Table 12.9.2.1.A. summarizes treatment-emergent events (at least moderate severity) that are of probable, possible or of unknown relationship to ABT-378/ritonavir or nelfinavir and with an incidence of greater than 2 percent.

Table 12.9.2.1.A. Treatment-emergent events that are of probable, or possible relationship to study drug and occurring in > 2 percent of patients

	Double Blind Phase	
Body System	**ABT-378/ritonavir (n=326)**	**Nelfinavir (N=327)**
Body as a Whole		
Abdominal pain	10 (3.1%)	8 (2.4%)
Asthenia	11 (3.4%)	9 (2.8%)
Headache	8 (2.5%)	6 (1.8%)
Digestive System		
Diarrhea	45 (13.8%)	47 (14.4%)
Nausea	21 (6.4%)	13 (4%)
Vomiting	7 (2.1%)	8 (2.4%)

HIV Related Events:

Fifty-seven patients in the ABT-378/ritonavir group and 51 patients in the nelfinavir group reported an HIV-related event during the first 24 weeks. The most common HIV-related events were oropharyngeal candidiasis, herpes simplex, and herpes zoster.

New AIDS-defining events:

The new AIDS-defining events (as defined by CDC class C event) are listed in the following table. Four patients in the ABT-378/ritonavir arm and 6 patients in the nelfinavir arm developed a new AIDS-defining event after one week of treatment. Patients who had the event at baseline or developed the event within the first week were not counted as a new AIDS-defining event, since we could not ensure that such conditions were not present at baseline. Three patients in each arm who achieved HIV RNA < 400 copies/mL at 24 weeks experienced a new AIDS-defining event following at least 1 week of treatment. The following table summarizes this analysis.

Summary of AIDS Defining Events

Patient #	Event	RX day	HIV RNA at week 24	Event at baseline (Yes/No)	< 400 copies/mL at week 24 (Yes/No)
ABT-378					
3091	MAI	5 and 6	< 400	?	NO
3123	Crypto	15	< 400	NO	YES
3188	MTB	2	< 400	NO	NO
3241	PCP	2	<400	YES	NO
3307	Crypto, CMV ret	5	Death	?	YES
3317	MAI	1	Premature DC	?	YES
3321	KS	113	>400	NO	YES
3390	KS	14	Premature DC	Yes	YES
2448	Toxo brain	53, 57	<400	YES	NO
3494	KS	143	<400	YES	NO
3551	PCP	5	<400	NO	NO
3574	PCP, MAI	1, 71	<400	NO	YES
3609	MAI	29	<400	NO	YES
NELFINAVIR					
3183	MAI	41	>400	NO	YES
3240	KS	85	<400	YES	NO
3364	Lympho	15, 20,22,37,42,63	>400	NO	YES
3459	Lympho	20	>400	NO	YES
3463	Lympho	140, 164	<400	NO	YES
3614	KS	1	>400	?	YES
3640	CMV ret	50	<400	NO	YES
3641	CMV ret	42	<400	NO	YES

12.9.2.2. Serious and Life-threatening Adverse Events

In the ABT-378/ritonavir group, a total of 44 serious adverse events were reported in 29 (8.9%) patients during the first 24 weeks of the study. Only 3 events were considered possibly or probably related to ABT-378/ritonavir. A total of 29 events were reported in 11 (3.4%) patients receiving nelfinavir. Two events were considered possibly or probably related to nelfinavir. Table 12.9.2.2.A. summarizes the serious adverse events that are possibly or probably related to study drug. Two patients prematurely discontinued study due to a serious adverse event. Both patients were in the nelfinavir group.

Table 12.9.2.2.A. Serious Adverse Events At Least Possibly Related

PATIENT	TREATMENT	ONSET	REASON	CAUSALITY	OUTCOME	RESOLUTION
3011	ABT-378	Day 73	Vasculitis	Possible	Hospitalization	ongoing
3159	ABT-378	Day 1	Dizziness Drug Interaction	Probably Probably	Required medical intervention	resolved
3358	ABT-378	Day 22	Deep thrombophlebitis	Possibly	Hospitalization Required medical/surgical intervention	ongoing
3145	ABT-378	Day 195	Pulmonary edema Atelectasis	Possibly	Hospitalization	resolved
3401	ABT-378	Day 271	Pancreatitis (see pancreatitis section for further details)	Possibly	Hospitalization	resolved
3184	Nelfinavir	Day 170	Leukopenia	Probably	Required medical/surgical Intervention Discontinued therapy	resolved
3635	Nelfinavir	Day 48	Diarrhea Vomiting Nausea	Possibly Possibly Possibly	Hospitalization Hospitalization Hospitalization	Resolved

Patient 3011 was a 26 year old male who was hospitalized for vasculitis and infectious colitis after 2 ½ months of ABT-378/ritonavir treatment. The patient had right wrist and left ankle swelling and a rash on his lower legs and forearms. All cultures were negative. IV cefoxitin was started and the rash and swollen joints improved. The rash was then thought to be due to sulfa medications for his toxoplasmosis. Several days later the patient was readmitted for worsening of the same symptoms. Biopsy of the leg showed vasculitis. The patient was re-hospitalized for worsening of the vasculitis. A colon biopsy was positive for treponema hyodysenteriae. Relationship of treponema infection and vasculitis is unknown.

Patient 3159 was a 37 year old male who experienced nefazodone toxicity approximately 1 day after receiving ABT-378/ritonavir. The patient experienced unsteadiness, orthostatic hypotension, "dropping items" and mild nausea. The final diagnosis was nefazodone toxicity potentiated by protease inhibitor therapy. This is an expected drug interaction with ritonavir. The ritonavir package insert lists in the WARNINGS section that cardiac and neurologic events have been reported with ritonavir when co-administered with nefazodone.

Patient 3358 was a 31 year old male who was hospitalized for deep vein thrombosis approximately 3 weeks after initiating ABT-378/ritonavir treatment. The patient developed pain and swelling of the left calf, 2+ edema, tenderness, and a positive Homan's sign of the left leg. Venous Doppleer studies revealed thrombosis of the popliteal vein and portions of the posterior tibial and peroneal veins. No other alternative etiologies were given.

Other Significant Adverse Events

Hepatitis:

One case of hepatitis was reported for patient 3191 after receiving ABT-378/ritonavir for approximately 5 months. The patient is also HCVAb+. The patient reported anorexia and fatigue, however the study drug was never interrupted for this event. The investigator felt that this event was related to hepatitis C infection. It is unclear if the hepatitis was also related to ABT-378/ritonavir. Patients receiving ABT-378/ritonavir who have underlying hepatitis B or C appear to be at an increased risk for transaminase elevations.

The patient had ALT values that were < 2 times the upper limit of normal during treatment. Bilirubin levels peaked at 2.2 mg/dL at a time when the ALT was 67 U/L.

The patient was subsequently hospitalized on May 20, 2000 for vomiting and progressive debilitation. His lipase was 926 U/L on admission and was thought to have pancreatitis. Chest X-ray showed pneumonia. The patient developed progressive respiratory deterioration and died 5 days later. Based on the available information, the investigator noted that a diagnosis of pancreatitis could not be made at this time. However, in the FDA analysis this is considered a case of pancreatitis for the ISS analysis.

Pancreatitis:

A total of 4 cases of pancreatitis were reported in this trial.

- Patient 3430 developed pancreatitis approximately 5 months after receiving ABT-378/ritonavir. His past medical history is unremarkable. Pancreatitis was diagnosed based on an elevated amylase level (249 U/L). However, at baseline his amylase was 241 U/L) and remained elevated. Study drug was not interrupted for this event. The patient's peak triglyceride level during treatment with ABT-378/ritonavir was 328 mg/dL. It is unclear if this event was a case of pancreatitis.

- Patient 3651 please refer Deaths for further details
- Patient 3191 please refer to hepatitis section for further details

- Patient 3401 noted mild back pain noted mild back pain on study visit 40. His amylase was 730 u/L and pancreatic amylase was 683 u/L. Three days later the patient was hospitalized due to severe epigastric pain and evaluation of pancreatitis. A NG tube was placed and the patient was "pain free." While in the hospital the patient was placed on amphotericin for cryptococcal skin lesions. Several days later his amylase returned to normal. The next day, the patients pain reoccurred and his amylase increased. The patient was subsequently discharged 13 days after initial hospitalization. At discharge his amylase was 189 u/L. A

relationship of this event to ABT-378/ritonavir can not be ruled out, however the patient was also receiving stavudine and lamivudine and Bactrim for 40 weeks.

Body Fat Composition Changes:

A total of 7 patients in the ABT-378/ritonavir group and 4 patients in the nelfinavir group reported body fat composition changes during the study. Most of these events were considered related to study drug by the investigator.

For the patients randomized to the ABT-378/ritonavir group, the body fat composition changes appeared after approximately 3 months of treatment (range 13 days to 5.75 months). There were two cases of gynecomastia, 1 report of lipomas, and 4 reports of increased abdominal girth/central adiposity with/without peripheral fat wasting or buffalo hump.

Adverse Events Associated with Discontinuation of Treatment

Serious Adverse Events:

No patient in the ABT-378/ritonavir group and two patients in the nelfinavir group prematurely discontinued study drug due to serious adverse events.

Non Serious Adverse Events:

Ten patients in each treatment group prematurely discontinued study drug due to an adverse event or HIV-related event. The most common events resulting in discontinuation were gastrointestinal symptoms.

12.9.2.4. Deaths

A total of 9 deaths occurred during the study; 5 deaths in the ABT-378/ritonavir group and 4 deaths in the nelfinavir group. All deaths were considered not related to the protease inhibitor by the investigator.

Patient 3307 was a 31 year old male who developed occipital headaches, sleepiness, chills and decreased vision 5 days after initiating ABT-378/ritonavir. He was subsequently hospitalized and diagnosed with cryptococcal meningitis. The patient died one month after beginning study drug.

Patient 3317 died from MAI with wasting syndrome approximately 7 months after receiving ABT-378/ritonavir.

Patient 3651, died secondary to acute pancreatitis, renal failure, GI bleed and hematuria. She was a 37 year old who presented to ER with abdominal pain, nausea, vomiting blood and blood in urine for several days. Four days later a CT with contrast showed an enlarged pancreas. Amylase was 575 u/L and lipase was 9752 u/L. It

was also noted that the patient had a possible transitional cell tumor. Amylase and lipase continued to rise; 1006 u/L and 15, 278 U/L, respectively. The patient's condition deteriorated and the patient died the next day. It is possible that this death may be related to study drug. To date this is the only case of fatal pancreatitis in an antiretroviral naïve patient. Although this case is concerning, it is reassuring that the overall incidence of pancreatitis seen in 5 adult clinical trials and the expanded access program of over 3000 patients is approximately <1%. This is similar to the overall incidence noted in HIV-infected patients. Of note, the incidence of pancreatitis for ABT-378/ritonavir is less than that seen with ddI and/or d4T.

A sudden death resulting from arteriosclerotic cardiovascular disease was reported for patient 3163 after approximately 9 ½ months with treatment of ABT-378/ritonavir. The police found the patient dead in bed. Drug paraphernalia was noted at the scene. The patient had a history of toxoplasmosis encephalitis. Autopsy report showed cerebral toxoplasmosis, arteriosclerotic cardiovascular disease with cardiomegaly, left ventricular hypertrophy and focally severe 3-vessel coronary atherosclerosis, pulmonary edema and pleural effusions. The toxicology report was noted as non-contributory. Triglyceride and cholesterol values at the last visit were reported as 457 mg/dL and 374 mg/dL, respectively. It appears that this death was not related to study drug, however relationship to study drug is still unclear.

Patient 3191 died on study day 335 due to community acquired pneumonia.

Nelfinavir Arm: deaths

One particularly interesting fatal clinical event among the patients receiving nelfinavir occurred in a 25-year-old female who died from lactic acidosis and pulmonary embolism approximately 152 days after beginning treatment. This patient developed acidosis, which worsened, and dialysis was begun 10 days later due to progressive acidosis and increasing fluid retention. Ultrasound revealed probable hepatomegaly and fatty infiltration of the liver. Sixteen days after admission the patient developed hypotension and hypoxemia and was found to have a pulmonary emboli. The patient continued to deteriorate with worsening mental status, renal function and acidosis. She died approximately 1 month after admission. Autopsy revealed diffuse alveolar damage, pulmonary thromboemboli with infarct and massive hepatomegaly with macrovesicular steatosis. The pathologist concluded "the underlying cause of death was most probably due to a combination of diffuse alveolar damage, and extensive hepatic macrovesicular steatosis, which were further complicated by lactic acidosis.

The other deaths in the nelfinavir arm were attributed to histoplasmosis infection, lymphoma and pneumonia. The death due to pneumonia occurred 12 weeks after nelfinavir treatment was stopped.

12.9.2.5. Laboratory Findings

12.9.2.5.1. Hematology

Two patients in the ABT-378/ritonavir group experienced hemoglobin < 8 g/dL and two patients experienced neutrophils < 0.75 x 10^9/L. None of the patients in the nelfinavir group experienced hemoglobin < 8 g/dL whereas 5 patients experienced neutrophils < 0.75 x 10^9/L.

Two subjects in the ABT-378/ritonavir group and 1 subject in the nelfinavir group prematurely discontinued study drug due to an adverse event related to an abnormal hematology value.

12.9.2.5.2. Biochemistry

The following table summarizes Grade 3 and 4 laboratory abnormalities. These events are discussed in further detail in this section

Grade 3 and 4 Laboratory Abnormalities Occurring in > 2% of Patients

Chemistry Variable	ABT-378/ritonavir	Nelfinavir
Amylase (> 2 x ULN)	6 (1.9%)	6 (1.9%)
ALT (> 215 U/L)	3(1%)	8 (2.5%)
AST (> 180 U/L)	1(0.6%)	8 (2.5%)
Cholesterol (> 300 mg/dL)	21 (6.7%)	9 (2.8%)
Triglycerides (> 750 mg/dL)	16 (5.1%)	3 (0.9%)

Glucose:

A total of 5 patients in the ABT-378/ritonavir group and 3 patients in the nelfinavir group developed glucose levels greater than 250 mg/dL. Two patients in each group had diabetes at baseline. None of these patients required medications to treat glucose abnormalities and none prematurely discontinued study drug for glucose abnormalities.

Lipids:

Twenty-five (8%) and twelve (4%) patients in the ABT-378/ritonavir and nelfinavir groups, respectively, had grade 3 or greater lipid abnormalities. There were no premature discontinuations of study drug due to these abnormalities.

Cholesterol:

Cholesterol abnormalities are summarized in Table 12.9.2.5.2.A.
The proportion of patients with cholesterol > 240 mg/dL was comparable for both treatment groups. However more patients on ABT-378 had levels exceeding 300

mg/dL. In addition, mean change from baseline in cholesterol at week 24 was comparable for both treatment groups.

Table 12.9.2.5.2.A. Cholesterol Abnormalities

	ABT-378/ritonavir	Nelfinavir
Cholesterol Value > 240 mg/dL	73 (23.4%)	79 (24.8%)
Cholesterol Value > 300 mg/dL	21 (6.7%)	9 (2.8%)
Mean Baseline (mg/dL)	159	158
Mean Change (mg/dL)	39	40
Mean Peak Values (mg/dL)	214	211

Triglyceride:

A greater proportion of patients developed triglycerides > 750 mg/dL in the ABT-378/ritonavir group compared to patients in the nelfinavir group. Five patients in the ABT-378/ritonavir group developed triglycerides > 1500 mg/dL of which 4 patients had triglycerides > 2001 mg/dL. Overall larger increases in triglycerides were observed among patients receiving ABT-378/ritonavir. Triglyceride abnormalities are further summarized in Table 12.9.2.5.2.B.

Table 12.9.2.5.2.B Elevations in Triglyceride Levels

	ABT-378/ritonavir	Nelfinavir
Triglyceride value > 750 mg/dL	16 (5.1%)	3 (0.9%)
Triglyceride value 1000-1499 mg/dL	5 (1.6%)	3 (0.9%)
Triglyceride value > 1500 mg/dL	5 (1.6%)	0
Triglyceride value > 2001 mg/dL	4 (1.3%)	0

The mean changes from baseline at week 24 for triglycerides are summarized in Table 12.9.2.5.2.C. Both mean change and mean peak triglyceride values were larger for patients in the ABT-378/ritonavir group compared to patients in the nelfinavir group.

Table 12.9.2.5.2.C. Mean change from baseline for triglyceride

	ABT-378/ritonavir	Nelfinavir
Mean Baseline (mg/dL)	166	162
Mean Change (mg/dL)	80	14
Mean Peak Values (mg/dL)	336	234

Seven patients in the ABT-378/ritonavir group received antihyperlipidemic agents as a result of elevated triglycerides/cholesterol. In comparison only one patient in the nelfinavir group received an antihyperlipidemic agent. Based on this limited data it appears that treatment with antihyperlipidemic agents were effective in reducing overall triglyceride and cholesterol levels.

Liver Function Tests:

Four patients in the ABT-378/ritonavir group and eleven patients in the nelfinavir group developed marked transaminase elevations. Marked transaminase elevations were defined as ALT > 180 U/L and AST > 215 U/L. No patients prematurely discontinued study drug due to transaminase elevations. Table 12.9.2.5.2.D summarizes the proportion of patients with transaminase abnormalities.

Table 12.9.2.5.2.D Grade 3 and 4 Adverse Laboratory Abnormalities

Chemistry Variable	ABT-378/ritonavir (n=312)	Nelfinavir (n=319)
ALT (> 215 U/L)	1%	2.5%
AST (> 180 U/L)	0.3%	2.5%

The majority of patients in the ABT-378/ritonavir group had improvement or stabilization of transaminases without interruption of study drug. Only one patient interrupted study drug.

The applicant reports that patients with baseline serologies positive for HBsAg or HCV Ab were at a significantly increased risk for developing grade 3+ transaminase elevations (risk ratios = 7.86 (AST) [1.35, 45.84] and 38.48 (ALT) [5.02, 295.30]).

ALT/Bilirubin:

No patient developed concomitant grade 3/4 elevations in ALT and bilirubin.

FDA calculated the proportion of patients with bilirubin > 1.2 who also had increases in ALT. The results are summarized in Table 12.9.2.5.2.E

Table 12.9.2.5.2.E Concomitant Bilirubin and ALT increases

	Isolated Bilirubin (bilirubin > 1.2 on only 1 study visit)		Sustained bilirubin (bilirubin > 1.2 on 2 or more consecutive study visits)	
Dose Group	ABT-378	Nelfinavir	ABT-378	Nelfinavir
Number of patients with ALT within normal limits	8	4	4	0
Number of patients with Grade 1-2 ALT elevations	4	1	5	1
Number of patients with > grade 3 ALT elevations	0	0	0	0

The majority of patients had an isolated or sustained bilirubin > 1.2 mg/dL with ALT values within normal limits or at a grade 1-2 elevation. No one developed concomitant grade 3+ ALT values and bilirubin > 1.2 mg/dL.

12.10 Safety Conclusions

Overall both treatment regimens were similarly tolerated. The most common adverse events, for either dose group, were gastrointestinal events such as abnormal stools, diarrhea, and nausea.

In the ABT-378/ritonavir group, a total of 44 serious adverse events were reported in 29 (8.9%) patients during the first 24 weeks of the study. Only 3 events were considered possibly or probably related to ABT-378/ritonavir. A total of 29 events were reported in 11 (3.4%) patients receiving nelfinavir.

Four cases of pancreatitis occurred in the ABT-378/ritonavir group, one of which resulted in death. It is unclear if these cases were related to drug or underlying diseases. However, since increases in triglycerides are a risk for pancreatitis and since ABT-378/ritonavir can increase triglycerides, continual evaluation of cases of pancreatitis during the post-marketing period will be essential.

There were 5 deaths in the ABT-378 group and 4 deaths in the nelfinavir treatment group. It is important to note that this population was relatively advanced compared to other studies of antiretroviral naïve patients.

Overall the development of laboratory abnormalities were comparable between dose groups with the exception of transaminase and lipid elevations. Transaminase elevations were slightly greater in the nelfinavir group. More patients in the ABT-378/ritonavir group developed triglyceride abnormalities. Changes in total cholesterol appeared to be comparable between treatments.

13.1 Study M98-888

13.2 Protocol Title

A Randomized, Open-Label, Phase III Study of ABT-378/ritonavir in Combination with Nevirapine and Two Nucleoside Reverse Transcriptase Inhibitors vs Investigator Selected Protease Inhibitors(s) (ISPI(s)) in Combination with Nevirapine and Two NRTIs in Antiretroviral-Experienced HIV-Infected Subjects

13.3 Study Design and Analysis Plans

This is an ongoing phase 3, open-label, randomized, multi-center, multi-country study to compare ABT-378/ritonavir in combination with nevirapine and two nucleoside reverse transcriptase inhibitors vs. ISP(s) in combination with nevirapine and two nucleoside reverse transcriptase inhibitors in antiretroviral-experienced HIV-infected subjects.

In this interim analysis, 118 antiretroviral-experienced patients with plasma HIV RNA between 1,000 copies/mL and 100,000 copies/mL were randomized to one of the following regimens:

Group A: One or two protease inhibitors selected by the principal investigator + nevirapine + two RTIs

Group B: ABT-378 400 mg/ritonavir 100 mg + nevirapine + two RTIs

The following table outlines the single and dual protease inhibitor combination and dosing recommendations when given with nevirapine + two RTIs.

SINGLE PROTEASE INHIBITOR	
Regimen	**Dose**
Indinavir	1000 mg q8h
Saquinavir (only Fortovase can be used for saquinavir single protease inhibitor regimens)	1200 mg TID
Ritonavir	600 mg BID
Nelfinavir	750 mg TID
DUAL PROTEASE INHIBITOR REGIMEN	
Ritonavir/Saquinavir	400 mg ritonavir/ 400 mg saquinavir BID
Ritonavir/Indinavir	400 mg ritonavir/400 mg indinavir BID
Nelfinavir/Saquinavir	1250 mg nelfinavir/1200 mg saquinavir BID or nelfinavir 750 mg/800 mg saquinavir TID

Hydroxyurea 500 mg BID could be added on day 1, at the discretion of the investigator, however investigational agents were excluded.

Patients will be followed for safety, plasma HIV RNA and CD4 cell counts at weeks 4, 8, 12, 16, 20, 24, 38, 40 and 48.

Of note, enrollment for this study is ongoing and 300 patients are to be enrolled.

13.4 Patient Population

13.5.1 Inclusion Criteria

Patients greater than 12 years of age with HIV RNA level between 1,000 copies/mL and 500,000 copies/mL and currently treated with an antiretroviral regimen containing a single protease inhibitor and two RTIs that has not been changed in at least 12 weeks will be included into the trial. In addition at least one RTI is available to which the subject is naïve is necessary for enrollment. Patients could not have been treated for an active OI within 30 days of screening nor requires and agrees not to take any medications that are contraindicated with protease inhibitors for the duration of the study. A Karnofsky Score of at least 70, no evidence of acute illness, and a negative pregnancy test or agreement to use a barrier method of birth control was also required for inclusion into the trial.

13.5.2. Exclusion Criteria

Patients with the following laboratory abnormalities were excluded from the study: hemoglobin < 8.0 mg/dL, absolute neutrophil count < 750 cells/mm^3, platelet count < 20,000, ALT/AST > 3x ULN, creatinine > 1.5 X ULN. Also patients who received an investigational drug within 30 days prior to screening (with the exception of amprenavir), or received treatment with more than 1 PI concurrently or received treatment with more than 1 PI for more than 6 weeks prior to their current regimen or received prior therapy with an NNRTI for more than 7 days were excluded from the trial.

13.6 Study Endpoints

13.6.1. Primary Study Endpoints

The primary efficacy endpoints for week 24 and 48 analyses are as follows:

Week 24: Proportion of subjects with plasma HIV RNA level below 400 copies/mL.

Week 48: Time until loss of virologic response

13.7. Results

13.7.1. Patient Disposition

For the interim report, a total of 118 patients were randomized into this trial. One hundred and eighteen patients who received at least one dose of ABT-378/ritonavir, completed 16 weeks of treatment of discontinued from study. A total of 50 patients, completed 24 weeks of treatment or have discontinued. Fifty nine patients were randomized to the ABT-378/ritonavir arm and 59 patients were randomized to the ISPI(s) group. Of note, enrollment for this study is ongoing and 300 patients are to be enrolled.

13.7.2. Protocol Deviations

Several protocol deviations occurred during the trial. Table 13.7.2.A. summarizes the protocol deviations. The applicant states that the protocol deviations are not expected to significantly influence the results of the study.

Table 13.7.2.A. Protocol Deviations

Protocol Deviation	ABT-378/ritonavir	ISPI(s)
Failure to meet specific entry criteria	2	1
Changed antiretroviral treatment within 12 week of screening	5	6
Not receiving PI + 2 NRTI at screening	4	5
Received more extensive prior PI therapy prior to screening (e.g. 2 PIs concurrently or > 6 weeks of another PI)	6	10
Did not receive nevirapine	2	2
Received excluded medications	1	1
Received non protocol PI regimen (amprenavir/saquinavir)	0	1

13.7.3. Reasons for Premature Discontinuation

Five patients in the ABT-378/ritonavir group and 13 patients in the ISPI(s) group discontinued at or before week 16/24. A summary of premature discontinuations can be found in Table 13.7.3.A. The applicant reviewed the reasons for premature discontinuation to determine if a bias based on treatment assignments impacted discontinuation from study. Of those who discontinued study medication, the median and mean time was longer for patients in the ISPI(s) group vs the ABT-378/ritonavir group.

Table 13.7.3.A. Premature Discontinuations

Original Assignment	ABT-378/ritonavir	ISPI(s)
Received at least one dose of study medication	59	59
Discontinued on or before week 24	7 (11.9%)	14 (23.7%)
Adverse event	1 (1.7%)#	5 (8.5%)
Death	0 (0.0%)	3 (5.1%)##
Lost to follow-up	0 (0.0%)	1 (1.7%)
Patient request/Personal Reasons	0 (0.0%)	2 (3.4%)**
Other (Non-compliant, intercurrent illness or investigator request)	5 (8.5%)*	1 (1.7%)***
Virologic Failure	1 (1.7%)	2 (3.4%)

Patient experienced AE on day 99 which lead to permanent discontinuation and subsequently died on day 106
patient died > 30 days after last dose of study drugs
* Includes admission criteria violation (1), other (1), and noncompliance (3)
** Consists of database category "Personal Reasons."
*** Includes noncompliance (1).

13.7.4. Demographic Data

The baseline demographics, including pre study antiretroviral therapy were comparable for the two treatment groups. There was a higher proportion of men and a higher mean baseline CD4 cell count in the ISPI(s) group, however these differences were not statistically significant. Please refer to Table 13.7.4.A. for further details

Table 13.7.4.A. Demographic Data

	ABT-378	ISPI(s)
Number of Patients	59	59
Mean age, Yrs	40.6	40.8
Men	85%	95%
Race or Ethnicity		
Caucasian	80%	90%
Black or African American	20%	8%
Asian/Pacific Islander	0%	2%
Hispanic	5%	12%
Pre-Study Antiretroviral Therapy		
NRTIs		
ZDV	72.9%	76.3%
Lamivudine	64.4%	74.6%
Stavudine	27.1%	40.7%
Didanosine	33.9%	30.5%
Combivir	23.7%	32.2%
Zalcitabine	20.3%	16.9%
Abacavir	1.7%	3.4%
PIs		
Indinavir	49.2%	42.4%
Nelfinavir	37.3%	39%
Ritonavir	6.8%	13.6%
Saquinavir (Invirase)	8.5%	10.2%
Saquinavir (Fortovase)	5.1%	5.1%
Amprenavir	1.7%	3.4%
Baseline mean plasma HIV RNA (PCR), $\log_{10}$ copies/mL	4	4.01
Baseline mean CD4 cell count (cells/mm^3)	291	354.8

Table 13.7.4.B. provides a summary of ISPI(s) regimens. Overall the most frequently selected single and dual PI regimens were nelfinavir (13.6%) and ritonavir/saquinavir (45.8%), respectively.

Table 13.7.4.B. Summary of ISPI(s) Regimens

Regimen	ISPI(s) N=59
Indinavir	4 (6.8%)
Nelfinavir	8 (13.6%)
Saquinavir	1 (1.7%)
Ritonavir/indinavir	13 (22%)
Ritonavir/saquinavir	27 (45.8%)
Saquinavir/Amprenavir (not a protocol specified regimen)	1 (1.7%)
Saquinavir/nelfinavir	5 (8.5%)

Six patients interrupted or discontinued treatment with nevirapine during the study and did not restart nevirapine. No patients took delavirdine or efavirenz at any time during the study.

13.7.5. Efficacy Outcomes

13.7.5.1. HIV RNA

Proportion < 400 copies/mL

Table 13.7.5.1.A summarizes the efficacy analyses at week 24 for the first 118 patients enrolled into the study. For the intent to treat analysis a statistically significant result was seen for the proportion of patients with HIV RNA < 400 copies/mL, favoring the ABT-378/ritonavir arm.

Table 13.7.5.1.A. Proportion < 400 copies/mL at week 24

Dose Group	HIV RNA < 400 copies/mL	
	Week 24	
	On Treatment	ITT (NC=F)
ABT-378/ritonavir	43/51 (84%)	43/59 (73%)
ISPI(s)	31/40 (78%)	31/59 (53%)
p-value comparing dose groups	0.408	0.022

The applicant conducted an analysis in which discontinuations for the ABT-378/ritonavir arm were considered failures and discontinuations from the ISPI(s) arm were considered successes. Results from this analysis showed similar proportions of patients with HIV RNA < 400 copies/mL (73% ABT-378/ritonavir and 80% ISPI(s)).

An analysis was conducted to determine if there were differences in the proportion of patients with HIV RNA < 400 copies/mL at week 24 for patients who received a single PI vs dual PIs in the ISPI(s) group. Results from this analysis showed that there were no statistically significant differences noted for patients receiving single PI vs dual PIs

at week 24 (single PI: 46.2%, dual PI 54.3%, overall ISPI(s) 53%). Since this is an interim analysis and the study has not been fully enrolled, all results should be interpreted with caution.

13.8.5.2. CD4 Cell Count

Mean change from baseline at week 24 was + 82 cells/mm^3 for the ABT-378/ritonavir arm and + 40 cells/mm^3 for the ISPI(s) group. Although larger increases in CD4 cell counts were noted in the ABT-378/ritonavir group, differences between the treatment arms were not statistically significant.

13.9 Safety Outcomes

A total of 118 patients were included in the safety analysis. Data from patients who discontinued drugs due to adverse events were reviewed to identify possible risk factors associated with adverse events. All serious adverse events were reviewed individually. There were a total of 4 deaths in this study.

13.9.1. Drug Exposure

The median duration of study drug exposure was 125 days for both groups

13.9.2. Adverse Events

13.9.2.1. Overview of Adverse Events

The most common adverse events were predominately gastrointestinal events such as diarrhea, nausea and vomiting. Asthenia and rash were also among the most commonly reported adverse events.

More patients in the ABT-378/ritonavir group (15/59, 25%) experienced rash compared to patients in the ISPI(s) group (8/59, 13.6%). Only two reports of rash were considered to be related to ABT-378/ritonavir treatment. It is thought that rash is predominately related to nevirapine use. Based on other pharmacokinetic studies ABT-378/ritonavir does not appear to increase nevirapine concentrations. Therefore, it is unclear why more patients experienced rash in the ABT-378 group compared to the ISPI(s) group.

Table 13.9.2.1.A. summarizes the treatment-emergent events (at least moderate severity) that are of probable, possible or of unknown relationship to ABT-378/ritonavir and with an incidence of > 2%. Of the events that were probably, possibly or unknown relationship to study drug, there was a greater incidence of nausea in the ISPI(s) group.

In addition, more patients in the ISPI(s) group required treatment with concomitant medications for their adverse events compared to patients in the ABT-378/ritonavir

group (80% vs 63%). Significantly more patients needed medications to treat GI intolerance in the ISPI(s) group (46% vs 24% p =0.020). A total of 14 and 12 patients had a temporary interruption in their treatment due to an adverse event in the ABT-378/ritonavir and ISPI(s) group, respectively. Adverse events were considered to be related to study drug in 3 patients in each treatment group.

Overall, the incidence of adverse events was similar for both treatment arms.

Table 13.9.2.1.A. Treatment-emergent events that are of probable, or possible relationship to study drug and occurring in > 2 percent of patients

Body System	ABT-378/ritonavir	ISPI(s)
Body as a Whole		
Asthenia	0	4 (6.8%)
Digestive		
Anorexia	0	3 (5.1%)
Diarrhea	6 (10.2%)	5 (8.5%)
Nausea	0	7 (11.9%)
Vomiting	1 (1.7%)	2 (3.4%)
Nervous		
Depression	0	2 (3.4%)

HIV-Related Events:

A total of 15 patients developed an HIV-related event; 7 patients in the ABT-378/ritonavir group and 8 patients in the ISPI(s) group. These events included candidiasis (thrush), cryptosporidiosis, oral hairy leukoplakia, herpes simplex, herpes zoster, Kaposi's sarcoma, MAI and CMV.

13.9.2.2. Serious and Life-threatening Adverse Events

A total of 18 serious adverse events were reported in 9 patients during the first 16/24 weeks. Two patients in the ABT-378/ritonavir group and 7 patients ISPI(s) group experienced a serious adverse event(s). The majority of these events were considered unrelated or probably not related to study drug.

One patient in the ABT-378 group experienced 3 events that were possibly related to ABT-378/ritonavir use. These events occurred due to a drug interaction with a contraindicated medication, an ergot alkaloid, which resulted in hospitalization and hemorrhagic colitis with eventual death resulting from a nosocomial staphylococcus sepsis. This patient had received methyergonovine for 10 days for prolonged menstruation. This case prompted the review team to develop a risk communication strategy regarding avoidance of potentially serious and life-threatening drug interactions. Please refer to section 16: Review of Proposed Labeling or the Executive Summary, section I.C. Risk Communication to Patients and Healthcare Professionals for further details.

Other Significant Adverse Events

Hepatitis

Three patients in the ISPI(s) group developed hepatitis. These events were considered not related to study drug. One patient tested positive for hepatitis B on study day 129. Please see section 13.9.2.4 ALT/AST for further details. None of the patients prematurely discontinued study drug due to these events.

Pancreatitis

Patient 8009, a 45-year-old male developed pancreatitis after approximately 5 ½ months of ABT-378, nevirapine, stavudine and didanosine therapy. The patient had a past history of elevated amylase levels and triglycerides. Treatment with ABT-378/ritonavir was restarted and pancreatitis has not recurred. Didanosine treatment was permanently discontinued.

Body Fat Composition Changes

Four and 3 patients reported body fat composition changes in the ABT-378/ritonavir and ISPI(s) groups, respectively.

Adverse Events Associated with Discontinuation of Treatment

Serious Adverse Events (not including deaths)

One patient in the ABT-378/ritonavir group prematurely discontinued treatment due to a serious adverse event (patient 8038: ergotism).

Non-serious Adverse Events

No patients in the ABT-378/ritonavir group prematurely discontinued treatment due to a non serious adverse event. Five patients in the ISPI(s) group prematurely discontinued treatment due to a non serious adverse event (headache/nausea/vomiting, allergic reaction, MAI, anorexia/nausea/asthenia, diarrhea)

13.9.2.3. Deaths

There were a total of 4 deaths during the first 16/24 weeks of the study. All the events were considered not related to study drug by the investigators. One patient died on the ABT-378/ritonavir arm due to sepsis (see section 13.9.2.2. for further details). Three deaths occurred on the ISPI(s) arm; cerebrovascular accident, gastrointestinal carcinoma and one death with an unknown cause at this time. The

death due to cerebrovascular accident occurred 30 days after last dose of study medications.

13.9.2.4. Laboratory Findings

13.9.2.4.1. Hematology

There were no significant differences between treatment groups at week 16 for any hematology value.

13.9.2.4.2. Biochemistry

The following table summarizes grade 3+ laboratory abnormalities. It should be noted that these safety conclusions should be interpreted with caution since these are interim results. Overall grade 3 and 4 laboratory abnormalities were similar between the two groups. However, more patients in the ISPIs group developed grade 3+ increases in ALT. Also more patients in the ABT-378/ritonavir group developed lipid abnormalities.

Grade 3 and 4 Adverse Laboratory Abnormalities

Chemistry Variable	ABT-378/Ritonavir N=59	ISPI(S) N=59
Amylase (> 2 x ULN)	1 (1.7%)	1 (1.7%)
ALT (> 5 x ULN)	1 (1.7%)	4 (6.8%)
AST (> 5 x ULN)	2 (3.4%)	2 (3.4%)
Bilirubin (> 2.9 U/L)	1 (1.7%)	2 (3.4%)
Cholesterol (> 300 mg/dL)	10 (16.9%)	8 (13.6%)
Glucose (> 250 mg/dL)	2 (3.4%)	2 (3.4%)
Triglycerides (> 750 mg/dL)	12 (20.3%)	10 (16.9%)

Significant differences were noted at week 16 for mean change from baseline for creatinine and uric acid. These changes are not considered clinically significant.

Amylase:

One patient in each treatment group experienced grade 3+ elevations in amylase. Both patients were asymptomatic. The patient in the ABT-378/ritonavir arm interrupted study drug due to these elevations. The investigator cites concomitant use of didanosine and stavudine and increased triglycerides as a contributing factor for the increased amylase. The patient in the ISPI(s) group did not interrupt study medication for this laboratory abnormality.

Glucose:

Two patients in each treatment group developed glucose abnormalities (> 250 mg/dL). Both patients in the ABT-378/ritonavir group and 1 patient in the ISPI(s) group were diabetic and were receiving either insulin or oral hypoglycemic agents at baseline. The patient in the ISPI(s) group who developed glucose > 250 mg/dL did

not require insulin or oral hypoglycemic agents. No subject prematurely discontinued study drug for glucose abnormalities.

Lipids:

A total of 26 patients developed grade 3+ lipid abnormalities during the study. No subjects prematurely discontinued study drug for lipid abnormalities. Four patients in the ABT-378/ritonavir group and two patients in the ISPI(s) group initiated a lipid lowering agent for their lipid abnormality.

Cholesterol:

The incidence of cholesterol > 240 mg/dL was comparable between treatment groups. The proportion of patients who developed cholesterol > 300 mg/dL was 2 times greater for patients in the ISPI(s) group compared to the ABT-378/ritonavir group. Of note, the majority of patients in the ISPI(s) group who developed cholesterol abnormalities were receiving ritonavir containing regimens; ritonavir/saquinavir 400 mg BID or ritonavir/indinavir 400 mg BID. It is important to note that these patients received another PI, in addition to ritonavir, which may contribute to further increases in cholesterol. The cholesterol abnormalities are further summarized in Table 13.9.2.4.2.A.

Table 13.9.2.4.2.A. Cholesterol Abnormalities

	ABT-378 (n=59)	ISPI(s)		
		All (n=59)	Ritonavir Containing Regimens (n=40)	Non-Ritonavir Containing Regimens (n=19)
Cholesterol Value > 240 mg/dL	21 (35.6%)	23 (39%)	19 (47.5%)	4 (21%)
Cholesterol Value > 300 mg/dL	10 (16%)	8 (13.5%)	7 (17.5%)	1 (5.3%)

The mean change from baseline for cholesterol is summarized in table 13.9.2.4.2.B. Mean change from baseline at week 16 for cholesterol was greater in the ISPI(s) group. Notably, larger changes from baseline were noted for subjects who received ritonavir containing regimens compared to those who did not in the ISPI(s) group.

Table 13.9.2.4.2.B. Mean change from baseline at week 16 for total cholesterol

	ABT-378 (n=59)	ISPI(s)		
		All (n=59)	Ritonavir Containing Regimens (n=40)	Non-Ritonavir Containing Regimens (n=19)
Mean Baseline (mg/dL)	186	185	188	178
Mean Change (mg/dL)	27	37	46	14
Mean Peak Values (mg/dL)	247	249	271	202

Triglyceride:

The proportion of patients who developed triglyceride values > 750mg/dL was comparable between treatment groups. Of note, all but one of the peak triglyceride values > 750 mg/dL occurred in patients receiving ritonavir containing regimens in the ISPI(s) group. More patients developed triglyceride values > 1500 mg/dL in the ABT-378/ritonavir group (n=6) compared to the ISPI(s) (n=2). In the ISPI(s) group both triglyceride abnormalities > 1500 mg/dL occurred in patients receiving ritonavir containing regimens. Triglyceride abnormalities are further summarized in Table 13.9.2.4.2.C.

Table 13.9.2.4.2.C. Elevations in Triglyceride Levels

	ABT-378 (n=59)	ISPI(s)		
		All (n=59)	Ritonavir Containing Regimens (n=40)	Non-Ritonavir Containing Regimens (n=19)
Triglyceride value > 750 mg/dL	12 (20%)	11 (18.6%)	10 (25%)	1 (5.3%)
Triglyceride value 1000-1499 mg/dL	1 (1.7%)	4 (6.7%)	4 (10%)	0
Triglyceride value > 1500 mg/dL	6 (10%)	2 (3.4%)	2 (5%)	0
Triglyceride value > 2001 mg/dL	4 (6.7%)	1 (1.7%)	1 (2.5%)	0

The mean changes from baseline at week 16 for triglycerides are summarized in Table 13.9.2.4.2.D. These changes were comparable between treatment groups.

Table 13.9.2.4.2.D. Mean change from baseline for triglyceride

	ABT-378 (n=59)	ISPI(s)		
		All (n=59)	Ritonavir Containing Regimens (n=40)	Non-Ritonavir Containing Regimens (n=19)
Mean Baseline (mg/dL)	253	223	237	199
Mean Change (mg/dL)	125	138	158	104
Mean Peak Values (mg/dL)	610	526	611	350

ALT/AST:

Two patients in each treatment group experienced AST elevations > 180 U/L during the study. One patient in the ABT-378/ritonavir group and 4 patients in the ISPI(s) group experienced ALT elevations > 215 U/L. In the ABT-378/ritonavir group one patient was positive for hepatitis C at baseline and the other patient was positive for both hepatitis B and C at baseline. In the ISPI(s) group, all patients were hepatitis negative at baseline, however one patient tested positive for hepatitis B on study day 129 (see section 13.9.2.2 for further details).

ALT/Bilirubin:

No patients in the ABT-378 group and two patients in the ISPI(s) group developed concomitant grade 3+ elevations in bilirubin and ALT. Patient 8114 received ritonavir/saquinavir treatment and had a bilirubin of 3 and ALT of 322 on study day 32. The bilirubin returned to within normal limits and the ALT abnormality declined to 58 U/L. Patient 8020 received indinavir treatment and had a bilirubin of 7.6 and ALT of 1602 on study day 135. The patient tested positive for hepatitis B during this time. The bilirubin and ALT abnormalities declined to 1.3 and 106 U/L respectively.

FDA also conducted an analysis on the proportion of patients with bilirubin > 1.2 and increases in ALT. The results of the analysis are summarized in Table 13.9.2.4.2.

Table 13.9.2.4.2. Concomitant Bilirubin and ALT increases

	Isolated Bilirubin (bilirubin > 1.2 on only 1 study visit)		Sustained bilirubin (bilirubin > 1.2 on 2 or more consecutive study visits, including retests)	
	ABT-378/ritonavir	ISPI(s)	ABT-378/ritonavir	ISPI(s)
Number of patients with ALT within normal limits	1	1	0	1
Number of patients with Grade 1-2 ALT elevations	1	0	1	0
Number of patients with > grade 3 ALT elevations	1	0	0	2

The two patients in the ISPI(s) group with sustained bilirubin abnormalities and grade 3+ ALT elevations are described in the section above.

Patient 8021 in the ABT-378/ritonavir group had an isolated bilirubin abnormality of 2.7 and an ALT value of 533 at week 16. The bilirubin abnormality was within normal limits at the next study visit and the ALT value was 57.

13.10 Safety Conclusions

The most common adverse events were gastrointestinal events such as diarrhea, nausea and vomiting. Asthenia and rash were also among the most commonly reported adverse events. With the exception of GI adverse events, no statistically significant differences between the two treatment groups were observed.

A total of 18 serious adverse events were reported in 9 patients during the first 16/24 weeks. Two patients in the ABT-378/ritonavir group and 7 patients ISPI(s) group experienced a serious adverse event(s). The majority of these events were considered unrelated or probably not related to study drug. There were a total of 4 deaths during the first 16/24 weeks of the study. All the events were considered not related to study drug by the investigators.

One patient died on the ABT-378/ritonavir arm due to sepsis, however this was at least indirectly related to a drug interaction with an ergot alkaloid.

The laboratory abnormalities of note are increases in lipids and transaminases. No patients prematurely discontinued study drug due to these laboratory abnormalities.

14.1. Study M99-046

14.2. Protocol Title

"ABT-378/ritonavir Early Access Program"

14.3. Study Design

This is a multi-center, multi-country, open-label, early access study for patients who are greater than 12 years of age.

Subjects are monitored for safety every 4 weeks through week 24 and every 8 weeks thereafter, for the duration of the study. Subjects will be required to visit the clinic as necessary to receive his/her re-supply of study drug.

The protocol requires that ABT-378/ritonavir be given with at least one or more RTI, NNRTI or protease inhibitor. The protocol does not allow ABT-378/ritonavir to be added as a single additional agent to a failing regimen. If possible, all components of a failing regimen are to be changed entirely at the onset of ABT-378/ritonavir therapy.

14.4. Results

14.4.1. Patient Disposition

In the June 1, 2000 submission the applicant provided information on 1290 patients that have confirmed documentation that they have been dosed with ABT-378/ritonavir. The majority of the patients enrolled were male (82.6%) and most were Caucasian (68.4%). The mean age was 41.2 years. Forty six percent of patients had a baseline CD4 < 50 cells/mm^3. Approximately 60% of patients reported a CD4 cell count nadir of < 50 cells/mm^3. Approximately 83% of patients had HIV RNA between 4 and 6 log copies/mL at entry. The median number of PIs, RTIs, and NNRTIs used in the past were 4, 5 and 1, respectively.

In the 3 month safety update, the applicant reported that a total of 3380 patients had received at least one dose of ABT-378/ritonavir. Table 14.4.1.A. summarizes the reasons for premature discontinuation.

Table 14.4.1.A Patient Disposition and Reasons for Premature Discontinuation

	Number of Patients
Subjects Dosed	3380
Premature Discontinuations	312 (9.2%)
Adverse Event/HIV-related Event	73 (2.2%)
Lost to Follow-Up	17 (<1%)
Withdrew Consent	37 (1.1%)
Administrative	14 (<1%)
Subject Death	60 (1.8%)
Other	124 (3.7%)
Continuing on Study	3069 (90.8%)

14.8. Safety Outcomes

The safety data from this expanded access program was reviewed to determine if any infrequent adverse events occurred that were not seen in the clinical trials. Overall there did not appear to be any increased incidence of adverse events noted in this program compared to clinical trials. This is typical because these programs often underestimate the incidence of adverse events due to the nature in which the data collected. It is difficult to assess causal relationships for adverse events and laboratory abnormalities in this patient population because of complications of advanced HIV disease and multiple concomitant medications

14.9.1. Drug Exposure

The mean duration of follow up as of June 15, 2000 is 2.3 months (range 0 – 8.7 months). Table 14.9.1.A. summarizes the duration of follow-up.

Table 14.9.1.A. Summary of Duration of Follow-up

Duration of Follow-up (months)	Number of Patients
< 1	892 (26.4%)
1 - < 2	811 (24%)
2 - < 3	630 (18.6%)
3 - < 4	433 (12.8%)
4 - < 5	290 (8.6%)
5 - < 6	191 (5.7%)
6 - < 7	74 (2.2%)
7 - < 8	27 (<1%)
8 - < 9	1 (<1%)

14.9.2. Adverse Events

14.9.2.1. Overview of Adverse Events

Per protocol, only serious adverse events were collected. A total of 563 serious adverse events were reported in 313 patients. Sixty three events were considered possibly or probably related to ABT-378/ritonavir treatment. Table 14.9.2.1.A. summarizes these events. (data cut off 6/15/00). The most common events considered possibly or probably related to ABT-378/ritonavir were abdominal pain, fever, increased LFTs, nausea, pancreatitis, rash, increased triglycerides and vomiting.

Other Significant Adverse Events

Pancreatitis:

A total of 21 cases of pancreatitis were reported in the expanded access program. Three cases resulted in death; however one of these patients died secondary to pneumonia and the investigator considered the event of pancreatitis to be "improved" at the time of death. The majority of these cases had other alternative etiologies such as past history of pancreatitis (n=12), use of concomitant medications such as stavudine, didanosine, Bactrim, pentamidine, etc (n=45), prior history of cholecystitis or alcohol use (n=8), or current OI or sepsis (n=5). One patient had a history of prior hypertriglyceridemia with efavirenz use and 3 patients had hypertriglyceridemia during the event of pancreatitis. A causal relationship has not been established for ABT-378/ritonavir and pancreatitis. However, we are concerned because large increases in triglycerides have been observed with ABT-378/ritonavir treatment (a known risk for pancreatitis)

14.9.2.3. Deaths

A total of 60 deaths were reported in the expanded access program. Of these, the dosing status of 6 patients is unknown at this time. An additional 17 patients died, however it was confirmed that they never received ABT-378/ritonavir. The majority of these deaths were HIV related and considered not related to ABT-378/ritonavir.

14.10 Safety Conclusions

Adverse events observed in the expanded access program are consistent with those previously noted in the phase 2/3 clinical trials. No new toxicities were noted in this study.

15. Integrated Summary of Efficacy and Safety for phase 2 and 3 trials (M97-720, M97-765, M98-957, M98-863 and M98-888):

Note for the ISE and ISS, the 533/133 mg dose group from study 957 was included in the pooled 400/100 mg dose groups. These dose groups were chosen for the pooled analyses because these were the doses proposed for marketing. The 200/100 mg dose group from study 720 was omitted from this summary because only 16 patients were received this dose.

15.1 Efficacy:

The antiviral activity of ABT-378/ritonavir has been established in both treatment naïve and treatment experienced patients. Table 11.1.1.A. summarizes the proportion of patients with HIV RNA < 400 copies/mL at week 24 for all phase 2 and 3 studies. In this analysis, the 400/100 mg and 533/133 mg dose groups from the phase 2 and 3 studies were pooled together. Overall, more PI naïve patients had HIV RNA < 400 copies/mL compared to treatment experienced patients. In the phase 3 studies more patients receiving ABT-378/ritonavir had HIV RNA < 400 copies/mL compared to the controls. Response rates have been sustained through 24-72 weeks in phase 2 trials.

Table 11.1.1.A. Proportion < 400 copies/mL at week 24 (ITT)

Dose Group	Naïve	Experienced
Phase 2		
400/100	45/51 (76%)	69/93 (74%)
400/200	23/33 (70%)	28/34 (82%)
Phase 3		
400/100	259/326 (79%)	43/59 (73%)
Nelfinavir (naïve only)	233/327 (71%)	N/A
PI choice (experienced only)	N/A	31/59 (53%)
Total (400/100 only)	304/377 (80.6%)	112/152 (73.6%)

Notably, the difference in virologic response rates for study 863 was greater (in favor of ABT-378/ritonavir vs nelfinavir) among the subgroups of patients with HIV RNA > 100,000 copies/mL or CD4 < 50 cells at baseline. Generally response rates in these subgroups have been less than that seen in the overall study. Results from this study suggest that ABT-378/ritonavir may be a preferred treatment for antiretroviral naïve patients with high baseline HIV RNA levels and/or low CD4 cell counts.

Response rates in antiretroviral experienced patients have typically been lower than that observed in treatment naïve patients. The applicant has demonstrated that the activity of ABT-378/ritonavir in combination regimens has antiviral activity in both first PI failures and multiple-PI experienced patients. Although the overall response rate from the phase 2 trials in PI experienced patients (756, and 957 = 73.6%) was lower than that observed in trials enrolling naive patients (720 and 863 =80.6%); these virologic response rates appear to be greater than that seen in other trials with similar patient populations. In addition, the 24-week virologic response rates in study 888 (interim analysis) were similar to that of the phase 2 trials in PI experienced patients.

In study 888 the response rate at week 24 was 73% for patients receiving ABT-378/ritonavir compared to 53% for the control arm. The differences in response rates may be due to the robust plasma concentrations achieved with ABT-378/ritonavir. These concentrations may be sufficient to treat PI experienced patients with HIV strains that exhibit reduced susceptibility at baseline. However, this study was open label and the results to date are an interim analysis on a portion of the targeted enrollment. Thus, results should be interpreted with caution until a final 48 week analyses can be completed. This will be submitted to the division in support of traditional approval at a later time.

The applicant conducted analyses by gender, race, and age. No statistically significant differences in the proportion of patients with HIV RNA < 400 copies/mL were noted by race. Also no consistent trends were seen between subgroups defined by gender or race.

CD4 cell counts:

Naïve patients had greater mean increases in CD4 cell counts compared to treatment experienced patients. This could be explained by the fact that patients with virologic failure sometimes maintain a CD4 cell count for a period following viral rebound. These patients may have less additional reserve for further CD4 increases.

No statistically significant differences in mean CD4 cell counts were observed between patients in subgroups defined by gender, age or race.

15.2 Safety:

Overview of Adverse Events:

The most common adverse events reported in patients who received 400/100 or 533/133 mg in the phase 2 and 3 studies were predominately gastrointestinal events and asthenia. Elevations in AST/ALT, triglycerides and total cholesterol were also observed. Overall, discontinuations were relatively infrequent. This is evident by the relatively low discontinuation rate that were related to ABT-378/ritonavir adverse events.

Table 15.2.A. summarizes treatment-emergent events (at least moderate severity that are of probable, possible or of unknown relationship to ABT-378/ritonavir for the pooled 400/100 mg arms and for naïve vs experienced patients.

Table 15.2.A. Treatment-emergent events that are of probable, or possible relationship to study drug and occurring in > 2%

	Naïve (n=377)	Experienced (n=152)	Pooled 400/100 Arms (n=529)
Abdominal pain	11 (2.9%)	2 (1.3%)	12 (2.5%)
Asthenia	15 (4%)	7 (4.6%)	22 (4.2%)
Headache	12 (3.2%)	2 (1.3%)	14 (2.6%)
Diarrhea	56 (14.9%)	20 (13.2%)	76 (14.4%)
Nausea	24 (6.4%)	1 (0.7%)	25 (4.7%)

The proportions of patients with adverse events were similar between naïve and experienced patients; however, more naïve patients experienced nausea compared to experienced patients.

Discontinuations due to Adverse Events:

Overall 3.2% (17/529) patients discontinued study due to a drug-related adverse event. The majority of the discontinuations were due to GI intolerance.

Deaths:

Six deaths occurred in patients receiving ABT-378/ritonavir 400/100 mg BID or 533/133 mg BID the phase 2 and 3 studies. Five deaths occurred in naïve patients from study 863 and one antiretroviral experienced patient died in trial 888. All deaths were considered not related to study drug; however, a death in study 888 may be indirectly related to a drug interaction with an ergot medication. Please also refer to Executive Summary section I.C. Risk Communication to Patients and Healthcare Professionals. In addition, in study 765 one patient died as a result of rhabdomyolysis, acute renal failure and pneumonia. It is unclear if this death was drug related. Although this case is concerning, no other cases of rhabdomyolysis were noted in clinical trials.

Laboratory Abnormalities:

Table 15.2.B. summarizes the proportions of patients with > grade 3 chemistry values. Overall the incidence of grade 3+ laboratory abnormalities were similar between naïve and experienced patients with the exception of GGT elevations and lipid abnormalities. Also the overall incidence of laboratory abnormalities were similar to controls (863: nelfinavir and 888: ISPIs), with the exception of lipid abnormalities. These abnormalities occurred more frequently in patients receiving ABT-378/ritonavir

Table 15.2.B. Grade 3 and 4 Adverse Laboratory Abnormalities

Chemistry Variable	Naïve (n=377)	Experienced (n=152)	Pooled 400/100 Arms (n=529)
Glucose (> 250 mg/dL)	6 (1.6%)	6 (4%)	12 (2.3%)
AST (> 5 x ULN)	8 (2.1%)	4 (2.6%)	12 (2.3%)
ALT (> 5 x ULN)	8 (2.1%)	5 (3.3%)	13 (2.5%)
GGT (> 5 x ULN)	2 (0.5%)	7 (4.6%)	9 (1.2%)
Cholesterol (> 300 mg/dL)	24 (6.4%)	25 (16.4%)	49 (9.3%)
Triglycerides (> 750 mg/dL)	20 (5.3%)	38 (25%)	58 (11%)
Triglycerides (> 1500 mg/dL)	1 (0.3%)	13 (8.5%)	14 (2.6%)
Amylase (> 2 x ULN)	6 (1.6%)	2 (1.3%)	8 (1.5%)

Transaminases:

Overall transaminase elevations occurred in approximately 2.5% of patients enrolled in the phase 2 and 3 trials. The incidence was similar in both naïve and experienced patients.

FDA reviewed ALT/AST data from various ritonavir trials in antiretroviral naïve and experienced patients to determine if a correlation exists between ritonavir dose and grade 3+ elevations in transaminases. The tables below summarizes the information. Overall the incidence of transaminase elevations were less in patients receiving ABT-378/ritonavir 400/100 mg than in those receiving ritonavir 600 mg in other studies.

Naïve Patients:

The incidence of grade 3+ transaminase elevations was considerably lower in study 863 compared to phase 2 studies. Data from a phase 2 study suggested that the incidence of transaminase elevations were similar when ABT-378 was given with 100 mg or 200 mg of ritonavir. It will be important to determine if the incidence of transaminase elevations increase in study 863 over time. Of note, duration of follow – up for studies 720 and 245 was greater than 72 weeks compared to 24 weeks of follow up in study 863. Furthermore, it has been confirmed in several studies that patients with underlying hepatitis B or C are at greater risk for transaminase elevations.

Transaminase Abnormalities: Cross Study Analysis (Naïve patients)

	ABT-378/ritonavir Study 863: Ritonavir 100 mg (n=326)	ABT-378/ritonavir Study 720 Ritonavir 100 mg (n=51)	ABT-378/ritonavir Study 720 Ritonavir 200 (n=33)	Ritoanvir Study 245: Ritonavir 600 mg (n=117)
AST > 180 U/L	0.3%	10.4%	3%	9.5%
ALT > 215 U/L	1%	7.5%	6%	7.8%

Experienced Patients:

For experienced patients, a relationship between transaminase elevations and ritonavir dose is not apparent. More patients in the 765 study who received ritonavir 200 mg experienced transaminase elevations compared to patients in study 247 who

received ritonavir 600 mg. This may be due to the small sample size for the ABT-378/ritonavir 400/200 mg dose group in study 765. The incidence of transaminase elevations for the ritonavir 100 mg groups were slightly lower then in the ritonavir 600 mg groups.

Transaminase Abnormalities: Cross Study Analysis (Experienced patients)

	ABT-378/ritonavir Study 888: Ritonavir 100 mg (n=59)	ABT-378/ritonavir Study 765 Ritonavir 100 mg (n=36)	ABT-378/ritonavir Study 765 Ritonavir 200 (n=33)	ABT-378/ritonavir Study 957 Ritonavir 100/133 mg (n=57)	Ritonavir Study 462: Ritonavir 400 mg + Saquinavir 400 mg (n=35)	Ritoanvir Study 247: Ritonavir 600 mg (n=541)
AST > 180 U/L	3.4%	5.6%	12.1%	0 %	6%	6.4%
ALT > 215 U/L	1.7%	8.3%	21.2%	3.6%	6%	8.5%

Lipids:

Lipid abnormalities occurred more frequently in patients with previous antiretroviral experience. The proportions of antiretroviral experienced patients who developed cholesterol > 300 mg/dL and triglycerides > 750 mg/dL was 2.5 and 5-fold higher, respectively, than that of the antiretroviral naïve patients. One naïve patient developed triglycerides > 1500 mg/dL compared to 13 antiretroviral experienced patients. Approximately 18 patients received lipid lowering agents for their lipid abnormalities.

FDA reviewed cholesterol/triglyceride data from various ritonavir trials in antiretroviral naïve and experienced patients to determine if there was correlation between ritonavir dose and grade 3+ lipid abnormalities. There did not appear to be a dose relationship for triglycerides or cholesterol elevation in antiretroviral experienced patients. A correlation may not be noted in this patient population because of prior use of protease inhibitors. The incidence of cholesterol abnormalities was about 2-fold less for naïve patients receiving ABT-378/ritonavir 400/100 mg vs ritonavir 600 mg. Based on historical comparisons, there was a 2.8 and 2 fold increase in the proportion of patients with triglycerides > 800 mg and > 1500 mg/dL for patients receiving ritonavir 600 mg vs 100 mg, respectively.

Cholesterol:

Naïve Patients:

Because the magnitude and pattern of changes in lipids are similar among historical comparisons between ABT-378/ritonavir and ritonavir 600 mg BID, it is likely that ritonavir is mainly responsible for the lipid abnormalities seen with ABT-378/ritoanvir. The table below summarizes the proportion of patients with cholesterol > 240 mg/dL in various trials using ritonavir in antiretroviral naive patients. In this cross study comparison it is unclear if increases in cholesterol are dose related. However, in cross study comparisons of treatment naïve patients, the proportion of patients who had a

cholesterol > 240 mg/dL was nearly double for those receiving ritonavir 600 mg compared to those receiving ritonavir 100 mg (with ABT-378). However, the proportion of patients with cholesterol > 240 mg/dL was even larger for those receiving 200 mg of ritonavir (with ABT-378) in study 720. These results may be a reflection of the relatively small sample size (n=33).

Cholesterol Abnormalities: Cross Study Analysis (Naïve patients)

	ABT-378/ritonavir Study 720 + 863 All pooled 100 mg ritonavir arms (n=377)	ABT-378/ritonavir Study 720 Ritonavir 200 mg dose group (n=33)	Ritoanvir Study 245: Ritonavir 600 mg (n=117)
Cholesterol Value > 240 mg/dL	26%	61%	44.8%

Experienced Patients:

There does not appear to be a dose relationship for cholesterol > 240 mg/dL for experienced patients receiving ritonavir 100 mg vs 600 mg. The incidence of cholesterol abnormalities were approximately 35% for both groups. It is difficult to assess if a dose relationship exists because of the small sample size in study 765 for the ritonavir 200 mg dose group and the concomitant use of saquinavir 400 mg BID in study 462. This dual PI combination appeared to have more increases in cholesterol compared to ritonavir treatment alone.

Cholesterol Abnormalities: Cross Study Analysis (Experienced patients)

	ABT-378/ritonavir Study 765 + 957 + 888 100/133 mg ritonavir arms (n=152)	ABT-378/ritonavir Study 765 200 mg dose group (n=33)	Ritonavir Study 462: Ritonavir 400 mg + Saquinavir 400 mg (n=35)	Ritonavir Study 247: Treatment Experienced Patients (600 mg BID) (n=541)
Cholesterol Value > 240 mg/dL	34.2%	63.6%	60%	36.5%

Triglycerides:

The table below summarizes the proportion of patients with triglycerides > 800 mg/dL and > 1500 mg in various trials with antiretroviral naive and experienced patients. There is a 2.8 and 2 fold increase in the proportion of patients with triglycerides > 800 mg and > 1500 mg/dL for patients receiving ritonavir 600 mg vs 100 mg with lopinavir, respectively.

Triglyceride Abnormalities: Cross Study Analysis

	ABT-378/ritonavir Study 720 + 863 All pooled 100 mg ritonavir arms (n=377)	ABT-378/ritonavir Study 720 Ritonavir 200 mg dose group (n=33)	Ritonavir Study 245: Ritonavir 600 mg (n=117)
Triglycerides > 800 mg/dL	6.1%	12%	17.2%
Triglycerides > 1500 mg/dL	0.26%	9%	2.6%

Experienced Patients:

The table below summarizes the proportion of patients with triglycerides > 800 mg/dL and > 1500 mg in various trials with antiretroviral experienced patients. There does not appear to be a dose relationship for triglyceride abnormalities in treatment experienced patients; however, the proportion of patients who experienced triglycerides > 800 mg/dL was slightly less in the 100 mg groups (25%) vs the 600 mg group (33.6%).

Triglyceride Abnormalities: Cross Study Analysis

	ABT-378/ritonavir Study 765 + 957 + 888 100/133 mg ritonavir arms (N=152)	ABT-378/ritonavir Study 765 200 mg dose group (n=33)	Ritonavir Study 462: Ritonavir 400 mg + Saquinavir 400 mg (n=35)	Ritonavir Study 247: Treatment Experienced Patients (600 mg BID) (n=541)
Triglycerides > 800 mg/dL	25%	30.3%	17.1%	33.6%
Triglycerides > 1500 mg/dL	8.3%	9.1%	11.4%	12.6%

EKG changes:

QT:

Analyses of mean/median QT (corrected) changes from baseline were conducted on pooled data from phase 2 studies which included several doses of ABT-378/ritonavir and one phase 3 study in which the new protease inhibitor was compared to a marketed PI (nelfinavir). For these analyses week 2 EKGs were compared to pretreatment baseline values. EKGs were done without regard to time of dosing. The pharmacokinetic data for these doses follows the phase 2 data. There was no apparent dose response in mean or median 2 week QTc. In study 863, approximately 250 patients per treatment arm had EKG data at week 2. No significant changes from baseline in QTc at week 2 were detected. Median and mean changes were similar between treatment groups.

Phase 2 (pooled from two dose-ranging studies, studies 720 and 765)

Dose	Mean change in QTc (msec)	95% C.I.	Median change in QTc
200/100 BID (n=16)	-5.06	-11.4, 1.34	-6
400/100 BID (n=77)	3.27	-0.17, 6.72	3
400/200 BID (n=55)	1.54	-4.88, 7.97	1

The PK data for the 400/100 and 400/200 doses from two phase 2 studies are as follows

Study/Dose	Cmax (ug/mL)	Cmin (ug/mL)	AUC12
Study # 1			
400/100	9.6	3.8	82
400/200	11.5	6.3	110
Study #2			
400/100	7.0	2.4	61
400/200	12.4	7.1	121

Phase 3 (study 863)

Drug/Dose	Mean change in QTc (msec)	95% C.I.	Median change in QTc
400/100 BID (n=253)	3.9	-0.93, 8.87	0.5
Nelfinavir (n=247)	3.1	-1.68, 7.96	0

(EKGs done at baseline and at week 24)

No patients in phase 2 or 3 had a QTc above 500 msec. Six patients in the phase 2 program and six in the phase 3 study had QTc intervals > 450 msec, but several of these had baseline values > 450 msec.

Although EKGs were not known to have been obtained at Cmax, there is some EKG data at higher doses (concentrations) than the to be marketed dose. This data would indicate that higher concentrations (than that expected with the to be marketed dose) do not appear to increase the risk of QTc prolongation.

PR:

The applicant's analyses of EKGs showed a statistically significant increase in PR interval in patients who received ABT-378/ritonavir compared to controls. However, these changes did not appear to be clinically significant. One patient developed an interval long enough to be considered first degree block (>210 msec), but he was asymptomatic and continued on ABT-378/ritonavir without adverse effect. It is not known whether this individual had any electrolyte abnormalities that may have contributed to the prolongation. The clinical significance of these findings appears to be minimal.

Other Significant Adverse Events:

Pancreatitis

There is concern that patients receiving ABT-378/ritonavir who develop marked elevations in triglyceride values (> 1000 mg/dL) may be at increased risk for pancreatitis. Patients with a history of pancreatitis may also be at increased risk for recurrence during ABT-378/ritonavir treatment. Therefore, continual evaluation of cases of pancreatitis during planned and ongoing studies and during post marketing is essential. A statement regarding pancreatitis has been included in the WARNING section of the package insert.

Clinical Trials:

The overall incidence of pancreatitis seen in the 5 adult clinical studies was 0.98% (7/716). This incidence is similar to the overall incidence in HIV-infected patients. Of note, the incidence of pancreatitis for ABT-378/ritonavir is less than what has been reported with ddI and/or d4T.

Four cases of pancreatitis were in antiretroviral experienced patients and 4 cases were in treatment naïve patients.

Two cases occurred approximately 5 ½ months after initiating treatment with ABT-378, nevirapine, stavudine and didanosine, the other case occurred after approximately 19 months on study. In both cases, ABT-378/ritonavir was restarted. Didanosine or didanosine and stavudine were replaced with other RTIs in both cases. In the fourth case, the patient had symptoms of pancreatitis 3 days prior to study drug initiation. The patient was hospitalized for lactic acidosis on study day 4 and pancreatitis was diagnosed during the hospitalization.

Another patient developed pancreatitis after 5 months of treatment, study drug was not interrupted and the event resolved. Another case of pancreatitis occurred in study 863. The patient had also been receiving d4T, 3TC and amphotericin B. The event resolved. Only one patient had triglyceride values > 750 mg/dL. One death as a result of pancreatitis occurred in a naïve patient.

Expanded Access:

A total of 21 cases of pancreatitis were reported in the expanded access program. Two cases resulted in death. The majority of these cases had other alternative etiologies such as past history of pancreatitis, and use of concomitant medications. One patient had a history of prior hypertriglyceridemia with efavirenz use and 3 patients had hypertriglyceridemia during the event of pancreatitis. Triglyceride values were not given for these patients; however, the investigator reported that "hypertriglyceridemia" was present. It is not known if these patients developed triglycerides > 1000 mg/dL, which is considered to be a risk factor for pancreatitis.

Hepatitis:

Three cases of hepatitis were reported in clinical trials. One patient developed hepatitis A and the second case was attributed to nevirapine use. ABT-378/ritonavir treatment was restarted without nevirapine and the event did not reoccur. In third case hepatitis was reported after receiving ABT-378/ritonavir for approximately 5 months. The patient is also HCVAb+. The patient reported anorexia and fatigue; however, the study drug was never interrupted for this event.

3 page(s) of revised draft labeling has been redacted from this portion of the review.

17. Accelerated Approval and Phase 4 Commitments

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies to verify and describe clinical benefit. The applicant agreed to submit the results from the final study analyses of the following two ongoing phase 3 studies of the safety and efficacy of KALETRA to support traditional approval: Study M98-863, "A Randomized, Double-Blind, Phase III Study of ABT-378/Ritonavir Plus Stavudine and Lamivudine vs. Nelfinavir Plus Stavudine and Lamivudine in Antiretroviral-Naïve HIV-Infected Subjects" and Study M98-888, "A Randomized, Open-Label, Phase III Study of ABT-378/ritonavir in Combination with Nevirapine and Two Nucleoside Reverse Transcriptase Inhibitors vs Investigator Selected Protease Inhibitor(s) in Combination with Nevirapine and Two NRTIs in Antiretroviral-Experienced HIV-Infected Subjects".

Phase 4:

Chemistry

- A commitment to reassess the drug substance specification and the drug product specification when stability studies on the first three commercial scale lots of the capsules have been completed. During this reassessment, release and stability data from both commercial and representative NDA lots will be considered. The applicant will submit this data, with the proposed specifications, through a prior approval supplement to NDA 21-226.

- A commitment to reassess the drug product specification when stability studies on the first three commercial scale lots of the oral solution have been completed. During this reassessment, release and stability data from both commercial and representative NDA lots will be considered. The applicant will submit this data, with the proposed specifications, through a prior approval supplement to NDA 21-251.

Microbiology

The applicant has agreed to provide the following information.

- Analyze isolates from patients with virologic failure on KALETRA to determine associations between protease mutations and *in vitro* shifts in susceptibility to define the resistance profile of lopinavir.

- Continue genotypic and phenotypic analysis of isolates from patients in ongoing Studies M97-765 and M98-957 who experience loss of virologic response.

- Assess the genotypic basis of drug susceptibility attributable to extragenic sites, such as the protease cleavage sites.

- Conduct *in vitro* combination activity studies.

- Evaluate the cross-resistance potential between KALETRA and amprenavir.

Pharmacology/toxicology

The applicant has agreed to provide the following information.

- Continue carcinogenicity studies and submit final report.

Clinical Pharmacology

The applicant has agreed to provide the following information.

- Evaluate KALETRA pharmacokinetics in subjects with mild and moderate hepatic impairment, to allow the determination of dosing recommendations, through the conduct of a pharmacokinetic study.

During the September 8, 2000 teleconference it was agreed that the applicant will attempt to enroll 6 patients with mild hepatic impairment and 6 patients with moderate hepatic impairment based on the Child-Pugh classification.

- Establish appropriate dosing recommendations for the coadministration of KALETRA with other approved protease inhibitors through the conduct of drug interaction studies.

During the September 8, 2000 teleconference, it was discussed that the dose recommendations will try to provide similar AUCs and increased Cmin compared to current regimens. Safety and efficacy will not be characterized in these studies. In addition, these studies will not make use of historical controls.

- Determine, in vivo, the extent to which KALETRA inhibits CYP2D6. Consideration will be given to conducting a drug interaction study with KALETRA and desipramine.

- Further evaluation of the pharmacokinetics of KALETRA and nevirapine in HIV-infected adults from Study M97-765

During the September 8, 2000 teleconference, it was agreed that pharmacokinetic samples taken at 0, 2, 4, 8, and 12 hours and will be compared with historical controls.

- Explore dosing recommendations for coadministration of KALETRA and rifampin, with additional ritonavir.

- Explore dosing recommendations for the coadministration of KALETRA plus approved protease inhibitor(s) plus efavirenz/nevirapine through analysis of data from the Expanded Access Program.

- Evaluate pharmacokinetic/pharmacodynamic relationships in Studies M98-957 and M99-049.

Clinical:

The applicant agreed to provide the following information.

- Continue to investigate the efficacy of once daily administration of KALETRA through the conduct of Study M99-056.

- Continue to evaluate the activity of higher doses of KALETRA in patients exhibiting virologic failure or showing reduced susceptibility to multiple protease inhibitors through the conduct of Study M99-049.

- Development of educational materials for patients and healthcare workers regarding avoidance of drug interactions.

- Continued evaluation of suspected protease inhibitor class adverse events including (a) establishment of an intercompany collaboration, or company based registry to collect data on patients who develop fractures or avascular hip necrosis while receiving antiretroviral therapy and (b) fat redistribution. This will include investigation of mechanisms for 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.

18. REGULATORY RECOMMENDATION

Based on the data submitted by Abbott Laboratories, it is recommended that this application receive an approval action. The information contained in this application fulfils the intent of the accelerated approval regulations. The results from 5 clinical trials in adults and the expanded access program clearly demonstrate a favorable safety and efficacy profile for both treatment naïve and treatment experienced patients.

/S/

Kimberly Struble, Pharm.D.
Regulatory Review Officer

Concurrence:
HFD-530/MOTL/Murray /S/ 10/11/00
HFD-530/DivDir/Jolson 10/23/00

cc:
Original NDA 21-226
Division File
HFD-530/RRO/Struble
HFD-530/MO/Murray
HFD-530/CSO/Lynche, Belioun
HFD-530/Stat/Soon
HFD-530/Biopharm/Reynolds, Kim
HFD-530/Chem/Miller, Lo
HFD-530/Pharm/Tox/Farrelly, Zhang