IX. Other Studies The following Phase I and Phase II studies were submitted in support of this application. Each study is briefly summarized, with an emphasis on safety information derived from the studies.

1. PROA 1002 A Phase I Trial to Evaluate the Safety, Pharmacokinetics and Antiviral Activity of 141W94 After Multiple Dosing in Subjects with HIV Infection

Summary: The study is a multi-dose, dose escalation study in 62 HIV-infected adults, CD_4 ——— , with no prior HIV protease inhibitor therapy. There was no placebo control group. Safety, pharmacokinetics and antiviral activity were assessed. In study phase A, cohorts I-V received ascending doses of 141W94 (monotherapy), and cohort VI received 141W94 + abacavir for 4 weeks. Although the initial phase of the study was of brief (4 wks) duration, analysis of HIV RNA indicated a dose-response relationship for APV monotherapy. In subsequent study phases, subjects were then rolled over to multidrug antiretroviral regimens, with or without 141W94.

Safety Results: There were no deaths. At the end of study phase A, when all cohorts were taken together, more frequent adverse events were diarrhea (31%), headache (25%), nausea (20%), malaise/fatigue (13%), rash (13%), nausea/vomiting (11%), neuropathy (10%), nasal signs/symptoms (7%), anxiety (5%), cough (5%), sleep disorders (5%), throat/tonsil discomfort/pain (5%).

> **Comment:** Because of its design and the small numbers of subjects enrolled, this study does not substantially contribute to the efficacy conclusions of this application. It does provide limited safety information which contributes to the safety data base of this application.

2. PROA 1003 A Randomized, Cross-over Study to Evaluate the Safety and Pharmacokinetics of 141W94, Zidovudine and Lamivudine Alone and in Combination After Single-dose Administration in HIV-Infected Subjects

Summary: This is a Phase I, open-label, randomized, single-dose four period cross-over PK study.

Safety Results: There were no deaths or serious adverse events. The most common adverse events thought to be drug-related were headache, nausea, neutropenia (asymptomatic), diarrhea and vertigo. Three of 9 subjects discontinued prematurely from the study due to events of renal calculus, dental bleeding and seborrhea; these events were not thought by the investigator to be related to study drug. The subject who developed renal calculus on study had a history of renal calculus at entry and received treatments I(141W94), VII (141W94+3TC) and III (3TC) on 12 Mar, 19 Mar, 26 Mar 96, respectively; right flank pain developed on 28 Mar 96.

> **Comment:** See Biopharm review for comments on this study. This study does not contribute to the major safety or efficacy conclusions of this application.

3. PROA 1007 A Mass Balance Study to Investigate the Metabolic Disposition of a Single Oral Dose of Radiolabelled [^{14}C]-141W94 in Healthy Male Subjects

Summary: This is an open-label, single-dose, mass balance study in 6 healthy male volunteers.

Safety Results: There were no deaths or other serious adverse events. There was one episode of vasovagal syncope. The most common adverse events included nausea, back pain, neck pain, intermittent headache, dizziness, and constipation. None of the adverse events was considered to be related to study drug.

> **Comment:** See Biopharm review for comments on this study. This study does not contribute

to the major safety or efficacy conclusions of this application.

4. PROA1010 A Phase I, open Label, Randomized, Balanced, Three Period, Cross over Study to Assess the Bioequivalence of a New 150 mg Soft Gelatin 141W94 Capsule With a ———— Content Relative to the Original ———— Content 150 mg Soft Gelatin Capsule and to Assess the Effect of Food upon the Oral Bioavailability of the New Capsule in Healthy Male Subjects

Summary: This is a single dose bioavailability study in 39 adult subjects. Single doses of original and new study formulation were to be administered to each subject, with new formulation to be tested in both the fasted and fed state, with a minimum 4-day washout period between doses. There was no placebo control.

Safety results: There were no serious adverse events, deaths or withdrawals of subjects due to adverse events during the conduct of the study. Seventeen of 39 subjects receiving one or more doses of 141W94 reported adverse events, all of mild or moderate intensity. The most common events were nausea (7 reports by 6 subjects) and oral/perioral numbness (5 reports, 5 subjects).

Comment: See Biopharmaceutics review. This study is not contributory to the major safety or efficacy conclusions of this application.

5. PROA1011 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 141W94 Oral Solution in Healthy Male Subjects

Summary: This is a single dose bioavailability study in 29 adult subjects. Single doses of the new 50 mg and 150 mg soft gelatin capsules and the oral solution were administered to each of 24 subjects who completed each of the 3 doses, with a minimum wash-out of 4 days between doses. There was no placebo control.

Safety results: There were no serious adverse events or deaths. Eight of 29 subjects reported a total of 9 adverse events, of mild or moderate intensity. The most frequent was headache (2 reports, 2 subjects) and sore throat (2 reports, 2 subjects).

Comment: See Biopharmaceutics review. This study is not contributory to the major safety or efficacy conclusions of this application.

6. PROA1012 A Study to Investigate Whether There is a Pharmacokinetic Interaction between 141W94 and Rifabutin and 141W94 and Rifampin following their Co-administration to Healthy Male Volunteers

Summary: This study investigates possible PK interactions between 141W94 and Rifabutin (RFB) (dosing cohort 1: 12 enrolled, 6 completed) and between 141W94 and Rifampin (RFP) (dosing cohort 2: 12 enrolled, 11 completed) in healthy, HIV-seronegative males. Dosing was as follows:

Table 39. Summary of Study Treatments

Treatment	Dosing Days	Dosing Cohort 1 (141W94-RFB)	Dosing Cohort 2 (141W94-RFP)
1	1-4 (4 days)	141W94 1200 mg BID for 7 doses-omitting final evening dose on Day 4	141W94 1200 mg BID for 7 doses-omitting final evening dose on Day 4
Washout Period		At least 7 days	At least 7 days
2	5-18 (14 days)	300 mg RFB every morning	
3	19-28 (10 days)	141W94 1200 mg BID + 300 mg RFB every morning	
4	5-18 (14 days)		600 mg RFP every morning

5	19-22 (4 days)		141W94 1200 mg BID+600 mg RFP every morning

Safety results: There were no deaths or serious adverse events. In the 141W94-RFB cohort, 5/12 subjects were withdrawn due to Adverse Events during the 141W94+RFB treatment; these events were chiefly flu-like symptoms and laboratory abnormalities (predominantly neutropenia and leukopenia), and were considered by the investigators to be consistent with elevated levels of RFB or its 25-RFB metabolite. A 6th subject was withdrawn due to a protocol violation. In the 141W94-RFP cohort, one subject was withdrawn due to rash, after completing 141W94, but before starting RFP treatment.

Adverse events occurring in 2 or more subjects are summarized in Table 40.

Table 40. Drug-related Adverse Events

	141W94/RFB			141W94/RFP		
Adverse Event	141W94	RFB	141W94/RFB	141W94	RFP	141W94/RFP
Oral numbness	3 (25)			8 (67)		
Headache	2 (17)	2 (17)	5 (45)			
Dizziness	3 (25)			2 (17)		
Oral/perioral paresthesias				2 (17)		
Nausea	4 (33)		4 (36)	4 (33)		3 (27)
Diarrhea			2 (18)			
Gastric upset			2 (18)	2 (17)		
Vomiting			3 (27)			
Flatulence				2 (17)		
Fever			4 (36)			
Pain in body			2 (18)			
Chills			2 (18)			
Weakness			2 (18)			
Abnormal urine color						
Myalgia		3 (25)	3 (27)			
Back pain			3 (27)			
Rash			2 (18)			
Decreased libido				2 (17)		

Comment: Regarding the interpretation of the PK data and the conclusions of this study, see the Biopharmaceutics review. Because of the study design and its relatively short duration, this study provides limited safety information. It does, however, suggest that oral numbness, and nausea are APV (141W94) associated, and perhaps also dizziness. The study is not contributory to the efficacy conclusions of this application.

7. PROA 1013 A Study to Investigate Whether there is a Pharmacokinetic Interaction between 141W94 and Clarithromycin Following Their Co-administration to Healthy Male Volunteers

Summary: This PK interaction study was designed to examine possible interactions between 141W94 and Clarithromycin (CLAR) in HIV-seronegative healthy male adult subjects. Fourteen were enrolled and 12 completed the study. There were three treatment periods, each lasting 4 days with no wash-out between treatment periods, and with dosing that included 141W94, CLAR, or the combination in one of three sequences, to which subjects had been randomized.

Safety results: There were no deaths and no serious adverse events. Two subjects withdrew from treatment. One withdrew during the second treatment period (141W94+CLAR) with complaints of nausea and vomiting, and another withdrew after completing the third treatment period (141W94+CLAR), but before blood sampling was complete. All adverse events were mild, except for two reported as moderate; of the latter, one subject complained of arthralgia/joint ache during treatment with CLAR, the other subject experienced back and rib pain while on 141W94+CLAR. Selected more frequent adverse events, independent of attribution, are

summarized:

Table 41. Subjects having selected, more frequent adverse events			
	141W94	Clarithromycin	141W94+Clarithromycin
Oral/perioral numbness	6 (43%)	0	10 (71)
Nausea	5 (36)	1 (8)	7 (50)

Comment: For the PK conclusions of this study, see the Biopharmaceutics review. Because of the relatively short duration and study design, this study provides relatively little safety information, but amprenavir (141W94) related adverse events are consistent with those seen in other studies. This study is not contributory to the efficacy conclusions of this application.

8. PROA2001 A Phase I/II Screening Trial to Identify Potential Partner Compounds to use in Combination with 141W94

Summary: The study is a randomized, open-label multicenter study to provide PK, safety and antiviral activity data on APV as monotherapy or in combination with other protease inhibitors (SAQ (saquinavir)+APV *vs* IDV (indinavir) +APV *vs* NFV (nelfinavir) +APV *vs* APV); 34 HIV-infected subjects having CD4>200 and HIV RNA >10,000 were enrolled. APV, 800 mg TID, was used in each study arm. The APV monotherapy was administered for the first 3 weeks of the study for PK evaluation, then 3TC/ZDV were added. This report provides the first 24 weeks of data from this study.

Safety Results: There were no deaths during the study. Serious adverse events. Three subjects had serious adverse events, all in the APV/NFV treatment group; none was thought by the investigator to be drug-related and no subjects were permanently discontinued from study treatment. Subject 305 had bradycardia, fatigue and stress at Week 12 (both study drugs interrupted) and again at Week 20; at this time, the study medications were permanently discontinued and the subject was withdrawn from the study. However, at the Week 12 follow-up visit, this subject again had bradycardia, and the investigator concluded that bradycardia was unrelated to study drug. Subject 308 had hypertriglyceridemia, and 317 had pneumonia.

Severe or Grade 3/4 adverse events. Subjects having severe or Gr 3/4 adverse events are summarized in Table 42.

Table 42. Grade 3/4 adverse events				
Treatment group	Subject No.	Event	Serious?	Severe/Gr 3/4
APV/IDV	369	hypertriglyceridemia, fever	N, N	N, N
	341	hypertriglyceridemia	N	N
APV/NFV	308	hypertriglyceridemia	Y	N
	317	pneumonia	Y	N
APV	312	oral/perioral lesions	N	Y
	381	asthma	N	N

No subjects developed *de novo* diabetes mellitus, but one having Gr 2 hyperglycemia at entry worsened to Gr 3 during the study, which in the investigator's opinion was related to study drug. Two subjects receiving APV/IDV developed urinary calculi; these were ascribed to study medications.

The most common adverse events were diarrhea, oral/perioral paresthesia, nausea, headache, gaseous symptoms, loose stools and rash.

Comment: This interim report provides information on the first 24 wks of this study. It is a small study, with fewer than 10 subjects per group. The dosing regimen for APV used in this study is 800 mg TID, not the 1200 mg BID regimen for which an indication is sought in this

NDA. For these reasons, the study is viewed as non-contributory to the major efficacy conclusion of this application. The safety information contributes to the safety data base of the application.

9. PROA 2002 A Phase II Study to Investigate the Safety, Tolerability, Pharmacodynamics and Antiviral Activity of Multiple Dosing of 141W94 in Combination with Zidovudine/3TC in Patients with HIV Infection

Summary: The study is randomized, partially blinded, and conducted in subjects (N=84) having no prior PI or 3TC therapy, and with CD_4>150 cells/mm^3 and HIV-RNA>10,000 copies/ml. Subjects were randomized to one of 4 treatment groups: (I) APV, 900mg BID,(open-label); (ii) APV 1050mg BID, (blinded); (iii) APV 1200 mg BID, (open-label) (iv) PLA (blinded); all subjects also received AZT+3TC. The blinded portion of the trial was conducted for 12 wks, then PLA recipients were rolled over to APV 1050mg BID. The study duration continued until the last subject had been treated for 48 weeks.

Safety Results:

(I) Deaths. There were no deaths during the study.

(ii) Serious adverse events. Serious adverse events judged by the investigator to be study drug-related are summarized in Table 43.

Table 43. Serious adverse events by study treatment and study period

Treatment/subject	Adverse Event	Study Drug discontinued?	Drug related?	Maximum intensity
PLA				
Weeks 0-12:				
468/M	increased lipase levels	decreased/stopped temporarily	no	Gr 4
607/M	neutropenia	no	yes	Gr 4
900 mg APV BID				
Weeks 0-12				
453/F	asthma	no	no	Gr 4
467/M	anemia	stopped permanently	yes	Gr 2
566/M	rash	stopped temporarily	yes	Gr 3
Week 13-end of study				
499/M	lower respiratory infection	no	no	Gr 1
	pleuritis	no	no	Gr 2
552/M	hepatitis A	decreased/stopped temporarily	no	Gr 4
609/M	hypertriglyceridemia	no	yes	Gr 4
	hypertriglyceridemia	no	yes	Gr 4
1050 mg APV BID				
Weeks 0-12				
none				
Weeks 13-end of study				
486/M	gastrointestinal ulcer	decreased/stopped temporarily	no	Gr 4
490/M	lower respiratory infection	decreased/stopped temporarily	no	Gr 4
494/M	viral infection (Epstein-Barr)	no	no	Gr 2
	B-cell lymphoma	stopped permanently	no	Gr 4
551/M	fracture	no	no	Gr 3
604/M	attempted suicide	no	no	Gr 2
606/M	anemia	decreased/stopped temporarily	yes	Gr 3

1200 mg APV BID				
Weeks 0-12				
454/M	pneumonia	no	no	Gr 3
457/M	Stevens-Johnson syndrome*	stopped permanently	yes	Gr 4
478/M	rash	stopped permanently	yes	Gr 4
581/M	rash	stopped permanently	yes	Gr 2
Week 13-end of study				
470/F	dehydration	decreased/stopped temporarily	no	Gr 3
	viral GI infection	stopped temporarily	no	Gr 3
478/F	rash	stopped permanently	yes	Gr 4

* onset described as occurring one day after study drug discontinued

Rashes that were serious or Gr 3/4 and that occurred during the first 12 weeks of the study had an early onset time for all treatment groups; none had onsets >10 days after the first dose. One subject receiving APV, 1200 mg BID developed a Gr 4 rash diagnosed as Stevens Johnson syndrome.

(iii) More frequent adverse events. The selected examples of more frequent adverse events occurring during the first 12 weeks of the study are summarized in Table 44.

Table 44. Selected more frequent adverse events

Treatment	PLA n=20	APV 900mg BID n=20	APV 1050mg BID n=21	APV 1200mg BID n=20	Total n=80
Event, no, (%)					
Rash	2 (10)	3 (15)	3 (14)	10 (50)	18 (23)
Paresthesia perioral	0	4 (20)	5 (24)	5 (25)	14 (18)
Vomiting	1 (5)	4 (20)	4 (19)	3 (15)	12 (15)

(iv) Adverse events of special interest. *Lipodystrophy.* No adverse event of lipodystrophy was noted during the study. *Diabetes mellitus and hyperglycemia.* Three subjects developed hyperglycemia or diabetes mellitus.

(v) Laboratory Gr 3/4 events. Clinical chemistry and hematology abnormalities emerging on treatment, from Week 0 to end of study are summarized in Table 45.

Table 45. Subjects having Gr 3/4 laboratory events, by treatment

Laboratory abnormality	Treatment		
	900mg APV BID	1050mg APV BID*	1200mg APV BID
	n=20	n=39	n=20
ALT, Gr 3/4	3 (15%)	0	1 (5)
AST, Gr 3/4	1 (5)	0	1 (5)
Bilirubin, Gr 4	1 (5)	0	0
Hyperglycemia, Gr 3	0	2 (5)	0
Hypertriglyceridemia, Gr 3/4	3 (15)	8 (21)	2 (10)
Anemia, Gr 3	0	1 (3)	0
Neutropenia, Gr 3/4	2 (10)	1 (30	0

*includes subjects receiving PLA from Wk 0-12, but rolled over to APV 1050 mg BID for the remainder of the study

Comment: The study has as its stated efficacy-related objective "To obtain preliminary evidence of the activity of APV administered in combination with ZDV/3TC...". Two-thirds of the subjects receiving APV were randomized to lower doses than that being proposed for marketing. The safety information contributes to the safety data base of the application, including longer term safety information. Two subjects who discontinued study drug due to adverse events did so because of Grade 4 rash, including one case of Stevens Johnson syndrome.

10. PROA2003 An Open Label, Single Center Trial to Evaluate the Efficacy and Safety of Quadruple Chemotherapy (Zidovudine, EPIVIR, 1592U89, and 141W94) in Subjects Infected with HIV-1 (GW QUAD)

Summary: This non-randomized, open-label, single-arm uncontrolled study in 24 HIV-infected adults with no prior treatment with 3TC or APV examines effects of a four-drug regimen (ZDV, 3TC, abacavir (ABC) and APV) on efficacy measures and on safety. This report is an interim evaluation of treatment effects through Study Week 24.

Safety results: There were no deaths. Serious adverse events occurring during the study included bacterial gastroenteritis (Gr 3/4), increased CPK (Gr 4), hypercholesterolemia (Gr 3), and cat scratch disease (severe). Three subjects discontinued study drug due to adverse events: No. 906, nausea and fatigue; No. 907, vomiting, neuropathy; No. 910, taste disorder, headache, nausea. The most frequent adverse events regarded by the investigator as being treatment-related included nausea, diarrhea, vomiting, headaches, fatigue and rash.

> **Comment:** Because of the study design and small numbers of subjects, this study does not contribute to the efficacy conclusions of this application. Although this is an interim study report, it does provide limited safety information which contributes to the safety data base of this application.

11. CNAB2006 A Phase II Open-Label Observational Study of Changes in Immune Function and Lymph Node Architecture During Long Term Suppression of Viraemia associated with Early Combination Therapy with 1592U89 and 141W94 in Antiretroviral Naive HIV-1 Infected Subjects with a CD4+ Cell count ≥400 cells/mm^3

Summary: The study is an open-label observational, nonrandomized study in 47 subjects, to compare a treatment cohort receiving abacavir (ABC) 300 mg BID and amprenavir (APV) 1200 mg BID to a long term non-progressor (LTNP) cohort receiving no antiretroviral therapy. Entry criteria were not the same for the two study groups. The study is in progress. This interim study report is based on data through a 15 May 98 cutoff, and is limited to a summary of safety information.

Safety Results: Six-month safety information is available in 29 subjects, and 10 had completed the Wk 48 assessment at the 15 May 98 cut-off. There were no deaths. Serious adverse events occurred only in ABC/APV recipients (Table 46):

Table 46. Serious adverse events at 15 May 98 data cutoff

Subject no.	Event
2055	inguinal abscess
	injury to right leg
2066	increased ALT
2068	arrhythmia, coronary artery disorder and myocardial infarction
2102	bronchitis
	hypertriglyceridemia/hypercholesterolemia
2116	increased ALT and AST

Seven subjects discontinued study drugs prematurely, all in the ABC/APV treatment group (Table 47).

Table 47. Subjects discontinuing study drugs prematurely (ABC/APV treatment group)

Subject no.	Reason for study drug discontinuation

2068	Adverse event
2075	rash
2099	rash
	pancreatitis
2110	
2058	Clinical progression
2123	Personal decision
2113	Personal decision
	Personal problems

Abacavir hypersensitivity developed in two stubjects (2068, 2075).

Subject 2099 with baseline Gr 3 amylase and Gr 1 ALT had variable amylase levels throughout the study, resulting in five interruptions of study medication prior to permanent discontinuation of study medication at Wk 24, with the diagnosis of pancreatitis.

Safety events of special interest. No hemolytic anemia or lipodystrophy syndrome were identified. *Increased bleeding in hemophiliacs*: no such subjects were enrolled. *Rash*. Seven subjects developed rash. Four were maintained on study medication; rash resolved spontaneously. Two had recurrent rash on ABC rechallenge (summarized above). One (2091) was successfully rechallenged, first with ABC then with APV, and remained on study medication. *Hypertriglyceridemia/hypercholesterolemia*. Subject 2084 had Gr 1 triglyceride and cholesterol elevations at baseline; at D 58 and D 114 respectively,Gr 3 triglycerides and Gr3 cholesterol were found. Subject 2102 had Gr 4 triglyceride elevation at screening and data cutoff. *Hyperglycemia/diabetes mellitus*. No significant changes from screening/baseline noted.

> **Comment:** Because of its design, this study does not contribute to the major efficacy conclusions of the application. Because of the non-randomized nature of the study and enrollment of different populations in the two study groups, a comparison of safety information between study groups is inappropriate. The uncontrolled safety information in this study contributes to the safety data base of the application.

12. CNAA 2007 A Phase II Study Evaluating the Safety and Antiviral Activity of Combination Therapy with 1592U89, 141W94 and DMP 266 (SUSTIVA) in HIV-1 Infected Subjects with Detectable HIV-1 Plasma RNA Despite Treatment with a Protease Inhibitor Containing Regimen

Summary: This is a phase II, open-label, single-arm multicenter study to evaluate the safety and antiviral activity of combination treatment with APV, ABC, and efavirenz (EFV) in subjects had evidence of partial/complete resistance to another protease inhibitor. These were mostly advanced patients who had been heavily pre-treated with other antiretroviral agents; 87% had > 2yrs of ART. Of 101 subjects enrolled, this preliminary study report provides safety information for 99 subjects who received at least one dose of assigned treatment (APV/ABC/EFV).

Safety Results: There were no deaths. Serious adverse events are summarized in Table 48.

Table 48. Serious adverse events (permanent discontinuation of therapy , event intensity, and investigator-assessed drug relationship)

Subject no.	Event (s)	Treatment discontinued?	Severe/Gr 3/4?	Drug-related?

13735	depression	n	y	n
13649	cancer of lung, pericardial effusion	n, n	n/a, y	n,n
13734	hypertriglyceridemia	n	y	y
13676	hypertriglyceridemia	n	y	y
13722	vomiting, diarrhea, headaches	y,y,y	y,y,y	y,y,y
13687	bacteremia, sepsis	n,n/a	n,y	n,n
13688	basal cell carcinoma of skin, hypertriglyceridemia	n,n	n,y	n,y
13689	hypertriglyceridemia	n	y	y
13692	HIV related cholangitis	n	n	n
13693	carcinoma in situ	n	n	n
13751	abscess of leg	n	n	n
13642	neutropenia, abdominal pain	n,n	y,y	y,y
13671	anxiety with panic, depression	y,y	y,y	y,y
13666	hypertriglyceridemia	n	y	y
13720	hypertriglyceridemia	n	y	y

Severe and Grade 3/4 adverse events that occurred in more than one subject are listed in Table 49.

Table 49. Severe and Grade 3/4 adverse events, occurring in more than one subject

Event	N (%)
hypertriglyceridemia	7 (7)
diarrhea	4 (4)
depressive disorders	3 (3)
anxiety	2 (2)
neutropenia	2 (2)
headaches	2 (2)
vomiting	2 (2)

Subjects who discontinued study drug due to an adverse event are summarized in Table 50.

Table 50. Adverse events leading to study drug discontinuation

Subject	Event	Serious (Y/N)	Drug-related (Y/N)
13710	rash, fever	n,n	y,y
13654	malaise, chills, fever	n,n,n	y,y,y
13700	rash	n	y
13723	fatigue, rash, rash	n,n,n	y,y,y
13727	diarrhea	n	y
13672	rash	n	y
13716	vomiting, nausea, dizziness, dyspnea, fiver, chills, pruritus	n,n,n,n,n,n,n	y,y,y,y,y,y,y
13722	diarrhea, vomiting, headaches	y,y,y	y,y,y
13751	rash, pruritus, fever, rash	n,n,n,n	y,y,y,y
13703	rash, rash	n,n	y,y
13704	pruritus, rash	n,n	y,y
13641	nausea, bloating	n,n	y,y
13650	fatigue, fever, rash	n,n	y,y
13695	rash	n	y
13698	fatigue, disturbance in concentration	n,n	y,y
13724	nausea, vomiting, rash	n,n,n	y,y,y
13725	fatigue	n	y
13671	anxiety with panic, depression	y,y	y,y
13668	rash, fever	n,n	y,y
13730	rash	n	y

Grade 3/4 laboratory toxicities on treatment are summarized in Table 51.

Table 51. Grade 3/4 laboratory toxicities

Laboratory measure	Grade	Number
Chemistry		
alkaline phosphatase	3	1
amylase	3	3
AST	3	1
hyperglycemia	3	2
hypertriglyceridemia	3	5
	4	5
Hematology		
neutropenia	3	5
total WBC decreased	3	1

Comment: Because of its design (open-label, single-arm), this study does not contribute to the efficacy conclusion of this application. The study does contribute to the safety data base.

Assessment, Phase I/II studies:

1. Safety. These Phase I/II contribute to the safety data base of this application. In aggregate, they provide similar safety information to that obtained in the controlled Phase III clinical trials.

2. Efficacy. These studies do not directly support the efficacy conclusions of the Phase III studies. In several studies, however evidence of antiviral activity was sought and was demonstrated. These studies are thus generally supportive of the efficacy conclusion of the Phase III studies.

X. Non-study-specific safety considerations

A. Excipient content of amprenavir formulations (capsules and oral solution)

Vitamin E. ——— glycol succinate (TPGS), a major excipient of both formulations of amprenavir, is hydrolyzed in the body to tocopherol (vitamin E), propylene glycol and succinic acid. It is only used infrequently as an excipient in drug formulation. Because of the limited experience in humans with TPGS as excipient, and because of the large amounts of TPGS in both amprenavir capsules or oral solution, the vitamin E exposure in amprenivir recipients is unusually high. The compositions of commercial 150 and 50 mg amprenavir soft gelatin capsules and oral solution (used in Phase 3 clinical trials and intended for marketing) and placebo soft gelatin capsules, are summarized (see Fax of 21 Dec 98, NDA Amendment of 2 Dec 98). (See Appendix 3 for additional information on capsule compositions used at earlier stages in amprenavir development.) All quantities are mg per capsule.

Component	APV capsule	placebo
Amprenavir	150.0 mg	0 mg
TPGS	———	———
PEG 400, NF		
Propylene glycol, USP	———	———
Fill weight		

The fill solution for the 50 mg capsule has an identical composition to that of the commercial 150 mg capsules. The placebo capsules have a composition that is almost identical to that of the corresponding drug product, with ——— replacing amprenavir.

Animal studies. Animal studies were not conducteded to specifically address whether administration of the excipient alone resulted in toxic effects, or excipient dose-dependent toxicities.

Vitamin E Reference Daily Intake and daily APV dose. Each 150 mg APV capsule contains 109 IU vitamin E; the total daily adult dose of APV (2400 mg) contains 1744 IU. The Reference Daily Intake (RDI) for vitamin E is: adults, 30 IU, pediatrics, approximately 10 IU. Thus, the vitamin E contained in total daly adult dose of APV is approximately 58-fold that of the RDI. The liquid formulation provides more than four times as much vitamin E as the capsule formulation at equivalent doses. A 20 kg child would receive almost 3000 IU vitamin E per day at the recommended dose of 22.5 mg/kg BID of the oral solution.

Literature review: There is a substantial literature on vitamin E administration, including assessment of vitamin E-associated toxicity. There is rather little information on vitamin E administration at the doses that will be provided by amprenavir capsules, 2400 mg/day. No data is available from the literature to address the long-term effects of vitamin E at the dose provided by the recommended APV dose, and particularly, in the HIV-infected population. The available information does indicate that high vitamin E doses may exacerbate the blood coagulation defect of vitamin K deficiency caused by anticoagulant therapy or malabsorption.

Clinical studies. Study 3001 compares APV *vs* PLA (soft gelatin capsules) in adults. Because the placebo capsules have an almost identical excipient content to APV capsules, and because rash, GI events (nausea, vomiting, diarrhea) and paresthesias are seen only in APV recipients, this permits clear attribution of these adverse events to amprenavir, not to excipient component(s). Clinical studies do not, however, directly address the contribution of excipients in amprenavir capsules to adverse events seen in humans. The most useful information at this time is that no adverse events have yet been identified that are either unexpected in the HIV-infected population and/or that are not also seen with approved therapies or found in these studies to be associated with amprenavir therapy.

B. Sulfonamide structure

The chemical structure of amprenavir includes a sulfonamide-like moiety. The adverse event profile of amprenavir is in some respects similar to that of other sulfonamides. The most notable of these is rash, which has occurred in 18-25% of amprenavir recipients in Phase 3 trials, in 28% of amprenavir recipients in all multidose trials; 4% of rash in amprenavir recipients is serious, including cases of Stevens Johnson syndrome. While rash occurs as an adverse event in patients receiving other HIV protease inhibitors, the rates of rash in amprenavir recipients is much higher.

At the FDA's request, the Applicant reviewed adverse events occurring in subjects with a documented history of sulfonamide allergy who had also received amprenavir therapy. The applicant's review also included a summary of adverse events for subjects who received amprenavir and sulfonamides concomitantly. In their analysis of the potential for sulfonamide-like related adverse events with amprenavir administration, the applicant noted several points. These are presented, with reviewers' comments.

1. *Three non-clinical toxicology studies provided no evidence that amprenavir administration resulted in sensitization.* Negative animal studies do not exclude the possibility that amprenavir sensitization in humans may occur.

2. *Cross-sensitivity among related compounds is about 20% and therefore, even if cross-sensitization occurred between sulfonamides and amprenavir, the rate of reactions occurring by this mechanism are unlikely to be clinically signficant.* Adverse events ascribed to cross-sensitization may indeed be infrequent in healthier HIV-infected individuals, but this statement does not address the potential for reactions occurring *de novo* after amprenavir administration and the subsequent sensitization to sulfonamides. Also, it does not address the known increased rate and severity of reactions noted in individuals with AIDS.

3. *Rates of sulfonamide-type adverse reactions were much higher in HIV-infected subjects receiving trimethoprim-sulfamethoxazole (TMS-SMX) as prophylaxis of treatment of Pneumocystis carinii pneumonia than those treated with amprenavir.* HIV-infected patients receiving TMP-SMX as prophylaxis or treatment experience allergic reactions to TMP-SMX at a very high rate, but these patients have relatively advanced HIV disease. The population included in the amprenavir safety database included a relatively healthy population of HIV-infected subjects, making the comparison an inappropriate one, as these are not comparable populations.

XI. NDA ——, Oral Solution

NDA —— is the application for approval for marketing of the amprenavir (formerly 141W94) oral solution. This NDA was submitted on 7 Dec 98, and consists of a single volume. It contains by cross-reference information contained in NDA 21-007. The amprenavir oral solution contains 15 mg amprenavir/ml of solution and is intended to be administered by the oral route.

NDA 21-039 consists primarily of Chemistry, Manufacturing and Controls (CMC) information for agenerase oral solution. This submission provides updated stability data, 6 months, for drug product. The annotated package insert and draft container labels are also submitted.

Clinical information in NDA 21-007(submitted 15 Oct 98) is included in NDA 21-039 by cross-reference. Additional clinical data from ongoing clinical trials in pediatrics patients, PROB 2004 and PROAB3004 were submitted to NDA 21-007 on 16 Nov 98.

Please see the NDA 21-007 review for a review and summary of the clinical data from pediatric trials in which the aprenavir oral solution was studied.

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XII. Summary of Safety and Efficacy

A. Dose selection

Dose-escalation and phamacokinetic studies and phamacodynamic modeling were used in dose selection.

1. Adult dose. In a dose-escalation study (PROA 1002), subjects (10-12 per dose) were given amprenavir monotherapy at total daily doses of 600-2400 mg/day (300 mg BID, 300 mg TID, 900 mg BID, 1050 mg BID, 1200 mg BID) for 4 weeks. The antiviral response by dose at Week 4, as measured by median change in plasma HIV RNA $\log_{10}$ copies/ml from baseline, was: 600 mg/ day: +0.14 $\log_{10}$ copies; 900 mg/day: -0.58 $\log_{10}$ copies; 1800 mg/day -1.26 $\log_{10}$ copies; 2100 mg/day: -1.83 $\log_{10}$ copies; 2400 mg/day: -1.59 $\log_{10}$ copies. A categorical analysis of safety showed a relationship between increases in $C_{min,ss}$ and headache or oral numbness.

Pharmacodynamic studies examining the relationship between minimum amprenavir concentration at steady state ($C_{min,ss}$) and decrease in virus titer, as measured by the time-weighted average of HIV-RNA AUC minus baseline (AAUCMB) estimated that a $C_{min,ss}$ of 0.23 µg/ml would provide 90% of the maximum antiviral activity (EC_{90}). The $C_{min,ss}$ for the 1050 mg BID and 1200 mg BID doses was 0.29 and 0.28 µg/ml, respectively and thus did not distinguish between these doses; small number of subjects at the 1200 mg BID dose had data available. Both doses exceeded the EC_{90}.

A subsequent dose comparison study (PROA 2002) studied 1800-2400 mg/day: 900mg BID, 1050mg BID, 1200mg BID vs PLA, on a background of AZT/3TC. A comparison of antiviral effects at Week 12 (protocol-specified efficacy comparison) did not establish convincing dose-related differences between doses.

Study PROA1010 was a single-dose PK study and included a comparison of the fasted and fed state. It showed that oral bioavailablity of amprenavir was reduced by a high-fat meal. The difference was such that, in conjunction with PD modeling, it was estimated that the the percent of maximal antiviral response observed over 4 weeks would be 93% vs 88% for median $C_{min,ss}$ for the 1200 mg BID dose taken in the fasted state vs high-fat meal. This food effect favored selection of the 1200 mg BID dose over the 1050 mg BID dose.

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 decrements in virus titer. It was estimated that a more than 2-fold increase in dose would be required to decrease the AAUCMB a further 0.11 $\log_{10}$ HIV RNA copies (the difference between the EC_{90} and EC_{99}). The safety of the 1200mg BID dose was considered to be acceptable.

2. Pediatric dose. The pharmacokinetics of the amprenavir oral solution was studied in children using BID and TID dosing regimens, with the rationale that a TID regimen may aid in tolerability and compliance in some pediatric patients. Comparative PK data using the oral solution in children and the capsule formulation in adults indicates that the amprenavir oral solution, when given 22.5 mg/kg, BID or 17 mg/kg TID, produce exposures in children (>4 years) that are similar to those seen in adults given the capsule formulation. The results of these studies also indicate that Amprenavir is 14% less bioavailable from the liquid formulation than from the capsulses, and therefore amprenavir capsules and amprenavir oral solution are not interchangeable on a milligram per milligram basis.

B. Safety

The material reviewed included (i) safety information provided in individual completed study reports submitted with the NDA, (ii) safety information in ongoing studies submitted to the NDA, (iii) the Integrated Summary of Safety (ISS) of the application, (iv) the 28 Oct 98 24-week Efficacy and Safety Update of ongoing studies, and

(v) the 23 Dec 98 Safety Update of ongoing studies.

1. Extent of exposure. A total of 2095 subjects were enrolled in 30 APV studies. According to the 23 Dec safety update, 1477 subjects had been treated with at least one dose of APV as of 1 Sept 98; 550 subjects had been with treated APV at the intended marketing dose for at least 24 weeks (Table 52).

Table 52. Extent of exposure to APV, 2400 mg/day (28 Dec 98 Safety Update)

Study	Subjects having ≥24 Wks Exposure
Non-phase 3 PROAB 1002, PROA 2001, PROAB 2002, PROA 2003, CNAB 2006, CNAA 2007, PROAB 3004, NZTA 4002, ACTG 347	28, 24, 11, 26, 23, 70, 8, 44, 70
Phase 3 studies: PROAB 3001, PROAB 3006	111, 135
Total	550

2. Deaths. Three deaths have been reported in all studies submitted to the NDA. These were not amprenavir-related.

3. Serious adverse events (see Appendix 2 and study summaries). Selected serious adverse events are noted below:

a. Rash. Rash was the most frequent amprenavir-associated serious adverse event and in several subjects resulted in hospitalization. Two subjects have thus far developed Stevens Johnson syndrome.

b. Psychiatry-related events. In studies 3006 and 3001, there were 6 amprenavir recipients who were hospitalized with one or more of the following: depression, attempted suicide, suicidal/homicidal ideation, drug or ethanol addiction or withdrawal syndrome, whereas there were 2 such subjects hospitalized with similar events in controls.

c. Hemolytic anemia. One subject was hospitalized for hemolytic anemia 12 weeks after initiation of APV, with brown urine, increased LFT's, and a fatty liver; the event was attributed by the investigator to APV.

d. Transaminase elevations (Grade 4). One subject had Grade 4 transaminase elevations while on amprenavir, which was interrupted; when rechallenged with amprenavir, Grade 4 transaminase elevations recurred.

e. Other Grade 4 lab events. Hypertriglyceridemia and CPK elevations were each reported in several patients.

4. Adverse events resulting in study drug discontinuation. These events include rash, gastrointestinal events (nausea, vomiting, diarrhea, abdominal pain) and paresthesias, both perioral and peripheral (Table 53). These adverse events limit drug tolerability, an effect seen in both Phase 3 studies. These were often graded as mild or moderate (Gr 1/2), but nevertheless had the important effect on discontinuation of amprenavir. Thus, these adverse events are likely to have major impact on amprenavir compliance, as determined by how long *and* how faithfully patients take amprenavir.

Table 53. Adverse event onset, duration, intensity and study drug modification, by event

Adverse Event	Days to onset-median	Duration, days-median	Intensity by Grade				Study Drug Modification (%)		
			Gr 1	Gr 2	Gr 3	Gr 4	No change	Temp. D/Ced	Perm. D/Ced
nausea	5	16	67%	28	5	0	81%	8	11
diarrhea	8	15	60	37	3	0	93	3	4
rash	10	10	40	51	7	1	43	47	11
oral paresthesias	2	48	95	5	0	0	97	2	1

headache	14	14	67	33	0	0	92	4	3
fatigue	10	29	75	22	2	0	93	4	4
vomiting	21	3	72	24	4	0	75	14	11
loose stools	7	36	86	14	0	0	98	0	2

5. More frequent adverse events. Clinical adverse events attributable to amprenavir (disproportionatly represented in amprenavir recipients in Studies 3001 and 3006) are rash, gastrointestinal events (diarrhea, nausea, vomiting), and paresthesias (oral/perioral and peripheral).

Events (all grades) reported in ≥ 5% of subjects and in an equal or greater proportion of APV recipients than in controls are summarized in Table 54.

Table 54. Adverse events reported in ≥ 5% of subjects in equal or greater proportion of APV recipients than in controls in both studies

	PROAB3001 (background therapy: AZT/3TC)		PROAB3006 (background therapy, NRTI's)	
	PLA (N=109)	APV (N=113)	APV (N=245)	IDV (N=241)
Adverse Event	n (%)	n (%)	n (%)	n (%)
Diarrhea	27 (25)	28 (25)	113 (46)	66 (27)
Nausea	54 (50)	83 (73)	94 (38)	62 (26)
Paresthesia (oral/perioral)	5 (5)	29 (26)	73 (30)	4 (2)
Vomiting	18 (17)	33 (29)	49 (20)	27 (11)
Rash	6 (6)	28 (25)	43 (18)	25 (10)
Paresthesia (peripheral)	3 (3)	6 (5)	22 (9)	17 (7)
Triglyceride increased	5 (5)	10 (9)	10 (4)	9 (4)

e. *Laboratory abnormalities.* When compared to placebo (Study 3001), a higher proportion of amprenavir recipients had hyperglycemia, hypertriglyceridemia and hypercholesterolemia. When compared to the indinavir treatment group (Study 3006), amprenavir recipients had similar proportions of subjects with these laboratory abnormalities.

C. Efficacy

The efficacy conclusion for amprenavir treatment is based on the 24 week (interim) analyses of the two Phase 3 studies, 3001 and 3006.

Study 3001 compares the efficacy of amprenavir to placebo (on a background of 3TC/ZDV) in therapy-naive HIV-infected patients by evaluating the proportion of subjects with undetectable plasma HIV-1 RNA (<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 HIV-1, and that APV adds benefit to approved therapy (ZDV/3TC); in a clinical endpoint study, ZDV/3TC was shown to provide significant survival benefit over ZDV alone.

The CD4 response in both treatment groups showed a progressive increase over time; at Week 24, APV recipients had 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.

Study 3006 compares the efficacy of amprenavir to indinavir (on a background of NRTIs) in therapy-experienced HIV-infected patients by evaluating the proportion of subjects with undetectable plasma HIV-1 RNA (<400 copies/ml). At Week 24, the FDA analysis showed that a higher proportion of amprenavir recipients failed randomized therapy than was the case for subjects randomized to indinavir. The analysis showed that when APV and IDV were given with NRTI's, the proportion of subjects having plasma HIV-1 RNA

reduced to undetectable levels (<400 copies/ml, assay limit of quantification, 400 copies/ml) and did not have a CDC class C event at Week 24 was 42.5% vs 53.2% for APV vs IDV, respectively, a difference of -10.8% (95% CI, -19.3%, -2.3%). The difference between the treatment arms was statistically significant (p=0.014).

The chief contribution to treatment failure in APV recipients was a greater frequency of adverse events leading to study drug discontinuation (chiefly gastrointestinal events, particularly nausea, vomiting, diarrhea, abdominal pain, and rash) than occurred in IDV recipients. Adverse events accounted for 8.5% of the total 10.8% difference between treatment groups. There was a greater increase in CD_4 cells in the IDV group than in APV recipients, but interpretation of these data was complicated by the numbers of subjects who had discontinued study drug at this time. One APV recipient and 3 IDV recipients had developed CDC class C events at this time.

Several features common to both studies are worth noting. In amprenavir recipients, adverse events (rash, gastrointestinal events, paresthesias) were similar in type and relative frequency in both studies and accounted for a disproportionate number of discontinuations in the amprenavir treatment groups. The large numbers of discontinuations in the amprenavir treatment groups complicated the interpretation of the efficacy analysis.

Both studies were conducted in relatively healthy HIV-infected individuals; in both studies, the median CD_4 cell count was approximately 400 cells/mm^3. CD_4 cell counts generally increased in both treatment groups in each of these studies. There was some variability of results over time. CD_4 responses from clinical trials in in this population (CD4 approximately 400) is quite limited, and cautious interpretation of CD4 results may thus be warranted. The CD4 responses in these Phase 3 studies are regarded as generally supportive of the efficacy conclusion based on HIV RNA.

The relatively healthy population enrolled likely accounts for the small number of clinical endpoints observed in both studies.

Besides these Phase 3 studies, there is supportive information from Phase 1/2 studies indicating that therapy combinations that includes amprenavir may have long-term effects on HIV; some individuals have plasma HIV RNA sustained at <400 copies/ml over many months.

XIII. Reviewer's assessment

A. Risk-benefit assessment

1. Risk. Risks associated with amprenavir therapy include toxicity-related events and the development of protease inhibitor resistant HIV under the selective pressure of amprenavir therapy. With respect to amprenavir toxicity, no APV-related deaths have yet been identified. Regarding serious toxicity, the chief amprenavir-associated severe or life-threatening toxicity recognized to date is rash, which can include Stevens Johnson syndrome. Single cases of hemolytic anemia and recurrent Gr 4 transaminase elevation with amprenavir rechallenge are of concern, but because of their isolated occurrence, are difficult to interpret at this time. Other toxicities include gastrointestinal toxicities (nausea, vomiting, diarrhea, abdominal pain) and paresthesias (oral/perioral and peripheral). These occur quite frequently and are significant not because they are life-threatening, but because of their impact on drug compliance, emergence of resistance, and thus on efficacy. Effects of these adverse events on circulating drug levels have not been defined. The amount of information on HIV resistance to amprenavir, and cross-resistance between amprenavir and other members of the protease inhibitor class of antiretrovirals is poorly defined and does not permit clear risk assessment in humans.

Other potential risks that remain to be defined are ones associated with chronic, high-dose vitamin E exposure, and sensitization and cross-sensitization with other sulfonamides.

2. Benefit. A previously conducted clinical endpoint study has shown that 3TC, when used in conjunction with AZT, provides a statistically significant survival benefit over AZT alone. In NDA 21-007, interim analysis of Study 3001 shows that amprenavir, when used in combination with AZT/3TC, adds benefit to approved therapy by maintaining an effect on HIV RNA which is sustained through Week 24. This benefit is defined as maintaining plasma HIV RNA to <400 copies/ml, which is regarded as a surrogate marker likely to result in suppression of HIV RNA at 48 weeks. Thus, when used in conjunction with other antiretroviral agents, the evidence supports the conclusion that amprenavir therapy has an effect on surrogate markers likely to be associated with clinical benefit in HIV-infected individuals. Study 3006 supports this conclusion, although the difference in antiviral activity at 24 weeks between amprenavir and indinavir recipients suggests that amprenavir may be less effective than indinavir, largely because amprenavir is less tolerable than indinavir.

B. Therapeutic use. As the fifth member of the protease inhibitor class of antiretrovirals to receive regulatory review, amprenavir provides a therapeutic option in a disease where new therapeutic agents continue to be needed. Its use is likely to be limited by its tolerability.

XIV. Phase IV commitments.

1. The applicant will continue to study and report the safety and efficacy of amprenavir used in combination with other antiretroviral agents to demonstrate the utility of amprenavir in various patient populations, including protease-inhibitor experienced and advanced HIV-infected (salvage) patients, by initiating or completing the following clinical trials:

- ACTG 398 Phase 2 randomized trial of amprenavir in combination with abacavir, efavirenz, and ———
- ACTG 400 Phase 2 open-label trial of antiviral therapy (efavirenz plus two nucleoside reverse transcriptase inhibitors plus at least one new protease inhibitor) for nelfinavir failures,
- PRO20005 Phase 2 open-label trial for treatment of HIV infection in subjects who have failed initial combination therapy with regimens containing indinavir or nelfinavir. This study assesses combination therapy with amprenavir, lamivudine, and abacavir plus either nelfinavir or indinavir for 48 weeks,
- CNAA2007: A Phase 2 study evaluating the safety and antiviral activity of combination therapy with amprenavir, abacavir, and efavirenz in HIV-1 infected subjects with detectable plasma HIV-1 RNA despite

treatment with a protease inhibitor-containing regimen for 48 weeks, and
• Safety data for patients with CD4 cell count < 100 at entry will be provided from ACTG398, ACTG400, PRO20005, CNAA2007, and the Agenerase Early Access program. In addition, the applicant agrees to submit a plan for review by the Division of Antiviral Drug Products (DAVDP) for studying patients with advanced HIV infection.

2. The applicant agrees to prepare and submit a supplemental NDA for traditional approval of Agenerase products. This application will include exploration of any gender-related differences in safety and efficacy outcome measures.

3. The applicant agrees to provide data on HIV-infected pediatric patients as agreed to in the Written Request dated April 7, 1999. In addition, the applicant agrees to further discussions with DAVDP of appropriate pre-clinical toxicology evaluations that would support the administration of amprenavir to neonates.

4. The applicant agrees to propose and conduct a study of a) the tolerability of amprenavir in patients with a known sulfonamide allergy, and b) the tolerability of sulfonamide therapy after patients have been treated with amprenavir.

5. The applicant agrees to propose and conduct an evaluation of the safety of chronic, high-dose Vitamin E administration in adults and pediatric patients receiving amprenavir, including the evaluation of vitamin E levels.

6. The applicant agrees to submit reports of completed carcinogenicity studies in a timely manner.

7. The applicant agrees to initiate or complete drug-drug interaction studies of amprenavir with ritonavir, efavirenz, nevirapine, methadone, and a representative female hormonal contraceptive product.

8. The applicant agrees to evaluate resistance to amprenavir and cross-resistance to other protease inhibitors in sequential HIV isolates from patients maintained on amprenavir in clinical trials, including:
• determination of *in vitro* susceptibility of HIV isolates to amprenavir,
• assessment of the genotypic basis of drug susceptibility attributable to the viral target genes and extragenic sites, such as the protease cleavage sites, and
• assessment of cross-resistance of amprenavir-resistant variants to other protease inhibitors and vice versa.

9. The applicant will investigate lipid metabolic pathways through *in vitro* studies. The applicant also agrees to investigate the possible mechanisms for the development of fat redistribution in patients receiving protease inhibitors, the incidence of this event, and the potential for long-term consequences. In addition, ongoing and future clinical trials should provide appropriate monitoring for these events and for any lipid-related disorders.

10. The applicant agrees to complete and submit a report of the results of the experiments

[ ]

XV. Recommended regulatory action

It is recommended that this application for accelerated approval of amprenavir be approved.

/S/

John R. Martin. M. D.
Medical Officer

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concurrences:
HFD-530/DivDir/ HJolson
HFD-530/TL/TCvetkovich
cc: NDA
HFD-530
HFD-530/DivDir/ HJolson
HFD-530/TL/TCvetkovich
HFD-530/CSO/MTruffa
HFD-530/Chem/GLunn
HFD-530/Micro/LMishra
HFD-530/Biopharm/VTammara, PRajagopalan
HFD-530/PharmTox/OMcMaster
HFD-530/Stats/GSoon
HFD-530/MO/JMartin

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Appendix 1. Listing of studies in humans submitted to the NDA, including numbers enrolled and numbers exposed to at least one dose of APV, by study.

Studies submitted to the NDA, conducted in adults and children, with numbers enrolled and exposed to amprenavir		
Protocol No.	No. Enrolled	No. exposed to at least 1 APV dose
Primary Safety Population		
PROAB 3001	232	180
PROAB 3006	504	432
TOTAL	736	432
Secondary Safety Population		
PROA1002	62	61
PROA2001	34	33
PROA2002	84	79
PROA2003	42	41
PROB2004*	27	24
CNAA2004	17	14
CNAB2006	47	41
CNAA2007	101	99
PROAB3004*	127	104
TOTAL	541	496
Other Supportive Data		
ACTG347	92	92
NZTA4002	304	151
NZTA4005	87	2
TOTAL	483	245
Clinical Pharmacology Studies		
PROA1001	18	12
PROA1003	42	28
PROA1004	18	18
PROA1005	12	12
PROA1006*	20	20
PROA1007	6	6
PROA1008	30	30
PROA1009	20	20
PROA1010	39	39
PROA1011	29	29
PROA1012	24	24
PROA1013	14	14
TOTAL	272	252
Other Studies		
PROB3005	34	34
Atilla	1	1
CH-97-02	17	6
NIH-94-1-0202	11	11
TOTAL	63	52
TOTAL, All Studies	2095	1477

* studies in children

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Appendix 2. Serious adverse events, and adverse events leading to discontinuation of study treatment.

A. Serious adverse events, information abstracted from SAE case narratives.

Serious adverse events occurring in Phase III trials (3001, 3006)					
Subj No	Age/ Sex	Event	Grade	SAE Onset[1]	Notes
PROA3001 (APV 1200 mg BID vs PLA, plus ZDV/3TC)					
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 after 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	Gr 4, hosp	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 Wk 12, study meds d/ced, 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	?	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 Mogigesic (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					
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 2 wks. 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
PROA3006 (APV 1200 mg BID vs IDV 800 mg TID, plus nucleosides)					
Subj No	Age/ Sex	Event	Grade	SAE Onset[1]	Notes
APV					
2472	35 M	hypertriglyceridemia	Gr 4	Wk 1	Gr 2 at entry; resolved by Wk 16, on study Rx
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
2592	44 M	hypoglycemia	hosp	Wk 21	recent dx of hyperglycemia; event resolved while maintained on study drug
2598	31 M	migraines, ? meningitis,	hosp	Wk 2	history of depression; CT: meningeal enhancement;LP: no bacteria invest: rel to study drugs
2634	53 M	seizure dyspnea, cough	hosp hosp	Wk 13 Wk 21	history: asthma, seizure disorder; pneumonia exacerbation of bronchial asthma
2668	40 M	LOC, bradycardia, hypotension	hosp	Wk 5	history: syncope, R BBB; eval (EKG) Lt ant block, mild mitral insuffic
2693	49 M	suicidal/homicidal ideation	hosp	Mo 8	history of depression
2697	27 F	angioedema, itchy eyes// abd pain, V, constip, UTI	Gr3/H hosp	Wk 8, Wk 22	history of schistosomiasis; hosp: recurr strongyloides vs "non-study drug rel.allergy" vs vasculitis under consideration// Invest: 2° to GI parasite
2701	29 M	erythema, legs; CPK Gr4	hosp	Wk 6	history of cocaine/crack use; Invest: AE's rel to study Rx and/or concurrent cellulitis/myositis
2728	39 M	GI bleed;epigastric pain; neck mass p. tooth extr; pneumonia gastritis	hosp, hosp hosp hosp	Wk 5 Wk 29 Wk 31 Mo 10	history of peptic ulcer, smoking, occ EtOH; also Gr 2 rash; 2nd hosp: to r/o retropharyngeal absess or septic phlebitis, resolved on antibiotics;
2731	30 M	disorientation, confusion, unsteady balance	hosp	D 0	never received randomized APV; invest: attrib SAE to BACTRIM DS .
2830	42 M	Meniere's disease	Gr3/H	Wk 33	resolved in 3 wks while maintained on study drug
3092	32 M	AST/ALT/t-bili incr	Gr 4,4,4	Wk 21	history of HBV inf; event diagnosed as HB reactivation, study drug interrupted
3277	28 M	abd pain, dysuria/ suprapubic, groin pain	hosp hosp	Wk 1, Mo 4	poss UTI infection; "no indication of kidney stones"; thickening of terminal ileum/cecum; poss CMVD or Crohn's disease
3307	48 M	metastatic sqam. cell CA	hosp	Mo 5	20 yr history of squamous cell Ca of anus
3338	46 M	ulcerated throat	hosp	Wk 11	culture-positive for Streptococcus
3348	27 F	N+V, AST/ALT incr	?	D 3	history: alcohol & drug abuse, hep C; APV d/ced 2° N+V, AST/ALT incr 17 da later; invest: poss rel to HCV
3369	43 M	hypertriglyceridemia	Gr 4	Wk 20	triglycerides incr at entry, fluctuated on study nc study regimen not modified
3445	34 F	head trauma, coma	hosp	Wk 11	history: drug abuse; eval: skull fracture, soft tissue; ?EtOH related
3453	31 F	pregnancy		Mo 2	also on ddI/3TC
3459	45 M	SGOT/SGPT incr	Gr 4	D 12	ongoing Hep C, transaminase incr at entry: invest: post rel to study drug
3460	56 M	laryngeal CA recurrence	hosp	D 24	-
3482	34 M	SGOT/SGPT incr	Gr 4	Mo 4	hx:cocaine abuse; rechall w/study drug->Gr 4 SGOT/SGPT 3wks later
3553	23 F	SGPT incr	Gr 4	Wk 2	history: ongoing Hep C inf
3638	30 M	hypertriglyceridemia	Gr 4	D 1 Da 85	resolved in 8 days/ resolved after 8 days
3717	41M	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 syndome, neurotic personality

6300	44 M	facial trauma (fractures)	hosp	Wk 3	trauma 2° to altercation
IDV					
2455	47 M	?pancreatitis (nausea, abd pain, fevers)	hosp	Wk 1	sonogram: probable pancreatitis; amylase, lipase not elevated; Investigator: due to flu, new onset lactose intolerance
2465	47 M	ALT incr	Gr 4	Mo 6	resolved following d/c of study meds (IDV/ddI/d4T)
2500	50 F	incr SGOT, SGPT	Gr 4	Da 1	elevations before first study treatment
2501	28 F	pregnancy			after initiation of study treatment
2511	28 M	hypertriglyceridemia	Gr 4	Wk 12	not fasted before sample taken; did not resolve
2579	46 M	detox: cocaine, ethanol	hosp	Wk 34	history of cocaine, marijuana use
2688	43 F	pneumonia, UTI	hosp	Wk 8	Invest: unrelated to study drug
2706	28 F	renal calculi	hosp	Wk 6	calculi not requiring hosp also on Wks 2, 5
2708	46 M	myocarditis	hosp	Wk 36	
2767	24 M	leukopenia/neutropenia	Gr 4	Wk 1	on concurrent ddI
2787	33 M	convulsions,somnolence, life-threaten hypoglycemia		Wk 6	hx: insulin-depend DM; pt thought to have confused the regular and the lon-acting insulin at the night-time dose
2788	41M	ALT/AST incr	Gr4, 3	Wk 12	recent hx: HbsAg+; AST/ALT incr asymptomatic initially, then tiredness, pale stools, amber urine on drug; Invest: rel to study drug
2814	24 F	probable renal calculus	hosp	Wk 29	
2818	29 M	infected hardware	hosp	?	S/p jaw surgery; surgery for infected mandibular hardware
2888	41 M	chest, jaw pain	hosp	Wk 2	Mild elevation of BP, but cardiac monitoring, EKG, exzymes, CXR wnl
2909	54 M	AST/ALT incr	Gr 4	Wk 3	history: recent HbsAg +; also on ddI + d4T;invest: rel.to meds or HBV
3031	37 M	thrombocytopenia	Gr 4	Wk 4	history of thrombocytopenia
3069	34 F	pregnancy		Mo 5	also on 3TC, d4T
3105	35 M	triglycerides incr	Gr 4	Wk 28	hx: bili incr, ? Gilbert's disease; triglycerides incr at entry, incr to Gr 4
3125	45 M	herniated disc	hosp	Wk 3	hosp for evaluation of foot pain, numbness
3289	52 M	non-Hodgkins lymphoma prostatism ascites, recurrent	Gr 4 hosp	Wk 6 Mo 5 Mo 7	high-grade B-cell type TURP liver biopsy: hepatitis, poss cholangitis and/or drug reaction
3308	46 M	cellulitis of leg basal cell CA	hosp Gr 1	Mo 2 Mo 7	preceding ingrown toenail, infected
3340	40 M	gastralgia, lymphoma	hosp	Wk 15	history of gastric ulceration; surgery: B-cell lymphoma of jejunum
3372	33 F	pregnancy			history: drug abuse, prior fetal malformation; pregnancy not terminated
3537	67 M	headache	Gr 3	Wk 5	h/a: disabling and incapacitating
3554	34 F	amylase incr	Gr 4	Da 16	history of amylase incr 2 yrs earlier; pancreatic amylase said by investigator to be normal
3637	52 M	pneumonia, N&V	hosp	Wk 7	history of EtOH abuse
3702	31 M	renal colic, hematuria	hosp	Wk 3	history of hemophilia
3732	42 M	anal ulceration	hosp	Da 15	history: spastic paraparesis, chronic constipation
4047	48 F	breast cancer	Gr 4	Wk 18	
4059	33 M	homicidal/suicidal ideas	hosp	Wk 10	history: impulse disorder, violent behavior; hosp eval: cocaine in urine
4077	24 M	SGPT incr	Gr 4	Wk 20	history of Hep C inf
4094	34 M	furuncle/cellulitis/abcess	hosp	Wk 14	hosp for drainage, therapy
4095	40 M	hyperbilirubinemia	Gr 4	Wk 8	total bili incr; on W16 AST/ALT also incr (gr 2); Invest: rel to study drug(s)
4338	47 M	hyperbilirubinemia	Gr 4	Wk 15	Invest: rel to study drug
6302	31 M	lung abscess wasting, rectal ulcer, dermatophytosis	hosp hosp	Wk 10 Mo 5	S. aureus from blood and sputum
Post-randomized therapy					
2581	32 F	pulmonary hypertension	hosp, death		history:asthma, pulm. hypertension; 2d APV, 10d later: 1d IDV, 5d later, 1d NFV; d/ced all 2° N+V; hosp 13 wks p. last PI for pulm. hypertension
2771	36 M	hypokalemia,severe N+V headache neutropenia, leukopenia	Gr4/H hosp Gr4/H	Wk 8 Wk 37 Mo 8	history of AIDS, histo; 10d APV, d/ced; 1 mo later, initiated IDV; AE's developed 2 mo p. initiation of study meds; no etiology for headache found invest: por rel to HIV, concurrent amphoterracin B

2860	32 F	renal calculi	hosp	Wk 11	Gr 3 rash after 12 d on APV; calculus symptomatic 6 wks post initiation on non-randomized IDV

relative to initiation of blinded study treatment

Serious adverse events, Phase I/II studies						
Subj No	Age/ Sex	Serious Adverse Event	Grade	SAE Onset[1]	Treatment	Notes
PROA 2001						
303	61 M	trauma, bike accident	hosp	W 45	APV+SQV	
305	37 M	bradycardia, fainting bipolar disorder	hosp	W 11 W 12	APV+NFV	bradycardia occurred on drug, on rechallenge, and 12 wks after study meds permanently discontinued; invest: bradycardia not related to study drugs (revised causality)
308	41 M	triglycerides incr	Gr 4	Wk 8	APV+NFV	resolved on study medications
317	38 F	pneumonia	hosp	Da 17	APV+NFV	responded to antibiotics
341	46 M	triglycerides incr	Gr 4	W 38	APV+IDV	hx: triglyc incr; resolved while maintained on study meds
346	44 M	triglycerides incr	Gr 4	W 29	APV+SQV	Gr 4->Gr 3 on study meds
356	35 M	AST incr	Gr 4	W 32	APV+NFV	Hx: HBV infect; ALT incr; invest: rel to HBV or study drugs
PROA 2003 (single arm, APV/ABC/3TC/ZDV)						
888	??M	cholesterol incr	Gr 4 (?G3)	W 16	APV/3nucs	hx: incr cholesterol & triglycerides; degreased to nl while on study meds: ULN correction->Gr 3 assignment
890	27 M	post-LP headache	hosp	D 1	none	SAE occurred prior to treatment
892	30 M	nausea,vomiting, adenopathy, diarrhea	hosp	W 17	APV/3nucs	dx: cat scratch disease, streptococcus inf
896	26 M	CPK incr	Gr 4	W 36	APV/3nucs	AST/ALT/LDH, Cr also incr; attrib to strenuous exercise
897	28 M	CPK incr	Gr 4	Wk 43	APV/3nucs	invest attrib:strenuous exercise program
904	29 M	fever, diarrhea, dehydr.	hosp	Wk 16	APV/3nucs	dx: bacterial gastroenteritis
911	32 M	CPK incr	Gr 4	Wk 43	APV/3nucs	resolved on meds; invest attrib: increase in exercise
913	32 M	CPK incr	Gr 4	Wk 12	APV/3nucs	resolved on meds; attrib: poss rel to strenuous exercise
918	39 M	CPK incr Gr4; AST Gr 3	Gr 4	Wk 28	APV/3nucs	off APV, Wk 7; NFV added Wk 9; invest: not rel to study drugs
920	19 F	pregnancy		D 14	APV/3nucs	also, rash on D 10; ultrasound: poss birth defect
921	34 M	CPK incr suicidal ideation	Gr ? Hosp	Wk 2 Mo 8	APV/3nucs	resolved on meds; attrib: strenuous exercise
923	33 M	CPK incr	Gr 4	Wk 12	APV/3nucs	resolved on meds; attrib: strenuous exercise
925	19 M	CPK incr	Gr 4	Wk 16	APV/3nucs	invest: attrib to strenuous excercise
926	30 M	neutropenia	Gr 4	Wk 1	APV/3nucs	invest: attrib to study drugs/ZDV
CNAA2004						
2237	41 M	bacteremia	hosp	Wk 19	APV/ABC	-
CNAA2007 (treatment= APV/ABC + EFV vs PLA, abbreviated as "APV+")						
13642	30 M	neutropenia abdominal pain	Gr 4 hosp	D 1 Wk 15	APV+	- pain resolved, non-diagnostic workup
13649	41 M	lung CA, pericardial effus	hosp	Wk 19	APV+	(I think this is the subject who subsequently died)
13650	36 M	esoph.candida,pancreat-itis,pneumonia,anemia	hosp	Wk 18	APV+	hosp 9 wks after completing study rx; invest: poss rel to ddI, paclitaxel, unrelated to study meds
13658	33 M	depression	hosp	Wk 21	APV+	also, elective hosp for varicose vein stripping
13661	33 F	AST/ALT incr	Gr 4	Wk 30		Wk 26: APV+ d/c'd, lack of efficacy; Wk 28: NFV/ddi/hydroxy-urea initiated; SAE Wk 30
13666	40 M	triglycerides incr	Gr 4	Wk 24	APV+	invest: attrib to study meds or to com meds RTV,SQV
13671	45 M	disabling depression, anxiety/panic disorder	?	Wk 2	APV+	hx: mild depression; attrib by invest to EFV
13676	45 M	triglycerides incr	Gr 4	Wk 7	APV+	hx: hypertriglyceridemia, Gr3@ screening, improved w/ no change in study meds; invest: attrib to study meds
13687	40 M	Kaposi's sarcoma, pulm	hosp	D 3	APV+	-
13688	35 M	triglycerides incr; basal cell CA-skin	Gr 4	Wk 16 D 10	APV+	invest: attrib t/g incr to study drugs -

13689	42 M	triglycerides incr	Gr 4	Wk 24	APV+	resolved while on study treatment
13692	29 M	cholangitis,biliary dilatat	?	Wk 1	APV+	-
13693	34 F	vulvar CA recurrence		Wk 2	APV+	history of localized vulvar CA
13694	32 M	B-cell lymphoma, death		Mo 7	APV+	
13703	44 M	triglycerides incr	Gr 4	Wk 16	APV+	d/cedABC, APV 15 and 14 wks prev, on IDV@SAE time
13706	43 M	attempted suicide	hosp	Wk 18	APV+	history of depression
13720	39 M	triglycerides incr	Gr 4	Wk 2	APV+	invest: poss rel to study drugs
13722	25 M	vomiting,diarrhea,dehydr	hosp	Wk 14	APV+	dx:colitis; invest: rel to study drugs or con meds RTV/SQV
13734	54 M	triglycerides incr	Gr 4	D 16	APV+	invest: attrib to study drugs
13735	43 M	depression,suicidal	hosp	W 7	APV+	-
13751	37 M	rash, myalgia, fever, abscess	hosp	D 10	APV+	recurr skin redness, pruritis on APV/EFV rechall
CNAB2006						
0033	37 M	AST/ALT incr	Gr 4	Mo 7	APV/ABC	study meds interrupted, SAEresolved
2055	71 M	abscess, inguinal skin graft 2° leg injury	hosp hosp	W 10 Mo 8	APV/ABC	invest: secondary to lymph node biopsy leg injury secondary to fall
2066	30 M	ALT incr	Gr 4	W 11	APV/ABC	HBV+ at beginning of study; invest: attrib to HBVD
2068	32 M	arrhythmia,coronary artery occlusion, myocardial infarction	hosp	D 18	APV/ABC	hx: obesity, high cholesterol and triglycerides, smoking, borderline hypertension; study meds permanently d/ced 2 days earlier due to recurr rash on rechall
2091	34 M	rash		?	APV/ABC	subsequently declassified as SAE
2102	40 M	bronchitis, pneumonitis triglycerides incr	hosp Gr 4	Mo 4 D 29	APV/ABC	invest: bronchitis attrib to viral infection Gr 4 at baseline
2116	26 F	ALT	Gr 4	W 20	APV/ABC	Hx: HCV infection; AST Gr 3;SAE attributed to HCV
PROA 1002 (Phase A: APV; Phase B: 3TC/ZDV; Phase C APV/3TC/ZDV)						
0002	45 M	pneumonia bronchitis	hosp hosp	12 Mo	3TC/ZDV APV+	Phase B at time of SAE, subsequently enrolled in Phase C 2nd hosp: 3 mo p. completion of study treatment
0004	30 F	uterine fibroma	hosp	12 Mo+	APV	Phase C at time of SAE
0016	35 M	attempted suicide	hosp	Wk 59		Phase B at time of hosp
0028	49 M	Gr 3 rash, urticaria	hosp	D 10	APV	Phase A at time of SAE
0030	27 M	seizures, h/a, photophob	hosp	12mo+	APV	Phase C at time of event; diagnosis: syphillis
0032	27 M	medication overdose		Mo 5	APV	Phase C at time of event; nausea, oral paresthesias
0035	33 M	nausea, vomiting				Phase B at time of event
0062	66 M	abd pain	hosp		APV	Phase C @hosp; invest: no pancreatitis, hepatits; pain unrelated to study drug
0075	36 F	thyroidectomy	hosp	Mo 18	APV	Phase C @ SAE; micronodular goiter x20yrs; worstened on therapy, unplanned thyroidectomy
0088	47 F	pneumonia	hosp			Phase B at time of event
0089	41 M	overdose, nausea	Gr 2		APV	Phase C at time of event; pharmacy error; 3 consecutive 1600mg doses
0121	37 M	rash,desquamation, fever, diarrhea,disarthria,	hosp	day 9	APV	Phase A; dx: toxicodermia; also thrombocytopenia, hemolysis
PROA 2002 (APV 900 vs APV 1050 vs aPV 1200 vs PLA/3TC/ZDV)						
0453	33 F	asthma attack		Wk 15	APV900	resolved with therapy, no change in study meds
0454	39 M	pneumonia	hosp	Wk 11	APV1200	resolved on therapy
0457	43 M	rash-Stevens Johnson		D 11	APV 1200	preceded (D 5) by diarrhea, nausea, fatigue, oral paresthesias, insomnia; accompanied by fever, tongue ulcers,buccal petechaiae, injeced conjunctiva
0467	35 M	anemia (Hb 7.7)	hosp	Wk 7	APV 900	invest: attributed to ZDV
0468	30 M	amylase, lipase incr		Wk 9	PLA	prior meds: ddI, d4T
0470	34 F	gastroenteritis, dehydr.	hosp	Wk 53	APV1200	-
0478	34 M	rash, fever,N+V,diarrhea, facial edema,sore throat, dehydration,tachycardia, dyspnea,coughheadache	hosp	Day 9	APV1200	invest: poss rel. to study medication; skin biopsies: purpuric dermatosis

0486	37 M	ulcer, perforated	hosp	Wk 57	APV1050	upper GI ulcer
0490	44 M	pneumonia	hosp	Wk 44	APV1050	-
0494	27 M	lymphoma		Wk 36	APV1050	-
0499	36 M	pneumonia	hosp	1 Yr	APV900	-
0551	37 M	wrist fracture	hosp	Mo 5	APV1050	-
0552	53 M	AST/ALT incr	Gr 4	Mo 14	APV 900	dx: HaV infection
0560	35 F	neutropenia	Gr 4		PLA	invest: lab test error
0566	30 M	rash		D8	APV 900	no systemic findings
0581	44 M	rash		D 9	APV1200	no systemic findings
0604	41 M	attempted suicide	hosp	Wk 28	APV1050	-
0606	36 M	anemia (Hb 6.9)	hosp		APV1050	rand. to PLA, r/o to o/l APV; AE 9days thereafter
0607	38 M	neutropenia	Gr 4	Wk 2	PLA	Gr 1 neutropenia before entry
0609	43 M	triglyceride incr	Gr 4	Mo 6	APV900	Gr 2 incr at entry, event resolved 1 mo later
PROB2004						
4550	9 M	thrombocytopenia	Gr 4	D 52	20mg/kg, BID	thrombocytopenic at b/l;con meds d4T/ddC; invest: AE rel to viral pneumonia and/or study meds
4554	4 M	MAI pneumonia, otitis media	hosp	Wk 5	20mg/kg, BID	also, ZDV,ddC,atovaquone
4559	10 F	rash,diffuse, maculopapular	Gr 2, hosp	D 6	15 mg/kg, TID	con meds: d4T, 3TC; findings included erythematous stomatitis and enanthema of mouth
4577	11 F	fever, viral infection lipase incr	hosp Gr 4	D 10	15 mg/kg, TID	hx: diarrhea x 4yrs, trauma (fall from horse) during screening; invest: events unrel. to study drug
PROA 3004						
1838	7 M	influenza A infection adenovirus infection	hosp, hosp	Mo 2 Mo 4	PLA capsules	hospitalized in both instances for diagnosis and treatment
2049	7 M	whelps on arms/legs pericarditis, viral	hosp hosp	Wk 5 Wk 10	PLA APV (o/l)	con meds: d4T, ddI; switched to o/l APV at Wk 7
2072	8 M	rash, maculopapular	hosp	Wk 15	PLA	viral exanthem suspected
7281	4 F	pneumonia	hosp	D -4	none	occurred 4 days before initiation of study therapy
7351	6 M	hypersensitivity rxn anemia	hosp hosp	? ?	ABC/APV	hypersensitivity rxn ascribed to ABC; drug doses not stated; time on treatment for each SAE not stated
PROB 3004						
7609	6 M	epistaxis, fever adenoidectomy	hosp hosp	D 13 Wk 3	"syrup, 25 ml,BID"	con meds: 3TC, d4T

Serious adverse events, other studies

Study No	Subj No	Age/ Sex	Serious Adverse Event	Grade	SAE Onset[1]	Treatment	Notes
PROA1001	0003	32 F	overdose	hosp	4th dosing period		overdose of phynylpropanolamine/guiafenesin
PROA1006	0654	10 F	hemoglobin decr	Gr 3	D 41	5 &10 mg/kg	entry: Gr 2 Hb, then Gr 2-3 thereafter
PROA1006	0681	6 M	cervical adenitis	hosp	D 8	5 &10 mg/kg	responded to I&D
PROA1006	0686	4 M	glucose incr	Gr 3	D1	15-20 mg/kg	SAE identified in pre-dose blood sample
PROA1006	0687	9 M	adenitis	hosp	D1	none	SAE occurred prior to treatment
PROB3005	5787	29 M	hemoglobin decr (5.7g/dL)		D 79	APV	also on ABC/ZDV/3TC; ZDV replaced w/ d4T
PROB3005	5942	37 M	rash,fever, Gr3, ALT/AST incr; biopsy site inf	hosp	Wk 3	APV/ABC/ ZDV/3TC	severe infection at site of lymph node biopsy; moderate rash
PROB3005	5948	32 M	rash,fever, incr AST/ALT		D11	APV	also,ABC/ZDV/3TC; ABC d/ced, rash resolved
PROB3005	5950	35 M	CPK incr	Gr 4	Mo 2	APV	also on ABC/ZDV/3TC; attrib to incr exercise
PROB3005	6769	32 M	rash,urticaria, malaise		D 1	APV	also on ABC/ZDV/3TC
PROB3005	6989	21 M	vomiting , rash	Gr 3,2	D 2	APV	also on ABC/ZDV/3TC
PROA3007	5484	45 M	triglycerides incr	Gr 4	Mo 14	APV	also on ABC/EFV/Adefovir; SAE 12 wks p. APV incr: 2400->3150mg/day
ACTG347	224-97	44 M	rash, confluent		D 10	APV/ZDV/3TC	max grade of rash not noted; attributed to APV

ACTG347	326-27	35 M	keratoconjuctivitis		D 2	APV/ZDV/3TC	invest: unable to judge if related to APV
ACTG347	460-97	45 F	seizures	hosp	D 41, D 59	APV/ZDV/3TC	hx: poorly controlled seizures 2° noncompliance w/meds; invest: poss rel to study drug
IRP016	8797	44 M	arthritis			APV/ABC	also on IL-2/PLA and IDV/PLA;
NZTA4002	1365	24 F	increased depression	hosp	Wk 17	APV/ABC	alsoAZT/3TC;switched from APV to NVF@Wk 3
NZTA4002	1488	42 F	neutropenia	Gr 4	Wk 16	APV	d/ced APV 4 wks before AE; on NFV
NZTA4002	1543	25 M	pyelonephritis, renal insufficiency		Wk 52	APV/ABC	switched from APV to NFV at Wk 25
NZTA4002	1682	60 M	renal insufficiency, weakness, neuropathy	hosp	D 9	APV/ABC/ ZDV/3TC	invest: SAEs not attributed to study treatment
NZTA4002	1793	33 M	Staph sepsis (catheter)	hosp	Wk 15	APV	also on ABC/3TC
NZTA4002	1846	37 F	serum potassium incr	Gr 4	Wk 8	APV	attrib to lab error
NZTA4002	1875	32 M	boils, 2° staph infection	hosp	Mo 2	APV	ABC/NFV/3TC/ZDV; also, ddI, d4T
NZTA4002	2441	37 M	anemia	Gr 4	Wk 10	APV+	attrib to ZDV
PANTALE2	1006	32 M	chills,malaise,sweating, dyspnea, rash		D 4-8	APV	also, ABC/NFV; also, worstening of diarrhea, nausea, abd distention; invest: attrib to ABC
PANTALE2	1018	41 M	rash, fatigue, pruritis, urticaria, fever		D 10	APV	also, ABC,NFV; invest: poss attrib to ABC

B. Case report forms reviewed of subjects having adverse events leading to permanent discontinuation of study drug

Subjects having AE leading to permanent discontinuation of study drug						
Study PROA 1002						
Subj No	Age/ Sex	APV dose	AE	Max Gr	T/p 1st/ last dose*	Notes
16	35 M	C I	stomach-burning	3	4d/	onset 15 min p. APV
17	26 M	C I	nausea	1	1d/	-
28	50 M	C II	rash	3	11d/1d	hospitalized
29	72 M	C II	nausea, diarrhea	2, 2	16d/, 16d/	-
31	28 M	C II	vomiting	2	13d/	-
35	33 M	C II	nausea, vomiting	3, 3	5d/, 5d/	-
65	32 M	C III	leg cramps, joint pain, headaches, neutropenia	2,2, 2,3	50d/, 50d, 52d/, 52d	-
74	46 F	C IV	abdominal pain, diarrhea	3, 2	2d/, 2d	-
87	34 M	C IV	rash, pins & needles (neuropathy)	1, 2	16d/, 19d/	pins and needles generalized over trunk
88	47 F	C IV	nausea	1	16d/	-
121	48 M	C VI	dysarthria, toxic erythema	2, 2	9d/, 10d	-
Study PROA 2001						
305	37 M	2250	bradycardia	2	150d/2d	CRF: "related" changed to "unrelated" to study drug
Study PROA 2002						
553	33 F	PLA	allergy	2	92d/	rash, pruritis, edema of lips, dry mouth, paresthesias of lips and limbs
626	32 M	PLA	hyperglycemia	3	313d/1d	-
564	42 M	PLA	diarrhea	1	239d/	-
512	44 M	PLA	rash	2	36d/	Gr 2 rash recurr on single-dose rechallenge
593	28 M	900BID	oral ulceration, UTI	1,1	379d/31d, 379d/31d	no CRF
566	30 M	900BID	erythroderma	1	22d/14d	Investigator: SAE: diffuse maculopapular rash with (illegible)
467	34 M	900BID	decr. hemoglobin	2	42d	transfused w/2U packed RBC, no bili incr recorded, 2+ blood in urine x1 (dipstick)
608	44 F	1050BID	epigastric pain	3	371d/	-

494	26 M	1050BID	B-cell lymphoma	4	498d/	-
581	44 M	1200BID	maculopapular rash, mouth ulcers	2, 1	9d/, 10d/1d	recorded by investigator as "Gr 2, serious" rash
554	21 M	1200BID	nausea, vomiting	3, 3	1d/, 39d	-
595	42 M	1200BID	hypertriglyceridemia	3	83d/	-
521	25 M	1200BID	rash, eye redness	2, 2	9d/, 9d/	-
478	34 M	1200BID	drug induced febrile rash	4, hosp	9d/	total body rash, T105F, nausea, vomiting, diarrhea, dehydr, facial edema, sore throat, unable to swallow, erythem conjunct, SOB, desquam (dry)
454	39 M	1200BID	incr AST, incr ALT	3, 3	121d/, 121d	-
457	43 M	1200BID	Stevens-Johnson syndrome	4	10d/1d	generalized rash, pruritis; earlier AE's included nausea, perioral paresthesias, abd numbness
463	32 M	1200BID	nausea	2	3d/	-
Study PROA 2003						
906	27 M	1200BID	nausea, fatigue, vomiting	2,1,1	1d/,1d/,2d/	patient's decision to stop meds
907	42 M	1200BID	vomiting, sensory neuropathy	1, 1	22d/, 91d/	-
910	34 M	1200BID	dysquesia, headache, nausea	1,1,1	1d/,4d/,5d/	-
CNAA 2004 *						
2049	29 F	1200BID (+ABC)	asthenia, pruritis, rash, dysphagia, fever, arthralgia, dizziness, muscle pain, nausea, chills	3,2,2 2,3,2 1,2,2 2	9d,9d,9d 9d,9d,6d 6d,6d,6d, 6d	-
*note: subjects 2083,2092,2106,2112,2180,2187 (for whom CRFs were provided) did not receive APV						
CNAB2006						
2068	32 M	?-ck	generalized rash	2	27 d/	-
2075	29 F		erythematous rash, various sites	1	25 d/	-
2099	36 M		pancreatitis	3	168 d/	-
CNAA 2007 (all subjects:APV/ABC/EFV)						
13710	46 M	1200BID	rash, fever	2,1	15d/,19d/	-
13654	51 M	1200BID	chills, fever, malaise	2,1,2	15d/ (all)	-
13700	38 M	1200BID	rash, maculopapular	2	9d/	drunk/hangover feeling also noted
13723	46 F	1200BID	fatigue, rash, rash	3,2,1	8d/, 26d/	-
13727	45 M	1200BID	diarrhea	3	7d/	-
13672	44 M	1200BID	pruritic rash	2	10d	w/d also attrib. to insomnia
13716	34 F	1200BID	vomiting, nausea, dizziness, dyspnea, fever, chills, pruritis	1,1,1 1,1,2 2	8d/,8d/,8d/ 12d/,12d/, 13d/,14d/	-
13722	25 M	1200BID	diarrhea, vomiting, headaches	4,4,4	97d/,97d/, 98d/	-
13751	37 M	1200BID	rash,pruritis,fever,rash	2,2,2 2	12d/,41d/, 41d/,41d/	rash recurr on rechall w/APV+EFV
13703	44 M	1200BID	rash, rash	2,2	9d/,18d/	-
13704	37 M	1200BID	rash, pruritis	2,2	11d/,11d/	facial edema, SOB, and fever also noted
13641	43 M	1200BID	nausea, bloating	1,1	2d/,101d/	-
13650	35 M	1200BID	fatigue,fever,rash	2,2,2	8d/,10d/, 10d/	AE's (fatigue, fever, rash) upgraded to Gr 3 in CRF
13695	44 M	1200BID	rash	2	8d/	-
13696	41 M	1200BID	fever, burning skin, rash	1,2,2	11d/1d-all	-
13698	38 M	1200BID	fatigue,disturb. of concentration	2,2	61d/,61d	-
13724	39 F	1200BID	nausea,vomiting,rash	1,1,1	13d/ (all)	-
13725	37 M	1200BID	fatigue	1	21d/	-
13671	45 M	1200BID	anxiety w/panic, depression	3,3	15d/ (all)	attributed by investigator to EFV
13668	40 M	1200BID	rash, fever	2,1	10d/ (all)	-
13720	39 M	1200BID	rash	2	11d/	-
PROAB3001 (PLA vs APV/AZT/3TC)						

1690	42 M	PLA	rash	2	13d/	-
1727	36 M	PLA	rash	2	192d/	-
1459	36 M	PLA	nausea, vomiting	2,2	195d/ (all)	-
1077	33 M	PLA	nausea, diarrhea	2,2	2d/ (all)	-
1288	44 M	PLA	nausea, vomiting	2,2	207d/ (all)	w/d AE's reflect modifications to CRF
1101	33 M	PLA	nausea	2	167d/	-
1060	40 M	PLA	anemia	3	85d/	-
1361	24 M	PLA	rash, maculopapular	2	131d/	hospitalized because of rash
1420	32 M	PLA	headache, epigast pain, flatulence	1,1,1	15/,21/,27/	-
1697	51 M	1200BID	hemolysis	4	84d/	incr LFT's & bili @ time of hemolytic episode
1806	55 M	1200BID	nausea	2	12d/	-
1808	43 M	1200BID	rash	2	11d	-
1083	34 M	1200BID	nausea, burning sense in stomach	2,1	4d/ (all)	-
1085	34 M	1200BID	nausea	3	2d/	-
1088	36 M	1200BID	rash	3	8d/	-
1295	37 M	1200BID	nausea, flatus, loose stools, fatigue, headaches	2,1,1 1,2	1d/3d/9d/ 9d/,10d	-
1099	37 F	1200BID	diarrhea, stomach pain, nausea	1,2,2	1d/,20d/, 20d/	-
1106	48M	1200BID	gastric upset, nausea	2,2	32d/ (all)	-
1206	44 M	1200BID	decr hemoglobin	4	55d/	-
1224	41 M	1200BID	nausea, vomiting,diarrhea	1,1,1	1d/ (all)	-
1040	25 F	1200BID	pruritis, rash	2,3	37d/ (all)	recurred on rechallenge
1058	25 F	1200BID	nausea	2	28d	preceded by Gr 2 rash which resolved
1498	27 M	1200BID	nausea,vomiting	3,3	64d/ (all)	-
1501	36 M	1200BID	hypertonia, gastric pain	2,2	103d/ (all)	-
1438	30 F	1200BID	vomiting	2	-/-	-
1436	25 M	1200BID	oral pain, nausea, vomiting, epigastric pain	2,2,2 2	2d/ (all)	-
1362	28 M	1200BID	nausea	1	3d/	preceded by rash
1785	31 M	1200BID	nausea, vomiting	1,2	3d/, 22d/	-
PROAB3006 (APV vs IDV/nucleosides)						
2581	32 F	1200QD	nausea, vomiting	2,2	1d/, 1d/	no CRF
2582	37 M	1200BID	diarrhea, nausea	2,3	3d/,8d/	-
4040	38 M	1200BID	nausea	1	1d/	-
2554	43 M	1200BID	incr bowel mvmts, diarrhea, nausea,malaise	1,1,1 2	10d/,28d/, 50d/, 50d/	-
2697	27 F	1200BID	angioedema	1	60d/	-
2701	28 M	1200BID	incr CPK, erythema of extremities	4,na	39d/1d (all)	-
2446	38 M	1200BID	inappropriate behavior	3	44d	-
2454	39 F	1200BID	nausea	3	1d	-
2713	35 M	1200BID	fatigue	2	4d/	-
2592	44 M	1200BID	diarrhea	2	13d/	-
2598	31 M	1200BID	migraine	3	13d/1d	-
3128	43 M	1200BID	neuropathy	2	84d/	-
6509	54 M	1200BID	rash, macular	2	13d/	
3181	28 M	1200BID	myalgia,headache,diarrhea,abd cramps,decr appetite,hot/cold flashes,nausea,fatigue	1,2,2 2,2,2 2,2	9d/, 10d/	-
3183	47 M	1200BID	paresthesias	1	118d/	-
4352	42 M	1200BID	rash	2	10d/	-
2860	32 F	1200BID	rash	3	10d/	also,vomiting, chest pressure
3028	34 F	1200BID	rash	1	171d/	generalized macular rash, Gr 2
2771	35 M	1200BID	vomiting	1	32d	-

3735	38 F	1200BID	nausea, abd pain, bladder calculus, bladder calculus	2,2 2,3	1d/,1d/ 15d/3d, 46d/34d	-
3348	27 F	1200BID	vomiting, nausea	2,2	2d/,2d/	N&V downgraded from Gr 3 to 2
3447	36 M	1200BID	oral paresthesia,diarrhea,malaise, nausea	2,2,2 2	2d/,2d/,2d/ 57d	-
3482	33 M	1200BID	incr GOT, incr GPT	4,4	86d/,86d	hepatitis, cocaine over dose noted in CRF
3438	36 F	1200BID	vomiting	2	119d/	-
3445	34 M	1200BID	craniocerebral injury	3	81d/	-
3748	35 F	1200BID	headache, vomiting	2,2	5d/ (all)	-
3749	57 M	1200BID	abd. discomfort	2	/	-
4082	46 M	1200BID	abd. burning, liver pain, vomiting	2,1,1	1d/,75d/, 76d/1d	-
4091	29 M	1200BID	flatulence	1	14d/	-
6300	44 M	1200BID	nausea	3	1d/	
3706	57 F	1200BID	nausea, vomiting	3,3	56d/ (all)	-
3708	35 F	1200BID	toxic erythema	3	11d/	-
3287	61 M	1200BID	fever, conjuctivitis, sore mouth, sinusitis,rash generalized, rash	1,1,1 1,3,1	10d/, 20d	-
3162	42 M	1200BID	dysphagia	2	1d	difficulty swallowing 141
3572	55 F	1200BID	rash	2	26d	-
4118	31 M	1200BID	nausea, vomiting	3,1	16d/	-
3720	25 M	1200BID	diarrhea	2	70d	-
2727	39 M	1200BID	altered sensorium,hot flashes, nausea	1,1,2	1d/ (all)	-
3459	45 M	1200BID	nausea, incr GOT, incr GPT	1,4,4	2d/12d/12d	Hep C infection noted on SAE page of CRF
3478	41 M	1200BID	rash, maculopapular	2	8d/	-
2706	28 F	IDV	renal calculus	3	42d	-
2888	41 M	IDV	nephrolithiasis	3	132d	-
2890	27 M	IDV	renal calculi	1	16d/	-
2476	34 M	IDV	renal calculi	2	75d	-
2865	33 M	IDV	groin pain, renal colic	2,2	31d/ (all)	-
4095	40 M	IDV	hyperbilirubinemia	4	57d/	G4 total bili, fatigue,jaundice
3702	31 M	IDV	renal colic, hematuria	3,2	23d/ (all)	-
3327	54 M	IDV	nausea	2	8d/	-
2833	24 F	IDV	nausea	1	1d/	also G2:rash,tingling,numb,weak,dizzy
3259	44 M	IDV	fatigue, malaise, nausea, vomiting, weight loss, depression	2,2,1 1,2,2	58d/, 84d/ 105d/	-
3537	67 M	IDV	headache	3	40d/	-
3477	27 F	IDV	renal colic	2	84d	CRF apparently incomplete
3480	35 M	IDV	vomiting	2	35d/	-
3485	25 M	IDV	renoureteral colic	2	57d	-

Appendix 3. Amprenavir and placebo capsule composition

The compositions of APV capsules and placebos are as follows. All quantities are mg per capsule. At some stage in the development process a new [redacted] was discovered. It was found that this [redacted] was the most stable but it was also less soluble than the other [redacted] Accordingly the capsules were reformulated to use [redacted]

Reformulated (commercial) 150 mg capsules

Component	Capsule	placebo
Amprenavir	150.0	-
TPGS		
PEG 400, NF		
Propylene glycol, USP		
Fill weight		

Original 150 mg capsules

Component	Capsule	placebo
Amprenavir	150.0	-
TPGS		
PEG 400, NF		
Propylene glycol, USP		
Fill weight		

[redacted]

Component	Capsule	placebo
Amprenavir		
TPGS		
PEG 400, NF		
Propylene glycol, USP		
Fill weight		

The fill solution for the 50 mg capsule has an identical composition to that of the commercial 150 mg capsules.

Conclusion: The placebos have compositions that are almost identical to those of the corresponding drug product with [redacted] replacing amprenavir.

Sources: Fax of 12/21/98 and Amendment of 12/2/98