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Pharmacokinetics of Lopinavir and Ritonavir After Multiple Dose Administration of Lopinavir/Ritonavir Tablet Co-administered with Efavirenz

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Introduction

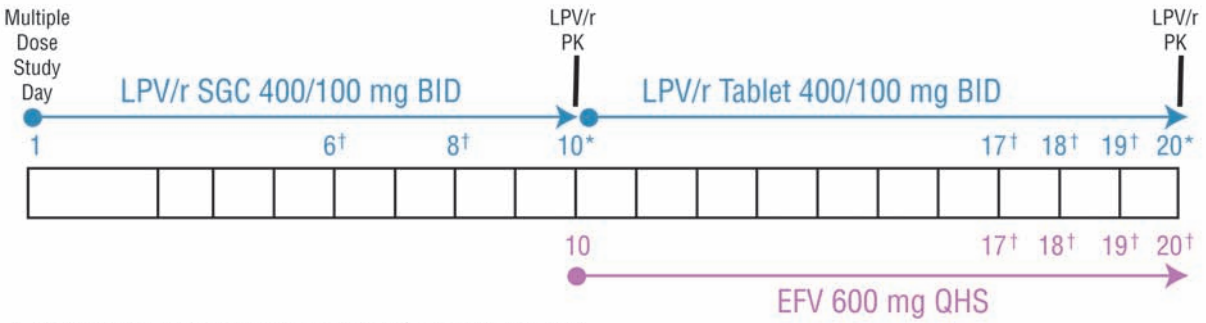
- Lopinavir/ritonavir (LPV/r) is indicated in combination with other antiretroviral agents for the treatment of HIV infection.
- A new LPV/r tablet was recently developed that reduces pill count, does not require refrigeration and may be taken without meals.[1]
- In previous studies with HIV-1 infected patients and HIV negative subjects, efavirenz (EFV) increased the clearance of lopinavir (LPV) when dosed as the soft gelatin capsule (SGC) by approximately 20% through Cytochrome P450 (CYP) 3A4 induction.[2]
- A previous study of LPV/r tablets 600/150 mg dosed twice daily (BID) with EFV produced LPV and ritonavir (RTV) concentrations that were 35% and 60–92% higher, respectively, than following LPV/r tablet 400/100 mg BID without EFV. Modeling and simulation suggested that a tablet dose of 400/100 mg BID may provide adequate LPV levels.[3]

Objective

The purpose of this study was to assess LPV concentrations following co-administration of the tablet 400/100 mg BID with 600 mg EFV every evening (QHS). These concentrations were compared to those predicted by prior simulation and those previously demonstrating efficacy.

Study Methods and Design

- Healthy subjects (N=21) were enrolled into this multiple-dose, non-fasting, open-label drug interaction study if they met the following criteria:
  - General good health, HIV negative
  - No concomitant medication
  - Body mass index (BMI) was 18 to 29 kg/m^2, inclusive
- The SGC was chosen as the reference, as it was the approved solid dosage form in Europe at the time of the study.
- The LPV/r tablet was administered following moderate-fat meals (20–30% from fat) to mirror administration of the SGC on Study Days 1 to 10.



* LPV/r 12-hour pharmacokinetic sampling on Study Days 10 and 20.
† LPV/r trough sampling on Study Days 6, 8, 17, 18 and 19; EFV sampling on Study Days 17, 18, 19 and 20.

Introduction continued

Pharmacokinetic Analysis

- Blood samples were collected for LPV and RTV assay as follows:
  - Study Days 10 and 20: prior to the morning dose (0 hour) and at 1, 2, 4, 6, 8, 10 and 12 hours after the morning dose,
  - Study Days 6, 8, 17, 18 and 19: prior to the morning dose (trough levels).
- Blood samples for EFV assay were collected in the morning on Study Days 17, 18, 19 and 20, approximately 9 hours after EFV dosing.
- Drug concentrations were measured by validated LC/MS/MS methods:
  - LPV lower limit of quantitation (LOQ) ≤ 19.42 ng/mL
  - RTV LOQ ≤ 11.15 ng/mL
  - EFV LOQ ≤ 0.100 µg/mL
- LPV and RTV PK parameters were calculated with standard non-compartmental analysis using WinNonlin® v. 5.0.1 software (Pharsight Corp., Mountain View, CA) to estimate the maximum observed concentration (C_{max}), time to C_{max} (T_{max}), plasma concentration prior to the morning dose (C_{trough}) and area under the plasma concentration time curve during a dosing interval (AUC_{12}).

Statistical Analysis

For LPV and RTV pharmacokinetics, a paired t-test was performed for T_{max} and the natural logarithms of C_{max}, C_{trough} and AUC_{12} to compare the difference between the administration of LPV/r alone on Study Day 10 and concomitant administration of LPV/r and EFV on Study Day 20. Within the paired t-test analysis framework on the logarithms of C_{max}, C_{trough} and AUC_{12}, the bioavailability for Study Day 20 relative to that for Study Day 10 was assessed.

The AUC_{12}, C_{max} and C_{trough} were also compared with those predicted by simulation and those previously observed in LPV/r clinical trials.

Safety Analysis

Safety and tolerability were assessed throughout the study based on reported adverse events, vital signs and clinical laboratory measurements.

Results

Demographics

Subjects	Healthy Adults
Sex	18 males (86%)
	3 females (14%)
Race/Ethnicity	15 white (71%)
	6 black (29%)
Age (years)*	43 ± 10 (21 – 54)
Weight (kg)*	81 ± 13 (58 – 104)
Height (cm)*	178 ± 11 (153 – 195)

* Mean ± standard deviation (range)

Pharmacokinetic Results

- Pharmacokinetic analyses were performed on 17 subjects with data available for both Study Day 10 and Study Day 20.
  - Three subjects were discontinued from the study due to adverse events; they are further described under Safety Results.
  - One subject was excluded from pharmacokinetic analyses because concentrations on Study Day 20 suggested that study drug was not ingested.
- The observed plasma concentration vs. time profiles for LPV/r SGC BID alone and tablet with EFV are shown in Figure 1 for LPV and Figure 2 for RTV.

Results continued

Figure 1. Lopinavir Concentration-Time Profiles with and without Efavirenz

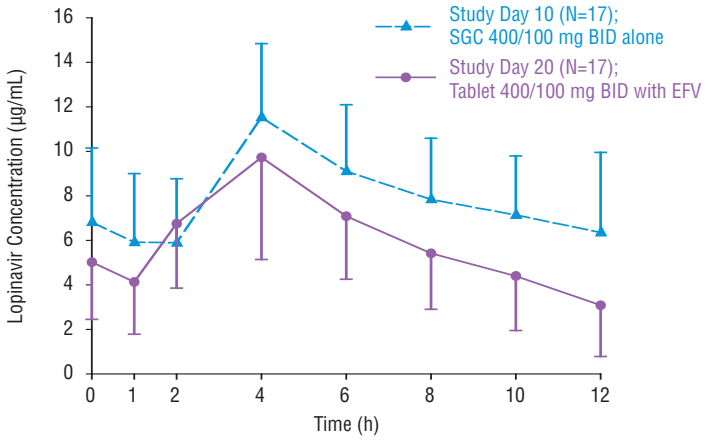
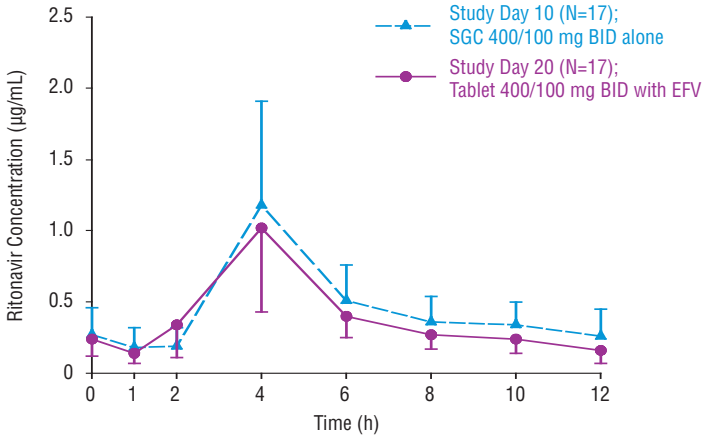


Figure 2. Ritonavir Concentration-Time Profiles with and without Efavirenz



Pharmacokinetic parameter estimates of LPV and RTV for LPV/r SGC BID without EFV and tablet with EFV are shown in Table 1.

Table 1. Pharmacokinetic Parameters of LPV and RTV

		LPV/r SGC 400/100 mg BID Alone	LPV/r Tablet 400/100 mg BID with EFV
		Study Day 10 (N=17)	Study Day 20 (N=17)
Parameter	**(Units)**	**Lopinavir**	
T_{max}	(h)	4.6 ± 2.6	3.9 ± 0.9
C_{max}	(µg/mL)	11.77 ± 3.29	10.46 ± 3.95*
C_{trough}	(µg/mL)	6.81 ± 3.34	5.04 ± 2.65*
AUC_{12}	(µg•h/mL)	95.7 ± 33.7	76.8 ± 29.8*
CL/F†	(L/h)	4.7 ± 1.6	5.9 ± 2.1
		Ritonavir	
T_{max}	(h)	4.5 ± 1.5	4.1 ± 0.5
C_{max}	(µg/mL)	1.21 ± 0.70	1.02 ± 0.58
C_{trough}	(µg/mL)	0.27 ± 0.19	0.24 ± 0.12
AUC_{12}	(µg•h/mL)	5.6 ± 2.8	4.8 ± 2.0*
CL/F†	(L/h)	22.1 ± 10.4	24.6 ± 10.4

Values in table are shown as arithmetic mean ± SD.
* Statistically significantly different from LPV/r alone (paired t-test, p<0.05).
† Parameter was not tested statistically.

Trough concentrations of LPV and RTV for LPV/r SGC BID alone and tablet with EFV are shown in Table 2.

Table 2. LPV and RTV Trough Concentrations (µg/mL)

LPV/r SGC 400/100 mg BID Alone			LPV/r Tablet 400/100 mg BID + EFV 600 mg QHS			
Day 6 (N=17)	Day 8 (N=17)	Day 10 (N=17)	Day 17 (N=17)	Day 18 (N=17)	Day 19 (N=17)	Day 20 (N=17)
Lopinavir						
6.97 ± 3.56	7.51 ± 3.53	6.81 ± 3.34	5.44 ± 3.21	5.39 ± 2.91	5.40 ± 2.98	5.04 ± 2.65
Ritonavir						
0.23 ± 0.19	0.28 ± 0.18	0.27 ± 0.19	0.23 ± 0.12	0.21 ± 0.12	0.22 ± 0.14	0.24 ± 0.12

Relative bioavailability and 90% confidence intervals for the ratios of central values for LPV and RTV are shown in Table 3.

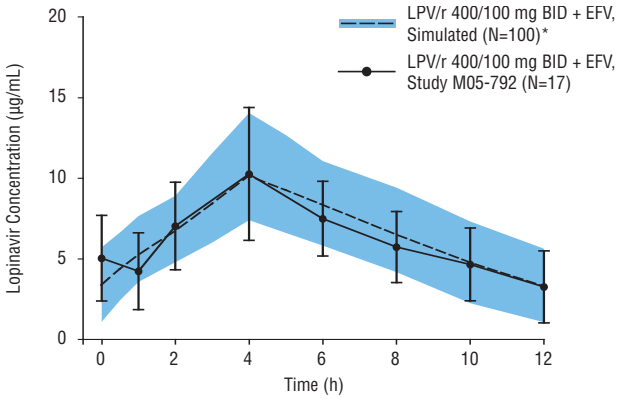
Table 3. Relative Bioavailability and 90% Confidence Intervals for the Ratios of Central Values for LPV and RTV

Test vs. Reference	PK Parameter	(Units)	Central Values* Test	Central Values* Reference	Relative Bioavailability Point Estimate**	Relative Bioavailability 90% Confidence Interval
		Lopinavir				
LPV/r tablet + EFV	C_{max}	(µg/mL)	9.83	11.31	0.869	0.809–0.933
vs.	C_{trough}	(µg/mL)	4.41	6.02	0.732	0.634–0.845
LPV/r SGC alone	AUC_{12}	(µg•h/mL)	72.13	90.65	0.796	0.753–0.841
		Ritonavir				
LPV/r tablet + EFV	C_{max}	(µg/mL)	0.88	1.03	0.856	0.726–1.010
vs.	C_{trough}	(µg/mL)	0.21	0.22	0.967	0.815–1.149
LPV/r SGC alone	AUC_{12}	(µg•h/mL)	4.40	5.05	0.872	0.794–0.958

* Geometric mean.
** Point estimate is the ratio of the geometric means (Test: Reference).

- Efavirenz plasma concentrations (mean ± SD) 9 hours after EFV administration on Study Days 17, 18, 19 and 20 were 2.82 ± 0.79, 2.62 ± 0.58, 2.97 ± 0.79 and 3.11 ± 0.83 µg/mL, respectively.
  - These concentrations are within the range of concentrations reported during a dosing interval (C_{min} to C_{max}) as detailed on the product label for 600 mg EFV QD.4
- Observed and simulated LPV concentration-time profiles following multiple-dose administration of the LPV/r tablet with EFV are shown in Figure 3.

Figure 3. Observed and Simulated Lopinavir Concentration-Time Profiles Following Multiple-Dose Administration of the LPV/r Tablet with EFV



* Shown as mean (dashed line), 5th and 95th percentile (lower and upper limit of the shaded area)

Observed and predicted LPV PK parameters following co-administration of LPV/r tablet with EFV are shown in Table 4.

Results continued

Table 4. Observed and Predicted Lopinavir Pharmacokinetic Parameters Following Co-administration of LPV/r Tablet 400/100 mg BID with EFV 600 mg QHS

PK Parameters	Simulation[3] N=100	Study M05-792 N=17
C_{max} (µg/mL)	10.50 ± 1.85	10.46 ± 3.95
AUC_{12} (µg•h/mL)	84.9 ± 17.8	76.8 ± 29.8
C_{trough} (µg/mL)	3.75 ± 1.54	5.04 ± 2.65

LPV and RTV PK after LPV/r as the SGC 400/100 mg BID administered with and without CYP3A-inducing non-nucleoside reverse transcriptase inhibitors (EFV and nevirapine, NVP) and as the tablet administered with EFV are shown in Table 5.

Table 5. Comparison of LPV Pharmacokinetics After LPV/r Tablet Administration with Efavirenz (600 mg QD) to Previously Demonstrated Efficacious Concentrations

Study	M05-792	M03-580	M97-765[5]	M98-957[6]	M98-888[7]	M97-720[8]
Regimen	400/100 mg BID + EFV	600/150 mg BID + EFV	400/100 mg BID + NVP	400/100 mg BID + EFV	400/100 mg BID + NVP	400/100 mg BID
LPV/r	Tablet	Tablet	SGC with Food	SGC with Food	SGC with Food	SGC with or without Food
Population	HIV– (N=17)	HIV– (N=23)	HIV+ Single PI-experienced (N=7)	HIV+ Multiple PI-experienced (N=24)	HIV+ Single PI-experienced (N=18)	HIV+ Treatment-naïve (N=21)
T_{max} (h)	3.9 ± 0.86	4.3 ± 0.7	5 ± 2	4.00 ± 1.87	5.4 ± 3.3	3 ± 2
C_{max} (µg/mL)	10.5 ± 3.95	14.4 ± 2.58	7.03 ± 1.96	8.15 ± 3.04	7.82 ± 3.16	9.58 ± 4.41
AUC_{12} (µg•h/mL)	76.8 ± 29.8	124 ± 26.9	61.01 ± 19.03	61.8 ± 26.4	65.43 ± 30.79	82.8 ± 44.5
C_{trough} (µg/mL)	5.04 ± 2.65	7.75 ± 2.69	2.35 ± 1.64[†]	3.66 ± 2.64	4.10 ± 3.94	5.49 ± 4.02

Safety Results

- Co-administration of LPV/r and EFV was noted to be safe and well-tolerated. There were no serious adverse events reported during the study. There were no adverse events judged by the investigator as moderate or greater in severity for LPV/r SGC without EFV. Two adverse events judged as moderate in severity (hyperhidrosis and pallor) were recorded for one subject receiving LPV/r tablet with EFV.
- The proportion of subjects reporting at least one treatment-emergent adverse event was higher with LPV/r tablet with EFV than with LPV/r SGC without EFV, a difference driven, in part, by EFV-related adverse events.
- Diarrhea was reported more frequently in subjects receiving the LPV/r SGC without EFV (67%) than in subjects receiving the LPV/r tablet formulation with EFV (19%).
- Three subjects discontinued from the study due to the occurrence of at least one adverse event (2 subjects rash, 1 subject ALT elevation). All three were receiving LPV/r with EFV at time of adverse event onset.

Conclusions

- The observed LPV and RTV concentrations from the current study confirmed the concentrations predicted by the modeling and simulation of the impact of co-administration of EFV on the pharmacokinetics of the LPV/r tablet.
  - Co-administration of EFV with the LPV/r tablet decreased LPV AUC_{12} and C_{trough} by approximately 20 and 27%, respectively, compared to the LPV/r SGC administered without EFV.
  - The reduction in LPV exposure was similar to that observed in both healthy and HIV-1 infected subjects receiving the combination of EFV and LPV/r as the SGC formulation.
- The concentrations with 400/100 mg tablet + EFV are within the range of concentrations previously demonstrated to be efficacious in clinical trials of antiretroviral-naïve and experienced subjects.[5–8]
  - The clinical implication of the modest reduction in LPV concentration should be considered in the context of the relatively high LPV concentrations typically achieved relative to the IC_{50} for wild-type virus and the patient's prior antiretroviral therapy.
- Consistent with previous studies of the LPV/r tablet formulation, diarrhea was reported more frequently in subjects receiving the LPV/r SGC without EFV (67%) than in subjects receiving the LPV/r tablet formulation with EFV (19%).

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