

Agenerase NDA 21-007&21-039

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Group I: APV (1200mg BID)+ ZDV (300mg BID) + 3TC (150mg BID)

Group II: APV placebo (BID) + ZDV (300mg BID) + 3TC (150mg BID)

To be enrolled in the study, subjects had to be naïve to all HIV protease inhibitors, must not have received greater than 4 weeks of therapy with any reverse transcriptase inhibitor (RTI), and must not have had a previous diagnosis of the acquired immunodeficiency syndrome (AIDS).

Subjects: 232 subjects (26F; 206M; mean age 36.6 years; mean body weight: 77 kg), with 116 subjects per treatment group, were enrolled in this study.

Formulations: APV: 150mg or — soft gelatin capsules; Matching placebo: 150 and — mg; ZDV: 300 mg tablets and 100mg capsules; 3TC: 150mg tablets; and ABC: 300mg tablets were used in this study.

Drug Name	Batch No.	
	US Sites	European Sites
APV (active)	031629/A, 032175, 032780, 032781, SF046502, SF048601, SF030308	150mg (032170/A) T97/228A (32176) T97/241A
	029899 SF031542	— mg SF031542 (029899) T97/128A (029899) T97/048A
APV (placebo)	031735/A 002758	150mg (031735/A) T97/150A (031730/A)
	029897 E900208 E900217	— mg E900208 (29897) T97/049A (29897) T97/129A
ZDV	5N2710 602766	300mg (3297A) T97/234A (3297A) E07B39 (3297A) T97/050A (3205/A) T96/232A
	5Y2760	100mg (3271K/A) T97/145A (3206B) T97/226A ACT-3048N/A
3TC	5Z1210, 6ZM0279 6ZM0280, 6ZM0747	150mg W0296FB
ABC	W0017KM, W0117NA, W0127NC, WA97B35AA, WA97B37AA	300 mg WA97B36AA, WA97B35AA, W0068BF

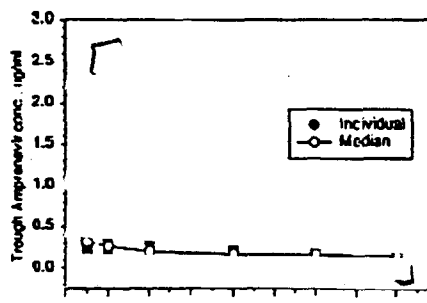
RESULTS:

Pharmacokinetic Data Analysis: The sponsor intends to do population based PK and PK-PD analyses after the completion of study. However, in this submission, interim results of PK and PK-PD analyses were reported with summary statistics for individual trough concentrations over the 16 week evaluation for a total of 71 subjects (62M, 9F), but no formal statistical comparisons were attempted. Median amprenavir trough concentrations versus AAUCMB for log₁₀ HIV-1 RNA levels and CD4+ cell counts was performed to detect if a relationship between exposure and efficacy was apparent.

Summary statistics for the APV trough concentrations by visit and individual trough concentrations are presented in the following table and figure:

Week	N	Trough APV concentration, µg/ml					
		Mean	S.D	CV, %	Median	Minimum	Maximum
1	22	0.333	0.203	61	0.310		
2	41	0.353	0.461	131	0.262		
4	35	0.237	0.243	102	0.193		
8	33	0.242	0.361	149	0.164		
12	32	0.182	0.120	66	0.155		

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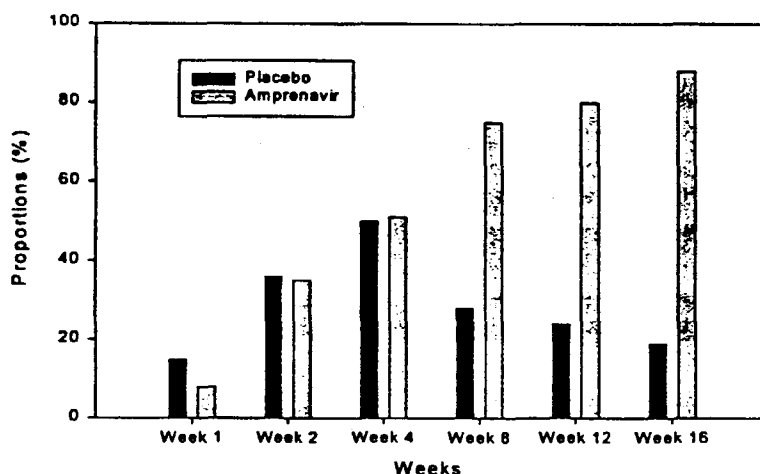
Between and within subject variability was observed to be high (CV range: 61 to 149% and 7 to 173%, respectively), which could be due to discrepancies in the times that doses and samples were recorded compared to the actual times of these events. This reviewer notes that the above figure demonstrated a trend of decreasing concentration of APV over the initial eight week period and then stabilizing through week 16. The time variant pharmacokinetics observed in this study are consistent with similar changes observed in PROA1002 and could be possibly due to lowering of α -1-acid glycoprotein (AAG) levels during antiretroviral therapy with APV. Free APV concentration in the plasma would be expected to modestly increase over time due to the lowering of AAG levels during therapy resulting in lower total APV concentrations. Other possible explanations include decreased absorption due to formulation problems, induction, compliance, and possible drug-drug interactions. In addition, the observed mean and median total APV concentrations at 16 weeks reported in this study were approximately 5-6 fold higher than the median *in vivo* IC50 from clinical isolates (0.028mg/mL;

The sponsor reported that no apparent difference in mean trough concentrations between males and females was observed. But median trough concentrations were lower in females, as trough concentrations were below the detection limit in 4/9 females. Similarly, blacks (n=10) and hispanics (n=7) tended to have modestly lower mean trough APV concentrations than whites (n=52). However, the small sample size precludes definitive interpretation.

The sponsor performed PK-PD correlation using the simple Emax and inhibitory Emax model. A modest correlation was observed between APV median trough concentrations and the changes in plasma HIV-1 RNA ($r^2=0.24$), but no significant relationship was observed between APV median trough concentration and changes in CD4+ cell counts.

Efficacy: For the 16-Week analysis, the primary efficacy endpoint was antiviral activity, defined as the proportion of subjects with plasma HIV-1 RNA <400 copies/mL who did not progress to a CDC Class C event or death. This analysis revealed that the triple combination of APV plus 3TC/ZDV was superior ($p<0.001$) to placebo plus 3TC/ZDV through 16 weeks of treatment in antiretroviral therapy-naïve subjects as depicted in the following figure.

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Safety: The two combination treatment regimens (APV/3TC/ZDV and placebo plus 3TC/ZDV) were generally well tolerated. The most common drug-related AEs were nausea, gaseous symptoms, fatigue, oral/perioral paresthesia, vomiting, headache, rash, and diarrhea. Only nausea, oral/perioral paresthesia, rash, and vomiting were higher in subjects treated with APV/3TC/ZDV compared to 3TC/ZDV alone. Nausea was the most common AE that led to discontinuation of study medication (1, 3TC/ZDV; 11, APV/3TC/ZDV); only three cases of rash were treatment-limiting (1, 3TC/ZDV; 2, APV/3TC/ZDV). Only one subject had a recurrence of rash after re-introduction of study drug.

In conclusion, the reviewer observed time variant pharmacokinetics of amprenavir which could be attributed to lowering of α -1-acid glycoprotein (AAG) levels during antiretroviral therapy with APV, decreased absorption due to formulation problems or induction, compliance, and possible drug-drug interactions.

Title: A study to compare the pharmacokinetics of a single, oral, 600 mg dose of amprenavir in healthy volunteers and patients with cirrhosis [(Protocol no.: PROB1008) NDA 21007 Volume 3.11].

Objectives: (i) To compare the pharmacokinetics of a single 600 mg dose of amprenavir following oral administration in healthy volunteers and subjects with cirrhosis (ii) To determine the dosing recommendations based on changes in hepatic function.

Subjects: 30 subjects were enrolled in the study.

	Healthy	Moderate cirrhosis	Severe cirrhosis
Male / Female	7 / 3	7 / 3	6 / 4
Mean age, years	51	51	52
Mean body weight, kg	79.5	80.4	73.9
Median Child-Pugh score (range)		5.0 (5 - 6)	9.0 (8 - 12)

Study Design: Subjects enrolled in this study received a single 600 mg oral dose amprenavir. The Applicant states that a decrease in clearance was anticipated in patients with cirrhosis and a dose of 600 mg was chosen to limit exposure in these subjects. Subjects received the treatments under fasted conditions.

Formulation: Amprenavir soft gelatin capsules (150 mg, batch number 6R2782) were used in this study.

Sample Collection: Blood samples were obtained at predose, and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 15 and 24 hours after amprenavir administration to healthy subjects. In subjects with cirrhosis, five additional samples were collected at 34, 48, 58, 72 and 96 hours.

Pharmacokinetic Data Analysis: Pharmacokinetic parameters were estimated by non-compartmental methods. The C_p -t profiles for amprenavir are shown in Figure 15 and pharmacokinetic parameters are presented in Table 1.

Table 1. Mean (%CV) pharmacokinetic parameters of amprenavir.

	Healthy subjects	Subjects with	
		Moderate cirrhosis	Severe cirrhosis
C_{max} , ng/mL	4900 (28)	6483 (35)	9434 (28)
T_{max} , h	0.98 (31)	1.08 (38)	1.08 (80)
$AUC_{0-\infty}$, ng.h/mL	11999 (37)	25761 (57)	38656 (37)
Half-life, h	5.56 (25)	7.81 (65)	7.93 (50)
CL_T/F , mL/min	946 (37)	564 (73)	295 (35)
V/F, L	462 (49)	458 (147)	196 (56)

Since amprenavir is extensively metabolized in the liver, hepatic impairment significantly affected the single dose pharmacokinetics of amprenavir. The changes in the pharmacokinetics are shown in Table 2.

Table 2. Geometric LS Mean ratio and 90% confidence interval.

	Subjects with mod. cirrhosis / Healthy subjects	Subjects with sev. cirrhosis / Healthy subjects
C_{max}	1.28 (0.95, 1.74)	1.96 (1.34, 2.87)
$AUC_{0-\infty}$	2.46 (1.76, 3.44)	4.51 (3.06, 6.67)
Half-life	1.26 (0.91, 1.75)	1.33 (0.89, 1.99)
CL_T/F	0.41 (0.29, 0.57)	0.22 (0.15, 0.33)
V/F	0.66 (0.39, 1.11)	0.32 (0.16, 0.62)

Statistical analyses:

Relationship between Child-Pugh score and pharmacokinetic parameters

As shown in Figure 16, there is clear relationship between hepatic impairment and exposure to amprenavir. The mean C_{max} and AUC_{∞} increased with increasing hepatic impairment and clearance decreased with increasing hepatic impairment. The Applicant has performed linear regression of various pharmacokinetic parameters with respect to Child-Pugh score (a score of zero was assigned to healthy subjects). The Applicant has proposed a dose adjustment schedule for patients with hepatic impairment based on linear regression of AUC_{∞} with respect to Child-Pugh score. As per the Applicant's recommendation, HIV infected patients with a Child-Pugh score of 5 – 8 and 9 – 15 will receive 450 mg

BID and 300 mg BID, respectively. The recommended dose for HIV patients with no hepatic impairment is 1200 mg BID.

Reviewer's remarks: In the opinion of this Reviewer, regression of a continuous variable against a discreet variable may not be appropriate. Further, assigning a Child-Pugh score of '0' to all healthy subjects is not acceptable. However, the dose adjustments proposed by the Applicant may also be justified by the following observation made by the Reviewer. As shown in Table 2, AUC_{∞} increased by 2.5- and 4.5- fold in subjects with moderate and severe hepatic impairment, respectively. In order to achieve similar exposure in these subjects when compared to healthy subjects, $1/2.5 (= 0.40)$ and $1/4.5 (= 0.22)$ of the recommended dose may be administered to subjects with moderate and severe hepatic impairment, respectively. This corresponds to a dose of 480 mg BID and 265 mg BID for subjects with moderate (C-P score 5 – 8) and severe (C-P score 9 – 12) hepatic impairment, respectively. Based on available strengths, the doses can be rounded to 450 mg BID and 300 mg BID (as proposed by the Applicant).

Relationship between AUC_{∞} and albumin, prothrombin time and bilirubin

The Applicant evaluated the relationship between AUC_{∞} and albumin, prothrombin time and bilirubin. An ANOVA model was employed taking into account the gender and mean baseline value for albumin, prothrombin time and bilirubin. Among the three lab data, bilirubin was found to have a significant ($p=0.01$) association with AUC_{∞} . The p values for albumin and prothrombin time were 0.26 and 0.52, respectively.

The relationship between AUC_{∞} and bilirubin was further evaluated using E_{max} models. The Applicant used the simple E_{max} and the sigmoid E_{max} models with five different weighting schemes. Simple E_{max} model with no weights was found to best describe the data. The parameter estimates for the model are shown in Figure 17. This relationship between amprenavir and bilirubin suggests that these two species may share a common metabolic pathway.

α 1- acid glycoprotein score analysis

Since amprenavir is primarily bound to α 1- acid glycoprotein, the Applicant measured the serum levels of α 1-acid glycoprotein in each subject. A score was assigned to each subject according to the following formula:

$$\alpha 1\text{- acid glycoprotein score} = (\text{value} - (H+L)/2) / (H - L)$$

where, H and L are the upper and lower limits of the normal range, respectively.

The mean α 1- acid glycoprotein scores were -0.176, -0.392 and -0.624 in healthy subjects, subjects with moderate and severe cirrhosis, respectively. These differences were statistically significant ($p=0.013$ and 0.003 for the moderately and severely impaired groups). The Applicant states that the above formula was used to "avoid a high difference observed for α 1-acid glycoprotein normal range between each laboratory". The Applicant has not provided the individual values for α 1-acid glycoprotein.

The Applicant states that the decrease in α 1- acid glycoprotein is most likely due to hepatic impairment, as this protein is synthesized in the liver. As a result of lower protein concentrations, the free fraction of amprenavir may have increased, leading to an increase in total clearance. However, since the total clearance decreased in subjects with hepatic impairment, it appears that such impairment affected amprenavir pharmacokinetics to a greater degree than did protein binding.

In conclusion, the results of this study indicate that hepatic impairment significantly affects the pharmacokinetics of amprenavir. Exposure as measured by AUC_{∞} , increased by 2.5 and 4.5 fold in subjects with moderate and severe hepatic impairment, respectively. Dose adjustments should be made to subjects with hepatic impairment. Subjects with Child-Pugh scores of 5 – 8 and 9 – 12 should receive amprenavir at doses of 450 mg BID and 300 mg BID, respectively.

The relationship between total bilirubin and AUC_{∞} of amprenavir can be reasonably described by simple E_{max} model. Increase in total bilirubin resulted in increased exposure to amprenavir. Serum $\alpha 1$ - acid glycoprotein levels were lower in subjects with hepatic impairment. Despite a possible increase in free drug concentration, total clearance was lower in these subjects as a result of hepatic impairment.

Title: A randomized, crossover study to evaluate the safety and pharmacokinetics of 141W94, zidovudine and lamivudine alone and in combination after single-dose administration in HIV-infected subjects [(Protocol no.: PROA1003) NDA 21007 Volume 8.1].

Objectives: (i) To determine the pharmacokinetics and safety of single doses of amprenavir, zidovudine (ZDV) and lamivudine (3TC) when administered alone and in two and three drug combinations. (ii) To assess whether pharmacokinetic interactions exist between amprenavir, ZDV and 3TC after single dose administration.

Subjects: A total of 42 HIV-positive subjects (without AIDS) were enrolled in the study and 33 subjects completed all four treatment periods. Fourteen subjects were randomized to each of the three cohorts. Ten, 11 and 12 subjects completed Cohorts I, II and III, respectively.

Nine subjects discontinued the study prematurely and did not complete all four treatments. Three subjects withdrew from the study due to adverse events. One subject with a medical history of seborrhea experienced worsening of facial seborrhea. A second subject with a medical history of renal stones and migraine headaches was discontinued after confirmation of presence of renal calculus. The third subject was withdrawn from the study due to profuse dental bleeding. These adverse events were not considered to be study related by the investigator.

Three subjects were discontinued from the study because of protocol violations (One subject was treated for a urinary tract infection 24 hours prior to study drug dosing and two subjects tested positive in drug screens). One subject did not return to receive the second treatment and two subjects were discontinued following a decision by the Applicant to close a study center.

Study Design: The study was conducted in a randomized, four-period crossover fashion. Subjects were randomly assigned to one of the following three cohorts and received four (out of a total of eight) treatments mentioned in the following table. Within each cohort, subjects were randomized to a treatment sequence according to a 4 x 4 William's square design.

Cohort no.	Treatment no.	Dose, mg		
		Amprenavir	Zidovudine	Lamivudine
I	1	600 mg		
	2		300 mg	
	4	600 mg	300 mg	
	7	600 mg	300 mg	150 mg
II	1	600 mg		
	3			150 mg
	5	600 mg		150 mg
	7	600 mg	300 mg	150 mg
III	2		300 mg	
	3			150 mg
	6		300 mg	150 mg
	8	Placebo	300 mg	150 mg

Subjects received a single dose of each antiviral agent and the treatments were separated by a washout period of at least 7 days. All treatments were administered under fasted conditions with 8 fluid ounces of water.

Formulation: Amprenavir soft-gelatin capsules (150 mg, batch number 5P2740), zidovudine capsules (100 mg, Retrovir®) and lamivudine tablets (150 mg, Epivir®) were used in this study.

Sample Collection: Blood samples were obtained at predose and at 0.25, 0.50, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hours after each treatment. Urine was collected during the following time intervals: 0 – 4, 4 – 8, 8 – 12 and 12 – 24 hours after each treatment.

Pharmacokinetic Data Analysis: Pharmacokinetic parameters were estimated by non-compartmental methods. The Applicant performed the following statistical analyses on log-transformed pharmacokinetic parameters. The initial analysis involved evaluating each cohort individually, in which each cohort was viewed as an independent four-way crossover study. The following general model was used:

$$\text{PK parameter} = \mu + \text{subject} + \text{treatment} + \text{period} + \text{carryover}$$

According to the Applicant, there was no evidence of carryover effect in the 'by-cohort' analyses. After removing the carryover term, there were no significant period effects. As a result, the Applicant performed the primary analyses on pooled data (across cohorts for a given treatment) and Treatment 6 was combined with Treatment 8. Appropriate models were then used for amprenavir, ZDV, and 3TC pharmacokinetic parameters.

The plasma concentration - time profiles for amprenavir, ZDV, ZDV glucuronide and 3TC under various treatments are shown in Figures 18, 19, 20 and 21, respectively. When compared to the respective reference treatments, the plasma profiles were superimposable for all analytes. The pharmacokinetic parameters for amprenavir, ZDV ZDV-glucuronide and 3TC are presented in Tables 1, 2, 3 and 4, respectively. Although the Sponsor had combined Treatments 6 and 8 for the purposes of statistical analyses, this Reviewer has presented the pharmacokinetic parameters from these two treatments separately for the sake of clarity.

By employing the statistical method described above, the Applicant has calculated the geometric LS mean ratio for two and three drug combinations with respect to reference treatment (not shown in the tables below). The Applicant has also calculated the 90% confidence intervals for the geometric LS mean ratio. The ratios and the 90% confidence intervals were, in most instances, within acceptable limits and did not indicate occurrence of significant drug interaction.

Table 1. Mean (%CV) pharmacokinetic parameters of amprenavir

	Amprenavir (n = 26)	Amprenavir + ZDV (n = 12)	Amprenavir + 3TC (n = 11)	Amprenavir + ZDV + 3TC (n = 23)
C _{max} , µg/mL	5.32 (34)	5.76 (24)	5.32 (50)	5.18 (35)
AUC _∞ , µg.h/mL	12.47 (44)	14.30 (42)	12.99 (52)	11.97 (43)
Half-life, h	6.78 (72)	5.94 (40)	7.53 (63)	8.52 (82)
CL _T /F, L/h	58.23 (48)	47.81 (37)	59.11 (52)	60.78 (49)

Table 2. Mean (%CV) pharmacokinetic parameters of ZDV

	ZDV (n = 26)	ZDV + amprenavir (n = 12)	ZDV + 3TC (n = 13)	ZDV + 3TC + placebo (n = 12)	ZDV + 3TC + amprenavir (n = 23)
C _{max} , µg/mL	1.38 (41)	1.93 (37)	1.52 (43)	1.20 (34)	1.67 (43)
AUC _∞ , µg.h/mL	1.79 (24)	2.45 (32)	1.72 (27)	1.60 (28)	2.15 (27)
Half-life, h	1.96 (55)	2.23 (77)	1.43 (39)	1.58 (38)	1.97 (38)
CL _T /F, L/h	177.24 (24)	134.38 (33)	186.90 (30)	204.0 (34)	148.19 (24)

Table 3. Mean (%CV) pharmacokinetic parameters of ZDV- glucuronide

	ZDV (n = 26)	ZDV + amprenavir (n = 12)	ZDV + 3TC (n = 13)	ZDV + 3TC + placebo (n = 12)	ZDV + 3TC + amprenavir (n = 22)
C _{max} , µg/mL	5.73 (48)	5.45 (55)	5.07 (25)	4.57 (34)	4.39 (42)
AUC _∞ , µg.h/mL	8.18 (39)	9.21 (43)	6.65 (26)	6.39 (31)	8.01 (35)
Half-life, h	1.74 (82)	1.87 (58)	1.39 (43)	1.39 (30)	2.75 (184)

When compared to administration of ZDV alone, ZDV AUC_∞ increased by 20 to 37% and C_{max} increased by 21 to 40% when ZDV was administered with amprenavir. This increase in ZDV exposure is not considered to be clinically significant.

Table 4. Mean (%CV) pharmacokinetic parameters of 3TC

	3TC (n = 25)	3TC + amprenavir (n = 11)	3TC + ZDV (n = 13)	3TC + ZDV + placebo (n = 12)	3TC + ZDV + amprenavir (n = 23)
C _{max} , µg/mL	1.35 (34)	1.15 (37)	1.31 (33)	1.34 (26)	1.12 (31)
AUC _∞ , µg.h/mL	5.33 (22)	4.85 (19)	5.36 (19)	5.35 (23)	4.93 (20)
Half-life, h	7.97 (25)	8.35 (46)	7.87 (23)	7.39 (29)	8.20 (33)
CL _T /F, L/h	29.34 (20)	31.97 (20)	28.79 (16)	29.2 (21)	31.58 (20)

Since clinically significant differences were not observed in plasma concentration profiles, the Applicant did not assay the urine samples.

In conclusion, two and three drug combinations of amprenavir, ZDV and 3TC were investigated in this study. The results of this single dose study do not indicate occurrence of a clinically significant drug interaction between any of the three drugs investigated in this protocol. It should also be noted that patients enrolled

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in a Phase 3 study have received amprenavir (1200 mg BID), ZDV (300 mg BID) and 3TC (150 mg BID) for at least 24 weeks.

Title: A study to investigate whether there is a pharmacokinetic interaction between 141W94 and ketoconazole following their co-administration to healthy male volunteers [(Protocol no.: PROA1005)]

Objectives: (i) To determine the reciprocal pharmacokinetic interaction when single doses of amprenavir and ketoconazole are administered concomitantly. (ii) To evaluate the use of the erythromycin breath test as a predictor of the rate of clearance of amprenavir and to measure the degree of inhibition of CYP3A4 caused by ketoconazole and amprenavir.

Subjects: 12 healthy male subjects (mean age: 25 years, mean weight: 77 kg) were enrolled in the study.

Study Design: The study was conducted in a randomized, three-way crossover fashion. Subjects enrolled in this study received the following treatments.

Treatment 1 : Single dose of 1200 mg of amprenavir
Treatment 2 : Single dose of 400 mg of ketoconazole
Treatment 3 : Single doses of 1200 mg of amprenavir and 400 mg of ketoconazole

The treatments were separated by a washout period of at least 7 days. Subjects received the treatments under fasted conditions with 8 fluid ounces of water. Erythromycin breath test was administered at screening and two hours postdose after each treatment.

Formulation: Amprenavir soft gelatin capsules (150 mg, batch number 6R2782) and ketoconazole tablets (200 mg, Nizoral[®]) were used in this study.

Sample Collection: Blood samples were obtained at predose, and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hours after each treatment.

Analytical Methodology:

Pharmacokinetic Data Analysis: Pharmacokinetic parameters were estimated by non-compartmental methods. The C_p -t profiles for amprenavir and ketoconazole are shown in Figure 22 and pharmacokinetic parameters are presented in Table 1.

Table 1. Mean (%CV) pharmacokinetic parameters of amprenavir and ketoconazole

	Amprenavir parameters		Ketoconazole parameters	
	Treatment 1	Treatment 3	Treatment 2	Treatment 3
C_{max} , µg/mL	6.99 (24)	6.04 (36)	7.29 (32)	8.54 (26)
T_{max} , h	1.20 (32)	1.85 (56)	2.10 (41)	3.00 (24)
AUC_{0-last} , µg.h/mL	20.89 (22)	27.91 (32)	34.80 (31)	49.04 (24)
$AUC_{0-∞}$, µg.h/mL	21.98 (22)	29.50 (33)	35.18 (31)	49.51 (24)
Half-life, h	8.73 (72)	6.56 (33)	1.86 (24)	2.27 (18)
$CL_{r/F}$, mL/min	966 (30)	755 (36)	216 (47)	144 (30)
V/F, L	705 (70)	422 (45)	35 (46)	29 (35)

The increase in amprenavir $AUC_{∞}$, 31%, was statistically significant. The 90% CI for the geometric mean LS ratio was 1.20 – 1.42. The decrease in amprenavir C_{max} , 16%, was also statistically significant and the 90% confidence interval for the ratio was 0.75 – 0.94. The individual values for the ratio of Treatment 3 / Treatment 1 pharmacokinetic parameters for amprenavir are shown in Figure 23a. As seen in this figure, C_{max} was consistently lower in most subjects and $AUC_{∞}$ was higher in all subjects after concomitant administration. The differences in half-life values were not statistically significant. This Reviewer noted that in several subjects, the last three data points were used for the determination of terminal phase half-life of amprenavir and the 2 hour difference in half-life may be attributed to imprecise estimation of true terminal phase half-life.

The increase in ketoconazole $AUC_{∞}$, 44%, was statistically significant. The 90% CI for the geometric mean LS ratio was 1.31 – 1.59. A statistically significant increase in ketoconazole C_{max} , 19%, with a 90% confidence interval for the geometric mean LS ratio of 1.08 – 1.33 was also noted. The individual values for the ratio of Treatment 3 / Treatment 2 pharmacokinetic parameters for ketoconazole are shown in Figure 23b.

According to the Sponsor, the overall results indicate that the interaction between amprenavir and ketoconazole may occur at different sites or by different mechanisms. A reason for decreased amprenavir C_{max} is not clear at this time. The likely reason for increase in exposure to amprenavir and ketoconazole following concomitant administration is an increase in systemic bioavailability due to inhibition of CYP3A4.

The mean (%CV) erythromycin breath test values (% erythromycin metabolized per hour) after various treatments are given below.

Screening	Treatment 1 (amprenavir)	Treatment 2 (ketoconazole)	Treatment 3 (amprenavir + ketoconazole)	Follow-up
1.95 (18)	0.46 (45)	0.53 (30)	0.28 (34)	2.00 (16)

As expected, amprenavir and ketoconazole inhibited CYP3A4 enzyme activity. However, there was no correlation between erythromycin breath test values and the clearance of amprenavir or that of ketoconazole.

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In conclusion, the results of this study indicate that after single dose administration of amprenavir and ketoconazole, the amprenavir AUC increased by 31% and amprenavir C_{max} decreased by 16%. Similarly, concomitant administration increased ketoconazole AUC and C_{max} by 44% and 19%, respectively. The clinical implication of the pharmacokinetic interaction observed in this study is not known.

Title: A study to investigate whether there is a pharmacokinetic interaction between 141W94 and clarithromycin following their co-administration to healthy male volunteers [(Protocol no.: PROA1013) NDA 21007 Volume 3.9].

Objectives: (i) to determine the effects of co-administration of amprenavir and clarithromycin on the pharmacokinetics of these drugs; (ii) to evaluate the potential use of the erythromycin breath test (ERMBT) as a predictor of the rate of clearance of amprenavir; and (iii) to measure, using the ERMBT, the degree of inhibition of cytochrome P450 3A4 caused by amprenavir and clarithromycin.

Subjects: 14 healthy male subjects (mean age: 27 years, mean weight: 75 kg) were enrolled in the study. Twelve subjects completed the study. One subject withdrew consent and the other discontinued treatment due to AEs (nausea and vomiting)

Study Design: The study was conducted in a randomized, three-period crossover fashion. Subjects enrolled in this study received the following treatments.

Treatment 1: 1200 mg amprenavir BID; a total of seven doses over four days

Treatment 2: 500 mg clarithromycin BID; a total of seven doses over four days

Treatment 3: 1200 mg amprenavir and 500 mg clarithromycin, BID;
a total of seven doses each over four days.

There was no washout period between the treatments. Subjects received the treatments under fasted conditions. Randomization was performed according to two 3 x 3 Latin Squares. The pharmacokinetics of the amprenavir and / or ketoconazole were determined on Study Days 4, 8 and 12. Erythromycin breath test was administered at baseline and two hours after the seventh dose of each treatment.

Formulation: Amprenavir soft gelatin capsules (150 mg, batch number 6R2782) and clarithromycin tablets (500 mg, Biaxin[®]) were used in this study.

Sample Collection: Blood samples were obtained at predose, and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hours after each treatment. Urine samples were collected during 0-4, 4-8, 8-12 and 12-24 hours for determining the amount of clarithromycin and 14-hydroxy clarithromycin excreted after Treatments 2 and 3.

Pharmacokinetic Data Analysis: Pharmacokinetic parameters were estimated by non-compartmental methods. The log-transformed pharmacokinetic parameters were analyzed using ANOVA with treatment, period and sequence as fixed effects and subject-within-sequence as the random effect. The two one-sided tests were performed to compare the pharmacokinetic parameters. The C_p -t profiles for amprenavir are shown in Figure 24 and the pharmacokinetic parameters are presented in Table 1.

Table 1. Mean (%CV) pharmacokinetic parameters of amprenavir

	Amprenavir parameters		Geo. LS Mean ratio (90% CI)
	Treatment 1 (n = 14)	Treatment 3 (n = 12)	Treatment 3 / Treatment 1
C_{max} , µg/mL	8.98 (26)	10.10 (26)	1.15 (1.01 – 1.31)
T_{max} , h	1.25 (53)	1.34 (38)	
AUC _{0-∞} , µg.h/mL	29.08 (26)	32.93 (25)	1.18 (1.08 – 1.29)
C_{avg} , µg/mL	2.42 (26)	2.74 (25)	1.18 (1.08 – 1.29)
C_{min} , µg/mL	0.41 (45)	0.53 (38)	1.39 (1.31 – 1.47)
CL_T/F , mL/min	754 (38)	649 (30)	0.85 (0.78 – 0.93)

The increases in geometric LS mean amprenavir AUC, C_{max} and C_{min} were 18%, 15% and 39%, respectively. The Treatment 3 : Treatment 1 ratio of individual amprenavir C_{max} and AUC are shown in Figure 25.

The C_p -t for clarithromycin and 14-hydroxy clarithromycin are shown in Figure 26 and the corresponding pharmacokinetic parameters are presented in Table 2.

Table 2. Mean (%CV) pharmacokinetic parameters of clarithromycin and 14-hydroxy clarithromycin

	Clarithromycin parameters		14-hydroxy clarithromycin parameters	
	Treatment 2 (n = 13)	Treatment 3 (n = 12)	Treatment 2 (n = 13)	Treatment 3 (n = 12)
C_{max} , µg/mL	2.70 (29)	2.36 (19)	0.84 (28)	0.58 (48)
T_{max} , h	2.46 (73)	4.79 (29)	3.31 (35)	5.50 (69)
AUC _{0-∞} , µg.h/mL	22.31 (29)	20.92 (21)	7.70 (26)	4.87 (24)
C_{min} , µg/mL	1.06 (33)	1.09 (28)	0.47 (38)	0.44 (38)
CL_T/F , mL/min	405 (30)	417 (25)		
CL_R , mL/min	121 (32)	159 (21)		
Ae(0-24h), mg	158 (35)	194 (19)	60 (11)	50 (21)

The decreases in geometric LS mean clarithromycin AUC and C_{max} were 4% and 10%, respectively. The Treatment 3 : Treatment 2 ratio of individual clarithromycin C_{max} and AUC are shown in Figure 27. The mean clarithromycin trough concentrations and total clearance were essentially identical for Treatments 2 and 3. However, a 34% increase in clarithromycin renal clearance was noted in Treatment 3. The AUC and C_{max} of the 14-hydroxy metabolite were decreased by 35% and 32%, respectively.

The mean (%CV) erythromycin breath test values (% erythromycin metabolized per hour) after various treatments are given below.

Screening	Treatment 1 (amprenavir)	Treatment 2 (clarithromycin)	Treatment 3 (amprenavir + clarithromycin)	Follow-up
2.23 (36)	0.36 (39)	0.75 (32)	0.31 (26)	2.07 (28)

One subject was excluded from the statistics due to an anomalous baseline value of 0.44. There was no correlation between erythromycin breath test values and clearance of amprenavir. The inhibition of CYP 3A4 enzyme activity was 85% due to amprenavir and 67% due to clarithromycin. The erythromycin

breath tests indicate that clarithromycin (Trt. 3) did not have any additional effect on the inhibition of CYP 3A4.

In conclusion, concomitant administration of amprenavir and clarithromycin resulted in a 18%, 15% and 39% increase in amprenavir AUC, C_{max} and C_{min} , respectively. This minor increase in exposure can be attributed to inhibition of CYP 3A4 by clarithromycin.

Concomitant administration of clarithromycin and amprenavir had no effect on clarithromycin exposure. However, a 10% decrease in mean clarithromycin C_{max} and 34% increase in clarithromycin renal clearance was noted. Since food has been reported to decrease clarithromycin C_{max} and increase renal clearance, the Applicant hypothesizes that amprenavir may have produced these effects due to its — formulation. Statistically significant changes were noted in mean 14-hydroxy clarithromycin C_{max} (↓ 32%) and AUC (↓ 35%).

The clinical relevance of the pharmacokinetic interaction between amprenavir and clarithromycin is not known. When administered concomitantly, an adjustment in the dose of these drugs is not recommended at this time.

Title: A study to investigate whether there is a pharmacokinetic interaction between 141W94 and rifabutin and 141W94 and rifampin following their co-administration to healthy male volunteers [(Protocol no.: PROA1012) NDA 21007 Volume 3.5.].

Objectives: (i) to determine the drug interaction effects when amprenavir is concomitantly administered with rifabutin or rifampin; (ii) to evaluate the potential use of the erythromycin breath test (ERMBT) as a predictor of the rate of clearance of amprenavir; (iii) to evaluate, using the ERMBT, whether amprenavir is an inhibitor or an inducer of CYP3A4 activity in man; and (iv) to compare, using the ERMBT, the effects of rifabutin and rifampin mediated induction of CYP3A4 activity on the rate of clearance of amprenavir.

Subjects: 24 (12 per cohort) healthy male subjects (mean age: 27 years, mean weight: 76 kg) were enrolled in the study. Six subjects withdrew from the study due to adverse events. The adverse events are discussed later in this review.

Study Design: Subjects enrolled in this study were assigned to one of two dosing cohorts and received the following treatments.

Cohort	Treatment code (Dosing days)	Treatment
1	A (1 – 4)	Amprenavir 1200 mg BID for three and half days Washout period : At least 7 days
	B (5 – 18)	300 mg of rifabutin once daily for 14 days
	C (19 – 28)	Amprenavir 1200 mg BID + Rifabutin 300 mg once daily for 10 days
2	A (1 – 4)	Amprenavir 1200 mg BID for three and half days Washout period : At least 7 days
	D (5 – 18)	600 mg of rifampin once daily for 14 days
	E (19 – 22)	Amprenavir 1200 mg BID + Rifampin 600 mg once daily for 4 days

In both cohorts, there was a washout period of at least 7 days after Treatment A. Subjects received all treatments under fasted conditions with 12 fluid ounces of water. Erythromycin breath test was administered at baseline and two hours postdose on Dosing Days 4, 11, 18 and 28 (Cohort 1) and 22 (Cohort 2).

Reviewer's remarks: For practical purposes, this study can be regarded as two separate drug interaction studies and the results will be reviewed separately.

Formulation: Amprenavir soft gelatin capsules (150 mg, batch number 6R2782), rifabutin capsules (150 mg, Mycobutin®) and rifampin capsules (300 mg, Rifadin®) were used in this study.

Sample Collection:

Amprenavir: Blood samples were obtained at predose, and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10 and 12 hours after Treatments A, C and E

Rifabutin and rifampin: Blood samples were obtained at predose, and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hours after Treatments B and C or D and E. Urine samples were obtained during the following time intervals: 0 – 4, 4 – 8, 8 – 12 and 12 – 24 hours after Treatments B and C or D and E.

Pharmacokinetic Data Analysis:

Amprenavir – rifabutin pharmacokinetic interaction

Twelve subjects were enrolled in Cohort 1 and all twelve subjects received Treatment A. One subject missed two consecutive doses of rifabutin (Treatment B) and, therefore, discontinued from the study. The remaining eleven subjects completed Treatment B, but five subjects withdrew from the study during Treatment C (amprenavir plus rifabutin) due to adverse events. Details on the adverse events are presented below:

Subj.	Demographics	Adverse event *	Day withdrawn from study
732	29 year old White male	Mild fever, headache, myalgia	Withdrawn on Day 8 of Treatment C. Treated with ibuprofen, AEs resolved in 3 days
733	18 year old White male	Mild sinus headache, mild episodes of weakness, dizziness and shortness of breath. All reported after discontinuation of Treatment C	Withdrawn one day after receiving Treatment C. All AEs resolved at follow-up visit.
735	21 year old White male	Mild episode of nausea and vomiting on the first day of Treatment C. Mild episodes of diarrhea and tiredness.	Withdrawn on first day of Treatment C. AEs Resolved in 4 days
740	26 year old Asian male	Mild episodes of nausea, vomiting, back pain, fever, headache, myalgia and moderate episode of exhaustion one day after starting Treatment C.	Withdrawn two days after reporting AEs. Treated with acetaminophen.
742	28 year old White male	Severe fever (duration 1 day), severe headache (duration 11 days), chills and body pain (duration 3 days) starting with initiation of Treatment C.	Withdrawn the next day after reporting AEs. Treated with ibuprofen and dihydrocodone.

* Other adverse events reported during Treatments A and B.

Pharmacokinetic parameters were estimated by non-compartmental methods. The C_p -t profiles for amprenavir, rifabutin and 25-desacetyl rifabutin are shown in Figure 28 and the pharmacokinetic parameters are presented in Table 1.

Table 1. Mean (%CV) pharmacokinetic parameters of amprenavir and rifabutin

COHORT 1	Amprenavir parameters		Rifabutin parameters		25-desacetyl rifabutin parameters	
	Treatment A (n = 12)	Treatment C (n = 6)	Treatment B (n = 11)	Treatment C (n = 6)	Treatment B (n = 11)	Treatment C (n = 6)
C_{max} , µg/mL	9.32 (20)	8.71 (24)	0.40 (35)	0.83 (23)	0.032 (27)	0.226 (9)
T_{max} , h	1.15 (43)	1.08 (32)	2.37 (25)	3.41 (36)	2.77 (30)	3.00 (58)
AUC _{0-∞} , µg.h/mL	27.96 (19)	22.13 (27)	3.47 (24)	9.52 (23)	0.24 (27)	2.77 (12)
C_{min} , µg/mL	0.39 (42)	0.27 (25)	0.06(37)	0.21 (22)	0.002 (146)	0.066 (32)
CL_T/F , mL/min	742 (22)	967 (31)	1510 (21)	543 (17)		
CL_R , mL/min			60.0 (25)	53.5 (20)		
Ac(0-24h), mg			12.2 (24)	29.8 (16)	1.76 (27)	16.59 (16)

Reviewer's remarks: In presenting the results of this study, the Applicant has pooled amprenavir pharmacokinetic parameters from Cohorts 1 and 2. As a result, amprenavir pharmacokinetic parameters obtained after Treatment C were compared to those obtained from all 24 subjects who received Treatment A. However, for sake of clarity, this Reviewer has shown pharmacokinetic parameters from the 12 subjects enrolled in Cohort 1 in Table 1. It was noted that the mean values derived from 12 subjects in Cohort 1 are not different from the mean values (from 24 subjects) reported by the Applicant.

For amprenavir, the geometric LS mean ratios (Treatment 3 : Treatment 1) for C_{max} and AUC were 0.93 (90% CI : 0.79 - 1.10) and 0.85 (90% CI : 0.72 - 1.00), respectively. After concomitant administration with rifabutin, the mean amprenavir C_{min} decreased by 15%. This decrease may be due to CYP 3A4 induction by rifabutin. Since data are not balanced, individual amprenavir C_{max} and AUC values are shown in Figure 29.

Co-administration of amprenavir had a statistically and clinically significant impact on the pharmacokinetics of rifabutin. Rifabutin C_{max} and AUC increased by 2.19- (90% CI: 1.82 - 2.64) and 2.93- fold (90% CI: 2.56 - 3.35), respectively. The renal clearance of rifabutin did not change when administered with amprenavir. Concomitant administration of amprenavir had a profound impact on the pharmacokinetics of 25-desacetyl rifabutin. The ratio of geometric LS means for the metabolite C_{max} , AUC and C_{min} were 7.39 (90% CI: 5.87 - 9.29), 13.35 (90% CI: 10.93 - 16.30) and 32.92 (90% CI: 26.6 - 39.2), respectively. The amount of 25-deacetyl rifabutin eliminated in the urine increased by 10-fold upon concomitant administration with amprenavir. It is likely that the increase in rifabutin and 25-desacetyl rifabutin levels is due to inhibition of CYP 3A4 activity by amprenavir.

Amprenavir plus rifabutin treatment was poorly tolerated by subjects enrolled in the study. The adverse events reported by patients receiving amprenavir and rifabutin may be attributed to increased levels of rifabutin.

Amprenavir – rifampin pharmacokinetic interaction

One subject (21 year old White male) withdrew from the study due to macropapular rash beginning the day after completing amprenavir treatment. The rash began in his forearm and spread to his hands, back, abdomen, legs and feet. There was no fever and the adverse event resolved without treatment after 9 days. This subject had no prior history of allergies. This adverse event was determined as being possibly related to the drug. Amprenavir AUC (25.1 $\mu\text{g}\cdot\text{h}/\text{mL}$) in this subject was less than the average AUC value of 28.4 $\mu\text{g}\cdot\text{h}/\text{mL}$.

Pharmacokinetic parameters were estimated by non-compartmental methods. The C_p -t profiles for amprenavir and rifampin are shown in Figure 30 and the pharmacokinetic parameters are presented in Table 2.

Table 2. Mean (%CV) pharmacokinetic parameters of amprenavir and rifampin

COHORT 2	Amprenavir parameters		Rifampin parameters		25-desacetyl rifampin parameters	
	Treatment A (n = 12)	Treatment E (n = 11)	Treatment D (n = 11)	Treatment E (n = 11)	Treatment D (n = 11)	Treatment E (n = 11)
C_{max} , $\mu\text{g}/\text{mL}$	9.75 (31)	3.10 (49)	9.10 (42)	9.05 (40)	0.70 (29)	0.66 (46)
T_{max} , h	1.10 (55)	0.79 (38)	1.50 (49)	1.59 (39)	2.22 (37)	2.32 (20)
AUC _{0-24h} , $\mu\text{g}\cdot\text{h}/\text{mL}$	28.43 (30)	5.40 (39)	29.26 (30)	30.16 (38)	3.12 (41)	3.02 (46)
$CL_{T/F}$, mL/min	774 (35)	4273 (43)	371 (30)	376 (36)		
CL_R , mL/min			18.98 (26)	14.72 (21)		
$A_e(0-24h)$, mg			32.93 (38)	25.66 (33)	7.92 (40)	6.53 (31)

When administered with rifampin, there was a statistically and clinically significant decrease in amprenavir C_{max} , AUC and C_{min} . These three pharmacokinetic parameters decreased by 70% (90% CI: 0.24 - 0.38), 82% (90% CI: 0.16 - 0.22) and 92% (90% CI: 0.05 - 0.11), respectively. The resulting plasma amprenavir levels are considered sub-therapeutic and, therefore, it is recommended that rifampin should not be administered with amprenavir. Amprenavir did not have a significant impact on rifampin pharmacokinetics. Rifampin and 25-desacetyl rifampin pharmacokinetic parameters were virtually identical under Treatments 2 and 3.

Erythromycin breath test

The mean (%CV) erythromycin breath test values (% erythromycin metabolized per hour) for dosing cohorts 1 and 2 are given in the following table.

	Screening	Amprenavir (Dosing Day 4)	RFB / RFP (Dosing day 11)	RFB / RFP (Dosing Day 18)	Amprenavir + RFB / RFP (Dosing Day 28 / 22)	Follow-up
Cohort 1	2.54 (26)	0.44 (44)	4.73 (17)	4.92 (22)	0.65 (28)	2.66 (20)
Cohort 2	2.08 (22)	0.37 (39)	3.43 (20)	3.16 (15)	1.68 (18)	2.25 (20)

Consistent with observations made in other studies, administration of amprenavir resulted in lower ERMBT values due to inhibition of CYP 3A4 by amprenavir. As expected, treatment with rifabutin and rifampin resulted in increased CYP 3A4 activity when compared to baseline (ERBMT values increased by 80 to 85% in the case of rifabutin and increased by 56 to 64% for rifampin). Significant decrease in mean ERMBT value, when compared to baseline values, was observed when treated with amprenavir

and rifabutin, but values were only slightly reduced after treatment with amprenavir with rifampin. Erythromycin breath test did not predict clinically relevant drug interactions in this study.

Effect on WBC

It was observed that total white blood cell counts were affected by administration of rifabutin (Applicant points out that this is consistent with previous reports) and was exacerbated by addition of amprenavir. The mean WBC values ($\times 10^3 / \text{mm}^3$) are shown below.

Baseline(n = 24)	5.98	Baseline (n = 24)	5.98
Amprenavir (n = 24)	6.22	Amprenavir (n = 24)	6.22
Rifabutin Day 11 (n = 12)	4.75	Rifampin Day 11 (n = 11)	6.18
Rifabutin Day 18 (n = 11)	3.88	Rifampin Day 18 (n = 9)	5.73
Amprenavir + rifabutin (n = 10)	3.24	Amprenavir + rifampin (n = 11)	5.11
Follow-up (n = 21)	5.44	Follow-up (n = 21)	5.44

This was discussed with the Medical Officer and the Applicant has agreed to incorporate the following sentence in the label: "A complete blood count should be performed weekly and as clinically indicated in order to monitor for neutropenia in patients receiving amprenavir and rifabutin".

Conclusions: The results of this study indicate:

- (a) Co-administration of amprenavir and rifabutin results in a 15% decrease in amprenavir exposure and a clinically significant increase in rifabutin and 25-desacetyl rifabutin exposures. The combination treatment was poorly tolerated by subjects possible due to increased rifabutin levels. Concomitant administration of amprenavir and rifabutin should be avoided. When rifabutin is medically necessary, the Applicant recommends that the dose of rifabutin may be reduced by 50% when given with amprenavir. This is acceptable.
- (b) Co-administration of amprenavir and rifampin results in a clinically significant decrease in amprenavir concentrations and no change in rifampin pharmacokinetics. It is recommended that rifampin should not be administered with amprenavir.

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APPENDIX 2

SECTION C DISSOLUTION

Reference is made to the CMC End-of-Phase II meeting held between representatives of the Division of Antiviral Drug Products and representatives of Glaxo Wellcome Inc on May 28, 1997.

As requested by Dr. Barbara Davit, Biopharmaceutics Reviewer, information is presented here regarding the dissolution method and proposed specification for Amprenavir Soft Gelatin Capsules, 50 mg and 150 mg. In addition, dissolution profile data for multiple batches used in clinical trials and in stability studies are presented.

The dissolution conditions for Amprenavir Soft Gelatin Capsules, 50 mg and 150 mg are listed below.

Apparatus: USP paddle apparatus (apparatus 2)

Medium: []

Stirring Speed: —

Temperature: —


Amprenavir Soft Gelatin Capsules, 50 mg and 150 mg are liquid-filled soft gelatin capsules containing amprenavir drug substance fully solubilized in the fill solution. The dissolution of Amprenavir Soft Gelatin Capsules, 50 mg and 150 mg is primarily controlled by the dissolution of the gelatin capsule shell. Once the gelatin capsule shell dissolves, the fill contents containing the solubilized amprenavir drug substance are released. A stirring speed of — is satisfactory to dissolve the gelatin capsule shell and disperse the fill solution, and represents a mild agitation condition as recommended in "Guidance for Industry, Dissolution Testing of Immediate Release Solid Oral Dosage Forms", CDER, August, 1997. In addition, the dissolution medium — simulates physiological conditions without enzymes, as suggested in the same guidance document.

The proposed NDA dissolution specification for Amprenavir Soft Gelatin Capsules, 50 mg and 150 mg is $Q = \text{---}$ in 30 minutes. Please note that Glaxo Wellcome will discontinue the collection of dissolution profiles at the next stability timepoint and will only collect dissolution data at 30 minutes.

C1. BATCHES TESTED

Dissolution profiles have been collected for multiple batches used in clinical trials and for stability studies. All data were collected using the currently registered dissolution method, which utilizes — as the dissolution medium, paddles at — and — as the sample analysis technique. The fill formulation for batches of Amprenavir Soft Gelatin Capsules, 50 mg and 150 mg is provided in Table C1.

Table C1 Fill Solution Composition of Amprenavir Soft Gelatin Capsules, 50 mg and 150 mg

Component	Quantity % w/w	Quantity/Dosage Unit for 50 mg (mg)	Quantity/Dosage Unit for 150 mg (mg)	Function
Amprenavir		50	150	Active Ingredient
TPGS				
PEG 400				
Propylene Glycol				
Approximate Fill Weight				

Results, as described in Tables C2 and C3, show complete and consistent dissolution at 30 minutes for all samples tested. Although dissolution at 15 minutes is essentially complete, capsule-to-capsule variability is observed in the 15-minute values. In addition, dissolution testing at 45 minutes does not provide a significant increase in dissolution over 30 minutes and does not provide additional scientific information or benefit. Therefore, a specification of $Q = \text{---}$ at 30 minutes is proposed.

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Table C2 Dissolution Profile Data for Amprenavir Soft Gelatin Capsules, 150 mg

Batch #	Description	Batch Use	Average Percent Amprenavir Dissolved (n = 6)		
			15 min	30 min	45 min
SF060606	150 mg, Tampa	clinical			
SF060608	150 mg, Tampa	clinical			
031629/A	150 mg	clinical			
031730/A	150 mg	clinical			
031731/A	150 mg	clinical			
031733/A	150 mg	clinical			
031897/A	150 mg	clinical			
032166/A	150 mg, <u> </u> NDA	clinical/stability			
032166/A	150 mg	clinical			
032168/A	150 mg, NDA	clinical/stability			
032170/A	150 mg, NDA	clinical			
032172	150 mg	clinical/stability			
032175	150 mg	clinical			
032176	150 mg	clinical			
032780	150 mg	clinical			
032781	150 mg	clinical			
032783	150 mg	clinical			
E7402A	150 mg	develop/stability			
E7402A	150 mg, MN1, 30/60	develop/stability			
E7402A	150 mg, MN1, 40/75	develop/stability			
E7402A	150 mg, MN1, <u> </u>	develop/stability			
E7402A	150 mg, MN1, F/T	develop/stability			
E7402A	150 mg, MN3, 30/60	develop/stability			
E7402A	150 mg, MN3, 40/75	develop/stability			

Notes:

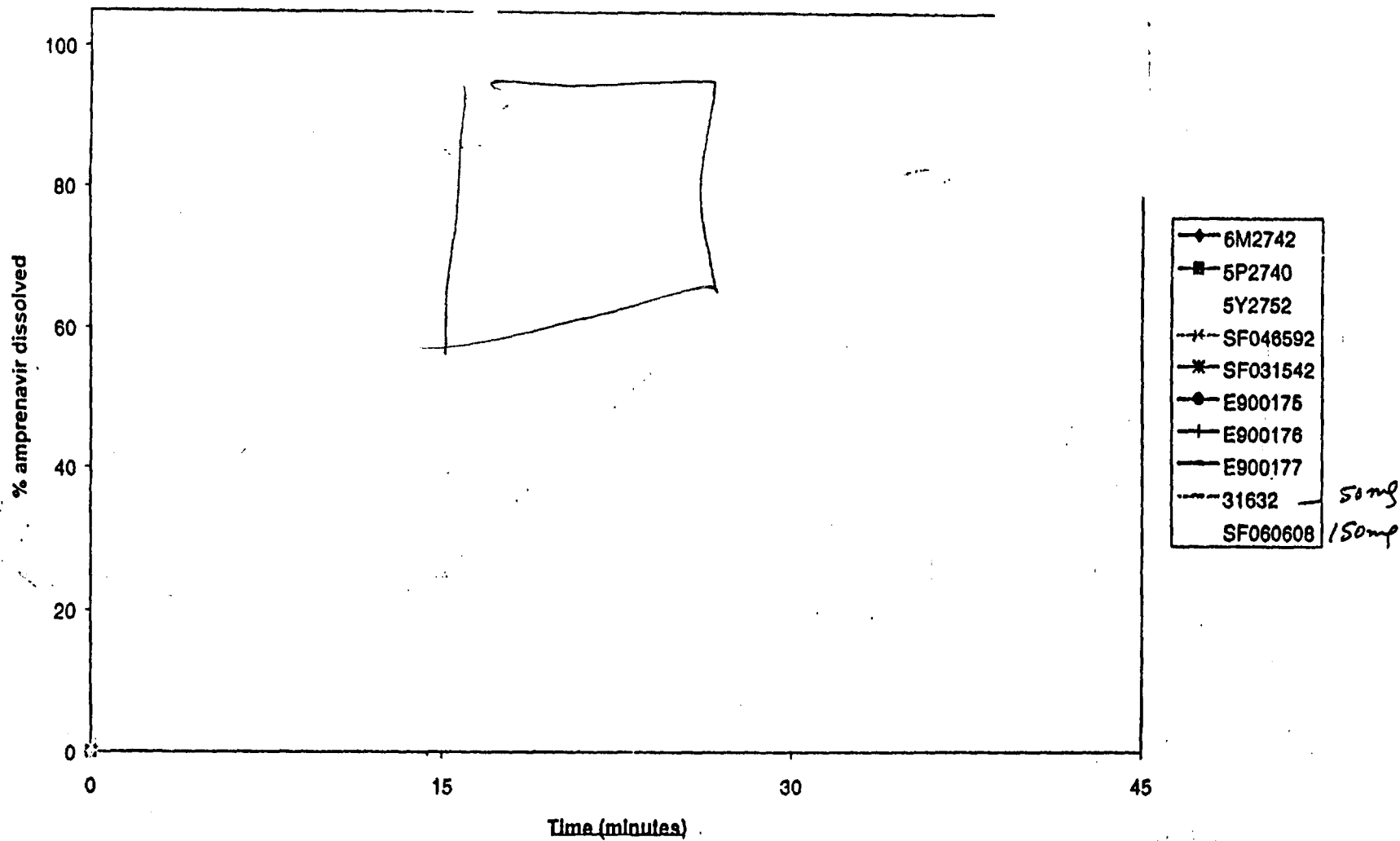
1. Samples are unprinted initials/release unless specified in the table. MN1 = 1 month and MN3 = 3 month stability.
2. Samples were manufactured at RP Scherer, Beinheim, France unless otherwise noted in the table.
3. "NDA" refers to batches manufactured for NDA stability.
4. "Tampa" refers to batches manufactured at RP Scherer, St. Petersburg, Florida facility.
5. "Develop" refers to development scale batches.
6. F/T = freeze/thaw samples . UV = UV Light exposed protected.
7. = Fluorescent Light
8. 25/60, 30/60, and 40/75 are sample storage temperature/percent relative humidity conditions.

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Dissolution Profile Amprenavir Soft Gelatin Capsules



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Table 2. Individual Pharmacokinetic Parameters of Amprenavir (PROA 1010)

Individual Pharmacokinetic Parameters by Treatment												
Treatment	Tmax	Cmax	AUCinf	Treatment	Tmax	Cmax	AUCinf	Treatment	Tmax	Cmax	AUCinf	
	(h)	(ug/mL)	(ug ² /mL)		(h)	(ug/mL)	(ug ² /mL)		(h)	(ug/mL)	(ug ² /mL)	
1	1	13.05	45.34	2	0.8	10.16	28.24	3	1	5.81	17.67	
1	1	10.72	29.71	2	0.8	14.56	31.97	3	2.5	4.98	21.01	
1	2	6.18	20.29	2	1	6	17.59	3	2.5	2.31	13.42	
1	1.5	10.7	51.66	2	1	8.49	38.8	3	1.5	6.78	41.3	
1	2	4.79	17.69	2	1	5.54	17.33	3	1	7.1	18.71	
1	1.07	12.71	37.22	2	1	12.95	33.52	3	1.5	7.3	24.08	
1	1	6.54	27.01	2	0.8	9.29	21.95	3	0.8	5.91	22.96	
1	0.8	14.16	49.29	2	0.8	14.71	50.07	3	1.5	10.29	36.37	
1	1	5.51	16.84	2	0.8	5.92	15.88	3	1.5	4.21	15.94	
1	1	10.49	27.66	2	0.5	9.03	22.75	3	1	7.04	22.01	
1	0.8	9.8	26.49	2	1	8.42	24.12	3	0.5	6.01	17.22	
1	2.5	7.59	26.07	2	2	5.22	21.95	3	1.5	5	19.75	
1	3	7.99	23.16	2	0.8	11.62	27.37	3	1.5	6.76	15.55	
1	2	7.64	21.54	2	1	10.9	23.7	3	1	6.21	16.14	
1	1.5	8.2	39.68	2	1	6.61	27.05	3	1.5	3.38	17.95	
1	1	9.48	33.01	2	0.8	13.17	36.85	3	1	9.36	32.66	
1	1	10.53	25.64	2	0.8	9.72	25.68	3	2	4.33	15.16	
1	1.5	7.38	19.96	2	1	6.93	16.42	3	1.5	2.84	9.38	
1	0.8	12.3	38.14	2	1	10.52	27.2	3	2.5	5.88	24.6	
1	1	10.65	28.61	2	0.8	11.77	29.45	3	1.5	3.94	16.93	
1	0.8	11.91	28.13	2	0.5	8.66	25.18	3	1	7.12	17.92	
1	0.8	7.79	20.77	2	0.8	8.67	23.22	3	1	5.56	13.61	
1	1.5	13.6	54.41	2	4	9.36	66.5	3	3	11.04	76.61	
1	1	5.34	15.97	2	0.8	10.19	21.6	3	1	6.52	14.03	
1	1	9.08	27.74	2	0.8	8.91	23.34	3	0.8	8.63	18.52	
1	1	6.29	13.52	2	0.8	10.04	18.88	3	0.8	5.75	12.52	
1	2	7.74	29.01	2	1.5	5.39	16.1	3	2	3.28	15.16	
1	1.5	9.67	30.5	2	0.8	15.25	44.04	3	1	5.82	21.02	
1	1	7.84	24.88	2	1	11.24	28.51	3	2	3.75	17.49	
1	1	11.87	43.69	2	1.5	9.76	29.72	3	1.5	3.88	15.85	
1	1.5	10.19	36.42	2	0.5	13.39	34.17	3	2	17.43	34.46	
1	1	10.15	43.51	2	2.5	7.69	33.97	3	3	2.77	17.81	
1	1.5	9.96	30.14	2	1.5	6	21.69	3	1	7.39	25.35	
1	0.8	5.25	16.27	2	0.8	11.51	20.68	3	0.5	7.45	15.98	
1	2	8.56	30.99	2	0.8	13.18	35.33	3	2.53	3.11	16.15	
1	1	11.41	32.58	2	0.8	10.6	30.1	3	0.8	11.39	30.7	
Mean	1.3	9.3	30.1		1.1	9.8	28.1		1.5	6.3	21.7	
SD	0.5	2.5	10.4		0.6	2.8	10.2		0.7	3.0	11.8	
Geo. Mean		8.9	28.4			9.4	26.6			5.7	19.9	

Table 4. Individual Pharmacokinetic Parameters of Amprenavir (PROA 1011)

Treatment	Time (h)	Conc (ng/mL)	AUCinf (ng·h/mL)	AUCinf (ng·h/mL)	VZf (L)	Lambda Z (1/h)	T1/2f (h)	CL/F (mL/min)	Subject Number
4 X 150 mg 141	1.5	2.07	7.06	7.33	623	0.132	5.27	1345	S337
4 X 150 mg 141	1	3.94	9.31	9.4	322	0.198	3.5	1064	S340
4 X 150 mg 141	1	4.58	8.42	8.83	339	0.201	3.46	1122	S346
4 X 150 mg 141	1.5	1.96	5.27	5.34	702	0.144	4.83	1871	S347
4 X 150 mg 141	1	2.17	4.52	4.59	837	0.156	4.44	2179	S348
4 X 150 mg 141	0.75	6.7	7.17	7.39	1005	0.081	8.58	1354	S353
4 X 150 mg 141	0.75	2.82	4.77	4.98	1406	0.084	8.26	2008	S354
4 X 150 mg 141	1.5	2.3	5.6	5.66	357	0.297	2.33	1768	S356
4 X 150 mg 141	0.75	3.64	8.33	8.68	302	0.128	5.83	1152	S357
4 X 150 mg 141	0.75	5.69	12.54	12.77	454	0.103	6.7	783	S362
4 X 150 mg 141	0.75	6.31	9.16	9.41	360	0.114	6.09	1063	S363
4 X 150 mg 141	0.5	3.85	5.87	5.16	887	0.131	5.29	1937	S338
4 X 150 mg 141	1	4.86	13.81	13.87	194	0.236	2.94	765	S341
4 X 150 mg 141	2	3.87	13.7	14.39	325	0.129	5.1	695	S342
4 X 150 mg 141	1.5	3.53	8.25	8.45	497	0.143	4.85	1184	S343
4 X 150 mg 141	1	6.24	9.91	11.24	878	0.081	11.39	890	S344
4 X 150 mg 141	1	4.82	13.65	13.73	188	0.233	2.98	729	S350
4 X 150 mg 141	0.5	6.64	11.42	11.49	287	0.182	3.81	870	S352
4 X 150 mg 141	1	4.13	8.87	9.06	490	0.135	5.13	1104	S355
4 X 150 mg 141	1	2.4	4.74	5.64	2079	0.051	13.55	1772	S358
4 X 150 mg 141	0.75	6.82	15.21	15.43	245	0.159	4.34	641	S359
4 X 150 mg 141	1.5	4.52	12.36	12.79	419	0.112	6.19	782	S361
4 X 150 mg 141	0.75	6.89	14.05	14.21	249	0.17	4.89	704	S364
4 X 150 mg 141	0.75	4.15	5.85	6.06	819	0.121	5.73	1650	S365
Mean	1.8	4.4	9.1	9.4	615.6	0.1	5.6	1227.9	
SD	0.4	1.6	3.4	3.5	437.8	0.1	2.6	480.6	
GM	1.0	4.1	8.5	8.8	506.7	0.1	5.1	1142.5	
12 X 50 mg 141	1.5	1.97	6.43	6.95	1064	0.081	8.54	1409	S337
12 X 50 mg 141	0.53	7.92	17.75	18.27	312	0.105	6.59	547	S340
12 X 50 mg 141	0.75	7.2	11.57	11.67	358	0.144	4.53	857	S346
12 X 50 mg 141	1.5	1.44	2.71	2.85	2300	0.092	7.57	3509	S347
12 X 50 mg 141	1	1.97	4.31	4.29	814	0.168	4.13	2280	S348
12 X 50 mg 141	0.75	4.04	6.61	6.88	1132	0.077	9	1453	S353
12 X 50 mg 141	1	2.54	3.99	4.12	1231	0.118	5.86	2426	S354
12 X 50 mg 141	0.75	3.61	6.08	6.15	611	0.146	4.34	1625	S356
12 X 50 mg 141	1	3.57	10.85	11.29	363	0.146	4.74	886	S357
12 X 50 mg 141	1	3.35	12.44	12.5	263	0.183	3.8	800	S362
12 X 50 mg 141	1	5.67	9.59	9.74	490	0.126	5.52	1025	S363
12 X 50 mg 141	0.5	6.42	7.46	7.65	723	0.106	6.29	1308	S338
12 X 50 mg 141	1	4.62	13.05	13.3	244	0.185	3.74	752	S341
12 X 50 mg 141	2	4.35	9.19	9.27	293	0.221	3.14	1079	S342
12 X 50 mg 141	1.5	3.52	12.25	12.66	519	0.091	7.6	789	S343
12 X 50 mg 141	1	4.34	7.68	8.5	1305	0.054	12.81	1177	S344
12 X 50 mg 141	1	2.04	8.6	8.96	443	0.151	4.59	1116	S350
12 X 50 mg 141	0.75	6.31	11.24	11.39	369	0.143	4.85	878	S352
12 X 50 mg 141	0.75	5.2	10.59	10.85	421	0.131	5.28	922	S355
12 X 50 mg 141	1	2.6	5.56	6.15	1515	0.084	10.77	1625	S358
12 X 50 mg 141	0.75	3.64	7.81	7.92	267	0.284	2.44	1262	S359
12 X 50 mg 141	1	6.85	15.8	16.15	284	0.131	5.3	619	S361
12 X 50 mg 141	1	4.55	14.81	15.04	250	0.159	4.35	665	S364
12 X 50 mg 141	0.5	3.82	6.26	6.47	644	0.14	4.96	1546	S365
Mean	1.8	4.3	9.3	9.5	676.5	0.1	5.9	1774.4	
SD	0.4	1.8	3.9	3.9	512.4	0.1	2.5	676.2	
GM	0.9	3.9	8.4	8.7	541.7	0.1	5.5	1145.6	
40 mL X 15 mg/mL 141	1.5	1.64	5.4	6.22	1186	0.081	8.52	1689	S337
40 mL X 15 mg/mL 141	0.75	3.23	8.27	8.66	707	0.098	7.87	1155	S340
40 mL X 15 mg/mL 141	0.5	3.01	6.79	6.88	687	0.144	4.82	1454	S346
40 mL X 15 mg/mL 141	1	1.79	3.97	4.19	1619	0.088	7.84	2385	S347
40 mL X 15 mg/mL 141	1	1.58	3.94	4.82	850	0.176	3.95	2489	S348
40 mL X 15 mg/mL 141	0.5	4.92	5.46	5.75	1503	0.07	9.98	1740	S353
40 mL X 15 mg/mL 141	0.5	2.6	4.19	4.42	1488	0.091	7.59	2265	S354
40 mL X 15 mg/mL 141	0.5	4.82	5.73	5.92	1054	0.096	7.21	1689	S356
40 mL X 15 mg/mL 141	0.5	2.83	6.48	7.75	1236	0.063	11.83	1294	S357
40 mL X 15 mg/mL 141	0.75	5.3	13.11	13.34	459	0.066	10.46	728	S362
40 mL X 15 mg/mL 141	0.5	6.83	7.87	8.14	806	0.092	7.54	1229	S363
40 mL X 15 mg/mL 141	0.52	2.44	3.43	3.55	1927	0.084	7.91	2816	S338
40 mL X 15 mg/mL 141	0.75	1.82	6.29	6.33	387	0.245	2.83	1579	S341
40 mL X 15 mg/mL 141	0.75	5.25	16.39	16.58	204	0.177	5.91	603	S342
40 mL X 15 mg/mL 141	0.5	4.81	11.09	12.07	966	0.052	13.47	828	S343
40 mL X 15 mg/mL 141	1	3.83	6.21	6.95	1236	0.07	9.93	1438	S344
40 mL X 15 mg/mL 141	1.5	1.83	5.27	5.35	520	0.216	3.21	1868	S350
40 mL X 15 mg/mL 141	0.75	4.12	7.77	7.98	755	0.1	6.97	1252	S352
40 mL X 15 mg/mL 141	0.75	3.77	8.36	14.18	2916	0.015	47.77	705	S355
40 mL X 15 mg/mL 141	0.5	2.36	4.49	5.64	3054	0.035	19.98	1765	S358
40 mL X 15 mg/mL 141	0.5	4.89	13.78	14.83	446	0.091	7.65	675	S359
40 mL X 15 mg/mL 141	1	4.87	10.84	10.57	600	0.095	7.33	946	S361
40 mL X 15 mg/mL 141	0.75	4.39	11.37	11.56	439	0.118	5.86	865	S364
40 mL X 15 mg/mL 141	0.75	1.99	4.27	4.71	1475	0.086	8.83	2123	S365
Mean	0.8	3.4	7.5	8.2	1110.0	0.1	9.6	1479.2	
SD	0.3	1.3	3.5	3.8	728.5	0.1	6.9	633.8	
GM	0.7	3.2	6.8	7.4	915.2	0.1	7.8	1350.2	

Table 5. Individual Pharmacokinetic Parameters of Amprenavir by Race (PROA 1011)

Race	Treatment	Tmax (h)	Cmax (ug/mL)	AUCinf (ug ² /mL)	VZF (L)	T1/2 ^β (h)	CL/F (mL/min)
Black	4 X 150 mg 141	1.5	2.07	7.33	623	5.27	1365
Black	4 X 150 mg 141	1	3.94	9.4	322	3.5	1064
Black	4 X 150 mg 141	1	4.58	8.83	339	3.46	1132
Black	4 X 150 mg 141	1.5	1.96	5.34	782	4.83	1871
Black	4 X 150 mg 141	1	2.17	4.59	837	4.44	2179
Black	4 X 150 mg 141	0.75	6.7	7.39	1005	8.58	1354
Black	4 X 150 mg 141	0.75	2.82	4.98	1436	8.26	2008
Black	4 X 150 mg 141	1.5	2.3	5.66	357	2.33	1768
Black	4 X 150 mg 141	0.75	3.64	8.68	502	5.03	1152
Black	4 X 150 mg 141	0.75	5.69	12.77	454	6.7	783
Black	4 X 150 mg 141	0.75	6.31	9.41	560	6.09	1063
	Mean	1.0	3.8	7.7	656.3	5.3	1430.8
	SD	0.3	1.8	2.5	339.9	2.0	454.7
	GM	1.0	3.5	7.3	588.4	5.0	1366.0
Black	12 X 50 mg 141	1.5	1.97	6.95	1064	8.54	1439
Black	12 X 50 mg 141	0.53	7.92	18.27	312	6.59	547
Black	12 X 50 mg 141	0.75	7.2	11.67	358	4.83	857
Black	12 X 50 mg 141	1.5	1.44	2.85	2300	7.57	3509
Black	12 X 50 mg 141	1	1.97	4.39	814	4.13	2280
Black	12 X 50 mg 141	0.75	4.04	6.88	1132	9	1453
Black	12 X 50 mg 141	1	2.54	4.12	1231	5.86	2426
Black	12 X 50 mg 141	0.75	3.61	6.15	611	4.34	1625
Black	12 X 50 mg 141	1	3.57	11.29	363	4.74	886
Black	12 X 50 mg 141	1	5.35	12.5	263	3.8	800
Black	12 X 50 mg 141	1	5.67	9.76	490	5.52	1025
	Mean	1.0	4.1	8.6	812.5	5.9	1531.5
	SD	0.5	2.2	4.6	604.9	1.8	890.3
	GM	0.9	3.6	7.5	650.7	5.7	1327.0
Black	40 mL X 15 mg/mL 14	1.5	1.64	6.22	1186	8.52	1609
Black	40 mL X 15 mg/mL 14	0.75	3.23	8.66	707	7.07	1155
Black	40 mL X 15 mg/mL 14	0.5	3.01	6.88	607	4.82	1454
Black	40 mL X 15 mg/mL 14	1	1.79	4.19	1619	7.84	2385
Black	40 mL X 15 mg/mL 14	1	1.58	4.02	850	3.95	2489
Black	40 mL X 15 mg/mL 14	0.5	4.92	5.75	1503	9.98	1740
Black	40 mL X 15 mg/mL 14	0.5	2.6	4.42	1488	7.59	2265
Black	40 mL X 15 mg/mL 14	0.5	4.02	5.92	1054	7.21	1689
Black	40 mL X 15 mg/mL 14	0.5	2.83	7.73	1236	11.03	1294
Black	40 mL X 15 mg/mL 14	0.75	5.3	13.74	659	10.46	728
Black	40 mL X 15 mg/mL 14	0.5	6.03	8.14	806	7.58	1229
	Mean	0.7	3.4	6.9	1065.0	7.8	1639.7
	SD	0.3	1.5	2.8	365.8	2.2	554.1
	GM	0.7	3.0	6.5	1007.4	7.5	1549.5
White	4 X 150 mg 141	0.5	3.25	5.16	887	5.29	1937
White	4 X 150 mg 141	1	4.86	13.07	194	2.94	765
White	4 X 150 mg 141	2	3.87	14.39	325	5.4	695
White	4 X 150 mg 141	1.5	3.53	8.45	497	4.85	1184
White	4 X 150 mg 141	1	6.24	11.24	878	11.39	890
White	4 X 150 mg 141	1	4.82	13.73	188	2.98	729
White	4 X 150 mg 141	0.5	6.64	11.49	287	3.81	870
White	4 X 150 mg 141	1	4.13	9.06	490	5.13	1104
White	4 X 150 mg 141	1	2.4	5.64	2079	13.55	1772
White	4 X 150 mg 141	0.75	6.82	15.43	245	4.36	648
White	4 X 150 mg 141	1.5	4.52	12.79	419	6.19	782
White	4 X 150 mg 141	0.75	6.89	14.21	249	4.09	704
White	4 X 150 mg 141	0.75	4.15	6.06	819	5.73	1650
	Mean	1.0	4.8	10.8	581.3	5.8	1056.2
	SD	0.4	1.4	3.6	516.7	3.1	448.1
	GM	0.9	4.6	10.2	446.6	5.3	982.3
White	12 X 50 mg 141	0.5	6.42	7.65	723	6.39	1308
White	12 X 50 mg 141	1	4.62	13.3	244	3.74	752
White	12 X 50 mg 141	2	4.35	9.27	293	3.14	1079
White	12 X 50 mg 141	1.5	3.52	12.68	519	7.6	789
White	12 X 50 mg 141	1	4.34	8.5	1305	12.81	1177
White	12 X 50 mg 141	1	2.04	8.96	443	4.59	1116
White	12 X 50 mg 141	0.75	6.31	11.39	369	4.85	878
White	12 X 50 mg 141	0.75	5.2	10.85	421	5.28	922
White	12 X 50 mg 141	1	2.6	6.15	1515	10.77	1625
White	12 X 50 mg 141	0.75	3.64	7.92	267	2.44	1262
White	12 X 50 mg 141	1	6.65	16.15	284	5.3	619
White	12 X 50 mg 141	1	4.55	15.04	250	4.35	665
White	12 X 50 mg 141	0.5	3.82	6.47	664	4.96	1546
	Mean	1.0	4.5	10.3	561.3	5.9	1056.8
	SD	0.4	1.4	3.2	408.7	3.0	322.2
	GM	0.9	4.2	9.9	463.8	5.3	1011.6
White	40 mL X 15 mg/mL 14	0.52	2.44	3.55	1927	7.91	2816
White	40 mL X 15 mg/mL 14	0.75	1.82	6.33	387	2.83	1579
White	40 mL X 15 mg/mL 14	0.75	5.25	16.58	204	3.91	603
White	40 mL X 15 mg/mL 14	0.5	4.81	12.07	966	13.47	828
White	40 mL X 15 mg/mL 14	1	3.83	6.95	1236	9.93	1438
White	40 mL X 15 mg/mL 14	1.5	1.83	5.35	520	3.21	1868
White	40 mL X 15 mg/mL 14	0.75	4.12	7.98	755	6.97	1252
White	40 mL X 15 mg/mL 14	0.75	3.77	14.18	2916	47.77	705
White	40 mL X 15 mg/mL 14	0.5	2.36	5.66	3054	19.98	1765
White	40 mL X 15 mg/mL 14	0.5	4.89	14.83	446	7.65	675
White	40 mL X 15 mg/mL 14	1	4.07	10.57	600	7.33	946
White	40 mL X 15 mg/mL 14	0.75	4.39	11.56	439	5.86	865
White	40 mL X 15 mg/mL 14	0.75	1.99	4.71	1475	8.03	2123
	Mean	0.8	3.5	9.3	1148.1	11.1	1343.3
	SD	0.3	1.2	4.3	949.9	11.9	668.1
	GM	0.7	3.3	8.3	843.9	8.1	1201.7

Table 6. Individual Pharmacokinetic Parameters of Amprenavir (PROA 1007)

Plasma Pharmacokinetic Parameter Values with Summary Statistics

AMClow (ng%h/mL)	AMCContrap (h)	CL/F (L/min)	Qmax (ng/mL)	Lambda (1/h)	WLF (h)	t1/2 (h)	tmax (h)
9.70	1.3	1003	3.37	0.074	989	9.32	1.50
3.07	2.7	3237	1.10	0.141	1440	4.31	0.53
41.03	0.3	855	1.04	0.176	781	5.31	1.02
9.44	2.4	1007	1.04	0.093	640	7.44	1.00
3.70	1.9	1477	1.31	0.175	781	4.31	1.50
40.70	1.1	760	1.31	0.155	373	6.34	1.50
n							
6	6	6	6	6	6	6	6
Mean	1.75	1016.3	2.05	0.14	722.17	5.41	1.34
SD	0.60	1044.3	1.20	0.05	412.37	3.27	0.51
CV%	34.30	65.03	44.90	32.70	37.40	60.53	34.16
Median	1.10	1003.0	1.04	0.15	706.50	4.30	1.50
min.	0.3	855	1.04	0.074	291	3.27	0.53
max.	2.7	3237	1.31	0.176	1440	5.31	1.02
Geometric Mean	1.34	1102.1	2.11	0.13	434.37	5.27	1.00
95% CI (lower)	0.71	747.53	1.20	0.09	241.96	3.35	0.50
95% CI (upper)	2.73	2555.3	4.04	0.20	1156.0	7.03	1.50

Individual and Summary Blood/Plasma Radioactivity and Estimated Red Blood Cell Concentration

Subject	AMClow	Qmax
Blood/Plasma_Radioactivity		
4207	86.3%	67.4%
4208	82.5%	63.0%
4209	85.0%	65.7%
4210	75.4%	60.7%
4211	77.1%	64.10%
4212	76.0%	58.3%
n		
6	6	6
Mean	80.0%	65.26%
SD	3.27%	3.30%
CV%	4.08%	5.07%
Median	77.9%	64.10%
min.	75.1%	58.3%
max.	86.3%	67.4%
n		
6	6	6
Mean	66.0%	45.26%
SD	3.27%	3.30%
CV%	4.94%	6.07%
Median	77.9%	64.10%
min.	75.1%	58.3%
max.	86.3%	67.4%
n		
6	6	6
Mean	66.0%	45.26%
SD	3.27%	3.30%
CV%	4.94%	6.07%
Median	77.9%	64.10%
min.	75.1%	58.3%
max.	86.3%	67.4%

Individual Pharmacokinetic Parameter Values of Radioactivity on 14194 Equivalents with Summary Statistics

Subject	Sex	AMClow (ng%h/mL)	AMCContrap (h)	WLFContrap (h)	CL/F (L/min)	Qmax (ng/mL)	Lambda (1/h)	t1/2 (h)	tmax (h)
Blood_Radioactivity									
4207	M	32.33	25.79	20.2	309	4.47	0.070	24.73	1.50
4208	M	16.04	11.32	11.9	532	1.47	0.035	17.74	0.53
4209	M	31.31	27.47	14.9	300	4.74	0.035	21.34	2.02
4210	M	24.25	17.01	29.9	412	4.21	0.035	17.04	1.00
4211	M	0.65	6.98	19.3	1154	1.04	0.042	4.00	1.50
4212	M	24.33	19.75	18.7	411	4.02	0.030	18.45	1.50
n									
6	6	6	6	6	6	6	6	6	6
Mean		22.29	18.09	22.94	510.00	3.47	0.05	17.04	1.34
SD		9.38	8.05	4.44	324.21	1.37	0.04	6.01	0.51
CV%		40.26	44.52	19.05	61.17	39.10	0.05	30.10	30.10
Median		24.28	18.30	19.75	411.50	4.12	0.04	17.11	1.50
min.		0.65	6.98	14.9	300	1.47	0.020	4.00	0.53
max.		32.31	27.47	32.7	1154	4.74	0.042	24.75	2.02
Geometric Mean		22.29	18.09	22.94	510.00	3.47	0.05	17.04	1.34
95% CI (lower)		12.52	9.40	14.44	274.44	1.95	0.02	6.50	0.50
95% CI (upper)		34.14	26.34	29.44	790.16	5.26	0.08	29.62	2.50
n									
6	6	6	6	6	6	6	6	6	6
Mean		20.70	14.16	15.05	414.03	3.34	0.04	10.23	1.07
SD		10.56	9.21	4.73	222.32	2.15	0.05	3.40	0.52
CV%		50.70	65.34	31.40	53.93	64.37	0.12	33.05	48.04
Median		11.04	10.00	15.00	310.00	4.51	0.04	11.49	1.50
min.		11.02	10.41	10.1	255	2.02	0.052	3.93	1.00
max.		29.19	22.21	21.3	646	7.12	0.124	11.42	2.50
Geometric Mean		20.70	14.16	15.04	414.03	3.34	0.04	10.23	1.07
95% CI (lower)		14.44	11.01	11.00	211.99	2.05	0.04	5.00	0.50
95% CI (upper)		43.10	24.16	21.11	600.46	6.23	0.12	15.40	2.50

Individual and Summary Recovery of Radioactivity as Percent of Dose from Urine and Feces with Total Recovery

Subject	Sex	Urine (%)	Feces (%)	Total (%)
4207	M	12.33	25.79	38.12
4208	M	16.04	11.32	27.36
4209	M	31.31	27.47	58.78
4210	M	24.25	17.01	41.26
4211	M	0.65	6.98	7.63
4212	M	24.33	19.75	44.08
n				
6	6	6	6	6
Mean		18.09	18.09	36.18
SD		9.38	8.05	17.43
CV%		51.90	44.52	48.20
Median		18.30	19.75	38.05
min.		6.98	14.9	21.88
max.		32.31	27.47	59.78
Geometric Mean		18.09	18.09	36.18
95% CI (lower)		9.40	14.44	23.84
95% CI (upper)		26.34	29.44	55.78

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Table 8

Plasma Aprenavir Pharmacokinetic Parameter Values at dose 3

Subject	Cohort	AUC ₀₋₂₄ , ng·h/mL	C ₀ , ng/mL	C ₁₂ , ng/mL	C ₂₄ , ng/mL	CL _R , mL/min	AUC ₀₋₂₄ /AUC _{inf}	t _{max} , h
1	300 BID	5.76	0.48	0.11	3.24	868	0.997	0.75
2	300 BID	11.74	0.98	0.13	6.62	426	1.135	1.50
3	300 BID	6.00	0.50	0.10	2.35	833	1.213	1.00
4	300 BID	4.66	0.39	0.05	2.27	1073	0.715	1.50
5	300 BID	2.54	0.30	0.10	1.21	1412	0.824	1.75
11	300 BID	1.73	0.14	0.01	1.10	2087	0.523	1.50
14	300 BID	5.03	0.49	0.07	2.49	858	1.592	1.00
15	300 BID	1.93	0.16	0.03	1.01	2589	0.997	1.50
17	300 BID	4.05	0.34	0.05	2.12	1235	1.913	0.75
25	300 TID	4.34	0.54	0.11	1.95	1153	0.571	1.00
26	300 TID	2.53	0.44	0.08	1.48	1418	0.396	1.50
27	300 TID	3.39	0.42	0.05	2.21	1474		1.00
29	300 TID	0.96	1.12	0.41	3.61	358	1.043	1.25
32	300 TID	5.42	0.68	0.14	1.81	923	1.395	1.50
33	300 TID	1.91	0.24	0.06	0.94	2618	0.912	0.98
34	300 TID	3.97	0.50	0.09	1.87	1260	0.511	1.02
35	300 TID	4.59	0.57	0.11	2.58	1090		1.00
37	300 TID	3.41	0.43	0.08	1.50	1464	0.823	1.48
49	900 BID	7.15	0.60	0.08	3.53	2097	1.344	2.00
51	900 BID	12.56	1.05	0.07	7.47	1194	1.323	3.00
52	900 BID	11.81	0.98	0.50	2.30	1270		1.98
63	900 BID	13.82	1.15	0.14	5.23	1086	0.636	1.00
64	900 BID	11.37	0.95	0.19	4.54	1319	0.972	1.00
65	900 BID	13.80	1.15	0.21	5.99	1087	0.724	2.50
73	1200 BID	32.95	2.75	0.51	9.81	607	0.605	1.50
75	1200 BID	3.02	0.23	0.12	0.92	6421	0.382	0.75
86	1200 BID	13.90	1.16	0.29	4.23	1439	0.663	2.00
88	1200 BID	16.15	1.35	0.21	4.63	1238	0.554	2.43
89	1200 BID	26.31	2.19	0.28	7.23	740	0.417	2.00
97	1050 BID	17.43	1.45	0.29	6.37	1004	0.930	1.50
98	1050 BID	27.53	2.29	0.59	8.04	636	0.852	0.75
99	1050 BID	14.97	1.25	0.30	7.51	1169	0.807	0.55
100	1050 BID	20.27	1.69	0.26	7.48	863	0.519	2.48
101	1050 BID	29.97	2.50	0.67	12.07	584	0.718	0.85
109	1050 BID	10.77	0.90	0.12	5.57	1624	0.854	1.00
110	1050 BID	20.84	1.74	0.27	9.41	839	0.739	0.50
112	1050 BID	21.11	1.76	0.34	7.38	839	0.558	1.00
113	1050 BID	10.13	0.84	0.14	5.42	1727	0.456	0.95
133	900 BID+ABC	30.41	2.53	0.57	12.78	493		1.50
135	900 BID+ABC	8.65	0.72	0.15	3.73	1735		1.50
137	900 BID+ABC	14.99	1.25	0.14	6.81	1801		2.50
138	900 BID+ABC	12.13	1.01	0.16	4.62	1237		2.00

Table 9. Individual Pharmacokinetic Parameters of Amprenavir and Indinavir after single oral dosing (PROA 2001)

Pharmacokinetic Parameters of Amprenavir and Indinavir After Single Oral Dosing (Phase IA)

Amprenavir				Indinavir			
Subject	C _{max} µg/mL	t _{max} h	AUC _{0-∞} µg/mL·h	Subject	C _{max} µg/mL	t _{max} h	AUC _{0-∞} µg/mL·h
303	5.5671	1	13.50	303	3.075	1	5.15
305	8.2787	0.75	26.98	305	7.804	0.75	17.00
306	8.4244	0.75	33.23	306	7.058	0.75	13.57
307	6.4855	2	23.83	307	6.658	0.75	15.75
308	8.2071	1	24.60	308	8.016	0.75	16.21
310	5.5270	3	26.79	310	3.290	1	9.40
311	5.0831	2.5	23.38	311	4.286	0.75	10.81
312	7.8335	0.75	23.14	312	8.823	0.75	19.67
315	8.1905	1	35.40	315	6.094	0.75	12.83
317	8.4509	1.5	32.90	317	1.943	0.75	4.47
318	5.6437	2.5	20.31	318	1.432	0.75	2.24
319	8.2357	0.5	19.42	319	5.546	0.75	6.98
Mean	7.1607	1.44	25.32	Mean	5.502	0.79	11.18
SD	1.3671	0.85	6.24	SD	2.729	0.10	5.59
Median	8.0120	1.00	24.22	Median	5.820	0.75	11.87
Min	5.0831	0.50	13.90	Min	1.432	0.75	2.24
Max	8.4509	3.00	35.40	Max	8.823	1.00	19.67
CV %	19.1	58.9	24.6	CV %	49.6	12.3	49.9
95% CI			21.36, 29.29	95% CI	3.77, 7.24		7.53, 14.73
Reference 1 (normalized mean*)			12.78	Reference (mean)	7.17		17.11
Mean ratio			1.98	Mean ratio	0.77		0.65
Reference 2 (normalized mean*)			21.49				
Mean ratio			1.18				

Reference 1: PROA 1002, 900 mg
 Reference 2: PROA 1001, 900 mg
 * mean AUC_{0-∞} has been normalized to an 800 mg dose

Table 10. Individual Pharmacokinetic Parameters of Amprenavir at Steady-State (PROA 2001)

Subject	Combination	C _{max,ss} µg/mL	t _{max,ss} h	C _{min,ss} µg/mL	AUC ₀₋₂₄ µg/mL·h	CLF mL/min
303	APV + SOV	2.495	2	1.2343	9.50	1403
305	APV + NFV	9.129	0.5	0.795	18.85	707
306	APV	5.596	1	0.2080	14.07	948
307	APV + IDV	8.763	0.75	0.5388	23.09	578
308	APV + NFV	4.198	0.5	0.657	12.18	1095
312	APV	9.905	1	0.7783	27.97	477
315	APV	5.888	1.5	0.1947	12.05	1107
317	APV + NFV	4.319	1	-	20.24	659
318	APV + IDV	9.788	1	0.6296	31.66	421
319	APV + SOV	3.706	1.5	0.2653	12.06	1106
322	APV + NFV	6.833	0.5	0.482	11.29	1162
323	APV	14.915	0.5	0.4302	25.61	521
324	APV + IDV	7.148	1	0.3504	23.98	556
325	APV + SOV	4.791	1.5	0.1517	13.67	975
329	APV + IDV	6.758	1.07	0.1211	17.33	769
341	APV + IDV	8.078	0.75	0.3478	22.46	594
342	APV + IDV	7.674	1	0.2413	10.71	1244
346	APV + SOV	7.256	0.5	0.3717	11.99	1112
353	APV + SOV	6.832	0.5	0.3081	10.79	1236
355	APV + NFV	5.358	1	1.300	18.74	712
356	APV + NFV	6.157	1.25	1.791	22.58	591
358	APV	5.026	2	0.0894	9.25	1441
360	APV	9.463	0.83	0.6494	21.35	624
362	APV + IDV	9.400	1	0.8358	20.09	664
363	APV + SOV	3.188	1	0.0858	7.86	1695
364	APV + SOV	3.432	1	0.2065	8.95	1490
366*	APV + IDV	5.276	0.5	0.3431	18.47	722
369*	APV + IDV	8.763	1.5	0.6051	23.22	574
365	APV	3.243	3	0.2273	6.82	1512
372*	APV	3.759	1	0.2974	10.72	1242

Contd... Table 10. Individual Pharmacokinetic Parameters of Indinavir, Saquinavir, and Nelfinavir at Steady-State (PROA 2001)

800 mg indinavir TID + 800 mg amprenavir TID

Indinavir	C _{max,ss} µg/mL	t _{max,ss} h	C _{min,ss} µg/mL	AUC ₀₋₂₄ µg/mL·h	CLF mL/min
307	6.527	0.75	0.129	13.13	1016
318	7.208	1	0.137	14.01	952
324	8.244	0.75	0.089	19.11	698
329	7.808	1.07	0.035	15.11	883
341	6.735	0.75	0.163	12.86	1037
342	6.435	1	0.197	10.05	1327
362	7.137	0.75	0.132	12.04	1107
368	4.904	0.5	0.086	7.70	1733
369	8.082	1	0.182	18.69	713
Mean	7.013	0.84	0.130	13.63	1052
SD	1.031	0.19	0.052	3.70	321
Median	7.137	0.75	0.132	13.13	1016
Min	4.904	0.5	0.035	7.70	698
Max	8.244	1.07	0.197	19.11	1733
CV%	14.7	22.2	39.7	27.1	30.5
95% CI	6.22, 7.81	0.70, 0.98	0.09, 0.17	10.79, 16.47	805, 1298
Heterence	8.982	0.8	0.179	21.85	610
Ratio	0.78	1.05	0.73	0.62	1.72

800 mg saquinavir TID + 800 mg amprenavir TID

Saquinavir	C _{max,ss} µg/mL	t _{max,ss} h	C _{min,ss} µg/mL	AUC ₀₋₂₄ µg/mL·h	CLF mL/min
303	0.918	3	0.0744	2.566	5198
319	3.010	1.5	0.2235	6.702	1989
325	2.450	2	0.0688	5.852	2278
346	0.614	0.83	0.0377	1.027	12985
353	0.221	0.5	0.0139	0.425	31398
363	0.462	0.75	0.0285	0.649	20554
364	0.360	1	0.0512	0.856	15577
Mean	1.148	1.4	0.0711	2.552	12854
SD	1.114	0.9	0.0705	2.629	10794
Median	0.614	1.0	0.0512	1.027	12985
Min	0.221	0.5	0.0139	0.425	1989
Max	3.010	3.0	0.2235	6.702	31398
CV%	97.1	64.3	99.2	101.8	84.0
95% CI	0.12, 2.18	0.56, 2.18	0.01, 0.14	0.15, 5.01	2871, 22837
Heterence	0.9495	2	0.137	3.206	4159
Ratio	1.21	0.68	0.52	0.81	3.09

750 mg nelfinavir TID + 800 mg amprenavir TID

Nelfinavir	C _{max,ss} µg/mL	t _{max,ss} h	C _{min,ss} µg/mL	AUC ₀₋₂₄ µg/mL·h	CLF mL/min
305	2.77	3.08	1.70	18.57	673
308	3.25	3	1.68	18.08	691
317	5.8	4	3.82	35.88	348
322	1.72	4	0.82	10.12	1235
355	4.46	5	1.75	22.33	559
356	3.36	3.25	0.44	15.18	823
Mean	3.58	3.72	1.70	20.03	722
SD	1.41	0.77	1.17	8.76	298
Median	3.36	3.63	1.68	18.33	682
Min	1.72	3	0.44	10.12	348
Max	5.80	5	3.82	35.88	1235
CV%	39.4	20.6	68.9	43.8	41.2
95% CI	2.10, 5.05		0.47, 2.93	10.83, 29.23	409, 1034
Heterence	3.18		1.49	17.4	718
Ratio	1.12		1.14	1.15	1.00

MS-Nelfinavir

	C _{max,ss} µg/mL	t _{max,ss} h	C _{min,ss} µg/mL	AUC ₀₋₂₄ µg/mL·h	AUC _{0-24,MSV} / AUC ₀₋₂₄
305	0.242	1.53	0.120	1.51	0.081
308	0.215	4	0.080	1.01	0.056
317	0.442	5	0.298	2.83	0.079
322	0.38	5	0.163	2.03	0.201
355	1.03	5	0.224	3.97	0.178
356	0.561	4.25	0.044	1.95	0.128
Mean	0.48	4.13	0.155	2.22	0.120
SD	0.30	1.35	0.094	1.05	0.058
Median	0.41	4.63	0.141	1.99	0.105
Min	0.22	2	0.044	1.01	0.056
Max	1.03	5	0.30	3.97	0.201
CV%	62.5	32.6	60.9	47.5	48.8

Table 11. Individual Pharmacokinetic Parameters of Amprenavir in Pediatrics After Single Dose (PROA 1006)

Listing of Pharmacokinetic Parameter Values

Subj	Study Treatment	Body Weight (kg)	Dose (mg/kg)	Total Dose (mg)	AUC inf (mg/L·h)	AUC last (mg/L·h)	AUC est (%)	Cmax (mg/L)	t1/2 (h)	Lambda z (1/h)	CL/F (mL/min)	Vz/F (L)	tmax (h)	Ratio Cmax	Ratio AUCinf	Ratio Dose																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																						
651	5 mg	39.7	5.04	200	5.89	5.77	7.02	4.53	5.9	0.117	566	291	1.50	1.48	2.34	2.00																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																						
	10 mg	40.3	9.93	400	13.79	12.30	10.81	6.71	15.0	0.046	483	629	0.60				652	5 mg	21.9	4.57	100	2.56	2.42	5.75	2.39	5.8	0.119	650	327	1.00	1.35	1.50	2.25	10 mg	21.5	10.47	225	3.85	3.67	4.67	3.24	6.9	0.101	974	579	1.00	653	5 mg	24.4	5.12	125	4.21	3.91	7.01	3.10	16.3	0.042	495	700	0.95	1.11	0.91	2.00	10 mg	25.2	9.92	250	3.82	3.72	2.79	3.43	4.5	0.153	1090	426	1.00	654	5 mg	29.1	5.15	150	4.61	4.09	11.29	2.95	9.6	0.072	543	450	1.00	2.00	2.28	2.00	10 mg	30.7	9.77	300	10.48	10.31	2.57	5.91	6.2	0.112	477	255	1.05	655	5 mg	25.6	4.88	125	2.18	2.15	1.20	2.66	1.3	0.556	957	103	0.50	2.40	3.15	2.00	10 mg	26.0	9.62	250	6.86	6.68	1.70	6.39	8.6	0.081	607	452	0.50	658	5 mg	14.7	5.04	175	3.94	2.98	24.39	1.98	17.4	0.040	740	1118	0.50	5.04	4.35	2.00	10 mg	14.1	10.26	350	17.15	17.05	0.60	9.97	4.8	0.144	340	141	1.00	659	5 mg	28.1	5.34	150	3.60	3.27	9.10	3.76	4.8	0.145	694	288	0.50	1.79	3.03	1.83	10 mg	28.3	9.72	275	10.91	10.00	1.08	6.73	4.5	0.156	420	162	0.50	660	5 mg	24.2	5.17	125	5.58	5.22	6.41	3.02	8.4	0.083	373	270	1.50	4.82	3.80	2.00	10 mg	23.6	10.59	250	21.24	21.18	0.27	14.54	1.7	0.420	196	28	1.00	662	15 mg	25.0	15.00	375	13.49	13.30	1.40	8.76	5.5	0.125	463	222	0.50	0.67	1.13	1.33	20 mg	25.3	19.76	500	15.23	14.24	6.50	5.85	8.1	0.085	547	384	2.00	663	15 mg	23.3	15.02	350	18.59	15.68	15.65	6.28	18.2	0.038	314	493	0.50	1.04	2.39	1.29	20 mg	22.6	19.91	450	44.37	41.67	6.08	6.52	6.9	0.101	169	100	4.00	681	5 mg	18.1	5.52	100	12.25	11.98	2.21	5.26	2.7	0.257	136	32	1.00	0.41	0.38	2.00	10 mg	19.1	10.47	200	4.65	4.31	7.32	2.14	3.5	0.200	717	215	1.50	682	5 mg	21.5	4.65	100	12.00	11.87	1.14	8.36	2.0	0.340	139	25	1.03	0.19	0.12	2.00	10 mg	21.1	9.48	200	1.46	1.36	7.02	1.56	6.7	0.103	2276	1321	0.50	683	15 mg	19.5	15.38	300	9.86	9.61	2.60	6.13	6.8	0.101	507	300	1.00	3.18	2.91	1.25	20 mg	19.2	19.53	375	28.71	27.30	5.24	19.53	12.0	0.058	218	227	1.00	684	15 mg	62.1	14.90	925	32.10	27.70	13.72	13.32	13.2	0.053	480	548	2.05	1.03	1.46	1.35	20 mg	62.6	19.97	1250	46.76	38.88	16.86	13.67	17.7	0.039	446	683	1.50	685	15 mg	26.4	15.15	400	14.19	13.92	1.92	3.19	4.6	0.152	470	186	1.50	1.45	0.51	1.31	20 mg	26.3	19.96	525	7.25	7.11	1.93	4.62	5.9	0.118	1207	616	1.50	686	15 mg	14.5	15.52	225	7.83	7.71	1.47	6.06	4.1	0.171	479	165	0.83	1.14	1.13	1.33	20 mg	14.9	20.13	300	8.87	8.65	2.45	6.91	6.1	0.113	564	300	0.50	687	15 mg	26.5	15.09	400	12.41	12.25	1.30	5.49	6.0	0.117	537	277	2.02	1.91	1.89	1.38	20 mg	27.4	20.07	550	23.44	22.97	1.99	10.88	6.1	0.113	391	208	1.00	688	15 mg	21.8	14.91	325	8.32	8.14	2.20	8.31	7.5	0.092	651	424	0.97	0.69	1.34	1.38	20 mg	22.1	20.36	450	11.13	10.78	3.12	5.73	5.8	0.119	674	339	1.75	689	15 mg	28.2	15.07	425	8.99	7.36	18.13	4.87	11.5	0.061	788	781	0.50	1.57	2.17	1.35	20 mg	28.5	20.18	575	19.55	17.43	10.86	7.63	9.0	0.077	490	381	1.00	690	15 mg	32.9	15.20	500	11.41	11.30	0.98	6.36	2.9	0.244	730	180	1.55	0.98	1.19	1.30	20 mg	33.1	19.64	650	13.52	13.00	3.87	6.24	5.2
652	5 mg	21.9	4.57	100	2.56	2.42	5.75	2.39	5.8	0.119	650	327	1.00	1.35	1.50	2.25																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																						
	10 mg	21.5	10.47	225	3.85	3.67	4.67	3.24	6.9	0.101	974	579	1.00				653	5 mg	24.4	5.12	125	4.21	3.91	7.01	3.10	16.3	0.042	495	700	0.95	1.11	0.91	2.00	10 mg	25.2	9.92	250	3.82	3.72	2.79	3.43	4.5	0.153	1090	426	1.00	654	5 mg	29.1	5.15	150	4.61	4.09	11.29	2.95	9.6	0.072	543	450	1.00	2.00	2.28	2.00	10 mg	30.7	9.77	300	10.48	10.31	2.57	5.91	6.2	0.112	477	255	1.05	655	5 mg	25.6	4.88	125	2.18	2.15	1.20	2.66	1.3	0.556	957	103	0.50	2.40	3.15	2.00	10 mg	26.0	9.62	250	6.86	6.68	1.70	6.39	8.6	0.081	607	452	0.50	658	5 mg	14.7	5.04	175	3.94	2.98	24.39	1.98	17.4	0.040	740	1118	0.50	5.04	4.35	2.00	10 mg	14.1	10.26	350	17.15	17.05	0.60	9.97	4.8	0.144	340	141	1.00	659	5 mg	28.1	5.34	150	3.60	3.27	9.10	3.76	4.8	0.145	694	288	0.50	1.79	3.03	1.83	10 mg	28.3	9.72	275	10.91	10.00	1.08	6.73	4.5	0.156	420	162	0.50	660	5 mg	24.2	5.17	125	5.58	5.22	6.41	3.02	8.4	0.083	373	270	1.50	4.82	3.80	2.00	10 mg	23.6	10.59	250	21.24	21.18	0.27	14.54	1.7	0.420	196	28	1.00	662	15 mg	25.0	15.00	375	13.49	13.30	1.40	8.76	5.5	0.125	463	222	0.50	0.67	1.13	1.33	20 mg	25.3	19.76	500	15.23	14.24	6.50	5.85	8.1	0.085	547	384	2.00	663	15 mg	23.3	15.02	350	18.59	15.68	15.65	6.28	18.2	0.038	314	493	0.50	1.04	2.39	1.29	20 mg	22.6	19.91	450	44.37	41.67	6.08	6.52	6.9	0.101	169	100	4.00	681	5 mg	18.1	5.52	100	12.25	11.98	2.21	5.26	2.7	0.257	136	32	1.00	0.41	0.38	2.00	10 mg	19.1	10.47	200	4.65	4.31	7.32	2.14	3.5	0.200	717	215	1.50	682	5 mg	21.5	4.65	100	12.00	11.87	1.14	8.36	2.0	0.340	139	25	1.03	0.19	0.12	2.00	10 mg	21.1	9.48	200	1.46	1.36	7.02	1.56	6.7	0.103	2276	1321	0.50	683	15 mg	19.5	15.38	300	9.86	9.61	2.60	6.13	6.8	0.101	507	300	1.00	3.18	2.91	1.25	20 mg	19.2	19.53	375	28.71	27.30	5.24	19.53	12.0	0.058	218	227	1.00	684	15 mg	62.1	14.90	925	32.10	27.70	13.72	13.32	13.2	0.053	480	548	2.05	1.03	1.46	1.35	20 mg	62.6	19.97	1250	46.76	38.88	16.86	13.67	17.7	0.039	446	683	1.50	685	15 mg	26.4	15.15	400	14.19	13.92	1.92	3.19	4.6	0.152	470	186	1.50	1.45	0.51	1.31	20 mg	26.3	19.96	525	7.25	7.11	1.93	4.62	5.9	0.118	1207	616	1.50	686	15 mg	14.5	15.52	225	7.83	7.71	1.47	6.06	4.1	0.171	479	165	0.83	1.14	1.13	1.33	20 mg	14.9	20.13	300	8.87	8.65	2.45	6.91	6.1	0.113	564	300	0.50	687	15 mg	26.5	15.09	400	12.41	12.25	1.30	5.49	6.0	0.117	537	277	2.02	1.91	1.89	1.38	20 mg	27.4	20.07	550	23.44	22.97	1.99	10.88	6.1	0.113	391	208	1.00	688	15 mg	21.8	14.91	325	8.32	8.14	2.20	8.31	7.5	0.092	651	424	0.97	0.69	1.34	1.38	20 mg	22.1	20.36	450	11.13	10.78	3.12	5.73	5.8	0.119	674	339	1.75	689	15 mg	28.2	15.07	425	8.99	7.36	18.13	4.87	11.5	0.061	788	781	0.50	1.57	2.17	1.35	20 mg	28.5	20.18	575	19.55	17.43	10.86	7.63	9.0	0.077	490	381	1.00	690	15 mg	32.9	15.20	500	11.41	11.30	0.98	6.36	2.9	0.244	730	180	1.55	0.98	1.19	1.30	20 mg	33.1	19.64	650	13.52	13.00	3.87	6.24	5.2	0.134	801	358	1.50																										
653	5 mg	24.4	5.12	125	4.21	3.91	7.01	3.10	16.3	0.042	495	700	0.95	1.11	0.91	2.00																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																						
	10 mg	25.2	9.92	250	3.82	3.72	2.79	3.43	4.5	0.153	1090	426	1.00				654	5 mg	29.1	5.15	150	4.61	4.09	11.29	2.95	9.6	0.072	543	450	1.00	2.00	2.28	2.00	10 mg	30.7	9.77	300	10.48	10.31	2.57	5.91	6.2	0.112	477	255	1.05	655	5 mg	25.6	4.88	125	2.18	2.15	1.20	2.66	1.3	0.556	957	103	0.50	2.40	3.15	2.00	10 mg	26.0	9.62	250	6.86	6.68	1.70	6.39	8.6	0.081	607	452	0.50	658	5 mg	14.7	5.04	175	3.94	2.98	24.39	1.98	17.4	0.040	740	1118	0.50	5.04	4.35	2.00	10 mg	14.1	10.26	350	17.15	17.05	0.60	9.97	4.8	0.144	340	141	1.00	659	5 mg	28.1	5.34	150	3.60	3.27	9.10	3.76	4.8	0.145	694	288	0.50	1.79	3.03	1.83	10 mg	28.3	9.72	275	10.91	10.00	1.08	6.73	4.5	0.156	420	162	0.50	660	5 mg	24.2	5.17	125	5.58	5.22	6.41	3.02	8.4	0.083	373	270	1.50	4.82	3.80	2.00	10 mg	23.6	10.59	250	21.24	21.18	0.27	14.54	1.7	0.420	196	28	1.00	662	15 mg	25.0	15.00	375	13.49	13.30	1.40	8.76	5.5	0.125	463	222	0.50	0.67	1.13	1.33	20 mg	25.3	19.76	500	15.23	14.24	6.50	5.85	8.1	0.085	547	384	2.00	663	15 mg	23.3	15.02	350	18.59	15.68	15.65	6.28	18.2	0.038	314	493	0.50	1.04	2.39	1.29	20 mg	22.6	19.91	450	44.37	41.67	6.08	6.52	6.9	0.101	169	100	4.00	681	5 mg	18.1	5.52	100	12.25	11.98	2.21	5.26	2.7	0.257	136	32	1.00	0.41	0.38	2.00	10 mg	19.1	10.47	200	4.65	4.31	7.32	2.14	3.5	0.200	717	215	1.50	682	5 mg	21.5	4.65	100	12.00	11.87	1.14	8.36	2.0	0.340	139	25	1.03	0.19	0.12	2.00	10 mg	21.1	9.48	200	1.46	1.36	7.02	1.56	6.7	0.103	2276	1321	0.50	683	15 mg	19.5	15.38	300	9.86	9.61	2.60	6.13	6.8	0.101	507	300	1.00	3.18	2.91	1.25	20 mg	19.2	19.53	375	28.71	27.30	5.24	19.53	12.0	0.058	218	227	1.00	684	15 mg	62.1	14.90	925	32.10	27.70	13.72	13.32	13.2	0.053	480	548	2.05	1.03	1.46	1.35	20 mg	62.6	19.97	1250	46.76	38.88	16.86	13.67	17.7	0.039	446	683	1.50	685	15 mg	26.4	15.15	400	14.19	13.92	1.92	3.19	4.6	0.152	470	186	1.50	1.45	0.51	1.31	20 mg	26.3	19.96	525	7.25	7.11	1.93	4.62	5.9	0.118	1207	616	1.50	686	15 mg	14.5	15.52	225	7.83	7.71	1.47	6.06	4.1	0.171	479	165	0.83	1.14	1.13	1.33	20 mg	14.9	20.13	300	8.87	8.65	2.45	6.91	6.1	0.113	564	300	0.50	687	15 mg	26.5	15.09	400	12.41	12.25	1.30	5.49	6.0	0.117	537	277	2.02	1.91	1.89	1.38	20 mg	27.4	20.07	550	23.44	22.97	1.99	10.88	6.1	0.113	391	208	1.00	688	15 mg	21.8	14.91	325	8.32	8.14	2.20	8.31	7.5	0.092	651	424	0.97	0.69	1.34	1.38	20 mg	22.1	20.36	450	11.13	10.78	3.12	5.73	5.8	0.119	674	339	1.75	689	15 mg	28.2	15.07	425	8.99	7.36	18.13	4.87	11.5	0.061	788	781	0.50	1.57	2.17	1.35	20 mg	28.5	20.18	575	19.55	17.43	10.86	7.63	9.0	0.077	490	381	1.00	690	15 mg	32.9	15.20	500	11.41	11.30	0.98	6.36	2.9	0.244	730	180	1.55	0.98	1.19	1.30	20 mg	33.1	19.64	650	13.52	13.00	3.87	6.24	5.2	0.134	801	358	1.50																																																								
654	5 mg	29.1	5.15	150	4.61	4.09	11.29	2.95	9.6	0.072	543	450	1.00	2.00	2.28	2.00																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																						
	10 mg	30.7	9.77	300	10.48	10.31	2.57	5.91	6.2	0.112	477	255	1.05				655	5 mg	25.6	4.88	125	2.18	2.15	1.20	2.66	1.3	0.556	957	103	0.50	2.40	3.15	2.00	10 mg	26.0	9.62	250	6.86	6.68	1.70	6.39	8.6	0.081	607	452	0.50	658	5 mg	14.7	5.04	175	3.94	2.98	24.39	1.98	17.4	0.040	740	1118	0.50	5.04	4.35	2.00	10 mg	14.1	10.26	350	17.15	17.05	0.60	9.97	4.8	0.144	340	141	1.00	659	5 mg	28.1	5.34	150	3.60	3.27	9.10	3.76	4.8	0.145	694	288	0.50	1.79	3.03	1.83	10 mg	28.3	9.72	275	10.91	10.00	1.08	6.73	4.5	0.156	420	162	0.50	660	5 mg	24.2	5.17	125	5.58	5.22	6.41	3.02	8.4	0.083	373	270	1.50	4.82	3.80	2.00	10 mg	23.6	10.59	250	21.24	21.18	0.27	14.54	1.7	0.420	196	28	1.00	662	15 mg	25.0	15.00	375	13.49	13.30	1.40	8.76	5.5	0.125	463	222	0.50	0.67	1.13	1.33	20 mg	25.3	19.76	500	15.23	14.24	6.50	5.85	8.1	0.085	547	384	2.00	663	15 mg	23.3	15.02	350	18.59	15.68	15.65	6.28	18.2	0.038	314	493	0.50	1.04	2.39	1.29	20 mg	22.6	19.91	450	44.37	41.67	6.08	6.52	6.9	0.101	169	100	4.00	681	5 mg	18.1	5.52	100	12.25	11.98	2.21	5.26	2.7	0.257	136	32	1.00	0.41	0.38	2.00	10 mg	19.1	10.47	200	4.65	4.31	7.32	2.14	3.5	0.200	717	215	1.50	682	5 mg	21.5	4.65	100	12.00	11.87	1.14	8.36	2.0	0.340	139	25	1.03	0.19	0.12	2.00	10 mg	21.1	9.48	200	1.46	1.36	7.02	1.56	6.7	0.103	2276	1321	0.50	683	15 mg	19.5	15.38	300	9.86	9.61	2.60	6.13	6.8	0.101	507	300	1.00	3.18	2.91	1.25	20 mg	19.2	19.53	375	28.71	27.30	5.24	19.53	12.0	0.058	218	227	1.00	684	15 mg	62.1	14.90	925	32.10	27.70	13.72	13.32	13.2	0.053	480	548	2.05	1.03	1.46	1.35	20 mg	62.6	19.97	1250	46.76	38.88	16.86	13.67	17.7	0.039	446	683	1.50	685	15 mg	26.4	15.15	400	14.19	13.92	1.92	3.19	4.6	0.152	470	186	1.50	1.45	0.51	1.31	20 mg	26.3	19.96	525	7.25	7.11	1.93	4.62	5.9	0.118	1207	616	1.50	686	15 mg	14.5	15.52	225	7.83	7.71	1.47	6.06	4.1	0.171	479	165	0.83	1.14	1.13	1.33	20 mg	14.9	20.13	300	8.87	8.65	2.45	6.91	6.1	0.113	564	300	0.50	687	15 mg	26.5	15.09	400	12.41	12.25	1.30	5.49	6.0	0.117	537	277	2.02	1.91	1.89	1.38	20 mg	27.4	20.07	550	23.44	22.97	1.99	10.88	6.1	0.113	391	208	1.00	688	15 mg	21.8	14.91	325	8.32	8.14	2.20	8.31	7.5	0.092	651	424	0.97	0.69	1.34	1.38	20 mg	22.1	20.36	450	11.13	10.78	3.12	5.73	5.8	0.119	674	339	1.75	689	15 mg	28.2	15.07	425	8.99	7.36	18.13	4.87	11.5	0.061	788	781	0.50	1.57	2.17	1.35	20 mg	28.5	20.18	575	19.55	17.43	10.86	7.63	9.0	0.077	490	381	1.00	690	15 mg	32.9	15.20	500	11.41	11.30	0.98	6.36	2.9	0.244	730	180	1.55	0.98	1.19	1.30	20 mg	33.1	19.64	650	13.52	13.00	3.87	6.24	5.2	0.134	801	358	1.50																																																																																						
655	5 mg	25.6	4.88	125	2.18	2.15	1.20	2.66	1.3	0.556	957	103	0.50	2.40	3.15	2.00																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																						
	10 mg	26.0	9.62	250	6.86	6.68	1.70	6.39	8.6	0.081	607	452	0.50				658	5 mg	14.7	5.04	175	3.94	2.98	24.39	1.98	17.4	0.040	740	1118	0.50	5.04	4.35	2.00	10 mg	14.1	10.26	350	17.15	17.05	0.60	9.97	4.8	0.144	340	141	1.00	659	5 mg	28.1	5.34	150	3.60	3.27	9.10	3.76	4.8	0.145	694	288	0.50	1.79	3.03	1.83	10 mg	28.3	9.72	275	10.91	10.00	1.08	6.73	4.5	0.156	420	162	0.50	660	5 mg	24.2	5.17	125	5.58	5.22	6.41	3.02	8.4	0.083	373	270	1.50	4.82	3.80	2.00	10 mg	23.6	10.59	250	21.24	21.18	0.27	14.54	1.7	0.420	196	28	1.00	662	15 mg	25.0	15.00	375	13.49	13.30	1.40	8.76	5.5	0.125	463	222	0.50	0.67	1.13	1.33	20 mg	25.3	19.76	500	15.23	14.24	6.50	5.85	8.1	0.085	547	384	2.00	663	15 mg	23.3	15.02	350	18.59	15.68	15.65	6.28	18.2	0.038	314	493	0.50	1.04	2.39	1.29	20 mg	22.6	19.91	450	44.37	41.67	6.08	6.52	6.9	0.101	169	100	4.00	681	5 mg	18.1	5.52	100	12.25	11.98	2.21	5.26	2.7	0.257	136	32	1.00	0.41	0.38	2.00	10 mg	19.1	10.47	200	4.65	4.31	7.32	2.14	3.5	0.200	717	215	1.50	682	5 mg	21.5	4.65	100	12.00	11.87	1.14	8.36	2.0	0.340	139	25	1.03	0.19	0.12	2.00	10 mg	21.1	9.48	200	1.46	1.36	7.02	1.56	6.7	0.103	2276	1321	0.50	683	15 mg	19.5	15.38	300	9.86	9.61	2.60	6.13	6.8	0.101	507	300	1.00	3.18	2.91	1.25	20 mg	19.2	19.53	375	28.71	27.30	5.24	19.53	12.0	0.058	218	227	1.00	684	15 mg	62.1	14.90	925	32.10	27.70	13.72	13.32	13.2	0.053	480	548	2.05	1.03	1.46	1.35	20 mg	62.6	19.97	1250	46.76	38.88	16.86	13.67	17.7	0.039	446	683	1.50	685	15 mg	26.4	15.15	400	14.19	13.92	1.92	3.19	4.6	0.152	470	186	1.50	1.45	0.51	1.31	20 mg	26.3	19.96	525	7.25	7.11	1.93	4.62	5.9	0.118	1207	616	1.50	686	15 mg	14.5	15.52	225	7.83	7.71	1.47	6.06	4.1	0.171	479	165	0.83	1.14	1.13	1.33	20 mg	14.9	20.13	300	8.87	8.65	2.45	6.91	6.1	0.113	564	300	0.50	687	15 mg	26.5	15.09	400	12.41	12.25	1.30	5.49	6.0	0.117	537	277	2.02	1.91	1.89	1.38	20 mg	27.4	20.07	550	23.44	22.97	1.99	10.88	6.1	0.113	391	208	1.00	688	15 mg	21.8	14.91	325	8.32	8.14	2.20	8.31	7.5	0.092	651	424	0.97	0.69	1.34	1.38	20 mg	22.1	20.36	450	11.13	10.78	3.12	5.73	5.8	0.119	674	339	1.75	689	15 mg	28.2	15.07	425	8.99	7.36	18.13	4.87	11.5	0.061	788	781	0.50	1.57	2.17	1.35	20 mg	28.5	20.18	575	19.55	17.43	10.86	7.63	9.0	0.077	490	381	1.00	690	15 mg	32.9	15.20	500	11.41	11.30	0.98	6.36	2.9	0.244	730	180	1.55	0.98	1.19	1.30	20 mg	33.1	19.64	650	13.52	13.00	3.87	6.24	5.2	0.134	801	358	1.50																																																																																																																				
658	5 mg	14.7	5.04	175	3.94	2.98	24.39	1.98	17.4	0.040	740	1118	0.50	5.04	4.35	2.00																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																						
	10 mg	14.1	10.26	350	17.15	17.05	0.60	9.97	4.8	0.144	340	141	1.00				659	5 mg	28.1	5.34	150	3.60	3.27	9.10	3.76	4.8	0.145	694	288	0.50	1.79	3.03	1.83	10 mg	28.3	9.72	275	10.91	10.00	1.08	6.73	4.5	0.156	420	162	0.50	660	5 mg	24.2	5.17	125	5.58	5.22	6.41	3.02	8.4	0.083	373	270	1.50	4.82	3.80	2.00	10 mg	23.6	10.59	250	21.24	21.18	0.27	14.54	1.7	0.420	196	28	1.00	662	15 mg	25.0	15.00	375	13.49	13.30	1.40	8.76	5.5	0.125	463	222	0.50	0.67	1.13	1.33	20 mg	25.3	19.76	500	15.23	14.24	6.50	5.85	8.1	0.085	547	384	2.00	663	15 mg	23.3	15.02	350	18.59	15.68	15.65	6.28	18.2	0.038	314	493	0.50	1.04	2.39	1.29	20 mg	22.6	19.91	450	44.37	41.67	6.08	6.52	6.9	0.101	169	100	4.00	681	5 mg	18.1	5.52	100	12.25	11.98	2.21	5.26	2.7	0.257	136	32	1.00	0.41	0.38	2.00	10 mg	19.1	10.47	200	4.65	4.31	7.32	2.14	3.5	0.200	717	215	1.50	682	5 mg	21.5	4.65	100	12.00	11.87	1.14	8.36	2.0	0.340	139	25	1.03	0.19	0.12	2.00	10 mg	21.1	9.48	200	1.46	1.36	7.02	1.56	6.7	0.103	2276	1321	0.50	683	15 mg	19.5	15.38	300	9.86	9.61	2.60	6.13	6.8	0.101	507	300	1.00	3.18	2.91	1.25	20 mg	19.2	19.53	375	28.71	27.30	5.24	19.53	12.0	0.058	218	227	1.00	684	15 mg	62.1	14.90	925	32.10	27.70	13.72	13.32	13.2	0.053	480	548	2.05	1.03	1.46	1.35	20 mg	62.6	19.97	1250	46.76	38.88	16.86	13.67	17.7	0.039	446	683	1.50	685	15 mg	26.4	15.15	400	14.19	13.92	1.92	3.19	4.6	0.152	470	186	1.50	1.45	0.51	1.31	20 mg	26.3	19.96	525	7.25	7.11	1.93	4.62	5.9	0.118	1207	616	1.50	686	15 mg	14.5	15.52	225	7.83	7.71	1.47	6.06	4.1	0.171	479	165	0.83	1.14	1.13	1.33	20 mg	14.9	20.13	300	8.87	8.65	2.45	6.91	6.1	0.113	564	300	0.50	687	15 mg	26.5	15.09	400	12.41	12.25	1.30	5.49	6.0	0.117	537	277	2.02	1.91	1.89	1.38	20 mg	27.4	20.07	550	23.44	22.97	1.99	10.88	6.1	0.113	391	208	1.00	688	15 mg	21.8	14.91	325	8.32	8.14	2.20	8.31	7.5	0.092	651	424	0.97	0.69	1.34	1.38	20 mg	22.1	20.36	450	11.13	10.78	3.12	5.73	5.8	0.119	674	339	1.75	689	15 mg	28.2	15.07	425	8.99	7.36	18.13	4.87	11.5	0.061	788	781	0.50	1.57	2.17	1.35	20 mg	28.5	20.18	575	19.55	17.43	10.86	7.63	9.0	0.077	490	381	1.00	690	15 mg	32.9	15.20	500	11.41	11.30	0.98	6.36	2.9	0.244	730	180	1.55	0.98	1.19	1.30	20 mg	33.1	19.64	650	13.52	13.00	3.87	6.24	5.2	0.134	801	358	1.50																																																																																																																																																		
659	5 mg	28.1	5.34	150	3.60	3.27	9.10	3.76	4.8	0.145	694	288	0.50	1.79	3.03	1.83																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																						
	10 mg	28.3	9.72	275	10.91	10.00	1.08	6.73	4.5	0.156	420	162	0.50				660	5 mg	24.2	5.17	125	5.58	5.22	6.41	3.02	8.4	0.083	373	270	1.50	4.82	3.80	2.00	10 mg	23.6	10.59	250	21.24	21.18	0.27	14.54	1.7	0.420	196	28	1.00	662	15 mg	25.0	15.00	375	13.49	13.30	1.40	8.76	5.5	0.125	463	222	0.50	0.67	1.13	1.33	20 mg	25.3	19.76	500	15.23	14.24	6.50	5.85	8.1	0.085	547	384	2.00	663	15 mg	23.3	15.02	350	18.59	15.68	15.65	6.28	18.2	0.038	314	493	0.50	1.04	2.39	1.29	20 mg	22.6	19.91	450	44.37	41.67	6.08	6.52	6.9	0.101	169	100	4.00	681	5 mg	18.1	5.52	100	12.25	11.98	2.21	5.26	2.7	0.257	136	32	1.00	0.41	0.38	2.00	10 mg	19.1	10.47	200	4.65	4.31	7.32	2.14	3.5	0.200	717	215	1.50	682	5 mg	21.5	4.65	100	12.00	11.87	1.14	8.36	2.0	0.340	139	25	1.03	0.19	0.12	2.00	10 mg	21.1	9.48	200	1.46	1.36	7.02	1.56	6.7	0.103	2276	1321	0.50	683	15 mg	19.5	15.38	300	9.86	9.61	2.60	6.13	6.8	0.101	507	300	1.00	3.18	2.91	1.25	20 mg	19.2	19.53	375	28.71	27.30	5.24	19.53	12.0	0.058	218	227	1.00	684	15 mg	62.1	14.90	925	32.10	27.70	13.72	13.32	13.2	0.053	480	548	2.05	1.03	1.46	1.35	20 mg	62.6	19.97	1250	46.76	38.88	16.86	13.67	17.7	0.039	446	683	1.50	685	15 mg	26.4	15.15	400	14.19	13.92	1.92	3.19	4.6	0.152	470	186	1.50	1.45	0.51	1.31	20 mg	26.3	19.96	525	7.25	7.11	1.93	4.62	5.9	0.118	1207	616	1.50	686	15 mg	14.5	15.52	225	7.83	7.71	1.47	6.06	4.1	0.171	479	165	0.83	1.14	1.13	1.33	20 mg	14.9	20.13	300	8.87	8.65	2.45	6.91	6.1	0.113	564	300	0.50	687	15 mg	26.5	15.09	400	12.41	12.25	1.30	5.49	6.0	0.117	537	277	2.02	1.91	1.89	1.38	20 mg	27.4	20.07	550	23.44	22.97	1.99	10.88	6.1	0.113	391	208	1.00	688	15 mg	21.8	14.91	325	8.32	8.14	2.20	8.31	7.5	0.092	651	424	0.97	0.69	1.34	1.38	20 mg	22.1	20.36	450	11.13	10.78	3.12	5.73	5.8	0.119	674	339	1.75	689	15 mg	28.2	15.07	425	8.99	7.36	18.13	4.87	11.5	0.061	788	781	0.50	1.57	2.17	1.35	20 mg	28.5	20.18	575	19.55	17.43	10.86	7.63	9.0	0.077	490	381	1.00	690	15 mg	32.9	15.20	500	11.41	11.30	0.98	6.36	2.9	0.244	730	180	1.55	0.98	1.19	1.30	20 mg	33.1	19.64	650	13.52	13.00	3.87	6.24	5.2	0.134	801	358	1.50																																																																																																																																																																																
660	5 mg	24.2	5.17	125	5.58	5.22	6.41	3.02	8.4	0.083	373	270	1.50	4.82	3.80	2.00																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																						
	10 mg	23.6	10.59	250	21.24	21.18	0.27	14.54	1.7	0.420	196	28	1.00				662	15 mg	25.0	15.00	375	13.49	13.30	1.40	8.76	5.5	0.125	463	222	0.50	0.67	1.13	1.33	20 mg	25.3	19.76	500	15.23	14.24	6.50	5.85	8.1	0.085	547	384	2.00	663	15 mg	23.3	15.02	350	18.59	15.68	15.65	6.28	18.2	0.038	314	493	0.50	1.04	2.39	1.29	20 mg	22.6	19.91	450	44.37	41.67	6.08	6.52	6.9	0.101	169	100	4.00	681	5 mg	18.1	5.52	100	12.25	11.98	2.21	5.26	2.7	0.257	136	32	1.00	0.41	0.38	2.00	10 mg	19.1	10.47	200	4.65	4.31	7.32	2.14	3.5	0.200	717	215	1.50	682	5 mg	21.5	4.65	100	12.00	11.87	1.14	8.36	2.0	0.340	139	25	1.03	0.19	0.12	2.00	10 mg	21.1	9.48	200	1.46	1.36	7.02	1.56	6.7	0.103	2276	1321	0.50	683	15 mg	19.5	15.38	300	9.86	9.61	2.60	6.13	6.8	0.101	507	300	1.00	3.18	2.91	1.25	20 mg	19.2	19.53	375	28.71	27.30	5.24	19.53	12.0	0.058	218	227	1.00	684	15 mg	62.1	14.90	925	32.10	27.70	13.72	13.32	13.2	0.053	480	548	2.05	1.03	1.46	1.35	20 mg	62.6	19.97	1250	46.76	38.88	16.86	13.67	17.7	0.039	446	683	1.50	685	15 mg	26.4	15.15	400	14.19	13.92	1.92	3.19	4.6	0.152	470	186	1.50	1.45	0.51	1.31	20 mg	26.3	19.96	525	7.25	7.11	1.93	4.62	5.9	0.118	1207	616	1.50	686	15 mg	14.5	15.52	225	7.83	7.71	1.47	6.06	4.1	0.171	479	165	0.83	1.14	1.13	1.33	20 mg	14.9	20.13	300	8.87	8.65	2.45	6.91	6.1	0.113	564	300	0.50	687	15 mg	26.5	15.09	400	12.41	12.25	1.30	5.49	6.0	0.117	537	277	2.02	1.91	1.89	1.38	20 mg	27.4	20.07	550	23.44	22.97	1.99	10.88	6.1	0.113	391	208	1.00	688	15 mg	21.8	14.91	325	8.32	8.14	2.20	8.31	7.5	0.092	651	424	0.97	0.69	1.34	1.38	20 mg	22.1	20.36	450	11.13	10.78	3.12	5.73	5.8	0.119	674	339	1.75	689	15 mg	28.2	15.07	425	8.99	7.36	18.13	4.87	11.5	0.061	788	781	0.50	1.57	2.17	1.35	20 mg	28.5	20.18	575	19.55	17.43	10.86	7.63	9.0	0.077	490	381	1.00	690	15 mg	32.9	15.20	500	11.41	11.30	0.98	6.36	2.9	0.244	730	180	1.55	0.98	1.19	1.30	20 mg	33.1	19.64	650	13.52	13.00	3.87	6.24	5.2	0.134	801	358	1.50																																																																																																																																																																																																														
662	15 mg	25.0	15.00	375	13.49	13.30	1.40	8.76	5.5	0.125	463	222	0.50	0.67	1.13	1.33																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																						
	20 mg	25.3	19.76	500	15.23	14.24	6.50	5.85	8.1	0.085	547	384	2.00				663	15 mg	23.3	15.02	350	18.59	15.68	15.65	6.28	18.2	0.038	314	493	0.50	1.04	2.39	1.29	20 mg	22.6	19.91	450	44.37	41.67	6.08	6.52	6.9	0.101	169	100	4.00	681	5 mg	18.1	5.52	100	12.25	11.98	2.21	5.26	2.7	0.257	136	32	1.00	0.41	0.38	2.00	10 mg	19.1	10.47	200	4.65	4.31	7.32	2.14	3.5	0.200	717	215	1.50	682	5 mg	21.5	4.65	100	12.00	11.87	1.14	8.36	2.0	0.340	139	25	1.03	0.19	0.12	2.00	10 mg	21.1	9.48	200	1.46	1.36	7.02	1.56	6.7	0.103	2276	1321	0.50	683	15 mg	19.5	15.38	300	9.86	9.61	2.60	6.13	6.8	0.101	507	300	1.00	3.18	2.91	1.25	20 mg	19.2	19.53	375	28.71	27.30	5.24	19.53	12.0	0.058	218	227	1.00	684	15 mg	62.1	14.90	925	32.10	27.70	13.72	13.32	13.2	0.053	480	548	2.05	1.03	1.46	1.35	20 mg	62.6	19.97	1250	46.76	38.88	16.86	13.67	17.7	0.039	446	683	1.50	685	15 mg	26.4	15.15	400	14.19	13.92	1.92	3.19	4.6	0.152	470	186	1.50	1.45	0.51	1.31	20 mg	26.3	19.96	525	7.25	7.11	1.93	4.62	5.9	0.118	1207	616	1.50	686	15 mg	14.5	15.52	225	7.83	7.71	1.47	6.06	4.1	0.171	479	165	0.83	1.14	1.13	1.33	20 mg	14.9	20.13	300	8.87	8.65	2.45	6.91	6.1	0.113	564	300	0.50	687	15 mg	26.5	15.09	400	12.41	12.25	1.30	5.49	6.0	0.117	537	277	2.02	1.91	1.89	1.38	20 mg	27.4	20.07	550	23.44	22.97	1.99	10.88	6.1	0.113	391	208	1.00	688	15 mg	21.8	14.91	325	8.32	8.14	2.20	8.31	7.5	0.092	651	424	0.97	0.69	1.34	1.38	20 mg	22.1	20.36	450	11.13	10.78	3.12	5.73	5.8	0.119	674	339	1.75	689	15 mg	28.2	15.07	425	8.99	7.36	18.13	4.87	11.5	0.061	788	781	0.50	1.57	2.17	1.35	20 mg	28.5	20.18	575	19.55	17.43	10.86	7.63	9.0	0.077	490	381	1.00	690	15 mg	32.9	15.20	500	11.41	11.30	0.98	6.36	2.9	0.244	730	180	1.55	0.98	1.19	1.30	20 mg	33.1	19.64	650	13.52	13.00	3.87	6.24	5.2	0.134	801	358	1.50																																																																																																																																																																																																																																												
663	15 mg	23.3	15.02	350	18.59	15.68	15.65	6.28	18.2	0.038	314	493	0.50	1.04	2.39	1.29																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																						
	20 mg	22.6	19.91	450	44.37	41.67	6.08	6.52	6.9	0.101	169	100	4.00				681	5 mg	18.1	5.52	100	12.25	11.98	2.21	5.26	2.7	0.257	136	32	1.00	0.41	0.38	2.00	10 mg	19.1	10.47	200	4.65	4.31	7.32	2.14	3.5	0.200	717	215	1.50	682	5 mg	21.5	4.65	100	12.00	11.87	1.14	8.36	2.0	0.340	139	25	1.03	0.19	0.12	2.00	10 mg	21.1	9.48	200	1.46	1.36	7.02	1.56	6.7	0.103	2276	1321	0.50	683	15 mg	19.5	15.38	300	9.86	9.61	2.60	6.13	6.8	0.101	507	300	1.00	3.18	2.91	1.25	20 mg	19.2	19.53	375	28.71	27.30	5.24	19.53	12.0	0.058	218	227	1.00	684	15 mg	62.1	14.90	925	32.10	27.70	13.72	13.32	13.2	0.053	480	548	2.05	1.03	1.46	1.35	20 mg	62.6	19.97	1250	46.76	38.88	16.86	13.67	17.7	0.039	446	683	1.50	685	15 mg	26.4	15.15	400	14.19	13.92	1.92	3.19	4.6	0.152	470	186	1.50	1.45	0.51	1.31	20 mg	26.3	19.96	525	7.25	7.11	1.93	4.62	5.9	0.118	1207	616	1.50	686	15 mg	14.5	15.52	225	7.83	7.71	1.47	6.06	4.1	0.171	479	165	0.83	1.14	1.13	1.33	20 mg	14.9	20.13	300	8.87	8.65	2.45	6.91	6.1	0.113	564	300	0.50	687	15 mg	26.5	15.09	400	12.41	12.25	1.30	5.49	6.0	0.117	537	277	2.02	1.91	1.89	1.38	20 mg	27.4	20.07	550	23.44	22.97	1.99	10.88	6.1	0.113	391	208	1.00	688	15 mg	21.8	14.91	325	8.32	8.14	2.20	8.31	7.5	0.092	651	424	0.97	0.69	1.34	1.38	20 mg	22.1	20.36	450	11.13	10.78	3.12	5.73	5.8	0.119	674	339	1.75	689	15 mg	28.2	15.07	425	8.99	7.36	18.13	4.87	11.5	0.061	788	781	0.50	1.57	2.17	1.35	20 mg	28.5	20.18	575	19.55	17.43	10.86	7.63	9.0	0.077	490	381	1.00	690	15 mg	32.9	15.20	500	11.41	11.30	0.98	6.36	2.9	0.244	730	180	1.55	0.98	1.19	1.30	20 mg	33.1	19.64	650	13.52	13.00	3.87	6.24	5.2	0.134	801	358	1.50																																																																																																																																																																																																																																																																										
681	5 mg	18.1	5.52	100	12.25	11.98	2.21	5.26	2.7	0.257	136	32	1.00	0.41	0.38	2.00																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																						
	10 mg	19.1	10.47	200	4.65	4.31	7.32	2.14	3.5	0.200	717	215	1.50				682	5 mg	21.5	4.65	100	12.00	11.87	1.14	8.36	2.0	0.340	139	25	1.03	0.19	0.12	2.00	10 mg	21.1	9.48	200	1.46	1.36	7.02	1.56	6.7	0.103	2276	1321	0.50	683	15 mg	19.5	15.38	300	9.86	9.61	2.60	6.13	6.8	0.101	507	300	1.00	3.18	2.91	1.25	20 mg	19.2	19.53	375	28.71	27.30	5.24	19.53	12.0	0.058	218	227	1.00	684	15 mg	62.1	14.90	925	32.10	27.70	13.72	13.32	13.2	0.053	480	548	2.05	1.03	1.46	1.35	20 mg	62.6	19.97	1250	46.76	38.88	16.86	13.67	17.7	0.039	446	683	1.50	685	15 mg	26.4	15.15	400	14.19	13.92	1.92	3.19	4.6	0.152	470	186	1.50	1.45	0.51	1.31	20 mg	26.3	19.96	525	7.25	7.11	1.93	4.62	5.9	0.118	1207	616	1.50	686	15 mg	14.5	15.52	225	7.83	7.71	1.47	6.06	4.1	0.171	479	165	0.83	1.14	1.13	1.33	20 mg	14.9	20.13	300	8.87	8.65	2.45	6.91	6.1	0.113	564	300	0.50	687	15 mg	26.5	15.09	400	12.41	12.25	1.30	5.49	6.0	0.117	537	277	2.02	1.91	1.89	1.38	20 mg	27.4	20.07	550	23.44	22.97	1.99	10.88	6.1	0.113	391	208	1.00	688	15 mg	21.8	14.91	325	8.32	8.14	2.20	8.31	7.5	0.092	651	424	0.97	0.69	1.34	1.38	20 mg	22.1	20.36	450	11.13	10.78	3.12	5.73	5.8	0.119	674	339	1.75	689	15 mg	28.2	15.07	425	8.99	7.36	18.13	4.87	11.5	0.061	788	781	0.50	1.57	2.17	1.35	20 mg	28.5	20.18	575	19.55	17.43	10.86	7.63	9.0	0.077	490	381	1.00	690	15 mg	32.9	15.20	500	11.41	11.30	0.98	6.36	2.9	0.244	730	180	1.55	0.98	1.19	1.30	20 mg	33.1	19.64	650	13.52	13.00	3.87	6.24	5.2	0.134	801	358	1.50																																																																																																																																																																																																																																																																																																								
682	5 mg	21.5	4.65	100	12.00	11.87	1.14	8.36	2.0	0.340	139	25	1.03	0.19	0.12	2.00																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																						
	10 mg	21.1	9.48	200	1.46	1.36	7.02	1.56	6.7	0.103	2276	1321	0.50				683	15 mg	19.5	15.38	300	9.86	9.61	2.60	6.13	6.8	0.101	507	300	1.00	3.18	2.91	1.25	20 mg	19.2	19.53	375	28.71	27.30	5.24	19.53	12.0	0.058	218	227	1.00	684	15 mg	62.1	14.90	925	32.10	27.70	13.72	13.32	13.2	0.053	480	548	2.05	1.03	1.46	1.35	20 mg	62.6	19.97	1250	46.76	38.88	16.86	13.67	17.7	0.039	446	683	1.50	685	15 mg	26.4	15.15	400	14.19	13.92	1.92	3.19	4.6	0.152	470	186	1.50	1.45	0.51	1.31	20 mg	26.3	19.96	525	7.25	7.11	1.93	4.62	5.9	0.118	1207	616	1.50	686	15 mg	14.5	15.52	225	7.83	7.71	1.47	6.06	4.1	0.171	479	165	0.83	1.14	1.13	1.33	20 mg	14.9	20.13	300	8.87	8.65	2.45	6.91	6.1	0.113	564	300	0.50	687	15 mg	26.5	15.09	400	12.41	12.25	1.30	5.49	6.0	0.117	537	277	2.02	1.91	1.89	1.38	20 mg	27.4	20.07	550	23.44	22.97	1.99	10.88	6.1	0.113	391	208	1.00	688	15 mg	21.8	14.91	325	8.32	8.14	2.20	8.31	7.5	0.092	651	424	0.97	0.69	1.34	1.38	20 mg	22.1	20.36	450	11.13	10.78	3.12	5.73	5.8	0.119	674	339	1.75	689	15 mg	28.2	15.07	425	8.99	7.36	18.13	4.87	11.5	0.061	788	781	0.50	1.57	2.17	1.35	20 mg	28.5	20.18	575	19.55	17.43	10.86	7.63	9.0	0.077	490	381	1.00	690	15 mg	32.9	15.20	500	11.41	11.30	0.98	6.36	2.9	0.244	730	180	1.55	0.98	1.19	1.30	20 mg	33.1	19.64	650	13.52	13.00	3.87	6.24	5.2	0.134	801	358	1.50																																																																																																																																																																																																																																																																																																																																						
683	15 mg	19.5	15.38	300	9.86	9.61	2.60	6.13	6.8	0.101	507	300	1.00	3.18	2.91	1.25																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																						
	20 mg	19.2	19.53	375	28.71	27.30	5.24	19.53	12.0	0.058	218	227	1.00				684	15 mg	62.1	14.90	925	32.10	27.70	13.72	13.32	13.2	0.053	480	548	2.05	1.03	1.46	1.35	20 mg	62.6	19.97	1250	46.76	38.88	16.86	13.67	17.7	0.039	446	683	1.50	685	15 mg	26.4	15.15	400	14.19	13.92	1.92	3.19	4.6	0.152	470	186	1.50	1.45	0.51	1.31	20 mg	26.3	19.96	525	7.25	7.11	1.93	4.62	5.9	0.118	1207	616	1.50	686	15 mg	14.5	15.52	225	7.83	7.71	1.47	6.06	4.1	0.171	479	165	0.83	1.14	1.13	1.33	20 mg	14.9	20.13	300	8.87	8.65	2.45	6.91	6.1	0.113	564	300	0.50	687	15 mg	26.5	15.09	400	12.41	12.25	1.30	5.49	6.0	0.117	537	277	2.02	1.91	1.89	1.38	20 mg	27.4	20.07	550	23.44	22.97	1.99	10.88	6.1	0.113	391	208	1.00	688	15 mg	21.8	14.91	325	8.32	8.14	2.20	8.31	7.5	0.092	651	424	0.97	0.69	1.34	1.38	20 mg	22.1	20.36	450	11.13	10.78	3.12	5.73	5.8	0.119	674	339	1.75	689	15 mg	28.2	15.07	425	8.99	7.36	18.13	4.87	11.5	0.061	788	781	0.50	1.57	2.17	1.35	20 mg	28.5	20.18	575	19.55	17.43	10.86	7.63	9.0	0.077	490	381	1.00	690	15 mg	32.9	15.20	500	11.41	11.30	0.98	6.36	2.9	0.244	730	180	1.55	0.98	1.19	1.30	20 mg	33.1	19.64	650	13.52	13.00	3.87	6.24	5.2	0.134	801	358	1.50																																																																																																																																																																																																																																																																																																																																																																				
684	15 mg	62.1	14.90	925	32.10	27.70	13.72	13.32	13.2	0.053	480	548	2.05	1.03	1.46	1.35																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																						
	20 mg	62.6	19.97	1250	46.76	38.88	16.86	13.67	17.7	0.039	446	683	1.50				685	15 mg	26.4	15.15	400	14.19	13.92	1.92	3.19	4.6	0.152	470	186	1.50	1.45	0.51	1.31	20 mg	26.3	19.96	525	7.25	7.11	1.93	4.62	5.9	0.118	1207	616	1.50	686	15 mg	14.5	15.52	225	7.83	7.71	1.47	6.06	4.1	0.171	479	165	0.83	1.14	1.13	1.33	20 mg	14.9	20.13	300	8.87	8.65	2.45	6.91	6.1	0.113	564	300	0.50	687	15 mg	26.5	15.09	400	12.41	12.25	1.30	5.49	6.0	0.117	537	277	2.02	1.91	1.89	1.38	20 mg	27.4	20.07	550	23.44	22.97	1.99	10.88	6.1	0.113	391	208	1.00	688	15 mg	21.8	14.91	325	8.32	8.14	2.20	8.31	7.5	0.092	651	424	0.97	0.69	1.34	1.38	20 mg	22.1	20.36	450	11.13	10.78	3.12	5.73	5.8	0.119	674	339	1.75	689	15 mg	28.2	15.07	425	8.99	7.36	18.13	4.87	11.5	0.061	788	781	0.50	1.57	2.17	1.35	20 mg	28.5	20.18	575	19.55	17.43	10.86	7.63	9.0	0.077	490	381	1.00	690	15 mg	32.9	15.20	500	11.41	11.30	0.98	6.36	2.9	0.244	730	180	1.55	0.98	1.19	1.30	20 mg	33.1	19.64	650	13.52	13.00	3.87	6.24	5.2	0.134	801	358	1.50																																																																																																																																																																																																																																																																																																																																																																																																		
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Draft Labeling
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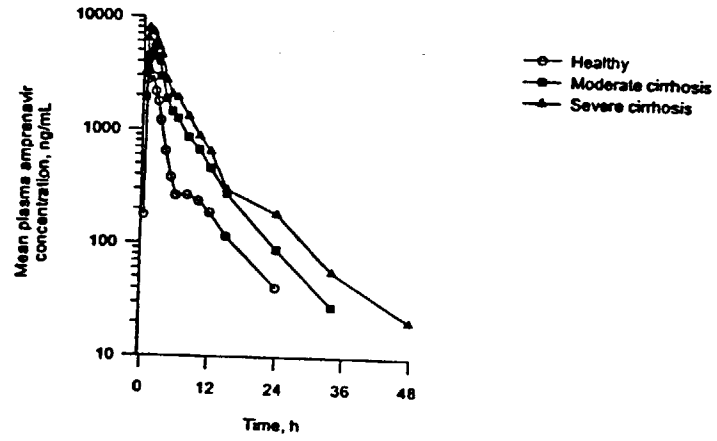


Figure 15

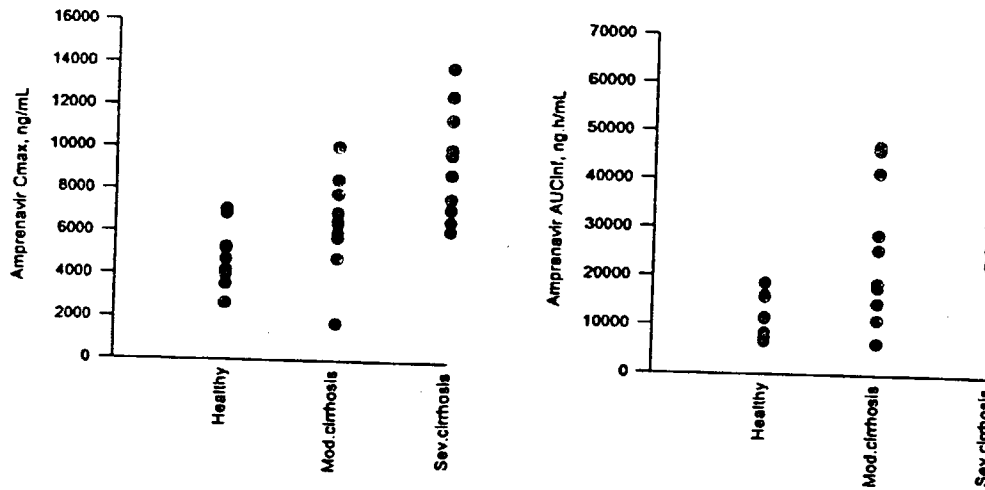


Figure 16

**APPEARS THIS WAY
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Agenerase NDA 21-007&21-039
 Vijay Tammara
 Prabhu Rajagopalan
 Individual data (PROB1008)

C_{max} , ng/mL			AUC_{∞} , ng.h/mL			CL/F, mL/min		
Healthy	Moderate cirrhosis	Severe cirrhosis	Healthy	Moderate cirrhosis	Severe cirrhosis	Healthy	Moderate cirrhosis	Severe cirrhosis

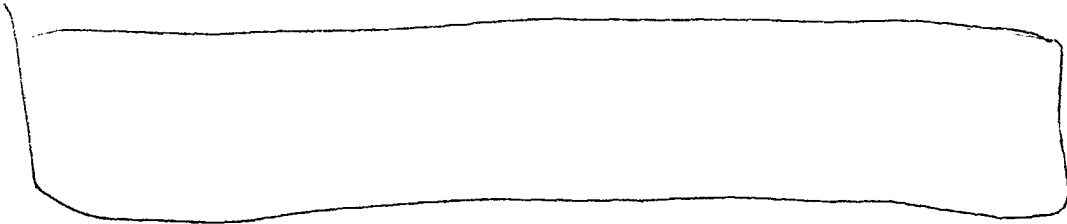
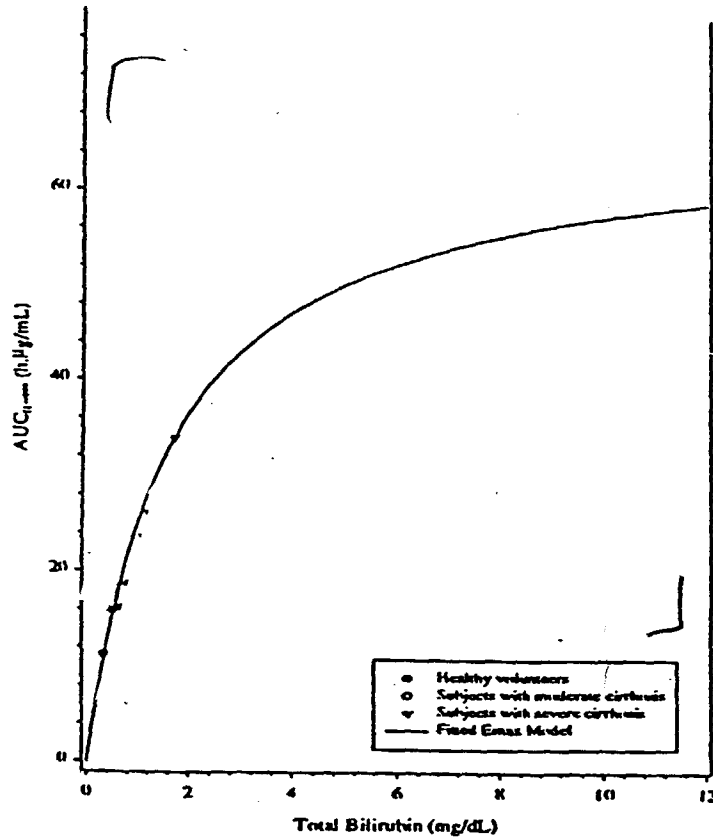


FIGURE 17



Parameter	Estimate	SE	%CV
$AUC_{(max)}$, $\mu\text{g.h/mL}$	66.46	9.36	14.1
BIL_{50} , g/dL	1.65	0.49	29.7
R^2	0.65		

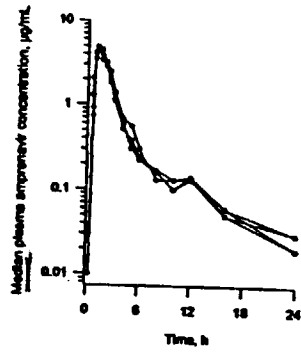


Figure 18

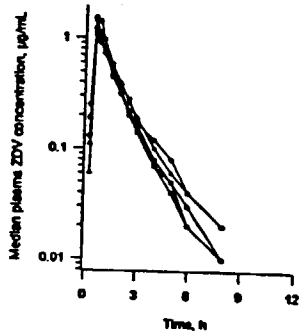


Figure 19

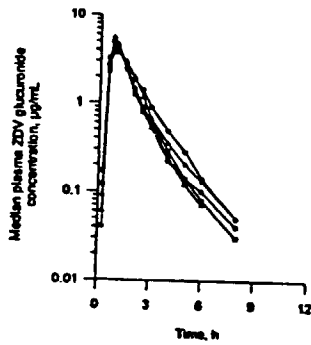


Figure 20

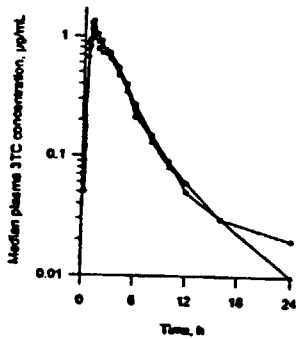


Figure 21

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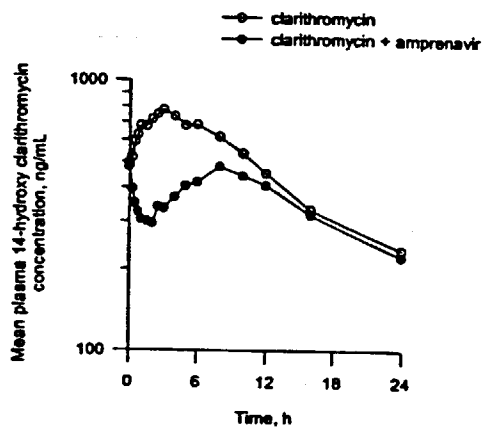
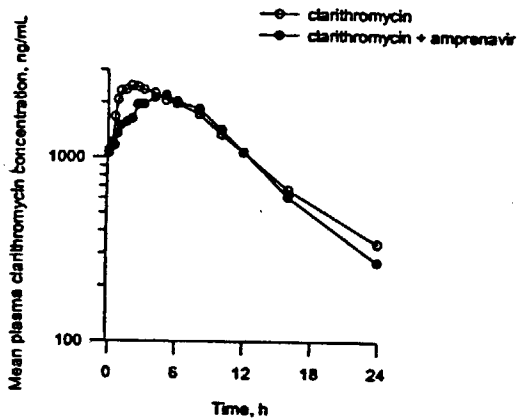


Figure 26

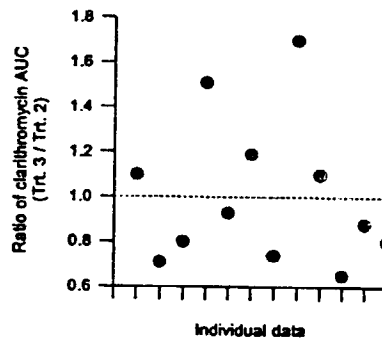
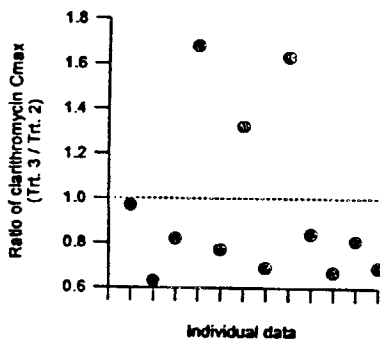


Figure 27

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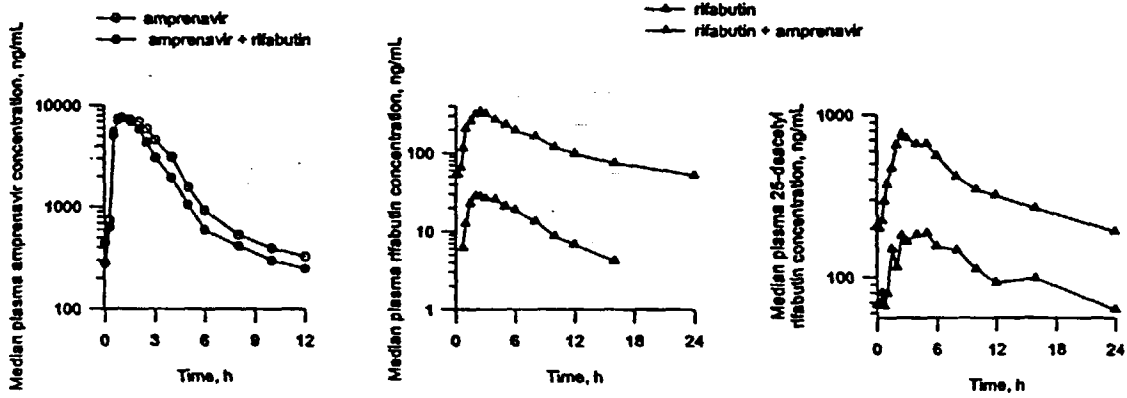


Figure 28

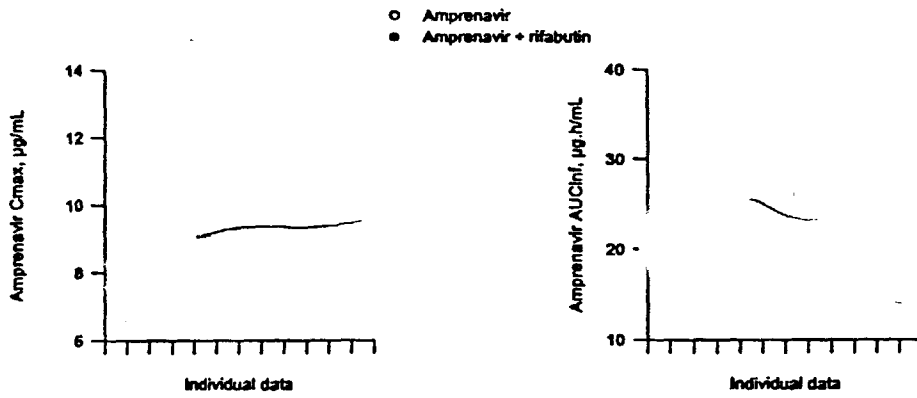


Figure 29

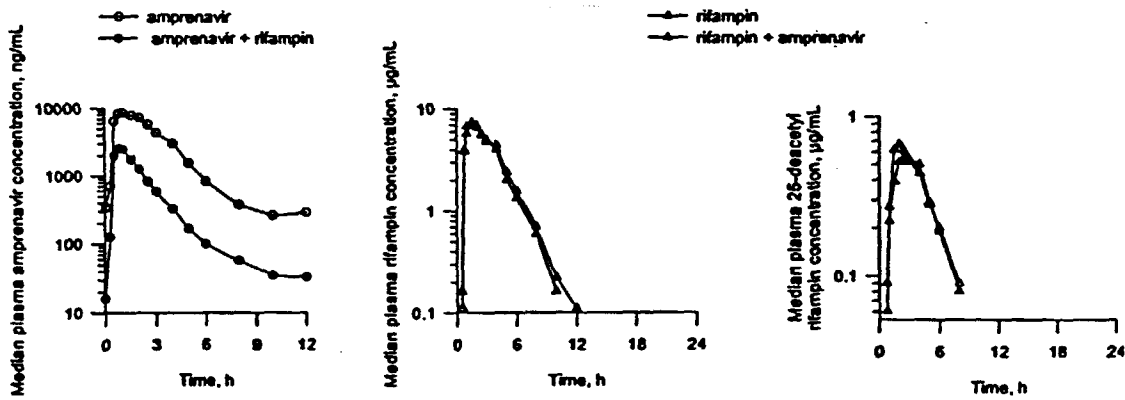


Figure 30

APPENDIX 1

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Figures and Individual Data

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Figure 1. Mean Plasma Concentration -Time Profiles for Amprenavir (PROA 1004)

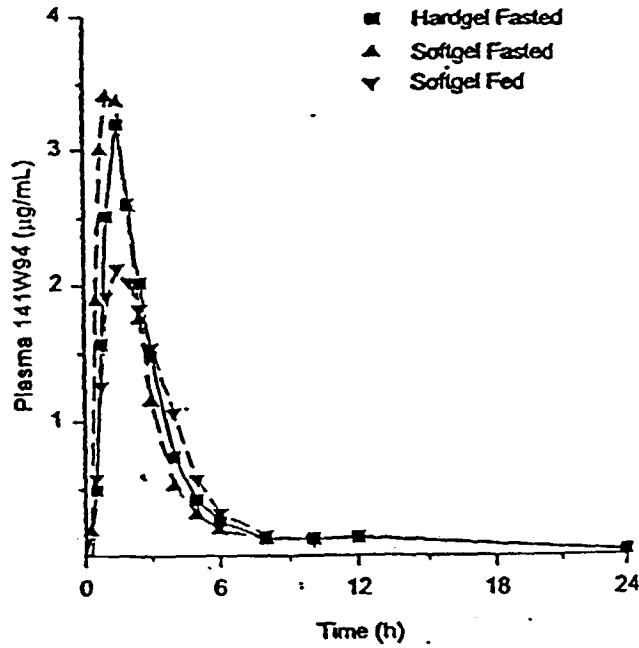


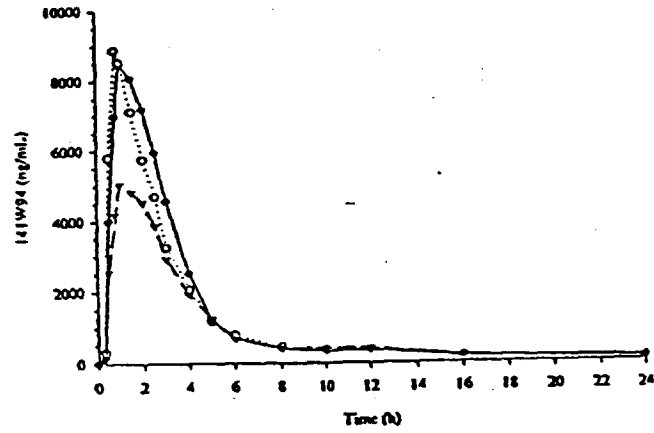
Table 1. Individual Pharmacokinetic Parameters of Amprenavir (PROA 1004)

Individual 141W94 C _{max} (µg/mL) values with summary statistics				Individual 141W94 AUC _(0-inf) (µg·h/mL) values with summary statistic			
Subject	TREATMENT 1 141W94 4x150mg hard fasted	TREATMENT 2 141W94 4x150mg soft fasted	TREATMENT 3 141W94 4x150mg soft fed	Subject	TREATMENT 1 141W94 4x150mg hard fasted	TREATMENT 2 141W94 4x150mg soft fasted	TREATMENT 3 141W94 4x150mg soft fed
Geometric LSMean	3.27	4.10	2.75	Geometric LSMean	9.32	9.58	8.26
95% CI (lower)	2.62	3.28	2.20	95% CI (lower)	7.20	7.39	6.37
95% CI (upper)	4.08	5.11	3.43	95% CI (upper)	12.08	12.41	10.70
Arithmetic LSMean	3.66	4.36	3.12	Arithmetic LSMean	10.40	10.67	9.83
95% CI (lower)	2.93	3.63	2.39	95% CI (lower)	7.81	8.08	7.23
95% CI (upper)	4.39	5.09	3.85	95% CI (upper)	13.00	13.27	12.42
Median	3.55	4.47	3.10	Median	10.04	10.45	8.93
Minimum				Minimum			
Maximum				Maximum			
Arithmetic Mean	3.66	4.36	3.12	Arithmetic Mean	10.41	10.67	9.83
SD	1.75	1.45	1.56	SD	4.74	4.72	6.27
CV	47.78	33.17	50.02	CV	45.58	44.18	63.84
Geometric Mean	3.27	4.10	2.75	Geometric Mean	9.32	9.58	8.26
Mean of logs	1.18	1.41	1.01	Mean of logs	2.23	2.26	2.11
SD of logs	0.50	0.38	0.54	SD of logs	0.50	0.50	0.61

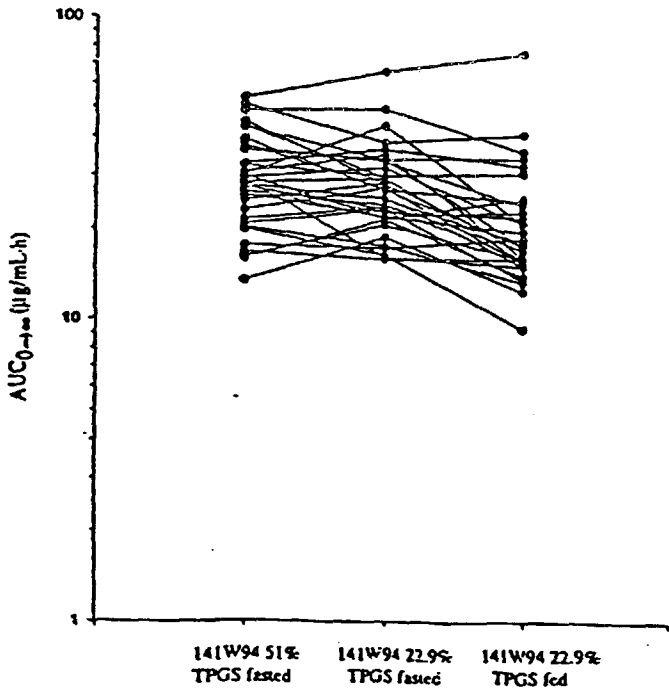
Individual 141W94 t _{max} (h) values with summary statistics			
Subject	TREATMENT 1 141W94 4x150mg hard fasted	TREATMENT 2 141W94 4x150mg soft fasted	TREATMENT 3 141W94 4x150mg soft fed
Median	1.50	1.00	1.75
Minimum			
Maximum			

LSMEAN = Least Square Mean, adjusted for design imbalance if present.
SD = standard deviation.
CV = coefficient of variation.

Figure 2. Mean Plasma Concentration -Time Profiles and Comparative plots for Amprenavir (PROA 1010)



Comparative semi-log plot of 141W94 $AUC_{0-\infty}$ ($\mu\text{g/mL}\cdot\text{h}$)



Comparative semi-log plot of 141W94 C_{max} ($\mu\text{g/mL}$)

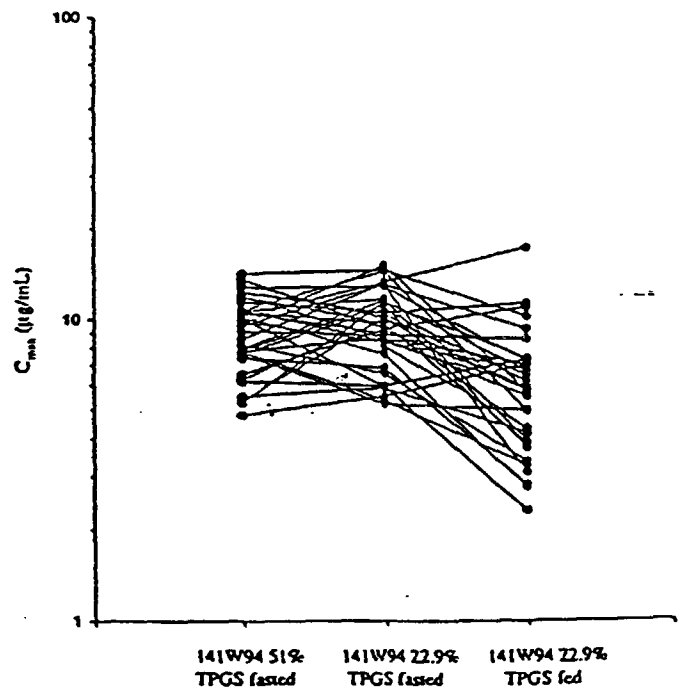


Figure 3. Mean Plasma Concentration -Time Profiles by Race for Amprenavir (PROA 1010)

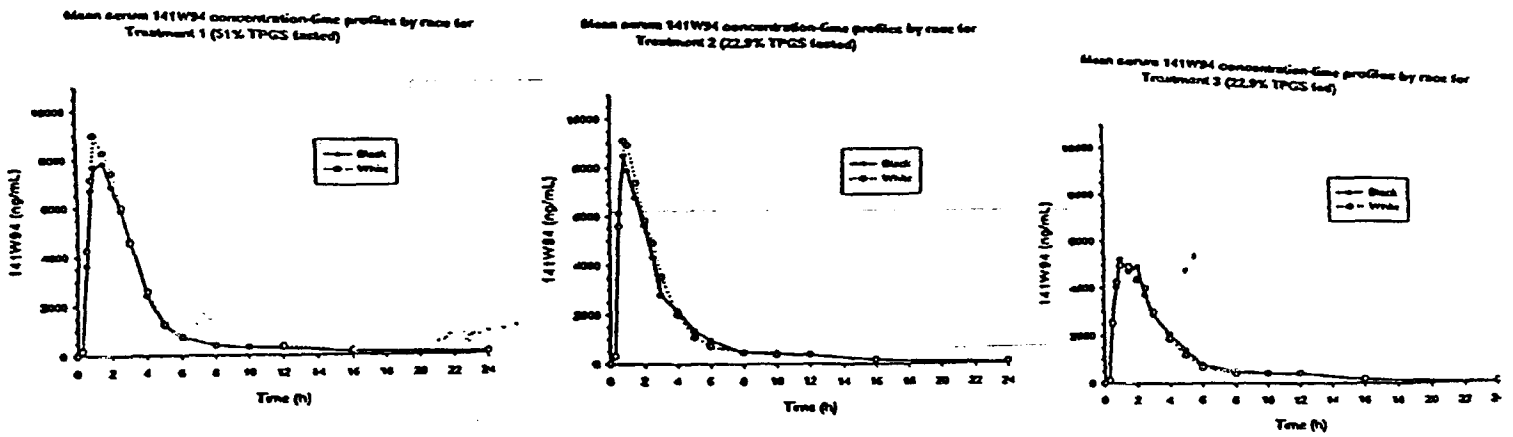


Table 3. Individual Pharmacokinetic Parameters of Amprenavir by Race (PROA 1010)

Race	Treatment	Tmax (h)	Cmax (ug/mL)	AUCinf (ug·h/mL)	CLF (mL/min)
TRT1	Mean	1.4	9.1	29.1	780.3
Blacks	SD	0.6	2.6	11.3	273.7
	Geo.Mean	1.3	8.7	27.2	734.4

Race	Treatment	Tmax (h)	Cmax (ug/mL)	AUCinf (ug·h/mL)	CLF (mL/min)
TRT2	Mean	1.1	9.6	27.3	819.6
Blacks	SD	0.9	2.2	12.3	239.7
	Geo.Mean	0.9	9.3	25.6	781.0

Race	Treatment	Tmax (h)	Cmax (ug/mL)	AUCinf (ug·h/mL)	CLF (mL/min)
TRT3	Mean	1.4	6.7	21.7	1172.6
Blacks	SD	0.6	3.7	16.8	427.7
	Geo.Mean	1.3	6.0	18.6	1073.2

Race	Treatment	Tmax (h)	Cmax (ug/mL)	AUCinf (ug·h/mL)	CLF (mL/min)
TRT1	Mean	1.3	9.3	30.6	730.6
Whites	SD	0.5	2.6	10.5	267.6
	Geo.Mean	1.2	8.9	29.0	689.8

Race	Treatment	Tmax (h)	Cmax (ug/mL)	AUCinf (ug·h/mL)	CLF (mL/min)
TRT2	Mean	1.1	9.9	28.6	767.4
Whites	SD	0.4	3.1	9.0	237.4
	Geo.Mean	1.0	9.4	27.3	733.1

Race	Treatment	Tmax (h)	Cmax (ug/mL)	AUCinf (ug·h/mL)	CLF (mL/min)
TRT3	Mean	1.5	6.0	21.8	1073.2
Whites	SD	0.7	2.9	11.4	357.7
	Geo.Mean	1.4	5.5	20.7	967.7

Figure 4. Mean Plasma Concentration -Time Profiles and Comparative plots for Amprenavir (PROA 1011)

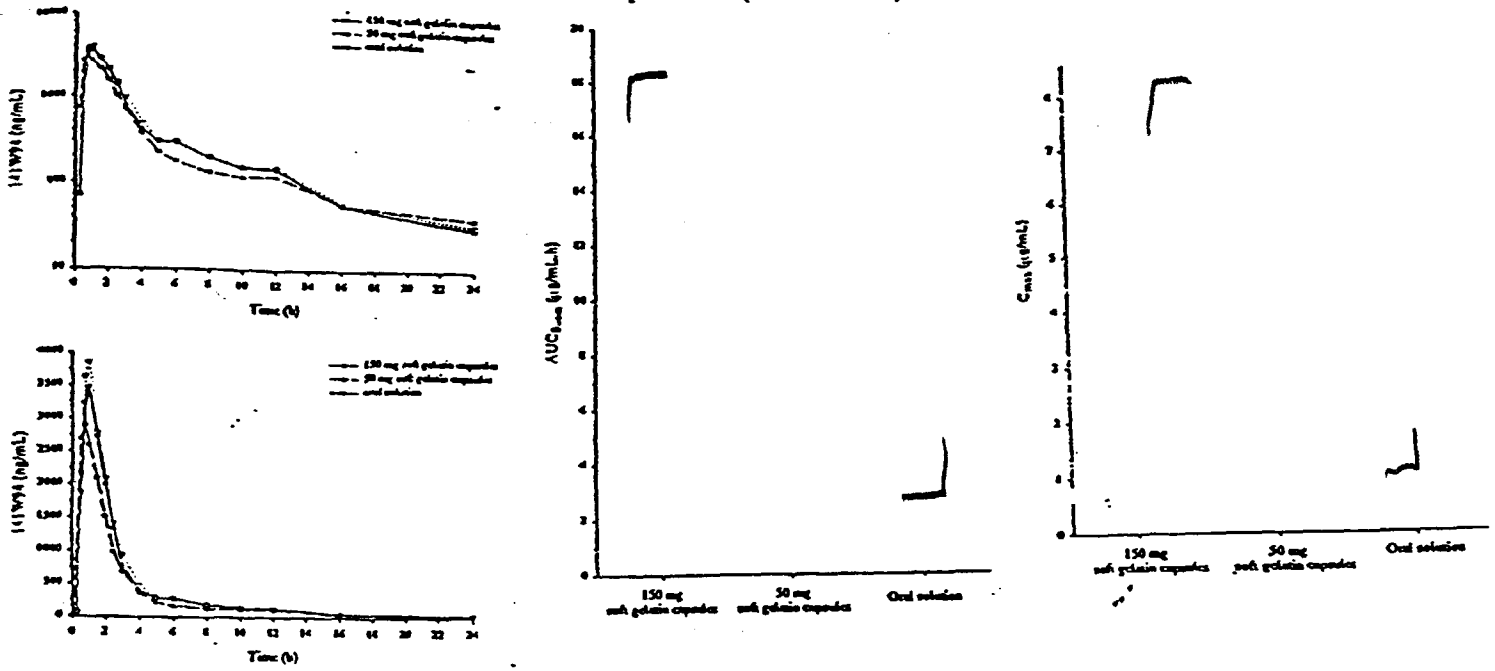


Figure 5. Mean Plasma Concentration -Time Profiles by Race for Amprenavir (PROA 1011)

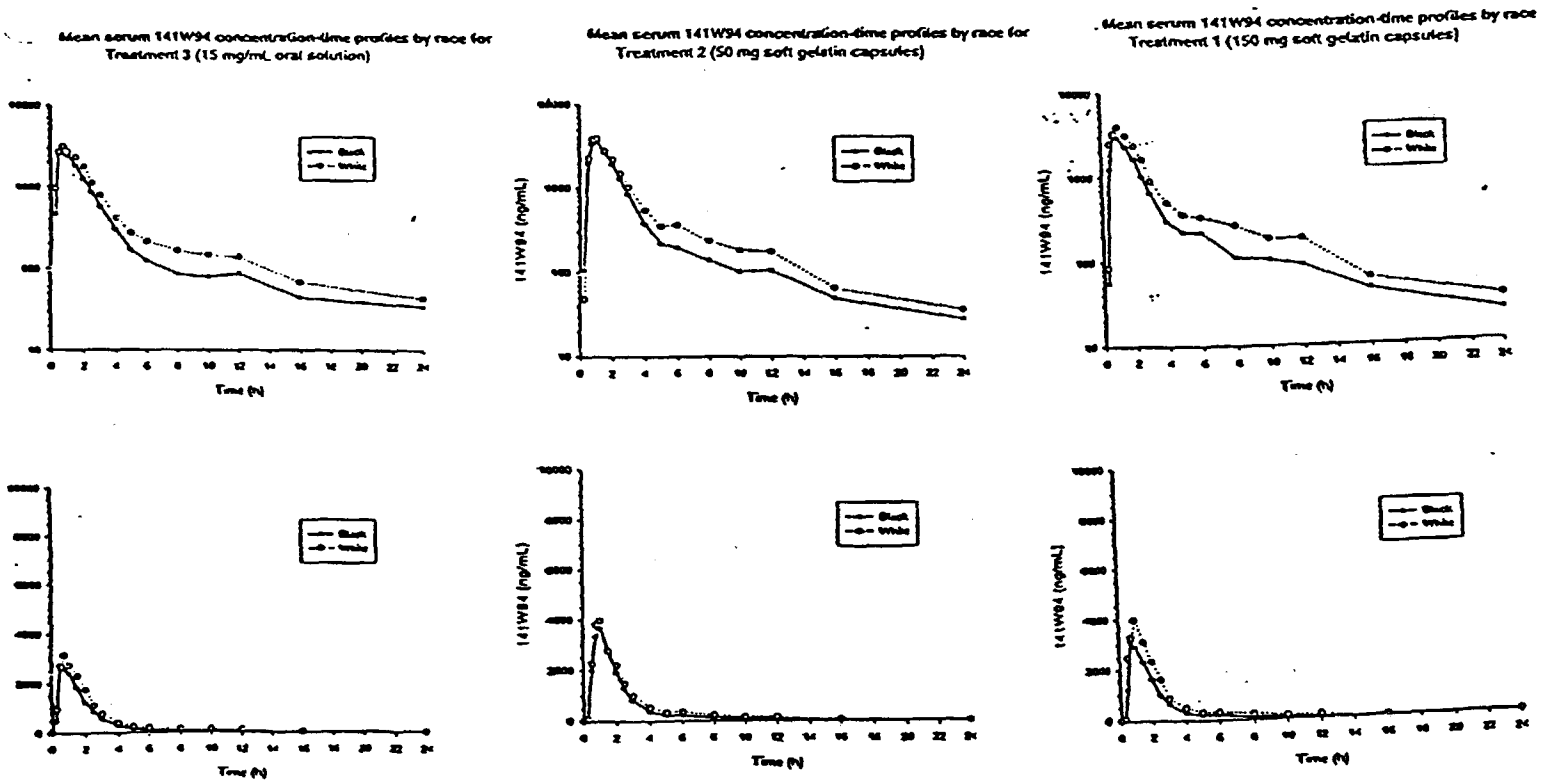


Figure 6. Metabolic Pathway of Amprenavir (PROA 1007)

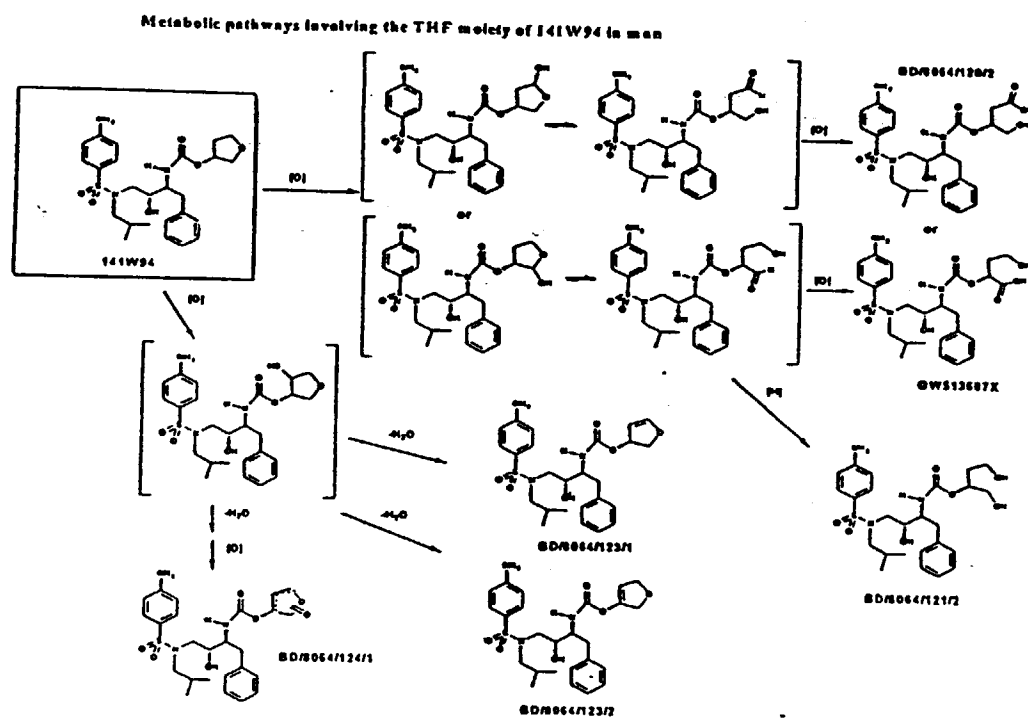


Figure 1D. Metabolic pathways of 141W94 in man

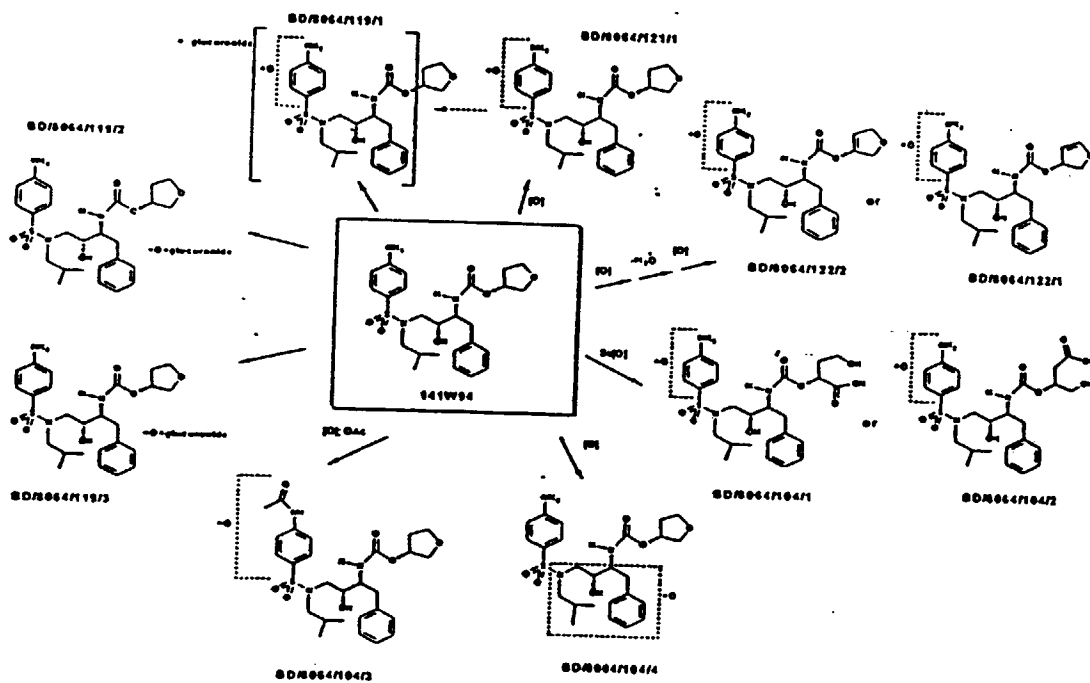
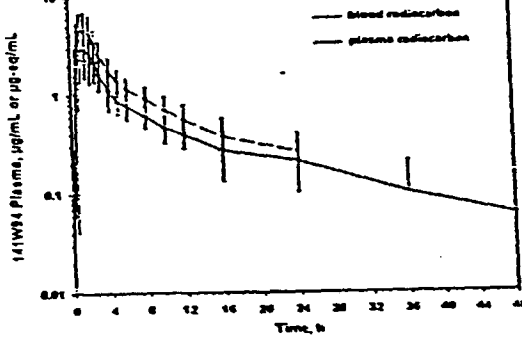
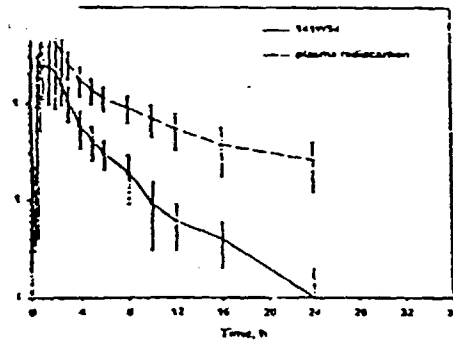
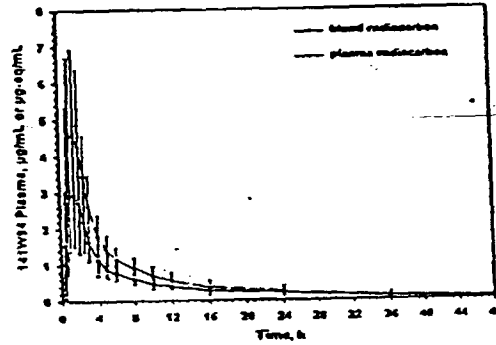
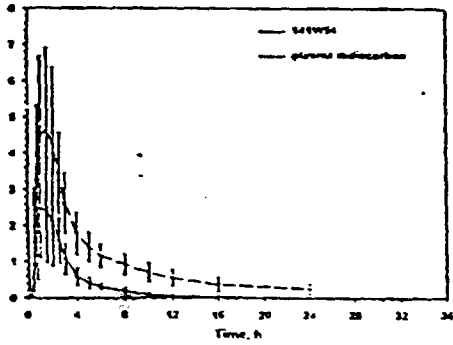


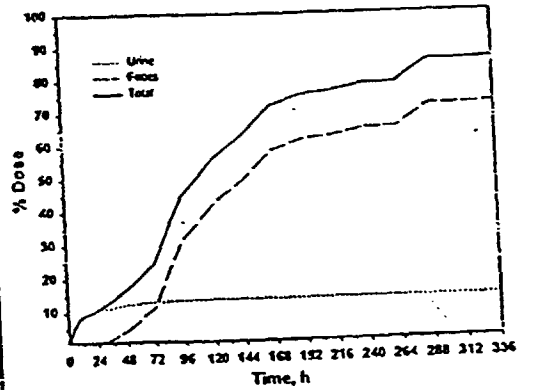
Figure 3. Mean Plasma Concentration -Time Profiles of Amprenavir and Plasam Radioactivity; Mean Cumulative Excretion of Radioactivity (PROA 1007)

Mean \pm Standard Deviation Plasma Concentration vs. Time Profiles of 141W94 ($\mu\text{g}/\text{mL}$) and Plasma Radioactivity ($\mu\text{g}\text{-eq}/\text{mL}$) after Oral Administration of [^{14}C]-141W94 (600 μg , 95.76 μCi)

Mean \pm Standard Deviation Plasma and Blood Radioactivity vs. Time Profiles of 141W94 ($\mu\text{g}\text{-eq}/\text{mL}$) after Oral Administration of [^{14}C]-141W94 (600 μg , 95.76 μCi)



Mean Cumulative Excretion of Radioactivity after Oral Administration of [^{14}C]-141W94 (600 μg , 95.76 μCi)



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Figure 8 Mean Plasma Concentration -Time Profiles for Amprenavir after Single Doses of 150, 300, 600, 900, and 1200 mg (PROA 1001)

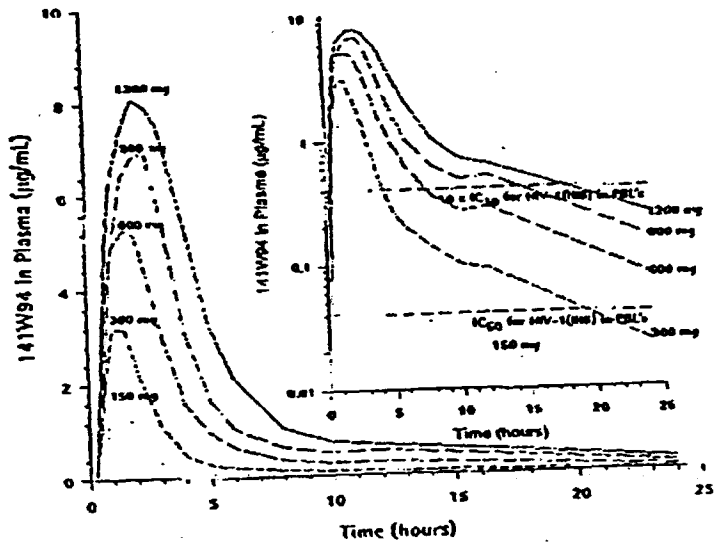
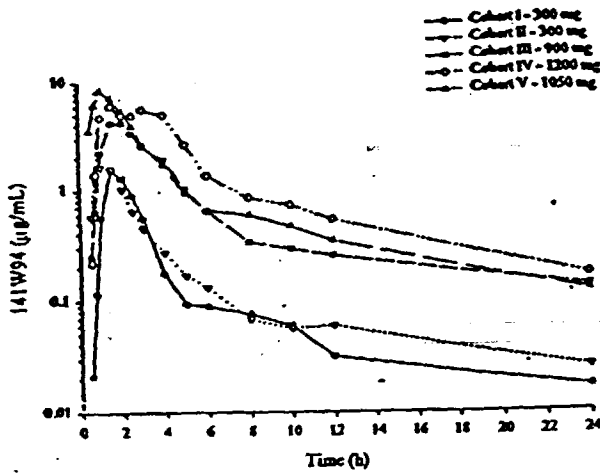


Table 7. Individual Pharmacokinetic Parameters of Amprenavir (PROA 1001)

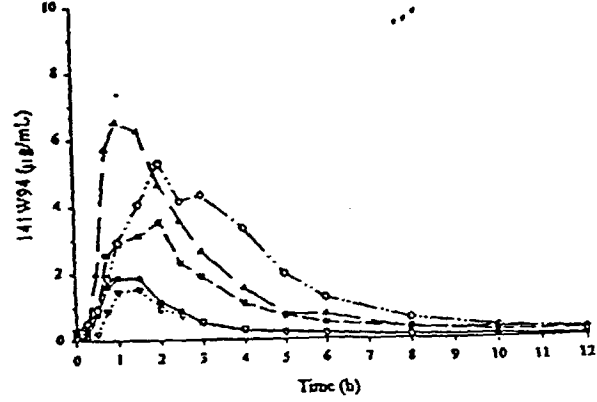
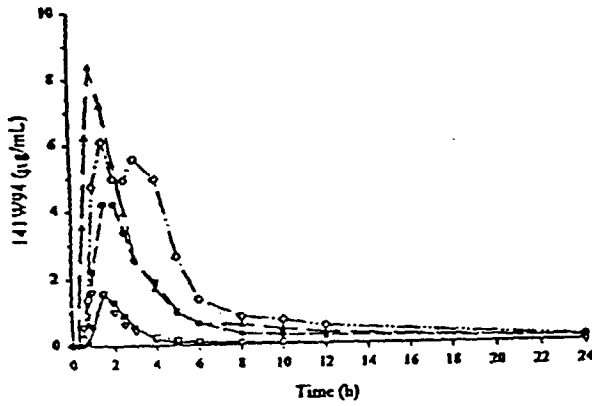
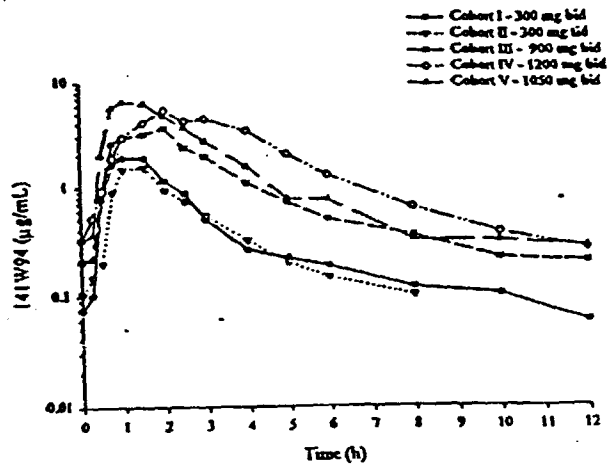
Parameter	Mean	SD	CV	Min	Q1	Q2	Q3	Max	CV
1200 mg	1200.0	0.1	2.1	9.5	47.1	344.8	367.8	4.3	
900 mg	900.0	2.7	6.8	4.6	31.6	213.3	288.9	1.7	
600 mg	600.0	0.7	1.9	7.8	43.7	468.1	346.7	4.5	

Figure 9. Mean Plasma Concentration -Time Profiles of Amprenavir (PROA 1002)

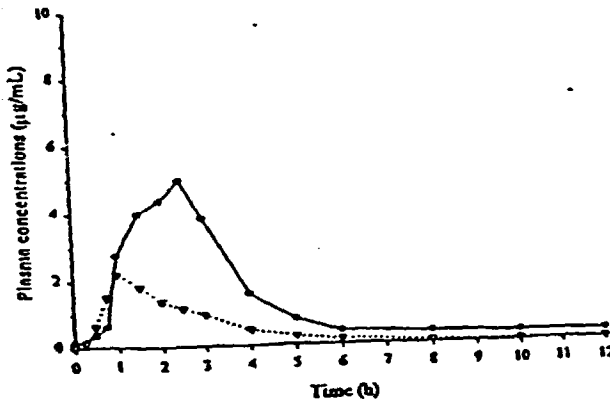
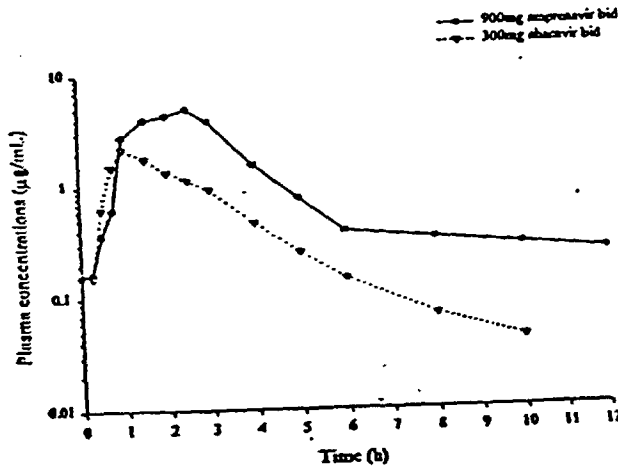
concentrations of amprenavir in plasma after single, oral dosing



concentrations of amprenavir in plasma at steady-state



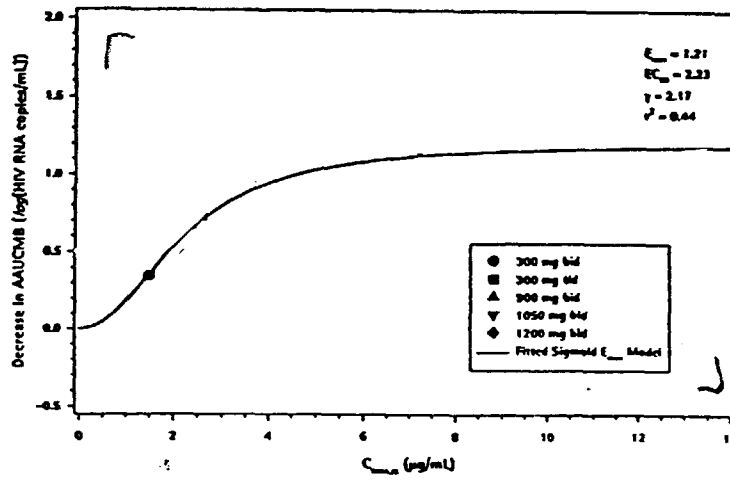
Media concentrations of amprenavir and abacavir in plasma at steady-state



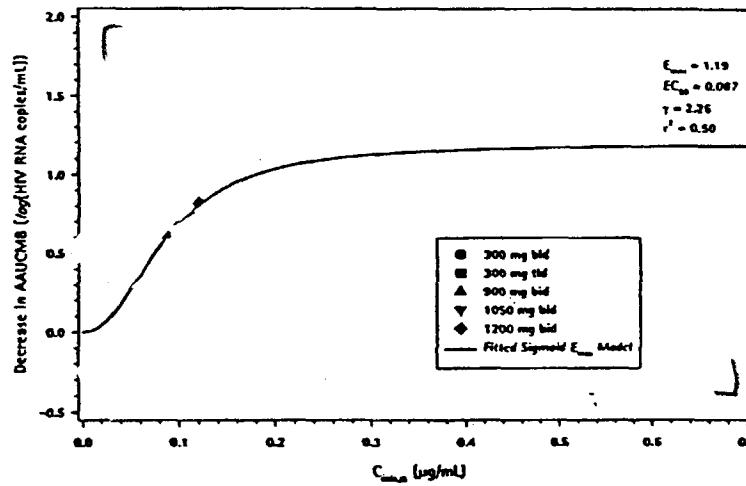
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Figure 10. Fitted Curves for the Selected Sigmoid Emax Model (PROA 1007)

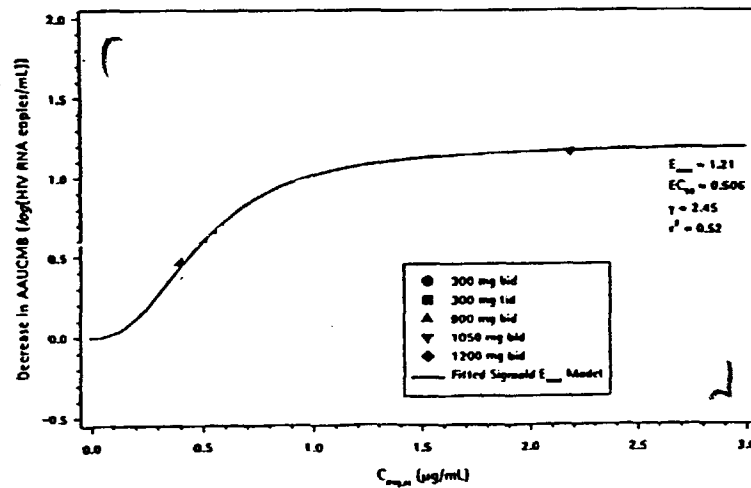
Plot of $C_{max,ss}$ versus Decrease in AAUCMB



Plot of $C_{min,ss}$ versus Decrease in AAUCMB



Plot of $C_{avg,ss}$ versus Decrease in AAUCMB

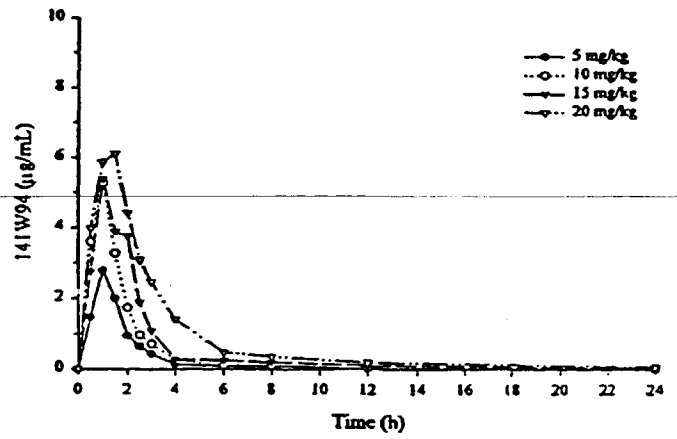
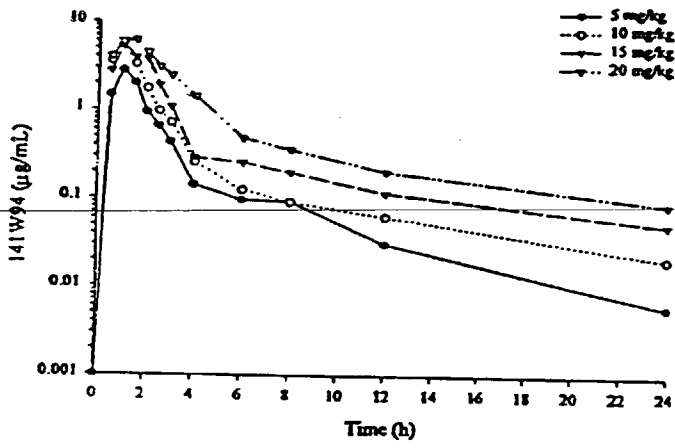


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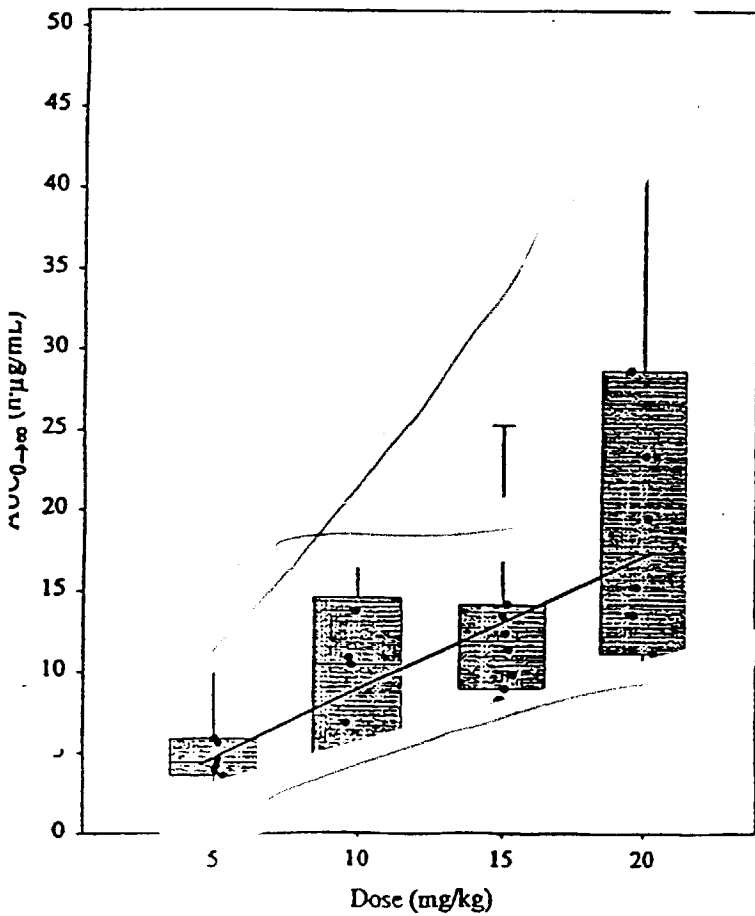
111

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Figure 13. Mean Plasma Concentration -Time Profiles and Comparative Plots of Amprenavir in Pediatrics (PROA 1006)



Comparative Linear Box Plots of 141W94



Comparative Linear Box Plot of 141W94 C_{max} (µg/mL)

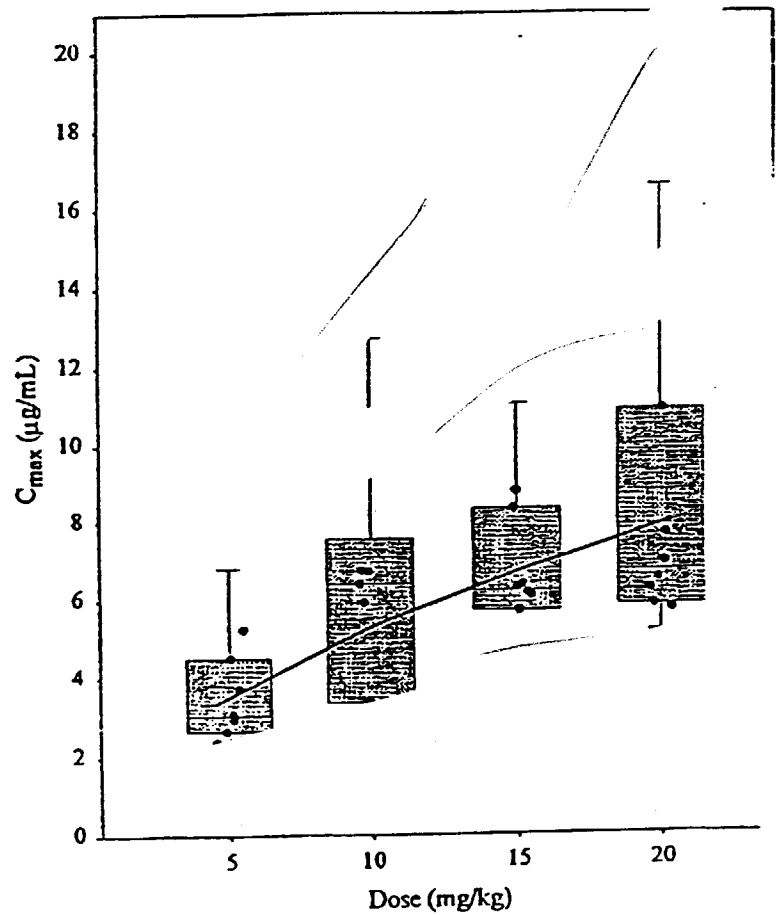


Figure 14. Mean Plasma Concentration -Time Profiles of Amprenavir in Pediatrics at Steady-State (Week 2; PROA 1006)

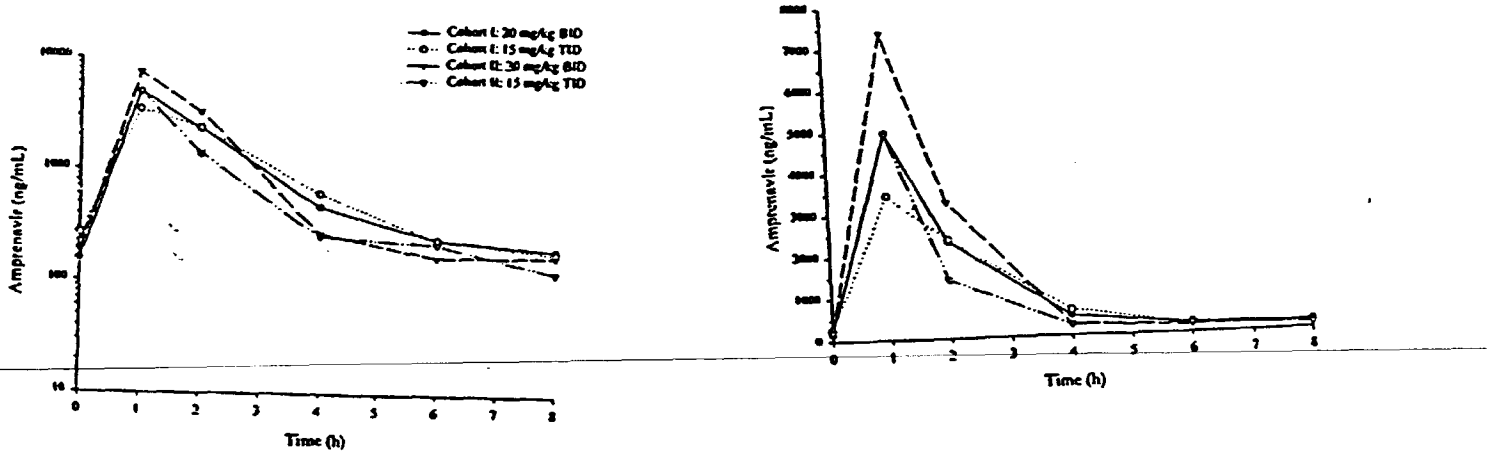
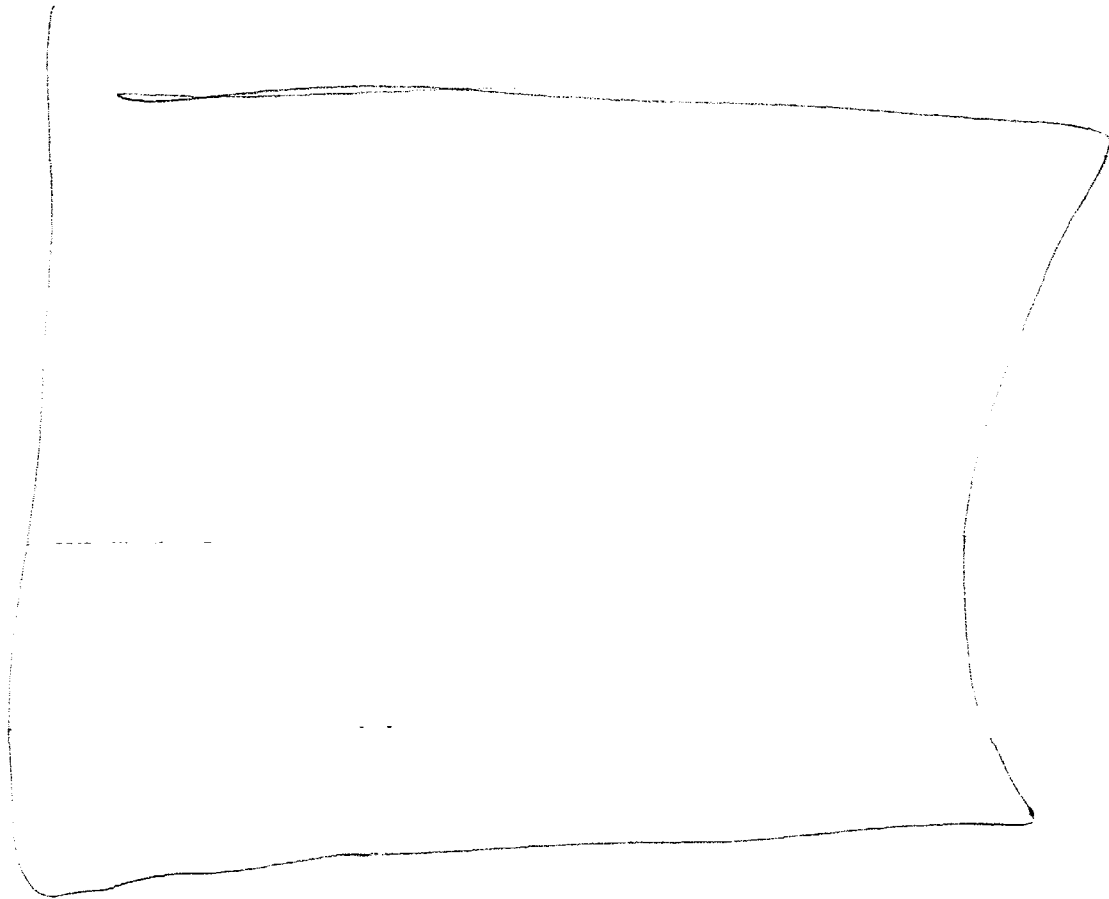
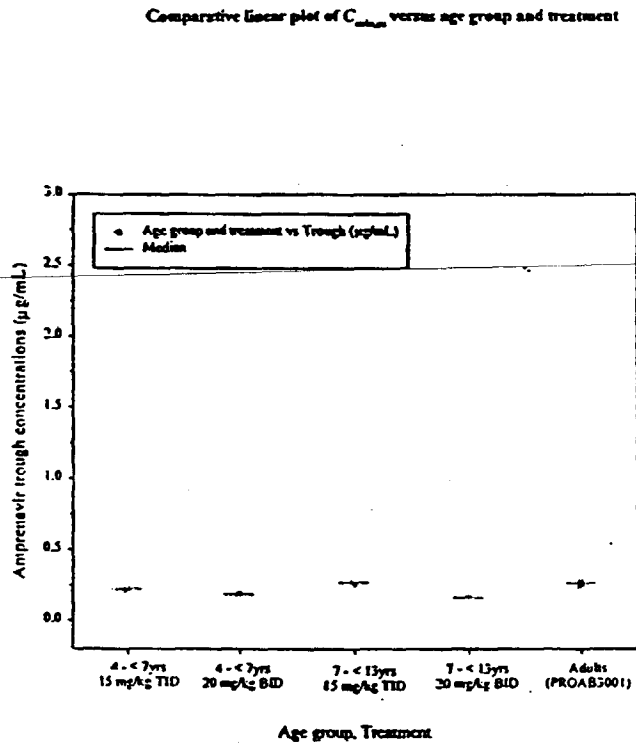


Table 12. Individual Pharmacokinetic Parameters of Amprenavir in Pediatrics at Steady-State (Week 2; PROA 1006)

Subj	Age	Sex	Race	Body Weight (kg)	Treatment	Total Dose (mg)	Actual Dose (mg/kg)	AUC ₀₋₂₄ (h·ug/mL)	C _{avg,ss} (ug/mL)	C _{max,ss} (ug/mL)	C _{min,ss} (ug/mL)	Lambda z (1/h)	CL/F (mL/min/kg)	t _{1/2} (h)	t _{max} (h)
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14a.
Figure 14a. Comparative Plot of C_{min} Vs Age Group and treatment (PROB 2004)



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