Baseline HIV RNA Level and CD4 Cell counts Randomized Subjects				
	Treatment Regimen: ddI/d4T/PI			
	ATV (QD)			NFV (TID)
	200 mg	400 mg	500 mg	750 mg
	N = 104	N = 103	N = 110	N = 103
HIV RNA level (log10 c/mL):				
Mean (SE)	4.75 (0.06)	4.65 (0.06)	4.74 (0.07)	4.79 (0.06)
Median	4.64	4.71	4.74	4.82
Range				
Missing	1	2	1	2
Qualifying HIV RNA: N (%)				
< 30,000	41 (39)	39 (38)	40 (36)	39 (38)
≥ 30,000	63 (61)	64 (62)	70 (64)	64 (62)
CD4 cell count (cells/mm3):				
Mean (SE)	331 (16)	357 (18)	361 (19)	341 (16)
Median	323	326	339	343
Range				
Missing	1	2	1	2
CD4 cell count distribution: N (%)				
< 200	23 (22)	16 (16)	22 (20)	23 (22)
≥ 200 □ < 350	38 (37)	43 (42)	35 (32)	30 (29)
≥ 350 □ < 500	30 (29)	22 (21)	26 (24)	31 (30)
≥ 500	12 (12)	20 (19)	26 (24)	17 (17)
Missing	1 (1)	2 (2)	1 (1)	2 (2)

6.2.3.5 Subject Disposition

A total of 420 HIV-infected subjects were randomized in this clinical trial. Ten randomized subjects in this study never started therapy, two in the atazanavir 200 mg regimen, two in the atazanavir 400 mg regimen, three in the atazanavir 500 mg regimen, and three in the NFV 750 mg regimen. Overall, 64 (15%) of subjects discontinued prior to week 48 .

Subject Disposition – Randomized Subjects				
	Treatment Regimen: ddI/d4T/PI			
	ATV (QD)			NFV (TID)
	200 mg	400 mg	500 mg	750 mg
	N = 104	N = 103	N = 110	N = 103
Randomized	104 (100)	103 (100)	110 (100)	103 (100)
Never treated	2 (2)	2 (2)	3 (3)	3 (3)
Treated	102 (98)	101 (98)	107 (97)	100 (97)
Discontinued prior to	17 (16)	15 (15)	16 (15)	16 (16)
Week 48				
Adverse event	4 (4)	3 (3)	9 (8)	5 (5)
Death	1 (< 1)	--	--	--
Disease progression or relapse	1 (< 1)	1 (< 1)	--	--
Lost to follow-up	6 (6)	5 (5)	2 (2)	3 (3)
Noncompliance	1 (< 1)	3 (3)	3 (3)	3 (3)
Pregnancy	1 (< 1)	--	--	--
Protocol violation	--	--	1 (< 1)	--
Subject withdrew	--	3 (3)	1 (< 1)	2 (2)
Treatment failure or lack of efficacy	3 (3)	--	--	3 (3)

6.2.3.6 **Eligibility Violations and Protocol Deviations**

Seventeen subjects had one or more violations of protocol eligibility requirements: one subject on ATV 200, five subjects on ATV 400, six subjects on ATV 500, and five subjects on NFV. Violations included baseline labs out of range, no prior inclusion or exclusion lab values, no prior CD4 values and no prior viral load. One subject had a history of prior ART.

Protocol deviations of randomized subjects are summarized in the following table:

Protocol Deviations Randomized Subjects				
	Treatment Regimen: ddI/d4T/PI			
	ATV (QD)			NFV (TID)
	200 mg	400 mg	500 mg	750 mg
Type of Deviation[a]	N = 104	N = 103	N = 110	N = 103
Any deviation	35 (34)	42 (41)	45 (41)	38 (37)
Randomized twice	3 (3)	1 (< 1)	1 (< 1)	2 (2)
Randomization more than 14 days after screening	8 (8)	14 (14)	15 (14)	12 (12)
Start of dose more than 3 days after randomization	15 (14)	22 (21)	17 (15)	22 (21)
Never received monotherapy	8 (8)	8 (8)	4 (4)	7 (7)
Received more than 21 days of monotherapy	4 (4)	1 (< 1)	2 (2)	--
Received treatment different from assigned for > 3 days	5 (5)	4 (4)	6 (5)	--
Unblinded for Grade 4 bilirubin but not dose-reduced	1 (< 1)	1 (< 1)	--	--
Not unblinded for Grade 4 hyperbilirubinemia	--	1 (< 1)	5 (5)	--

6.2.3.7 **Efficacy Endpoints and Outcomes**

Please refer to Dr. Hammerstrom's review for a complete analysis of efficacy data. The following table summarizes treatment outcomes through 48 weeks for randomized subjects in study 007. Atazanavir 400 mg QD was similar to nelfinavir 750 mg TID in terms of percentage with HIV RNA viral load below the limit of quantification, the mean change in HIV RNA from baseline and CD4 mean change from baseline.

The results for percentage of patients with HIV RNA below limit of quantification are based on the Time to Loss of Virologic Response analysis. The TLOVR analysis is an intent-to-treat analysis that examines endpoints using the following definitions of treatment failure for patients who have achieved HIV RNA levels below the limit of quantification:

For all subjects with confirmed HIV RNA levels below an assay limit, the time to failure is the earliest time when a specific event had occurred. These events are

- Death
- Permanent discontinuation of the study drug or loss to follow-up
- Introduction of a new ARV drug (unless a background drug is changed for reasons of toxicity or intolerance that are clearly attributable to that drug)
- Confirmed HIV RNA levels above or equal to an assay

Treatment Outcomes at Week 48 Randomized Subjects		
	Treatment Outcomes at Week 48	
	Atazanavir	Nelfinavir
Outcome	N=103	N=103
Percent of Patients Responding		
HIV RNA < 400 copies/mL	60	60
HIV RNA < 50 copies/mL	17	16
HIV RNA Mean change from Baseline (log10 copies/mL)	-1.83	-1.91
CD4 Mean change from Baseline	221	185

6.2.4 Clinical Trial AI424008

"Evaluation of the Safety and Antiviral Efficacy of a Novel HIV-1 Protease Inhibitor, Atazanavir, in Combination with d4T and 3TC as Compared to a Reference Combination Regimen"

6.2.4.1 Study Design and Subject Population

This study was an active-controlled, three arm study designed to evaluate and compare the safety, tolerability, and antiviral efficacy of atazanavir at 400 mg and 600 mg QD with NFV 1250 mg BID, in combination with d4T and 3TC through 48 weeks in antiretroviral naïve subjects who had a CD4 cell count ≥ 100 cells/mm^3 (or ≥ 75 cells/mm^3 with no prior history of any AIDS-defining diagnoses) and a plasma HIV RNA > 2,000 c/mL (Roche Amplicor). The dose level of atazanavir was blinded. Randomization was stratified for HIV RNA level (< 30,000 c/mL; ≥ 30,000 c/mL). This study enrolled 467 patients.

6.2.4.2 Endpoints

Primary Efficacy Outcome Measure:

- The magnitude and durability of the reduction of plasma HIV RNA in terms of the change from baseline, expressed in log10, was assessed for each treatment group over 48 weeks of therapy.

Secondary Efficacy Outcome Measures:

- The proportion of subjects with HIV RNA levels < 400 copies/mL and below the limits of detection of the ultrasensitive assay (< 50 copies/mL);
- The magnitude and durability of rises in CD4 cell counts in terms of the change from baseline was assessed for each treatment group.

6.2.4.3 Analysis Plan

This study was powered (> 95%) to demonstrate similarity of antiviral efficacy of two atazanavir doses of 400 mg, and 600 mg compared to nelfinavir when administered as a triple combination therapy. The primary endpoint was the change from baseline in HIV RNA levels through 48 weeks of treatment compared using the Time-Averaged Differences (TAD). The TAD between each atazanavir regimen and nelfinavir regimen in the change from baseline in log10 HIV RNA levels through 48 weeks of triple therapy was computed along with 97.5% confidence intervals. Analyses were stratified by qualifying HIV RNA level obtained prior to randomization (< 30,000 c/mL; ≥ 30,000 c/mL). The proportion of subjects classified as responders at levels of HIV RNA < 400 c/mL and < 50 c/mL were analyzed using Virologic Response (randomized subjects: VR-R and completers: VR-C) and Treatment Response Without Prior Failure (randomized subjects: TRWPF) analyses.

6.2.4.4 Study Population

Overall, the baseline demographic characteristics of the randomized subjects were comparable. The study population was predominantly white (55%) and male (63%), with a median age of 34 years. In general, there was equal distribution of demographic characteristics across regimens.

Baseline Characteristics - Randomized Subjects			
	Treatment Regimen: d4T/3TC/PI		
	ATV (QD)		**NFV (BID)**
	400 mg	**600 mg**	**1250 mg**
Characteristic	**N = 181**	**N = 195**	**N = 91**
Age (years):			
Mean (SE)	34.3 (0.7)	34.7 (0.6)	35.3 (1.0)
Median	33	34	34
Range	18 - 64	18 - 58	19 - 69
Gender: N (%)			
Male	110 (61)	125 (64)	57 (63)
Female	71 (39)	70 (36)	34 (37)
Race: N (%)			
White	100 (55)	104 (53)	52 (57)
Black/Mixed	47 (26)	59 (30)	24 (26)
Asian/Pacific Islander	27 (15)	26 (13)	12 (13)
American/Alaskan Native	--	1 (< 1)	--

Baseline Characteristics - Randomized Subjects			
	Treatment Regimen: d4T/3TC/PI		
	ATV (QD)		NFV (BID)
	N = 181	N = 195	N = 91
Region: N (%)			
Europe	53 (29)	61 (31)	28 (31)
Africa	38 (21)	40 (21)	23 (25)
North America	26 (14)	31 (16)	11 (12)
South America	40 (22)	38 (19)	17 (19)
Asia	24 (13)	25 (13)	12 (13)
IV Drug Use: N (%)[b]	11 (6)	16 (8)	6 (7)
AIDS: N (%)	18 (10)	24 (12)	9 (10)
Weight (kg):			
Mean (SE)	67.9 (1.0)	70.7 (1.0)	66.7 (1.4)
Median	66.0	69.0	65.0
Range			

Baseline HIV RNA levels and CD4 cell counts were comparably distributed across treatment regimens. Median baseline HIV RNA levels were 4.70 - 4.77 log10 c/mL across regimens, with 29% - 32% of subjects having qualifying levels < 30,000 c/mL. Median baseline CD4 cell counts (273 cells/mm3) were comparable across regimens with 55% - 65% of subjects having CD4 cell counts of 200 - < 500 cells/mm^3.

Baseline HIV RNA Level and CD4 Cell Count – Randomized Subjects			
	Treatment Regimen: d4T/3TC/PI		
	ATV (QD)		NFV (BID)
	400 mg	600 mg	1250 mg
	N = 181	N = 195	N = 91
HIV RNA level (log10 c/mL):			
Mean (SE)	4.74 (0.05)	4.73 (0.05)	4.73 (0.07)
Median	4.77	4.70	4.71
Range			
Missing	1	--	--
Qualifying HIV RNA strata: N (%)			
< 30,000 c/mL	55 (30)	63 (32)	26 (29)
≥ 30,000 c/mL	126 (70)	132 (68)	65 (71)
CD4 cell count (cells/mm^3):			
Mean (SE)	294 (12)	302 (11)	283 (16)
Median	260	283	273
Range			
Missing	1	--	--

6.2.4.5 Subject Disposition

A total of 467 HIV-infected subjects were randomized in this clinical trial. Overall, 54 (12%) subjects discontinued prior to week 48. Fewer subjects receiving nelfinavir discontinued for adverse events.

Subject Disposition - Randomized Subjects			
	Number of Subjects (%)		
	Treatment Regimen: d4T/3TC/PI		
	ATV (QD)		NFV (BID)
	400 mg	600 mg	1250 mg
	N = 181	N = 195	N = 91
Randomized	**181 (100)**	**195 (100)**	**91 (100)**
Never treated	3 (2)	--	--
Treated	**178 (98)**	**195 (100)**	**91 (100)**
Discontinued prior to Week 48	22 (12)	21 (11)	11 (12)
Adverse event	7 (4)	9 (5)	3 (3)
Death	1 (< 1)	1 (< 1)	--
Disease progression or relapse	1 (< 1)	1 (< 1)	--
Lost to follow-up	5 (3)	7 (4)	2 (2)
Noncompliance	2 (1)	2 (1)	1 (1)
Pregnancy	2 (1)	--	1 (1)
Subject withdrew	2 (1)	--	1 (1)
Treatment failure/lack of efficacy	2 (1)	1 (< 1)	3 (3)
Continuing on treatment	149 (82)	162 (83)	74 (81)
Completed treatment	--	1 (< 1)	--

6.2.4.6 Eligibility Violations and Protocol Deviations

Eighteen subjects had violations of protocol eligibility requirements and 86 subjects had other protocol deviations. In general, while protocol amendments were in preparation or awaiting approval, waivers of specific protocol eligibilities were provided by the applicant if they corresponded with the new amended criteria.

Eligibility Violations - Randomized Subjects			
	Number of Subjects (%)		
	Treatment Regimen:		
	ATV (QD)		NFV (BID)
	400 mg	600 mg	1250 mg
Type of Violation	**N = 181**	**N = 195**	**N = 91**
Any violation[a]	6 (3)	4 (2)	8 (9)
HIV RNA level < 2,000 c/mL	1 (< 1)	--	--
CD4 cell count < 100 cells/mm^3 (< 75 with no prior AIDS)	1 (< 1)	1 (< 1)	2 (2)
Baseline laboratory values out of range	3 (2)	2 (1)	5 (5)
Prior antiretroviral treatment	--	1 (< 1)	--
History of grade 2 or bilateral peripheral neurologic symptoms	--	--	2 (2)
Positive pregnancy test	--	1 (< 1)	--
No prior inclusion or exclusion laboratory values	1 (< 1)	--	--
No prior CD4 values	1 (< 1)	--	--
No prior viral load values	1 (< 1)	--	--

Protocol violations are summarized in the following table:

Protocol Deviations - Randomized Subjects			
	Number of Subjects (%)		
	Treatment Regimen: d4T/3TC/PI		
	ATV (QD)		NFV (BID)
	400 mg	600 mg	1250 mg
Type of Deviation	**N = 181**	**N = 195**	**N = 91**
Any deviation	32 (18)	41 (21)	13 (14)
Randomization more than 14 days after screening	10 (6)	19 (10)	3 (3)
Start of dose more than 3 days after randomization	13 (7)	10 (5)	10 (11)
Treatment different from assigned (> 3 days)	2 (< 1)	7 (4)	--
Grade 4 total bilirubin without dose reduction	7 (4)	8 (4)	--
Dose reduction without Grade 4 total bilirubin	1 (< 1)	2 (1)	--

6.2.4.7 Efficacy Endpoint Outcomes

Please refer to Dr. Hammerstrom's review for a complete analysis of efficacy data. The following table summarizes treatment outcomes through 48 weeks for randomized subjects in study 008. Atazanavir 400 mg QD was similar to nelfianvir 1250 mg BID in terms of percentage with HIV RNA viral load below the limit of quantification, the mean change in HIV RNA from baseline and CD4 mean change from baseline.

The results for percentage of patients with HIV RNA below limit of quantification are based on the Time to Loss of Virologic Response analysis. The TLOVR analysis is an intent-to-treat analysis that examines endpoints using the following definitions of treatment failure for patients who have achieved HIV RNA levels below the limit of quantification:

For all subjects with confirmed HIV RNA levels below an assay limit, the time to failure is the earliest time when a specific event had occurred. These events are

- Death
- Permanent discontinuation of the study drug or loss to follow-up
- Introduction of a new ARV drug (unless a background drug is changed for reasons of toxicity or intolerance that are clearly attributable to that drug)
- Confirmed HIV RNA levels above or equal to an assay

Treatment Outcomes at Week 48 Randomized Subjects		
	Treatment Outcomes at Week 48	
	Atazanavir 400 mg	**Nelfinavir 1250 mg bid**
Outcome	N=181	N=91
Percent of Patients Responding		
HIV RNA < 400 copies/mL	67%	59%
HIV RNA < 50 copies/mL	33%	38%
Virologic failure	24%	27%
Rebound	14%	14%
Never suppressed through wk 48	10%	13%
HIV RNA Mean change from Baseline (log10 copies/mL)	-1.88	-1.87
CD4 Mean change from Baseline	234	211

7 Integrated Review of Safety

7.1 Brief Statement of Findings

In general, use of atazanavir appeared to be well-tolerated with relatively few subjects discontinuing for treatment-related adverse events potentially attributable to atazanavir use. No adverse event potentially related to treatment that led to discontinuation occurred in more than 2% of subjects in any trial; treatment-related events leading to discontinuation included hyperbilirubinemia/jaundice, abnormal liver enzyme tests, rash/allergic reaction, lipodystrophy, lactic acidosis syndrome and peripheral neuropathy. Some of these adverse events are currently attributed to the NRTI component of antiretroviral therapy.

Adverse events that were most commonly reported in clinical trials across all treatment regimens included infection, nausea, vomiting, headache, diarrhea, and abdominal pain. Other common events included peripheral neurologic symptoms, fatigue, insomnia, and rash.

Use of atazanavir appeared to be associated with less diarrhea relative to nelfinavir and lopinavir/ritonavir. It did appear, however, to result in more events of rash relative to these two PI comparators. Rash appeared to occur less commonly in atazanavir-treated subjects as compared to efavirenz.

The most common laboratory abnormality associated with use of atazanavir is hyperbilirubinemia; the mechanism causing this abnormality appears to be inhibition of UDP-glucuronosyl transferase 1A1 (UGT 1A1), an enzyme responsible for glucuronidation of bilirubin. In clinical trials utilizing a 400 mg dose of atazanavir, any grade of hyperbilirubinemia occurred in 75-91% of patients and grade 3-4 elevations were observed in 20-47% of patients. This resulted in an indirect hyperbilirubinemia that appeared to be generally distinguishable from hyperbilirubinemia due to hepatic injury or inflammation.

Hyperbilirubinemia did not appear to be associated with an increased risk of hepatic injury. Discontinuations and/or deaths due to hepatitis, hepatotoxicity, or liver enzyme abnormalities appeared to occur with similar frequencies in atazanavir-treated subjects as compared to other protease inhibitors or efavirenz; the incidence of hepatotoxicity associated with atazanavir use appears to fall within the range observed with currently marketed ARV medications.

A strategy of dose reduction for patients with confirmed elevations of bilirubin greater than five times the upper limit of normal was employed during clinical trials of atazanavir. Unfortunately, insufficient data on the efficacy of patients who dose-reduced was collected to recommend this as a management strategy.

While clinical jaundice and/or scleral icterus were reported in roughly 15-20% of patients, these symptoms or laboratory confirmed grade 4 hyperbilirubinemia led to dose

reduction and/or discontinuation of atazanavir in ≤ 5% of patients. From the perspective of patient acceptability this side-effect appears to be well-tolerated; however, it may be postulated that more discontinuations may occur in general clinical practice as patients enrolled in clinical trials have unique motivations to continue treatment and the strategy of dose reduction will not be recommended.

Atazanavir does not appear to be associated with the hyperlipidemia that is commonly observed with use of other protease inhibitor or efavirenz-containing antiretroviral (ARV) regimens. As a result, use of atazanavir may result in fewer patients initiating lipid-lowering medication, allowing them to avoid the adverse effects associated with this class of medications, the additional pill burden and potential drug interactions. It is unknown at this time whether this treatment benefit will result in a reduced risk of cardiovascular events. At this time, it does not appear that the favorable lipid profiles observed in subjects taking atazanavir results in a reduced incidence of lipodystrophy; spontaneous reports of lipodystrophy appeared to be similar between atazanavir and comparators through one to two years of treatment.

Limited data from a phase 2 rollover study showed that switching from a nelfinavir-based regimen to atazanavir after 72 weeks of therapy appeared to result in return of lipid profiles to pretreatment baseline. However, in a phase 3 study of treatment experienced patients, triglycerides remained elevated above what may be considered pre-treatment levels despite atazanavir use. In addition, use of atazanavir did not prevent isolated subjects from developing severe elevations of triglycerides. This suggests that factors other than current protease inhibitor use may impact upon at least triglyceride levels and that this treatment benefit may not be sustained with long-term use of atazanavir.

Preclinical studies of atazanavir suggested a potential for prolongation of the QT interval, the mechanism believed to underlie the development of torsades de pointes, a potentially life-threatening arrhythmia. However, a placebo-controlled, three-treatment, three-period crossover study of healthy volunteers designed to evaluate the effects of atazanavir on the QT interval did not show any significant effect. This study is limited by the lack of a positive control group and by failure to reach exposures of five to ten-fold that seen with the to-be-marketed dose. However, review of extensive ECG data from clinical trials revealed no signal for an increased risk of prolongation of the QT interval relative to comparator regimens and review of adverse events revealed no events likely related to prolongation of the QT interval.

During evaluation of the effects of atazanavir on the QT interval it was also found that atazanavir produced concentration and dose-dependent prolongation of the PR interval. In pharmacokinetic studies designed to evaluate the effects of atazanavir on ECG parameters, the incidence of first degree AV block was common and occurred in over 50% of subjects receiving 800 mg of atazanavir.

In clinical trials of atazanavir asymptomatic first degree AV block was observed with similar frequency in atazanavir-treated subjects (5.9%) versus PI comparators (5.2 –

10%). First degree AV block appeared to be less common in subjects receiving efavirenz (3%).

In the expanded access protocol a patient taking atazanavir concomitantly with verapamil, delavirdine, and other medications, was hospitalized with a junctional rhythm. ARV medications were held, however, the patient continued to receive verapamil. One day following admission to the hospital, the junctional rhythm persisted. The junctional rhythm was most likely due to markedly elevated levels of verapamil; however, this case does highlight the clinical importance of drug-drug interactions with the comcomitant use of CYP3A substrates, particularly calcium channel blockers.

A second subject enrolled in rollover study 007/041 ingested a large number of atazanavir, lamivudine, and stavudine pills in a suicide attempt. ECG revealed a severely prolonged PR interval with bifascicular block. ARV medications were discontinued and prolongation of the PR interval and bifascicular block resolved after five days.

In summary, while pharmacokinetic studies revealed moderate dose-dependent prolongation of the PR interval, significant clinical events were uncommon. Asymptomatic first degree AV block was the most common abnormality observed.

7.2 Material Utilized in this Review

This NDA was received in electronic format on December 20, 2002. A Safety Update was received in electronic format on February 28, 2003. The following modules/items were included in this NDA and/or Safety Update and were reviewed for the clinical section of this review: Labeling, Investigators and Study Sites, Clinical Overview, Clinical Summaries, Case Report Tabulations, and Case Report Forms. Reviewed Clinical Study Reports included reports for studies 007, 008, 009, 020, 041, 044, 034, 043 (24 week data), 045 (16 week data), 037, 038, 049, 069, 074, 900, and pharmacokinetic study 076. Reviewed ECG Study Reports included reports for studies 020, 034, 043, and 045.

The following items were also reviewed: Comparison of HIV-1 RNA Levels in Study 034 Using Roche amplicor Version 1.0 and 1.5, Summary of HIV-1 RNA Collection, Processing and Handling,

In addition, submissions were received to the NDA on the following dates and were reviewed;

April 11, 2003	May 1, 2003
April 14, 2003	May 23, 2003
April 24, 2003	May 30, 2003

7.3 Description of Patient Exposure

Overall, a total of 2299 subjects received atazanavir for periods ranging from 1 day to greater than 108 weeks. A total of 737 healthy subjects were enrolled in clinical

pharmacology studies; 703 of these subjects were treated with atazanavir alone or with another protocol specified drug. A total of 2425 HIV-infected subjects were treated in the clinical studies; 1596 received at least one dose of atazanavir in combination with other ARV medications and 892 subjects received comparator regimens. These numbers were determined to be adequate to evaluate the safety of atazanavir as a component of HAART for the chronic treatment of HIV infection.

Of the 1596 subjects who received atazanavir in clinical trials, 1087 were treatment-naive subjects and 509 were treatment-experienced subjects. The proposed dose of 400 mg once daily was received by 683 treatment-naive and 363 treatment-experienced subjects. Over 200 subjects received doses which provided exposures greater than that of the 400 mg target dose. In addition, 44 pediatric subjects were enrolled in the PACTG study, and 170 subjects were enrolled in four collaborative studies and one early access program.

7.4 Safety Findings from Clinical Studies

7.4.1 Special Safety Considerations – Hyperbilirubinemia and Hepatotoxicity

Elucidation of Mechanism of Hyperbilirubinemia
Elevations in bilirubin in subjects receiving atazanavir were noted early during the phase 1 development of ATV and confirmed in phase 2 and 3 clinical studies. In order to elucidate the mechanism of hyperbilirubinemia, studies were conducted by the applicant to investigate the following potential causes:

1) Increased production of bilirubin in spleen and peripheral tissues.
2) Displacement of bilirubin from albumin during transport to the liver.
3) Decreased uptake of bilirubin by liver cells from plasma.
4) Displacement of bilirubin from cytosolic binding protein (ligandin) in liver cells.
5) Inhibition of bilirubin conjugation mediated by the uridine diphosphate-glucuronosyl transferase 1A1 (UGT 1A1) isozyme.

Data from these studies support an unconjugated hyperbilirubinemia. Elevated total bilirubin, when fractionated, was primarily indirect (unconjugated) and reversible upon discontinuation of ATV. This finding suggests that the mechanism of hyperbilirubinemia attributable to ATV occurs prior to glucuronidation (conjugation). At clinically relevant concentrations, ATV, bound to purified UGT 1A1 isozymes, inhibited the conjugation of bilirubin. Evidence for hemolysis, another potential cause of unconjugated hyperbilirubinemia, was not seen; clinical markers such as LDH, reticulocytes, and hemoglobin were stable. Displacement from carriers (eg, albumin, GST) was not observed. By elimination, these experiments suggest that the predominant mechanism of the primarily unconjugated hyperbilirubinemia seen with ATV exposure is inhibition of UGT 1A1.

The lack of a hepatotoxic process, as reflected by no increases in direct bilirubin, was also supported by the absence of detectable bilirubin in the urine of healthy subjects after multiple doses of ATV. Together, these findings support the hypothesis that no inhibition

of bilirubin secretion occurs at the level of canalicular transport. On this basis, the applicant concluded that the predominant mechanism of hyperbilirubinemia is inhibition of UGT 1A1.

Safety Evaluation - Hyperbilirubinemia

Several concerns emerged during the development of ATV regarding the incidence and degree of hyperbilirubinemia seen in clinical trials and these concerns will be the focus of the review of atazanavir and inhibition of UGT 1A1.

Concerns raised regarding hyperbilirubinemia associated with ATV administration are the following:

- General patient tolerability of this side-effect given the degree and frequency seen in clinical trials.
- The efficacy and safety of the management strategy of dose reduction for grade 4 hyperbilirubinemia used in these trials.
- Risks potentially associated with chronic hyperbilirubinemia in HIV-infected patients.
- Any potentially increased risk for hepatoxicity due to chronic inhibition of UDP-glucuronosyl transferase and any potentially unrecognized mechanisms of hepatotoxicity.

For the following discussion, please note that the following toxicity grading scale for hyperbilirubinemia was used for grading hyperbilirubinemia in the atazanavir clinical development program:

Grade 1 – 1.1 – 1.5 x ULN
Grade 2 – 1.6 – 2.5 x ULN
Grade 3 – 2.6 – 5.0 x ULN
Grade 4 – > 5.0 x ULN

Standard normal ranges of laboratory values may vary slightly from lab to lab, however, for total bilirubin levels the normal range is generally defined as ≤ 1 - 1.5 mg/dL. The normal range for direct bilirubin is generally defined as ≤ 0.2 - 0.5 mg/dL.

Incidence of Hyperbilirubinemia in Phase 2 and 3 Clinical Trials

Increases in total bilirubin levels were observed in the vast majority of subjects treated with ATV in contrast to relatively few subjects treated with comparator drugs. In study 034, the mean total bilirubin for ATV-treated subjects was approximately 3-fold higher at week 48 compared to baseline. The mean direct bilirubin levels for ATV-treated subjects increased slightly from baseline and did not increase as total bilirubin increased.

Mean Total and Direct Bilirubin on Atazanavir				
	Study 034		Study 043	
	Baseline N = 404		Baseline N=109	
	Mean (mg/dL)	Standard Error	Mean (mg/dL)	Standard Error
Total Bilirubin	0.5	.01	.63	.03
Direct Bilirubin	0.1	.00	.09	.01
	48 weeks N = 335		24 weeks N=98	
Total Bilirubin	1.7	.06	1.39	.10
Direct Bilirubin	0.3	.01	.2	.1

Mean Total and Direct Bilirubin in Study 034 by Category of Total Bilirubin Elevation	
Total Bilirubin < 2.5 mg/dL	N=3170
Mean total bilirubin (SD)	1.2 (.58)
Mean direct bilirubin (SD)	0.22 (.10)
Total Bilirubin 2.5 - 5 mg/dL	N=634
Mean total bilirubin (SD)	3.3 (.64)
Mean direct bilirubin (SD)	0.36 (.14)
Total Bilirubin ≥ 5 mg/dL	N=66
Mean total bilirubin (SD)	6.3 (1.4)
Mean direct bilirubin (SD)	0.35 (.52)

The incidence of hyperbilirubinemia was clearly dose-dependent as demonstrated in dose-finding phase 2 studies.

Incidence of Grade 3–4 Hyperbilirubinemia				
Number of Subjects/Total (%)				
Dose	**200 mg**	**400 mg**	**500 mg**	**600 mg**
Study	**007**	**007/008**	**007**	**008**
	N= 101	N=277	N=104	N=195
Grade 3-4 Bilirubin	20/101 (20)	114/277 (41)	51/104 (49)	113/195 (58)

The following table shows the incidence of all total bilirubin increases (Grade 1 - 4) and the incidence of Grade 3 - 4 increases for ARV treatment-naive and treatment-experienced subjects treated with ATV 400 mg, ATV 300mg/RTV 100 mg and comparators:

Proportion of Subjects with Hyperbilirubinemia in Phase 2 and 3 Clinical Studies					
Percentage of Subjects					
ARV Treatment-Naive Studies	**034**	**034**	**007/41 008/44**	**007/41 008**	
	ATV 400 mg	**EFV 600 mg**	**ATV 400 mg**	**NFV**	
	N = 404	**N = 401**	**N = 279**	**N = 191**	
Grade 1 - 4	86	3	91	12	
Grade 3 - 4	33	<1	47	3	
ARV Treatment-Experienced Studies	**043**	**043**	**045**	**045**	**045**
	ATV 400 mg	**LPV/RTV**	**ATV 300 mg RTV 100 mg**	**ATV/SQV**	**LPV/RTV**
	N = 144	**N = 146**	**N = 119**	**N = 109**	**N = 117**
Grade 1 - 4	74	10	86	55	7
Grade 3 - 4	20	0	35	13	0

Follow-up in these trials ranges from 16 weeks (study 045) to 108 weeks (studies 007/041 and 008/044). The lower incidence of hyperbilirubinemia in treatment-experienced subjects may reflect, in part, the shorter duration of follow-up in these studies.

Subjects began to experience grade 3-4 bilirubin elevations by week 2; approximately one-third to one-half of treatment-naïve subjects experienced grade 3-4 elevations through 48 weeks of therapy. In the majority of subjects, grade 3-4 bilirubin elevations were measured by 12 - 16 weeks of treatment and continued as long as ATV was administered. The incidence of grade 3-4 elevations continued to rise slowly through 108 weeks of treatment.

Clinical Signs of Hyperbilirubinemia

Jaundice and scleral icterus were reported for subjects treated with ATV but rarely for subjects treated with comparators. The incidence of these two adverse events in ARV treatment-naive and treatment-experienced trials is shown in the following table:

Incidence of Jaundice and Scleral Icterus in Treated Subjects in Phase 2 and 3 Clinical Studies

	Number of Subjects (%)				
ARV Treatment-Naive Studies	**034**	**034**	**007/41 008/44**	**007/041 008**	
	ATV 400 mg	**EFV 600 mg**	**ATV 400 mg**	**NFV**	
	N = 404	**N = 401**	**N = 279**	**N = 191**	
Jaundice[a]	45 (11)	0 (0)	26 (9)	0 (0)	
Scleral icterus[a]	45 (11)	8 (2)	22 (8)	0 (0)	
ARV Treatment-Experienced Studies	**043**	**043**	**045**	**045**	**045**
	ATV 400 mg	**LPV/RTV**	**ATV 300 mg RTV 100 mg**	**ATV 400 mg SQV 1200 mg**	**LPV/RTV**
	N = 144	**N = 146**	**N = 119**	**N = 109**	**N = 117**
Jaundice[a]	14 (10)	0 (0)	12 (10)	5 (5)	0 (0)
Scleral icterus[a]	8 (6)	0 (0)	10 (8)	3 (3)	0 (0)

[a] Subjects may have had both jaundice and scleral icterus; therefore, the overall number of subjects with these events is not necessarily cumulative.

The incidence of jaundice was similar for ARV treatment-naive (9% - 11%) and treatment-experienced subjects (10%), however, follow-up for subjects in the treatment-experienced trials was significantly shorter. The incidence of jaundice was not increased on the ATV 300 mg/RTV 100 mg (10%) treatment regimen relative to treatment with ATV 400 mg (5% - 11%) through 16 weeks of follow-up.

In general, this adverse event appeared to be well tolerated by subjects and led to treatment discontinuation in relatively few subjects.

Co-Infection with Hepatitis B/C

According to the applicant, hepatotoxicity, characterized by increased rates of cytolysis, is frequent in HIV-infected patients who are treated with HAART. Compared to HIV-infected individuals that are not co-infected with hepatitis B or C, patients with co-infection that are treated with HAART have about a 2.5-fold greater relative risk of developing liver enzyme elevations.

To assess the medical impact of co-infection with HBV and/or HCV on hepatic enzymes for subjects treated with ATV, all subjects in phase 3 studies underwent hepatitis B and C testing. Analyses compared serum liver function test results for ATV-treated subjects with those who received a comparator agent in subjects with or without baseline evidence of either chronic HBV infection (HBs Ag positive) or HCV infection (HCV Ab-positive).

Not unexpectedly, subjects with chronic viral hepatitis are more likely than those without chronic viral hepatitis to have hepatic transaminase elevations. There were no notable differences in the incidence of total bilirubin elevations between HBV or HCV positive and negative subjects. Data comparing co-infected patients to those without chronic hepatitis for registrational trials 034 and 043 are summarized in the following tables:

Grade 1-4 Liver Function Abnormalities by Baseline Hepatitis B or C Co-Infection Phase 3 Treated Subjects

	Number with Abnormalities/Evaluable (%)			
	034[a]		043[b]	
LFT	**ATV 400**	**EFV**	**ATV 400**	**LPV/RTV**
Hepatitis B/C Status	**N = 404**	**N = 401**	**N = 144**	**N = 146**
ALT (SGPT)				
Negative	70/346 (20)	85/330 (26)	34/114 (30)	34/127 (27)
Positive	29/49 (59)	37/58 (64)	16/27 (59)	11/17 (65)
AST (SGOT)				
Negative	47/346 (14)	57/330 (17)	34/114 (30)	34/127 (27)
Positive	25/49 (51)	28/58 (48)	15/27 (56)	11/17 (65)
Total Bilirubin				
Negative	302/346 (87)	9/330 (3)	81/114 (71)	12/127 (9)
Positive	36/49 (73)	3/58 (5)	23/27 (85)	3/17 (18)

[a] Median time on therapy of 52 weeks.

[b] Median time on therapy of 24 weeks.

Grade 3 - 4 Liver Function Abnormalities By Baseline Hepatitis B or C Co-Infection Phase 3 Treated Subjects				
	Number with Abnormalities/Evaluable (%)			
	034[a]		043[b]	
LFT	**ATV 400**	**EFV**	**ATV 400**	**LPV/RTV**
Hepatitis B/C Status	**N = 404**	**N = 401**	**N = 144**	**N = 146**
ALT (SGPT)				
Negative	8/346 (2)	2/330 (<1)	6/114 (5)	1/127 (<1)
Positive	6/49 (12)	8/58 (14)	2/27 (7)	0/17 (0)
AST (SGOT)				
Negative	2/346 (<1)	5/330 (2)	2/114 (2)	2/127 (2)
Positive	5/49 (10)	3/58 (5)	2/27 (7)	0/17 (0)
Total Bilirubin				
Negative	115/346 (33)	2/330 (<1)	22/114 (19)	0/127 (0)
Positive	14/49 (29)	0/58 (0)	6/27 (22)	0/17 (0)
[a] Median time on therapy of 52 weeks.				
[b] Median time on therapy of 24 weeks.				

Dose Modifications and Treatment Discontinuation Due to Hyperbilirubinemia
Clinical protocols outlined a dose reduction strategy for subjects with isolated hyperbilirubinemia (i.e., elevated bilirubin without an increase in ALT/AST from baseline) or clinical jaundice. Subjects were monitored for the development of isolated hyperbilirubinemia or clinical jaundice. Criteria for dose reduction were as follows:

- Subjects with confirmed elevations in total bilirubin > 5 x ULN were to be dose reduced.
- Subjects with clinical jaundice (scleral icterus or cutaneous jaundice) and elevated total bilirubin > 5 x ULN were to be dose reduced without confirmation of the serum bilirubin level.
- Subjects with clinical jaundice (scleral icterus or cutaneous jaundice) and with total bilirubin < 5 x ULN may have been dose reduced if the subject and/or investigator viewed the jaundice as unacceptable, and only after discussion and agreement by the BMS medical monitor.

Subjects with elevation of conjugated (direct) bilirubin > 2 x ULN in association with ALT/AST > 3 x ULN were to be discontinued from the study.

Subjects receiving 400 mg of atazanavir were dose-reduced to 200 mg. Subjects receiving atazanavir 300 mg/ritonavir 100 mg were dose reduced to atazanavir 200 mg/ ritonavir 100 mg; if grade 4 hyperbilirubinemia persisted, subjects were dose-reduced to atazanavir 200 mg/ ritonavir 50 mg.

Hyperbilirubinemia and/or its associated clinical signs, jaundice and/or scleral icterus, resulted in dose reductions of regimens containing ATV 400 mg or ATV 300 mg/RTV 100 mg in up to 5% of treated patients:

Dose Reduction Due to Hyperbilirubinemia or Jaundice					
	Number of Subjects (%)				
Clinical Trial	**034**	**007/041 008/044**	**043**	**045**	**045**
Event Leading to Dose Reduction[a]	**ATV 400 mg**	**ATV 400 mg**	**ATV 400 mg**	**ATV 300 mg RTV 100 mg**	**ATV 400 mg SQV 1200 mg**
	N = 404	**N = 279**	**N = 144**	**N = 119**	**N = 109**
Hyperbilirubinemia	20 (5)	15 (5)	2 (1)	3 (3)	0 (0)
Jaundice	1 (<1)	0 (0)	3 (2)	0 (0)	0 (0)

[a] Subjects may have had more than one event; therefore, the overall number of subjects discontinuing due to these events is not necessarily cumulative.

The following table summarizes discontinuations from the study that were due to hyperbilirubinemia, jaundice, or scleral icterus:

Discontinuation of Study Therapy Due to Hyperbilirubinemia, Jaundice and Scleral Icterus - Treated Subjects					
	Number of Subects (%)				
Clinical Trial	**034**	**007/41 008/44**	**043**	**045**	**045**
Event Leading to Discontinuation of Treatment[a]	**ATV 400 mg**	**ATV 400 mg**	**ATV 400 mg**	**ATV 300 mg RTV 100 mg**	**ATV 400 mg SQV 1200 mg**
	N = 404	**N = 279**	**N = 144**	**N = 119**	**N = 109**
Hyperbilirubinemia	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)
Jaundice	1 (<1)	1 (<1)	1 (<1)	0 (0)	0 (0)
Scleral icterus	2 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)

[a] Subjects may have had more than one event; therefore, the overall number of subjects discontinuing due to these events is not necessarily cumulative.

In summary, while clinical jaundice and/or scleral icterus were reported in approximately 10-20% of patients, these symptoms or laboratory confirmed hyperbilirubinemia led to dose reduction and/or discontinuation of atazanavir in ≤ 5% of patients. From the perspective of patient acceptability this side-effect appears to be well-tolerated; however, it may be postulated that more discontinuations may occur in general clinical practice as patients enrolled in clinical trials have unique motivations to continue treatment.

Dose Reduction as a Management Strategy for Hyperbilirubinemia
The primary concern regarding dose reduction as a management strategy for hyperbilirubinemia is the maintenance of efficacy at a reduced dose of ATV. Response rates for LOQ ≤ 400 c/mL in ATV-treated treatment-naive subjects after dose reduction or dose interruptions due to hyperbilirubinemia were similar to the overall response rate (26/35, 74% and 23/31, 74%, respectively, vs. 452/663, 68%). For LOQ ≤ 50 c/mL, the response rates after dose reductions were similar to the overall rate (12/35, 34% vs. 217/663, 33%).

A total of 7 subjects in the ARV treatment-experienced studies 043 and 009 (not listed in table) underwent dose reduction for hyperbilirubinemia. Of these seven subjects, two responded (29%) at LOQ = 400 c/mL and 1/7 (14%) at LOQ = 50 copies/mL. This is compared to 55% and 34% of subjects receiving atazanavir in study 043 (LOQ = 400 c/mL and LOQ = 50 c/mL respectively).

As expected, treatment-experienced subjects were more likely to experience treatment failures when dose-reduced as compared to treatment-naïve subjects. Although the overall numbers of patients experiencing these events is low, this result would be expectd based on the assumption that treatment-experienced subjects are more likely to have resistant HIV strains and would be more susceptible to treatment failure with lower exposures to atazanavir.

Given these observations and the fact that newly-infected subjects have been shown to have a rising incidence of resistance to any class of ARV drug, dose reduction as a management strategy for hyperbilirubinemia should not be accepted.

Assessment of Risks Associated with Hyperbilirubinemia
The background for this section was obtained primarily from the review of hyperbilirubinemia associated with ATV done by the applicant's consultant, ———

Insight into the risks associated with chronic isolated hyperbilirubinemia can be obtained from the observations of several inheritable genetic diseases: Gilbert's syndrome (GS), and Crigler-Najjar syndromes types I and II (CN-I and II). In these diseases bilirubin UDP-glucuronosyl transferase activity ranges from modestly reduced (GS) to completely absent (CN-I). Only two adverse consequences of unconjugated hyperbilirubinemia have been reported in these patient groups; bilirubin encephalopathy/kernicterus, seen routinely in CN-I subjects and rarely in CN-II patients, and an increased incidence of gallstones in association with Gilbert's syndrome which is generally only seen in the setting of hemolysis.

Chronic unconjugated hyperbilirubinemia of ≤ 4 mg/dL is common in Gilbert's syndrome. Values in the range of 5 - 12 mg/dL are observed in CN-II, or in patients with both Gilbert's syndrome and a hemolytic state. Occasionally, chronic unconjugated bilirubin elevations as high as 20 mg/dL may occur in patients with CN-II. Patients with

CN-I typically experience unconjugated bilirubin concentrations of ≥ 20 mg/dL that begin in the neonatal period and persist for life.

According to the applicant's consultant, ——— no literature reports exist that suggest that bilirubin exposures of the level experienced by GS patients pose any risk of bilirubin encephalopathy in the absence of additional, acquired hepatic or nutritional illness. An increased incidence of gallstones in association with GS in the setting of hemolysis has been reproted.

In general, the literature suggests that bilirubin encephalopathy and kernicterus occur in the neonatal period or infancy when unconjugated bilirubin concentrations either rapidly approach or exceed 18-20 mg/dL. While this may also be seen in adolescents and adults in this range, it more often requires bilirubin concentrations in the 30-40 mg/dl range. Overall, available data suggests that in adolescents and adults with normal albumin levels, prolonged exposure to unconjugated bilirubin levels of ≤ 16 mg/dL does not result in toxicity.

In chronically-ill patients with hypoalbuminemia associated with AIDS, hepatic disease, and/or concomitant nutritional deficits, the predicted safety level for bilirubin may be lower, since neurologic sequelae largely reflect the concentration of non-protein bound unconjugated bilirubin. ——— postulates that, at an albumin level of 2 g/dL, unconjugated bilirubin levels chronically in excess of 10 mg/dL are a theoretical risk of concern and those in excess of 15 mg/dL should probably mandate therapeutic intervention.

Incidence of Hyperbilirubinemia ≥ 10 mg/dL in Clinical Trials

The occurrence of total bilirubin levels ≥ 10 mg/dL in clinical trials of atazanavir was uncommon. Only ten patients experienced any level of total bilirubin ≥ 10 mg/dL. In seven of the ten cases, a bilirubin in excess of this level was reported on only one occasion. In one case two total bilirubins greater than 10 mg/dL were observed one day apart. One subject had total bilirubin levels greater than 10 mg/dL on two occasions; once prior to study randomization and once nine days after initiating study therapy. One subject in study 008 appeared to have a total bilirubin in excess of 10 mg/dL (direct bilirubin > 5 mg/dL), as well as grade 4 LFTs for approximately 2 months; this patient was diagnosed with acute hepatitis A. LFTs normalized after 2 months; the patient remained on study during this time.

Hyperbilirubinemia of greater than 10 mg/dL was seen in association with elevations of direct bilirubin and other LFTs in five subjects; two of theses patients were ultimately discontinued from the study. One subject, as noted above, was diagnosed with acute hepatitis A and remained on treatment until the abnormal LFTs normalized. One subject with chronic hepatitis C remained on study throughout the treatment period despite having persistent grade 3-4 elevations of LFTs for approximately 10 months (LFTs in the normal range prior to study treatment). The last patient experienced his first TB > 10 mg/dL prior to randomization; TB and other LFTs briefly rose after starting treatment, but normalized rapidly.

Hyperbilirubinemia occurred as an isolated event in the remaining five patients; four of these subjects had direct bilirubin levels of 0.3 mg/dL or less and in a fifth patient diagnosed with symptomatic hyperlactatemia a direct bilirubin of 0.6 mg/dL was recorded.

In summary, total bilirubin elevations in excess of levels placing patients theoretically at risk for bilirubin encephalopathy were uncommon and generally transient.

Hyperbilirubinemia and Hepatotoxicity
The following data was reviewed to explore whether ATV use is associated with an increased risk of hepatotoxicity.

Discontinuations Due to Liver Enzyme Abnormalities or Hepatitis
No increase in discontinuations and/or death due to hepatotoxicity relative to comparators was apparent in clinical trials of ATV. The following table summarizes discontinuations due to the development or worsening of abnormal liver enzyme tests (without lactic acidosis syndrome/symptomatic hyperlactatemia):

Discontinuations and/or Death Due to Liver Enzyme Abnormalities/Toxicity Phase 2 and 3 Clinical Studies					
	Number of Subjects (%)				
ARV Treatment-Naive Studies	**034**	**034**	**007/41 008/44**	**007/041 008**	
	ATV 400 mg	**EFV 600 mg**	**ATV all doses**	**NFV**	
	N = 404	**N = 401**	**N = 673**	**N = 191**	
Discontinuation	2 (<1)	1 (<1)	11 (2)	4 (2)	
Death	0	0	1 (< 1)	0	
ARV Treatment-Experienced Studies	**043**	**043**	**045**	**045**	**045**
	ATV 400 mg	**LPV/RTV**	**ATV 300 mg RTV 100 mg**	**ATV 400 mg SQV 1200 mg**	**LPV/RTV**
	N = 144	**N = 146**	**N = 119**	**N = 109**	**N = 117**
Discontinuation	1 (<1)	0	1 (<1)	0	0
Death	0	0	0	0	0
ARV Treatment-Experienced Studies	**009**	**009**	**009**		
	ATV 400 mg SQV 1200 mg	**ATV 600 mg SQV 1200 mg**	**RTV 400 mg SQV 400 mg**		
	N= 32	**N=27**	**N=23**		
Discontinuation	0	0	3 (13)		
Death	0	0	0		

One atazanavir 200 mg subject in study 007 died with the immediate cause of death specified as liver failure; this was described as hepato-renal syndrome secondary to multi-organ failure and complications of HIV disease, possibly non-Hodgkins lymphoma (autopsy indeterminate). With the exception of five deaths in studies 007 and 008 [four ATV (<1%), one NFV (<1%)] related to lactic acidosis, no other subjects died due to causes associated with hepatotoxicity; lactic acidosis syndrome/symptomatic hyperlactatemia are adverse events attributed to the mitochondrial toxicity of NRTIs.

Of the 15 subjects discontinuing atazanavir for worsening of liver function or hepatitis (without documented LAS/SHL) on therapy, 10 had chronic hepatitis B or C. One subject had acute hepatitis B. One subject had a prior history of hepatic steatosis. The three remaining subjects had no apparent risk factors for hepatotoxicity. Five of the eight subjects discontinuing treatment for worsening of liver function on comparator regimens had chronic hepatitis B or C, one subject was hepatitis B core antibody positive but surface antigen and antibody negative, and one subject had acute hepatitis B. One subject receiving ritonavir/saquinavir had no apparent risk factors for hepatotoxicity.

LFT Abnormalities in Clinical Trials

Grade 3 - 4 bilirubin elevations were uncommonly associated with Grade 3 - 4 ALT and/or AST elevations, suggesting that hyperbilirubinemia was not a consequence of a hepatotoxic process. The following table shows elevated bilirubin and ALT/AST for the phase 3 studies 034, 043, and 045:

Grade 3 - 4 ALT/AST and Total Bilirubin Elevations in Phase 3 Studies- Treated Subjects

	Observed/Evaluable (%)					
	034	**043**	**045**	**034**	**043**	**045**
	ATV 400 mg	**ATV 400 mg**	**ATV 300 RTV 100**	**ATV 400 mg**	**ATV 400 mg**	**ATV 300 RTV 100**
	N = 404	**N = 144**	**N = 119**	**N = 404**	**N = 144**	**N = 119**
	No Grade 3 - 4 Total Bilirubin			**Grade 3 - 4 Total Bilirubin**		
No Grade 3 - 4 ALT/AST	262/402 (65)	107/142 (75)	76/119 (64)	125/402 (31)	26/142 (18)	40/119 (34)
Grade 3 - 4 ALT/AST	9/402 (2)	7/142 (5)	1/119 (<1)	6/402 (1)	2/142 (1)	2/119 (2)

A total of 10 subjects (< 1%) in the three phase 3 studies had both grade 3 - 4 total bilirubin and grade 3 - 4 ALT/AST: six subjects in 034, two subjects in 043 and two subjects on the ATV 300 mg/RTV 100 mg arm of 045. Of the six subjects in 034, three had grade 3 - 4 values of bilirubin and ALT/AST that were measured > 50 days apart, and three had concurrent grade 3 - 4 bilirubin and ALT/AST. Of the latter subjects, one was hospitalized, received four units of packed red blood cells and was discontinued from the study because of jaundice and anemia; the other two subjects continued on study with active hepatitis C infection. Of the two subjects in 043, one had grade 1 ALT and AST at

baseline, developed grade 3 jaundice, grade 3 ALT and grade 4 AST and was discontinued from the study for the grade 4 AST and hyperbilirubinemia. The other subject had normal ALT at baseline, had a transient on-study grade 3 ALT measurement which had decreased to grade 2 at the next visit and remained on-study with mild scleral icterus. Of the two subjects in 045, one was asymptomatic at the time of the elevations and had a documented history of alcohol abuse. The other had a transient increase that had decreased by the next study visit. Both subjects remained on the study.

Three of the clinical trials (007, 008, and 034) had subjects receiving identical NRTI background therapy allowing for direct comparison of the rate of LFT abnormalities on treatment. Hepatitis B and C status in studies 007 and 008 were comparable across treatment regimens. In studies 007 and 008 more subjects receiving atazanavir had any grade elevation of LFTs as compared to nelfinavir (data similar for 200 mg dosing cohort; data not shown). Overall, the incidence of LFT abnormalities was lower in study 008 as compared to 007, likely reflecting the difference in NRTI backgrounds. Data are summarized in the following two tables:

Liver Function Test Abnormalities - Treated Subjects						
Treatment Regimens: ATV or NFV and ddI/d4T						
Study 007						
	Number of Subjects with Abnormal Values/Number at Risk (%)					
	ATV (QD)		**ATV (QD)**		**NFV (TID)**	
	400 mg		**500 mg**		**750 mg**	
	N = 101		**N = 107**		**N = 100**	
	Grade 1 - 4	**Grade 3 - 4**	**Grade 1 - 4**	**Grade 3 - 4**	**Grade 1 - 4**	**Grade 3 - 4**
AST/SGOT	64/100 (64)	14/100 (14)	60/104 (58)	8/104 (8)	46/100 (46)	4/100 (4)
ALT/SGPT	63/100 (63)	14/100 (14)	58/104 (56)	8/104 (8)	47/100 (47)	6/100 (6)
Total Bilirubin	89/100 (89)	44/100 (44)	97/104 (93)	56/104 (54)	13/100 (13)	1/100 (1)
Alk. Phos.	16/100 (16)	--	13/104 (13)	--	8/100 (8)	--

Liver Function Test Abnormalities - Treated Subjects						
Treatment Regimens: ATV or NFV and 3TC/d4T						
Study 008						
	Number of Subjects with Abnormal Values/Number at Risk (%)					
	ATV (QD)		ATV (QD)		NFV (BID)	
	400 mg		600 mg		750 mg	
	N = 178		N = 195		N = 91	
	Grd 1 - 4	Grd 3 - 4	Grd 1 - 4	Grd 3 - 4	Grd 1 - 4	Grd 3 - 4
AST/SGOT	75/177 (42)	6/177 (3)	85/195 (44)	7/195 (4)	25/91 (27)	6/91 (7)
ALT/SGPT	85/177 (48)	9/177 (5)	87/195 (45)	11/195 (6)	27/91 (30)	8/91 (9)
Total Bilirubin	162/177 (92)	79/177 (45)	187/195 (96)	120/195 (62)	9/91 (10)	4/91 (4)
Alk Phos	17/177 (10)	--	14/195 (7)	--	6/91 (7)	1/91 (1)

In study 007, grade 3-4 abnormalities were more common in atazanavir treated subjects, while in study 008 grade 3-4 abnormalities were slightly more common in nelfinavir-treated subjects. When treatment arms from the two trials were combined, discontinuations for LFT abnormalities were similar for atazanavir versus nelfinavir treated subjects.

In study 034, with the expected exception of bilirubin results, abnormalities of serum liver function tests were comparable between atazanavir and efavirenz treated subjects.

Liver Function Abnormalities - Treated Subjects Study 034				
	Number of Subjects/Number at Risk (%)			
	ATV ZDV+3TC		EFV ZDV+3TC	
	N = 404		N = 401	
Laboratory Test	**Grade 1 - 4**	**Grade 3-4**	**Grade 1-4**	**Grade 3-4**
ALT/SGPT	100/402 (25)	15/402 (4)	122/395 (31)	10/395 (3)
AST/SGOT	74/402 (18)	7/402 (2)	85/395 (22)	8/395 (2)
Total Bilirubin	344/402 (86)	131/402 (33)	12/395 (3)	2/395 (<1)
Alkaline Phosphatase	31/402 (8)	0/402 (0)	47/395 (12)	0/395 (0)

The frequency of transaminase elevations in HBV and/or HCV co-infected subjects was generally comparable between ATV and comparators, with the exception of study 043 in which Grade 3 - 4 ALT elevations were more common among both hepatitis negative and positive subjects treated with ATV (5% and 7%, respectively) than subjects treated with LPV/RTV (< 1% and 0%, respectively). However, it must be kept in mind that nucleoside backbone therapy in study 043 was individualized, thus making direct comparison difficult.

In summary, the hyperbilirubinemia observed during the development program of atazanavir appeared to be predominantly indirect, well-tolerated by study subjects, reversible with discontinuation of therapy, and distinguishable from hyperbilirubinemia associated with hepatic toxicity or dysfunction. Use of atazanavir did not appear to result in an increased incidence of hepatotoxicity relative to selected PIs or to efavirenz.

7.4.2 Special Safety Issues – Lipid Profiles

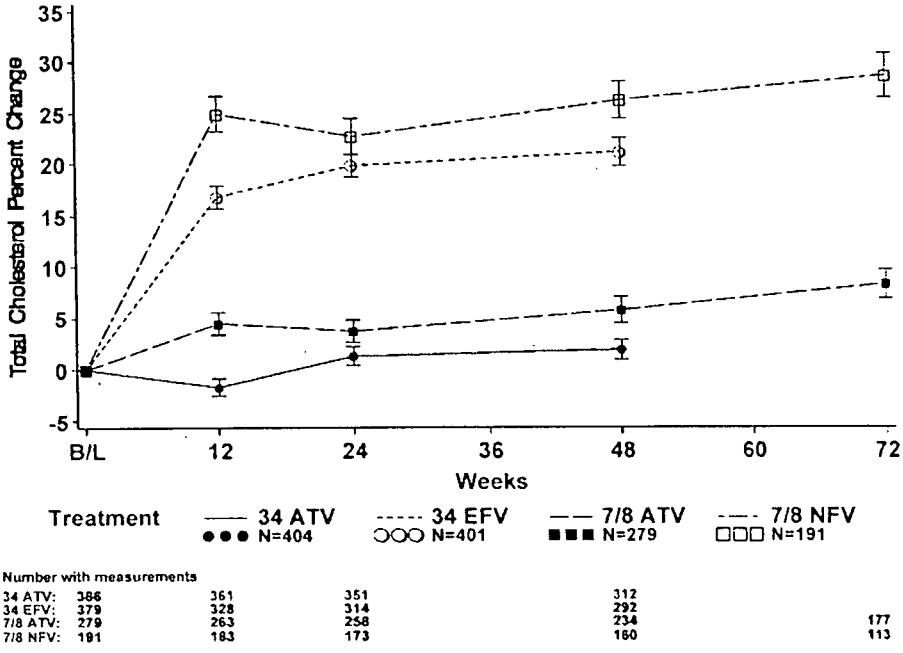
Hyperlipidemia is a recognized side effect of HAART that often limits the success of or further complicates HAART regimens. Significant increases in serum cholesterol and triglycerides occur with the use of currently marketed protease inhibitors and other ARV agents.

Lipid Metabolism in ARV Treatment-Naive Treated Subjects
Results from treatment-naïve studies 007, 008, and 034 demonstrated a favorable lipid profile for ATV-treated subjects as compared to NFV or EFV treated subjects through 72 and 48 weeks of treatment, respectively. Lipid profiles were assessed through measurement of total cholesterol, low-density lipoprotein (LDL)-cholesterol, and triglyceride changes from baseline. Studies 007 and 008 were not specifically designed to address lipid changes in treated subjects so data from these trials are based only on those subjects who had fasting lipid profiles performed; as a result, the findings from these studies must be interpreted with caution.

Mean total cholesterol in the ATV 400 mg, NFV, and EFV treatment groups was similar at baseline. Differences between ATV and comparator regimens became apparent by week 4 and continued throughout the treatment period. At week 72 for subjects treated in studies 007 and 008, mean increase from baseline in total cholesterol for NFV-treated subjects was 29% compared to 8% for ATV-treated subjects. In study 034, the mean increase from baseline in total cholesterol for EFV-treated subjects was 21% compared to 2% for ATV-treated subjects. The 95% CI for the difference (ATV - EFV) in mean percent change from baseline in total cholesterol excluded zero ($p < 0.0001$).

Data on total cholesterol in treatment-naïve trials is in summarized in the following figure. It is interesting to note that total cholesterol levels are slightly higher on 007/008 treatment arms as compared to 034 treatment arms. This may reflect the contribution of the nucleoside analogue background to elevations of total cholesterol.

Mean Percent Change in Total Cholesterol From Baseline
ARV Treatment-Naive Treated Subjects



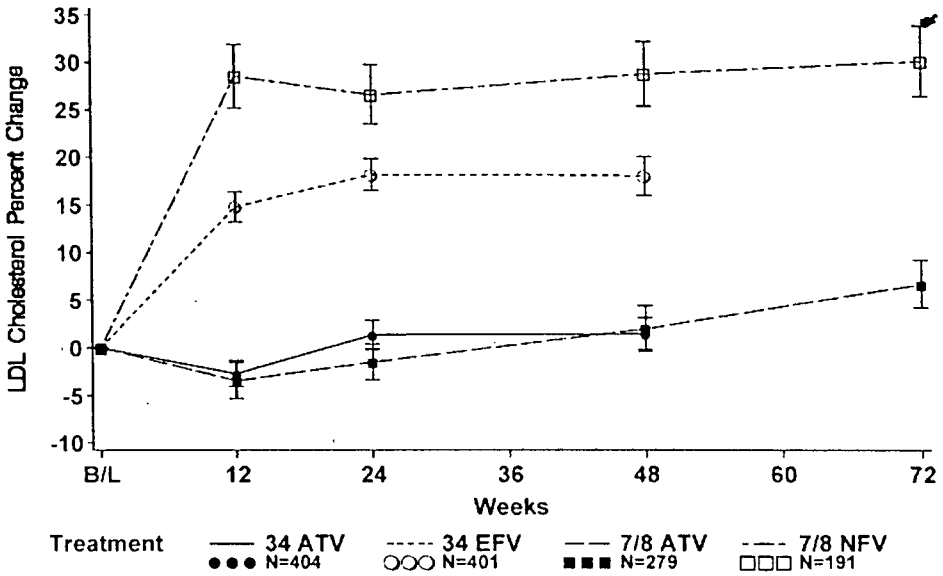
LDL Cholesterol

Analysis of mean percent changes from baseline indicated that subjects on the EFV and NFV treatment regimens had substantial increases in LDL cholesterol by week 12 and that these increases were sustained through 48 weeks for EFV and 72 weeks for NFV.

At week 72 for subjects treated in studies 007 and 008, the mean increase from baseline in LDL cholesterol for NFV-treated subjects was 30% compared to 7% for ATV-treated subjects. The proportion of subjects who had week 72 LDL cholesterol concentrations ≥ 160 mg/dL was greater on NFV (17%) as compared to ATV (5%).

Similar results were observed at week 48 on study 034. The mean increase from baseline in LDL cholesterol for EFV-treated subjects was 18% compared to 1% for ATV-treated subjects. The 95% CI for the difference in mean percent change from baseline in LDL cholesterol excluded zero (-17.6%, -10.7%, $p < 0.0001$). At week 48 for study 034, fewer subjects on the ATV regimen (3%) had fasting LDL cholesterol ≥ 160 mg/dL compared to EFV (8%, $p < 0.05$).

Mean Percent Change in Fasting LDL Cholesterol From Baseline - ARV Treatment-Naive Treated Subjects



Number with measurements

34 ATV:	383	368	345	272	
34 EFV:	378	326	312	253	
7/8 ATV:	194	153	147	145	95
7/8 NFV:	135	108	102	98	72

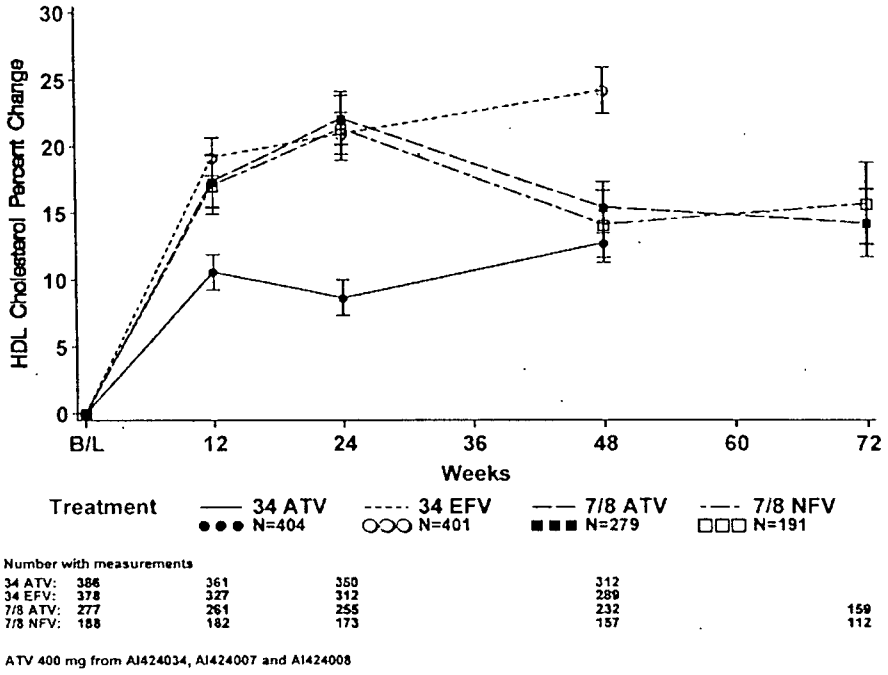
ATV 400 mg from AI424034, AI424007 and AI424008

HDL Cholesterol:

Baseline mean HDL cholesterol concentrations were evenly distributed across the ATV 400 mg, NFV, and EFV regimens. For all treatment regimens, HDL cholesterol increased by week 12.

At week 48, a 13% mean increase was observed for subjects receiving ATV 400 mg on study 034. However, the EFV treatment regimen had a significantly higher increase (24%) in HDL cholesterol at week 48 ($p < 0.0001$). At week 72, the HDL cholesterol increased from baseline by 16% for NFV-treated subjects and by 14% for ATV 400 mg in studies 007/008 combined.

Mean Percent Change in HDL Cholesterol From Baseline - ARV Treatment-Naive Treated Subjects

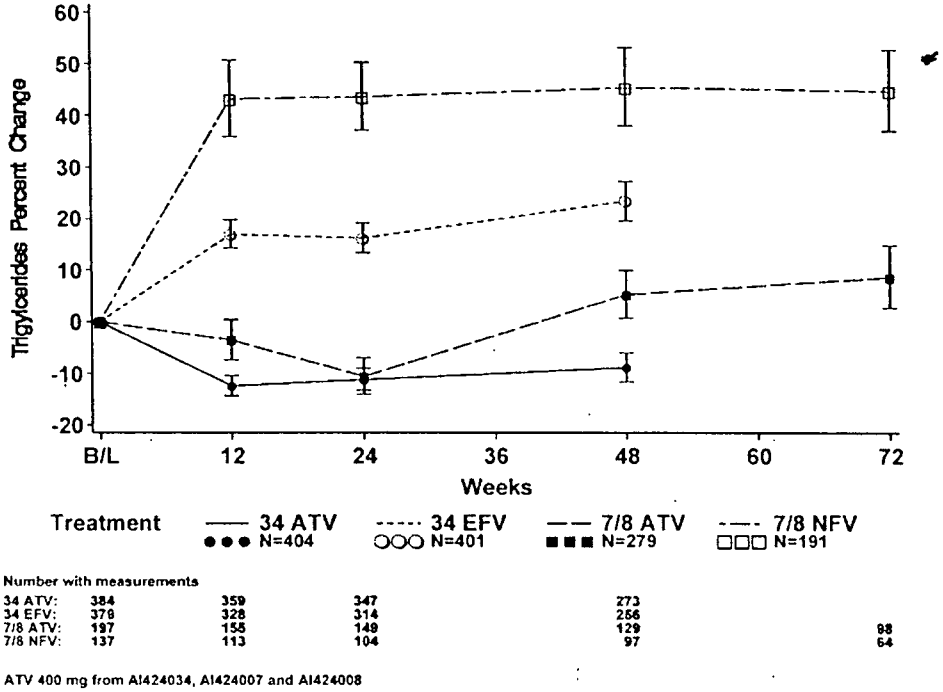


Fasting Triglycerides:
Baseline mean fasting triglyceride concentrations were slightly lower on the NFV treatment regimen (102 mg/dL) compared to the ATV 400 mg treatment regimen (124 mg/dL) for studies 007 and 008. In study 034, baseline fasting mean triglyceride concentrations were slightly lower on the EFV treatment regimen (129 mg/dL) compared to the ATV 400 mg treatment regimen (138 mg/dL).

At week 72, substantial mean increases were observed in triglycerides for NFV-treated subjects relative to ATV-treated subjects (45% compared to 9%). Differences between ATV and comparator regimens were observed by week 4 and continued throughout the treatment period. At week 48, significant mean increases ($p < 0.0001$) were observed for EFV-treated subjects (23%) compared with ATV-treated subjects, who experienced a small decrease in triglyceride concentrations (-9%). Fasting triglyceride concentrations increased rapidly and were sustained through 72 weeks for NFV and 48 weeks for EFV.

Despite the favorable triglyceride profile that was generally observed in atazanavir-treated patients, this finding did not preclude the development of severe elevations of triglycerides (defined as > 751 mg/dL) in these patients; two percent of treated patients receiving ATV 400 mg QD or nelfinavir in studies 007 and 008 developed triglyceride elevations of this severity.

Mean Percent Change in Fasting Triglycerides From Baseline - ARV Treatment-Naive Treated Subjects



Lipid Metabolism in ARV Treatment-Experienced Subjects Who Switched From Nelfinavir to ATV

Study 044 was an open-label (initially blinded to ATV dose), observational, roll-over/switch study designed to assess the long-term safety, tolerability, and continued antiviral efficacy of ATV in initially antiretroviral treatment-naive subjects who completed a minimum of 48 weeks of therapy with ATV or NFV in study 008. In addition, 044 was designed to assess changes in serum lipid concentrations in subjects who switched from NFV to ATV. All subjects received ATV in 044 for a median of 38 weeks. Overall, a large proportion of subjects treated in 008 continued treatment in 044 (346/464); unfortunately, sufficient numbers of data are missing from subjects that these results must be interpreted with caution.

At study entry, the NFV to ATV cohort had higher lipid levels compared with the ATV treatment cohorts. By week 12 of ATV treatment, lipid concentrations in this cohort were comparable with the other treatment regimens and remained comparable through week 24.

In the NFV to ATV treatment regimen at week 12, significant differences were observed in the mean percent change from entry in total cholesterol (-16.1%), HDL cholesterol (5%), fasting LDL cholesterol (-20.6%), and fasting triglycerides (-27.7%). These

differences were maintained through week 24. Median week 12 levels of total cholesterol (165 mg/dL), fasting LDL cholesterol (94 mg/dL), and fasting triglycerides (86 mg/dL) in this cohort were comparable to the median baseline levels of subjects enrolling in study 008 (168 mg/dL, 91 mg/dL, and 93 mg/dL, respectively).

Lipid Metabolism in ARV Treatment-Experienced Subjects

Two studies, 009 and 043, were conducted in treatment-experienced population. Study 045 was conducted in an ARV highly treatment-experienced population; results from study 045 will be discussed in a separate section of this review. Study 009 will not be discussed in this section due to the low numbers of subjects that were enrolled.

Total Cholesterol:

The mean total cholesterol for ATV-treated subjects in study 043 was slightly higher than LPV/RTV-treated subjects at baseline. At week 24, the mean change in total cholesterol for LPV/RTV-treated subjects was 18% compared to -2% for ATV-treated subjects; the 95% CI for the difference estimate (ATV - LPV/RTV) excluded zero ($p < 0.0001$). Analysis of mean percent changes from baseline indicated that subjects on the LPV/RTV treatment regimen had rapid and substantial increases in total cholesterol by week 4 that were sustained through week 24.

Fasting LDL Cholesterol:

Baseline mean LDL cholesterol was 104 mg/dL on the ATV treatment regimen and 100 mg/dL in the LPV/RTV treatment regimen. At week 24, the mean increase in LDL cholesterol for LPV/RTV-treated subjects was 8% compared to a mean decrease of 6% for ATV-treated subjects; the mean LDL cholesterol for ATV-treated subjects was 92 mg/dL for atazanavir treated subjects versus 106 mg/dl for LPV/RTV-treated subjects.

At week 24, the negative estimate for the pairwise difference (ATV - LPV/RTV) in the mean percent change from baseline in fasting LDL cholesterol favored the ATV treatment regimen using the LOCF for subjects who initiated lipid reduction therapy or who discontinued (-14.2%, 97.5% CI: -23.0%, -5.4%; $p < 0.0001$). When sensitivity analyses without the LOCF were performed, the difference remained significant (97.5% CI: -21.1%, -3.4%; $p < 0.025$).

HDL Cholesterol

At week 24 on study 043, HDL cholesterol had increased by modest amounts (15% on ATV; 17% on LPV/RTV) on both treatment regimens.

Fasting Triglycerides:

At week 24, the mean increase in serum triglycerides for LPV/RTV-treated subjects was 57% compared to a mean decrease of 2% for ATV-treated subjects; the difference of the means was statistically significant ($p < 0.0001$). Analysis of mean percent changes from baseline indicated that subjects on the LPV/RTV treatment regimen had rapid and substantial increases in fasting serum triglycerides by week 4 that were sustained through week 24.

The mean fasting triglycerides of treatment-experienced subjects at baseline (ATV-treated subjects; mean 207 mg/dL) was significantly higher than that observed in treatment-naïve subjects in studies 007, 008, and 034. Treatment with ATV did not result in a reduction of triglycerides to what may be considered treatment-naive or pre-treatment levels.

Frequency and Severity of Hyperlipidemia Using NCEP ATP-III Classification: Fasting LDL Cholesterol

For treatment-experienced subjects in study 043, the proportion of subjects with fasting LDL cholesterol grouped by NCEP category was slightly different between the two regimens at baseline.

At week 24, the proportion of subjects who experienced LDL cholesterol concentrations in the high or very high (≥ 160 mg/dL) category was higher on the LPV/RTV treatment regimen.

Fasting LDL Cholesterol Categories (mg/dL) Study 043			
		Observed/Evaluable (%)	
		Treatment Regimen	
		ATV	LPV/RTV
Week	Category	N = 109	N = 114
B/L	< 100	51/109 (47)	64/114 (56)
	100 - < 130	33/109 (30)	27/114 (24)
	130 - < 160	18/109 (17)	16/114 (14)
	160 - < 190	5/109 (5)	6/114 (5)
	≥ 190	2/109 (2)	1/114 (<1)
24	< 100	53/91 (58)	41/83 (49)
	100 - < 130	32/91 (35)	19/83 (23)
	130 - < 160	6/91 (7)	17/83 (20)
	160 - < 190	0/91 (0)	4/83 (5)
	≥ 190	0/91 (0)	2/83 (2)

Fasting Triglycerides

For treatment-experienced subjects in study 043, the proportion of subjects with fasting triglycerides grouped by NCEP category were similar between the two regimens at baseline.

At week 24, the proportion of subjects who experienced fasting triglyceride concentrations above 400 mg/dL was higher on the LPV/RTV treatment regimen,

although the one patient who developed triglyceride elevation > 1250 mg/dL was receiving atazanavir.

Fasting Triglycerides Categories (mg/dL)			
		Observed/Evaluable (%)	
		Treatment Regimen	
		ATV	LPV/RTV
Week	Category	N = 109	N = 114
B/L	< 250	82/109 (75)	87/114 (76)
	250 - < 401	20/109 (18)	19/114 (17)
	401 - < 751	3/109 (3)	7/114 (6)
	751 - 1250	4/109 (4)	1/114 (<1)
	> 1250	0/109 (0)	0/114 (0)
24	< 250	71/92 (77)	48/83 (58)
	250 - < 401	13/92 (14)	22/83 (27)
	401 - < 751	7/92 (8)	12/83 (14)
	751 - 1250	0/92 (0)	1/83 (1)
	> 1250	1/92 (1)	0/83 (0)

Cardiovascular Events

Three myocardial infarctions were reported in atazanavir-treated patients and three were reported in patients receiving comparators. One subject receiving RTV/SQV underwent three vessel coronary bypass surgery. As can be observed by these numbers, significant cardiovascular events were uncommon in atazanavir clinical trials and duration of follow-up too short to reach any conclusions regarding the reduction of cardiovascular risk with use of atazanavir as compared to other protease inhibitors or efavirenz.

Lipodystrophy

Lipodystrophy, a term used to describe a number of clinical signs generally characteristic of fat redistribution, has been described in HIV-infected patients receiving HAART. Manifestations of this phenomenon vary widely, and include both lipoatrophy and lipohypertrophy. The former includes wasting in the arms, legs and face, while the latter includes fat accumulation in the neck, upper back (dorsocervical fat pad or buffalo hump), and abdomen (truncal obesity), lipoma, and breast enlargement in men and women. Fat redistribution is often not clinically detected until one or two years of exposure to HAART.

The pathogenesis of fat redistribution and the role of antiretroviral therapy remains unclear, but is likely multifactorial. Hypotheses have included mitochondrial toxicity of nucleosides and interference of PIs with enzymes and receptors involved in fat and glucose metabolism. Fat redistribution had been reported even prior to the use of

antiretroviral agents. The relationship between fat redistribution and metabolic alterations such as dyslipidemia and insulin resistance is also unclear.

The phase 2 and 3 programs for ATV included measurements of waist-to-hip ratios as a marker for lipodystrophy. In addition, DEXA scanning and CT scanning were incorporated into the phase 3 program of ATV. No clinically significant changes from baseline in waist-to-hip ratio among the treatment-naive subjects was observed on any of the treatment regimens.

Despite this, lipodystrophy events (includes all events of lipoatrophy, lipohypertrophy, or both) were reported in 9% of ATV-treated subjects and in 7% of EFV-treated subjects at 48 weeks in study 034. In study 007/41, with a median time on therapy of 111 weeks for ATV and 105 weeks for NFV, the overall incidence of any lipodystrophy event was 13% in ATV-treated subjects (all doses) and 10% in NFV-treated subjects. Generalized weight loss and weight gain were also reported with similar frequency between atazanavir and comparators in these trials.

In summary, use of atazanavir appeared to be associated with less hyperlipidemia as compared to efavirenz and selected protease inhibitors. Use of atazanavir in treatment-experienced subjects in study 043 did not result in a return of fasting triglycerides to levels observed in treatment-naive subjects, suggesting that factors other than current protease inhibitor use may also contribute to the development of at least hypertriglyceridemia. In addition, the favorable lipid profile seen in atazanavir arms of clinical trials did not translate into fewer events of patient and investigator reported lipodystrophy events relative to comparators through one to two years of treatment in treatment-naïve subjects. The impact of this favorable lipid profile on cardiovascular risk is unknown.

7.4.3 Special Safety Issues – Effects on ECG Parameters

In Vitro Studies

Safety pharmacology evaluations were first conducted to assess atazanavir's potential to prolong the QT interval. Atazanavir was tested *in vitro* at concentrations of 0, 3, 10, and 30 μM for effects on rabbit Purkinje action potentials. There was a dose-dependent increase in the mean action potential duration at 50% and 90% repolarization (24% and 13% at 30 μM, respectively); this is approximately four times the Cmax and 17 times the steady-state concentration in humans given ATV at 400 mg/day. Weak inhibition of sodium currents (IC50 > 30 μM) and moderate inhibition of calcium currents (IC50 of 10.4 μM) were also identified in *in vitro* studies. Other protease inhibitors evaluated simultaneously were found to alter action potential duration and ion currents with potency equivalent to or greater than that of ATV.

ATV was also evaluated in the *in vitro* IKr (HERG) and IKs potassium current assays along with several other HIV protease inhibitors for comparison. ATV produced weak inhibition of IKr current at concentrations up to 30 μM (15% at 30 μM); the IC50 was not established because only 15% inhibition was observed at the highest concentration.

Nelfinavir, saquinavir, and lopinavir inhibited IKr current amplitude with IC50s of 7.9, 17.6, and 22.0 μM, respectively. Indinavir and ritonavir were less active (IC50s > 30 μM) and inhibited IKr current at 30 μM by 23% and 46%, respectively. In the IKs assay, neither ATV, nor any of the PIs evaluated, produced significant inhibition of IKs current (IC50s > 30 μM).

No direct drug-related effects on cardiac function were noted in chronic dog studies of up to 9 months duration. Plasma concentrations of ATV at the high dose of 180 mg/kg/day in the 9-month toxicity study were up to three times the Cmax and seven times the AUC in humans given ATV at 400 mg/day.

Studies Assessing the Effects of Atazanavir on ECG Parameters in Healthy Subjects
Seven uncontrolled clinical studies were performed in healthy subjects to evaluate the effect of ATV exposure on ECG parameters and to evaluate potentially significant drug-drug interactions with regard to ECG parameters: 021, 039, 055, 057, and 058 at 400 mg QD, 056 at 300 mg in combination with ritonavir 100 mg QD, and 040 at three dose levels (200 mg, 400 mg and 800 mg QD). One placebo-controlled study (076) of 400 mg and 800 mg doses was also performed. This review will focus on study 076 as the design of this study facilitates more definitive evaluation of the effects of atazanavir on the QTc interval. For a complete review of these studies, please see Dr. J. Zheng's biopharmaceutics review.

In study 076, 12 ECGs were obtained over a 24 hour period on the day prior to first study drug administration and at steady-state (day 6), and included timepoints that corresponded to pre-dose, maximal QTc interval, and maximum concentration (Tmax).

QTc calculations were made using Bazett's correction or Fridericia's correction. Statistical analyses performed by the applicant were primarily on Delta QTc Max and Delta PR Max, as defined below:

- QTc Max was defined as the longest QTc interval recorded after dosing on each study day
- Baseline QTc Max was defined as the average of the QTc intervals recorded prior to study drug administration at the same clock time as QTc Max
- Delta QTc Max was defined as the difference between QTc Max and Baseline QTc Max
- PR Max was defined as the longest PR interval recorded after dosing on each study day
- Baseline PR Max was defined as the average of the PR intervals recorded prior to study drug administration at the same clock time as PR Max
- Delta PR Max was defined as the difference between PR Max and Baseline PR Max

Analysis of Effect of Atazanavir on the QTc and PR Interval – Study 076
This was a double-blind, randomized, placebo-controlled, multiple-dose, three-period, three-treatment crossover study, balanced for residual effects, in healthy subjects. Seventy-two (72) subjects were assigned subject numbers sequentially; each subject was

to receive the following three treatments (A, B, C) for 6 days with a washout period of 14 days between treatments, in one of six randomly assigned treatment sequences.

A: 4 x 200 mg matching placebo capsules QD.
B: 2 x 200 mg atazanavir capsules and 2 x 200 mg matched placebo capsules QD.
C: 4 x 200 mg atazanavir capsules QD.

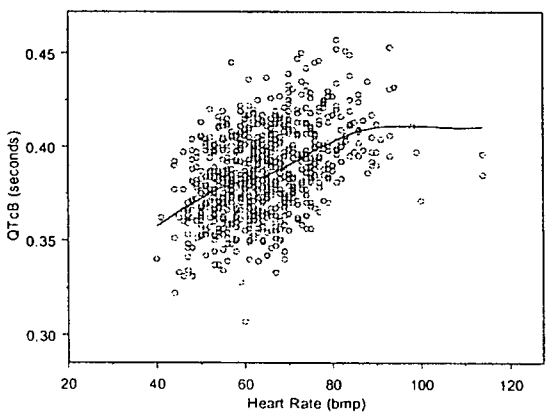
In this study, unlike previous studies designed to evaluate QTc changes, a dose dependent increase in heart rate was observed. This was likely detected due to the larger number of subjects enrolled and due to the minimum of 14 days required as a washout period between treatments. The mean change in heart rate from baseline at the 800 mg dose of atazanavir was about 8 msec and the mean change from placebo was about 6 msec.

The following table summarizes mean heart rates observed in study 076:

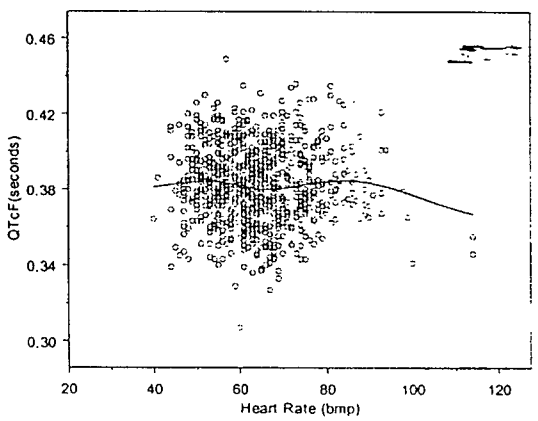
Treatment Period	Mean Heart Rate BPM (SE)
Pre-Study (Baseline)	63 (.36)
Placebo	64 (.37)
ATV 400 mg	66 (.36)
ATV 800 mg	70 (.34)

In the setting of dose dependent changes in heart rate, Fridericia's correction formula may be considered to be a more appropriate correction formula to use, as it provides a more consistent correction over a range of heart rates. The following two plots show the corrected QT interval plotted versus heart using all QTc values collected during the placebo treatment period in study 076:

QTc Intervals Versus Heart Rate Calculated with Bazett's and Fridericia's Correction Formulas



Bazett's



Fridericia's

Prior to the discovery that ATV administration was associated with a dose dependent increase in heart rate, all QTc calculations were made using Bazett's correction formula, a formula which tends to overcorrect the QT interval at higher heart rates, and undercorrect at lower heart rates. This formula was used in the development program of atazanavir as historically it has been used most frequently in evaluation of the QT interval. For the sake of completeness, changes in the QTc interval using both correction formulas will be presented.

QTc Interval - Bazett's Correction
The following table summarizes QTc changes using Bazett's correction.

Treatment A – Placebo
Treatment B – 400 mg atazanavir
Treatment C – 800 mg atazanavir

Summary of Results for the ANCOVA of QTcB Changes from Baseline					
	Treatments			Treatment Differences	
Delta QTcB (msec)	Adjusted Means			Point Estimate for Mean Differences (95% C.I.)	
	A	B	C	B-A	C-A
Delta QTcB Max	18.7	13.6	19.9	-5.1 (-9.2, -1.1)	1.2 (-2.9, 5.2)
Delta QTcB at Tmax	-13.2	-16.6	-5.3	-3.4 (-8.4, 1.7)	7.9 (2.8, 12.9)
Delta QTcB Avg	-2.5	-3.0	2.9	-0.5 (-3.4, 2.4)	5.4 (2.4, 8.3)

QTc Interval – Fridericia's Correction
The following table summarizes QTc changes using Fridericia's correction.

Summary of Results for the ANCOVA of QTcB Changes from Baseline					
	Treatments			Treatment Differences	
Δ QTcF (msec)	Adjusted Means			Point Estimate for Mean Differences (95% C.I.)	
	Placebo	400	800	400 - Placebo	800 - Placebo
Δ QTcF Max	12.2	6.1	8.8	-6.1 (-9.5, -2.7)	-3.4 (-6.8, <0.1)
Δ QTcF at Tmax	-8.8	-15.1	-8.3	-6.3 (-10.5, -2.1)	0.5 (-3.8, 4.7)
Δ QTcF Avg	-3.4	-6.4	-5.0	-3.0 (-5.6, -0.3)	-1.6 (-4.2, 1.1)

between 800 mg and placebo was 5.4 msec (95% CI 2.4, 8.3). The difference in the mean changes from baseline in the QTcB interval at Tmax was 7.9 msec (95% CI 2.8, 12.9).

Changes in mean QTcB intervals of > 5 msec are considered potentially clinically significant. While these signals were seen only at the 800 mg dose, co-administration of atazanavir with other medications metabolized by CYP 3A4 may lead to drug levels that could potentially result in significant prolongation of the QT interval.

When data from study 076 is analyzed using Fridericia's correction formula significant changes in QTc parameters are not observed. An analysis of covariance of QTcF changes from baseline showed that the placebo-corrected difference in the mean changes from baseline of the average QTcF interval between 800 mg and placebo was –1.6 msec (95% CI – 4.2, 1.1). The difference in the mean changes from baseline in the QTcF interval at Tmax was 0.5 msec (95% CI 0.5, 4.7).

Evaluation of the PR Interval

Study 076 and other PK studies conducted to evaluate the effects of atazanavir of ECG parameters revealed a dose dependent prolongation of the PR interval. The following table summarizes changes in the mean PR interval across the three dosing cohorts in study 076:

Changes in Maximum PR Interval And Incidence of First Degree AV Block – Study 076

Dose	# of Subjects	Baseline PR Max Mean (SD)	PR Max Mean (SD)	Δ PR Max from Baseline Mean (SD)	Subjects w/ AV block Evaluable/Total (%)
Placebo	67	154 (17)	166 (17)	13 (11)	1/67 (1)
400 mg	65	155 (19)	180 (18)	24 (15)	9/65 (14)
800 mg	66	152 (17)	212 (31)	60 (25)	39/66 (59)

The frequency of subjects with 1st degree AV-block (PR > 200 msec) was 3/72 (4%) prior to dosing, 1/67 (1%) for placebo, 9/65 (14%) for ATV at 400 mg, and 39/66 (59%) for ATV at 800 mg.

Eight subjects developed prolonged PR interval greater than 250 msec with increases over baseline ranging between 52 and 168 msec; all of these PR prolongations were observed at the 800 mg dose of atazanavir. No subjects were observed to have higher than first degree AV-block. The highest recorded PR interval was 328 msec in a female subject receiving 800 mg of atazanavir.

Analysis of Effect of a Ritonavir-Enhanced Dose of Atazanavir on the PR Interval – Study 056

Atazanavir is a cytochrome CYP3A substrate and inhibitor that undergoes hepatic and gut-associated elimination. Ritonavir, which is a potent inhibitor of the CYP3A enzyme, increases atazanavir exposure several-fold. Ritonavir has evolved in HIV therapy to become a pharmacologic enhancer of other drugs metabolized by the CYP3A enzyme in order to increase drug exposures, and as a result, increase the likelihood of treatment success. In addition, this approach helps decrease pill burden, and as a result, improves treatment compliance.

Atazanavir 400 mg when administered with 100 mg of ritonavir, produces atazanavir exposures similar to that seen when atazanavir is administered at a dose of 800 mg once daily. Due to the potential for PR and QT prolongation that was most apparent at the 800 mg dose in other PK studies, the applicant chose a 300 mg dose of atazavanir to co-administer with 100 mg of ritonavir. Use of this drug combination is currently undergoing evaluation in the phase 3 clinical study 045 for highly treatment experienced patients.

In this healthy volunteer study atazanavir 300 mg was administered once daily for ten days, followed by co-administration of atazanavir 300 mg/ritonavir 100 mg once daily for 10 days. When atazanavir 300 mg was co-administered with ritonavir 100 mg in this study, the atazanavir Cmax was increased by about 32% relative to atazanavir 400 mg once daily in study 040. The AUC was increased by about 2.5-fold. Changes in the PR Max are summarized in the following table:

Summary Statistics for Change from Baseline PR Max to PR Max

	Study Day		
	Day 10 (n=30)	**Day 15 (n=28)**	**Day 20 (n=28)**
Baseline PR Max (msec) Mean (SD)	156 (12)	157 (16)	156 (15)
PR Max (msec) Mean (SD)	174 (14)	176 (16)	187 (15)
Δ PR Max (msec) Mean (SD)	18 (10)	19 (16)	31 (38)

Five subjects out of thirty (17%) had at least one ECG with PR > 200 msec while receiving the ritonavir-boosted dose of atazanavir. One male subject had a PR interval of 358 msec on one occasion; this subject had no other ECGs with a PR > 200 msec.

Summary of ECG Evaluations in Pharmacokinetic Studies

In summary, following multiple, once-daily administrations of ATV alone to healthy subjects in the dose range of 200 mg to 800 mg, ATV was associated with a concentration-dependent prolongation of the PR interval. Maximum PR intervals included PR intervals of 324 msec and 458 msec in two females receiving 800 mg ATV.

Following multiple, once-daily administration of ATV alone to healthy subjects in the dose range of 200 mg to 800 mg, ATV was associated with a mild concentration-dependent effect on the QTc interval when analyzed using Bazett's correction formula. No significant changes in the QTc interval were observed when data was analyzed using Fridericia's correction formula, the more appropriate formula to use in the setting of a dose dependent increase in the heart rate. Subjects receiving atazanavir in phase 2 and 3 clinical trials did not appear to experience an excess of clinical events potentially related to prolongation of the QT interval as compared to subjects in comparator arms of these trials. Only two subjects in clinical trials of atazanavir have experienced QTc intervals greater than 500 msec, and both were receiving comparator regimens. No cases of torsades de pointes or sudden death have occurred in any trials conducted during the development of atazanavir.

Summary of Cardiovascular Evaluation in Clinical Trials
Phase 3 studies 043 and 045 (antiretroviral-experienced subjects) were designed to evaluate ECG parameters by obtaining a baseline ECG measurement prior to study drug administration and by measuring serial ECG parameters (pre-dose, 2-3 hours post-dose, and 6-12 hours post-dose) multiple times over the 48 week treatment period. However, these studies did not include a washout period prior to enrollment, and therefore, prior drugs may have influenced the baseline measurement.

The rollover phase 2 studies 007/041 and 008/044, and the phase 3 study of treatment-naive subjects (034), were amended to include ECG measurements. Three serial ECGs (pre-dose [trough], 2 -3 hours post-dose, and 6 - 12 hours post-dose) were collected. The interpretation of the ECG results was limited by two factors. First, no pre-study baseline measurement was available for comparison and in addition, many subjects had been receiving concomitant medications for various durations at the time of the ECG recordings. Secondly, the timing of the ECGs did not take into account diurnal variation.

In these five clinical studies, a total of 1773 subjects (1241 males and 532 females) had at least one ECG tracing performed. Of these 1773 subjects, 911 (619 males and 292 females) were receiving ATV at the recommended 400 mg dose. ECG results will be reviewed by study.

Study 034
Of randomized subjects, 678/810 subjects were evaluable for this ECG analysis. There were 353 (226 males and 127 females) assigned to ATV and 325 (221 males and 104 females) assigned to EFV.

QTc Interval: The potential of the study regimens to affect the QTc interval was assessed by cross-tabulations of the maximum QTc (Max QTc) observed on either of the ECG recordings taken after dosing. These cross tabulations are presented by regimen and gender, and use the following categories:

For males: $QTc \leq 430$, $430 < QTc \leq 450$, and $QTc > 450$ msec