CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-567

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21567	Submission Date(s): Dec 20, 2002
Brand Name	Reyataz®
Generic Name	Atazanavir sulfate
Primary Reviewer	Jenny H. Zheng, Ph.D.
In Vitro Metabolism Reviewer	Derek Zhang, Ph.D.
Team Leader	Kellie Reynolds, Pharm.D.
OCPB Division	DPE III
ORM division	DAVDP
Applicant	Bristol-Myers Squibb Company
Relevant IND(s)	IND ———
Submission Type; Code	Priority (P1)
Formulation; Strength(s)	100/150/200 mg capsule
Indication	Treatment of HIV infection in combination with other antiretroviral drugs

1. EXECUTIVE SUMMARY

Atazanavir, a protease inhibitor, is proposed for treatment of HIV infection. Atazanavir 400 mg once daily was studied in treatment-naïve and treatment-experienced subjects. Phase II and III trials in this NDA support the antiviral activity of atazanavir, which was similar to nelfinavir or efavirenz in combination with two NRTIs in treatment-naïve patients, but was inferior to lopinavir/ritonavir in treatment-experienced patients. The following safety issues were evaluated: drug-drug interactions, QTc and PR prolongation, and hyperbilirubinemia.

1.1 Recommendation

The Clinical Pharmacology and Biopharmaceutics information provided by the applicant is acceptable. The outstanding issues that need to be addressed are listed in the Phase IV Commitments Section.

1.2 Phase IV Commitments

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

2. Evaluate the pharmacokinetics of atazanavir when coadministered with histamine H2 receptor antagonist.

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

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

5. Evaluate the pharmacokinetics of atazanavir in subjects with renal impairment to allow the determination of dosing recommendations through the conduct of a pharmacokinetic study.

2. TABLE OF CONTENTS

3. SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Atazanavir is an azapeptide HIV-1 protease inhibitor. Atazanavir exhibits anti-HIV-1 activity with a mean 50% effective concentration (EC_{50}) in the absence of human serum of 2 to 5 nM against a variety of HIV wild type isolates, and 7.8 nM in the presence of 40% human serum. The Cmin of atazanavir after 400 mg dose is about 45-fold higher than protein-binding adjusted EC_{50}. The clinical pharmacology and pharmacokinetic profile of atazanavir has been defined in healthy and HIV-infected subjects. These studies show atazanavir has the following clinical pharmacology characteristics:

- Atazanavir exposures are about 50% (geometric mean) lower in HIV-infected subjects as compared to healthy subjects. The following table summarizes the steady-state PK parameter values for atazanavir at 400 mg QD in the fed state in healthy and HIV-infected subjects.

PK Parameters	Healthy Subjects (n = 14)	HIV-Infected Subjects (n = 13)
C_{max} (ng/mL)		
Geometric Mean (CV%)	5199 (26)	2298 (71)
T_{max} (hr)		
Median	2.5	2.0
Range		
AUC (ng.hr/mL)		
Geometric Mean (CV%)	28132 (28)	14874 (91)
t-Half (hr)		
Mean (SD)	7.9 (2.9)	6.5 (2.6)
C_{min} (ng/mL)		
Geometric Mean (CV%)	152 (88)	120 (109)

- As compared to fasted conditions, a light meal increased Cmax and AUC of atazanavir by 57% and 70%, respectively; while a high fat meal had no effect on the Cmax, but increased AUC by 35%.

- Steady-state is achieved between Days 4 and 8 in both healthy and HIV-infected subjects with an accumulation index of 2 to 3.

- Atazanavir exhibits concentration independent protein binding to albumin and α-1-acid glycoprotein of approximately 86%.

- Atazanavir was found to distribute into the cerebrospinal (CSF) and seminal fluid. The CSF/plasma ratio for atazanavir in HIV-infected subjects (n=4) ranged between 0.0021 and 0.0226 and seminal fluid/plasma ratio (n=5) ranged between 0.11 and 4.42.

- Atazanavir is extensively metabolized in humans. The major biotransformation pathways of atazanavir in humans consist of monooxygenation and dioxygenation. Other minor biotransformation pathways consist of glucuronidation, N-dealkylation, hydrolysis and oxygenation with dehydrogenation. In human plasma, atazanavir constitutes the major portion of radioactivity, but BMS-421419, BMS-551160 and a keto metabolite (M41) each constitutes approximately 10% of the plasma radioactivity. Neither metabolite demonstrated in vitro antiviral activity.

- In vitro studies using human liver microsomes suggested that atazanavir is metabolized by CYP3A4. However, the 20 μM ketoconazole used in the in vitro study is too high and could inhibit other CYPs. In addition, in vivo studies have shown conflicting results. Therefore, the metabolic pathway, including enzymes involved, may not be fully characterized for atazanavir.

- Atazanavir is a competitive inhibitor of CYP3A4 (Ki, inhibition rate constant = 2.35 μM) and UGT1A1 (Ki=1.9 μM) at clinically relevant concentrations. Atazanavir also competitively inhibits CYP1A2 and CYP2C9 with the Ki values of 12 μM.

- Atazanavir may be a substrate of P-gp and a weak inhibitor of P-gp, with an IC_{50} value of ~29 μM based on in vitro Caco-2 cell model studies.

- Approximately 13% of atazanavir was excreted in the urine with approximately 7% of the dose excreted as unchanged drug. Approximately 79% of atazanavir was recovered in the feces, suggesting that biliary elimination is a major pathway for the elimination of atazanavir and/or a fraction of the dose is unabsorbed.

- Pharmacokinetics in subjects with renal impairment was not studied and is listed in the Phase IV commitments.

- Atazanavir exposure in subjects with moderate to severe hepatic impairment was 45% higher after 400 mg dose and 31% lower after 200 mg dose as compared to the exposure in subjects with normal hepatic function after 400 mg dose. In addition, atazanavir exposure is dose proportional in subjects with hepatic impairment. Therefore, a dose reduction to 300 mg is suggested for patients with moderate hepatic impairment. Atazanavir should not be used in patients with severe hepatic impairment, due to the small number of subjects with severe hepatic impairment studied (n = 2). No dose reduction is needed for patients with mild hepatic impairment.

- There was no PK difference between female and male subjects when parameters were normalized by body weight.

- Elderly subjects have 17% higher AUC and Cmax compared to younger subjects. After body weight adjustment, a similar difference still exists. However, the difference is not considered clinically significant.

- Atazanavir results in concentration-dependent increase of total and indirect bilirubin levels, primarily due to inhibition of UGT 1A1.

- The magnitude of the bilirubin increase in the presence of atazanavir is UGT 1A1 genotype dependent, with more significant increase of bilirubin levels in subjects with genotype 6/7 than genotype 6/6.

- Atazanavir is associated with dose- and concentration-dependent prolongations of the PR interval of the ECG. First degree A-V block was the most frequently observed ECG abnormality in the treatment naïve subjects with the 400 mg atazanavir QD dose.

- Atazanavir is associated with dose-dependent increases in the QT interval with Bazett's correction (QTcB). However, dose-dependent increases in QT interval are not present with Fridericia's correction (QTcF). Atazanavir also increases heart rate. The analysis with subjects in placebo group shows that QTcB increased with increased heart rates, while Fridericia's corrected QT (QTcF) is constant with increased heart rates. Therefore, Fridericia's correction may be more appropriate than Bazett's correction. The QTc prolongation is not clinically significant at 400 mg QD dose based on both correction factors. In addition, the QTc prolongation is not clinically significant at 800 mg QD dose based on Fridericia's correction.

- Population PK/PD analysis was used for dose selection. The interim population PK/PD analysis was conducted using the data collected during the two-week monotherapy phase at the beginning of the trial. Since this analysis was interim and

the patients' food status at the time of the dose was unknown, the Phase I model available for the interim analysis was developed using fasted data. The results of this population PK/PD analysis was not accepted due to:

- assuming that pharmacokinetics of atazanavir in HIV-1 infected patients is the same as that in healthy subjects, which is not true;
- using fasted data to select the dose. However, it is known that atazanavir exposure is higher after administered under fed conditions as compared to fasted conditions.

- Population PK analysis results were cited by the sponsor regarding the effect of race on pharmacokinetics of atazanavir. However, the results of the population PK/PD analysis was not accepted due to
  - uncertainty of the meal time relative to dosing;
  - all the PK parameters and inter- and intra-individual variability were fixed to the population mean estimates obtained from the Phase I healthy subjects model, while there may be 50% lower atazanavir exposure in HIV-infected as compared to healthy subjects; and
  - the concentrations estimated did not accurately predict the observed concentrations.

  In addition, subject covariates were not formally evaluated in the population pharmacokinetic analysis.

- The applicant studied drug-drug interactions between atazanavir and possible coadministered CYP3A4 substrates or drugs that inhibit or induce CYP3A4. In addition, drug-drug interactions between atazanavir and other possible coadministered drugs that could cause QT or PR prolongation were also studied. The following tables show the pharmacokinetic results of drug-drug interaction studies.

Drug Interactions: Pharmacokinetic Parameters for Atazanavir in the Presence of Coadministered Drugs

Coadministered Drug	Coadministered Drug Dose/Schedule	REYATAZ Dose/Schedule	n	Ratio (90% Confidence Interval) of Atazanavir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect =1.00		
				C_{max}	AUC	C_{min}
atenolol	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)	0.74 (0.65, 0.86)
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)	1.91 (1.66, 2.21)
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)	0.16 (0.10, 0.27)
	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)	1.03 (0.61, 1.73)
diltiazem	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)	0.98 (0.90, 1.07)
efavirenz	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)	0.07 (0.05, 0.10)
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)	1.48 (1.24, 1.76)
ketoconazole	200 mg QD, d 7-13	400 mg QD, d 1-13	14	0.99 (0.77, 1.28)	1.10 (0.89, 1.37)	1.03 (0.53, 2.01)
rifabutin	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)	1.13 (0.68, 1.87)
ritonavir[b]	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)	11.89 (10.23, 13.82)

[a] One subject did not receive REYATAZ.

[b] Compared with atazanavir 400 mg QD historical data, administration of atazanavir/ritonavir 300/100 mg QD increased the atazanavir geometric mean values of C_{max}, AUC, and C_{min} by 18%, 103%, and 671%, respectively. The geometric mean values of atazanavir pharmacokinetic parameters when coadministered with ritonavir were: C_{max} = 6129 ng/mL, AUC = 57039 ng·h/mL, and C_{min} = 1227 ng/mL.

Drug Interactions: Pharmacokinetic Parameters for Coadministered Drugs 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	C_{min}
atenolol	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)	1.02 (0.88, 1.19)
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)	0.38 (0.35, 0.43) OH-clarithromycin: 2.64 (2.36, 2.94)
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)	NA d4T: 1.04 (0.94, 1.16)
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)	0.41 (0.37, 0.47) desacetyl-diltiazem: 0.45 (0.41, 0.49)
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)	ethinyl estradiol: 1.91 (1.57, 2.33) norethindrone: 3.62 (2.57, 5.09)
rifabutin	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)	3.43 (1.98, 5.96) 25-O-desacetyl-rifabutin: 75.6 (30.1, 190.0)
saquinavir (soft gelatin capsules)[c]	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)	6.86 (5.29, 8.91)
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)	lamivudine: 1.12 (1.04, 1.21) zidovudine: 0.69 (0.57, 0.84) zidovudine glucuronide: 0.82 (0.62, 1.08)

[a] One subject did not receive REYATAZ.
[b] Not the recommended therapeutic dose of atazanavir.
[c] The combination of atazanavir and saquinavir 1200 mg QD produced daily saquinavir exposures similar to the values produced by the standard therapeutic dosing of saquinavir at 1200 mg TID. However, the C_{max} is about 79% higher than that for the standard dosing of saquinavir (soft gelatin capsules) alone at 1200 mg TID.

NA = not available.

- Atazanavir has an additive PR prolongation effect when coadministered with clarithromycin and diltiazem.
- Dose adjustments or precautions are recommended when atazanavir is coadministered with the following drugs.

Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interactions

Concomitant Drug Class: Specific Drugs	Effect on Concentration of Atazanavir or Concomitant Drug	Clinical Comment
HIV Antiviral Agents		
Nucleoside Reverse Transcriptase Inhibitors (NRTIs): didanosine buffered formulations	↓ atazanavir	Coadministration with REYATAZ did not alter exposure to didanosine; however, exposure to atazanavir was markedly decreased by coadministration of REYATAZ with didanosine buffered tablets (presumably due to the increase in gastric pH caused by buffers in the didanosine tablets). In addition, it is recommended that didanosine be administered on an empty stomach; therefore, REYATAZ should be given (with food) 2 h before or 1 h after didanosine buffered formulations (see **CLINICAL PHARMACOLOGY: Drug-Drug Interactions**). (Although no interaction is expected with didanosine EC capsules, because didanosine EC capsules are to be given on an empty stomach and REYATAZ is to be given with food, they should be administered at different times.)
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs): efavirenz	↓ atazanavir	If REYATAZ is to be coadministered with efavirenz, which decreases atazanavir exposure, it is recommended that REYATAZ 300 mg with ritonavir 100 mg be coadministered with efavirenz 600 mg (all as a single daily dose with food), as this combination results in atazanavir exposure that approximates the mean exposure to atazanavir produced by 400 mg of REYATAZ alone. REYATAZ without ritonavir should not be coadministered with efavirenz.
Protease Inhibitors: saquinavir (soft gelatin capsules)	↑ saquinavir	Appropriate dosing recommendations for this combination, with respect to efficacy and safety, have not been established.
Protease Inhibitors: ritonavir	↑ atazanavir	Coadministration of REYATAZ and ritonavir is currently under clinical investigation. If REYATAZ is coadministered with ritonavir, it is recommended that REYATAZ 300 mg once daily be given with ritonavir 100 mg once daily with food.
Other Agents		
Antacids and buffered medications	↓ atazanavir	Reduced plasma concentrations of atazanavir are expected if antacids, including buffered medications, are administered with REYATAZ. REYATAZ should be administered 2 hours before or 1 hour after these medications.
Antiarrhythmics: amiodarone, lidocaine (systemic), quinidine	↑ amiodarone, lidocaine (systemic), quinidine	Coadministration with REYATAZ has the potential to produce serious and/or life-threatening adverse events and has not been studied. Concentration monitoring of these drugs is recommended if they are used concomitantly with REYATAZ.
Anticoagulants: warfarin	↑ warfarin	Coadministration with REYATAZ has the potential to produce serious and/or life-threatening bleeding and has not been studied. It is recommended that INR (International Normalization Ratio) be monitored.
Antidepressants: tricyclic antidepressants	↑ tricyclic antidepressants	Coadministration with REYATAZ has the potential to produce serious and/or life-threatening adverse events and has not been studied. Concentration monitoring of these drugs is recommended if they are used concomitantly with REYATAZ.
Antimycobacterials: rifabutin	↑ rifabutin	A rifabutin dose reduction of up to 75% (eg, 150 mg every other day or 3 times per week) is recommended.

Calcium channel blockers: diltiazem	↑ diltiazem and desacetyl-diltiazem	Caution is warranted. A dose reduction of diltiazem by 50% should be considered. ECG monitoring is recommended.
eg, felodipine, nifedipine, nicardipine, and verapamil	↑ calcium channel blocker	Caution is warranted. Dose titration of the calcium channel blocker should be considered. ECG monitoring is recommended.
Erectile dysfunction agents: sildenafil	↑ sildenafil	Coadministration may result in an increase in sildenafil-associated adverse events, including hypotension, visual changes, and priapism. Use with caution at a reduced dose of 25mg every 48 hours and monitor for adverse events.
HMG-CoA reductase inhibitors: atorvastatin	↑ atorvastatin	The risk of myopathy including rhabdomyolysis may be increased when protease inhibitors, including REYATAZ, are used in combination with atorvastatin. Caution should be exercised.
H_2-Receptor antagonists	↓ atazanavir	Reduced plasma concentrations of atazanavir are expected if H_2-receptor antagonists are administered with REYATAZ. This may result in loss of therapeutic effect and development of resistance. To lessen the effect of H_2-receptor antagonists on atazanavir exposure, it is recommended that an H_2-receptor antagonist and REYATAZ be administered as far apart as possible, preferably 12 hours apart.
Immunosuppressants: cyclosporin, sirolimus, tacrolimus	↑ immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when coadministered with REYATAZ.
Macrolide antibiotics: clarithromycin	↑ clarithromycin ↓ 14-OH clarithromycin ↑ atazanavir	Increased concentrations of clarithromycin may cause QTc prolongations; therefore, a dose reduction of clarithromycin by 50% should be considered when it is coadministered with REYATAZ. In addition, concentrations of the active metabolite 14-OH clarithromycin are significantly reduced; consider alternative therapy for indications other than infections due to *Mycobacterium avium* complex.
Oral contraceptives: ethinyl estradiol and norethindrone	↑ ethinyl estradiol ↑ norethindrone	Mean concentrations of ethinyl estradiol, when coadministered as a 35-μg dose with REYATAZ, are increased to a level between mean concentrations produced by a 35-μg and a 50-μg ethinyl estradiol dose. Decreased HDL or increased insulin resistance may be associated with increased mean concentrations of norethindrone, when coadministered with REYATAZ, particularly in diabetic women. Caution should be exercised. It is recommended that the lowest effective dose of each oral contraceptive component be used.

- Atazanavir drug interactions with CYP2C9 substrates (e.g. warfarin) or CYP1A2 substrate (e.g. theophylline) have not been studied. Caution should be exercised.
- Drugs that are contraindicated or not recommended for coadministration with atazanavir are listed in the following table:

Drugs That Should Not Be Administered with REYATAZ

Drug class: Specific Drugs	Clinical Comment
Antimycobacterials: rifampin	Decreases plasma concentrations and AUC of most protease inhibitors by about 90%. This may result in loss of therapeutic effect and development of resistance.
Antineoplastics: irinotecan	Atazanavir inhibits UGT and may interfere with the metabolism of irinotecan, resulting in increased irinotecan toxicities.
Benzodiazepines: midazolam, triazolam	CONTRAINDICATED due to potential for serious and/or life-threatening events such as prolonged or increased sedation or respiratory depression.
Calcium Channel Blockers: bepridil	Potential for serious and/or life-threatening adverse events.
Ergot Derivatives: dihydrorergotamine, ergotamine, ergonovine, methylergonovine	CONTRAINDICATED due to potential for serious and/or life-threatening events such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI Motility Agent: cisapride	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
HMG-CoA Reductase Inhibitors: lovastatin, simvastatin	Potential for serious reactions such as myopathy including rhabdomyolysis.
Neuroleptic: pimozide	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Protease Inhibitors: indinavir	Both REYATAZ and indinavir are associated with indirect (unconjugated) hyperbilirubinemia. Combinations of these drugs have not been studied and coadministration of REYATAZ and indinavir is not recommended.
Proton-Pump Inhibitors	Concomitant use of REYATAZ and proton-pump inhibitors is not recommended. Coadministration of REYATAZ with proton-pump inhibitors is expected to substantially decrease REYATAZ plasma concentrations and reduce its therapeutic effect.
Herbal Products: St. John's wort (*Hypericum perforatum*)	Patients taking REYATAZ should not use products containing St. John's wort (*Hypericum perforatum*) because coadministration may be expected to reduce plasma concentrations of atazanavir. This may result in loss of therapeutic effect and development of resistance.

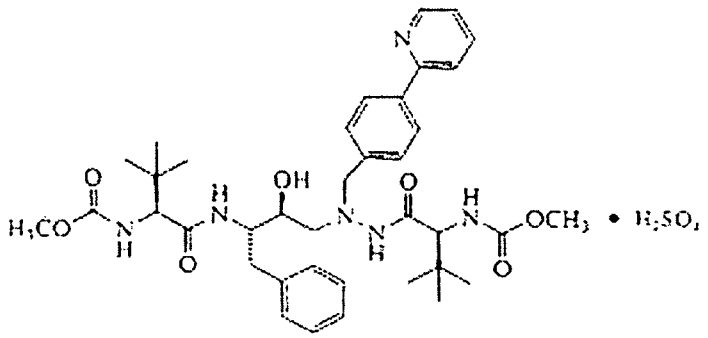
4. QUESTION BASED REVIEW

4.1 General Attributes

4.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

The structure and physical properties of atazanavir sulfate are shown below:

Structural Formula: $C_{38}H_{52}N_6O_7 \cdot H_2SO_4$



Chemical Name: (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)

Molecular Weight: 704.9 daltons

pH-solubility profile: At strongly acidic pH, the solubility values are between 3.2 and 5.2 mg/mL. Solubilities decreased with increasing pH and remained virtually unchanged (0.002 mg/mL) in the pH range of 4.3 to 12.1, which is consistent with the ionization of the molecule (pKa = 4.7).

pH	Solubility (mg/mL) *
0.8	3.2
1.1	3.7
1.7	4.3
1.9	5.2
3.0	0.77
3.1	0.37
4.3	0.001
5.2	0.002
8.7	0.002
12.1	0.001

* All solubility values are reported in free base equivalents

Apparent Permeability: ≥100 nm/sec

The quantitative composition of the to-be-marketed atazanavir sulfate capsules are shown in the following table:

Ingredient	Quantity per dosage form (mg/capsule) 100[a] mg Capsule	150[a] mg Capsule	200[a] mg Capsule	Function	Compendial Reference
Atazanavir Sulfate[b]				Active Ingredient	NC[c]
Lactose, Monohydrate[d]				Filler	NF[e]
Crospovidone				Disintegrant	NF
Magnesium Stearate[f]				Lubricant	NF
Hard Gelatin Capsule Shell[g]				Capsule shell	NC
TOTAL	180.2	270.3	360.4		

[a] Expressed as the free base.

[b] Based on a purity of 100% for atazanavir sulfate

[c] Non compendial.

[d] Amount may vary based on purity of atazanavir sulfate.

[e] National Formulary.

[f]

[g] The composition of the hard gelatin capsule shell is presented in section [II.C.2].

4.1.2 What is the proposed mechanism of drug action and therapeutic indication?

Atazanavir is an azapeptide HIV-1 protease inhibitor. The compound selectively inhibits the virus-specific processing of viral Gag-Pol proteins in HIV-1 infected cells, thus preventing formation of mature virions. Atazanavir exhibits anti-HIV-1 activity with a mean 50% effective concentration (EC_{50}) in the absence of human serum of 2 to 5 nM against a variety of HIV wild type isolates, and 7.8 nM in the presence of 40% human serum. The Cmin of atazanavir after 400 mg dose is about 45-fold higher than protein-binding adjusted EC_{50}.

4.1.3 What is the proposed dosage and route of administration?

The proposed dosing regimen for atazanavir is 400 mg once daily taken orally with food, in adult patients. The label also recommends dose modifications for drug-drug interactions and in patients with hepatic impairment.

Drug-drug interactions:

Efavirenz. When coadministered with efavirenz, it is recommended that atazanavir 300 mg and ritonavir 100 mg be given with efavirenz 600 mg (all as a single daily dose with food). Atazanavir without ritonavir should not be coadministered with efavirenz.

Didanosine. When coadministered with didanosine buffered formulations, atazanavir should be given (with food) two hours before or one hour after didanosine.

Patients with hepatic impairment:

Atazanavir should be used with caution in patients with mild to moderate hepatic A dose reduction to 300 mg once daily should be considered in patients with moderate hepatic Atazanavir should not be used in patients with severe hepatic

4.1.4 What efficacy and safety information contribute to the assessment of clinical pharmacology and biopharmaceutics study data?

Two pivotal Phase III studies (AI424034 and AI424043) provide safety and efficacy data.

Study AI424034:
This was a Phase III, randomized, double-blind, double-dummy, active-controlled, multinational, two-arm study designed to compare the antiviral efficacy and safety of ATV with zidovudine + lamivudine (ZDV + 3TC) vs. efavirenz (EFV)/ZDV+3TC in HIV-infected subjects who had received no prior antiretroviral treatment (or limited prior treatment). The antiviral efficacy of ATV 400 mg QD was similar to EFV for proportions of subjects responding to treatment with HIV RNA < 400 c/mL through 48 weeks of therapy.

Study AI424043:
This was a randomized, open-label, active-controlled, multinational, two arm study to compare the antiviral activity, metabolic changes, safety, and tolerability of ATV 400 mg QD vs. LPV/RTV 400 mg/100 mg BID, each in combination with two nucleosides, in HIV-infected subjects who had failed prior antiretroviral treatment(s) that included one PI. Subjects received two NRTIs to which their screening viral isolate was sensitive. The proportion of subjects with HIV RNA < 400 c/mL at Week 24 was 61% on the ATV treatment regimen and 81% on the LPV/RTV treatment regimen, favoring the LPV/RTV treatment regimen.

Two Phase II studies (AI424007 and 008) supported the antiviral efficacy of atazanavir in treatment naïve patients. Highly treatment-experienced subjects having failed at least two regimens containing drugs from all three classes were enrolled in Study AI424045. A

ritonavir-boosted dose of atazanavir (atazanavir/ritonavir 300/100 mg QD), 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. The efficacy data from this trial will not be used to make a regulatory decision on this NDA, because 24-week data were not submitted for review.

Safety:
The most notable adverse events related to atazanavir were hyperbilirubinemia and associated jaundice (10% on 200 mg, 8%-13% on 400 mg, 16% on 500 mg and 22% on 600 mg) and scleral icterus (2% on 200 mg; 6%-11% on 400 mg; 5% on 500 mg; and 13% on 600 mg).

Atazanavir is associated with concentration dependent increase in the PR interval, and first degree A-V block was the most frequently observed ECG abnormality in the treatment naïve subjects (AI424034: ATV 400, 5%; EFV, 3%; AI424007/041: ATV, 1%; NFV, 2%; AI424008/044: ATV 400, 12%). Atazanavir demonstrated dose dependent prolongation of the QT intervals, particularly at the 800 mg dose, using Bazett's correction. However, the dependency tended to disappear by using Fridericia's correction. The QT prolongation at the dose of 400-800 mg atazanavir QD was not clinically significant based on Fridericia's correction. Atazanavir appears to be associated with a modest dose-dependent increase in heart rate.

Atazanavir produced less change in total cholesterol, fasting LDL, and triglycerides compared to nelfinavir, efavirenz, and lopinavir/ritonavir. However, the favorable lipid profile did not appear to result in fewer reported lipodystrophy events in atazanavir-treated subjects as compared to efavirenz and nelfinavir.

4.2 General Clinical Pharmacology

4.2.1 What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

The surrogate efficacy endpoints for HIV-1 infection are plasma HIV viral load and CD4 cell counts. The viral load tends to be more predictive of the progression of HIV infection than CD4 cell counts. The primary efficacy endpoint for the pivotal clinical studies was the proportion of subjects with a treatment response (HIV RNA < 400 c/mL) without prior failure (TRWPF) through Week 48 (Study AI424034) or through Week 24 (Study AI424043).

Total bilirubin and direct bilirubin were measured to detect if subjects had hyperbilirubinemia, and if hyperbilirubinemia was due to direct or indirect bilirubin increase. It is believed that increased direct bilirubin but not indirect bilirubin is associated with a hepatotoxic process. Hyperbilirubinemia can result in jaundice and scleral icterus.

4.2.2 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

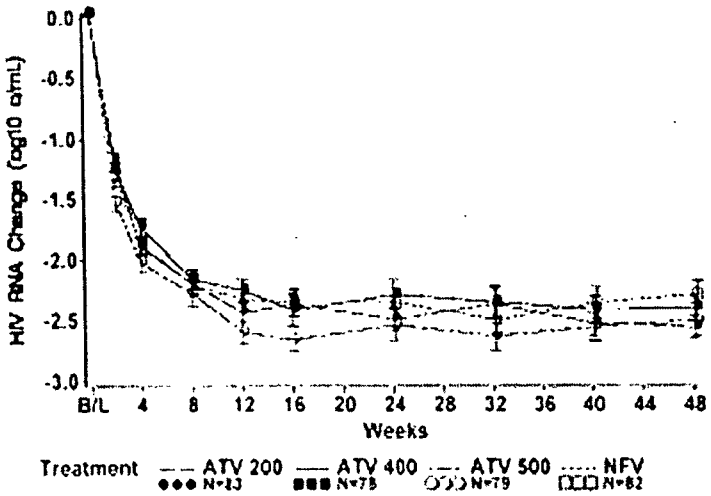
The concentrations of atazanavir in human plasma were determined by a ——— method using ——— detection. The assays are acceptable. See section 4.6 for further details. No active metabolites are present in the plasma.

4.2.3 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?

The sponsor attempted to establish an exposure-response relationship for efficacy using a population PK/PD analysis. However, the population PK analysis was not acceptable. (See section 4.2.3.3)

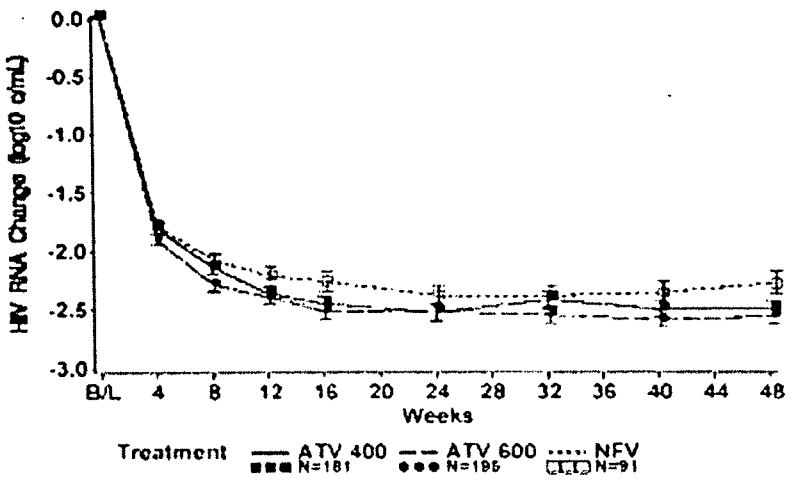
Efficacy

The Phase II study AI424007 showed that the antiviral activity of ATV at all three doses studied (200, 400, and 500 mg QD) was similar to NFV (750 mg TID) in treatment-naïve patients as measured by the primary endpoint of HIV RNA change from baseline through Week 48.



Source: AI424007 48 Week Clinical Study Report

Another Phase II Study (AI424008) showed that antiviral activity of ATV at the two doses studied (400 and 600 mg QD) was similar to NFV (1250 mg BID) in treatment-naïve patients as measured by the primary endpoint of HIV RNA change from baseline through Week 48.



Source: AI424008 48 Week Clinical Study Report

Therefore, there was no dose-response relationship for atazanavir efficacy from dose of 200 mg to 600 mg QD in treatment naïve patients. The rationale for selection of the 400 mg QD dose is in Section 4.2.3.3.

Bilirubin

Bilirubin levels (both total and indirect (unconjugated)) tended to increase as atazanavir plasma trough concentrations increased, and returned to baseline following discontinuation of atazanavir. In order to elucidate the mechanism of hyperbilirubinemia, studies were conducted by the applicant to investigate the following potential causes:

Increased production of bilirubin in spleen and peripheral tissues: Evidence for hemolysis was not apparent as the clinical markers, LDH, reticulocytes, and hemoglobin, were each stable. In a follow-up Gunn rat study conducted to further investigate any effect of ATV on hemolysis, rats administered up to 600 mg/kg of ATV by gavage had little increase in bilirubin.

Displacement of bilirubin from albumin during transport to the liver: Equilibrium dialysis determined that ATV did not affect the binding of bilirubin to albumin at physiological concentrations over the anticipated therapeutic concentration range.

Decreased uptake of bilirubin by liver cells from plasma: Rat hepatocyte studies showed that ATV has no effect on bilirubin uptake versus control at concentrations (30 - 100 µM) several-fold higher than the Cmax (10 µM) in humans.

Displacement of bilirubin from the cytosolic binding protein (ligand) in liver cells: In circular dichroism studies evaluating the ability of ATV to displace bilirubin from any of several glutathione-S-transferase isoforms (GSTs), ATV had no effect on the binding of bilirubin to any of several GSTs at concentrations of 100 µM, several-fold higher than the highest maximal concentrations (Cmax) in humans (up to 10 µM).

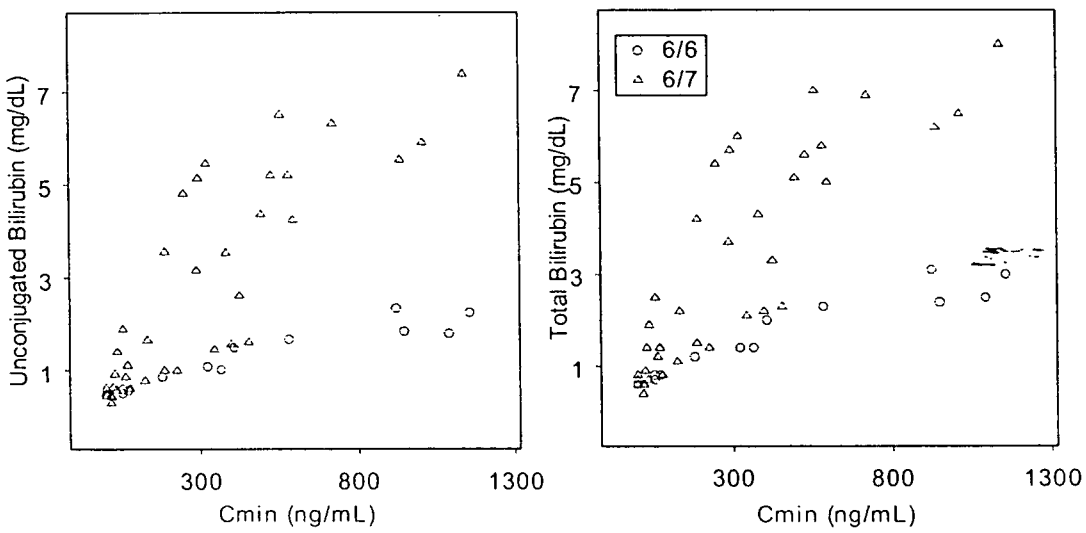
Inhibition of Adenosine Triphosphate (ATP)-dependent conjugated bilirubin into bile canaliculi: In the early clinical trials, it was also noted at higher levels of

hyperbilirubinemia that the conjugated (direct) component of bilirubin was elevated to levels above the upper limit of normal. These levels potentially suggested a hepatotoxic process in the presence of ATV. The applicant indicated that the auto-analyzer method used to determine bilirubin levels overestimated conjugated bilirubin values. Plasma samples from pharmacokinetic study 028 were reassessed by ——— which directly measures each bilirubin fraction. The values of the conjugated bilirubin component of the provided samples were substantially lower when measured by ——. In addition, no detectable bilirubin was observed in the urine of healthy subjects after multiple doses of ATV. On this basis, the applicant concluded that there was no reason to investigate the inhibition of ATP-dependant bilirubin glucuronide secretion into bile canaliculi at the level of transporters

Inhibition of bilirubin conjugation mediated by the UGT 1A1 isozyme: ATV, like indinavir, inhibits the glucuronidation of bilirubin in a heterologously expressed human UGT 1A1 *in vitro* system, as well as in human liver microsomes. At clinically relevant concentrations, ATV, bound to purified UGT 1A1 isozymes, inhibited the conjugation of bilirubin.

These studies suggest that the predominant mechanism of the primarily unconjugated hyperbilirubinemia seen with ATV exposure is inhibition of UGT 1A1. However, according to BMS consultant ———, the degree of inhibition seen in *in vitro* experiments seems too small to account for the degree of hyperbilirubinemia observed clinically, suggesting either that this particular assay system does not reflect quantitatively the changes in UGT 1A1 function that occur *in vivo* or that other mechanisms may also contribute.

The magnitude of unconjugated bilirubin increase is higher in subjects with UDP-GT 1A1 genotype 6/7 as compared to genotype 6/6.

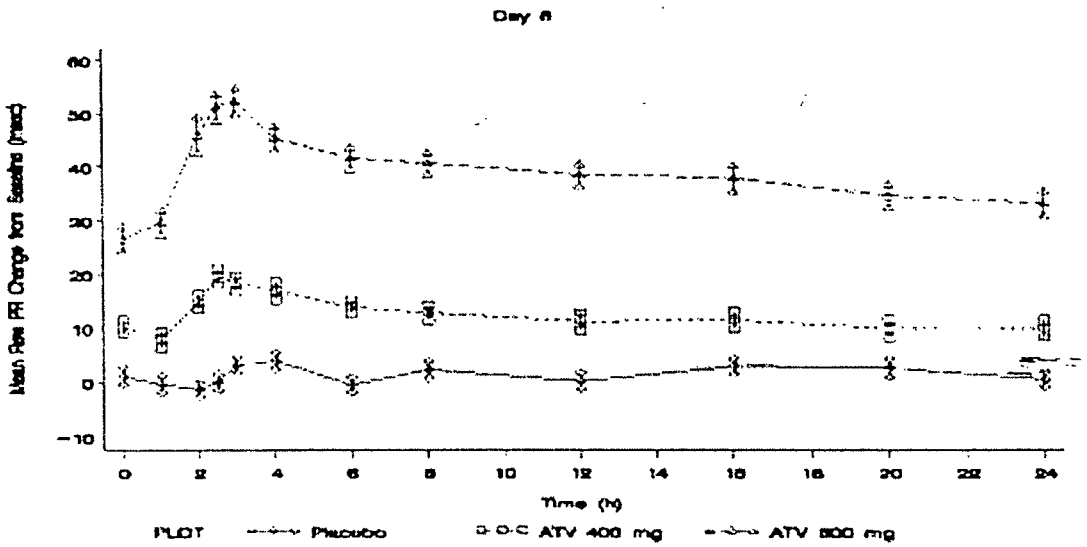


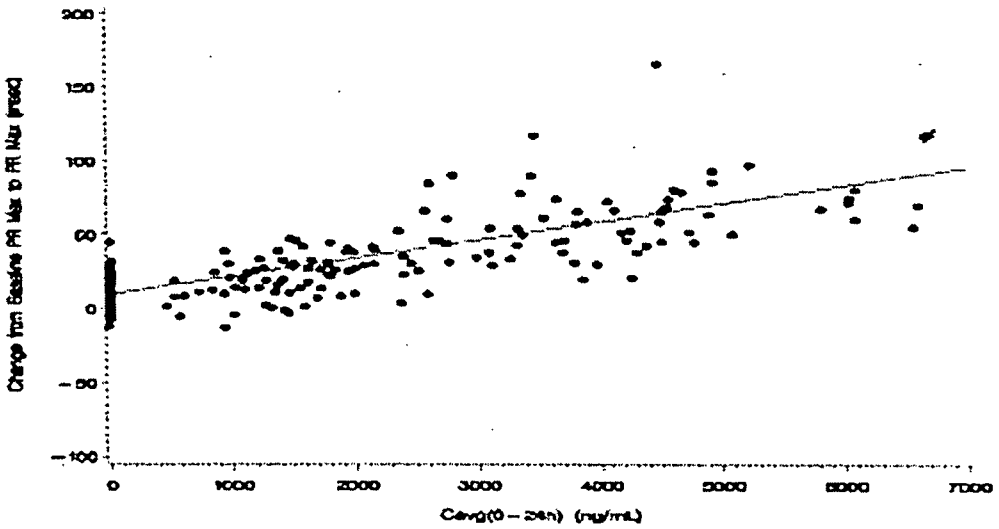
In summary, the hyperbilirubinemia seen during the development program of atazanavir is primarily due to increased indirect bilirubin caused by atazanavir, and does not appear to result in an increased incidence of hepatoxicity relative to nelfinavir, lopinavir/ritonavir

or to efavirenz. Advisory Committee felt that the hyperbilirubinemia associated with atazanavir is not a toxicity, but is a cosmetic problem.

PR interval

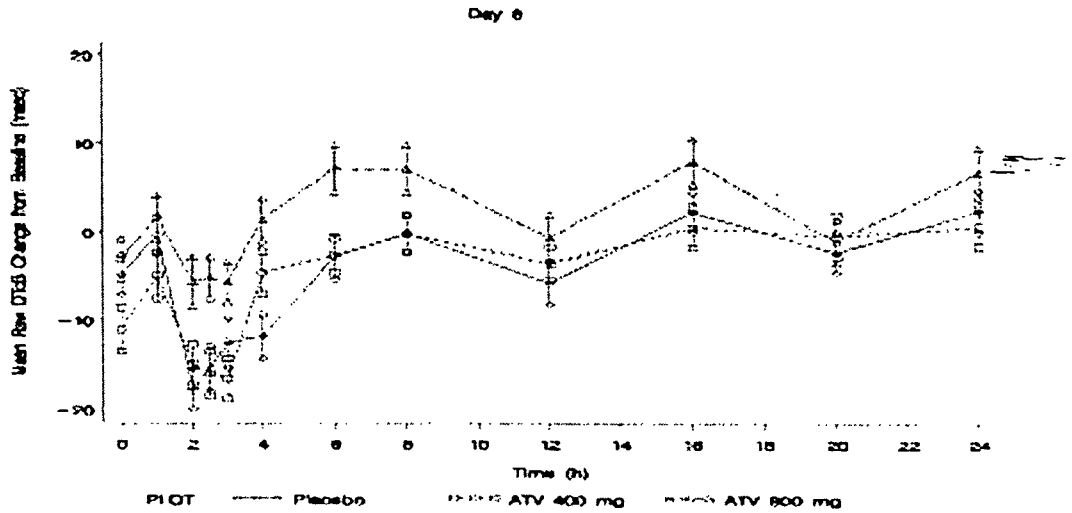
Study AI424076 showed that atazanavir was associated with dose- and concentration-dependent prolongations of the PR interval of the ECG. The prolongation was most apparent at the 800 mg dose. For each additional 1000 ng/mL of atazanavir Cavg(0-24h), the estimated derived PR changes from baseline ranged between 11.5 and 13.4 msec. All upper bounds of the 95% confidence intervals for the slopes of the linear regressions of PR changes from baseline on Cavg(0-24h) were above zero. The largest upper bound for the 95% confidence intervals for the slopes of the linear regressions of PR changes from baseline on Cavg(0-24h) was 15.2 msec per 1000 ng/mL. The Cavg(0-24h) for healthy subjects with the 400 mg dose in this study is 1379 ng/ml, which could cause 21 msec increase of PR interval. The analysis of covariance of PR changes from baseline showed that the placebo-corrected (difference between the adjusted mean for atazanavir and the adjusted mean for placebo), mean time-matched change from baseline to PR Max (Δ PR Max) was +12.4 msec for the 400 mg dose and +47.0 msec for the 800 mg dose of atazanavir. The placebo-corrected, time-matched mean change from baseline to PR at Tmax (Δ PR at Tmax) was +18.0 msec for the 400 mg dose and +52.6 msec for the 800 mg dose of atazanavir. However, 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 A-V block was the most frequently observed ECG abnormality in the treatment naïve subjects with the 400 mg atazanavir QD dose.

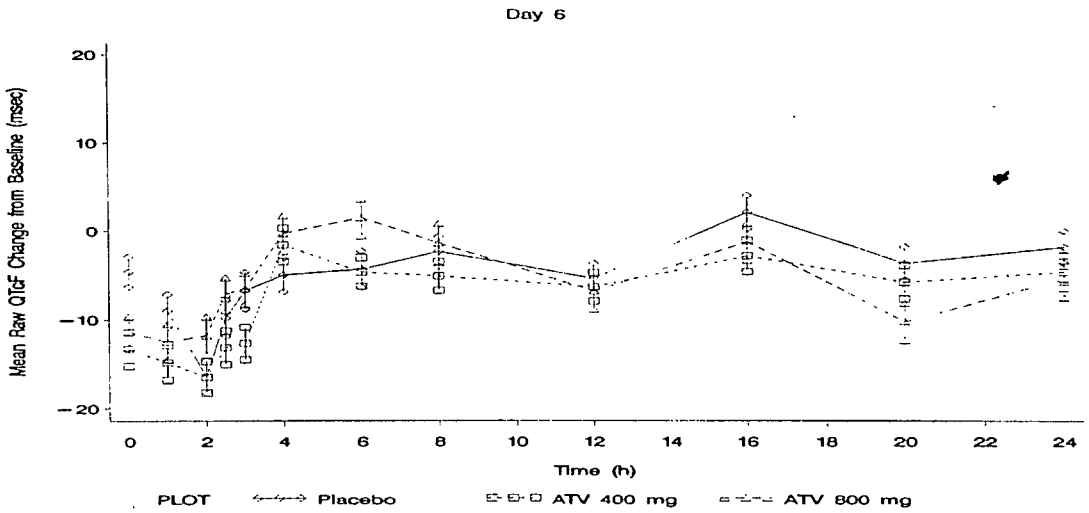


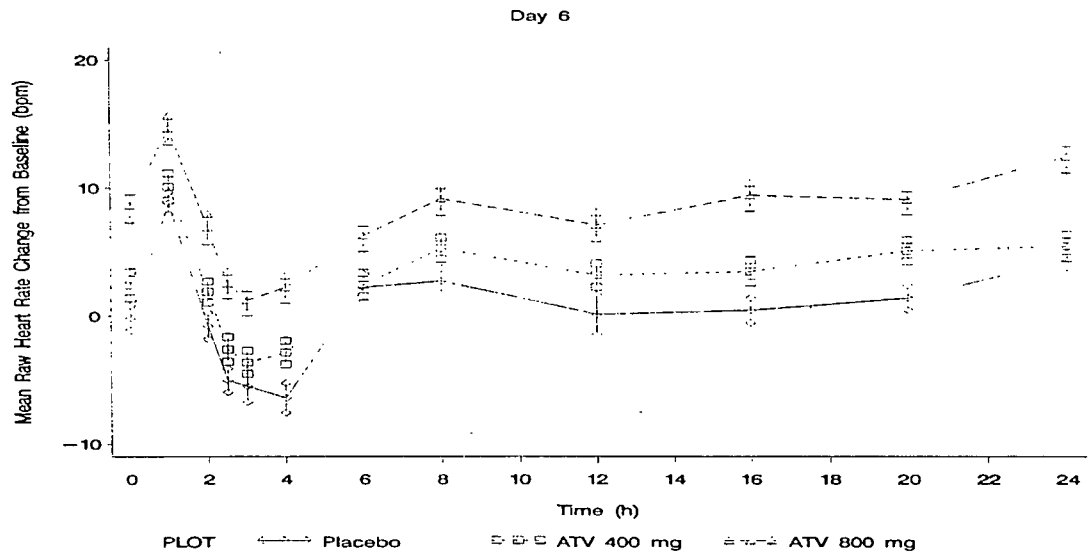


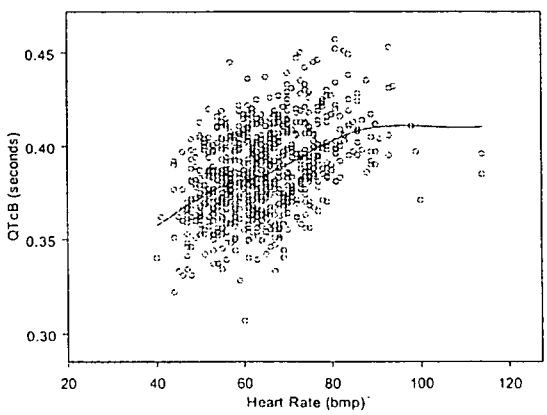
QT interval

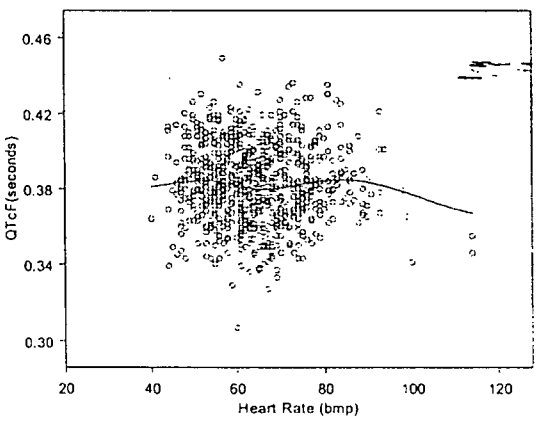
Study AI424076 showed that atazanavir was associated with a dose-dependent increase in QT interval with Bazett's correction (QTcB). However, dose-dependent increase of QT interval disappeared with Fridericia's correction (QTcF). Atazanavir also increase heart rate. The analysis with subjects in placebo group shows that QTcB increased with increased heart rates, while Fridericia's corrected QT (QTcF) is constant with increased heart rates. Therefore, Fridericia's correction may be more appropriate than Bazett's correction. With both Bazett's and Fridericia's correction, the frequency of borderline or prolonged Δ QTc was lower for subjects when on atazanavir at 400 mg than when on placebo.




Day 6
Mean Raw QTcF Change from Baseline (msec)
20
10
0
−10
−20
0
2
4
6
8
10
12
14
16
18
20
22
24
Time (h)
PLOT
Placebo
ATV 400 mg
ATV 800 mg


Day 6
Mean Raw Heart Rate Change from Baseline (bpm)
20
10
0
−10
0
2
4
6
8
10
12
14
16
18
20
22
24
Time (h)
PLOT
Placebo
ATV 400 mg
ATV 800 mg


QTcB (seconds)
0.45
0.40
0.35
0.30
20
40
60
80
100
120
Heart Rate (bmp)


QTcF (seconds)
0.46
0.42
0.38
0.34
0.30
20
40
60
80
100
120
Heart Rate (bmp)

4.2.3.1 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Atazanavir Cmax and AUC(TAU) increased more than proportionally to dose after multiple dose administration of atazanavir in healthy subjects under fed conditions (Study AI424040), as shown in the following table.

Pharmacokinetic Parameter	Dose		
	200 mg (n = 23)	400 mg (n = 22)	800 mg (n = 22)
Cmax (ng/mL) Geometric Mean (C.V. %)	1206.04 (94.16)	4224.97 (43.01)	9665.24 (25.53)
AUC(TAU) (ng·h/mL)[a] Geometric Mean (C.V. %)	6130.98 (54.94)	23468.58 (42.11)	72338.29 (35.55)
Tmax (h) Median (Min, Max)	2.00	2.00	2.00
T-HALF (h) Mean (SD)	5.31 (1.39)	7.06 (2.09)	9.91 (6.14)

[a] TAU = 24 h

Similar pharmacokinetic nonlinearity was also observed in HIV-infected subjects after multiple dose administration of atazanavir under fed conditions.

Dose proportionality was not evaluated after single dose administration of atazanavir under fed conditions.

4.2.3.2 Do PK parameters change with time following chronic dosing?

Studies in HIV-infected patients showed that following oral administration, atazanavir half-life is similar on Day 1 and Day 29, and AUC(inf) after single dose is similar to AUC(0-24) at steady-state. Therefore, apparent clearance does not change following chronic dosing. In healthy subjects, atazanavir half-life is similar after single-dose administration and multiple administration of atazanavir. An in vitro study has shown that, over the concentration range of 100 to10000 ng/ml, the extent of human serum protein binding of BMS-232632 was constant. Therefore, volume of distribution of BMS-232632 may not be changed after multiple dose administration.

4.2.3.3 Are the dose and dosing regimen consistent with the known relationship between dose-concentration-response?

The dosing regimen is consistent with the known relationship between dose and response. The initial population PK/PD analysis was conducted based on 2-week

monotherapy data from Study AI424007, to select a dose for Phase III studies. The interim analysis showed that doses at and above 400 mg were associated with a higher probability of achieving the target change from baseline of HIV RNA, and the 400 mg dose was associated with a lower probability of achieving a total bilirubin value > 2.5 mg/dL as compared to 500 mg and 600 mg dose. Therefore, 400 mg QD was selected for pivotal clinical trials. However, the study was conducted under fasted conditions and may not apply to fed conditions, which were used in pivotal Phase III clinical trials. The final population PK/PD analyses using 24 week and 48 weeks results (under fed conditions) showed that there was not concentration-response for efficacy. However, we do not accept the population analysis results due to the following reasons:

- uncertainty of the meal time relative to dosing;
- all the PK parameters and inter- and intra-individual variability were fixed to the population mean estimates obtained from the Phase I healthy subjects model, while there may be 50% lower atazanavir exposure in HIV-infected as compared to healthy subjects; and
- the concentrations estimated did not accurately predict the observed concentrations.

Dose-response data show that there was no dose-response relationship for atazanavir efficacy from dose of 200 mg to 600 mg QD in naïve patients. The virologic response rates for naïve patients who dose reduced to 200 mg due to hyperbilirubinemia was similar to the overall response in this population with the 400 mg dose. The data suggest that dose reduction does not impact the clinical efficacy of atazanavir in naïve patients. However, the limited number of subjects with dose reductions does not provide sufficient data to recommend dose reduction as a management approach. The virologic response rate for treatment experienced patients who dose reduced to 200 mg due to hyperbilirubinemia was relatively lower than the overall response in treatment experienced patients with the 400 mg dose. No resistance data are available for 200 mg dose, but lower dose generally correlated with higher chance of resistance. Therefore, the selected dose of 400 mg QD is acceptable, based on efficacy and safety data and a possible higher resistance associated with a lower dose in both treatment-naïve and experienced patients. The Medical Officer indicated that the highest dose for atazanavir with acceptable adverse events is 600 mg QD.

4.2.4 How does the PK of atazanavir in healthy volunteers compare to that in patients?

4.2.4.1 What are the basic PK parameters?

The steady-state PK parameter values for ATV at 400 mg in the fed state in healthy or HIV-infected subjects are provided in the following table.

APPEARS THIS WAY
ON ORIGINAL

PK Parameters	Healthy Subjects (n = 14)	HIV-Infected Subjects (n = 13)
C_{max} (ng/mL)		
Geometric Mean (CV%)	5199 (26)	2298 (71)
Mean (SD)	5358 (1371)	3152 (2231)
Range		
T_{max} (hr)		
Median	2.5	2.0
Range		
AUC (ng.hr/mL)		
Geometric Mean (CV%)	28132 (28)	14874 (91)
Mean (SD)	29303 (8263)	22262 (20159)
Range		
T-Half (hr)		
Mean (SD)	7.9 (2.9)	6.5 (2.6)
Range		
C_{min} (ng/mL)		
Geometric Mean (CV%)	159 (88)	120 (109)
Mean (SD)	218 (191)	273 (298)[a]
Range		

Source: AI424013 Clinical Study Report and AI424008 Pharmacokinetic Study Report

[a] n = 12

The data showed that atazanavir Cmax and AUC were about 50% lower (geometric mean) in HIV-infected subjects as compared to healthy subjects. In study AI424008, one subject had an extremely high AUC (75882 ng.hr/ml). This extreme value results in a much higher arithmetic mean in patients. Cmin values appeared similar in these two subject groups.

4.2.4.2 Does mass balance study suggest the major route of elimination is renal or hepatic?

The mass balance study in humans (n =3) showed that the mean cumulative total recovery of radioactivity in excreta after 168 hours post dose administration was 91.9%. Urinary excretion accounted for 13.1% of the dose, and fecal excretion accounted for 78.8% of the dose. Unchanged drug accounted for approximately half of the urinary radioactivity (about 7% of the administered dose). Since the absolute bioavailability of atazanavir was not determined, it is not known what percentage of absorbed dose was eliminated unchangedly in the urine. In the feces, approximately 15% of the radioactivity was due to unchanged drug and the rest is attributed to at least 3 monohydroxylated metabolites and 4 dihydroxylated metabolites.

4.2.5 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

There was great inter-subject variability of PK parameters when atazanavir was taken under fasted conditions. Food tended to reduce the PK variability of atazanavir. In healthy subjects, the coefficient of variation in the Cmax and AUC(inf) decreased from 66% and 69%, respectively, in the fasted state to 29% and 37%, respectively, in the presence of a light meal and to 33% and 43%, respectively, when the drug was taken with a high fat meal (AI424003). The intra-subject C.V. for Cmax was 58% and the intra-subject C.V. for AUC(TAU) was 41% in healthy subjects under fed conditions (AI424040). The pharmacokinetic variability in patients was higher than healthy subjects at the 400 mg dose, and was 53% -71% for Cmax and 54% -91% for AUC under fed conditions.

4.3 Intrinsic Factors

4.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics? What dosage regimen adjustments, if any, are recommended for each of these subgroups

The effect of age, gender, and hepatic dysfunction were studied after single dose administration of atazanavir under fed conditions. Each individual factor is discussed in the following sections.

4.3.1.1 Age/Gender

A study of the pharmacokinetics of atazanavir was performed in young (n=29, 14 female and 15 male) and elderly (n=30, 15 for each gender) healthy subjects. There was no PK difference between female and male subjects if parameters were normalized by body weight. Elderly subjects have 17% higher AUC and Cmax compared to younger subjects. After body weight adjustment, a similar difference still exists. However, the difference is not clinically significant.

4.3.1.2 Hepatic impairment

Atazanavir is metabolized and eliminated primarily by the liver. Atazanavir has been studied in adult patients with moderate (n = 14) to severe (n = 2) hepatic impairment (Child-Pugh B and C) after a single 400-mg dose. The summary statistics for the pharmacokinetic parameters are shown in the following tables.

Pharmacokinetic Parameter	400 mg		200 mg
	Normal (N = 16)	Hepatic (N = 16)	Hepatic (N = 15)
Cmax (ng/mL) Geometric Mean (C.V.%)	1334.4 (51.2)	1391.0 (58.1)	826.7 (53.3)
AUC(INF) (ng·h/mL) Geometric Mean (C.V.%)	8071.1 (58.5)	11738.6 (62.6)	5548.2 (49.8)
Tmax (h) Median (Minimum, Maximum)	3.0	2.0	2.0
T-HALF (h) Mean (S.D.)	6.4 (1.5)	12.1 (2.9)	11.6 (3.2)

The data showed that atazanavir exposure in subjects with hepatic impairment was 45% higher after 400 mg dose, and 31% lower after 200 mg dose as compared to the exposure in subjects with normal hepatic function after 400 mg dose. In addition, atazanavir exposure may be dose proportional in subjects with hepatic impairment. Therefore, dose reduction to 300 mg is recommended for patients with moderate hepatic impairment. The applicant suggested that ATV not be used in patients with severe hepatic impairment, due to the small number of subjects with severe hepatic impairment in the study (n = 2), which is acceptable. The applicant also proposed a dose reduction to 300 mg QD for patients with mild hepatic impairment. However, no study was conducted in this population. We suggest no dose adjustment for subjects with mild hepatic impairment due to the following reasons:

1) atazanavir Cmax in subjects with moderate to severe hepatic impairment was similar to that in normal subjects,
2) the exposure increase due to mild hepatic impairment should be less than 45%, and
3) the Cmax and AUC with the highest safe dose (600 mg QD) is 67% and 70 % higher than that with clinically used 400 mg QD dose.

4.3.1.3 Renal impairment

In healthy subjects, the renal elimination of unchanged atazanavir was approximately 7% of the administered dose. There are no pharmacokinetic data available on patients with renal insufficiency. Pharmacokinetics of atazanavir in subjects with renal impairment will be evaluated as a Phase IV commitment because the percentage of the absorbed atazanavir dose that is eliminated unchanged in the urine is unknown.

4.3.1.4 Pediatric patients

The pharmacokinetics of atazanavir are being studied after multiple doses in pediatric patients, stratified by age. There are insufficient data at this time to recommend a dose.

4.3.1.5 Race

The applicant claimed that a population pharmacokinetic analysis showed no effect of race on the pharmacokinetics of atazanavir. However, subject covariates were not evaluated in the population pharmacokinetic analysis. In addition, the population PK/PD results were not acceptable (see Section 4.2.3.3). Therefore, there are insufficient data to determine whether there are any effects of race on the pharmacokinetics of atazanavir.

4.4 Extrinsic Factors

4.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

Refer to Drug-Drug Interactions section (Section 4.4.2) for the potential effects of other drugs on atazanavir and of atazanavir on other drugs. Refer to Section 4.5.3 for food effect.

4.4.2 Drug-Drug Interactions

4.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

CYP3A4 appears to be the CYP enzyme responsible for the oxidation of atazanavir in human liver microsomes, as evidenced by the 100% and 71% inhibition by ketoconazole and troleandomycin, respectively. The production of all metabolites appears to be inhibited completely by the addition of ketoconazole and troleandomycin (except the carbamate hydrolysis metabolite being slightly less affected by troleandomycin). Additional evidence was provided in a correlation analysis relating the rates of oxidation of BMS-232632 and testosterone in human liver microsomes. The correlation between these two activities is highly significant ($r = 0.97$) which suggests that CYP3A4 metabolizes atazanavir (In vitro correlation of the oxidation of BMS-232632 and of testosterone in human liver microsomes. Report no. 910065007).

Addition of inhibitors for CYPs 1A2, 2A6, 2B6, 2D6, and 2E1 produced minor effects ranging from 0% to 16% inhibition for atazanavir. These effects are judged to be not significant.

Inhibition results cannot be clearly assessed from the addition of sulfaphenazole, a CYP2C9 inhibitor and tranylcypromine, a CYP2C19 inhibitor, because they were co-eluted with several metabolites of BMS-232632. However, their effects on the remaining peaks in the metabolite profile were minimal. These peaks were produced at levels comparable to controls. These facts, along with the results found for CYP3A4, suggest that CYP2C9 and CYP2C19 are not significant enzymes in the metabolism of atazanavir.

However, there are some concerns with the design of the in vitro studies that complicate interpretation of the results. The investigators used a high concentration of ketoconazole (20 μM) in the in vitro incubations. At such a high concentration, ketoconazole inhibits other enzymes- there are reports that it may inhibit some of the CYP2C enzymes. Most laboratories use incubations with 1 μM or less of ketoconazole

to determine whether a drug is metabolized by CYP3A4. Due to the problems with the CYP2C9 and CYP2C19 results discussed in the previous paragraph, we cannot rule out metabolism by those enzymes. The inhibition by troleandomycin is supportive of CYP3A4 involvement, but use of a high concentration of troleandomycin (100 μM) is not optimal. The high correlation with oxidation of testosterone is also supportive of CYP3A4 involvement, but correlation results are generally considered the weakest evidence and need to be supported by other studies (use of probe inhibitors, such as ketoconazole).

The inhibitory potential of atazanavir on the activity of human liver microsomal CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5 and CYP4A9/11 was studied. The *in vitro* studies showed that atazanavir is not a reversible inhibitor of CYP2A6, CYP2C19, CYP2D6, CYP2E1, and CYP4A9/11. However, it competitively inhibits CYP1A2, CYP2C9 and CYP3A4/5 with Ki values of 12.1, 12.7 and 2.35 μM, respectively (I/Ki: ~ 0.25, ~ 0.25, and ~ 1.28). Atazanavir is also a mechanism-based inhibitor of CYP3A4/5. In addition, BMS-551160, one of the circulating metabolites of atazanavir, inhibited CYP2C19 with an average IC_{50} value of 4.9 μM.

The inhibitory potential of atazanavir on the activity of bilirubin glucuronidation in human liver microsomes and cDNA-expressed human UGT 1A1 was studied. Atazanavir appears to be a potent inhibitor of UGT 1A1.

4.4.2.2 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

A permeability study using Caco-2 monolayers showed that the basolateral-to-apical/apical-to-basolateral transport ratio was about 4, suggesting that atazanavir may be a substrate of efflux pumps (e.g., P-gp).

A P-glycoprotein inhibition study using digoxin (a P-gp substrate) in Caco-2 cells demonstrated that atazanavir is a weak inhibitor of P-gp with an IC_{50} value of ~29 μM.

4.4.2.3 Are there other metabolic/transporter pathways that may be important?

No study was conducted to evaluate other metabolic/transporter pathways. Although in vitro studies suggest atazanavir is a CYP3A substrate, there are conflicting in vivo study results. The metabolic pathway, including enzymes involved, may not be fully characterized for atazanavir. See the discussion following the two tables in Section 4.4.2.4.

4.4.2.4 What interaction data are available? What is the impact?

As discussed in the previous sections, in vitro studies showed that atazanavir is a CYP3A4 substrate and inhibitor, and a potent inhibitor to UGT 1A1. In vitro studies also showed that atazanavir may be a substrate and a weak inhibitor of P-gp. The applicant studied drug-drug interactions between atazanavir and possible coadministered CYP3A4 substrate or drugs that inhibit or induce CYP3A4. Atazanavir also causes dose- and concentration-dependent prolongation of PR intervals and possible prolongation of QT intervals. Therefore, the applicant also studied drug-drug interactions between atazanavir and other possible coadministered drugs that could cause QT or PR prolongation. The following tables show the pharmacokinetic results of drug-drug interaction studies.

Drug Interactions: Pharmacokinetic Parameters for Atazanavir in the Presence of Coadministered Drugs

Coadministered Drug	Coadministered Drug Dose/Schedule	REYATAZ Dose/Schedule	n	Ratio (90% Confidence Interval) of Atazanavir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00		
				C_{max}	AUC	C_{min}
atenolol	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)	0.74 (0.65, 0.86)
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)	1.91 (1.66, 2.21)
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)	0.16 (0.10, 0.27)
	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)	1.03 (0.61, 1.73)
diltiazem	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)	0.98 (0.90, 1.07)
efavirenz	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)	0.07 (0.05, 0.10)
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)	1.48 (1.24, 1.76)
ketoconazole	200 mg QD, d 7-13	400 mg QD, d 1-13	14	0.99 (0.77, 1.28)	1.10 (0.89, 1.37)	1.03 (0.53, 2.01)
rifabutin	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)	1.13 (0.68, 1.87)
ritonavir[b]	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)	11.89 (10.23, 13.82)

[a] One subject did not receive REYATAZ.

[b] Compared with atazanavir 400 mg QD historical data, administration of atazanavir/ritonavir 300/100 mg QD increased the atazanavir geometric mean values of C_{max}, AUC, and C_{min} by 18%, 103%, and 671%, respectively. The geometric mean values of atazanavir pharmacokinetic parameters when coadministered with ritonavir were: C_{max} = 6129 ng/mL, AUC = 57039 ng·h/mL, and C_{min} = 1227 ng/mL.

The above table shows pharmacokinetic parameters for atazanavir in the presence of coadministered drugs. It is interesting that, although clarithromycin, ketoconazole and ritonavir are all potent CYP3A4 inhibitors, only ritonavir significantly increased atazanavir concentrations. Clarithromycin is also a P-gp inhibitor, while ritonavir is reported as a P-gp inhibitor in vitro but not in vivo. It is not clear whether other transporters and enzymes are involved in atazanavir absorption or elimination. Conflicting results were also observed for two CYP3A4 inducers efavirenz and rifabutin. Efavirenz reduced atazanavir Cmax and AUC by 59% and 74%, respectively, while rifabutin did not reduce atazanavir concentrations.

Ritonavir

The applicant proposed that when atazanavir is coadministered with ritonavir, 300 mg/100 mg atazanavir/ritonavir QD should be used. The proposed regimen results in 18%, 103% and 671% increase of Cmax, AUC and Cmin, respectively, as compared to atazanavir 400 mg QD. The atazanavir/ritonavir combination regimen is being used in a Phase III trial in treatment experienced population (AI424045). The information is included in the Clinical Pharmacology and Precausion sections of the label but not in Dosage and Administration Section, because 24 weeks efficacy data and safety data were not submitted yet.

Efavirenz

When atazanavir is coadministered with efavirenz, ritonavir is needed to offset the efavirenz induction effect. It is recommended that atazanavir 300 mg with ritonavir 100 mg be coadministered with efavirenz 600 mg (all as a single daily dose with food), atazanavir without ritonavir should not be coadministered with efavirenz.

Buffered didanosine and drugs that affect gastric pH

Exposure to atazanavir was markedly decreased by coadministration of atazanavir with didanosine buffered tablets, presumably due to the increase in gastric pH caused by buffers in the didanosine tablets. If these two drugs are separated by at least 1 hour, the effect on atazanavir concentration disappeared. Therefore, atazanavir should be given (with food) 2 h before or 1 h after didanosine buffered formulations. The treatment schedule applies to other antacids and buffered medications. Reduced plasma concentrations of atazanavir are expected if H_2-receptor antagonists are administered with atazanavir. This may result in loss of therapeutic effect and development of resistance. To lessen the effect of H_2-receptor antagonists on atazanavir exposure, it is recommended that an H_2-receptor antagonist and atazanavir be administered as far apart as possible, preferably 12 hours apart. Concomitant use of atazanavir and proton-pump inhibitors is not recommended. Coadministration of atazanavir with proton-pump inhibitors is expected to substantially decrease atazanavir plasma concentrations and reduce its therapeutic effect.

Other Drugs that Inhibit or induce CYP3A

We do not know the effects of other CYP3A inducer or inhibitor, which have not been studied, on atazanavir. Inhibition of CYP3A my increase atazanavir concentrations but we don't expect big effect due to ketoconazole results. Induction of CYP3A my decrease atazanavir concentrations. However, efavirenz but not rifabutin reduced atazanavir concentrations.

Drug Interactions: Pharmacokinetic Parameters for Coadministered Drugs 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	C_{min}
atenolol	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)	1.02 (0.88, 1.19)
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)	0.38 (0.35, 0.43) OH-clarithromycin: 2.64 (2.36, 2.94)
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)	NA D4T: 1.04 (0.94, 1.16)
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)	0.41 (0.37, 0.47) desacetyl-diltiazem: 0.45 (0.41, 0.49)
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)	Ethinyl estradiol: 1.91 (1.57, 2.33) norethindrone: 3.62 (2.57, 5.09)
rifabutin	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)	3.43 (1.98, 5.96) 25-O-desacetyl-rifabutin: 75.6 (30.1, 190.0)
saquinavir (soft gelatin capsules)[c]	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)	6.86 (5.29, 8.91)
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)	Lamivudine: 1.12 (1.04, 1.21) zidovudine: 0.69 (0.57, 0.84) zidovudine glucuronide: 0.82 (0.62, 1.08)

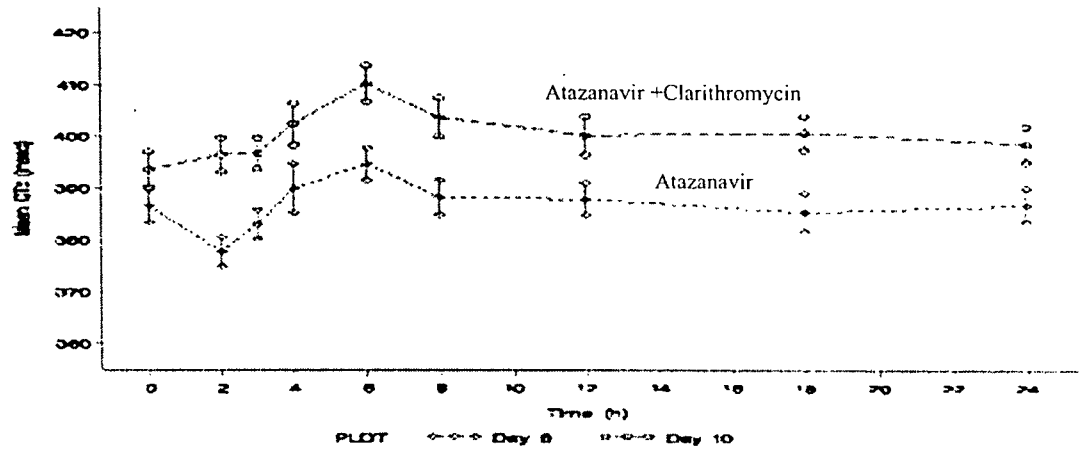
[a] One subject did not receive REYATAZ.
[b] Not the recommended therapeutic dose of atazanavir.
[c] The combination of atazanavir and saquinavir 1200 mg QD produced daily saquinavir exposures similar to the values produced by the standard therapeutic dosing of saquinavir at 1200 mg TID. However, the C_{max} is about 79% higher than that for the standard dosing of saquinavir (soft gelatin capsules) alone at 1200 mg TID.
NA = not available.

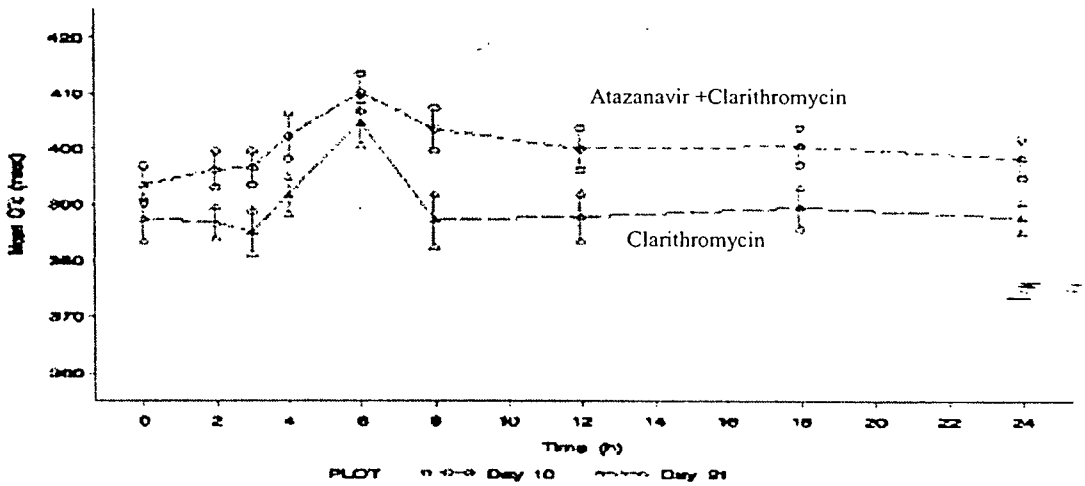
The above table shows the pharmacokinetic parameters for coadministered drugs in the presence of atazanavir. Atazanavir increased exposure of CYP3A4 substrates

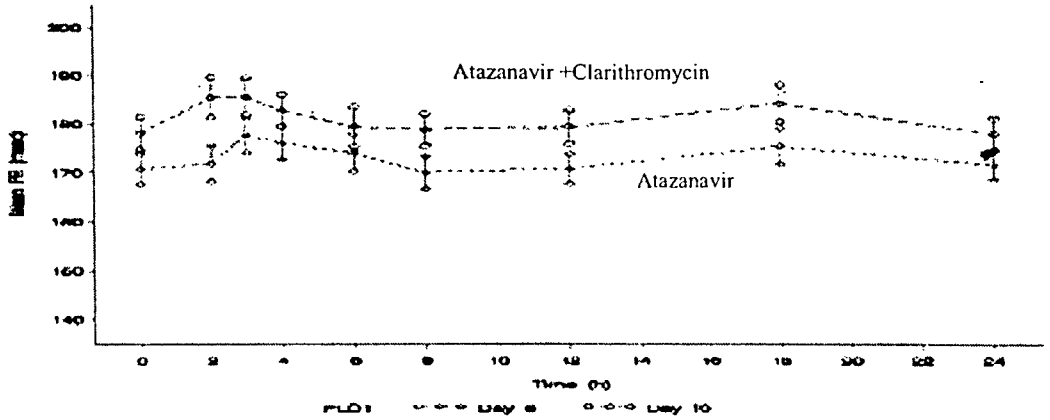
clarithromycin, diltiazem, ethinyl estradiol, norethindrone, rifabutin, and saquinavir to various degrees.

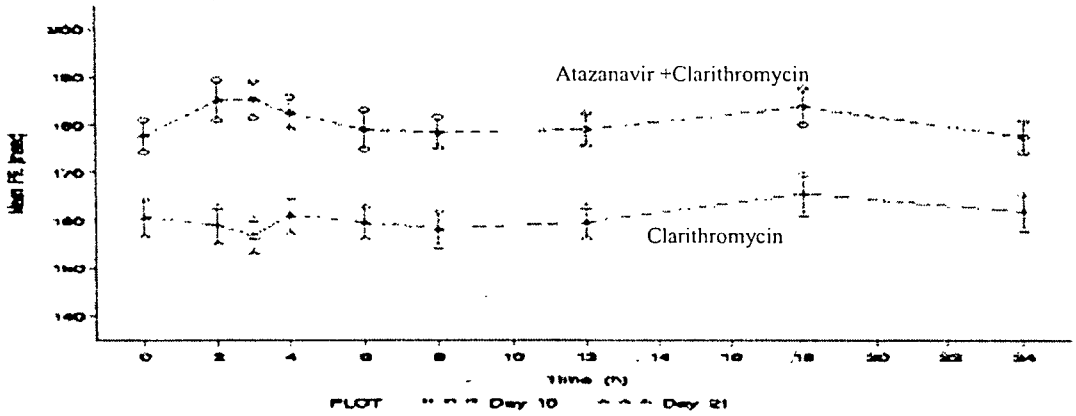
Clarithromycin

Atazanavir increased clarithromycin AUC by 94% (90% C.I.: 75% -116%) and reduced 14-OH clarithromycin by 70% (90% C.I.: 66% - 74%). In addition, coadministered clarithromycin and atazanavir had additive effects on the QTc and PR interval, as compared to the effect due to either drug alone. Since QTc was calculated by Bazett's formula, and atazanavir increased heart rate as shown in Study AI424076, the actural effect of atazanavir on QTc may not be significant.







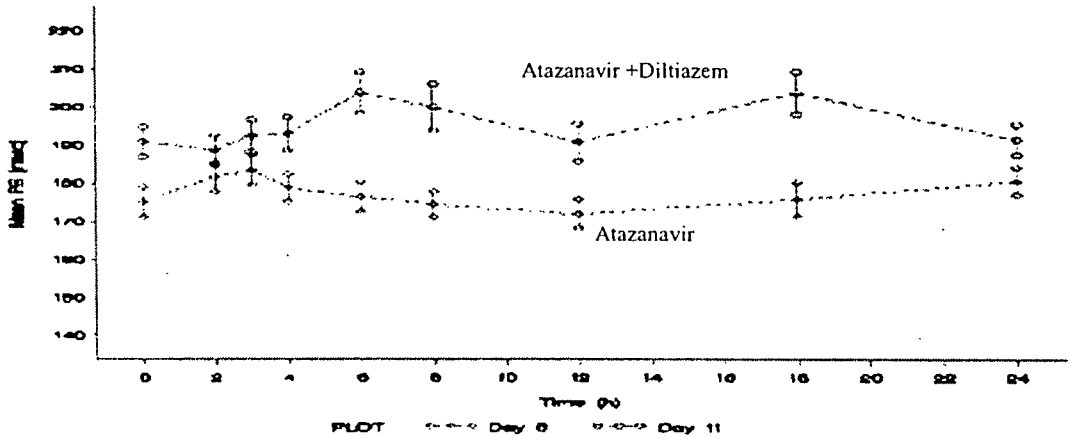


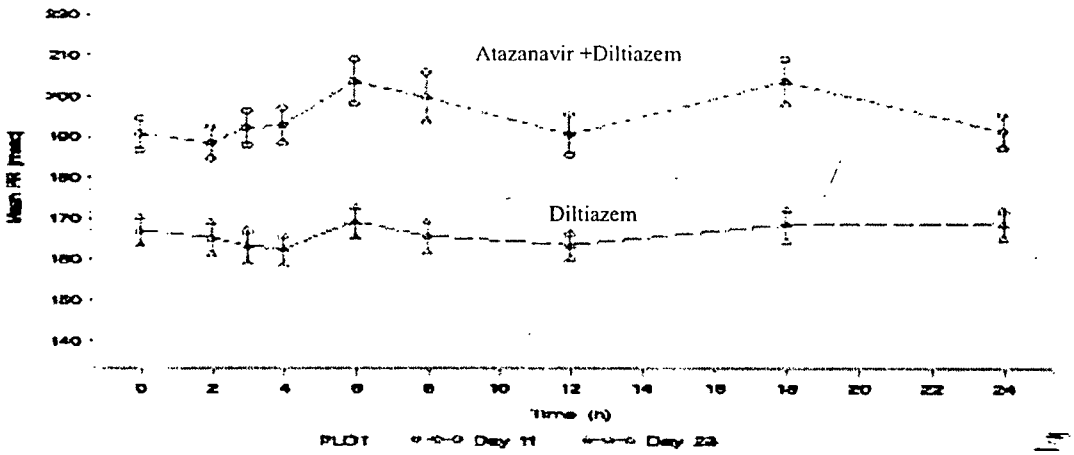
The applicant proposed a reduction in clarithromycin dose by half (250 mg BID), which is acceptable for treatment of Mycobacterium avium complex. (MAC). However, 14-OH clarithromycin have activities for organisms other than MAC. Therefore, alternative therapy of indications other than MAC needs to be considered,

Diltiazem

Atazanavir increased diltiazem concentrations by approximately 100%. When atazanavir and diltiazem were co-administered, more severe PR prolongation was observed, than when either drug was administered alone.

Study day	PR interval (msec)	
	200-250	>250
	Count (%)	Count (%)
6 (atazanavir)	10 (33%)	0 (0%)
11 (atazanavir + diltiazem)	14 (46.7%)	4 (13.3%)
23 (diltiazem)	3 (11%)	0 (0%)





The applicant suggested a reduction of diltiazem dose by half. When considering the impact of dose reduction, it is important to remember that diltiazem has nonlinear pharmacokinetics, as diltiazem exposure increases more than dose-proportionally. If atazanavir and diltiazem are co-administered in patients receiving a higher diltiazem dose and for a longer duration, more severe prolongation of the PR interval may result. When atazanavir / ritonavir 300/100 mg is used, atazanavir Cmax and AUC could be increased by 17%-53% and 91%-170%, respectively, and thus increase the risk of PR prolongation further. Therefore, in addition to 50% dose reduction of diltiazem, caution should be warranted and ECG monitoring is recommended. For other calcium channel blockers (e.g. felodipine, nifedipine, nicardipine, and verapamil), dose titration of the

calcium channel blocker should be considered and ECG monitoring is also recommended.

Oral contraceptives

Coadministration of once-daily doses of Ortho-Novum® 7/7/7 and atazanavir at 400 mg resulted in a 67% and 110% increase in the Cmax and AUC of norethindrone, respectively, and a 15% and 48% increase in the Cmax and AUC of ethinyl estradiol, respectively, compared to the administration of Ortho-Novum® 7/7/7 alone. Mean concentrations of ethinyl estradiol, when coadministered as a 35-µg dose with atazanavir, are increased to a level between mean concentrations produced by a 35-µg and a 50-µg ethinyl estradiol dose. Decreased HDL or increased insulin resistance may be associated with increased mean concentrations of norethindrone, when coadministered with atazanavir, particularly in diabetic women. After discussion with medical and clinical pharmacology reviewers for Division of Reproductive and Urologic Drug Products (DRUDP), we agree with the applicant that the lowest effective dose of each oral contraceptive component be used.

Rifabutin

The pharmacokinetics of rifabutin and its metabolite following 150 mg QD doses of rifabutin with different doses of atazanavir and with or without 100 mg ritonavir appeared similar. The exposure produced by rifabutin at 150 mg QD in the presence of atazanavir (with or without ritonavir) was higher than that for the standard 300 mg QD doses of rifabutin suggesting that the 150 mg QD dose of rifabutin may need to be modified. The applicant recommended a reduction of rifabutin dose up to 75% (e.g., 150 mg every other day or 3 times per week), which is acceptable.

Saquinavir

Atazanavir increases saquinavir concentrations by 4-fold. The combination of atazanavir and saquinavir 1200 mg QD produced saquinavir daily exposures similar to the values produced by the standard therapeutic dosing of saquinavir (Fortovase ®) at 1200 mg TID. However, the Cmax is about 79% higher than that for the standard dosing of saquinavir alone at 1200 mg TID. Coadministration of 400 mg SQV + 400 mg RTV BID has also being used in clinical practice, although it is not an approved regimen. RTV increased SQV AUC and Cmax by 121% and 64% using this regimen as compared to standard dosing of saquinavir alone at 1200 mg TID. Therefore, the Cmax for saquinavir coadministered with atazanavir is about 23% higher than that for 400 mg saquinavir combined with 400 mg RTV BID, with lowered AUC. Combination of saquinavir 1200 mg and atazanavir 400 mg QD is used in an ongoing Phase III trial (Study AI424045). The preliminary data showed that the combination of saquinavir/atazanavir 1200/400 mg QD was less effective than atazanavir/ritonavir 300/100 mg QD. Appropriate dosing recommendations for this combination, with respect to efficacy and safety, have not been established.

Other drugs that have not been studied but could cause drug-drug interactions are summarized in the Summary Section. In particular caution is warrented when atazanavir is coadministered with CYP3A substrates that have narrow therapeutics indices.

4.5 General Biopharmaceutics

4.5.1 What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

The only difference between capsules used in major clinical pharmacology, Phase II and III studies and the proposed to-be-marketed capsules is a 0.2% difference in the theoretical fill weight. Therefore, the applicant referred the capsules used in Phase II and III studies as to-be-marketed formulations. No BE study is needed.

4.5.2 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The data showed that administration of a single dose of 400 mg of atazanavir with a meal high in calories and fat (721 kcal and 47% fat) had no effect on the Cmax atazanavir, but increased AUC by 35%. Administration of a single dose of 400 mg of atazanavir with a meal low in calories and fat (357 kcal and 20% fat) increased the Cmax and AUC of atazanavir by 57% and 70%, respectively. It is not clear if orange juice, a possible P-gp inhibitor (*Takanaga, et. al., JPET 293:230-236, 2000*), present in the light meal contributed to the increased bioavailability.

The label indicates patients should take atazanavir 400 mg QD with a meal. The Phase III clinical trials were also conducted under fed conditions.

4.5.3 How do the dissolution conditions and specifications assure in vivo performance and quality of the product?

The applicant and FDA agree on the following method and specification:

Apparatus: Paddle, USP dissolution apparatus 2
Rotation: 50 rpm
Temperature: 37 ± 0.5°C
Medium: 1000 mL of 0.025 N HCl
Q = ___ in 30 minutes

Dissolution rate is the same for all three capsule strengths. We reached agreement on the dissolution method and medium during the IND stage. The rationale is summarized here.

Selection of dissolution medium (IND ___ SN 100)

Atazanavir had very low solubility at pH<2 (See section 4.1.1). The applicant evaluated the following media:

pH 1.0; 0.1N HCl
pH 1.6; 0.025N HCl
pH 2.0; 0.1N HCl
pH 2.6; Citrate buffer
pH 6.8; Phosphate buffer

0.025 N HCl was selected because the higher concentration of HCl leads to the formation of a plug that results in dissolution variability.

Selection of dissolution apparatus and rotation speed

In 0.025 N HCl, the atazanavir dissolution profiles were almost identical using USP apparatus 2 (paddle) at 50 rpm

(IND SN 100)

The applicant originally planned to use a paddle rotation speed of rpm (IND SN 237), due to its more gradual dissolution profile and better discriminatory ability. However, in a later submission (IND SN 335) the applicant changed to a 50 rpm paddle rotation speed for the following reasons:

1. The 50-rpm method is robust. Unlike the rpm method, it is not dependent on the use of a particular type of sinker.
2. The 50-rpm method can differentiate between storage conditions, storage time, and packaging configurations.
3. The 50-rpm method is discriminatory with respect to which they claim is the most critical processing parameter in the manufacture of the capsules.

Selection of dissolution specification

The applicant originally proposed a specification of Q= in 30 minutes. However, the submitted data did not support this specification. The data are summarized below.

Strength	Batch (n)	Range of % dissolved values				
		10 min	20 min	30 min	45 min	60 min
100 mg	8MEE177 (6)					
150 mg	8MCE137 (12)					
	8MCE129 (12)					
200 mg	8MBM119 (12)					
	8MHM292 (6)					
	8MJC275 (6)					
	8MJC276 (6)					
	8MKM358 (6)					

Based on the above data, we asked the applicant to revise the specification to Q= in minutes. In response, (NDA 21-567; June 6, 2003) the applicant indicated that during long-term stability some slowing in dissolution was noticed, especially upon exposure to accelerated conditions of high humidity and high temperature. Their investigation

indicated that the slower dissolution was due to cross-linking of the capsule shell. Some samples required addition of —— to the dissolution medium to restore the rapid and typical in vitro dissolution. For some of those batches, a Q= — in 30 minutes is required to avoid excessive S2 and S3 testing.

We agree that a Q of —— in 30 minutes is acceptable.

Additional dissolution evaluations

We asked the applicant to consider developing a method that provides a more gradual dissolution profile. Such a method may be useful if they want to make post approval changes that allow comparison of dissolution profiles. The current method will not be useful in such situations. The applicant agreed.

4.5.4 What is the basis of the approval for all the strengths of atazanavir capsules?

All proposed strengths were used in Phase II and Phase III clinical trials. The composition of the three capsule strenghs is proportional.

4.6 Analytical Section

4.6.1 Which moieties have been selected for analysis and why?

Atazanavir was selected for analysis, because it is the only active moiety circulating in the plasma after atazanavir administration.

4.6.2 For all moieties measured, is free, bound or total measured? What is the basis for that decision, if any, and is it appropriate?

Total atazanavir concentration was measured. Atazanavir is a highly bound drug, thus, free concentrations of drug will be too low to measure with this assay. The fraction of atazanavir bound to plasma proteins does not change with plasma atazanavir concentrations across the relevant range.

4 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

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

Jenny H. Zheng, Ph.D.
Reviewer, Clinical Pharmacology/Biopharmaceutics
Division of Pharmaceutical Evaluation III, OCPB

Derek Zhang, Ph.D.
Reviewer, Clinical Pharmacology/Biopharmaceutics
Division of Pharmaceutical Evaluation III, OCPB

Concurrence:

Kellie S. Reynolds, Pharm. D
Team Leader, Antiviral Drug Products Section
Division of Pharmaceutical Evaluation III, OCPB

cc: HFD-530 /NDA 21567
/MO/KMarcus
CSO/VReddy
HFD-880 /JHZheng
HFD-880 /DZhang
HFD-880 /TL/KReynolds

6. APPENDICES

6.1 Individual Study Review

Table of Contents

Pharmacokinetics and Disposition of [^{14}C]BMS-232632
In Healthy Male Volunteers (Protocol AI424-029)

Objective: To assess the pharmacokinetics, metabolism, and routes and extent of elimination of a single oral dose of [^{14}C]BMS-232632 in healthy male volunteers.

Population: 12 healthy male subjects.

Study Design: This was an open-label, non-randomized, single dose study. A cohort of 8 subjects was initially enrolled. The applicant suspected there were problems associated with fecal sample preparation, and thus a second cohort of 4 subjects was later enrolled into the study. Subjects received a single 400 mg oral dose of [^{14}C]BMS-232632 on Study Day 1 within 5 minutes after a light meal.

Formulation [^{14}C]BMS-232632 (as the bisulfate salt; BMS-232632-05, containing 100 µCi of radioactivity per vial) was supplied as a white to off-white powder (Batch # N00158) packaged in vials of 400 mg/vial.

Pharmacokinetic Sampling: Blood samples for pharmacokinetic assessments of BMS-232632 and radioactivity were collected prior to dosing and at 0.25, 0.5, 0.75, 1.0, 1.5, 2, 3, 4, 6, 8, 12, 24, 48 72, 96, 120, 144, and 168 hours after dosing. Once daily sample collections continued after 168 hours until discharge when the cumulative fecal recovery was ≤1% of the total radioactive dose. Blood samples for biotransformation analyses were collected prior to dosing and at 1 and 8 hours post-dose. Blood samples for determination of RBC-associated radioactivity were collected prior to dosing, and at 1.5, 4, and 12 hours post-dose. Urine samples were collected prior to dosing, and during 0-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144,
and 144-168 hours after dosing. Twenty-four (24) hour urinary collections continued after 168 hours until discharge when the cumulative fecal recovery was ≤1% of the total radioactive dose. Fecal samples were collected prior to dosing, and during 0-24, 24-48, 48-72, 72-96, 96-120, 120-144, and 144-168 hours after dosing. Twenty-four (24) hour fecal collections continued after 168 hours until discharge when the cumulative fecal recovery was ≤1% of the total radioactive dose.

Sample Assay: Plasma and urine samples were assayed for BMS-232632 content by a validated [redacted] method. Blood, plasma, urine, and feces were assayed for radioactivity by liquid scintillation counting. Plasma and urine samples were counted directly after addition of the scintillation cocktail without any pretreatment. Blood samples and fecal homogenates were pretreated with a tissue solubilizer for digestion followed by the addition of sodium pyruvate/glacial acetic acid mixture prior to the addition of the scintillation cocktail. For Subjects in Cohort A, water (about 2 to 5 times by weight) was added to the feces and then homogenized. For Subjects in Cohort B, fecal samples were homogenized with a methanol:water mixture (1:1 by volume) instead of water. The results for the standard curve and QCs indicated that the plasma and urine assay methods were precise and accurate for BMS-232632. See QBR for details.

Pharmacokinetic Results: Summary statistics for the pharmacokinetic parameters of BMS-232632 and radioactivity including the urinary recovery of BMS-232632 or total radioactivity (%UR) and the fecal recovery of total radioactivity (%FE) are presented in the table below.

Pharmacokinetic Parameter	Cohort	
	Cohort A (n = 8)	Cohort B (n = 3)
BMS-232632		
Cmax (ng /mL) Geometric Mean (C.V.%)	1269.60 (62.99)	2755.16 (12.15)
AUC(INF) (ng·h/mL) Geometric Mean (C.V.%)	7042.07 (62.57)	13809.25 (28.90)
Tmax (h) Median (Min, Max)	3.0 [redacted]	4.0 [redacted]
T-HALF (h) Mean (S.D.)	36.14 (20.29)	37.26 (11.64)
%UR Mean (S.D.)	4.09 (4.17)	6.64 (1.93)
Radioactivity		
Cmax (ng equiv/mL) Geometric Mean (C.V.%)	1897.97 (59.33)	3756.95 (11.07)
AUC(INF) (ng equiv·h/mL) Geometric Mean (C.V.%)	19191.21 (54.67)	31577.92 (19.63)
Tmax (h) Median (Min, Max)	4.0 [redacted]	4.0 [redacted]
T-HALF (h) Mean (S.D.)	8.09 (2.40)	7.82 (1.38)
%UR Mean (S.D.)	8.70 (2.95)	13.11 (2.41)
%FE Mean (S.D.)	56.27 (24.23)	78.80 (2.14)

[a] One subject was excluded from the summary statistics because of high pre-dose radioactivity. Suggesting the subject's participation in a previous ^{14}C study.

Relative to Cohort B, lower and more variable total recovery of radioactivity was observed for subjects in Cohort A. The low total recovery of radioactivity in Cohort A was unexpected based on the recovery (mean = 69-82%) in rats and dogs following oral or intravenous administration in preclinical studies. The sponsor indicated that it could be due to less than optimal processing of fecal samples (homogenization with water prior to radioactivity measurement). Since BMS-232632 converts from a soluble sulfate salt to an insoluble free base at pH > 4, it is possible that the insoluble material may have precipitated, preventing a representative sampling from the homogenate and subsequent quantitation. Therefore, the fecal samples from subjects in Cohort B were processed with a methanol:water mixture instead of water, as BMS-232632 is freely soluble in organic solvents. The applicant indicated that the radioactivity recovery values from Cohort B are considered to be the appropriate values. In the feces, approximately 15% of the radioactivity was due to unchanged drug and the rest is attributed to at least 3 monohydroxylated metabolites and 4 dihydroxylated metabolites.

Reviewer's comment: The applicant indicated that investigation showed that drug administration and sample collection did not appear to contribute to the low and variable recovery of radioactivity. However, the 100% increase of BMS-232632 exposure and radioactivity observed in plasma of Cohort B suggests that there might be some problems associated with drug administration and/or sample

collection. It also noted that there were higher variabilities in parameter estimates associated with Cohort A. The exposure in Cohort B is comparable to that in male subjects in Study AI424-014 (age and gender effect study, 400 mg with a similar light meal). Therefore, the reviewer agreed that the radioactivity recovery values from Cohort B are the more appropriate values.

Unchanged drug accounted for approximately half of the urinary radioactivity (mean = 7% of the dose). The remainder of the radioactivity in the urine was due to the metabolites which included BMS-421419 [4-(2-pyridyl) benzoic acid] and its glucuronide (15% of the urinary radioactivity), 2 dihydroxylated metabolites, and at least 3 monohydroxylated metabolites.

The metabolites appeared to be rapidly formed since the median Tmax of total radioactivity coincided with the median Tmax of the parent drug. The sponsor indicated the mean T-HALF of BMS-232632 was longer than that of total radioactivity, because the —— assay method for BMS-232632 was more sensitive than liquid scintillation counting, resulting in longer quantification of BMS-232632 than radioactivity. The T-HALF of BMS-232632 in this study (36-37h) was longer than determined in other studies (6 – 8 h). The difference could be due to longer plasma sampling time in current study (o 10 days) as compared to previous studies (≤ 48h). The concentrations of BMS-232632 were appreciably lower after 48h (< 5 ng/mL) in this study, indicating that the T-HALF estimate is based on very low levels of the drug in the circulation. The low level may indicate a slow release of the drug from deeper tissues. The AUC values of BMS-232632 and radioactivity indicated that approximately 50% of the drug derived material circulating in the plasma was due to metabolites of BMS-232632.

The *in vivo* RBC-associated radioactivity data in this study were variable, with several negative values. The values that were positive (2.4-81.4% for Cohort A; 4.8-22.7% for Cohort B) were more variable than the previously determined *in vitro* RBC binding values (24.3-32.7%). The reasons for the high variability and the negative values are unclear.

Conclusions:

- Radioactivity was almost completely recovered (92% of the dose) in the urine and feces within 7 days after a single oral solution dose of [^{14}C]BMS-232632 in 3 subjects with properly processed fecal samples.
- The majority of the radioactivity (79% of the dose) was recovered in the feces, indicating that BMS-232632 and its metabolites are eliminated predominantly by biliary excretion and/or a fraction of the dose is unabsorbed.
- In the feces, approximately 15% of the radioactivity was due to unchanged drug and the rest is attributed to at least 3 monohydroxylated metabolites and 4 dihydroxylated metabolites.
- A small amount of radioactivity (13% of the dose) was recovered in the urine, and parent BMS-232632 accounted for half of the urinary radioactivity. The results indicated that urinary excretion plays a minor role in the overal elimination of BMS-232632 and its metabolites. However, the percentage of the absorbed dose that is excreted in urine is not known.
- The AUC values of BMS-232632 and radioactivity indicated that approximately 50% of the drug derived material circulating in the plasma was due to metabolites of BMS-232632.

- A single 400 mg oral dose of [^{14}C]BMS-232632 administered to male subjects was safe and well tolerated.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

A Randomized, Double-Blind, Placebo-Controlled, Single-Dose, Dose-Escalation Study to Evaluate the Safety and Pharmacokinetics of BMS-232632 in the Healthy Subjects (Protocol AI424-001)

Objective:

1. To evaluate the safety, tolerability and pharmacokinetics of a single-dose of BMS-232632 in healthy male subjects following administration of three dosage forms: capsule, oral solution and Gelucire® prototype capsule formulation.
2. To determine the relative bioavailability among the various formulations.

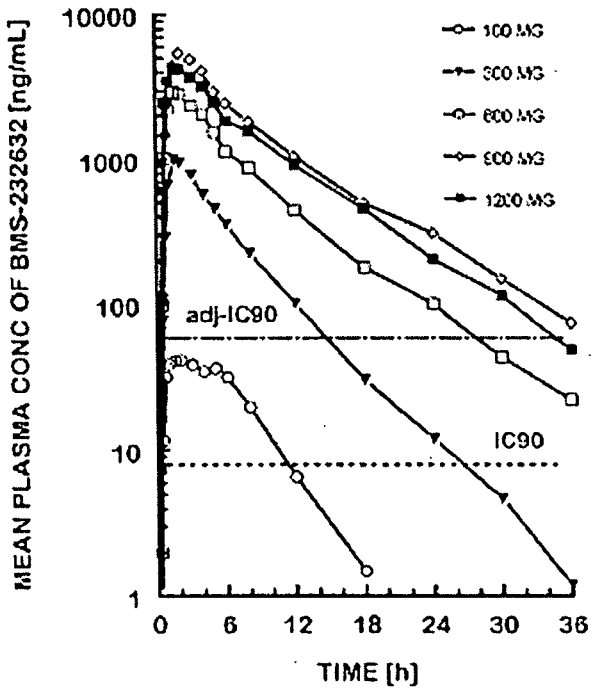
Population: 40 healthy white male subjects, aged from 18 to 45 years.

Study Design: This was a randomized, double-blind, placebo-controlled, single-dose, dose-escalation study. The range of doses studied were 100, 300, 600, 900, and 1200 mg. Eight healthy males were enrolled in each dose panel and randomized to drug or placebo in a 3:1 ratio. (6 active and 2 placebo in each dose panel). Each subject received a single dose of study drug on each of two occasions under fasted conditions, first in capsule form (Period 1) and second as an oral solution or a Gelucire® capsule (Period 2). A washout period of at least 7 days occurred between the two periods. Subjects in the 100 mg and 600 mg dose panels received the oral solution as the second dose and subjects in the 300, 900 and 1200 mg groups received a prototype Gelucire® capsule as the second dose. Plasma samples for pharmacokinetic analysis were collected prior to dosing, and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 18, 24, 30 and 36 hours after each dose of study drug.

Formulation: The gelatin capsule formulation contains 50 mg (Batch N97181) or 200 mg BMS-232632 (Batch N97184) as the bisulfate salt. The capsule formulations contain 0.2% w/w magnesium stearate as compared to 0.4% w/w magnesium stearate used in the to-be-marketed formulations. The Gelucire® capsule contains 100 mg BMS-232632 (Batch N97187) as the bisulfate salt. Powder for oral solution was supplied in vials containing 100 (Batch N97189) or 600 mg (Batch N97190) of BMS-232632 as the free base and Denatonium Benzoate NF (Bitrex™ Granules). The vials were reconstituted immediately before administration in a compounded solution of water and ethanol (BP). The contents were administered to each subject using an oral syringe.

Sample Assay: Plasma samples from all dose levels were assayed for BMS-232632 content by a validated —— method. The standard curve and QC data indicated that the plasma assay method was precise and accurate, and that BMS-232632 was stable in the plasma samples during shipment and storage. See QBR for details.

Pharmacokinetic Results: The mean plasma concentration-time profiles and the mean pharmacokinetic parameters of BMS-232632 following administration of 100 to 1200 mg doses of the capsule formulation are shown in the following figure and table. The IC_{90} (8 ng/mL) is the in vitro concentration of BMS-232632 producing 90% inhibition of HIV replication. The adj-IC_{90} is IC_{90} adjusted for human serum protein binding of 86.5%. For BMS-232632 capsule doses in a ratio of 1:3:6:9:12, the geometric means for the Cmax and AUC(INF) were in the ratios of 1:9:67:126:68 and 1:18:63:143:78.



Pharmacokinetic Parameter	Dose Level				
	100 mg (n=6)	300 mg (n=5)[a]	600 mg (n=6)	900 mg (n=6)	1200 mg (n=6)
CMAX (ng/mL) Geo. Mean (CV)	47 (42%)	884 (61%)	3128 (31%)	5897 (13%)	3175 (81%)
AUC(INF) (ng·h/mL) Geo. Mean (CV)	278 (65%)	4943 (44%)	17490 (47%)	39748 (28%)	21651 (87%)
T-HALF (h) Mean (SD)	2.81 (1.01)	3.82 (0.80)	6.14 (2.30)	5.88 (1.61)	5.54 (1.23)
TMAX (h) Median (Min, Max)	1.00	1.50	1.50	2.00	1.50

a one subject vomited and was excluded from the PK analysis

The results show that following oral administration of various doses as the capsule formulation, BMS-232632 was rapidly absorbed with a dose dependent clearance. In the range of 100 mg to 900 mg, Cmax and AUC values increased more than dose proportionally suggesting saturable intestinal and hepatic metabolism at high doses. From 900 mg to 1200 mg, Cmax and AUC decreased by about 50%. The applicant did not discuss the rationale for the exposure decrease with increased dose. An in vitro study has shown that, over the concentration range of 100 to 10000 ng/ml, the extent of human serum protein binding of BMS-232632 was constant. Therefore, the PK nonlinearlity of BMS-232632 may not be due to a change of the volume of distribution of BMS-232632, but could be due to saturable absorption. In addition, there were high variabilities associated with the PK parameters at the 1200 mg dose. The results

showed that single oral doses of 600 mg to 1200 mg BMS-232632 have 24-hour concentrations above adj-IC_{90}.

A comparison of the mean pharmacokinetic parameters of BMS-232632 administered as a capsule vs. the oral solution are summarized in the following table:

Pharmacokinetic Parameter	Dose Level			
	100 mg		600 mg	
	Capsule (n = 6)	Solution (n = 6)	Capsule (n = 6)	Solution (n = 6)
CMAX (ng/mL) Geo. Mean (CV)	47 (42%)	82 (69%)	3128 (31%)	4827 (32%)
AUC(INF) (ng·h/mL) Geo. Mean (CV)	278 (65%)	520 (72%)	17490 (47%)	24378 (31%)
T-HALF (h) Mean (SD)	2.81 (1.01)	2.87 (1.17)	6.14 (2.30)	5.41 (1.84)
TMAX (h) Median (Min, Max)	1.00	1.50	1.50	1.00
CMAX Ratio (%) Geo. Mean (CV)	57 (45%)	--	65 (34%)	--
AUC(INF) Ratio (%)[a] Geo. Mean(CV)	53 (32%)	--	72 (47%)	--

a $F_{REL\_CAPSULE}$

The data showed that based on the AUC ratios, the bioavailability ($F_{REL\_CAPSULE}$) of BMS-232632 from the capsule formulation, relative to the solution formulation, was 53% and 72% following doses of 100 and 600 mg, respectively.

A comparison of the mean pharmacokinetic parameters of BMS-232632 administered as a capsule vs. the Gelucire® capsule (prototype) are summarized in the following table:

Pharmacokinetic Parameter	Dose Level					
	300 mg		900 mg		1200 mg	
	Capsule (n = 5)[a]	Prototype (n = 6)	Capsule (n = 6)	Prototype (n = 5)[b]	Capsule (n = 6)	Prototype (n = 6)
CMAX (ng/mL) Geo. Mean (CV)	884 (61%)	1332 (45%)	5897 (13%)	3662 (28%)	3175 (81%)	7342 (36%)
AUC(INF) (ng·h/mL) Geo. Mean (CV)	4943 (44%)	6335 (42%)	39748 (28%)	37496 (38%)	21651 (87%)	60267 (58%)
T-HALF (h) Mean (SD)	3.83 (0.80)	5.21 (1.66)	5.88 (1.61)	6.11 (2.35)	5.54 (1.23)	6.70 (1.75)
TMAX (h) Median (Min, Max)	1.50	1.50	2.00	2.00	1.50	2.50
CMAX Ratio (%) Geo. Mean (CV)	--	136[c] (76%)	--	94 (18%)	--	231 (69%)
AUC(INF) Ratio (%)[c] Geo. Mean (CV)	--	115[a] (65%)	--	91 (18%)	--	278 (62%)

a one subject vomited and was excluded from the PK analysis
b one subject withdrew from the study and was excluded from the PK analysis
c $F_{REL\_PROTOTYPE}$

Based on the AUC ratios, the bioavailability ($F_{REL\_PROTOTYPE}$) of BMS-232632 from the prototype formulation (Gelucire® capsule), relative to the capsule formulation, was 115%, 91%, and 278% following doses of 300, 900 and 1200 mg, respectively.

The applicant claimed that adverse events did not increase in frequency with increasing dose and were not associated with a particular formulation. The majority of the adverse events were mild in intensity with 2 reported as moderate and 1 reported as severe. Increased bilirubin ranging from Grade 1 to Grade 3 was reported in 7 subjects who received BMS-232632 doses from 600 mg to 1200 mg.

Conclusions:

- Following oral administration of single doses of 100 to 900 mg as a capsule, the peak plasma concentrations and AUC values of BMS-232632 increase more than dose proportionally. However, from 900 mg to 1200 mg, Cmax and AUC decreased by about 50%.
- The mean apparent terminal half-life of BMS-232632 ranged from 3 to 6 hours following oral administration.
- The bioavailability of BMS-232632 from the capsule formulation, relative to the solution formulation, was 53% and 72% following doses of 100 and 600 mg, respectively.
- The bioavailability of BMS-232632 from the prototype formulation (Gelucire® capsule), relative to the capsule formulation, was 115%, 91%, and 278% following doses of 300, 900 and 1200 mg, respectively.
- Increased bilirubin was associated with single dose administration of 600 mg to 1200 mg BMS-232632.

A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Dose Escalation Study to Evaluate the Safety and Pharmacokinetics of BMS-232632 in Healthy Subjects (Protocol AI424-002)

Objective:

- To evaluate the pharmacokinetics, safety and tolerability of multiple oral doses of BMS-232632 in healthy male subjects.
- To determine if induction of the cytochrome P450 enzyme system (specifically CYP3A) occurred due to the administration of BMS-232632.

Population: A total of 66 healthy male subjects, 18 to 45 years with a Body Mass Index > 18 and < 30 kg/m^2 and serum creatinine, total serum lipase and liver enzymes at or below the upper limit of normal, were enrolled in the study. A total of 49 subjects received BMS-232632 capsules and 17 subjects received placebo capsules. Twelve subjects discontinued prior to completion of the study. Six subjects discontinued due to treatment-emergent AEs, two subjects withdrew consent, one subject was discontinued due to non-compliance and three subjects discontinued for personal reasons.

Study Design: Seven cohorts (200 mg QD, 400 mg QD, 600 mg QD (only for 7 days), 500 mg QD, 200 mg BID, 100 mg BID, and 800 mg QD for 14 consecutive days) were studied. One cohort (600 mg QD) was initially halted (after 8-day dosing) due to a protocol specific stopping rule and a second 600 mg cohort was dosed (before 800 mg QD dose) successfully. The original and replacement 600 mg QD cohorts are referred to as 600 mg QD (1) and 600 mg QD (2), respectively in the report. Eight subjects were enrolled in each cohort and randomized to receive BMS-232632 or placebo in a 3:1 ratio (6 active and 2 placebo per cohort). The QD doses and the morning doses for the BID regimen were given after an overnight fast. The evening doses of the BID regimen were given at least 2 hours before a meal.

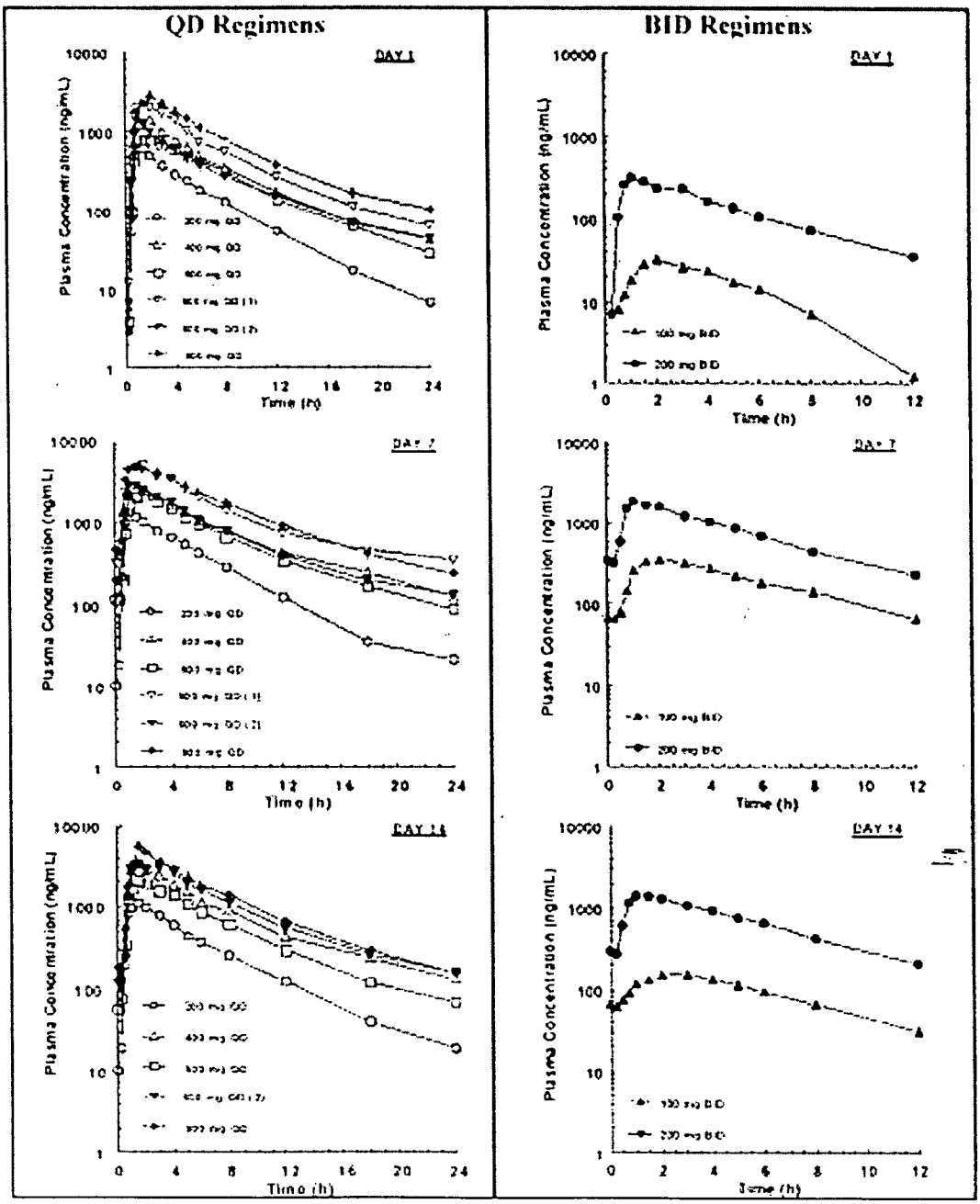
Formulation: 200 mg capsules (Batches N97184 and N98065) and 50 mg capsules (Batches N98064). The formulations contain 0.2% w/w magnesium stearate as compared to 0.4% w/w magnesium stearate used in the to-be-marketed formulations.

Pharmacokinetic Sampling: Blood samples for full pharmacokinetic analysis of BMS-232632 and its metabolite BMS-421419 were collected on Days 1, 7, and 14 and for pre-dose levels on Days 3, 5, 9, 11 and 13. For QD cohorts, blood samples were collected prior to dosing and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 18, and 24 hours after dosing. On Day 14, additional samples were collected at 30, 36, and 48 hours after dosing. For BID cohorts, blood samples were collected prior to dosing and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, and 12 hours after dosing. On Day 14, additional samples were collected at 18, 24, 30, 36, and 48 hours after dosing. Urine samples were obtained from the subjects in the 800 mg QD cohort prior to dosing and during periods of 0-4, 4-8, 8-12, and 12-24 hours after dosing on Days -1, 3, 7, 11 and 13 for 6 - hydroxycortisol/cortisol ratios. In addition, the Day 11 urine samples were used for assessment of urinary recovery of BMS-232632 and the presence of conjugated metabolites of BMS-232632.

Sample Assay: Plasma and urine samples were assayed for BMS-232632 concentrations by validated —— methods. Plasma BMS-421419 was analyzed by a valid —— method. The standard curve and QC data indicated that the plasma and urine assay methods were precise and accurate. See QBR for details.

Pharmacokinetic Results:

The mean plasma concentration-time profiles and the mean pharmacokinetic parameters of BMS-232632 following BMS-232632 QD or BID regimens are shown in the following figure and table.



Pharmacokinetic Parameter	Cohort	Study Day					
		Day 1 (n = 6)[a]		Day 7 (n = 6)[b]		Day 14 (n = 6)[c]	
Cmax (ng/mL) Geometric Mean (C.V. %)	200 mg QD	704	(52)	1081	(90)	598	(83)
	400 mg QD	1110	(86)	3003	(27)	3302	(54)
	500 mg QD	295	(176)	1696	(166)	1860	(60)
	600 mg QD (1)[d]	2378	(46)	5005	(42)	--	
	600 mg QD (2)	908	(84)	1899	(67)	3415	(55)
	800 mg QD	3227	(30)	4516	(44)	4908	(51)
	100 mg BID	18	(117)	313	(59)	154	(33)
	200 mg BID	294	(80)	1652	(55)	1487	(33)
AUC(TAU) (ng·h/mL)[e] Geometric Mean (C.V. %)	200 mg QD	2748	(43)	5387	(74)	3052	(71)
	400 mg QD	5611	(73)	16757	(34)	17427	(51)
	500 mg QD	1631	(193)	10757	(67)	11336	(52)
	600 mg QD (1)[d]	10563	(67)	27818	(71)	--	
	600 mg QD (2)	4726	(68)	12544	(62)	19591	(55)
	800 mg QD	15869	(40)	30851	(40)	26308	(51)
	100 mg BID	108	(108)	2005	(50)	1052	(28)
	200 mg BID	1143	(84)	8539	(48)	7727	(32)
Tmax (h) Median (Min, Max)	200 mg QD	1.25		1.25		1.50	
	400 mg QD	1.50		1.25		1.50	
	500 mg QD	1.50		2.00		1.50	
	600 mg QD (1)[d]	1.00		1.50			
	600 mg QD (2)	1.00		1.00		1.50	
	800 mg QD	1.50		1.50		1.50	
	100 mg BID	1.25		1.25		2.00	
	200 mg BID	0.88		1.00		1.00	
T-HALF (h) Mean (S.D.)	200 mg QD	3.46	(0.69)	4.07	(0.72)	4.95	(1.19)
	400 mg QD	5.54	(0.92)	7.74	(2.79)	5.42	(1.43)
	500 mg QD	4.63	(0.89)	5.85	(1.24)	5.70	(1.27)
	600 mg QD (1)[d]	5.17	(1.27)	9.77	(10.53)	--	
	600 mg QD (2)	6.33	(2.08)	7.69	(4.02)	5.00	(1.00)
	800 mg QD	6.12	(1.34)	5.73	(0.64)	5.15	(0.63)
	100 mg BID	2.26	(0.38)	4.04	(0.84)	5.34	(1.01)
	200 mg BID	3.53	(0.54)	3.87	(0.99)	5.14	(1.49)

[a] n = 5 for AUC(TAU) and T-HALF in the 100 mg BID cohort, n = 7 for all parameters in the 600 mg QD (2)

[b] n = 5 for AUC(TAU) and T-HALF in the 600 mg QD (1) cohort, n = 7 for all parameters in the 600 mg QD (2)

[c] n = 5 for all parameters in the 100 mg BID and 200 mg BID cohorts

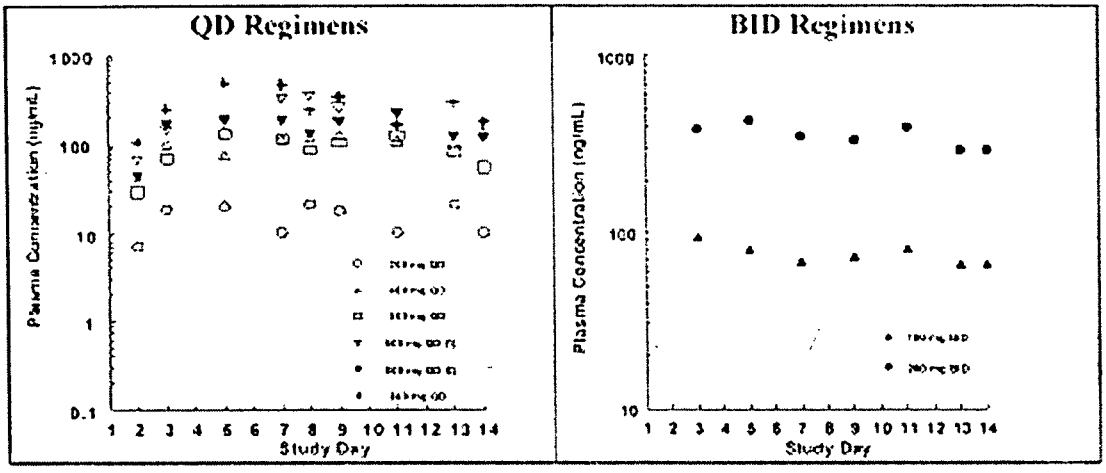
[d] All subjects discontinued by Study Day 9

[e] TAU = 12 h for BID regimen and 24 h for QD regimen

The data show that there was huge intersubject variability in PK parameter estimates. High variability was especially evident with the two cohorts that received 600 mg QD doses. Therefore, it is hard to determine if there is a dose-proportional increase in exposure. The T-HALF and Tmax are close to that seen in the previous single dose study (Study AI424-001). The accumulation index ranged from 1- to 18-fold after 7 or 14 days of BMS-232632 QD or BID regimens.

Cohort	n	Geometric Mean (C.V.%) Accumulation Index			
		Day 7/Day 1	n	Day 14/Day 1	
200 mg QD	6	1.96	(70.92)	6	1.11 (79.42)
400 mg QD	6	2.99	(100.68)	6	3.11 (117.04)
500 mg QD	6	6.59	(126.32)	6	6.95 (134.70)
600 mg QD (1)[a]	5	2.75	(90.50)	0	--
600 mg QD (2)	7	2.65	(58.68)	6	4.45 (142.08)
800 mg QD	6	1.94	(51.27)	6	1.66 (87.73)
100 mg BID	5	18.40	(114.63)	4	15.21 (113.07)
200 mg BID	6	7.47	(61.25)	5	6.13 (66.98)

Mean plasma trough levels are shown in the following figure:



The Cmin data suggest that steady-state concentrations were achieved within 3-5 days after either once or twice daily dosing of BMS-232632. The free plasma levels of BMS-232632 (based on protein binding of 86.5%) remained above the EC_{90} (8 ng/mL) for 24 h following QD doses of ≥400 mg and BID doses of 200 mg only. Therefore, pharmacokinetic data from the current study suggest that daily doses of 400 mg or above may be more effective than doses below 400 mg in the treatment of HIV infection.

A circulating metabolite, BMS-421419, was detected in the plasma of the subjects. The levels of the metabolite were very low (<10%) compared to the parent compound. Furthermore, this metabolite did not have any anti-HIV activity.

Urine samples were collected from subjects in the 800 mg QD cohort to detect conjugated metabolites of BMS-232632. Urinary recovery of unchanged drug was about 7%. The concentrations of BMS-232632 following β-glucuronidase incubation were comparable to the values before incubation with β-glucuronidase. The lack of increase in BMS-232632 levels with β-glucuronidase treatment indicates that there are no glucuronide conjugates of BMS-232632 present in the urine.