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APPLICATION NUMBER:

21-567

MEDICAL REVIEW

NDA 21-567

Medical Review
NDA 21-567

Date submitted: **December 20, 2002**
Date Received: **December 26, 2002**
Date Assigned: **December 26, 2002**
Date Completed: **June 20, 2003**

Applicant: Bristol-Myers Squibb Pharmaceuticals
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660

Drug:
Generic: atazanavir
Trade: Reyataz®
Chemical: dimethyl (3S,8S,9S,12S)-9-benzyl-3,12-di-tert-butyl-8-hydroxy-4,11-dioxo-6-[4-(2-pyridyl)benzyl]-2,5,6,10,13-pentaazatetradecanedioate, sulfate (1:1)

Drug class: antiviral agent

Route of administration: oral

Dosage form: 100 mg, 150 mg, and 200 mg capsules

Proposed Indication: treatment of HIV infection

Related INDs: [redacted]

Related NDAs: None

Medical Reviewer: Kendall Marcus, M.D.

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Executive Summary

1 Recommendations

1.1 Recommendations on Approvability

Based on review of the data submitted by Bristol-Myers Squibb in support of NDA 21-567, it is recommended that this application for atazanavir capsules for once daily administration to HIV-1 infected patients, in combination with other antiretroviral agents, be approved.

In an intent-to-treat analyses, the percentage of patients achieving HIV viral load below limits of quantification at 48 weeks of treatment appeared to be similar between atazanavir as compared to efavirenz or nelfinavir in three studies of treatment-naïve subjects. In one treatment-experienced study of patients failing a PI-based regimen, atazanavir was inferior to lopinavir/ritonavir at 24 weeks; however, multiple analyses performed by FDA and the applicant indicated that atazanavir has activity in this population of patients.

Use of atazanavir appeared to be well-tolerated with relatively few subjects discontinuing for treatment-related adverse events potentially attributable to atazanavir use. Discontinuations due to treatment-related adverse events were infrequent; they included hyperbilirubinemia/jaundice, abnormal liver enzyme tests, rash/allergic reaction, lipodystrophy, lactic acidosis syndrome and peripheral neuropathy. In general, each of these events led to discontinuation of fewer than 1-2% of subjects. Some of these adverse events are currently attributed to the nucleoside analogue component of antiretroviral therapy. Other uncommon but clinically important events leading to study discontinuation of atazanavir-treated patients were hypertriglyceridemia, hyperglycemia, and cardiac conduction abnormalities.

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 to these observations, it was noted that patients

taking atazanavir-based regimens still occasionally developed severe elevations of lipids, particularly triglycerides. These observations suggest 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-based regimens.

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 (greater than 2.5 times the upper limit of normal) were observed in 20-47% of patients. As measured by commercially available assays, inhibition of UGT 1A1 resulted in a predominantly indirect hyperbilirubinemia that was reversible with discontinuation of atazanavir; in the absence of concurrent hepatic injury or inflammation, elevations in direct bilirubin were minimal regardless of the degree of indirect hyperbilirubinemia observed.

Hyperbilirubinemia did not appear to be associated with an increased risk of hepatic injury. Discontinuations and/or deaths due to hepatic injury 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 $\leq$ 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.

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. A placebo-controlled, three-treatment, three-period crossover study of healthy volunteers did not show any significant effect of atazanavir on the QT interval. In addition, 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 concnetration 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 the most common ECG abnormality observed; it was observed in 5.9% of atazanavir-treated subjects (n=920), 5.2% of lopinavir/ritonavir treated patients (n=252), 10.4% of nelfinavir-treated patients (n=48), and in 3.0% of efavirenz-treated patients (n=329).

A 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 the abnormalities observed on ECG resolved after five days.

In the expanded access study 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 drug-drug interaction study of atazanavir and diltiazem revealed additive effects on the PR interval and increased levels of diltiazem.

In summary, while pharmacokinetic studies revealed a concentration and dose dependent prolongation of the PR interval, significant clinical events were uncommon and appeared to occur in the setting of high atazanavir exposures. Asymptomatic first degree AV block was the most common abnormality observed.

And finally, approval of this application will allow patients access to a protease inhibitor that needs to be taken only once daily and has a low "pill burden" (two pills each day). For selected patients, this may positively impact treatment compliance, and as a result, treatment success.

1.2.1 Recommendations on Postmarketing Studies

The applicant has agreed to complete the following phase IV commitments:

Microbiology:

1) Submit analysis of protease cleavage sites in ATV- resistant patients from ongoing studies 034, 043 and 045.

2) Test the activity *in vitro* of atazanavir against multiple clinical isolates of non-clade B subtypes of HIV-1 and HIV-2.

Pharmacology/Toxicology:

3) Complete ongoing carcinogenicity studies in mice and rats and submit final reports.

Clinical Pharmacology:

4) Conduct drug-drug interaction study to explore dosing recommendations for the coadministration of atazanavir and nevirapine and of atazanavir/ritonavir and nevirapine.

5) Evaluate the pharmacokinetics of atazanavir when co-administered with histamine H2 receptor antagonist.

6) Evaluate the pharmacokinetics and safety of atazanavir when coadministered with interferon and ribavirin in patients infected with hepatitis C virus.

7) Determine, *in vivo*, the extent to which atazanavir inhibits CYP1A2 or CYP2C9, preferably with warfarin, or with theophylline.

8) Conduct a pharmacokinetic study of atazanavir in subjects with renal impairment to allow the determination of dosing for this population..

Clinical

9) Assess the long term antiviral efficacy and safety of atazanavir in ARV treatment naive and stable switch patients through the conduct of studies -034, -044, -041 and -067.

10) Assess the efficacy and safety of atazanavir when pharmacokinetically boosted with low dose ritonavir in protease inhibitor treatment naive patients.

11) Using objective measurements (e.g., DEXA and CT scanning, etc.) evaluate the role of atazanavir in fat redistribution through 96 weeks of therapy through the conduct of studies -034/-077 (DEXA and CT scan) and -043 (CT scan).

12) Evaluate the suspected protease inhibitor class-associated effects of fat redistribution and metabolic abnormalities through the conduct of studies -034/-077 and -043.

13) Follow a cohort of patients who failed on ATV treatment and developed the I50L mutation on new physician-selected PI regimens for 48 weeks compared to an NNRTI-failure/PI-naïve patient cohort and determine treatment response, baseline genotypes and phenotypes, and genotypes and phenotypes of virologic failures.

Chemistry:

14) A test (USP<781>) for optical rotation will be developed by fourth quarter 2003. Data will begin to be collected for all commercial batches. Once sufficient data are generated, the data will be reviewed to determine a numerical acceptance criterion and drug substance specification will be updated accordingly.

2 Summary of Clinical Findings

2.1 Overview of Clinical Program

Proposed Trade name:	Reyataz®
Generic name:	atazanavir
Formulation:	100 mg, 150 mg, and 200 mg capsules
Dosage:	400 mg by mouth, once daily
Indication:	Reyataz™, in combination with other antiretroviral agents, is indicated for the treatment of HIV-1 infection.

The submitted application contained safety and efficacy information from twenty-four clinical pharmacology studies conducted in healthy subjects with the capsule formulation and two studies conducted in special populations (young/elderly, male/female and hepatically-impaired subjects) to guide dosing in these subjects.

Ten clinical studies conducted by the applicant and one study conducted by the Pediatric AIDS Clinical Trial Group comprise the core clinical program of this application. In addition to these studies, data from four small studies conducted by other sponsors were submitted in support of this application.

Following completion of initial phase 1 pharmacokinetic and safety studies, the applicant conducted two phase 2 dose-finding studies. In study AI424007 (007), 420 treatment-naïve subjects were randomized to receive either atazanavir 200 mg, 400 mg, or 500 mg once daily or nelfinavir 750 mg tid, each in combination with didanosine and stavudine. This trial was blinded only to atazanavir dose. In a second phase 2 dose-finding study, AI424008 (008), 467 subjects were randomized to receive atazanavir 400 mg, atazanavir 600 mg or nelfinavir 1250 mg bid, each in combination with stavudine and lamivudine. This study was also blinded only to atazanavir dose.

A small phase 2 study of treatment-experienced subjects compared atazanavir 400 mg and 600 mg, each given with saquinavir 1200 mg once daily, to ritonavir 400 mg/saquinavir 400 mg given twice daily. Each treatment arm was administered with a background of two NRTIs.

Two rollover studies were conducted for patients completing phase 2 studies in order to collect long-term safety data. Subjects completing studies 007 and 009 were enrolled in AI424041 (041). In this study, patients receiving atazanavir in study 007 were assigned to receive open-label atazanavir 400 mg. Patients receiving nelfinavir in study 007

continued on the same regimen. Patients completing treatment in 009 continued to receive their previously assigned regimen in 041.

Subjects completing study 008 were given the option to enroll in study 044. In this study subjects originally assigned to atazanavir continued on the same regimen, while subjects receiving nelfinavir were switched to atazanavir. This was done in order to assess changes in lipid profiles after 72 weeks of nelfinavir therapy. A total of 346/467 patients originally enrolled in study 008 enrolled in study 044.

Phase 3 studies included AI424034 (034) and AI424043 (043). Study 034 was a multinational, randomized, double-blind, double-dummy, active-controlled, two-arm study comparing atazanavir to efavirenz for the treatment of ARV-naïve subjects. A total of 810 subjects were randomized to receive either atazanavir 400 mg QD, efavirenz placebo and fixed-dose ZDV/3TC (Combivir®) or efavirenz 600 mg QD, atazanavir placebo and Combivir®. Combivir® was administered open label. Antiviral response was assessed through 48 weeks of treatment.

Study 043 was a randomized, multinational, open-label, active-controlled, two-arm study in subjects who had failed protease inhibitor based ARV regimens. A total of 300 subjects were randomized to receive either atazanavir or lopinavir/ritonavir in combination with two NRTIs. The selection of NRTIs was based on phenotypic susceptibility data for the subject's viral isolate obtained at the screening visit and the physician's choice at the time of randomization. Twenty-four week data for 229 of the 300 randomized subjects was provided in the initial NDA submission, and twenty-four week data on all subjects was provided in a safety update submitted 2 months into the review clock.

Study AI424045 (045) is a randomized, multinational, open-label, active-controlled, three arm study of highly treatment-experienced patients who had failed at least two ARV regimens containing drugs from all three classes at the time of enrollment. A total of 357 patients were randomized in this study. Data on efficacy through 16 weeks of therapy for approximately 100 subjects was submitted with the NDA. Sixteen week safety and efficacy data for all randomized subjects was submitted with a safety update provided two months into the six month review clock; this data was reviewed for safety, but not specifically for efficacy.

Other studies presented in this application include a pediatric study conducted by the PACTG, an expanded access protocol, and four small collaborative studies conducted by other sponsors. These studies are described elsewhere in this review. Key studies reviewed in this application are summarized in the following table:

Summary of Clinical Trials

Study	Design	Regimens (mg)	Comparator (mg)	Background	# Randomized	Pt Population	Endpoint
007	Randomized Blinded to ATV dose	ATV 200 400 500	Nelfinavir 750 tid	ddI/d4T	420	Treatment naive	TAD* in log10 HIV RNA Δ from B/L
008	Randomized Blinded to ATV dose	ATV 400 600	Nelfinavir 1250 bid	d4T/3TC	467	Treatment naive	TAD
009	Randomized	ATV 400 SQV 1200 ATV 600 SQV 1200	RTV 400 SQV 400	Optimized background	85	Treatment experienced	TAD
041	Rollover study for 007 and 009 to collect long-term safety data	ATV 400	NFV 750 tid	Background therapy received in previous trial	222	Subjects completing 007 and 009	Collection of long-term safety data
044	Rollover study for 008 to collect additional safety data	ATV 400 ATV 600	Patients receiving NFV in 008 switched to ATV 400 to assess lipids	Background therapy received in previous study	346	Subjects completing study 008	Collection of long-term safety data
034	Randomized Double-blind Placebo controlled	ATV 400	EFV 600 mg	AZT/3TC	810	Treatment naïve	Percent BLQ
043	Randomized Open-label	ATV 400	LPV/RTV	Optimized background of 2 NRTIs	300	Patients who failed a PI regimen	TAD
045	Randomized Open-label	ATV 300 RTV 100 ATV 400 SQV 1200	LPV/RTV	Tenofovir and 1 NRTI based on results of phenotypic testing	358	Highly treatment experienced patients having failed drugs in all three classes	TAD
900	Expanded Access Protocol	ATV 400 ATV 300 RTV 100	None	Based on physician choice		Open enrollment	None
020	Pediatric	ATV dose ranging	None	Based on MD choice	48	Age 3 mo to 21 years	PK/PD and safety

*TAD – Time-averaged difference from baseline

2.2 Efficacy Summary

The applicant has demonstrated in three clinical trials of ARV treatment-naive patients that atazanavir, when added to a background regimen of two nucleoside reverse transcriptase inhibitor (NRTIs), produces a statistically and clinically significant reduction in HIV viral load, including a significant increase in the proportion of patients whose HIV viral load is undetectable by Roche Amplicor assays. This clinical benefit is sustained through at least 48 weeks.

The trials were conducted across several continents within a diverse adult population. There was no convincing evidence that the observed clinical benefit is reduced in any of the racial, gender, or age categories examined.

The applicant tested atazanavir for 24 weeks in one trial with patients who had failed at least one regimen containing a protease inhibitor. In that trial, atazanavir was statistically and clinically significantly inferior to Kaletra® when each was added to a background regimen of two NRTIs. Meta-analysis supports the inference that atazanavir would have been superior to placebo with respect to the proportion of subjects whose HIV viral load was undetectable had it been ethical to include such an arm in the trial.

There was no convincing evidence in this experienced population that atazanavir effects differed significantly among racial, gender, or age categories.

2.3 Safety Summary

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 highly active antiretroviral therapy (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 373 treatment-experienced subjects. Over 200 subjects received doses that provided exposures greater than that of the 400 mg target dose. In addition, 48 pediatric subjects were enrolled in the PACTG study, and 170 subjects were enrolled in four collaborative studies and one early access program.

Use of atazanavir appeared to be well-tolerated with relatively few subjects discontinuing for treatment-related adverse events potentially attributable to atazanavir use. Discontinuations due to treatment-related adverse events were infrequent; they included hyperbilirubinemia/jaundice, abnormal liver enzyme tests, rash/allergic reaction, lipodystrophy, lactic acidosis syndrome and peripheral neuropathy. In general, each of

these events led to discontinuation of fewer than 1-2% of subjects. Some of these adverse events are currently attributed to the NRTI background of HAART. Other clinically important events leading to discontinuation of atazanavir-treated patients were hypertriglyceridemia, hyperglycemia, and cardiac conduction abnormalities.

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

Subjects receiving atazanavir frequently reported jaundice/scleral icterus; these events were uncommon in subjects receiving comparator regimens. 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 often in atazanavir-treated subjects as compared to efavirenz.

Three areas of concern with regards to safety emerged during the atazanavir development program. The first is the frequency of hyperbilirubinemia seen in atazanavir-treated subjects; this adverse event is dose dependent and appears to be due to inhibition of UDP-glucuronosyl transferase 1A1, an enzyme responsible for the conjugation of bilirubin. In clinical trials over three-fourths of all patients experienced an elevation of bilirubin while taking atazanavir, and approximately five percent of patients experienced grade 4 increases (five times the upper limit of normal) resulting in a protocol-mandated dose reduction. Dose reduction as a management strategy will not be recommended for clinical practice due to insufficient data on the efficacy of a reduced dose.

Treatment discontinuations for jaundice and/or scleral icterus were uncommon despite a 15-20% incidence of these events. 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.

The hyperbilirubinemia observed in atazanavir-treated subjects was predominantly indirect, regardless of the degree of hyperbilirubinemia observed. Significant elevations of direct bilirubin appeared to occur predominantly in association with other indices of hepatic injury or inflammation.

In two phase 2 studies that compared atazanavir to nelfinavir, each with identical NRTI background therapy, the frequency of all grades of transaminase elevations was higher in atazanavir arms. The incidence of grade 3-4 transaminase elevations was higher in atazanavir arms in one of these studies, but lower in atazanavir arms in the second study. When treatment arms from the two studies were combined, discontinuations for liver enzyme abnormalities was similar between atazanavir and nelfinavir treated subjects.

In the phase 3 study 034 that compared atazanavir to efavirenz in treatment-naïve patients, the incidence of all grades of transaminase abnormalities was similar between the two treatments. In the phase 3 study 043 of treatment-experienced patients, atazanavir subjects experienced more grade 3-4 LFT elevations than lopinavir/ritonavir subjects. Although there was an imbalance in hepatitis B or C co-infection between treatment arms (ATV 20%, LPV/RTV 12%), this did not explain the differences. Slight differences in background NRTI therapy also existed in this study, with use of ddI and d4T being slightly more common in atazanavir subjects. In the phase 3 study 045 of highly treatment experienced patients grade 3-4 abnormalities were comparable between ATV/RTV, ATV/SQV and LPV/RTV-treated subjects.

Discontinuations due to hepatitis or liver enzyme abnormalities (excluding lactic acidosis syndrome/symptomatic hyperlactatemia [LAS/SHL] cases) appeared to occur with similar frequency between atazanavir and comparator regimens. One percent of subjects receiving any dose of atazanavir and one percent of subjects receiving a comparator regimen discontinued for hepatitis or liver enzyme abnormalities.

In summary, the hyperbilirubinemia seen during the development program of atazanavir appeared to be unconjugated (in the absence of concurrent hepatotoxic or inflammatory processes), was well tolerated by patients and did not appear to result in an increased incidence of hepatotoxicity relative to selected PIs or to efavirenz.

The second area of concern is effects of atazanavir on ECG parameters. 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. In addition, 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.

Evaluation of the effects of atazanavir on the PR interval in the previously described study did reveal moderate dose-dependent prolongation of the PR interval. The following table summarizes mean changes in the maximum PR interval and the incidence of first degree AV block seen in this healthy volunteer study:

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)

In the five phase 2 and 3 clinical trials that collected ECG data, first degree heart block was seen in 54 of 920 subjects (5.8%) receiving the recommended 400 mg dose of atazanavir. This incidence is comparable to that seen for protease inhibitor comparators: 5.2% for subjects receiving lopinavir/ritonavir and 10% for subjects receiving nelfinavir. It is higher than the incidence observed in subjects receiving efavirenz (3%).

The ACC/AHA/NASPE 2002 Guidelines for Implantation of Cardiac Pacemakers and Antiarrythmic Devices recommend pacemaker placement for first degree AV block greater than 300 msec in patients with left ventricular dysfunction and symptoms of congestive heart failure; in these patients a shorter AV interval results in hemodynamic improvement. PR interval prolongations of this magnitude were uncommon in clinical trials of atazanavir 400 mg, with a PR interval greater than 300 msec being observed on one occasion in one subject.

PR intervals of this magnitude were observed on several occasions in healthy volunteer pharmacokinetic studies. In a drug-drug interaction study of atazanavir and diltiazem, one subject receiving 400 mg atazanavir concomitantly with 180 mg diltiazem was observed to have a PR interval greater than 300 msec; this was likely due to a combination of PR interval prolongation due to elevated levels of diltiazem and prolongation of the PR interval by atazanavir. Two healthy volunteers receiving 800 mg atazanavir and one healthy volunteer receiving atazanavir/ritonavir 300/100 were observed to have PR intervals greater than 300 msec.

Cardiac conduction abnormalities other than first degree AV block that were potentially attributable to atazanavir were also uncommon. In clinical trials, one subject who intentionally ingested approximately 29 gm of atazanavir developed a severely prolonged PR interval and bifascicular block that resolved five days following withdrawal of treatment. Another patient receiving atazanavir through the expanded access protocol was hospitalized with a junctional rhythm eleven days after starting ARV therapy with atazanavir (CYP 3A inhibitor), delavirdine (CYP 3A inhibitor), lamivudine and tenofovir, while concomitantly receiving verapamil (CYP3A substrate) for hypertension. 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 concomitant use of CYP3A substrates, particularly calcium channel blockers. In study 034 bundle branch block was reported in one ATV subject and one EFV subject; neither of these events were reported as significant adverse events or resulted in discontinuation from study.

In summary, while pharmacokinetic studies designed to evaluate effects of atazanavir revealed moderate dose dependent prolongation of the PR interval, clinical events were uncommon. Asymptomatic first degree AV block was the most common ECG abnormality observed. It is likely that this effect of atazanavir will impact predominantly those patients who develop high serum concentrations of atazanavir, particularly those with significant left ventricular dysfunction or pre-existing cardiac conduction abnormalities.

And finally, atazanavir does not appear to be associated with the hyperlipidemia that is commonly observed with use of other protease inhibitor or efavirenz-containing 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.

2.4 Dosing, Regimen, and Administration

Reyataz® will be indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents. Patients will take two 200 mg capsules once daily with food.

Efficacy of a 400 mg dose was not found to be significantly different from the efficacy of a 500 mg or 600 mg dose, and had a more favorable adverse event profile in terms of the incidence of hyperbilirubinemia. Atazanavir 400 mg QD was found to be inferior to lopinavir/ritonavir in a trial of PI-experienced patients, although multiple analyses showed that it still had activity in this population of patients. A ritonavir-boosted dose of atazanavir (ATV/RTV 300/100) is currently undergoing evalution in a phase 3 trial of highly treatment experienced patients.

2.5 Drug-Drug Interactions

Please see Dr. Jenny Zheng's review for detailed information regarding drug-drug interactions. Atazanavir is metabolized in the liver by CYP3A and is a competitive inhibitor of CYP3A at clinically relevant concentrations. In addition, it also an inhibitor of UGT1A1. Drugs that induce CYP3A activity such as rifampin may be expected to lower atazanavir plasma concentrations and drugs that inhibit CYP3A such as ritonavir may be expected to increase atazanavir plasma levels. In addition, coadministration of atazanavir and other drugs metabolized by CYP3A (i.e. calcium channel blockers, HMG-CoA reductase inhibitors, immunosuppressants, sildenafil) may result in increased plasma concentrations of these other drugs.

Atazanavir was extensively evaluated in pharmacokinetic studies for the potential for clinically significant drug interactions with a variety of medications. The results of these studies are summarized in the following two tables:

Drug Interactions: Pharmacokinetic Parameters for Reyataz® in the Presence of Coadministered Drugs (3A4 inhibitor, inducer, substrate or drugs affecting PR intervals)					
Coadministered Drug	**Coadministered Drug Dose/Schedule**	**Reyataz® Dose/Schedule**	**n**	**Ratio (90% Confidence Interval) of Reyataz® Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00**	
				C_{max}	**AUC**
Atenolol (prolongs PR interval)	50 mg QD, d 7-11 and d 19-23	400 mg QD, d 1-11	19	1.00 (0.89, 1.12)	0.93 (0.85, 1.01)
clarithromycin	500 mg QD, d 7-10 and d 18-21	400 mg QD, d 1-10	29	1.06 (0.93, 1.20)	1.28 (1.16, 1.43)
didanosine (ddI) (buffered tablets) plus stavudine (d4T)	ddI: 200 mg x 1 dose, d4T: 40 mg x 1 dose	400 mg x 1 dose simultaneously with ddI and d4T	32[a]	0.11 (0.06, 0.18)	0.13 (0.08, 0.21)
	ddI: 200 mg x 1 dose, d4T: 40 mg x 1 dose	400 mg x 1 dose 1 hour after ddI + d4T	32[a]	1.12 (0.67, 1.18)	1.03 (0.64, 1.67)
Diltiazem (prolongs PR interval)	180 mg QD, d 7-11 and d 19-23	400 mg QD, d 1-11	30	1.04 (0.96, 1.11)	1.00 (0.95, 1.05)
Efavirenz (3A4 inducer)	600 mg QD, d 7-20	400 mg QD, d 1-20	27	0.41 (0.33, 0.51)	0.26 (0.22, 0.32)
efavirenz and ritonavir	efavirenz 600 mg QD 2 h after Reyataz® and ritonavir 100 mg QD simultaneously with Reyataz®, d 7-20	400 mg QD, d 1-6 then 300 mg QD d 7-20	13	1.14 (0.83, 1.58)	1.39 (1.02, 1.88)
Ketoconazole (3A4 inhibitor)	200 mg QD, d 1-13	400 mg QD, d 7-13	14	0.99 (0.77, 1.28)	1.10 (0.89, 1.37)
Rifabutin (3A4 inducer)	150 mg QD, d 15-28	400 mg QD, d 1-28	7	1.34 (1.14, 1.59)	1.15 (0.98, 1.34)
Ritonavir (3A4 inhibitor)	100 mg QD, d 11-20	300 mg QD, d 1-20	28	1.86 (1.69, 2.05)	3.38 (3.13, 3.63)
[a] One subject did not receive Reyataz®					

Drug Interactions: Pharmacokinetic Parameters for Coadministered Drugs (3A4 substrates, drugs affecting PR intervals) in the Presence of Reyataz®					
Coadministered Drug	Coadministered Drug Dose/Schedule	Reyataz® Dose/Schedule	n	Ratio (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters with/without Reyataz®; No effect = 1.00	
				C_{max}	AUC
Atenolol (prolongs PR interval)	50 mg QD, d 7-11 and d 19-23	400 mg QD, d 1-11	19	1.34 (1.26, 1.42)	1.25 (1.16, 1.34)
Clarithromycin (prolongs QT interval)	500 mg QD, d 7-10 and d 18-21	400 mg QD, d 1-10	21	1.50 (1.32, 1.71) OH-clarithromycin: 0.28 (0.24, 0.33)	1.94 (1.75, 2.16) OH-clarithromycin: 0.30 (0.26, 0.34)
Didanosine (ddI) (buffered tablets) plus stavudine (d4T)	ddI: 200 mg x 1 dose, d4T: 40 mg x 1 dose	400 mg x 1 dose simultaneous with ddI and d4T	32[a]	ddI: 0.92 (0.84, 1.02) d4T: 1.08 (0.96, 1.22)	ddI: 0.98 (0.92, 1.05) d4T: 1.00 (0.97, 1.03)
Diltiazem (prolongs PR interval)	180 mg QD, d 7-11 and d 19-23	400 mg QD, d 1-11	28	1.98 (1.78, 2.19) desacetyl-diltiazem: 2.72 (2.44, 3.03)	2.25 (2.09, 2.16) desacetyl-diltiazem: 2.65 (2.45, 2.87)
ethinyl estradiol & norethindrone	Ortho-Novum® 7/7/7 QD, d 1-29	400 mg QD, d 16-29	19	ethinyl estradiol: 1.15 (0.99, 1.32) norethindrone: 1.67 (1.42, 1.96)	ethinyl estradiol: 1.48 (1.31, 1.68) norethindrone: 2.10 (1.68, 2.62)
Rifabutin (3A4 substrate)	300 mg QD, d 1-10 then 150 mg QD, d 11-20	600 mg QD[b], d 11-20	3	1.18 (0.94, 1.48) 25-O-desacetyl-rifabutin: 8.20 (5.90, 11.40)	2.10 (1.57, 2.79) 25-O-desacetyl-rifabutin: 22.01 (15.97, 30.34)
Saquinavir (soft gelatin capsules)	1200 mg QD, d 1-13	400 mg QD, d 7-13	7	4.39 (3.24, 5.95)	5.49 (4.04, 7.47)
Lamivudine + zidovudine	150 mg lamivudine + 300 mg zidovudine BID, d 1-12	400 mg QD, d 7-12	19	lamivudine: 1.04 (0.92, 1.16) zidovudine: 1.05 (0.88, 1.24) zidovudine glucuronide: 0.95 (0.88, 1.02)	lamivudine: 1.03 (0.98, 1.08) zidovudine: 1.05 (0.96, 1.14) zidovudine glucuronide: 1.00 (0.97, 1.03)

[a] One subject did not receive Reyataz®.
[b] Not the recommended therapeutic dose of atazanavir.

2.6 Special Populations

2.6.1 Race and Gender

Efficacy
Clinical trials were conducted across several continents within a diverse adult population. There was no convincing evidence in treatment-naïve or in treatment-experienced studies that the observed clinical benefit is reduced in any of the racial or gender categories examined.

Safety
Sub-population analyses were performed for adverse events of all grades, serious adverse events, adverse events leading to treatment discontinuation, and laboratory test parameters. Clinically relevant differences between gender and race are summarized here.

In general, men and women receiving atazanavir experienced comparable AE profiles; however, males had higher incidences of the following AEs compared with females: peripheral neurologic symptoms (13% vs. 4%), jaundice (12% vs. 4%), and fatigue (11% vs. 4%). Grade 3 - 4 AEs were infrequent for both genders. Males reported a greater than 1% difference compared with females for the following Grade 3 - 4 events: jaundice (2% vs. 0%) and headache (2% vs. 0%).

Females tended to have more frequent hematologic abnormalities than males (low hemoglobin, 16% vs. 2%; low WBC, 43% vs. 24%). Males were found to have more frequent ALT (41% vs. 28%), AST (38% vs. 26%), CK (21% vs. 13%), amylase (22% vs. 14%), and serum uric acid (11% vs. 1%) abnormalities than females. Males also reported higher incidences of total cholesterol (51% vs. 39%) and triglyceride (40% vs. 13%) abnormalities and hyperglycemia (17% vs. 7%) than females.

In general, there were no discernable differences among racial groups for SAEs or adverse events leading to treatment discontinuation.

Asian/Pacific Islanders had higher incidences of headache (38% vs. 11% - 22%), lipodystrophy (15% vs. 4% - 9%), fever (15% vs. 6% - 7%), and allergic reaction (15% vs. 0% - < 1%) than other racial groups.

Black/mixed subjects had higher incidences of hemoglobin (13% vs. 0% - 5%), WBC (40% vs. 8% - 32%), neutrophil (33% vs. 8% - 18%), CK (31% vs. 8% - 19%), and serum uric acid (26% vs. 4% - 15%) abnormalities, and hyperglycemia (28% vs. 8% - 16%) than other racial groups. Asian/Pacific Islanders had a higher incidence of lipase abnormalities (23% vs. 11% - 15%), total bilirubin (92% vs. 75% - 77%) and total cholesterol (62% vs. 39% - 53%) elevations than other racial groups.

2.6.2 Pediatrics

A pharmacokinetic and safety study of the pediatric HIV-infected population is currently being conducted by the Pediatric AIDS Clinical Trial Group. A total of 48 subjects have been enrolled. Unfortunately, due to the wide variability of pharmacokinectic data accumulated to date, dosing has not yet been defined for any age group. At this time, the safety profile of atazanavir in pediatric patients appears generally similar to that in adults.

2.6.3 Renally and Hepatically-Impaired Patients

Renal Impairment
No studies were performed to examine the rate of elimination of atazanavir after administration to renally impaired patients. In addition it is unknown what percentage of the absorbed dose (as opposed to the administered dose) of atazanavir is renally excreted; As a result, no recommendations will be made in product labeling for dosing of atazanavir in patients with decreased creatinine clearance. However, as this drug is predominantly excreted through other pathways, it is not expected that renal impairment will significantly impact atazanavir exposures.

Hepatic Impairment
Atazanavir has been studied in adult patients with moderate to severe hepatic impairment (14 Child-Pugh Class B and 2 Class C subjects) after a single 400-mg dose. The mean AUC and mean half-life were 42% and 88% greater in patients with impaired hepatic function than in healthy subjects. On this basis, a dose of ATV 300 mg once-daily will be recommended for patients with moderate or severe hepatic impairment.

2.6.4 Pregnancy
Atazanavir has been assigned pregnancy category B. At maternal doses producing the systemic drug exposure levels equal to (in rabbits) or two times (in rats) those at the human clinical dose (400 mg/day), atazanavir did not produce teratogenic effects. At maternally toxic drug exposure levels two times those at the human clinical dose, atazanavir caused body weight loss or weight gain suppression in the offspring.

Hyperbilirubinemia occurred in most patients undergoing treatment with atazanavir. It is not known if administration to the mother during pregnancy will exacerbate physiological hyperbilirubinemia and lead to kernicterus in neonates and young infants.

There are no adequate and well-controlled studies of atazanavir in pregnant women. A number of women became pregnant while receiving atazanavir in clinical trials. In general, women who carried their pregnancies to term received atazanavir for 4-6 weeks while pregnant. When pregnancy was diagnosed, they were discontinued from study and received other medications as prescribed by their physicians for the remainder of the pregnancy. No maternal or fetal complications were reported in this group of women.

Two women enrolled in clinical trials of atazanavir became pregnant on study and received atazanavir for at least 36 weeks while pregnant; each woman delivered a healthy

infant. One woman receiving atazanavir in combination with didanosine and stavudine developed a clinical syndrome consistent with lactic acidosis, as well as other medical problems, shortly following delivery. Atazanavir should be used in pregnancy only if the potential benefit justifies the potential risk.

2.6.4 **Age**

In a pharmacokinetic study of young versus elderly subjects, there were no clinically important pharmacokinetic differences observed due to age. In a safety analysis, age could not be evaluated because there were few subjects > 65 years of age in enrolled in clinical studies.

Clinical Review

1 Introduction and Background

1.2 Established and Proposed Trade Name of Drug, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

This application is for the protease inhibitor atazanavir, which has the approved trade name of Reyataz®. The sponsor submitted this application to support the indication for Reyataz® for the treatment of HIV-1 infection in combination with other antiretroviral agents. The proposed dose is two 200 mg capsules once daily with food. This medication should be administered in combination with other antiretroviral agents as part of highly active antiretroviral therapy (HAART).

1.3 State of Armamentarium for Indication

There are currently 17 drugs approved for the treatment of HIV infection. Despite the advances made in the treatment of HIV disease with the advent of HAART and the marked decrease in mortality due to HIV disease observed in the USA over the past 7 years, treatment success remains limited by acute and chronic toxicities of antiretroviral agents, increasing drug resistance and due to issues related to adherence.

With regard to adherence, it has been found that missing from at least one out of four doses of medication to as few as one out of twenty doses may result in reduced efficacy of a treatment regimen. Compliance in turn can be influenced by side effects, the dosing schedule of a regimen, food restrictions, and the number of pills (pill burden) that a patient must take each day.

Simplifying treatment regimens so that they need to be taken only once a day has been postulated by some physicians caring for HIV-infected patients to be a reasonable approach to improve compliance. In addition, it is thought that a once-daily regimen will also facilitate the administration of directly observed therapy (DOT), a treatment strategy that has resulted in improved outcomes and decreased transmission rates for tuberculosis.

One concern, however, is that missing the dose of a once-daily medication may put patients at greater risk of developing drug resistance as compared to the risk associated with missing a single dose of a twice daily medication. Subjects on once daily regimens may experience failure rates that are higher than those experienced by subjects receiving regimens that are dosed more frequently. To date, there has been no evidence substantiating that once daily regimens lead to greater compliance than other regimens.

1.4 Important Milestones in Product Development

The IND for atazanavir was first submitted to FDA in September 1998. After completing phase 1 safety and pharmacokinetic studies, phase 2 dose-finding studies were initiated in March 1999; a dose of 400 mg once daily was chosen as a result of these studies. The first phase 3 study of treatment-naïve subjects was initiated in February 2001. At an end-of-phase meeting held on April 17, 2001, FDA and the applicant agreed upon the general design of two other phase 3 studies; a study of atazanavir 400 mg QD in PI-experienced subjects and a phase 3 study of ATV/RTV 300/100 and ATV 400/SQV 1200 in highly-treatment experienced subjects having failed ARV containing drugs from all three classes. A pre-NDA meeting was held in July 2002. At that time, it was determined that the applicant had sufficient safety and efficacy data to submit the NDA, with the exception of an adequately designed pharmacokinetic study evaluating the effects of atazanavir on the QT interval. The applicant agreed to conduct such a study and submit it no later than two months into the review clock of the NDA.

1.5 Important Issues with Pharmacologically Related Agents

Acute and chronic toxicities associated with protease inhibitor administration include liver enzyme abnormalities, hepatotoxicity, hyperlipidemia, fat redistribution and impaired glucose tolerance/diabetes. Atazanavir appears to have less of an effect on lipid profiles than other protease inhibitors. Other class effects of these medications appear to occur with similar frequency in atazanavir-treated subjects over one to two years of treatment. These adverse events are discussed in greater detail in the safety section of this review.

2 Significant Findings from Chemistry, Animal Pharmacology/Toxicology, and Microbiology

2.1 Chemistry

Please see Dr. Dan Boring's review for detailed information regarding the chemistry, manufacturing, and controls of Reyataz®.

The chemical name for atazanavir sulfate is (3S,8S,9S,12S)-3,12-Bis(1,1-dimethylethyl)-8-hydroxy-4,11-dioxo-9-(phenylmethyl)-6-[[4-(2-pyridinyl)phenyl]methyl]- 2,5,6,10,13-pentaazatetradecanedioic acid dimethyl ester, sulfate (1:1). Its molecular formula is C38H52N6O7 •H2SO4, which corresponds to a

While the plasma exposures were less dose-responsive, the metabolic profiles between animals and humans and presence of major metabolites in both were shown to be somewhat similar. Thus, additional utility of the animal toxicity studies may be justified here regarding concerns on the safety profile of those metabolites present in humans upon which information gained from the animal studies could be considered useful.

The atazanavir induced-hyperbilirubinemia in patients has triggered significant medical attention paid to concurrent liver enzyme increases during clinical trials and concerns over the drug's potential to produce more severe liver necrosis, and even total liver failure. Safety data from the animal studies appeared to support clinical findings that hepatotoxicity is a cross-species phenomenon; in rats and dogs this occurred in a dose-proportional and treatment duration-proportional manner.

This NDA has provided adequate preclinical safety information in support of its approval. The sponsor has employed feasible levels of dosage and numbers of animals of both sexes in their studies and assay systems. The sponsor has explored the toxicity of the drug and adequately addresses issues regarding the modes and mechanisms of each toxicity uncovered. While the toxicity testing on atazanavir is still ongoing (i.e. carcinogenicity studies in both mice and rats), it is concluded that the NDA has provided sufficient preclinical safety information to allow for prediction of potential toxicity in humans with the judicious use of this drug in humans.

2.3 Microbiology

Please see Dr. Lisa Naeger's review for detailed information regarding the microbiology of Reyataz®. Dr. Naeger's conclusions are summarized in this section of the review.

Atazanavir is an HIV-1 protease inhibitor that specifically and selectively blocks the cleavage of viral precursor proteins preventing maturation of viral particles. ATV exhibits anti-HIV activity in cell culture with an EC_{50} of 2 to 5 nM against a variety of HIV isolates in several host cell-types. The anti-HIV activity of atazanavir is diminished 5-fold by human serum and 8-fold by ∝-1 acid glycoprotein.

Drug combination studies using ATV with PIs – ritonavir, indinavir, saquinavir, nelfinavir, amprenavir or with NRTIs – stavudine, didanosine, zidovudine, and lamivudine demonstrated additive effects without enhanced cytotoxicity. Drug combination studies using ATV with NNRTIs and abacavir demonstrated antagonistic to additive effects.

HIV-1 resistant to ATV was selected from *in vitro* selection experiments in three different HIV-1 strains. These ATV-resistant HIV-1 isolates showed a 6- to 183-fold decrease in susceptibility to ATV compared to wild type. Genotypic analyses indicated that I50L, A71V, N88S, M46I and I84V substitutions appeared to be key changes with possible roles in ATV resistance. Direct evidence for a role of the I50L mutation in ATV resistance was obtained by constructing recombinant viruses with the protease gene from clinical isolates. ATV resistance corresponded to the presence of I50L and A71V in the

protease coding sequence. Results showed that the I50L mutation, sometimes combined with A71V and other changes, appears to be a signature substitution for ATV and mediates increased susceptibility to other PIs by an unknown mechanism.

Genotypic and phenotypic evaluation of clinical isolates from ATV-treated patients designated as virologic failures with decreased ATV susceptibility (>2.5-fold) demonstrated that ATV can display different resistance patterns depending on the PI-treatment experience of the patient population. When ATV was used as the only PI in patients with no previous antiretroviral experience, clinical isolates developed a unique I50L mutation frequently accompanied by an A71V mutation. The I50L mutation resulted in ATV resistance, impaired viral growth and increased susceptibility to other approved PIs including amprenavir where resistance is mediated through the I50V mutation.

In contrast to naïve patients, isolates from treatment-experienced patients treated with ATV and SQV did not contain the I50L mutation but acquired several additional amino acid changes including I84V, L90M, M46I or N88S/D. These additional mutations in protease also conferred cross-resistance to other PIs. A higher percentage of the clinical isolates from ATV treatment arms with the PI mutations A71V, I84V, L90M, M46I, or N88S/D at baseline were virologic failures as compared to isolates from other treatment arms with similar mutations. These results suggest that these mutations in the HIV-1 protease are unfavorable to ATV antiviral activity and may reduce virologic response to ATV treatment clinically.

Out of 551 PI-experienced clinical isolates evaluated, ATV susceptibility was retained against > 80% of isolates resistant to 1-2 other PIs, primarily NFV-resistant isolates. There was a clear trend toward loss of ATV susceptibility as isolates demonstrated resistance to three or more PIs. ATV sensitivity was retained against only 5% of isolates resistant to five PIs. Therefore, ATV susceptibility of clinical isolates resistant to one or more PIs from patients never exposed to ATV decreased as the level of cross-resistance to other PIs increased. ATV-resistant isolates were highly cross-resistant to NFV, IDV, SQV, and RTV and moderately cross-resistant to APV and LPV. From treatment-experienced trials, 63% percent of the isolates that developed ATV-resistance remained susceptible to APV and 53% of the isolates were susceptible to LPV while less than 20% of these isolates remained susceptible to IDV, RTV, or SQV and none remained susceptible to NFV.

In summary, mutations I50L, A71V, I84V, N88S/D, M46I and L90M appear to confer ATV resistance and reduce the clinical response to ATV. ATV is cross-resistant with other PIs and there is a clear trend toward loss of ATV susceptibility with isolates resistant to three or more PIs.

3 Human Pharmacokinetics and Pharmacodynamics

3.1 Pharmacokinetics

Please see Dr. Jenny Zheng's review for detailed information regarding the pharmacokinetics and pharmacodynamics of Reyataz®. Dr. Zheng's conclusions are summarized in this section of the review.

Important clinical pharmacology and biopharmaceutices findings are as follows:

- The geometric mean of atazanavir exposures are about 50% lower in HIV-infected subjects as compared to healthy adult volunteers. The mean Cmax in a pK study of HIV-infected patients was 2298 ng/mL. The Tmax occurred at 2.0 hours, the half-life was 6.5 hours, and the Cmin was 120 ng/mL.
- A light meal increased the Cmax and AUC of ATV by 57% and 70%, respectively, while a high fat meal had no effect on the Cmax, but increased the AUC by 35%.
- Steady state is achieved between days 4 and 8 in both healthy and HIV-infected subjects.
- The major biotransformation pathways of ATV in humans consists of monooxygenation and dioxygenation. Other minor pathways consist of glucuronidation, N-dealkylation, hydrolysis and oxygenation with dehydrogenation.
- Three minor metabolites were identified, however, none displays antiviral activity.
- In vitro studies using human liver microsomes demonstrated that ATV is metabolized by CYP3A.
- ATV is a competitive inhibitor of CYP3A and UGT1A1 at clinically relevant concentrations. ATV also competitively inhibits CYP1A2 amd CYP2C9.
- Approximately 13% of ATV was excreted in the urine with approximately 7% of the dose excreted as unchanged drug. About 79% of atazanavir was recovered in the feces, suggesting that biliary elimination is a major pathway for the elimination of ATV and/or a fraction of the dose is unabsorbed.
- No difference in pK was observed between male and female subjects when adjusted for body weight.
- Elderly subjects have a 17% higher AUC and Cmax compared to younger subjects. This difference is not considered clinically significant.
- Atazanavir results in concentration-dependent increase in total and indirect bilirubin due to inhibition of UGT 1A1.
- ATV exposure in subjects with moderate to severe hepatic impairment was 45% higher after the 400mg dose and 31% lower after the 200 mg dose as compared to the exposure in subjects with normal hepatic function after a 400 mg dose. Therefore, dose reduction to 300 mg may be considered for patients with moderate hepatic impairment. It will be recommended that patients with severe hepatic impairment not receive atazanavir.

3.2 Pharmacodynamics

Population PK/PD analysis was used for dose selection and labeling of the effect of race on the pharmacokinetics of atazanavir. The interim population PK/PD analysis was

conducted using two week data and was under fasted conditions, and may not apply to dose administration under fed conditions.

The applicant conducted final population PK/PD analysis under fed conditions. However, this analysis was not accepted due to

- Uncertainty of the meal time relative to dosing;
- PK parameters and inter- and intra-individual variability were fixed to the population mean estimates obtained from the phase 1 healthy subjects model, while it appears that ATV exposures in HIV-infected subjects may be about 50% lower; and
- The concentrations estimated did not accurately predict the observed concentrations.

4 Description of Clinical Data and Sources

4.1 Sources of Clinical Data

This NDA contains data from 15 clinical trials conducted with atazanavir. Pivotal trials in review of this NDA are described below:

AI424007 was a two-stage, randomized, active-controlled, four arm study designed to compare the safety, tolerability, and antiviral activity of 1) atazanavir at 3 different doses with NFV over 2 weeks of monotherapy; and 2) atazanavir at 200 mg, 400 mg, and 500 mg QD in combination with d4T and ddI versus NFV in combination with d4T and ddI over 46 additional weeks. Treatment was blinded only to atazanavir dose. Treatment naïve subjects were enrolled.

AI424008 (008) 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, in combination with d4T and 3TC through 48 weeks in antiretroviral naïve subjects. Treatment was blinded to atazanavir dose.

AI424034 (034) is a multinational, randomized, double-blind, double-dummy, active-controlled, two-arm study of ARV treatment-naïve subjects. A total of 805 subjects were randomized to receive atazavanir 400 mg QD, efavirenz placebo and open-label, fixed-dose zidovudine and lamivudine (Combivir™) or efavirenz 600 mg QD, atazanavir placebo and Combivir™. Forty-eight week data was submitted for this trial.

AI424043 (043) is a randomized, multinational, open-label, active-controlled, two-arm study in subjects who had failed ARV therapy regimens containing no more than two protease inhibitors. A total of 300 subjects were randomized to receive either atazanavir or lopinavir/ritonavir in combination with two NRTIs. The selection of NRTIs was based on the phenotypic susceptibility data for the subject's viral isolate obtained at the screening visit and the physician's choice at the time of randomization. Twenty-four week data for the protocol-specified cohort of 229 subjects was submitted with this NDA.

4.3 Postmarketing Experience

Dr. Jose Gattell, an investigator for study 007 which enrolled 15/422 randomized subjects, served on a BMS advisory board for HIV for which he received an honoraria of —— per year.

As an investigator, Dr. Calvin Cohen enrolled 1/300 subjects in study 043 and 1/358 randomized subjects for study 045. He has received honoria from BMS in excess of —— for giving HIV-related talks.

As an investigator, Dr. Ken Lichenstein enrolled 1/300 subjects in study 043. He has received honoria in excess of —— for giving presentations sponsored by BMS and for serving on BMS advisory boards.

No response to requests for financial disclosure were provided by fewer than ten percent of sub-investigators. The most common reason provided by study sites was that the sub-investigator no longer worked at the study site.

In summary, due to the small numbers of subjects enrolled by investigators with financial interests in Bristol-Myers Squibb, it was determined that participation by these investigators in clinical studies of atazanavir would not impact safety or efficacy findings of any of these studies.

6 Integrated Review of Efficacy

6.1 Brief Statement of Conclusions

The applicant has demonstrated in three clinical trials of ARV treatment-naive patients that atazanavir, when added to a background regimen of two nucleoside reverse transcriptase inhibitor (NRTIs), produces a statistically and clinically significant reduction in HIV viral load, including a significant increase in the proportion of patients whose HIV viral load is undetectable by the Roche Amplicor assay. This clinical benefit is sustained to at least 48 weeks.

The trials were conducted across several continents within a diverse adult population. There was no convincing evidence that the observed clinical benefit is reduced in any of the racial, gender, or age categories examined.

The applicant tested atazanavir for 24 weeks in one trial with patients who had failed at least one prior regimen containing a protease inhibitor. In that trial, atazanavir was statistically and clinically significantly inferior to Kaletra® when each was added to a background regimen of two NRTIs. Meta-analysis supports the inference that atazanavir

would have been statistically significantly superior to placebo with respect to the proportion of subjects whose HIV viral load was undetectable had it been ethical to include such an arm in the trial.

Please refer to Dr. Tom Hammerstrom's review for further details regarding FDA's review of the efficacy data submitted with this application.

6.2 Detailed Review of Trials by Indication

6.2.1 Clinical Trial AI424034 (034)

"A Phase III Study Comparing the Antiviral Efficacy and Safety of BMS-232632 with Efavirenz; Each in Combination with Fixed Dose Zidovudine-Lamivudine"

6.2.1.1 Study Design and Subject Population

This study was a multinational, randomized, double-blind, double-dummy, active-controlled, two-arm study comparing atazanavir to efavirenz for the treatment of ARV-naïve subjects. Subjects were randomized to receive either atazanavir 400 mg QD, efavirenz placebo and fixed-dose open-label zidovudine and lamivudine (Combivir®) or efavirenz 600 mg QD, atazanavir placebo and Combivir®. Qualifying subjects had plasma HIV RNA levels ≥ 2,000 c/mL and CD4 cell counts ≥ 100 cells/mm^3 (or ≥ 75 cells/mm^3 with no prior history of any AIDS-defining diagnoses). Randomization was stratified by qualifying HIV RNA (< 30,000 c/mL; ≥ 30,000 c/mL).

6.2.1.2 Endpoints

The primary efficacy outcome measure was the proportion of subjects with HIV RNA levels < 400 c/ml through week 48. Secondary efficacy outcomes measures included the following:

- The proportion of subjects with HIV RNA < 50 c/ml through week 48.
- The time to treatment failure (TRWPF).
- The magnitude and durability of the reduction in plasma log10 HIV RNA in terms of the Time-Averaged Difference from baseline.
- The magnitude and durability of increases in CD4 cell counts in terms of the Time Averaged Difference from baseline.

6.2.1.3 Analysis Plan

Efficacy analyses performed by the applicant were based on all treated subjects and were stratified by qualifying HIV RNA (< 30,000 c/mL; ≥ 30,000 c/mL). This study was designed with 90% power to demonstrate that the proportions of subjects with HIV RNA < 400 c/mL through week 48 for ATV/ZDV+3TC and EFV/ZDV+3TC were similar. For the primary analysis the proportions were determined to be similar if the lower 95% confidence limit for the difference (ATV - EFV) was greater than -10%. Time to treatment failure for LOQ = 400 c/mL was compared using hazard ratios and 95% CI from Cox proportional hazards models. The Time-Averaged Differences (TAD) between ATV/ZDV+3TC and EFV/ZDV+3TC in the change from baseline in HIV RNA levels and CD4 cell counts through week 48 were computed with 95% CIs.

ATV/ZDV+3TC and EFV/ZDV+3TC in the change from baseline in HIV RNA levels and CD4 cell counts through week 48 were computed with 95% CIs.

6.2.1.4 Study Population

A total of 1042 HIV-infected subjects were enrolled and 810 (77%) were randomized to treatment. Five randomized subjects never started therapy, one on the ATV regimen and four on the EFV regimen. A total of 805 subjects (99%) were treated.

In general, baseline characteristics for all treated subjects were comparable between treatment regimens. The study population was predominantly male (65%) and had a median age of 33 years. Non-white racial groups comprised 67% of the population.

Baseline Characteristics - Treated Subjects		
	Treatment Regimen	
	ATV ZDV+3TC	**EFV ZDV+3TC**
Characteristics	N = 404	N = 401
Age (Years)		
Mean (SE)	34 (0.4)	34 (0.5)
Median	33	33
Min, Max	18, 71	18, 73
Missing	0	0
Gender: N (%)		
Male	257 (64)	265 (66)
Female	147 (36)	136 (34)
Race: N (%)		
Hispanic/Latino	152 (38)	142 (35)
White	136 (34)	130 (32)
Asian/Pacific Islanders	58 (14)	69 (17)
Black	54 (13)	53 (13)
Other: Ile Maurice	1 (<1)	0
Other: Mixed	1 (<1)	4 (<1)
Other: Mixed Race	1 (<1)	1 (<1)
Other: Native American	1 (<1)	0
Other: Colored	0	1 (<1)
Other: Ethiopian	0	1 (<1)
Region: N (%)		
South America	142 (35)	133 (33)
Europe	111 (27)	111 (28)
Asia	57 (14)	68 (17)
North America	56 (14)	53 (13)
Africa	38 (9)	36 (9)
h/o IVDA [N (%)]:	22 (5)	23 (6)
AIDS [N (%)]:	17 (4)	24 (6)

The median HIV RNA level and CD4 cell count for all treated subjects were 4.88 log10 c/mL and 282 cells/mm^3, respectively, and were comparable between regimens. Forty-two percent of all treated subjects had baseline HIV RNA levels ≥ 100,000 c/mL.

Baseline HIV RNA Level and CD4 Cell Count - Treated Subjects		
	TREATMENT REGIMEN	
	ATV ZDV+3TC	EFV ZDV+3TC
	N = 404	N = 401
HIV RNA Level (log10 c/mL)		
Mean (SE)	4.86 (0.031)	4.81 (0.032)
Median	4.87	4.91
Min, Max		
HIV RNA Distribution (c/mL): N (%)		
< 30000	112 (28)	104 (26)
30000 - < 100000	123 (30)	126 (31)
≥ 100000	169 (42)	171 (43)
CD4 Cell Count (cells/mm3)		
Mean (SE)	313 (9.2)	330 (10.6)
Median	286	280
Min, Max		
CD4 Distribution (cells/mm3): N (%)		
50 - < 200	125 (31)	109 (27)
200 - < 350	138 (34)	151 (38)
350 - < 500	94 (23)	84 (21)
≥ 500	47 (12)	57 (14)

6.2.1.5 Subject Disposition

Of those treated, 144 subjects (18%) discontinued prior to the week 48 visit. More subjects on the EFV regimen compared with the ATV regimen discontinued treatment before week 48 (20% vs.16%). The higher rate of discontinuation from the EFV regimen was due to slightly higher incidences of adverse events, death, and subject withdrawal.

Subject Disposition - Randomized Subjects			
	NUMBER OF SUBJECTS (%)		
	TREATMENT REGIMEN		
	ATV ZDV+3TC	EFV ZDV+3TC	Total
Randomized	405	405	810
Never treated	1 (<1)	4 (<1)	5 (<1)
Treated	404 (>99)	401 (99)	805 (99)
Discontinued prior to 48 week visit	65 (16)	79 (20)	144 (18)
Adverse event	26 (6)	34 (8)	60 (7)
Death	0	2 (<1)	2 (<1)
Lost to follow-up	15 (4)	17 (4)	32 (4)
Needed therapy prohibited by protocol	2 (<1)	0	2 (<1)
Non-compliance	6 (1)	5 (1)	11(1)
Physician's decision	0	1 (<1)	1 (<1)
Pregnancy	1 (<1)	2 (<1)	3 (<1)
Protocol violation while on study	2 (<1)	3 (<1)	5 (<1)
Subject withdrew	6 (1)	7 (2)	13 (2)
Treatment failure/lack of efficacy	7 (2)	8 (2)	15 (2)

6.2.1.6 Eligibility Violations and Protocol Deviations

Eleven subjects (five on ATV and six on EFV) had violations of protocol eligibility requirements. One subject was on AZT and ddI one year (this subject was withdrawn two weeks after starting study drug because of this eligibility violation); three subjects were on AZT 6 months, 4 months and 31 days, respectively; and one subject was on nelfinavir 30 days. The latter four subjects were granted permission to participate by a BMS Medical Monitor.

One hundred and eighty-one subjects (22%) experienced protocol deviations. These deviations were comparably distributed between treatment regimens (23% on ATV and 21% on EFV). The deviations were generally minor. The majority of the protocol deviations were randomization more than 14 days after screening. The majority of subjects had their labs re-tested within the 14 day window and should not have been considered protocol deviations. One hundred and twenty-one subjects were considered to

have had greater than 14 but less than 30 days between screening and randomization and one subject had greater than 30 days.

Forty-four subjects had greater than three days between randomization and the start of dosing. Two subjects had greater than 14 days (each ≤ 34 days) between randomization and the start of dosing. The remaining 41 subjects began dosing 4 - 11 days after screening for reasons that included: misunderstanding by site personnel as to when subjects should begin dosing, difficulties with the randomization system, scheduling conflicts, and subject decision to delay dosing.

Nineteen subjects received the wrong active or placebo container. Eight subjects (four on each regimen) received the incorrect active dose for one or two months. Eleven subjects (five on ATV; six on EFV) received the wrong placebo for one or two months.

6.2.1.7 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 034. Atazanavir was similar to efavirenz 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	Efavirenz
Outcome	N=405	N=405
Percent of Patients Responding		
HIV RNA < 400 copies/mL	67%	62%
HIV RNA < 50 copies/mL	32%	37%
Virologic failure	20%	21%
Rebound	17%	16%
Never suppressed through wk 48	3%	5%
HIV RNA Mean change from Baseline (log10 copies/mL)	-2.05	-1.94
CD4 Mean change from Baseline	176	160

6.2.2 Clinical Trial AI424043 (043)

"A Randomized Open-Label Study of the Antiviral Efficacy and Safety of Atazanavir versus Lopinavir/Ritonavir (LPV/RTV), Each in Combination with Two Nucleosides in Subjects who Have Experienced Virologic Failure with Prior Protease Inhibitor-Containing HAART Regimen(s)"

6.2.2.1 Study Design and Subject Population

This is a randomized, multinational, open-label, active-controlled, two-arm study in antiretroviral-experienced subjects designed to determine the antiviral activity, metabolic changes, and tolerability of atazanavir as compared to LPV/RTV, each in combination with two NRTIs, over the initial 24 weeks with a final analysis at 48 weeks. Atazanavir and LPV/RTV were administered in combination with two NRTIs: didanosine (ddI), stavudine (d4T), lamivudine (3TC), zidovudine (ZDV), or abacavir (ABC) in combination as ZDV + 3TC, d4T + 3TC, ZDV + ddI, d4T + ddI, or ABC + appropriate NRTI (ddI, d4T, or 3TC). The selection of NRTIs was based on the phenotypic susceptibility data for the subject's viral isolate obtained at the screening visit and the physician's choice at the time of randomization. Subjects with confirmed intolerance to one or more of their originally prescribed nucleosides were permitted to substitute the nucleosides provided that the pre-study phenotypic analysis demonstrated susceptibility.

A total of 300 subjects were randomized, with 290 subjects treated. This interim report describes results through 24 weeks for the protocol-specified cohort of 229 subjects.

Eligible subjects were HIV-infected men and women, 16 years of age or older, who had failed prior antiretroviral treatment(s) that included one PI; key enrollment criteria

included a plasma HIV RNA viral load ≥ 1,000 c/mL, CD4 cell count ≥ 50 cells/mm³ and current treatment with a PI-containing highly active antiretroviral therapy (HAART) regimen at the time of study enrollment. The failing regimen must have been administered for at least 12 weeks at the initiation of dosing. Subjects must have had a documented virologic response to at least one HAART regimen (either ≥ 1.0 log10 decline or HIV RNA < 400 c/mL for AMPLICOR . HIV-1 Monitor Assay Version 1.5 Ultrasensitive method or < 500 c/mL by Chiron bDNA).

6.2.2.2 Endpoints

Primary Efficacy Outcome Measure

- The magnitude and durability of the reduction in plasma HIV RNA from baseline, in terms of the Time-Average Difference (TAD), through week 24 (and week 48).

Secondary Efficacy Outcome Measures

- The proportion of subjects with ≥ 1.0 log10 decrease in HIV RNA levels from baseline or HIV RNA < 50 c/mL (or < 400 c/mL) at Weeks 24 and 48;
- The proportion of subjects with HIV RNA levels < LOQ (LOQ = 400 c/mL and 50 c/mL) at weeks 24 and 48;
- The magnitude of increases in CD4 cell counts from baseline, in terms of the TAD, through weeks 24 and 48;
- Pharmacokinetic parameters of atazanavir, EC50 of HIV strains and the magnitude of change in HIV RNA during and after dose reduction at weeks 24 and 48.

6.2.2.3 Analysis Plan

The following describes the analysis plan of the applicant for this study. For a detailed review of efficacy data by FDA, please see Dr. Tom Hammerstrom's statistical review.

Analyses conducted by the applicant was based on subjects who initiated therapy and included all data obtained on the originally assigned protease inhibitor. Analyses were stratified by NRTI backbone combination (ZDV/3TC, d4T/3TC, ddI/ZDV, ddI/d4T, ABC/NRTI). The primary efficacy analysis compared treatment regimens for the TAD in reduction of log 10 HIV RNA from baseline through week 24, with a two-sided 97.5% confidence interval. Other secondary analyses compared the week 24 CD4 cell count changes from baseline and HIV RNA response between treatment regimens [> 1 log 10 HIV RNA decrease from baseline or < LOQ (LOQ = 400 c/mL and 50 c/mL)].

6.2.2.4 Study Population

In general, baseline characteristics for all randomized subjects were comparable between treatment regimens. The study population was predominately male (79%) and had a median age of 37 years. Non-white racial groups comprised 58% of the population. Most subjects were from South America (51%) or North America (40%). Of the 121 randomized subjects from North America, 64 subjects (53%) were from the US/Puerto Rico. The incidences of prior IV drug use and history of CDC Class C AIDS-defining clinical events were comparable between the treatment regimens. An imbalance did exist

in the hepaitits B/C co-infection status between treatment regimens (ATV; 20%, LPV/RTV; 12%).

The median baseline HIV RNA level for all randomized subjects was 4.17 log10 c/mL and was comparable between treatment regimens. Less than half of subjects had baseline HIV RNA levels ≥ 30,000 c/mL (ATV, 31%; LPV/RTV, 41%). The median baseline CD4 cell count was 273 cells/mm^3 and was comparable between the treatment regimens.

The following table summarizes subject characteristics at baseline:

Subject Characteristics at Baseline - Randomized Subjects		
	Treatment Regimen	
	ATV	LPV/RTV
CHARACTERISTICS	N = 150	N = 150
Age (Years)		
Mean (SE)	38 (0.7)	39 (0.7)
Median	36	38
Min, Max	20, 65	23, 64
Mssing	0	0
Gender: N (%)		
Male	115 (77)	123 (82)
Female	35 (23)	27 (18)
Race: N (%)		
Hispanic/Latino	76 (51)	78 (52)
White	64 (43)	61 (41)
Black	9 (6)	11 (7)
Asian/Pacific Islanders	1 (<1)	0
Region: N (%)		
South Amerca	77 (51)	77 (51)
North America	60 (40)	61 (41)
Europe	13 (9)	12 (8)
IV Drug Use : N (%)	8 (5)	8 (5)
AIDS: N (%)	35 (23)	41 (27)

HIV RNA Level and CD4 Cell Count at Baseline Randomized Subjects		
	Treatment Regimen	
	ATV	LPV/RTV
	N = 150	N = 150
HIV RNA Level (log10 c/mL)		
Mean (SE)	4.10 (0.065)	4.15 (0.068)
Median	4.18	4.14
Min, Max		
Missing	0	0
HIV RNA Distribution(c/mL): N (%)		
< 30,000	104 (69)	89 (59)
30,000 - < 100,000	24 (16)	35 (23)
≥ 100,000	22 (15)	26 (17)
CD4 Cell Count (cells/mm3)		
Mean (SE)	327 (17.0)	321 (16.4)
Median	288	261
Min, Max		
Missing	0	0
CD4 Distribution (cells/mm3): N(%)		
< 50	1 (<1)	0
50 - < 200	43 (29)	46 (31)
200 - < 350	55 (37)	53 (35)
350 - < 500	25 (17)	26 (17)
≥ 500	26 (17)	(17)

6.2.2.5 Subject Disposition

A total of 485 HIV-infected subjects were enrolled, and 300 subjects (62%) were randomized to treatment. Of the 300 subjects who were randomized, 290 subjects were treated (ATV, 144 subjects; LPV/RTV, 146 subjects). More subjects on the ATV treatment regimen discontinued treatment due to treatment failure or lack of efficacy (14 subjects, 9%), compared to no subjects on the LPV/RTV treatment regimen. Subject disposition is summarized in the following table:

Subject Disposition (Week 24 Analysis)		
Randomized Subjects		
	Number of Subjects (%)	
	Treatment Regimen	
	ATV	**LPV/RTV**
	N=150	N=150
Randomized	150	150
Never Treated	6(4)	4(3)
Treated	144(96)	146(97)
D/C'd Prior to Week 24 Visit	**10 (7)**	**10 (7)**
Adverse Event	1 (<1)	4 (3)
Death	1 (<1)	0
Lost to Follow-up	0	2 (1)
Non-Compliance	1 (<1)	1 (<1)
Protocol Violation	3 (2)	1 (<1)
Subject Withdrew	0	2 (1)
Treatment Failure/Lack of Efficacy	4 (3)	0
D/C'd After Week 24 Visit	**13 (9)**	**1 (<1)**
Adverse Event	1 (<1)	0
Non-Compliance	1 (<1)	0
Subject Withdrew	1 (<1)	1 (<1)
Treatment Failure/Lack of Efficacy	10 (7)	0
Continuing on Treatment	**121 (81)**	**134 (89)**

6.2.2.6 Eligibility Violations and Protocol Deviations

One hundred seven subjects (ATV, 57 subjects; LPV/RTV, 50 subjects), approximately one-third of randomized subjects, violated some protocol eligibility requirements. These violations did not affect the validity of the study. The type and incidence of these violations were comparable between the treatment regimens. The majority of the protocol eligibility violations were in four categories: CD4 cell count outside the window of four weeks prior to randomization (17% overall; ATV, 18%; LPV/RTV, 17%); HIV RNA level outside the window of four weeks prior to randomization (16% overall; ATV, 17%; LPV/RTV, 15%); laboratory data outside the window of four weeks prior to screening (16% overall; ATV, 16%; LPV/RTV, 16%); or at least one HIV RNA level < 1000 c/mL (8% overall; ATV, 9%; LPV/RTV, 8%). In many cases, eligibility violations occurred due to delayed resistance testing (phenotype and genotype) results, causing delays in subject randomization. In these instances, investigators would have had to repeat screening laboratory tests to be within the four week window, but this was not done.

Six subjects were identified as having violated the exclusion criteria of receiving less than 12 weeks of a PI-containing regimen prior to baseline. Five of these subjects were randomized in error and never received study drug. One subject had an unknown start date of antiretroviral treatment prior to screening; the start date was being clarified at the time of this report.

Four subjects were identified as not having received PI-containing therapy in the three months immediately prior to the start of study therapy. One subject was identified in error due to incorrect treatment dates recorded in the database. One subject had received a PI-containing regimen, but the regimen closest to randomization was d4T, ddI, and efavirenz. Two subjects received nevirapine, d4T, and 3TC prior to randomization.

One hundred seventy-nine subjects (ATV, 86 subjects; LPV/RTV, 93 subjects) experienced protocol deviations. These deviations were minor and were not considered to affect the validity of the study. The type and incidence of these deviations were comparable between the treatment regimens. The majority of the protocol deviations were in two categories: randomization more than four weeks after screening (53% overall; ATV, 52%; LPV/RTV, 53%) or start of dose more than three days after randomization (16% overall; ATV, 15%; LPV/RTV, 18%). The majority of these delays in randomization or dosing were due to delayed phenotypic results, delayed screening laboratory results, or general scheduling conflicts.

Electrocardiogram (ECG) data for one site are not available due to a technological malfunction. The site was provided with ECG equipment that allowed the site to send ECG measurements directly to the central reading service via telephone modem only. Although the equipment indicated that the data were being properly transmitted, these data were never received by the central reading service. This equipment did not have printing capability, so hard copies of ECG tracings were not available. This error affected ECG measurements for ten subjects (ATV, 5 subjects; LPV/RTV, 5 subjects).

6.2.2.7 Efficacy Endpoint Outcomes

The following table summarizes outcomes of treatment for the first 229 randomized patients through 24 weeks of treatment in study 043 as analyzed by FDA. While atazanavir was inferior to lopinavir/ritonavir in analyses of both the TAD and proportion with HIV RNA viral load below the limits of quantification, analyses performed by both FDA and the applicant did support that atazanavir has antiviral activity in this population of patients. Please see Dr. Tom Hammerstrom's review for a complete review of the efficacy of atazanavir in study 043.

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 24 Randomized Subjects		
	Treatment Outcomes at Week 24	
	Atazanavir	LPV/RTV
Outcome	N=114	N=115
Percent of Patients Responding		
HIV RNA < 400 copies/mL	54%	75%
HIV RNA < 50 copies/mL	34%	50%
HIV RNA Mean change from Baseline	-1.73	-2.16
(log10 copies/mL)		
CD4 Mean change from Baseline	101	121

Exploratory post-hoc analyses were performed by the applicant to potentially correlate observed treatment differences in efficacy with prognostic baseline characteristics; the results are presented here. These analyses (longitudinal virologic suppression, proportions with HIV RNA < 400 c/mL at week 24) were performed within the following subgroups of subjects:

- PI phenotypic sensitivity (PI sensitive; PI resistant)
- Number of prior PI therapies (one prior PI; more than one prior PI)
- Number of PI mutations
- Number of NRTI mutations (no NRTI mutations; at least one NRTI mutation)

For presentation of these analyses, the applicant chose the TAD for the reduction of HIV RNA from baseline through week 24.

Phenotypic Sensitivity

A post-hoc exploratory analysis was performed to evaluate the effect of phenotypic sensitivity to the randomized PI on antiviral activity. Subjects were identified as having isolates fully sensitive (< 2.5 x IC50 of control: ATV, 84 subjects; LPV/RTV, 101 subjects) or resistant (> 2.5 x IC50 of control: ATV, 26 subjects; LPV/RTV, 12 subjects) to their randomized PI.

Overall, HIV RNA changes from baseline and response rates were greater for subjects who were sensitive to the randomized PI. However, the differences observed within the subgroups were consistent with the overall analysis. A detailed analysis of treatment response by genotypic mutations can be found in the microbiology review.

Number of Prior PI Therapies
A post-hoc exploratory analysis was performed to evaluate the effect of having had one or more prior PI therapies on antiviral activity. Eighty-five subjects on the ATV treatment regimen and 83 subjects on the LPV/RTV treatment regimen had received one prior PI therapy. Twenty-eight subjects on the ATV treatment regimen and 31 subjects on the LPV/RTV treatment regimen had received more than one prior PI therapy.

Greater changes from baseline in HIV RNA and higher response rates were observed for subjects who had a history of one prior PI compared with subjects with a history of more than one PI. Differences for subjects treated with LPV/RTV were not as apparent between subgroups, leading to smaller differences between the treatment regimens for subjects with a history of one prior PI.

Number of PI Mutations
A post-hoc exploratory analysis was not performed by the applicant because only about 25% of subjects had at least four PI mutations at baseline. Please see the microbiology review for a detailed analysis of PI mutations and atazanavir treatment response.

Number of NRTI Mutations
A post-hoc exploratory analysis was performed to evaluate the effect of having at least one NRTI (genotype) mutation on antiviral activity. Thirty-two subjects on the ATV treatment regimen and 26 subjects on the LPV/RTV treatment regimen had no NRTI mutations. Eighty-two subjects on the ATV treatment regimen and 89 subjects on the LPV/RTV treatment regimen had at least one NRTI mutation.

No significant difference was observed between treatment regimens when no NRTI mutations were present. When NRTI mutations were present the treatment difference between regimens was similar to the overall analysis. On the ATV treatment regimen, subjects with no identified NRTI mutations had greater decreases in HIV RNA and slightly higher response rates than subjects with at least one NRTI mutation. In contrast, no significant difference was apparent in LPV/RTV-treated patients in treatment response if NRTI mutations were present or absent.

6.2.3 Study AI424007
"Evaluation of the Safety and Antiviral Efficacy of a Novel HIV-1 Protease Inhibitor, Atazanavir, Alone and in Combination with d4T and ddI as Compared to a Reference Combination Regimen"

6.2.3.1 Study Design and Subject Population
This study was a randomized two-stage, active-controlled, four arm study designed to evaluate and compare the safety, tolerability, and antiviral activity of 1) atazanavir at 200

mg, 400 mg, and 500 mg QD with NFV 750 mg TID over 2 weeks of monotherapy; and 2) atazanavir at the 3 different doses in combination with d4T and ddI with NFV in combination with d4T and ddI over 46 additional weeks. Eligible subjects were HIV-infected, antiretroviral-naïve patients who had a CD4 cell count of ≥ 100 cells/mm^3 (≥ 75 cells/mm^3 in subjects with no prior AIDS-defining diagnoses) and a plasma HIV RNA viral load > 2,000 copies/mL. The study was blinded only to the dose of atazanavir. Randomization was stratified for HIV RNA level (< 30,000 c/mL; ≥ 30,000 c/mL).

6.2.3.2 Endpoints

Primary Efficacy Outcome Measure

- The magnitude and durability of the reduction in plasma HIV RNA from baseline, in terms of the change from baseline, expressed in log10, through 48 weeks of therapy.

Secondary Efficacy Outcome Measures

- The proportion of subjects with HIV RNA levels < LOQ (LOQ = 400 c/mL and 50 c/mL) at week 48;
- The magnitude of increases in CD4 cell counts from baseline, in terms of the mean change from baseline;
- The time to virologic response, defined as a confirmed decrease in RNA levels to < 400 copies/mL.

6.2.3.3 Analysis Plan

Stage 2 of the study was powered (> 95%) to demonstrate similarity of antiviral activity of three atazanavir doses of 200 mg, 400 mg, and 500 mg compared to nelfinavir when administered as a triple combination therapy. The primary endpoint was the magnitude of reduction in HIV RNA levels from baseline over 48 weeks of treatment compared using the Time-Averaged Difference (TAD); the TAD between each atazanavir regimen and nelfinavir regimen in change from baseline in log 10 HIV RNA level over 48 weeks of therapy were computed along with a 98.3% confidence interval.

Analyses were stratified by qualifying HIV RNA level obtained prior to randomization (< 30,000 mL and ≥ 30,000 c/mL). Week 2 changes from baseline in HIV RNA were also compared. The percent of subjects classified as responders at levels of HIV RNA < ~~400~~ 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.

6.2.3.4 Study Population

Overall, the baseline demographic characteristics of the subjects were comparable. The study population was predominantly male (64%), with a median age of 34 years. Non-white racial groups comprised 44% of the population. In general, populations were equally distributed across treatment regimens.

	Treatment Regimen: ddI/d4T/PI			
	ATV (QD)			NFV (TID)
	200 mg	400 mg	500 mg	750 mg
Characteristic	**N = 104**	**N = 103**	**N = 110**	**N = 103**
Age (years):				
Mean (SE)	34.7 (0.9)	33.8 (0.7)	35.5 (0.9)	35.3 (0.9)
Median	34	34	34	34
Range	19 - 68	20 - 54	18 - 72	21 - 59
Gender: N (%)				
Male	73 (70)	63 (61)	67 (61)	67 (65)
Female	31 (30)	40 (39)	43 (39)	36 (35)
Race: N (%)				
White	63 (61)	58 (56)	58 (53)	58 (56)
Black/Mixed	36 (35)	40 (39)	40 (36)	36 (35)
Hispanic/Latino	5 (5)	5 (5)	11 (10)	6 (6)
Arabian	--	--	--	1 (1)
Asian/Pacific Islanders	--	--	1 (1)	1 (1)
Turkish	--	--	--	1 (1)
Region: N (%)				
Europe	38 (37)	35 (34)	38 (35)	40 (39)
South Africa	33 (32)	32 (31)	35 (32)	32 (31)
North America	18 (17)	21 (20)	22 (20)	17 (17)
South America	15 (14)	15 (15)	15 (14)	14 (14)
IV Drug Use: N (%)	17 (16)	15 (15)	11 (10)	14 (14)
AIDS: N (%)	6 (6)	5 (5)	4 (4)	4 (4)

Baseline HIV RNA levels (log10 c/mL) were comparable for all treatment regimens. Qualifying HIV RNA strata were also comparable across treatment regimens with 35% to 40% of subjects having baseline levels of < 30,000 c/mL. Baseline HIV RNA summary data for all randomized and treated subjects are presented.