MEMORANDUM

DATE: April 14, 2003

TO: Advisory Committee Members and Guests

FROM: Atazanavir Review Team

THROUGH: Debra Birnkrant, M.D.
Division Director
Division of Antiviral Drug Products

SUBJECT: Background Package for NDA 21-567: atazanavir sulfate

I. Summary of Regulatory Issues and Purpose of Meeting

This document provides background information for the May 13, 2003, Antiviral Drugs Advisory committee meeting on atazanavir sulfate. On this day, the committee will be asked to consider efficacy and safety data submitted to support the approval of atazanavir for the treatment of HIV infection.

The FDA analyses of the safety and efficacy data submitted in the NDA support the applicant's findings. Phase 2 and 3 trials submitted in support of this NDA provide evidence that the antiviral activity of atazanavir is similar to nelfinavir or efavirenz in combination with two NRTIs in treatment-naïve patients. In a registrational study of treatment-experienced subjects, atazanavir was inferior to lopinavir/ritonavir both in terms of viral load reduction and percentage of patients with viral load below limits of quantification; however, multiple analyses performed by FDA and the applicant support that atazanavir has antiviral activity in this population.

Highly treatment-experienced subjects having failed at least two regimens containing drugs from all three classes were enrolled in study 045. A ritonavir-boosted dose of atazanavir, and atazanavir given in combination with saquinavir were compared to lopinavir/ritonavir, each with tenofovir and an NRTI. Preliminary results support the similarity of the ritonavir-boosted dose of atazanavir to lopinavir/ritonavir, while the ATV/SQV arm appears to be inferior. These data are preliminary and efficacy data from this trial will not be used to make a regulatory decision on this NDA.

The Division is convening this meeting to solicit the committee's comments on the breadth of the proposed treatment indication, and the risk-benefit analysis of the use of atazanavir as it relates to the following safety issues: 1) the incidence and degree of hyperbilirubinemia seen in clinical trials, 2) prolongation of the QT and PR interval, and 3) lipid profiles observed in atazanavir subjects as compared to efavirenz and selected protease inhibitors. Given the diversity of these issues, we have invited several committee guests with expertise in fields relating to these safety issues.

The applicant is proposing a broad indication for the treatment of HIV infection based on the results of the two registrational trials. While atazanavir was comparable to currently marketed ARV medications in treatment-naïve studies, it appeared inferior to lopinavir/ritonavir in treatment-experienced patients. We would like to hear comments from the committee regarding the proposed treatment indication for atazanavir.

With regard to safety issues, three areas of concern 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, an enzyme responsible for the conjugation of bilirubin. Over three-fourths of all patients experienced an elevation of bilirubin while on treatment, and approximately five percent of patients experienced grade 4 (five x upper limit of normal) increases requiring dose modification per study protocols. Treatment discontinuations for jaundice and/or scleral icterus were uncommon despite a 15% incidence of these events.

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. Discontinuations due to abnormal LFTs or hepatotoxicity (lactic acidosis syndrome/symptomatic hyperlactatemia [LAS/SHL] cases were examined separately) appeared to occur with similar frequency between atazanavir and comparator regimens.

In two phase 2 studies that compared atazanavir to nelfinavir, each with identical NRTI background therapy, the frequency of all grades of transaminase abnormalities 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.

In registrational study 034 which compared atazanavir to efavirenz in treatment-naïve patients, the incidence of all grades of transaminase abnormalities was similar between treatment arms. In registrational study 043 of treatment-experienced patients, atazanavir subjects experienced more grade 3-4 LFT abnormalities 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 summary, the hyperbilirubinemia seen during the development program of atazanavir did not appear to result in an increased incidence of hepatotoxicity relative to selected PIs or to efavirenz. During the meeting we will be seeking your assessment of the clinical data with regard to hyperbilirubinemia and the risk of hepatotoxicity associated with atazanavir use. We would like your general impression of the clinical implications of these data and your recommendations for additional preclinical or clinical studies to address the potential for hepatotoxicity.

The second safety issue relates to effects of atazanavir on the QT and PR interval. Effects of drugs on the QT interval have become an increasing focus of the FDA; QT prolongation and the subsequent development of Torsades de Pointes (TdP) have been one of the most common reasons for drug withdrawal in recent years. While the risk-benefit analysis of taking an antiretroviral medication versus the possibility of developing an extremely rare but potentially life-threatening arrhythmia may appear to be clear-cut, the Division believes that we have moved into management of HIV infection as a chronic disease. As such, all risks associated with medication use should be well delineated.

Evaluation of the QT interval includes "correction" of the QT interval for heart rate, as the QT interval decreases with increasing heart rate. In this document, corrected QT intervals (QTc) were derived using a correction formula known as Bazett's; this has been the correction method historically used by the FDA and the one on which criteria for evaluation of the QT interval have been based. Evaluation of the QT interval is a specialized and evolving field and will not be discussed at length in this document; further information will be provided at the Advisory Committee meeting with the goal of allowing attendees to participate in a discussion of the QT effects of atazanavir.

In brief, a placebo-controlled pharmacokinetic study designed to evaluate effects of atazanavir on ECG parameters revealed a dose-dependent prolongation of the QT interval. Prolongation that may be considered a signal for increased risk for development of TdP was seen at a dose of 800 mg given once daily. This dose produced an exposure that is three-fold greater than that seen with the proposed dose of 400 mg. The ritonavir boosted dose of atazanavir 300 mg that is being investigated for use in treatment-experienced patients has not been fully evaluated in a placebo-controlled pharmacokinetic study, but data suggest that this dose may also be associated with prolongation of the QT interval.

In order to further evaluate cardiac risks, ECGs were collected from five clinical trials. Use of atazanavir did not appear to result in an increased incidence of QTc interval prolongation relative to comparators. There were no clinical events of sudden death, or report of arrhythmias that appeared to be related to prolongation of the QT interval; however, these types of clinical events are rare, and likely would not be seen in clinical trials of the size seen in this application.

During evaluation of the effects of atazanavir on the QT interval it was also found that atazanavir produced dose-dependent prolongation of the PR interval. 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 first degree AV block was observed with similar frequency in atazanavir subjects versus PI comparators. First degree AV block appeared to be less common in subjects receiving efavirenz. In study 034 bundle branch block was reported in one ATV subject and one EFV subject. In the expanded access protocol a patient taking atazanavir concomitantly with verapamil, delavirdine, and other medications, was hospitalized with angina and a junctional rhythm.

In summary, while pharmacokinetic studies revealed moderate effects of atazanavir on the PR interval, clinical events related to prolongation of the PR interval were rare. First degree AV block was the most common abnormality observed. Effects on the QT interval at the proposed dose appeared to be minimal. We will be seeking comments from the Advisory Committee on the risk-benefit analysis of the use of atazanavir with regard to these issues.

The final safety issue relates to lipid metabolism. It was noted during phase 2 studies of treatment-naïve subjects that treatment with nelfinavir resulted in greater increases in lipid parameters relative to atazanavir. These studies were not designed specifically to measure these changes; however, this finding was confirmed in phase 3 studies of both treatment-naïve and treatment-experienced patients.

The applicant analyzed lipid data from all studies in multiple ways. Mean changes from baseline were calculated and categorical analyses were performed using NCEP guidelines to define categories of lipid elevation. Data regarding initiation of lipid-lowering agents during studies were recorded. Calculations were made using Last Observation Carried Forward (LOCF) for subjects initiating lipid lowering therapy during the trial and sensitivity analyses were performed without using LOCF.

In general, atazanavir produced less change in total cholesterol, fasting LDL, and triglycerides than all comparators; these differences were found to be statistically significant. Atazanavir subjects initiated lipid lowering therapy less frequently than patients on comparator regimens. After 72 weeks of nelfinavir therapy, lipid levels of subjects who switched from nelfinavir to atazanavir returned to pretreatment levels.

Two concerns have emerged with regard to lipid parameters. The first is whether this finding will be maintained over longer durations of therapy and across multiple treatment regimens. In study 043 fasting triglycerides did not appear to decrease significantly in the atazanavir treatment arm to what may be considered pre-treatment (or treatment naive) levels. This may suggest that other factors in addition to protease inhibitor use may contribute to hypertriglyceridemia. The other concern is whether this apparent lack of effect on lipid parameters will translate into health benefits for patients in terms of a lower incidence of lipodystrophy and cardiovascular disease. Spontaneous reporting of lipodystrophy events in these clinical trials does not suggest a reduction of these events in subjects taking atazanavir.

We will be seeking the committee's comments on this potential treatment advantage of atazanavir.

II. Clinical Development Summary

This NDA contains clinical data collected primarily from nine clinical studies, including the two registrational studies, AI424034 (034) and AI424043 (043). Study 034 was an international, multi-center, double-blind, randomized, placebo-controlled trial comparing atazanavir to efavirenz, each given with AZT/3TC, in treatment-naïve HIV-infected subjects. Study 043 was an international, multi-center, randomized, open-label trial comparing atazanavir to lopinavir/ritonavir, each with an optimized NRTI background, in HIV-infected subjects who had failed a PI-containing regimen.

Several supportive studies were also submitted, including studies AI424007 (007) and AI424008 (008), two dose-finding studies comparing atazanavir to nelfinavir. Studies AI434041 (041) and AI424044 (044) were rollover studies for the dose-finding studies and were designed to collect long-term safety data. Also notable is study AI424045 (045), a multi-center, randomized open-label trial comparing a ritonavir-boosted dose of atazanavir, and atazanavir given in combination with saquinavir, to lopinavir/ritonavir, each with tenofovir and an NRTI, in highly treatment-experienced HIV-infected subjects who had failed at least two regimens containing ARV medications from all three classes.

Other trials include a PACTG pediatric protocol (020), an expanded access protocol (900), and a small phase 2 trial of treatment-experienced patients (009).

Summaries of these trials are provided in the table presented on the following page:

Summary of Clinical Trials

Study	Design	Regimens (mg)	Comparator (mg)	Background	# Enrolled	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	Patients receiving NFV in 008 switched to ATV 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	43	Age 3 mo to 21 years	PK/PD and safety

*TAD – Time-averaged difference from baseline

III. Summary of Efficacy

A. Dose Selection

A dose of 400 mg was chosen based on results from phase 2 dose-ranging studies 007 and 008. No significant differences in efficacy were seen after 48 weeks of treatment with 200 mg, 400 mg, 500 mg, and 600 mg doses of atazanavir; however, an initial two-week monotherapy treatment phase with atazanavir showed that doses of 400 mg or greater had higher probabilities of producing a 1.5 $\log_{10}$ reduction from baseline. The choice of 400 mg provided a balance between efficacy and the incidence of hyperbilirubinemia.

B. Study Design and Baseline Demographics for Registrational Trials

As mentioned previously, study 034 was an international, multi-center, double-blind, randomized, placebo-controlled trial comparing atazanavir to efavirenz, each given with AZT/3TC, in treatment-naïve HIV-infected subjects. Study 043 was an international, multi-center, randomized, open-label trial comparing atazanavir to lopinavir/ritonavir, each with an optimized NRTI background, in HIV-infected subjects who had failed a PI containing regimen.

Baseline characteristics of subjects enrolled in these studies are summarized on the following page.

Baseline Characteristics: Studies 034 and 043

	Study 034	Study 043
# of Subjects Randomized	810	300
# of Subjects Treated	805	290
Age (Years)		
Mean	34	38
Median	33	37
Range	18, 73	20, 65
Sex (%)		
Male	65	79
Female	35	21
Race (%)		
Caucasian	33	41
Hispanic	37	52
Black	13	7
Asian/Other	17	<1
CD4 Cell Count (cells/mm^3)		
Mean	322	320
Median	282	268
HIV RNA (log_{10} copies/mL)		
Mean	4.84	4.14
Median	4.88	4.19
N < 100,000 (%)	58	83
N ≥ 100,000 (%)	42	17
Mean Time on Prior Antiretroviral Therapy (weeks)		
PIs	N/A	144 (100% of subjects)
NRTIs		184 (100% of subjects)
NNRTIs		94 (14% of subjects)

C. Primary Efficacy Endpoints

The primary efficacy endpoint in study 034 was percentage of patients with HIV RNA levels below the limit of quantification of 400 copies/mL at 48 weeks. The primary efficacy endpoint for study 043 was the magnitude of viral suppression as assessed by the change from baseline in plasma HIV RNA levels (expressed in log10) through 24 weeks. Multiple secondary analyses were performed for each study.

D. HIV RNA Results

The following two tables summarize efficacy results for selected trials. The first table provides efficacy results for atazanavir 400 mg in studies 007, 008, and 034. In these studies, atazanavir was similar to efavirenz and nelfinavir in a Time to Loss of Virologic Response (TLOVR) analysis using both 400 copies/mL and 50 copies/mL as limits of detection.

At 24 weeks in study 043, subjects receiving atazanavir had a mean decrease of 1.73 log10 c/mL as compared to a mean decrease of 2.16 log10 copies/mL for lopinavir/ritonavir patients. The time-averaged difference (TAD) estimate (ATV - LPV/RTV) for the change from baseline in HIV RNA level through 24 weeks was 0.31 log10 c/mL (97.5% CI: 0.06, 0.55), favoring lopinavir/ritonavir.

Preliminary efficacy results at 16 weeks of a limited number of enrolled subjects in study 045 were provided in this NDA. A ritonavir-boosted dose of atazanavir 300 mg appeared to be similar to LPV/RTV, each given with tenofovir and an optimized NRTI. Atazanavir given in combination with saquinavir appeared to be inferior.

Time to Loss of Virologic Response (TLOVR)
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

Summary of Efficacy Treatment-Naïve Studies
Time to Loss of Virologic Response (TLOVR)

	Study 034		Study 007		Study 008	
HIV RNA	**ATV AZT/3TC**	**EFV AZT/3TC**	**ATV ddI/d4T**	**NLF ddI/d4T**	**ATV d4T/3TC**	**NLF d4T/3TC**
	Number of Subjects/Total (%)					
< 400 copies/mL	281/404 (70)	258/401 (64)	48/78 (62)	50/82 (61)	123/181 (68)	54/91 (59)
< 50 copies/mL	131/404 (32)	150/401 (37)	26/78 (33)	23/82 (28)	60/181 (33)	35/91 (38)
TAD_{48}	-2.67	-2.74	-2.42	-2.33	-2.51	-2.31

Summary of Efficacy – Treatment-Experienced Studies
Time to Loss of Virologic Response (TLOVR)

	Study 043 - 24 weeks		Study 045 – 16 weeks		
HIV RNA	**ATV 2 NRTIs**	**LPV/RTV 2 NRTIs**	**ATV 300 RTV 100 TNF/NRTI**	**ATV 400 SQV 1200 TNF/NRTI**	**LOP RTV TNF/NRTI**
	Number of Subjects/Total (%)				
< 400 copies/mL	69/114 (61)	93/115 (81)	21/37 (57)	17/34 (50)	21/35 (60)
< 50 copies/mL	47/114 (41)	60/115 (52)	14/37 (38)	10/34 (29)	7/35 (20)
TAD_{16}	---	---	-1.74	-1.70	-1.87
TAD_{24}	-1.73	-2.16	---	---	---

E. CD4 Cell Counts

In general, CD4 counts increased over time across all treatment regimens and were comparable between treatment arms within each study. In study 034, the mean increase at week 48 was 176 cells/mm^3 on the ATV regimen and 160 cells/mm^3 on the EFV regimen. In study 043, the mean increase from baseline in CD4 cell count at week 24 was 101 cells/mm^3 on the ATV treatment regimen and 121 cells/mm^3 on the LPV/RTV treatment regimen. While each of these differences was statistically significant, they are not felt to have clinical significance due to the small magnitude of the differences.

IV. Drug Interactions

The following two tables summarize the results of drug interactions studies performed by the applicant. Drugs were chosen for study based on the likelihood that drugs would be co-administered with atazanavir and the potential for clinically relevant drug interactions.

Table 1: Drug Interactions: Pharmacokinetic Parameters for Atazanavir in the Presence of Coadministered Drugs (3A4 inhibitor, inducer, or drugs affecting QTc and PR intervals)

Coadministered Drug	Coadministered Drug Dose/Schedule	TRADENAME Dose/Schedule	n	Ratio (90% Confidence Interval) of Atazanavir 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 TRADENAME and ritonavir 100 mg QD simultaneously with TRADENAME, 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 TRADENAME.

Table 2: Drug Interactions: Pharmacokinetic Parameters for Coadministered Drugs (3A4 substrates, drugs affecting QTc and PR intervals) in the Presence of TRADENAME

Coadministered Drug	Coadministered Drug Dose/Schedule	TRADENAME Dose/Schedule	n	Ratio (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters with/without TRADENAME; No effect = 1.00	
				C_{max}	AUC
Atenolol (prolongs PR interval, not metabolized by 3A)	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	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	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 TRADENAME.
[b] Not the recommended therapeutic dose of atazanavir.

V. **Summary of Clinical Virology**

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 *in vitro* susceptibility to other approved PIs including amprenavir where resistance is mediated through the I50V mutation.

In contrast to naïve patients, isolates from 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 I84V, L90M, A71V, N88S/D or M46I at baseline were virologic failures compared to isolates from other treatment arms. 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, N88S/D, I84V, and L90M appear to confer ATV resistance and reduce the clinical response to ATV. ATV is cross-resistant with other PIs and there is clear trend toward loss of ATV susceptibility with isolates resistant to three or more PIs.

VI. Safety Summary

Study 034 - General Safety
Clinical adverse events were common in study subjects; at least 95% of all subjects on both treatment regimens reported at least one adverse event. The majority of all AEs were mild to moderate only (Grade 1 - 2). Grade 3 - 4 events occurred in about 16% of subjects on both regimens.

The most common adverse events of any grade that were reported with a comparable incidence on both treatment regimens were infection, nausea, headache, vomiting, diarrhea, abdominal pain, somnolence, insomnia, and fever.

Adverse events that occurred with a higher frequency on the ATV regimen included jaundice (11% vs. 0%) and scleral icterus (11% vs. 2%). Adverse events that occurred with a higher frequency on the EFV regimen included dizziness (39% vs. 13%), abnormal dreams (10% vs. 6%), nervousness (3% vs. < 1%), rash (29% vs. 23%), and vasodilatation (7% vs. 3%).

Sixty-five subjects discontinued therapy because of adverse events (28 subjects on the ATV regimen and 37 subjects on the EFV regimen). The most frequent events leading to discontinuation in the ATV regimen were anemia (2%), nausea (1%) and vomiting (1%). Three subjects on the ATV regimen discontinued for scleral icterus or jaundice. The most frequent events leading to discontinuation on the EFV regimen were rash (2%), CNS events (2%), and nausea (1%).

Study 043 - General Safety
The regimens appeared to be well-tolerated with 2 subjects in each treatment arm discontinuing for adverse events prior to the week 24 visit (one atazanavir subject discontinued for scleral icterus and lipoatrophy, and the second atazanavir subject discontinued for grade 4 transaminases and grade 3 bilirubin). The majority of AEs were mild to moderate in severity; Grade 3 - 4 adverse events were observed in approximately 10% of subjects in each treatment arm.

The most common adverse events of any grade that were reported with a comparable incidence between the treatment regimens were headache, nausea, peripheral neurologic symptoms, abdominal pain, fatigue, insomnia, vomiting, and lipodystrophy.

Adverse events that were observed more frequently on the ATV treatment regimen as compared with the LPV/RTV treatment regimen included rash (13% vs. 7%), dizziness (8%; vs. 3%), extremity pain (8% vs. 1%), jaundice (10% vs. 0%), and scleral icterus (6% vs. 0%). Adverse events that were observed more frequently on the LPV/RTV

treatment regimen as compared with the ATV treatment regimen included diarrhea (32% vs. 10%), infection (40% vs. 35%), somnolence (9% vs. 3%), and anorexia (5% vs. <1%).

Special Safety Considerations

Lipid Profiles

As mentioned previously it was noted during phase 2 studies of treatment-naïve subjects that treatment with nelfinavir resulted in greater increases in lipid parameters relative to atazanavir. This finding was confirmed in phase 3 studies of both treatment-naïve and treatment-experienced patients. In addition, subjects who switched from nelfinavir to atazanavir after 72 weeks of treatment experienced a return to baseline lipid parameters by 12 weeks on treatment.

The following tables summarize the means of data collected at each timepoint for lipid parameters during studies 034 and 043.

Lipid Parameters – Study 034		
	Atazanavir	**Efavirenz**
	AZT/3TC	**AZT/3TC**
	N=404	**N=401**
	Mean	
	N=386	N=379
Total Chol – B/L	164	162
	N=321	N=302
48 weeks	168	195
	N=383	N=378
Fasting LDL - B/L	98	98
	N=283	N=264
48 weeks	98	114
	N=386	N=379
HDL – B/L	39	38
	N=321	N=302
48 weeks	43	46
	N=384	N=379
Fasting TG – B/L	138	129
	N=283	N=266
48 weeks	124	168

Lipid Parameters – Study 043		
	Atazanavir	**Lopinavir/Ritonavir**
	Dual NRTI background	**Dual NRTI background**
	N=109	N=114
	Mean	
	N=109	N=114
Total Chol – B/L	179	172
	N=94	N=84
24 weeks	169	199
	N=109	N=114
Fasting LDL – B/L	104	100
	N=91	N=83
24 weeks	92	106
	N=109	N=114
HDL – B/L	37	37
	N=94	N=84
24 weeks	41	45
	N=109	N=114
Fasting TG – B/L	207	196
	N=92	N=83
24 weeks	207	260

LDL Cholesterol
In treatment naïve studies, subjects receiving efavirenz and nelfinavir treatment regimens had substantial increases in LDL cholesterol by week 12; these increases persisted through 48 weeks for efavirenz and 72 weeks for nelfinavir in studies 007/008. Data from rollover study 007/041 confirmed that atazanavir produced less effect on lipid parameters than nelfinavir through 108 weeks of treatment.

In treatment-naïve study 034, the mean increase from baseline in LDL cholesterol for efavirenz-treated subjects was 18 % as compared to 1% for ATV-treated subjects ($p < .0001$). At week 48 for study 034, more subjects on the efavirenz regimen had fasting LDL cholesterol ≥ 160 mg/dL as compared to atazanavir (8% versus 3%, $p < .005$).

At week 24, in treatment-experienced study 043, the mean increase in LDL cholesterol for LPV/RTV-treated subjects was 8% compared to a mean decrease of 6% for ATV-treated patients. By week 24, 7% of LPV/RTV subjects had fasting LDL > 160 mg/dL as compared to none of the atazanavir subjects.

HDL Cholesterol
In study 034, mean baseline HDL cholesterol concentrations were similar between atazanavir and efavirenz treatment arms. By week 48, the efavirenz regimen had a significantly higher mean increase from baseline in HDL cholesterol as compared to atazanavir (24% versus 13%, $p < 0.0001$).

In study 043 mean increases in HDL were similar (ATV 14%, LPV/RTV 13%).

Fasting Triglycerides
In study 034, baseline fasting mean triglyceride concentrations were slightly lower on the efavirenz regimen (129 mg/dL) as compared to the atazanavir regimen (138 mg/dL). At week 48, significant mean increases ($p < 0.0001$) were observed for efavirenz-treated subjects (23%) as compared to atazanavir-treated subjects, who experienced a small decrease in triglyceride concentrations (-9%).

In studies 007/008 combined, substantial mean increases were observed in triglycerides for NFV-treated subjects relative to ATV-treated subjects (45% versus 9%). These differences were seen by week 4 and were sustained throughout the treatment period.

At week 24 in study 043, the mean increase in serum triglycerides for LPV/RTV-treated subjects was 57 % compared to a mean decrease of 2% for ATV-treated subjects ($p < .0001$). Despite this, triglyceride levels of atazanavir patients appeared to be higher than levels seen in atazanavir-treated patients enrolled in naïve studies. This may suggest that factors other than current protease inhibitor use also contribute to hyperlipidemia in HIV-infected subjects.

Lipodystrophy
Review of lipodystrophy events in this document will be limited to treatment-naïve studies 007 and 034. Data on lipodystrophy events in treatment-experienced trials may be confounded by prior ARV therapy and by variable NRTI backgrounds.

Lipodystrophy events were inconsistently reported; some were reported only as lipodystrophy, while other reports were specific as to the area of weight loss or weight gain. Because of this, reports were not grouped by categories of lipoatrophy, lipohypertrophy or both. As some events may have been reported simply as weight loss or weight gain due to lack of awareness of these events at the time studies were conducted, these reports were also reviewed.

Spontaneous reports of any event of lipodystrophy, generalized weight loss or weight gain appeared to be similar between atazanavir and comparators in these trials. Events did appear to increase with increasing duration of therapy.

Incidence of Lipodystrophy, Weight Loss, and Weight Gain

Study	034		007		007/041	
	ATV 400 mg AZT/3TC N=404	EFV 600 mg AZT/3TC N=401	ATV all doses ddI/d4T N=310	NFV 2500 mg ddI/d4T N=100	ATV all doses ddI/d4T N=310	NFV 2500 mg ddI/d4T N=100
	Number of subjects (%)					
Any Event	61 (15)	47 (12)	46 (15)	11 (11)	68 (22)	18 (18)
Lipodystrophy	37 (9)	29 (7)	14 (4)	4 (4)	41 (13)	10 (10)
Weight gain	12 (3)	3 (1)	4 (1)	1 (1)	4 (1)	1 (1)
Weight loss	12 (3)	16 (4)	31 (10)	7 (7)	41 (13)	11 (11)

In summary, use of atazanavir appeared to have less of an impact on lipid parameters as compared to efavirenz and selected protease inhibitors. Fasting triglycerides in treatment-experienced subjects in study 043 did not return to levels seen in treatment-naive subjects, suggesting that factors other than protease inhibitor use may also contribute to the development of hyperlipidemia. In addition, the favorable lipid profile did not appear to result in fewer reported lipodystrophy events in atazanavir-treated subjects as compared to efavirenz and nelfinavir.

Special Safety Considerations – 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 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 evaluations of these mechanisms supported an unconjugated hyperbilirubinemia. Elevated total bilirubin, when fractionated, was primarily indirect (unconjugated) and reversible upon discontinuation of ATV. This finding suggested 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 (e.g., albumin, GST) was not observed. By elimination, these experiments suggested that the predominant mechanism of the primarily unconjugated hyperbilirubinemia seen with ATV exposure is inhibition of UGT 1A1.

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. For purposes of this review, the normal range of total bilirubin is ≤ 1.0 mg/dL and the normal range for direct bilirubin is ≤ 0.2 mg/dL.

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 regimens. The mean total bilirubin for ATV-treated subjects was approximately 3-fold higher at week 48 as compared to baseline.

The following table summarizes total and direct bilirubin levels collected at all timepoints in study 034. Regardless of the degree of hyperbilirubinemia observed at a given timepoint, minimal changes were seen in direct bilirubin, supporting inhibition of UDP-glucuronosyl transferase as the mechanism of hyperbilirubinemia. Mean direct bilirubin levels for ATV-treated subjects increased slightly from baseline. This was generally observed regardless of the degree of elevation in total bilirubin. When significant elevations of direct bilirubin were observed they generally occured simultaneously with other indices of hepatic injury or inflammation.

Mean Total and Direct Bilirubin of All Bilirubin Measurements in Study 034 by Categorical Analysis	
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. Please note that dose reduction as a management strategy for grade 4 hyperbilirubinemia was utilized in clinical trials of atazanavir, however, insufficient data was obtained from clinical trials on the efficacy of a reduced dose of atazanavir to support its use in clinical practice.

Incidence of Grade 3–4 Hyperbilirubinemia and Dose Reduction by ATV Dose				
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)
Dose Reduction for Grade 4 Elevation	0/102 (0)	15/277 (5)	10/107 (9)	24/195 (12)

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 for patients receiving ATV 400 mg is shown in the following table:

Atazanavir – 400 mg			
Number of Subjects (%)			
Study	**007/41 008/44 N=277**	**034 N=404**	**043 N=109**
Jaundice	26 (9)	45 (11)	14 (10)
Scleral Icterus	22 (8)	45 (11)	8 (6)
Total Subjects*	45 (16)	58 (14)	21 (15)

* Subjects may have reported one or both of these adverse events.

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 the 16 weeks of follow-up available for study 045.

While clinical jaundice and/or scleral icterus were reported in roughly 15% 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.

Three of the clinical trials (007, 008, and 034) had subjects receiving identical nucleoside analogue 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 study 007 at 72 weeks of follow-up, more subjects receiving atazanavir had any grade elevation of LFTs as compared to nelfinavir. This finding was also observed in study 008, although the overall incidence of LFT abnormalities was lower, likely reflecting the different NRTI background therapy. In 007 grade 3-4 abnormalities were more frequent in atazanavir arms, while in study 008, they were more common in the nelfinavir arm. In registrational study 034, with the expected exception of bilirubin elevations, abnormalities of serum liver function tests were comparable between ATV-treated subjects and EFV-treated subjects.

In study 043, an imbalance existed at baseline between the two treatment regimens in the number of subjects with a history of hepatitis B or C (ATV 20%, LPV/RTV 12%); slight differences in NRTI background therapy also existed between the two regimens. The majority of liver function test abnormalities on study were Grade 1 - 2 and were comparable between the treatment regimens. Grade 3 – 4 ALT and AST elevations occurred in 6% and 3% of subjects, respectively, on the ATV treatment regimen and < 1% and 1% of subjects, respectively, on the LPV/RTV treatment regimen. Grade 3 - 4 elevations in ALT were more common among hepatitis negative subjects treated with

ATV (5%) than subjects treated with LPV/RTV (< 1%). One subject with hepatitis B receiving atazanavir/ddI EC/d4T discontinued for grade 3-4 LFTs.

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 hepatitis, liver function abnormalities or damage (excluding lactic acidosis syndrome/symptomatic hyperlactatemia cases [LAS/SHL]):

Discontinuations and/or Deaths Due to Hepatic Abnormalities (w/o LAS/SHL)					
Phase 2 and 3 Clinical Studies					
	Number of Subjects (%)				
ARV Treatment-Naive Studies	**034**	**034**	**007/41 008/44**	**007/041 008**	
	ATV 400	**EFV 600**	**ATV all doses**	**NFV**	
	N = 404	**N = 401**	**N = 673**	**N = 191**	
D/C	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	**LPV/RTV**	**ATV 300 RTV 100**	**ATV 400 SQV 1200**	**LPV/RTV**
	N = 144	**N = 146**	**N = 119**	**N = 109**	**N = 117**
D/C	1 (<1)	0	1 (<1)	0	0
Death	0	0	0	0	0
ARV Treatment-Experienced Studies	**009**	**009**	**009**		
	ATV 400 SQV 1200	**ATV 600 SQV 1200**	**RTV 400 SQV 400**		
	N= 32	**N=27**	**N=23**		
D/C	0	0	3 (13)		
Death	0	0	0		

One atazanavir 200 mg subject in study 007 died four weeks after treatment discontinuation 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-Hodgkin's lymphoma (autopsy indeterminate). With the exception of five deaths related to lactic acidosis (four ATV, one NFV), no other subjects died due to causes associated with hepatotoxicity; LAS/SHL are adverse events attributed to the mitochondrial toxicity of NRTIs.

Of the 15 subjects discontinuing atazanavir for worsening of liver function or hepatitis (without 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.

In summary, hyperbilirubinemia seen in clinical trials was predominantly indirect, and resulted in dose reduction and/or treatment discontinuation in relatively few subjects (≤ 5%). With the exception of hyperbilirubinemia, the incidence of LFT abnormalities and discontinuations for hepatotoxicity, hepatitis, or LFT abnormalities in subjects receiving atazanavir appeared to fall within the range of that seen with other marketed protease inhibitors and non-nucleoside reverse transcriptase inhibitors.

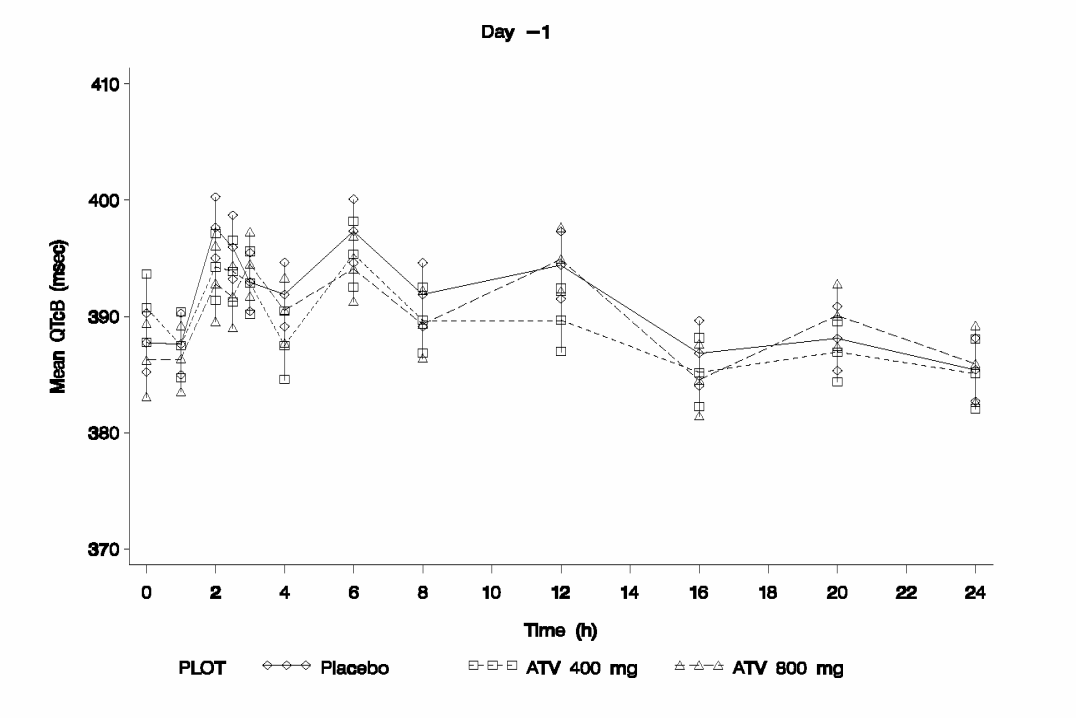
Cardiac Issues

As mentioned previously in this document, evaluation of the QT interval includes "correction" of the QT interval for heart rate, as the QT interval decreases with increasing heart rate. Corrected QT intervals (QTc) were derived using a correction formula known as Bazett's; this has been the correction method historically used by the FDA and the one on which criteria for evaluation of the QT interval have been based. Several weeks ago, the Division requested that the applicant recalculate data from two studies using a correction formula known as Fridericia's; while this correction formula has not been used by the FDA to evaluate potential QT effects in the past, it was felt that presentation of this data would provide a balanced analysis of QT effects. This data will be presented only by the applicant.

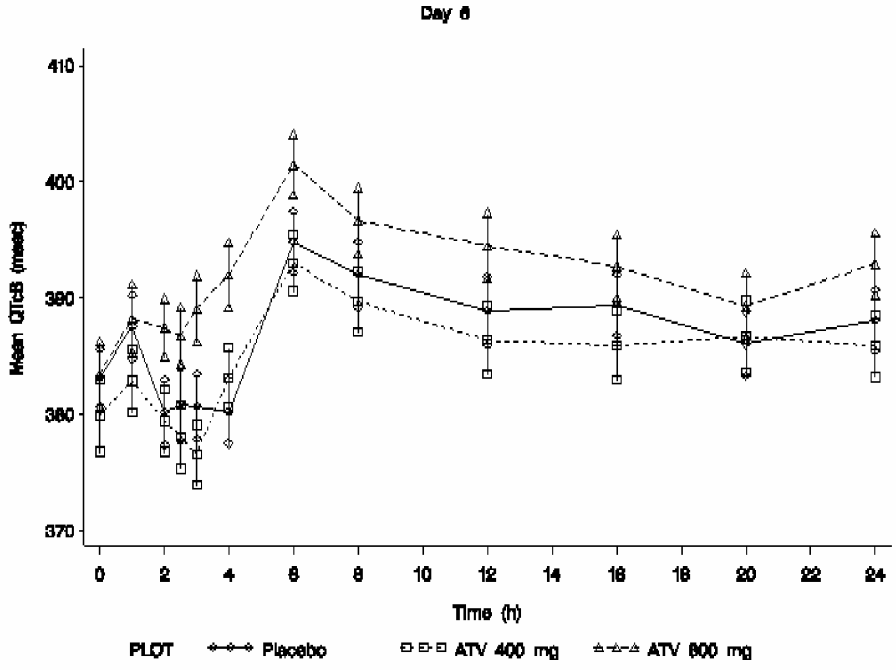
Several pharmacokinetic studies were undertaken by the applicant to evaluate the effects of atazanavir on the QT interval after preclinical studies revealed a weak signal for potential to prolong the QT interval. We will focus here on study 076, a three-treatment, three-period crossover study in which 72 subjects were randomized to receive multiple once-daily doses of atazanavir at 400 mg, 800 mg, or a placebo in six different sequences, with a washout period between doses of ≥ 14 days. The results we will focus on here will be changes in the average Bazett's corrected QT interval over 24 hours of dosing (QTcB Avg) and the changes in the Bazett's corrected QT interval at the time of maximal atazanavir concentration (QTcB at Tmax).

The following two graphs display the means of the QTc interval across a 24-hour period prior to dosing and then at day 6 of drug administration.

Plot of Mean QTcB From Time of Dosing on Day –1 (Baseline) Study 076



Plot of Mean QTcB from Time of Dosing on Day 6 Study 076



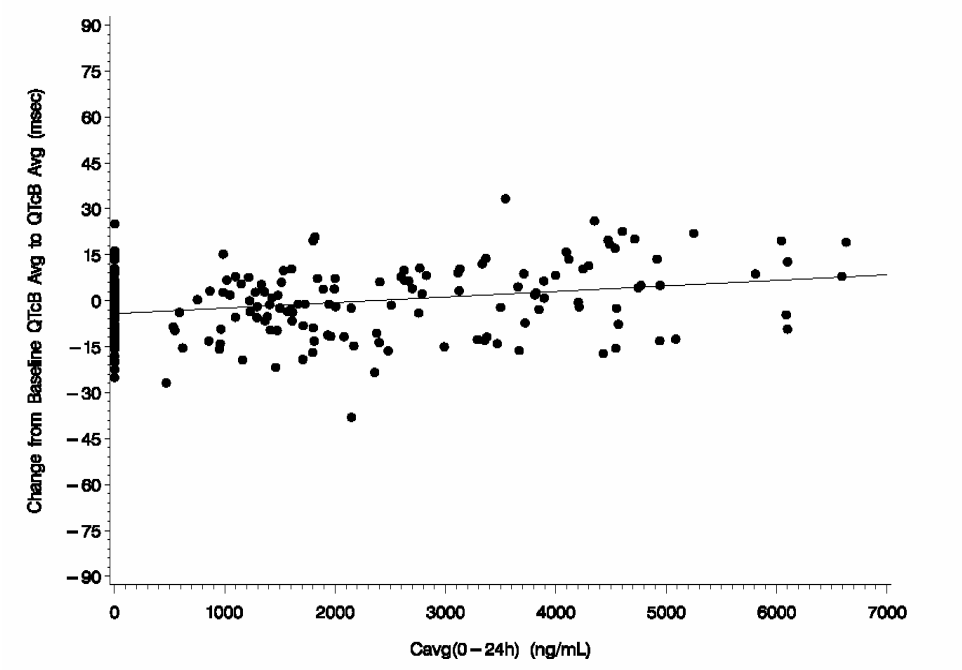
As can be seen in the previous figures, differences in the mean QTcB interval become apparent at the 800 mg dose at the time that corresponds to the maximum concentration of atazanavir (Tmax [2-2.5 hrs]). An analysis of covariance of QTcB changes from baseline showed that the placebo-corrected difference in the mean changes from baseline of the average QTcB interval 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.

Summary statistics for derived QTcB changes from baseline in each treatment group are summarized in the following table. A scatter plot of QTc Avg changes from baseline versus ATV concentration follows this table.

Summary of Selected Derived QTcB Changes from Baseline			
Dose	Subjects (#)	Δ QTcB Avg (msec) Mean (SD)	Δ QTcB at Tmax (msec) Mean (SD)
Placebo	67	-2.5 (10)	-15 (20)
400 mg	65	-3.0 (10)	-17 (20)
800 mg	66	2.9 (13)	-4 (22)

Scatter Plot and Fitted Regression Line of Derived QTc Avg Changes from Baseline vs. Measures of Average ATV Concentration



Summary of Cardiovascular Evaluation of the QT Interval 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. Interpretation of the ECG results was limited by several 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. And lastly, a single baseline ECG measure likely does not provide an accurate measure of a baseline value from which to calculate delta signals.

For this section categories of QT prolongation will be reviewed, using the following categories to assess potential signals for QT prolongation:

Normal QTc Interval Criteria

QTc Interval (msec)	Males	Females
Normal	< 430	< 450
Borderline	430 – 450	450 – 470
Prolonged	> 450	> 470

Absolute QTc Signals
QTc > 450 msec
QTc > 470 msec
QTc > 500 msec

Changes from Baseline (Delta) Signals
QTc increase from baseline ≥ 30 msec
QTc increase from baseline ≥ 60 msec

Study 034 - In study 034 subjects from each treatment arm had similar numbers of subjects with QTc prolongation.

Maximum Post-Dose QTc (msec)

		Females	
	< 450	**450 – 470**	**> 470**
Atazanavir	121/127 (95)	6/127 (5)	0/127 (0)
Efavirenz	99/103 (96)	3/103 (3)	1/103 (1)
		Males	
	< 430	**430 – 450**	**>450**
Atazanavir	202/225 (90)	19/225 (8)	4/225 (2)
Efavirenz	198/221 (90)	17/221 (8)	6/221 (3)

One male subject receiving efavirenz experienced a QTc > 500 msec. Nine of the eleven subjects with QTc prolongation were receiving drugs mentioned as possible contributors to QTc interval prolongation in the literature, specifically trimethoprim/sulfamethoxasole, amitriptyline, and fluconazole; their contribution to QT prolongation in this population is unknown.

Changes from Trough QTc to Post-Dose Maximum QTc

	≤ 30	**30 - 60**	**≥ 60**
Atazanavir	304/352 (86)	44/352 (13)	4/352 (1)
Efavirenz	303/324 (94)	21/324 (6)	0/324 (0)

In study 034 no cardiovascular (CV) events led to death and no events of sudden death were reported. CV events leading to treatment discontinuation occurred only in the efavirenz arm (1 event each of MI, HTN, syncope, palpitations, and vasodilatation). Four CV events coded as SAEs by investigators occurred and all were in efavirenz arm (1 MI, 2 syncope, 1 HTN). Grade 3-4 CV events occurred in 3 atazanavir treated patients (1 event each of hypotension, syncope, and bradycardia). The 3 events occurring in atazanavir were related to one event of meningoencephalitis (bradycardia), and two events of grade 3-4 anemia (hypotension and syncope).

All other CV events occurred with roughly equal frequency between arms with the exception of vasodilatation which was more frequent in the EFV arm. AEs potentially related to arrhythmia were reviewed (w/exception of dizziness) and found to be generally mild, self-limiting, and attributable to causes other than arrhythmia.

Study 043 – In this study two atazanavir subjects and seven lopinavir/ritonavir subjects had post-baseline QTc prolongation. None of these subjects were on concomitant medications known to prolong the QT interval. Slightly more patients on LPV/RTV had post-dose maximum changes from baseline QTc greater than 60 msec.

Changes From Trough QTc to Post-Dose Maximum QTc

	≤ 30	**30 - 60**	**≥ 60**
Atazanavir	77/107 (72)	28/107 (26)	2/107 (2)
Lopinavir/Ritonavir	77/115 (67)	31/115 (27)	7/115 (6)

No cardiovascular events led to death or discontinuation from study. One LPV/RTV subject experienced an MI on study; no other CV events were reported as SAEs or as grade 3-4 events. Other reported CV events that were considered to be potentially related to study therapy by investigators included one event of extrasystole in an ATV patient and one event of palpitations in a LPV/RTV patient; no ECGs were recorded at the time of these events.

PR Interval

Evaluation of the effects of atazanavir on the PR interval in the previously described study 076 revealed a 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 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)

PR intervals > 250 msec were observed in eight subjects receiving 800 mg of atazanavir in study 076. A PR interval of 324 msec was observed in one female subject receiving the 800 mg dose.

In another pharmacokinetic study designed to study ECG effects, a female subject was discontinued from the study when she developed an asymptomatic prolongation of the PR interval of > 400 msec on an 800 mg dose of ATV.

Study 034 - At trough drug concentrations, the mean PR interval was 5 msec shorter for subjects receiving EFV compared with subjects receiving ATV. Minimal changes in the mean post-dose PR intervals from trough were observed on both treatment regimens. Maximum recorded PR intervals on atazanavir ranged from 265-307 msec.

Seven of 324 evaluable subjects (2.2%) treated with EFV and 16 of 352 evaluable subjects (4.5%) treated with ATV experienced first degree AV block (PR > 200 msec) on at least one ECG. One subject receiving atazanavir reported bundle branch block and one patient receiving efavirenz reported bifasicular block. Neither event was reported as a Grade 3-4 event, an SAE, or resulted in discontinuation from therapy.

Study 043 – No differences in mean PR intervals were noted between atazanavir and lopinavir/ritonavir subjects. Mean PR intervals at all time points were similar. The mean PR interval at the time corresponding to Cmax for atazanavir was 157 msec for both ATV and LPV/RTV. Six percent of subjects in both treatment arms experienced first degree AV block. No other conduction abnormalities were reported in this study.

As mentioned previously in this document, one subject receiving atazanavir in combination with DLV/TNF/3TC through the expanded access protocol was hospitalized with atypical angina and a junctional rhythm. Medications included verapamil and mirtazapine; ARV medications were discontinued following hospital admission, however, verapamil and other medications were continued. Junctional rhythm persisted despite discontinuation of atazanavir. The patient was found unresponsive during hospital admission with an idioventricular rhythm; preliminary autopsy revealed a 95% LAD without evidence of infarct.

It is likely the junctional rhythm in this patient was multifactorial. It may have been due, in part, to high serum levels of both verapamil and atazanavir that occurred with co-administration of delavirdine, a CYP 3A4 inhibitor. Persistence of this rhythm after discontinuation of atazanavir would suggest that factors other than atazanavir use contributed to the development of this rhythm in this patient.

In summary, while pharmacokinetic studies designed to evaluate effects of atazanavir revealed moderate effects on the PR interval, clinical events related to prolongation of the PR interval were uncommon. First degree AV block was the most common abnormality observed. Effects on the QT interval appeared to be minimal.

VII. **Questions for the Advisory Committee**

Listed below are a number of questions for you to consider during the discussion period.

1) Are the available data sufficient to support approval of atazanavir for the treatment of HIV infection?

   If no, what additional studies are recommended?

   If yes, please address the following questions.

2) Does the degree of hyperbilirubinemia seen with atazanavir administration raise any significant safety concerns?

3) Does prolongation of the PR and QT interval raise any significant safety concerns?

4) Does the committee believe that the effect of atazanavir on lipid parameters offers patients a unique advantage over other treatment options?

5) Please provide your risk/benefit assessment of atazanavir and its implications for clinical use.

6) Please provide us with recommendations for any Phase 4 studies of atazanavir.