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Effect of Amprenavir on the Steady-State Pharmacokinetics of Lopinavir/ritonavir in HIV+ and Healthy Subjects

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ABSTRACT

Background: Lopinavir/ritonavir (LPV/r) and amprenavir (APV) may be coadministered in a dual HIV protease inhibitor (PI) regimen. Low-dose ritonavir (RTV) substantially enhances APV. LPV/r and APV inhibit CYP3A and induce metabolism.

Methods: In the LPV/r Early Access Program (EAP), a single steady-state pre-dose LPV concentration (C_{trough}) was measured in 47 HIV+ subjects on anti-HIV therapy including LPV/r 400/100 mg BID (or 533/133 mg BID + efavirenz or nevirapine) and either indinavir (IDV, n=16), saquinavir (SQV, n=6), APV (n=21) or no second PI (n=4). ANOVA was performed on LPV C_{trough}. In a second study, healthy subjects (n=12) received LPV/r 400/100 mg BID on Days 1-21, APV 750 mg BID on Days 12-21; APV was continued at 1200 mg BID alone on Days 22-35. Plasma samples were collected over 12h on Days 11, 21 and 35. Noncompartmental PK methods were used. Effect of coadministration was assessed by paired t-test.

Results: APV with LPV/r in HIV+ subjects resulted in lower LPV C_{trough} *vs.* LPV/r with either SQV or IDV. The mean LPV C_{trough} when coadministered with APV was 2.9 ± 1.5 µg/mL *vs.* 5.4 ± 3.3 µg/mL when given with other PIs ($p<0.05$ for APV *vs.* IDV or SQV). In a healthy subject study, LPV C_{max}, AUC and C_{min} were lower during APV. Ratio of geometric means (90% CI) for LPV AUC was 0.62 (0.56, 0.70) and for C_{min} was 0.43 (0.34, 0.56). Mean LPV C_{trough} was 6.0 ± 1.9 µg/mL (median C_{trough}/protein-binding-adjusted IC_{50} for *wt*-HIV or IQ=88) when used alone and 3.0 ± 1.4 µg/mL (median IQ=45) with APV 750 mg BID. RTV was similarly lower. Conversely, mean APV C_{trough} with LPV/r was 1.4 ± 0.5 µg/mL *vs.* 0.24 ± 0.10 µg/mL with APV 1200 mg BID alone.

Conclusions: LPV concentrations were lower during APV in HIV+ subjects participating in the LPV/r EAP. This finding was confirmed in a controlled, healthy subject study. Higher doses of LPV/r combined with APV are being explored.

INTRODUCTION

- Kaletra® (lopinavir/ritonavir or LPV/r) and Agenerase® (amprenavir or APV) are HIV-protease inhibitors (PIs) approved worldwide for treatment of HIV in combination with other antiretroviral agents.
- Adult clinical dose of LPV/r is 400/100 mg BID; APV dose is 1200 mg BID.
- At clinical concentrations, LPV/r and APV inhibit CYP3A-mediated metabolism and are also metabolic inducers.
- Ritonavir (RTV) substantially enhances APV concentrations.

OBJECTIVE

- To assess the steady-state pharmacokinetic interaction between APV and LPV/r
  - in a subgroup of HIV+ subjects participating in the LPV/r Early Access Program (EAP).
  - in a well-controlled study in healthy subjects, confirming results from LPV/r EAP.

STUDY DESIGN

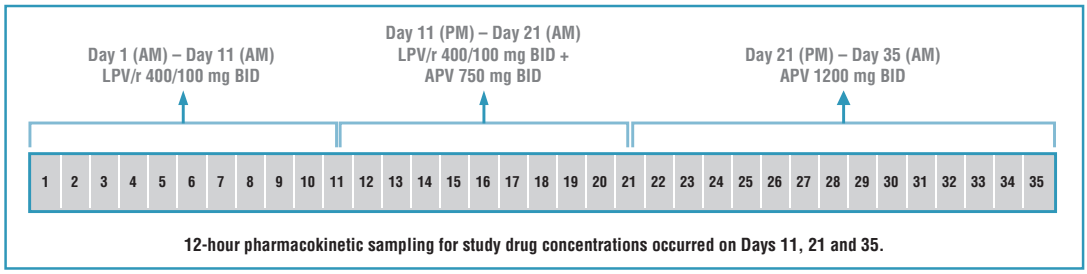
Study 1

- A total of 47 HIV+ subjects in the LPV/r EAP participated in an optional pharmacokinetic substudy and had usable plasma samples.
- Subjects received LPV/r 400/100 mg BID or 533/133 mg BID + a non-nucleoside reverse transcriptase inhibitor (NNRTI: efavirenz or nevirapine) and one of the following additional protease inhibitors (PI) at a range of BID dosing regimens:
  - indinavir (IDV, n=16)
  - saquinavir (SQV, n=6)
  - APV (n=22)
  - no additional PI (n=4)
- APV dose range: 600-1200 mg BID
- Subjects were to have received LPV/r and accompanying antiretroviral agents without interruption or regimen change for a minimum of 14 days prior to pharmacokinetic pre-dose (trough) sampling; all PIs were to be taken with food.

Study 2

- Multiple-dose, open-label, single-center, non-fasting sequential study.
- Healthy male and female subjects (N=14) were enrolled.
- Subjects received a standardized diet consisting of approximately 30% calories from fat.
- 11 subjects completed; 2 subjects discontinued on Days 20 and 21 due to rash and 1 subject discontinued on Day 10 due to a positive drug screen.

STUDY DESIGN



12-hour pharmacokinetic sampling for study drug concentrations occurred on Days 11, 21 and 35.

METHODS

Study 1

- Plasma samples were obtained as trough concentrations drawn approximately 12 hours after the previous evening dose of LPV/r.
- APV, LPV and RTV concentrations were measured by LC/MS/MS.
  - APV limit of quantitation (LOQ) = 1.0 ng/mL
  - LPV LOQ = 5.0 ng/mL
  - RTV LOQ = 1.0 ng/mL
- ANOVA was performed on LPV C_{trough} with classification by additional PI and NNRTI use.
- Point estimates and tests of population central values for the levels of additional PI and NNRTI use were obtained within the framework of the ANOVA model.
- The covariates age, weight and gender were not statistically significant at the 0.05 level, thus were not included in the model.

Study 2

- Within a dosing interval, plasma samples were collected pre-dose and at 1, 2, 3, 4, 6, 8, 10 and 12 hours post-dose on Study Days 11, 21 and 35.
- APV, LPV and RTV concentrations measured by LC/MS/MS.
  - APV LOQ = 5.0 ng/mL
  - LPV LOQ = 25.6 ng/mL
  - RTV LOQ = 5.0 ng/mL
- Noncompartmental methods were used to calculate pharmacokinetic parameters.
- Effect of APV on LPV/r and effect of LPV/r on APV (APV was not dose-normalized) were assessed using a paired t-test on the log-transformed pharmacokinetic data.
- Point estimates and 90% confidence intervals (CI) for the bioavailability of the combination regimen relative to APV or LPV/r alone were obtained for log-transformed C_{max}, C_{min}, C_{trough} and AUC.

Demographics

Subjects	Study 1 HIV+		Study 2 Healthy
N	47*	22**	12***
Age (yrs)	43 (31 – 61)	45 (34 – 61)	39 (22 - 55)
Weight (kg)	76 (42 – 104)	76 (62 – 95)	82 (58 - 104)
Height (cm)	176 (158 – 191)	176 (160 – 191)	177 (155 - 201)
Gender	41 Male, 6 Female	20 Male, 2 Female	8 Male, 4 Female
Race	29 Caucasian, 8 Hispanic, 9 Black, 1 Asian/Pacific Islander	14 Caucasian, 4 Hispanic, 3 Black, 1 Asian/Pacific Islander	8 Caucasian, 4 Black

* All subjects included in EAP PK substudy analysis.
** Data from 22 subjects were used in the evaluation of APV and 21 subjects in the evaluation of LPV/r.
*** Data from 12 subjects were used in the evaluation of LPV/r and 11 subjects in the evaluation of APV.
Age, weight and height presented as mean (range).

RESULTS

Study 1, EAP PK Substudy

Addition of APV to LPV/r resulted in

- Lower trough levels of LPV
  - Mean LPV trough plasma concentrations were 5.2 µg/mL (n=26) in the absence of APV (IDV, SQV or no additional PI) and 2.9 µg/mL (n=21) in combination with APV, representing a 44% lower trough concentration.
  - Median LPV inhibitory quotient assuming *wt*-HIV (IQ=C_{trough}/protein binding-adjusted IC_{50} *wt*-HIV of 0.07 µg/mL)* was 71 for regimens without APV *vs.* 44 with APV.
  - P-values for comparison of LPV/r trough plasma concentrations in the presence of IDV (n=16) or SQV (n=6) *vs.* those in the presence of APV were 0.023 and 0.005, respectively.
- Higher trough levels of APV
  - Mean APV trough plasma concentrations were 1.7 µg/mL, 5-fold higher than the reported trough of 0.32 µg/mL after APV 1200 mg BID in Agenerase® labelling.
  - Median APV IQ assuming *wt*-HIV (IQ = C_{trough}/protein binding-adjusted IC_{50} *wt*-HIV of 0.28 µg/mL)* was 5.6 when combined with LPV/r.
  - Considering sample size limitations, APV trough concentrations:
    - Appeared not to differ whether or not an inducing NNRTI was coadministered [mean APV 1.7 µg/mL without EFV/NVP (n=14) *vs.* 1.6 µg/mL with EFV/NVP (n=8), p=0.55]
    - Do not appear easily distinguishable within the dosing range of 600 to 1200 mg BID

      Mean APV C_{trough}:
      – 1.7 µg/mL for APV 600 mg BID (n=5)
      – 1.4 µg/mL for APV 750 mg BID (n=10)
      – 1.8 µg/mL for APV 1200 mg BID (n=5)

*Molla A, et al. *Virology* 1998;250:255-262.

RESULTS

Table 1. Lopinavir Mean ± SD PK Estimates

	EAP Study LPV/r + APV HIV+ Subjects (N=21)	LPV/r 400/100 mg BID Alone Healthy Subjects (N=12)	LPV/r 400/100 mg BID + APV 750 mg BID Healthy Subjects (N=12)
C_{max} (µg/mL)	ND	10.33 ± 1.31	7.53 ± 1.79*
T_{max} (h)	ND	4.5 ± 1.2	4.3 ± 0.9
C_{min} (µg/mL)	ND	4.64 ± 1.34	2.09 ± 0.85*
C_{trough} (µg/mL)	2.86 ± 1.55	5.97 ± 1.86	3.03 ± 1.04*
IQ (C_{trough} / IC_{50})#&	44 (2.1 – 77)	88 (32 – 126)	45 (20 – 75)
AUC_{12} (µg•h/mL)	ND	86.4 ± 14.1	54.5 ± 12.4*
$t_{1/2}$ (h)^	ND	7.43 ± 2.35	5.71 ± 1.63*
CL/F (L/h)&	ND	4.75 ± 0.83	7.69 ± 1.72

* Statistically significantly different from LPV/r alone (paired t-test, $p<0.05$).
\# IQ (inhibitory quotient) is based on LPV C_{trough}/protein binding-adjusted *wt*-HIV IC_{50}=0.07 µg/mL; presented as median (range).
^ Presented as harmonic mean and pseudostandard deviation; statistical tests based on β; calculated from C_{max} to C_{12}.
& Parameter not tested statistically.
ND = Not determined.

Figure 1. Lopinavir Individual C_{trough} Values Relative to Protein-Binding Adjusted IC_{50} in HIV+ and Healthy Subjects

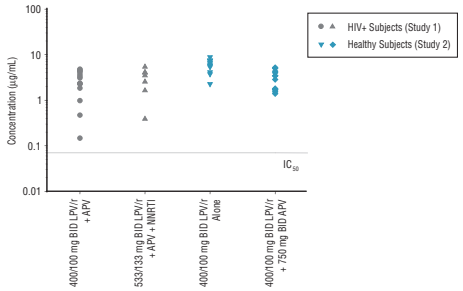


Figure 2. Lopinavir Mean (SD) Concentration-Time Profiles in Healthy Subjects

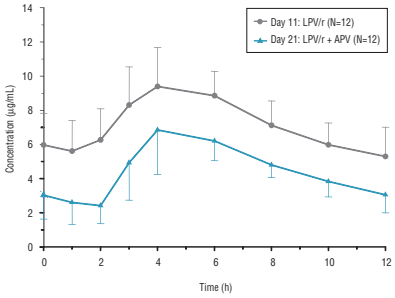


Table 2. Bioavailability of Lopinavir During APV Coadministration Relative to LPV/r Alone in Healthy Subjects

Test *vs.* Reference (N=12)	Parameter	Central Values* Test	Central Values* Reference	Relative Bioavailability Point Estimate†	Relative Bioavailability 90% CI
Study Day 21 *vs.* Study Day 11	C_{max}	7.363	10.252	0.718	0.650 – 0.793
	C_{min}	1.908	4.408	0.433	0.338 – 0.555
	C_{trough}	2.726	5.636	0.484	0.409 – 0.572
	AUC_{12}	53.233	85.333	0.624	0.557 – 0.699

* Antilogarithm of the least squares means for logarithms.
† Antilogarithm of the mean of the paired differences for logarithms.

Figure 3. Ritonavir Mean (SD) Concentration-Time Profiles in Healthy Subjects

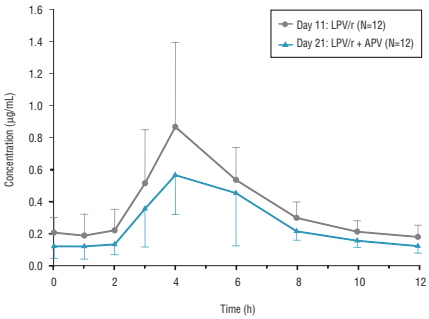
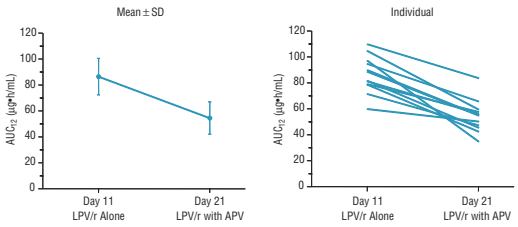


Figure 4. Lopinavir Mean ± SD and Individual AUC_{12} Values in Healthy Subjects



RESULTS

Figure 5. Lopinavir Mean ± SD and Individual C_{min} Values in Healthy Subjects

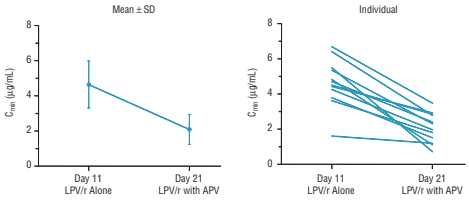


Table 3. Amprenavir Mean ± SD PK Estimates

	EAP (Study 1) LPV/r + APV BID** HIV+ Subjects (N=22)	APV 1200 mg BID Alone Healthy Subjects (N=11)	APV 750 mg BID + LPV/r 400/100 mg BID Healthy Subjects (N=11)
C_{max} (µg/mL)	ND	3.10 ± 1.24	3.37 ± 0.95
T_{max} (h)	ND	2.1 ± 0.8	2.0 ± 0.8
C_{min} (µg/mL)	ND	0.21 ± 0.06	0.96 ± 0.32*
C_{trough} (µg/mL)	1.68 ± 0.72	0.24 ± 0.10	1.38 ± 0.46*
IQ (C_{trough} / IC_{50})#&	5.6 (2.1 – 12.2)	0.8 (0.5 – 1.8)	4.9 (2.6 – 8.6)
AUC_{12} (µg•h/mL)	ND	11.3 ± 3.3	19.4 ± 5.4*
$t_{1/2}$ (h)^	ND	2.67 ± 0.38	7.67 ± 2.32*
CL/F (L/h)&	ND	114.3 ± 29.6	42.2 ± 14.6

** Amprenavir dosing regimen ranged from 600 to 1200 mg BID.
* Statistically significantly different from APV alone (paired t-test, p<0.05).
# IQ (inhibitory quotient) is based on APV C_{trough}/protein binding-adjusted *wt*-HIV IC_{50}=0.28 µg/mL; presented as median (range).
^ Presented as harmonic mean and pseudostandard deviation; statistical tests based on β; calculated from C_{max} to C_{12}.
& Parameter not tested statistically.
ND = Not determined.

Figure 6. Amprenavir Individual C_{trough} Values Relative to Protein-Binding Adjusted IC_{50} in HIV+ and Healthy Subjects

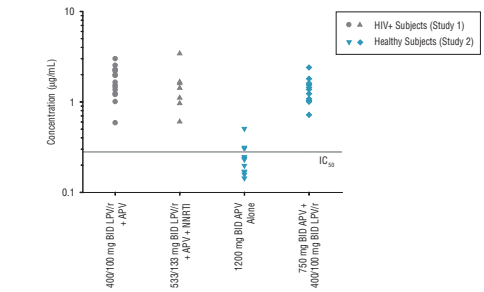


Figure 7. Amprenavir Mean (SD) Concentration-Time Profiles in Healthy Subjects

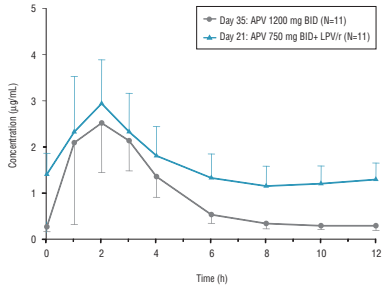


Table 4. Bioavailability of APV 750 mg BID + LPV/r Relative to APV 1200 mg BID Alone in Healthy Subjects

Test *vs.* Reference (N=11)	Parameter	Central Values* Test	Central Values* Reference	Relative Bioavailability Point Estimate†	Relative Bioavailability 90% CI
	C_{max}	3.231	2.883	1.121	0.905 – 1.388
Study Day 21	C_{min}	0.911	0.199	4.568	3.507 – 5.950
vs. Study Day 35	C_{trough}	1.318	0.226	5.821	4.698 – 7.213
	AUC_{12}	18.639	10.856	1.717	1.412 – 2.087

* Antilogarithm of the least squares means for logarithms.
† Antilogarithm of the mean of the paired differences for logarithms.

DISCUSSION AND CONCLUSIONS

- Results from a pharmacokinetic substudy in the LPV/r Early Access Program suggest:
  - LPV C_{trough} was reduced by about 44% during coadministration with APV relative to coadministration with IDV or SQV.
  - APV C_{trough} was substantially increased by about 5-fold when coadministered with LPV/r relative to historical data from the clinical dose of APV 1200 mg BID.
- Results from a well-controlled multiple-dose interaction study in healthy subjects:
  - Confirmed that LPV concentrations were reduced during APV 750 mg BID + LPV/r 400/100 mg BID; median LPV IQ was reduced from 88 to 45.
  - Demonstrated that APV C_{min} was increased by 4.6-fold during LPV/r when administered at 750 mg BID relative to APV 1200 mg BID alone; median APV IQ increased from 0.9 to 4.9.
- APV C_{trough} from APV 750 mg BID in combination with LPV/r 400/100 mg BID appears to be similar to or somewhat lower than that reported historically during APV/RTV 600/100 mg BID.
- The dose of LPV/r may need to be increased during coadministration of APV, particularly in patients with extensive protease inhibitor experience or with reduced viral susceptibility to lopinavir.