6.3.5.A. summarizes the serious adverse events that are possibly or probably related to study drug. Events occurring after week 24 are depicted in bold type.

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Table 6.3.5.A. Serious Adverse Events At Least Possibly Related

PATIENT	TREATMENT	ONSET	REASON	CAUSALITY	OUTCOME	RESOLUTION
3011	Lopinavir/ritonavir	Day 73	Vasculitis	Possible	Hospitalization	resolved
3159	Lopinavir/ritonavir	Day 1	Dizziness Drug Interaction	Probably Probably	Required medical intervention	resolved
3358	Lopinavir/ritonavir	Day 22	Deep thrombophlebitis	Possibly	Hospitalization Required medical/surgical intervention	ongoing
3145	Lopinavir/ritonavir	Day 195	Pulmonary edema Atelectasis	Possibly	Hospitalization	resolved
3651	Lopinavir/ritonavir	Day 193	Pancreatitis (see pancreatitis section for further details)	possibly	Hospitalization; death	Death
3401	Lopinavir/ritonavir	Day 271	Pancreatitis (see pancreatitis section for further details)	Possibly	Hospitalization	resolved
3184	Nelfinavir	Day 170	Leukopenia	Probably	Required medical/surgical Intervention Discontinued therapy	resolved
3608	Nelfinavir	Day 241	LFT abnormal	Possible	Required medical/surgical Intervention	Resolved
3683	Nelfinavir	Day 281	Acidosis; peripheral neuritis	Possible	Required medical/surgical Intervention Discontinued therapy	Ongoing
3635	Nelfinavir	Day 48	Diarrhea Vomiting Nausea	Possibly Possibly Possibly	Hospitalization Hospitalization Hospitalization	Resolved

### 6.3.6 Deaths

A total of 8 deaths were reported in the original NDA; 5 in the lopinavir/ritonavir group and 3 in the nelfinavir group. No new deaths were reported in this sNDA. Below is a summary of the deaths in the lopinavir/ritonavir group from the original NDA.

- Patient 3307 was a 31 year old male who developed occipital headaches, sleepiness, chills and decreased vision 5 days after initiating lopinavir/ritonavir. He was subsequently hospitalized and diagnosed with cryptococcal meningitis. The patient died one month after beginning study drug. This event was not attributed to lopinavir/ritonavir treatment.
- Patient 3317 died from MAI with wasting syndrome approximately 7 months after receiving lopinavir/ritonavir.
- Patient 3651, died secondary to acute pancreatitis, renal failure, GI bleed and hematuria. She was a 37-year-old who presented to ER with abdominal pain, nausea, hematemesis and hematuria for several days. Four days later a CT with contrast showed an enlarged pancreas. Amylase was 575 u/L and lipase was 9752 u/L. It was also noted that the patient had a possible transitional cell tumor. Amylase and lipase continued to rise; 1006 u/L and 15,278 U/L, respectively. The patient's condition deteriorated and the patient died the next day. It is possible that this death may be related to study drug. To date this is the only case of

fatal pancreatitis in an antiretroviral naïve patient receiving lopinavir/ritonavir in a clinical trial. Although this case is concerning, it is reassuring that the overall incidence of pancreatitis seen in 5 adult clinical trials and the expanded access program of over 3000 patients is approximately <1%. This is similar to the overall incidence noted in HIV-infected patients. Of note, the incidence of pancreatitis for lopinavir/ritonavir is less than that seen with ddl and/or d4T.

- A sudden death resulting from arteriosclerotic cardiovascular disease was reported for patient 3163 after approximately 9 ½ months with treatment of lopinavir/ritonavir. The police found the patient dead in bed. Drug paraphernalia were noted at the scene. The patient had a history of toxoplasmosis encephalitis. Autopsy report showed cerebral toxoplasmosis, arteriosclerotic cardiovascular disease with cardiomegaly, left ventricular hypertrophy and focally severe 3-vessel coronary atherosclerosis, pulmonary edema and pleural effusions. The toxicology report was noted as non-contributory. Triglyceride and cholesterol values at the last visit were reported as 457 mg/dL and 374 mg/dL, respectively. It appears that this death was not related to study drug, however relationship to study drug is still unclear.
- Patient 3191 died on study day 335 due to community acquired pneumonia. This death was not related to lopinavir/ritonavir treatment.

### 6.3.7 Laboratory Abnormalities

The FDA analysis primarily focused on the incidence of grade 3 and grade 4 laboratory abnormalities and mean change from baseline for selected laboratory tests. Generally grade 3 and 4 laboratory abnormalities were similar between lopinavir/ritonavir and nelfinavir with few exceptions. Greater proportions of patients in the nelfinavir group (4.1%) developed a grade 3 or 4 increase in AST compared to the lopinavir/ritonavir group (2.2%); however, the proportions of patients with ALT abnormalities was similar between treatment arms. Whereas, a greater proportion of patients in the lopinavir/ritonavir group (9%) developed a grade 3 or 4 increase in total cholesterol compared to the nelfinavir group (5%). These differences were not statistically significant. A statistically significant greater proportion of patients in the lopinavir/ritonavir group (9.3%) developed triglycerides > 750 mg/dL compared to the patients in the nelfinavir group (1.3%). Table 6.3.7.A. summarizes the grade 3 and 4 laboratory abnormalities through week 48.

**Table 6.3.7.A. Grade 3 and 4 Laboratory Abnormalities Occurring in > 2% of Patients**

Chemistry Variable	Weeks 0-48	
	Lopinavir/ritonavir (N=312)	Nelfinavir (N=318)
Amylase (> 2 x ULN)	10 (3.2%)	7 (2.2%)
ALT (> 215 U/L)	12 (3.8%)	12 (3.8%)
AST (> 180 U/L)	7 (2.2%)	13 (4.1%)
Cholesterol (> 300 mg/dL)	28 (9%)	16 (5%)
Triglycerides (> 750 mg/dL)	29 (9.3%)	4 (1.3%)
Glucose (> 250 mg/dL)	7 (2.2%)	5 (1.6%)
Uric acid (> 12 mg/dL)	7 (2.2%)	5 (1.6%)

Discontinuations due to laboratory abnormalities were infrequent. Through week 48, two patients and no patients discontinued from the lopinavir/ritonavir and nelfinavir groups respectively due to laboratory abnormalities.

## Review of Selected Abnormalities

### Hematologic Parameters

Grade 3 and 4 hematologic abnormalities are displayed in Table 6.3.7.B. In the lopinavir/ritonavir group two additional patients developed an aPTT abnormality after week 24. Also after week 24, 3 new patients experienced a decrease in hemoglobin value and 3 new patients experienced a decrease in neutrophil counts, in the lopinavir/ritonavir and nelfinavir groups, respectively. In the lopinavir/ritonavir group all patients with a grade 3 or 4 abnormality for hemoglobin or neutrophil counts were also noted to have had low baseline values.

One patient in each group prematurely discontinued study due to an abnormal hematology value. Patient 3321 in the lopinavir/ritonavir group discontinued due to moderate lymphadenopathy. This event was considered not related to lopinavir/ritonavir by the investigator. Patient 3184 in the nelfinavir group discontinued due to leukopenia. This event was considered related to nelfinavir.

**Table 6.3.7.B. Grade 3 and 4 Hematologic Abnormalities**

Hematology Value	Weeks 0-48	
	Lopinavir/ritonavir (N=311)	Nelfinavir (N=319)
Prothrombin Time (> 22.35 sec)	2 (0.6%)	0
Activated Partial Thromboplasin Time (>86.95 sec)	3 (1%)	0
Hemoglobin (< 8 g/dL)	5 (1.6%)	0
Neutrophils (<0.75 x 10 <sup>9</sup> /L)	2 (0.6%)	8 (2.5%)

### Amylase

In the original NDA, 6 patients in each treatment group experienced a grade 3 or 4 increase in amylase values. In this sNDA, 4 additional patients in the lopinavir/ritonavir group and one additional patient in the nelfinavir group experienced a grade 3 or 4 increase in amylase values. Therefore, through week 48, a total of 17 patients developed a grade 3 or 4 amylase abnormality; 10 patients in the lopinavir/ritonavir group and 7 patients in the nelfinavir group. Eight of the 10 patients in the lopinavir/ritonavir group had elevated amylase levels at baseline (range 106 U/L to 247 U/L). No patients in the lopinavir/ritonavir group discontinued study drug for increases in amylase values. Two patients interrupted study drug due to increases in amylase values and the remaining 6 patients did not interrupt study drug.

Four patients with amylase elevations developed pancreatitis. These events occurred in the first 24 weeks of study. For study weeks 24-48 no patients with amylase elevations developed pancreatitis. In addition, none of the patients had concomitant grade 3 or 4 elevations in triglycerides.

### Lipids

Forty-two (13%) and twenty (6%) of patients in the lopinavir/ritonavir and nelfinavir groups, respectively had grade 3 or greater lipid abnormalities. No subjects prematurely discontinued study drug due to these abnormalities. It is important to note that all post baseline lipid values were collected without regard to fasting.

**Cholesterol:**

The proportion of patients with cholesterol > 240 mg/dL was comparable for both treatment groups. However more patients in the lopinavir/ritonavir group had cholesterol levels exceeding 300 mg/dL. This difference was not statistically significant. In addition, mean change in cholesterol at week 48 was comparable for both treatment groups. No patients discontinued study due to cholesterol elevations.

**Table 6.3.7.C. Cholesterol Abnormalities**

	Lopinavir/ritonavir (N=312)	Nelfinavir (N=318)
Grade 1 or no elevation < 240 mg/dL	194 (62%)	204 (64%)
Grade 2 240 –300 mg/dL	90 (29%)	98 (31%)
Grade 3 301-400 mg/dL	22 (7.1%)	15 (5%)
Grade 4 > 400 mg/dL	6 (1.9%)	0
Cholesterol Value > 240 mg/dL	115 (37%)	112 (35%)
Cholesterol Value > 300 mg/dL	28 (9%)	16 (5%)
Mean Change (mg/dL)	53	48

Source FDA analyses and applicant tables 12.4m and 12.4h

**Triglycerides:**

A statistically significant greater proportion of patients developed triglycerides > 750 mg/dL in the lopinavir/ritonavir group compared to patients in the nelfinavir group. Eight patients in the lopinavir/ritonavir group developed triglycerides > 1500 mg/dL of which 6 patients had triglycerides > 2001 mg/dL. A statistically significant mean increase from baseline for triglycerides was observed in the lopinavir/ritonavir group compared to the nelfinavir group. No patients discontinued for elevations in triglycerides and only one patient in the lopinavir/ritonavir group interrupted study drug due to elevated triglycerides. No patients developed pancreatitis as a result of elevated triglyceride values. Triglyceride abnormalities are further summarized in Table 6.3.7.D.

**Table 6.3.7.D Elevations in Triglyceride Levels**

	Lopinavir/ritonavir (N=312)	Nelfinavir (N=318)
Grade 1 or no elevation < 400 mg/dL	209 (67%)	260 (82%)
Grade 2 400-750 mg/dL	74 (24%)	54 (17%)
Grade 3 751 – 1200 mg/dL	15 (5%)	4 (1%)
Grade 4 >1200 mg/dL	14 (5%)	0
Triglyceride value > 750 mg/dL	29 (9%)	4 (1%)
Triglyceride value > 1500 mg/dL	8 (3%)	0
Triglyceride value > 2001 mg/dL	6 (2%)	0
Mean Change (mg/dL)	124	46

Fifteen patients in the lopinavir/ritonavir group received antihyperlipidemic agents as a result of elevated triglycerides/cholesterol. In comparison only four patients in the nelfinavir group received an antihyperlipidemic agent. Based on this limited data it appears that for the majority of patients treatment with antihyperlipidemic agents was effective in reducing overall triglyceride and/or cholesterol levels.

### Transaminases

No significant differences were observed between treatment groups for grade 3 or 4 elevations in AST or ALT or in mean changes from baseline. Table 6.3.7.E summarizes the grade 3 and 4 transaminase abnormalities. Two patients in the lopinavir/ritonavir arm discontinued study due to elevated transaminase levels.

**Table 6.3.7.E Grade 3 and 4 Laboratory Abnormalities**

Chemistry Variable	Lopinavir/ritonavir (n=312)	Nelfinavir (n=318)
ALT (> 215 U/L)	12 (4%)	12 (4%)
AST (> 180 U/L)	7 (2%)	13 (4%)
Mean Change ALT (U/L)	-3.1	-0.2
Mean Change AST (U/L)	-4.3	-1.4

FDA conducted several analyses regarding transaminase elevations and baseline hepatitis B or C. The incidence of baseline hepatitis B or C was similar between treatment groups. Approximately 17% and 21% of patients in the lopinavir/ritonavir and nelfinavir groups has baseline hepatitis B or C, respectively. More patients in the nelfinavir group (n=13) with baseline hepatitis B or C experienced a grade 3 or 4 increase in ALT or AST compared to patients in the lopinavir/ritonavir group (n=6).

The applicant reports that patients with baseline hepatitis B or C were found to be at a significantly increased risk of developing grade 3 or 4 transaminase elevations in both the lopinavir/ritonavir group (risk ratio = 3.49; 95% CI 1.30, 9.38) and the nelfinavir group (risk ratio = 10.16; 95% CI 3.76, 27.47). The applicant also states that in the lopinavir/ritonavir group the risk of grade 3 or 4 transaminase elevations was greater in patients with baseline hepatitis B (risk ratio 4.08; 95% CI 1.26, 13.19) versus baseline hepatitis C (risk ratio 2.19; 95% CI 0.65, 7.34). Interestingly the converse was true for the nelfinavir group. Patients with baseline hepatitis C had a greater risk of transaminase elevations (risk ratio 7.18; 95% CI 3.26, 18.71) compared to patients with baseline hepatitis B (risk ratio 2.84; 95% CI 0.89, 9.03).

### ALT/Bilirubin:

One patient in the lopinavir/ritonavir group developed concomitant grade 3+ elevations in ALT and total bilirubin. These laboratory abnormalities were due to acute hepatitis A infection and not drug related.

### Thyroid Parameters:

In nonclinical studies, mild but dose-related hypertrophy of follicular cells in the thyroid gland along with decreased T<sub>4</sub> levels and elevated TSH were observed in rats. All changes in rats were reversible following a one month recovery period. Similar effects were noted when ritonavir was administered to rats for 2 years. These changes did not progress to thyroid neoplasia. Given these preclinical findings, TSH, T<sub>3</sub> and T<sub>4</sub> levels were measured at baseline and week 48 for both treatment groups.

Mean decreases from baseline to week 48 in T4 values were significantly greater in the lopinavir/ritonavir group compared to the nelfinavir group (-0.80 mcg/dL vs -0.43 mcg/dL, p=0.003). No significant differences were noted in the mean change from baseline between treatment groups at weeks 48 for either T3 or TSH.

No patients discontinued study or interrupted study drugs for changes in TSH, T3 or T4. Two patients in the nelfinavir group initiated treatment with levothyroxine during study. Both of these patients had elevated TSH levels at baseline.

#### **EKG changes:**

The cardiovascular profile of lopinavir/ritonavir was evaluated in 4 studies in rats and dogs. Cardiac effects were noted in a 3 month dog study, however these changes appeared to be secondary to changes in plasma electrolyte concentrations attributed to GI intolerance. ECG changes were noted in 7 dogs, of which 3 dogs were either euthanized or died. Subsequently the dogs received an aggressive dietary supplementation and ECG or electrolyte changes were not observed.

In order to fully evaluate the cardiotoxic potential of lopinavir, the applicant performed ECGs on all patients in the phase 2 program and at baseline and weeks 24 and 48 for patients in study 863. In addition 4 animal studies were conducted. It was noted that only modest, if any effects on cardiovascular system, receptor or ion channel functions were found at therapeutic or super therapeutic doses/plasma concentrations. Decreases in heart rate and mean arterial pressure accompanied by an increase in the PR interval was noted in the pentobarbital-anesthetized beagle dog study. The QTc interval was unchanged in these animals.

#### **QT:**

In the original NDA review, FDA conducted analyses of mean/median QT (corrected) changes from baseline on pooled data from phase 2 studies that included several doses of lopinavir/ritonavir and one phase 3 study in which the lopinavir/ritonavir was compared to a marketed PI (nelfinavir). For these analyses week 2 EKGs were compared to pre treatment EKGs. It is assumed that the EKGs were done without regard to time of dosing. The pharmacokinetic data for these doses follows the phase 2 data. There was no response in 2 week QTc changes over a range of AUC<sub>12</sub> values of 6.

#### **Phase 2 (pooled from two dose-ranging studies, studies 720 and 765)**

Dose	Mean change in QTc (msec)	95% C.I.	Median change in QTc
200/100 BID (n=16)	-5.06	-11.4, 1.34	-6
400/100 BID (n=77)	3.27	-0.17, 6.72	3
400/200 BID (n=55)	1.54	-4.88, 7.97	1

The PK data for the 400/100 and 400/200 doses from two phase 2 studies are as follows

Study/Dose	C <sub>max</sub> (ug/mL)	C <sub>min</sub> (ug/mL)	AUC <sub>12</sub>
Study # 1			
400/100	9.6	3.8	82
400/200	11.5	6.3	110
Study #2			
400/100	7.0	2.4	61
400/200	12.4	7.1	121

The table below describes the mean and median changes from baseline for the QT and QTc interval for both treatment groups at weeks 24 and 48 in study 863.

**Study M98-863: Mean and Median Changes from Baseline in ECG variables with 95% Confidence Interval for Mean Change from Baseline**

Variable	Week	Treatment Group	N	Mean Change from baseline (msec)	Median Change from Baseline (msec)	95% Confidence Interval for Mean Change from Baseline
QT Interval	24	ABT-378/r	252	+9.762	+4.0	(4.44, 15.08)
		nelfinavir	256	+9.520	+4.0	(4.65, 14.39)
	48	ABT-378/r	236	+8.178	+6.0	(0.53, 15.83)
		nelfinavir	229	+10.764	+6.0	(5.19, 16.34)
QTc Interval	24	ABT-378/r	229	+3.986	+1.0	(-0.83, 8.80)
		nelfinavir	225	+3.189	+1.0	(-1.88, 7.76)
	48	ABT-378/r	213	+4.312	+5.0	(-1.18, 9.81)
		nelfinavir	208	+7.785	+5.0	(2.50, 13.07)

The mean change in QTc for the lopinavir/ritonavir group increased slightly from 3.9 to 4.3 msec between week 24 and 48. Whereas in the nelfinavir group the mean change in QTc increased between week 24 and 48 (3.1 to 7.7 msec). However the median change from baseline was the same for both treatment groups at week 24 and week 48.

The applicant also evaluated the maximum change from baseline for QTc intervals in 30 msec increments. The changes were similar between both treatment groups. Overall 18 patients (11 lopinavir/ritonavir, 7 nelfinavir) had a QTc interval between 451 and 499 msec. Two patients in each treatment group had baseline QTc intervals > 450 msec. No patient had a QTc > 500 msec.

Adverse events associated with abnormal ECG findings were similar in both treatment groups. A summary of the proportion of patients with events associated with abnormal ECG values is presented in the table below. All events in the lopinavir/ritonavir group were considered not related to study drug. One patient in the nelfinavir group (#3166) prematurely discontinued study due to moderate palpitations. This event was considered possibly related to study drug.

**AEs Associated with Abnormal ECG Values**

	Lopinavir/ritonavir (n=326)	Nelfinavir (n=327)
Arrhythmia	1 (0.3%)	0
Atrial fibrillation	1 (0.3%)	0
AV block first degree	1 (0.3%)	0
ECG abnormal	1 (0.3%)	0
Palpitation	0	5 (1.5%)
PR interval prolonged	1 (0.3%)	0

Source: NDA vol 1 pg 280 table 12.5d, SAS dataset AE

Although the mean and median change from baseline for the QTc interval increased over time and differences were noted between the two groups, the clinical significance of these findings appears to be minimal. In addition there appears to be no indication of a dose response for lopinavir/ritonavir. Although the EKGs were not known to have been obtained at Cmax, we feel that there is some data at higher doses (concentrations) than the to be marketed dose. This data would indicate the higher concentrations do not appear to increase the risk of QTc prolongation.

**PR:**

The applicant's analyses of EKGs showed a statistically significant increase in PR interval in patients who received lopinavir/ritonavir compared to nelfinavir. A summary of this information can be found in the table below. However, these changes did not appear to be clinically significant. Overall 16 patients had a PR interval  $\geq$  210- msec, 9 patients in the lopinavir/ritonavir group and 7 patients in the nelfinavir group. Three patients in the lopinavir/ritonavir group had a baseline PR interval > 210 msec. All patients continued on study drugs without adverse events. The clinical significance of these findings appeared to be minimal in this study.

**Study M98-863: Mean and Median Changes from Baseline in ECG variables with 95% Confidence Interval for Mean Change from Baseline**

Variable	Week	Treatment Group	N	Mean Change from baseline (msec)	Median Change from Baseline (msec)	95% Confidence Interval for Mean Change from Baseline
PR Interval	24	ABT-378/r	253	+5.704	+3.0	(2.98, 8.43)
		Nelfinavir	257	+1.152	+0.0	(-1.64, 3.94)
	48	ABT-378/r	239	+4.088	+3.0	(1.15, 7.03)
		Nelfinavir	230	-1.757	+0.0	(-4.67, 1.16)

**Safety Summary:**

Both treatment regimens appeared to be well tolerated throughout 48 weeks. Premature discontinuation due to adverse events were similar between treatment groups; approximately 5-6%. For either treatment group, the most common adverse events were predominately gastrointestinal events such as diarrhea, and nausea. Discontinuations for these events occurred in < 1% of patients in either treatment group.

More patients in the lopinavir/ritonavir group compared to patients in the nelfinavir group experienced asthenia, vomiting, eczema, taste perversion, ear disorder, neuropathy, convulsion and skin ulcer. Whereas more patients in the nelfinavir group compared to patients in the lopinavir/ritonavir group developed urticaria.

No new cases of pancreatitis, drug-related hepatitis or deaths were reported during study weeks 24-48. Overall, 4 cases of pancreatitis were reported prior to week 24. Eight deaths were reported during the study; 5 in the lopinavir/ritonavir group and 3 in the nelfinavir group. One patient in the lopinavir/ritonavir group died of pancreatitis and this event was considered to be related to study drug. The remaining 4 deaths were not related to study drug.

The common laboratory abnormalities for both treatment groups included elevations in transaminases and lipids. A statistically significantly greater proportion of patients in the lopinavir/ritonavir group compared to patients in the nelfinavir group developed triglycerides > 750 mg/dL. The incidence of grade 3 or 4 increases in cholesterol and transaminases was not significantly different between treatment groups. Discontinuations for laboratory abnormalities were also infrequent. Only two patients in the lopinavir/ritonavir group discontinued for a laboratory abnormality. Both patients discontinued due to elevated transaminases.

The adverse event and laboratory abnormality profile seen in the original NDA was consistent with that observed in this sNDA. No new safety concerns were seen with continued dosing of lopinavir/ritonavir through week 48.

## 7.0 Review of Efficacy/Clinical Virology in Antiretroviral Experienced Patients

### 7.1 Clinical Trial M98-957

"A Phase II Study of ABT-378/Ritonavir and Efavirenz in HIV Infected Subjects Experienced with Multiple Protease Inhibitors"

#### 7.1.1. Study Design

This is an ongoing a phase II, open-label, randomized, multiple dose, parallel arm, pharmacokinetic interaction study. Fifty subjects who are NNRTI naïve and have received multiple protease inhibitors were randomized into one of the following treatment arms:

Arm A: ABT-378/ritonavir 400/100 mg BID + efavirenz 600 mg QD + RTIs (determined by investigator)

Arm B: Day 1-13:  
ABT-378/ritonavir 400/100 mg BID + efavirenz 600 mg QD + RTIs (determined by investigator)

Day 14 onward:  
ABT-378/ritonavir 533/133 mg BID + efavirenz 600 mg QD + RTIs (determined by investigator)

Based on pharmacokinetic and safety data, the applicant amended the study such that all patients in Arm A were dose increased to 533/133 mg BID. This amendment occurred after all subjects reached the week 24 visit.

Adverse events, physical exam, laboratory monitoring for toxicity, and immunologic and virologic assessments of efficacy were performed at regular intervals .

Adverse Events and laboratory abnormalities were assessed by the standardized ACTG Toxicity Grading Table.

#### 7.1.2 Analysis Plan

The primary efficacy variable for this report was the time to loss of virologic response through Week 48.

- Proportion of subjects with plasma HIV RNA level below the LOQ \_\_\_\_\_ at each study visit.
- Change from baseline (to each study visit) in plasma HIV RNA level, CD4 and CD8 cell count.
- The (time-normalized) area under the curve minus baseline (AUCMB) through Week 16, Week 24 and Week 48 for plasma HIV RNA level, CD4 and CD8 cell count.
- Time to loss of virologic response

#### Cross-resistance:

The relationship between baseline genotype, baseline susceptibility and virologic response rates were assessed in 56 patients through week 48.

**Safety:**

The primary safety endpoint was the incidence of patients with grade 3 or greater adverse events and laboratory abnormalities. The secondary safety endpoints were the proportion of patients who discontinued study drug due to adverse events, time to first study drug dose modification and time to study drug discontinuation and changes in weight and Karnofsky performance status. All patients who received at least 1 dose of study drug were assessed for safety. Treatment-emergent events were compared between arms using COSTART terms

**7.1.3. Study Population and Patient Disposition**

Inclusion/Exclusion criteria were: > 18 years of age, HIV RNA > 1000 copies/mL, current treatment with an antiretroviral regimen containing at least one protease inhibitor that had not been changed in the last 8 weeks and prior history of sequential or concurrent treatment with at least two different protease inhibitors for a period of at least 12 weeks and no evidence of acute illness or documentation of abnormal laboratory parameters as defined by the protocol.

A total of 75 patients were screened for this study. Fifty-seven patients were randomized and dosed, 29 to the 400/100 dose and 28 to the 533/133 dose. Patients in the 400/100 mg dose group received the 533/133 mg dose between weeks 24 and 48.

Baseline demographics are displayed in Table 7.1.3.A. The baseline demographic characteristics were similar for both treatment groups with respect to gender, race, age, baseline mean HIV RNA levels, or baseline mean CD<sub>4</sub> cell counts. Patients were predominantly male (79%), Caucasian (88%), mean age of 41 years (25-63) with a mean HIV RNA of 4.5 log<sub>10</sub> copies/mL and mean CD4 cell count of 278 cells/mm<sup>3</sup>. Of note, more patients in the 400/100 mg group received prior treatment with ritonavir and fewer patients in the 400/100 mg group received prior treatment with stavudine.

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Table 7.1.3.A Demographic Data

	400/100	533/133
Number of Patients	29	28
Mean age, Yrs	41.1	42.6
Men	76%	82%
Race or Ethnicity		
Caucasian	25	25
Black or African American	2	3
Unspecified	2	0
Prior number of antiretrovirals (mean)	7.17 (3-10)	7.29 (4-10)
Prior Antiretroviral Therapy		
Indinavir	24 (82.8%)	25 (89.3%)
Nelfinavir	16 (55.2%)	17 (60.7%)
Ritonavir	26 (89.7%)	18 (64.3%)
Saquinavir	20 (69%)	21 (75%)
Abacavir	4 (13.8%)	6 (21.4%)
Didanosine	24 (82.8%)	21 (75%)
Lamivudine	27 (93.1%)	25 (89.3%)
Stavudine	24 (82.8%)	28 (100%)
Zalcitabine	13 (44.8%)	13 (46.4%)
Zidovudine	28 (96.6%)	25 (89.3%)
Hydroxyurea	2 (6.9%)	5 (17.9%)
Baseline Antiretroviral Therapy		
Abacavir	2 (6.9%)	2 (7.1%)
Didanosine	8 (27.6%)	11 (39.3%)
Lamivudine	18 (62.1%)	15 (53.6%)
Stavudine	14 (48.3%)	16 (57.1%)
Zalcitabine	1(3.4%)	0
Zidovudine	13 (44.8%)	10 (35.7%)
Hydroxyurea	3 (10.3%)	2 (7.1%)
Baseline mean plasma HIV RNA (PCR), log <sub>10</sub> copies/mL	4.6	4.4
Baseline median CD4 cell count (cells/mm <sup>3</sup> )	230	325

The proportion of patients discontinuing treatment and the primary reasons for discontinuation are summarized in Table 7.1.3.B. Overall, 5 subjects discontinued due to an adverse event, 4 subjects due to virologic failure, one subject died, and one subject discontinued due to personal reasons. Of note, 7 subjects who prematurely discontinued from the 400 mg/100 mg dose arm, 6 subjects discontinued prior to the conversion to the higher dose and one subject discontinued after conversion (personal reasons).

Table 7.1.3.B. Patient Disposition Through Week 48

	400/100	533/133	Overall (combined 400/100 and 533/133 mg dose groups)
# patients received at least 1 dose of study drug	29	28	57
Discontinued by week 48	7 (24%)	4 (14%)	11 (20%)
<b>Reasons for Discontinuation</b>			
AE	3 (10%)	2 (7%)	5 (9%)
Lack of Virologic Response	3 (10%)	1 (4%)	4 (7%)
Death	0	1 (4%)	1 (2%)
Personal reasons	1 (3%)	0	1 (2%)

## 7.2 Review of Efficacy

The proportion of patients with HIV RNA < 400 and < 50 copies/mL are summarized in Table 7.2.A. HIV RNA values were analyzed according to the originally randomized dose arm. Patients in the 400/100 mg group were converted to the 533/133 mg dose group between weeks 24 and 48.

The majority of patients achieved HIV RNA levels < 400 and < 50 copies/mL despite having received at least 3 prior protease inhibitors. There were no significant differences between the two dose groups.

Table 7.2.A. Proportion &lt; 400 and &lt; 50 copies/mL at Week 48

	400/100 (n=29)	533/133 (N=28)	Overall (combined 400/100 and 533/133 mg dose groups) (N=57)
< 400 copies/mL	17/29 (59%)	20/28 (71%)	37/57 (65%)
< 50 copies/mL	17/29 (59%)	15/28 (54%)	32/57 (56%)

Increases in CD4 cell counts were seen over 48 weeks. Overall the mean change from baseline to week 48 in CD4 Cell counts was approximately 92 cells. Table 7.2.B. summarizes the mean change from baseline to week 48. There were no significant differences between dose groups.

Table 7.2.B. Mean change from baseline to week 48 in CD4 Cell counts

	400/100 (n=29)	533/133 (N=28)	Overall (combined 400/100 and 533/133 mg dose groups) (N=57)
Mean change from baseline (cells/mm <sup>3</sup> )	+116	+67	+92

**Virology Substudies:**

Cross-resistance: Clinical studies

The relationship between baseline genotype, baseline susceptibility and virologic response rates were assessed in 56 patients. Results of these analyses are described below.

**Genotypic Analyses:**

All 56 patients' baseline and week 48 HIV RNA results were reviewed. Six patients were censored for this analysis because these patients discontinued treatment for reasons other than loss of virologic response. Four patients did not have a week 48 HIV RNA result, however these patients were included in the analysis because loss of virologic response was noted at an earlier time point.

The following mutations in the HIV protease were evaluated in order to determine if there was an association between specific mutational patterns and virologic response rates; (L10F/I/R/V, K20M/R, L24/I, M46I/L, F53L, 154L/T/V, L63P, A71I/L/T/V, V82A/F/T, I84V and L90M). These mutations were associated with a statistically significant reduction in susceptibility to lopinavir in vitro in an analysis submitted by the applicant.

Overall 12 patients experienced a loss of virologic response by week 48. Within this study, no specific mutational patterns were associated with a loss of virologic response. However, it did appear that at least one primary protease mutation (82, 84, and 90) plus multiple other mutations at baseline were associated with a lack or loss of virologic response. Twenty-five patients had less than or equal to 5 mutations at baseline. Response rates (proportion < 400 copies/mL) for these patients were 96% (24/25) compared to 67% (18/27) for patients with greater than 5 mutations at baseline. The mean and median number of mutations for patients with HIV RNA < 400 copies/mL at 24 weeks, were 4.7 and 5, respectively. The mean and median number of mutations for patients with HIV RNA > 400 copies/mL, were 7. These results suggest that the presence 6 or more protease mutations at baseline may be associated with reduced response rates. Further studies are needed to assess the association between specific mutational patterns and virologic response rates.

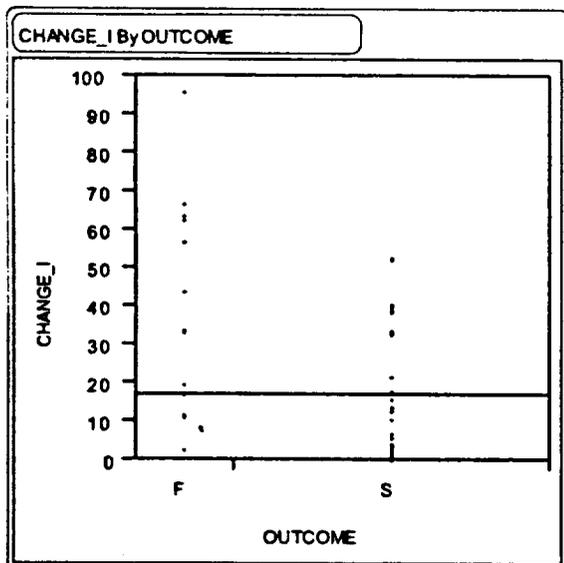
**Phenotypic Analyses:**

The virologic response to lopinavir/ritonavir therapy was evaluated with respect to baseline phenotype. The applicant proposed to include the following information in the label.

**Applicants Proposed Phenotypic Analyses for Package Insert -**

Baseline Phenotype	Response Rate	
	< 400 copies/mL	< 50 copies/mL
< 10 fold	25/27 (93%)	22/27 (81%)
10 – 40 fold	11/15 (73%)	9/15 (60%)
> 40 fold	2/8 (25%)	2/8 (25%)

FDA conducted several exploratory analyses to evaluate virologic response rates by several baseline phenotype groups. Below is a figure of virologic outcome (x-axis, F= failure, S= success (< 400 copies/mL) by baseline phenotype (y-axis). Identifying appropriate baseline phenotype subgroups was difficult because of the limited number of patients in this trial. However, based on the figure below it appears that baseline susceptibility cut off between 30-50 had an impact on response. Although limited in numbers, patients with a baseline susceptibility of 30-40 fold had response rates similar to those with a baseline susceptibility of 10-30 fold. Therefore, we agree that the data support the applicant's proposal for the package insert.



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It is important to note that these baseline phenotype groups are not meant to represent definitive clinical susceptibility cut offs for lopinavir. More data are needed in order to determine the susceptibility breakpoints for lopinavir. This information is to give clinicians information on the likelihood of virologic success based on baseline susceptibility to lopinavir for protease inhibitor, NRTI experienced, NNRTI naive patients initiating treatment with lopinavir/ritonavir and efavirenz.

#### 7.4 Review of Safety in Antiretroviral Experienced Patients

In general, the FDA analysis of the safety data confirmed the applicant's findings. There were only minor differences between the two analyses, which did not affect the overall results and conclusions.

A total of 57 patients were included in the safety analysis. Data from patients who discontinued drugs due to adverse events were reviewed to identify possible risk factors associated with adverse events. All serious adverse events were reviewed individually.

The median duration of study drug exposure was 378 days for both treatment groups. The applicant states that over 80% of the patients in each treatment group received study drug for greater than 48 weeks. All subjects received lopinavir/ritonavir 533/133 mg BID at a time point after the week 24 visit. Twenty-three patients in the 400/100 mg BID dose group converted to the 533/133 mg BID dose group between days 223 and 363 (median day 280).

##### 7.3.1 Overview of Adverse Events

Overall 97% of patients experienced at least one adverse event during the 48 weeks of the study. The most common adverse events of any severity and relationship to study drug were predominately related to the CNS system, digestive system and the body as a whole, specifically, diarrhea (39%), dizziness (30%), asthenia (23%), flu syndrome (23%), pain (23%) and abnormal dreams (19%). Ten patients in the 400/100 mg dose group who converted to the 533/133 mg dose experienced a new adverse event. The events did not cluster in any particular COSTART body system. None of the patients who converted to the 533/133mg dose prematurely discontinued for an adverse event.

Table 7.3.1.A. summarizes treatment-emergent events (at least moderate severity) that are of probable, possible or of unknown relationship to lopinavir/ritonavir and with an incidence of greater than 2 percent. Only six new events that were considered related to study drug occurred between weeks 24-48. These events included abdominal pain, diarrhea, depression and nervousness.

**Table 7.3.1.A. Treatment-emergent events that are of probable, or possible relationship to study drug and occurring in > 2 percent of patients**

Body System	400/100 (n=29)	533/133 (n=28)	Total (N=57)
<b>Body As a Whole</b>			
Abdominal pain	0	3 (10.7%)	3 (5.3%)
Asthenia	2 (6.9%)	4 (14.3%)	6 (10.5%)
Headache	0	2 (7.1%)	2 (3.5%)
Pain	0	2 (7.1%)	2 (3.5%)
<b>Digestive</b>			
Diarrhea	3 (10.3%)	4 (14.3%)	7 (12.3%)
Flatulence	0	2 (7.1%)	2 (3.5%)
<b>Nervous</b>			
Depression	1 (3.4%)	1 (3.6%)	2 (3.5%)
Insomnia	0	2 (7.1%)	2 (3.5%)
Nervousness	0	2 (7.1%)	2 (3.5%)
<b>Special Senses</b>			
Tinnitus	0	2 (7.1%)	2 (3.5%)
<b>Urogenital</b>			
Abnormal ejaculation*	0	1 (4.3%)	1 (2.2%)

\*percentages based on total number of males in each dose group

### 7.3.2. Other Events of Interest:

#### Hepatic Events:

##### Hepatitis:

No cases of hepatitis were reported through week 48.

#### 6.3.3.2. Pancreatitis:

One case of pancreatitis was reported in the original NDA. Patient 526 was a 34-year-old female who was hospitalized for pancreatitis and lactic acidosis after 4 days of lopinavir/ritonavir 400/100 mg therapy. CT scan revealed pancreatitis. Symptoms of pancreatitis were noted 3 days prior to study drug initiation. The patient was diagnosed with lactic acidosis that worsened despite bicarbonate supplementation. Her lactic acid level was 16 mmol/L. The patient has a past medical history of hepatic steatosis, cholecystectomy, urethral lithiasis, moderate anemia, hematuria, lymphedema, obesity and hypertriglyceridemia. It was thought that the pancreatitis was due to other medications and not lopinavir/ritonavir because the symptoms began 3 days prior to study drug initiation. The lactic acidosis worsened despite interruption of ABT-378/ritonavir. No new cases of pancreatitis developed between study weeks 24-48.

#### 6.3.3.3 Metabolic Complications:

##### Body Fat Composition Changes:

In the original NDA, 2 patients reported body fat changes during the first 24 weeks. In this sNDA two additional patients reported body fat changes. All patients had received months of prior antiretroviral agents, including protease inhibitors as specified in the inclusion criteria.

##### New-onset diabetes:

One case of new onset diabetes was reported during study week 24-48. Patient 501, a 50 year old male developed new onset diabetes after approximately 10 months of lopinavir/ritonavir 400/100 mg BID therapy. The event was considered to be mild in severity and the event was treated with diet and exercise.

**Bone Events:**

One fracture was reported during the study. A 60 year old male sustained a rib fracture on study 278. The fracture was a result of accidental injury and not related to lopinavir/ritonavir use.

**7.3.4 Drug Discontinuations Due to Adverse Events:**

Discontinuations due to adverse events were similar for both dose groups. Overall five patients (9%) prematurely discontinued study due to an adverse event. In the original NDA, two patients in each treatment group prematurely discontinued. In this sNDA an additional patient in the 400/100 mg dose group discontinued study between weeks 24-48. It is important to note that this patient did not convert to the 533/133 mg BID dose. Three patients prematurely discontinued study for neuropsychiatric adverse events. One subject discontinued due to lactic acidosis. The remaining patient discontinued for preexisting hyperlipidemia.

**7.3.5 Serious and Life-threatening Adverse Events**

Overall, ten subjects experienced one or more serious adverse event through study week 48. A total of 12 serious adverse events were reported in 6 patients. Four events were considered related to lopinavir/ritonavir. Table 7.3.5.A. summarizes the serious adverse events that are possibly or probably related to study drug. One patient prematurely discontinued study due to a serious adverse event. Three of the events have not resolved as of the last available information provided on these patients.

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**Serious Adverse Events At Least Possibly Related**

PATIENT	ONSET	REASON	CAUSALITY	OUTCOME
520	166	Kidney calculus	Possible	Hospitalization
526	5	Lactic acidosis	Possible	Prolonged hospitalization
	10	Pain	Possible	Permanent disability
	66	Liver fatty Deposit*	Possible	Hospitalization

\*event occurred > 30 days after last dose

**7.3.6 Deaths**

One death occurred during the study. A 45 year old female, died of aspiration pneumonia and sepsis on study day 302, 55 days after interrupting study drugs for polyneuropathy and dehydration. Based on the case report, it appears that this death was not related to study drug.

**7.3.7. Laboratory Abnormalities**

The FDA analysis primarily focused on the incidence of grade 3 and grade 4 laboratory abnormalities and mean change from baseline for selected laboratory tests. The most common laboratory abnormalities were hypercholesterolemia and hypertriglyceridemia. Only 4 of the 23 patients who converted to the 533/133-mg dose group developed an initial grade 3/ 4-laboratory abnormality. Three patients developed hyperlipidemia and one patient develop a grade 3 elevation in amylase. One patient discontinued for a grade 3 or 4 laboratory abnormality. Table 7.3.7.A. summarizes the grade 3 and 4 laboratory abnormalities through week 48.

**Table 7.3.7.A. Grade 3 and 4 Adverse Laboratory Abnormalities**

Chemistry Variable	400/100	533/133	Total
Glucose (> 250 mg/dL)	3 (10.3%)	0	3 (5.3%)
ALT (> 215 x U/L)	0	2 (7.1%)	2 (3.5%)
AST (> 180 U/L)	0	2 (7.1%)	2 (3.5%)
Cholesterol (> 300 mg/dL)	10 (34.5%)	13 (46.5%)	23 (40.4%)
Triglycerides (> 800 mg/dL)	12 (41.4%)	11 (39.3%)	23 (40.4%)
Amylase (> 2 x ULN)	1 (3.4%)	4 (14.3%)	5 (8.8%)

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## Review of Selected Abnormalities

### Hematologic Parameters

With the exception of neutropenia, no subjects developed a grade 3 or 4 hematologic abnormality. Four patients, two in each dose group, experienced a grade 3+ decrease in neutrophil values.

Adverse events related to hematologic abnormalities were reported for 6 patients. None of the events were considered to be drug related by investigators and no patients discontinued study for these events. Four patients developed leukopenia and two patients developed anemia.

### Amylase

A total of 5 patients developed a grade 3 or 4 elevation in amylase. In the original NDA, 2 patients reported grade 3+ increases in amylase. Both patients were in the 533/133 mg dose group. Patient 555 had an isolated increase in amylase that returned to within normal limits at the next study visit. Patient 526 developed pancreatitis. Please refer to pancreatitis section for further details. In this sNDA one patient in the 400/100 mg dose group and 2 additional patients in the 533/133 mg dose group develop a grade 3+ increase in amylase. Baseline amylase values were above the upper limit of normal for 2 patients.

### Lipids

Fourteen (48%) and 16 (57%) of patients in the 400/100 mg and 533/133 mg dose groups, respectively had grade 3 or greater lipid abnormalities. No subjects prematurely discontinued study drug due to these abnormalities. One patient interrupted study drug due to elevated cholesterol and triglycerides. It is important to note that all post baseline lipid values were collected without regard to fasting.

### Cholesterol:

More patients in the 533/133 mg dose group compared to the 400/100 mg dose group experienced a grade 3 or 4 elevation in cholesterol. Three patients in the 400/100 mg dose group who converted to the 533/133 mg dose group developed a grade 3 elevation in cholesterol. In addition, mean change from baseline for cholesterol at week 48 was comparable for both treatment groups; however at other time points there were larger mean increases from baseline in cholesterol for the 533/133 mg dose group. Cholesterol abnormalities are further summarized in Table 7.3.7.B.

**Table 7.3.7.B. Cholesterol Abnormalities**

	400/100 mg (N=29)	533/133 mg (N=28)
Grade 1 or no elevation < 240 mg/dL	11 (38%)	5 (18%)
Grade 2 240 -300 mg/dL	8 (26%)	10 (36%)
Grade 3 301-400 mg/dL	8 (26%)	11 (39%)
Grade 4 > 400 mg/dL	2 (7%)	2 (7%)
Cholesterol Value > 240 mg/dL	18 (62%)	23 (82%)
Cholesterol Value > 300 mg/dL	10 (34%)	13 (46%)
Mean Change (mg/dL)	78.72	59.45

Source FDA analyses and applicant table 12.4.d

The applicant conducted an analysis to assess the risk of developing grade 3 or 4 elevations in cholesterol based on baseline cholesterol values. The applicant reported that subjects with total cholesterol values > 200 mg/dL at baseline were found to be at an increased risk of developing a grade 3 or 4 cholesterol abnormalities than subjects with baseline values < 200 mg/dL (relative risk + 2.4; 95% CI: 1.22-4.74).

#### Triglycerides:

The incidence of grade 3 or 4 elevations in triglycerides was similar for both treatment groups. In addition, mean change from baseline for triglycerides at week 48 was comparable for both treatment groups; however at other time points there were larger mean increases from baseline in triglycerides for the 533/133 mg dose group. No patients developed pancreatitis as a result of elevated triglyceride values. Triglyceride abnormalities are further summarized in Table 7.3.7.C.

**Table 7.3.7.C Elevations in Triglyceride Levels**

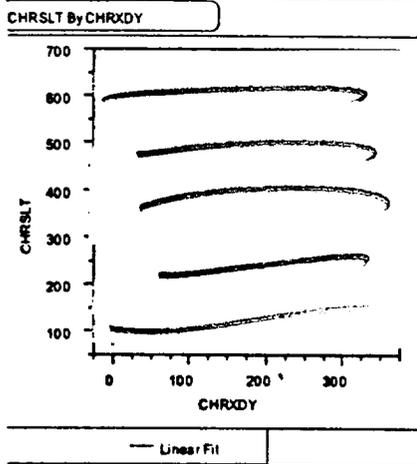
	400/100 mg (N=29)	533/133 mg (N=28)
Grade 1 or no elevation < 400 mg/dL	10 (34%)	7 (25%)
Grade 2 400-750 mg/dL	7 (24%)	10 (36%)
Grade 3 751 – 1200 mg/dL	8 (28%)	3 (11%)
Grade 4 >1200 mg/dL	4 (14%)	8 (29%)
Triglyceride value > 750 mg/dL	12 (41%)	11 (39%)
Triglyceride value > 1500 mg/dL	1 (3%)	4 (14%)
Triglyceride value > 2001 mg/dL	1 (3%)	2 (7%)
Mean Change (mg/dL)	232.89	197.21

The applicant also conducted an analysis to assess the risk of developing grade 3 or 4 elevations in triglyceride based on baseline triglyceride values. The applicant reported that subjects with total triglyceride values > 400 mg/dL at baseline were found to be at an increased risk of developing a grade 3 or 4 triglyceride abnormalities than subjects with baseline values < 400 mg/dL (relative risk + 2.18; 95% CI: 1.24-3.83).

Fifteen patients in the lopinavir/ritonavir group received antihyperlipidemic agents as a result of elevated triglycerides/cholesterol. Based on this limited data it appears that for the majority of patients treatment with antihyperlipidemic agents were effective in reducing overall triglyceride and/or cholesterol levels. However, four patients had triglyceride and/or cholesterol values at week 48 that were higher than their corresponding pre-intervention values.

Figures 1 and 2 are scatter plots displaying cholesterol and triglyceride data on the y-axis (CHRSLT) and study duration on the x-axis (CHRXDYS). Overall, cholesterol values increased slightly over time whereas triglyceride values did not appear to increase over time. Although cholesterol and triglyceride values did not increase substantially over time, it is important to note that some patients did have large increases in cholesterol and triglycerides over time. As cited in the PRECAUTIONS section of the package insert, treatment with KALETRA has resulted in large increases in the concentration of total cholesterol and triglycerides. Triglyceride and cholesterol testing should be performed prior to initiating KALETRA therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate.

Figure 1: Increases in Cholesterol Over Time

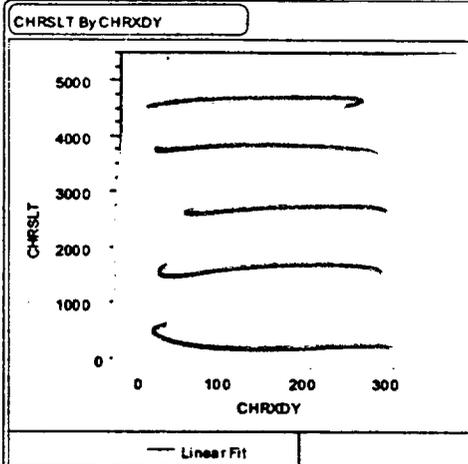


Linear Fit

CHRSLT = 229.525 + 0.07678 CHRXYD

Summary of Fit	
RSquare	0.016834
RSquare Adj	0.015264
Root Mean Square Error	63.25332
Mean of Response	239.5056
Observations (or Sum Wgts)	628

Figure 2: Increases in Triglycerides Over Time



Linear Fit

CHRSLT = 473.387 + 0.02755 CHRXYD

Summary of Fit	
RSquare	0.00004
RSquare Adj	-0.00155
Root Mean Square Error	469.8719
Mean of Response	469.807
Observations (or Sum Wgts)	629

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### Transaminases

No patients in the 400/100 mg dose group developed a grade 3 or 4 transaminase abnormality. Three subjects in the 533/133 mg dose group developed a grade 3+ elevation in AST and/or ALT. All 3 patients had chronic hepatitis Band/or C. All 3 patients remained symptomatic despite elevated transaminases. One subject (#506) was hospitalized and study drugs were temporarily interrupted due to elevated transaminases. The investigator considered the event related to concurrent antiretroviral medications or preexisting chronic hepatitis and not related to lopinavir/ritonavir use. Transaminases for this patient decreased with continued dosing but remained above the ULN throughout the study. No patients discontinued study due to ALT/AST abnormalities. Table 7.3.7.D summarizes the grade 3 and 4 transaminase abnormalities.

**Table 7.3.7.D Grade 3 and 4 Laboratory Abnormalities**

Chemistry Variable	400/100 mg (N=29)	533/133 mg (N=28)
ALT (> 215 U/L)	0	2 (7%)
AST (> 180 U/L)	0	2 (7%)

### ALT/Bilirubin:

No patient developed concomitant grade 3 or 4 elevations in ALT and bilirubin.

### Safety Summary:

Treatment with both doses of lopinavir/ritonavir appeared to be well tolerated throughout 48 weeks. Overall five patients prematurely discontinued study due to adverse events. For either dose group, the most common adverse events of any severity and relationship to study drug reported predominately events related to the CNS system, digestive system and the body as a whole, specifically, diarrhea (39%), dizziness (30%), asthenia (23%), flu syndrome (23%), pain (23%) and abnormal dreams (19%).

No new cases of pancreatitis or drug-related hepatitis were reported during study weeks 24-48. One case of pancreatitis was reported prior to week 24. One death occurred during the study and the death was not considered drug related.

The common laboratory abnormalities for both dose groups included elevations in cholesterol and triglycerides. The incidence of grade 3 or 4 increases in cholesterol and triglycerides were not significantly different between dose groups. No patients discontinued study for a laboratory abnormality. Two patients interrupted study drug for a grade 3+ laboratory abnormality; one for hyperlipemia and one for elevations in ALT and AST.

The adverse event and laboratory abnormality profile seen in the original NDA was consistent with that observed in this sNDA. No new safety concerns were seen with continued dosing of lopinavir/ritonavir through week 48.

## 8.0 Safety Update

### Background:

The applicant was requested to provide a detailed review of cases of hemolytic anemia, thrombocytopenia, thrombotic thrombocytopenic purpura (TTP), hepatic failure, renal failure and rhabdomyolysis reported in the phase 1, 2 and 3 trials, the expanded access program (EAP) and during postmarketing. Please refer to submissions dated December 3, 2001 for further information. This submission contains the requested reports in any Kaletra phase 1-3 clinical trial or during the postmarketing phase up to October 1, 2001.

### Review methods:

During a pre approval safety conference with OPDRA, we requested OPDRA to monitor the postmarketing reports of TTP, thrombocytopenia, and hemolytic anemia. These events were seen in the expanded access program but not during the clinical trials. In addition we evaluated any additional cases that occurred in ongoing clinical trials in order to determine if information regarding these cases was warranted in the package insert. Also the current Kaletra label has statements in the Precaution section regarding hepatic impairment and toxicity. We reviewed postmarketing cases of hepatic failure in order to determine if revised wording regarding hepatic toxicity was warranted. Cases of rhabdomyolysis were reviewed in detail because of the potential drug interaction between Kaletra and statins.

Of note, cases with onset prior to the first dose of lopinavir/ritonavir were excluded from the analyses. Also cases reported in the patient-named programs were included with the postmarketing cases.

### Results:

Listed below is a summary for the reports of hematologic events, hepatic failure, renal failure and rhabdomyolysis. Based on the information provided by the applicant no new labeling was warranted for hematologic events, renal failure or cases of rhabdomyolysis. The PRECAUTIONS section was revised to include statements regarding postmarketing reports of hepatic decompensation in patients with hepatitis B or C after initiation of lopinavir/ritonavir. Although these cases were confounded by advanced HIV disease and/or multiple concomitant medications, it is recommended that clinicians consider increased AST/ALT monitoring in these patients, especially during the first several months of lopinavir/ritonavir treatment.

### *Hematologic events: Thrombocytopenia/hemolytic anemia/thrombotic thrombocytopenic purpura.*

The majority of the hematologic events was observed in patients receiving concomitant agents known to cause these events or observed in patients with other possible alternative etiologies. Several cases lacked relevant information to confirm diagnosis. Based on the information provided by the applicant, new product labeling is not warranted at this time for these hematologic events. The table below shows the number of each reported in clinical trials or during the post-marketing phase. Also a summary of the cases submitted is provided in the following sections.

### Number of Cases of Hematologic Events

	Phase 1-3 Trials	Expanded Access Program	Post-marketing Reports (includes Patient Named programs)
Thrombocytopenia	2	14	8
TTP	0	5	2
Hemolytic Anemia	1	2	8

***Thrombocytopenia:***

Overall 24 cases of thrombocytopenia have been reported.

The applicant reported two cases of thrombocytopenia from the phase 1-3 clinical trial database. One subject developed severe thrombocytopenia after 384 days of lopinavir/ritonavir treatment in the setting of chemotherapy for Burkitt's lymphoma. The second case of thrombocytopenia was seen in a pediatric patient with Burkitt's lymphoma. This patient subsequently died.

Fourteen cases of thrombocytopenia were reported in the expanded access program. Six patients had a prior history of thrombocytopenia. Three of the six patients had resolution of thrombocytopenia either without interruption of lopinavir/ritonavir treatment or after dechallenge/rechallenge without recurrence. Four patients had evidence of infection that may have contributed to bone marrow suppression. One patient also received other concomitant medications known to cause thrombocytopenia. Lastly a pediatric patient experienced thrombocytopenia that improved with immunosuppressive therapy after discontinuation of lopinavir/ritonavir treatment.

Eight cases were identified through post-marketing reports. All 8 patients received medications known to cause thrombocytopenia. Three cases were also confounded by infections.

***TTP:***

Overall 7 cases of TTP have been reported. No cases of TTP were reported in any phase 1-3 clinical trial. Four potential cases of TTP were reported in the expanded access program. In all cases documentation of the diagnosis was incomplete. One subject had a prior history of TTP with reactivation in the setting of an intercurrent, infection, another subject recovered without interruption of lopinavir/ritonavir.

Two cases of TTP were reported during the post-marketing. One case occurred two weeks after initiation of lopinavir/ritonavir treatment. No concomitant medications or laboratory data was provided in the reports. In the second case, treatment for TTP was initiated 5 weeks after abacavir and lopinavir/ritonavir were started. No other manifestations characteristic of TTP were reported.

***Hemolytic Anemia:***

A total of 11 cases of hemolytic anemia have been reported. One case of hemolytic anemia was reported in a clinical trial, however this event resolved 13 days after onset with ongoing lopinavir/ritonavir. This patient was noted to have a positive Coomb's test. Two events were identified in the expanded access program. One case occurred in a 55 year old male following one month of lopinavir/ritonavir treatment. The patient also received glyburide, an agent that has been associated with hemolytic anemia. Lopinavir/ritonavir treatment was discontinued and the event was considered to be resolved. However the subject was rehospitalized for recurrence of hemolytic anemia, with fever, malaise and cough. The patient was found to have massive splenomegaly, anemia, thrombocytopenia and megakaryocytic hyperplasia. The patient subsequently died 7 days later. The second case occurred in a patient with a history of hemolytic anemia. Treatment with lopinavir/ritonavir was interrupted during the event and was reintroduced without recurrence.

Eight cases were reported during the postmarketing phase. Two reports were described as severe anemia requiring transfusion; two reports were seen in patients receiving concomitant medications known to cause hemolytic anemia.

**Summary:**

The applicant submitted a review of the medical literature regarding hematologic disorders in HIV infected patients and calculated incidence rates of serious hematologic events in the clinical trials and the expanded access program. Results from this analysis are found in the table below. In