A 42-Week Open-Label Study to Assess the Pharmacokinetics, Antiretroviral Activity, and Safety of Amprenavir or Amprenavir plus Ritonavir in Combination with Abacavir and Lamivudine for Treatment of HIV-Infected Patients

Robin Wood,[1] Joseph Eron,[7] Keikawus Arasteh,[2] Eugenio Teofilo,[3] Christian Trepo,[4] Jean-Michel Livrozet,[5] Jane Yeo,[6] Judith Millard,[8] Mary Beth Wire,[9] and Odin J. Naderer[9]

[1]Somerset Hospital, University of Cape Town, South Africa; [2]Epimed/Auguste-Victoria-Krankenhaus, Berlin, Germany; [3]Servico de Medicina 3, Lisboa, Portugal; [4]Hôpital Hôtel Dieu, and [5]Hôpital Edoard Herriot, Lyon, France; [6]HIV Clinical Development and Medical Affairs, GlaxoSmithKline, Greenford, Middlesex, United Kingdom; [7]University of North Carolina at Chapel Hill, and [8]HIV Clinical Development and Medical Affairs and [9]Clinical Pharmacology Discovery Medicine, GlaxoSmithKline, Research Triangle Park, North Carolina

The pharmacokinetics, antiviral activity, and safety of an amprenavir-ritonavir (APV-RTV) 600/100 mg b.i.d. regimen and an APV-RTV 1200/200 mg q.d. regimen were studied in a human immunodeficiency virus (HIV)–infected population. The geometric least-square mean ratio (90% confidence interval) of steady-state trough concentrations, compared with that of the amprenavir 1200 mg b.i.d. regimen, was 6.08 (4.94–7.49) for the twice-daily APV-RTV regimen, and it was 4.19 (2.90–6.08) for the daily APV-RTV regimen. The regimens were well tolerated, which supports APV-RTV as an option for twice-daily or daily therapy for HIV.

Amprenavir (APV; Agenerase; GlaxoSmithKline) is an HIV protease inhibitor with potent antiretroviral activity [1–3] and a favorable safety [4] and cross-resistance profile [5–7] when administered as part of a combination regimen. Ritonavir (RTV; Norvir; Abbott Laboratories) is frequently coadministered with HIV protease inhibitors at subtherapeutic doses because of its pharmacokinetic-enhancing characteristics [8–11]. Previous pharmacokinetic simulations have suggested that APV-RTV dosages of 600/100 mg b.i.d. and 1200/200 mg q.d. would achieve a concentration that exceeds the IC_{50} for HIV isolates from both protease inhibitor–naive patients and patients who had received multiple protease inhibitors [12]. The primary objective of this study was to evaluate plasma pharmacokinetic parameters of APV for these 2 APV-RTV combination regimens, compared with those of an APV 1200 mg b.i.d. regimen, in HIV-infected patients.

Methods. APV20001 was an open-label study conducted in 11 centers in Europe, 8 in the United States, and 1 in South Africa. Two phases were conducted: an initial 6-week, randomized phase comparing APV and its phosphate ester prodrug GW433908 [13], followed by an open-label phase of up to 42 weeks in duration. Here, we report the data collected in the open-label phase. The primary end point was to evaluate plasma pharmacokinetic parameters of APV after repeated dosing with 2 APV-RTV combination regimens or APV at a dosage of 1200 mg b.i.d. Secondary end points were the safety and tolerability of the 2 APV-RTV dose combinations.

Patients entering the open-label phase initially received APV, 1200 mg b.i.d., with abacavir (Ziagen; GlaxoSmithKline), 300 mg b.i.d., and lamivudine (Epivir; GlaxoSmithKline), 150 mg b.i.d., prior to the randomized study. During the study, patients could either continue to receive this regimen or switch to 1 of the following 2 APV-RTV regimens, after consultation with their doctor: 600/100 mg b.i.d. or 1200/200 mg q.d. Both APV-RTV combination regimens were administered in combination with abacavir and lamivudine.

Patients were eligible if they had previously completed the 6-week randomized study. Male and nonpregnant, female HIV-1–infected patients were eligible to participate if they were 18–65 years of age and were protease inhibitor–naive. Exclusion criteria included current alcohol or illicit drug use; a clinical diagnosis of AIDS (i.e., Centers for Disease Control and Prevention [CDC; Atlanta, GA] category C); or receipt of protocol-specified medications that induced or were extensively metabolized by cytochrome P450 3A4. All patients gave written informed consent to participate in the study.

Pharmacokinetic assessments occurred 2–4 weeks after patients initiated the APV 1200 mg b.i.d. regimen and 2 weeks after patients were switched to 1 of the APV-RTV combination regimens. Patients attended the clinic the night before samples were to be obtained, received their evening dose (if they were receiving a twice-daily regimen), and began an overnight fast.

Received 17 February 2003; accepted 27 March 2004; electronically published 26 July 2004.

Presented in part: 8th European Conference on Clinical Aspects and Treatment of HIV Infection, Athens, Greece, 28–31 October 2001 (poster 218).

Reprints or correspondence: Dr. Odin J. Naderer, 5 Moore Dr., 17.2237, PO Box 13398, Research Triangle Park, NC 27709 (ojn98495@gsk.com).

Clinical Infectious Diseases 2004;39:591–4

1058-4838/2004/3904-0030$15.00

The following morning, patients received their morning dose, and serial whole-blood samples were collected during the following 12 h at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 h after dosing. Patients fasted for an additional 3 h after taking their morning dose and were discharged after the sample was collected at 12 h after dosing.

Pharmacokinetic plasma samples were analyzed for APV concentrations by GlaxoSmithKline International Bioanalysis BioMet (Research Triangle Park, NC) using a validated method of high-performance liquid chromatography with tandem mass spectrometric detection following solid-phase extraction. The validated calibration range was 10–5000 ng/mL, bias was a maximum of $\pm 3.2\%$, and the coefficient of variation was $\leq 9.3\%$.

Plasma HIV-1 RNA load was measured using the Amplicor HIV-1 Ultrasensitive Monitor test, version 1.0 (Roche; ultrasensitive limit of detection, 50 copies/mL). Samples with plasma HIV-1 RNA loads of >75,000 copies/mL were retested using the Amplicor HIV-1 Monitor test standard assay, version 1.0 (Roche; lower limit of detection, 400 copies/mL). $CD4^+$ cell counts were measured using flow cytometry.

Adverse events and standard hematological and clinical chemistry parameters were recorded at each visit. Adverse events were graded for their relationship to a study drug and for severity on a scale of 1–4 (in which 4 was the most intense). No power calculation was made to recommend the sample size for the open-label phase of the study.

The "pharmacokinetic" population consisted of patients for whom data were available on plasma APV pharmacokinetic parameter values for APV at a dosage of 1200 mg b.i.d. and an APV-RTV combination regimen. The "safety and efficacy" population consisted of all patients who entered the open-label phase of the study with documented evidence of having received an APV-RTV combination regimen.

The maximum steady-state plasma concentration ($C_{max,ss}$) was derived from observed values. The steady-state concentration at the end of a dosing interval ($C_{min,ss}$) was calculated as the mean of the predose and 12-h postdose plasma APV concentrations for the twice-daily regimens and as the predose value for the once-daily regimen. The area under the steady-state plasma APV concentration–time curve during a dosing interval ($AUC_{\tau,ss}$) was calculated by the log-linear trapezoidal method. For the daily regimen, the predose concentration was carried forward to serve as the 24-h time point in the $AUC_{\tau,ss}$ calculation.

In a separate analysis of variance (ANOVA) model, within-subject comparisons of the steady-state plasma APV pharmacokinetic parameters were conducted between the APV 1200 mg b.i.d. regimen and one of the APV-RTV combination regimens. Plasma APV pharmacokinetic parameters were logarithmically transformed before statistical analysis was performed, and the comparisons were expressed as ratios on the original scale. The geometric least-square mean ratio and associated 90% CI were estimated for each plasma APV pharmacokinetic parameter.

Results. Fifty-four patients entered the open-label study. Forty patients switched treatment to receive an APV-RTV combination regimen: 22 patients received a dosage of 600/100 mg b.i.d., and 18 patients received a dosage of APV-RTV 1200/200 mg q.d.

The pharmacokinetic analysis included 30 patients who initiated an APV-RTV combination regimen: 18 who received the 600/100 mg b.i.d. dosage and 12 who received the 1200/200 mg q.d. dosage. For 5 subjects, plasma APV concentration data were not available for both the APV and APV-RTV regimens. Three subjects were excluded from analysis because of presumed nonadherence to therapy (i.e., their predose APV concentration was at least 10-fold lower than their 12-h concentration). Two patients were excluded from analysis because of dosing errors.

Significant elevations in plasma APV exposure were observed for the APV-RTV combination regimens, compared with those observed for the APV 1200 mg b.i.d. regimen (table 1). Coadministration of APV-RTV at a dosage of 600/100 mg b.i.d. resulted in a 64% increase in plasma APV $AUC_{\tau,ss}$, a 6.1-fold increase in plasma APV $C_{min,ss}$, and a 30% reduction in plasma APV $C_{max,ss}$ (table 1). Coadministration of APV-RTV at a dosage of 1200/200 mg q.d. resulted in a similar (62%) increase in plasma APV $AUC_{\tau,ss}$, a 4.2-fold increase in plasma APV $C_{min,ss}$, and no change in plasma APV $C_{max,ss}$ (table 1).

At the time of their switch to an APV-RTV regimen, 36 (90%) of 40 patients had an HIV RNA level of <400 copies/mL. Upon completion of the study, subjects had been exposed to APV-RTV for a median of 32 weeks (range, 7–43 weeks). At the patients' last study visit while receiving APV-RTV therapy, 36 (90%) of 40 patients had an HIV RNA level of <400 copies/mL, and 35 (88%) of 40 had a level of <50 copies/mL.

Overall, 21 (39%) of 54 patients receiving APV at a dosage of 1200 mg b.i.d. experienced at least 1 adverse event of at least moderate severity (grade ≥ 2) after starting treatment. The most frequently reported adverse events were diarrhea, nausea, and vomiting (3 patients each). Seven (13%) of 54 patients reported adverse events that were judged attributable to a study drug. The most frequently reported drug-related adverse events were diarrhea and nausea (2 patients each). After switching to an APV-RTV combination regimen, 16 (40%) of 40 patients experienced at least 1 treatment-emergent adverse event. The most frequently reported was anorexia (in 3 patients). Of the patients who switched, 8 (20%) of 40 reported adverse events judged attributable to a study drug. The most frequently reported drug-attributed adverse events were anorexia and headache, each reported by 1 patient in each treatment group. There

Table 1. Summary of plasma pharmacokinetic parameters for amprenavir (APV) and comparison of treatment with different regimens.

Parameter	Geometric mean (95% CI), by regimen			Geometric least-square mean ratio (90% CI), by regimen	
	APV-RTV 600/100 mg b.i.d. $n = 18$	APV-RTV 1200/200 mg q.d. $n = 12$	APV 1200 mg b.i.d. $n = 30$	APV-RTV 600/100 mg b.i.d. vs. APV 1200 mg b.i.d. $n = 18$	APV-RTV 1200/200 mg q.d. vs. APV 1200 mg b.i.d. $n = 12$
$AUC_{\tau,ss}$, μg/h/mL[a]	28.4 (21.8–36.9)	68.2 (60.0–77.7)	17.0 (14.2–20.3)	1.64[b] (1.37–1.97)	1.62[b] (1.35–1.94)
$C_{max,ss}$, μg/mL[c]	5.15 (4.07–6.53)	7.75 (6.95–8.65)	6.85 (5.63–8.32)	0.70[b] (0.56–0.86)	1.04 (0.83–1.30)
$C_{min,ss}$, μg/mL[d]	1.51 (1.15–2.00)	1.40 (1.10–1.78)	0.25 (0.19–0.33)	6.08[b] (4.94–7.49)	4.19[b] (2.90–6.08)

NOTE. RTV, ritonavir.

[a] $AUC_{\tau,ss}$, area under the steady-state plasma APV concentration-time curve over a dosing interval (τ) where $\tau = 12$ h for the b.i.d. regimens and 24 h for the q.d. regimen.

[b] Statistically significant difference, compared with APV 1200 mg regimen, as the 90% CI does not include 1.

[c] $C_{max,ss}$, the maximum steady-state plasma APV concentration during a dosing interval, where the interval was 12 h for the b.i.d. regimens and 24 h for the q.d. regimen.

[d] $C_{min,ss}$, the steady-state plasma APV concentration at the end of a dosing interval, where the interval was 12 h for the b.i.d. regimens and 24 h for the q.d. regimen.

were 5 serious adverse events during the study, but none was related to the study drug. Four patients receiving APV at a dosage of 1200 mg b.i.d. experienced serious adverse events: psychiatric depression, recurrent muscle abscess, vomiting, and lower respiratory tract infection. One patient receiving APV-RTV daily experienced fatal non-Hodgkin lymphoma.

The incidence of clinically significant changes in laboratory parameters was low. Grade 3–4 abnormalities in laboratory values experienced by at least 5% of patients receiving the APV-RTV regimens were abnormal creatine phosphokinase levels (by 5 [12.5%] of 40 patients) and abnormal gamma glutamyl transferase levels (by 2 [5%] of 40). One patient (2.5% of 40 patients) in the APV-RTV group had abnormal triglyceride levels (grade 3).

Discussion. The antiretroviral activity and tolerability profile of a protease inhibitor depends largely on its pharmacokinetic profile. The $C_{min,ss}$ should remain above the minimum concentration required to inhibit viral replication (i.e., the IC_{50}), and the $C_{max,ss}$ should remain as low as possible to minimize toxicity.

In this nonrandomized study, APV-RTV at either of 2 dosing schedules appeared to have persistent antiretroviral activity consistent with the enhanced pharmacokinetic parameters of APV observed with these treatments. Geometric least-square mean values for $C_{min,ss}$ for both APV-RTV combination regimens were significantly higher (4–6-fold) than the value for the APV 1200 mg b.i.d. regimen. As predicted by a previous simulation, both APV-RTV combination regimens maintained plasma APV concentrations in excess of the mean IC_{50} for APV against HIV both for patients who were protease inhibitor–naive and in those who had received multiple protease inhibitors [12]. In addition, since the $C_{max,ss}$ values for both APV-RTV combination regimens were similar or lower than that for the APV 1200 mg b.i.d. regimen, no increase in the incidence of adverse events would be expected. There was no increase in the incidence of adverse events of at least moderate severity (grade ≥ 2) reported by patients receiving an APV-RTV combination regimen after switching from the APV 1200 mg b.i.d. regimen. In addition, there were minimal changes in laboratory parameters. Thus, these safety data revealed no new safety concerns concerning the use of APV in combination with RTV.

In conclusion, compared with an APV 1200 mg b.i.d. regimen, both the APV-RTV 600/100 mg b.i.d. and APV-RTV 1200/200 mg q.d. regimens demonstrated significant increases in plasma APV $C_{min,ss}$ and $AUC_{\tau,ss}$, whereas $C_{max,ss}$ values were not increased. No new safety issues were identified. These results, combined with the distinct resistance profile of APV, support the use of APV-RTV combination regimen as an option for initial HIV therapy that includes a protease inhibitor.

Acknowledgments

We thank Justin Cook for editing and writing assistance during preparation of the manuscript.

The following investigators recruited patients for this study: Keikawus Arasteh, Epimed/Auguste-Viktoria-Krakenhaus, Berlin, Germany; Antonio Diniz, Hospital de Pulido Valente, Lisboa, Portugal; Joseph Eron, University of North Carolina at Chapel Hill; Richard Haubrich, UCSD Treatment Center, San Diego, California; Jean-Michel Livrozet, Hôpital Edoard Herriot, Lyon, France; Richard Pollard, The University of California–Davis, Sacramento, California; Françoise Raffi, CHRU de Nantes, Nantes, France; Hans-Jurgen Stellbrink, Universitaetsklinikum Eppendorf, Hamburg, Germany; Eugenio Teofilo, Servico de Medicina 3, Lisboa, Portugal; Christian Trepo, Hôpital Hôtel Dieu, Lyon, France; Robin Wood, Somerset Hospital, Cape Town, South Africa.

Financial support. GlaxoSmithKline Research and Development supported this study.

Conflict of interest. J.E. is an ad hoc consultant for GlaxoSmithKline. J.Y., J.M., M.B.W., and O.J.N. are employees of GlaxoSmithKline. R.W., K.A., E.T., C.T., J.M.L.: No conflict.

References

1. Goodgame JC, Pottage JC Jr, Jablonowski H, et al. Amprenavir in combination with lamivudine and zidovudine versus lamivudine and zidovudine alone in HIV-1 infected antiretroviral-naive adults. Antivir Ther **2000**; 5:215–25.
2. Haubrich R, Thompson M, Schooley R, et al. A phase II safety and efficacy study of APV in combination with zidovudine and lamivudine in HIV-infected patients with limited antiretroviral experience. AIDS **1999**; 13:2411–20.
3. Murphy R, Gulick R, DeGruttola V, et al. Treatment with APV alone or APV with zidovudine and lamivudine in adults with human immunodeficiency virus infection. J Infect Dis **1999**; 179:808–16.
4. Pedneault, Brothers LC, Pagano G, et al. Safety profile and tolerability of APV in the treatment of adult and pediatric patients with HIV infection. Clin Ther **2000**; 22:1378–94.
5. Tisdale M, Myers RE, Maschera B, Parry NR, Oliver NM, Blair ED. Cross-resistance analysis of human immunodeficiency virus type 1 variants individually selected for resistance to five different protease inhibitors. Antimicrob Agents Chemother **1995**; 39:1704–10.
6. Alford JL, McQuiaid TC, Partaledis JA, et al. Amprenavir-resistant mutants show reduced viral fitness: correlation of protease mutations, cleavage site mutations, enzyme kinetics, viral polyprotein processing and viral growth kinetics [abstract 44]. In: Program and abstracts of the 3rd International Workshop on HIV Drug Resistance and Treatment Strategies (San Diego, CA), **1999**.
7. Markland W, Zuchowski L, Black J, et al. Kinetic and structural analysis of HIV-1 protease mutations: APV resistance, cross-resistance and resensitisation [abstract 24]. In: Program and abstracts of the 2nd International Workshop on Drug Resistance and Treatment Strategies (Lake Maggiore, Italy), **1998**.
8. Sham HL, Kempf DJ, Molla A, et al. ABT-378, a highly potent inhibitor of the human immunodeficiency virus protease. Antimicrob Agents Chemother **1998**; 42:3218–24.
9. Saag MS, Kilby M, Ehrensing E, Buss N, Oo CY. Modulation of saquinavir steady-state pharmacokinetics with "baby" doses of RTV in healthy volunteers [abstract 829]. In: Program and abstracts of the 7th European Conference on Clinical Aspects and Treatment of HIV Infection (Lisbon, Portugal), **1999**.
10. Hsu A, Granneman GR, Cao G, et al. Pharmacokinetic interactions between RTV and indinavir in healthy volunteers. Antimicrob Agents Chemother **1998**; 42:2784–91.
11. Sadler B, Pilieor P, Preston S, Lou Y, Sale M, Stein D. Pharmacokinetic (PK) drug-interaction between amprenavir (APV) and ritonavir (RTV) in HIV-seronegative subjects after multiple, oral dosing [abstract 77]. In: Program and abstracts of the 7th Conference on Retroviruses and Opportunistic Infections (San Francisco, CA), **2000**.
12. Sale M, Sadler BM, Stein DS. Pharmacokinetic modeling and simulations of interaction of amprenavir and ritonavir. Antimicrob Agents Chemother **2002**; 46:746–54.
13. Wood R, Arasteh K, Stellbrink HJ, et al. Six-week randomized controlled trial to compare the tolerabilities, pharmacokinetics, and antiviral activities of GW433908 and amprenavir in human immunodeficiency virus type 1–infected patients. Antimicrob Agents Chemother **2004**; 48:116–23.