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Ritonavir Increases Plasma Amprenavir (APV) Exposure to a Similar Extent when Coadministered with either Fosamprenavir or APV

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To compare the effect of ritonavir on plasma amprenavir pharmacokinetics, healthy adults received either fosamprenavir (700 mg twice a day [BID]) or amprenavir (600 mg BID) alone and in combination with ritonavir (100 mg BID). Ritonavir increased plasma amprenavir pharmacokinetic parameters to a similar extent when coadministered with either fosamprenavir or amprenavir.

Fosamprenavir (FPV) is a human immunodeficiency virus type 1 (HIV-1) protease inhibitor approved in the United States (as Lexiva), the European Union (as Telzir), and in other countries for the treatment of HIV-1 infection in combination with other antiretroviral agents. FPV has demonstrated antiviral efficacy, durability, and tolerability in antiretroviral therapy-naïve (2, 3) and protease inhibitor-experienced subjects (R. C. Elston, P. Yates, M. Tisdale, N. Richards, S. White, and E. DeJesus, Abstr. XV Int. AIDS Conf., abstr. MoOrB1055, 2004). FPV, the phosphate ester prodrug of amprenavir (APV), is rapidly and extensively converted to APV in vivo (1, 5). FPV was developed to replace the large capsule, high pill burden, and undesirable excipient requirements associated with the previous soft-gelatin capsule formulation of APV (Agenerse).

Similar plasma APV exposures are observed for equimolar FPV-ritonavir (RTV) and APV-RTV regimens across pharmacokinetic studies (4, 6), suggesting that RTV has similar effects on plasma APV pharmacokinetics when coadministered with either FPV or APV; however, the specific drug interaction between FPV and RTV had not been tested formally. Thus, this study was designed to assess the effect of RTV on plasma APV pharmacokinetics following coadministration with FPV at 700 mg twice a day (BID) and following coadministration with APV at 600 mg BID.

In this randomized, open-label, two-period, 2 × 2 crossover study, healthy subjects received either FPV at 700 mg BID and FPV at 700 mg BID plus RTV at 100 mg BID or APV at 600 mg BID and APV at 600 mg BID plus RTV at 100 mg BID for 14 days during confinement, with a 28-day washout between treatments. On day 14, fasting plasma pharmacokinetic samples were collected at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, and 12 h after morning dosing. Samples were analyzed for APV and FPV concentrations by Advion Biosciences (Ithaca, NY) using validated high-performance liquid chromatography with tandem mass spectrometry for detection following solid-phase extraction (lower limit of quantification of 10 ng/ml for APV; bias, ≤11% [accuracy], and coefficient of variation, <8% [precision]; lower limit of quantification of 5 ng/ml for FPV; bias, ≤2% [accuracy], and coefficient of variation, ≤9% [precision]).

Pharmacokinetic analysis of plasma APV concentration-time data was conducted using the noncompartmental model 200 (for extravascular administration) of WinNonlin (version 3.1) Software (Pharsight Corporation, Mountain View, CA). Plasma APV area under the curve at steady state ($AUC_{\tau,ss}$), maximum concentration at steady state ($C_{max,ss}$), time to C_{max} ($T_{max,ss}$), and concentration at the end of the dosing interval at steady state ($C_{\tau,ss}$) were estimated. All statistical calculations were performed using SAS. Assuming an intrasubject standard deviation of 0.29 and estimated plasma APV AUC ratios for APV plus RTV-APV and FPV plus RTV-RTV of 3.34, 12 evaluable subjects for each comparison were estimated to provide 90% confidence intervals (CIs) with lower and upper limits within approximately 30% of the estimated ratio.

FPV and APV treatments were compared using analysis of variance, considering treatment, period, and α-1-acid glycoprotein concentration as fixed effects and subject as a random effect. The ratio of geometric least square (GLS) means and

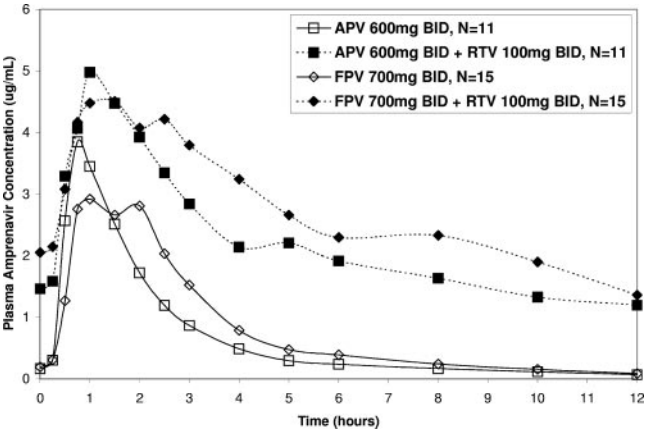

FIG. 1. Median plasma APV concentration-time profiles.

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TABLE 1. Plasma APV pharmacokinetic parameter summary

Pharmacokinetic parameter	Geometric mean (95% confidence interval)			
	APV (n = 11)	APV + RTV (n = 11)	FPV (n = 15)	FPV + RTV (n = 15)
$AUC_{\tau,ss}$ (μg · h/ml)	8.21 (6.38–10.6)	26.2 (22.3–30.9)	9.51 (7.81–11.6)	33.2 (28.0–39.5)
$C_{max,ss}$ (μg/ml)	3.66 (2.76–4.84)	4.69 (3.97–5.54)	3.19 (2.64–3.85)	4.92 (4.19–5.77)
$C_{\tau,ss}$ (μg/ml)	0.122 (0.071–0.207)	1.32 (1.11–1.57)	0.135 (0.099–0.183)	1.77 (1.48–2.13)
$T_{max,ss}$[a] (h)	0.75 (0.50–1.50)	1.00 (0.75–1.50)	1.00 (0.50–3.00)	1.50 (0.75–4.00)

[a] T_{max} data are medians (range).

associated 90% CIs for RTV-containing treatments relative to those with FPV or APV alone were estimated. To compare the effect of RTV on plasma APV pharmacokinetics following coadministration with FPV versus with APV, the GLS mean ratio for (FPV plus RTV)/FPV was compared to the GLS mean ratio for (APV plus RTV)/APV (i.e., compound ratio) using the same analysis of variance model described above. Safety and tolerability were assessed by adverse events, clinical laboratory evaluations, vital signs, and electrocardiographic assessments.

Thirty-two healthy adults gave written consent and 26 subjects (22 males and 10 females) completed the study. Ages ranged from 19 to 52 years and body weights ranged from 53.7 to 104.6 kg. Six subjects withdrew from the study prematurely (four due to adverse events and two due to personal reasons unrelated to the study). Median plasma APV concentration-time profiles are shown in Fig. 1. Plasma FPV concentrations were below the quantification limit (0.005 μg/ml) in the majority of samples and ranged from below the quantification limit to 0.029 μg/ml; thus, FPV pharmacokinetic parameters were not generated and no statistical comparisons were made for FPV. Plasma APV pharmacokinetic parameters and treatment comparisons are summarized in Tables 1 and 2. Plasma APV pharmacokinetic parameter values were similar for equimolar APV and FPV regimens and were increased to a similar extent when coadministered with RTV, as evidenced by the similar GLS mean ratios and compound ratios.

Study treatments were generally well tolerated over 14 days. All adverse events were of mild or moderate intensity and the most frequently reported adverse events included rash (44%), loose stools (38%), nausea (31%), pruritus (31%), and headache (22%). Overall, there appeared to be more adverse events reported with APV (92%), followed by APV plus RTV (87%), FPV plus RTV (69%), and FPV (60%). When stratified by body system, gastrointestinal (especially nausea), skin (especially rash), and neurologic adverse events appeared more common for APV plus RTV compared to all other treatments. Four subjects receiving APV or APV plus RTV were withdrawn from the study due to adverse events: two due to maculopapular rash, one due to pruritus, and one due to urticaria. All four adverse events were mild in severity, were considered drug related, and resolved in 11 days or less. No subjects were withdrawn from the FPV groups due to adverse events. No serious adverse events or deaths occurred during the study. No vital signs or electrocardiographic results were reported as adverse events during the study.

FPV was developed to replace the large capsule, high pill burden, and undesirable excipient requirements associated with the previous soft-gelatin capsule formulation of APV (Agenerse). FPV can replace APV based upon comparable plasma APV exposures achieved for molar equivalent FPV and APV dosage regimens (5), comparable plasma APV exposures achieved for molar equivalent FPV-RTV and APV-RTV dosage regimens (as demonstrated in this study), data supporting the hypothesis that metabolic drug interactions established for APV can be extrapolated to FPV (as demonstrated in this study), similar antiviral activity over 4 weeks of dosing with FPV or APV in antiretroviral-naïve HIV-1-infected patients (5), robust clinical trials demonstrating the safety and efficacy of FPV (2, 3), and an adverse event profile for FPV that is similar to or better than that observed with APV (2, 3, 5).

TABLE 2. Relative effect of RTV on plasma APV pharmacokinetics when coadministered with FPV or APV[a]

Pharmacokinetic parameter	Ratio of GLS means (90% confidence interval)		Compound ratio FPV + RTV/FPV: APV + RT/APV
	APV + RTV/APV (n = 11)	FPV + RTV/FPV (n = 15)	
$AUC_{\tau,ss}$ (μg · h/ml)	3.16 (2.83–3.53)	3.40 (3.09–3.75)	1.08 (0.93–1.24)
$C_{max,ss}$ (μg · h/ml)	1.27 (1.11–1.46)	1.51 (1.34–1.70)	1.19 (0.99–1.43)
$C_{\tau,ss}$ (μg/ml)	10.73 (7.82–14.73)	12.68 (9.67–16.64)	1.18 (0.78–1.79)

[a] APV was used at 600 mg BID for 14 days. APV + RTV, APV at 600 mg BID and RTV at 100 mg BID for 14 days. FPV, 700 mg BID for 14 days. FPV + RTV, FPV 700 mg BID + RTV at 100 mg BID for 14 days. Each FPV oral film-coated 700-mg tablet is the molar equivalent of 600 mg APV.

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