The mean plasma concentration time profiles are presented in Figure 4 and pharmacokinetic parameters for individuals are presented in Table 4. The mean pharmacokinetic parameters for all treatments are presented in the following table:

Parameter	Treatment 1 (n=24) 150-mg capsule (Ref)	Treatment 2 (n=24) 50-mg capsule (Test)	Treatment 3 (n=24) 15 mg/mL oral solution(Test)
$AUC_{0-\infty}$ (μg*hr/mL)			
Mean ± SD	9.4 ± 3.5	9.5 ± 3.9	8.2 ± 3.8
GM	8.8	8.7	7.4
GM Ratio	–	0.99 (2/1)	0.84 (3/1); 0.85 (3/2)
90% CI	–	0.90, 1.14 (2/1)	0.76,0.95 (3/1); 0.77, 0.96 (3/2)
C_{max} (μg/mL)			
Mean ± SD	4.4 ± 1.6	4.3 ± 1.8	3.4 ± 1.3
GM	4.1	3.9	3.2
GM Ratio	–	0.95 (2/1)	0.78 (3/1); 0.82 (3/2)
90% CI	–	0.82,1.13 (2/1)	0.71,0.93 (3/1); 0.73, 0.96 (3/2)
T_{max} (hr)			
Mean ± SD	1.0 ± 0.4	1.0 ± 0.4	0.8 ± 0.3
CL/F (mL/min)			
Mean ± SD	1227.9 ± 480.6	1274.4 ± 676.2	1479.2 ± 623.8
GM	1142.5	1145.6	1350.2
GM Ratio	—	1.0 (2/1)	1.18 (3/1); 1.18 (3/2)
p-value	—	0.84 (2/1)	0.05 (3/1); 0.03 (3/2)
Vz/F (L)			
Mean ± SD	615.6 ± 437.0	676.5 ± 512.4	1110.0 ± 728.5
GM	506.7	541.7	915.2
GM Ratio	—	1.07 (2/1)	1.81 (3/1); 1.68 (3/2)
p-value	—	0.55 (2/1)	0.0001(3/1); 0.0001 (3/2)
Tl/2 (hr)			
Mean ± SD	5.6 ± 2.6	5.9 ± 2.5	9.6 ± 8.9
GM	5.1	5.5	7.8
GM Ratio	—	1.08 (2/1)	1.53 (3/1); 1.42 (3/2)
p-value	—	0.40 (2/1)	0.0001 (3/1); 0.0006 (3/2)

New 150-mg Vs New 50-mg Soft Gelatin Capsule (Treatment 1 Vs 2): Statistical analyses indicate that four150-mg amprenavir new soft gelatin capsules ———) are bioequivalent to twelve 50-mg amprenavir new soft gelatin capsules ——— . The 90% confidence intervals for $AUC_{0-\infty}$ and Cmax were within — and no difference in the mean Tmax for the original and new formulations was observed.

New 50-mg Soft Gelatin Capsule Vs New 15 mg/mL Oral Solution (Treatment 2 Vs 3): There were statistically significant decreases in $AUC_{0-\infty}$ and Cmax observed (by 14% and 18%, respectively) when amprenavir was administered as a new oral solution compared to the new 50-mg soft gelatin capsule. The 90% confidence intervals for $AUC_{0-\infty}$ and Cmax were outside the — range and the mean Tmax for the new oral solution was 0.2 h faster compared to the new 50-mg soft gelatin capsule. Thus, the 50-mg soft gel capsule is not bioequivalent to the 15 mg/mL oral solution. Further, statistically significant differences ($p \leq 0.03$) were also noted in apparent clearance (CL/F), apparent volume of distribution (Vz/F), and elimination half-life ($T_{1/2}$).

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New 150-mg Soft Gelatin Capsule Vs New 15 mg/mL Oral Solution (Treatment 1 Vs 3):
The results were similar to the comparison of the new oral solution to the 50-mg soft gelatin capsule as above.

Ethnic Differences: The mean plasma concentration time profiles reflecting ethnic differences are presented in Figure 5 and pharmacokinetic parameters for individuals by treatment are presented in Table 5. The mean pharmacokinetic parameters for all treatments are presented in the following table:

Race		Tmax (h)	Cmax (µg/mL)	AUCinf (µg*h/mL)	Vz/F (L)	$T_{1/2}$ (h)	CL/F (mL/min)
Blacks	Mean	0.9	3.8	7.7	844.5	6.3	1534.0
	SD	0.3	1.8	3.4	470.6	2.2	644.8
	GM	0.9	3.4	7.1	727.9	6.0	1410.9
Whites	Mean	0.9	4.3	10.1	763.6	7.6	1152.1
	SD	0.4	1.4	3.7	705.7	7.6	505.9
	GM	0.9	4.0	9.4	559.1	6.1	1060.9
B/W	GM Ratio	0.99	0.84	0.75	1.30	0.98	1.33
	p-value		0.09	0.001	0.03	0.84	0.03

Statistically significant decrease in $AUC_{0-\infty}$ (25%) and increases in CL/F and Vz/F (33% and 30%, respectively) were observed for amprenavir in Blacks compared to Whites. This could be due to lower mean α-aminoacid glycoprotein (AAG) concentrations in Blacks (77.2 ± 13.8 mg/dL) compared to Whites (90.0 ± 20.2 mg/dL). Since amprenavir is highly protein bound, specifically to AAG, lower concentrations of AAG would result in an increase in the free fraction of drug available to the clearance organs. However, no information is available on the clinical significance of such differences. No statistically significant differences were noted for Cmax, Tmax, and $T_{1/2}$ in Blacks compared to Whites.

Safety: All three treatments were well tolerated and no serious adverse events were reported.
In conclusion, the new 150-mg soft gelatin capsule is bioequivalent to the new 50-mg soft gelatin capsule. The new 15 mg/mL oral solution is not bioequivalent to either 50-mg or 150-mg soft gelatin capsule and the rate and extent of absorption is decreased by 19 and 14%, respectively. Statistically significant differences in $AUC_{0-\infty}$, CL/F, and Vz/F were observed for amprenavir in Blacks compared to Whites.

TITLE: A Mass Balance Study to Investigate the Metabolic Disposition of a Single, Oral Dose of Radiolabelled ^{14C}141W94 in Healthy Male Subjects [PROA1007, NDA 21,007, Vol. 5.8]

Background: The sponsor conducted this study to obtain definitive information on the metabolic profile, extent of absorption, and elimination of drug–related material in man following a single oral dose administration of radiolabelled 141W94.

The primary objectives of this study were to determine the metabolic profile and the total recovery of

drug–related material after single oral dose administration of ^{14C}141W94 in man.

Study Design: This was a Phase I, open–label, single dose, mass balance study in six healthy male volunteers. Each subject received a single, oral 95.76 µCi/600 mg dose of ^{14C}141W94 on Day 1 and a single, *intravenous* 3 µCi/0.03 mg dose of ^{14C}*N*–methyl-erythromycin at the follow–up visit.

Subjects: A total of 6 healthy, HIV–seronegative male subjects (3 Blacks, 3 Whites; mean age: 29 years; mean weight: 78 kg) participated and completed this study.

Formulations: — -mg ——— capsules (batch number A98B1) containing ^{14C}141W94 with a specific activity of 0.152 µCi/mg were used in this study.

Sample Collection:
Blood: Blood samples were collected at predose, and at 0.25, 0.5, 0.75, 1, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36,and 48 hours. The sponsor performed real-time radioactivity analysis and, if plasma radioactivity measured was greater than twice the background radiation count, then additional samples were collected at 24 hour intervals up to 240 hours.

CSF: CSF samples were obtained by lumbar puncture at pre-dose and at 1, 2, 3, 4, and 6 hrs post-dosing.

Urine: Urine samples were collected at pre-dose, and at 0-4, 4-8, 8-12,12-24, 24-48, 48-72, and 72-96 hour blocks. As above, if required, additional samples at 24 hr intervals were collected up to 240 hrs.

Feces: Fecal samples were collected at pre-dose and at 24 hr interval up to 96 hrs. As above, if required, additional samples at 24 hr intervals were collected up to 240 hrs.

RESULTS:
Pharmacokinetic Data Analysis: Pharmacokinetic parameters were estimated by noncompartmental methods. The proposed metabolic pathway is displayed in Figure 6. The mean plasma concentration-time profiles and mean cumulative excretion are presented in Figure 7 and pharmacokinetic parameters for individuals are presented in Table 6. The mean ± sd pharmacokinetic parameters are presented in the following table:

Parameter	141W94 in Plasma	Radioactivity as 141W94 equivalents Blood	Plasma	B/P * 100
$AUC_{0-\infty}$ (µg*hr/mL)	8.2 ± 3.7	23.3 ± 9.4	28.7 ± 10.6	80.1 ± 5.3
C_{max} (µg/mL)	2.9 ± 1.6	3.5 ± 1.4	5.4 ± 2.2	65.3 ± 4.0
T_{max} (hr)	1.3 ± 0.5	1.3 ± 0.5	1.7 ± 0.5	
CL/F (mL/min)	1616.2 ± 1064.5	530.0 ± 324.2	414.8 ± 227.3	
Vz/F (L)	722.2 ± 412.4	—	—	—
T1/2 (hr)	5.6 ± 2.3	17.8 ± 6.8	10.3 ± 3.7	—

Following oral administration, amprenavir was rapidly absorbed with a mean Tmax of 1.3 hours. The plasma concentrations of amprenavir declined monoexponentially and were quantifiable in all subjects at 24 hrs after drug administration. Comparison of the mean $AUC_{0-\infty}$ of amprenavir in plasma to the radioactivity measured in plasma as amprenavir equivalents indicates that about 30% of the circulating radioactivity is due to unchanged drug. Additionally, greater apparent clearance of amprenavir compared to total radioactivity, suggests that the metabolite concentrations exceed that of parent drug. Plasma metabolite profiles obtained by the sponsor showed the presence of metabolite resulting from di-oxidation of the tetrahydrofuran moiety (BD/8064/120/2 or GW513607) and three glucuronide conjugates of mono–oxidation products of amprenavir as plasma circulating metabolites. The mean blood to plasma ratios for $AUC_{0-\infty}$ and Cmax were 80 and 65%, respectively. It was observed that amprenavir distributes in to erythrocytes as evidenced by similar concentrations in red blood cells and plasma (5.3 ± 2.1 vs 5.4 ± 2.2).

Concentrations of radioactivity in the CSF were below the limit of quantitation in all subjects (n=3) where CSF (at least one sample for each subject) was collected.

Concentrations of amprenavir in urine were not determined because <2% of dose is excreted in urine as unchanged drug. Radioactivity in urine and fecal samples were analyzed by —— The mean cumulative excretion of radioactivity as urine, feces, and total as % of dose is shown in Figure 7.

Based on ———————— 13.7 ± 2.3 and 72.1 ± 8.8% of the administered radioactivity was eliminated in urine and feces over a period of 144 and 240 hours, respectively. Thus total recovery was 86% of administered radioactivity over a period of 240 hours and 14% was unaccounted for. Approximately 75% of the radioactivity recovered in urine and feces was within 24 and 144 hours, respectively.

Urine profiling accounted for 14% of the administered dose and detected unchanged drug and ten metabolites but were in insufficient quantity to determine the percentage of radioactivity present as each species.

Feces profiling accounted for approximately 72% of the administered radioactivity. Metabolite resulting from di-oxidation of the tetrahydrofuran moiety (BD/8064/120/2 or GW513607; 62%) and another metabolite resulting from di-oxidation of the tetrahydrofuran moiety and an additional oxidation of the aniline portion of the molecule (BD/8064/104/1 or BD/8064/104/2; 32%) were the major metabolites detected in feces. Unchanged drug and eight other metabolites were detected and accounted for the remaining 6%. The percentage of radioactive dose that was eliminated as unchanged drug was below the limit of quantitation in urine and feces.

In conclusion, upon oral administration, amprenavir was rapidly absorbed with a mean Tmax of 1.3 hrs. Mean ratio of unchanged amprenavir plasma $AUC_{0-\infty}$ to plasma radioactivity was 30%, suggesting total metabolite concentrations will exceed that of the parent drug. Detection of radioactivity in the CSF was below the limit of detection in all subjects.

Following oral administration, mean total recovery of radioactivity was 86% (Urine 14%, feces 72%) over a period of 240 hours. Of the 72% of radioactivity dose recovered in the feces, two metabolites,

BD/8064/120/2 or GW513607 and BD/8064/104/1 or BD/8064/104/2 accounted for approximately 94% of the excreted dose in feces.

TITLE: A Phase I Trial to Evaluate the Safety and Pharmacokinetics of Amprenavir (141W94) [PROA1001; ———

Background: The sponsor conducted this study to evaluate the safety and pharmacokinetics of single oral doses of 141W94 and is a dose escalation study. The doses studied were found to have no effect in the preclinical toxicological species, based on mg/kg dosing.

The primary objectives of this study were to determine the pharmacokinetics of 141W94 and also evaluate safety after single oral doses in HIV-infected patients.

Study Design: This was a Phase I, single–center, double-blind, placebo-controlled, parallel, dose escalation study conducted in 18 HIV–infected patients.

Period 1: One 150-mg ——— amprenavir capsule or one 150-mg placebo ——— capsule

Period 2: Two 150-mg ——— amprenavir capsules or two 150-mg placebo ——— capsules

Period 3: Four 150-mg ——— amprenavir capsules or four 150-mg placebo ——— capsules

Period 4: Six 150-mg ——— amprenavir capsules or six 150-mg placebo ——— capsules

Period 5: Eight 150-mg ——— amprenavir capsules or eight 150-mg placebo ——— capsules

Each treatment was separated by a four-day wash-out period.

Subjects: A total of 18 HIV–infected subjects (15M; 3F; mean age: 32 years; mean weight: 67 kg) were enrolled and completed this study. Subjects were randomized to receive either 141W94 or placebo. Twelve subjects received five single oral doses of 141W94 and six subjects received five single oral doses of placebo in a parallel fashion.

Formulations: 150-mg ——— capsules of 141W94 (———lot number BIN 4U2794) and Placebo (lot number BIN 4U2795) were used in this study.

RESULTS:
Pharmacokinetic Data Analysis: Pharmacokinetic parameters were obtained by noncompartmental methods.

The mean plasma concentration time profiles are presented in Figure 8 and pharmacokinetic parameters for individuals are presented in Table 7. The mean pharmacokinetic parameters for all treatments are presented in the following table:

Dose (mg)	Cmax (µg/mL)	tmax (hr)	t½ (hr)	$AUC_{0-\infty}$ (µg*h/mL)	CL/F (mL/min)	Vz/F (L)	CLR (mL/min)	C_8 (ng/mL)	C_{12} (ng/mL)	Cumulative Urinary Excretion of 141W94 (% dose)
150										
Mean	2.0	1.1	8.0	4.0	808.6	482.3	3.4	37.2	24.3	0.38
SD	1.1	0.4	5.0	2.2	458.1	274.9	1.2	26.2	19.1	0.21
GM	1.7	1.1	6.8	3.5	707.6	418.5	3.1	28.5	18.9	---
300										
Mean	3.5	1.3	7.1	9.1	757.1	459.9	3.1	123.2	88.9	0.58
SD	1.6	0.5	3.5	5.2	469.2	350.7	1.5	91.6	60.6	0.29
GM	3.2	1.2	6.3	7.8	640.4	351.9	2.8	88.5	68.5	---
600										
Mean	6.3	1.6	8.0	21.2	650.8	428.5	3.7	348.8	271.7	0.95
SD	3.2	0.6	3.3	12.8	381.1	250.7	0.9	273.4	241.2	0.59
GM	5.6	1.5	7.4	18.0	555.2	357.4	3.6	260.7	191.4	---
900										
Mean	7.8	1.9	7.8	32.7	546.9	335.8	3.9	614.0	491.8	1.06
SD	2.4	0.7	3.7	16.0	231.0	138.3	0.9	575.5	353.9	0.61
GM	7.4	1.8	7.1	29.8	502.8	310.2	3.8	443.0	410.7	---
1200										
Mean	9.1	2.1	9.5	47.1	518.8	387.8	4.7	1029.4	604.0	1.31
SD	2.7	0.8	6.8	21.6	255.3	288.9	1.7	791.1	355.8	0.67
GM	8.7	1.9	7.8	42.7	468.1	316.7	4.5	765.4	508.9	---

The above results indicate that less than dose-proportional increases in mean Cmax and greater than dose-proportional increases in mean $AUC_{0-\infty}$ were observed between 150- and 1200-mg doses. These observed increases in $AUC_{0-\infty}$ could be due to saturation of first-pass metabolism or P-glycoprotein mediated transport in the intestine. Apparent oral clearance (CL/F) and apparent volume of distribution (Vz/F) decreased with increasing dose. The terminal half-life was relatively constant across doses. The mean plasma concentrations of 141W94 at 8 and 12 h after dosing of 900- and 1200-mg were greater than 10-times the *in vitro* IC_{50} for HIV-1_{IIIB} in peripheral blood leukocytes (40 ng/mL). There was minimal renal elimination of unchanged drug as evidenced by consistent low renal clearance of 141W94 across doses. The mean cumulative amount of 141W94 excreted unchanged in urine increased with dose and ranged from 0.38 to 1.31% over 24 hrs.

Safety: All five single doses were well tolerated and no serious adverse events were reported.

In conclusion, less than dose-proportional increases in mean Cmax and greater than dose-proportional increases in mean $AUC_{0-\infty}$ were observed between 150- and 1200-mg doses and a minimal amount of unchanged drug was excreted renally.

Agenerase NDA 21-007&21-039
Vijay Tammara
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TITLE: A Phase I/II Trial to Evaluate the Safety, Pharmacokinetics, and Antiviral Activity of Amprenavir (141W94) After Multiple Dosing in Subjects with HIV Infection [PROA1002; NDA 21007; # 003, Vol. 5.1].

Background: The sponsor demonstrated that amprenavir (APV) is safe and well tolerated when administered as single, oral doses of up to 1200 mg. This Phase I study was designed to evaluate the safety and pharmacokinetics of multiple oral dosing with amprenavir alone; in combination with abacavir (ABC); in combination with zidovudine (ZDV) and lamivudine (3TC); and in combination with ABC, ZDV, and 3TC. Several dose levels of amprenavir were evaluated, from 300 mg BID to 1200 mg BID.

The primary objectives of this study conducted in three phases were: Phase A: to determine the steady–state pharmacokinetics of APV alone and in combination with ABC after multiple oral dosing; to characterize the relationship between exposure to APV and antiviral response after 4 weeks of mono-therapy and in combination with ABC; and to assess safety and tolerance of multiple oral doses of APV alone and in combination with ABC. Phase B: to obtain evidence of subsequent antiretroviral effect of double combination of ZDV and 3TC and the triple combination of ZDV, 3TC, and ABC administered following four weeks of APV monotherapy or APV in combination with ABC administered during Phase A. Phase C: to obtain preliminary evidence of antiretroviral activity and also to assess safety and tolerance of APV administered in combination with either ZDV and 3TC or ZDV, 3TC and ABC.

Study Design: This was a Phase I international, multi–center, open–label, non–randomized trial conducted over three distinct phases (Phases A, B, and C) in HIV–infected adult subjects with CD4+ cell counts between 150 and 400 cells/mm^3, inclusive. Subjects were required to discontinue antiretroviral therapy two weeks prior to study enrollment and could not have received any previous therapy with an HIV protease inhibitor.

Intensive single–dose and steady–state pharmacokinetic sampling was conducted during Phase A. No pharmacokinetic samples were obtained during Phase B. Single pharmacokinetic samples were obtained throughout Phase C, during regularly scheduled clinic visits. Only the pharmacokinetic and pharmacodynamic data collected during Phase A are discussed in this review.

Phase A was designed to evaluate the safety, pharmacokinetics, and antiviral activity of multiple doses of APV administered alone (Cohorts I–V) or in combination with ABC (Cohort VI) for 4 weeks. Subjects with previous 3TC-therapy experience were not eligible for Cohort VI. Eligible participants were enrolled into one of six dose cohorts, with ten subjects planned for each cohort, for a planned total of sixty subjects.

Following successful completion of Phase A, APV therapy was discontinued and subjects were given the option to receive combination therapy of ZDV/3TC (Phase B). Subjects who received the combination of APV/ABC in Phase A (Cohort VI) received ZDV/3TC/ABC therapy during Phase B. Subjects who were intolerant of either ZDV or 3TC were not eligible for Phase B of this study. Subjects remained in Phase B until an effective dose for APV was chosen, based on Phase A data and completion of APV toxicology studies, at which time the subjects were given the option to enter Phase C.

Subjects entering Phase C received either the triple antiretroviral therapy ZDV/3TC/APV (Cohorts I–V) or the quadruple antiretroviral therapy ZDV/3TC/APV/ABC (Cohort VI). Some subjects in Cohorts V

and VI progressed from Phase A directly to Phase C (as a result of timing of these cohorts).

Subjects in Cohorts I–V received a single dose of amprenavir at the prescribed dose on Day 1 and began their regular regimen on Day 2. Subjects in Cohort VI began their prescribed multiple–dose, two–drug regimen on Day 1. The six dosing cohorts for Phases A-C were as follows.

Phase A	Dose	Total Daily Dose
Cohort I	300-mg APV BID	600-mg APV
Cohort II	300-mg APV TID	900-mg APV
Cohort III	900-mg APV BID	1800-mg APV
Cohort IV	1200-mg APV BID	2400-mg APV
Cohort V	1050-mg APV BID	2100-mg APV
Cohort VI	900-mg APV BID + 300-mg ABC BID	1800-mg APV + 600-mg ABC
Phase B		
Cohorts I -V	ZDV 300-mg + 3TC 150-mg BID	600-mg ZDV + 300-mg 3TC
Cohort VI	ZDV 300-mg + 3TC 150-mg BID+300-mg ABC	600-mg ZDV + 300-mg 3TC + 600-mg ABC
Phase C		
Cohorts I-V	ZDV 300-mg + 3TC 150-mg BID + 1200-mg APV BID	600-mg ZDV + 300-mg 3TC + 2400-mg APV
Cohort VI	ZDV 300-mg + 3TC 150-mg BID +1200-mg APV + 300-mg ABC BID	600-mg ZDV + 300-mg 3TC + 2400-mg APV + 600-mg ABC

Subjects: A total of 62 subjects (9 F, 53 M; mean age: 37 years; mean weight: 72 kg) were enrolled into Phase A and 56 subjects completed the study. 10 subjects in Cohorts I, III, and V; 11 subjects in Cohort II; 8 subjects in Cohort IV; and 7 subjects in Cohort VI completed the study. Enrollment into Cohorts I–V was sequential; Cohort VI ran parallel to Cohort V. A total of 53 subjects entered Phase B (9 subjects in Cohort I, 11 in Cohort II, 9 in Cohort III, 8 in Cohort IV, 9 in Cohort V, and 7 in Cohort VI). A total of 37 subjects entered Phase C (4 subjects in Cohort I, 7 in Cohort II, 4 in Cohort III, 5 in Cohort IV, 10 in Cohort V, and 7 in Cohort VI). Plasma concentration profiles were obtained from 53 subjects on Day 1 and from 55 subjects at Week 3.

Formulations: 150-mg ~~~ capsules of APV, ~~~ batch numbers 5N2700 and 4U2794), 150-mg (batch numbers SOF 31275, 5Y2752, 6R2782, SF046592, SF046593, and SF060606) or 200 mg (batch number SOF SF031542) soft gelatin capsules, 100-mg tablets of ABC (succinate salt, batch numbers CPL 5Y2745 and CPL 6W6006), 100-mg capsules of ZDV (batch number CAP 5Y2750), 150-mg tablets of 3TC (batch number TAB 5Z1210) were used in this study.

Sample Collection: Plasma samples for determination of APV concentrations were obtained on Day 1 (Cohorts I-V) and during the scheduled visit during Week 3 (all cohorts). Plasma samples were collected before (pre–dose) and 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3, 4, 5, 6, 8, 10, 12, and 24 hours after dosing on Day 1. At Week 3, plasma samples were collected before and 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3, 4, 5, 6, 8, 10, and 12 hours after dosing. Plasma samples collected during Week 3 for Cohort VI were also assayed for ABC.

RESULTS:

Pharmacokinetic Data Analysis: Pharmacokinetic parameters were obtained by noncompartmental methods for single dose and at steady-state from Phase A. The relationship between steady–state pharmacokinetic parameters and the decrease in time-weighted average area under the curve of log_{10}(HIV-1 RNA) minus the baseline (AAUCMB) was examined using simple and sigmoid Emax models, with and without a baseline effect. Results from Phase C have not yet been reported.

Of the 53 single dose profiles, 36 could be used for the estimation of all PK parameters. Two profiles could not be used for any analysis (Subject 122 and 77): subject 122, mistakenly had a Day 1 instead of a Week 3 pharmacokinetic profile collected; subject 77 in Cohort IV appears to have received more than one dose on Day 1 and had a Cmax of 15.0 µg/mL 24 hours after dosing. Profiles from 15 subjects did not allow adequate estimation of elimination rate constant and hence PK parameters except Cmax and Tmax. Subjects 49 and 66 in Cohort III received 450 mg of amprenavir on Day 1 instead of the protocol–specified 900 mg dose.

The mean plasma concentration time profiles are presented in Figure 9 and pharmacokinetic parameters for individuals are presented in Table 8. The mean ± sd pharmacokinetic parameters on Day 1 and Week 3 for all cohorts are presented in the following tables:

DAY 1

Parameter	Cohorts				
	I & II (300-mg)	III (450-mg)	III (900-mg)	V (1050-mg)	IV (1200-mg)
$AUC_{0-\infty}$ (µg*hr/mL)	5.7 ± 2.4	7.5 ± 3.0	17.6 ± 3.7	27.1 ± 9.2	35.7 ± 22.9
N	14	2	5	8	7
GM	5.2	7.2	17.3	25.5	28.8
C_{max} (µg/mL)	2.6 ± 1.7	3.1 ± 1.0	5.3 ± 1.9	8.4 ± 2.1	8.5 ± 4.5
N	22	2	8	10	9
GM	2.2	3.0	7.9	8.0	8.1
T_{max} (hr)	1.5 ± 0.7	1.7 ± 0.3	1.5 ± 0.5	1.3 ± 0.3	1.8 ± 0.6
N	22	2	8	10	9
GM	1.5	1.7	1.5	1.3	1.8
CL/F (mL/min)	1059 ± 493	1095 ± 444	889 ± 229	734 ± 311	900 ± 774
N	14	2	5	8	7
GM	966	1049	869	686	694
Vz/F (L)	708 ± 445	1588 ± 1715	856 ± 591	617 ± 739	787 ± 1223
N	14	2	5	8	7
GM	616	1026	692	399	395
T1/2 (hr)	9.1 ± 6.8	14.3 ± 12.3	10.6 ± 6.7	8.1 ± 5.8	7.2 ± 4.0
N	16	2	5	8	7
GM	7.4	11.3	9.2	6.7	6.6

The dose proportionality was examined for Cmax and $AUC_{0-\infty}$ using the linear regression equation (log y= a+ b * log(dose)). It was observed that Cmax (slope = 0.9) and $AUC_{0-\infty}$ (slope = 1.2) increased less than and greater than proportional, respectively, and are not statistically significant. There was a corresponding decrease in CL/F with dose. Half-life (T1/2) was dose independent.

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WEEK 3

Parameter	Cohorts					
	I (300-mg BID; n=9)	II (300-mg TID; n=9)	III (900-mg BID; n=6)	V (1050-mg BID; n=9)	IV (1200-mg BID; n=5)	VI (900-mg APV BID + 300-mg ABC; n=4)
AUCss (µg*h/mL) GM	5.0 ± 2.9 4.3	4.4 ± 1.9 4.1	11.8 ± 2.5 11.5	19.2 ± 6.87 18.1	18.5 ± 11.6 14.3	16.5 ± 9.6 14.8
Cmax ss (µg/mL) GM	2.3 ± 1.1 2.0	2.0 ± 0.8 1.9	4.5 ± 1.8 4.2	7.7 ± 2.1 7.5	5.4 ± 3.3 4.2	7.0 ± 4.0 6.2
Cavg ss (µg/mL) GM	0.42 ± 0.2 0.36	0.55 ± 0.2 0.51	0.98 ± 0.2 0.96	1.6 ± 0.6 1.51	1.5 ± 0.9 1.2	1.4 ± 0.8 1.2
Cmin ss (µg/mL) GM	0.07 ± 0.04 0.05	0.12 ± 0.11 0.10	0.20 ± 0.16 0.16	0.33 ± 0.18 0.29	0.28 ± 0.15 0.25	0.25 ± 0.22 0.20
Tmax ss GM	1.25 ± 0.4 1.2	1.2 ± 0.3 1.2	2.2 ± 1.2 2.2	1.1 ± 0.6 1.0	1.9 ± 1.0 2.0	1.9 ± 0.5 1.9
CL/Fss GM	1353 ± 836 1156	1329 ± 566 1232	1342 ± 382 1306	1031 ± 406 966	2133 ± 2532 1403	1116 ± 516 1015

The-dose proportionality was examined for Cmaxss and AUCss using the linear regression equation (log y= a+ b * log(dose)). Slightly less than proportional increases in Cmaxss (slope = 0.8) and AUCss (slope = 0.9) were observed between 300- and 1200-mg BID doses and CL/F was dose independent. The increase in the estimate of CL/F observed in Cohort IV (1200-mg BID) was due mainly to the influence of Subject 75 who had an exceptionally small AUCss (3.0 µg*hr/mL) and high CL/Fss (6621 mL/min) for the 1200 mg BID dose administered. Without Subject 75, the mean would be reduced from 2133 mL/min to 1011 mL/min, which is similar to the 1031 mL/min observed for the 1050 mg BID treatment.

The accumulation index is less than 1.2 suggesting that no significant accumulation of amprenavir occurs upon multiple dosing. Based on the ~ 9 hr half-life, accumulation is less than expected. This suggests that there is increased clearance of unbound drug either, due to autoinduction of metabolism or transport, or that the free fraction in plasma increases due to a reduction in α-1-acid glycoprotein (AAG).

The sponsor also performed a step–wise regression with variables, percent change in AAG, *ln*(dose), baseline HIV RNA, baseline CD4 cell count, the change in CD4 count, and the change in log10 (HIV RNA), and observed that only the percent change in AAG was significantly associated with the AUCratio (p = 0.014). Further, it was observed that the baseline AAG concentrations decreased by about 20% during the 3 weeks between the single–dose and steady–state pharmacokinetic profiles. Thus, higher doses of amprenavir, which produce the greatest antiviral effect, could lead to a decrease in AAG, which, in turn, leads to an increase in free drug concentrations in plasma thereby countering the decrease in apparent total clearance observed at higher single doses.

The results from the above table (comparison of cohort III to cohort VI), indicate that in the presence of abacavir, mean Cmaxss, AUCss, Cavgss, and Cminss of amprenavir increased by 55, 40, 40, and 25% respectively. This indicates that abacavir affects the pharmacokinetics of amprenavir. Due to small sample size (n=4) and high between subject variability (CV ≥ 58%), statistical significance was not evaluated. This observation is different from sponsor's conclusion. The mechanism and the clinical significance of such an interaction is unknown. However, precaution should be exercised when they are administered in combination.

The sponsor compared the pharmacokinetics of abacavir from a historical control (Study CNAA2001; NDA 20-977) to those measured in cohort VI and concludes that there was no influence of amprenavir on the pharmacokinetics of abacavir. The mean pharmacokinetic parameters of abacavir from cohort VI and historical control are presented in the following table:

Parameter	Cohort VI (300-mg ABC BID + 900-mg APV BID; n=5)	CNAA2001 (300-mg ABC BID monotherapy at week 4; n=20)
AUCss (μg*h/mL)	5.9 ± 1.7	6.0 ± 2.0
Cmax ss (μg/mL)	2.3 ± 0.4	3.0 ± 0.9
Cavg ss (μg/mL)	0.5 ± 0.08	0.5 ± 0.1
Cmin ss (μg/mL)	0.01 ± 0.005	0.04 ± 0.04
Tmax ss	1.1 ± 0.3	1.0 ± 0.5
CL/Fss	860 ± 130	897 ± 260

The results indicate the APV did not affect the pharmacokinetics of ABC. *In vitro* studies indicated that APV does not inhibit metabolic enzymes except for CYP 3A4. Thus, APV may not alter the metabolism via the route that abacavir is metabolized. However, this reviewer notes that such a comparison across different patient population may not be ideal.

PHARMACODYNAMIC RESULTS

Relationship Between Concentration and Efficacy

The sponsor evaluated the PK-PD correlation between Cminss, Cavgss, and Cmaxss and antiviral activity (Plasma HIV-RNA) over four weeks. The pharmacokinetic variables were fitted to the decrease in the time-weighted average area under the curve of $\log_{10}$(HIV-1 RNA) minus the baseline (AAUCMB) using a simple Emax model, a simple Emax model with baseline effect, a sigmoid Emax model, and a sigmoid Emax model with baseline effect. The sigmoid Emax model was the best fit for all three expressions of amprenavir concentrations Cminss, Cavgss, and Cmaxss, based upon its having the lowest AIC of the four models tested. All models provided a statistically significant fit to the data ($p < 0.0001$). The fitted curves for the selected sigmoid Emax models along with the observed data are presented graphically for Cminss, Cavgss, and Cmaxss in Figure 10. The r^2 values for these models were 0.44 or higher. The final parameter estimates are summarized in the following table:

Parameter	$C_{min,ss}$	$C_{avg,ss}$	$C_{max,ss}$
E_{max} (-$\log_{10}$ HIV RNA copies/mL))	1.19 (13)	1.21 (14)	1.21 (17)
EC_{50} (μg/mL)	0.087 (19)	0.506 (19)	2.233 (25)
γ (unitless)	2.26 (46)	2.45 (47)	2.17 (50)

The sponsor used the final model to predict the concentrations of amprenavir needed to achieve 50%, 75%, 90%, 95%, and 99% of the maximum decrease in AAUCMB which are presented in

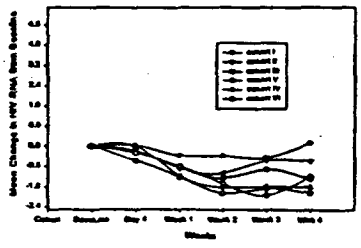
the following table:

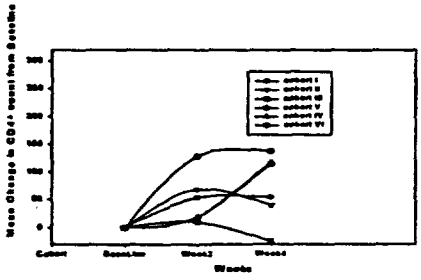
	$C_{min,ss}$ (µg/mL)	Decrease in AAUCMB (log_{10}[copies/mL])	$C_{avg,ss}$ (µg/mL)	Decrease in AAUCMB (log_{10}[copies/mL])	$C_{max,ss}$ (µg/mL)	Decrease in AAUCMB (log_{10}[copies/mL])
EC_{50}	0.087	0.60	0.506	0.60	2.233	0.61
EC_{75}	0.141	0.89	0.793	0.90	3.702	0.91
EC_{90}	0.228	1.07	1.243	1.09	6.139	1.09
EC_{95}	0.318	1.13	1.687	1.15	8.661	1.15
EC_{99}	0.658	1.18	3.310	1.19	18.510	1.20
E_{max}	-	1.19	-	1.21	-	1.21

The mean Cminss for amprenavir after the 1050 and 1200 mg BID doses were observed to be 0.33 and 0.28 µg/mL, respectively. Both exceed the EC90 predicted for Cminss (0.23 µg/mL). Further, it was reported that the Cminss achieved after 1200 mg BID is 10–fold greater than the median *in vitro* IC50 for clinical isolates of HIV (0.023 mg/mL; range [redacted] mg/mL). However, this reviewer notes that the AAUCMB used in the pharmacodynamic analysis was only measured during the four weeks of monotherapy with amprenavir. Since other protease inhibitors in clinical trials have taken 16 to 20 weeks to reach maximal effects, the Emax calculated in these models may be an underestimate of the potential antiviral activity.

In addition, the effect of small differences in exposure on plasma HIV–1 RNA would require evaluation over a longer duration of treatment. Hence, the utility of these models may not be ideal at this time, except for dose selection for further evaluation in clinical trials.

Efficacy Results: HIV-RNA levels were determined by Roche Amplicor assay with a lower limit of quantitation of 400 copies/mL. Mean change in plasma log (HIV-RNA) and CD4+ count from base line for each cohort over 4 weeks is shown below:





From the above figures, it can be seen that plasma HIV-RNA tended to decrease with increasing APV dose, whereas CD4+ count increased. In cohort I, patients had a decrease in plasma HIV-RNA in the

first three weeks of therapy but then rebounded towards baseline at week 4. Maximum decrease was observed in cohort VI. For the APV monotherapy, the best response at week 4 in terms of decreased plasma HIV-RNA and increased CD4+ cell count was observed in cohorts IV and V, respectively. Therefore, a 1200-mg BID dose was carried forward into Phase III clinical trials.

Relationship Between Concentration and Safety: The sponsor performed categorical and logistic regression analysis to correlate steady state plasma concentration to adverse events. The results are presented in the following tables:

Categorical Analysis of Occurrence of Adverse Events with Parameter and p-Values

Adverse Event	n	$C_{max,ss}$	$C_{avg,ss}$	$C_{min,ss}$
Nausea and/or Vomiting	12	0.21	0.05	0.15
Headache	11	0.01	0.07	0.34
Diarrhea	12	0.44	0.92	0.92
Rash	4	0.96	0.28	0.96
Oral Numbness	5	0.02	0.02	0.18

Logistic Regression of Pharmacokinetic Variables with the Occurrence of Adverse Events

		Odds Ratios and 95% Confidence Intervals		
Adverse Event	n[a]	$C_{max,ss}$ (per 1 µg/mL)	$C_{avg,ss}$ (per 50 ng/mL)	$C_{min,ss}$ (per 50 ng/mL)
Nausea and/or vomiting	12	0.90 (0.69,1.13)	0.98 (0.97,1.03)	0.81 (0.57,1.03)
Headache	11	1.16 (0.93,1.47)	1.04 (0.99,1.09)	1.11 (0.90,1.36)
Diarrhea	12	0.97 (0.75,1.20)	0.99 (0.94,1.04)	0.90 (0.68,1.11)
Rash	4	0.81 (0.45,1.18)	0.97 (0.86,1.05)	1.02 (0.70,1.34)
Oral Numbness	5	1.31 (0.99,1.82)	1.06 (0.99,1.13)	1.10 (0.83,1.41)

The categorical analysis results using the median of the distribution of each pharmacokinetic parameter value for grouping of the exposure, indicated significant associations of increasing Cmaxss with the reporting of headache or oral numbness. Oral numbness was also significantly associated with Cavgss. Nausea and/or vomiting had a trend towards higher occurrence with higher Cavgss .

There were no significant associations with the occurrence of AEs in the logistic regression analysis using each pharmacokinetic parameter as a continuous variable.

Safety: Adverse events were recorded as Grade 1, 2, 3, and 4. Most adverse events were of Grade 1 or 2; few Grade 3 adverse events and no Grade 4 events were recorded. The Grade 3 events that occurred were nausea, nausea and vomiting, abdominal discomfort and pain, and skin rash, resulting discontinuation of 6 patients. No dose-related trend was observed in adverse events. Four weeks of APV monotherapy and/or combination therapy with ABC was well tolerated with few treatment-limiting adverse events.

In conclusion, mean Cmax and $AUC_{0-\infty}$ increased less than and greater than proportional, respectively, with dose following single dose and multiple doses. The accumulation index is less than 1.5, indicating no significant accumulation of amprenavir up on multiple dosing. Abacavir affected the pharmacokinetics of amprenavir, whereas amprenavir did not affect the pharmacokinetics of abacavir.

The 1200-mg BID dose after three weeks of therapy provided a mean Cminss for amprenavir (0.28 μg/mL) that was 10–fold higher than its mean *in vitro* IC_{50} (corrected for protein binding) from clinical isolates (0.023 μg/mL) and greater than the *in vivo* trough concentration estimated in the pharmacodynamic model to provide 90% of the maximum antiviral effect over four weeks (EC_{90} = 0.228 mg/mL). Based on this study, 1200-mg BID dose was selected for Phase III clinical trials.

TITLE: A Phase I/II Screening Trial to Identify Potential Partner Compounds to use in Combination with Amprenavir in Subjects with HIV Infection [PROA2001; NDA 21007; # 003, Vol. 8.7 - 8.9].

Background: The sponsor demonstrated that amprenavir (APV) is safe and well tolerated when administered as single, oral doses of up to 1200 mg. This Phase I/II study was designed to evaluate the safety and pharmacokinetics of multiple oral dosing of amprenavir in combination with other protease inhibitors, and to rule-out those combinations that demonstrate significant antagonistic antiviral effects and/or safety concerns.

The primary objectives of this study conducted in three phases were: Phase IA: to determine the single dose pharmacokinetics and possible drug-drug interaction of amprenavir (APV) and indinavir (IND) when administered in combination by comparing to historical single dose controls of each drug alone; and to assess safety and tolerance of single oral doses of APV and IND in combination.

Phase I/II: to determine the steady–state pharmacokinetics and safety and tolerability of APV in combination with saquinavir (SQV), IND, and nelfinavir (NFV) after multiple oral dosing and vice versa; and to evaluate APV in combination with other antiretroviral agents to identify those regimens for further investigations.

Study Design: This was a multi–center, open–label, randomized trial conducted over three distinct phases (Phases IA, I, and II) in HIV–infected, protease inhibitor-naïve, adult subjects with CD4+ cell counts ≥ 200 cells/mm^3 and plasma HIV-1 RNA concentrations >10,000 copies /mL.

The study was conducted in two phases at all sites (Phase I and II), with a single center participating in an additional Phase of the study (Phase IA). Phase IA was a single–dose interaction study with APV and IND to determine the dose of IND to be used in Phases I and II of this study. Based on the results of Phase IA, a dose of 800 mg TID was selected for both APV and IND. Subjects completing Phase IA were eligible for randomization during Phase I if they met all inclusion and exclusion criteria. Randomization occurred once pharmacokinetic data from Phase IA had been analyzed and safety data reviewed.

In Phase I, subjects were randomly assigned to one of four treatment groups:
Treatment Group A: SQV (800 mg TID) + APV (800 mg TID)
Treatment Group B: IND (800 mg TID) + APV (800 mg TID)
Treatment Group C: NFV (750 mg TID) + APV (800 mg TID)
Treatment Group D: APV (800 mg TID)

Subjects in Group A and C took APV at the same time as either SQV or NFV, with food. Subjects in Group B and D took APV either 1 hour before or 2 hours after a meal. Subjects in Group B took APV at the same time IDV was taken.

In Phase I, subjects received 3 weeks of dosing in order to gain information on steady–state pharmacokinetics, acute antiviral activity, and tolerability. Pharmacokinetic studies were conducted during Week 2 of this phase. Those subjects who tolerated the study medication during Phase I were continued into Phase II of the study on the double protease regimens in order to evaluate tolerability and durability of response over a 48–week treatment period. Patients in Group D alone continued on APV plus zidovudine (ZDV) and lamivudine (3TC).

At the time this study was initiated, subjects received APV 800 mg tid. However, during the study, the — mg capsule formulation was replaced by a 150 mg capsule, ——————— therefore, the dose was changed to 750 mg tid.

Only the pharmacokinetic data collected during Phase IA and I, and first 24 week efficacy and safety results are discussed in this review.

Subjects: A total of 34 subjects (8F, 26M; mean age: 40.5 years; mean weight: 75.6 kg) were enrolled. 12 subjects were enrolled into Phase IA and completed the study. 10 subjects from Phase IA continued in to Phase I and an additional 24 were enrolled. 31 subjects completed Phase I of the study and 23 subjects completed week 24. 3 subjects withdrew their consent prior to week 1, one subject withdrew consent prior to week 4, and 6 were lost to follow-up.

Formulations:
APV: — mg (Batch Number SOF SF031542) or 150 mg soft gelatin capsules (Batch Numbers SOF SF046592, SOF SF060606)
SQV: 200 mg soft gel capsules (Batch Numbers SOF C187286–01, SOF C188207)
IND: 200 mg capsules (Batch Numbers CAP 0639DFC032C002, CAP 0639DFC032C006)
NFV: 250 mg tablets (Batch Numbers TAB 077458, TAB MNT3611, TAB MPT8541) were used in this study.

Sample Collection:
Phase IA: Plasma samples for determination of APV and IND concentrations were obtained at pre–dose and at 0.25, 0.50, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6 and 8 h post–dosing.

Phase I: During Weeks 1 and 3, single plasma samples for determination of APV, IND, SQV and NFV concentrations were collected at the same time as samples for determination of plasma HIV ribonucleic acid (RNA) concentrations. During Week 2, blood samples for determination of APV, IND, SQV and NFV and one of its metabolites (M8–NFV) concentrations were obtained at pre–dose, 0.25, 0.50, 0.75, 1, 1.5, 2, 3, 4, 5, 6 and 8 h post–dosing.

RESULTS:
Pharmacokinetic Data Analysis: Pharmacokinetic parameters were obtained by noncompartmental methods for single dose and at steady-state from Phase IA and I. Results from Phase II have not yet been

reported. The sponsor performed ANOVA to calculate geometric least–squares mean (LS Mean) and 95% CI (Proc Mixed in SAS). Pharmacokinetic parameters obtained from subjects who received 750 mg APV (Subjects 368, 369 and 372) were normalized to an 800-mg dose prior to descriptive summarization and statistical analyses. A secondary analysis taking into account treatment, race, weight, age, α1 –acid glycoprotein (AAG), albumin, bilirubin and HIV risk factor (intravenous drug abuse *versus* all others) as fixed effects was also carried out on APV parameters. Mean pharmacokinetic parameters for IND, SQV and NFV were compared to historical data reported in the literature.

Phase IA

The mean plasma concentration time profiles for APV and IND following single doses are presented in Figure 11 and pharmacokinetic parameters for individuals are presented in Table 9. The mean ± sd pharmacokinetic parameters for APV and IND following single doses of APV and IND in combination are presented in the following table:

	Amprenavir			Indinavir	
Parameter	PROA2001 (Current Study)	PROA 1002 (Historical Control)[a]	PROA 1001 (Historical Control)[a]	PROA2001 (Current Study)	Historical Control
AUC_{0-8} (μg*hr/mL) Ratio	25.32 ± 6.24 —	12.8 ± 5.4 1.98	21.5 ± 4.7 1.18	11.2 ± 5.6 —	17.1 ± 6.9 0.65
C_{max} (μg/mL) Ratio	7.2 ± 1.4	—	—	5.5 ± 2.7	7.2 ± 2.9 0.76
T_{max} (hr)	1.4 ± 0.8	—	—	0.8 ± 0.1	—

a Mean AUC 0-8 has been normalized to an 800-mg dose

The APV pharmacokinetic parameters from the present study were compared to historical controls (PROA1001 and PROA1002; AUC_{0-8} was normalized to an 800-mg dose using 900-mg single dose APV data). A 98% increase in mean AUC_{0-8} for APV was observed compared to the value obtained in PROA1002. However, the mean AUC_{0-8} for APV in the present study was not statistically different from the value reported in PROA1001 (18% increase from reference value). This may be due to variability between study populations. Further, it was observed that mean AUC_{0-8} and Cmax were decreased by 35 and 25%, respectively, for IND compared to the historical control data. This could be attributed to variability in across study population and possibly due to the —— formulation of APV.

Phase I: APV, SQV, IDV and NFV multiple dose pharmacokinetics:

The mean plasma concentration time profiles for APV, SQV, IND, and NFV following multiple doses are presented in Figure 12 and pharmacokinetic parameters for individuals are presented in Table 10. The mean ± sd pharmacokinetic parameters of APV, SQV, IND, and NFV at steady-state when administered in combination are presented in the following tables:

APV:

Parameter	Treatment A APV+SQV n=7	Treatment B APV+IND n=9	Treatment C APV+NFV n=6	Treatment D APV alone n=9	Ratio A/D GM ratio 90%CI	Ratio B/D GM ratio 90%CI	Ratio C/D GM ratio 90%CI
AUCss (μg-hr/mL)							
Mean	10.69	21.53	17.31	16.88	0.68	1.33	1.00
%CV	19	27	26	43	0.51,0.91	1.02,1.73	0.81,1.47
GM	10.52	20.46	16.76	15.39			
95% CI	8.14,13.59	16.33,25.65	12.71,22.11	12.28,19.29			
$Cmax_{ss}$ (μg/mL)							
Mean	4.54	8.14	6	7.5	0.63	1.18	0.86
%CV	41	16	31	50	0.46,0.96	0.87,1.58	0.62,1.20
GM	4.23	7.93	5.78	6.74			
95% CI	3.18,5.84	6.18,10.22	4.24,7.88	5.23,8.88			
$Cmin_{ss}$ (μg/mL)							
Mean	0.37	0.45	1.01	0.38	0.88	1.25	2.80
%CV	104	50	53	61	0.48,1.54	0.73,2.16	1.52,5.48
GM	0.27	0.39	0.90	0.31			
95% CI	0.16,0.45	0.25,0.62	0.48,1.67	0.20,0.49			
Cl/F(mL/min)							
Mean	1288	671	824	936	1.48	0.75	0.92
%CV	20	35	30	42	1.10,1.94	0.58,0.98	0.68,1.24
GM	1267	652	796	888			
95% CI	981,1637	520,817	803,1049	891,1086			
$tmax_{ss}$ (h)							
Mean	1.14	0.95	0.79	1.29	—	—	—
%CV	49	29	42	60			

The results from the above table indicate that AUCss, Cmaxss, and Cminss were decreased by 32, 37, and 14%, respectively, with a corresponding increase in mean CL/F (46%) for APV when coadministered with SQV. In this study SQV treatment was given with food. In an earlier study (PROA1010), it was shown that the food affects the rate and extent of absorption of APV. Thus, the observed decrease in AUCss, Cmaxss, and Cminss for APV could be attributed in part to a food effect. In that case, the decrease in AUC due to the co-administration with SQV would be less.

When coadministered with IND, an increase of 33, 18, and 25% in AUCss, Cmaxss, and Cminss, respectively, for APV was observed with a corresponding decrease in CL/F (25%). Both APV and IND are metabolized by CYP 3A4, and IND is more a potent inhibitor of CYP 3A4 than APV (based on *in vitro* evaluation), thereby possibly resulting in increased concentrations of APV.

In contrast, when NFV was coadministered with APV, no significant changes in the pharmacokinetics of APV were observed except for a significant increase in Cminss by 189%.

SQV:

	AUCss (µg-hr/mL)	$Cmax_{ss}$ (µg/mL)	$tmax_{ss}$ (h)	$Cmin_{ss}$ (µg/mL)	Cl/F(mL/min)
Mean	2.58	1.15	1.4	0.071	12854
SD	2.63	1.11	0.9	0.071	10794
95%CI	0.15,5.01	0.12,2.18	0.56,2.18	0.01,0.14	871,22837
Reference (mean)	3.21	0.96	2	0.14	4237
Means ratio	0.81	1.21	0.68	0.52	3.03

The results indicate that AUCss and Cminss for SQV were decreased by 19 and 48%, respectively, and there was a 21% increase in Cmaxss when SQV was given with APV compared to SQV given alone (historical control). These results were not statistically significant. However, this reviewer notes that the comparison of pharmacokinetic data across different study populations may not be ideal.

IND:

	AUCss (µg-hr/mL)	$Cmax_{ss}$ (µg/mL)	$tmax_{ss}$ (h)	$Cmin_{ss}$ (µg/mL)	Cl/F(mL/min)
Mean	13.63	7.01	0.84	0.13	1052
SD	3.70	1.03	0.19	0.06	321
95%CI	10.79,16.47	6.22,7.81	0.70,0.98	0.09,0.17	805,1298
Reference (mean)	21.86	8.98	0.80	0.18	610
Means ratio	0.62	0.78	1.05	0.73	1.72

Statistically significant decreases in AUCss, Cmaxss, and Cminss by 38, 22, and 27%, respectively, with an associated increase in CL/F (72%) were observed for IND when IND was administered with APV relative to when IND was given alone (historical data). Similar changes were seen earlier following a single dose. These differences from historical data could be due to between–study comparisons and/or effect of ——— formulation of APV, as food significantly decreases IND Cmax and AUC. Since the single and multiple dose data are similar, hepatic enzyme induction would not have occurred after a single dose, the decrease in IND concentrations cannot be due to an increase in P450 metabolism.

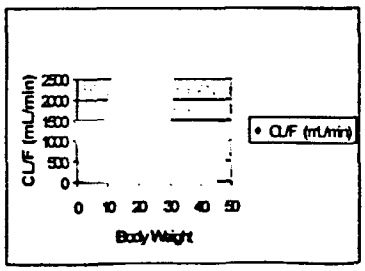
	Children				Adults (PROA 1001)
Parameter	5 mg/kg (n=10)	10 mg/kg (n=9)	15 mg/kg (n=10)	20 mg/kg (C) (n=10)	1200-mg (n=12) (A)
$AUC_{0-\infty}$ (µg*h/mL) GM GM Ratio (A/C)	5.7 ± 3.6 4.9 —	10.3 ± 6.2 8.7 —	13.7 ± 7.2 12.5 —	21.9 ± 14.1 18.3 —	47.1 ± 21.6 42.7 2.3
Cmax (µg/mL) GM GM Ratio (A/C)	3.8 ± 1.9 3.5 —	6.6 ± 3.8 5.7 —	6.9 ± 2.8 6.5 —	8.8 ± 4.6 7.9 —	9.1 ± 2.7 8.7 0.9
Tmax (hr)	0.9 ± 0.4	0.9 ± 03	1.1 ± 0.6	1.6 ± 1.0	2.1 ± 0.8
CL/F (mL/min) GM Wt. Norm.CL/F Ratio [1]	529 ±259 450 25.4±14.3 —	589 ±293 524 20.2 ± 12.4 0.8	542 ± 142 525 18.6 ± 6.4 0.9	551 ± 299 479 24.8 ± 17.2 1.3	519 ± 255 468 8.1 ± 4.0 0.33
$T_{1/2}$ (hr)	7.4 ± 5.4 5.5	6.2 ± 3.9 5.3	8.0 ± 4.8 6.9	8.3 ± 3.9 7.7	9.5 ± 6.8 7.8
Vz/F (L)	360 ±334 215	321 ± 209 238	358 ± 201 314	360 ± 177 318	388 ± 289 317

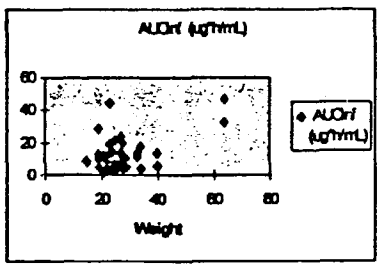
1 Ratio of Wt. Norm. CL/F for each dose level in children and children to adults at 20/mg kg and 1200 mg dose level

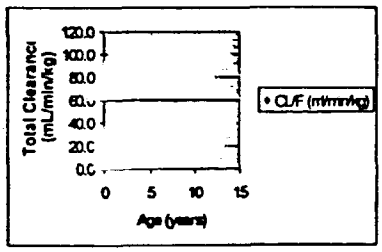
The dose proportionality was examined for Cmax and $AUC_{0-\infty}$ using the linear regression equation (log y= a+ b * log(dose)). It was observed that Cmax (slope = 0.6) and $AUC_{0-\infty}$ (slope = 0.9) increased less than proportional. CL/F (normalized to body weight) and $T_{1/2}$ were dose independent. There was considerable between-subject variability in all pharmacokinetic parameters and the coefficients of variation (CV) were greater than 50%. Since APV is metabolized hepatically via CYP3A4, increased variability is expected in children due to hepatic maturation. Faster metabolism is also expected in children.

Reviewer Remarks: The sponsor reported that the pharmacokinetic parameters observed in this study were similar to those observed in a study of single, oral doses of 150 to 1200 mg of amprenavir in HIV-infected adults. This reviewer calculated the Geometric mean ratios for $AUC_{0-\infty}$ and Cmax for adults (1200-mg single dose) relative to children (20 mg/kg, which is approximately equal to adult dose based on body weight) and observed that $AUC_{0-\infty}$ was two-fold greater in adults than children, while Cmax was similar. This reviewer also calculated and plotted the body weight normalized clearance values obtained after 20 mg/kg in children relative adults who received 1200-mg single dose. It was observed that body weight normalized clearance in children was three times faster than in the adults. This supports the earlier observation that children have lower $AUC_{0-\infty}$ compared to adults. This could be due to the fact that children metabolize the drug more rapidly than the adults and could also be due to decreased absorption. Similar observations were noted when comparing 5, 10, and 15-mg/kg data from this study to the data in adults at 300, 600, and 1050-mg single doses (PROA1001). Thus, based on this information, children may require 2-3 times more drug than adults based on body weight to achieve similar exposure.

Body Weight Vs CL/F; Body Weight Vs AUC_{inf} and CL/F/kg vs Age in children at all doses







NFV:

	AUCss (μg-hr/mL)	$Cmax_{ss}$ (μg/mL)	$tmax_{ss}$ (h)	$Cmin_{ss}$ (μg/mL)	Cl/F(mL/min)
Mean	20.0	3.58	3.72	1.70	722
SD	8.76	1.41	0.77	1.17	298
95%CI	10.83,29.23	2.10,5.05		0.47,2.93	408,1034
Reference (mean)	17.4	3.18		1.49	718
Means ratio	1.15	1.12		1.14	1.0

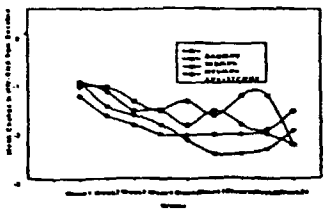
No change in the NFV pharmacokinetic results were observed in this study when compared to historical data.

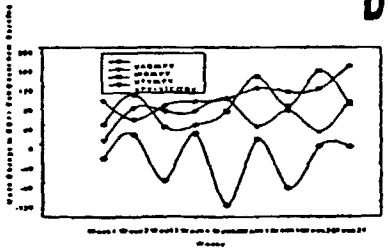
The sponsor performed a secondary statistical analysis taking into account AAG, age, albumin, bilirubin, HIV risk factor, race, treatment, and weight as fixed effects on log–transformed APV pharmacokinetic parameters and the results are summarized in the following table:

Fixed Effects	AUC_{ss} p-value	CL/F p-value	$C_{max,ss}$ p-value	$C_{min,ss}$ p-value
AAG	0.0040	0.0040	0.0263	0.7160
Age	0.4490	0.4477	0.2282	0.5536
Albumin	0.7502	0.7501	0.1110	0.7502
Bilirubin	0.8499	0.8486	0.6399	0.6365
HIV risk factor	0.5075	0.5087	0.4202	0.1046
Race	0.9294	0.9260	0.4595	0.3189
Treatment	0.0042	0.0042	0.0146	0.1259
Weight	0.6391	0.6378	0.1187	0.0633

The results showed that, except for AAG and treatment, all of the above–mentioned covariates had no effect on the pharmacokinetic parameters of amprenavir. AAG levels and treatment had a statistically significant effect on AUCss ($p \leq 0.0040$), CL/F ($p \leq 0.0040$) and Cmaxss ($p \leq 0.0263$). The significant treatment effect simply indicates that the different protease inhibitors had different effects on APV pharmacokinetics. While preliminary analyses of previous studies have suggested that there are racial differences in the pharmacokinetics of amprenavir, race had no effect on APV pharmacokinetics in the present study.

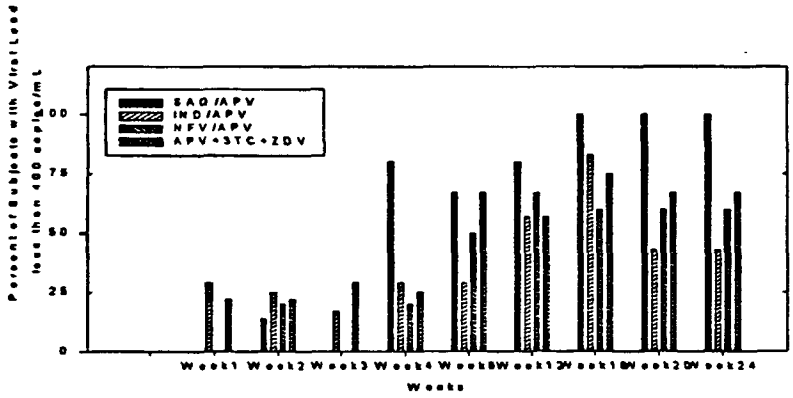
Efficacy Results: HIV-RNA levels were determined by Roche Amplicor assay with a lower limit of quantitation of 400 copies/mL. Mean changes in plasma log (HIV-RNA) and CD4+ count from base line for each treatment over 24 weeks are shown below:





The mean plasma HIV-RNA concentrations decreased rapidly to the threshold limit of the assay in all treatment groups. Mean reductions from baseline of approximately –2.0 log10 copies/mL were observed in the SAQ/APV and IND/APV groups from week 4 through 24, whereas these changes were slightly lower in the NFV/APV and APV+3TC+ZDV group. Similarly, a mean increase from baseline CD4+ cell counts was observed in all three double protease inhibitor treatment groups, at each study week. In contrast, decreases in CD4+ cell counts were observed in the APV+3TC+ZDV group. Reductions in plasma HIV-RNA and increases in CD4+ cell counts suggest that dual combination therapy with APV plus a protease inhibitor may be useful and needs further evaluation.

Proportion of subjects with plasma HIV-RNA <400 copies /mL provides another view of efficacy as shown below:



The results indicate that the majority of subjects had plasma HIV-RNA concentrations <400 copies/mL at week 16.

Safety: Safety results demonstrated that all treatments of APV combined with protease inhibitors or 3TC/ZDV were well tolerated. The most common drug related adverse events observed were nausea, gaseous symptoms, headache, and rash.

In conclusion, APV concentrations were generally decreased by SQV after multiple dosing and modestly increased by IDV after single and multiple dosing. With NFV there was a significant increase in Cminss of APV but no effect on Cmaxss or AUCss. APV produced a 38% decrease in IDV plasma concentrations, comparable to the effect of a meal, and no changes in the steady–state pharmacokinetics of NFV and SQV. No racial differences were observed in the steady–state pharmacokinetic parameters of APV. A statistically significant relationship was observed between the total concentrations of APV (bound and unbound drug) and α1 –acid glycoprotein concentrations, with decreasing AAG associated with decreasing total concentrations of APV.

Title: A Phase I, Open–Label, Dose–Escalation Clinical Study to Assess the Pharmacokinetics and Tolerability of Single, Oral Doses of Amprenavir in HIV–Infected Children [PROA1006, NDA 21,007, Vol. 1]

Background: Amprenavir is a promising new HIV–1 protease inhibitor that has produced substantial decreases in plasma viremia in adults given a dose of 1200 mg twice daily. The sponsor intends to make this new drug available to both adult and pediatric patients. Thus, information on the safety and pharmacokinetics of amprenavir in the pediatric population was required in order to select a dose that would be appropriate for this group of patients in subsequent efficacy trials. The present study was undertaken in order to provide this information. The doses selected for this study (5, 10, 15, and 20 mg/kg) were chosen to bracket the range of individual doses employed in the dosing regimens studied in adult Phase I/II single and multiple dose studies (300-1200 mg).

The primary objectives this study were to determine the single dose pharmacokinetics and safety of amprenavir in HIV-infected children ≤13 years of age.

Study Design: This was a Phase I, open–label, dose–escalation trial designed to assess the pharmacokinetics and tolerability of single, oral doses of amprenavir soft gel capsules in HIV–infected children. Two groups of 10 HIV–infected subjects less than 13 years of age each received 2 single escalating doses of amprenavir separated by a minimum 7–day washout period.
Plasma samples were collected over 24 hrs at regular intervals.

Group I: received 5 and 10 mg/kg; Group II: received 15 and 20 mg/kg.

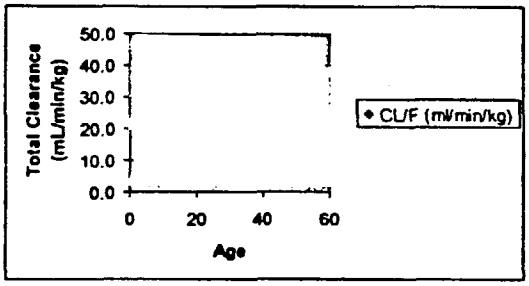
Subjects: Twenty clinically stable HIV–1 infected children (9F, 11M; mean age: 8.4 years (range 4 to 12 years); mean body weight 27.4 kg) were enrolled and completed the study.

Formulation: – and 150-mg soft gelatin capsules (batch numbers (BIN) SOF 6M2742 and SOF 5Y2752, respectively) were used in this study.

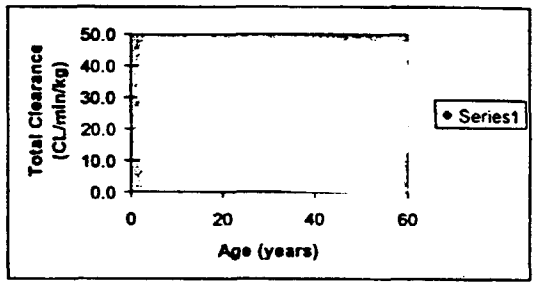
RESULTS:
Pharmacokinetic Data Analysis: Pharmacokinetic parameters were obtained by noncompartmental methods. One subject vomited after receiving 10 mg/kg dose and hence the data from this subject were excluded in calculating pharmacokinetic parameters.

The mean plasma concentration time profiles are presented in Figure 13 and pharmacokinetic parameters for individuals are presented in Table 11. The mean pharmacokinetic parameters for all treatments are presented in the following table:

CL/F/kg Vs Age (5-20 mg/kg in children and 1200 mg in adults)



CL/F/kg Vs Age (20 mg/kg in children and 1200 mg in adults)



The sponsor performed simulations based upon the 20 mg/kg dose given twice daily and predicted that the steady–state trough concentrations (Cminss) will be about 360 ng/mL. This concentration was comparable to that observed in a multiple–dose study in adults receiving amprenavir as monotherapy at 1200 mg twice daily (280 ng/mL).

Safety: : Safety results demonstrated that all treatments of APV were well tolerated.

In conclusion, $AUC_{0-\infty}$ and Cmax increased less than proportionally. CL/F and $T_{1/2}$ were dose independent. Weight normalized total clearance was three times greater in children compared to adults (receiving approximately equivalent doses based on body weight), indicating that children may require higher dose to achieve similar exposure as adults.

Title: A Phase II Trial to Assess the Preliminary Antiviral Effect, Pharmacokinetics, Safety and Tolerability of Multiple Oral Doses of Amprenavir Liquid Formulation in Combination with NRTIs in HIV Infected Children Below 13 Years Old [PROB 2004; NDA 21007; Vol. 1].

Background: Based on the pharmacokinetic information in children from study PROA 1006 and data from adult studies, the sponsor conducted this multiple dose study in children to determine the pharmacokinetic and safety profiles of amprenavir (APV) in children. In addition the anti–retroviral effect of APV in combination with approved nucleoside reverse trascriptase inhibitors (NRTIs) in PI naïve and experienced children was evaluated.

The primary objectives of this study were: to assess the anti–retroviral effect, safety and tolerability of APV oral solution, in combination with approved NRTIs, in HIV infected children over the 48 week period and to determine and compare the pharmacokinetics of two dosing regimen of APV oral solution, 20mg/kg BID and 15mg/kg TID, in HIV infected children below 13 years old.

Study Design: This was a Phase II, randomized, open label, parallel group, multicentre trial designed to assess the pharmacokinetics and tolerability of multiple oral doses of APV oral solution (15mg/mL) in combination with approved NRTIs for a period of 48 weeks in one of two dosing regimen: Group I: 20mg/kg BID APV oral solution; Group II: 15mg/kg TID APV oral solution.

Recruitment was sequential according to age into 3 cohorts: Cohort I: 7 years – <13 years; Cohort II: 4 years – <7 years; and Cohort III: 2 years – <4 years). In this interim report, the sponsor provided the

pharmacokinetic, safety, and efficacy results of children from cohorts I and II. Subjects could be PI naïve or experienced; and NRTI naive or experienced. Prior treatment with non nucleoside reverse transcriptase inhibitor (NNRTI) therapy was permitted but had to be stopped at least 28 days before study Day 1.

Subjects: 42 clinically stable HIV–1 infected children (15F, 22M; mean age: 7.6 years (range 4 to 12 years; mean body weight 25.2 kg) were enrolled and 37 completed the study. Two subjects withdrew consent before the start of the study, one subject withdrew consent at Day 5 of the study, one subject was withdrawn on day 9 due to adverse event (grade 2 rash), and one subject had a deferred APV start date.

On day 15 (Week 2), blood samples were drawn for the steady–state PK analyses: prior to the morning dose and 1, 2, 4, 6, 8, and 12 hours after dosing.

Formulation: APV Oral solution (15 mg/mL; Batch No. A97B123 and A97B210 (——→ flavor) was used in this study.

Sample Collection: Plasma samples were taken for PK analysis at every visit (pre dose, weeks 2, 4, 8, 12, 16 and every 8 weeks thereafter until Week 48); the steady–state PK profile was measured at week 2, and samples for population PK were taken throughout the study.

RESULTS:

Pharmacokinetic Data Analysis: Pharmacokinetic parameters were obtained by noncompartmental methods. The mean plasma concentration time profiles are presented in Figure 14 and pharmacokinetic parameters for individuals are presented in Table 12. The mean ± sd (%CV) pharmacokinetic parameters for all treatments are presented in the following table:

Parameter	Children		Adults (PROA 1002)
	4 to ≤ 13 years	4 to ≤ 13 years	1200-mg BID (n=5)
	20 mg/kg BID (n=20)	15 mg/kg TID (n=17)	
AUCss (μg*h/mL)	15.5 ± 9.1 (59%)	8.7 ± 3.1 (36%)	18.5 ± 11.6 (62%)
Cmaxss (μg/mL)	6.7 ± 3.4 (51%)	4.0 ± 1.6 (37%)	5.4 ± 3.3 (61%)
Cavgss (μg/mL)	1.3 ± 0.76 (59%)	1.1 ± 0.4 (36%)	1.5 ± 0.9 (60%)
Cminss (μg/mL)	0.241 ± 0.237 (98%)	0.273 ± 0.258 (95%)	0.28 ± 0.15 (54%)

The results indicate that mean Cmaxss and AUCss are lower in TID regimen compared to BID regimen. These differences could be due to different regimen and variability between subjects (CV ranges between 36-59%). The reviewer observed no difference in mean Cavgss and Cminss between regimens within cohort or pooled across cohort. The sponsor also reported that no statistical difference was noted in Cavgss or Cminss between cohorts I and II in either dose group. Since no differences could be detected between the age cohorts, data from all subjects were pooled within regimen. In the earlier interim report where data from 22 subjects were used, mean CL/F (normalized to body weight) was observed to be greater in children compared to adults, but no such difference was observed among children of different age groups. This observation is consistent with the observation made in the earlier single dose study in children (PROA 1006). However, the sponsor did not report the Cl/F data for all the subjects in this interim report and stated that the information will be provided in the final study report.

The sponsor also compared the individual week 2 trough concentration data from this study with the trough concentrations obtained in the ongoing pivotal clinical trial (PROAB3001, n=41) in adults and reported that they were comparable (Figure 14a). This reviewer notes that the comparison of individual trough concentrations across patient population with a small sample size and high between subject variability may not provide adequate and meaningful information.

Efficacy: A total of 13 subjects achieved a reduction in plasma HIV-1 RNA to below 10,000 copies/mL by week 4. Both treatment regimens in combination with NRTI induced a good viral response. The sponsor reported that by the data cut-off date (week 16), decrease in plasma HIV-RNA (>0.7 $\log_{10}$ copies /mL) was observed in 8/14 subjects in the 20 mg/kg BID group and 6/9 subjects in the 15 mg/kg TID group. However, due to the small number of subjects and short exposure duration (week 16), a meaningful conclusion can not be drawn regarding efficacy at this stage.

Safety: APV oral solution in combination with various NRTIs was well tolerated in these HIV-infected children, except for four children in whom clinically significant adverse events were noted. These include thrombocytopenia, severe rash, and anorexia.

In conclusion, the data support the use of 20 mg/kg BID or 15 mg/kg TID when amprenavir is given as capsules and 22.5 mg/kg BID or 17 mg/Kg TID when amprenavir is given as the oral solution.

Title: A Phase III, Open Label Trial to Evaluate the Safety, Antiviral Efficacy and Pharmacokinetics of Amprenavir Plus Current Therapy in HIV–1 Infected Children [PROAB3004, NDA 21007, Vol. 3]

This study was a randomized trial initially, then was amended to be an open label trial. The protocol was designed to evaluate the safety, antiviral efficacy and durability of antiviral response of APV when added to NRTI therapy in HIV–infected subjects aged six months (180 days) to 18 years. The dose for subjects ≥ 13 years of age with a weight ≥ 50 kg who were able to tolerate capsules was 1200-mg BID orally; for subjects who were able to tolerate capsules and were ≥13 years of age but with a weight < 50kg, the dose was 20mg/kg BID orally. Subjects < 13 years who were able to tolerate capsules received a dose of 20mg/kg BID orally. The dose of APV was 22.5 mg/kg BID using the 15mg/mL oral solution for subjects unable to swallow capsules. All the formulations used were to be marketed formulations.

In this submission, the sponsor presents an interim report of efficacy and safety analysis. The sponsor reported that all pharmacokinetic samples will be assayed and formal pharmacokinetic analysis will be provided in the final study report.

Title: A Phase II study to investigate the safety, tolerability, pharmacodynamics and antiviral activity of multiple dosing amprenavir (APV) in combination with zidovudine (ZDV)/3TC in patients with HIV infection [PROA2002, NDA 21007, Vol. 8.11]

This was a randomized, partially blinded, parallel–group, Phase II study in 80 subjects assigned to one of four APV or placebo treatment arms: (Group A 900mg BID, Group B 1050mg BID, Group C 1200mg BID, Group D APV–placebo matched to 1050mg BID). Subjects also received 300mg BID ZDV and 150mg BID 3TC. After Week 12, subjects in the control group received open label APV, 1050mg BID, instead of APV–placebo. Subjects were monitored before entry, at Day 1, Day 4 and then at Weeks 1, 2, 3, 4, 6, 8, and 4–weekly thereafter until the last subject had completed 48 weeks on study.

Plasma samples for pharmacokinetic/pharmacodynamic evaluation were taken in conjunction with all scheduled virology samples between Day 4 and Week 48 except for weeks 2 and 12 where plasma samples were taken just prior to each subject's regular morning dosing time.

The sponsor reported that this is an interim pharmacokinetic/pharmacodynamic analysis of the data available so far. A separate report on the analysis of the remaining data will be issued at a later stage, when the analysis of all the samples collected in this study is completed. The results of this interim report are summarized as follows:

Large inter and intra subject variability was observed, with CVs as high as 70% and 240%, respectively, for the median trough levels within the different treatment groups. There appeared to be no significant differences between trough levels after different dosing regimens of APV or between subjects of different ethnic origin or gender (N=46: 38 M; 8 F; 4 Blacks; 37 Whites, 5 others). No significant relationship was found between the trough levels of amprenavir at steady–state and the changes in the plasma HIV–1 RNA and CD4+ cell counts over the first 12 weeks of treatment, in the subset of the pharmacokinetically evaluable subjects.

Further, this reviewer noted that APV administered at oral BID doses of 900, 1050, and 1200-mg, in a triple combination with ZDV/3TC had a potent antiviral effect over the 12 week study period.

This study will be reviewed further when the final formal pharmacokinetic/pharmacodynamic analysis is submitted by the sponsor.

Title: A Phase III Trial to Evaluate the Safety and Antiviral Efficacy of Amprenavir in Combination with Retrovir and Epivir Compared to Retrovir and Epivir Alone in Patients with HIV Infection [PROAB3001, NDA 21007, Vol. 5.9]

The primary objectives of this study were to: compare the antiviral activity and durability of antiviral response of the triple combination of amprenavir (APV)/Retrovir (zidovudine, ZDV)/Epivir (lamivudine, 3TC) versus the double combination of 3TC/ZDV based on changes in viral load measured as human immunodeficiency virus (HIV)–1 RNA and CD4+ cells at 16 weeks.

The secondary objectives were: to assess the safety and tolerability of multiple oral doses of APV in combination with ZDV and 3TC; and in subjects who change therapy, to assess the antiviral effect of APV in combination with abacavir (ABC), and/or approved antiretrovirals; and to collect plasma samples for APV concentration analyses for a population–based pharmacokinetic and/or pharmacodynamic analysis.

Study Design: This study was designed as a randomized, double–blind, placebo–controlled, multicenter study conducted in the US and Europe to compare the safety, tolerance, viral load reduction, and CD4+ lymphocyte response at 16 weeks and the durability of response at 48 weeks in HIV–infected subjects treated with APV/3TC/ZDV versus 3TC/ZDV alone. Subjects were randomly assigned to one of the following two treatment groups, stratified by screening plasma HIV–1 RNA level (10,000–30,000, >30,000–100,000, or >100,000 copies/mL):