

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-906

MEDICAL REVIEW

MEMORANDUM**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: 10-27-05

FROM: Jeffrey S. Murray M.D., M.P.H.
Deputy, Division of Antiviral Products

SUBJECT: Division Director's memorandum for NDA 21-906, Kaletra tablets

TO: DAVP Division files

I fully concur with the clinical review, written by clinical analyst and acting team leader Kimberly Struble PharmD, that Kaletra (lopinavir/ritonavir) tablets should be approved in combination with other antiretrovirals for the treatment of HIV. Kaletra is a fixed dose combination product consisting of two HIV protease inhibitors, lopinavir and ritonavir; lopinavir is responsible for the virologic efficacy of the FDC while low doses of ritonavir (also a metabolic inhibitor) substantially increase the plasma concentrations of lopinavir. Kaletra capsules and oral solution were first approved in September 2000. Department of Health and Human Services HIV treatment guidelines recommend Kaletra as a component of one of several preferred regimens for initiation of HIV therapy. Kaletra is also widely used as a component of second-line HIV therapy.

This NDA for Kaletra tablets was granted a priority review because of the expected advantages over the existing capsule formulation. These advantages compared to the capsule formulation are:

- Lower pill burden (4 pills daily instead of 6)
- Tablets can be administered without regard to food
- Tablets do not require refrigeration
- Dose adjustments of the tablets are not necessary in treatment naïve subjects concomitantly receiving certain NNRTIs and PIs

To support approval of the new tablet formulation Kaletra, Abbott Laboratories had intended to show that the tablets were bioequivalent to the approved capsules. However, bioequivalence studies showed that the new tablets yielded modestly greater concentrations than the capsules. Bioequivalence was met for AUC but exceeded the upper confidence bound for C_{max}. The point estimate for AUC and C_{max} after administration of the tablet formulation was 18% and 24% higher, respectively, than that of the approved capsule. This is a modest increase and if observed in the setting of a drug interaction would be unlikely to prompt a recommendation for a dose adjustment. However, during development

meetings for the tablet formulation FDA asked Abbott to provide in the NDA clinical safety data of higher exposures of Kaletra to show that higher plasma exposures of Kaletra are not associated with a substantial increase in adverse events. In response to FDA's request, Abbott submitted data pooled from four previously conducted dose-ranging clinical studies in which Kaletra was administered at higher doses. The conclusion of these analyses, as reviewed by Dr. Struble, was that exposures in the range of the tablet formulation were unlikely to significantly change the currently known safety profile of Kaletra. In addition, in cross-study comparisons of the tablet and capsule formulation, Abbott provided evidence that suggests the tablet formulation may have improved gastrointestinal tolerability compared to the capsules. They hypothesize that the difference may be related to changes in the other components of the drug products. FDA views these cross-study comparisons suggesting a potential tolerability advantage of the tablets as hypothesis-generating and recommended that Abbott confirm these findings in a controlled clinical study of the tablet and capsule formulation. Abbott agreed to complete such a study as a post-marketing commitment.

CLINICAL REVIEW

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Reviewer Name Kimberly A Struble, PharmD
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Established Name Lopinavir/Ritonavir (LPV/RTV)
Trade Name Kaletra
Therapeutic Class Antiviral
Applicant Abbott Laboratories

Priority Designation P

Formulation Tablets
Dosing Regimen Antiretroviral-naïve: 400/100 mg
twice daily or 800/200 once daily
Antiretroviral-experienced:
400/100 mg twice daily
Indication Treatment of HIV infection
Intended Population HIV-1 infected patients

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1 EXECUTIVE SUMMARY

This executive summary contains the recommendations and summary of clinical findings for a new tablet formulation of KALETRA (lopinavir/ritonavir; LPV/RTV). This application includes data from five pharmacokinetic studies in healthy volunteers and data from HIV-1 infected patients to support the higher exposures achieved with the tablet formulation compared to the marketed capsule formulation.

1.1 Recommendation on Regulatory Action

From a clinical perspective, the data presented in this NDA support approval for the new tablet formulation of Kaletra. Although the new tablet formulation is not bioequivalent to the currently marketed Kaletra capsule formulation, results from cross-study comparisons indicate the steady-state pharmacokinetics of LPV and RTV after administration of LPV/RTV 400/100 mg twice daily (BID) as the to-be-marketed tablet formulation were similar to the pharmacokinetic data observed in previous multiple-dose studies in healthy subjects using the marketed capsule formulation. Of note, the point estimates for lopinavir AUC and C_{max} are 18% and 24% higher with the tablet formulation compared to the marketed capsule formulation.

Safety data from studies in HIV-infected patients were used to support the approval of the new tablet formulation. Safety data from four phase II studies evaluating regimens that produced higher lopinavir and ritonavir concentrations compared to the approved 400/100 mg capsule regimen were submitted for review. Based on the analyses provided by Abbott, we concluded the slightly higher increases in LPV and RTV produced by the new tablet formulation will not likely alter the safety profile of LPV/RTV.

In addition, no new safety signals were identified from clinical studies evaluating single or multiple doses of the tablet formulation in healthy subjects. The preliminary multiple-dose tablet formulation data appears to suggest a decreased rate and severity of gastrointestinal adverse events, specifically diarrhea, compared to the marketed capsule formulation. However, these results are based on a limited number of healthy volunteers and are based on cross-study comparisons. The lower incidence of gastrointestinal-related events observed with the tablet formulation may be due to the lack of oleic acid in the tablet formulation. Additional phase IV studies are planned to determine if the incidence of GI events are less with the new tablet formulation. See section 1.2.2 for further details.

The new tablet formulation provides advantages over the marketed capsule formulation for HIV-1 infected patients. Specifically, the tablet formulation:

- does not require refrigeration,
- can be administered without regard to meals
- does not require dose adjustments for concomitant use with certain NNRTIs and PIs in treatment-naïve patients

- has a decreased pill burden compared to the capsule formulation (2 tablets BID or 4 tablets QD in treatment-naïve patients only vs 3 capsules BID or 6 capsules QD in treatment-naïve patients only)

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No specific Risk Management Activities were requested from the applicant.

1.2.2 Required Phase 4 Commitments

Abbott agreed to submit the final clinical study report for M05-730 entitled "A Phase 3, Randomized, Open-label study of Lopinavir/ritonavir Tablets Versus Soft Gel Capsules and Once Daily Versus Twice Daily Administration, when Coadministered with NRTIs in Antiretroviral Naïve HIV-1 Infected Subjects" on or before June 30, 2008.

Other Phase 4 Requests

No other phase 4 studies were requested with this sNDA.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

In this NDA, data from five pharmacokinetic studies in healthy volunteers were submitted:

1. M01-360: Bioavailability of multiple tablet formulations of LPV and RTV relative to the currently marketed capsule formulation
2. M01-381: Bioavailability of multiple tablet formulations of LPV and RTV relative to the currently marketed capsule formulation in fasting versus non-fasting conditions
3. M03-580: Comparison of the single-dose bioavailability of the tablet formulation relative to the currently marketed capsule formulation and assessment of the multiple-dose pharmacokinetics and safety of the tablet formulation with efavirenz
4. M03-616: Comparison of the single-dose bioavailability of the tablet formulation relative to the currently marketed capsule formulation following a high fat and moderate fat meal or under fasting conditions
5. M04-703: Comparison of the single-dose bioavailability of three lots of a tablet formulation relative to the currently marketed capsule formulation

Data from the following HIV-infected patient studies were included to support the higher exposures achieved with the tablet formulation compared to the marketed capsule formulation. Of note the point estimates for lopinavir AUC and Cmax are 18% and 24% higher with the tablet formulation compared to the marketed capsule formulation.

Study	Lopinavir/ritonavir Dosing (mg)	Subjects Treated (n)	Duration of treatment (weeks) Median (IQR)
Currently Marketed Regimen			
M97-720	400/100 q12h	51	54 (54-54)
Regimens with higher LPV and RTV levels than currently marketed regimen			
M97-720	400/200 q12h	33	54 (54-54)
M97-720	200/100 q12h	16	54 (54-54)
M97-765	400/200 q12h	34	156 (93-164)
M98-940	300/75 mg/m ² q12h	29	97 (96-108)
M99-049	400/300 q12h	17	24 (9-29)
M99-049	667/167 q12h	19	20 (14-36)

1.3.2 Efficacy

No efficacy data were reviewed for the approval of this NDA. Based on the pharmacokinetic parameters of the tablet formulation as compared to the marketed capsule formulation, the tablet formulation is expected to have an efficacy profile similar to the capsule formulation. This conclusion is based on the following:

- The point estimate for LPV AUC is approximately 18% higher for the tablet compared to the marketed capsule formulation
- Lower variability in lopinavir exposures for the tablet formulation compared to the marketed capsule formulation was observed.

1.3.3 Safety

No new or unexpected safety signals were identified in the application. The slightly higher increases in LPV and RTV produced by the new tablet formulation will not likely alter the safety profile of LPV/RTV. This conclusion is based on the review of safety data for higher LPV exposures where HIV-1 infected patients received 400/200 mg BID and 667/167 mg BID. LPV exposures following 400/200 mg BID, 667/167 mg BID and 400/300 mg BID were >20% higher than that of 400/100 BID. As a result, the anticipated events with the tablet formulation are expected to be less frequent and milder in nature than those observed in studies with higher dose LPV/RTV regimens.

1.3.4 Dosing Regimen and Administration

The recommended dosing regimen for LPV/RTV tablets is 400/100 mg once daily or twice daily in treatment-naïve patients and 400/100 mg twice daily in treatment-experienced patients. These recommendations are identical to those approved in September 2000 and April 2005.

1.3.5 Drug-Drug Interactions

Increasing the dose of Kaletra tablets to 600/150 mg (3 tablets) BID co-administered with efavirenz significantly increased LPV plasma concentrations approximately 35% and increased RTV plasma concentrations approximately 56% to 92% compared to Kaletra tablets 400/100 mg BID without efavirenz. Based on these data, we concluded a dose increase was not necessary for all patients. A dose increase should be considered for patients who need higher LPV concentrations. As a result the following information was included in the package insert: a dose increase of LPV/RTV to 600/150 mg should be considered when used in combination with efavirenz, nevirapine, amprenavir, or nelfinavir in treatment-experienced patients where reduced susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). KALETRA 400/100 mg tablets can be used twice daily in combination with these drugs with no dose adjustment in antiretroviral-naïve patients.

1.3.6 Special Populations

No new dosing considerations for special populations are included in this NDA. The maximum recommended dose in children > 40 kg is 400/100 mg twice daily (5.0 ml of the oral solution or two tablets).

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

LPV is a peptidomimetic HIV-1 protease inhibitor (PI) that selectively inhibits the virus-specific processing of viral Gag and Gag-Pol polyproteins in HIV-1 infected cells, thus preventing formation of mature infectious virions. The mechanism of action of LPV/RTV is similar to other PIs used in the treatment of HIV infection. Currently, the approved dosing regimen for treatment-naïve patients is 800/200 mg given orally once daily or is 400/100 mg twice daily and the approved dosing regimen for treatment-experienced patients is 400/100 mg twice daily.

2.2 Currently Available Treatment for Indications

At present, 21 antiretroviral drug products are approved in the US for the treatment of HIV infection, some in multiple formulations and fixed drug combinations. Four classes of

antiretroviral agents exist. The classes are based on the mechanism of action in the HIV life cycle: nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs) and fusion inhibitors.

Eight NRTI's are approved and marketed in the US: zidovudine (Retrovir®), didanosine (Videx®), zalcitabine (Hivid®), stavudine (Zerit®), lamivudine (Epivir®), abacavir (Ziagen®), emtricitabine (Emtriva®), and tenofovir (Viread®). The approved NNRTIs include delavirdine (Rescriptor®), nevirapine (Viramune®), and efavirenz (Sustiva®). The PI class is comprised of the following agents: indinavir (Crixivan®), ritonavir (Norvir®), saquinavir (Invirase® and Fortovase®), nelfinavir (Viracept®), amprenavir (Agenerase®), atazanavir (Reyataz®), lopinavir/ritonavir fixed dose combination (Kaletra®), fosamprenavir (Lexiva®), and tipranavir (Aptivus). Finally, enfuvirtide (Fuzeon®), a GP41 fusion inhibitor, is approved for use in the US.

The Department of Health and Human Services (DHHS) guidelines for use of antiretroviral agents in HIV-1 infected adults and adolescents include LPV/RTV + lamivudine (or emtricitabine) + zidovudine as the preferred PI-based regimen for antiretroviral-naïve subjects. In addition, LPV/RTV in combination with lamivudine or emtricitabine + (zidovudine or stavudine or abacavir or tenofovir or didanosine) is a recommended alternative PI-based regimen. Other alternative PI-based regimens for antiretroviral-naïve subjects include atazanavir, fosamprenavir, fosamprenavir/ritonavir, indinavir/ritonavir, nelfinavir, saquinavir/ritonavir in combination with NRTIs (lamivudine or emtricitabine + zidovudine or stavudine or abacavir or tenofovir or didanosine).

2.3 Availability of Proposed Active Ingredient in the United States

LPV/RTV tablets are not approved in any country. LPV/RTV capsules and oral solution formulations are approved in 74 countries for the treatment of HIV infection. The package insert has undergone several revisions since the September 15, 2000 approval, including a once daily dosing regimen for treatment-naïve patients, results from numerous drug-drug interaction studies, dosing information in special populations (hepatic and renal impairment) and addition of long-term safety and efficacy (144-204 weeks) results from the phase I/II trials.

2.4 Important Issues With Pharmacologically Related Products

Class-related AEs/laboratory abnormalities and potential for significant drug-drug interaction potential are common for the approved PIs. RTV is the PI with the largest number and greatest magnitude of drug-drug interactions due to its potent inhibition of CYP3A metabolism. For the drug product Kaletra, LPV is the active antiretroviral agent and RTV serves as a pharmacologic enhancer by inhibiting the metabolism of LPV via the CYP3A system. Because LPV is co-formulated with RTV, the potential exists for

numerous drug-drug interactions, some with clinical significance. Various interaction studies between LPV/RTV and other commonly used medications in HIV-infected subjects were conducted. Results from these interaction studies and other potentially significant drug interactions are prominently displayed in the package insert. As with other PIs, the LPV/RTV label includes warnings and precautions for new onset diabetes, hyperglycemia, increased bleeding episodes in patients with hemophilia and fat redistribution.

2.5 Presubmission Regulatory Activity

A pre-NDA CMC meeting was held with Abbott on February 4, 2003.

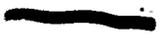
A pre-NDA meeting was held on December 17, 2004. During this meeting FDA agreed the proposed clinical, clinical pharmacology and CMC data were acceptable to support filing of an NDA for the tablet formulation. At this time, Abbott's proposal for no dose adjustments with NNRTIs was acceptable for filing; however, FDA requested more detailed modeling information and data using the 400/100 mg capsule as a reference.

2.6 Other Relevant Background Information

LPV/RTV is a co-formulation product containing two PIs. LPV is the active antiretroviral agent and RTV serves as a pharmacologic enhancer by inhibiting the metabolism of LPV via the CYP3A system. Both the soft gel capsule and oral solution formulations of Kaletra were granted accelerated approval on September 15, 2000. The basis for accelerated approval were results from one phase III trial in antiretroviral-naïve and an interim phase III report in PI-experienced subjects showing substantial declines in HIV-1 RNA levels and increases in CD4 cell counts over 24 weeks. In addition, results from three phase I/II trials through 24-72 weeks were provided. Review of efficacy supplements containing 48-week data from an adult Phase III clinical trial (21-226, SE8-003) and the on-going pediatric study (21-251, SE8-004) were completed in January, 2002, and results were incorporated into the product label. Traditional approval was granted in November 2002.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Please refer to Dr. Ko-Yu Lo's review for additional details. The tablet formulation was developed using  technology. KALETRA film-coated tablets are available for oral administration in a strength of 200 mg of lopinavir and 50 mg of ritonavir with the following inactive ingredients: copovidone, sorbitan monolaurate, colloidal silicon dioxide, and sodium stearyl fumarate. The following are the ingredients in the film coating: hypromellose, titanium dioxide, polyethylene glycol 400, hydroxypropyl cellulose, talc, colloidal silicon dioxide, polyethylene 3350, yellow ferric oxide E172, and polysorbate 80.

Based on the review of the CMC data, the review team concluded a statement in the package insert and on the container was warranted to alert healthcare providers and patients that the tablet

formulation may be more sensitive to moisture than other products. Data showing that reversion from the desired physical state (solid solution) to some amount of crystalline lopinavir/ritonavir occurs after 20 days exposure to high humidity (75% relative humidity). This physical change may present some risk to patients, because the crystalline lopinavir or ritonavir is expected to be less bioavailable compared to the solid solution. In addition, a change to the crystalline form would not likely be visibly noticeable by patients or pharmacists. Therefore, the following statements were included in the package insert and on the container.

Dispense in original container. For patient use: exposure of this product to high humidity outside the original container for longer than 14 days is not recommended.

3.2 Animal Pharmacology/Toxicology

Please refer to Dr. KM Wu's review for additional details. Abbott provided a nonclinical summary to support the levels of the excipients copovidone. Each tablet contains [REDACTED] of copovidone; therefore patients receive a total of [REDACTED] of copovidone per day. Of note, the highest tablet content of copovidone listed in the FDA Inactive Ingredient list is [REDACTED]. Abbott provided data to show copovidone represents a negligible safety risk to patients receiving Kaletra tablets. Overall, we agree with Abbott's assessments and findings.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

This NDA is an electronic submission and contains clinical reports for the five bioavailability studies in healthy volunteers. In addition, to address the potential safety concerns arising from increase LPV exposure, Abbott provided an integrated summary of safety and limited pharmacokinetic data from four studies in HIV-infected patients. These studies evaluated LPV/RTV doses greater than 400/100 mg bid. Please refer to section 1.3.1 for a brief overview of the clinical program.

4.2 Review Strategy

No new efficacy data are provided in this NDA. Please refer to the Clinical Pharmacology review by Dr. Derek Zhang for review of the five pharmacokinetic studies in healthy volunteers to demonstrate the relative bioequivalence and bioavailability of the tablet formulation compared to the marketed capsule formulation. [REDACTED] and SAS software was used to evaluate the safety data.

In the clinical review, the five pharmacokinetic studies were reviewed for safety. In addition, the integrated summary of safety from the four studies in HIV-infected patients were reviewed and summarized in this document. The data from these studies were reviewed in detail during the review of other sNDAs or review of final study reports or phase IV commitment reports.

4.3 Data Quality and Integrity

Following internal discussions within the Division, audits or site visits by the Division of Scientific Investigations were not requested.

4.4 Compliance with Good Clinical Practices

All study protocols were written to conform to accepted ethical standards and were reviewed and approved by Institutional Review Boards overseeing each investigative site prior to enrollment of subjects.

4.5 Financial Disclosures

Abbott submitted signed copies of Form FDA 3454 and adequately provided the required information regarding disclosed financial arrangements by the investigators. Based on the disclosure information provided, no significant issues were raised regarding the integrity of the data presented in this NDA.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Please refer to Dr. Derek Zhang's review for specific details regarding the pharmacokinetic of the tablet formulation. Dr. Zhang concluded the following:

Single dose bioequivalence study results indicate the to-be-marketed tablet formulation is not bioequivalent to the currently marketed capsule formulation. The to-be-marketed tablets did not meet the bioequivalence criteria relative to the reference capsule with respect to lopinavir and ritonavir's C_{max} when administered with a moderate-fat meal with the point estimate of 1.23 and 1.35, and the 90% confidence intervals of 1.19 to 1.28, and 1.26 to 1.44, respectively. Although lopinavir and ritonavir's area under the concentration time curve (AUC_{∞}) ratios (tablet vs. capsule) were within 80-125%, the point estimates were about 20% higher and the upper limits of 90% confidence intervals were close to 1.25. However, the results from cross-study comparison indicate the steady-state pharmacokinetics of lopinavir and ritonavir after administration of lopinavir/ritonavir 400/100 mg BID as the to-be-marketed tablet formulation were similar to that seen in previous multiple-dose studies in healthy subjects using SGC formulations. Please refer to the table below for details.

Relative Bioavailability and 90% Confidence Intervals for Lopinavir and Ritonavir from a Meta-Analysis of the Combined Data from Study M03-616 and Study M04-703 (Moderate Fat Meal Conditions)

Regimen Test vs. Reference	Pharmacokinetic Parameter	Central Value*		Relative Bioavailability	
		Test	Reference	Point Estimate ⁺	90% Confidence Interval
Lopinavir					
Tablet vs. SGC	C _{max}	8.0	6.5	1.235	1.188 – 1.285
	AUC _t	95.8	80.9	1.184	1.131 – 1.239
	AUC _∞	96.2	81.5	1.181	1.129 – 1.236
Ritonavir					
Tablet vs. SGC	C _{max}	0.6	0.4	1.349	1.263 – 1.441
	AUC _t	4.3	3.6	1.202	1.146 – 1.261
	AUC _∞	4.4	3.7	1.193	1.139 – 1.249

* Antilogarithm of the least squares means for logarithms.

+ Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

Note: All formulations administered as a single 400/100 mg dose under moderate-fat meal conditions.

Relative to fasting, administration of Kaletra tablets with a high fat meal increased LPV AUC by 19% and no increase in C_{max} was observed. No clinically significant changes in C_{max} and AUC were observed following administration of Kaletra tablets under fed conditions compared to fasted conditions. Additionally, the effect of food (moderate-fat or high-fat meals) on the new tablet formulation is lower than the effect of food on the marketed capsule formulation. Based on these data, Kaletra tablets can be taken with or without food.

Pharmacodynamics

The pharmacodynamic effects of LPV/RTV on HIV RNA are well characterized through the conduct of numerous clinical trials and extensively described in the medical literature. No new pharmacodynamic findings for LPV/RTV are presented in this NDA.

5.2 Exposure-Response Relationships

No new exposure-response (efficacy) relationships regarding LPV/RTV are presented in this NDA. For safety analyses with respect to increased LPV exposures following administration with the tablet formulation please refer to Section 7, Integrated Review of Safety for additional details.

6 INTEGRATED REVIEW OF EFFICACY

No efficacy data were included in this application. The new tablet formulation results in higher exposures compared to the capsule formulation; therefore, the tablet formulation is expected to have an efficacy profile similar to the capsule formulation.

6.1 Indication

No new indication is sought with this NDA.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Healthy Volunteer Studies:

The safety analyses include all subjects who received at least one dose of study medication. The safety database for the tablet formulation includes 190 healthy adult subjects from five studies. One hundred and five subjects received up to three single 400/100 mg doses of the tablet formulation and 15 subjects received a single 800/200 mg dose. Of the 190 subjects, 23 subjects received 400/100 mg twice daily alone for 11 days followed by 650/150 mg twice daily with efavirenz for 15 days.

Adverse event (AE) and laboratory data were collected for each subject in the five clinical studies at the protocol defined study visits. Investigators assigned a severity grade and relationship to study drug. Serious adverse events were collected in accordance with regulations and include those events which resulted in death, life-threatening situation, hospitalization (or prolonged), persistent or significant disability, congenital anomaly or other medically important event. All AEs were subsequently coded according to preferred terms using COSTART. The AEs were grouped by body system.

HIV-infected Patient Studies:

The point estimates for lopinavir AUC and C_{max} are 18% and 24% higher with the tablet formulation compared to the marketed capsule formulation. As a result, Abbott provided a detailed summary of the pharmacokinetic and safety data from studies in HIV-infected patients where higher lopinavir and ritonavir concentrations compared to the approved 400/100 mg capsule regimen were observed. Four clinical studies were used for this analysis and these studies met any one of the following criteria as outlined by Abbott.

- LPV/RTV dosing regimen different from the currently approved regimen
- Pharmacokinetic evaluations were performed in at least a subset of subjects receiving the non-approved regimen
- The non-approved regimen resulted in higher mean AUC and C_{max} for LPV and RTV compared to the currently marketed LPV/RTV 400/100 mg BID capsule formulation
- The non-approved regimen was administered for at least 48 weeks during which safety data were routinely collected

This evaluation included four studies as outlined in section 1.3.1. These data were reviewed in support of previous NDA and sNDA submissions or during the clinical review of final study reports or phase IV commitment reports. As a result, the data were not reviewed in further detail and a summary of the findings are provided in this review.

Safety Findings from Healthy Volunteer Studies:

Adverse Events:

No deaths were reported in the healthy volunteer studies. Two subjects experienced serious adverse events. Both events were not considered related to LPV/RTV. One subject fractured his right elbow due to a fall two weeks after study discharge. The second subject developed coronary artery disease requiring hospitalization and bypass surgery. This subject received one single dose each of the tablet and capsule formulation. The subject also had a history of tobacco use < 1 pack/day for 28 years). I agree both cases are not likely due to single dose of LPV/RTV use.

Overall, 13 subjects prematurely discontinued from the five pharmacokinetic studies; of which five of the discontinuations were due to adverse events. The adverse events leading to premature discontinuation included, viral infection, urinary tract infection, viral gastroenteritis, coronary bypass surgery (see above), and periodontal abscess. The remaining reasons for premature discontinuation included positive drug screen (6), positive alcohol screen (1), and urgent family business (1).

Abbott presented the single dose safety data as the mean frequency of treatment-emergent events. The frequency was weighted by the number of subjects per treatment period in order to compare the events observed after a single 400/100 mg dose of the tablet versus capsule formulation. Overall the mean frequency of treatment-emergent adverse events was similar after single doses of the tablet and capsule formulations. The most commonly reported events with the tablet formulation were diarrhea (26%), abdominal pain (6%), and nausea (4%). In comparison the most commonly reported events with the capsule formulation were diarrhea (23%), abdominal pain (7%), and nausea (4%). The mean frequency of moderate or severe events with the tablet formulation was headache (0.6%) and diarrhea (0.3%). For the capsule formulation, the mean frequency for headache was similar to the tablet formulation (4%), whereas, the mean frequency for diarrhea was slightly higher with the capsule formulation (1.5% vs 0.3%).

In the single dose studies with LPV/RTV 800/200 mg tablets, the most commonly reported events were headache (13%) and diarrhea (13%). For the capsule formulation, diarrhea was higher (27%) following a single dose of LPV/RTV 800/200 mg.

The adverse events observed in multiple dose studies with the tablet formulation dosed as 400/100 mg twice daily for 11 days or 650/150 mg twice daily + efavirenz for 15 days are presented in the table below. The majority of the events were gastrointestinal related and the most commonly reported events were diarrhea (17%), abdominal pain (13%), and headache (13%). Of note all the events reported were mild in severity and no moderate or severe events were reported for the tablet formulation.

Treatment-Emergent Adverse Event Observed in Subjects Receiving Multiple Dose LPV/RTV Tablet Formulation

Adverse Event	Multiple Dose 400/100 mg Twice Daily Tablet (n=23)	Multiple Dose 650/150 mg Twice Daily Tablet + Efavirenz 600 mg Once Daily (n=23)
Abdominal pain	3 (13%)	0
Accidental injury	2 (9%)	1 (4%)
Asthenia	0	3 (13%)
Headache	3 (13%)	3 (13%)
Pain	0	2 (9%)
Diarrhea	4 (17%)	5 (22%)
Eructation	2 (9%)	0
Flatulence	1 (4%)	2 (9%)
Nausea	2 (9%)	2 (9%)
Abnormal dreams	0	4 (17%)
Ataxia	0	6 (26%)
Dizziness	0	12 (52%)
Hallucinations	0	4 (17%)
Hypesthesia	0	2 (9%)
Pharyngitis	1 (4%)	5 (22%)
Rhinitis	2 (9%)	0
Rash	0	2 (9%)

Source: NDA Table 6, Table 2.7.4_3.7, and electronic dataset

In addition, Abbott conducted a cross-study analysis comparing the adverse event profile with the tablet formulation from study M03-580 and data from three studies (M01-273, M01-299, and M01-341) with the capsule formulation in healthy volunteers administered for 10-11 days. The table below summaries the pooled analysis conducted by Abbott.

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Summary for the Pooled Analysis of Treatment-Emergent Adverse Events in Healthy Volunteers

Adverse Event	400/100 mg Tablet Formulation N=23	400/100 mg Capsule Formulation N=44
Abdominal pain	3 (13%)	9 (20%)
Asthenia	0	10 (23%)
Headache	3 (13%)	10 (23%)
Diarrhea	4 (17%)	22 (50%)
Flatulence	1 (4%)	6 (14%)
Nausea	2 (9%)	10 (23%)
Taste perversion	1 (4%)	5 (11%)

Source: NDA Table 8 and electronic dataset

Overall no new safety signals were identified from clinical studies evaluating single or multiple doses of the tablet formulation in healthy subjects. The preliminary multiple-dose tablet formulation data appears to suggest a decreased rate and severity of gastrointestinal adverse events, specifically diarrhea compared to the marketed SGC formulation; however, these results are based on a limited number of healthy volunteers and are based on cross study comparisons. The lower incidence of gastrointestinal-related events observed with the tablet formulation may be due to the lack of oleic acid in the tablet formulation compared to the capsule formulation.

During a PreNDA meeting, FDA recommended Abbott conduct a comparative post-marketing study (tablet vs. capsule) to confirm these findings and suggested an 8-12 week study to evaluate the incidence of diarrhea and continue the study for approximately 16 weeks to evaluate potential lipid and hepatic abnormalities. In response to this request Abbott submitted a new protocol for a study in antiretroviral-naïve patients to compare the safety and tolerability of lopinavir/ritonavir tablets versus the currently marketed soft gelatin capsules when dosed once daily and twice daily for eight weeks and to compare the safety, tolerability and efficacy of once daily and twice dosing of the tablet formulation for 48 weeks. This study will provide valuable information for short-term (8 week) safety comparisons between the two formulations and long-term dosing with the new tablet formulation administered once or twice daily. These data are also important because Abbott intends to discontinue the marketed capsule formulation within months after the approval of the tablet formulation.

Laboratory Abnormalities

The majority of the laboratory abnormalities observed were not clinically significant and these values were just outside the normal reference range. These abnormalities tended to occur during the wash-out periods or off study. Five subjects experienced laboratory abnormalities that met Abbott’s criteria for “very high or very low.” Abbott’s criteria for “very high or very low” are similar to Grade 3 and 4 events per the DAIDS Toxicity Grading Scheme. One subject prematurely discontinued due to a laboratory abnormality as described below. In addition, increases in triglycerides and cholesterol were observed. These changes were expected and consistent with those observed in other LPV/RTV trials.

- Study M03-580
 - Subject 115 developed ALT value of 323 IU/L six days after completion of LPV/RTV 400/100 mg BID on days 8-17 then 600/150 mg BID in combination with EFV on days 18-32. During the study his ALT values were within normal limits. His repeat ALT values at 7, 12, 13 and 15 days post dosing were 227, 82, 71, and 56 IU/L, respectively. The investigator cites alcohol use following the study may have contributed to the ALT increases.
 - Subjects 117 and 121 developed increases in cholesterol of 302 and 315 mg/dL, respectively.
 - Subject 129 had elevated triglycerides of 901 mg/dL and 754 mg/dL on study 18 and one day after study completion, respectively. His baseline value was 80 mg/dL and twelve days after study completion his triglycerides further decreased to 224 mg/dL.
- Study M03-616
 - Subject 120 had an abnormal urinalysis (positive leukocyte esterase and > 50 WBC/hpf) consistent with a urinary tract infection. This patient discontinued from study and was treated for the infection.

Safety Findings from HIV-Infected Patient Studies:

As mentioned in section 1.3.1, safety data from four HIV-infected patient studies were included to support the higher exposures achieved with the tablet formulation compared to the marketed capsule formulation. The point estimates for lopinavir AUC and C_{max} are 18% and 24% higher with the tablet formulation compared to the marketed capsule formulation when administered with a moderate-fat meal. The safety data from the four studies outlined in section 1.3.1 were previously submitted to the Agency and reviewed in support of other sNDAs or as final study reports. Abbott provided a safety analysis to show the effect of LPV or RTV AUC and C_{max} on selected events (diarrhea, nausea, vomiting, Grade 3/4 increases in AST, ALT and lipids) in a subset of patients for whom both pharmacokinetic and safety data were available. A total of 88 subjects were included in this analysis; 45 from M97-720, 12 from M97-765, and 31 from M99-049. These data provide support that despite the higher exposures with the tablet formulation, the safety profile for the tablet formulation is predicted to be similar to the events observed in other studies. The regimens used in this analysis produced LPV AUC and C_{max} values 33-99% and 20-69%, respectively, higher compared to the capsule formulation dosed at 400/100 mg BID. In addition, these regimens also produced RTV AUC and C_{max} values 42% -639% and 40%-605%, respectively, higher compared to the capsule formulation. Please refer to Appendix A for a summary of the AUC and C_{max} values for dose regimens where higher LPV and RTV exposures were achieved compared to the approved 400/100 mg capsule twice daily dose. Overall, the anticipated events with the tablet formulation are expected to be less frequent and milder in nature than those observed in studies with higher dose LPV/RTV regimens with the capsule formulation.

Abbott provided the table below summarizing the treatment-emergent adverse events of any severity for the selected adverse events of interest. I agree with Abbott's assessment that no consistent relationship between AUC₁₂ of either LPV or RTV and the frequency of GI-events

was observed for the selected GI-events, regardless of severity or of at least moderate in severity. Notably, this finding is based on a cross-study comparison of studies with various patient populations, treatment regimens and study designs; however, these data do provide reassurance that the events seen with the tablet formulation are not likely to be worse than those already observed in a variety of LPV/RTV clinical trials.

Similar findings were seen for the selected laboratory abnormalities with few exceptions. No consistent relationship between AUC_{12} of either LPV or RTV and the frequency of AST or ALT elevations were observed. No relationship was seen for LPV AUC and the frequency of Grade 3 and 4 increases in cholesterol and triglycerides. As expected, and seen in other evaluations, an association of Grade 3 and 4 increases in cholesterol and triglycerides were seen with regimens producing higher concentrations of RTV. The highest frequency of lipid abnormalities was seen in patients receiving LPV/RTV 400/300 mg twice daily.

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Cross Study Comparison of the Incidence of Selected AEs and Laboratory Abnormalities
 Occurring in $\geq 10\%$ of Patients Through Week 48 (All Studies)

	Dose Regimen LPV/RTV BID					
	400/100 mg M97-720	400/200 mg M97-720	400/200 mg + NVP M97-765	300/75 mg/m ² M98-940	400/300 mg M99-049	667/167 mg M99-049
Difference in LPV AUC₁₂ compared to 400/100 mg BID^a		+33%	+47%	+41%	+75%	+99%
Difference in RTV AUC₁₂ compared to 400/100 mg BID^a		+187%	+211%	+42%	+639%	+153%
Abdominal pain	$\leq 2\%$	6%	$\leq 2\%$	$\leq 2\%$	$\leq 2\%$	$\leq 2\%$
Abnormal stools	10%	$\leq 2\%$	6%	$\leq 2\%$	$\leq 2\%$	$\leq 2\%$
Diarrhea	20%	24%	24%	$\leq 2\%$	24%	11%
Nausea	6%	30%	6%	$\leq 2\%$	12%	16%
Vomiting	$\leq 2\%$	12%	$\leq 2\%$	$\leq 2\%$	12%	$\leq 2\%$
AST^b	14%	0	12%	5%	12%	16%
ALT^b	10%	3%	21%	0	12%	16%
Total Cholesterol (>300 mg/dL)	6%	15%	33%	5%	41%	26%
Triglycerides (> 750 mg/dL)	6%	15%	30%	0	65%	21%

^areference 400/100 mg bid from study M97-720

^b(> 5 x ULN adults or > 10 x ULN pediatrics)

Source: Tables 51 and 53 NDA

Abbott also conducted first and second order logistic regression models to test the association of LPV or RTV AUC₁₂ and the incidence of the selected events and laboratory abnormalities as noted above. According to Abbott, no statistically significant association was seen for diarrhea, nausea or vomiting and LPV AUC. Triglyceride elevations were significantly associated with RTV AUC, whereas, cholesterol elevations were marginally associated with higher RTV AUC values. No significant associations were seen with both LPV or RTV values and ALT/AST increases.

In summary, I agree with Abbott's assessments in that the slightly higher increases in LPV and RTV produced by the new tablet formulation will not likely alter the safety profile of LPV/RTV. No new or unexpected safety signals were identified in the review.

3 Page(s) Withheld

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8 APPENDIX A

	Dose Regimen LPV/RTV BID					
	400/100 mg M97-720 ^{a,b}	400/200 mg M97-720 ^b	400/200 mg + NVP M97-765 ^c	300/75 mg/m ² M98-940 ^d	400/300 mg M99-049	667/167 mg M99-049
Lopinavir						
AUC ₁₂ (µg.h/mL)	82.8 ± 44.5	110.3 ± 31.9	121.8 ± 76.2	116.4 ± 57.1	144.9 ± 58.8	164.5 ± 53.8
Difference compared to 400/100 mg BID		+33%	+47%	+41%	+75%	+99%
C _{max} (µg.h/mL)	9.58 ± 4.41	11.52 ± 3.32	12.45 ± 7.08	12.45 ± 7.08	14.5 ± 5.5	16.2 ± 4.5
Difference compared to 400/100 mg BID		+20%	+30%	+30%	+51%	+69%
Ritonavir						
AUC ₁₂ (µg.h/mL)	3.8 ± 1.8	10.9 ± 2.3	11.8 ± 6.5	5.38 ± 3.26	28.1 ± 16.4	9.6 ± 4.4
Difference compared to 400/100 mg BID		+187%	+211%	+42%	+639%	+153%
C _{max} (µg.h/mL)	0.60 ± 0.35	1.75 ± 0.29	1.66 ± 0.93	0.84 ± 0.55	4.23 ± 2.87	1.28 ± 0.58
Difference compared to 400/100 mg BID		+192%	+177%	+40%	+605%	+113%

^a400/100 BID group from M97-720 is used as reference

^bWeek 3 or 4 PK data

^cWeek 6 PK data

^dsubjects who did not receive NVP