Poster PE4.3/2

Effect of Efavirenz on Lopinavir/ritonavir Pharmacokinetics from a New Tablet Formulation

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Introduction

A new tablet formulation of lopinavir/ritonavir (LPV/r) was developed to decrease the daily pill count from 6 soft gelatin capsules (SGC) to 4 tablets and to eliminate the need for refrigeration.

Compared to the SGC, the tablet formulation has significantly reduced food effect as well as decreased pharmacokinetic variability.[1]

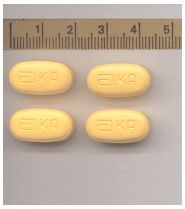
In previous studies with HIV-1 infected patients, efavirenz (EFV) increased the clearance of LPV from the SGC approximately 20% through Cytochrome P450 3A4 (CYP3A) induction.[2]

As a result of 31% lower lopinavir trough concentration (C_{trough}) values when 400/100 mg twice daily (BID) SGC was co-administered with EFV 600 mg QD, a 33% dose increase to LPV/r 533/133 mg BID is recommended when the SGC is co-administered with EFV.

Drug loading for the LPV/r 200/50 mg tablet allows for a dose of either 400/100 mg or 600/150 mg (2 or 3 tablets) BID co-administered with CYP3A-inducing antiretroviral agents, including EFV.

SGC

Tablet



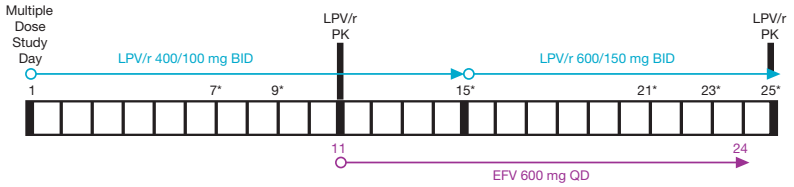
Objectives

To assess the multiple dose pharmacokinetics (PK) and tolerability of LPV/r 400/100 mg BID as the tablet when administered to healthy adults for 10 days.

To compare the PK of LPV/r 600/150 mg BID tablet + EFV to LPV/r 400/100 mg BID tablet alone.

Study Methods and Design

- Healthy subjects (N=23) were enrolled into this multiple-dose, non-fasting, open-label drug interaction study if they met the following criteria:
  - General good health
  - No concomitant medication
  - Body weight was within ± 15% of the applicable range based on height, sex and body frame
- LPV/r tablet was administered following moderate-fat meals (20-30% from fat) as the SGC is currently recommended to be taken with food.



* LPV/r trough sampling on Study Days 7, 9, 15, 21, and 23; EFV trough sampling on Study Days 21, 23 and 25.

Pharmacokinetic Analysis

- Blood samples were collected for LPV, ritonavir (RTV) and EFV assay as follows:
  - PK for LPV and RTV on Study Days 11 and 25 at pre-dose (0 hour) and at 2, 4, 6, 8, 10 and 12 hours following morning dose.
  - Trough concentrations (0 hour) for LPV and RTV on Study Days 7, 9, 11, 15, 21 and 23.
  - Trough concentrations (0 hour) for EFV on Study Days 21, 23 and 25.
- Drug concentrations were measured by validated LC/MS/MS methods:
  - LPV limits of quantitation (LOQ) ≤ 20.4 ng/mL
  - RTV LOQ ≤ 10.8 ng/mL
  - EFV LOQ = 0.10 µg/mL
- LPV and RTV PK Parameters were calculated with standard non-compartmental analysis using WINNONLIN v. 4.1 software (Pharsight Corp., Mountain View, CA) to estimate the maximum observed concentration (C_{max}), minimum observed concentration (C_{min}), C_{trough}, and area under the plasma concentration time curve during a dosing interval (AUC_{12}).

Statistical Analysis

- The bioavailability of LPV and RTV from the LPV/r 600/150 mg BID tablet + EFV relative to LPV/r 400/100 mg BID tablet alone was assessed by a two one-sided test procedure via 90% confidence intervals obtained from the analysis of the natural logarithms of C_{max}, C_{trough}, C_{min} and AUC_{12} within the framework of the ANOVA model using the SAS system v. 6.12 software (SAS Institute, Cary, NC).

Safety Analysis

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

Simulations of LPV/r 400/100 mg BID Tablet + EFV

- The bioavailability of LPV/r 400/100 mg BID tablet + EFV was predicted using Trial Simulator and compared to observed PK from the LPV/r 400/100 mg BID dose administered as the SGC in HIV-1 infected patients.
- The Trial Simulator model was adapted for the tablet from a model created for the SGC.[3] Absorption characteristics were modified as the tablet is absorbed more efficiently than the SGC.[1] Based on previous study results, co-administration with EFV was modeled as approximately a 20% increase in LPV clearance.[2]
- The tablet model was validated by comparing the predicted PK with observed PK from 400/100 mg BID tablet alone.

Results

Demographics

Subjects	Healthy Adults
Sex	22 males (96%) 1 female (4 %)
Race/Ethnicity	16 White (70%) 4 Black (17%) 3 Hispanic (13%)
Age (years)*	36.7 ± 11.5 (19 – 53)
Weight (kg)*	80.2 ± 11.9 (64 – 101)
Height (cm)*	179.4 ± 7.0 (163 – 192)

* Mean ± standard deviation (range)

Pharmacokinetics

The observed plasma concentration vs. time profiles from LPV/r 400/100 mg BID tablet alone and LPV/r 600/150 mg BID tablet + EFV are shown in Figure 1 for LPV and Figure 2 for RTV.

Figure 1. LPV Plasma Concentration, Mean (SD)

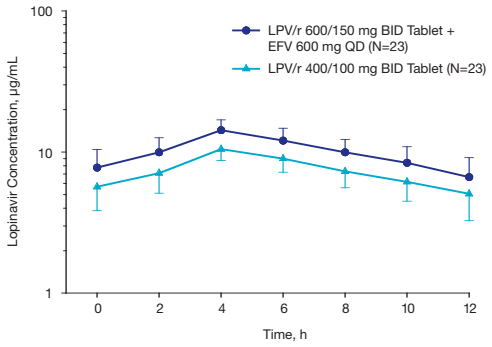
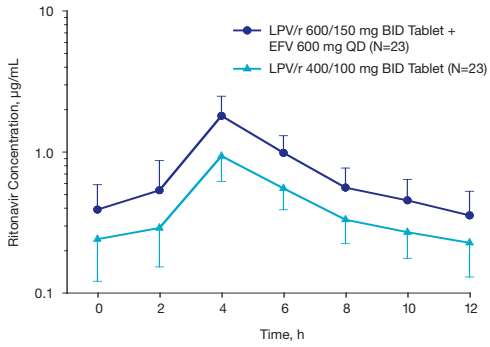


Figure 2. RTV Plasma Concentration, Mean (SD)



Pharmacokinetic parameter estimates of LPV and RTV from LPV/r 400/100 mg BID tablet and LPV/r 600/150 mg BID tablet + EFV are shown in Table 1.

Table 1. LPV and RTV Pharmacokinetics With and Without EFV

Pharmacokinetic Parameters (units)		400/100 mg BID Tablet Alone (N=23)	600/150 mg BID Tablet + Efavirenz (N=23)
Lopinavir			
C_{max}	(µg/mL)	10.56 ± 1.73	14.39 ± 2.58*
T_{max}	(h)	4.4 ± 0.8	4.3 ± 0.7
C_{min}	(µg/mL)	4.86 ± 1.61	6.55 ± 2.42*
C_{trough}	(µg/mL)	5.66 ± 1.83	7.75 ± 2.69*
AUC_{12}	(µg•h/mL)	90.6 ± 18.7	123.5 ± 26.9*
$t_{1/2}^{\#}$	(h)	6.86 ± 2.12	6.70 ± 2.21
Ritonavir			
C_{max}	(µg/mL)	0.94 ± 0.32	1.83 ± 0.64*
T_{max}	(h)	4.0 ± 0.0	4.2 ± 0.6
C_{min}	(µg/mL)	0.19 ± 0.08	0.28 ± 0.10*
C_{trough}	(µg/mL)	0.24 ± 0.12	0.39 ± 0.20*
AUC_{12}	(µg•h/mL)	5.22 ± 1.40	9.41 ± 2.87*
$t_{1/2}^{\#}$	(h)	3.77 ± 0.88	3.28 ± 0.73

* Statistically significantly different from reference (400/100 mg BID tablet, paired t-test, $p<0.05$).

Harmonic mean ± pseudo standard deviation; parameter was not tested statistically.

A comparison of exposures to LPV and RTV following 400/100 mg BID tablet alone and 600/150 mg BID tablet + EFV is shown in Table 2.

Table 2. LPV and RTV Relative Bioavailability With and Without EFV

Test vs. Reference	Pharmacokinetic Parameter	Central Values[&] Test	Central Values[&] Reference	Relative Bioavailability Point Estimate[#]	Relative Bioavailability 90% Confidence Interval
		Lopinavir			
600/150 mg BID Tablet + EFV vs. 400/100 mg BID Tablet Alone	C_{max} (µg/mL)	14.1	10.4	1.356	1.275 – 1.442
	C_{min} (µg/mL)	6.1	4.6	1.320	1.207 – 1.444
	C_{trough} (µg/mL)	7.3	5.4	1.362	1.256 – 1.477
	AUC_{12} (µg•h/mL)	120.4	88.7	1.357	1.284 – 1.435
		Ritonavir			
600/150 mg BID Tablet + EFV vs. 400/100 mg BID Tablet Alone	C_{max} (µg/mL)	1.7	0.9	1.921	1.678 – 2.199
	C_{min} (µg/mL)	0.3	0.2	1.564	1.405 – 1.742
	C_{trough} (µg/mL)	0.3	0.2	1.604	1.399 – 1.840
	AUC_{12} (µg•h/mL)	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.

When comparing the pharmacokinetics of LPV/r 600/150 mg BID tablet + EFV to LPV/r 400/100 mg BID tablet alone:

- LPV C_{max} and AUC_{12} were increased by 36%
- RTV C_{max} and AUC_{12} were increased 92% and 78%

Simulation of the LPV/r 400/100 mg BID tablet + EFV regimen suggests that LPV concentrations may be similar to those observed with the LPV/r 400/100 mg BID SGC without EFV in HIV-1 infected patients, Table 3.

Table 3. Simulation of LPV/r 400/100 mg Tablet BID + EFV

Formulation	Tablet	SGC		
Dose Regimen	LPV/r 400/100 mg	LPV/r 400/100 mg BID Alone Observed	LPV + RTV 400/100 mg BID + EFV mg QD Simulation	Alone Observed in HIV-1 Infected Patients[4]
Parameters (units)		(N=23)		(N=21)
C_{max}	(µg/mL)	10.56 ± 1.73	10.50 ± 1.85	9.58 ± 4.41
C_{trough}	(µg/mL)	5.66 ± 1.83	3.75 ± 1.54	5.49 ± 4.02
AUC_{12}	(µg•h/mL)	90.6 ± 18.7	84.9 ± 17.8	82.8 ± 44.5

Data expressed as mean ± SD.

A cross-study comparison of the multiple dose PK of LPV/r 400/100 mg BID tablet to two studies with the SGC is shown in Table 4.

Table 4. A Cross-study Comparison of Multiple Dosing of the LPV/r 400/100 mg BID Tablet and SGC in Healthy Adults

Formulation	Tablet	SGC		
Days of Dosing	11	11	11	
Parameters (units)		(N=23)	(N=12)	(N=13)
		Lopinavir		
C_{max}	(µg/mL)	10.56 ± 1.73	10.33 ± 1.31	10.87 ± 2.74
T_{max}	(h)	4.4 ± 0.8	4.5 ± 1.2	5.2 ± 2.5
C_{min}	(µg/mL)	4.86 ± 1.61	4.64 ± 1.34	6.15 ± 2.88
C_{trough}	(µg/mL)	5.66 ± 1.83	5.97 ± 1.86	7.66 ± 3.22
AUC_{12}	(µg•h/mL)	90.6 ± 18.7	86.4 ± 14.1	100.3 ± 35.6
$t_{1/2}$	(h)	6.86 ± 2.12	7.43 ± 2.35	9.27 ± 4.01
		Ritonavir		
C_{max}	(µg/mL)	0.94 ± 0.32	0.96 ± 0.46	1.14 ± 0.49
T_{max}	(h)	4.0 ± 0.0	4.2 ± 0.9	4.8 ± 2.3
C_{min}	(µg/mL)	0.19 ± 0.08	0.13 ± 0.05	0.17 ± 0.09
C_{trough}	(µg/mL)	0.24 ± 0.12	0.21 ± 0.10	0.28 ± 0.15
AUC_{12}	(µg•h/mL)	5.22 ± 1.40	4.62 ± 1.46	5.48 ± 1.37
$t_{1/2}$	(h)	3.77 ± 0.88	3.23 ± 0.74	3.62 ± 0.99

Adverse Events (AEs)

The most common AEs reported by 2 or more subjects by treatment group are listed in Table 5.

- All AEs were mild in severity
- More subjects reported central nervous system (CNS) AEs for LPV/r + EFV (74%) than LPV/r alone (0%). No notable increase in gastrointestinal AEs was seen for LPV/r + EFV compared to LPV/r alone.
- The rate of any grade of diarrhea with LPV/r tablets alone (17%) was less than half that seen in previous Phase 1 studies with LPV/r administered as multiple doses of the SGC alone (36–69%), Table 6.

Table 5. Adverse Events Reported by Two or More Subjects in any Treatment Group*

Adverse Event	LPV/r 400/100 mg BID Tablet (N=23)	LPV/r 600/150 mg BID Tablet + EFV (N=23)
Abdominal Pain	3 (13%)	0
Accidental Injury	2 (8.7%)	1 (4.3%)
Asthenia	0	3 (13%)
Headache	3 (13%)	3 (13%)
Pain	0	2 (8.7%)
Diarrhea	4 (17.4%)	5 (21.7%)
Eructation	2 (8.7%)	0
Flatulence	1 (4.3%)	2 (8.7%)
Nausea	2 (8.7%)	2 (8.7%)
Abnormal Dreams	0	4 (17.4%)
Ataxia	0	6 (26.1%)
Dizziness	0	12 (52.2%)
Hallucinations	0	4 (17.4%)
Hyperesthesia	0	2 (8.7%)
Pharyngitis	1 (4.3%)	5 (21.7%)
Rhinitis	2 (8.7%)	0
Rash	0	2 (8.7%)
Any AE	13 (56.5%)	20 (87%)

* All AEs were mild.

Table 6. Cross-study Comparison of Gastrointestinal Adverse Events in Healthy Adults After Multiple Doses of LPV/r

	Tablet	SGC		
Adverse Event	400/100 mg BID N=23	400/100 mg BID N=16	400/100 mg BID N=14	400/100 mg BID N=14
Abdominal Pain	3 (13%)	4 (25%)	2 (14.3%)	3 (21.4%)
Diarrhea	4 (17.4%)	11 (68.8%)	6 (42.9%)	5 (35.7%)
Eructation	2 (8.7%)	4 (25%)	0	0
Flatulence	1 (4.3%)	3 (18.8%)	1 (7.1)	2 (14.3%)
Nausea	2 (8.7%)	5 (31.3%)	3 (21.4%)	2 (14.3%)

Conclusions

In a cross-study comparison, 2 LPV/r tablets (400/100 mg) BID alone produced a similar pharmacokinetic profile as 3 SGCs (400/100 mg) BID alone with fewer gastrointestinal adverse events during multiple dosing in healthy adults.

3 LPV/r tablets (600/150mg) BID + EFV produces LPV and RTV AUCs that are 36 and 78% higher than those observed with the 400/100 mg BID tablet regimen alone.

- Despite this increase in exposure, the regimen was generally well-tolerated with no increase in gastrointestinal AEs compared to the 400/100 mg BID tablet alone.

2 LPV/r tablets (400/100mg) BID + EFV may result in LPV and RTV levels comparable to those observed with LPV/r 400/100mg BID administered as the SGC without CYP3A-inducing antiretroviral agents.

- Simulation of a LPV/r 400/100mg BID tablet + EFV regimen predicts 10% and 2% higher LPV C_{max} and AUC_{12} compared to LPV/r 400/100 mg BID administered as the SGC without CYP3A-inducing antiretroviral agents.
- The slight increase in LPV/r bioavailability with the tablet may compensate for the inductive effect of EFV.

Acknowledgements

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