CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-906

CLINICAL PHARMACOLOGY/ BIOPHARMACEUTICS REVIEW(s)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-906	Submission Date(s): April 28, 2005
Brand Name	Kaletra
Generic Name	Lopinavir/Ritonavir
Reviewer	Yuanchao (Derek) Zhang, Ph.D.
Team Leader	Kellie S. Reynolds, Pharm.D.
OCPB Division	Division of Pharmaceutical Evaluation III
OND Division	DAVP
Sponsor	Abbott
Relevant NDA(s)	21-226 and 21-251
Relevant IND(s)	51,715
Submission Type; Code	505 (b) (1), 1P
Formulation; Strength(s)	Film-Coated Tablet; 200 mg/50 mg
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-1 infection

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1 Executive Summary

The sponsor submitted a New Drug Application for Kaletra (lopinavir 200 mg/ritonavir 50 mg) film-coated tablets for the treatment of HIV-1 infection. The proposed to-be-marketed tablet formulation has several advantages over the currently marketed soft gel capsule (SGC) formulation, such as reduced pill burden, diminished food effect, and less restrictive storage requirements.

1.1 Recommendation

The clinical pharmacology and biopharmaceutics information provided by the sponsor is acceptable. There are no major clinical pharmacology and biopharmaceutics issues related to the approval of this application.

1.2 Post Marking Commitments

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Single dose BE studies indicate that the to-be-marketed tablet formulation is about 20% more bioavailable than the currently marketed capsules under non-fasting conditions. However, the results from a cross-study comparison indicate that 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.

No new exposure-response information regarding lopinavir/ritonavir are presented in this NDA. The proposed dose regimens for Kaletra tablets are identical to those for capsule formulation approved in September 2000 and April 2005. The currently approved dose regimens for Kaletra SGC formulation are 400/100 mg lopinavir/ritonavir twice daily or 800/200 mg lopinavir/ritonavir once daily in treatment-naïve patients and 400/100 mg lopinavir/ritonavir twice daily in treatment-experienced patients. The original approval was based on the clinical trials M97-720 and M97-765 where Kaletra dose regimens 200/100 mg BID, 400/100 mg BID and 400/200 mg BID were studied. 400/100 mg dose regimen provides efficacious drug exposure for patients with wild-type virus and some resistant virus, but 400/100 mg dose regimen may not be adequate for patients with more resistant virus. Although the 400/200 mg BID regimen provided higher lopinavir trough concentrations, it was not tolerated as well as the 400/100 mg regimen. The main tolerability issues were GI-related. Triglycerides were also increased to a greater degree at the 400/200 mg dose.

The new tablet formulation with slightly higher exposures compared to the capsule formulation is expected to have an efficacy profile similar to the capsule formulation. 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. Safety data for higher LPV exposure are provided from patients who received 400/200 mg BID capsule formulation (M97-765) and 667/167 mg BID (M99-049). LPV exposure following 400/200 mg BID and 667/167 mg BID were >20% higher than that of 400/100 BID.

For safety analyses with respect to increased LPV exposures following administration of the tablet formulation please refer to Medical Officer, Dr. Kim Struble's review for additional details.

Please refer to the Clinical Pharmacology and Biopharmaceutics reviews of Kaletra capsule formulation (NDA 21-226) for more detailed information (September 2000 and April 2005).

Relative Bioavailability of Tablet Formulation vs. Capsule Formulation

Single dose BE study results indicate that 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. When study drugs were administered with a moderate-fat meal, the point estimates (tablet vs. capsule) for lopinavir and ritonavir's C_{max} were 1.23 and 1.35, with 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 (see Table 1 below).

Although single dose results indicate the tablet is not BE to the capsule, the results from cross-study comparison indicate that 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 (see Table 2 below).

Table 1. 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.

Table 2. Historical Comparison of Lopinavir and Ritonavir Pharmacokinetics After 400/100 mg BID in Healthy Subjects Following a Moderate-Fat Meal

Formulation		Tablet	LPV SGC & RTV SGC#			Marketed Capsules		
Study Number		M03-580	M97-650	M97-741	M97-806	M01-273	M01-299	M01-341
Days of Dosing		11	6[a]	8	11	16[b]	11	11
Parameters (units)		(N=23)	(N=7)	(N=7)	(N=11)	(N=15)	(N=12)	(N=13)
Lopinavir								
T_{max}	(h)	4.4 ± 0.8	4.3 ± 1.4	4.3 ± 2.7	4.9 ± 1.0	4.8 ± 2.6	4.5 ± 1.2	5.2 ± 2.5
C_{max}	(µg/mL)	10.56 ± 1.75	9.58 ± 1.76	10.78 ± 2.67	10.28 ± 2.95	8.02 ± 2.23	10.33 ± 1.31	10.87 ± 2.74
AUC_{12}	(µg•h/mL)	90.6 ± 18.7	88.2 ± 17.78	103.2 ± 27.8	87.8 ± 30.1	73.7 ± 23.5	86.4 ± 14.1	100.3± 35.6
C_{min}	(µg/mL)	4.86 ± 1.61	5.31 ± 1.58	5.96 ± 2.35	4.66 ± 2.25	4.28 ± 2.12	4.64 ± 21.34	6.15 ± 2.88
CL/F	(L/h)	4.61 ± 1.03	4.73 ± 1.03	4.10 ± 0.99	5.27 ± 2.07	–	4.75 ± 0.83	4.32 ± 1.09
Ritonavir								
T_{max}	(h)	4.0 ± 0.0	4 ± 1	4.3 ± 2.7	4.4 ± 1.2	4.9 ± 2.5	4.2 ± 0.9	4.8 ± 2.3
C_{max}	(µg/mL)	0.94 ± 0.32	0.85 ± 0.41	0.55 ± 0.23	0.80 ± 0.33	0.81 ± 0.45	0.96 ± 0.46	1.14 ± 0.49
AUC_{12}	(µg•h/mL)	5.22 ± 1.40	5.07 ± 2.10	4.19 ± 1.43	4.2 ± 1.4	4.74 ± 2.20	4.62 ± 1.46	5.48 ± 1.37
C_{min}	(µg/mL)	0.19 ± 0.08	0.17 ± 0.07	0.14 ± 0.06	0.13 ± 0.08	0.15 ± 0.09	0.13 ± 0.05	0.17 ± 0.09
CL/F	(L/h)	20.8 ± 6.6	23.0 ± 10.2	26.1 ± 8.0	26.8 ± 10.6	–	23.2 ± 5.5	19.5 ± 5.5

a. 300 mg lopinavir and 100 mg ritonavir administered for 10 days followed by 400 mg lopinavir and 100 mg ritonavir administered for 6 days.
b. Single-dose desipramine was administered on Days 1 and 16.
Separate capsules of lopinavir (LPV) and ritonavir (RTV) were administered.

Food Effect on the Bioavailability of Tablet Formulation

A moderate-fat meal improved the bioavailability of lopinavir from both the new tablet formulation and the marketed capsule formulation compared to administration under fasting conditions. However, the increases in lopinavir C_{max} (32.3% for the capsule vs. 17.6% for the new tablet) and AUC_{∞} (61.5% for the capsule vs. 26.9% for the new tablet) following a moderate-fat meal were much more pronounced for the marketed capsule than for the new tablet formulation. Comparable results were observed for ritonavir.

Administration of the new tablet formulation with a high-fat meal increased lopinavir AUC by 19%, but not C_{max}, when compared to administration of the tablet formulation under fasting conditions. These results indicate that 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.

The proposed label recommendation that Kaletra tablets be taken with or without food is acceptable.

Drug Interactions with efavirenz, nevirapine, fosamprenavir, and nelfinavir

The current label for Kaletra SCG formulation recommends a dose increase to lopinavir/ritonavir 533/133 mg BID in patients taking CYP3A-inducing antiretroviral agents such as nevirapine, efavirenz, nelfinavir, amprenavir, or fosamprenavir. The recommendation is based on a drug interaction study with efavirenz. Co-administration of lopinavir/ritonavir 400/100 mg BID as 3 SGCs with efavirenz decreased the lopinavir AUC and Cmin by approximately 20 and 40%, respectively, while efavirenz concentrations were not significantly altered. A similar interaction was observed during co-administration of lopinavir/ritonavir SGC with nevirapine and other CYP3A-inducing antiretroviral agents. Administration of lopinavir/ritonavir 533/133 mg BID with efavirenz provided similar lopinavir concentrations as administration of lopinavir/ritonavir 400/100 mg BID without an inducing agent.

Due to the increased drug loading of the to-be-marketed tablet formulation compared to the SGC, a dose of 533/133 mg is not possible with the tablet formulation. Therefore, drug interaction study between efavirenz and Kaletra tablet formulation 600/150 mg (3 tablets) was assessed in Study M03-580.

When the to-be-marketed tablet formulation at a dose of [redacted] mg BID was co-administered with efavirenz, steady-state lopinavir Cmax, AUC12h and Cmin values were 36%, 36% and 32% higher, respectively, than after a 400/100 mg BID regimen administered as the to-be-marketed tablet alone. Ritonavir Cmax, AUC12h and Cmin values were 92%, 78% and 56% higher, respectively, than the corresponding values for a 400/100 mg BID regimen administered alone.

We predict that co-administration of lopinavir/ritonavir 400/100 mg BID as 2 tablets with efavirenz would result in similar effects to those of co-administration of lopinavir/ritonavir 400/100 mg BID as 3 SGCs with efavirenz: a decrease in the lopinavir AUC and Cmin by approximately 20 and 40%, respectively. No evidence suggests the effect of efavirenz will be different for Kaletra tablet than for Kaletra SGC.

Thus a dose increase of Kaletra tablets to 600/150 mg should be considered when used in combination with efavirenz, nevirapine, fosamprenavir without ritonavir, or nelfinavir in treatment-experienced patients where reduced susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). Safety data for the lopinavir/ritonavir 400/200 mg BID, 400/300 BID and 667/167 mg BID regimens support the higher exposure that will result from 600/150 mg BID with efavirenz or other inducing agents. The lopinavir exposure provided by 400/100 mg BID of the tablet in combination with efavirenz should be well above the IC50 in treatment naïve patients. Also, due to the potential for decreased tolerability of higher lopinavir or ritonavir exposure, the dose increase is not recommended for treatment naïve patients.

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2 Question Based Review (QBR)

2.1 General Attributes of the Drug

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

The dosage form is an immediate release film coated tablet containing 200 mg of lopinavir and 50 mg of ritonavir. The tablet product has a higher drug load than the current soft gelatin capsule (SGC) product, which reduces the daily pill burden from 6 to 4 units. The tablet product is sufficiently stable to be stored at room temperature throughout shelf-life without the requirement of refrigerated storage (Please refer to Chemistry Reviewer, Dr. Ko-Yu Lo's review for additional details).

Table 3. Quantitative Composition of Lopinavir/ritonavir Tablet

Ingredients	Unit Formula (Per Tablet)	Primary Function	Compendia Status
Extrusion			
Drug Substances			
Lopinavir [a]	200.0 mg	Active	In-house
Ritonavir [a]	50.0 mg	PK Enhancer	In-house
Excipients			
Copovidone, K value 28	[redacted]	[redacted]	NF
Sorbitan monolaurate			NF
Colloidal silicon dioxide			NF
Post Extrusion			
Sodium stearyl fumarate			NF
Colloidal silicon dioxide			NF
Film coating powder [b]			In-house
Purified water [c]			USP
Total Tablet Weight	1242.0 mg	N/A	N/A

[redacted]

For other questions in this section, please refer to the Clinical Pharmacology and Biopharmaceutics review of Kaletra capsule formulation (NDA 21-226).

2.2 General Clinical Pharmacology

Single dose BE studies indicate that the to-be-marketed tablet formulation is about 20% more bioavailable than the currently marketed capsules under non-fasting conditions. However, the results from a cross-study comparison indicate that 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.

No new exposure-response information regarding lopinavir/ritonavir are presented in this NDA. The proposed dose regimens for Kaletra tablets are identical to those for capsule formulation approved in September 2000 and April 2005. The currently approved dose regimens for Kaletra SGC formulation are 400/100 mg lopinavir/ritonavir twice daily or 800/200 mg lopinavir/ritonavir once daily in treatment-naïve patients and 400/100 mg lopinavir/ritonavir twice daily in treatment-experienced patients. The original approval was based on the clinical trials M97-720 and M97-765 where Kaletra dose regimens 200/100 mg BID, 400/100 mg BID and 400/200 mg BID were studied. 400/100 mg dose regimen provides efficacious drug exposure for patients with wild-type virus and some resistant virus, but 400/100 mg dose regimen may not be adequate for patients with more resistant virus. Although the 400/200 mg BID regimen provided higher lopinavir trough concentrations, it was not tolerated as well as the 400/100 mg regimen. The main tolerability issues were GI-related. Triglycerides were also increased to a greater degree at the 400/200 mg dose.

The new tablet formulation with slightly higher exposures compared to the capsule formulation is expected to have an efficacy profile similar to the capsule formulation. 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. Safety data for higher LPV exposure are provided from patients who received 400/200 mg BID capsule formulation (M97-765) and 667/167 mg BID (M99-049). LPV exposure following 400/200 mg BID and 667/167 mg BID were >20% higher than that of 400/100 BID.

For safety analyses with respect to increased LPV exposures following administration of the tablet formulation please refer to Medical Officer, Dr. Kim Struble's review for additional details.

Please refer to the Clinical Pharmacology and Biopharmaceutics reviews of Kaletra capsule formulation (NDA 21-226) for more detailed information (September 2000 and April 2005).

2.3 Intrinsic Factors

Please refer to the Clinical Pharmacology and Biopharmaceutics review of Kaletra capsule formulation (NDA 21-226).

2.4 Extrinsic Factors

2.4.1. Drug-Drug Interactions

The current label for Kaletra SCG formulation recommends a dose increase to lopinavir/ritonavir 533/133 mg BID in patients taking CYP3A-inducing antiretroviral agents such as nevirapine, efavirenz, nelfinavir, amprenavir, or fosamprenavir. The recommendation is based on a drug interaction study with efavirenz. Co-administration of lopinavir/ritonavir 400/100 mg BID as 3 SGCs with efavirenz decreased the lopinavir AUC and Cmin by approximately 20 and 40%, respectively, while efavirenz concentrations were not significantly altered. A similar interaction was observed during co-administration of lopinavir/ritonavir SGC with nevirapine and other CYP3A-inducing antiretroviral agents. Administration of lopinavir/ritonavir 533/133 mg BID with efavirenz provided similar lopinavir concentrations as administration of lopinavir/ritonavir 400/100 mg BID without an inducing agent.

Due to the increased drug loading of the to-be-marketed tablet formulation compared to the SGC, a dose of 533/133 mg is not possible with the tablet formulation. Therefore, drug interaction study between efavirenz and Kaletra tablet formulation 600/150 mg (3 tablets) was assessed in Study M03-580.

When the to-be-marketed tablet formulation at a dose of [redacted] mg BID was co-administered with efavirenz, steady-state lopinavir Cmax, AUC12h and Cmin values were 36%, 36% and 32% higher, respectively, than after a 400/100 mg BID regimen administered as the to-be-marketed tablet alone. Ritonavir Cmax, AUC12h and Cmin values were 92%, 78% and 56% higher, respectively, than the corresponding values for a 400/100 mg BID regimen administered alone.

Higher lopinavir exposure is likely due to the combination of increased doses of both lopinavir and ritonavir. The increased ritonavir exposure likely contributes to further subdue the inducing effect of efavirenz. Efavirenz concentrations measured in this study suggest that the higher lopinavir and ritonavir exposures observed in Study M03-580 are not likely due to insufficient efavirenz levels. The results of the interaction study are shown in Table 4.

Table 4. The Effect of Efavirenz on Lopinavir and Ritonavir (Study M03-580)

Pharmacokinetic Parameter	Central Values*		Relative Bioavailability	
	LPV/r 600/150 mg BID + EFV 600 mg QD	LPV/r 400/100 mg BID alone	Point Estimate#	90% Confidence Interval
Lopinavir				
C_{max}	14.1	10.4	1.356	1.275 – 1.442
C_{min}	6.1	4.6	1.320	1.207 – 1.444
C_{trough}	7.3	5.4	1.362	1.256 – 1.477
AUC_{12}	120.4	88.7	1.357	1.284 – 1.435
Ritonavir				
C_{max}	1.7	0.9	1.921	1.678 – 2.199
C_{min}	0.3	0.2	1.564	1.405 – 1.742
C_{trough}	0.3	0.2	1.604	1.399 – 1.840
AUC_{12}	8.9	5.0	1.778	1.620 – 1.952

* Antilogarithm of the least squares means for logarithms.

\# Antilogarithm of the difference (co-administration of lopinavir/ritonavir with efavirenz minus lopinavir/ritonavir alone) of the least squares means for logarithms.

Based on the fact that the steady-state pharmacokinetics of lopinavir and ritonavir after administration of lopinavir/ritonavir 400/100 mg BID as the to-be-marketed tablet formulation (M03-580) were similar to that seen in previous multiple-dose studies in healthy subjects using SGC formulations, we predict that co-administration of lopinavir/ritonavir 400/100 mg BID as 2 tablets with efavirenz would result in similar effects to those of co-administration of lopinavir/ritonavir 400/100 mg BID as 3 SGCs with efavirenz: a decrease in the lopinavir AUC and C_{min} by approximately 20 and 40%, respectively. No evidence suggests the effect of efavirenz will be different for Kaletra tablet than for Kaletra SGC.

Based on modeling, Abbott predicted that compared to the SGC 400/100 mg BID regimen alone, a regimen of the to-be-marketed lopinavir/ritonavir tablet 400/100 mg BID with efavirenz would result in slightly higher mean lopinavir C_{max} and AUC, approximately 10% and 2%, respectively, and 30% lower lopinavir C_{min}. Thus, FDA and Abbott predict a 30-40% decrease in lopinavir C_{min} following co-administration of Kaletra tablets (400/100 BID) with efavirenz. Table 5 summarizes the available and predicted Kaletra-Efavirenz interaction data.

Table 5. Summary of Known and Predicted Kaletra-Efavirenz Drug Interactions

	Cmax	AUC	Cmin
SGC			
400/100 + EFV vs. 400/100	LPV 15%↓	LPV 25% ↓	LPV 40%↓
	RTV ↔	RTV ↔	RTV ↔
533/133 +EFV vs. 400/100	LPV 12% ↑	LPV 8%↑	LPV 6%↑
	RTV 44%↑	RTV 46%↑	RTV 55%↑
Tablet			
600/150 +EFV vs. 400/100	LPV 35%↑	LPV 35%↑	LPV 35%↑
	RTV 90%↑	RTV 80% ↑	RTV 47-62% ↑
FDA prediction: 400/100 +EFV vs. 400/100 SGC	LPV 15%↓	LPV 25% ↓	LPV 40%↓
Abbott prediction: 400/100 +EFV vs. 400/100 SGC	LPV 10%↑	LPV 2%↑	LPV 30%↓

Thus a dose increase of Kaletra tablets to 600/150 mg should be considered when used in combination with efavirenz, nevirapine, fosamprenavir without ritonavir, or nelfinavir in treatment-experienced patients where reduced susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). Safety data for the lopinavir/ritonavir 400/200 mg BID, 400/300 BID and 667/167 mg BID regimens support the higher exposure that will result from 600/150 mg BID with efavirenz or other inducing agents. The lopinavir exposure provided by 400/100 mg BID of the tablet in combination with efavirenz should be well above the IC50 in treatment naïve patients. Also, due to the potential for decreased tolerability of higher lopinavir or ritonavir exposure, the dose increase is not recommended for treatment naïve patients.

For other questions regarding drug interactions, please refer to the Clinical Pharmacology and Biopharmaceutics review of Kaletra capsule formulation (NDA 21-226). All other drug interaction information is the same for the tablet and SGC formulations.

2.5 General Biopharmaceutics

Note: BE assessments are based on administration with a moderate-fat meal. Most safety and efficacy data in the original NDA for the SGC were collected following administration with food, so the fed BE assessment is acceptable. See the individual study reports for fasted data.

2.5.1. What is the relative bioavailability of the proposed to-be-marketed tablet formulation to the currently marketed capsule formulation?

Single dose BE study results indicate that 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. When study drugs were administered with a moderate-fat meal, the point estimates (tablet vs. capsule) for lopinavir and ritonavir's C_{max} were 1.23 and 1.35, with 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 that 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.

No new exposure-response information regarding lopinavir/ritonavir are presented in this NDA. The proposed dose regimens for Kaletra tablets are identical to those for capsule formulation approved in September 2000 and April 2005. The currently approved dose regimens for Kaletra SGC formulation are 400/100 mg lopinavir/ritonavir twice daily or 800/200 mg lopinavir/ritonavir once daily in treatment-naïve patients and 400/100 mg lopinavir/ritonavir twice daily in treatment-experienced patients. The original approval was based on the clinical trials M97-720 and M97-765 where Kaletra dose regimens 200/100 mg BID, 400/100 mg BID and 400/200 mg BID were studied. 400/100 mg dose regimen provides efficacious drug exposure for patients with wild-type virus and some resistant virus, but 400/100 mg dose regimen may not be adequate for patients with more resistant virus. Although the 400/200 mg BID regimen provided higher lopinavir trough concentrations, it was not tolerated as well as the 400/100 mg regimen. The main tolerability issues were GI-related. Triglycerides were also increased to a greater degree at the 400/200 mg dose.

The new tablet formulation with slightly higher exposures compared to the capsule formulation is expected to have an efficacy profile similar to the capsule formulation. 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. Safety data for higher LPV exposure are provided from patients who received 400/200 mg BID capsule formulation (M97-765) and 667/167

mg BID (M99-049). LPV exposure following 400/200 mg BID and 667/167 mg BID were >20% higher than that of 400/100 BID.

Five bioavailability studies that evaluated the to-be-marketed tablet formulation in healthy volunteers are presented in this NDA:

1. M01-306 and M01-381 (two pilot bioavailability studies): Tablet formulation DC-C was selected for further development based on its similar bioavailability relative to the SGC under non-fasting conditions, limited food effect, and formulation simplicity.

2. M03-580 (a pilot bioavailability study): Compared the single-dose bioavailability of the tablet formulation from a partial production scale (pilot) lot to the currently marketed capsule formulation and assessed the multiple-dose pharmacokinetics and safety of the tablet formulation with efavirenz.

3. M03-616 (a pivotal bioavailability study): Compared single-doses of the tablet formulation at production scale to the SGC formulation to the marketed SGC in a larger number of subjects and also assessed the food effect of the to-be-marketed formulation under fasting, moderate-fat, and high-fat conditions.

4. M04-703 (a pivotal bioavailability study): To avoid cross-study comparison between the lots, the to-be-marketed tablet formulation pilot and production scale lots were compared directly in M04-703, also compared to the marketed SGC formulation.

Results from the pilot Study M03-580 showed that following the 400/100 mg dose administration, the new tablet from a partial production scale lot was bioequivalent to the marketed capsule under non-fasting conditions. However, Study M03-616 (pivotal BE study) demonstrated the new tablet exhibited greater bioavailability with respect to lopinavir C_{max} and AUC relative to the marketed capsule. Under non-fasting conditions, lopinavir C_{max} and AUC values for the new tablet were 29% and 27% higher, respectively, than those for the marketed capsules.

Extensive investigation of the CMC characteristics of the partial and full production-scale lots were conducted to explore potential reasons for the somewhat different relative bioavailability results found in Study M03-580 and Study M03-616. The investigation concluded that there were no significant differences between the lots. To avoid cross-study comparison between the lots, the to-be-marketed tablet formulation pilot and production scale lots used in Study M03-580 and Study M03-616 were compared directly in Study M04-703, and each was again compared to the marketed SGC formulation. A second lot of the to-be-marketed tablet formulation was independently manufactured at production scale and included in Study M04-703 to assess potential lot-to-lot variability in bioavailability resulting from the manufacturing processes.

Results from Study M04-703 were consistent with results from Study M03-580 and Study M03-616:

1. Tablets from the pilot scale lot previously tested in Study M03-580 met the bioequivalence criteria relative to the reference capsule.

2. Tablets from the production scale Lot 1 previously tested in Study M03-616 did not meet the bioequivalence criteria relative to the reference capsule. Lopinavir's C_{max} was higher for the tablet, with the point estimate of 1.23 and the 90% confidence intervals of 1.16 to 1.30. Although lopinavir's AUC ratio (tablet vs. capsule) was within 80-125%, the point estimate was 10% higher and the 90% confidence interval was close to 1.25.

3. Tablets from the production scale Lot 2 also met the bioequivalence criteria relative to the reference capsule. However, lopinavir C_{max} and AUC ratios (tablet vs. capsule) were 13% to 17% higher and the 90% confidence intervals were close to 1.25.

The new tablets from the two production scale lots and the pilot scale lot were bioequivalent to one another.

Table 6. Lopinavir Bioavailability from Different Lots of the Tablet Formulation Relative to the Marketed SGC

Regimens	Study	PK Parameter	Central Values*		Relative Bioavailability	
			Test	Reference	Point Estimate+	90% Confidence Interval
Tablet Production Scale Lot 1 *vs.* SGC	M04-703	C_{max}	8.1	6.6	1.227	1.158 – 1.300
		AUC_t	95.7	84.5	1.132	1.062 – 1.208
		AUC_∞	96.2	85.2	1.129	1.059 – 1.204
	M03-616	C_{max}	8.2	6.3	1.295	1.230 – 1.362
		AUC_t	96.7	76.0	1.272	1.197 – 1.351
		AUC_∞	97.1	76.5	1.269	1.195 – 1.348
Tablet Production Scale Lot 2 *vs.* SGC	M04-703	C_{max}	7.7	6.6	1.170	1.104 – 1.241
		AUC_t	93.2	84.5	1.102	1.034 – 1.176
		AUC_∞	93.6	85.2	1.099	1.031 – 1.172
Tablet Pilot Scale Lot *vs.* SGC	M04-703	C_{max}	7.4	6.6	1.125	1.062 – 1.191
		AUC_t	85.0	84.5	1.006	0.944 – 1.073
		AUC_∞	85.5	85.2	1.004	0.942 – 1.070
	M03-580	C_{max}	6.2	6.4	0.971	0.879 – 1.073
		AUC_t	71.0	69.4	1.023	0.909 – 1.151
		AUC_∞	71.5	69.8	1.024	0.909 – 1.153

* 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.

Table 7. Ritonavir Bioavailability from Different Lots of the Tablet Formulation Relative to the Marketed SGC

Regimens	Study Number	PK Parameter	Central Values*		Relative Bioavailability	
			Test	Reference	Point Estimate+	90% Confidence Interval
Tablet Production Scale Lot 1 *vs.* SGC	M04-703	C_{max}	0.6	0.4	1.378	1.242 – 1.530
		AUC_t	4.3	3.8	1.151	1.075 – 1.232
		AUC_∞	4.5	3.9	1.147	1.075 – 1.226
	M03-616	C_{max}	0.5	0.4	1.396	1.286 – 1.517
		AUC_t	4.1	3.2	1.270	1.189 – 1.356
		AUC_∞	4.2	3.3	1.254	1.177 – 1.336
Tablet Production Scale Lot 2 *vs.* SGC	M04-703	C_{max}	0.6	0.4	1.291	1.163 – 1.433
		AUC_t	4.3	3.8	1.152	1.076 – 1.234
		AUC_∞	4.4	3.9	1.147	1.074 – 1.225
Tablet Pilot Scale Lot *vs.* SGC	M04-703	C_{max}	0.5	0.4	1.157	1.044 – 1.283
		AUC_t	3.8	3.8	1.007	0.941 – 1.078
		AUC_∞	3.9	3.9	1.010	0.946 – 1.079
	M03-580	C_{max}	0.4	0.5	0.952	0.746 – 1.214
		AUC_t	3.4	3.4	1.008	0.807 – 1.167
		AUC_∞	3.5	3.6	0.991	0.865 – 1.135

* 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.

Table 8. 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.

Lower variability in lopinavir exposures for the tablet formulation compared to the marketed capsule formulation was observed.

A single dose of lopinavir/ritonavir 800/200 mg administered as the to-be-marketed tablet was bioequivalent to the SGC for lopinavir as the 90% confidence intervals for C_{max} and AUC_{∞} were contained within the 0.80 to 1.25 range. Ritonavir levels from the to-be-marketed tablet slightly exceeded those from the SGC since the upper limits of the 90% confidence intervals were greater than 1.25 and ranged from 1.253 for C_{max} to 1.260 for AUC_{∞}. This results support the sponsor's proposed dose regimen of 800/200 mg lopinavir/ritonavir tablet once daily in treatment-naïve patients.

Table 9. Relative Bioavailability and 90% Confidence Intervals for Lopinavir and Ritonavir following Administration of a Single Dose of Kaletra 800/200 mg

Test vs. Reference (Regimen)	Parameter	Central Values*		Relative Bioavailability	
		Test	Reference	Point Estimate+	90% Confidence Interval
Lopinavir					
800/200 mg Tablet vs. SGC	C_{max}	13.1	11.5	1.140	1.044 – 1.244
	AUC_t	202.2	173.1	1.168	1.121 – 1.217
	AUC_{∞}	203.7	173.9	1.172	1.126 – 1.219
Ritonavir					
800/200 mg Tablet vs. SGC	C_{max}	1.8	1.6	1.133	1.024 – 1.253
	AUC_t	14.0	11.9	1.174	1.090 – 1.264
	AUC_{∞}	14.1	12.0	1.173	1.091 – 1.260

* Antilogarithm of the least squares means for logarithms.

\+ Antilogarithm of the difference (tablet minus capsule) of the least squares means for logarithms.

2.5.2. What is the effect of food on the bioavailability (BA) of Kaletra tablet formulation? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

A moderate-fat meal improved the bioavailability of lopinavir from both the new tablet formulation and the marketed capsule formulation compared to administration under fasting conditions. However, the increases in lopinavir C_{max} (32.3% for the capsule vs. 17.6% for the new tablet) and AUC_{∞} (61.5% for the capsule vs. 26.9% for the new tablet) following a moderate-fat meal were much more pronounced for the marketed capsule than for the new tablet formulation. Comparable results were observed for ritonavir.

Administration of the new tablet formulation with a high-fat meal increased lopinavir AUC, but not C_{max}, when compared to administration of the tablet formulation under fasting conditions. The 90% confidence intervals of lopinavir C_{max} were within 80-125%, while the 90% confidence intervals for lopinavir AUC extended above 1.25. These results suggest that 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.

The proposed label recommends Kaletra tablets are to be taken with or without food.

Table 10. Relative Bioavailability and 90% Confidence Intervals for the Assessment of Food Effect on Lopinavir and Ritonavir Following Administration of Kaletra Tablets

Regimens	Study Number	PK Parameter	Central Values*		Relative Bioavailability	
			Test	Reference	Point Estimate+	90% Confidence Interval
Lopinavir						
Moderate-Fat vs. Fasting	M03-616	C_{max}	8.2	7.0	1.176	1.111 – 1.244
		AUC_{∞}	97.1	76.5	1.269	1.191 – 1.352
High-Fat vs. Fasting	M03-616	C_{max}	6.9	7.0	0.993	0.877 – 1.124
		AUC_{∞}	87.1	73.3	1.189	1.029 – 1.373
Ritonavir						
Moderate-Fat vs. Fasting	M03-616	C_{max}	0.5	0.5	1.049	0.943 – 1.167
		AUC_{∞}	4.2	3.7	1.149	1.063 – 1.241
High-Fat vs. Fasting	M03-616	C_{max}	0.5	0.5	1.103	0.920 – 1.323
		AUC_{∞}	4.4	3.6	1.239	1.068 – 1.436

* Antilogarithm of the least squares means for logarithms.

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

Note: Single doses were administered as lopinavir/ritonavir 400/100 mg (two 200/50 mg to-be-marketed tablets).

2.5.3. How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?

The proposed and current dissolution methods and specifications for Kaletra tablet and capsule are as follows, respectively:

To-Be-Marketed Tablet:

Apparatus: USP Apparatus 2 (paddle)
Agitation: 75 rpm
Medium: 0.06M POE10LE (Polyoxyethylene 10 Lauryl Ether)
Temperature: 37°C
Profile Times: 15, 30, 60, 90, 120 and 150 minutes with medium replacement
Proposed Specification: Q = [redacted] in 90 minutes

Capsule:

Apparatus: USP Apparatus 2 (paddle)
Agitation: 50 rpm
Medium: 0.05M POE10LE (with 0.01M sodium phosphate, pH 6.8)
Temperature: 37°C
Profile Time: 30 minutes with medium replacement
Specification: Q = [redacted] in 30 minutes

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✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio-1

The proposed dissolution method and specification for Kaletra tablet are acceptable.

For other questions in this section, please refer to the Clinical Pharmacology and Biopharmaceutics review of Kaletra capsule formulation (NDA 21-226).

2.6. Analytical Section

2.6.1 What bioanalytical methods are used to assess concentrations?

Two validated assay methods were used to determine concentrations of lopinavir and ritonavir in human plasma. Method 1 used solid phase extraction followed by [redacted] high-performance liquid chromatography (HPLC) [redacted] -tandem mass spectrometric (MS/MS) detection for the early pilot studies (M01-306 and M01-381). The limit of quantitation (LOQ) for lopinavir was established at 5.25 ng/mL. The LOQ of ritonavir was established to be 4.14 ng/mL. For assay precision and accuracy, the lopinavir mean QC concentrations for the accepted values ranged from 103.5 to 106.6% of their theoretical values, while CVs ranged from 5.9 to 8.9%. The ritonavir mean QC concentrations for the accepted values ranged from 98.9 to 110.3% of their theoretical values, while CVs ranged from 3.2 to 9.2%. Method 2 used a [redacted] extraction followed by HPLC with [redacted] and MS/MS detection for the later studies (M03-580, M03-616 and M04-703). The LOQs for lopinavir and ritonavir were established at [redacted] respectively. For assay precision and accuracy, the lopinavir mean QC concentrations for the accepted values ranged from [redacted] of their theoretical values, while CVs ranged from [redacted] The ritonavir mean QC concentrations for the accepted values ranged from 102.6 to 107.7% of their theoretical values, while CVs ranged from 2.8 to 6.1%.

These analytical methods are acceptable.

3. Major Labeling Recommendations

[redacted]

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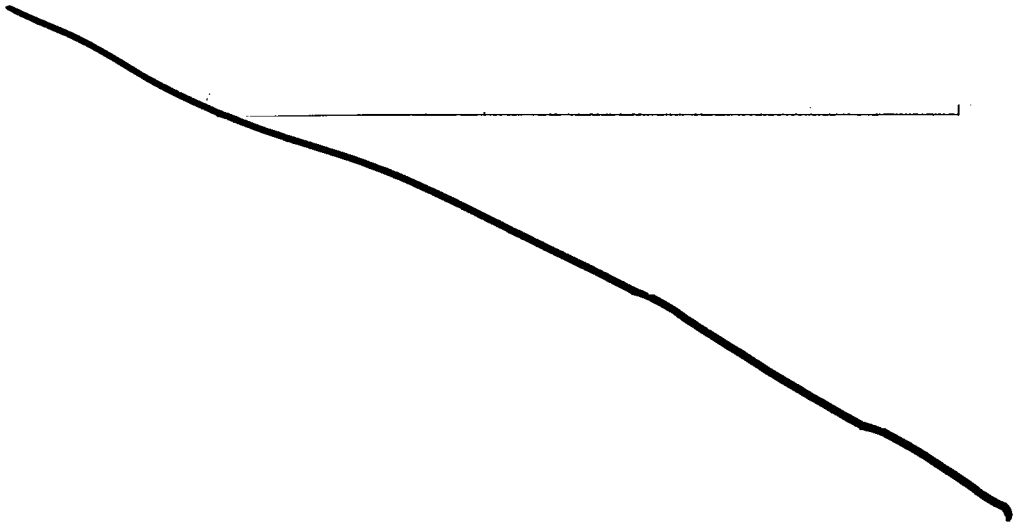
✓ Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Clin Pharm/Bio-*2



4.2 Individual Study Review (5)

M01-306

TITLE: Assessment of the Bioavailability of Multiple Tablet Formulations of Lopinavir and Ritonavir Relative to a Soft Gelatin Capsule Co-formulation of Lopinavir/Ritonavir

OBJECTIVES: The objective of this study was to assess the bioavailability of multiple tablet formulations of lopinavir and ritonavir relative to Kaletra soft gelatin capsule (SGC) formulation under non-fasting conditions.

SUBJECTS AND STUDY DESIGN: This was a phase 1, randomized, open-label, single-dose, four period, single center study. The study had two arms. Arm 1 had a conventional four period crossover design in which four single-dose regimens were administered. For Arm 2, the first three periods had a conventional three period crossover design in which three single-dose regimens were administered to the subjects, and in Period 4 all the subjects received the same single-dose formulations. Five subjects were assigned to each of the four sequences of Arm 1, and six subjects were assigned to each of the three sequences of Arm 2. The sequences of dosing regimens were such that upon completion of the study each subject had received all four dosing regimens administered to his/her arm. A washout interval of at least 7 days separated the doses in each of the four study periods. Adult male and female volunteers (n= 38) in general good health were selected to participate in the study according to the subject selection criteria of the protocol.

Arm 1

Sequence Groups I, II, III and IV:

(n=20 subjects)

Dosing Regimen A: Two lopinavir/ritonavir 186.7/46.7 mg co-formulated extruded tablets (Formulation E-C)

Dosing Regimen B: Two lopinavir/ritonavir 200/50 mg co-formulated compressed tablets (Formulation DC-C)

Dosing Regimen C: Two lopinavir/ritonavir 186.7/46.7 mg co-formulated extruded tablets (Formulation E-E)

Dosing Regimen D: Three lopinavir/ritonavir 133.3/33.3 mg co-formulated Soft Gelatin Capsules [Reference formulation]

Arm 2

Sequence Groups V, VI, and VII:

(n=18 subjects)

Dosing Regimen E: Two lopinavir 200 mg compressed tablets plus two ritonavir 50 mg compressed tablets (Formulations DC-A & DC-B)

Dosing Regimen F: Two lopinavir/ritonavir 200/50 mg co-formulated compressed tablets (Formulation DC-AB)

Dosing Regimen G: Three lopinavir/ritonavir 133.3/33.3 mg co-formulated Soft Gelatin Capsules (SGC) [Reference formulation]

Dosing Regimen H: Two lopinavir/ritonavir 200/50 mg co-formulated compressed tablets (Formulation DC-E)

Subjects received a standardized diet for all meals during the study. On Study Day 1 of a period, a moderate-fat breakfast consisting of 500 to 600 Kcal with 20 to 30% of calories from fat was served approximately 30 minutes prior to dosing.

INVESTIGATOR AND STUDY LOCATION: [redacted]

FORMULATION: Lopinavir/ritonavir tablet formulations DC-A, DC-B, DC-AB, DC-C, DC-E, E-C, and E-E, Kaletra soft gel capsules

SAMPLE COLLECTION: Blood samples were collected prior to dosing (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 30 and 36 hours after dosing in each study period.

ASSAY: Plasma concentrations of lopinavir and ritonavir were determined using a validated [redacted] method with liquid chromatography/mass spectrometry (LC/MS) analysis at Abbott Laboratories, Abbott Park, IL. The lower limit of quantification of lopinavir and ritonavir was 11.29 nglmL and 11.26 ng/mL, respectively, using 0.20 mL plasma sample.

PHARMACOKINETIC DATA ANALYSIS: Non-compartmental methods by a validated pharmacokinetic analysis program were used. Summary statistics of pharmacokinetic parameters such as geometric means and coefficients of variation for Cmax, Tmax and AUC were provided for each group. The geometric mean ratios with 90% confidence intervals were calculated between groups.

PHARMACOKINETIC RESULTS:

Table 1. Mean ± SD Pharmacokinetic Parameters of Lopinavir and Ritonavir (Arm 1)

		Arm 1			
Formulation (Regimen)		E-C (A)	DC-C (B)	E-E (C)	Reference (D)
Dose[#]		373.4/93.4	400/100	373.4/93.4	400/100
Pharmacokinetic Parameters		Test Tablets (N = 20)	Test Tablets (N = 20)	Test Tablets (N = 20)	Reference Capsules (N = 20)
		Lopinavir			
T_{max}	(h)	4.4 ± 1.9	4.9 ± 1.7	4.2 ± 1.2*	5.3 ± 2.5
C_{max}	(μg/mL)	6.21 ± 1.58*	5.55 ± 1.27	6.61 ± 1.71*	5.36 ± 1.29
C_{12}	(μg/mL)	3.24 ± 1.11*	3.00 ± 1.17	3.52 ± 1.10*	3.04 ± 1.24
AUC_t	(μg•h/mL)	73.1 ± 25.8*	66.5 ± 23.8	77.5 ± 24.5*	65.1 ± 25.3
AUC_∞	(μg•h/mL)	73.5 ± 26.1*	67.0 ± 24.2	78.0 ± 25.1*	65.9 ± 26.5
$t_{1/2}$[$]	(h)	2.59 ± 0.51	2.56 ± 0.58	2.55 ± 0.59	2.60 ± 0.62
CL/F[†]	(L/h)	5.8 ± 2.4	6.9 ± 2.8	5.4 ± 2.0	7.1 ± 2.9
V_p/F[†]	(L)	22 ± 10	26 ± 10	20 ± 7	27 ± 9
		Ritonavir			
T_{max}	(h)	4.1 ± 1.2*	4.5 ± 1.1	4.2 ± 1.2*	5.3 ± 2.8
C_{max}	(μg/mL)	0.43 ± 0.18*	0.37 ± 0.16	0.49 ± 0.25*	0.35 ± 0.15
C_{12}	(μg/mL)	0.12 ± 0.08	0.12 ± 0.08	0.13 ± 0.08*	0.13 ± 0.10
AUC_t	(μg•h/mL)	3.38 ± 1.71*	3.16 ± 1.67	3.71 ± 1.84*	3.04 ± 1.68
AUC_∞	(μg•h/mL)	3.50 ± 1.74*	3.28 ± 1.69	3.83 ± 1.87*	3.18 ± 1.71
$t_{1/2}$[$]	(h)	4.25 ± 0.75*	4.33 ± 0.86	4.25 ± 0.74*	4.53 ± 0.80
CL/F[†]	(L/h)	34.4 ± 19.1	38.8 ± 18.6	30.4 ± 14.0	40.5 ± 19.4
V_p/F[†]	(L)	206 ± 98	238 ± 95	182 ± 68	265 ± 123

Dose presented in mgs of lopinavir/ritonavir.

* Statistically significantly different from reference (Regimen D, ANOVA, $p < 0.05$).

$ Harmonic mean ± pseudo-standard deviation; evaluations of $t_{1/2}$ were based on statistical tests for β.

† Parameter was not tested statistically.

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Table 2. Mean ± SD Pharmacokinetic Parameters of Lopinavir and Ritonavir (Arm 2)

		Arm 2			
Formulation (Regimen)		**DC-A & DC-B (E)**	**DC-AB (F)**	**Reference (G)**	**DC-E (H)**
Dose#		**400/100**	**400/100**	**400/100**	**400/100**
Pharmacokinetic Parameters		**Test Tablets (N = 18)**	**Test Tablets (N = 18)**	**Reference Capsules (N = 18)**	**Test Tablets (N = 17)¢**
		Lopinavir			
T_{max}	(h)	4.3 ± 1.2*	4.9 ± 1.6*	6.7 ± 3.2	3.8 ± 1.4* (4.0)@
C_{max}	(μg/mL)	4.37 ± 1.22	5.22 ± 1.07*	4.53 ± 1.45	6.31 ± 1.18* (5.96)@
C_{12}	(μg/mL)	2.04 ± 0.95*	3.05 ± 0.80	3.07 ± 0.89	3.46 ± 0.87 (3.26)
AUC_t	(μg•h/mL)	46.7 ± 19.5*	63.8 ± 15.6	63.6 ± 18.0	75.8 ± 15.0* (73.1)@
AUC_{∞}	(μg•h/mL)	46.9 ± 19.5*	64.2 ± 15.8	64.0± 18.3	76.0 ± 15.2* (73.2)
$t_{1/2}$$	(h)	2.55 ± 0.56	2.54 ± 0.67	2.51 ± 0.55	2.45 ± 0.47 (2.44)
CL/F†	(L/h)	11.4 ± 8.9	6.6 ± 1.7	6.8 ± 2.0	5.5 ± 1.2 (5.5)
Vβ/F†	(L)	42 ± 26	26 ± 9	25 ± 8	20 ± 6 (20)
		Ritonavir			
T_{max}	(h)	4.1 ± 1.1*	5.0 ± 1.7*	6.2 ± 2.7	3.9 ± 1.3* (4.0)@
C_{max}	(μg/mL)	0.21 ± 0.11*	0.36 ± 0.10*	0.30 ± 0.15	0.46 ± 0.14* (0.44)@
C_{12}	(μg/mL)	0.06 ± 0.04*	0.12 ± 0.06	0.13 ± 0.05	0.12 ± 0.06 (0.11)
AUC_t	(μg•h/mL)	1.69 ± 1.08*	2.89 ± 1.04	2.70 ± 0.87	3.38 ± 1.00* (2.92)@
AUC_{∞}	(μg•h/mL)	1.84 ± 1.10*	3.03 ± 1.06	2.89 ± 0.87	3.53 ± 1.01* (3.10)@
$t_{1/2}$$	(h)	4.67 ± 1.29	4.53 ± 1.11*	5.22 ± 1.18	4.14 ± 0.66* (4.32)@
CL/F†	(L/h)	93.0 ± 86.6	36.7 ± 12.0	38.0 ± 12.3	30.6 ± 8.5 (32.3)
Vβ/F†	(L)	659 ± 635	246 ± 80	311 ± 172	183 ± 44 (177)

Dose presented in mgs of lopinavir/ritonavir.

* Statistically significantly different from reference (Regimen G, ANOVA, $p < 0.05$).

@ Statistically significantly different from reference (Regimen G, sign test, $p < 0.05$).

$ Harmonic mean ± pseudo-standard deviation: evaluations of $t_{1/2}$ were based on statistical tests for β.

† Parameter was not tested statistically.

¢ Mean ± SD values represent all subjects excluding Subject 121; median values in parenthesis represent all subjects.

Table 3. Lopinavir Relative Bioavailability

Formulation (Regimen) Test *vs.* Reference	Parameter	Central Values* Test	Central Values* Reference	Relative Bioavailability Point Estimate+	Relative Bioavailability 90% Confidence Interval
E-C (A) *vs.* SGC (D)	C_{max}	6.4	5.2	1.240	1.141 – 1.347
	C_{12}	3.3	2.8	1.170	1.050 – 1.304
	AUC_{∞}	73.7	60.9	1.211	1.100 – 1.334
DC-C (B) *vs.* SGC (D)	C_{max}	5.4	5.2	1.040	0.957 – 1.130
	C_{12}	2.8	2.8	0.988	0.886 – 1.101
	AUC_{∞}	62.6	60.9	1.028	0.933 – 1.132
E-E (C) *vs.* SGC (D)	C_{max}	6.8	5.2	1.315	1.210 – 1.429
	C_{12}	3.6	2.8	1.285	1.153 – 1.432
	AUC_{∞}	79.1	60.9	1.299	1.179 – 1.430
DC-A & DC-B (E) *vs.* SGC (G)	C_{max}	4.2	4.3	0.973	0.863 – 1.097
	C_{12}	1.7	2.9	0.587	0.474 – 0.728
	AUC_{∞}	41.8	61.6	0.679	0.590 – 0.782
DC-AB (F) *vs.* SGC (G)	C_{max}	5.1	4.3	1.193	1.059 – 1.346
	C_{12}	2.9	2.9	1.003	0.809 – 1.243
	AUC_{∞}	62.4	61.6	1.012	0.880 – 1.165
DC-E (H)^ *vs.* SGC (G)	C_{max}	6.2	4.2	1.461	1.266 – 1.686
	C_{12}	3.4	2.9	1.168	1.003 – 1.361
	AUC_{∞}	74.5	60.7	1.228	1.097 – 1.374

* Antilogarithm of the least squares means for logarithms.

\+ Antilogarithm of the difference (tablet minus capsule) of the least squares means for logarithms.

^ Formulation DC-E (Regimen H) without Subject 121.

Table 4. Ritonavir Relative Bioavailability

Formulation (Regimen) Test *vs.* Reference	Parameter	Central Values*		Relative Bioavailability	
		Test	Reference	Point Estimate+	90% Confidence Interval
E-C (A) *vs.* SGC (D)	C_{max}	0.4	0.3	1.337	1.166 – 1.533
	C_{12}	0.1	0.1	1.038	0.925 – 1.163
	AUC_{∞}	3.3	2.8	1.190	1.075 – 1.318
DC-C (B) *vs.* SGC (D)	C_{max}	0.3	0.3	1.092	0.953 – 1.252
	C_{12}	0.1	0.1	0.958	0.854 – 1.074
	AUC_{∞}	2.9	2.8	1.041	0.940 – 1.153
E-E (C) *vs.* SGC (D)	C_{max}	0.5	0.3	1.509	1.316 – 1.729
	C_{12}	0.1	0.1	1.164	1.038 – 1.305
	AUC_{∞}	3.7	2.8	1.317	1.189 – 1.459
DC-A & DC-B (E) *vs.* SGC (G)	C_{max}	0.2	0.3	0.662	0.528 – 0.829
	C_{12}	0.0	0.1	0.398	0.307 – 0.517
	AUC_{∞}	1.5	2.8	0.531	0.429 – 0.657
DC-AB (F) *vs.* SGC (G)	C_{max}	0.3	0.3	1.318	1.052 – 1.651
	C_{12}	0.1	0.1	0.905	0.697 – 1.174
	AUC_{∞}	2.9	2.8	1.041	0.841 – 1.288
DC-E (H)^ *vs.* SGC (G)	C_{max}	0.4	0.3	1.705	1.371 – 2.120
	C_{12}	0.1	0.1	0.961	0.794 – 1.162
	AUC_{∞}	3.4	2.7	1.262	1.142 – 1.395

* Antilogarithm of the least squares means for logarithms.

\+ Antilogarithm of the difference (tablet minus capsule) of the least squares means for logarithms.

^ Formulation DC-E (Regimen H) without Subject 121.

SAFETY RESULTS: See Medical Officer's review.

CONCLUSIONS AND DISCUSSION: When administered as a single dose under non-fasting conditions, each of the five test tablet lopinavir/ritonavir co-formulations produced similar or greater lopinavir and ritonavir bioavailability with respect to Cmax and AUC relative to the marketed SGC formulation. The co-formulated compressed tablet formulation DC-C was bioequivalent to the reference SGC since the 90% confidence intervals with respect to lopinavir Cmax and AUC were contained within the 0.80 to 1.25 range. The co-formulated compressed tablet formulation DC-AB produced similar AUC compared to the SGC, but Cmax was higher. The point estimate for Formulation DC-E was 20% higher for both lopinavir Cmax and AUC compared to the reference SGC. Formulations DC-C, DC-E and DC-AB were selected for further study based on relative bioavailability and ease of manufacture.

M01-381

TITLE: Assessment of the Bioavailability of Multiple-Tablet Co-Formulations of Lopinavir/Ritonavir Relative to a Soft Gelatin Capsule Co-Formulation of Lopinavir/Ritonavir in Fasting Versus Non-Fasting Conditions

OBJECTIVES: The objective of this study was to assess the bioavailability of multiple-tablet co-formulations of lopinavir/ritonavir relative to the approved soft gelatin capsule (SGC) formulation under fasting conditions. The food effect of each of the tablet formulations was also assessed.

SUBJECTS AND STUDY DESIGN: This was a phase 1, randomized, single-dose, open-label, four period, single-center bioavailability study in 48 healthy subjects. Each regimen was administered as a single dose of two lopinavir/ritonavir 200/50 mg co-formulated tablets or a single dose of three lopinavir/ritonavir 133.3/33.3 mg SGC co-formulated capsules (reference formulation). All subjects were to receive the reference SGC under fasting conditions and each test formulation was to be administered under fasting conditions to two-thirds and under non-fasting conditions to one-third of the subjects. Subjects were randomized to receive four of the following seven regimens:

Regimen A:	Two lopinavir/ritonavir 200/50 mg co-formulated compressed tablets (Formulation DC-C) under fasting conditions
Regimen B:	Two lopinavir/ritonavir 200/50 mg co-formulated compressed tablets (Formulation DC-C) following a moderate-fat breakfast
Regimen C:	Two lopinavir/ritonavir 200/50 mg co-formulated compressed tablets (Formulation DC-E) under fasting conditions
Regimen D:	Two lopinavir/ritonavir 200/50 mg co-formulated compressed tablets (Formulation DC-E) following a moderate-fat breakfast
Regimen E:	Two lopinavir/ritonavir 200/50 mg, separately extruded lopinavir and ritonavir, compressed tablets (Formulations DC-AB) under fasting conditions
Regimen F:	Two lopinavir/ritonavir 200/50 mg, separately extruded lopinavir and ritonavir, compressed tablets (Formulations DC-AB) following a moderate-fat breakfast
Regimen G:	Three lopinavir/ritonavir 133.3/33.3 mg co-formulated SGCs (Reference) under fasting conditions

INVESTIGATOR AND STUDY LOCATION [redacted]

FORMULATION: Lopinavir/ritonavir tablet formulations BC-AB, DC-C, DC-E, Kaletra soft gel capsules

SAMPLE COLLECTION: Blood samples for the determination of lopinavir/ritonavir were collected prior to dosing (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 30, and 36 hours after the dose in each study period.

ASSAY: Plasma concentrations of lopinavir and ritonavir were determined using a validated [redacted] method with liquid chromatography/mass spectrometry (LC/MS) analysis at Abbott Laboratories, Abbott Park, IL. The lower limit of quantification of lopinavir and ritonavir was 25.56 nglmL and 4.97 ng/mL, respectively, using 0.20 mL plasma sample.

PHARMACOKINETIC DATA ANALYSIS: Non-compartmental methods by a validated pharmacokinetic analysis program were used. Summary statistics of pharmacokinetic parameters such as geometric means and coefficients of variation for Cmax, Tmax and AUC were provided for each group. The geometric mean ratios with 90% confidence intervals were calculated between groups.

PHARMACOKINETIC RESULTS:

Table 1. Lopinavir and Ritonavir Mean ± SD Pharmacokinetic Parameter

Pharmacokinetic Parameters (units)		Regimen A (DC-C) Fasting (N=32)	Regimen B (DC-C) NF (N=15)	Regimen C (DC-E) Fasting (N=30)	Regimen D (DC-E) NF (N=13)	Regimen E (DC-AB) Fasting (N=30)	Regimen F (DC-AB) NF (N=17)	Regimen G (SGC) Fasting (N=46)
Lopinavir								
T_{max}	(h)	3.4 ± 1.3*	4.7 ± 1.6+	2.9 ± 1.1*	4.9 ± 2.1+	3.6 ± 1.0	4.6 ± 1.5+	4.2 ± 1.7
C_{max}	(µg/mL)	6.48 ± 1.98*	6.60 ± 2.11	8.58 ± 2.45*	8.18 ± 2.64	5.43 ± 1.97	7.32 ± 1.49+	5.49 ± 2.17
C_{12}	(µg/mL)	2.79 ± 1.48	3.53 ± 1.32+	3.77 ± 1.22*	4.43 ± 1.73	2.33 ± 1.24	3.76 ± 1.24+	2.44 ± 1.40
AUC_t	(µg•h/mL)	70.0 ± 33.0*	75.5 ± 30.5	93.0 ± 32.0*	107.1 ± 46.0	53.9 ± 22.7	81.7 ± 19.4+	59.6 ± 32.7
AUC_∞	(µg•h/mL)	70.4 ± 34.0*	76.0 ± 30.5	94.0 ± 33.0*	108.1 ± 46.9	54.4 ± 22.9	82.6 ± 19.6+	60.4 ± 33.7
$t_{½}$#	(h)	3.03 ± 0.74	2.74 ± 0.45	2.78 ± 0.58*	2.72 ± 0.72+	2.97 ± 0.59	2.81 ± 0.77	3.11 ± 0.63
CL/F$	(L/h)	7.0 ± 3.2	7.4 ± 8.2	4.7 ± 1.5	4.6 ± 2.4	9.2 ± 5.3	5.1 ± 1.3	11.4 ± 14.2
Ritonavir								
T_{max}	(h)	3.3 ± 0.9*	4.5 ± 1.2+	2.9 ± 0.9*	4.4 ± 1.3+	3.5 ± 0.8*	4.5 ± 1+	4.2 ± 1.8
C_{max}	(µg/mL)	0.44 ± 0.20*	0.49 ± 0.19	0.73 ± 0.39*	0.60 ± 0.25	0.40 ± 0.22	0.55 ± 0.36	0.40 ± 0.28
C_{12}	(µg/mL)	0.11 ± 0.06	0.13 ± 0.07+	0.13 ± 0.06	0.17 ± 0.10	0.09 ± 0.05	0.14 ± 0.07+	0.10 ± 0.07
AUC_t	(µg•h/mL)	3.40 ± 1.61	3.78 ± 1.76	4.72 ± 1.95*	4.97 ± 2.35	2.89 ± 1.48	4.16 ± 1.95+	3.03 ± 1.97
AUC_∞	(µg•h/mL)	3.49 ± 1.66	3.83 ± 1.76	4.78 ± 1.96*	5.03 ± 2.36	2.95 ± 1.49	4.27 ± 2.00+	3.11 ± 2.01
$t_{½}$#	(h)	4.78 ± 1.19	4.08 ± 0.63	4.20 ± 0.74*	4.53 ± 0.78	4.65 ± 1.17	4.66 ± 1.41	4.76 ± 1.22
CL/F$	(L/h)	35.9 ± 17.9	41.7 ± 55.8	24.5 ± 9.5	24.5 ± 11.6	45.6 ± 31.6	27.3 ± 10.1	52.4 ± 54.9

* Statistically significantly different from Regimen G (ANOVA, $p < 0.05$).

\+ Statistically significantly different from Fasting (ANOVA, $p < 0.05$).

\# Harmonic mean ± pseudo standard deviation; evaluations of $t_{½}$ were based on statistical tests for β.

$ Parameter was not tested statistically.

NF = Non-fasting (moderate-fat).

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Table 2. Lopinavir Relative Bioavailability

Formulation (Regimen) Test *vs.* Reference	Parameter	Central Values*		Relative Bioavailability	
		Test	Reference	Point Estimate+	90% Confidence Interval
Tablet *vs.* Capsule, Fasting					
DC-C (A) *vs.* SGC (G)	C_{max}	6.1	4.9	1.250	1.076 – 1.452
	C_{12}	0.3	0.3	1.067	0.818 – 1.392
	AUC_{∞}	61.6	49.8	1.238	1.045 – 1.466
DC-E (C) *vs.* SGC (G)	C_{max}	8.0	4.9	1.635	1.402 – 1.907
	C_{12}	0.5	0.3	1.632	1.242 – 2.144
	AUC_{∞}	85.4	49.8	1.716	1.443 – 2.041
DC-AB (E) *vs.* SGC (G)	C_{max}	5.3	4.9	1.074	0.921 – 1.252
	C_{12}	0.3	0.3	0.966	0.735 – 1.269
	AUC_{∞}	53.0	49.8	1.066	0.895 – 1.267
Tablet, Non-Fasting *vs.* Fasting					
DC-C (B) *vs.* DC-C (A)	C_{max}	6.3	6.1	1.032	0.837 – 1.273
	C_{12}	0.5	0.3	1.629	1.123 – 2.362
	AUC_{∞}	74.0	61.6	1.201	0.948 – 1.522
DC-E (D) *vs.* DC-E (C)	C_{max}	7.5	8.0	0.939	0.751 – 1.174
	C_{12}	0.6	0.5	1.275	0.857 – 1.895
	AUC_{∞}	90.6	85.4	1.061	0.825 – 1.366
DC-AB (F) *vs.* DC-AB (E)	C_{max}	6.9	5.3	1.316	1.076 – 1.611
	C_{12}	0.6	0.3	2.227	1.557 – 3.187
	AUC_{∞}	76.8	53.0	1.449	1.154 – 1.820

* Antilogarithm of the least squares means for logarithms.

\+ Antilogarithm of the difference (tablet minus capsule) of the least squares means for logarithms.

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Table 3. Ritonavir Relative Bioavailability Results

Regimens Test *vs.* Reference	Parameter	Central Values* Test	Central Values* Reference	Relative Bioavailability Point Estimate+	Relative Bioavailability 90% Confidence Interval
Tablet *vs.* Capsule, Fasting					
DC-C (A) *vs.* SGC (G)	C_{max}	0.4	0.3	1.267	1.051 – 1.529
	C_{12}	0.0	0.0	0.980	0.872 – 1.100
	AUC_{∞}	3.0	2.6	1.173	1.010 – 1.363
DC-E (C) *vs.* SGC (G)	C_{max}	0.6	0.3	1.980	1.634 – 2.399
	C_{12}	0.0	0.0	1.093	0.970 – 1.231
	AUC_{∞}	4.3	2.6	1.698	1.456 – 1.979
DC-AB (E) *vs.* SGC (G)	C_{max}	0.3	0.3	1.119	0.924 – 1.356
	C_{12}	0.0	0.0	0.993	0.882 – 1.118
	AUC_{∞}	2.8	2.6	1.081	0.928 – 1.260
Tablet, Non-Fasting *vs.* Fasting					
DC-C (B) *vs.* DC-C (A)	C_{max}	0.4	0.4	1.107	0.852 – 1.439
	C_{12}	0.0	0.0	1.225	1.041 – 1.441
	AUC_{∞}	3.6	3.0	1.197	0.971 – 1.476
DC-E (D) *vs.* DC-E (C)	C_{max}	0.5	0.6	0.847	0.641 – 1.120
	C_{12}	0.0	0.0	1.126	0.947 – 1.339
	AUC_{∞}	4.3	4.3	0.994	0.796 – 1.243
DC-AB (F) *vs.* DC-AB (E)	C_{max}	0.5	0.3	1.303	1.012 – 1.676
	C_{12}	0.0	0.0	1.315	1.125 – 1.538
	AUC_{∞}	3.7	2.8	1.342	1.097 – 1.641

* Antilogarithm of the least squares means for logarithms.

\+ Antilogarithm of the difference (tablet minus capsule) of the least squares means for logarithms.

SAFETY RESULTS: See Medical Officer's review.

CONCLUSIONS AND DISCUSSION: When administered under fasting conditions, each of the three compressed tablet formulations (formulations DC-C, DC-E and DC-AB) produced similar or greater lopinavir and ritonavir bioavailability relative to the marketed SGC formulation.

Comparison of the tablet formulation DC-C under non-fasting relative to fasting conditions suggested that there was less food effect with this tablet formulation relative to the capsule; 10-20% increase compared to 56% with the SGC (Study M99 – 073).

Formulation DC-C was selected for further development based on its similar bioavailability relative to the SGC under non-fasting conditions, limited food effect, and formulation simplicity.

M03-580

TITLE: Comparison of the Single-Dose Bioavailability of a Tablet Formulation of Lopinavir/Ritonavir Relative to the Currently Marketed Capsule Formulation and Assessment of the Multiple-Dose Pharmacokinetics and Safety of the Co-Administration of a Lopinavir/Ritonavir Tablet Formulation with Efavirenz

OBJECTIVES: The objectives of this study were to: 1. Compare the single-dose bioavailability of lopinavir/ritonavir 400/100 mg from a scale-up lot of an experimental tablet formulation to that obtained from the currently marketed capsule formulation. 2. Compare the single-dose bioavailability of lopinavir/ritonavir 800/200 mg from a scale-up lot of an experimental tablet formulation to that obtained from the currently marketed capsule formulation. 3. Assess the multiple-dose pharmacokinetics and safety of lopinavir/ritonavir 600/150 mg twice daily (BID) dosed as the experimental table formulation and co-administered with 600 mg efavirenz (tablet) once daily (QD).

SUBJECTS AND STUDY DESIGN: This was a phase 1, single- and multiple-dose, non-fasting, open-label, bioavailability and drug interaction study.

Part 1 of the study was a single-dose, two-period crossover comparison of the bioavailability of lopinavir/ritonavir 400/100 mg (Regimens A and B) and 800/200 mg (Regimens C and D) from an experimental tablet formulation to that of the currently marketed capsule formulation. Subjects were randomly assigned in equal numbers to four groups; within each group, the subjects received one of the two formulations on Study Day 1 and the other formulation on Study Day 6 under non-fasting conditions.

Part 2 (Regimen E) of the study was to assess the multiple-dose pharmacokinetics and safety of co-administration of the lopinavir/ritonavir tablet formulation with efavirenz in a subset of subjects from Part 1. Subjects received lopinavir/ritonavir 400/100 mg (2 tablets) BID from the morning of Study Day 8 through the morning of Study Day 18. Efavirenz 600 mg QD was co-administered with lopinavir/ritonavir 400/100 mg BID (2 tablets) on the evening of Study Day 18 through the evening of Study Day 21. Efavirenz 600 mg QD was co-administered with lopinavir/ritonavir 600/150 mg BID (3 tablets) on the morning of Study Day 22 through the morning of Study Day 32.

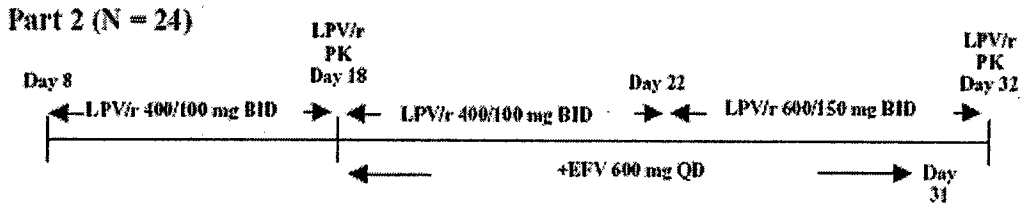
30 subjects were enrolled and completed the Part 1 of the study. 23 subjects were enrolled and completed the Part 2 of the study.

The study design schemes are shown below:

Part 1 (N = 32)

Sequence Group	N	Regimen	
		Study Day 1	Study Day 6
Ia	8	A	B
Ib	8	B	A
IIa	8	C	D
IIb	8	D	C

Regimen A: Single dose of 400/100 mg lopinavir/ritonavir tablet formulation (two 200/50 mg tablets)
Regimen B: Single dose 400/100 mg lopinavir/ritonavir marketed capsule formulation (three 133.3/33.3 mg capsules)
Regimen C: Single dose of 800/200 mg lopinavir/ritonavir tablet formulation (four 200/50 mg tablets)
Regimen D: Single dose of 800/200 mg lopinavir/ritonavir marketed capsule formulation (six 133.3/33.3 mg capsules)



Regimen E:

Study Days 8 through 18	Lopinavir/ritonavir 400/100 mg (two 200/50 mg tablets) BID. This regimen began with the morning dose on Study Day 8 and ended with the morning dose on Study Day 18.
Study Days 18 through 21	Co-administration of efavirenz 600 mg (one 600 mg tablet) QD and lopinavir/ritonavir 400/100 mg (two 200/50 mg tablets) BID. This regimen began with the evening dose on Study Day 18 and ended with the evening dose on Study Day 21.
Study Days 22 through 32	Co-administration of efavirenz 600 mg (one 600 mg tablet) QD and lopinavir/ritonavir 600/150 mg (three 200/50 mg tablets) BID. This regimen began with the doses on Study Day 22 and ended with the morning dose of lopinavir/ritonavir on Study Day 32.

Breakfast and dinner were served approximately 30 minutes prior to administration of lopinavir/ritonavir. Subjects received a standardized diet for all meals during the study. On Study Days 1 and 6 of Part 1, all subjects were served an identical breakfast consisting of approximately 500 Kcal with 20-30% calories from fat. In Part 2 of the study, lopinavir/ritonavir was administered at approximately 7:00 and 19:00 under non-fasting conditions with a meal of low fat content (20-30% Kcal from fat). All remaining study meals provided approximately 30% calories from fat. Efavirenz was administered at approximately 22:00 on an empty stomach, at least 2 hours after completion of dinner.

The demographic characteristics of subjects included in Part 1, regimens A and B

	Mean ± SD (N = 15)	Min – Max
Age (years)	36 ± 11	20 – 49
Weight (kg)	81 ± 13	63 – 101
Height (cm)	180 ± 9.3	163 – 192
Sex	15 Males (100%)	
Race	9 White (60%), 4 Black (27%), 2 Hispanic (13%)	

The demographic characteristics of subjects included in Part 1, regimens C and D

	Mean ± SD (N = 15)	Min – Max
Age (years)	36 ± 12	19 – 53
Weight (kg)	77 ± 10	58 – 96
Height (cm)	175 ± 6.2	158 – 183
Sex	12 Males (80%), 3 Females (20%)	
Race	12 White (80%), 1 Black (7%), 2 Hispanic (13%)	

The demographic characteristics of subjects included in Part 2, regimen E

	Mean ± SD (N = 23)	Min – Max
Age (years)	37 ± 11	19 – 53
Weight (kg)	80 ± 12	64 – 101
Height (cm)	179 ± 7.0	163 – 192
Sex	22 Males (96%), 1 Female (4%)	
Race	16 White (70%), 4 Black (17%), 3 Hispanic (13%)	

INVESTIGATOR AND STUDY LOCATION: Thao Doan, M.D., Abbott Clinical Pharmacology Research Unit, Waukegan, IL

FORMULATION: Katetra tablet formulation DC-C, 200/50 mg, lot number 95-096-4P, Kaletra soft gelatin capsules, 133.3/33.3 mg, lot number 85-048-4P, Sustiva tablets, 600 mg

SAMPLE COLLECTION: Blood samples for lopinavir and ritonavir assay were collected on Study Days 1 and 6 prior to dosing (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 30 and 36 hours after dosing, and on Study Days 18 and 32 prior to dosing (0 hour) and at 2, 4, 6, 8, 10 and 12 hours after morning dosing. Blood samples were also collected prior to the morning dose (trough levels) on Study Days 14, 16, 28 and 30. Blood samples for efavirenz assay were collected on the morning of Study Days 28, 30 and 32, approximately 9 hours post efavirenz dosing.

ASSAY: Plasma concentrations of lopinavir and ritonavir were determined using a validated high performance liquid chromatography analytical method with tandem mass spectrometric detection at Abbott Laboratories, Abbott Park, IL. The lower limits of quantitation (LOQs) for lopinavir were established at 18.7 and 20.4 ng/mL, and the LOQs for ritonavir were established at 10.8 and 11.2 ng/mL, using a 0.100 mL plasma sample. Plasma concentrations of efavirenz were determined using a validated high performance liquid chromatography analytical method with ultraviolet detection at [redacted]. The lower limit of quantitation for efavirenz was established at 0.100 µg/mL, using a 100 µL plasma sample.

The coefficient of variation (CV) values were ≤ 9.9%; the mean % bias values ranged from -3.2 to 8.0%.for lopinavir. The CV values were ≤13.3%; the mean % bias values ranged from -3.2 to 7.8% for ritonavir. The CV values were ≤2.35% for efavirenz.

PHARMACOKINETIC DATA ANALYSIS: The pharmacokinetic parameter values of lopinavir and ritonavir were estimated using non-compartmental methods. Summary statistics of pharmacokinetic parameters such as geometric means and coefficients of variation for C_{max}, T_{max} and AUC_{12} were provided for each group. The geometric mean ratios with 90% confidence intervals were calculated between treatments.

PHARMACOKINETIC RESULTS:

Part 1:

Table 1. Mean ± SD Pharmacokinetic Parameters of Lopinavir, Part 1

Pharmacokinetic Parameters (units)		Part 1, LPV/r Single-Dose Regimens			
		Regimen A 400/100 mg tablet (N = 15)	Regimen B 400/100 mg capsule (N = 15)	Regimen C 800/200 mg tablet (N = 15)	Regimen D 800/200 mg capsule (N = 15)
C_{max}	(µg/mL)	6.41 ± 1.25	7.10 ± 2.89	13.74 ± 4.92**	11.72 ± 2.43
T_{max}	(h)	4.1 ± 1.3*	5.6 ± 1.4	5.5 ± 2.3	6.1 ± 2.1
AUC_t	(µg•h/mL)	76.7 ± 26.8	80.6 ± 38.1	212.5 ± 68.6**	180.6 ± 50.8
AUC_∞	(µg•h/mL)	77.0 ± 26.8	81.0 ± 38.2	214.2 ± 69.6**	181.4 ± 51.5
C_{12}	(µg/mL)	3.93 ± 1.63	4.35 ± 2.20	--	--
C_{24}	(µg/mL)	--	--	3.98 ± 2.01	4.00 ± 2.54
$t_{1/2}^{\$}$	(h)	2.57 ± 0.43	2.40 ± 0.49	2.49 ± 0.68	2.36 ± 0.49
$CL/F^{\#}$	(L/h)	5.97 ± 2.66	6.70 ± 4.96	4.21 ± 1.71	4.83 ± 1.76

* Statistically significantly different from Regimen B (ANOVA, $p < 0.05$).

** Statistically significantly different from Regimen D (ANOVA, $p < 0.05$).

$ Terminal elimination $t_{1/2}$ presented as harmonic mean ± pseudostandard deviation; evaluations of $t_{1/2}$ were based on statistical tests for β.

\# Parameter was not tested statistically.

Table 2. Mean ± SD Pharmacokinetic Parameters of Ritonavir, Part 1

Pharmacokinetic Parameters (units)		Part 1, LPV/r Single-Dose Regimens			
		Regimen A 400/100 mg tablet (N = 15)	Regimen B 400/100 mg capsule (N = 15)	Regimen C 800/200 mg tablet (N = 15)	Regimen D 800/200 mg capsule (N = 15)
C_{max}	(µg/mL)	0.46 ± 0.16	0.54 ± 0.33	1.96 ± 0.86**	1.72 ± 0.74
T_{max}	(h)	4.5 ± 1.0*	5.3 ± 1.2	4.8 ± 1.0**	5.5 ± 0.9
AUC_t	(µg•h/mL)	3.76 ± 1.59	3.98 ± 2.07	15.96 ± 7.61**	13.16 ± 5.64
AUC_∞	(µg•h/mL)	3.87 ± 1.61	4.10 ± 2.06	16.06 ± 7.60**	13.28 ± 5.64
C_{12}	(µg/mL)	0.17 ± 0.09	0.21 ± 0.14	--	--
C_{24}	(µg/mL)	--	--	0.09 ± 0.06	0.11 ± 0.12
$t_{1/2}^{\$}$	(h)	4.14 ± 0.71	4.20 ± 0.79	3.63 ± 0.55	3.79 ± 0.60
$CL/F^{\#}$	(L/h)	31.2 ± 15.2	31.9 ± 18.4	16.8 ± 11.9	18.7 ± 11.4

* Statistically significantly different from reference regimen (Regimen B, ANOVA, $p < 0.05$).

** Statistically significantly difference from reference regimen (Regimen D, ANOVA, $p < 0.05$).

$ Terminal elimination $t_{1/2}$ presented as harmonic mean ± pseudostandard deviation; evaluations of $t_{1/2}$ were based on statistical tests for β.

\# Parameter was not tested statistically.

Table 3. Relative Bioavailability and 90% Confidence Intervals for the Bioequivalence Summary, Part 1

LPV/r Dose	Pharmacokinetic Parameter	Central Values*		Relative Bioavailability	
		Test Tablet	Reference Capsule	Point Estimate#	90% Confidence Interval
Lopinavir					
400/100 mg Regimen A *vs.* Regimen B	C_{max}	6.2	6.4	0.971	0.879 – 1.073
	AUC_t	71.0	69.4	1.023	0.909 – 1.151
	AUC_∞	71.5	69.8	1.024	0.909 – 1.153
800/200 mg Regimen C *vs.* Regimen D	C_{max}	13.1	11.5	1.140	1.044 – 1.244
	AUC_t	202.2	173.1	1.168	1.121 – 1.217
	AUC_∞	203.7	173.9	1.172	1.126 – 1.219
Ritonavir					
400/100 mg Regimen A *vs.* Regimen B	C_{max}	0.4	0.5	0.952	0.746 – 1.214
	AUC_t	3.4	3.4	1.008	0.870 – 1.167
	AUC_∞	3.5	3.6	0.991	0.865 – 1.135
800/200 mg Regimen C *vs.* Regimen D	C_{max}	1.8	1.6	1.133	1.024 – 1.253
	AUC_t	14.0	11.9	1.174	1.090 – 1.264
	AUC_∞	14.1	12.0	1.173	1.091 – 1.260

* Antilogarithm of the least squares means for logarithms.

\# Antilogarithm of the difference (tablet minus capsule) of the least squares means for logarithms.

Table 4. Total Variabilities for Lopinavir and Ritonavir, Part 1

Pharmacokinetic Parameter	Variability (%CV)			
	Part 1, LPV/r Single-Dose Regimens			
	Regimen A 400/100 mg tablet (N = 15)	Regimen B 400/100 mg capsule (N = 15)	Regimen C 800/200 mg tablet (N = 15)	Regimen D 800/200 mg capsule (N = 15)
Lopinavir				
C_{max}	20	41	36	21
AUC_t	35	47	32	28
AUC_∞	35	47	33	28
Ritonavir				
C_{max}	36	61	44	43
AUC_t	42	52	48	43
AUC_∞	42	50	47	42

Figure 1. Mean (SD) Lopinavir Plasma Concentration-Time Profiles after Single Dose Administration of Lopinavir/ritonavir 400/100 mg(Regimens A and B) Part 1

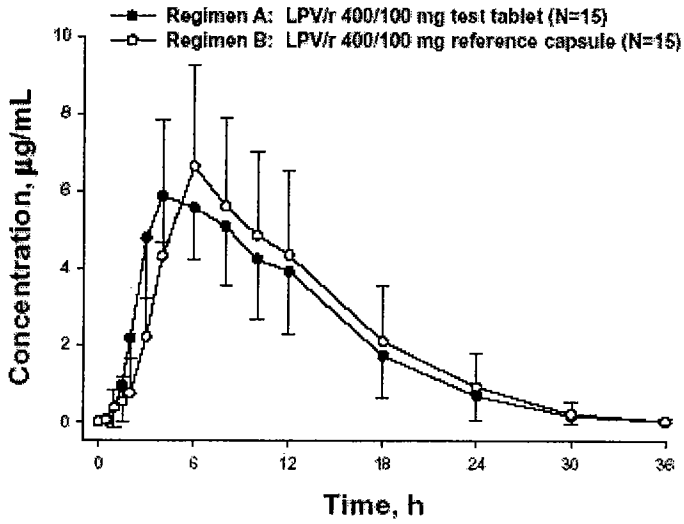


Figure 2. Mean (SD) Lopinavir Plasma Concentration-Time Profiles after Single Dose Administration of Lopinavir/ritonavir 800/200 mg(Regimens C and D) Part 1

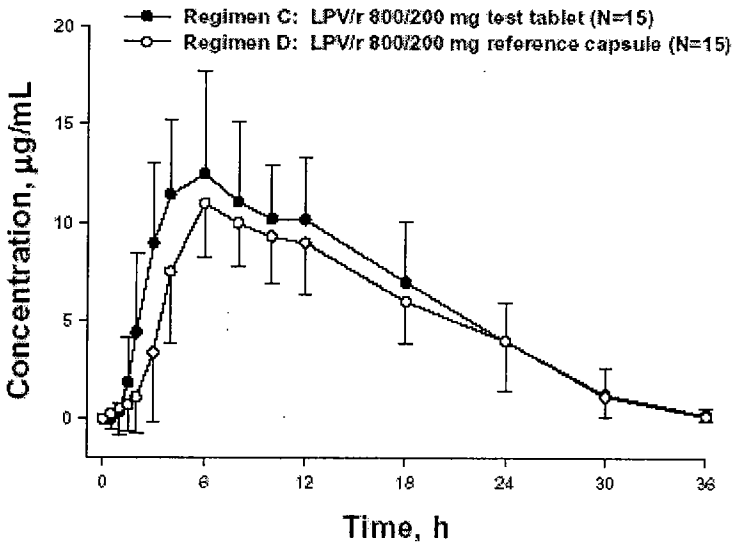


Figure 3. Mean (SD) Ritonavir Plasma Concentration-Time Profiles after Single Dose Administration of Lopinavir/ritonavir 400/100 mg(Regimens A and B) Part 1

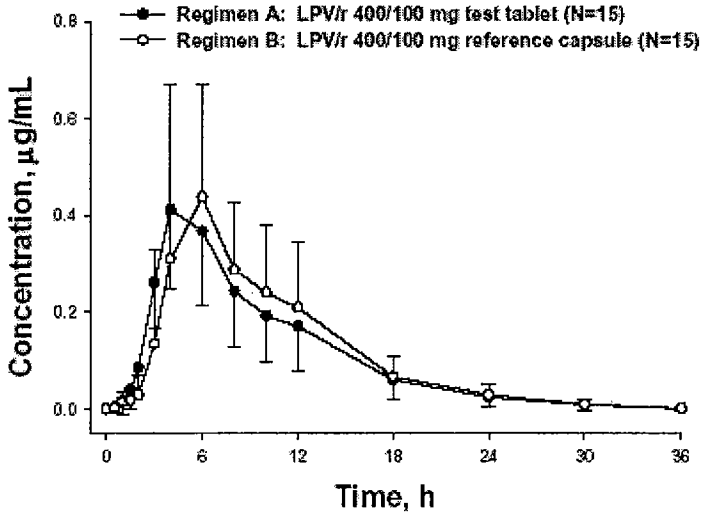
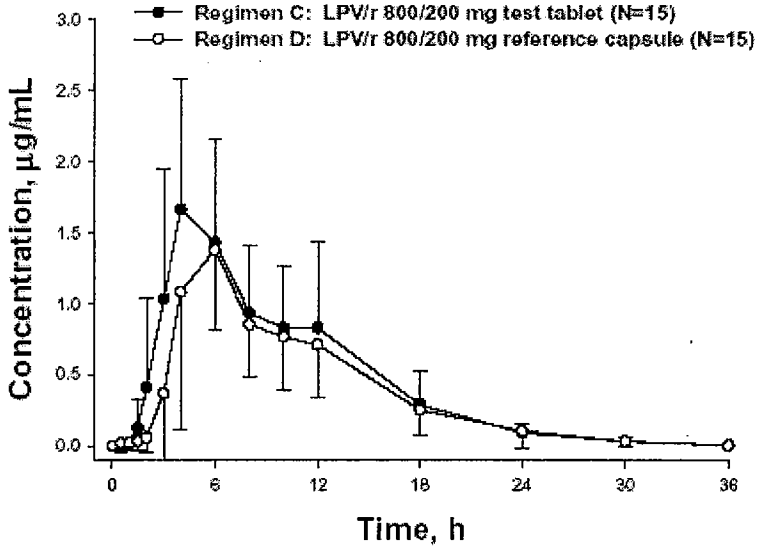


Figure 4. Mean (SD) Ritonavir Plasma Concentration-Time Profiles after Single Dose Administration of Lopinavir/ritonavir 800/200 mg(Regimens C and D) Part 1



Part 2:

Table 5. Mean ± SD Pharmacokinetic Parameters of Lopinavir, Part 2

Pharmacokinetic Parameters (units)		Part 2, LPV/r Multiple-Dose Tablet, Regimen E	
		600/150 mg BID Co-Administered with EFV 600 mg QD, Study Day 32 (N=23)	400/100 mg BID Alone, Study Day 18 (N=23)
C_{max}	(µg/mL)	14.39 ± 2.58*	10.56 ± 1.73
T_{max}	(h)	4.3 ± 0.7	4.4 ± 0.8
C_{min}	(µg/mL)	6.55 ± 2.42*	4.86 ± 1.61
C_{trough}	(µg/mL)	7.75 ± 2.69*	5.66 ± 1.83
AUC_{12}	(µg•h/mL)	123.5 ± 26.9*	90.6 ± 18.7
$t_{1/2}^{\$\#}$	(h)	6.70 ± 2.21	6.86 ± 2.12
$CL/F^{\#}$	(L/h)	5.14 ± 1.46	4.61 ± 1.03

* Statistically significantly different from lopinavir/ritonavir alone (paired t-test, $p < 0.05$).

\$ Peak-to-trough elimination $t_{1/2}$ presented as harmonic mean ± pseudostandard deviation.

\# Parameter was not tested statistically.

Table 6. Mean ± SD Pharmacokinetic Parameters of Ritonavir, Part 2

Pharmacokinetic Parameters (units)		Part 2, LPV/r Multiple-Dose Tablet, Regimen E	
		600/150 mg BID Co-Administered with EFV 600 mg QD, Study Day 32 (N=23)	400/100 mg BID Alone, Study Day 18 (N=23)
C_{max}	(µg/mL)	1.83 ± 0.64*	0.94 ± 0.32
T_{max}	(h)	4.2 ± 0.6	4.0 ± 0.0
C_{min}	(µg/mL)	0.28 ± 0.10*	0.19 ± 0.08
C_{trough}	(µg/mL)	0.39 ± 0.20*	0.24 ± 0.12
AUC_{12}	(µg•h/mL)	9.41 ± 2.87*	5.22 ± 1.40
$t_{1/2}^{\$\#}$	(h)	3.28 ± 0.73	3.77 ± 0.88
$CL/F^{\#}$	(L/h)	17.9 ± 7.1	20.8 ± 6.6

* Statistically significantly different from lopinavir/ritonavir alone (paired t-test, $p < 0.05$).

\$ Peak-to-trough elimination $t_{1/2}$ presented as harmonic mean ± pseudostandard deviation.

\# Parameter was not tested statistically.

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Table 7. Lopinavir and Ritonavir Relative Bioavailability and 90% Confidence Intervals, Part 2

Pharmacokinetic Parameter	Central Values*		Relative Bioavailability	
	LPV/r 600/150 mg BID + EFV 600 mg QD	LPV/r 400/100 mg BID alone	Point Estimate#	90% Confidence Interval
Lopinavir				
C_{max}	14.1	10.4	1.356	1.275 – 1.442
C_{min}	6.1	4.6	1.320	1.207 – 1.444
C_{trough}	7.3	5.4	1.362	1.256 – 1.477
AUC_{12}	120.4	88.7	1.357	1.284 – 1.435
Ritonavir				
C_{max}	1.7	0.9	1.921	1.678 – 2.199
C_{min}	0.3	0.2	1.564	1.405 – 1.742
C_{trough}	0.3	0.2	1.604	1.399 – 1.840
AUC_{12}	8.9	5.0	1.778	1.620 – 1.952

* Antilogarithm of the least squares means for logarithms.

\# Antilogarithm of the difference (co-administration of lopinavir/ritonavir with efavirenz minus lopinavir/ritonavir alone) of the least squares means for logarithms.

Table 8. Total Variability for Lopinavir and Ritonavir, Part 2

Pharmacokinetic Parameter	Variability (%CV)	
	Part 2, Lopinavir/ritonavir Multiple-Dose Regimen E	
	600/150 mg BID Co-Administered with Efavirenz 600 mg QD (N=23)	400/100 mg BID Alone (N=23)
Lopinavir		
C_{max}	18	16
C_{min}	37	33
C_{trough}	35	32
AUC_{12}	22	21
Ritonavir		
C_{max}	35	34
C_{min}	36	41
C_{trough}	50	50
AUC_{12}	30	27

Table 9. Mean ± SD Efavirenz 9-Hour Concentrations

	LPV/r 600/150 mg BID tablets + EFV 600 mg QD		
Study Day	28	30	32
EFV Dosing Day	10	14	16
Time after Dose (h)	9	9	9
N	23	23	23
Mean ± SD (μM)	10.25 ± 4.89	10.66 ± 5.74	10.57 ± 5.31

Figure 5. Lopinavir Plasma Concentration-Time Profiles, Part 2

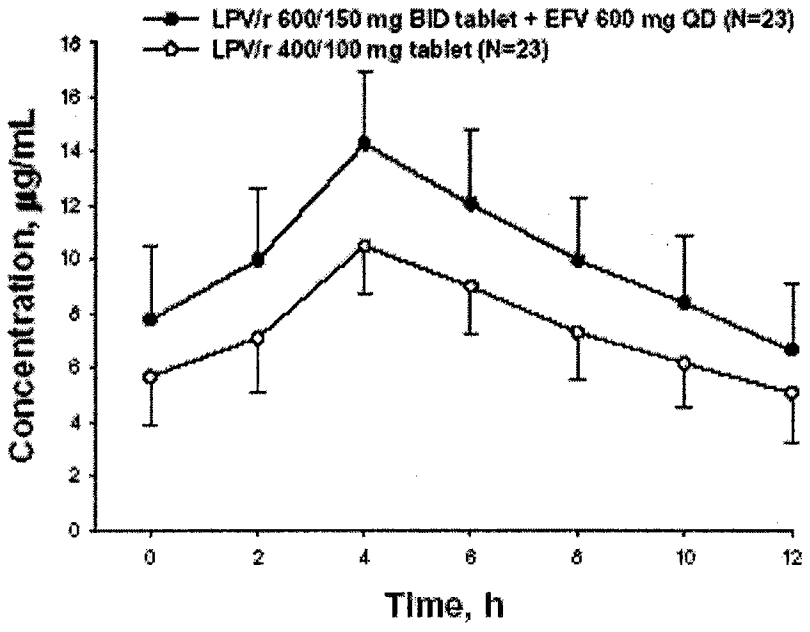

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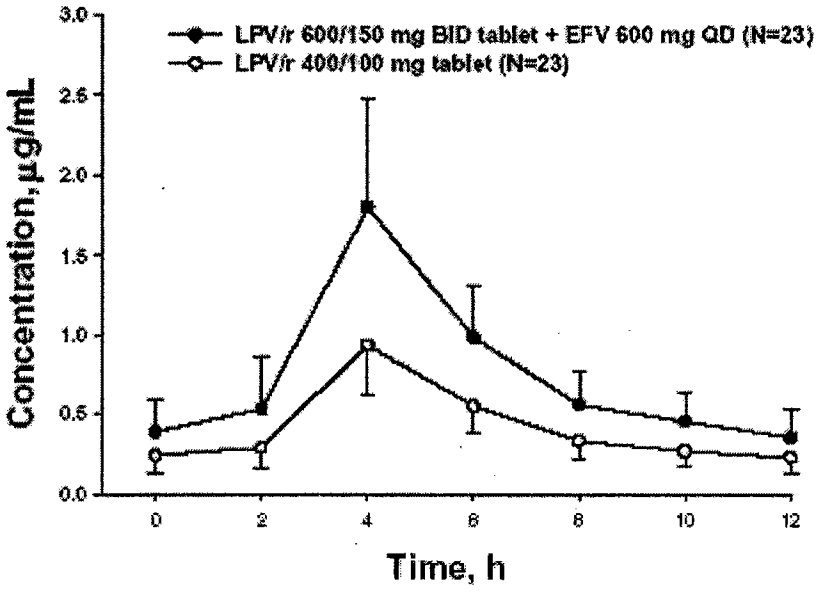
Figure 6. Ritonavir Plasma Concentration – Time Profiles, Part 2



SAFETY RESULTS: See Medical Officer's review.

CONCLUSIONS AND DISCUSSION: Following single-doses of lopinavir/ritonavir 400/100 mg under non-fasting conditions, the tablet and capsule formulations were bioequivalent for lopinavir. The two formulations also met bioequivalence criteria following single-doses of lopinavir/ritonavir 800/200 mg under non-fasting conditions for lopinavir. However, the experimental tablet formulation exhibited higher lopinavir bioavailability than the capsule formulation. The central values for lopinavir Cmax and AUC were 14% and 17% higher, respectively.

Following single-doses of lopinavir/ritonavir 400/100 mg under non-fasting conditions, the tablet and capsule formulations were not bioequivalent for ritonavir. Although ritonavir's area under the concentration time curves (AUCt and AUC∞) ratios (tablet vs. capsule) were within 80-125%. The lower limit of 90% confidence intervals for ritonavir's Cmax ratio (tablet vs. capsule) was below 80%, 74.6%. Following single-doses of lopinavir/ritonavir 800/200 mg under non-fasting conditions, the tablet and capsule formulations were not bioequivalent for ritonavir. The central values of Cmax and AUC were 13% and 17% higher for the experimental tablets after 800/200 mg doses under non-fasting conditions.

Co-administration of lopinavir/ritonavir 400/100 mg BID as 3 SGCs with the CYP3A-inducing antiretroviral agent efavirenz has been shown to decrease the lopinavir area under the curve (AUC) and minimum plasma concentration (Cmin) by approximately 20 and 40%, respectively, while efavirenz concentrations were not significantly altered. An increase in the lopinavir/ritonavir dose to 533/133 mg BID was recommended when co-administered with nevirapine or efavirenz based on a cross-study comparison. A similar interaction was observed during co-administration of lopinavir/ritonavir SGC with nevirapine and expected for other CYP3A-inducing antiretroviral agents such as nevirapine, efavirenz, nelfinavir, amprenavir, or fosamprenavir.

Thus, for patients taking CYP3A-inducing antiretroviral agents such as nevirapine, efavirenz, nelfinavir, amprenavir, or fosamprenavir concurrently with lopinavir/ritonavir, the current product labeling for Kaletra SGC formulation recommends increasing the lopinavir/ritonavir dose to 533/133 mg BID.

Due to the increased drug loading of the to-be-marketed tablet formulation compared to the SGC, a dose of 533/133 mg is not possible with the tablet formulation. Therefore, drug interaction study between efavirenz and Kaletra tablet formulation 600/150 mg (3 tablets) was assessed in this study.

When the to-be-marketed tablet formulation at a dose of [redacted] mg BID was co-administered with efavirenz, lopinavir Cmax, AUC_{12h} and Cmin values were 36%, 36% and 32% higher, respectively, than after a 400/100 mg BID regimen administered as the to-be-marketed tablet alone. The central values for ritonavir Cmax, AUC_{12h} and Cmin were 92%, 78% and 56% higher, respectively, than the corresponding values for a 400/100 mg BID regimen administered alone. A single blood sample to monitor efavirenz concentrations was collected 9 hours after dosing on Study Day 16. The mean ± SD efavirenz concentration in the 23 subjects who participated in Part 2 of Study M03-580 was 10.57 ± 5.31 µM and is within the steady state Cmax (12.9 ± 3.7 µM) and Cmin (5.6 ± 3.2 µM) reported in the efavirenz product label. Efavirenz concentrations measured in this study suggest that the higher lopinavir and ritonavir exposures observed in Study M03-580 are not likely due to insufficient efavirenz levels.

Higher lopinavir exposure is likely due to the combination of increased doses of both lopinavir and ritonavir. The increased ritonavir exposure may decrease the inducing effect of efavirenz.

Based on the observation (see table below) that 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, we predict that co-administration of lopinavir/ritonavir 400/100 mg BID as 2 tablets with efavirenz would result in similar effects to those of co-administration of lopinavir/ritonavir 400/100 mg BID as 3 SGCs with efavirenz: a decrease in the lopinavir AUC and Cmin by approximately 20 and 40%, respectively. No evidence suggests the effect of efavirenz will be different for Kaletra tablet than for Kaletra SGC.

Thus a dose increase of Kaletra tablets 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).

In order to simplify the labelling, Kaletra SGC formulation recommends increasing the lopinavir/ritonavir dose to 533/133 mg BID in all patients including antiretroviral-naïve patients.

Increasing the dose of Kaletra tablets to 600/150 mg (3 tablets) BID co-administered with efavirenz significantly increased the lopinavir plasma concentrations approximately 35% and ritonavir concentrations approximately 56% to 92% compared to Kaletra tablets 400/100 mg BID without efavirenz. In order to limit the Kaletra dose increase to patients who need the higher lopinavir concentrations, Kaletra tablets 400/100 mg dose can be used twice daily in combination with these drugs with no dose adjustment in antiretroviral-naïve patients.

Historical Comparison of Lopinavir and Ritonavir Pharmacokinetics After 400/100 mg BID in Healthy Subjects Following a Moderate-Fat Meal

Formulation		Tablet	LPV SGC & RTV SGC#			Marketed Capsules		
Study Number		M03-580	M97-650	M97-741	M97-806	M01-273	M01-299	M01-341
Days of Dosing		11	6[a]	8	11	16[b]	11	11
Parameters (units)		(N=23)	(N=7)	(N=7)	(N=11)	(N=15)	(N=12)	(N=13)
Lopinavir								
T_{max}	(h)	4.4 ± 0.8	4.3 ± 1.4	4.3 ± 2.7	4.9 ± 1.0	4.8 ± 2.6	4.5 ± 1.2	5.2 ± 2.5
C_{max}	(µg/mL)	10.56 ± 1.73	9.58 ± 1.76	10.78 ± 2.67	10.28 ± 2.95	8.02 ± 2.23	10.33 ± 1.31	10.87 ± 2.74
AUC_{12}	(µg•h/mL)	90.6 ± 18.7	88.2 ± 17.78	103.2 ± 27.8	87.8 ± 30.1	73.7 ± 23.5	86.4 ± 14.1	100.3± 35.6
C_{min}	(µg/mL)	4.86 ± 1.61	5.31 ± 1.58	5.96 ± 2.35	4.66 ± 2.25	4.28 ± 2.12	4.64 ± 21.34	6.15 ± 2.88
CL/F	(L/h)	4.61 ± 1.03	4.73 ± 1.03	4.10 ± 0.99	5.27 ± 2.07	–	4.75 ± 0.83	4.32 ± 1.09
Ritonavir								
T_{max}	(h)	4.0 ± 0.0	4 ± 1	4.3 ± 2.7	4.4 ± 1.2	4.9 ± 2.5	4.2 ± 0.9	4.8 ± 2.3
C_{max}	(µg/mL)	0.94 ± 0.32	0.85 ± 0.41	0.55 ± 0.23	0.80 ± 0.33	0.81 ± 0.45	0.96 ± 0.46	1.14 ± 0.49
AUC_{12}	(µg•h/mL)	5.22 ± 1.40	5.07 ± 2.10	4.19 ± 1.43	4.2 ± 1.4	4.74 ± 2.20	4.62 ± 1.46	5.48 ± 1.37
C_{min}	(µg/mL)	0.19 ± 0.08	0.17 ± 0.07	0.14 ± 0.06	0.13 ± 0.08	0.15 ± 0.09	0.13 ± 0.05	0.17 ± 0.09
CL/F	(L/h)	20.8 ± 6.6	23.0 ± 10.2	26.1 ± 8.0	26.8 ± 10.6	–	23.2 ± 5.5	19.5 ± 5.5

a. 300 mg lopinavir and 100 mg ritonavir administered for 10 days followed by 400 mg lopinavir and 100 mg ritonavir administered for 6 days.

b. Single-dose desipramine was administered on Days 1 and 16.

Separate capsules of lopinavir (LPV) and ritonavir (RTV) were administered.

M03-616

TITLE: Comparison of the Single-Dose Bioavailability of a New Tablet Formulation of Lopinavir/Ritonavir Relative to the Currently Marketed Capsule Formulation

BACKGROUND: Results from the pilot Study M03-580, the single-dose bioavailability of the new tablet formulation from a partial scale-up lot compared to the marketed capsule formulation at doses of 400/100 mg, suggested that the new tablet was bioequivalent to the marketed capsule following administration of 400/100 mg under non-fasting conditions.

In the current study, the bioavailability of a production-scale lot of the new tablet formulation was compared to that from the marketed capsule formulation under fasting and non-fasting conditions after single doses of lopinavir/ritonavir 400/100 mg.

OBJECTIVES: The objectives of this study were to: 1. Compare the single-dose bioavailability of lopinavir/ritonavir 400/100 mg from a 200/50 mg new tablet formulation to that obtained from the currently marketed 133.3/33.3 mg capsule formulation under fasting and non-fasting (moderate-fat foods) conditions. 2. Evaluate the effects of high-fat breakfasts on the 400/100 mg dose of the new tablet formulation of lopinavir/ritonavir.

SUBJECTS AND STUDY DESIGN: This was a phase 1, single-dose, open-label, bioavailability study with a five-period, randomized design. The first four periods were conducted according to a complete-crossover design. Subjects were randomized in equal numbers to four sequences of regimens A, B, C and D for Periods 1 through 4. Five subjects from each sequence group who completed Periods 1 through 4 were randomly chosen to participate in Period 5 and received regimen E. A washout interval of at least 7 days separated the doses of the five study periods. Study drug was administered as a single dose in the morning on Study Day 1 of each period as follows:

Regimen A: Three 133.3/33.3 mg capsules (marketed) following a moderate-fat breakfast.
Regimen B: Three 133.3/33.3 mg capsules (marketed) administered under fasting conditions.
Regimen C: Two 200/50 mg tablets (new) following a moderate-fat breakfast.
Regimen D: Two 200/50 mg tablets (new) administered under fasting conditions.
Regimen E: Two 200/50 mg tablets (new) following a high-fat breakfast.

Subjects received a standardized diet for all meals during the study. On Study Day 1 of a period in which a subject received regimen A or C, a moderate-fat breakfast consisting of 500 to 600 Kcal with 20 to 30% of calories from fat, was served approximately 30 minutes prior to dosing. In Period 5 (Regimen E), on Study Day 1, a high-fat breakfast consisting of approximately 1000 Kcal with 50 to 55% of calories from fat was served approximately 30 minutes prior to dosing. Subjects in regimens B and D (fasting regimens) did not receive breakfast on Study Day 1.

Healthy adult male and female subjects (N = 64) were planned and 63 subjects were enrolled in the study. Fifty-seven subjects (42 males and 15 females) completed Periods 1 through 4. Twenty subjects of the 57 subjects who completed Periods 1 through 4 participated in Period 5 of the study.

Demographic summary for subjects who entered the study:

	Mean ± SD (N = 63)	Min – Max
Age (years)	36 ± 11	19 – 55
Weight (kg)	77 ± 10	60 – 101
Height (cm)	175 ± 9	147 – 191
Sex	46 Males (73%), 17 Females (27%)	
Race	44 White (70%), 10 Black (16%), 9 Hispanic (14%)	

INVESTIGATOR AND STUDY LOCATION: Thao Doan, MD, Abbott Clinical Pharmacology Research Unit, Waukegan, IL

FORMULATION: Katetra tablet formulation DC-C, 200/50 mg, lot number 03-502-AR, Kaletra soft gelatin capsules, 133.3/33.3 mg, lot number 07-469-2E-21

SAMPLE COLLECTION: Blood samples for lopinavir and ritonavir assay were collected prior to dosing (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 30 and 36 hours after dosing on Study Day 1 in each period.

ASSAY: Plasma concentrations of lopinavir and ritonavir were determined using a validated high performance liquid chromatography analytical method with tandem mass spectrometric detection at Abbott Laboratories, Abbott Park, IL. The lower limits of quantitation for lopinavir and ritonavir were established at 20.4 and 11.2 ng/mL, respectively, using a 0.100 mL plasma sample.

PHARMACOKINETIC DATA ANALYSIS: The pharmacokinetic parameter values of lopinavir and ritonavir were estimated using non-compartmental methods. Summary statistics of pharmacokinetic parameters such as geometric means and coefficients of variation for Cmax, Tmax and AUC were provided for each group. The geometric mean ratios with 90% confidence intervals were calculated between groups.

PHARMACOKINETIC RESULTS:

Table 1. Mean ± SD Pharmacokinetic Parameters of Lopinavir (regimens A, B, C and D)

Pharmacokinetic Parameters (units)		LPV/r 400/100 mg Single-Dose Regimens (Periods 1 through 4)			
		Regimen A Capsule Moderate-Fat (N = 59)	Regimen B Capsule Fasting (N = 60)	Regimen C Tablet Moderate-Fat (N = 59)	Regimen D Tablet Fasting (N = 62)
C_{max}	(µg/mL)	6.56 ± 1.78^{+}	5.35 ± 2.34	8.38 ± 2.15$^{*\wedge}$	7.16 ± 1.99^{+}
T_{max}	(h)	6.4 ± 2.9^{+}	4.2 ± 2.0	3.9 ± 0.8*	3.6 ± 1.4^{+}
$C_{12}^{\#}$	(µg/mL)	4.35 ± 1.80	2.46 ± 1.53	4.49 ± 1.47	3.46 ± 1.46
AUC_t	(µg•h/mL)	82.6 ± 29.3^{+}	56.4 ± 31.4	101.9 ± 33.4$^{*\wedge}$	81.6 ± 30.5^{+}
AUC_∞	(µg•h/mL)	83.1 ± 29.5^{+}	56.9 ± 31.6	102.3 ± 33.6$^{*\wedge}$	82.0 ± 30.6^{+}
$t_{½}^{\$}$	(h)	2.64 ± 0.50^{+}	2.88 ± 0.60	2.53 ± 0.47	2.63 ± 0.44^{+}
$CL/F^{\#}$	(L/h)	5.57 ± 2.50	10.81 ± 9.55	4.28 ± 1.30	5.62 ± 2.25

* Statistically significantly different from Regimen A (Mixed Effects Analysis, $p < 0.05$).

\+ Statistically significantly different from Regimen B (Mixed Effects Analysis, $p < 0.05$).

^ Statistically significantly different from Regimen D (Mixed Effects Analysis, $p < 0.05$).

$ Presented as harmonic mean ± pseudostandard deviation; evaluations based on statistical tests for β.

\# Parameter was not tested statistically.

Table 2. Mean ± SD Pharmacokinetic Parameters of Lopinavir (regimens C, D and E)

Pharmacokinetic Parameters (units)		LPV/r 400/100 mg Single-Dose Regimens		
		Regimen C Tablet moderate-fat (N = 20)	Regimen D Tablet fasting (N = 20)	Regimen E Tablet high-fat (N = 20)
C_{max}	(µg/mL)	8.34 ± 1.74	7.40 ± 2.79	7.08 ± 1.76*
T_{max}	(h)	4.0 ± 0.6	3.2 ± 0.7	5.4 ± 1.8*+
C_{12}#	(µg/mL)	4.32 ± 1.12	3.30 ± 1.57	4.60 ± 1.26
AUC_t	(µg•h/mL)	96.8 ± 21.9	79.9 ± 35.6	88.3 ± 17.9*
AUC_∞	(µg•h/mL)	97.2 ± 21.9	80.2 ± 35.6	88.8 ± 17.8*
$t_{½}$$	(h)	2.57 ± 0.47	2.57 ± 0.35	2.49 ± 0.47
CL/F#	(L/h)	4.35 ± 1.14	5.97 ± 2.64	4.68 ± 0.94

* Statistically significantly different from Regimen C (ANOVA, $p < 0.05$).

\+ Statistically significantly different from Regimen D (ANOVA, $p < 0.05$).

$ Presented as harmonic mean ± pseudostandard deviation; evaluations based on statistical tests for β.

\# Parameter was not tested statistically.

Table 3. Mean ± SD Pharmacokinetic Parameters of Ritonavir (regimens A, B, C and D)

Pharmacokinetic Parameters (units)		LPV/r 400/100 mg Single-Dose Regimens (Periods 1 through 4)			
		Regimen A Capsule moderate-fat (N = 59)	Regimen B Capsule fasting (N = 60)	Regimen C Tablet moderate-fat (N = 59)	Regimen D Tablet fasting (N = 62)
C_{max}	(µg/mL)	0.44 ± 0.25+	0.38 ± 0.26	0.58 ± 0.26*+	0.57 ± 0.28+
T_{max}	(h)	6.3 ± 2.7+	4.1 ± 1.6	4.0 ± 0.7*^	3.4 ± 1.2+
C_{12}#	(µg/mL)	0.19 ± 0.14	0.10 ± 0.08	0.15 ± 0.09	0.13 ± 0.10
AUC_t	(µg•h/mL)	3.80 ± 1.90+	2.86 ± 1.82	4.65 ± 2.16*^	4.08 ± 1.94+
AUC_∞	(µg•h/mL)	3.94 ± 1.90+	2.99 ± 1.84	4.78 ± 2.17*^	4.21 ± 1.96+
$t_{½}$$	(h)	4.61 ± 0.91	4.69 ± 1.09	4.36 ± 0.84*^	4.52 ± 0.86
CL/F#	(L/h)	31.8 ± 16.9	51.0 ± 40.6	24.3 ± 9.2	29.0 ± 14.0

* Statistically significantly different from Regimen A (Mixed Effects Analysis, $p < 0.05$).

\+ Statistically significantly different from Regimen B (Mixed Effects Analysis, $p < 0.05$).

^ Statistically significantly different from Regimen D (Mixed Effects Analysis, $p < 0.05$).

$ Presented as harmonic mean ± pseudostandard deviation; evaluations based on statistical tests for β.

\# Parameter was not tested statistically.

Table 4. Mean ± SD Pharmacokinetic Parameters of Ritonavir (regimens C, D and E)

Pharmacokinetic Parameters (units)		LPV/r 400/100 mg Single-Dose Regimens		
		Regimen C Tablet Moderate-Fat (N = 20)	Regimen D Tablet Fasting (N = 20)	Regimen E Tablet High-Fat (N = 20)
C_{max}	(µg/mL)	0.60 ± 0.27	0.57 ± 0.34	0.57 ± 0.22
T_{max}	(h)	4.0 ± 0.6	3.2 ± 0.6	5.4 ± 2.0*+
C_{12}#	(µg/mL)	0.14 ± 0.07	0.12 ± 0.08	0.20 ± 0.11
AUC_t	(µg•h/mL)	4.43 ± 1.67	3.99 ± 2.20	4.55 ± 1.53+
AUC_∞	(µg•h/mL)	4.56 ± 1.68	4.10 ± 2.23	4.68 ± 1.56+
$t_{½}$$	(h)	4.22 ± 0.72	4.40 ± 0.82	4.06 ± 0.74+
CL/F#	(L/h)	25.1 ± 10.1	31.9 ± 17.3	23.7 ± 7.8

* Statistically significantly different from Regimen C (ANOVA, $p < 0.05$).

\+ Statistically significantly different from Regimen D (ANOVA, $p < 0.05$).

$ Presented as harmonic mean ± pseudostandard deviation; evaluations based on statistical tests for β.

\# Parameter was not tested statistically.

Table 5. Lopinavir Relative Bioavailability and 90% Confidence Intervals for Bioequivalence Evaluation (regimens A, B, C and D)

Comparison	Pharmacokinetic Parameter	Central Values*		Relative Bioavailability	
		Test	Reference	Point Estimate#	90% Confidence Interval
C (tablet mod-fat) *vs.* A (capsule mod-fat)	C_{max}	8.2	6.3	1.295	1.230 – 1.362
	AUC_t	96.7	76.0	1.272	1.197 – 1.351
	AUC_∞	97.1	76.5	1.269	1.195 – 1.348
D (tablet fasting) *vs.* B (capsule fasting)	C_{max}	7.0	4.8	1.457	1.314 – 1.615
	AUC_t	76.2	46.9	1.627	1.439 – 1.839
	AUC_∞	76.5	47.4	1.616	1.431 – 1.824
C (tablet mod-fat) *vs.* D (tablet fasting)	C_{max}	8.2	7.0	1.176	1.111 – 1.244
	AUC_t	96.7	76.2	1.269	1.191 – 1.352
	AUC_∞	97.1	76.5	1.269	1.191 – 1.352
A (capsule mod-fat) *vs.* B (capsule fasting)	C_{max}	6.3	4.8	1.323	1.191 – 1.470
	AUC_t	76.0	46.9	1.623	1.429 – 1.843
	AUC_∞	76.5	47.4	1.615	1.425 – 1.831

* Antilogarithm of the least squares means for logarithms.

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

mod-fat = moderate-fat meal conditions.

Table 6. Ritonavir Relative Bioavailability and 90% Confidence Intervals for Bioequivalence Evaluation (regimens A, B, C and D)

Comparison	Pharmacokinetic Parameter	Central Values*		Relative Bioavailability	
		Test	Reference	Point Estimate#	90% Confidence Interval
C (tablet mod-fat) *vs.* A (capsule mod-fat)	C_{max}	0.5	0.4	1.396	1.286 – 1.517
	AUC_t	4.1	3.2	1.270	1.189 – 1.356
	AUC_∞	4.2	3.3	1.254	1.177 – 1.336
D (tablet fasting) *vs.* B (capsule fasting)	C_{max}	0.5	0.3	1.707	1.495 – 1.950
	AUC_t	3.5	2.2	1.579	1.402 – 1.778
	AUC_∞	3.7	2.4	1.532	1.376 – 1.706
C (tablet mod-fat) *vs.* D (tablet fasting)	C_{max}	0.5	0.5	1.049	0.943 – 1.167
	AUC_t	4.1	3.5	1.156	1.066 – 1.253
	AUC_∞	4.2	3.7	1.149	1.063 – 1.241
A (capsule mod-fat) *vs.* B (capsule fasting)	C_{max}	0.4	0.3	1.283	1.112 – 1.480
	AUC_t	3.2	2.2	1.438	1.273 – 1.624
	AUC_∞	3.3	2.4	1.403	1.256 – 1.567

* Antilogarithm of the least squares means for logarithms.

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

mod-fat = moderate-fat meal conditions.

Table 7. Relative Bioavailability and 90% Confidence Intervals for the Assessment of Food Effect on Lopinavir and Ritonavir Following Administration of New Tablets (regimens C, D and E)

Comparison	Pharmacokinetic Parameter	Central Values*		Relative Bioavailability	
		Test	Reference	Point Estimate#	90% Confidence Interval
Lopinavir					
C (moderate-fat) *vs.* D (fasting)	C_{max}	8.2	7.0	1.176	1.111 – 1.244
	AUC_t	96.7	76.2	1.269	1.191 – 1.352
	AUC_∞	97.1	76.5	1.269	1.191 – 1.352
E (high-fat) *vs.* C (moderate-fat)	C_{max}	6.9	8.2	0.844	0.780 – 0.913
	AUC_t	86.6	94.3	0.918	0.859 – 0.982
	AUC_∞	87.1	94.7	0.919	0.861 – 0.982
E (high-fat) *vs.* D (fasting)	C_{max}	6.9	7.0	0.993	0.877 – 1.124
	AUC_t	86.6	73.0	1.187	1.028 – 1.371
	AUC_∞	87.1	73.3	1.189	1.029 – 1.373
Ritonavir					
C (moderate-fat) *vs.* D (fasting)	C_{max}	0.5	0.5	1.049	0.943 – 1.167
	AUC_t	4.1	3.5	1.156	1.066 – 1.253
	AUC_∞	4.2	3.7	1.149	1.063 – 1.241
E (high-fat) *vs.* C (moderate-fat)	C_{max}	0.5	0.6	0.973	0.853 – 1.109
	AUC_t	4.3	4.1	1.042	0.977 – 1.111
	AUC_∞	4.4	4.3	1.040	0.977 – 1.107
E (high-fat) *vs.* D (fasting)	C_{max}	0.5	0.5	1.103	0.920 – 1.323
	AUC_t	4.3	3.5	1.247	1.071 – 1.453
	AUC_∞	4.4	3.6	1.239	1.068 – 1.436

* Antilogarithm of the least squares means for logarithms.

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

Table 8. Total Variabilities for Lopinavir and Ritonavir

Pharmacokinetic Parameters	Variability (%CV) LPV/r 400/100 mg Single-Dose Regimens (Periods 1 through 4) Regimen A Capsule Moderate-Fat (N = 59)	Regimen B Capsule Fasting (N = 60)	Regimen C Tablet Moderate-Fat (N = 59)	Regimen D Tablet Fasting (N = 62)
Lopinavir				
C_{max}	27	44	26	28
AUC_t	35	56	33	37
AUC_∞	35	56	33	37
Ritonavir				
C_{max}	56	67	45	49
AUC_t	50	64	46	48
AUC_∞	48	61	45	46

Pharmacokinetic Parameters	Variability (%CV) LPV/r 400/100 mg Single-Dose Regimens Regimen C Tablet Moderate-Fat (N = 20)	Regimen D Tablet Fasting (N = 20)	Regimen E Tablet High-Fat (N = 20)
Lopinavir			
C_{max}	21	38	25
AUC_t	23	45	20
AUC_∞	23	44	20
Ritonavir			
C_{max}	45	59	39
AUC_t	38	55	34
AUC_∞	37	54	33

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Figure 1 Mean (+SD) Lopinavir Plasma Concentration-Time Profiles after Single Dose Administration of Lopinavir/ritonavir 400/100 mg (regimens A, B, C and D)

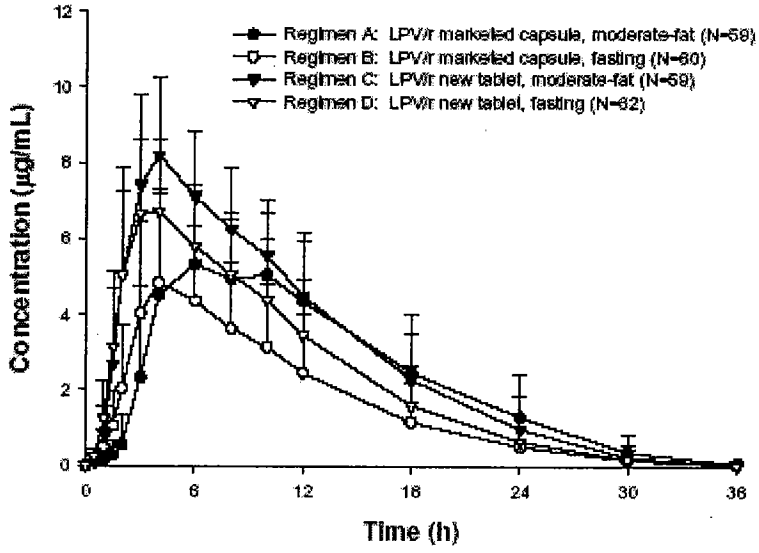


Figure 2. Mean (+SD) Lopinavir Plasma Concentration-Time Profiles after Single Dose Administration of Lopinavir/ritonavir 400/100 mg (regimens C, D and E)

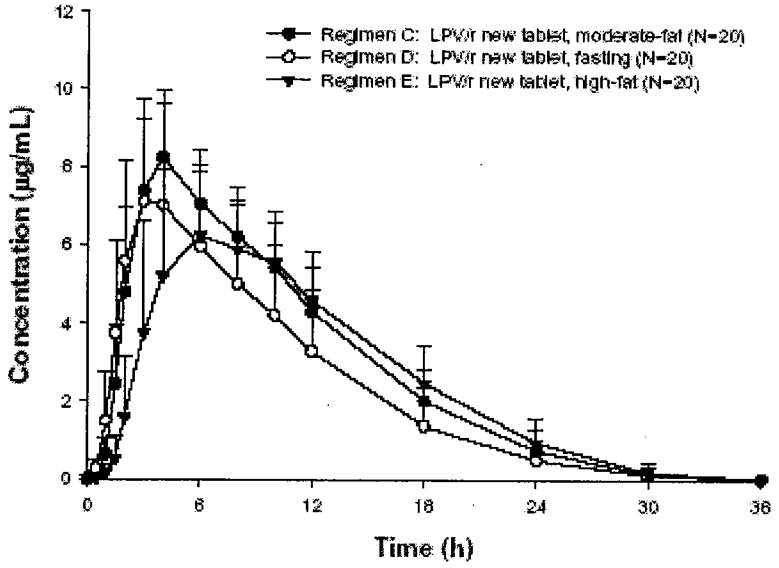


Figure 3. Mean (+SD) Ritonavir Plasma Concentration-Time Profiles after Single Dose Administration of Lopinavir/ritonavir 400/100 mg (regimens A, B, C and D)

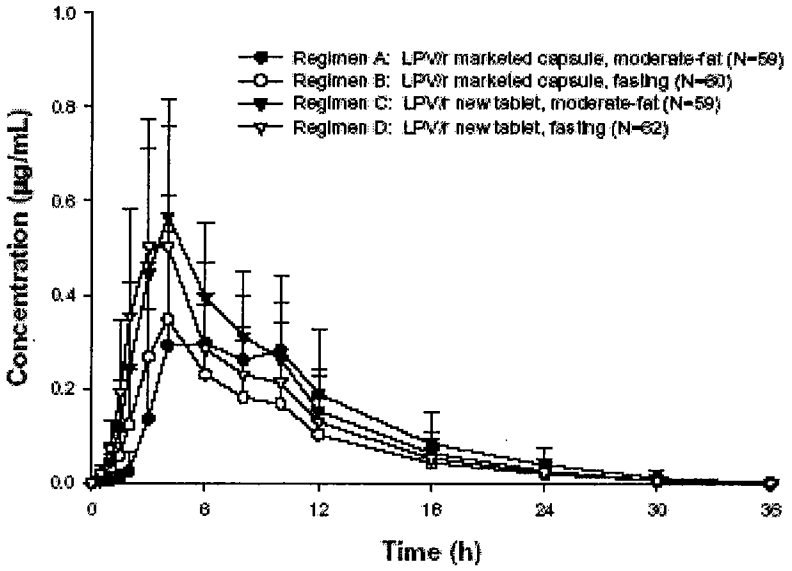
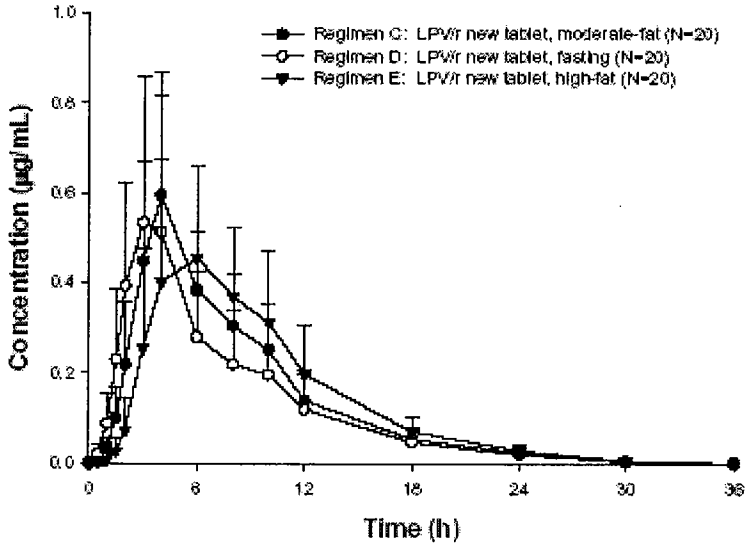


Figure 4. Mean (+SD) Ritonavir Plasma Concentration-Time Profiles after Single Dose Administration of Lopinavir/ritonavir 400/100 mg (regimens C, D and E)



SAFETY RESULTS: See Medical Officer's review.

CONCLUSIONS AND DISCUSSION: When the new tablet formulation was administered following a moderate-fat meal, lopinavir exhibited higher bioavailability relative to the currently-marketed capsules administered following the same meal. The point estimates were 27.2% to 29.5% higher and the 90% confidence intervals for the relative bioavailability of lopinavir from the new tablet formulation compared to the marketed capsules extended above 1.25 for both AUC and Cmax. Similarly, when the new tablet formulation was administered under fasting conditions, lopinavir exhibited higher bioavailability relative to the capsules administered under fasting conditions. The point estimates were 45.7% to 62.7% higher and the 90% confidence intervals were above 1.25 for both Cmax and AUC. Comparable results were observed for ritonavir.

A moderate-fat meal improved the bioavailability of lopinavir from the new tablet formulation and the marketed capsule formulation compared to administration under fasting conditions. However, the increases in lopinavir Cmax (32.3% for the capsule vs. 17.6% for the new tablet) and AUC_{∞} (61.5% for the capsule vs. 26.9% for the new tablet) following a moderate-fat meal were much more pronounced for the marketed capsule than for the new tablet formulation. Comparable results were observed for ritonavir. Administration of the new tablet formulation with a high-fat meal increased lopinavir AUC, but not Cmax, when compared to administration of the tablet formulation under fasting conditions.

The results from this study suggest that 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.

The relative bioavailability results found in Study M03-616 were different from those in Study M03-580. Results from the pilot Study M03-580 showed that following administration of the 400/100 mg dose under non-fasting conditions, the new tablet from a partial production scale lot was bioequivalent to the marketed capsule with respect to lopinavir. However, the current study demonstrated the new tablet (production-scale lot) exhibited greater bioavailability with respect to lopinavir Cmax and AUC relative to the marketed capsule. Under non-fasting conditions, lopinavir Cmax and AUC values for the new tablet were 29% and 27% higher, respectively, than those for the marketed capsules.

M04-703

TITLE: Comparison of the Single-Dose Bioavailability of Three Lots of a Tablet Formulation of Lopinavir/Ritonavir Relative to the Currently Marketed Capsule Formulation

BACKGROUND: Results from the pilot Study M03-580 showed that following administration of the 400/100 mg dose under non-fasting conditions, the new tablet from a partial production scale lot was bioequivalent to the marketed capsule with respect to lopinavir. However, Study M03-616 demonstrated the new tablet (production-scale lot) exhibited greater bioavailability with respect to lopinavir Cmax and AUC relative to the marketed capsule. Under non-fasting conditions, lopinavir Cmax and AUC values for the new tablet were 29% and 27% higher, respectively, than those for the marketed capsules.

Extensive investigation of the CMC characteristics of the partial and full production-scale lots were conducted to explore potential reasons for the somewhat different relative bioavailability results found in Study M03-580 and Study M03-616. The investigation concluded that there were no significant differences between the lots. To avoid cross-study comparison between the lots, the to-be-marketed tablet formulation pilot and production scale lots used in Study M03-580 and Study M03-616 were compared directly in Study M04-703, and each was again compared to the marketed SGC formulation.

A second lot of the to-be-marketed tablet formulation was independently manufactured at production scale and included in Study M04-703 to assess potential lot-to-lot variability in bioavailability resulting from the manufacturing processes.

OBJECTIVES: The objective of this study was to compare the single-dose bioavailability of lopinavir/ritonavir 400/100 mg from three lots of a 200/50 mg new tablet formulation, to that obtained from the currently-marketed 133.3/33.3 mg capsule formulation under non-fasting conditions.

SUBJECTS AND STUDY DESIGN: This was a phase 1, single-dose, open-label study with a four-period, randomized, complete-crossover design. Subjects were randomly assigned in equal numbers to receive one of four sequences of regimen A (new tablet formulation production scale lot 1 tested in M03-616, two 200/50 mg tablets), regimen B (new tablet formulation production scale lot 2, two 200/50 mg tablets), regimen C (new tablet formulation pilot lot, tested in M03-580, two 200/50 mg tablets) and regimen D (marketed capsule formulation, three 133.3/33.3 mg capsules) under non-fasting conditions in the morning on Study Day 1 of each period. A washout interval of 7 days separated the doses of the four study periods.

Subjects received a standardized diet for all meals during the study. On Study Day 1 of a period, a moderate-fat breakfast consisting of 500 to 600 Kcal with 20 to 30% of calories from fat was served approximately 30 minutes prior to dosing.

Demographic summary for subjects included in the of the pharmacokinetic analyses

	Mean ± SD (N=46)	Min – Max
Age (years)	33.0 ± 10.1	19 - 52
Weight (kg)	75.5 ± 9.2	55 – 90
Height (cm)	174.4 ± 9.1	149 - 191
Sex	32 Males (70%), 14 Females (30%)	
Race	37 White (80%), 7 Black (15%), 2 Hispanic (4%)	

INVESTIGATOR AND STUDY LOCATION: Thao Doan, MD, Abbott Clinical Pharmacology Research Unit, Waukegan, IL

FORMULATION: Katetra tablet formulation DC-C, 200/50 mg, lot numbers 03-502-AR, 03-503-AR and 95-096-4P, Kaletra soft gelatin capsules, 133.3/33.3 mg, lot number 05-214-2E-22

SAMPLE COLLECTION: Blood samples for lopinavir and ritonavir assay were collected prior to dosing (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 30 and 36 hours after dosing in each study period.

ASSAY: Plasma concentrations of lopinavir and ritonavir were determined using a validated high performance liquid chromatography analytical method with tandem mass spectrometric detection at Abbott Laboratories, Abbott Park, IL. The lower limits of quantitation for lopinavir and ritonavir were established at 19.7 ng/mL and 11.1 ng/mL, respectively, using a 0.1 mL plasma sample.

PHARMACOKINETIC DATA ANALYSIS: The pharmacokinetic parameter values of lopinavir and ritonavir were estimated using non-compartmental methods. Summary statistics of pharmacokinetic parameters such as geometric means and coefficients of variation for Cmax, Tmax and AUC were provided for each group. The geometric mean ratios with 90% confidence intervals were calculated between regimens.

PHARMACOKINETIC RESULTS:

Table 1. Mean ± SD Pharmacokinetic Parameters of Lopinavir

Pharmacokinetic Parameters (units)		Regimens£ A: New Tablets Production Scale Lot 1 Tested in M03-616 (N=45)	B: New Tablets Production Scale Lot 2 (N=45)	C: New Tablets Pilot Lot Tested in M03-580 (N=46)	D: Marketed Capsules (N=45)
T_{max}	(h)	5.0 ± 1.6*	5.2 ± 1.6*	5.0 ± 1.8*	6.9 ± 3.1
C_{max}	(µg/mL)	8.29 ± 2.19*#	7.94 ± 2.10*	7.65 ± 1.69*	6.92 ± 2.09
C_{12}	(µg/mL)	4.72 ± 1.41#	4.76 ± 1.59#	4.24 ± 1.40*	4.80 ± 1.97
AUC_t	(µg•h/mL)	100.4 ± 33.1*#	98.7 ± 34.2*#	90.0 ± 29.0	91.6 ± 35.4
AUC_∞	(µg•h/Ml)	101.0 ± 33.5*#	99.2 ± 34.4*#	90.5 ± 29.2	92.5 ± 37.2
$t_{½}$¢	(h)	2.61 ± 0.55	2.64 ± 0.52	2.69 ± 0.50	2.67 ± 0.62
CL/F†	(L/h)	4.42 ± 1.54	4.64 ± 2.07	4.99 ± 2.01	5.21 ± 2.87

£ All four regimens were administered as a single lopinavir/ritonavir 400/100 mg dose.

* Statistically significantly different from Regimen D (ANOVA, $p < 0.05$).

\# Statistically significantly different from Regimen C (ANOVA, $p < 0.05$).

¢ Harmonic mean ± pseudo-standard deviation; evaluations of $t_{½}$ were based on statistical tests for β.

† Parameter was not tested statistically.

Table 2. Mean ± SD Pharmacokinetic Parameters of Ritonavir

Pharmacokinetic Parameters (units)		Regimens£ A: New Tablets Production Scale Lot 1 Tested in M03-616 (N=45)	B: New Tablets Production Scale Lot 2 (N=45)	C: New Tablets Pilot Lot Tested in M03-580 (N=46)	D: Marketed Capsules (N=45)
T_{max}	(h)	4.7 ± 1.4*	5.1 ± 2.0*	4.8 ± 1.6*	6.5 ± 2.7
C_{max}	(µg/mL)	0.63 ± 0.24*#	0.60 ± 0.26*	0.56 ± 0.24*	0.51 ± 0.30
C_{12}	(µg/mL)	0.17 ± 0.09	0.18 ± 0.09#	0.15 ± 0.08*	0.21 ± 0.15
AUC_t	(µg•h/mL)	4.59 ± 1.72*#	4.64 ± 1.87*#	4.14 ± 1.64	4.23 ± 2.02
AUC_∞	(µg•h/mL)	4.72 ± 1.74*#	4.75 ± 1.89*#	4.27 ± 1.65	4.35 ± 2.03
$t_{½}$¢	(h)	4.32 ± 0.93^	4.06 ± 0.68*#	4.39 ± 0.84	4.32 ± 0.73
CL/F†	(L/h)	24.6 ± 11.1	25.6 ± 13.5	28.3 ± 14.9	29.4 ± 17.0

£ All four regimens were administered as a single lopinavir/ritonavir 400/100 mg dose.

* Statistically significantly different from Regimen D (ANOVA, $p < 0.05$).

^ Statistically significantly different from Regimen B (ANOVA, $p < 0.05$).

\# Statistically significantly different from Regimen C (ANOVA, $p < 0.05$).

¢ Harmonic mean ± pseudo-standard deviation; evaluations of $t_{½}$ were based on statistical tests for β.

† Parameter was not tested statistically.

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Table 3. Lopinavir and Ritonavir Relative Bioavailability and 90% Confidence Intervals for the Bioequivalence Assessment (regimens A, B, C and D)

Regimens Tablet *vs.* Capsule	Pharmacokinetic Parameter	Central Value*		Relative Bioavailability	
		Test	Reference	Point Estimate+	90% Confidence Interval
		Lopinavir			
A *vs.* D	C_{max}	8.1	6.6	1.227	1.158 – 1.300
	AUC_t	95.7	84.5	1.132	1.062 – 1.208
	AUC_∞	96.2	85.2	1.129	1.059 – 1.204
B *vs.* D	C_{max}	7.7	6.6	1.170	1.104 – 1.241
	AUC_t	93.2	84.5	1.102	1.034 – 1.176
	AUC_∞	93.6	85.2	1.099	1.031 – 1.172
C *vs.* D	C_{max}	7.4	6.6	1.125	1.062 – 1.191
	AUC_t	85.0	84.5	1.006	0.944 – 1.073
	AUC_∞	85.5	85.2	1.004	0.942 – 1.070
		Ritonavir			
A *vs.* D	C_{max}	0.6	0.4	1.378	1.242 – 1.530
	AUC_t	4.3	3.8	1.151	1.075 – 1.232
	AUC_∞	4.5	3.9	1.148	1.075 – 1.226
B *vs.* D	C_{max}	0.6	0.4	1.291	1.163 – 1.433
	AUC_t	4.3	3.8	1.152	1.076 – 1.234
	AUC_∞	4.4	3.9	1.147	1.074 – 1.225
C *vs.* D	C_{max}	0.5	0.4	1.157	1.044 – 1.283
	AUC_t	3.8	3.8	1.007	0.941 – 1.078
	AUC_∞	3.9	3.9	1.010	0.946 – 1.079

* Antilogarithm of the least squares means for logarithms.

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

Table 4. Lopinavir and Ritonavir Relative Bioavailability and 90% Confidence Intervals for the Bioequivalence Assessment (regimens A, B and C)

Regimens Tablet *vs.* Tablet	Pharmacokinetic Parameter	Central Value*		Relative Bioavailability	
		Test	Reference	Point Estimate+	90% Confidence Interval
		Lopinavir			
A *vs.* B	C_{max}	8.1	7.7	1.048	0.989 – 1.111
	AUC_t	95.7	93.2	1.027	0.964 – 1.095
	AUC_∞	96.2	93.6	1.027	0.964 – 1.095
A *vs.* C	C_{max}	8.1	7.4	1.091	1.030 – 1.156
	AUC_t	95.7	85.0	1.125	1.055 – 1.199
	AUC_∞	96.2	85.5	1.125	1.055 – 1.199
B *vs.* C	C_{max}	7.7	7.4	1.041	0.982 – 1.103
	AUC_t	93.2	85.0	1.095	1.028 – 1.168
	AUC_∞	93.6	85.5	1.095	1.027 – 1.167
		Ritonavir			
A *vs.* B	C_{max}	0.6	0.6	1.068	0.963 – 1.185
	AUC_t	4.3	4.3	0.998	0.933 – 1.069
	AUC_∞	4.5	4.4	1.001	0.938 – 1.069
A *vs.* C	C_{max}	0.6	0.5	1.191	1.074 – 1.321
	AUC_t	4.3	3.8	1.142	1.067 – 1.222
	AUC_∞	4.5	3.9	1.136	1.064 – 1.213
B *vs.* C	C_{max}	0.6	0.5	1.115	1.006 – 1.237
	AUC_t	4.3	3.8	1.144	1.069 – 1.224
	AUC_∞	4.4	3.9	1.135	1.063 – 1.212

* Antilogarithm of the least squares means for logarithms.

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

Table 5. Total Variability

Parameter	Variability (%CV) A: New Tablets Production Scale Lot 1 Tested in M03-616 (N=45)	B: New Tablets Production Scale Lot 2 (N=45)	C: New Tablets Pilot Lot Tested in M03-580 (N=46)	D: Marketed Capsules (N=45)
		Lopinavir		
C_{max}	26	26	22	30
AUC_t	33	35	32	39
AUC_∞	33	35	32	40
		Ritonavir		
C_{max}	38	43	43	59
AUC_t	37	40	40	48
AUC_∞	37	40	39	47

SAFETY RESULTS: See Medical Officer's review.

CONCLUSIONS AND DISCUSSION: In general, results from Study M04-703 were consistent with results from Study M03-580 and Study M03-616.

Tablets from the pilot scale lot previously tested in Study M03-580 met the bioequivalence criteria relative to the reference capsule with respect to lopinavir.

Tablets from production scale Lot 2 met the bioequivalence criteria relative to the reference capsule with respect to lopinavir. However, the point estimates for Cmax and AUC ratios (tablet vs. capsule) were 10% to 17% higher and the upper limits of 90% confidence intervals were close to 1.25.

Tablets from the production scale Lot 1 previously tested in Study M03-616 did not meet the bioequivalence criteria relative to the reference capsule with respect to lopinavir. Cmax was 23% higher. Althrough area under the concentration time curve (AUC) ratios (tablet vs. capsule) were within 80-125%, the point estimates were 13% higher and the upper limits of 90% confidence intervals were close to 1.25.

The new tablets from the two production scale lots (Regimens A and B) and the pilot scale lot (Regimen C) were bioequivalent to one another with respect to lopinavir.

Ritonavir results were comparable to lopinavir results.

In conclusion, single dose BE study results indicate that the to-be-marketed tablet formulation is about 20% more bioavailable than the currently marketed capsules under non-fasting conditions.

The new tablet formulation results in slight higher exposures compared to the capsule formulation; therefore, the tablet formulation is expected to have an efficacy profile similar to the capsule formulation. 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. For safety analyses with respect to increased LPV exposures following administration with the tablet formulation please refer to Medical Officer, Dr. Kim Struble's review for additional details.

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Derek Zhang
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Kellie Reynolds
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