8.7.2.5.2. Biochemistry

Table 8.7.2.5.2.A. summarizes the proportions of patients with > grade 3 chemistry values during the first 72 weeks for the 400/100 mg dose groups. Selected Laboratory abnormalities are further discussed in detail in this section.

Table 8.7.2.5.2.A. Grade 3 and 4 Laboratory Abnormalities for 400/100 mg Dose Group

Chemistry Variable	All 400/100 mg Dose Groups (n=51)
Glucose (>250 mg/dL)	1 (2%)
Uric Acid (> 12 mg/dL)	1 (2%)
Total bilirubin (>2.9 x ULN)	1 (2%) [patient diagnosed with Hepatitis A]
AST (>5 x ULN)	7 (13.7%)
ALT (>5 X ULN)	5 (9.8%)
GGT (>5 X ULN)	2 (4%)
Total Cholesterol (> 300 mg/dL)	3 (5.8%)
Triglycerides (> 800 mg/dL)	2 (4%)

Amylase:

Four patients in the 400/200 mg dose group experienced increases in amylase levels to ≥ grade 3(>2 X ULN). All four patients continued dosing and no adverse events were associated with these elevations. Patient 245 had the largest increase in amylase and also > grade 3 amylase values at baseline.

Bilirubin:

Three patients had bilirubin levels > 2. One patient was diagnosed with hepatitis A. Another patient had a peak bilirubin of 2 however the visits before and after the peak level were within normal limits. The third patient had a bilirubin level of 0.5 on day 141, 2.4 on day 170, 2 on day 182 and 1.4 on day 337. It is unclear if the intermittent elevations in bilirubin were due to ABT-378/ritonavir. ALT/AST values were within normal limits for this patient.

Glucose:

Three patients had glucose values > 250 mg/dL during the study. Of note patients 104 and 212 had pre-existing diabetes mellitus. In addition patient 212 and 217 were receiving steroid medications at the time of the glucose elevations. No patients discontinued study drug due to increases in glucose. All three patients were treated with oral hypoglycemics throughout the study.

Lipids:

Twenty patients had grade 3 or 4 elevations in triglycerides and/or cholesterol values during the first 72 weeks. Overall 6 patients had both grade 3/ 4 elevations in triglycerides and cholesterol. No patient interrupted or reduced the dose of study drug

due to grade 3 or 4 lipid increases. Please also refer to section 15: ISS for additional information on cross study comparisons for lipid abnormalities.

Cholesterol

Overall 46% and 14% of patients experienced cholesterol values > 240 mg/dL and > 300 mg/dL, respectively. Cholesterol abnormalities are summarized in Table 8.7.2.5.2.C. In the pooled 400/100 mg dose groups, 35% and 10% of patients had cholesterol values > 240 mg and > 300 mg/dL respectively.

Table 8.7.2.5.2.C. Cholesterol Abnormalities

	GROUP I		GROUP II		
	200/100	400/100	400/100	400/200	Pooled 400/100
	N=16	N=16	N=35	N=33	N=51
Cholesterol Value > 240 mg/dL	8 (50%)	8 (50%)	10 (29%)	20 (61%)	18 (35%)
Cholesterol Value > 300 mg/dL	2 (13%)	2 (13%)	3 (9%)	7 (21%)	5 (10%)

The mean change from baseline for total cholesterol at week 48 was approximately 50 mg/dL for all dose groups. The mean change from baseline for total cholesterol is summarized in Table 8.7.2.5.2.D. Mean increases in cholesterol did not appear to be dose related.

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Table 8.7.2.5.2.D. Mean change from baseline for total cholesterol

	GROUP I		GROUP II		
	200/100	400/100	400/100	400/200	Pooled 400/100
	N=16	N=16	N=35	N=33	N=51
Mean Baseline (mg/dL)	160	161	155	163	162
Mean Change (mg/dL)	51	38.5	36	46	36
Mean Peak Values (mg/dL)	238.5	236.8	228.9	259.6	231.4

Triglyceride:

Overall 11% and 3% of patients had triglyceride values > 800 mg/dL and > 1500 mg/dL respectively. Triglyceride abnormalities are summarized in Table 8.7.2.5.2.F. In the pooled 400/100 mg dose groups, 2% of patients had triglyceride values > 800 mg/dL and one (2%) patient had a triglyceride value > 1500 mg/dL.

Table 8.7.2.5.2.F Elevations in Triglyceride Levels

	GROUP I		GROUP II		
	200/100	400/100	400/100	400/200	Pooled 400/100
	N=16	N=16	N=35	N=33	N=51
Triglyceride value > 800 mg/dL	3 (10%)	1 (6%)	3 (8.5%)	4 (12%)	4 (7.8%)
Triglyceride value 1000-1499 mg/dL	1 (6%)	1 (6%)	1 (2.8%)	0	2 (4%)
Triglyceride value > 1500 mg/dL	0	0	0	3 (9%)	0
Triglyceride value > 2001 mg/dL	0	0	0	2 (6%)	0

The applicant states that there were no statistically significant differences observed for mean changes from baseline in triglycerides between the two dose groups in group I or group II. Table 8.7.2.5.2.G. summarizes mean change from baseline for triglyceride.

Table 8.9.2.5.2.G. Mean change from baseline for triglyceride

	GROUP I		GROUP II		
	200/100	400/100	400/100	400/200	Pooled 400/100
	N=16	N=16	N=35	N=33	N=51
Mean Baseline (mg/dL)	186	153	129	164	136
Median Change (mg/dL)	110.5	73.5	64	65	66
Mean Peak Values (mg/dL)	476	386	381	546	382

Six patients received antihyperlipidemic agents as a result of elevated triglycerides/cholesterol. Based on this limited data it appears that statins were effective in reducing lipid levels back toward baseline.

Liver Function Tests:

There were no grade 3 or 4 increases in AST/ALT values in group I. In group II: 400/100 mg dose group, seven patients (20%) had grade 3 + increases in AST levels.

Five patients (14.3%) in the 400/100 mg dose group had grade 3 or 4 increases in ALT levels compared to two patients (5.7%) in the 400/200 mg group. No patients discontinued ABT-378/ritonavir treatment due to increases in ALT/AST levels. Increases in transaminases did not appear to increase with duration of treatment

Approximately 66% of patients with grade 3 or 4 transaminase elevations returned to near baseline levels with either continued therapy or after interruption and rechallenge. Two patients' levels remained intermittently elevated on continued ABT-378/ritonavir treatment. These patients were asymptomatic. Only one patient with increased ALT/AST levels discontinued treatment; however, the reason cited for premature discontinuation was for noncompliance and not for transaminase elevations.

At week 72, one patient (patient 240) had Grade 3+ transaminase elevations and was the only patient to permanently discontinue study due to elevated transaminases. This patient had intermittently elevated transaminases until study day 505 at which time levels increased to grade 3+. This patient was HBsAG+ at baseline. Of note the patient began serostim treatment 45 days prior to grade 3 elevations in transaminases.

The applicant conducted an analysis on the proportion of patients with positive baseline serologies for viral hepatitis and grade 3 or 4 transaminase elevations. Forty-five percent (5/11) of patients with baseline serologies positive for HBsAG or HCV antibodies experienced grade 3 or 4 transaminase elevations compared to 5% (4/89) of patients who had negative baseline serologies for HBsAG or HCV antibodies. The applicant states that patients with positive baseline serologies for viral hepatitis were found to be at increased risk for grade 3 or 4 elevations in ALT/AST [relative risk = 10.11; 95% CI 3.18 – 32.17].

ALT/Bilirubin:

An analysis was conducted by the FDA to examine the number of patients who had both grade 3 /4 ALT and grade 3 /4 total bilirubin elevations during the first 48 weeks. One patient experienced both grade 4 ALT and bilirubin elevations. However this patient was diagnosed with hepatitis A by serology. This event was considered not related to ABT-378/ritonavir treatment.

FDA also conducted an analysis on the proportion of patients with concomitant bilirubin > 1.2 and increases in ALT. The results of the analysis are summarized in Table 8.7.5.2.H. Patients experiencing either isolated, intermittent or sustained bilirubin and grade 3 or 4 increases in ALT are further discussed below. Overall, it is difficult to assess if concomitant increases in bilirubin and ALT are related to ABT-378/ritonavir therapy, however it does appear that patients with underlying hepatitis infection may be at greater risk for abnormalities in bilirubin/transaminases.

Table 8.7.5.2.H Concomitant Bilirubin and ALT increases

	Isolated Bilirubin (bilirubin > 1.2 on only 1 study visit)	Intermittent bilirubin (bilirubin > 1.2 on more than 1 study visit but bilirubin not sustained for 2 or more consecutive visits)	Sustained bilirubin (bilirubin > 1.2 on 2 or more consecutive study visits)
Number of patients	11	3	10
Number of patients with ALT within normal limits	7	3	7
Number of patients with Grade 1/2 ALT elevations	3	0	2*
Number of patients with > grade 3 ALT elevations	1	0	1 (patient diagnosed with hep A)

*Patient experienced peak ALT > grade 3+

Aside from the patient with acute hepatitis A, 2 patients experienced sustained bilirubin elevations > 1.2 mg/dL and concomitant grade 1/ 2 ALT elevations. Patient 238 was HCV + at baseline and had a baseline bilirubin of 0.9 mg/dL and ALT of 91 U/L. On week 16, his bilirubin and ALT increased to 1.7 mg/dL and 204 U/L, respectively. His bilirubin returned to within normal limits several weeks later and remained within normal limits at the last follow up, grade 1/ 2 ALT elevations continued and peaked to 285 U/L at week 48.

Patient 267 was HBV/HCV negative at baseline and had a baseline bilirubin of 0.9 mg/dL and ALT of 79 U/L. His bilirubin increased to 1.6 mg/dL on week 4 and remained elevated from weeks 12-24, 36 and 48. During this time his ALT ranged from 37 U/L to 66 U/L.

Metabolic Complications/Abnormal Fat Redistribution

Information from clinical trials and reports in the medical literature suggest an association between the development of metabolic abnormalities, such as increases in serum glucose, triglycerides and/or cholesterol and syndromes of abnormal fat redistribution and the use of antiretroviral therapy. There is still debate if the metabolic and body composition abnormalities are a single syndrome or if these abnormalities represent several different syndromes that may not be necessarily related. In an effort to evaluate the potential correlation between metabolic complications and abnormal fat redistribution, FDA conducted analyses to determine the number of patients with metabolic and body composition abnormalities compared to those patients with only body composition abnormalities. Four of the five patients who reported body composition changes, experienced cholesterol > 240 mg/dL. All patients had increases in triglycerides, however all levels were < 800 mg/dL.

In a separate analysis 2 patients experienced 2 or more metabolic abnormalities in the absence of body composition changes. One patient experienced > grade 3 increases in glucose, cholesterol and triglycerides and one patient experienced > grade 3 increases in glucose and cholesterol. Given the small number of patients enrolled in this trial it is difficult to assess the relationship between metabolic and body composition abnormalities in patients receiving antiretroviral therapy.

Thyroid Function Tests:

The applicant states that mild decreases from baseline were observed in mean T4 levels for all dose groups. However, changes in TSH levels for individual patients appeared to be evenly distributed and of low magnitude. The applicant cites an independent review of the preclinical and clinical data by an endocrinologist, Dr. Mark Molitch who concluded that these changes were physiologically insignificant across this population. We agree with these conclusions.

8.7.3. Safety Conclusions

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

- Overall the most common adverse events reported for all dose groups were predominately gastrointestinal events, asthenia and headache. Specifically, the most common adverse events reported for the 400/100 mg dose groups were abnormal stools, diarrhea, nausea, asthenia and headache. Moderate or severe nausea and vomiting related to ABT-378/ritonavir occurred at a higher rate (statistically significant) in the 400/200 mg group than the 400/100 mg group.

- One patient prematurely discontinued study for a drug related adverse event.

- A total of 47 serious adverse events were reported in 23 patients during the first 72 weeks of the study. Only 2 events were considered possibly or probably related to ABT-378/ritonavir. One patient prematurely discontinued study due to a serious adverse event. Eighteen (38%) of the serious adverse events occurred in patients receiving 400/100 mg dose, of which only one event was considered possibly related to ABT-378/ritonavir.

- Elevations in triglycerides and cholesterol occurred in all dose groups. Patients in the 400/200 mg dose group experienced a numerically higher rate (not statistically significant) of grade 3 or 4 lipid elevations compared to patients in the 400/100 mg group. Changes in lipids may be related to the ritonavir component of this product. No patients discontinued study due to lipid abnormalities.

- Elevations in liver function tests were also observed. Only one patient prematurely discontinued study due to transaminase abnormalities at week 72. Patients with positive baseline serologies for HBsAg or HCV antibodies were at increased risk for grade 3 or 4 transaminase elevations.

- There were no deaths during the first 72 weeks.

9.1 Study M97-765

9.2 Protocol Title

Randomized, multi-center study of ABT-378/ritonavir in combination with two nucleoside reverse transcriptase inhibitors and nevirapine in protease inhibitor experienced HIV-infected males and females

9.3 Study Design and Analysis Plans

This was a blinded, randomized, multi-center trial in seventy antiretroviral experienced patients with HIV RNA levels between 1,000 and 100,000 copies/mL. Patients were required to be currently treated with a PI and one or two RTIs that have not changed in the last 12 weeks prior to enrollment. Patients were randomized to one of the following dose groups:

Group 1: ABT-378/ritonavir 400/100 mg BID
Group 2: ABT-378/ritonavir 400/200 mg BID

The PI in each patient's existing regimen was discontinued on day –1. For days 1-14, patients received their assigned ABT-378/ritonavir regimen in combination with the RTIs they were receiving in their existing regimen. This allowed one to isolate the effect of ABT-378 on HIV RNA reduction over two weeks. On day 15, each patient's RTI regimen was changed to a new regimen that included at least on new RTI that the patient had not previously received. Nevirapine was also added to each patient's regimen on day 15.

9.4 Patient Population

Inclusion/Exclusion criteria were: > 18 years of age, NNRTI naïve, naïve to at least one RTI, current treatment with a regimen containing a PI and 1 or 2 RTIs that had not changed in the 12 weeks prior to screening, HIV RNA between 1,000 and 100,000 copies/mL, no evidence of acute illness or documentation of abnormal laboratory parameters as defined by the protocol.

9.5 Study Endpoints

The primary efficacy analysis was proportion of patients with HIV RNA < 400 copies/mL at week 24 and the time to loss of virologic response through week 48.

9.6 Results

9.6.1. Patient Disposition

A total of 74 patients were randomized into this trial. Seventy patients received at least one dose of ABT-378/ritonavir. Thirty-six patients received ABT-378/ritonavir 400/100 mg BID and 34 patients received ABT-378/ritonavir 400/200 mg BID. See Table 9.6.3.A. for further details.

9.6.2 Protocol Deviations

The protocol deviations appeared to be minor violations related to measurements or examinations that did not occur within a time window specified in the protocol, a missing laboratory test, or an exclusionary value at screening. These deviations would not be expected to adversely impact the overall interpretation of the study results.

9.6.3. Reasons for Premature Discontinuation

Overall 7 patients in 400/100 mg dose group and 6 patients in the 400/200 mg dose group prematurely discontinued study prior to week 72. Table 9.6.3.A. summarizes the reasons for premature discontinuation.

Table 9.6.3.A. Patient Disposition and Premature Discontinuations

Original Assignment	400/100 mg	400/200 mg
Received at least one dose of study medication	36	34
Number of Patients beyond 72 weeks	29	28
Personal Reasons	2	0
Death	0	2
AE/HIV related event	3	1
Patient noncompliant	1	1
Lost to follow-up	0	2
Other	1	0

9.6.4. Demographic Data

Table 9.6.4.A. shows demographic data, baseline HIV RNA and CD4 cell counts for each dose group. There were no significant differences in the baseline characteristics between groups.

Table 9.6.4.A. Demographic Data

	400/100	400/200
Number of Patients	36	34
Mean age, Yrs	41	40
Men	34 (94%)	29 (85%)
Race or Ethnicity		
Caucasian	29	22
Black or African American	7	10
Asian/Pacific Islander	0	2
Baseline Antiretroviral Therapy		
RTI:		
DDI	7 (19.4%)	0
3TC	28 (77.8%)	33 (97.1%)
d4T	22 (61.1%)	17 (50%)
ZDV	14 (38.9%)	16 (47.1%)
PI:		
Amprenavir	1 (2.8%)	0
Indinavir	15 (41.7%)	16 (47.1%)
Nelfinavir	14 (38.9%)	11 (32.4%)
Ritonavir	1 (2.8%)	3 (8.8%)
Saquinavir	5 (13.9%)	4 (11.8%)
Baseline mean plasma HIV RNA (PCR), $\log_{10}$ copies/mL	4.1	4.0
Baseline median CD4 cell count (cells/mm^3)	371	372

Table 9.6.4.B summarizes the baseline phenotypic susceptibility to protease inhibitors at study entry. Phenotypic data were available for 57/70 (81%) of patients. The applicant determined that 63% of patients were phenotypically resistant to their baseline PI. Phenotypic resistance was defined at $\geq$ 4 fold increase in EC_{50} relative to

wild type virus. Also 32% of patients were cross-resistant to at least 3 of the 4 licensed PIs.

Table 9.6.4.B. Number of Patients with Changes in Phenotypic Susceptibility

Baseline PI	Fold-Change in EC_{50} to Baseline PI (Relative to Wild Type)			
	< 4 fold change	≥ 4 fold change	Mean Change	Range
Indinavir (n=24)	8	16	7.4	[redacted]
Nelfinavir (n=21)	8	13	19.1	[redacted]
Saquinavir (n=9)	5	4	9.5	[redacted]
Ritonavir (n=3)	3	0	23	[redacted]

9.6.5. Efficacy Outcomes

9.6.5.1. HIV RNA

Proportion < 400 copies/mL

Table 9.6.5.1.A. summarizes the efficacy analyses. The on-treatment and intent to treat (noncompleters = failure/NC=F) analyses are presented below. Overall 70% and 73% of patients had HIV RNA < 400 copies/mL at week 48 and 72, respectively. There were no differences between dose groups at week 24, 48 or 72.

Table 9.6.5.1.A. Week 24 and 48 Proportion < 400 copies/mL

Dose Group	HIV RNA < 400 copies/mL					
	Week 48			Week 72		
	On Treatment	ITT (NC=F)	>400 copies/mL*	On Treatment	ITT (NC=F)	>400 copies/mL*
400/100	23/29 (79%)	24/36 (67%)	N=6 Mean: 8786 copies/mL Range: [redacted] copies/mL	27/30 (90%)	27/36 (75%)	N=3 Mean: 24787 copies/mL Range: [redacted]
400/200	25/27 (93%)	25/34 (74%)	N=3 Mean: 8601 copies/mL Range: [redacted] copies/mL	24/28 (86%)	24/34 (71%)	N=4 Mean 1893 Copies/mL Range: [redacted] Copies/Ml
p-value comparing dose groups	0.254	0.607		0.701	0.790	

*Missing HIV RNA values and premature discontinuations not included

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Mean Change From Baseline:

Decreases in mean HIV RNA were seen at all time points. The mean change from baseline at week 2 was –1.21 log_{10} copies/mL for the 400/100 mg dose group and –1.07 log_{10} copies/mL for the 400/200 mg dose group. These changes were observed prior to the additions of nevirapine and new RTIs.

9.6.5.2. CD4 Cell Count

The mean change from baseline to week 72 was 132 and 172 cells for the 400/100 and 400/200 dose groups, respectively. These differences were not statistically significant.

9.7 Safety Outcomes

A total of 70 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 2 deaths in this study.

9.7.1. Drug Exposure

The median duration of exposure was 541 days for the 400/100 mg dose group and 544 days for the 400/200 mg dose group.

9.7.2. Adverse Events

9.7.2.1. Overview of Adverse Events

All 70 patients experienced at least one adverse event during the first 72 weeks of the study. The most common adverse events were predominately gastrointestinal events such as diarrhea, nausea and abnormal stools. Asthenia was also among the most commonly reported adverse events. Elevations in AST/ALT, triglycerides and total cholesterol were observed in both dose groups.

Table 9.7.2.1.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 > 5%.

Table 9.7.2.1.A Treatment-emergent events that are of probable, or possible relationship to study drug and occurring in > 5 percent of patients

	400/100	400/200
Number of patients	**36**	**34**
Body System		
Asthenia	1 (2.8%)	3 (8.8%)
Digestive		
Abnormal Stools	1 (2.8%)	2 (5.9%)
Diarrhea	8 (22.2%)	8 (23.5%)
Nausea	1 (2.8%)	2 (5.9%)
Musculoskeletal		
Myalgia	2 (5.6%)	0
Skin/Appendages		
Rash	2 (5.6%)	0

Source: NDA 21-226 vol 28 table 12.2B and vol 83 table 12.2.B

Rash:

Ten and 11 patients experienced rash in the 400/100 mg and 400/200 mg dose groups, respectively. The applicant stated that 16 of these patients experienced only a mild rash and 4 patients experienced a moderate rash. It appears that the majority of the rashes may have been related to nevirapine. One patient was hospitalized for a severe rash attributed to nevirapine use. The patient subsequently resumed ABT-378/ritonavir 3 days after the event and nevirapine was permanently discontinued.

AIDS Defining Events:

There were no CDC class C, AIDS defining events; however, there were a comparable number of HIV-related events observed in both dose groups, including oral candidiasis, and herpes zoster.

9.7.2.2. Serious and Life-threatening Adverse Events

A total of 28 serious adverse events were reported in 13 patients during the first 72 weeks. Five patients (13.9%) in the 400/100 mg dose group and 8 patients (23.5%) in the 400/200 mg dose group experienced a serious adverse event(s). The majority of these events were considered unrelated or probably not related to ABT-378/ritonavir. Only 3 events were considered possibly related to ABT-378/ritonavir. Table 9.2.2.A. summarizes the serious adverse events that are possibly related to ABT-378/ritonavir. Only one patient prematurely discontinued study due to a serious adverse event. This patient experienced a MI one day after initiating ABT-378/ritonavir therapy. The investigator felt that this event was not related to study drugs. The 3 month safety update lists one patient that was hospitalized on day 610 for abdominal pain and distension accompanied by nausea. These events were considered not related to study drugs.

Table 9.7.2.2.A. Serious Adverse Events At Least Possibly Related

DOSE GROUP	PATIENT	REASON	CAUSALITY	OUTCOME
400/100	423	Diarrhea	Possibly	Hospitalized
400/200	304	Cholecystitis	Possibly	Hospitalized
400/200	417	Rhabdomyolysis	Possibly	Prolonged Hospitalization; Death

Source NDA 21226: vol 28 Table 12.3b

For information on patient 417 please see section 9.7.2.4.

Other Significant Adverse Events

Hepatitis

One case (patient 318) of hepatitis was reported and considered not related to ABT-378/ritonavir treatment. The patient was randomized to receive ABT-378/ritonavir 400/100 mg on August 5, 1998. Approximately 2 months later his ALT, AST and GGT peaked at 245 U/L, 153 U/L and 567 U/L respectively. The patient was also noted to have "clay-colored stools and dark urine." All study drugs were stopped and retest of laboratory values showed improvement in ALT, AST and GGT to 119 U/L, 68 U/L and 527 U/L respectively. All study drugs, except nevirapine, were reintroduced 8 days later with no recurrence of hepatitis. ALT/AST levels remained stable (not exceeding grade 2 toxicity) for approximately 5 months until study drugs were permanently discontinued for persistent intermittent loose stools. The investigator's assessment that the event was related to nevirapine appears accurate, since the event did not recur after all study drugs except nevirapine were restarted. No other cases of hepatitis were reported.

Pancreatitis

There were 2 cases of pancreatitis. The first case was reported 5 months after study entry. The investigator felt that this event was related to ddI use, however an ABT-378 effect can not be ruled out. Patient 307 was receiving ABT-378/ritonavir 400/100 mg BID + nevirapine + ddI +d4T at the time of the event. Didanosine was permanently discontinued and replaced with 3TC one month after the event.

The other case occurred in a 36 year old male after 19 months of therapy with ABT-378/ritoanvir, nevirapine, stavudine and didanosine. The pancreatitis resolved and ABT-378/ritonavir was restarted with nevirapine, zidovudine and abacavir.

It is difficult to evaluate the causal relationship between pancreatitis and ABT-378/ritonavir from these cases. In both cases, patients received concomitant medications that are known to cause pancreatitis.

Body Fat Composition Changes

Similar to that reported for study 720, the applicant conducted a search of the adverse event database to identify potential events of lipodystrophy and other body fat composition changes.

Eight patients, 6 patients in the 400/200 mg dose group and 2 patients in the 400/100 mg dose group, reported body fat composition changes consisting of facial thinning, increase in abdominal girth, etc. In each case, study drug was not interrupted or discontinued.

Urogenital System:

One patient developed mild flank back pain and amber colored urine on days 49-52 and 64-66. On day 70 an IVP revealed "a normal study with the possibility of nonobstructing left ureteral calculus present at the ureterovesical junction." The investigator assessment that this event is possibly related to ABT-378/ritonavir or alternatively due to a kidney stone and dehydration appears reasonable.

9.7.2.3 Adverse Events Associated with Discontinuation of Treatment

Serious Adverse Events

One patient prematurely discontinued study due to a serious adverse event. This patient experienced a myocardial infarction one day after initiating ABT-378/ritonavir therapy. The investigator felt that this event was not related to study drugs. Given the onset of the event, it would be unlikely that this event was related to ABT-378/ritonavir.

Nonserious Adverse Events

Two patients in the 400/100 mg group and one patient in the 400/200 mg group discontinued study due to a nonserious adverse event. Two discontinued secondary to GI disturbances and one due to rash. All the events were considered to be probably related to study drugs.

9.7.2.4. Deaths

There were two deaths during the first 72 weeks. Both patients received ABT-378/ritonavir 400/200 mg. The causes of death are summarized below.

Patient 417 was hospitalized after approximately 7 months of ABT-378/ritonavir treatment for pneumonia. During this hospitalization, ABT-378/ritonavir treatment was interrupted. On admission the patient was also found to have elevated AST (558 U/L

rose to 822 U/L), ALT (113 U/L), and LDH (2635 U/L). Bilirubin levels were normal. In addition two the liver enzyme abnormalities he had acute renal failure with a creatinine of 2.2 mg/dL which rose to 11.5 mg/dL two days later. CPK on admission was 22,000 U/L. The patient was thought to have rhabdomyolysis. Transaminase levels returned to normal; however, acute renal failure progressed with creatinine rising to 24.3 mg/dL 7 days after admission. The patient died approximately 8 days after admission due to progressive renal failure. The investigator thought the events of pneumonia and rhabdomyolysis was probably not related to study drug; however, the applicant considered these events to be possibly related given the lack of a clinically verifiable alternative etiology. Further complicating this case, the patient was hospitalized at month 2 of study for PML.

It is unclear if this death was drug related. No other cases of rhabdomyolysis were noted in clinical trials. Events of acute renal failure and rhabdomyolysis will be monitored in other trials and during the postmarketing period.

The second death was due to metastatic lung cancer diagnosed 9 weeks after study in a patient with a heavy smoking history.

9.7.2.5. Laboratory Findings

9.7.2.5.1. Hematology

Two patients experienced adverse events relating to abnormal hematology values (leukopenia, anemia). No patient prematurely discontinued due to these values.

9.7.2.5.2. Biochemistry

The following table summarizes the proportions of patients with > grade 3 chemistry values. Selected Laboratory abnormalities are further discussed in detail in this section.

Table 9.9.3.A. Grade 3 and 4 Adverse Laboratory Abnormalities

Chemistry Variable	400/100 mg n=36	400/200 n=33*
Glucose (> 250 mg/dL)	1 (2.8%)	2 (6.1%)
Creatinine (>3 x ULN)	0	1 (3%)**
Uric Acid (> 12 mg/dL)	0	1 (3%)***
AST (> 5 x ULN)	2 (5.6%)	4 (12.1%)
ALT (> 5 x ULN)	3 (8.3%)	7 (21.2%)
GGT (> 5 x ULN)	7 (19.4%)	12 (36.4%)
Cholesterol (> 300 mg/dL)	7 (19.4%)	12 (36.4%)
Triglycerides (> 800 mg/dL)	7 (19.4%)	10 (30.3%)
Amylase (> 2 x ULN)	2 (5.6%)	1 (3%)

source NDA 21226 vol. 28 table 12.4c

*one patient did not have post baseline laboratory values and was excluded from all chemistry analyses

**creatinine elevation please refer to section 9.7.2.4 patient 417

*** one patient had uric acid elevation of 12.7 mg/dL. This patient had a previous history of hyperuricemia, gout and degenerative arthritis.

Amylase:

Two patients in the 400/100 mg group and one in the 400/200 mg group experienced ≥ grade 3 increases in amylase levels (> 2x ULN), none had symptomatic pancreatitis.

Glucose:

One patient in the 400/100 mg group and two patients in the 400/200 mg group experienced ≥ grade 3 increases in glucose levels (> 250 mg/dL). Two patients had pre-existing diabetes mellitus at baseline. Glucose values decreased to near baseline for all patients. No patient discontinued study due to glucose elevations.

Lipids:

No patient interrupted or reduced the dose of study drug due to grade 3 or 4 lipid increases. However, some patients required therapeutic intervention for their lipid abnormalities. Refer to section 15, integrated summary of safety for additional information on cross study comparisons for lipid abnormalities.

Cholesterol:

Overall, 44.4% and 63.6% of patients experienced cholesterol elevations > 240 mg/dL in the 400/100 mg and 400/200 mg dose groups, respectively

The mean change from baseline for cholesterol was approximately 29 mg/dL and 51 mg/dL for the 400/100 mg and 400/200 mg dose groups, respectively. Mean peak values were 234 mg/dL and 272 mg/dL for the 400/100 and 400/200 mg dose groups, respectively. There appeared to be greater increases in mean cholesterol levels for the 400/200 mg dose group. Statistically significant differences were observed for mean change from baseline at several time points. The applicant stated that patients with baseline cholesterol > 200 mg/dL were found to be at increased risk for developing grade 3 or 4 elevations in cholesterol [risk ratio 4.33; 95% C.I. 1.89-9.92).

Triglycerides:

Overall, 11% and 30% of patients developed triglyceride values > 800 mg/dL in the 400/100 mg and 400/200 mg dose groups respectively. Triglyceride abnormalities are further summarized in Table 9.7.2.5.2.C.

Table 9.7.2.5.2.C Elevations in Triglyceride Levels

	400/100 mg	400/200 mg
	N=36	N=33*
Triglyceride value > 800 mg/dL	4 (11%)	10 (30.3%)
Triglyceride value 1000-1499 mg/dL	1 (2.8%)	3 (9.1%)
Triglyceride value > 1500 mg/dL	3 (8.3%)	3 (9.1%)
Triglyceride value > 2001 mg/dL	0	2 (6%)

*one patient did not have post baseline chemistry value and is excluded from all analyses

The mean changes from baseline at week 72 for triglycerides were 82 mg/dL and 203 mg/dL for the 400/100 mg and 400/200 mg dose groups, respectively. Statistically significant differences were noted for mean change from baseline at weeks 2, 60 and 72. The applicant reports that patients with baseline triglycerides > 400 mg/dL were found to be at increased risk for developing grade 3 or 4 elevations in triglycerides [risk ratio=4.16; 95% CI 2.13-8.11).

Nine patients received antihyperlipidemic agents as a result of elevated triglycerides/cholesterol. Based on this limited data it appears that treatment with antihyperlipidemic agents, such as HMG CoA reductase inhibitors ("statins") or gemfibrizol were effective in reducing overall triglyceride and cholesterol levels.

Liver Function Tests:

Overall 8.7% and 14.5% of patients had grade 3 or 4 elevations in AST and ALT values, respectively. Although not statistically significant, there appeared to be larger increases in ALT for the 400/200 mg dose group compared to the 400/100 mg dose group (400/100 mg: 8.3%; 400/200 mg: 21.2%).

Twelve patients developed grade 3 or 4 transaminase elevations. Only one patient developed grade 3+ transaminase elevations after week 48. Notably, no patient permanently discontinued study drug due to these abnormalities. All but 4 patients with elevations in ALT/AST had return of these values to near baseline. Two of the 4 patients with elevated AST/ALT were HCV antibody positive.

In addition, 9 patients (16.9%: 10/59) who had negative baseline serologies for HBsAg or HCV antibodies developed grade 3 or 4 transaminase elevations compared to two patients (20%: 2/10) with baseline serologies positive for HBsAG or HCV antibodies. Clinical hepatitis was reported for one patient, however this event was attributed to nevirapine use. Please refer to section 9.7.2.2 for further details.

The applicant reported that patients with baseline AST/ALT greater than the upper limit of normal were found to be at greater risk for developing grade 3 or 4 transaminase elevations [risk ratio = 4.21; 95% CI. 1.66-10.70].

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ON ORIGINAL

ALT/Bilirubin:

No patient experienced concomitant grade 3/4 elevations in both ALT and total bilirubin.

FDA calculated the proportion of patients with any elevation in bilirubin (> 1.2) concomitant with increases in ALT. The results are summarized in Table 9.7.2.5.2.E. Only one patient experienced a sustained bilirubin > 1.2 mg/dL with concomitant grade 3 or 4 increases in ALT. This patient is discussed below. One patient with isolated elevated bilirubin and one patient with sustained bilirubin elevations developed a peak ALT of grade 3 or 4; however, these peak values did not occur at the same study visit as the bilirubin elevations. Overall, it is difficult to assess if concomitant increases in bilirubin and ALT were related to ABT-378/ritonavir therapy.

Table 9.7.2.5.2.E Concomitant Bilirubin and ALT increases

	Isolated Bilirubin (bilirubin > 1.2 on only 1 study visit)	Intermittent bilirubin (bilirubin > 1.2 on more than 1 study visit but bilirubin not sustained for 2 or more consecutive visits)	Sustained bilirubin (bilirubin > 1.2 on 2 or more consecutive study visits)
Number of patients	8	2	4
Number of patients with ALT within normal limits	4	1	1
Number of patients with Grade 1-2 ALT elevations	4*	1	2*
Number of patients with > grade 3 ALT elevations	0	0	1

*1 pt in each group had peak ALT of grade 3+ during the study

Patient 321 had a peak total bilirubin of 3.2 mg/dL with AST of 262 U/L and ALT of 565 U/L on study day 78. This patient had a history of intermittent elevations in transaminases since June 1994 as well as ongoing alcohol abuse and was found to be reactive for hepatitis C antibody. Bilirubin levels subsequently decreased below the ULN by study day 134 and remained below ULN through study day 519. The investigator felt that the first two ALT/AST elevations were due to hepatitis C or alcohol use. No other GI events suggestive of symptomatic hepatitis were reported. On study day 371 the investigator discontinued nevirapine, zidovudine and zalcitabine and initiated stavudine and abacavir. It is possible that transaminase elevations may have been related to nevirapine use.

GGT:

GGT elevations > 300 mg/dL were reported in 19.4% and 36.4% of patients in the 400/100 mg and 400/200 mg dose groups, respectively. Seven patients experienced concomitant grade 3+ elevations in both GGT and ALT or AST. No patient prematurely discontinued study due to GGT elevations. GGT elevations have also been reported with nevirapine.

Thyroid Function Tests:

The applicant states that mild decreases from baseline were observed in mean T4 levels for all dose groups. However, changes in TSH levels for individual patients appeared to be randomly distributed and of low magnitude. The applicant cites an independent review of the preclinical and clinical data by an endocrinologist, Dr. Mark Molitch, who concluded that these changes were physiologically insignificant across this population. His conclusions appear to be reasonable based on the data reviewed.

9.9.3 Safety Conclusions

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

- The most common adverse events were predominately gastrointestinal events such as diarrhea, nausea and abnormal stools. Asthenia was also among the most commonly reported adverse events.

- A total of 28 serious adverse events were reported in 13 patients during the first 728 weeks. Only 3 events were considered possibly related to ABT-378/ritonavir. One patient prematurely discontinued study due to a serious adverse event. This patient experienced a MI one day after initiating ABT-378/ritonavir therapy. The investigator felt that this event was not related to study drugs.

- Two patients in the 400/100 mg group and one patient in the 400/200 mg group discontinued study due to a nonserious adverse event.

- There were two deaths during the first 48 weeks; one patient's death was attributed to pneumonia, rhabdomyolysis and renal failure and the second was related to metastatic lung cancer. These patients received ABT-378/ritonavir 400/200 mg. Both were considered not related to ABT-378/ritonavir by the investigator. However, the applicant considers the case of pneumonia and rhabdomyolysis possibly related given the lack of a clinically verifiable alternative etiology.

- Elevations in triglycerides and cholesterol were seen in both dose groups. No patient discontinued study due to lipid abnormalities. Statistically significant differences in cholesterol and triglycerides were observed at multiple time points during the study.

- Elevations in transaminases were also observed in both dose groups. Although not statistically significant, there appeared to be larger increases in ALT for the 400/200 mg dose group compared to the 400/100 mg dose group (400/100 mg: 8.3%; 400/200 mg: 21.2%). Transaminase elevations were not dose limiting

events for ABT-378/ritonavir. Most patients were able to continue randomized treatment.

10.1 Study M98-957

10.2 Protocol Title

A Phase II Study of ABT-378/Ritonavir and Efavirenz in HIV Infected Subjects Experienced with Multiple Protease Inhibitors

10.3 Study Design and Analysis Plans

This is a phase II, open-label, randomized, multiple dose, parallel arm, pharmacokinetic interaction study. Fifty subjects who are NNRTI naïve and have received multiple protease inhibitors were randomized into one of the following treatment arms:

Arm A: ABT-378/ritonavir 400/100 mg BID + efavirenz 600 mg QD + RTIs (determined by investigator)

Arm B: Day 1-13:
ABT-378/ritonavir 400/100 mg BID + efavirenz 600 mg QD + RTIs (determined by investigator)

Day 14 onward:
ABT-378/ritonavir 533/133 mg BID + efavirenz 600 mg QD + RTIs (determined by investigator)

Based on pharmacokinetic and safety data, the applicant amended the study such that all patients in Arm A were dose increased to 533/133 mg BID. This amendment occurred after all subjects reached the week 24 visit.

10.4 Patient Population

10.4.1 Inclusion/Exclusion Criteria

Inclusion/Exclusion criteria were: > 18 years of age, HIV RNA > 1000 copies/mL, current treatment with an antiretroviral regimen containing at least one protease inhibitor that had not been changed in the last 8 weeks and prior history of sequential or concurrent treatment with at least two different protease inhibitors for a period of at least 12 weeks and no evidence of acute illness or documentation of abnormal laboratory parameters as defined by the protocol.

10.5 Study Endpoints

- Proportion of subjects with plasma HIV RNA level below the limit of quantitation (400 copies/mL) at each study visit

10.7. Results

10.7.1. Patient Disposition

A total of 75 patients were screened for this study. Fifty-seven patients were randomized and dosed, 29 to the 400/100 dose and 28 to the 533/133 dose. Twenty-five patients in each dose group remained on study at week 24. Overall a total of 7 patients prematurely discontinued prior to week 24.

10.7.2. Protocol Deviations

Three subjects had protocol deviations that included not receiving at least 2 PIs prior to enrollment, received an NNRTI up to 1 day prior to enrollment and switched dosing frequency of nelfinavir and saquinavir within 8 weeks prior to study.

10.7.3. Reasons for Premature Discontinuation

Overall 7 patients prematurely discontinued from study; 4 patients in the 400/100 dose group and 3 patients in the 533/133 dose group. Two patients discontinued in each dose group due to an adverse event.

10.7.4. Demographic Data

Baseline characteristics were similar between dose groups with the exception that more patients in the 400/100 mg group received prior treatment with ritonavir and fewer patients in the 400/100 mg group received prior treatment with stavudine.

Table 10.7.4.A. Demographic Data

	400/100	533/133
Number of Patients	29	28
Mean age, Yrs	41.1	42.6
Men	76%	82%
Race or Ethnicity		
Caucasian	25	25
Black or African American	2	3
Unspecified	2	0
Prior number of antiretrovirals (mean)	7.17 (3-10)	7.29 (4-10)
Prior Antiretroviral Therapy		
Indinavir	24 (82.8%)	25 (89.3%)
Nelfinavir	16 (55.2%)	17 (60.7%)
Ritonavir	26 (89.7%)	18 (64.3%)
Saquinavir	20 (69%)	21 (75%)
Abacavir	4 (13.8%)	6 (21.4%)
Didanosine	24 (82.8%)	21 (75%)
Lamivudine	27 (93.1%)	25 (89.3%)
Stavudine	24 (82.8%)	28 (100%)
Zalcitabine	13 (44.8%)	13 (46.4%)
Zidovudine	28 (96.6%)	25 (89.3%)
Hydroxyurea	2 (6.9%)	5 (17.9%)
Baseline Antiretroviral Therapy		
Abacavir	2 (6.9%)	2 (7.1%)
Didanosine	8 (27.6%)	11 (39.3%)
Lamivudine	18 (62.1%)	15 (53.6%)
Stavudine	14 (48.3%)	16 (57.1%)
Zalcitabine	1(3.4%)	0
Zidovudine	13 (44.8%)	10 (35.7%)
Hydroxyurea	3 (10.3%)	2 (7.1%)
Baseline mean plasma HIV RNA (PCR), $\log_{10}$ copies/mL	4.6	4.4
Baseline median CD4 cell count (cells/mm^3)	230	325

10.7.5. Efficacy Outcomes

10.7.5.1. HIV RNA

There was a numerical but not a statistical difference in the proportion of patients with HIV RNA < 400 copies/mL at week 24. The results of the on treatment and ITT analyses are displayed in the table below.

Proportion of Patients with HIV RNA < 400 copies/mL at week 24

Dose Group	HIV RNA < 400 copies/mL	
	Week 24	
	On Treatment	ITT (M=F)
400/100	20/25 (80%)	20/29 (69%)
533/133	23/25 (92%)	23/28 (82%)
p-value	0.417	0.358

Coadministration of ABT-378/ritonavir 400/100 and efavirenz yielded a reduction in the ABT-378 Cmin of approximately 44%. Based on the efficacy results and pharmacokinetic information from the ABT-378/ritonavir + efavirenz interaction study, all patients in the 400/100 dose group had their dose increased to 533/133 mg. ABT-378/ritonavir 533/133 mg in the presence of efavirenz yielded ABT-378 Cmin values that were similar to those observed in a phase 2 study of 400/100 without efavirenz.

Mean change from baseline in HIV RNA for both dose groups was – 1.64.

Virology Substudies:

Cross-resistance: Clinical studies

The relevance of baseline genotypic mutational patterns, baseline susceptibility and virologic response rates were assessed in 56 patients. Results of these analyses are described below.

Genotypic Analyses:

All 56 patients' baseline and week 24 HIV RNA results were reviewed. Four patients were censored for this analysis because these patients discontinued treatment for reasons other than loss of virologic response. Three patients did not have a week 24 HIV RNA result, however these patients were included in the analysis because loss of virologic response was noted at an earlier time point.

The following mutations in the HIV protease were evaluated in order to determine if there was an association between specific mutational patterns and virologic response rates; (L10F/I/R/V, K20M/R, L24/I, M46I/L, F53L, 154L/T/V, L63P, A71I/L/T/V, V82A/F/T, I84V and L90M). These mutations were associated with a statistically

significant reduction in susceptibility to lopinavir in vitro in an analysis submitted by the applicant.

Ten patients had a loss of virologic response. Of these patients, 7 were randomized to the 400/100 mg dose group and 3 were randomized to the 533/133 mg dose group.

Within this study, no specific mutational patterns were associated with a loss of virologic response. However, it did appear that at least one primary protease mutation (82, 84, and 90) plus multiple other mutations at baseline were associated with a lack or loss of virologic response. Twenty-five patients had less than or equal to 5 mutations at baseline. Response rates (proportion < 400 copies/mL) for these patients were 96% (24/25) compared to 67% (18/27) for patients with greater than 5 mutations at baseline. The mean and median number of mutations for patients with HIV RNA < 400 copies/mL at 24 weeks, were 4.7 and 5, respectively. The mean and median number of mutations for patients with HIV RNA > 400 copies/mL, were 7. These results suggest that the presence 6 or more protease mutations at baseline may be associated with reduced response rates.

Also it is important to note that the majority of patients with a loss of virologic response received the 400/100 mg dose. This may be due to lower ABT-378 levels as a result of an interaction between ABT-378/ritonavir and efavirenz. Further studies are needed to assess the association between specific mutational patterns and virologic response rates.

Phenotypic Analyses:

Baseline susceptibility to lopinavir and virologic response rates at week 24 were evaluated. Patients with a less than 10 fold reduction in susceptibility to lopinavir at baseline had a better virologic outcome than patients with $\geq$ 10 fold reduction in susceptibility to lopinavir at baseline. The proportion of patients with HIV RNA < 400 copies/mL was 93% (27/29) for patients with < 10 fold reduction in susceptibility to lopinavir at baseline compared to 65% (15/23) for patients with $\geq$ 10 fold reduction in susceptibility to lopinavir at baseline.

10.7.5.2. CD4 Cell Count

The mean increase at 24 weeks from baseline for CD4 cell counts was 48 and 41 cells/mm^3 for the 400/100 and 533/133 mg groups, respectively.

10.8 Safety Outcomes

A total of 57 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 no deaths in this study.

10.8.1. Drug Exposure

The median duration of treatment was 196 days for both dose groups.

10.8.2. Adverse Events

Overall 93% of patients experienced at least one adverse event during the first 24 weeks of the study. The most common adverse events reported for either dose groups were predominately gastrointestinal events such as abnormal stools, diarrhea, and nausea. Other common adverse events included dizziness, pain, abnormal dreams, asthenia, flu syndrome, headache, insomnia, pharyngitis and rash. The applicant noted a statistically significant difference between dose groups for those events, which were at least moderate in intensity and possibly, probably, or unknown relationship to study drug. More of these events were noted in the 533/133 group; however, the difference was apparent in the first 14 days of treatment when all subjects were still receiving 400/100 mg. Therefore this difference did not appear to be related to ABT-378/ritonavir exposures. Also efavirenz concentrations did not differ in the two dose groups.

Table 10.8.2.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 10.8.2.A. Treatment-emergent events that are of probable, or possible relationship to study drug and occurring in > 2 percent of patients

	400/100 (n=29)	533/133 (n=28)
Body System		
Body as a Whole		
Abdominal pain	0	2 (7.1%)
Asthenia	2 (6.9%)	4 (14.3%)
Headache	0	2 (7.1%)
Pain	0	2 (7.1%)
Digestive		
Diarrhea	2 (6.9%)	4 (14.3%)
Flatulence	0	2 (7.1%)
Nervous		
Insomnia	0	5 (17.9%)
Special Senses		
Tinnitus	0	2 (7.1%)
Urogential		
Abnormal ejaculation	0	1 (4.3%)

10.8.2.2. Serious and Life-threatening Adverse Events

A total of 12 serious adverse events were reported in 6 patients. Four events were considered related to ABT-378/ritonavir. Table 10.8.2.2.A. summarizes the serious adverse events that are possibly or probably related to study drug. One patient

prematurely discontinued study due to a serious adverse event. Two of the events have not resolved as of the last available information provided on these patients.

Table 10.8.2.2.A. Serious Adverse Events At Least Possibly Related

PATIENT	ONSET	REASON	CAUSALITY	OUTCOME	RESOLVED?
400/100 mg					
520	166	Kidney calculus	Possible	Hospitalization	Ongoing
533/133					
526	5	Lactic acidosis	Possible	Prolonged hospitalization	Resolved
	10	Pain	Possible	Permanent disability	Ongoing
	66	Liver fatty Deposit*	Possible	Hospitalizaiton	Resolved

*event occurred > 30 days after last dose

Patient 520 experienced nephrolithiasis after 5 months of ABT-378/ritonavir 400/100 mg BID treatment. His past medical history is significant for nephrolithiasis requiring nephrolithotomy on indinavir therapy. The patient was hospitalized with right abdominal pain and nausea and removal of kidney calculus. The patient had hematuria at baseline, which may suggest the presence of a kidney calculus. Therefore, it is possible that this event may not be related to ABT-378/ritonavir.

Patient 526 was a 34 year old female who was hospitalized for pancreatitis and lactic acidosis after 4 days of ABT-378/ritoanvir 400/100 mg therapy. CT scan revealed pancreatitis. Symptoms of pancreatitis were noted 3 days prior to study drug initiation. The patient was diagnosed with lactic acidosis that worsened despite bicarbonate supplementation. Her lactic acid level was 16 mmol/L. The patient has a past medical history of hepatic steatosis, cholecystectomy, urethral lithiasis, moderate anemia, hematuria, lymphoedema, obesity and hypertriglyceridemia. It was thought that the pancreatitis was due to other medications and not ABT-378/ritoanvir. The applicant felt that these events might have been due to zidovudine use pancreatitis and not due to ABT-378/ritoanvir. The lactic acidosis worsened despite interruption of ABT-378/ritonavir.

This patient was hospitalized again for leg pain, hepatic steatosis and depression after 2 months after stopping of ABT-378/ritonavir therapy. The patient also had an elevated bilirubin and "icterious" which was attributed to hepatic steatosis. It is possible that the event of hepatic steatosis may have been attributed previous NRTIs. Also the leg pain may have been due to prior d4T use or myeloradiculitis. Of note these events occurred 2 months after ABT-378/ritonavir therapy was discontinued.

Other Significant Adverse Events

Hepatitis:

There were no cases of hepatitis reported during the study.

Pancreatitis:

One case of pancreatitis was reported during the first 24 weeks. Please refer to section 10.8.9.2. patient 526 for further details.

Diabetes:

No cases of new onset diabetes were observed during the first 24 weeks.

Body Fat Changes:

Two patients reported body fat changes during the first 24 weeks. However both patients had received months of prior antiretroviral agents, including protease inhibitors as specified in the inclusion criteria.

Adverse Events Associated with Discontinuation of Treatment

Serious Adverse Events:

One patient prematurely discontinued treatment due to a serious adverse event. Patient 526 discontinued due to lactic acidosis. Please refer to section 10.9.9.2 for further details.

Non-serious Adverse Events:

Three subjects prematurely discontinued treatment due to a non serious adverse event. In the 400/100 mg dose group, patient 505 discontinued due to multiple GI and CNS events approximately 5 days after study initiation and patient 554 discontinued due to agitation and euphoria approximately 18 days after study entry.

In the 533/133 dose group, patient 534 discontinued treatment due to multiple CNS events, and rash approximately 11 days after beginning ABT-378/ritonavir treatment.

10.8.2.3. Deaths

No deaths were reported in the first 24 weeks of this study.

Patient 513, a 45 year old female, died on study day 301 due to sepsis. Based on the case report, it appears that this death was not related to study drug.

10.8.2.4. Laboratory Findings

10.8.2.4.1. Hematology

The applicant noted that there were no consistent statistically significant differences between dose groups for any hematology variable.

Two patients in each dose group developed neutrophils < 0.75 X 10^9/L. Anemia was reported for one patient in each dose group. None of these laboratory abnormalities were considered drug related. No patient discontinued for these events.

10.8.2.4.2. Biochemistry

Amylase:

Only 2 patients reported grade 3+ increases in amylase. Both patients were in the 533/133 mg dose group. Patient 555 had an isolated increase in amylase that returned to within normal limits at the next study visit. Patient 526 developed pancreatitis. Please refer to pancreatitis section for further details.

Glucose:

Three subjects in the 400/100 mg dose group developed glucose > 250 mg/dL. All 3 patients had pre-existing diabetes at baseline at glucose levels > 200 mg/dL prior to study drug initiation.

Lipids:

A total of 25 patients developed grade 3+ lipid abnormalities. Only one patient interrupted study drug due to a lipid abnormality. No subjects discontinued study due to these events. Please also refer to section 15: ISS for additional information on cross study comparisons for lipid abnormalities.

Cholesterol:

Overall 67% of patients developed cholesterol abnormalities > 240 mg/dL. More patients in the 533/133 dose group developed cholesterol > 240 and 300 mg/dL. Cholesterol abnormalities are summarized in Table 10.9.2.4.2.A.

Table 10.8.2.4.2.A. Cholesterol Abnormalities

	400/100	533/133
Cholesterol Value > 240 mg/dL	15 (52%)	23 (82.1%)
Cholesterol Value > 300 mg/dL	8 (27.6%)	10 (35.7%)

The mean change from baseline at week 24 for cholesterol was 49 mg/dL and 61 mg/dL for the 400/100 mg and 533/133 mg dose groups, respectively. These differences were statistically significant.

Triglyceride:

The proportion of patients who developed triglyceride values > 750 mg/dL was similar between dose groups. Three patients in the 533/133 mg dose group compared to one patient in the 400/100 mg dose group developed triglyceride values > 1500 mg/dL. The majority of patients who developed triglycerides > 1500 mg/dL had triglycerides > 2001 mg/dL. Triglyceride abnormalities are further summarized in Table 10.8.2.4.2.C.

Table 10.8.2.4.2.C Elevations in Triglyceride Levels

	400/100	533/133
Triglyceride value > 750 mg/dL	9 (31%)	10 (35.7%)
Triglyceride value 1000-1499 mg/dL	3 (10.3%)	4 (14.3%)
Triglyceride value > 1500 mg/dL	1 (3.4%)	3 (10.7%)
Triglyceride value > 2001 mg/dL	1 (3.4%)	2 (7.1%)

The mean changes from baseline at week 24 for triglycerides were 115 mg/dL and 221 mg/dL for the 400/100 and 533/133 mg dose groups, respectively. These differences were statistically significant.

Eight patients in the 533/133 mg dose group and 3 patients in the 400/100 mg dose group received antihyperlipidemic agents to treat their lipid abnormalities. Overall it appears that these agents may be effective in lowering cholesterol and triglycerides back toward baseline.

Transaminases:

Only one patient in the 533/133 mg dose group developed grade 3+ transaminase elevation. Patient 517 had a peak ALT of 280 U/L on day 55. This patient was positive for hepatitis C at baseline. ALT decreased toward baseline on the next study visit, however ALT increased and remained elevated throughout the study. Bilirubin or alkaline phosphatase was not increased. The patient did not interrupt or discontinue study medications.

An additional report of hospitalization due to elevated transaminases (ALT = 806, AST = 355) was listed in the 3 month safety update. Patient 506 has a history of chronic hepatitis B and C. The patient was asymptomatic but all antiretrovirals were stopped after the week 32 study visit. The patient was hospitalized for a planned liver biopsy. The biopsy showed active moderate hepatitis. At the time of hospital discharge the transaminase levels were still elevated despite study drug interruption.

The patient resumed study drug approximately two months later. The last available laboratory data shows an improvement in transaminase levels (ALT= 241, AST = 107). It has been noted in other trials that patients with underlying hepatitis B or C may be at increased risk for further transaminase elevations.

ALT/Bilirubin:

No patients developed concomitant grade 3+ elevations in bilirubin and ALT.

Patient 542 had a peak bilirubin of 3.2 mg/dL at week 24. ALT values were grade 1 at baseline and throughout the study. Final values for bilirubin and ALT were 1.7 mg/dL and 34 U/L respectively. It is unclear if elevations in bilirubin in this patient were related to study drug.

10.9 Safety Conclusions

Two patients in each dose group discontinued due to an adverse event. The majority of these events were CNS effects. CNS events are known toxicities for efavirenz. The applicant noted a statistically significant difference between dose groups for events that were at least moderate in intensity and possibly, probably, or unknown relationship to study drug. More of these events were noted in the 533/133 group; however, the difference was apparent in the first 14 days of treatment when all subjects were still receiving 400/100 mg. Therefore this difference did not appear to be related to ABT-378/ritonavir exposures. Also efavirenz concentrations did not differ in the two dose groups.

One death due to sepsis occurred during the trial. The death was considered not related to ABT-378/ritonavir.

Abnormalities in cholesterol and triglycerides occurred as in other trials of ABT-378/ritonavir. No patient prematurely discontinued for a laboratory abnormality in this study. Grade 3+ laboratory abnormalities are summarized in Table 10.10.

Table 10.9. Grade 3 and 4 Adverse Laboratory Abnormalities

Chemistry Variable	400/100	533/133
Glucose (> 250 mg/dL)	3 (10.3%)	0
ALT (> 5 x ULN)	0	1 (3.6%)
Cholesterol (> 300 mg/dL)	8 (27.6%)	10 (35.7%)
Triglycerides (> 800 mg/dL)	9 (31%)	10 (35.7%)
Amylase (> 2 x ULN)	0	2 (7.1%)

11.1 Integrated Summary of Efficacy and Safety for Phase 2 trials (M97-720, M97-765 and M98-957) and Dose Selection

Note for the ISE and ISS for the phase 2 trials, 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 are the to be marketed doses. The 200/100 mg dose group from study 720 was omitted from this summary because only 16 patients received this dose.

11.1.1. Efficacy

Proportion < 400 copies/mL

The 400/100 mg and 400/200 mg dose groups from the phase 2 studies (M97-720 M97-765, M98-957) were pooled for the following integrated efficacy analysis.

Table 11.1.1.A. summarizes the proportion of patients with HIV RNA < 400 copies/mL at week 24 for three phase 2 studies. The intent to treat (non completers = failure NC=F) analyses are displayed. Overall, the response rate at week 24 was comparable for both dose groups and for antiretroviral naïve and experienced patients. Eighty percent and 75% of patients had HIV RNA < 400 copies/mL at week 24 in the 400/100 mg and 400/200 mg dose groups, respectively.

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

Dose Group	Naïve	Experienced	Total
400/100	45/51 (88%)	69/93 (74%)	108/144 (75%)
400/200	23/33 (70%)	28/34 (82%)	51/64 (80%)

Table 11.1.B. summarizes the proportion of patients with HIV RNA < 400 copies/mL at weeks 48 and 72 for studies 720 and 765.

Table 11.1.1.B. Proportion < 400 copies/mL at weeks 48 and 72

Dose Group	Week 48			Week 72		
	Naïve	Experienced	Total	Naïve	Experienced	Total
400/100	45/51 (88%)	24/36 (67%)	69/87 (79%)	41/51 (80%)	27/36(75%)	68/87 (78%)
400/200	24/33 (82%)	25/34 (74%)	49/67 (73%)	27/33 (82%)	24/34 (71%)	51/67(76%)

Antiviral efficacy in studies 720 and 765 at both dose levels were demonstrated with 82% and 87% of patients in the 400/100 and 400/200 mg dose groups, respectively, achieving HIV RNA < 400 copies/mL at week 24. These responses were sustained through week 72 in which 78% and 76% of antiretroviral naïve and experienced patients had HIV RNA levels < 400 copies/mL.

CD4 Cell Counts:

Increases in CD4 cell counts were noted for patients randomized to all doses of ABT-378/ritonavir – 200/100, 400/100, 400/200 and 533/133 mg. Mean increases from baseline for patients randomized to 400/100 or 533/133 mg ranged from 41 cells/mm^3 at week 24 in study 957, to 342 cells/mm^3 at week 72 in study 720. It is expected that treatment naïve patients would have the largest CD4 increases.

11.1.2. 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 studies were predominately gastrointestinal events and asthenia. Elevations in AST/ALT, triglycerides and total cholesterol were also observed.

Table 11.1.2.A. summarizes treatment-emergent events (at least moderate severity that were 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 11.1.2.A. Treatment-emergent events that are of probable, or possible relationship to study drug and occurring in > 5%

	Naïve (n=51)	Experienced (n=93)	Pooled 400/100 Arms (n=144)
Asthenia	4 (7.8%)	6 (6.5%)	10 (6.9%)
Headache	4 (7.8%)	2 (2.2%)	6 (4.2%)
Abnormal stools	5 (9.8%)	1 (1.1%)	6 (4.2%)
Diarrhea	11 (22%)	14 (15%)	25 (17.7%)
Nausea	3 (5.9%)	1 (1.1%)	4 (2.8%)
Insomnia	0	5 (5.4%)	5 (3.5%)

The incidence of adverse events were similar between naïve and experienced patients. Overall 5.6% (8/144) patients discontinued study due to a drug related adverse event.

Table 11.1.2.B. summarizes the proportion of patients with > grade 3 chemistry values. More naïve patients developed transaminase elevations compared to antiretroviral experienced patients. Twice as many experienced patients developed GGT elevations compared to naive patients. This finding may in part be due to concomitant use of nevirapine in trials of experienced patients.

The proportion of antiretroviral experienced patients who developed cholesterol > 300 mg/dL and triglycerides > 750 mg/dL was approximately 3-fold that of antiretroviral naïve patients. No naïve patients developed triglycerides > 1500 mg/dL compared to 7 antiretroviral experienced patients.

Table 11.1.2.B. Grade 3 and 4 Adverse Laboratory Abnormalities

Chemistry Variable	Naïve (n=51)	Experienced (n=93)	Pooled 400/100 Arms (n=144)
Glucose (> 250 mg/dL)	1 (2%)	4 (4.3%)	5 (3.5%)
Uric Acid (> 12 mg/dL)	1 (2%)	0	1 (0.7%)
AST (> 180 mg/dL)	7 (13.7%)	2 (2.2%)	9 (6.3%)
ALT (> 215 mg/dL)	5 (9.8%)	4 (4.3%)	9 (6.3%)
GGT (> 300 U/L)	2 (3.9%)	7 (7.5%)	9 (6.3%)
Cholesterol (> 300 mg/dL)	5 (9.8%)	25 (27%)	30 (21%)
Triglycerides (> 750 mg/dL)	4 (7.8%)	26 (28%)	30 (21%)
Triglycerides (> 1500 mg/dL)	0	7 (7.5%)	7 (4.9%)
Bilirubin (>3.4 mg/dL)	1 (2%)	0	1 (0.7%)
Amylase (> 2 x ULN)	0	2 (2.2%)	2 (1.4%)

Three of the 144 patients (2.1%) who received either 400/100 or 533/133 mg ABT-378/ritonavir in phase 2 trials developed pancreatitis in the phase 2 program. All three were antiretroviral experienced patients.

Two cases of hepatitis were reported. 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.

11.1.3. Dose Selection:

400/100 mg dose

The dose chosen for phase 3 trials and the proposed marketing dose for ABT-378/ritonavir is 400/100 mg BID.

The objective of the phase 1 and 2 development of ABT-378 has been to maximize ABT-378 exposures. The contribution of ritonavir in this fixed combination product is for pharmacologic enhancement of ABT-378 levels, to prolong ABT-378 concentrations and to allow for less frequent dosing intervals. Less frequent dosing intervals may contribute to overall patient compliance and therefore prolonged viral suppression. It has been shown that ABT-378 concentrations are increased by up to 150-fold when coadministered with ritonavir doses of 50-300 mg. Based on concentrations of ritonavir at this dose, it does not contribute measurably to the overall virologic efficacy.

We feel that this combination product meets the requirements for fixed-combination prescription drugs in that the ritonavir component has been demonstrated to increase concentrations of ABT-378 up to 150 fold. Clinical studies have shown that ritonavir 100 mg BID is better tolerated than the approved dose of ritonavir (600 mg BID).

The applicant has undertaken a comprehensive dose finding phase I/II program. Doses of 200/100, 400/100 and 400/200 mg were further studied in phase 2 studies. Response rates were similar for all doses. The 400/100 mg BID dose regimen was chosen based on differences in rates of AE/laboratory abnormalities. Moderate or severe nausea and vomiting occurred at higher rates for the 400/200 mg vs the

400/100 mg dose groups in study 720. There also was a higher frequency of diarrhea and marked lipid elevations with the 400/200 mg dose. In addition dose selection was based on the ability to achieve high Cmin values throughout the dosing interval. Mean Cmin values for ABT-378/ritonavir 200/100 mg BID, 400/100 mg BID and 400/200 mg BID exceeded the protein binding –corrected EC50 for wild type HIV by 50, 70 and 100 fold, respectively. Therefore, the applicant chose a dose that would yield the highest ratio (concentration/EC50) and that was also best tolerated..

Overall the dosing regimen of 400/100 mg BID appears reasonable with respect to pharmacokinetics, safety and efficacy.

533/133mg dose with efavirenz and nevirapine

A dose increase of ABT-378/ritonavir to 533/133 mg BID when coadministered with efavirenz or nevirapine should be considered for treatment experienced patients for which reduced susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). Consideration for this dose increase is based on the following information.

- Pharmacokinetic results from several drug interaction studies/substudies in healthy volunteers and HIV infected adults given efavirenz and pediatric patients given nevirapine showed a reduction in ABT-378 concentrations by approximately 30%.
- Numerically higher response rates (not statistically significant) in patients receiving 533/133 mg dose compared to the 400/100 mg dose in study 957.

However, a dose increase may not be necessary for patients who have previously received one protease inhibitor and/or where reduced susceptibility is not suspected. This is supported by the results from study 765 in that similar response rates where noted for patients receiving 400/100 mg and 400/200 mg in combination with nevirapine.

12.1 Study M98-863

12.2. Protocol Title

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

12.3 Study Design and Analysis Plans

This was a randomized, double-blind, multi-country study in 686 antiretroviral naïve patients with HIV RNA levels > 400 copies/mL. Patients were randomized to one of two blinded treatment arms.

Group 1: 400 mg ABT-378/100 mg ritonavir BID + nelfinavir placebo + stavudine 40 mg BID + lamivudine 150 mg BID

Group 2: Nelfinavir 750 mg TID + ABT-378/ritonavir placebo + stavudine 40 mg BID + lamivudine 150 mg BID

12.4 Patient Population

12.4.1 Inclusion Criteria

Patients with who were greater than 12 years of age and had HIV RNA > 400 copies/mL, no evidence of acute illness, had not been treated for an active OI within 30 days of screening and did not require and agreed not to take any medications that are contraindicated with protease inhibitors for the duration of the study were included in the study.

12.4.2 Exclusion Criteria

Patients with a history of active substance abuse or psychiatric illness that could preclude compliance with protocol or had 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 were pregnant or lactating, received an investigational drug(s) within 30 days prior to study dosing or any antiretroviral within 30 days prior to screening and received > 14 days of any antiretroviral therapy were excluded from the study.

12.5 Study Endpoints

12.5.1. Primary Study Endpoints

- Week 24: Proportion of subjects with HIV RNA < 400 copies/mL
- Week 48: Time until loss of virologic response

12.6. Results

12.8.1. Patient Disposition

A total of 686 patients were randomized to this study. Six hundred and fifty three patients received at least one dose of ABT-378/ritonavir or nelfinavir. Please refer to Table 12.8.3.A. for further details.

12.8.2. Protocol Deviations

Several protocol deviations occurred during the trial. Most of the protocol deviations were related to receipt of antiretroviral therapy prior to enrollment, receipt of excluded concomitant medications during study, or enrollment with exclusionary laboratory values. The applicant states that the protocol deviations are not expected to significantly influence the results of the study. However a total of 11 patients received incorrect study drug due to dispensing errors. All patients received the incorrect study drug for less than 30 days. These deviations would not be expected to adversely impact the overall interpretation of the study results

12.8.3. Reasons for Premature Discontinuation

A total of 36 and 38 patients prematurely discontinued study drug from the ABT-378/ritonavir and nelfinavir groups, respectively. Table 12.8.3.A. summarizes the premature discontinuations. The applicant reports that a statistically significant difference was noted between the treatment groups with respect to proportion of patients who withdrew due to virologic failure; no patients in the ABT-378/ritonavir group and 10 (3.1%) in the nelfinavir group. It is important to note that the protocol

did not mandate that patients discontinue due to virologic failure. This finding raises some question regarding the adequacy of the blinding of this study. The applicant encapsulated nelfinavir tablets for the study. Three patients in the nelfinavir group opened the blinded nelfinavir capsules and therefore the blind was broken for these patients. It is unclear if more patients were able to determine if they were receiving nelfinavir/placebo.

Based on a review of selected patient records it appears that some patients returned approximately one third of the dispensed nelfinavir/placebo. This could be a reflection of poor adherence to the mid day dose.

It was also thought that more patients on the nelfinavir arm might have had higher rebound of HIV RNA levels during study and therefore discontinued due to virologic failure. However for those patients with HIV RNA greater than 400 copies/mL at week 24, the mean viral load was similar for both treatment groups ABT-378/ritonavir: mean 27,679 [redacted]; nelfinavir: mean 33,631 [redacted]

Clearly the blinding was not optimal because some patients were able to break the blind. However, the applicant was not able to obtain placebo for nelfinavir, over-encapsulating was a reasonable alternative. Given that the endpoint is objective, confirmed laboratory values, this does not raise serious problems with the validity of the overall study conclusions.

Table 12.8.3.A. Patient Disposition and Premature Discontinuations

Original Assignment	ABT-378/ritonavir	Nelfinavir
Total Number Randomized	343	343
Received at least one dose of study medication	326	327
Completed 24- week Blinded treatment	290	289
Total Discontinued	36 (11%)	38 (11.6%)
Lost to follow-up	9 (2.8%)	11 (3.4%)
Adverse event/HIV-related event	8 (2.5%)	10 (3.1%)
Virologic failure	0	10 (3.1%)
Other	7 (2.1%)	2 (0.6%)
Subject noncompliant	5 (1.5%)	3 (0.9%)
Personal reasons	5 (1.5%)	2 (0.6%)
Death	2 (0.6%)	2 (0.6%)
Required prohibited medication	1 (0.3%)	0

Source vol 125 page 96, statistical table 14.1_3.1: Vol 125 page 94, Statistical Tables 14.1_1.1 and 14.1_2.1

12.8.4. Demographic Data

Table 12.8.4.A. summarizes the demographic information for this trial. The groups appeared to be comparable.

Table 12.8.4.A. Demographic and Baseline Data

	ABT-378/Ritonavir	Nelfinavir
Number of Patients	326	327
Mean age, Yrs	38.4	37.3
Gender		
Male	260 (80%)	264 (81%)
Female	66 (20%)	63 (19%)
Race:		
Caucasian	226 (69%)	222 (68%)
Black	87 (27%)	86 (26%)
Asian/Pacific Islander	8 (2%)	12 (4%)
Native American/Alaskan Native	3 (<1%)	3 (<1%)
Mixed Race	2 (<1%)	2 (<1%)
Missing	0	2 (<1%)
Baseline mean plasma HIV RNA (PCR), log_{10} copies/mL	4.89	4.92
Baseline median CD4 cell count (cells/mm^3)	260	257

Source vol 125 pg 102 table 11.2a, statistical table 14.1_4.1; vol 125 page 104 table 11.2.b Statistical tables 14.1_8.1, and 14.1_9.1

12.8.5. Efficacy Outcomes

12.8.5.1. HIV RNA

A greater proportion of patients had HIV RNA < 400 copies/mL at week 24 in the ABT-378/ritonavir group compared to patients receiving nelfinavir. Table 12.8.5.1.A. summarizes the on treatment and intent to treat analysis.

Table 12.8.5.1.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 (n=326)	259/277 (92%)	259/326 (79%)
Nelfinavir (n=327)	232/285 (81%)	233/327 (71%)
p-value	0.15	<0.001

Lower virologic response rates for patients with baseline HIV RNA > 100,000 copies/mL or baseline CD4 counts less than 50 cells/mm^3 have been observed in some trials. Virologic response rates for these subgroups are shown in table 12.8.5.1.B. Statistically significant differences were noted between treatment groups for patients with baseline HIV RNA > 100,000 copies/mL and baseline CD4 cell counts < 50, favoring the ABT-378/ritonavir arm. Response rates were comparable between treatment arms for patients with baseline HIV RNA < 100,000 copies/mL and baseline CD4 cell counts > 50. Results from this trial suggest that ABT-378/ritonavir is

similarly efficacious regardless of baseline HIV RNA. As such, it may be a preferred treatment for patients with baseline HIV RNA > 100,000 copies/mL.

Table 12.8.5.1.B. Proportion of Patients with HIV RNA < 400 copies/mL by baseline HIV RNA and CD4 cell counts

	HIV RNA < 400 copies/mL (ITT)		
	Week 24		
	ABT-378/RTV	Nelfinavir	p-value
Baseline HIV RNA > 100,000 copies/mL	128/165 (78%)	100/161 (62%)	0.002
Baseline HIV RNA < 100,000 copies/mL	131/161 (81%)	133/166 (80%)	0.775
Baseline CD4 < 50 cells/mm^3	51/71 (72%)	27/55 (49%)	0.009
Baseline CD4 ≥ 50 cells/mm^3	208/255 (82%)	206/271 (76%)	0.120

The proportion of patients with HIV RNA < 50 copies was 65% in the ABT-378/ritonavir arm and 60% in the nelfinavir arm. These data are also supportive of the antiviral activity of ABT-378/ritonavir.

12.8.5.2. CD4 Cell Count

Mean change from baseline at week 24 for CD4 cell counts were similar for both treatment arms; mean change 154 cells/mm^3 for the ABT-378/ritonavir group vs 150 cells/mm^3 for the nelfinavir group.

12.9 Safety Outcomes

A total of 653 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 4 deaths in this study.

12.9.1. Drug Exposure

The median duration of study drug exposure was 196 days for both treatment groups. The applicant states that over 85% of the patients in each treatment group received study drug for greater than 24 weeks.

12.9.2. Adverse Events

12.9.2.1. Overview of Adverse Events

Overall 93.6% of patients experienced at least one adverse event during the first 24 weeks of the study. The most common adverse events reported for either dose group were predominately gastrointestinal events such as abnormal stools, diarrhea, and nausea. A greater proportion of patients in the ABT-378/ritonavir group experienced vomiting, taste perversion, hyperlipemia, eczema, neuropathy and UTIs compared to patients in the nelfinavir group. These differences were statistically significant.