CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-007
21-039

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW
TEAM LEADER ADDENDUM

NDA: 21-007 and 21-039
DRUG: Amprenavir (AGENERASE™)
FORMULATIONS: 50 and 150 mg capsules
15 mg/mL oral solution

The purpose of this addendum is to clarify the rationale for the pediatric dosing recommendations for amprenavir capsules and oral solution. For more details, see the full Clinical Pharmacology/Biopharmaceutics Review, completed by Dr. Vijay Tammara and Dr. Prabhu Rajagopalan.

The dosing recommendations are based on multiple-dose pharmacokinetic data collected from 37 pediatric patients (age 4 to ≤13 years) in study PROB 2004. These patients received amprenavir oral solution at a dose of 20 mg/kg BID or 15 mg/kg TID. The resulting pharmacokinetic data are summarized in the following table. The pharmacokinetic parameters from the pediatric patients are compared to pharmacokinetic parameters from adult patients receiving the recommended dose of amprenavir capsules, 1200 mg BID.

Steady-State Amprenavir Pharmacokinetic Parameters [Arithmetic mean ± SD (%CV)]

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

*AUC is 0 to 12 hours for BID regimens and 0 to 8 hours for the TID regimen. Thus, Cavg is a more relevant comparison of exposures.

The following items were considered when determining the appropriate dosing regimen for pediatric patients:

1. It is assumed that the most relevant parameters, when comparing pediatric and adult data, are Cavg (AUC/dosing interval) and Cmin. Cmax must also be considered. For some drugs, it may be difficult to find a pediatric dosing regimen that provides similar values for all three parameters (Cavg, Cmin, and Cmax) when compared to adult data.
2. Adult amprenavir pharmacokinetic data, following administration of the recommended dose, are available for only five HIV infected patients. The pharmacokinetic data are highly variable in the five adult patients.
3. The pharmacokinetic profile following TID dosing in pediatric patients differs from the profile following BID dosing in pediatric or adult patients, with a lower Cmax observed following the TID regimen. The applicant stated that they would like to include the TID dosing option for those pediatric patients that have a problem tolerating the larger BID dose (20 mg/kg) because the smaller TID dose (15 mg/kg) may allow improved tolerability and compliance.
4. The pediatric multiple-dose pharmacokinetic data were collected following administration of amprenavir oral solution. The results of a bioequivalence study conducted in adults indicate that amprenavir concentrations are, on average, 15% lower following administration of the oral solution compared to the capsules. Thus, following administration of amprenavir capsules to pediatric patients at 20 mg/kg BID or 15 mg/kg TID, the concentrations will be ~15% higher than those in the above table and will be closer to the adult values. Following administration of amprenavir oral solution to pediatric patients at the proposed adjusted

dosing regimens, 22.5 mg/kg BID or 17 mg/kg TID, the concentrations will be higher than those in the above table and will be closer to the adult values.

Based on the above considerations, the following dosing instructions for pediatric patients will be included in the amprenavir label:

Capsules: For patients between 4 and 12 years of age or for patients over 13 years of age with a weight of <50 kg, the recommended oral dose of Agenerase Capsules is 20 mg/kg twice daily or 15 mg/kg three times daily (to a maximum dose of 2400 mg).

Oral Solution: For patients between 4 and 12 years of age or for patients over 13 years of age with a weight of <50 kg, [redacted] is 22.5 mg/kg twice daily or 17 mg/kg three times daily (to a maximum dose of 2800 mg).

/S/ 4/7/99

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cc:

HFD 530	/NDAs 21-007 & 21-039
	/MO/JMartin
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HFD 880	/PK/VTammara
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HFD 880	/PKTL/KReynolds
HFD 880	/DPE III
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Agenerase NDA 21-007&21-039
Vijay Tammara
Prabhu Rajagopalan

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Amprenavir (Agenerase™)
50 and 150 mg Capsules
15 mg/mL Oral Solution

Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

NDA 21-007 (Capsules);

Submission Dates:
May 29, 1998; July 20, 1998;
October 15, 1998; November 16; 1998;
November 19, 1998; December 7, 1998;
December 14, 1998; January 12, 1999;
January 13, 1999; January 18, 1999;
February 26, 1999

NDA 21-039 (Oral Solution)

October 29, 1998; December 7, 1998;

[redacted]

October 6, 1997; March 30, 1998;
April 30, 1998; June 19, 1998;
July 23, 1998

Reviewers: **Vijay K. Tammara, Ph. D. and Prabhu Rajagopalan, Ph. D.**

Indication: **Treatment of HIV-Infection**
Classification: 1P
Type of Submission: Original – New Molecular Entity

Amprenavir (141W94; ((3S)-tetrahydro-3-furyl N-(1S,2R)-3-(4-amino-N-isobutylbenzene-sulphonamido)-1-benzyl-2-hydroxypropyl carbamate)) is a selective synthetic, potent protease inhibitor. The mechanism of action is presumably by preventing cleavage of gag and gag-pol polyproteins resulting in an inactive, noninfectious virus. The recommended dose of amprenavir in adults and adolescents (age 13-16 years) is 1200 mg BID and for pediatrics (age: 4-12 years) or patients over 13 years with body weight of ≤ 50 kg is 20 mg/kg BID or 15 mg/kg TID to a maximum of 2400 mg per day.

The sponsor has evaluated the efficacy and safety of amprenavir in the treatment of HIV infection in two Phase III adult studies. Study PROAB 3001 is a well controlled, multicenter trial conducted in therapy-naive adults. Patients were randomized to receive amprenavir (1200-mg BID), zidovudine and lamivudine or placebo, zidovudine, and lamivudine. Study PROAB 3006 is an open-label, well-controlled trial, which compares amprenavir (1200-mg BID) and indinavir (800-mg TID) in combination with nucleoside reverse trancriptase inhibitors (NRTIs) in NRTI-experienced, protease inhibitor-naïve adults. Week 16 data from these studies are available at this time. Study PROAB 3004 is an open-label, non-comparative trial in combination with two NRTIs in HIV infected children (aged 4 – 18 years). In this study pediatric patients received amprenavir capsules at 20 mg/kg BID (50 or 150-mg) or oral solution at a dose of 22.5 mg/kg BID (15 mg/mL). Week 16 and preliminary week 24 data from this study are available at this time. The sponsor is seeking approval of capsule and oral solution formulations of amprenavir.

The sponsor has adequately studied the pharmacokinetics of amprenavir at the recommended doses.

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I. SYNOPSIS

ABSORPTION:

Following oral administration, amprenavir is rapidly absorbed, with a mean ± sd Tmax value of 1.1 ± 0.5 hours. In 36 healthy (HIV-seronegative) subjects receiving the proposed market formulation of amprenavir soft gel capsules, the mean ± sd Cmax and $AUC_{0-\infty}$ values were 9.8 ± 2.8 μg/mL and 30.1 ± 10.4 μg*hr/mL, respectively, after a single oral dose of 1200-mg. In 24 healthy (HIV-seronegative) subjects receiving the proposed market formulation of amprenavir oral solution (15 mg/mL), the mean ± sd Cmax and $AUC_{0-\infty}$ values were 3.4 ± 1.3 μg/mL and 8.2 ± 3.8 μg*hr/mL, respectively, after a single oral dose of 600-mg. The ratio of geometric means of Cmax and $AUC_{0-\infty}$ of oral solution relative to soft gel capsules (150 or 50-mg) were 0.8 and 0.84, respectively. The absolute oral bioavailability of amprenavir in humans has not been established.

When administered with a high fat breakfast, the mean fed to fasted ratios for amprenavir Cmax and $AUC_{0-\infty}$ were 0.6 [90% CI: 0.54 - 0.67] and 0.75 [90% CI: 0.70 - 0.81], respectively. The mean Tmax was prolonged by 0.4 hrs (1.1 vs 1.5; ↑ by 36%). Thus, food affected the rate and extent of absorption (mean Cmax decreased by 40%, and mean $AUC_{0-\infty}$ decreased by 25%). These decreases were statistically significant and may have clinical significance.

In 5 HIV infected patients receiving amprenavir 1200-mg BID, the mean ± sd Cmaxss and AUCss values were 5.4 ± 3.3 μg/mL and 18.5 ± 11.6 μg*hr/mL, respectively. The accumulation index was less than 1.2, indicating little accumulation upon multiple dosing. Based on the ~ 9 hr half-life, accumulation is less than expected. This suggests that there is increased clearance of unbound drug either, due to autoinduction of metabolism or transport, or that the free fraction in plasma increases due to a reduction in α-1-acid glycoprotein (AAG).

Bioequivalency: The sponsor conducted 3 studies to assess bioequivalency between four formulations used in clinical trials. Amprenavir ——— capsules, soft gelatin capsules with ——— proposed market formulation; two strengths 150 and 50-mg) ——— and an oral solution (15 mg/mL) were used in Phase I, II, and III studies. The results of statistical analysis of the bioequivalency assessments are summarized below:

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Parameter	Formulation	GM [90% CI]
$AUC_{0-\infty}$	Capsule (reference, 150-mg)	
	Soft Gelatin Capsule (content; 150-mg; test)	1.03 [92 – 114]
	Soft Gelatin Capsule (ontent; 150-mg; reference)	
	Soft Gelatin Capsule ntent; 150-mg; test)	0.94 [87 – 101]
	Soft Gelatin Capsule (content; 150-mg; reference)	
	Soft Gelatin Capsule (content; 50-mg; test)	0.99 [90 – 114]
	Soft Gelatin Capsule content; 150-mg; reference)	
	Oral solution (15 mg/mL; test)	0.84 [76 – 95]
	Soft Gelatin Capsule (content; 50-mg; reference)	
	Oral solution (15 mg/mL; test)	0.85 [77 - 96]
Cmax	Capsule (reference, 150-mg)	
	Soft Gelatin Capsule (content; 150-mg; test)	1.25 [103 – 153]
	Soft Gelatin Capsule ontent; 150-mg; reference)	
	Soft Gelatin Capsule (content; 150-mg; test)	1.06 [94 – 117]
	Soft Gelatin Capsule (content; 150-mg; reference)	
	Soft Gelatin Capsule (content; 50-mg; test)	0.95 [82 – 113]
	Soft Gelatin Capsule (content; 150-mg; reference)	
	Oral solution (15 mg/mL; test)	0.78 [71 – 93]
	Soft Gelatin Capsule (content; 50-mg; reference)	
	Oral solution (15 mg/mL; test)	0.82 [73 - 96]

The results indicate that soft gelatin and capsules of amprenavir are bioequivalent in terms of $AUC_{0-\infty}$, but not in terms of Cmax.

The 150 mg soft gelatin capsule formulation containing is bioequivalent to the original 150 mg soft gelatin capsule formulation containing

The 150-mg soft gelatin capsule formulation containing is bioequivalent to the 50-mg soft gelatin capsule formulation containing

The oral solution formulation is not bioequivalent to the soft gel capsule formulation of either strength.

DOSE PROPORTIONALITY:

Following oral administration of amprenavir in HIV infected subjects, less than dose-proportional increases in mean Cmax and greater than dose-proportional increases in mean $AUC_{0-\infty}$ were observed between 150- and 1200-mg single doses. Following multiple dosing of amprenavir for 3 weeks in HIV infected subjects, less than proportional increases in mean Cmaxss and proportional increases in AUCss were observed between 300- and 1200-mg doses. Further, a trend of decreasing concentrations of APV over the initial eight-week period, followed by stabilization through week 16, was observed in the pivotal clinical trial following administration of APV 1200-mg BID. The time variant pharmacokinetics observed in this pivotal clinical study are consistent with similar changes observed in another Phase 2 multiple dose study. This could be possibly due to lowering of AAG levels during antiretroviral therapy with APV, decreased absorption due to formulation problems or induction, compliance, and possible drug-drug interactions.

DISTRIBUTION:

The apparent volume of distribution is 6 - 9 L/kg in healthy adult subjects and HIV infected patients, whereas in pediatrics (age: 4–12 years) it was observed to be 11 – 13 L/kg.

Protein binding and erythrocyte partitioning

In vitro studies indicate that protein binding was largely concentration independent over the clinically relevant concentration range of 0.5 to 10 μg/mL. Over this concentration range, 96 to 91% of drug was bound to plasma proteins. Binding studies with α1-acid glycoprotein and human serum albumin indicate that amprenavir has a higher affinity for α1-acid glycoprotein. At low concentrations of 0.1 to 1 μg/mL, partitioning of amprenavir into erythrocytes was not observed. However, partitioning into erythrocytes was noted at higher, therapeutically relevant drug concentrations. Partitioning into erythrocytes may be due to an increase in free fraction at higher drug concentrations.

METABOLISM AND ELIMINATION:

In vitro metabolism

In vitro metabolism studies indicate that amprenavir is metabolized by CYP3A4 enzyme. An additional study conducted by the Applicant has indicated that amprenavir inhibits CYP3A4 enzyme and to a lesser extent (10 to 20%) CYP2C19 and 2E1 enzymes. At clinically relevant concentrations, amprenavir did not inhibit CYP1A2, 2C9 and 2D6. Based on a study comparing the CYP3A4 inhibition of various protease inhibitors, the Applicant has rank ordered the protease inhibitors as follows: ritonavir > indinavir > nelfinavir > amprenavir > saquinavir.

In Vivo

In the mass balance study, following oral administration of amprenavir, mean total recovery of radioactivity was 86% over a period 240 hours (Urine 14%, feces 72%) and 14% was unaccounted for. Of the 72% of dose-related radioactivity recovered in the feces, two metabolites, BD/8064/120/2 or GW513607 (resulting from di-oxidation of the tetrahydrofuran moiety; 62%) and BD/8064/104/1 or BD/8064/104/2 (resulting from di-oxidation of the tetrahydrofuran moiety and an additional oxidation of the aniline portion of the molecule; 32%) accounted for approximately 94% of the excreted dose in feces.

HPLC analysis of urine samples obtained from a Phase I study (PROA 1001) indicated that less than 2% of amprenavir is eliminated unchanged in the urine.

Comparison of the mean $AUC_{0-\infty}$ of amprenavir in plasma to the radioactivity measured in plasma as amprenavir equivalents indicates that about 30% of the circulating radioactivity is due to unchanged drug.

The mean ± sd total apparent clearance was 8.1 ± 2.1 mL/min/kg and 24 mL/min/kg in adult and pediatric patients, respectively. The plasma half-life in these subjects was 8 – 9 hours.

PHARMACODYNAMICS:

Relationship Between Concentration and Efficacy

The sponsor evaluated the PK-PD correlation between Cminss, Cavgss, and Cmaxss and antiviral activity (Plasma HIV-RNA) over four weeks. The pharmacokinetic variables were fitted to the decrease in the time-weighted average area under the curve of $\log_{10}$(HIV-1 RNA) minus the baseline (AAUCMB) using a simple Emax model, a simple Emax model with baseline effect, a sigmoid Emax model, and a sigmoid Emax model with baseline effect. The sigmoid Emax model was the best fit for all three expressions of amprenavir concentrations Cminss, Cavgss, and Cmaxss, based upon its having the lowest AIC of the four models tested. All models provided a statistically significant fit to the data ($p < 0.0001$). The r^2 values for these models were 0.44 or higher. The mean Cminss for amprenavir after the 1050 and 1200 mg BID doses were observed to be 0.33 and 0.28 µg/mL, respectively. Both exceed the EC90 predicted for Cminss (0.23 µg/mL). Further, it was reported that the Cminss achieved after 1200 mg BID is 10–fold greater than the median *in vitro* IC50 (corrected for protein binding) for clinical isolates of HIV (0.023 mg/mL; range ———— mg/mL). Therefore, based on these results, the sponsor pursued a dose of 1200-mg BID in adult and pediatric (normalized to body weight) patients in principal Phase III clinical trials.

Relationship Between Concentration and Safety

The sponsor performed categorical and logistic regression analyses to correlate steady state plasma concentration to adverse events. The categorical analysis results, using the median of the distribution of each pharmacokinetic parameter value for grouping of the exposure, indicated significant associations of increasing Cmaxss with the reporting of headache or oral numbness. Oral numbness was also significantly associated with Cavgss. Nausea and/or vomiting had a trend towards higher occurrence with higher Cavgss. There were no significant associations with the occurrence of AEs in the logistic regression analysis using each pharmacokinetic parameter as a continuous variable.

SPECIAL POPULATIONS:

Pediatrics: The sponsor obtained pharmacokinetic data in pediatric patients (age: 4–12 years) following a single dose escalation study. The results of this study indicated that $AUC_{0-\infty}$ and Cmax increased less than and greater than proportionally, respectively. Mean CL/F (normalized to body weight) and $T_{1/2}$ were observed to be dose independent. Weight normalized total clearance was greater in children compared to adults (receiving approximately equivalent doses based on body weight).

The sponsor provided an interim report of an ongoing multiple dose study in pediatric patients. The results indicated that the pharmacokinetic parameters are comparable between cohorts (cohort I: age: 4-6 years; Cohort II: age: 7-12 years). Mean Cavgss and Cminss were similar between patients receiving TID regimen (15 mg/kg TID) and BID regimen (20 mg/kg BID) and are comparable to those observed in adults (1200-mg BID). Based on these data, amprenavir capsules are recommended to be administered in

pediatric patients (age: 4-12 years) at either 15 mg/kg TID or 20 mg/kg BID doses to a maximum of 2400-mg per day. Due to decreased bioavailability observed with the oral solution, the recommended dose is 17 mg/kg TID or 22.5 mg/kg BID.

Ethnic Differences: The sponsor performed a secondary statistical analysis taking into account AAG, age, albumin, bilirubin, HIV risk factor, race, treatment, and weight as fixed effects on log–transformed APV pharmacokinetic parameters in two multiple dose studies (PROA 1002 and 2001). The results of this analysis indicated that race had no effect on APV pharmacokinetics. A similar observation was made in one single dose study (PROA 1010), whereas in another single dose study (PROA 1011), a statistically significant decrease in $AUC_{0-\infty}$ (25%) and increases in CL/F and Vz/F (33% and 30%, respectively) were observed for amprenavir in Blacks compared to Whites. This could be due to lower mean AAG concentrations in Blacks (77.2 ± 13.8 mg/dL) compared to Whites (90.0 ± 20.2 mg/dL). Since amprenavir is highly protein bound, specifically to AAG, lower concentrations of AAG would result in an increase in the free fraction of drug available to the clearance organs. However, no information is available on the clinical significance of such differences.

Patients with Hepatic Impairment: The pharmacokinetics of amprenavir, following oral administration of a single 600-mg dose, were determined in healthy subjects and subjects with moderate (Child-Pugh score: 5 – 6) and severe (Child-Pugh score 8 – 12) hepatic impairment. The results of this single dose study indicate that AUC∞ of amprenavir in subjects with moderate and severe hepatic impairment increases by 2.46- and 4.51- fold, respectively. Therefore, in order to achieve exposures similar to subjects without hepatic impairment, subjects with moderate and severe hepatic impairment should receive 450 mg BID and 300 mg BID, respectively.

Gender: No formal pharmacokinetic study was conducted to evaluate if there are gender differences. A retrospective analysis of the data (PROA 1002 (7F; 29M) and PROA 1008 (10F, 20M)) indicated no gender differences in the pharmacokinetics of amprenavir.

Healthy Volunteers vs HIV Infected Patients: No formal pharmacokinetic study was conducted to evaluate if there are differences between healthy volunteers and HIV infected patients. A retrospective analysis of the data (PROA 1010 (39 healthy subjects) and PROA 1002 (7 HIV infected patients) indicated no differences in the pharmacokinetics of amprenavir between healthy subjects and HIV infected patients.

Drug interactions

Zidovudine and Lamivudine: The results of a single dose study in HIV infected patients (without AIDS) did not indicate occurrence of clinically significant pharmacokinetic interaction upon administration of two and three drug combinations of amprenavir, zidovudine and lamivudine.

Ketoconazole: The Applicant conducted a single dose study in healthy *male* subjects to assess the pharmacokinetic interaction between amprenavir and ketoconazole. The results of this study indicate that concomitant administration of amprenavir and ketoconazole increases amprenavir AUC by 31% and decreases amprenavir C_{max} by 16%. Concomitant administration of these drugs increased ketoconazole C_{max} and AUC by 44% and 19%, respectively. The clinical relevance of this single dose study is not known.

Clarithromycin: A multiple dose study was conducted in healthy *male* subjects to assess the pharmacokinetic interaction between amprenavir and clarithromycin. The results of this study indicate a minor increase in amprenavir AUC (18%) when administered with clarithromycin. Concomitant administration of amprenavir and clarithromycin did not affect exposure to clarithromycin, but resulted in a 10% decrease in clarithromycin C_{max}. The clinical relevance of the pharmacokinetic interaction is not known.

Rifabutin: The results of a multiple dose study conducted in healthy *male* subjects indicate that concomitant administration of amprenavir and rifabutin is poorly tolerated. Concomitant administration of amprenavir and rifabutin resulted in a 15% increase in amprenavir AUC and a clinically significant increase in rifabutin (2.93- fold) and 25-desacetyl rifabutin (13.35- fold) exposure. Concomitant administration of amprenavir and rifabutin should be avoided. When rifabutin is clinically necessary, rifabutin dose may be reduced by 50% when administered with amprenavir.

Rifampin: In a multiple dose study in healthy *male* subjects it was noted that rifampin significantly affects the pharmacokinetics of amprenavir. A 70% and 82% decrease was noted in amprenavir C_{max} and AUC when administered with rifampin. It is strongly recommended that rifampin not be administered with amprenavir. The pharmacokinetics of rifampin were not affected by concomitant administration with amprenavir.

Abacavir: In a multiple dose study in HIV infected patients it was noted that abacavir significantly affects the pharmacokinetics of amprenavir. A 55, 40, 40, and 25% increase in mean Cmaxss, AUCss, Cavgss, and Cminss of amprenavir was noted, respectively, when amprenavir (900 mg BID) was coadministered with abacavir (300 mg BID). However, due to small sample size (n=4) and high between subject variability (CV $\geq$ 58%), statistical significance was not evaluated. APV was observed not to have an affect on the pharmacokinetics of abacavir when compared with pharmacokinetics of abacavir alone from a historical control.

Saquinavir: In a multiple dose study in HIV infected patients it was noted that saquinavir (SQV-soft gelatin capsules) affects the pharmacokinetics of amprenavir. A 32, 37, and 14% decrease in mean AUCss, Cmaxss, and Cminss of amprenavir was noted, respectively, when amprenavir (800 mg TID) was coadministered with SQV (800 mg TID). Further, a 19 and 48% decrease in mean AUCss and Cminss, respectively, and a 21% increase in Cmaxss was noted for saquinavir when SQV was given with APV compared to SQV given alone (historical control).

Indinavir: In a multiple dose study in HIV infected patients it was noted that indinavir (IND) affects the pharmacokinetics of amprenavir. A 33, 18, and 25% increase in mean AUCss, Cmaxss, and Cminss of amprenavir was noted, respectively, when amprenavir (800 mg TID) was coadministered with IND (800 mg TID). Statistically significant decreases in AUCss, Cmaxss, and Cminss by 38, 22, and 27%, respectively, with an associated increase in CL/F (72%) were observed for IND when IND was administered with APV relative to when IND was given alone (historical data).

Nelfinavir: In a multiple dose study in HIV infected patients it was noted that nelfinavir (NFV; 750 TID) did not affect the pharmacokinetics of amprenavir (800 mg TID) except for a significant increase in Cminss by 189%. No change in the NFV pharmacokinetic results were observed in this study when compared to historical data.

Agenerase NDA 21-007&21-039
Vijay Tammara
Prabhu Rajagopalan
Dissolution Method

The following dissolution methodology and specification for Agenerase Soft gelatin capsules (SGC), as requested by the sponsor, are acceptable:

Apparatus: USP Apparatus 2 (paddles)
Medium: [redacted]
Volume:
Agitation:
Temperature:
Specification: Q = [redacted]
****

RECOMMENDATION:

These submissions (NDAs 21007 & 21-039; [redacted] have been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics and have been found to be acceptable for meeting the Office's requirements.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS BRIEFING

The briefing was held on February 01, 1999 and was attended by Debbie Birnkrant, Jerry Collins, John Martin, Narayana Battula, Lalji Mishra, Therese Cvetkovich, Stephen Miller, George Lunn, Greg Soon, Mei-Ling Chen, Raymond Miller, John Lazor, Kellie Reynolds, Prabhu Rajagopalan, and Vijay Tammara.

/S/ 3/30/99

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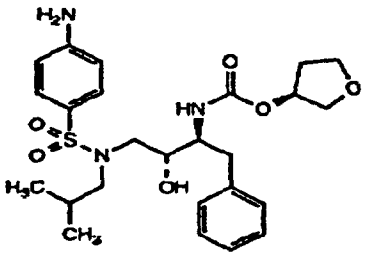
CC: HFD 530 /NDAs 21-007 & 21-039
/MO/Martin
/CSO/Truffa
HFD 880 /Tammara
HFD 880 /Rajagopalan
HFD 880 /TL/Reynolds
HFD 880 /DPE III
CDR /Barbara Murphy (for Drug files).

II. CHEMISTRY OVERVIEW

Physico-chemical Properties of Amprenavir:



Amprenavir is a carbamic acid derivative and its chemical name is ((3S)-tetrahydro-3-furyl N-(1S,2R)-3-(4-amino-N-isobutylbenzene-sulphonamido)-1-benzyl-2-hydroxypropyl carbamate)). It is a white to cream colored crystalline solid and its molecular weight is 505.64.

Solubility:

SOLVENT	SOLUBILITY MG/ML
Water	
0.1N HCl	
0.1N NaOH	
Polyethylene Glycol 400	
Propylene Glycol	
Ethanol	
Isopropanol	

Solution pH: The pH of an aqueous solution of amprenavir at 0.041 mg/mL is 7.5 ± 0.5

Partition coefficient: ———

pK_a: —

Chirality/Stereochemistry: Amprenavir is a single stereoisomer with the (3S, 1S, 2R) configuration

Dissolution Specification:

The following dissolution methodology and specification is proposed by the sponsor for 50 and 150 mg Capsules:

Apparatus: USP Apparatus 2 (paddles)
Medium: [redacted]
Volume:
Agitation:
Temperature:
Specification: Q = [redacted]

These specifications are acceptable.

Based on the solubility, pKa, and dissolution profiles (Appendix 2), this drug can be classified as poorly soluble and highly permeable.

III. ANALYTICAL METHODS

The details of the analytical methodology is provided in Appendix 1.

IV. DISSOLUTION

The dissolution methodology and dissolution profiles for to be marketed soft gelatin capsules are provided in Appendix 2.

V. FORMULATION

Final To-Be-Marketed Formulation Composition of Agenerase Soft Gelatin Capsules and Oral Solution:

Strength	50-mg	150-mg	15 mg/mL
Ingredients	Quantity (mg/capsule)	Quantity (mg/capsule)	Quantity per mL (mg)
Amprenavir	50	150	15
TPGS			
PEG 400			
Propylene glycol			
Acesulfame potassium			
Saccharin sodium			
Sodium Chloride			
Artificial grape bubble gum flavor			
Natural Pepperiment flavor			
Menthol			
Citric acid, anhydrous			
Sodium citrate dihydrate			
Solution of NaOH/HCl			
Total Fill Weight			

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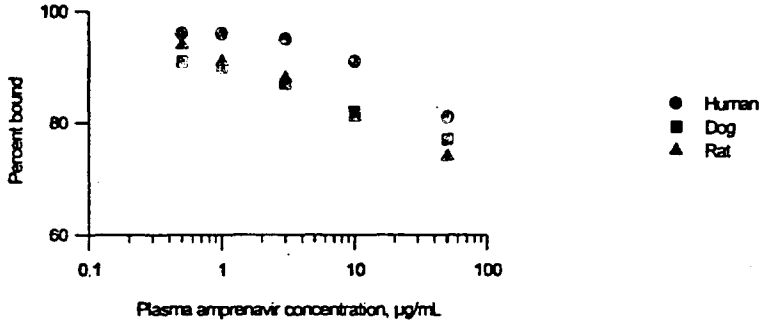
VI. IN VITRO STUDIES

Title: Plasma protein binding and erythrocyte partitioning in rats, dogs and humans with 141W94. [Volume 6.18]

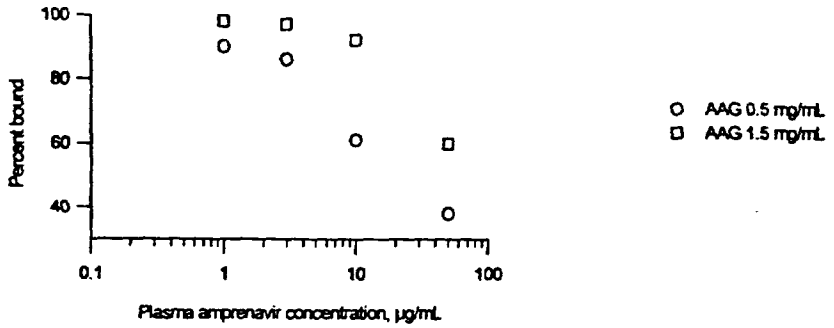
Protein binding:

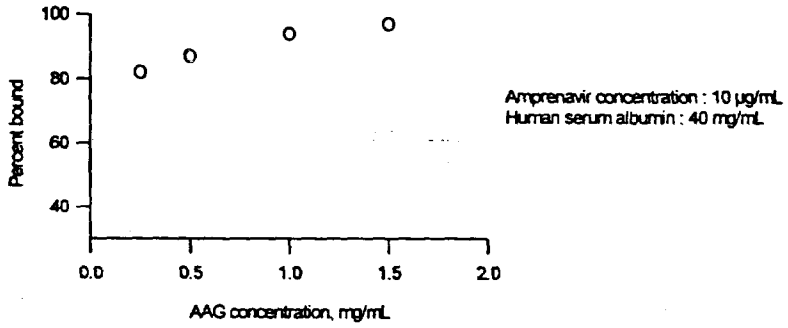
Plasma protein binding characteristics of amprenavir were examined at five concentrations (0.5, 1, 3, 10 and 50 µg/mL) of amprenavir in human, rat, and dog plasma using the equilibrium dialysis method. The clinically relevant concentration range is 0.1 to 10 µg/mL. ^{14}C-amprenavir was mixed with non-radiolabeled amprenavir to achieve concentrations mentioned above. In a pilot study, the Applicant determined that equilibrium was reached in 3 hours after incubation at 37° C. Plasma samples were dialyzed against 0.14 M phosphate buffer (pH 7.4) for 3 hours. At the end of dialysis, buffer and plasma samples were counted for total radioactivity and the protein bound fraction was calculated as $(C_{plasma} - C_{buffer})/C_{plasma}$.



The results of this study indicate that protein binding is concentration dependent in the range 0.5 – 50 µg/mL. However, over the clinically relevant concentration range of < 10 µg/mL, there is little change in protein binding. In human plasma, protein binding was 96%, 96% and 95% at 0.1, 1 and 3 µg/mL, respectively. At 10 µg/mL, the protein binding was species dependent and averaged 91, 82 and 81% in human, dog and rat plasma, respectively.

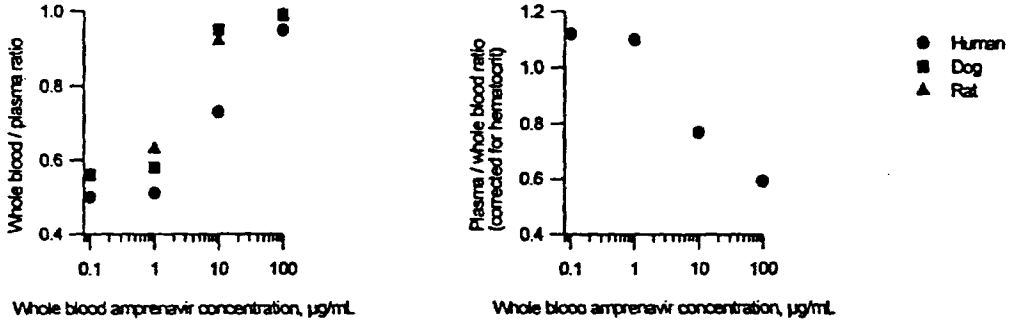
Protein binding was further characterized by incubating amprenavir with α1-acid glycoprotein (AAG) alone and with human serum albumin. The results from these experiments (shown below) indicate that amprenavir has a higher affinity for α1-acid glycoprotein when compared to albumin.





Erythrocyte partitioning:

The red blood cell partitioning of amprenavir was examined at concentrations of 0.1, 1, 10 and 100 µg/mL. ^{14}C-amprenavir was incubated in human, dog and rat whole blood at concentrations mentioned above. After a 3-hour incubation period, 1 mL of whole blood and 1 mL of plasma were analyzed for radioactive content and whole blood / plasma concentration ratios were obtained (left panel).



To explain the observations reported by the Applicant, this reviewer calculated the plasma / whole blood ratio (correction was applied for hematocrit). These data (values greater than 1 are theoretically not possible) indicate that at higher concentrations, as fraction of drug unbound to plasma protein increases, amprenavir partitions into red blood cells.

Agenerase NDA 21-007&21-039
Vijay Tammara
Prabhu Rajagopalan

Title: Identification of the cytochrome P450 isozymes involved in the metabolism of 141W94 [Volume 6.18].

The Applicant conducted studies with pooled human liver microsomes and microsomes that contained cDNA-expressed human cytochrome P450 3A4, 1A2 and 2D6 to identify the enzymes involved in the metabolism of amprenavir. Approximately 20 μM of ^{14}C-amprenavir was incubated with pooled human liver microsomes in phosphate buffer containing NADPH in the presence of known inhibitors for 10 or 45 minutes. Appropriate control (NADPH without inhibitor) incubations were also run. The results for ten minute incubations are tabulated below:

CYP enzyme	Inhibitor (concentration)	% amprenavir metabolized	% inhibition
	Control	19.4	
3A4	Troleandomycin (50 μM)	9.8	49.5
1A2	Furafylline (20 μM)	19.7	0
	Control	17.1	
2E1	Diethyldithiocarbamic acid (10 μM)	13.8	19.3
	Control	13.5	
2C19	S-mephenytoin (250 μM)	12.1	10.4
2C19	S-mephenytoin (20 μM)	16.2	-
2C9	Sulfaphenazole (20 μM)	16.4	-
	Control	15.0	
2D6	Quinidine (15 μM)	13.5	10.0

The results for 45 minute incubations are tabulated below:

CYP enzyme	Inhibitor (concentration)	% amprenavir metabolized	% inhibition
	Control	38.0	
3A4	Troleandomycin (50 μM)	21.3	43.9
	1-aminobenzotriol	1.0	97.4
	Control	39.5	
3A4	Ritonavir (5 μM)	3.0	92.4
	Ritonavir (20 μM)	2.4	93.9
	Ketoconazole (5 μM)	20.3	48.6
	Ketoconazole (20 μM)	8.3	79.0

In the presence of known specific inhibitors of CYP3A4, the *in vitro* metabolism of amprenavir is blocked by 44 to 94%. These results indicate that amprenavir is metabolized by CYP3A4. Dr. Collins points out the concentration of ketoconazole used in the above study is greater than the concentration generally used in this type of study. It is possible that amprenavir is also metabolized by an unknown cytochrome P450 enzyme. In the presence of inhibitors of CYP2D6 and 2E1, the metabolism of amprenavir was inhibited to a lesser extent (10 to 20%). The presence of inhibitors of CYP2C19, 2C9 and 1A2 did not have any effect on the metabolism of amprenavir. Further, it was observed that less than 2% is metabolized when amprenavir is incubated with cDNA-expressed CYP1A2 and 2D6 microsomes and 7 to 28% is metabolized when incubated with two different types of cDNA expressed CYP3A4 microsomes. These results support previous observations in human liver microsomes.

Additional experiments conducted by the Applicant revealed that amprenavir does not inhibit the activity of uridine glucuronyltransferase (as measured by formation of α-naphthyl glucuronide from α-naphthol).

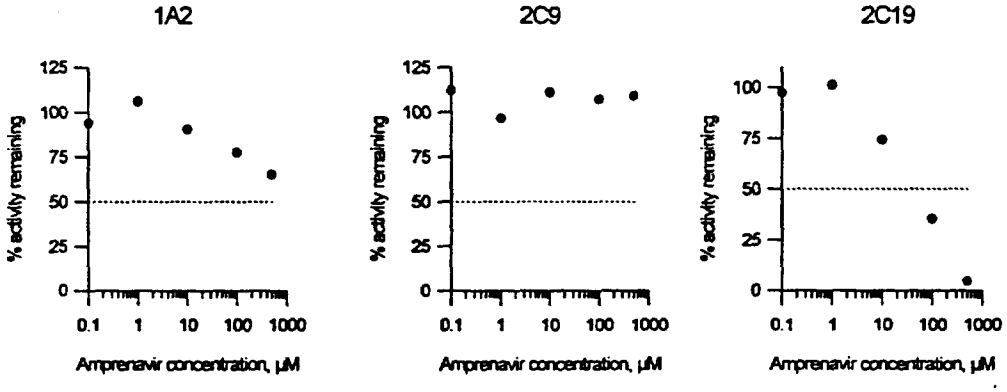
The results of the above *in vitro* studies indicate that CYP3A4 is the cytochrome P450 enzyme involved in the metabolism of amprenavir.

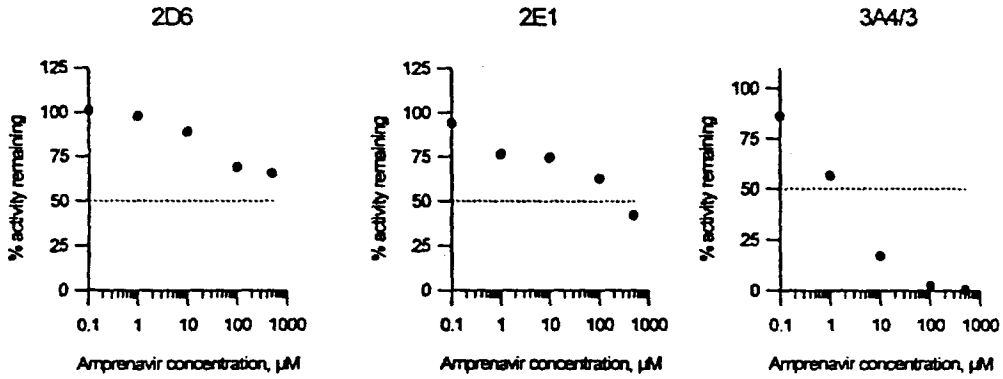
Title: Inhibition of human microsomal cytochrome P450 isozymes by 141W94 [Volume 6.19].

The inhibitory effect of amprenavir on human cytochrome P450 1A2, 2C9, 2C19, CD6, 2E1 and 3A4 were examined in this study. Details on the biochemical reaction monitored for each of the six CYP450 enzyme are provided in the following table.

CYP enzyme	Reaction monitored	Positive control
1A2	7-ethoxyresorufin O-deethylation	α-naphthoflavone
2C9	Tolbutamide methyl hydroxylation	Sulfaphenazole
2C19	S-mephenytoin 4-hydroxylation	Tranylcypromine
2D6	Dextromethorphan O-demethylation	Quinidine
2E1	p-Nitrophenol 3-hydroxylation	Diallyldisulfide
3A4	Erythromycin N-demethylation	Troleandomycin

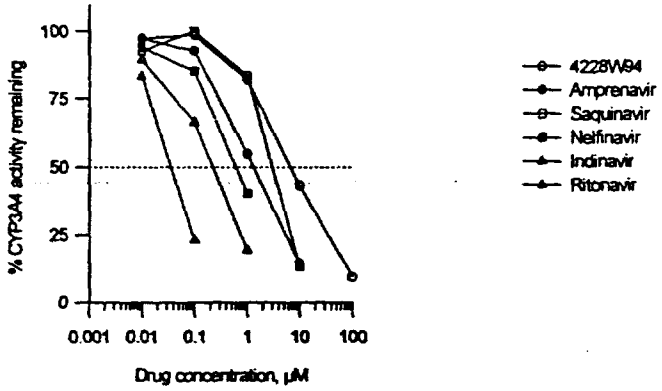
According to the Applicant, the substrate concentrations in the above assay were approximately equal to predetermined Km values. Inhibition of enzyme activity was determined at five concentrations of amprenavir 0.1, 1, 10, 100 and 500 μM. The clinical relevant amprenavir concentration range is 0.1 to 10 μg/mL (0.2 to 20 μM). Appropriate positive controls (as mentioned in the table) were used in this study. Percent enzyme inhibition was determined at each concentration and IC_{50} values were obtained from the following plots.





Amprenavir had little or no inhibitory activity against CYP1A2, 2C9 and 2D6 and the in vitro IC_{50} with respect to these three enzymes is greater than 500 µM. The IC_{50} values for inhibition of CYP 2E1, 2C19 and 3A4 activity were 280 µM, 47 µM and 1.4 µM, respectively. In a separate study, the Applicant had determined that the Ki value for amprenavir as a competitive inhibitor of erythromycin N-demethylation is 0.64 µM.

The Applicant performed an additional study with amprenavir, other approved protease inhibitors and compound 4228W94. In this study, the inhibition of erythromycin N-demethylation was examined in the presence of 0.01, 0.1, 1, 10 and 100 µM concentration of protease inhibitors. The results from this comparison study are shown below.



The IC_{50} for CYP3A4 inhibition was estimated to be 0.0372, 0.218, 0.675, 1.31, 3.08 and 7.06 µM for ritonavir, indinavir, nelfinavir, amprenavir, saquinavir and 4228W94, respectively.

These *in vitro* studies indicate that it is unlikely that amprenavir will inhibit CYP1A2, 2C9 and 2D6 enzymes and alter the pharmacokinetics of drugs metabolized by these enzymes. At clinically relevant concentrations, amprenavir does not have any effect on CYP2E1. Amprenavir has the potential to alter the pharmacokinetics of drugs metabolized by CYP3A4 and to a lesser extent pharmacokinetics of drugs metabolized by CYP2C19.

VII. PHARMACOKINETICS

Title: A Study to Evaluate the Bioavailability of a Soft Gelatin Capsule (Formulation No. CEN01A1) of Amprenavir Relative to the ——— Capsule (Formulation No CCM01A1) and the Effects of Food upon the Bioavailability of the Soft Gelatin Capsule [PROA1004; ———].

Background: The sponsor used 150-mg amprenavir ——— capsules in initial Phase I studies. However, this formulation was not satisfactory for use on a large scale and required storage under refrigerated conditions. To solve these problems, the sponsor developed a soft gelatin capsule, which is stable at room temperature and utilizes ——— amprenavir. Further, ——— amprenavir is soluble in TPGS (d–alpha tocopherol polyethylene glycol 1000 succinate), potentially enhancing the bioavailability of the compound. Thus, this study was designed to determine the bioequivalence of soft gelatin and ——— capsules of amprenavir. The sponsor used this opportunity also to evaluate the effect of food on the pharmacokinetics of amprenavir using soft gelatin capsules.

The primary objective of this study was to assess the bioequivalence of a soft gelatin capsule of amprenavir relative to the ——— capsule. The secondary objective was to evaluate effect of food on the pharmacokinetics of amprenavir using soft gelatin capsules.

Study Design: This was a Phase I, single–center, open–label, randomized, balanced, three–period, single dose, cross–over study conducted in 18 HIV–1 infected subjects.

Treatment 1: four 150-mg ——— amprenavir capsules (under fasting condition)
Treatment 2: four 150-mg soft gelatin amprenavir capsules (under fasting condition)
Treatment 3: four 150 mg soft gelatin amprenavir capsules (under fed condition, Standard FDA high fat breakfast).

Each treatment was separated by a seven-day washout.

Subjects: A total of 18 HIV-infected patients (3F; 15M; mean age: 32 years; mean weight: 72 kg) participated and completed this study.

Formulations: 150 mg capsules of amprenavir ——— capsule, batch number CAP 5N2700); amprenavir —— (soft gelatin capsules, batch number CAP 5P2740) were used in this study.

RESULTS:

<u>Pharmacokinetic Data Analysis</u>: Pharmacokinetic parameters were obtained by noncompartmental methods. The log-transformed pharmacokinetic parameters were statistically analyzed by the sponsor using Proc Mixed in SAS (ANOVA) for a three period crossover to account for period, sequence, and treatment (fixed effects) and subject within sequence (random effect) in the final model. This reviewer performed the two one-sided t-test and calculated the 90% CI for Cmax and $AUC_{0-\infty}$ for treatment 1 Vs 2 and treatment 2 Vs 3 using WinNonLinPro® Software. The results obtained by the reviewer are in agreement with those reported by the sponsor.

The mean plasma concentration time profiles are presented in Figure 1 and pharmacokinetic parameters for individuals are presented in Table 1. The mean pharmacokinetic parameters for all treatments are presented in the following table:

Treatment	$AUC_{0-\infty}$ (μg*hr/mL)				C_{max} (μg/mL)				T_{max} (hr)
	Mean ± SD	GM	Ratio (2/1 or 3/2)	90 % CI (p-value)	Mean ± SD	GM	Ratio (2/1 or 3/2)	90% CI (p-value)	Mean ± SD
1 ——— (Fasted)	10.4 ± 4.7	9.3	–	–	3.7 ± 1.8	3.3	–	–	1.5 ± 0.5
2 Soft Gel (Fasted)	10.7 ± 4.7	9.6	1.03	0.92, 1.14 (0.67)	4.4 ± 1.9	4.1	1.25	1.03, 1.53 (0.065)	1.0 ± 0.5
3 Soft Gel (Fed)	9.8 ± 6.3	8.3	0.86	0.78, 0.96 (0.24)	3.1 ± 1.6	2.8	0.68	0.55, 0.82 (0.002)	1.8 ± 0.8

The geometric least–squares mean ratios and 90% confidence intervals indicate that four 150- mg amprenavir ——— capsules are bioequivalent to four 150-mg amprenavir soft gelatin capsules in terms of $AUC_{0-\infty}$, but not in terms of Cmax. The modest increase in mean Cmax (by 19%) is explained by the lower Tmax, indicating a faster rate of absorption following soft gelatin capsule administration. This increase in Cmax may not have clinical relevance as ——— capsules were not studied in the pivotal clinical studies. The soft gel formulation used in this study is used in clinical trials but is not the to-be-marketed formulation. However, a bioequivalence study was conducted to link to-be-marketed formulation and clinically tested formulation and is discussed later (study PROA 1010).

Food effect: The results indicated that administration of the soft gelatin capsule with food affected the rate of absorption (mean Cmax decreased by 32% and mean Tmax prolonged by 0.8 hrs (80%)) significantly, and resulted in a 14% decrease in $AUC_{0-\infty}$. Dose-ranging and phase III studies of efficacy and safety were conducted in patients without dosing restrictions relative to food consumption.

Safety: All three treatments were well tolerated and no serious adverse events were reported.

In conclusion, soft gelatin and ——— capsules of amprenavir are bioequivalent in terms of $AUC_{0-\infty}$, but not in terms of Cmax. Further, soft gelatin capsules resulted in a faster rate of absorption as evidenced by shorter Tmax and higher Cmax. Food affected the absorption rate significantly and produced a small decrease in the extent of amprenavir absorption from the soft gelatin capsules. Amprenavir is well–tolerated when administered to HIV–1 infected subjects at single doses of 600 mg with or without food.

Title: A Phase I, Open–Label, Randomized, Balanced, Three Period, Cross–over Study to Assess the Bioequivalence of a New 150-mg Soft Gelatin Amprenavir (141W94) Capsule With a ——— ——— to the Original ——— 150-mg Soft Gelatin Capsule and to Assess the Effect of Food Upon the Oral Bioavailability of the New Capsule in Healthy Male Subjects [PROA1010, NDA 21007; Vol. 3.1].

Agenerase NDA 21-007&21-039
Vijay Tammara
Prabhu Rajagopalan

Background: In Phase II dose ranging studies and in phase III adult efficacy trials, the sponsor used 150-mg amprenavir soft gelatin capsules which contained [redacted] of Vitamin E derivative, known as TPGS (d-alpha tocopherol polyethylene glycol 1000 succinate), to [redacted] of amprenavir. However, a new, more stable and less soluble [redacted] of drug substance was discovered necessitating reformulation. Thus, the sponsor replaced the original 150- and 200-mg soft gelatin capsules in phase III adult efficacy trials with a new soft gelatin capsules with a [redacted] Since Phase III adult trials included both original and new soft gelatin capsules, a study had to be conducted to assess the bioequivalence between the original and new soft gelatin capsules of amprenavir. Thus, this study was designed to determine the bioequivalence of new soft gelatin and original soft gelatin capsules of amprenavir. This new soft gel capsule formulation is the to-be-marketed formulation and is also used in the pivotal clinical trials, replacing the original soft gelatin capsules. The sponsor also used this opportunity to evaluate the effect of food on the pharmacokinetics of amprenavir using new soft gelatin capsules.

The primary objective of this study was to assess the bioequivalence of the new 150-mg soft gelatin amprenavir capsule formulation with a [redacted] relative to the original [redacted] 150-mg soft gelatin amprenavir capsule formulation. The secondary objectives of the study were to assess the effect of food on the oral bioavailability of the new 150-mg soft gelatin amprenavir capsule and to evaluate potential racial differences in amprenavir pharmacokinetics among Blacks and Whites.

Study Design: This was a Phase I, single-center, open-label, randomized, balanced, three-period, single dose, cross-over study conducted in 36 healthy HIV-seronegative male subjects.

Treatment 1: eight 150-mg original soft gelatin amprenavir capsules ([redacted] , under fasting condition; 1200 mg of amprenavir)

Treatment 2: eight 150-mg new soft gelatin amprenavir capsules ([redacted] under fasting condition; 1200 mg of amprenavir)

Treatment 3: eight 150-mg new soft gelatin amprenavir capsules ([redacted] ; under fed condition, Standard FDA high fat breakfast; 1200 mg of amprenavir).

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

Subjects: A total of 39 healthy male subjects (14 Blacks, 25 Whites; mean age: 29 years; mean weight: 77 kg) participated in this study. Each of the subjects completed at least one of the three treatments and thirty-eight completed two out of three treatments. Only 36 completed all three treatments.

Formulations: 150-mg original soft gelatin capsules of amprenavir ([redacted] batch number BIN SF046592) and 150-mg new soft gelatin capsules of amprenavir ([redacted] ; batch number BIN SF060608) were used in this study.

RESULTS:

Pharmacokinetic Data Analysis: Pharmacokinetic parameters were obtained by noncompartmental methods. The log-transformed pharmacokinetic parameters were statistically analyzed by the sponsor using Proc Mixed in SAS (ANOVA) for a three period crossover to account for period, sequence, race, and treatment (fixed effects) and subject within sequence (random effect) in the final model. The sponsor included the pharmacokinetic data from all 39 subjects in the analysis. This reviewer reanalyzed the data excluding the three subjects that did not receive all the three treatments. One subject dropped out after receiving treatment 1 (not related to drug), another subject withdrew consent after receiving two treatments. The third subject was a protocol violator as he tested positive for opiates in the drug screen prior to his third dosing.

This reviewer performed the two one-sided t-test and calculated the 90% CI for Cmax and $AUC_{0-\infty}$ for treatment 1 Vs 2 and treatment 2 Vs 3 using WinNonLinPro® Software. The results obtained by the reviewer are in agreement with those reported by the sponsor.

The mean plasma concentration time profiles are presented in Figure 2 and pharmacokinetic parameters for individuals are presented in Table 2. The mean pharmacokinetic parameters for all treatments are presented in the following table:

Treatment	$AUC_{0-\infty}$ (µg*hr/mL)				C_{max} (µg/mL)				T_{max} (hr)
	Mean ± SD	GM	Ratio (2/1 or 3/2)	90 % CI	Mean ± SD	GM	Ratio (2/1 or 3/2)	90% CI (p-value)	Mean ± SD
1 Original soft gel Fasted (n=36)	30.1 ± 10.4	28.4	–	–	9.3 ± 2.5	8.9	–	–	1.3 ± 0.5
2 New soft gel fasted (n=36)	28.1 ± 10.2	26.6	0.94	0.87, 1.01	9.8 ± 2.8	9.4	1.06	0.94, 1.17	1.1 ± 0.6
3 New soft gel fed (n=36)	21.7 ± 11.8	19.9	0.75	0.70, 0.81	6.3 ± 3.0	5.7	0.61	0.54, 0.67	1.5 ± 0.7

Statistical analyses indicate that eight 150-mg amprenavir original soft gelatin capsules (containing — -- — are bioequivalent to eight 150-mg amprenavir new soft gelatin capsules (containing ———). The 90% confidence intervals for $AUC_{0-\infty}$ and Cmax were within —— and no difference in the mean Tmax for the original and new formulations was observed.

Food effect: The results indicated that administration of the amprenavir soft gelatin capsules with food affected the rate and extent of absorption (mean Cmax decreased by 40%, mean Tmax prolonged by 0.4 hrs (36%) and mean $AUC_{0-\infty}$ decreased by 25%). These decreases were statistically significant and may have clinical significance. Dose-ranging and phase III studies of efficacy and safety were conducted in

patients without dosing restrictions relative to food consumption. However, it is recommended that the high fat meal should be avoided when administering amprenavir.

Ethnic Differences: The mean plasma concentration time profiles reflecting ethnic differences are presented in Figure 3 and pharmacokinetic parameters for individuals by treatment are presented in Table 3. The mean pharmacokinetic parameters for all treatments are presented in the following table:

Race		Tmax (h)	Cmax (µg/mL)	$AUC_{0-\infty}$ (µg*h/mL)	CL/F (mL/min)
Blacks (n=14)	Mean	1.3	8.5	26.0	924.1
	SD	0.7	3.1	13.7	363.1
	Geo.Mean	1.1	7.9	23.5	850.6
Whites (n=22)	Mean	1.3	8.3	26.9	840.7
	SD	0.6	3.2	9.6	293.0
	Geo.Mean	1.2	7.7	25.3	791.5
B/W	GM Ratio	0.92	1.03	0.93	1.08
	p-value		0.48	0.48	0.47

There were no statistically significant differences in the $AUC_{0-\infty}$, Cmax, and CL/F for amprenavir in Blacks compared to Whites.

Safety: All three treatments were well tolerated and no serious adverse events were reported. The most common drug–related events were nausea and oral numbness (which occurred somewhat more frequently on the fasted arms, as opposed to the fed arm).

In conclusion, the new 150 mg soft gelatin capsule formulation containing [redacted] is bioequivalent to the original 150 mg soft gelatin capsule formulation containing [redacted]. Food affected the rate and extent of absorption of new soft gelatin capsules and may have clinical significance. Hence, it is recommended that the high fat meal should be avoided when administering amprenavir. There were no statistically significant differences in the $AUC_{0-\infty}$, Cmax, and CL/F for amprenavir, respectively, in Blacks compared to Whites.

Title: A Phase I, Open–Label, Randomized, Balanced, Three Period, Cross–over Study to Assess the Oral Bioavailability of the New 50 and 150 mg Soft Gelatin Capsules Relative to the New Amprenavir Oral Solution in Healthy Male Subjects [PROA1011; NDA 21007; Vol. 3.3].

Background: The sponsor developed a new 50-mg soft gelatin capsule and a new oral solution (15 mg/mL) as 150-mg soft gelatin capsule was not suitable for children and adults who have difficulty swallowing solid medications. The 50-mg soft gelatin capsule is a scaled version of the 150-mg gelatin capsule and has the same [redacted] content. The new 50 mg soft gelatin capsule, together with a new oral solution for younger children, who are unable to take solid medication, will be used in the Phase III efficacy trial (Study PROAB3004) in children. Thus, a study had to be conducted to assess the oral bioavailability of the new 50-mg capsule relative to the 150-mg capsule and the new 15 mg/mL oral solution relative to the new 50-mg soft gelatin capsule. All these formulations are to-be-marketed

formulations. This study was designed to determine the bioequivalence of new 50-mg soft gelatin capsules and oral solution relative to the 150-mg soft gelatin capsules of amprenavir.

The primary objectives of this study were to assess the bioequivalence of the new 50-mg soft gelatin capsule relative to the new 150 mg soft gelatin capsule of amprenavir; to assess the oral bioavailability of the new 15 mg/mL oral solution relative to the new 50-mg soft gelatin capsule; and to evaluate the tolerability and pharmacokinetics of amprenavir when administered as an oral solution. The secondary objectives of this study were: to assess the oral bioavailability of the new 15 mg/mL oral solution relative to the new 150-mg soft gelatin capsule and to evaluate potential racial differences in amprenavir pharmacokinetics among Blacks and Whites.

Study Design: This was a Phase I, single–center, open–label, randomized, balanced, three–period, single dose, cross–over study conducted in 24 healthy HIV–seronegative male subjects.

Treatment 1: four 150-mg new soft gelatin amprenavir capsules [redacted], under fasting condition; 600 mg of amprenavir)
Treatment 2: twelve 50-mg new soft gelatin amprenavir capsules [redacted] under fasting condition; 600 mg of amprenavir)
Treatment 3: 40 mL of the new 15 mg/mL amprenavir oral solution, [redacted] under fasting condition; 600 mg of amprenavir).

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

Subjects: A total of 29 healthy male subjects (12 Blacks, 17 Whites; mean age: 28 years; mean weight: 80.7 kg) participated in this study. Each of the subjects completed at least one of the three treatments and 26 completed two out of three treatments. Only 24 completed all three treatments.

Formulations: 150-mg original soft gelatin capsules of amprenavir [redacted] batch number BIN SF060608), 50-mg new soft gelatin capsules of amprenavir [redacted]; batch number BIN 031632), and 15 mg/mL oral solution of amprenavir [redacted] batch number BIN A97B123) were used in this study.

RESULTS:

Pharmacokinetic Data Analysis: Pharmacokinetic parameters were obtained by noncompartmental methods. The log-transformed pharmacokinetic parameters were statistically analyzed by the sponsor using Proc Mixed in SAS (ANOVA) for a three period crossover to account for period, sequence, race, and treatment (fixed effects) and subject within sequence and residual error (random effects) in the final model. The sponsor included the pharmacokinetic data from all 29 subjects in the analysis. This reviewer reanalyzed the data excluding the five subjects that did not receive all the three treatments. One subject dropped out after receiving treatment 1 (not related to drug), another subject withdrew consent after receiving treatment 2, and three subjects were withdrawn because of positive drug screen results (for marijuana, alcohol, and cocaine metabolites) prior to their second or third dosing. This reviewer performed the two one-sided t-test and calculated the 90% CI for Cmax and $AUC_{0-\infty}$ for treatment 1 Vs 2, treatment 2 Vs 3 and treatment 1 Vs 3 using WinNonLinPro® Software. The results obtained by the reviewer are in agreement with those reported by the sponsor.