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Application Number 21-007
21-039

MEDICAL REVIEW(S)

NDA 21-007
NDA 21-039

NDA 21-007 submitted: 16 Oct 98
NDA 21-039 submitted: 7 Dec 98
Review completed: 15 Apr 99
Revisions completed: 14 Jul 99

Medical Officer's Review - New Molecular Entity

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

Drug: Chemical: (3S)-tetrahydro-3-furyl N-((1S,2R)-3-(4-amino-N-isobutylbenzenesulfonamido)-1-benzyl-2-hydroxypropyl) carbamate
Generic: amprenavir
Trade: Agenerase™
Other: 141W94

Route: Oral

Dosage forms: Capsule, 50 mg, 150 mg
Oral Solution, 15 mg/ml

Proposed indication: AGENERASE (amprenavir) in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection

Related INDs: [redacted]

Related documents: Minutes of meetings:
13 Nov 96: End of Phase II meeting
21 Feb 97: Advisory Committee meeting (closed session)
27 Apr 98: Pre-NDA meeting

Major amendments:

28 Oct 98: Amendment: 24-Week Efficacy Update
16 Nov 98: Amendment: Pediatric Study Reports
20 Nov 98: Amendment: Response to Information Request
22 Dec 98: Amendment: Updated Efficacy Data (follow-up data)
23 Dec 98: Amendment: Safety Update
28 Jan 99: Amendment: Response to Information Request
1 Feb 99: Amendment: Expanded Access Study data

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I. Summary

Agenerase™ (amprenavir) is the fifth HIV protease inhibitor for the treatment of HIV infection to be submitted to the FDA for accelerated approval under 21CFR Subpart H (accelerated approval regulations). The NDA, (submitted 15 Oct 98) and subsequent Amendments were reviewed. The clinical portion of the submission contains information from 30 studies in more than 1900 adults and 140 children (Appendix 1) that provides data on the safety and efficacy of amprenavir on HIV-1 RNA levels and CD4 lymphocyte counts, surrogate endpoints that are reasonably likely to predict clinical benefit in HIV-infected patients. The applicant has requested accelerated approval of amprenavir for the indication: "AGENERASE (amprenavir) in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection".

Dose-escalation, phamacokinetic studies and phamacodynamic modeling were used in dose selection. In a dose-escalation study (PROA 1002), amprenavir monotherapy was administered at total daily doses of 600-2400 mg/day for 4 weeks. In this study, amprenavir provided the highest antiviral activity at daily doses of 2100 mg and 2400 mg, and at these doses amprenavir (APV) had an acceptable safety profile. Data on food effects showed reduced bioavailability of APV with a high-fat meal. The 1200 mg BID dose was chosen because a greater proportion of subjects receiving this dose were expected have trough concentrations of amprenavir at or above the EC_{90}, compared to lower doses. Higher doses were not considered because large increments of dose would be required to produce small decreases in circulating HIV RNA.

Two principle efficacy studies are being conducted; 24-week data were used to evaluate efficacy. Study 3001 is an ongoing, randomized, double-blind placebo-controlled comparison of APV *vs* placebo (PLA) on a background of zidovudine/lamivudine (ZDV/3TC) in relatively healthy (median, 422 CD_4 cells/mm^3), antiretroviral therapy-naive individuals. This study showed that APV was superior to PLA in reducing plasma HIV RNA to <400 copies/ml (assay limit of detection) at 24 weeks.

Study 3006 is an open-label, 48-week equivalence-design study comparing APV *vs* indinavir (IDV) on a background of nucleosides in relatively healthy (median,, 400 CD_4 cells/mm^3), antiretroviral-experienced, protease inhibitor-naive individuals. Analysis of 24-week data from this study showed that a higher proportion of IDV recipients remained below the assay limit of plasma HIV RNA detection, compared to APV. A large part of this difference is explained by a higher proportion of IDV recipients who remained on assigned therapy at this time, compared to those randomized to APV.

In the evaluation of safety, there were no amprenavir-related deaths. The primary amprenavir-associated toxicities were rash, gastrointestinal toxicity and paresthesia. Rash, although usually mild or moderate, can be severe (Grade 3-4), and can include Stevens Johnson syndrome. Gastrointestinal toxicities (nausea, vomiting, diarrhea, abdominal pain), together with rash, were important because they resulted in the premature discontinuation of amprenavir therapy in a relatively high proportion of recipients. Perioral and, less commonly, peripheral paresthesias were experienced by a significant minority of those receiving amprenavir treatment.

II. Regulatory Background and Materials Reviewed

The initial IND for amprenavir (originally designated as 141W94) was submitted to the FDA on 20 Jan 95. The End of Phase 2 meeting with the FDA was held on 13 Nov 96. A closed session Advisory Committee meeting was held on 21 Feb 97. At this time, the development plan for amprenavir was discussed, as was the use of durable suppression of plasma HIV RNA as the primary endpoint for Phase 3 studies. The pre-NDA meeting was held on 27 Apr 98. The NDA was submitted on 15 Oct 98.

Major submissions examined during the course of this review included study reports pre-submitted to the IND and the NDA, the NDA submission (15 Oct 98), and the following amendments: 24-week efficacy update (28 Oct 98), pediatric study reports (16 Nov 98), a response to information request (20 Nov 98), updated efficacy data (22 Dec 98), safety update (23 Dec 98), and expanded access study data (1 Feb 99).

Please refer also to the following reviews:
Chemistry/Manufacturing Controls: Dr. George Lunn
Microbiology: Dr. Narayana Battula
Animal Pharmacology/Toxicology: Dr. Owen McMaster
Biopharmaceutics: Drs. Prabu Rajagopalan, Vijay Tamarra
Statistics: Dr. Greg Soon
Division of Scientific Integrity: A. El Hage

III. Summary of NDA clinical section

The clinical section of this application includes the study reports of two randomized, controlled Phase 3 clinical trials in HIV-infected adults, and 28 other studies containing PK and safety information; of these, three studies were conducted in children. Table 1 summarizes major features of the two phase 3 studies that were submitted to support short-term safety and efficacy of amprenavir.

Table 1. Phase 3 randomized trials in adults

	PROAB 3001	PROAB 3006
Population	N=232, antiretroviral-naive	N=504, antiretroviral-experienced
Design	randomized, double-blind, placebo controlled	randomized, open-label, equivalence to indinavir
Centers	13 US, 10 Europe	33 US, 11 Canada, 34 Europe and Australia
Treatment comparison	APV vs PLA (ZDV/3TC background)	APV vs IDV (NRTI's background)
Primary endpoint	% with HIV RNA < 400 copies/ml at 16 weeks	% with HIV RNA < 400 copies/ml at 16 weeks
Baseline demographics		
age, median	36	38
sex	89% male	81% male
race	75% Caucasian	72% Caucasian
HIV-RNA (log_{10} copies/ml)	4.7	3.9
CD4 cells/mm^3 (median)	422	400

Other studies providing supportive evidence are listed in Appendix 1. A total of 2095 subjects had been enrolled in studies and 1477 had been exposed to at least one dose of amprenavir (APV) as of 1 Sept 98.

IV. Safety and Efficacy in Antiretroviral Naïve Adults

Clinical Trial PROAB 3001 "A Phase III Trial to Evaluate the Safety and Antiviral Efficacy of 141W94 in Combination with RETROVIR and EPIVIR compared to RETROVIR and EPIVIR Alone in Patients with HIV Infection"

The clinical trial report is included in NDA 21-007/M003/Volume 5.9-5.16, submitted 31 Aug 98, and M005/Vol 7.1, submitted 28 Sep 98. This study report contains Week 16 efficacy and safety data. In addition, an efficacy update containing Week 24 data was submitted on 28 October 98. In the following review, the term "16-week data" will refer to information provided in the NDA submission, and "24-week data" will refer to data from the Week 24 update.

A. Design. This is an ongoing randomized, double-blind Phase 3 study in 232 HIV-infected adult (≥18 years) subjects that evaluates the efficacy and safety of amprenavir (APV) *vs* placebo (PLA) when used in combination with zidovudine (ZDV) and lamivudine (3TC). The study is being conducted at 23 centers, 13 in the US and 10 in Europe. Sixteen and 24 week data were submitted in support of this accelerated approval application. Forty-eight week data will be submitted in the traditional approval application.

1. Population. Eligible subjects were ≥18 yrs of age (13 yrs if permitted by local regulatory authorities) treatment-naive, with baseline HIV RNA copies/ml in plasma ≥ 10,000/ml , and CD_4 cells ≥ 200/mm^3.

2. Study therapy. Subjects were randomized 1:1 to receive APV (1200 mg BID) or PLA; all received ZDV (300 mg BID) and 3TC (150 mg BID).

3. Randomization and stratification. Subjects were stratified by HIV RNA (10000-30000, >30000-100000, >100,000 copies/ml).

4. Discontinuation of study medication. Enrolled subjects are to continue randomized therapy until all subjects complete 48 weeks unless they met a protocol-defined switch criterion, defined as two consecutive (within 3 weeks) plasma levels of HIV RNA ≥400 copies/ml at Wk 16 or thereafter, or progression to CDC Class C event after 4 weeks on study. Subjects who meet a switch criterion can choose one of six options: (1) continue randomized therapy; (2) switch to open-label APV; (3) add abacavir (ABC); (4) change nucleoside RT inhibitor(s); (5) add another approved protease inhibitor; (6) change to any other approved protease inhibitor.

5. Endpoints and analysis. The primary efficacy endpoint is antiretroviral activity, defined as the proportion of subjects having <400 HIV RNA copies/ml (Roche AMPLICORE HIV-1 MONITOR assay) at 16 weeks who did not progress to a CDC Class C event or death. Prior to the time this Phase 3 study was designed, efficacy endpoints had not been based on virological response. With the review of accelerated approval applications since the time this study was designed, the FDA has concluded that longer-term data provide a more adequate basis for a regulatory decision than the 16 week virological data originally submitted to the NDA from this study. During the course of the review, the Sponsor complied with the Agency's request to provide 24-week data from this study.

For purposes of analysis of the intent-to-treat population, subjects were considered treatment failures as follows: (i) virologic failure (HIV RNA ≥400 copies/ml), or clinical AIDS progression events, or death, (ii) those switching randomized therapy for adverse events or any other reason after randomization, (iii) those with insufficient data to demonstrate virologic success at 24 weeks, including withdrawal of consent, lost to follow-up, or withdrawal for protocol violations.

Secondary efficacy analyses included plasma HIV RNA and CD4 AUC measures, the proportion of subjects with plasma HIV RNA <50 copies/ml, HIV disease progression, and HIV reverse transcriptase and protease

inhibitor genotype and phenotype evaluations. Safety evaluation included adverse events and clinical laboratory values.

6. Study size. As initially designed, the study was to enroll 290 subjects. During the course of the study, a view developed in the clinical and patient communities that maintaining HIV RNA below the detection limit of Roche assay (lower limit of quantification, 400 copies/ml) was a useful, and perhaps the most appropriate, goal of therapy. This view, together with the recognition that three drugs were often required to reduce HIV RNA to undetectable levels, resulted in a shift in clinical management of HIV infection towards the use of three-drug regimens that included a protease inhibitor. Initial therapy with two nucleosides became less generally acceptable, and the protocol was therefore amended to reduce the sample size to 230 subjects.

B. Results. Study population and subject disposition

1. Study Population. A total of 232 patients were enrolled and 221 received study drug. Baseline characteristics are summarized by study treatment in Table 2.

Table 2. Baseline demographics by study treatment

Treatment (with 3TC/ZDV)	PLA	APV
No. randomized	116	116
Population	Intent-to-treat	Intent-to-treat
Age, No. (%) Median (min, max)	116 35.6 (18, 63)	116 35.9 (22, 62)
Sex, female male	13 103	13 103
Race, No. (%) White Black Asian Hispanic Other	 85 (73) 11 (9) 0 18 (16) 2 (2)	 89 (77) 14 (12) 1 (<1) 9 (8) 3 (3)
CDC Classification, No. (%) A: asymptomatic or lymphadenopathy B: symptomatic, not AIDS C: AIDS	 88 (80) 22 (20) 0	 87 (78) 20 (18) 5 (4)
HIV RNA (log_{10} copies/ml), No. Median (min, max)	114 4.740 (3.06, 6.31)	112 4.608 (3.61, 6.09)
Baseline HIV RNA (copies/ml) 400-<10000 10000-30000 >30000-100000 >100000 missing	 5 (4) 37 (32) 42 (36) 30 (26) 2 (2)	 5 (4) 37 (32) 47 (41) 23 (20) 4 (3)
CD_4 cells/mm^3, No. Median (min, max)	113 409.0	113 435.0

Comment: The treatment groups are balanced with respect to sex, race, CDC classification, and baseline efficacy outcome measures (HIV RNA, CD_4 cells).

2. Conduct of the study and disposition of subjects

a. Subject recruitment by country and site. The study was conducted in Europe and the US. The large majority (82%) of subjects were enrolled at US sites. The three largest sites were in the US, where 125/232 (54%) of subjects were enrolled. Subject enrollment at European sites included Germany, 14; Greece, 5; Norway, 4; Portugal, 8; Spain, 4; UK, 7. In general, enrollment in each country and at each site was balanced between treatment groups, although one large US center had a somewhat greater number of subjects

enrolled in the APV treatment group (23 APV, 13 PLA).

Comment: Concentration of enrollment at a few sites means that the conduct of the study at these sites can be expected to have a substantial impact on the study conclusions.

b. Protocol violations. These are summarized in Table 3.

Table 3. Protocol violations - inclusion/exclusion criteria		
Treatment (enrolled)	PLA (116)	APV (116)
No. not meeting all entry criteria (%)	5 (4)	4 (3)
Exclusion		
Treatment with immunomodulators	0	2
Neutrophils <1000	2	0
Platelets < 75000	2	0
Prior protease inhibitor therapy	0	1
Clinical diagnosis of AIDS	0	1
AST or ALT >2x ULN	1	0
Violation	12	10
Treatment assigned, but never exposed to study medication	7	4
Previous or ongoing clinical diagnosis of AIDS at baseline	0	5
Suspended administration of study treatment for >28 consecutive days	3	0
Not PI naive, or adding another PI during randomized phase	1	1
Wrong treatment medication taken	1	0

Comment: More placebo recipients (vs APV) were assigned to, but did not receive study treatment, and more APV recipients had a previous or ongoing clinical diagnosis of AIDS at baseline. These differences are small, and may have no significant impact on the study conclusions.

c. Study discontinuations. As summarized in the NDA amendment containing 24-week data, subjects discontinuing from the study by Week 16 and at Week 24 are summarized in Table 4.

Table 4. Subjects discontinuing from study at Week 16 and at Week 24, by treatment group (Intent to treat population)				
	Week 16		Week 24	
	PLA	APV	PLA	APV
No. randomized	116	116	116	116
No. treated	109	112	109	112
No. discontinued randomized therapy	11	33	96	57
Reason for study medication discontinuation				
AE	3	17	3	18
Consent withdrawn	3	5	7	7
Lost to follow-up	3	7	3	7
Met switch criteria			81	21
Other	2	4	2	4

Comment: At Week 16, there were disproportionately more study discontinuations in the APV than in the PLA treatment group, due to adverse events and loss to follow up. At Week 24, disproportionately more subjects in the AZT/3TC/PLA treatment group had met switch criteria (treatment failure: viral load ≥400 copies/ml) and had discontinued blinded study treatment. The implications of these differences will be discussed in the context of the efficacy analysis.

C. Results: Efficacy

During the course of the review, the FDA requested that the applicant submit all virology and CD_4 cell data, to include Week 24 data for all subjects. Week 24 data is the basis for the FDA analysis. For a more detailed

treatment of the FDA analysis of surrogate endpoints (HIV-RNA and CD_4 cell counts), please see the Statistical Review. Several points are summarized here.

1. Primary analysis. The FDA analysis examined the Week 24 HIV-1 RNA status, instead of the Week 16 data provided in the initial NDA submission. Treatment failures were subjects with a viral load ≥400 copies/ml, or a new CDC Class C event or who had discontinued the randomized treatment. Subjects with missing data were regarded as failures. The result of this analysis is shown in Table 5.

Table 5. Subjects remaining on randomize treatment at Week 24, and HIV RNA <400 copies/ml (missing regarded as failures)				
Randomized treatment	Amprenavir (N=116)	Placebo (N=116)	Difference, % (95% CI)	p-value*
<400 copies/ml	62 (53.4%)	13 (11.2%)	42.2 % (31.8, 52.7)	<0.001

*stratified Cochran-Mantel-Haenszel test

Subjects who at Week 24 were treatment failures, or were regarded as failures, are summarized in Table 6.

Table 6. Treatment failures, or regarded as treatment failures, by category and treatment group, Week 24		
	APV (N=116)	PLA (N=116)
Progressed to new CDC Class C event	0	0
On treatment Week 24 HIV-1 RNA		
Missing	0 (0%)	1 (0.9 %)
≥400 copies/ml	6 (5.2)	18 (15.5)
Discontinued randomized therapy by Week 24 due to		
Adverse events	17 (14.1%)	4 (3.3)
Virological rebound	9 (7.4)	54 (44.6)
Before taking any study medication	4 (4.3)	7 (6.0)
Consent withdrawn, Lost to follow-up, Protocol violation, Other	18 (15.5)	19 (16.4)

In the placebo group, treatment failures were most often due to virological rebound, that is, a confirmed rise in HIV RNA to above the assay limit of quantitation in a subject who had previously had undetectable HIV RNA. In the amprenavir group, treatment failures were most often due to adverse events.

2. Secondary endpoint, CD_4 cells/mm^3. The numbers of subjects remaining on randomized therapy at Week 24 reflect the disproportionately large numbers of PLA recipients who discontinued randomized treatment at Week 20. Median CD_4 responses through Week 24 are summarized in Table 7.

Table 7. CD_4 cells/mm. Responses from baseline, by treatment group and study week (Intent to treat population)								
	CD_4 response by Study Week:							
Study Week	baseline	2	4	8	12	16	20	24
PLA, N median/change	106 405	100 +37	101 +60	98 +73	95 +93	89 +49	89 +56	82 +69
APV, N median/change	109 448	101 +24	100 +37	91 +51	81 +63	75 +55	73 +72	72 +113

There is a rise in median CD_4 cell responses in both treatment groups in the first 24 weeks. The PLA response is somewhat variable over time is and difficult to interpret. The APV response shows a more consistent pattern, with a progressive rise over time. At Week 16, a similar 49-55 cell CD_4 response is seen in both treatment arms. The median Week 24 responses differ by 44 cells, and are numerically higher in the APV group than PLA. The analysis of CD4 cells over 24 weeks using an Area Under Curve Minus Baseline (AUCMB) shows mean changes of +38.8 cells for APV and +26.5 cells for PLA; the p-value= 0.174 suggests that the treatment effect as judged by CD_4 cell count is not significantly different.

3. HIV-associated conditions. Subjects developing HIV-associated conditions during the first 16 weeks of the study are summarized in Table 8.

Table 8. HIV associated conditions, by treatment group		
Event class	PLA	APR
Category C: AIDS Indicator Condition		
Number of subjects	1 (<1)	1 (<1)
Herpes simplex	1 (<1)	0
Kaposi's sarcoma (cutaneous)	0	1 (<1)

Comment: At Week 16, the numbers of subjects who had developed AIDS-defining Category C events are quite small in both treatment groups.

D. Results: Safety

The following is based on information provided in the of the initial study report, the Integrated Summary of Safety (Vol. 10.15) of the NDA, the 28 Oct 98 efficacy update, the 22 Dec 98 safety update, and the 28 Jan 99 Response to Information Request.

1. Deaths. There were no deaths in this study, through the latest safety information provided in the 23 Dec 98 Safety Update.

2. Serious adverse events. The following adverse events (Table 9) were tabulated from narrative case summaries provided in the sources cited above.

Table 9. Serious adverse events, by assigned study therapy and subject number

Subj No	Age/ Sex	Event	Grade	SAE Onset[1]	Notes
PLA					
1037	26 M	neutropenia	Gr 4	2 wks	study treatment continued, AE unresolved
1077	33 M	hypertriglyceridemia	Gr 4		Gr 3/4 hypertriglyceridemia at entry, on therapy, 3 mo p. last study drug
1139	54	neutropenia	Gr 4	24 wks	ZDV interrupted, later replaced with d4T
1144	33 M	septic phlebitis	hosp	7 wks	phlebitis 2° to heel ulcer
1162	42 M	stroke, hemiparesis	hosp	1 da	history of hypertension prior to entry
1167	40 M	anemia	G4/H	12 wks	also, pancytopenia
1170	28 M	pneumonia	hosp	0	did not initiate study regimen; responded to antibiotics
1177	69 M	syncope		44 wks	history of smoking, severe COPD
1233	31 M	neutropenia	Gr 4	20 wks	ZDV d/ced, treatment with o/l d4T, APV, ABC
1250	39 M	glucose incr	Gr 4	14 mo	history of diabetes; investigator attributed to insulin non-compliance
1365	29 M	neutropenia	Gr 3	1 mo	study meds interrupted
1378	63 M	trauma, Achilles tendon	hosp	1 yr	-
1400	39 M	neutropenia	Gr 4	19 wks	simultaneous sample: normal; considered spurious abnormality
1450	25 F	pregnancy, abortion	hosp	12 wks	pregnancy found at Wk 12, study meds discontinued, spont. abortion 4 wks later (at approx 3 mo gestation)
1458	44 M	AST/ALT elevation hemorrhoids	Gr 3 hosp	4.5 mo 5.5 mo	Hbs-Ag found to be +; invest: rel. to preexist HBV, poss. rel. to study med
APV					
1040	25 F	rash urticarial	Gr 3	10 da	preceded by nausea,vomiting,diarrhea, serious rash recurrence on rechall.
1084	33 M	SGOT incr	Gr 4	15 mo	asymptomatic elevation - treated through event - decr to Gr 1
1206	44 M	decr. hemoglobin	Gr 4	8 wks	investigator ascribed event to ZDV, but rationale not provided
1258	36 F	hyperglycemia, new onset	hosp	23 wks	nausea, dec appetite @Wk 20, worsening @ Wk 23, glucose 590; invest: rel to study drug
1293	26 M	depression	hosp	9 wks	SAE rel. to job loss, other probs
1360	41 F	granulocytopenia	Gr 4	33 wks	Investigator: related to study medication
1365	29 M	granulocytopenia	Gr 3	4 wks	investigator: considered AE possibly related to study medication
1400	39 M	granulocytopenia	Gr 4	19 wks	parallel WBC test :just below nl limit; ? lab or shipping error
1686	36 M	lymphoma	Gr 4	29 wks	prior axillary mass, enlarged on therapy, LN biopsy:positive for tumor
1688	33 M	hepatitis A, acute, AST/ALT incr	Gr 4/4	not stated	abd pain, fatigue, nausea, aches, fever, dark urine, light stools, icterus, Gr 4 AST/ALT/BILI

1697	51 M	anemia, hemolytic	hosp	12 wks	Hx:DM,incrBP,TB,hepatitis,smoking;Sx:brwn urine,depression, disorientation, incr LFTs/bili/LDH/CPK, fatty liver; investigator: "rel to study drug"
1739	38 M	vein thrombosis, R. leg	hosp	8+ wks	Hx: on maint. warfarin therapy for prior deep vein thrombosis, R. leg
1745	31 M	SOB, wheezing	hosp	4 wks	Hx: asthma. Sx: p.allergy shots. Restart study meds->recurr resp insuffic
1772	31 M	vomiting, drowsy, car accident	hosp	5 wks	Took carisoprodol and ——— 'concomitant meds) to relieve back pain, symptoms began 45 min later. Invest: rel. to study drugs and conmeds
1779	22 F	tubo-ovarian abscess	hosp	10 wks	resolved following laparotomy diagnosis and antibiotic treatment
1784	44 M	epigastric pain, burning, diarrhea	hosp	4 wks	Hx: MI. No relief w/nitroglycerine. EKG, troponin I (x3) tests neg. Recurr (x2)chest pain 35 wks later (3 wks p. study drug d/c) Enz, EKG neg. Invest: esophageal spasm
Open label (treatment failures, rolled over to open-label therapy)					
1079	26 M	SGOT/SGPT incr	Gr 4	37 wks	ZDV/3TC/PLAx16wks, then APV/ABC/3TC/d4Tor ddI/ACV, HAV inf dx'ed
1252	47 M	rash, maculopapular	Gr 3, hosp	25 wks	ZDV/3TC/PLAx23wks, then o/l APV/ABC/3TC/ZDV for 2wks. Rash accompanied by nausea, vomiting, fever to 105°F
1283	41 F	neutropenia, bronchitis	hosp	30 wks	ZDV/3TC/PLAx16wks, then APV/ABC/3TC/ZDVx14wks
1361	24 M	rash, maculopapular	Gr 2 hosp	17 wks	ZDV/3TC/PLA x 16 wks, then 8 days o/l APV. Diffuse, disseminated maculopapular rash began 8 days post o/l APV
1715	30 M	AST/ALT elevations	Gr 4	28 wks	APV/ZDV/3TC/x27 wks, then o/l APV/ZDV/3TC/1592 x 1 wk; Lab: HAV+, other eval in progress; investigator: "rel to study drug"
1790	50 M	anemia, recurrent	hosp	(4 wks) 22 wks	ZDV or d4T/3TC/PLAx19wks, Wk 20: o/l APV/d4T Wk 22: ABC added Investigator: recurr anemia was related to study drugs

[1]weeks after initiation of randomized therapy

The following serious events are noteworthy:

Rash, Gr 3/4 and/or serious. The primary APV-related serious adverse event recognized in this study is rash. There were no rashes in PLA recipients recorded as SAE's in this study during the time the subjects were on PLA. Of the three subjects having the SAE of rash, all had received APV for 8-14 days when rash occurred. Two such subjects (1252, 1361) had recently been rolled over from PLA to open-label therapy containing APV; one had also received open-label abacavir, which is known to cause rash. One subject (1040) was rechallenged with APV, and had a serious rash on rechallenge. In summary, there was a numerical excess of serious rash in APV recipients.

Anemia, Gr 3/4 and/or serious. There were three such cases in amprenavir recipients, and one in placebo. Of amprenavir recipients, subject 1697, a 51 year old male, was hospitalized for hemolytic anemia 12 weeks after initiation of APV; he had brown urine, increased LFTs, a fatty liver and the event was ascribed to APV.

Other cases in which anemia did not appear to be explained by hemolysis are: Subject 1206, a 44 year old male, developed grade 4 anemia 8 weeks after initiating APV; anemia was variably attributed by the investigator to APV or ZDV. Subject 1790, a 50 year old male, was randomized to PLA, but rolled over to an APV-containing regimen at Week 20, 2 weeks before anemia recurrence, which was attributed by the investigator to APV.

AST/ALT increased, serious. Subject 1084, a 33 year old male, had a Grade 4 AST elevation 15 months after initiation of APV. This event was asymptomatic, the patient was treated through the event, and AST decreased to Grade 1.

Hyperglycemia, serious/Gr 4. Subject 1258, a 36 year old female, was hospitalized with the new onset of hyperglycemia 23 weeks after initiating APV; the investigator attributed this event to APV.

3. Adverse events leading to permanent discontinuation of study drug. These are summarized through Week 16 in Table 10.

Table 10. Subjects permanently discontinuing study drug due to adverse event, through Week 16		
Event by system	PLA (n=109)	APV (n=113)

No. of subjects with AE, discontinuing drug	4 (4%)	17 (15%)
GI		
No of subjects (%)	2 (2)	13 (12)
nausea	1 (1)	12 (11)
vomiting	0	4 (4)
abdominal pain	1 (1)	2 (2)
diarrhea	1 (1)	2 (2)
abdominal discomfort	0	2 (2)
gaseous/flatulence/eructations	1 (1)	1 (1)
dyspeptic symptoms	0	1 (1)
loose stools	0	1 (1)
oral discomfort, pain	0	1 (1)
Blood and Lymphatic		
No of subjects	1 (1)	2 (2)
anemia	1 (1)	1 (1)
hemolytic anemia and hemolysis	0	1 (1)
Neurology		
No. of subjects	1 (1)	2 (2)
headaches	1 (1)	1 (2)
hypertonia	0	1 (1)
Skin		
No. of subjects	1 (1)	2 (2)
rashes	1 (1)	2 (2)
pruritus	0	1 (1)
Non-site specific		
No. of subjects	0	1 (1)
fatigue	0	1 (1)

Comment: Toxicities leading to permanent discontinuation of study drug during the first 16 weeks of the study and occurring disproportionately in APV recipients involved the gastrointestinal system (12 vs 2%) and included nausea (11 vs 1%), vomiting (4 vs 0%), diarrhea (2 vs 1%). Other events leading to study drug discontinuation during this time that were numerically more frequent in APV recipients vs PLA included skin rash, anemia and fatigue, although the numbers of these events were quite small.

4. More common adverse events. Clinical adverse events reported in ≥ 5% of subjects, and in equal or greater proportion of APV recipients than in controls (from the Response to Request for Information, 28 Jan 99) are summarized in Table 11.

Table 11. Adverse events, all grades, reported in ≥ 5% of subjects in equal or greater proportion of APV recipients than in controls

	PLA (N=109)	APV (N=113)
Adverse Event	Percent	Percent
Nausea	50	73
Vomiting	17	29
Diarrhea	25	25
Paresthesia		
oral/perioral	5	26
peripheral	3	5
Rash	6	25
Psychiatric		
depressive disorders	3	10
mood disorders	1	7
Infections		
ENT	6	8
viral respiratory	12	20
Fever	6	8
Musculoskeletal		
arthralgia/articular rheumatism	5	6

Comment: The more common adverse events occurring more frequently in APV recipients than in PLA, for which another explanation is not evident include GI events, paresthesias, rash, and psychatric events. The other events either have an alternate explanation (viral respiratory) or show no particular excess in APV recipients.

5. Laboratory events. Laboratory abnormalities, all grades (from the Response to Request for Information, 28 Jan 99), occurring more frequently in APV recipients are summarized in Table 12.

Table 12. Laboratory adverse events, all grades, reported in ≥ 1% of subjects in a greater proportion of APV recipients than in controls , by study treatment

	PLA (N=113)	APV (N=109)
Event	Percent	Percent
Hyperglycemia	29	37
Hypertriglyceridemia	22	36
Hypernatremia	6	11
Albumin increased	1	6
Hypercholesterolemia	3	4
Platelets decreased	0	3

6. Gr 3/4 laboratory events (through 1 Sept 98, 23 Dec 98 Safety Update) are summarized in Table 13.

Table 13. Grade 3/4 laboratory events, by study treatment

Lab abnormality	PLA	APV
ALT incr	3	5
AST incr	4	4
Triglycerides incr	3	2
Bilirubin incr	2	3
Glucose incr	2	1
Amylase incr	2	2
Neutrophils decr	9	9
Hemoglobin decr	2	1
WBC decr	1	1

Comment: Hyperglycemia and hypertriglyceridemia appear increased in APV recipients, *vs* controls. There was no disproportionate increase in severe laboratory adverse events in APV recipients.

E. Study Conclusions

1. Efficacy. The chief efficacy conclusion of the interim analysis of this study is that at Week 24, amprenavir was more effective than placebo (when both were given with 3TC/ZDV) in reducing plasma HIV-1 RNA to undetectable levels (<400 copies/ml; assay limit of quantification, 400 copies/ml). At Week 24, the FDA analysis showed that 53.4% of APV recipients had HIV RNA < 400 copies/ml, versus 11.2% for placebo, a difference of 42.2% (95% CI, 31.8, 52.7%). Thus this study provides convincing evidence that APV has activity against this HIV-1, and that APV adds benefit to approved therapy (ZDV/3TC).

The treatment groups were similar with regard to CDC Category C (AIDS indicator) events, with one occurring in each group. The CD4 response in both treatment groups showed a progressive increase over time. At Week 24, APV recipients had numerically higher CD_4 cell counts than did placebo recipients, but several factors, including the numbers of subjects who continued randomized treatment at Week 20, limit the interpretability of the significance of this finding.

This study is ongoing until the last-enrolled subject has completed 48 weeks of study participation. It is

anticipated that this study, when completed, will be submitted in support of traditional approval for amprenavir.

2. Safety. The safety conclusions of this study may be summarized as follows:

(a) There were no deaths. Information is available to 23 Dec 98 (safety update).

(b) There were disproportionately more premature study drug discontinuations in the APV (28%) than in the PLA (9%) treatment group.

(c) Disproportionately more subjects receiving APV discontinued study drug due to an adverse event (15%) than did PLA recipients (4%).

(d) Toxicities leading to permanent discontinuation of study drug during the first 16 weeks of the study and occurring disproportionately in APV recipients (vs PLA) involved the gastrointestinal system(12 *vs* 2%) and included nausea (11 *vs* 1%), vomiting (4 *vs* 0%), diarrhea (2 *vs* 1%), as well as other GI findings. Other events leading to study drug discontinuation during this time that were numerically more frequent in APV recipients *vs* PLA included skin rash, anemia and fatigue, although the numbers of these events were quite small.

(e) Of serious adverse events, there was a numerical excess of rash events in subject receiving amprenavir, although these numbers were small. There were 3 cases of serious rash among APV recipients.

(f) Other serious adverse events may at least potentially be attributed to amprenavir, although their numbers were quite small. Among these were: hemolytic anemia (1), transaminase elevations (1), hyperglycemia, new onset (1).

(g) Common adverse events observed in 5% or more of amprenavir recipients and more frequently in this treatment group than controls are: nausea, vomiting, diarrhea/loose stools, paresthesias (predominantly oral/perioral, but also peripheral), rash, and psychiatric (depressive and mood disorders).

(h) Of commonly occurring laboratory events, hyperglycemia (37 *vs* 29%) and hypertriglyceridemia (36 *vs* 22%) occurred disproportionately in APV recipients, *vs* controls. There was no disproportionate increase in severe laboratory adverse events in APV recipients.

V. Safety and efficacy in adults with prior nucleoside anti-retroviral therapy experience

Clinical Trial PROA/B3006 "A Phase III Trial to Compare the Safety and Antiviral Efficacy of 141W94 with Indinavir in Combination with Nucleoside Reverse Transcriptase Inhibitor (NRTI) Therapy in NRTI Experienced, Protease Inhibitor (PI) Naive HIV-1 Infected Patients"

Information examined in the review of this study includes the interim Trial Report (Vols 8.24-8.34), the 28 Oct 98 Efficacy Update (Vols 2-3), the 22 Dec 98 Efficacy Amendment, and the 23 Dec 98 Safety Update.

A. Design. This is an ongoing randomized, open-label, multicenter, Phase 3, equivalence-design study in 504 HIV-infected, NRTI-experienced adult subjects that evaluates the efficacy and safety of amprenavir (APV) *vs* indinavir (IDV) when used in combination with NRTIs. The sponsor was not blinded to the treatment that subjects received, but was blinded to HIV-1 RNA PCR and CD4/CD8 results until the results were unblinded for presentation in the clinical study report. The study was conducted at 78 centers, 33 in the US, 11 in Canada, and 34 in Europe and Australia.

1. Population. Eligible subjects were to be ≥16 yrs of age, to have had at least 12 weeks of prior lifetime nucleoside experience, to be HIV protease inhibitor naive, and to have ≥400 HIV RNA copies/ml in plasma.

2. Study therapy. Subjects were to receive APV (1200 mg BID) or IDV (800 mg TID) on a background of NRTIs. Investigators were encouraged to change at least one NRTI at entry. If a subject was receiving non-nucleoside reverse transcriptase inhibitor (NNRTI) therapy, it was to be discontinued one day before starting study therapy.

3. Randomization and stratification. Subjects were randomized 1:1 study therapy and were stratified by HIV RNA (≥400-10000, >10,000-100,000, >100,000 copies/ml) and according to whether a change of at least one NRTI was initiated at entry.

4. Discontinuation of study medication. Subjects were to continue randomized protease inhibitor therapy in conjunction with background NRTI therapy until the last subject enrolled had completed 48 wks of therapy unless they met a protocol-defined switch criterion. Switch criteria were defined as two consecutive (within 3 wks) plasma levels of HIV RNA ≥400 copies/ml at Wk 16 or thereafter or progression to CDC Class C event after 4 wks on study. If, at Week 8, the viral load had not decreased by at least 0.7 $\log_{10}$ copies/ml from baseline, the subject could continue on randomized protease inhibitor (PI) or switch. If the PI was switched at any time, the subject was considered to have met a study endpoint.

In the event that the investigator considered that a change in protease inhibitor therapy was warranted, subjects discontinued their randomized protease inhibitor and received any licensed HIV protease inhibitor or APV. Additionally, protease-protease combination therapy or addition of licensed NNRTI could be considered if, in the investigator's judgement, a subject may derive benefit from these therapies. These agents were to be used only in combinations where data was available to support such use. Subjects who changed therapy were to continue to be followed until the last subject enrolled completes 48 weeks of therapy.

5. Endpoints and analysis. The primary endpoint was antiretroviral activity, defined as the proportion of subjects having <400 HIV RNA copies/ml (Roche AMPLICORE HIV-1 MONITOR assay) at 16 weeks (for the accelerated approval application) or at 48 wks (to be evaluated for traditional approval), who did not progress to a CDC Class C event or death. The FDA has only very recently based its regulatory decisions regarding antiretroviral drugs on HIV-1 virological responses. Experience to date suggests that longer term data (beyond 16 weeks) may be important in these decisions, and the Applicant was therefore asked to provide 24-week efficacy data, which was submitted during the course of the review.

For purposes of analysis of the intent-to-treat population, subjects were considered treatment failures as

follows: (i) virologic failure (HIV RNA ≥400 copies/ml), or clinical AIDS progression events, or death, (ii) those switching randomized therapy for adverse events or any other reason after randomization, (iii) those with insufficient data to demonstrate virologic success at 24 weeks, including withdrawal of consent, lost to follow-up, or withdrawal for protocol violations.

Other analyses were to be plasma HIV RNA and CD_4 AUC measures, the proportion of subjects with plasma HIV RNA <50 copies/ml, disease progression, and HIV-RT and PI genotype and phenotype evaluations. Safety evaluation included adverse events and clinical laboratory values.

B. Results: Study population and subject disposition

1. Study Population. A total of 504 patients are enrolled and 486 have received study drug. Baseline characteristics are summarized in Table 14.

Table 14. Baseline demographics by study treatment (Intent-to-treat population)

Treatment	APV	IDV
No. randomized	254	250
Age		
Mean (SD)	38.9 (9.4)	37.7 (8.8)
Median (min, max)	38.0 (20, 71)	36.0 (21, 67)
Sex		
female	48 (19%)	54 (22%)
male	206 (81)	196 (78)
CDC classification, N (%)		
A. asymptomatic or lymphadenopathy	158 (62)	152 (61)
B. symptomatic, not AIDS	66 (26)	63 (25)
C. AIDS	22 (9)	26 (10)
Randomized but not treated (missing)	8 (3)	9 (4)
Race		
White	184 (72)	179 (72)
Black	46 (18)	50 (20)
Asian	2 (<1)	2 (<1)
Hispanic	20 (8)	17 (7)
Other	2 (<1)	2 (<1)
HIV RNA (log_{10} copies/ml)		
N	253	244
Mean (SD)	3.929 (0.680)	3.973 (0.718)
Median (min, max)	3.871 (2.60, 6.06)	3.982 (2.60, 7.01)
Baseline HIV RNA (log_{10} copies/ml)		
<400	4 (2)	6 (2)
400-10,000	141 (56)	122 (49)
>10,000-100,000	89 (35)	97 (39)
>100,000	19 (7)	19 (8)
Missing	1 (<1)	6 (2)
CD_4 cells/ml		
N	253	242
Mean (SD)	395.5 (172.7)	420.5 (214.3)
Median (min, max)	389.5	412.3

2. Conduct of the study and disposition of subjects.

a. Subject recruitment and study treatment, by country and site. A total of 152 subjects were enrolled in seven European countries (Belgium, France, Greece, Portugal, Spain, Sweden, United Kingdom) at 25 sites. Five Australian sites enrolled 14 subjects, and 10 Canadian centers enrolled 90 subjects. The remainder, 248 subjects, were enrolled at 28 sites.

Comment: The number of sites is relatively large, and the number of subjects per site is

relatively small. No site(s) contributed a disproportionately large number of subjects. In general, the numbers of subjects at a particular site assigned to each of the study treatments are similar.

b. Violations of inclusion/exclusion criteria. In information submitted to the NDA (20 Nov 98 Supplement), the protocol violations are relatively few in number, similar in numbers and types between treatment groups, and were generally not likely to influence the interpretation of the study.

c. Randomized therapy discontinuations (24-Week efficacy update, Table 15).

Table 15. Subjects discontinuing from study by Week 24, by treatment group (Intent to treat population)		
	APV	IDV
No. randomized	254	250
No. treated	245	241
On randomized therapy, 13 Aug 98	158	189
No. (%) discontinued randomized therapy	87 (36)	52 (22)
Reason for study medication discontinuation		
AE	41	23
Met switch criteria	13	6
Consent withdrawn	9	6
Protocol Violation	2	1
Lost to follow-up	14	10
Other	8	5

Comment: Disproportionately more subjects discontinued from the APV treatment group *vs* IDV, chiefly due to adverse events. More APV vs IDV recipients (13 *vs* 6) had met switch criteria (confirmed HIV>400 copies/ml) by Week 24.

3. Background therapy at entry. Antiretroviral therapy on Day 1 is summarized in Table 16.

Table 16. Background anti-retroviral therapy on Entry Day 1		
	APV (N=245)	IDV (N=241)
ZDV	50 (21%)	35 (15%)
ddC	10 (4)	8 (3)
ddI	79 (33)	74 (31)
3TC	145 (60)	151 (63)
nevirapine	4 (2)	1 (<1)
d4T	193 (80)	195 (82)
delavirdine	2 (1)	1 (<1)
combivir (ZDV+3TC)	9 (4)	7 (3)

Comment: The three most frequently used antiretroviral agents were d4T (81%), 3TC (64%), and ddI (32%). Background antiretroviral therapy combinations at entry were similar between treatment groups.

C. Results:

Efficacy (FDA analysis) During the course of the review, the FDA requested that the applicant submit all virology and CD_4 cell data, to include Week 24 data for all subjects. For a more detailed treatment of the FDA analysis of surrogate endpoints (HIV-RNA and CD_4 cell counts), please see the Statistical Review. Several points are summarized here.

1. Primary analysis. Week 24 data is the basis for the FDA analysis. Treatment failures were subjects with a viral load ≥400 copies/ml, or a new CDC Class C event or who had discontinued the randomized treatment. Subjects with missing data were regarded as failures. The results of this analysis are shown in Table 17.

Table 17. Subjects remaining on randomized treatment at Week 24, and HIV RNA <400 copies/ml (missing regarded as failures)				
Randomized treatment	Amprenavir (N=254)	Indinavir (N=250)	Difference, % (95% CI)**	p-value*
<400 copies/ml	108 (42.5%)	133 (53.2%)	-10.8% (-19.3%, -2.3%)	0.014

*stratified Cochran-Mantel-Haenszel test
**randomized stratum adjusted difference with continuity correction

Subjects who at Week 24 were treatment failures, or were regarded as failures, are summarized in Table 18.

Table 18. Treatment failures, or regarded as treatment failures, by category and treatment group, Week 24		
	APV (N=254)	IDV (N=250)
Progressed to new CDC Class C event	1 (0.4%)	4 (1.6%)
On treatment at Week 24, and HIV-1 RNA is:		
Missing	11 (4.3)	17 (6.8)
≥400 copies/ml	45 (17.7)	40 (16.0)
Discontinued randomized therapy by Week 24 due to:		
Adverse events	41 (16.1)	19 (7.6)
Virological rebound	12 (4.7)	6 (2.4)
Before taking any study medication	9 (3.5)	9 (3.6)
Consent withdrawn, Lost to follow-up, Protocol violation, Other	27 (10.6)	22 (8.6)
Total	136 (57.5)	117 (46.8)

Comment: The difference in failure rates between amprenavir and indinavir treatment groups, 10.8%, is chiefly due to the difference in discontinuations due to adverse events (8.5%) in the APV treatment group.

2. CD4 cell counts. The median changes from baseline in CD_4 cells/mm^3, by treatment and study week (randomized phase), are summarized in Table 19.

Table 19. Median change in CD4 cells, through Wk 24, by treatment								
	Baseline	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24
APV cells, (N)	390/mm^3 (253)	+11 (216)	+16 (205)	+25 (199)	+23 (188)	+27 (160)	+37 (138)	+42 (154)
IDV cells, (N)	414/mm^3 (243)	+24 (222)	+31 (223)	+30 (213)	+40 (205)	+46 (184)	+66 (166)	+88 (176)

Comment: At Wk 24, there is a 46-cell difference in the CD_4 response between treatment groups, in favor of the IDV-containing treatment group.

3. CDC Class C clinical events are summarized in Table 18.

Comment: The numbers of CDC Category C events are small in both arms.

D. Results: Safety

The following is based on information provided in the initial study report, the Integrated Summary of Safety of the NDA, the 28 Oct 98 efficacy update, the 22 Dec 98 safety update, and the 28 Jan 99 Response to Information Request.

1. Deaths. There was one death in this study. A 32 year-old Black female with a history of asthma and pulmonary hypertension at entry died shortly thereafter due to pulmonary hypertension. Death was not drug-

related.

2. Serious Adverse Events (regardless of causality).

a. Serious adverse events. In the Applicant's analysis at 16 weeks, serious adverse events occurred in 21 *vs* 29 APV vs IDV recipients. The types and numbers of events were similar between treatment groups, except that there was a disproportion of psychiatry-related SAEs in amprenavir recipients (see below). In APV recipients, one had a serious rash, one had convulsions, and one had syncope.

b. The case narratives of all subjects having serious adverse events through the latest time for which data was available (1 Sept 98, in the 22 Dec 98 Safety Update) were reviewed (see Appendix 2). The following are listed because of their potential importance or disproportionate representation in amprenavir recipients.

i. LFT elevation. One subject had Grade 4 SGOT and SGPT increases during the fourth month of amprenavir therapy, and study therapy was stopped. When rechallenged with amprenavir, LFTs increased to Grade 4.

Comment: Because rechallenge with amprenavir resulted in recurrent Grade 4 transaminase increases, this event is reasonably attributable to amprenavir.

ii. Hypertriglyceridemia. Subjects with Grade 4 increases in triglycerides are listed in Table 20.

Table 20. Grade 4 Hypertriglyceridemia SAEs, by study treatment

Subj No	Age/ Sex	SAE Onset[1]	Notes
APV			
2472	35 M	Wk 1	Gr 2 at entry; resolved by Wk 16 while on study therapy
3369	43 M	Wk 20	Triglycerides incr at entry, fluctuated on study therapy; study regimen not modified
3638	30 M	Days 1, 85	First event resolved in 8 days, second event resolved after 8 days
IDV			
2511	28 M	Wk 12	not fasted before sample taken; did not resolve
3105	35 M	Wk 28	history of bili incr, ? Gilbert's disease; triglycerides incr at entry, incr to Gr 4

Comment: Grade 4 hypertriglyceridemia events in amprenavir recipients were not sustained episodes resulting in discontinuation of amprenavir.

iii. Depression. Subjects hospitalized with psychiatry-related events, in particular, depression, suicide-related events and/or drug detoxification events are summarized in Table 21.

Table 21. Psychiatry-related

Subj No	Age/ Sex	Event	Grade	SAE Onset[1]	Notes
APV					
2568	35 M	drug addiction depressed/suicide	hosp hosp	Wk 3 Wk 8	history of depression, suicidal ideation, drug abuse
2577	36 M	depression, exacerbation alcohol addiction	hosp hosp	Wk 5 Wk 32	history of depression, alcoholism, drug use, anxiety
2693	49 M	suicidal/homicidal ideation	hosp	Mo 8	history of depression
3717	41 M	EtOH withdrawal syndr/ attempted suicide	hosp/ hosp	Wk 3 Mo 5	history: alcoholism, anxiety/ suicide attempted using overdose of several drugs
3720	25 M	depressive syndrome	hosp	Wk 10	history: depressive syndrome, neurotic personality
IDV					

4059	33 M	homicidal/suicidal ideas	hosp	Wk 10	history: impulse disorder, violent behavior; hosp eval: cocaine in urine
2579	46 M	detox: cocaine, ethanol	hosp	Wk 34	history of cocaine, marijuana use

Comment: More amprenavir recipients were hospitalized for depression and related events (n=5) than in those treated with indinavir (n=2).

3. Severe (Gr 3/4) adverse events. Events occurring during the randomized phase, by system and event (Week 16 report) and more frequent in amprenavir recipients than controls are listed in Table 22.

Table 22. Severe, Grade 3/4 adverse events, occurring on randomized treatment, regardless of causality

	APV	IDV
Subjects with any severe, Grade 3/4 event	37	56
Hepatobiliary tract and pancreas, no.	5	23
increased LFTs	4	7
increased amylase	1	2
Gastrointestinal, no.	11	10
diarrhea	4	3
nausea	5	1
abdominal pain	1	3
vomiting	2	1
pseudomembranous colitis	1	0
inguinal pain	1	0
Endocrine and metabolic, no.	7	6
hypertriglyceridemia	5	4
hyperglycemia	0	3
diabetes mellitus	1	0
incr CPK	1	0
Blood and lymphatic	2	5
decreases white cells	1	2
thrombocytopenia	1	1
Neurology, no.	2	5
convulsions	1	0
migraines	1	0
Non-site specific	2	5
allergies/allergic reactions	1	1
viral infections	1	0
Lower respiratory, no.	2	3
infection	2	1
Psychiatry, no.	4	1
depressive disorders	2	0
suicide, attempted suicide	1	1
behavioral disorders	1	0
Skin	3	2
rashes	2	0
fungal skin infections	1	0
Urology	0	5
Musculoskeletal	0	3
Cardiovascular	2	0
syncope	2	0
Reproduction	0	2
Trauma, overdose, poisoning	2	0
craniocerebral injuries	1	0
wounds and lacerations	1	0
ENT	1	0
tonsil disorders	1	0

Comment: More Gr 3/4 GI events and skin rashes were seen in amprenavir recipients than controls. Two amprenavir recipients and no controls had syncope. More psychiatry-

related events were observed in amprenavir recipients than in those treated with indinavir (see below). LFT and amylase were increased in fewer APV recipients than in controls.

4. Adverse events (all grades), regardless of relationship to drug, by body system. More frequent adverse events occurring during randomized therapy in which the percent of amprenavir subjects with an event was greater than that of indinavir recipients are included in Table 23. Certain other events are selected for inclusion as well.

Table 23. Adverse events occurring with greater frequency in APV recipients than control, and selected adverse events of interest.

System, event	APV (N=245)	IDV (N=241)
Gastrointestinal, any (%)	197 (80%)	153 (63%)
diarrhea	113 (46)	66 (27)
nausea	94 (38)	62 (26)
vomiting	49 (20)	27 (11)
abdominal pain	27 (11)	33 (14)
gaseous symptoms/flatulence/eructations	39 (16)	19 (8)
loose stools	37 (15)	15 (6)
Neurological, any (%)	135 (55)	94 (39)
paresthesia oral/perioral	73 (30)	4 (2)
paresthesia peripheral	22 (9)	17 (7)
sleep disorders	20 (8)	16 (7)
paresthesia	10 (4)	5 (2)
hypnagogic effects	6 (2)	3 (1)
dysesthesia	3 (1)	0
Skin, any (%)	76 (31)	94 (39)
rashes	43 (18)	25 (10)
acne and folliculitis	11 (4)	2 (1)
skin signs and symptoms	2 (1)	0
urticaria	1	1
Non-site specific, any (%)	71 (29)	84 (35)
allergies/allergic reactions	8 (3)	11 (5)
edema and swelling	6 (2)	3 (1)
flushing	5 (2)	3 (1)
primary malignant neoplasia	1	0
Lower respiratory, any (%)	57 (23)	74 (31)
airways constriction/obstruction	1	0
asthma	1	0
lung disorders	1	0
Ear, nose and throat, any (%)	52 (21)	65 (27)
primary malignant ENT neoplasia	1	0
Musculoskeletal, any (%)	35 (14)	66 (27)
muscle stiffness/tightness/rigidity	2	0
Urology, any (%)	10 (4)	34 (14)
urinary calculi	0	7 (3)
micturition disorders	2	1
nocturia	2	1
Hepatobiliary tract and pancreas, any (%)	11 (4)	29 (12)
abnormal bilirubin levels	0	16 (7)
increased liver function tests	7 (3)	9 (4)
hepatobiliary signs	1	2
increased amylase levels	1	2
hepatitis	1	0
hepatitis B	1	0
pancreas disorders	0	1
Psychiatry, any (%)	16 (7)	21 (9)
anxiety	5 (2)	3 (1)
aggression and hostility	2	1
suicide and attempted suicide	2	1
alcohol use abuse and withdrawal	2	0
behavioral disorders	1	1

Endocrine and metabolic, any (%)	15 (6)	15 (6)
hypertriglyceridemia	10 (4)	9 (4)
hyperglycemia	2	4 (2)
diabetes mellitus	2	0
hypercholesterolemia	2	0
hypoglycemia	0	1
hypothyroidism	1	0
increased CPK	1	0
lipodystrophy signs and symptoms	1	0
Eye, any (%)	13 (5)	17 (7)
Reproduction, any (%)	6 (2)	19 (8)
Cardiovascular, any (%)	13 (5)	10 (4)
hypertension	3 (1)	0
palpitations	2	1
heart block	1	0
increased blood pressure	1	0
vascular disorders	1	0
vasculitis	1	0
Trauma overdose and poisoning, any (%)	9 (4)	14 (6)
Blood and lymphatic, any (%)	8 (3)	13 (5)
anemia	1	0

Comment: Adverse events that appear to be associated with amprenavir therapy include GI events (nausea, vomiting, diarrhea/loose stools, and gaseous symptoms), rash, and paresthesias (including oral/perioral and peripheral). Other adverse events occurring more frequently in amprenavir recipients than in subjects receiving indinavir are mostly those occurring too infrequently to assess whether a meaningful amprenavir association exists. The data from this study do not show increased hepatic or pancreatic enzymes.

Small numbers of amprenavir recipients developed hypertriglyceridemia, hyperglycemia, diabetes mellitus, hypercholesterolemia, hypothyroidism, increased CPK or signs and symptoms of lipodystrophy; these events are similar in type and frequency to those expected and observed with IDV. A single amprenavir recipient developed anemia.

Although adverse events occurring more frequently in indinavir recipients are for the most part not summarized in this table,urinary calculi were reported in 7 indinavir recipients and no amprenavir treated patients, and hyperbilirubinemia was reported in 16 subjects treated with indinavir and none receiving amprenavir.

5. Adverse events leading to study drug discontinuation. These are summarized in Table 24.

Table 24. Adverse events leading to study drug discontinuation, by system and event (Week 16)

Event, by System	APV	IDV
Gastrointestinal, no.	24	4
nausea	13	3
vomiting	8	2
diarrhea	6	0
abdominal pain	3	0
abdominal discomfort	1	0
dyspeptic symptoms	1	0
dysphagia	1	0
gaseous symptoms/flatulence/eructations	1	0
gastrointestinal motility symptoms	1	0
oral discomfort and pain	1	0

Neurology	7	1
headaches	2	1
decreased consciousness	1	0
migraines	1	0
neuropathy	1	0
paresthesia oral/perioral	1	0
paresthesia peripheral	1	0
Skin	8	0
rashes	8	0
Non site specific	6	1
fatigue	2	1
malaise	1	1
allergies and allergic reactions	1	0
anorexia	1	0
fever	1	0
flushing	1	0
hot and cold sensations	1	0
weight loss	0	1
Urology	0	6
Hepatobiliary tract and pancreas	2	1
increased LFTs	2	0
increased bilirubin	0	1
Psychiatry	1	1
behavioral disorders	1	0
depressive disorders	0	1
ENT	1	0
sinus disorders	1	0
Endocrine and metabolic	1	0
increased CPK	1	0
Eye	1	0
keratitis and conjunctivitis	1	0
Musculoskeletal	1	0
muscle pain	1	0
Trauma overdose and poisoning	1	0
craniocerebral injuries	1	0

Comment: In amprenavir recipients, substantially more adverse events led to study drug discontinuation than in controls. Adverse events that accounted for most study drug discontinuations included GI events (nausea, vomiting, diarrhea, abdominal pain or discomfort), skin rash, and neurological symptoms.

6. Adverse events, selected. Clinical information concerning events that are specifically associated with APV are summarized in Table 25.

Table 25. Clinical features of APV-specific adverse events

Adverse event	APV (N=245)	IDV (N=241)
Diarrhea (No.)	138	76
Onset day (median)	day 8	day 23
Duration (median)	33 days	25 days
Intensity (subjects with Gr 1,2,3)	85 (61%), 51 (36), 4 (3)	50 (66), 23 (30), 3 (4)
Action taken		
no change	132 (94%)	71 (93)
dosage adjusted/stopped temporarily	2 (1)	5 (7)
stopped permanently	6 (4)	0

Nausea (No.)	107	70
Onset day (median)	day 8	day 8
Duration (median)	13 days	15 days
Intensity (subjects with Gr 1,2,3)	83 (74%), 23 (21), 6 (5)	61 (81%), 13 (17), 1 (1)
Action taken		
no change	94 (84%)	71 (95)
dossage adjusted/stopped temporarily	5 (4)	1 (1)
stopped permanently	13 (12)	3 (4)
Vomiting (No.)	64	32
Onset day (median)	day 15	day 21
Duration (median)	20 days	12 days
Intensity (subjects with Gr 1,2,3)	53 (80%), 10 (15), 3 (5)	23 (68%), 10 (29), 1 (3)
Action taken		
no change	53 (80%)	32 (94)
dossage adjusted/stopped temporarily	5 (8)	0
stopped permanently	8 (12)	2 (6)
Rash (No.)	48	28
Onset day (median)	day 10	day 28
Duration (median)	10 days	8 days
Intensity (subjects with Gr 1,2,3)	24 (49%), 22 (45), 2 (4)	23 (77%), 7 (23), 0
Action taken		
no change	25 (51)	29 (97)
dossage adjusted/stopped temporarily	16 (33)	1 (3)
stopped permanently	8 (16)	0
Paresthesia oral/perioral (No.)	82	4
Onset day (median)	day 2	day 4
Duration (median)	30 days	85 days
Intensity (subjects with Gr 1,2)	81 (94%), 5 (6)	4 (100), 0
Action taken		
no change	85 (99%)	4 (100)
stopped permanently	1 (1)	0

Comment: These adverse events were much more common in amprenavir recipients than in controls. It is particularly noteworthy that each of these events led to study drug discontinuation in a higher proportion of amprenavir recipients than controls. The median onsets of gastrointestinal events (nausea, vomiting, diarrhea) occurred earlier (Days 8-15) in amprenavir recipients than in controls (Days 8-23), and generally tended to be of longer duration in amprenavir recipients.

7. Laboratory events. Laboratory abnormalities, all grades (from the Response to Request for Information, 28 Jan 99), occurring more frequently in APV recipients than controls are summarized in Table 26.

Table 26. Laboratory adverse events, all grades, reported in ≥ 1% of subjects in a greater proportion of APV recipients than in controls

	APV (N=245)	IDV (N=241)
Event	Percent	Percent
Hyperglycemia	47%	40%
Albumin increased	5%	3%

Comment: These differences between treatment groups appear to be minor.

E. Study Conclusions

1. Efficacy. In the FDA's analysis of this ongoing equivalence design study, the efficacy conclusions may be summarized as follows:

(a) At Week 24, a higher proportion of APV recipients failed randomized therapy at Study Week 24 than was the case for subjects randomized to IDV. The proportion of subjects having undetectable plasma HIV-1 RNA and no CDC class C event was 42.5% vs 53.2% for APV vs IDV, respectively (95% CI, -19.3%,

-2.3%). The difference between the treatment arms was statistically significant (p=0.014).

(b) There were disproportionately more premature study drug discontinuations due to adverse events in APV recipients, vs IDV (16.1% vs 7.6%, respectively). These adverse events accounted for 8.5% of the total 10.8% difference between treatment groups. In APV recipients, these events were chiefly gastrointestinal events, particularly nausea, vomiting, diarrhea, abdominal pain, and rash. In subjects discontinuing therapy secondary to adverse events, the effectiveness of therapy cannot be determined, and therefore these events are considered as treatment failures. The disproportion of adverse events leading to change in therapy in those randomized to APV vs IDV leads to difficulty in interpretation of the efficacy of amprenavir, relative to indinavir.

(c) At 24 weeks, there was a greater treatment effect on CD_4 cells in the IDV group than in APV recipients. Interpretation of these data was complicated by the numbers of subjects who had discontinued study drug at this time.

(d) At 24 weeks, one APV recipient and three IDV recipients had developed CDC class C events.

2. Safety. The safety conclusions of this study are summarized as follows:

(a) There was one death, due to pulmonary hypertension, which was unrelated to amprenavir therapy.

(b) Toxicities leading to permanent discontinuation of study drug during the first 16 weeks of the study and occurring disproportionately in APV recipients (vs IDV) included gastrointestinal events (nausea, vomiting, diarrhea, abdominal pain) and rash.

(c) Of serious adverse events, there was one subject who developed Grade 4 transaminase increases while receiving amprenavir, which recurred with amprenavir rechallenge. There were more hospitalizations for psychiatric events (depression, suicide attempts or ideation, alcohol/drug related events) in amprenavir recipients than in those receiving indinavir.

(d) Common adverse events associated with amprenavir therapy include GI events (nausea, vomiting, diarrhea/loose stools, and gaseous symptoms), rash, and paresthesias (including oral/perioral and peripheral).

Small numbers of amprenavir recipients developed hypertriglyceridemia, hyperglycemia, diabetes mellitus, hypercholesterolemia, hypothyroidism, increased CPK or signs and symptoms of lipodystrophy. A single amprenavir recipient developed anemia.

(e) Common laboratory events occurring more frequently in amprenavir recipients (vs IDV) were hyperglycemia and increased albumin; these differences between treatment groups were small.

VI. Expanded access studies

Beginning in the Fall of 1998, three protocols (PRO30010, PRO20011, PRO30012) in which patients were given early access to amprenavir were ongoing. On 1 Feb 99, the Applicant provided serious adverse event data from these studies through 31 Dec 98. At this time, a total of 1050 patients had been enrolled in these studies.

In PRO30010, the largest study (950 enrolled), these patients were 95% male, 75% Caucasian, median age 41 years, median CD_4 cells/mm^3 was 132 (range, ——— and median HIV RNA copies/ml in plasma was 85,000 (range, ——————— Study PRO30011(N=70) had similar demographics, while Study PRO30012 (N=29) enrolled patients with less advanced disease (median CD_4, 472 cells/mm^3).

Five patients experienced serious adverse events. These are summarized in Table 27.

Table 27. Serious adverse events reported during early access studies of amprenavir

Subj No	Age/ Sex	Serious Adverse Event	Onset	APV	Concomitant medications	Action-APV	
A0078160	38 M	septic shock, fever, nausea, vomiting, diarrhea, pancytopenia	15 d	1200 mg BID	ABC/3TC/ZDV/NVP/ACV	no change	
A0078979	42 M	pancreatitis,nausea, vomiting, incr lipase and amylase, abd pain	13 d	1200 mg BID	ABC/d4T/3TC/EFV/HUrea	discon-tinued	
A0077089	35 M	anaphylactic reaction, maculopapular rash, dyspnea	16 d	1200 mg BID	ABC/EFV	inter-rupted	positive ABC rechallenge
A0078080	35 M	allergic reaction, fever, myalgia, rash on upper body	6 d	1200 mg BID	ABC/d4T/ACV/Cotrim	inter-rupted	
A0078138	35 M	rash maculopapular, pruritus, erythema, poss erythema multiforme	5 d	1200 mg BID	ABC/3TC/ZDV/dapsone	discon-tinued	rash worse p/ABC dose while off APV

Comment: Because of the systemic manifestations and/or response to abacavir (ABC) dose, four of the five cases appear more appropriately attributed to ABC than to APV.

VII. Studies in pediatric patients

The applicant has provided pharmacokinetic and safety data in pediatric patients, 2 to 18 years of age. During the course of the review, PK but not safety information was provided on an additional (36) pediatric patients.

A. PROA 1006 "A Phase I, Open-Label, Dose Escalation Clinical Study to Assess the Pharmacokinetics and Tolerability of Single, Oral Doses of 141W94 in HIV-Infected Children"

This single dose, dose escalation PK study was conducted in 20 HIV-infected children (11 M, 9 F; mean age 8.4 yrs (range 4-12 yrs). Two groups of 10 subjects each received 2 single escalating doses of APV separated by a minimum 7-day washout period. Group I received 5 and 10 mg/kg; Group II received 15 and 20 mg/kg. Soft gelatin capsules, — and 150 mg dosage forms, were used.

PK results: For a summary of the PK results, please see Dr. Tammara's review.

Safety: Information from this single dose, dose escalation study does not contribute significantly to safety conclusions in the pediatric age group.

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B. PROB 2004 "A Phase II Trial to Assess the Preliminary Antiviral Effect, Pharmacokinetics, Safety and Tolerability of Multiple Oral Doses of 141W94 Liquid Formulation in Combination with NRTIs in HIV Infected Children Below 13 Years Old"

This multiple dose PK study of the oral solution of APV is ongoing. Data are available in 27 HIV-infected children, ages 4-12 (mean age 7.6 yrs, range 4-11 years), of whom 22 completed the study. The study is to recruit three age groups: Cohort I, 7-13 yrs; Cohort II, 4-7 yrs; Cohort III, 2-4 yrs. Cohorts are to be sequentially recruited, and randomized to dosing regimen, and treated for 48 weeks.

This interim report contains data on Cohorts I (n=16) and II (n=6). Two dosing regimens of the oral solution were tested: 20 mg/kg BID and 15 mg/kg TID. Subjects were to be given APV in combination with approved NRTIs.

1. Population.

The demographics and baseline characteristics of subjects studied are summarized in Table 28.

Table 28. Baseline demographic characteristics of treatment groups

	APV 20 mg/kg BID (N=15)	APV 15 mg/kg TID (N=12)
Age, median (range)	8 (4-11)	8 (4-11)
Weight, kg, median (range)	22.2 (15-46)	26 (13.6-46)
Sex, n (%) female male	 2 (13) 13 (87)	 6 (50) 6 (50)
Race, n (%) White Black Asian	 9 (60) 6 (40) 0	 8 (67) 3 (25) 1 (8)
HIV risk factors Transfusion Vertical/perinatal Other (nosocomial)	n=15 0 14 1	n=9 1 7 1

HIV subtype Clade B Non-B	 13 2	 12 0
CDC classification N: non-symptomatic A: mildly symptomatic B: moderately symptomatic C: severely symptomatic	n=15 2 5 6 2	n=9 2 1 3 3
Baseline HIV RNA, median (range) <400 400-<10,000 10,000-30,000 30,000-100,000 >100,000	5.11 1 0 2 4 7	4.89 0 1 1 4 3
Baseline CD4, median (range)	212	340
Prior PI exposure no yes	 9 6	 9 3

2. Prior and concurrent therapy. All but 2 subjects had been on prior NRTI therapy for more than 2 years. Most had been treated with multiple agents. During the study, all subjects were receiving 2 NRTIs + APV.

3. PK results. For a review of the PK results, please see the full Biopharmaceutics review (Drs. Tammara and Rajagopalan) and the Team Leader Addendum (Dr. Reynolds). Information from Study PROB2004 forms the basis for dosing recommendations in pediatric patients.

The following is abstracted from Dr. Reynolds' Team Leader Addendum. Summary data is shown in Table 29.

Table 29. Steady-state amprenavir PK parameters [arithmetic mean ±SD (%CV)]

PK parameter	Children		Adults (PROA 1002)
	4 to ≤ 13 yrs	4 to ≤ 13 yrs	
	oral solution, 20 mg/kg BID(n=20)	oral solution, 15 mg/kg TID (n=17)	capsules, 1200 mg BID(n=5)
AUC,ss (µ 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	0.273±0.258 (95%)	0.28±0.15 (54%)

It was assumed that the most relevant parameters (children *vs* adult) are Cavg and Cmin, but Cmax was also considered. Interpretation of adults *vs* children (Table 29) is limited because only 5 adults studied and the adult data is highly variable. The TID dosing option for children is included to enhance tolerability and compliance. The results of a bioequivalence study in adults indicate that APV concentrations are, on average, 15% lower following administration of the oral solution compared to the capsules. It was proposed that amprenavir oral solution be administered in children at 22.5 mg/kg BID or 17 mg/kg TID, giving concentrations that will be higher than those in Table 29 and will be closer to the adult values. Amprenavir capsules, when administered to children at 20mg/kg BID or 15 mg/kg TID, should give concentrations that are approximately 15% higher than those in the above table and be closer to the adult values.

4. Antiviral activity.

a. Change from baseline HIV RNA, by treatment week and treatment group is summarized in Table 30.

Table 30. HIV RNA (log_{10} copies/ml) by study week and treatment group

	APV 20 mg/kg BID (N=14)	APV 15 mg/kg TID (N=9)

Baseline, median (range)	5.1	4.89
Wk 4	-0.58 (n=13)	-1.72 (n=8)
Wk 8	-1.13 (n=10)	-0.54 (n=5)
Wk 12	-1.01 (n=4)	-0.72 (n=4)
Wk 16	-1.82 (n=3)	-2.43 (n=1)

b. Change from baseline HIV RNA, by treatment week and prior protease inhibitor experience is summarized in Table 31.

Table 31. HIV RNA (log_{10} copies/ml) by study week and prior protease inhibitor experience		
	PI-naive (n=15)	PI-experienced (n=8)
Baseline, median (range)	4.74	5.8
Wk 4	-1.72 (n=13)	-0.64 (n=8)
Wk 8	-1.82 (n=7)	-0.66 (n=8)
Wk 12	-1.17 (n=6)	-0.52 (n=2)
Wk 16	-1.83 (n=4)	(n=0)

Comment: There is a virological response to therapy, particular in those pediatric subjects who are naive to protease inhibitors.

5. Safety results.

a. Extent of exposure. Two subjects were exposed for 2-4 weeks, 14 for 4-12 weeks and 8 for 12-24 weeks.

b. Deaths. There were no deaths (through 17 Aug 98).

c. Adverse Events. Selected treatment-emergent AE's are summarized in Table 32. All adverse events were Gr 1-2, except for diarrhea, Gr 3 (n=1), fever Gr 3 (n=1), and thrombocytopenia Gr 4 (n=1).

Table 32. Adverse event (all grades) in pediatric subjects treated with the oral formulation of amprenavir, by regimen			
	APV 20 mg/kg BID (N=15)	APV 15 mg/kg, TID (N=9)	Total (N=24)
Subjects with any event , n (%)	11 (73)	7 (78)	18 (75)
Diarrhea	3 (20)	3 (33)	6 (25)
Loose stools	1 (7)	0	1 (4)
Rash	2 (13)	4 (44)	6 (25)
Fever	3 (20)	1 (11)	4 (17)
Cough	2 (13)	1 (11)	3 (13)
Abdominal pain	2 (13)	0	2 (8)
Vomiting	1 (7)	0	1 (4)

Comment: Systems most commonly affected by adverse events (GI, skin) in these children are similar to those involved in adults. Diarrhea and rash are prominent in this study as they are in the controlled trials in adults, but nausea is not listed here, and vomiting is reported in only one subject. Thus, observations in this study raise the possibility that there may be certain differences in the amprenavir adverse event profile in children, as compared to adults. There was no clear treatment group-related differences with respect to adverse events.

d. Serious Adverse Events. These are summarized in Table 33.

Table 33. Serious adverse events, by study treatment					
Treatment group	Subj. No.	SAE	Treatment Discontinued	Possible Drug-related*	Severe /Gr 3/4

20 mg/kg, BID (N=15)	45500	thrombocytopenia (Gr 4)	N	N	Y
	4554	anorexia	N	Y	N
		fever and fatigue	N	N	N
15 mg/kg, TID (N=9)	4577	severe abdominal trauma (prior to Day 1)	N	N	Y
	4577	diarrhea and fever (possible viral infection)	N	N	Y
	4559	rash, maculopapular, diffuse and pruritic (Gr 2, mucosa involved)	Y, permanent	Y	N

* Investigator assessment

e. Adverse events leading to study withdrawal. One subject withdrew from study due to rash (SAE's, above).

f. Laboratory events. These are summarized in Table 34.

Table 34. Laboratory events, by treatment regimen

	APV, 20 mg/kg, BID	APV, 15 mg/kg, TID
ALT Gr 1	1	0
AST Gr 1	1	1
Amylase Gr 1	1	3
Gr 2	1	0
Gr 3	1	0
Creatinine Gr 1	8	1
Hemoglobin Gr 1	3	4
Gr 2	2	2
Hyperglycemia Gr 1	1	0
Neutrophils Gr 1	2	0
Pancreatic amylase Gr 2	1	0
Platelets Gr 3	1	0
Gr 4	1	0
Triglycerides Gr 1	2	0
Serum lipase Gr 3	0	1

The subject with a Gr 3 amylase had a Gr 2 value at entry, which rose to Gr 3 by Day 1, then decreased. A second subject with a transient Gr 3 lipase and Gr 1 amylase had concurrent episodes of diarrhea and fever, thought possibly related to viral infection.

Of the four subjects with Gr 2 hemoglobin abnormalities, two normalized within 2 weeks, and 2 were still reduced at the time of data cut-off. No subject received any intervention to normalize these toxicities.

> **Comment:** Amylase increase, creatinine increase and hemoglobin decrease are the most frequent laboratory abnormalities. None of these were related to APV treatment in the controlled adult studies.

C. PROAB 3004 A Phase III Open Label Trial to Evaluate the Safety, Antiviral Efficacy and Pharmacokinetics of APV Plus Current Therapy in HIV-1 Infected Children

This study was originally designed as a randomized, double-blind placebo controlled Phase III efficacy trial in children. Twenty subjects were initially enrolled during the randomized phase of the trial. Because of difficulties in recruitment, the study was amended to an open-label, non-comparative design and study objectives were restricted to the collection of PK and safety data. This study is ongoing and the data presented has a 14 Aug 98 cutoff date.

Subjects who could swallow capsules received either the 150 mg or 50 mg soft gelatin capsules at a dose of 1200 mg BID or 20 mg/kg BID depending on age and weight. Subjects who could not swallow capsules received the APV oral solution (15 mg/ml) at a dose of 1.5 ml/kg, BID (22.5 mg/kg, BID)

1. Population (Table 35)

Table 35. Demographic and baseline characteristics	
	Total (N=81)
Age, median (range)	8 (3-17)
2-4 (no.)	3
4–7	24
7-13	43
13-18	11
Sex, n (%)	
female	43 (53)
male	38 (47)
Race, n (%)	
White	22 (27)
Black	35 (43)
Hispanic	23 (28)
Other	1 (1)
CDC classification	
>13 yrs	
A: asymptomatic/lymphadenopathy	4
B: symptomatic, not-AIDS cond	2
C: AIDS	5
<13 yrs	
N: non-symptomatic	3
A: mildly symptomatic	27
B: moderately symptomatic	20
C: severely symptomatic	17
Baseline HIV RNA, median (range)	n=73
400-<10,000	19
10,000-30,000	13
30,000-100,000	20
>100,000	21
Baseline CD4, median (range)	474

2. Prior and concurrent therapy. The majority of subjects had been treated with NRTI's for more than two years before study entry. The majority of subjects had been treated with at least one component of their background NRTI therapy. A minority of subjects had prior exposure to protease inhibitor therapy.

3. PK results. Please see Biopharmaceutics Review (Dr. Tamarra)

4. Antiviral activity (Table 36)

Table 36. Median HIV RNA change from baseline, by study week & treatment group*, collected data only (ITT population)					
	R-PLA (N=15)	R-APV (N=14)	N-APV (N=38)	E-APV (N=14)	Total (N=81)
Baseline, median (no)	4.78 (10)	4.54 (12)	4.22 (37)	4.89 (14)	4.63 (73)
Wk 2	-1.40 (1)	-1.34 (8)	-0.33 (2)	0.59 (2)	-1.00 (13)
Wk 4	-1.0 (8)	-0.89 (9)	-0.94 (33)	0.28 (11)	-0.89 (61)
Wk 8	-0.77 (6)	-0.55 (8)	-1.50 (19)	0.38 (4)	-0.94 (37)
Wk 12	-1.11 (6)	-0.66 (9)	-1.52 (2)	-	-0.94 (17)
Wk 16	(0)	-1.20 (8)	-	-	-1.20 (8)
Wk 20	-0.52 (2)	-0.36 (8)	-	-	-0.36 (10)
Wk 24	-	-0.45 (8)	-	-	-0.45 (8)

*R-PLA, R-APV: subjects enrolled during the randomized portion of the study to PLA or APV; N-APV, E-APV: subjects naive or experienced with respect to other protease inhibitors during the open lable portion of the study

5. Safety

a. Extent of exposure. Through 14 Aug 98, 74 subjects were exposed to at least 1 dose of APV, with a median duration of exposure of 58 days (range, 4-225 days). Sixty-four subjects <13 yrs of age and 10 subjects > 13 yrs were exposed for 57 days (range: 4-225 days) and 76 days (12-240 days) respectively.

Table 37. Extent of exposure by treatment duration	
APV exposure	Total (N=81)
<2 wks	2 (3)
2-4 wks	5 (7)
4-12 wks	50 (68)
12-24 wks	9 (12)
24-48 wks	8 (11)

b. Deaths. There were no deaths to 14 Aug 98.

c. Adverse events. Adverse events on treatment reported in >10% of subjects are summarized in Table 38.

Table 38. Adverse events on treatment, reported in >10% of subjects.	
Adverse event	Total N=74
Any AE	51 (69)
Vomiting	21 (28)
ENT infection	12 (16)
Rash	12 (16)
Nausea	11 (15)
Diarrhea	10 (14)

d. Serious adverse events. Two subjects had serious adverse events. One had viral pericarditis (Gr 2), and the other had epistaxis. Neither was discontinued from the study.

e. Severe or Gr 3/4 adverse events. Each of four subjects had a single Gr 3 event. These events were abdominal pain, neutropenia, inflammation of oral mucosa, and fever.

e. Adverse events leading to permanent discontinuation of study medication. Two subjects had such events, one each due to vomiting, and vomiting with diarrhea .

f. Laboratory events.

Treatment emergent, Grade 3/4 clinical chemistry abnormalities. One subject each had a Grade 3 increase in alkaline phosphatase, amylase, and CPK. No Grade 4 events are noted.

Treatment emergent, Grade 3/4 hematology abnormalities. One subject had Grade 3 neutropenia. There were no Grade 4 events.

D. Assessment (all pediatrics studies)

1. Efficacy. The efficacy portion of the Phase III pediatric efficacy study (PROAB 3004) was terminated early due to poor enrollment. Although the numbers of subjects are small, it appears that APV, when given in combination with other antiretroviral agents, has antiviral activity in pediatric subjects; this is particularly evident in subjects who are protease inhibitor-naive, but who have varying degrees of prior experience with antiretroviral agents.

2. Safety. Although the data are limited, it appears that APV has a similar safety profile in pediatric patients

as in adults.

3. Dosing instructions for pediatric patients (to be included in the label)

Capsules: For patients between 4 and 12 years of age or for patients over 13 years of age with a weight of <50kg, the recommended oral dose of amprenavir capsules is 20mg/kg BID or 15 mg/kg TID, to a maximun dose of 2400 mg.

Oral solution: For patients between 4 and 12 years of age or for patients ofver 13 years of age with a weight of <50kg, the recommended oral dose of amprenavir oral solution is 22.5 mg/kg BID or 17 mg/kg TID, to a maximun dose of 2800 mg.

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VIII. Studies in other special patient populations

A. Patients with hepatic failure.

PROB1008 A Study to Compare the Pharmacokinetics of a Single Oral 600 mg Dose of Amprenavir in Healthy Volunteers and Patients with Cirrhosis

Summary: This is a study designed to examine the pharmacokinetics of a single dose of APV in adult patients with cirrhosis; 30 subjects were recruited, including controls.

PK results: Please see Biopharmaceutics review (Dr. Tamarra)

Safety results: There were no deaths or serious adverse events. No consistent patterns in clinical adverse events or changes in pre-existing or new laboratory abnormalities were evident.

> **Comment:** This study is not contributory to the major safety or efficacy conclusions of this application.

B. Patients with renal failure. This population was not studied.