CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-226
21-251

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-226 and 21-251
GENERIC NAME: Lopinavir/ritonavir (Lopinavir = ABT-378)
TRADE NAME: Kaletra
FORMULATIONS: capsule (133.3 mg lopinavir and 33.3 mg ritonavir)
Oral solution (80 mg/mL lopinavir and 20 mg/mL ritonavir)
APPLICANT: Abbott Laboratories
SUBMISSION DATES: NDA 21-226: 12/29/99, 3/31/00, 6/1/00, 6/9/00, 8/31/00
NDA 21-251: 4/3/00, 5/31/00, 6/9/00

DRAFT REVIEW: September 1, 2000
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BACKGROUND:

Lopinavir is an HIV protease inhibitor with greater in vitro potency than ritonavir. The lopinavir EC_{50}, in 50% human serum, for wild-type HIV-1 is approximately 0.07 µg/mL. Lopinavir is almost completely metabolized by cytochrome P450 3A4 (CYP3A4). Coadministration with ritonavir inhibits the metabolism of lopinavir, dramatically increasing the plasma concentrations of lopinavir. Administration of lopinavir/ritonavir 400/100 mg BID to HIV infected patients yields lopinavir concentrations that are 15- to 20-fold higher than those of ritonavir. It is presumed that the antiviral activity of this combination is due to lopinavir.

This review focuses on the clinical pharmacology and biopharmaceutics aspects of lopinavir/ritonavir. The synopsis portion of this review addresses the questions listed below. Individual study reviews are on file with the Division of Pharmaceutical Evaluation III.

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What are the proposed dosing regimens for lopinavir/ritonavir?
Adults
400/100 mg (3 capsules or 5 mL) twice daily, taken with food. Increase to 533/133 mg BID, when administered with nevirapine or efavirenz.

Pediatric patients

Body weight 7 to <15 kg: 12/3 mg/kg twice daily, taken with food
Body weight 15 to <40 kg: 10/2.5 mg/kg twice daily, taken with food
Body weight ≥40kg: 400/100 mg twice daily, taken with food.

Increase when administered with nevirapine or efavirenz:
Body weight 7 to <15 kg: 13/3.25 mg/kg twice daily, taken with food
Body weight 15 to <50 kg: 11/2.75 mg/kg twice daily, taken with food
Body weight ≥50kg: 400/100 mg twice daily, taken with food.

What are the primary clinical trials, for demonstration of efficacy and safety?

Phase III pivotal clinical trial
M98-863: Subjects were HIV-infected, antiretroviral-naive

(n=326) Lopinavir 400 mg/ritonavir 100 mg BID
        + Stavudine 30 or 40 mg BID (based on weight) + lamivudine 150 mg BID

(n = 327) Nelfinavir 750 mg TID
        + Stavudine 30 or 40 mg BID (based on weight) + lamivudine 150 mg BID

<u>Supportive clinical trials</u>

M97-720: Phase I/II randomized, multi-center study of HIV-infected, antiretroviral naïve patients
The sponsor used this study for dose selection.

Group I
(n = 16) Lopinavir 200/ritonavir 100 mg BID + (beginning day 22) stavudine + lamivudine
(n = 16) Lopinavir 400/ritonavir 100 mg BID + (beginning day 22) stavudine + lamivudine

Group 2
(n = 35) Lopinavir 400/ritonavir 100 mg BID + (beginning day 1) stavudine + lamivudine
(n = 33) Lopinavir 400/ritonavir 200 mg BID + (beginning day 1) stavudine + lamivudine

M97-765: Phase I/II dose blinded, randomized, multi-center study in PI-experienced, NNRTI-naïve HIV-infected adults

(n = 36) Lopinavir 400/ritonavir 100 mg BID + 2 NRTIs + (beginning day 15) nevirapine
(n = 34) Lopinavir 400/ritonavir 200 mg BID + 2 NRTIs + (beginning day 15) nevirapine

Pediatric Study
M98-940: Phase I/II open-label, multi-center study in NNRTI-naïve, HIV-infected children

(n=48) Lopinavir 230/ritonavir 57.5 mg/m^2 BID + 2NRTIs, with or without nevirapine
(n=51) Lopinavir 300/ritonavir 75 mg/m^2 BID + 2NRTIs, with or without nevirapine

How did the sponsor select the lopinavir/ritonavir dosing regimen?

The sponsor's objectives for the development of a new HIV protease inhibitor were (1) a high Cmin/EC50 ratio and (2) a highly acceptable safety and tolerability profile. Lopinavir has an EC50 of 0.1 μM for wild type HIV in 50% human serum. When lopinavir is dosed alone, plasma lopinavir concentrations are low and variable. However, coadministration of ritonavir with lopinavir results in substantially higher plasma lopinavir concentrations, due to ritonavir's potent inhibition of CYP3A-mediated metabolism of lopinavir.

Results of Phase I studies indicated that higher exposures of lopinavir could be achieved by increasing either the lopinavir or ritonavir dose. The initial Phase II study in HIV-infected patients (M97-720) evaluated three lopinavir/ritonavir BID dosing regimens: 200/100 mg, 400/100 mg, and 400/200 mg. The study was conducted in antiretroviral naïve patients who also received stavudine and lamivudine. In a review of preliminary data from this trial, similar antiviral activity was seen for the three regimens. The applicant expected the regimens to perform similar to one another, based on the estimates of the Cmin/EC50 ratios for the regimens (30 to 40 for 200/100; 50 to 60 for 400/100; 80 to 90 for 400/200). There was a higher incidence of nausea and lipid elevations noted with the 400/200 mg BID regimen. The applicant also believes the lower 100 mg ritonavir dose has a lower potential for significant interactions with other drugs metabolized by CYP3A4. Although the performance of the 200/100 mg BID and 400/100 mg BID regimens was similar in M97-720, the applicant selected the 400/100 mg BID regimen for further clinical trials because it provides a higher lopinavir Cmin/EC50 ratio.

Although efficacy in M97-720 was similar for the 200/100 mg BID and 400/100 mg BID regimens, the applicant anticipated that the higher lopinavir concentrations provided by the 400/100 mg BID regimen may be necessary for efficacy in patients with more antiretroviral

therapy experience. Patients with more antiretroviral experience, particularly protease inhibitor experience, are likely to have more resistant virus, thus requiring higher drug concentrations for efficacy. Study M98-957 provides suppor. for this hypothesis. In M98-957, multiple protease inhibitor experienced HIV infected patients received lopinavir/ritonavir 400/100 mg BID or 533/133 mg BID, in combination with efavirenz 600 mg qd and 2 NRTIs. The average lopinavir exposure following administration of lopinavir/ritonavir 400/100 mg BID in combination with efavirenz were lower when compared to data from M97-720. The average lopinavir exposure following administration of lopinavir/ritonavir 533/133 mg BID in combination with efavirenz were slightly higher than the values observed in M97-720. Concentrations for both regimens were within the range observed in M97-720 following doses between 200/100 mg BID and 400/200 mg BID. In M98-957, for the proportion of patients with HIV RNA < 400 copies/mL analysis, a statistically significant difference was noted at week 16 in favor of the 533/133 arm. Based on the efficacy results and pharmacokinetic information from the lopinavir/ritonavir + efavirenz interaction study, all patients in the 400/100 dose group had their dose increased to 533/133 mg. Thus, a lopinavir concentration difference that did not appear to be clinically important in antiretroviral therapy naïve patients, did lead to differences in efficacy in a more experienced population. Because patients with various levels of previous treatment will receive lopinavir/ritonavir, it is appropriate for the applicant to select the higher of the well-tolerated doses, 400/100 mg BID, for further clinical study.

What are the chemical characteristics of lopinavir?

Molecular weight: 628.8
Nonionized across pH range
Solubility: Low aqueous solubility, >390 mg/mL in ethanol, ~218 mg/mL in propylene glycol

What are the basic pharmacokinetic characteristics of lopinavir (ADME) when administered without ritonavir?

In M96-552, healthy volunteers received single doses of lopinavir under fed conditions (24% of calories from fat). When administered without ritonavir, lopinavir exhibited poor and variable absorption. Over the dose range 200 to 800 mg, there was a greater than dose proportional increase in lopinavir C_{max} and AUC.

Mean (%CV) lopinavir pharmacokinetic parameters

Lopinavir dose	C_{max}, µg/mL	T_{max}, h	AUC, µg·h/mL	C_{12}, µg/mL
200 mg (n=10)	0.03 (74)	2.7 (45)	0.07 (77)	–
400 mg (n=10)	0.19 (81)	2.3 (48)	0.67 (101)	–
800 mg (n=10)	0.7 (69)	3.4 (32)	2.50 (77)	–

What are the basic pharmacokinetic characteristics of lopinavir (ADME) when administered with ritonavir?

In study M97-723, 5 healthy male subjects received a single oral dose of 400 mg of lopinavir and approximately 100 µCi of [^{14}C]lopinavir with 100 mg of ritonavir. Subjects were dosed approximately 30 minutes after completion of a standard breakfast. The results from this study indicate that:
   Based on AUC comparisons, the predominant component (approximately 89%) of plasma radioactivity was lopinavir.
   The elimination of lopinavir in humans is dependent on oxidative metabolism.
   Urinary excretion is a minor route of elimination for lopinavir. Approximately 10% of radioactivity was eliminated in urine, the majority as metabolites.

Single dose administration of lopinavir/ritonavir

In M96-552, the applicant evaluated lopinavir and ritonavir pharmacokinetic parameters following administration of various combinations of lopinavir (100 to 800 mg) with ritonavir (50 to 300 mg) to healthy male volunteers.
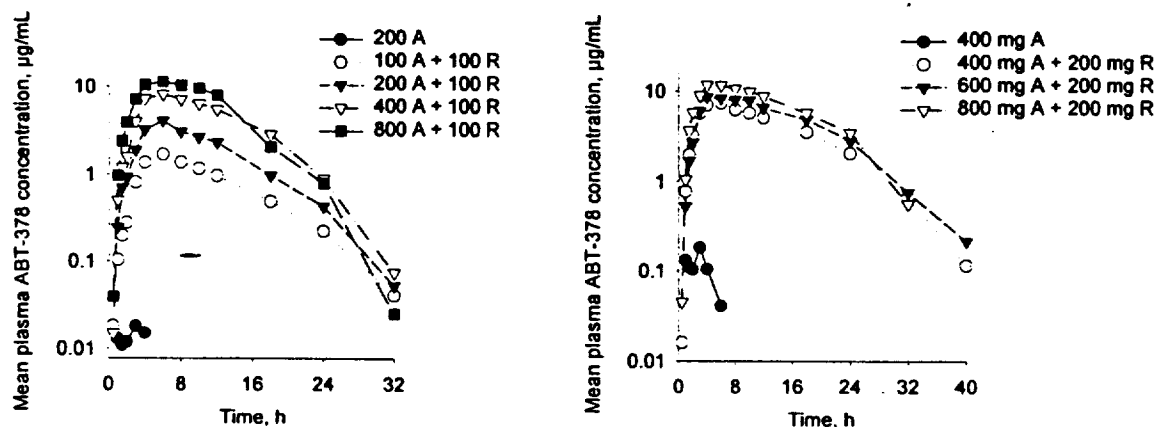
When compared to administration of lopinavir alone, concomitant administration with ritonavir had a profound impact on the pharmacokinetics of lopinavir. At least a 10-fold increase in lopinavir C_{max} and a 30- fold increase in lopinavir AUC was seen when administered with ritonavir. As an example, lopinavir pharmacokinetic parameters following administration of 400 mg lopinavir with several doses of ritonavir are summarized in the following table.

Mean (%CV) lopinavir pharmacokinetic parameters

lopinavir	Ritonavir	C_{max}, µg/mL	T_{max}, h	AUC, µg.h/mL	C_{12}, µg/mL	C_{24}, µg/mL
400 mg	0 mg	0.19 (81)	2.3 (48)	0.67 (101)	0	0
400 mg	50 mg	5.7 (36)	5.2 (25)	50.5 (45)	2.28 (59)	0.14 (119)
400 mg	100 mg	8.5 (23)	5.2 (20)	105.3 (33)	5.41 (30)	0.90 (65)
400 mg	200 mg	8.3 (26)	4.6 (28)	121.9 (36)	5.10 (24)	2.08 (89)

In general, lopinavir exposure appeared to increase in a dose proportional manner when administered with a fixed dose of ritonavir. For a fixed dose of lopinavir, an increase in the dose of ritonavir resulted in an increase in the exposure to lopinavir. The magnitude of increase was dependent on the dose of lopinavir. In general, the increase in lopinavir concentrations is less than proportional to the increase in ritonavir dose.

Multiple dose administration of lopinavir/ritonavir

In M96-650, the applicant evaluated lopinavir and ritonavir pharmacokinetic parameters following administration of various multiple dose combinations of lopinavir (200 to 600 mg) with ritonavir (50 to 300 mg) to healthy male volunteers.

When administered with fixed doses of ritonavir, the pharmacokinetic parameters of lopinavir increase in a less than dose proportional manner. Increasing the dose of ritonavir with fixed doses of lopinavir results in an increase in exposure to lopinavir. At a dose of 200 mg of lopinavir, an increase in ritonavir dose from 50 to 100 mg resulted in an average 60% increase in AUC∞ of lopinavir. At a dose of 400 mg of lopinavir, the increase in average AUC∞ was 15%. After multiple dosing of lopinavir and ritonavir, lopinavir doses of 200 to 600 mg did not

appear to affect the pharmacokinetics of 50 mg of ritonavir and lopinavir doses of 200 to 400 mg did not appear to affect the pharmacokinetics of 100 mg of ritonavir.

In M97-720, the applicant evaluated lopinavir and ritonavir pharmacokinetics following administration of three lopinavir/ritonavir dosing regimens to HIV infected subjects. Lopinavir/ritonavir was administered without regard for food in this study.

Mean (%CV) steady-state pharmacokinetic parameters of lopinavir

Dose	N	Cmax µg/mL	AUC12 µg.hr/mL	C12 µg/mL	CL/F L/hr	*T½ hr
200/100	16	6.65 (36)	55.9 (39)	2.72 (53)	4.5 (67)	6.76 ± 2.73
400/100	21	9.58 (46)	82.8 (53)	3.83 (89)	6.4 (69)	5.76 ± 2.39
400/200	8	11.5 (29)	110.3 (29)	6.27 (37)	3.8 (24)	10.93 ± 4.34

*T½ presented as harmonic mean ± pseudo-standard deviation

Increasing the dose of ritonavir from 100 mg to 200 mg along with 400 mg of lopinavir resulted in a 25%, 35% and 50% increase in lopinavir C_{max}, AUC and C_{min}.

Do lopinavir plasma concentrations demonstrate diurnal variation?

In M97-650, the applicant evaluated lopinavir diurnal variation following administration of various multiple dose combinations of lopinavir (200 to 600 mg) with ritonavir (50 to 300 mg) to healthy male volunteers. For several regimens, lopinavir AUC and Cmax were approximately 15% lower in the evening than in the morning. There was a larger difference observed for the C_{12hr} vs. C_{0hr} comparison. For the 200/50 mg BID, 400/50 mg BID and 600/50 mg BID regimens, the mean decrease for C_{12hr} vs. C_{0hr} was 42%. For the 300/100 mg BID and 400/100 mg BID regimens, the mean decrease for C_{12hr} vs. C_{0hr} was 21%.

How long does it take for lopinavir concentrations to reach steady-state?

Predose concentration data from 10 HIV infected patients who received lopinavir/ritonavir 400/100 mg BID in M97-720 suggest that lopinavir steady state concentrations are not achieved before Day 16. Concentrations decrease between Days 4 (7.99 ± 4.07 µg/mL) and 16 (4.19 ± 2.09 µg/mL); however, the decrease between Days 10 (4.85 ± 2.81 µg/mL) and 16 is small. These results are consistent with data from healthy volunteers in M96-650. There was a slight decrease in lopinavir exposure between Days 10 and 16. The applicant believes that the decrease in concentrations is due to induction of lopinavir metabolism by ritonavir. The applicant evaluated the potential for ritonavir and lopinavir to induce several enzymes in human hepatocytes from 5 donors. The results indicate that ritonavir induces CYP3A4, but lopinavir does not. Due to the small changes in lopinavir concentrations observed between Days 10 and 16, it is likely that lopinavir concentrations are very close to steady-state at Day 16. Pharmacokinetic data collected after 3 or 4 weeks are very similar to the Day 16 data.

What is the extent of lopinavir binding to plasma proteins?

Lopinavir plasma protein binding was determined using equilibrium dialysis. The percent of free lopinavir increased from 0.28% at 0.1 µg/mL to 0.5% at 10 µg/mL and 1.3% at 30 µg/mL. The clinically relevant concentration range is approximately 2.0 to 10.0 µg/mL. Lopinavir binds to both human serum albumin and alpha-1-acid glycoprotein.

Protein binding was measured for the Hour 6 plasma sample obtained on Day 16 after the evening dose in healthy volunteers (M96-650). For lopinavir, in the concentration range 2.1 to 12.6 µg/mL, protein binding ranged from 98.8 – 99.2% and was independent of concentration.

What is the effect of food on lopinavir concentrations?

Administration with food increases lopinavir plasma concentrations, as compared to administration under fasting conditions. Patients took lopinavir/ritonavir under nonfasting conditions in most clinical safety and efficacy studies, so the nonfasting administration is the reference treatment.

Proposed commercial capsule formulation

In M99-073, fasting state single–dose pharmacokinetics were compared to the nonfasting state (500 kcal, 25% from fat). Following lopinavir/ritonavir administration under fasting conditions, lopinavir Cmax was 23% lower (90% CI: 13.9 to 31.7%) and AUC was 36% lower (90% CI: 27.3 to 43.7%) than following administration under non-fasting conditions. The results of a similar evaluation in M99-072 indicated that the mean decreases in lopinavir Cmax and AUC when administered fasted vs. fed (628 kcal, 25% fat) were 13% and 28%, respectively.

In M99-073, subjects took a single dose of lopinavir/ritonavir with a high-fat meal (872 kcal, 56% from fat). After administration of lopinavir/ritonavir with a high-fat meal, plasma lopinavir C_{max} values were comparable to those seen after administration of a moderate-fat meal. However, AUC_{∞} was approximately 25% higher. Part of the increase in AUC_{∞} can be attributed to quantifiable plasma concentrations beyond 30 hours when administered with a high-fat meal; it is not known if such an increase would be seen at steady-state.

When compared under multiple dose conditions, lopinavir AUC_{12}, Cmax and Cmin were 32%, 31% and 49% lower, respectively, when administered under fasting conditions, as compared to nonfasting conditions.

Proposed commercial liquid formulation

In M99-073, fasting state single–dose pharmacokinetics were compared to the nonfasting state (500 kcal, 25% from fat). Following lopinavir/ritonavir administration under fasting conditions, lopinavir Cmax was 35% lower (90% CI: 26 to 43%) and AUC was 44% lower (90% CI: 37 to 51%) than following administration under non-fasting conditions.

After administration of lopinavir/ritonavir with a high-fat meal, plasma lopinavir C_{max} values were comparable to those seen after administration of a moderate-fat meal. However, AUC_{∞} was approximately 37% higher.

Separate lopinavir and ritonavir capsules

Patients received separate lopinavir and ritonavir capsules in some of the important Phase 2 studies. In M99-073, mean lopinavir Cmax and AUC were 7% and 27% lower, respectively, following administration under fasting conditions compared to nonfasting conditions (628 kcal, 25% fat).

What formulations were used in the important clinical safety and efficacy studies?

Pivotal phase 3 study (M98-963): Proposed commercial co-formulated lopinavir/ritonavir capsules (formulation #19)

Supportive phase 2 studies (M97-720 and M97-765): Separate lopinavir (formulation #6) and ritonavir (formulation #5) capsules. Patients switched to the proposed commercial formulation after week 60.

Pediatric study (M98-940): Proposed commercial oral solution.

When evaluating bioequivalence, is it necessary to satisfy bioequivalence criteria for ritonavir, in addition to lopinavir?

The antiviral activity of lopinavir/ritonavir is due to lopinavir. The plasma concentrations of ritonavir when administered at 100 mg BID are approximately 7% or less of those obtained after administration of the approved ritonavir 600 mg BID dose. Ritonavir is present as a CYP3A4 inhibitor, to increase lopinavir concentrations. The amount of ritonavir present in the formulation must be within 90 to 110% of the labeled amount.

Changes in ritonavir concentrations, to the extent that there would be a change in lopinavir efficacy, would be reflected in the lopinavir concentrations. Thus, it is not necessary to satisfy bioequivalence criteria for ritonavir, when administered in the lopinavir/ritonavir combination.

Are the separately formulated lopinavir and ritonavir capsules used in the Phase 2 studies bioequivalent to the proposed commercial coformulated capsules?

Study M99-072 (reference = separate capsules; test = coformulated capsules)

Fasting conditions:

Based on 90% confidence intervals for C_{max} (87 – 111) and AUC_∞ (88 – 111), the coformulated capsules were bioequivalent to separately administered capsules with respect to lopinavir. However, the formulations were not bioequivalent with respect to ritonavir. The confidence intervals for ritonavir C_{max} and AUC were (67 – 87) and (74 – 90), respectively.

Nonfasting conditions (628 kcal, 25% fat)

Based on the 90% confidence intervals for C_{max} (94 – 115) and AUC_∞ (90 – 113), the coformulated capsules were bioequivalent to the separately administered capsules with respect to lopinavir. The formulations were also bioequivalent with respect to ritonavir. The confidence intervals for ritonavir C_{max} and AUC were (80 – 105) and (82 – 100), respectively.

Is the proposed commercial liquid formulation bioequivalent to the proposed commercial coformulated capsule formulation?

M99-073
Fasting conditions

Lopinavir Mean (%CV) exposure measures, point estimate, and 90% CI

PK parameter	Formulation (Treatment)	Arithmetic mean (%CV)	Geometric mean	% point estimate [90% CI]
C_{max}, µg/mL	capsules (B)	4.98 (37)	4.51	100
	Liquid (D)	4.01 (51)	3.52	78.1 [68.6 – 88.8]
AUC_∞, µg.h/mL	capsules (B)	50.2 (47)	42.6	100
	Liquid (D)	40.8 (65)	33.2	77.8 [67.6 – 89.4]

Based on the 90% confidence intervals for C_{max} and AUC_∞, the liquid co-formulation of lopinavir/ritonavir is not bioequivalent to the co-formulated capsules. Lopinavir AUC_∞ and Cmax were approximately 22% lower following administration of the liquid formulation, compared to the capsules. In addition, ritonavir mean Cmax and AUC were 31% and 25%, respectively, lower following administration of the liquid.

Non-fasting conditions (500 kcal, 25% from fat)

Lopinavir Mean (%CV) PK parameters, point estimates, and 90% CI

PK parameter	Formulation	Arithmetic mean (%CV)	Geometric mean	% point estimate [90% CI]
C_{max}, µg/mL	capsules (A)	6.21 (39)	5.88	100
	Liquid (C)	5.84 (35)	5.41	92.0 [83.6 – 101.2]
AUC_∞, µg.h/mL	capsules (A)	72.0 (38)	66.7	100
	Liquid (C)	67.0 (45)	59.6	89.4 [80.5 – 99.2]

The relative bioavailability of the liquid co-formulation of lopinavir/ritonavir was approximately 90% when compared to the co-formulated capsules under nonfasting conditions.

The coformulated liquid formulation is not bioequivalent to the coformulated capsules. However, this does not affect the approvability of the liquid formulation. The applicant used the proposed commercial liquid formulation in the pediatric study M98-940. The pharmacokinetic results from M98-940 were used to determine appropriate pediatric doses.

The label will indicate that the two formulations are not bioequivalent and will indicate the relative bioavailability under fasting and nonfasting conditions.

Does lopinavir exposure differ between HIV infected patients and healthy volunteers, following administration of lopinavir/ritonavir?

Mean ± SD lopinavir pharmacokinetic parameters following administration of lopinavir/ritonavir 400/100 mg BID

Subjects	Study	N	AUC12 (µg.hr/mL)	Cmax (µg/mL)	Cmin (µg/mL)
HIV (-)	M97-650	7	88.2 ± 17.8	9.58 ± 1.76	5.31 ± 1.58
HIV (-)	M97-806	11	87.8 ± 30.1	10.36 ± 2.90	4.66 ± 2.25
HIV (+)	M97-720	21	82.8 ± 44.5	9.58 ± 4.41	3.83 ± 3.44

The lopinavir concentrations in HIV infected patients are similar to, but more variable than, concentrations in healthy volunteers. Patients in M97-720 were not very advanced in their disease. Patients in M97-765 were more advanced. Although their lopinavir plasma

concentrations were lower than those in M97-720, the observed difference may be due to the presence of the metabolic inducer nevirapine and the limited pharmacokinetic sampling scheme.

Does lopinavir exposure differ between males and females, following administration of lopinavir/ritonavir?

Analyses of covariance (ANCOVA) were performed for lopinavir ln(Cmax) and ln(AUC) using coformulated lopinavir/ritonavir data from across seven single dose bioavailability studies. For each of the studies, a single 400/200 mg or 400/100 mg dose of lopinavir/ritonavir was administered under nonfasting conditions. ANCOVA was performed with classification by study, and with body weight and age as continuous variables. The evaluation included 50 female and 144 male subjects. The mean ± SD body weight was 75.7 ± 11.0 kg (range: 54.5 to 100.3 kg).

Sex was not a significant factor for any of the lopinavir exposure measures. However, subjects with a higher body weight did tend to have lower AUC and Cmax. The effect was small.

Does lopinavir exposure differ between races, following administration of lopinavir/ritonavir?

The ANCOVA described above included pairwise comparisons to explore exposure measure differences for Blacks, Caucasians, and Hispanics. There were 157 Caucasian, 17 Hispanic and 20 Black subjects.

The Hispanic vs. Caucasian and the Black vs. Hispanic comparisons were not significant. However, compared to Caucasians, Blacks had a 14% lower central value for both Cmax (p=0.0204) and AUC (p=0.0531).

The observed difference between Blacks and Caucasians is not likely to be clinically significant. As a part of the statistical analyses in the pivotal trial (M98-863), the on-treatment proportions of patients with viral load below 400 were compared between Caucasians (148/160 = 92.5%) and Blacks (61/67 = 91%) and found to be comparable.

Does lopinavir exposure differ between older and younger adults?

As indicated, the ANCOVA included age as a continuous variable. However, across the bioavailability studies the average age was 32 years, with a range of 18 to 55 years. Within this range, there was no significant age effect on lopinavir exposure.

It is difficult to quantify an age related decline in hepatic function, and even more difficult to predict the effect the decline may have on drug elimination. There is no specific reason to expect that lopinavir pharmacokinetics will differ between older and younger adults, although it is not possible to rule out a difference. It is notable that HIV affects a predominantly young population. According to the Centers for Disease Control 1997-1998 accounting for demographics of AIDS diagnoses, a clear majority of patients are between 13 to 64 years of age, with 1.6% of reports in the 65+ age range. However, as survival of HIV infected patients increases, there may be more patients in the 65+ age range.

Do lopinavir pharmacokinetics change as a function of age in pediatric patients? What is the appropriate lopinavir/ritonavir dose in pediatric patients?

In M98-940, the applicant evaluated the lopinavir/ritonavir dosage regimen (230/57.5 mg/m^2) equivalent to the adult dose of 400mg/100mg BID and a regimen approximately 33% higher (300/75 mg/m^2) in HIV-infected pediatric patients. Patients who were antiretroviral naïve received stavudine and lamivudine with lopinavir/ritonavir. Antiretroviral experienced patients received nevirapine and one or two NRTIs with lopinavir/ritonavir. Lopinavir/ritonavir was given with food. 53 pediatric subjects between 6 months to 12 years of age provided pharmacokinetic data.

Although the data are variable, the results of this study indicate that lopinavir clearance, normalized for body weight, decreases with age. By age 12, clearance was similar to adult values (0.09 ± 0.06 L/hr/kg). Due to higher clearance, exposure tended to be lower in the youngest children. The table below would be more informative if data were presented divided by age groups (for example: 6 months to 1 year, 1 to 2 years, 2 to 6 years, 6 to 12 years). However, due to the high pharmacokinetic variability observed and the small number of patients per age group, dose, and nevirapine status, dividing the data by age does not present an accurate picture.

Mean ± SD pharmacokinetic parameters for lopinavir, compared to historical adult data from Study M97-720

Treatment	AUC$_{12}$ (µg.hr/mL)		Cmax (µg/mL)		Cmin (µg/mL)	
	No NVP	With NVP	No NVP	With NVP	No NVP	With NVP
230/57.5	72.6 ± 31.1	51.6 ± 27.8	8.16 ± 2.94	6.71 ± 3.32	3.35 ± 2.14	1.80 ± 1.68
300/75	116.4 ± 57.1	85.8 ± 36.9	12.45 ± 5.77	10.04 ± 3.26	6.53 ± 4.57	3.56 ± 3.45
Adults (400/100)	82.8 ± 44.5		9.58 ± 4.41		3.83 ± 3.44	

Based on these results, the applicant selected 300/75 mg/m^2 BID as the pediatric dose. The dose would not be increased when nevirapine or efavirenz were added. Note: although the effect of efavirenz on lopinavir/ritonavir was not evaluated in pediatric patients, it is presumed that the effect of the metabolic inducers nevirapine and efavirenz would be similar.

However, the 230/57.5 mg/m^2 BID dose appears to be more reasonable for pediatric patients who are not receiving nevirapine or efavirenz. For those patients receiving nevirapine or efavirenz, the dose should be increased to 300/75 mg/m^2 BID.

A mg/kg dosing scheme is easier than a mg/m^2 dosing scheme: the calculation is easier and mg/kg does not require a height or length measurement. Because the relationship between weight and body surface area changes as children grow, two mg/kg dose levels are needed.

Using the target mg/m^2 doses mentioned above, the following dosing scheme was determined:

> Body weight 7 to <15 kg: 12/3 mg/kg twice daily, taken with food
> Body weight 15 to <40 kg: 10/2.5 mg/kg twice daily, taken with food
> Body weight ≥40kg: 400/100 mg twice daily, taken with food.

> Increase when administered with nevirapine or efavirenz:
> Body weight 7 to <15 kg: 13/3.25 mg/kg twice daily, taken with food
> Body weight 15 to <50 kg: 11/2.75 mg/kg twice daily, taken with food
> Body weight ≥50kg: 400/100 mg twice daily, taken with food.

Does impaired renal function alter lopinavir pharmacokinetics?

The applicant did not investigate lopinavir pharmacokinetics in subjects with impaired renal function. Approximately 10% of a [^{14}C]-dose of 400 mg lopinavir in combination with 100mg ritonavir was eliminated in the urine, 2.2% as unchanged lopinavir. Renal impairment should not have a significant effect on lopinavir clearance or the elimination of its metabolites. It is acceptable for the applicant to not conduct a study in subjects with renal impairment. This is consistent with the *Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function.*

The applicant has not determined whether lopinavir clearance is altered by dialysis. Due to the poor water solubility and high extent of plasma protein binding, dialysis may not increase lopinavir (or ritonavir) clearance.

Does impaired hepatic function alter lopinavir pharmacokinetics?

The applicant did not investigate lopinavir pharmacokinetics in subjects with impaired hepatic function. Because CYP3A4 metabolizes both lopinavir and ritonavir, it is likely that hepatic disease will result in increased plasma lopinavir concentrations.

Data are not available to allow the selection of appropriate lopinavir/ritonavir dose adjustments in patients with hepatic impairment. The label will recommend that physicians make a benefit/risk assessment on an individual patient basis. The applicant should conduct a study to determine the appropriate dose for patients with hepatic impairment.

Based on in vitro drug metabolism studies, what drug-drug interactions are expected?

Cytochrome P450 enzymes involved in lopinavir metabolism

The Applicant evaluated the kinetics of lopinavir in liver microsomes from four humans over the concentration range 0.3 – 50 µM. The mean ± SD values for Km and Vmax were determined to be 6.8 ± 3.6 µM and 9.4 ± 5.5 nmol substrate metabolized/mg protein/minute, respectively.

The involvement of human cytochrome P450 1A2, 2A6, 2C9/10, 2C19, CD6, 2E1 and 3A4 enzymes in the metabolism of lopinavir was investigated in this study. The concentration of lopinavir used in these experiments was 7 µM (5.6 µg/mL), which is approximately equal to the Km value previously determined. The concentration of lopinavir used is also within the clinically relevant concentration range (when administered with ritonavir).

The results indicate that lopinavir is primarily metabolized by CYP3A4. Thus, coadministration of a CYP3A4 inducer or inhibitor may alter lopinavir concentrations. Lopinavir will be coadministered with the potent CYP3A4 inhibitor ritonavir, which may change the potential for drug-drug interactions via CYP3A4. Other CYP3A4 inhibitors may not further inhibit lopinavir metabolism. Although it was anticipated that the presence of ritonavir may "protect" lopinavir from the effects of CYP3A4 inducers, in vivo drug interaction studies indicate this is not true.

Lopinavir/ritonavir inhibition of cytochrome P450 enzyme activity

Previous studies have shown that ritonavir is a very potent inhibitor of CYP3A4 and is an inhibitor of CYP2D6, CYP2C9 and CYP2C19. The applicant conducted CYP enzyme inhibition

studies in human liver microsomes to determine the inhibition potential of ritonavir, lopinavir, and combinations of lopinavir/ritonavir. IC_{50} values were determined for two lopinavir/ritonavir combinations (3:1 and 29:1). The typical clinically observed ratio of lopinavir:ritonavir in the plasma is 15:1 to 20:1. For lopinavir alone, percent inhibition was determined at one concentration, usually 30 µM.

IC_{50} (µM) of lopinavir/ritonavir combination

CYP enzyme	Substrate (concentration)	Lopinavir:ritonavir ratio		Ritonavir (Historical data)
		3:1	29:1	
1A2	Phenacetin (60 µM)	No effect	No effect	> 50
2A6	Coumarin (5 µM)	No effect	No effect	No effect
2B6	S-mephenytoin (500 µM)	> 30	> 30	8.1
2C9	Tolbutamide (100 µM)	13.7	23.0	8.0
2C19	S-mephenytoin (75 µM)	28.7	38.0	13.0
2D6	Dextromethorphan (20 µM)	13.5	29.0	2.5
2E1	Chlorzoxazone (100 µM)	No effect	No effect	No effect
3A4	Terfenadine (10 µM)	1.1	4.6	0.14

% Control Activity (CYP2D6 activity, substrate = Dextromethorphan)

Inhibitor	Concentration	Mean ± SD % control activity
Ritonavir	3.3 µM	45.4 ± 18.5
Lopinavir	30 µM	58.3 ± 4.3
3:1 lopinavir: ritonavir	20 µM	47.5 ± 11.3
3:1 lopinavir: ritonavir	30 µM	27.5 ± 3.9
29:1 lopinavir: ritonavir	20 µM	51.4 ± 18.1
29:1 lopinavir: ritonavir	30 µM	47.6 ± 4.2
Quinidine	0.5 µM	35.5 ± 14.5

The IC_{50} values for the lopinavir/ritonavir combinations are composite values. For example, the 2D6 IC_{50} value for the 3:1 combination is 13.5 µM. 25% of the concentration is ritonavir and 75% is lopinavir. This approach seems unusual, but may give a gross appreciation of the inhibitory potential of lopinavir/ritonavir combinations. What is of interest is the inhibitory potential of each component, in the presence of the other component, relative to component's plasma concentration.

The inhibitory potential of lopinavir/ritonavir, compared to ritonavir alone, appears similar for CYP2C9, CYP2C19, CYP2D6, and CYP3A4.

Lopinavir/ritonavir is not expected to inhibit CYP1A2, CYP1A6, CYP2B6, or CYP2E1.

Lopinavir/ritonavir induction of cytochrome P450 enzyme activity

Based on in vivo data at higher doses of ritonavir (500 to 600 mg), it is presumed that ritonavir induces metabolism via CYP3A4, CYP1A2 and some UDP-glucuronosyltransferase enzymes. The applicant conducted studies in human hepatocytes from 5 donors to determine whether ritonavir or lopinavir induce activities of CYP3A4, CYP1A2 and glucuronosyltransferase.

This study confirmed the inductive effect of ritonavir on CYP3A4. Ritonavir did not induce CYP1A2 or glucuronosyltransferase. Lopinavir did not induce any of the three enzymes studied.

When lopinavir/ritonavir is administered in combination with other protease inhibitors, are dose adjustments needed?

<u>Saquinavir</u>

Coadministration of saquinavir does not alter lopinavir/ritonavir pharmacokinetics. Coadministration of lopinavir/ritonavir increases saquinavir concentrations.

In M97-806, healthy volunteers received a single saquinavir 800 mg dose with steady-state lopinavir/ritonavir 400/100 mg BID. The results were compared to saquinavir pharmacokinetics in HIV patients who received 1200 mg TID (approved Fortovase dose). The comparison is confounded by the fact that saquinavir concentrations at 1200 mg TID are twice as high for HIV infected patients as they are for healthy volunteers. It is not known whether this difference will exist in the presence of the potent CYP3A4 inhibitor ritonavir.

Following administration of saquinavir 800 mg BID in combination with lopinavir/ritonavir, saquinavir AUC_{24}, C_{max}, and C_{min} in healthy volunteers will be approximately 26 µg.hr/mL, 1.3 µg/mL, and 0.32 µg/mL, respectively. These exposure measures are higher than those observed following administration of the approved saquinavir dose (1200 mg TID) without lopinavir/ritonavir. Although it is not possible to predict the magnitude of the change, saquinavir exposure is expected to be even higher in HIV-infected patients receiving lopinavir/ritonavir with 800 mg BID saquinavir.

Results from M97-741 indicate that coadministration of lopinavir/ritonavir (± efavirenz) increases saquinavir AUC and C_{max} by approximately 40- and 10- fold, respectively. Due to small numbers, this study is difficult to interpret.

The Kaletra label can include a general statement that saquinavir 800 mg BID in combination with lopinavir/ritonavir will provide saquinavir exposure higher than observed following saquinavir 1200 mg TID alone. The appropriate dose of saquinavir in combination with lopinavir/ritonavir has not been determined.

<u>Indinavir</u>

Coadministration of indinavir does not alter lopinavir/ritonavir pharmacokinetics. Coadministration of lopinavir/ritonavir increases indinavir concentrations.

In M97-806, healthy volunteers received a single indinavir 600 mg dose with steady-state lopinavir/ritonavir 400/100 mg BID. The results were compared to indinavir pharmacokinetics in HIV patients who received 800 mg TID (approved Crixivan dose).

Following administration of indinavir 600 mg BID in combination with lopinavir/ritonavir, indinavir AUC_{24}, C_{max} and C_{min} in healthy volunteers will be approximately 45 µg.hr/mL, 3.5 µg/mL and 0.44 µg/mL. Indinavir exposure is similar in healthy volunteers and HIV-infected patients. Thus, this combination will provide indinavir AUC_{24} that is similar to AUC_{24} with the approved dose. C_{max} will be reduced by >50%, the significance of this decrease is not known. C_{min} will be approximately double that observed with the approved dose.

M97-741 provides similar results regarding the interaction between indinavir and lopinavir/ritonavir

The Kaletra label can include a statement regarding the expected indinavir concentrations following indinavir Ɩ.ʃ.0 mg BID in combination with lopinavir/ritonavir. The label will indicate that the significance of the reduction in indinavir Cmax is not known.

Nelfinavir

Results from M97-741 indicate that coadministration of lopinavir/ritonavir (± efavirenz) decreases nelfinavir AUC, Cmax and Cmin. Concentrations of the active nelfinavir M8 metabolite are increased. Due to small numbers, the fact that efavirenz may confound the interaction, and the fact that nelfinavir single dose pharmacokinetics do not predict multiple dose pharmacokinetics, this study is difficult to interpret.

It is not possible to include nelfinavir interaction data in the Kaletra label.

Amprenavir

In M99-085, healthy volunteers received amprenavir 450 or 750 mg BID in combination with steady-state lopinavir/ritonavir 400/100 mg BID.

An 11 to 19% decrease in lopinavir exposure measures was observed when lopinavir/ritonavir was coadministered with 450 mg or 750 mg of amprenavir. Lopinavir C_{min} decreased by 19%.

When compared to historical data from HIV infected patients receiving the approved amprenavir 1200 mg BID regimen, amprenavir C_{max} and AUC values were lower (55% and 18%, respectively) when amprenavir was dosed at 750 mg BID with lopinavir/ritonavir. However, the decreases in amprenavir exposure are greater (amprenavir AUC and C_{min} decreased by 40 to 45% and C_{max} decreased by 73%) when compared to previous data for healthy volunteers. As with saquinavir, it is difficult to predict whether the differences between healthy volunteers and HIV infected patients will exist in the presence of the potent CYP3A4 inhibitor ritonavir.

Preliminary results from ⚊⚊⚊⚊⚊⚊⚊ indicate that amprenavir AUC is 67% higher, Cmax is 16% lower and Cmin is 5-fold higher following administration of amprenavir 600 mg BID with ritonavir 100 mg BID, compared to amprenavir 1200 mg BID alone.

The 750 mg amprenavir results may be placed in the label, including wording regarding the cross-study comparisons in different populations. The label will indicate that the significance of the interaction is not known, and that the appropriate regimen for this combination is not known. The results from ⚊⚊⚊⚊⚊ give us more confidence that the amprenavir 750 mg BID dose is not too low.

When lopinavir/ritonavir is administered in combination with non-nucleoside reverse transcriptase inhibitors, are dose adjustments needed?

Nevirapine

Three studies provide nevirapine-lopinavir/ritonavir drug interaction information

In the parallel study M97-704, healthy volunteers received lopinavir/ritonavir 400/100 mg BID (n=9), nevirapine 200 mg BID (n=6), or nevirapine 200 mg BID with lopinavir/ritonavir 400/100 mg BID (n=5). The ratio of the average value of the pharmacokinetic parameters is close to

unity in most cases, suggesting that major changes in the pharmacokinetics of lopinavir, ritonavir or nevirapine are not expected when these drugs are administered concomitantly. However, due to the wide confidence intervals it is not possible to rule out an interaction.

In the Phase 2 study M97-765, lopinavir pharmacokinetic data are available for 7 HIV infected patients who received lopinavir/ritonavir 400/100 mg BID with nevirapine 200 mg BID and for 5 patients who received lopinavir/ritonavir 400/200 mg BID with nevirapine 200 mg BID.

Following administration of lopinavir 400/100 mg BID for 6 weeks, lopinavir AUC_{12} was $61.0 \pm$ 19 µg.hr/mL. This value is approximately 27% lower than the AUC_{12} observed in the HIV infected patients (n = 21) in M97-720. Part of the difference between the two studies may be due to the limited sampling strategy used in M97-765.

Pediatric patients in M98-940 received lopinavir/ritonavir in combination with nevirapine and NRTIs or with only NRTIs. At both lopinavir/ritonavir dose regimens evaluated, lopinavir concentrations were 27 to 29% lower in the patients who received nevirapine, compared to those who did not receive nevirapine.

Results from M97-765 and M98-940 indicate that it is appropriate to increase the lopinavir dose to 533/133 mg BID when coadministered with nevirapine.

Efavirenz

In the parallel study M97-741, healthy volunteers received lopinavir/ritonavir 400/100 mg BID (n=9), efavirenz 600 mg QD (n=18), or efavirenz 600 mg QD with lopinavir/ritonavir 400/100 mg BID (n=18). Concomitant administration of lopinavir/ritonavir and efavirenz resulted in a 10 to 15% decrease in efavirenz C_{max}, C_{min} and AUC and also resulted in a decrease in lopinavir C_{min} and AUC. The point estimate and 90% confidence intervals for lopinavir (No efavirenz/with efavirenz) C_{max}, C_{min} and AUC_{12} were 0.97 [0.78 – 1.22], 0.61 [0.38 – 0.98] and 0.81 [0.64 – 1.03], respectively.

In M98-957, pharmacokinetic data are available for HIV infected patients who received lopinavir/ritonavir at 400/100 mg BID or 533/133 mg BID, in combination with efavirenz 600 mg QD and NRTIs. The efavirenz trough values observed in this study are higher than observed previously in HIV-infected patients who received efavirenz 600 mg QD.

Mean (%CV) lopinavir pharmacokinetic parameters (Study M98-957)

Dose	n	C_{max} (µg/mL)	AUC_{12} (µg.h/mL)	C_{12} (µg/mL)
400/100	24	8.15 (37)	61.8 (43)	2.16 (74)
533/133	26	10.73 (61)	89.8 (73)	4.07 (99)

The mean lopinavir pharmacokinetic parameter values following administration of lopinavir/ritonavir 400/100 mg BID in combination with efavirenz were lower when compared to historical data (M97-720). The mean lopinavir pharmacokinetic parameter values following administration of lopinavir/ritonavir 533/133 mg BID in combination with efavirenz were slightly higher than the values observed in M97-720. Safety and data for lopinavir/ritonavir 533/133 mg BID in combination with efavirenz 600 mg QD from this study are acceptable.

The results from M98-957 and M97-741 indicate that when lopinavir/ritonavir are coadministered with efavirenz, the lopinavir/ritonavir dose should be increased to 533/133 mg BID.

Delavirdine

No data are available regarding the magnitude of any interaction between lopinavir/ritonavir and delavirdine. Delavirdine is a potent CYP3A4 inhibitor; it significantly decreases the metabolism of all approved protease inhibitors, including ritonavir. It is possible that coadministration with delavirdine will significantly increase lopinavir plasma concentrations.

When lopinavir/ritonavir is administered in combination with nucleoside reverse transcriptase inhibitors, are dose adjustments needed?

No formal drug interaction studies were conducted with the NRTIs and lopinavir/ritonavir. None of the NRTIs are inducers or inhibitors of CYP3A4 metabolism. Approved NRTIs, other than zidovudine and abacavir, are partly eliminated by nucleoside salvage pathways and are largely eliminated renally. Thus, the pharmacokinetics of lamivudine, didanosine, stavudine, and zalcitabine should not be affected significantly by lopinavir/ritonavir coadministration.

Lopinavir/ritonavir may induce the activity of UDP-glucuronosyl transferase, so it may decrease zidovudine and abacavir plasma concentrations. The clinical significance of this is not known. In a previously reviewed study, coadministration of ritonavir 500 mg BID decreased zidovudine concentrations by 25%. No dosage adjustment is recommended during concurrent ritonavir and zidovudine use.

Didanosine is formulated with a buffer for physical stability and must be taken at least 30 minutes before or two hours after a meal. Lopinavir/ritonavir should be administered with food. Due to the instructions regarding administration relative to food, didanosine and lopinavir/ritonavir doses must be spaced appropriately.

Dose adjustments are not needed when NRTIs are administered with lopinavir/ritonavir. Instructions regarding administration with didanosine will be included in the label.

When lopinavir/ritonavir is administered in combination with drugs used to prevent or treat opportunistic infections, are dose adjustments needed?

Rifampin

The results of M99-107 indicate that concentrations of lopinavir and ritonavir are reduced substantially when coadministered with rifampin. Lopinavir AUC was decreased by 75%. Rifampin should not be administered to patients receiving lopinavir/ritonavir.

Rifabutin

The results of M99-113 indicate that the elimination of rifabutin and 25-O-desacetylrifabutin is inhibited by concomitant administration of lopinavir/ritonavir. For rifabutin, there was a 2- to 5-fold increase in exposure measures (AUC, Cmax, Cmin). For 25-O-desacetylrifabutin, there was a 24- to 95-fold increase in exposure measures.

Concomitant administration of rifabutin did not alter lopinavir/ritonavir pharmacokinetics.

Dose adjustment is required for rifabutin. A dosing recommendation similar to the one provided in the label for ritonavir would be appropriate for this product. Thus, if rifabutin is coadministered with lopinavir/ritonavir, a reduction in the rifabutin dosing regimen by at least three-quarters of the usual dose of 300 mg per day is recommended (i.e., a maximum dose of 150 mg every other day or three times per week). Additionally, increased monitoring for adverse events is warranted in patients receiving the combination. Further dosage reduction of rifabutin may be necessary.

Ketoconazole and other azole antifungal agents

In M99-057, concomitant administration of lopinavir/ritonavir and ketoconazole resulted in a significant increase (3- fold) in ketoconazole AUC. Ketoconazole did not appear to have a clinically significant effect on the pharmacokinetics of lopinavir/ritonavir. These results are similar to the interaction observed when 500 mg ritonavir is administered with ketoconazole. Consistent with the ritonavir label, it is recommended that patients receiving lopinavir/ritonavir not receive doses of ketoconazole greater than 200 mg per day.

Although not studied, it is likely that concentrations of itraconazole, another azole antifungal agent metabolized by CYP3A4, would be increased by lopinavir/ritonavir. Consistent with the ritonavir label, it is recommended that patients receiving lopinavir/ritonavir not receive doses of itraconazole greater than 200 mg per day.

Fluconazole is eliminated renally and is a less potent CYP3A4 inhibitor. A significant pharmacokinetic interaction between fluconazole and lopinavir/ritonavir is not expected.

Clarithromycin

The applicant did not conduct an interaction study between lopinavir/ritonavir and clarithromycin. Interaction studies with ritonavir and other protease inhibitors have demonstrated that concentrations of clarithromycin increase with coadministration, and concentrations of the active 14-OH metabolite are decreased substantially. The ritonavir label indicates that the clarithromycin dose should be decreased in patients with severe renal impairment that receive clarithromycin and ritonavir. A similar statement should be in the lopinavir/ritonavir label.

Other agents

Many other agents used for opportunistic infections are not expected to have a significant pharmacokinetic interaction with lopinavir/ritonavir, because they are not significantly metabolized by and do not affect CYP3A4 significantly. These agents include trimethoprim/sulfamethoxazole, dapsone, ethambutol, isoniazid, and azithromycin. It is notable that a recent drug interaction study conducted by ▬▬indicates that coadministration of azithromycin with nelfinavir increases azithromycin concentrations by approximately 2-fold, but does not alter azithromycin elimination half-life. Another study indicated that there is no interaction between azithromycin and indinavir. Because indinavir and nelfinavir both inhibit CYP3A4 and p-glycoprotein, a mechanism for the interaction is not known. In addition, azithromycin is not metabolized significantly by CYP3A4. The implications for an interaction between azithromycin and other protease inhibitors is not known.

Does coadministration of lopinavir/ritonavir alter the pharmacokinetics of the components of oral contraceptives?

In M98-969, concomitant administration of lopinavir/ritonavir decreased ethinyl estradiol and norethindrone concentrations. Mean ethinyl estradiol exposure measures were decreased by 40 to 60%. Mean norethindrone exposure measures were decreased by 17 to 32%. Therefore, female patients receiving lopinavir/ritonavir should NOT use oral contraceptives as the primary method of birth control.

Does coadministration of lopinavir/ritonavir alter the pharmacokinetics of methadone?

In M99-085, concomitant administration of lopinavir/ritonavir and methadone resulted in a substantial decrease in methadone plasma concentrations. Methadone mean AUC was decreased by 53% (90% CI: 47 to 58%) and mean Cmax was decreased by 45% (90% CI: 36 to 52%). Therefore, the dose of methadone may need to be adjusted in patients receiving lopinavir/ritonavir.

Does coadministration of lopinavir/ritonavir alter the pharmacokinetics of HMG-CoA reductase inhibitors ("statins")?

The applicant evaluated the effect of lopinavir/ritonavir on the pharmacokinetics of atorvastatin and pravastatin in M99-057.

Pravastatin (20 mg QD for 4 days) did not affect the pharmacokinetics of lopinavir/ritonavir. Concomitant administration of lopinavir/ritonavir and pravastatin increased the exposure to pravastatin and its metabolite SQ 31906 by approximately 30%. This is generally not considered clinically significant; however, patients receiving a dose of 40 mg QD of pravastatin should be monitored for adverse events.

Atorvastatin (20 mg QD for 4 days) did not affect the pharmacokinetics of lopinavir/ritonavir. Concomitant administration of lopinavir/ritonavir and atorvastatin results in a significant increase in the exposure to atorvastatin. Atorvastatin AUC and Cmax were increased by approximately 6- and 5-fold, respectively. If concomitant administration of lopinavir/ritonavir and atorvastatin is necessary, then the lowest possible dose of atorvastatin (10 mg) should be considered and patients should be carefully monitored for adverse events.

The elimination of lovastatin and simvastatin are highly dependent on CYP3A4. These agents should not be administered with lopinavir/ritonavir (or other protease inhibitors). The elimination of cerivastatin is less dependent on CYP3A4, but an interaction similar to the one with atorvastatin is possible. Thus, if concomitant administration of lopinavir/ritonavir and cerivastatin is necessary, then the lowest possible dose of cerivastatin should be considered and patients should be carefully monitored for adverse events. Fluvastatin is not metabolized by CYP3A4, an interaction is not expected.

Are there any medications that should be contraindicated in patients receiving lopinavir/ritonavir?

Medications for which a large increase in concentrations may occur when administered with lopinavir/ritonavir, leading to severe or life threatening events, should be contraindicated.

The following CYP3A4 substrates should be contraindicated: triazolam, midazolam, ergotamine, dihydroergotamine, and pimozide. These drugs are contraindicated with other HIV protease inhibitors.

The following CYP2D6 substrates should be contraindicated: flecanide and propafenone. These drugs are contraindicated with ritonavir (Norvir). In vitro drug metabolism studies indicate that lopinavir/ritonavir may be a potent CYP2D6 inhibitor. To remove these agents from the contraindication list, the applicant should provide in vivo evidence that the potential for a significant interaction is small.

What other drugs may have a significant pharmacokinetic interaction when coadministered with lopinavir/ritonavir?

Concentrations of the following CYP3A4 substrates may be increased: amiodarone, quinidine, bepridil, systemic-lidocaine, nifedipine, felodipine, nicardapine, cyclosporine, tacrolimus, sirolimus, sildenafil.

Concentrations of CYP2D6 substrates may also be increased.

The following CYP3A4 inducers may decrease lopinavir concentrations: phenytoin, phenobarbital, carbamazepine, dexamethasone, and St. John's wort.

Were the analytical procedures used to determine drug concentrations in this NDA acceptable?

Two methods were used to determine simultaneously lopinavir and ritonavir concentrations in plasma. One method used liquid-liquid extraction with UV detection (LC/UV) and the other used either liquid-liquid or solid phase extraction and tandem mass spectroscopy (LC/MS/MS). Both methods have adequate linearity (correlation coefficient>0.99), precision (%CVs <8%), accuracy, reproducibility, and sensitivity (LOQ ▬▬▬ for validation) for both lopinavir and ritonavir. The applicant provided adequate documentation of method validation and in-study validation.

Has the applicant developed an appropriate dissolution method and specification?

The applicant proposes the following method and specification. These are acceptable.
    Apparatus: Paddle, USP dissolution apparatus 2
    Rotation: 50 rpm
    Temperature: 37 ± 0.5°C
    Medium: ▬▬▬▬▬▬▬▬▬▬▬▬
    Q = ▬▬in 30 minutes (for lopinavir and ritonavir)

To select a medium, the applicant evaluated the effect of pH and surfactant concentration.

<u>Effect of surfactant concentration</u>
The applicant evaluated ▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬

Thus, the applicant selected 0.05 M. This is acceptable.

Effect of pH

The applicant evaluated ——————— ¹ acetate buffer (pH 4.0) and phosphate buffer (pH 6.8). In order to disperse the ————— material of the dosage form, each medium was prepared with ——————

Results:

       Phosphate buffer at pH 6.8: mean % dissolved <50% at 45 minutes
       ————— incomplete and variable dissolution at 45 minutes
       Acetate buffer at pH 4.0: Profiles are acceptable. However, the measured pH of the
       ———————————— Dissolution profiles were similar for acetate buffer at
       pH 4.0 and ᵢ ——————— ˙ solution. Addition of acetate buffer does not provide any
       benefit to profiles for lopinavir or ritonavir.

Thus, the applicant selected the ————— solution. This is acceptable.

SPECIFICATION:

Lot 51-139-AR-R1 was used in both pivotal BE studies (M99-072 and M99-073). The dissolution profiles for this lot indicate that the 20 minute time point is almost acceptable, but there is more variability than for the 30 minute timepoint. Several dosage units would almost not pass at 20 minutes. The true plateau in the profile is reached by 30 minutes.

The specification of Q = —— in 30 minutes is acceptable.

What clinical pharmacology/biopharmaceutics related Phase IV commitments should the sponsor fulfill?

1. Evaluate lopinavir/ritonavir pharmacokinetics in subjects with hepatic impairment, to allow the determination of dosing recommendations.
2. Establish appropriate dosing recommendation for the coadministration of ritonavir/lopinavir with the other approved protease inhibitors.
3. Determine, in vivo, the extent to which lopinavir/ritonavir inhibits CYP2D6.
4. Collect additional data addressing the effect of nevirapine on lopinavir/ritonavir, in adult patients.
5. Explore dosing recommendations for coadministration of lopinavir/ritonavir and rifampin, with additional ritonavir.
6. Explore dosing recommendations for the coadministration of lopinavir/ritonavir + approved protease inhibitor(s) + efavirenz/nevirapine.
7. Evaluate PK/PD relationships in studies M98-957 and M99-049 (ongoing Phase III studies).

Recommendation: The clinical pharmacology and biopharmaceutics information submitted to NDA 21-226 and NDA 21-251 is acceptable.

/S/   ✓ 1?–10–2000

Kellie Schoolar Reynolds, Pharm.D.   ⊔
Pharmacokinetics Team Leader/Reviewer
Antiviral Drug Products Team
Division of Pharmaceutical Evaluation 3
Office of Clinical Pharmacology and Biopharmaceutics

/S/   10/10/2000

Jooran S. Kim, Pharm.D.
Pharmacokinetics Reviewer
Antiviral Drug Products Team
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Office of Clinical Pharmacology and Biopharmaceutics

Note: Prabhu Rajagopalan, Ph.D. conducted the initial review of all individual study reports, except M98-940 and M97-806. He left the agency prior to the action on this application.

Concurrence: /S/   10/11/2000

Arzu Selen, Ph.D.
Deputy Division Director
Division of Pharmaceutical Evaluation 3
Office of Clinical Pharmacology and Biopharmaceutics

CC:
HFD-530   /NDA 21-226 and 21-251
          /MO/KStruble
HFD-880   /PKTL/KReynolds
          /PK/JKim

**Regulatory Review Officer's Review of New Drug Application 21-226
Lopinavir/ritonavir 133/33 mg:**

Pre Submission Date: December 29, 1999
Date Submitted: June 1, 2000
Date Completed:

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

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

APPEARS THIS WAY
ON ORIGINAL

Table of Contents:

1. RESUME

Abbott Laboratories submitted this NDA to seek FDA approval for ABT-378/ritonavir 400/100 mg twice daily for the treatment of HIV infection. At the time of accelerated approval for many other antiretroviral drugs, determination of efficacy was often based on studies conducted in treatment naïve patients. However, this applicant undertook a development program that evaluated ABT-378/ritonavir in several different patient populations, including treatment naïve patients, patients who had virologic failure following their first protease inhibitor (PI) and patients who had previously been treated with multiple PI-containing regimens.

In addition the safety and activity of ABT-378/ritonavir has been demonstrated in patients with baseline HIV RNA > 100,000 copies/mL and CD4 cell counts < 50 in 5 phase 2 and 3 studies ranging from 24 – 72 weeks in duration.

The applicant's NDA filing for ABT-378/ritonavir 400/100 mg BID is based on the following:

- Treatment Naïve:
  - One phase two study to evaluate 3 doses of ABT-378/ritonavir (200/00 mg BID, 400/100 mg BID and 400/200 mg BID) in combination with stavudine and lamivudine for 72 weeks
  - An ongoing phase 3 study to evaluate ABT-378/ritonavir + stavudine + lamivudine vs Nelfinavir + stavudine + lamivudine (data out at 24 weeks).
- First PI failure:
  - One phase 2 study to evaluate 2 doses of ABT-378/ritonavir (400/100 mg BID and 400/200 mg BID) in combination with nevirapine, stavudine and lamivudine for 72 weeks.
  - An ongoing phase 3 study to evaluate ABT-378/ritonavir + nevirapine + RTIs vs Investigator Selected PIs (single or dual) + nevirapine + RTIs (24 weeks interim analyses).
- Multiple PI-experienced:
  - One phase 2 study to evaluate 2 does of ABT-378/ritonavir (400/100 mg BID + 533/133 mg BID) + efavirenz + RTIs for 24 weeks.

In addition, ABT-378/ritonavir was administered to over 3,000 patients with limited treatment options in an expanded access program. This program provides supplemental safety data.

This review will focus on studies conducted in adult patients. The activity of ABT-378/ritonavir was also evaluated in 100 treatment naïve and treatment experienced pediatric patients. Please refer to the review by Dr. Linda Lewis in NDA 21-251 for further details.

In summary, ABT-378/ritonavir has demonstrated activity that is at least as comparable to that of other marketed PI drugs. This has been demonstrated across a spectrum of patients ranging from treatment naïve to multiple-PI experienced, in pediatric patients and in patients with increased risk of progression or advanced disease (HIV-RNA > 100,000 copies/mL and CD4 counts < 50 cells/mm^3, respectively). In addition, the tolerability of this drug product appears to be comparable to that of nelfinavir and much better tolerated than standard doses of ritonavir. The most common adverse events and laboratory abnormalities were gastrointestinal (GI) intolerance, transaminase elevations and lipid abnormalities. Since this drug product contains ritonavir, drug interactions are an important safety concern and are appropriately addressed in the package inserts and in risk communication programs.

2. MATERIAL REVIEWED

This written review was based on the electronic data sets provided by the applicant and the following volumes:

NDA presubmission: December 29, 1999 and March 31, 2000
NDA submission: June 1, 2000

- Volume 1-2:   Labeling, application summary
- Volume 94-159 and 10-182:   Clinical and statistical data, ISE, ISS, Case report
                              forms and tabulations

The following amendments were also reviewed.

December 28, 1999	June 21, 2000	September 7, 2000
January 12, 2000	June 28, 2000	September 13, 2000
March 31, 2000	July 7, 2000	September 14, 2000
April 10, 2000	July 27, 2000 (2)	September 15, 2000 (3)
May 17, 2000	August 2, 2000	
May 31, 2000	August 7, 2000	
June 7, 2000	August 16, 2000	
June 9, 2000	August 30, 2000	

Financial Disclosure:

3. CHEMISTRY, MANUFACTURING AND CONTROL

ABT-378 is a peptidomimetic HIV protease inhibitor. ABT-378 is coformulated with ritonavir in a soft gelatin capsule. Lopinavir is a white to light tan powder and is insoluble in water. The recommended storage is at 36°F - 46°F (2°C - 8°C) until dispensed, however refrigeration is not required if used within 2 months and stored below 77°F (25°C). Please refer to Dr. Ko-Yu Lo's chemistry review for further details on the drug.

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4. PHARMACOLOGY AND TOXICOLOGY

4.1. Animal Toxicology Study Summaries

The applicant conducted the required animal toxicology and toxicokinetic studies of ABT-378 alone or in combination with ritonavir. The evaluations have included studies in mice, rats, and dogs. The most significant target organ for toxicity was the liver. Mild changes were also noted in the thyroid, erythron and testis. In addition, ECG changes were evaluated in dogs. Please refer to Dr. Hau Zhang's review for further details.

4.1.1. Hepatotoxicity

Changes in liver histology were observed in rodents and dogs. These changes were accompanied by ALT, AST, ALP or GGT elevations. Hepatocellular changes appeared to be reversible after a one month recovery period in dogs; however, these changes persisted through the one month recovery period in rats. Increases in cholesterol were seen in rats and mice and increases in triglycerides were seen in mice only. These elevations were considered possibly secondary to hepatic effects.

Increases in transaminases and lipids have been observed in human clinical trials. No patients discontinued for these laboratory abnormalities. These changes are readily monitored in clinical trials. In some cases lipid abnormalities required therapeutic intervention.

4.1.2. Thyroid

Mild but dose-related hypertrophy of follicular cells in the thyroid gland along with decreased T_4 and elevated TSH levels 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.

Changes in T_4 and TSH levels in humans were not clinically significant.

4.1.3. Cardiovascular

The cardiovascular profile of ABT-378/ritonavir was evaluated in 4 studies in rats and dogs. ECG changes Cardiac effects were noted in a 3-month dog study; however, these appeared to be secondary to alterations in plasma electrolyte concentrations resulting from poor GI tolerability in dogs. ECG changes were noted in 7 dogs, of which 3 dogs were either euthanized or died. In a subsequent studies the dogs received aggressive dietary supplementation and ECG and electrolyte changes were reduced.

In order to fully evaluate the cardiotoxic potential of ABT-378, the applicant performed ECGs on all patients in the phase 2 program. ECGs were perfor..ied at baseline and at subsequent time points, including week 24 for patients in study 863. In addition, 4 animal studies were conducted. Only modest effects on the cardiovascular system, receptor or ion channel functions were found at therapeutic or supratherapeutic 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. (See section 15: ISS for further details in humans)

4.2. Teratology and Reproductive Toxicity Studies

Some developmental toxicity was observed at maternally toxic dosages; however, no drug-induced malformations were observed.

4.3. Mutagenicity, Genotoxicity, and Carcinogenicity Studies

No mutagenic or clastogenic effects were detected in the mutagenicity studies. The Ames tests and in vitro cytogenetics in human lymphocytes with ABT-378 alone or in combination with ritonavir were negative.

Two-year oral carcinogenicity studies with ABT-378/ritonavir are currently ongoing. Carcinogenicity studies with ritonavir alone have recently been completed.

5. MICROBIOLOGY

The mean EC_{50} of lopinavir against five different HIV-1 laboratory strains was 19 nM. The applicant has provided analyses on genotypic correlates of reduced phenotypic susceptibility to ABT-378/ritonavir in viruses selected by other protease inhibitors and the activity of ABT-378/ritonavir in patients with previous protease inhibitor therapy. Please refer to Dr. Julian O'Rear's review for further details.

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6. CLINICAL BACKGROUND

6.1. Related INDs

51,175 – ABT-378/ritonavir capsules
55,984 – ABT-378/ritonavir oral solution

6.2. Foreign Experience

ABT-378/ritonavir has not been approved in any foreign country. Some of the studies submitted in this NDA had clinical trial sites in Europe, South America and South Africa.

6.3. Human Pharmacology, Pharmacokinetics and Pharmacodynamics

6.3.1. Pharmacokinetics

Please refer to the Biopharmaceutics review prepared by Drs. Prabhu Rajagapolan and Kellie Reynolds for further details.

6.3.1.1.   Absorption and Bioavailability
Lopinavir is essentially completely metabolized by CYP3A. Ritonavir inhibits the metabolism of lopinavir, thereby increasing the plasma levels of lopinavir.
In multiple dose studies the mean peak plasma concentration (C_{max}) of lopinavir was 9.6 ± 4.4 µg/mL, at approximately 4 hours after administration. The mean steady-state trough concentration prior to the morning dose was 5.5 ± 4.0 µg/mL. Lopinavir AUC over a 12 hour dosing interval averaged 82.8 ± 44.5 µg•h/mL.

Administration of a single 400/100 mg dose of ABT-378/ritonavir capsules with a moderate fat meal (500-682 Kcal, 22.7 to 25.1% calories from fat) was associated with a mean increase of 48 and 23% in lopinavir AUC and C_{max}, respectively, relative to fasting. For ABT-378/ritonavir oral solution, the corresponding increases in lopinavir AUC and C_{max} were 80 and 54%, respectively. Relative to fasting, administration of ABT-378/ritonavir with a high fat meal (872 Kcal, 55.8% from fat) increased lopinavir AUC and C_{max} by 97 and 43%, respectively, for capsules, and 130 and 56%, respectively, for oral solution. ABT-378/ritonavir should be taken with food in order to enhance bioavailability and decrease pharmacokinetic variability.

6.3.1.2.   Distribution

Lopinavir is approximately 98-99% bound to plasma proteins.

6.3.1.3. Metabolism:

Lopinavir is extensively metabolized by the hepatic cytochrome P450 system, almost exclusively by the CYP3A isozyme. Therefore, ABT-378/ritonavir has a potential to interact with many CYP3A inhibitors, inducers and substrates. The applicant also states that ABT-378/ritonavir is a weak inhibitor of CYP2D6 *in vitro;* thus, KALETRA is not likely to produce clinically significant drug interactions with drugs metabolized by CYP2D6 at the recommended dose but this needs to be demonstrated in vivo. Also ABT-378/ritonavir does not inhibit CYP2C9, CYP2C19, CYP2E1, CYP2B6 or CYP1A2 at clinically relevant concentrations.

6.3.1.4. Elimination

ABT-378/ritonaivr is metabolized extensively and excreted in the feces. Only 2% of the ABT-378 dose is recovered in the urine unchanged. It is unlikely that ABT-378/ritonavir will be affected in patients with renal impairment or by hemodialysis. However ABT-378/ritonavir concentrations may be increased in patients with hepatic impairment. This will be studies as a phase 4 commitment.

6.3.2. Drug Interactions

6.3.2.1. Drug Interaction Studies with ABT-378/ritonavir

Drug interaction studies were performed with ABT-378 and other drugs likely to be co-administered or drugs that had the potential to interact based on known metabolism of the agents. Twelve drug interaction studies were submitted with the NDA for review. ABT-378/ritonavir was found to increase plasma concentrations of atorvastatin, ketoconazole, rifabutin, and other marketed PIs. Efavirenz, nevirapine and rifampin decreased ABT-378 concentrations. ABT-378 also decreased methadone and ethinyl estradiol concentrations.

6.3.3. Special Populations

6.3.3.1. Pediatric Patients

The applicant submitted an NDA (NDA 21-251) for an oral solution for use in pediatric patients. The pharmacokinetics, safety and efficacy of oral ABT-378/ritonavir has been evaluated in 100 treatment naïve and experienced pediatric patients. Please refer to Dr. Linda Lewis' review for further details.

7. BRIEF DESCRIPTIONS OF CLINICAL TRIALS

A brief summary of all clinical trials submitted in this NDA is presented in the table below. These will be reviewed in detail in section 8.

Study Number	Patient Population (N)	Doses Studied/Control Arm	Design	Section in Review
Phase 2				
M97-720	Naïve (N=100)	200/100 + d4T + 3TC 400/100 + d4T + 3TC 400/200 + d4T + 3TC	Randomized, Open-Label, Dose Ranging	8.1 – 8.7.3
M97-765	Experienced (N=70)	400/100 + NVP +RTIs 400/200 + NVP +RTIs	Blinded, Randomized, Dose Ranging	9.1 – 9.9.3
M98-957	Experienced (N=57)	400/100 + EFV +RTIs 533/133 + EFV +RTIs	Randomized, Open-label	10.1 – 10.9
Phase 3				
M98-863	Naïve (N=686)	400/100 + d4T + 3TC Nelfinavir + d4T + 3TC	Randomized, Double-Blind	12.1 – 12.10
M98-888	Experienced (N=300) Interim results on 118	400/100 + NVP + RTIs PI Choice + NVP + RTIs	Randomized, Open-label	13.1 – 13.10

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CLINICAL TRIALS:

8.1 Study M97-720

8.2 Protocol Title

Phase I/II Study of ABT-378/Ritonavir in Combination with Reverse Transcriptase Inhibitors in Antiretroviral Naïve HIV-Infected Patients

8.3 Study Design

This was a randomized, multi-center study of ABT-378/ritonavir in combination with stavudine and lamivudine in HIV infected patients. Thirty-two antiretroviral naïve patients with HIV RNA $\geq$ 5,000 copies/mL were randomized in group I to receive one of the following blinded treatment arms:

Group I:

ABT-378/ritonavir 200/100 mg BID + d4T + 3TC
ABT-378/ritonavir 400/100 mg BID + d4T + 3TC

Stavudine and lamivudine were added on day 22.

Following a safety review after 4 weeks of dosing by the first 16 patients in group II, approximately 70 patients were randomized to one of the following blinded treatment arms.

Group II:

ABT-378/ritonavir 400/100 mg BID + d4T + 3TC
ABT-378/ritonavir 400/200 mg BID + d4T + 3TC

Stavudine and lamivudine were given on day 1 in group II.

All patients ongoing at week 48 were converted to open-label ABT-378 400/100 mg between week 48 and 72.

8.4 Patient Population

8.4.1 Inclusion Criteria

Inclusion/Exclusion criteria were: > 18 years of age, antiretroviral naïve, HIV RNA $\geq$ 5,000 copies/mL, no evidence of acute illness or documentation of abnormal laboratory parameters as defined by the protocol.

8.5   Study Endpoints

The primary efficacy analysis was proportion of patients with HIV RNA < 400 copies/mL at week 24 and the time to loss of virologic response through week 48.

8.6. Results

8.6.1. Patient Disposition

At total of 107 patients were randomized (see Table 8.6.3.A. for the number randomized to each treatment group). One hundred patients received at least one dose of ABT-378/ritonavir. Overall 51 patients received the 400/100 mg BID dose. It is important to note that all patients ongoing at week 48 were converted to open-label ABT-378 400/100 mg between weeks 48 and 72. The applicant states that conversion to the 400/100 mg dose was mostly completed between the week 48 and week 60 visits.

8.6.2. Protocol Deviations

Protocol deviations appeared to minor violations, related to measurements or assessments that did not occur within a time window specified in the protocol. In addition there were a number of laboratory tests missing at various timepoints. These deviations would not be expected to adversely impact the overall interpretation of the study results.

8.6.3. Reasons for Premature Discontinuation

Overall 13% of all patients who received at least one dose of study drug discontinued treatment at or before week 72. Table 8.6.3.A. also summarizes the reasons for premature discontinuation. Four patients prematurely discontinued study due to an adverse event. Overall 6 patients (12%) in the 400/100 dose groups discontinued study drug prior to week 72.

Table 8.6.3.A. Patient Disposition and Premature Discontinuations

Original Assignment	Group I		Group II	
	200/100 mg BID	400/100 mg BID	400/100 mg BID	400/200 mg BID
Received at least one dose of study medication	16	16	35	33
Discontinued at or before week 72	1*	2	4	6
Personal reasons	0	0	1	0
AE/HIV related event	1	0	1	2
Patient noncompliant	0	0	1	3
Lost to follow-up	0	1	1	1
Other	0	1	0	0

*patient discontinued at the week 72 visit

8.6.4. Demographic Data

Table 8.6.4.A shows demographic data, baseline HIV RNA levels and CD4 cell counts. There were no significant differences in the baseline characteristics for dose groups within group I or group II.

Table 8.6.4.A. Demographic Data

	Group I		Group II	
	200/100 mg BID	400/100 mg BID	400/100 mg BID	400/200 mg BID
Number of Patients	16	16	35	33
Mean age, Yrs	36	33	35	35
Men	100%	88%	97%	97%
Race or Ethnicity Caucasian Black or African American	 75% 25%	 69% 31%	 74% 26%	 64% 36%
Baseline mean plasma HIV RNA (PCR), $\log_{10}$ copies/mL	4.88 (3.7 – 5.9)	4.96 (3.7 – 6.1)	4.78 (3.3 – 6.1)	4.97 (3.9 – 6.7)
Number of patients with baseline HIV RNA > 100,000 copies/mL	8 (50%)	8 (50%)	14 (40%)	15 (45%)
Baseline median CD4 cell count (cells/mm³)	471	330	343	275

8.6.5. Efficacy Outcomes

8.6.5.1. HIV RNA

Proportion < 400 and 50 copies/mL

Table 8.6.5.1.A. and B summarize the efficacy analyses. Only the on-treatment and intent to treat (noncompleter = failure/NC=F) analyses are presented below. Other intent to treat (last observation carried forward and missing data = failure) analyses yielded similar results to the NC=F analysis.

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Table 8.6.5.1.A. Week 24, 48 and 72 Proportion < 400 copies/mL

| Dose Group | Proportion of Patients with HIV RNA < 400 copies/mL | | | | | |
| | Week 48 | | | Week 72 | | |
	On Treatment	ITT (NC=F)	> 400* copies/mL	On Treatment	ITT (NC=F)	> 400* copies/mL
Group I: 200/100	16/16 (100%)	16/16 (100%)	0	14/14 (100%)	14/16 (88%)	0
Group I: 400/100	13/14 (93%)	13/16 (81%)	2 (1572 and 6791 copies/mL)	11/13 (85%)	11/16 (69%)	2 (410, 4372 copies/mL)
p-value comparing dose groups	0.467	0.226		0.394	0.394	
Group 2: 400/100	32/32 (100%)	32/35 (91%)	0	30/30 (100%)	30/35 (86%)	0
Group 2: 400/200	24/30 (80%)	24/33 (73%)	7 (range 427 – 191780 copies/mL)	27/27 (100%)	27/33 (82%)	0
p-value comparing dose groups	0.010	0.059		>0.999	0.749	
Pooled 400/100 mg dose groups	45/46 (98%)	45/51 (88%)	2	41/43 (95%)	41/51 (80%)	2

* Missing HIV RNA measurements or premature discontinuations not included

A statistically significant (p<0.05) result for a comparison between dose groups was noted at week 48 for the on-treatment analysis in group 2. However, it is important to note that 5 patients in the 400/200 mg dose group had HIV RNA < 502 copies/mL. Based on this, the applicant's explanation that this difference between the 400/100 and 400/200mg doses is not likely a related to biologic activity or tolerability between doses appears reasonable.

Table 8.6.5.1.B. Week 24, 48 and 72 Proportion < 50 copies/mL

Dose Group	Proportion < 50 copies/mL				
	Week 48			Week 72	
	On Treatment	ITT (NC=F)	> 50 copies/mL*	On Treatment	ITT (NC=F)
Group I: 200/100	16/16 (100%)	16/16 (100%)	0	13/14 (93%)	13/16 (81%)
Group I: 400/100	9/14 (64%)	9/16 (56%)	5 (4 pts < 400 copies/mL, 1 pt 143050 copies/mL)	11/13 (85%)	11/16 (69%)
p-value comparing dose groups	0.014	0.007			
Group 2: 400/100	30/32 (94%)	30/35 (86%)	1 (180 copies/mL)	29/30 (97%)	29/35 (83%)
Group 2: 400/200	21/30 (70%)	22/33 (66%)	8 (6 pts < 400 copies/mL)	23/27 (85%)	23/33 (70%)
p-value comparing dose groups	0.020	0.050			
Pooled 400/100 mg dose groups	39/46 (85%)	39/51 (76%)	6 (5 pts < 400 copies/mL)	40/43 (93%)	40/51 (78%)

*Missing HIV RNA measurements or premature discontinuations not included

FDA conducted analyses on the proportion of patients in the 400/100 mg dose groups with HIV RNA < 400 copies/mL and < 50 copies/mL at week 48. These analyses were stratified by baseline HIV RNA (< 100,000 copies/mL and > 100,000 copies/mL). The results of these analyses are displayed in table below. The week 72 HIV RNA results appear similar for patients with baseline HIV RNA < 100,000 copies/mL and > 100,000 copies/mL. Of note, one patient with a baseline HIV RNA > 100,00 copies/mL who had a loss of virologic response had a week 72 HIV RNA of 410 copies/mL.

Dose Group	< 400 copies/mL at week 72 (On treatment)	< 50 copies/mL at week 72 (ITT NC=F)
Pooled 400/100 mg dose groups Baseline HIV RNA > 100,000 copies/mL	18/20 (90%)	18/22 (82%)
Pooled 400/100 mg dose groups Baseline HIV RNA < 100,000 copies/mL	23/23 (100%)	22/28 (79%)
Pooled 400/100 mg dose groups	45/46 (98%)	39/51 (76%)

*Patient 122 did not have a baseline HIV RNA and therefore was not included in these analyses.

Mean Change From Baseline:

Decreases in mean HIV RNA were seen at all time points. For group 1: ABT-378/ritonavir was given as monotherapy for the first 3 weeks. The mean change from baseline was −1.84 $\log_{10}$ copies/mL for the 200/100 mg dose group and −1.86 $\log_{10}$ copies/mL for the 400/100 mg dose group. Despite ABT-378/ritonavir given as monotherapy for the first 3 weeks there does not appear to be a difference between group I or group II with respect to HIV RNA response. Decreases in HIV RNA levels were maintained through week 72.

8.6.5.2 CD4 Cell Count

Table 8.6.5.2. summarizes the mean change from baseline to week 48 and 72 for CD4 cell counts. CD4 changes were comparable for both dose groups.

Dose Group	Mean Change from Baseline Week 48 (cell/µL)	Mean Change from Baseline Week 72 (cell/µL)
Group 1: 200/100	208	269
Group 1: 400/100	277	342
Group 2: 400/100	227	217
Group 2: 400/200	200	264

8.7 Safety Outcomes

A total of 100 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. There were no deaths during the first 72 weeks of this study.

8.7.1. Drug Exposure

The median duration of exposure was 545 days for all dose groups.

8.7.2. Adverse Events

8.7.2.1. Overview of Adverse Events

All 100 patients experienced at least one adverse event during the first 72 weeks of the study. The most common adverse events reported were predominately gastrointestinal events such as abnormal stools, diarrhea, and nausea. Asthenia and headache were also among the most commonly reported adverse events. Elevations in AST/ALT, triglycerides and total cholesterol were observed in all dose groups.

Table 8.7.2.1.A. summarizes treatment-emergent events (at least moderate severity) that are of probable, possible or of unknown relationship to ABT-378/ritonavir and with an incidence of greater than 2 percent.

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Table 8.7.2.1.A. Treatment-emergent events that are of probable, or possible relationship to study drug and occurring in > 2 percent of patients

	Group I		Group II		Pooled 400/100 Arms
	200/100	400/100	400/100	400/200	
Number of patients	16	16	35	33	51
Body System					
Abdominal pain	3 (18.8%)	0	1 (2.9%)	3 (9.1%)	1 (2%)
Asthenia	1 (6.3%)	2 (12.5%)	2 (5.7%)	2 (6.1%)	4 (7.8%)
Headache	1 (6.3%)	2 (12.5%)	2 (5.7%)	2 (6.1%)	4 (7.8%)
Digestive					
Abnormal stools	3 (18.8%)	3 (18.8%)	2 (5.7%)	0	5 (9.8%)
Diarrhea	2 (12.5%)	4 (25%)	6 (17.1%)	9 (27.3%)	10 (19.6%)
Dyspepsia	2 (12.5%)	1 (6.3%)	0	0	1 (2%)
Nausea	2 (12.5%)	0	3 (8.6%)*	10 (30.3%)*	3 (5.9%)
Vomiting	1 (6.3%)	0	0	4 (12.1%)	0
Skin/appendages					
Rash	0	0	2 (5.7%)	1 (3%)	2 (3.9%)

*statistically significant difference (p=0.031)
source NDA 21226 vol 1 table 12.2.b and vol 43 table 12.2.b

HIV Related Events:

Overall 15 patients experienced an HIV-related event during the first 72 weeks. Nine patients in the 400/100 mg dose groups experienced an HIV-related event. These events included oral candidiasis, chronic ulcers, herpes zoster, KS, wasting syndrome, hairy leukoplakia, and lymphoma.

8.7.2.2. Serious and Life-threatening Adverse Events

A total of 47 serious adverse events were reported in 23 patients during the first 72 weeks of the study. Only 2 events were considered possibly or probably related to ABT-378/ritonavir. Two patients prematurely discontinued study due to a serious adverse event. Eighteen (38%) of the serious adverse events occurred in patients receiving 400/100 mg dose, of which only one event was considered possibly related to ABT-378/ritonavir. One event of pneumothorax was reported during the 3 month safety update. This event was considered not related to study drugs.

One patient (patient 130) was hospitalized for enterocolitis with microabcesses and granulomata approximately 11 weeks after beginning ABT-378/ritonavir. This patient had a past medical history significant for gastroenteritis. This event could not be definitively linked to an infectious agent via culture; therefore the investigator stated that this event was possibly related to study drug. The applicant also states that this patient had a baseline CD4 count of < 100 and granulomata were seen on pathology. Therefore, atypical mycobacterial infection with an inflammatory reaction resulting from immune reconstitution is a possible etiology.

Another patient (patient 264) was hospitalized for fever, sweating and asthenia attributed to disseminated MAI ten days after the beginning of the study. The patient

also experienced diarrhea (8-12 times per day) and had a history of fever (> 101) for 4 months prior to study and a history of intermittent diarrhea, asthenia and night sweats for 3 months prior to study. During hospitalization study drugs were interrupted and subsequently restarted two days later. The hospitalization was prolonged by diarrhea and concurrent dehydration upon rechallenge of study drugs. Therefore the investigator's assessment that the events of diarrhea and dehydration were probably related to study drug appears reasonable; however a possible relationship to MAI cannot be ruled out.

Other Significant Adverse Events

Hepatitis

One case (patient 269) of acute hepatitis A infection (confirmed by serology) was reported as a serious adverse event and was considered not related to ABT-378/ritonavir. No other cases of clinical hepatitis were reported.

Body Fat Composition Changes

The applicant conducted a search of the adverse event database to identify potential events of lipodystrophy and other body fat composition changes. The following terms were used: buffalo, Cushing, dorsocervical, enlarged, girth, gynecomastia, hump, lipodystrophy, lipoma, moon and obesity.

Five patients reported body fat composition changes during 6-18 months after study initiation. Two patients were randomized to the 200/100 mg dose group, two patients were in the 400/100 mg dose group and one patient was in the 400/200 mg dose group. No patient discontinued therapy due to these changes

8.7.2.3. Adverse Events Associated with Discontinuation of Treatment

Serious Adverse Events

Two patients permanently discontinued study due to a serious adverse event during the 48-week study period. The first patient (patient 211), was hospitalized and subsequently discontinued from study due to lymphoma and a life threatening DVT (right lower extremity) and the second patient (patient 210) discontinued study drugs after approximately 12 months of ABT-378/ritonavir therapy to undergo alcohol detoxification.

Nonserious Adverse Events:

Two patients prematurely discontinued study drug due to a non-serious adverse event during the first 72 weeks. Patient 104 discontinued for severe hyperglycemia on day

539. This patient had pre-existing diabetes. Please refer to section 8.7.2.5.2 for further details.

Patient 240 discontinued study on day 521 due to non-compliance. The patient had a positive baseline serology for HBsAg and a history of chronic hepatitis B and increased transaminases at discontinuation. Please refer to section 8.9.2.5.2 for further details.

8.7.2.4. Deaths

No deaths occurred during the first 72 weeks of the study.

8.7.2.5. Laboratory Findings

8.7.2.5.1. Hematology

The applicant claims there were statistically significant mean decreases from baseline in RBC count over the 72 week study period. However, these changes were not considered clinically significant because hemoglobin and hematocrit levels increased from baseline.

Mean increases in MCV were seen for all dose groups. Increases in MCV have been associated with RTIs such as d4T. At week 72, MCV increases ranged from 13.7 to 19.3 μM^3. These increases were statistically significant for the 400/100 mg and 400/200 mg dose groups. Although there were statistically significant increases in MCV, the applicant did not consider these clinically significant because they were not accompanied by anemia. Patients with an increase of MCV > 105 μM^3 did not have decreases in either hemoglobin or hematocrit.

Statistically significant increases from baseline were seen for prothrombin time in the 400/100 dose groups. The applicant considered these changes to be not clinically significant due to the low magnitude of changes (0.31-0.60 seconds). Three patients experienced prothrombin times above the upper limit of normal, however no adverse events were reported.

Statistically significant increases in WBC, lymphocytes, monocytes and platelet counts were seen for at least 3 of the 4 dose groups. The only sustained statistically significant difference observed over the 72 week study period were increases from baseline for platelet counts. Patients in group I: 400/100 mg dose group had greater increases compared to patients in group I: 200/100 mg dose group.