



# Lopinavir/ritonavir (LPV/r) 500/125 mg BID Plus Efavirenz Approximate the Pharmacokinetic Exposure of LPV/r 400/100 mg BID Administered Alone in Healthy Adult Subjects

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## Background

Co-administration of lopinavir/ritonavir (LPV/r) 200/50 mg tablets at a dose of 400/100 mg or 600/150 mg BID with efavirenz (EFV) 600 mg results in 13–20% lower or 36% higher LPV exposure, respectively, compared to LPV/r 400/100 mg BID administered without efavirenz. A new LPV/r 100/25 mg tablet has recently been approved by the FDA, making possible a dose of LPV/r 500/125 mg. This study (M10-066) compared the LPV/r pharmacokinetic parameters of 500/125 mg BID with EFV vs. 400/100 mg BID alone.

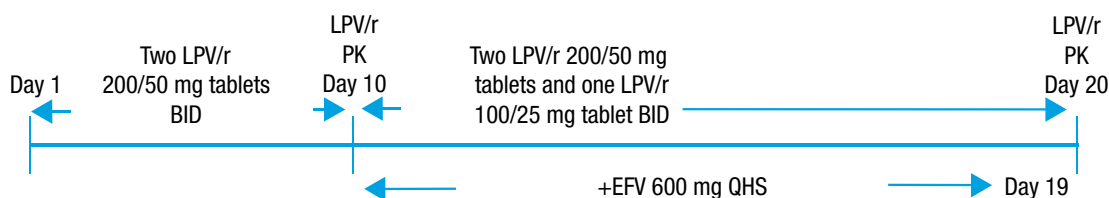
## Objective

The objective of this study was to assess the pharmacokinetics and safety profiles of LPV/r tablet 500/125 mg BID when co-administered with efavirenz dosed 600 mg every evening compared to LPV/r tablet 400/100 mg BID in healthy subjects.

## Methods

Nineteen healthy HIV negative adult subjects received LPV/r tablet 400/100 mg BID for 10 days (nonfasting) followed by LPV/r tablet 500/125 mg BID (nonfasting) + 600 mg EFV QHS (fasting) for 10 days (Figure 1). Serial blood samples were collected over the dosing interval for LPV/r concentrations on Days 10 and 20. Pharmacokinetic parameters of lopinavir and ritonavir [ $C_{max}$  (maximum observed plasma concentration),  $C_{min}$  (minimum observed plasma concentration during a dosing interval),  $C_{trough}$  (plasma concentration prior to the morning dose),  $T_{max}$  (time to maximum observed plasma concentration) and  $AUC_{12}$  (area under the plasma concentration-time curve from 0–12 hours after dosing)] were calculated using WinNonlin version 5.2 (Pharsight, Mountain View, CA). For lopinavir and ritonavir pharmacokinetics, a paired t-test was performed for  $T_{max}$ , and the natural logarithms of  $C_{max}$ ,  $C_{trough}$ ,  $C_{min}$  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 framework of paired t-test analysis on the logarithms of  $C_{max}$ ,  $C_{min}$ ,  $C_{trough}$  and  $AUC_{12}$ , the bioavailability for Study Day 20 relative to that for Study Day 10 was assessed using 90% confidence intervals. A mixed linear model was used to assess the steady state of lopinavir and ritonavir trough plasma concentrations for LPV/r alone (Study Days 7, 8, 9 and 10) and for LPV/r with EFV (Study Days 17, 18, 19 and 20). Safety and tolerability were assessed throughout the study.

Figure 1. Study M10-066 Design



### Inclusion Criteria

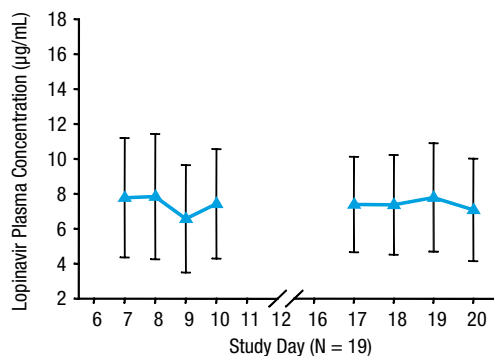
- Male or female between 18 and 55 years.
- If female, subject was either postmenopausal for at least 1 year, surgically sterile, or practicing birth control.
- Negative pregnancy test result for females.
- Screening Body Mass Index (BMI) was 19 to 29 kg/m<sup>2</sup>.
- General good health.

Lopinavir and ritonavir pharmacokinetic sampling for 12 hours following the LPV/r morning dose on Study Days 10 and 20: prior to dosing (0 hour) and at 1, 2, 4, 6, 8, 10 and 12 hours after morning dosing. Lopinavir and ritonavir trough concentration sampling on the mornings of Study Days 7, 8, 9, 10, 17, 18, 19 and 20. Efavirenz concentrations on the mornings of Study Days 17, 18, 19 and 20 (approximately 9 hours after evening dosing).

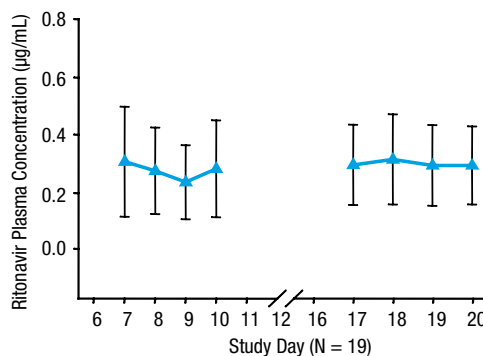
## Results

Mean (SD) trough concentrations on Study Days 7, 8, 9 and 10 (N = 19) and on Study Days 17, 18, 19 and 20 (N = 19) for lopinavir and ritonavir are shown in Figures 2a and 2b, respectively.

**Figure 2a. Mean (SD) Lopinavir Trough Concentrations**



**Figure 2b. Mean (SD) Ritonavir Trough Concentrations**



- Lopinavir levels approached steady state by Study Day 7 as the concentrations prior to the morning dose on Study Day 7 were not significantly different from those on Study Day 10 ( $p = 0.5686$  for Study Days 7 vs. 10).
- Likewise, tests of lopinavir trough concentrations on Study Days 17, 18, 19 and 20 suggest that lopinavir levels approached steady state by Study Day 17 ( $p = 0.3077$  for Study Days 17 vs. 20).
- Tests of ritonavir trough concentrations on Study Days 7, 8, 9 and 10 suggest that ritonavir levels approached steady state by Study Day 7 for LPV/r 400/100 mg BID alone ( $p = 0.4959$  for Study Day 7 vs. 10).
- Ritonavir trough concentrations on Study Days 17, 18, 19 and 20 suggest that ritonavir levels approached steady state by Study Day 17 for LPV/r 500/125 mg BID with EFV 600 mg QHS ( $p = 0.8437$  for Study Days 17 vs. 20).

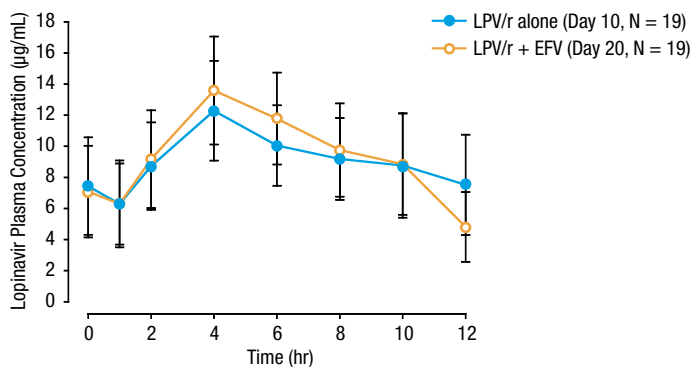
**Table 1. Mean  $\pm$  SD Pharmacokinetic Parameters of Lopinavir and Ritonavir**

Pharmacokinetic Parameters (units)	LPV/r 400/100 mg BID Alone	LPV/r 500/125 mg BID with EFV
	Study Day 10 (N = 19)	Study Day 20 (N = 19)
	Lopinavir	
$T_{max}$ (h)	4.2 $\pm$ 2.0	4.3 $\pm$ 1.2
$C_{max}$ ( $\mu$ g/mL)	12.38 $\pm$ 3.13	13.84 $\pm$ 3.25*
$C_{min}$ ( $\mu$ g/mL)	6.08 $\pm$ 2.63	5.55 $\pm$ 2.41
$C_{trough}$ ( $\mu$ g/mL)	7.43 $\pm$ 3.14	7.08 $\pm$ 2.94
$AUC_{12}$ ( $\mu$ g <hmath>\cdoth/mL)</hmath>	111.1 $\pm$ 32.2	117.4 $\pm$ 32.5
		Ritonavir
$T_{max}$ (h)	4.0 $\pm$ 0.0	4.1 $\pm$ 0.5
$C_{max}$ ( $\mu$ g/mL)	1.12 $\pm$ 0.58	1.42 $\pm$ 0.75*
$C_{min}$ ( $\mu$ g/mL)	0.18 $\pm$ 0.12	0.18 $\pm$ 0.09
$C_{trough}$ ( $\mu$ g/mL)	0.28 $\pm$ 0.17	0.29 $\pm$ 0.14
$AUC_{12}$ ( $\mu$ g <hmath>\cdoth/mL)</hmath>	6.2 $\pm$ 2.6	7.3 $\pm$ 3.1*

\* Statistically significantly different from LPV/r alone (paired t-test,  $p < 0.05$ ).

The mean (SD) plasma concentration-time profiles after administration of LPV/r 400/100 mg BID alone (Study Day 10) and LPV/r 500/125 mg BID with efavirenz (Study Day 20) for lopinavir and ritonavir are presented in Figures 3a and 3b, respectively.

**Figure 3a. Mean (SD) Lopinavir Plasma Concentration-Time Profiles**



**Figure 3b. Mean (SD) Ritonavir Plasma Concentration-Time Profiles**

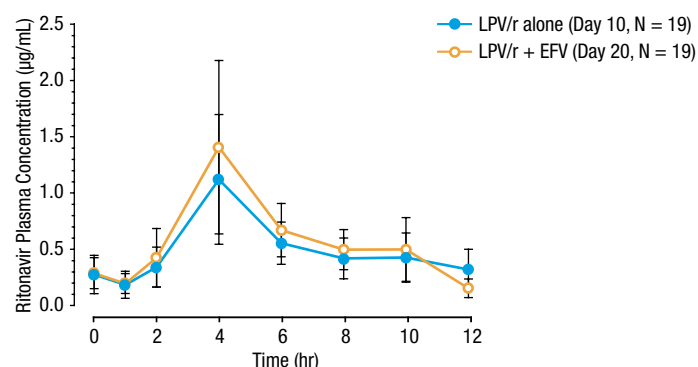


Table 2. Relative Bioavailability and 90% Confidence Intervals for the Ratios of Central Values for Lopinavir and Ritonavir

Test vs. Reference	PK Parameter	Central Values*		Relative Bioavailability	
		Test	Reference	Point Estimate <sup>#</sup>	90% Confidence Interval
<b>Lopinavir</b>					
LPV/r + EFV vs. LPV/r alone	T <sub>max</sub>	4.32	4.21	–	–
	C <sub>max</sub>	13.49	12.04	1.121	1.023 – 1.228
	AUC <sub>12</sub>	113.16	106.80	1.060	0.956 – 1.174
	C <sub>trough</sub>	6.46	6.77	0.954	0.822 – 1.108
	C <sub>min</sub>	4.97	5.52	0.902	0.784 – 1.037
<b>Ritonavir</b>					
LPV/r + EFV vs. LPV/r alone	T <sub>max</sub>	4.11	4.00	–	–
	C <sub>max</sub>	1.28	1.01	1.261	1.057 – 1.504
	AUC <sub>12</sub>	6.84	5.71	1.199	1.050 – 1.369
	C <sub>trough</sub>	0.25	0.23	1.113	0.910 – 1.361
	C <sub>min</sub>	0.16	0.15	1.103	0.924 – 1.315

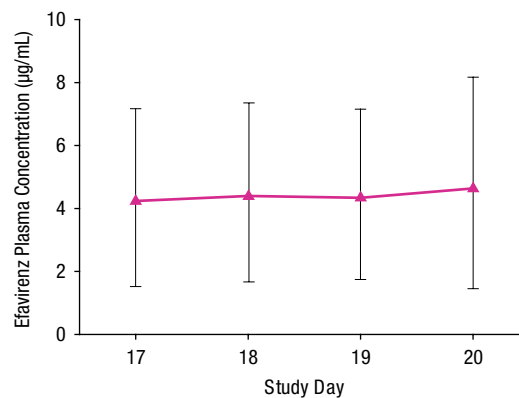
\* Arithmetic mean for T<sub>max</sub> and geometric mean for C<sub>max</sub>, AUC<sub>12</sub>, C<sub>trough</sub> and C<sub>min</sub>.

<sup>#</sup> Point estimate is the ratio of the geometric means.

- Co-administration of efavirenz with LPV/r tablet 500/125 mg BID resulted in similar lopinavir T<sub>max</sub>, C<sub>min</sub>, C<sub>trough</sub> and AUC<sub>12</sub> compared to LPV/r 400/100 mg BID alone (p ≥ 0.2163).
- Lopinavir C<sub>max</sub> after administration of efavirenz with LPV/r 500/125 mg BID was 12% higher than lopinavir C<sub>max</sub> after administration of LPV/r 400/100 mg BID (p = 0.0441). Co-administration of efavirenz with LPV/r 500/125 mg BID resulted in higher ritonavir C<sub>max</sub> and AUC<sub>12</sub> values than LPV/r 400/100 mg alone (p = 0.0355 and p = 0.0291, respectively). There were no statistically significant differences in ritonavir T<sub>max</sub>, C<sub>min</sub> or C<sub>trough</sub> between the two regimens (p ≥ 0.3306).

Mean (SD) concentrations 9 hours after dosing on Study Days 17, 18, 19 and 20 (N = 19) for efavirenz are shown in Figure 4.

Figure 4. Mean (SD) Efavirenz Plasma Concentrations



- Efavirenz concentrations on Study Days 17, 18, 19 and 20 suggest that efavirenz levels approached steady state by Study Day 17 when dosed as EFV 600 mg QHS with LPV/r 500/125 mg BID (p = 0.1398 for Study Days 17 vs. 20).

## Results continued

Comparison across studies: A summary of the point estimates and 90% confidence intervals of lopinavir/ritonavir co-administered with efavirenz relative to LPV/r 400/100 mg administered alone is presented in Table 3.

**Table 3. Cross-Study Comparison of Lopinavir Exposure – Central Values and 90% Confidence Intervals**

Pharmacokinetic Parameter	LPV/r BID + EFV QHS		
	Central Values (90% CI)		
	400/100 mg* Study M05-792 <sup>1</sup> , N = 17	500/125 mg <sup>#</sup> Study M10-066, N = 19	600/150 mg <sup>#</sup> Study M03-580 <sup>2</sup> , N = 23
C <sub>max</sub> (µg/mL)	0.869 (0.809 – 0.933)	1.121 (1.023 – 1.228)	1.356 (1.275 – 1.442)
C <sub>min</sub> (µg/mL)	0.585 (0.492 – 0.695)	0.902 (0.784 – 1.037)	1.320 (1.207 – 1.444)
C <sub>trough</sub> (µg/mL)	0.732 (0.634 – 0.845)	0.954 (0.822 – 1.108)	1.362 (1.256 – 1.477)
AUC <sub>12</sub> (µg•h/mL)	0.796 (0.753 – 0.841)	1.060 (0.956 – 1.174)	1.357 (1.284 – 1.435)

All test regimens were administered as lopinavir/ritonavir tablets.

\* Lopinavir/ritonavir 400/100 mg BID Soft Gelatin Capsule (SGC) as reference.

<sup>#</sup> Lopinavir/ritonavir 400/100 mg BID tablet as reference.

- When LPV/r 400/100 mg (two 200/50 mg tablets) was administered with efavirenz, lopinavir exposures (C<sub>max</sub>, C<sub>trough</sub>, and AUC<sub>12</sub>) were found to be 13–27% lower than when LPV/r 400/100 mg (three 133/33 mg SGCs) was administered alone. When the lopinavir/ritonavir dose was increased to 600/150 mg (three 200/50 mg tablets) and administered with efavirenz, lopinavir exposures (C<sub>max</sub>, C<sub>trough</sub>, and AUC<sub>12</sub>) were 36% higher than when LPV/r 400/100 mg BID (two 200/50 mg tablets) was administered alone. The current study confirms that the lopinavir/ritonavir dose of 500/125 mg BID (two 200/50 mg tablets + one 100/25 mg tablet) administered with efavirenz most closely approximates the pharmacokinetic exposure of LPV/r 400/100 mg BID (two 200/50 mg tablets) administered alone.

**Table 4. Summary of Treatment-Emergent Adverse Events Reported by Three or More Subjects in Any One Regimen by System Organ Class and MedDRA Preferred Term**

System Organ Class MedDRA Preferred Term	LPV/r 400/100 mg BID alone (N = 23)	LPV/r 500/125 mg BID with EFV (N = 21)
<b>Any Event</b>	16 (70%)	21 (100%)
<b>Gastrointestinal Disorders</b>		
Abdominal Pain	3 (13%)	3 (14%)
Abdominal Pain Upper	0 (0%)	5 (24%)
Diarrhea	12 (52%)	6 (29%)
Nausea	1 (4%)	5 (24%)
<b>General Disorders and Administration Site Conditions</b>		
Fatigue	1 (4%)	4 (19%)
Feeling Hot	0 (0%)	5 (24%)
<b>Nervous System Disorders</b>		
Dizziness	1 (4%)	17 (81%)
Headache	5 (22%)	5 (24%)
<b>Psychiatric Disorders</b>		
Abnormal Dreams	1 (4%)	7 (33%)
<b>Respiratory, Thoracic and Mediastinal Disorders</b>		
Dyspnea	0 (0%)	3 (14%)
<b>Vascular Disorders</b>		
Hot Flush	0 (0%)	3 (14%)

## Conclusions

- Co-administration of LPV/r tablet 500/125 mg BID with EFV closely approximates the pharmacokinetic exposure (C<sub>max</sub>, AUC<sub>12</sub>, C<sub>trough</sub> and C<sub>min</sub>) observed with the LPV/r tablet 400/100 mg BID administered alone.
- Overall, ritonavir exposures were modestly higher in subjects receiving the LPV/r 500/125 mg tablet BID with efavirenz relative to the LPV/r tablet 400/100 mg BID administered alone.
- The regimens were generally well tolerated by the subjects. Adverse events and laboratory abnormalities were consistent with those previously described in subjects receiving either lopinavir/ritonavir or efavirenz. Assessment of safety parameters did not identify any additional safety concerns when the medications were co-administered.

## References

- Klein CE, Chiu YL, Causemaker SK, et. al. Pharmacokinetics of lopinavir and ritonavir after multiple dose administration of lopinavir/ritonavir tablet co-administered with efavirenz. 8th International Congress on Drug Therapy in HIV Infection. 2006. Poster #366. Glasgow, UK
- Klein CE, Zhu T, Chiu YL, et. al. Effect of efavirenz on lopinavir/ritonavir pharmacokinetics from a new tablet formulation. 10th European AIDS Clinical Society Conference. 2005. Poster PE4.3/2. Dublin, Ireland.