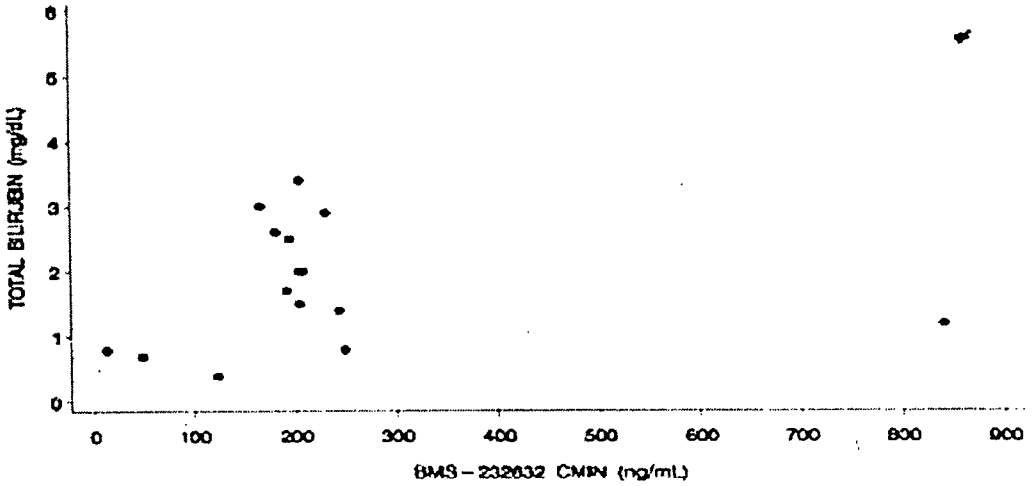
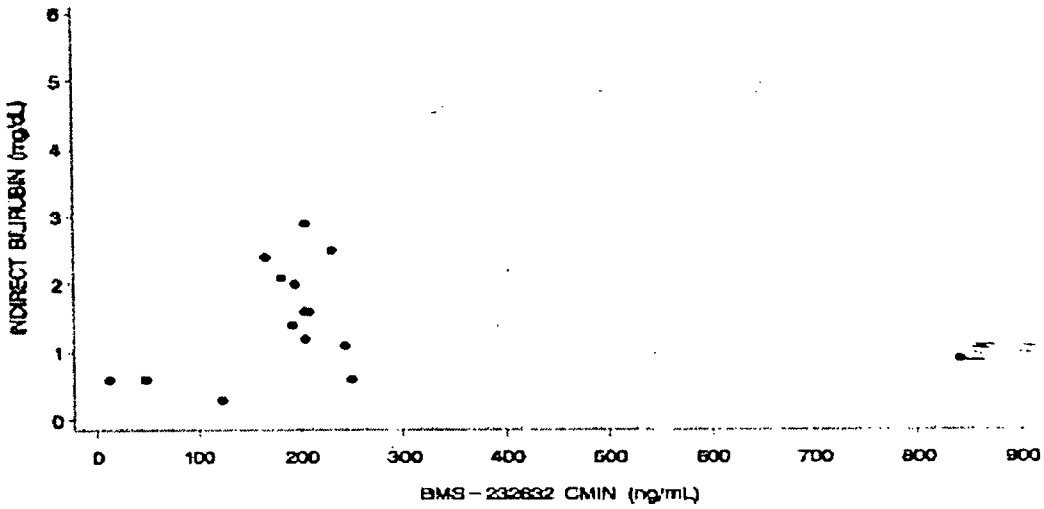
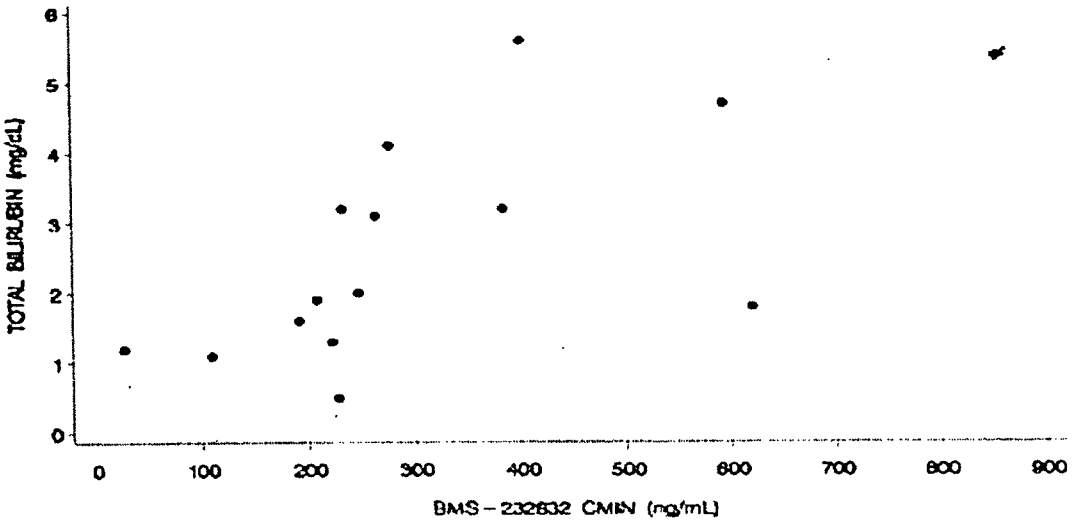
SCATTER PLOT OF DAY 7 PRE-DOSE TOTAL BILIRUBIN LEVELS VS DAY 7 BMS-232632 CMIN



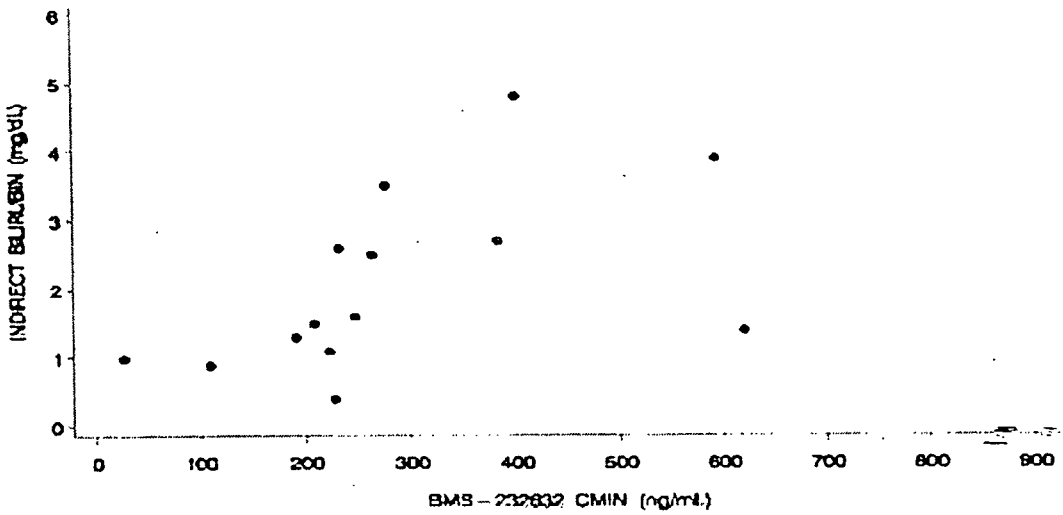
SCATTER PLOT OF DAY 7 PRE-DOSE INDIRECT BILIRUBIN LEVELS VS DAY 7 BMS-232632 CMIN



SCATTER PLOT OF DAY 14 PRE-DOSE TOTAL BILIRUBIN LEVELS VS DAY 14 BMS-232632 CMIN



SCATTER PLOT OF DAY 14 PRE-DOSE INDIRECT BILIRUBIN LEVELS VS DAY 14 BMS-232632 CMIN



Conclusion:

- Ketoconazole 200 mg QD did not affect the pharmacokinetics of BMS-232632. However, since ketoconazole is a potent CYP3A4 inhibitor and BMS-232632 is a CYP3A4 substrate, it is not known whether ketoconazole 400 mg QD affects the pharmacokinetics of BMS-232632.

- BMS-232632 may increase the Cmax and AUC of ketoconazole. However, the increase may not be clinically significant.

- No apparent relationship was observed between bilirubin levels (total and indirect) and BMS-232632 trough plasma concentrations on Day 7. Bilirubin levels (total and indirect) tended to increase with increasing trough plasma concentrations of BMS-232632 (in the presence of ketoconazole) on Day 14.

Evaluation of the Steady-State Interaction between BMS-232632 and Efavirenz (Sustiva ®) (Protocol AI424016)

Objective: To determine whether efavirenz, when co-administered with BMS-232632, affects the pharmacokinetics of BMS-232632.

Population: Thirty-one healthy subjects (21 male, 10 female) who met the eligibility criteria participated in the study. Age ranged from 18 to 56 years (mean = 32 years). Twenty-seven subjects completed the study. Four subjects withdrew their consent and requested to discontinue treatment due to central nervous system (CNS) effects believed to be associated with efavirenz.

Study Design: This was an open-label, non-randomized study with administration of BMS-232632 400 mg QD with a light meal for 6 days, followed by 14 days of simultaneous administration of BMS-232632 400 mg QD and efavirenz 600 mg QD with a light meal.

Formulation: BMS-232632 was supplied as 200 mg capsules (Batches N98178 and C99274). Efavirenz was supplied as Sustiva® 200 mg capsules (Batch RAO21A).

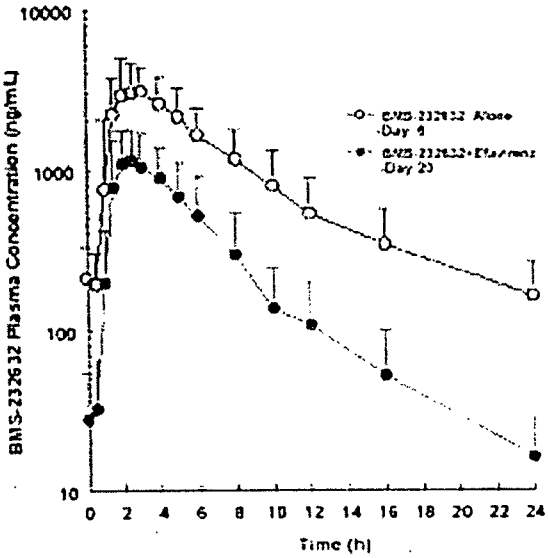
Pharmacokinetic Sampling: Blood samples were collected for BMS-232632 and efavirenz prior to dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, and 24 h after dosing on Days 6 and 20. Additional blood samples were collected on Days 2, 4, 12, 15, and 18 prior to the morning doses.

Analytical Analysis: Plasma concentrations of BMS-232632 and efavirenz were determined using validated —— methods. The standard curve and QC data indicated that the plasma assay method for BMS-232632 and efavirenz was precise and accurate. See QBR for details.

Pharmacokinetic Results:

BMS-232632

The following figure and tables show the mean plasma concentration-time profiles, the mean (SD) pharmacokinetic parameters, and the results of statistical analysis of BMS-232632, respectively.



Pharmacokinetic Parameter (BMS-232632)	Treatment[a]	
	B (Day 6) (n = 27)	B + E (Day 20) (n = 27)
Cmax (ng/mL) Geometric Mean (C.V. %)	3368.50 (38.42)	1374.74 160.39)
AUC(TAU) (ng·h/mL)[b] Geometric Mean (C.V. %)	20658.82 (41.31)	5462.35 159.59)
Tmax (h) Median (Min, Max)	2.00	2.50
T-HALF (h) Mean (S.D.)	6.97 (2.12)	5.09 (2.33)

Pharmacokinetic Parameter	Geometric Means[a]		Ratio (90% Confidence Interval)
	B	B + E	(B + E) / B
Cmax (ng/mL)	3368.50	1374.74	0.408 (0.329, 0.506)
AUC(TAU) (ng·h/mL)[b]	20658.82	5462.35	0.264 (0.217, 0.322)

[a] Treatment codes: B = BMS-232632 400 mg QD
B + E = BMS-232632 400 mg QD co-administered with efavirenz 600 mg QD

[b] TAU = 24 h

Summary statistics for BMS-232632 Cmin (ng/mL):

Treatment[a]	Study Day				
	Day 2 (n = 27)	Day 4 (n = 27)	Day 5 (n = 27)	Day 6 (n = 27)	Day 7 (n = 27)
B Mean (S.D.)	75.29 (46.99)	177.74 (150.81)	195.37 (136.95)	239.01 (137.54)	177.75 (102.97)
Treatment	**Study Day**				
	Day 12 (n = 27)	Day 15 (n = 27)	Day 18 (n = 27)	Day 20 (n = 27)	Day 21 (n = 26)
B + E Mean (S.D.)	50.93 (56.72)	25.89 (27.26)	18.31 (18.03)	26.34 (22.81)	17.71 (14.73)

The data show that efavirenz significantly reduced the AUC, Cmax and Cmin of BMS-232632. However, the half-life of BMS-232632 alone was comparable to its half-life when administered with efavirenz.

Efavirenz

The following table shows the mean (SD) pharmacokinetic parameters of efavirenz.

Pharmacokinetic Parameter (BMS-232632)	Treatment[a]
	B + E (Day 20) (n = 27)[b]
Cmax (ng/mL) Geometric Mean (C.V. %)	4958.23 (22.29)
AUC(TAU) (ng•h/mL)[c] Geometric Mean (C.V. %)	66569.38 (31.28)
Tmax (h) Median (Min, Max)	3.00
T-HALF (h) Mean (S.D.)	75.22 (45.33)

[a] Treatment codes: B = BMS-232632 400 mg QD
B + E = BMS-232632 400 mg QD co-administered with efavirenz 600 mg QD

[b] n = 26 for AUC(TAU)

[c] TAU = 24 h

Summary statistics for efavirenz Cmin (ng/mL):

Treatment[a]	Study Day				
	Day 12 (n = 27)	Day 15 (n = 27)	Day 18 (n = 27)	Day 20 (n = 27)	Day 21 (n = 26)
B + E Mean (S.D.)	1778.20 (512.71)	1926.60 (608.58)	1837.15 (629.06)	2031.37 (721.37)	2066.49 (921.89)

[a] Treatment code: B + E = BMS-232632 400 mg QD co-administered with efavirenz 600 mg QD

The data show that the geometric mean of Cmax and AUC(TAU) of efavirenz, when co-administered with BMS-232632, were 21.7% and 16.5% higher, respectively, as compared to efavirenz administered alone to HIV-infected subjects [Cmax = 4072 ng/mL; AUC(TAU) = 57150 ng.h/mL, under fasted conditions]. The half-life of efavirenz in the current study [mean = 75 hours (20-280 hours)] was longer than that reported in literature (40 - 55 hours). The increases in Cmax, Cmin and half-life were probably due to the light meals used in this study. Previous studies for efavirenz have shown that meals increase efavirenz exposure.

Bilirubin

An *in vitro* investigation demonstrated that BMS-232632 inhibits bilirubin glucuronidation by UDP-GT via a predominantly competitive process. Total bilirubin and indirect bilirubin were increased after BMS-232632 400 mg once daily treatment (Day 5). However, as shown in the following table, the levels of bilirubin decreased below the baseline after discontinuation of BMS-232632/efavirenz regimen (Day 21, 24 hours after the last dose), which was unexpected as even a lower exposure to BMS-232632 is expected to

Pharmacokinetic/ Pharmacodynamic Parameter[a]	Treatment[b]		
	Day -1 (n = 31)	Day 5 (n = 30)	Day 21 (n = 26)
Total Bilirubin (mg/dL) Mean (S.D.)	0.54 (0.31)	2.42 (1.69)	0.26 (0.11)
Indirect Bilirubin (mg/dL) Mean (S.D.)	0.41 (0.26)	2.18 (1.68)	0.17 (0.10)
BMS-232632 Cmin (ng/mL) Mean (S.D.)	--	185.44 (132.89)	17.71 (14.73)
Efavirenz Cmin (ng/mL) Mean (S.D.)	--	--	2066.49 (921.89)

AI424-016

Source: Supplemental Table S 11.4.1B

[a] Cmin and bilirubin values were obtained prior to dosing

[b] Treatments: Day 5 = BMS-232632 400 mg QD

Day 12 = Co-administration of BMS-232632 400 mg QD and efavirenz 600 mg QD

increase the levels of bilirubin. This observation suggests that efavirenz may have an inductive effect on UDP-GT.

Conclusion:

- Co-administration of efavirenz resulted in an appreciable decrease in the exposure of BMS-232632, probably due to induction of CYP3A4 caused by efavirenz. Therefore, efavirenz should not be given with BMS-232632 unless they are coadministered with ritonavir as a boosting agent.
- Comparison to data in Sustiva® label shows that the mean Cmax and AUC(TAU) of efavirenz, when co-administered with BMS-232632, was 21.7% and 16.5% higher, respectively, than that when efavirenz administered alone to HIV-infected subjects, which could be due to light meals used in this study.

APPEARS THIS WAY
ON ORIGINAL

Study to Evaluate the Effect of Efavirenz With and Without Ritonavir on the Pharmacokinetics of Atazanavir Administered with a Light Meal (Protocol AI424051)

Objective:

- To assess the exposure of atazanavir when given at 600 mg QD followed 2 hours later by efavirenz at 600 mg QD for 14 days, relative to the exposure of atazanavir when given at 400 mg QD for 6 days, in the presence of a light meal.
- To assess the exposure of atazanavir when given at 300 mg QD concomitantly with ritonavir at 100 mg QD followed 2 hours later by efavirenz at 600 mg QD for 14 days, relative to the exposure of atazanavir when given at 400 mg QD for 6 days, in the presence of a light meal.

Population: Thirty-four healthy subjects (32 male and 2 female), aged from 18 to 46 years, with an average of 31 years.

Study Design: This was an open-label, multiple-dose, randomized study. All Subjects were administered atazanavir at 400 mg QD for the first six days of the study. On Day 7, 50% subjects each were randomly assigned to either atazanavir at 600 mg QD followed 2 hours later by efavirenz at 600 mg QD for 14 days (Days 7-20) or to co-administered atazanavir at 300 mg QD and ritonavir at 100 mg QD followed 2 hours later by efavirenz at 600 mg QD for 14 days (Days 7-20). All atazanavir and ritonavir doses were given within 5 minutes after a 300-calorie evening snack, followed by administration of efavirenz 2 hours later.

Formulation: Atazanavir, 100 and 200 mg capsules (Batch N00097 and N00024, respectively); Sustiva ® (Efavirenz) 200 mg capsules (Lot #EPK348A); and Norvir® (Ritonavir) 200 mg capsules (Lot #817742E21).

Pharmacokinetic Sampling: Blood samples for pharmacokinetic assessment were collected prior to dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16 and 24 h after dosing on Days 6, and 20. Additional blood samples for trough levels (Cmin) were obtained prior to the evening dose on Days 2, 4, 12, 15, 17, and 19.

Analytical Analysis: Plasma samples were assayed for atazanavir, its metabolites BMS-421419 and BMS-551160, efavirenz, and ritonavir by validated [redacted] methods. The standard curve and QC data indicated that the plasma assay methods for atazanavir, BMS-421419, BMS-551160, efavirenz, and ritonavir were precise and accurate. See QBR for details.

Pharmacokinetic Results:

Atazanavir and metabolites

The two metabolites of atazanavir, BMS-421419 and BMS-551160 are formed via N-alkylation presumably by CYP3A4. These metabolites were observed previously in a ^{14}C ADME study. Both metabolites constituted approximately 19-25% and 30-38% of plasma radioactivity at 3 and 8 h after single 400 mg dose of atazanavir, respectively. The pharmacokinetics of atazanavir, BMS-421419 and BMS-551160 are presented below:

Pharmacokinetic Parameter	Regimen A[a]		Regimen B[a]	
	Day 6 (n = 10)	Day 20 (n = 10)	Day 6 (n = 13)	Day 20 (n = 13)
Atazanavir				
Cmax (ng/mL) Geometric Mean (C.V.%)	2918 (40)	3187 (37)	3244 (31)	3713 (27)
AUC(TAU)[b] (ng·h/mL) Geometric Mean (C.V.%)	24027 (47)	18922 (39)	27212 (28)	37726 (31)
Tmax (h) Median (Min, Max)	4.0 ———	2.5 ———	4.0 ———	2.5 ———
T-HALF (h) Mean (S.D.)	6.27 (1.96)	4.37 (1.18)	5.63 (1.00)	6.60 (2.16)
BMS-421419				
Cmax (ng/mL) Geometric Mean (C.V.%)	58 (50)	89 (37)	46 (37)	28 (36)
AUC(TAU)[b] (ng·h/mL) Geometric Mean (C.V.%)	1102 (45)	1530 (29)	871 (39)	408 (39)
Tmax (h) Median (Min, Max)	5.0 ———	4.0 ———	5.0 ———	2.0 ———
BMS-551160				
Cmax (ng/mL) Geometric Mean (C.V.%)	220 (28)	430 (34)	187 (37)	127 (49)
AUC(TAU)[b] (ng·h/mL) Geometric Mean (C.V.%)	4408 (26)	8386 (38)	3778 (38)	2126 (55)
Tmax (h) Median (Min, Max)	12.0 ———	12.0 ———	12.0 ———	2.5 ———

[a] Regimens A = Atazanavir at 400 mg for 6 days (Days 1-6) followed by atazanavir at 600 mg QD and, 2 hours later, efavirenz at 600 mg QD, for 14 days (Days 7-20).

B = Atazanavir at 400 mg for 6 days (Days 1-6) followed by co-administration of atazanavir at 300 mg QD, ritonavir at 100 mg QD and, 2 hours later, efavirenz at 600 mg QD, for 14 days (Days 7-20).

[b] TAU = 24 h

The geometric means, ratios of the geometric means, and the 95% confidence intervals for the ratios of geometric means for atazanavir, BMS-421419 and BMS-551160 are presented below:

Pharmacokinetic Parameter	Regimens[a]	Geometric Mean Day 6	Geometric Mean Day 20	Day 20/Day 6 Ratio Point Estimate (95% C.I.)	
Atazanavir					
Cmax (ng/mL)	A	2918	3187	1.09	(0.75, 1.58)
	B	3244	3713	1.14	(0.83, 1.58)
AUC(TAU)[b] (ng·h/mL)	A	24027	18922	0.79	(0.56, 1.11)
	B	27212	37726	1.39	(1.02, 1.88)
BMS-421419					
Cmax (ng/mL)	A	58	89	1.54	(1.34, 1.77)
	B	46	28	0.62	(0.55, 0.70)
AUC(TAU)[b] (ng·h/mL)	A	1103	1530	1.39	(1.23, 1.57)
	B	871	408	0.47	(0.42, 0.52)
BMS-551150					
Cmax (ng/mL)	A	220	430	1.95	(1.72, 2.22)
	B	187	127	0.68	(0.61, 0.76)
AUC(TAU)[b] (ng·h/mL)	A	4408	8386	1.90	(1.66, 2.18)
	B	3778	2126	0.56	(0.50, 0.63)

[a] Regimens A = Atazanavir at 400 mg for 6 days (Days 1-6) followed by atazanavir at 600 mg QD and, 2 hours later, efavirenz at 600 mg QD, for 14 days (Days 7-20).

B = Atazanavir at 400 mg for 6 days (Days 1-6) followed by co-administration of atazanavir at 300 mg QD, ritonavir at 100 mg QD and, 2 hours later, efavirenz at 600 mg QD, for 14 days (Days 7-20).

[b] TAU = 24 h

The data show that co-administration of atazanavir at 600 mg followed 2 hours later by efavirenz at 600 mg resulted in a 21% decrease in the AUC of atazanavir and a 39% and 90% increase in the steady-state AUC of the metabolites, BMS-421419 and BMS-551160, respectively, compared to atazanavir 400 mg alone. The decrease in atazanavir exposure observed following co-administration of atazanavir at 600 mg with efavirenz at 600 mg was probably due to the inductive effect of efavirenz on CYP3A4, as was observed in Study AI424016. The observed atazanavir AUC after atazanavir 400 mg alone is comparable to the values observed with 400 mg atazanavir QD in healthy subjects (Study AI424040, AUC =23469 ng.h/mL), but the Cmax is 23% to 31% lower than that in Study AI424040 (Cmax = 4225 ng/mL).

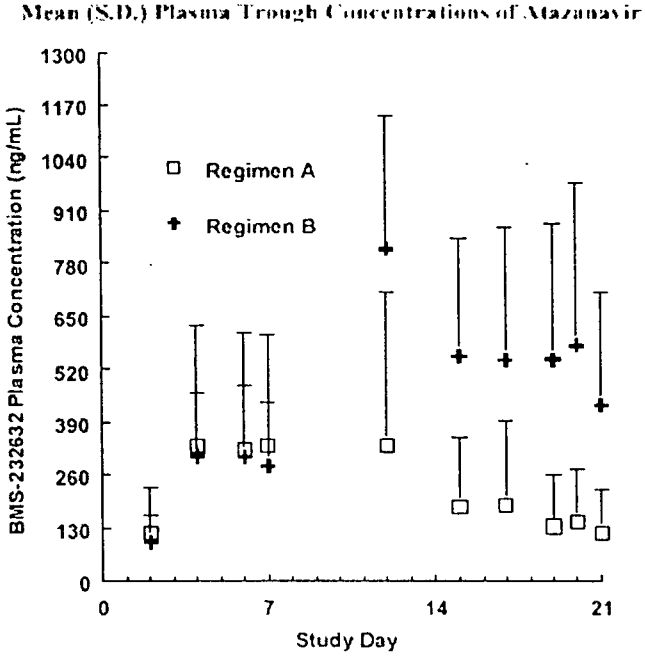
Co-administration of atazanavir at 300 mg and ritonavir at 100 mg followed 2 hours later by efavirenz at 600 mg resulted in a 39% increase in the steady-state AUC of atazanavir and a 53% and 44% decrease in the AUC of BMS-421419 and BMS-551160, respectively. The increase in atazanavir exposure observed with the co-administration of atazanavir at 300 mg and ritonavir at 100 mg with efavirenz at 600 mg was probably due to inhibition of CYP3A4 by ritonavir which may have offset the inductive effect of efavirenz. The inductive effect of efavirenz was also observed in Study AI424039.

The decrease in atazanavir exposure accompanied by an increase in the metabolite exposure suggests involvement of CYP3A4 in the formation of the metabolites, BMS-421419 and BMS-551160 of atazanavir.

The results showed that the exposure of the metabolite relative to the parent, when corrected for molecular weights was approximately 14% and 29% for BMS-421419 and BMS-551160, respectively. Relative to known circulating drug-related material, the exposure of the metabolite in the plasma was approximately 10% and 20% for BMS-421419 and BMS-551160, respectively. However, the half-lives for these metabolites were much longer as compared to their parent drug.

The in vitro data showed that both metabolites are inactive against HIV and exhibit no inhibitory effect on CYP P450 isozymes. However, the in vitro safety pharmacology studies showed that these metabolites also produced significant cardiac electrophysiological effects as their parent drug. In addition, the effect of the metabolites on UDP-GT is unknown.

The mean atazanavir Cmin values also reduced when atazanavir was combined with efavirenz. The mean values declined to about 50% of the reference 400 mg dose. The mean atazanavir Cmin values increased when atazanavir was combined with efavirenz and ritonavir.



Efavirenz and Ritonavir

Pharmacokinetic Parameter	Regimen A[a]	Regimen B[a]
	Day 20 (n = 10)	Day 20 (n = 13)
Efavirenz		
Cmax (ng/mL) Geometric Mean (C.V. %)	4798 (25)	5122 (26)
AUC(TAU)[b] (ng.h/mL) Geometric Mean (C.V. %)	73273 (32)	64683 (38)
Tmax (h) Median (Min, Max)	4.00	2.00
Ritonavir		
Cmax (ng/mL) Geometric Mean (C.V. %)	N/A	1347 (39)
AUC(TAU)[b] (ng.h/mL) Geometric Mean (C.V. %)	N/A	8832 (42)
Tmax (h) Median (Min, Max)	N/A	4.00
T-HALF (h) Mean (S.D.)	N/A	3.15 (0.47)

[a] Regimens A = Atazanavir at 400 mg for 6 days (Days 1-6) followed by atazanavir at 600 mg QD and, 2 hours later, efavirenz at 600 mg QD, for 14 days (Days 7-20).

B = Atazanavir at 400 mg for 6 days (Days 1-6) followed by co-administration of atazanavir at 300 mg QD, ritonavir at 100 mg QD and, 2 hours later, efavirenz at 600 mg QD, for 14 days (Days 7-20).

[b] TAU = 24 h

The mean (range) steady state AUC of efavirenz in Regimen A [AUC = 77610 (46859 - 117387) ng.h/mL] was comparable to that observed in Study AI424016 [AUC(TAU) = 69033 (43840 - 150113 ng.h/mL)]. Comparison to data in the Sustiva® label shows that the mean Cmax and AUC(TAU) of efavirenz, when co-administered with BMS-232632, was 20.9% and 35.8% higher, respectively, than that when efavirenz administered alone to HIV-infected subjects [Cmax = 4072 ng/mL; AUC(TAU) = 57150 ng.h/mL], under fasted conditions. The efavirenz mean (range) for Cmax and AUC observed in Regimen B [Cmax = 5281.4 ng/mL, AUC = 68499 (39379 - 136466) ng.h/mL] was 29.7% and 20.0% higher, respectively, than that when efavirenz administered alone to HIV-infected subjects. Ritonavir is known to increase the exposure to efavirenz by 21%. Therefore, atazanavir alone may not affect efavirenz exposure.

The mean (range) steady state AUC of ritonavir in the current study in Regimen B [AUC = 9581 (5092 - 16076) ng.h/mL] was 29% lower as compared to Study AI424028 [AUC = 13585 (8819 - 20192) ng.h/mL] where subjects were administered 400 mg of atazanavir with 100 mg of ritonavir for 10 days. The lower ritonavir exposure could be related to the inductive effect of efavirenz.

Bilirubin

Mean total bilirubin values increased, as expected, from a screening value of 0.64 mg/dl to 2.92 mg/dl at Day 7 of atazanavir administration (prior to dosing with efavirenz, with or without ritonavir - the applicant only provided combined data for Regimens A and B). Thereafter, the mean total bilirubin values began to decrease to 2.57 mg/dl by Day 14 and to 0.84 mg/dl by Day 22, when atazanavir is administered with efavirenz, with and without ritonavir. The previous study (AI424039) showed that total bilirubin tend to increase with the trough concentrations of atazanavir and ritonavir, but decrease with the trough concentrations of efavirenz. Therefore, the applicant suggested that the decline in bilirubin values by Day 22 of co-administration, as compared with Day 6 reflected the induction of the enzyme responsible for the glucuronidation of unconjugated bilirubin, principally by efavirenz.

> *Reviewer's Comment: Although ritonavir is reported to be an inducer of glucuronidation, there are no reports regarding induction ability of efavirenz. The applicant did provide the separated bilirubin data for Regimen A and B. Because bilirubin data were reported with all other laboratory results, it is difficult for the reviewer to analyze the data. We asked the applicant to submit an electronic PK/PD database to include all the bilirubin data. The applicant failed to do so. By examination of the individual bilirubin data, I found that with ritonavir on board, efavirenz could not effectively reduce the bilirubin level. Without ritonavir, efavirenz significantly reduced the bilirubin level. The results were consistent with the previous study AI424016.*

Conclusion:

- Co-administration of once daily doses of atazanavir at 600 mg and efavirenz at 600 mg resulted in a 21% decrease in the steady-state AUC of atazanavir and a 39% and 90% increase in the AUC of the metabolites, BMS-421419 and BMS-551160, respectively, compared to the administration of atazanavir at 400 mg alone.
- Co-administration of once daily doses of atazanavir at 300 mg and ritonavir at 100 mg with 600 mg of efavirenz resulted in 39% increase in the steady state AUC of atazanavir and a 53% and 44% decrease in the AUC of BMS-421419 and BMS-551160, respectively, compared to the administration of atazanavir at 400 mg alone. The regimen could be used when atazanavir is coadministered with efavirenz.
- The identified atazanavir metabolites, BMS-421419 and BMS-551160, accounts for approximately 10% and 20% of identified drug related material (metabolites + parent drug) in plasma, respectively.

Objective: To assess the effects of both 100 mg once-daily (QD) and 200 mg QD concomitant doses of ritonavir on the steady-state pharmacokinetics of both 200 mg QD and 400 mg QD regimens of BMS-232632.

Population: A total of thirty-two (32) male subjects, aged 29 to 50 years (average = 32 years), participated in the study.

Study Design: This was an open-label, randomized, pilot interaction study of BMS-232632 and ritonavir. Subjects were randomly assigned to one of the following 4 treatment groups:

A. BMS-232632 200 mg QD for 6 days followed by concomitantly administered BMS-232632 200 mg + ritonavir 100 mg QD for 10 days;
B. BMS-232632 200 mg QD for 6 days followed by concomitantly administered BMS-232632 200 mg + ritonavir 200 mg QD for 10 days;
C. BMS-232632 400 mg QD for 6 days followed by concomitantly administered BMS-232632 400 mg + ritonavir 100 mg QD for 10 days; or
D. BMS-232632 400 mg QD for 6 days followed by concomitantly administered BMS-232632 400 mg + ritonavir 200 mg QD for 10 days.

All doses of study drug were given within 5 minutes of a light meal.

Formulation: BMS-232632 was supplied as 200 mg capsules (Batch #C99274) Ritonavir was supplied by the Investigator as commercially available 100 mg capsules (Norvir®) imprinted with the corporate logo (Lot No. 61647E21).

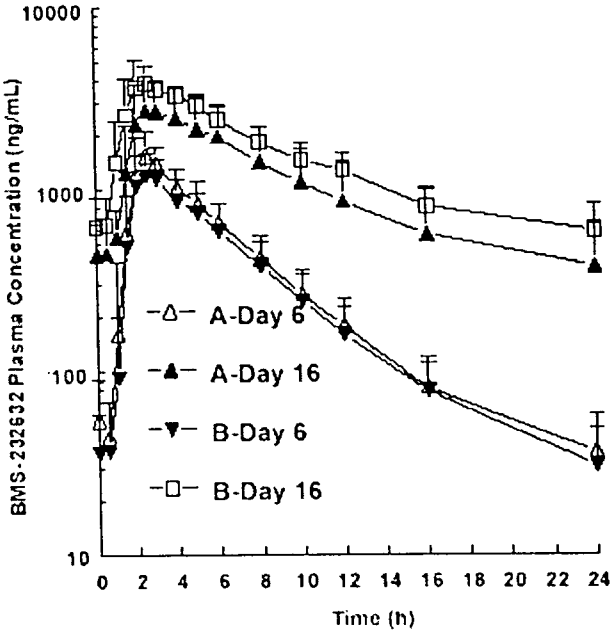
Pharmacokinetic Sampling: Blood samples were obtained at the following times:
Day 6: One sample (BMS-232632 only) prior to dosing and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16 and 24 h after dosing;
Day 16: Two samples (BMS-232632 and ritonavir) prior to dosing and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36 and 48 h after dosing;
Days 2, 4, 6 and 7 (BMS-232632 only) and Days 8, 11, 14, 16 and 17 (BMS-232632 and ritonavir): Prior to dosing (trough samples).

Analytical Analysis: Plasma samples were assayed for BMS-232632 content by a validated [redacted] method. Plasma concentrations of ritonavir were determined by a validated [redacted] method. The standard curve and QC data indicated that the plasma assay methods for BMS-232632 and ritonavir were precise and accurate. See QBR for details.

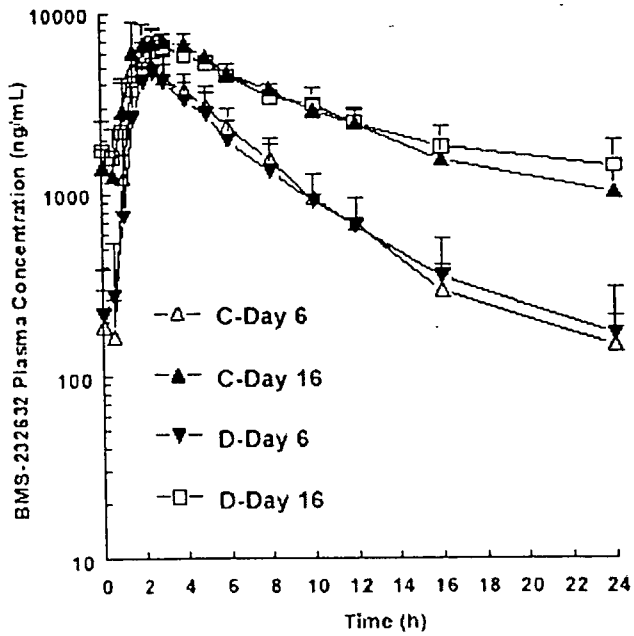
Pharmacokinetic Results:

BMS-232632
The mean plasma concentration-time profiles, the mean (SD) pharmacokinetic parameters, and the pharmacokinetic statistical analysis results for BMS-232632 are shown in the following figure and table, respectively.

Groups A and B



Groups C and D



Pharmacokinetic Parameter (BMS-232632)	Regimen Group[a]							
	A		B		C		D	
	Day 6 (n = 6)[b]	Day 16 (n = 6)[b]	Day 6 (n = 8)	Day 16 (n = 8)	Day 6 (n = 8)	Day 16 (n = 8)	Day 6 (n = 8)	Day 16 (n = 8)
Cmax (ng/mL) Geometric Mean (CV, %)	1595.79 (29.07)	2434.74 (47.05)	1312.40 (25.00)	4372.74 (17.11)	5690.30 (19.47)	7689.50 (13.68)	4683.87 (36.51)	7064.52 (16.70)
AUC(TAU) (ng·h/mL)[c] Geometric Mean (CV, %)	7687.58 (32.90)	21678.65 (54.26)	6826.74 (38.27)	35770.48 (17.70)	30494.59 (20.71)	69578.30 (14.96)	26372.08 (34.46)	69126.17 (19.60)
Tmax (h) Median (Min, Max)	2.50	2.50	2.50	2.00	2.00	2.25	2.50	2.50
T-HALF (h) Mean (SD)	4.65 (1.08)	8.36 (2.20)	4.43 (0.71)	10.64 (3.27)	4.81 (0.55)	7.04 (1.78)	5.75 (1.72)	9.68 (2.70)

Pharmacokinetic Parameter (BMS-232632)	Regimen Group[a]	Geometric Mean		Day 16/Day 6 Ratio	
		Day 6	Day 16	Point Estimate (90% C.I.)	
Cmax (ng/mL)	A	1595.79	2434.74	1.5	(1.130, 2.060)
	B	1312.40	4372.74	3.3	(2.569, 4.321)
	C	5690.30	7689.50	1.4	(1.042, 1.752)
	D	4683.87	7064.52	1.5	(1.163, 1.956)
AUC(TAU)[b] (ng·h/mL)	A	7687.58	21678.65	2.8	(2.111, 3.767)
	B	6826.74	35770.48	5.2	(4.078, 6.733)
	C	30494.59	69578.30	2.3	(1.776, 2.932)
	D	26372.08	69126.17	2.6	(2.040, 3.368)

a A = BMS-232632 at 200 mg QD for 6 days followed by co-administration of BMS-232632 at 200 mg QD and ritonavir at 100 mg QD for 10 days.
B = BMS-232632 at 200 mg QD for 6 days followed by co-administration of BMS-232632 at 200 mg QD and ritonavir at 200 mg QD for 10 days.
C = BMS-232632 at 400 mg QD for 6 days followed by co-administration of BMS-232632 at 400 mg QD and ritonavir at 100 mg QD for 10 days.
D = BMS-232632 at 400 mg QD for 6 days followed by co-administration of BMS-232632 at 400 mg QD and ritonavir at 200 mg QD for 10 days

b n = 6 as two subjects discontinued from the study before Day 6

c TAU = 24 h

The data show that the magnitude of increase in exposure (AUC) of BMS-232632 was comparable when either 100 mg (2.3 fold) or 200 mg (2.6 fold) of ritonavir was administered with 400 mg of BMS-232632, but was greater when 200 mg of BMS-232632 was administered with 200 mg (5.2 fold) of ritonavir as compared to 100 mg (2.8 fold) of ritonavir. The increase in plasma concentrations of BMS-232632 upon concomitant administration of ritonavir is presumed to be due to the inhibition of the CYP

3A4-mediated metabolism of BMS-232632, although interaction with transporters cannot be ruled out.

Atazanavir Cmax and AUC values after 200 mg administration of atazanavir alone is 9%-32% and 12%-26% higher, respectively, as compared to that after the same atazanavir dose in Study AI424040. Atazanavir Cmax and AUC values after 400 mg administration of atazanavir alone is 11%-35% and 12%-30% higher, respectively, as compared to that after the same atazanavir dose in Study AI424040, but is compared to that observed in Study AI424013.

Ritonavir

The following tables summarize the pharmacokinetic parameters of ritonavir.

Pharmacokinetic Parameter	Regimen Group			
	A	B	C	D
	Day 16 (n = 6)	Day 16 (n = 8)	Day 16 (n = 8)	Day 16 (n = 8)
Cmax (ng/mL) Geometric Mean (C.V. %)	1775.55 (46.55)	5531.43 (37.85)	2326.81 (26.20)	4462.78 (26.20)
AUC(TAU) (ng·h/mL) Geometric Mean (C.V. %)	10684.16 (45.88)	30626.64 (24.84)	13074.00 (30.17)	27401.15 (12.83)
Tmax (h) Median (Min, Max)	4.00	4.00	4.00	5.00
T-HALF (h) Mean (SD)	5.45 (1.22)	6.20 (1.36)	5.08 (1.31)	5.19 (0.70)

Ritonavir Cmin

Study Day	Regimen Group			
	A (n = 6)	B (n = 8)	C (n = 8)	D (n = 8)
Day 8 Geometric Mean (C.V.%)	46.42 (76.07)	158.48 (89.20)	53.58 (69.94)	159.60 (45.23)
Day 11 Geometric Mean (C.V.%)	53.54 (43.47)	159.71 (61.09)	55.10 (77.35)	142.58 (43.41)
Day 14 Geometric Mean (C.V.%)	52.92 (46.61)	138.80 (57.93)	55.96 (53.36)	136.01 (43.78)
Day 16 Geometric Mean (C.V.%)	49.39 (59.53)	131.89 (60.80)	52.02 (50.07)	129.66 (49.80)
Day 17 Geometric Mean (C.V.%)	43.06 (55.61)	103.59 (50.57)	29.18 (54.34)	112.01 (38.50)

Ritonavir pharmacokinetics were comparable upon co-administration of ritonavir with either 200 mg or 400 mg of BMS-232632. This indicates that if BMS-232632 had a pharmacokinetic effect on ritonavir, the effect was not dependent on the dose of BMS-232632.

Bilirubin

The following table summarizes the statistics for bilirubin levels and corresponding BMS-232632 Cmin

Regimen	Study Day[b]	n	PK/PD Parameter		
			Total Bilirubin (mg/dL) Mean (SD)	Indirect Bilirubin (mg/dL) Mean (SD)	BMS-232632 Cmin (ng/mL) Mean (SD)
A	Baseline	6	0.62 (0.25)	0.48 (0.21)	--
	Day 6	6	1.32 (0.69)	1.08 (0.62)	54.08 (36.72)
	Day 16	6	2.82 (1.54)	2.48 (1.63)	434.43 (222.39)
B	Baseline	8	0.51 (0.10)	0.38 (0.07)	--
	Day 6	8	0.86 (0.47)	0.71 (0.41)	36.33 (22.27)
	Day 16	8	2.38 (1.61)	2.08 (1.59)	618.60 (278.51)
C	Baseline	8	0.61 (0.24)	0.44 (0.17)	--
	Day 6	8	1.73 (0.98)	1.51 (0.96)	186.20 (117.95)
	Day 16	8	4.16 (2.08)	3.88 (2.21)	1402.04 (1397.84)
D	Baseline	8	0.85 (0.33)	0.63 (0.27)	--
	Day 6	8	2.13 (1.26)	1.85 (1.22)	215.97 (171.25)
	Day 16	8	4.81 (1.95)	4.55 (1.97)	1740.98 (832.30)

The data are consistent with the results from other studies. It shows that there was a tendency towards an increase in bilirubin levels with the increase in plasma trough concentrations of BMS-232632. All elevations in bilirubin returned to baseline upon discontinuation of study drug.

Conclusion:

- Ritonavir increased the Cmax, Cmin, and AUC of BMS-232632 appreciably as compared to the values following BMS-232632 administered alone, presumably due to inhibition of BMS-232632 metabolism mediated by CYP3A4.
- The magnitude of increase in BMS-232632 exposure (AUC) was similar when 400 mg of BMS-232632 was co-administered with 100 mg (2.3 fold) or 200 mg (2.6 fold) of ritonavir. However, the magnitude of increase in BMS-232632 exposure was greater when 200 mg of BMS-232632 was co-administered with 200 mg of ritonavir (5.2 fold) as compared to the 100 mg dose (2.8 fold).
- Ritonavir pharmacokinetics were related to the dose of ritonavir but were similar whether ritonavir was administered with 200 mg or 400 mg of BMS-232632, indicating that the pharmacokinetic effect of BMS-232632, if any, was independent of the dose of BMS-232632.
- Bilirubin levels tended to increase as plasma trough concentrations of BMS-232632 increased.

Safety and Pharmacokinetic Interaction Study of Atazanavir and Ritonavir in Healthy Subjects (AI424056)

Objective:

1. To assess the added effect of ritonavir, when co-administered with atazanavir, on the QTc interval (specifically on the change from baseline QTc Max to QTc Max), as compared with the effect due to administration of atazanavir alone.
2. To assess the effect of ritonavir, when co-administered with atazanavir, on the steady-state pharmacokinetics of atazanavir.

Population: 31 subjects (23 male, 8 female) entered the study. Twenty-eight (28) subjects (22 males, 6 females) completed the study. Only 30 subjects received study drug, as 1 subject (016) was discontinued after subject number assignment but prior to receiving the first dose.

Study Design: This was an open-label, non-randomized, multiple-dose study in healthy subjects. Subjects received atazanavir 300 mg QD for 10 days (Days 1-10), followed by co-administration of atazanavir 300 mg QD and ritonavir 100 mg QD for 10 days (Days 11-20). All doses were given within 5 minutes after a standard light meal.

Formulation: Atazanavir was supplied as 100 mg capsules (Batch #C99178). Ritonavir was supplied as marketed 100 mg Norvir® capsules (Lot #762172E21).

Pharmacokinetic/Pharmacodynamic Sampling: Blood samples for pharmacokinetic assessments were collected prior to dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16 and 24 h after dosing on Days 10, 15, and 20. Additional blood samples for trough levels (Cmin) were obtained prior to the evening dose on Days 4, 8, 13, and 18.

Blood samples for bilirubin evaluation were collected at screening; on Day -1 (within 24 hours prior to dosing); prior to study drug administration on Day 10 and prior to discharge on Day 21, while urine samples were only collected at screening and discharge.

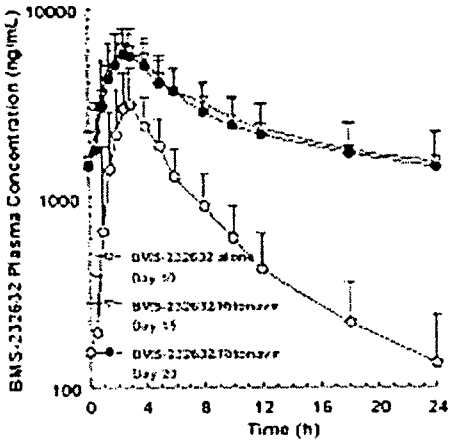
Twelve (12)-lead ECGs were recorded at screening; on Day -1 at the clock times corresponding to pre-dose, 2, 3, 4, 6, 8, 12, 18 and 24 hours after dosing; on Days 10, 15 and 20, at pre-dose, 2, 3, 4, 6, 8, 12, 18 and 24 hours after dosing and at discharge on Day 21. The 24 hour ECG on Day 20 was used as the discharge ECG for subjects who completed the study. ECGs were to be recorded prior to blood sampling.

Analytical Analysis: Plasma samples were assayed for BMS-232632 and ritonavir concentrations by a validated ——— method. The standard curve and QC data indicated that the plasma assay methods for BMS-232632 and ritonavir were precise and accurate. See QBR for details.

Pharmacokinetic Results:

Atazanavir

The mean plasma concentration-time profiles, the mean (SD) pharmacokinetic parameters, and the pharmacokinetic statistical analysis results for BMS-232632 are shown in the following figure and table, respectively.



Pharmacokinetic Parameter (Atazanavir)	Treatment [a]		
	B	B + R	
	Day 10 (n = 28)	Day 15 (n = 28)	Day 20 (n = 28)
Cmax (ng/mL) Geometric Mean (C.V.%)	3288.15 (47.65)	6455.81 (26.17)	6128.71 (31.49)
AUCTAU (ng·h/mL) [b] Geometric Mean (C.V.%)	16874.51 (41.05)	63348.41 (30.47)	57038.59 (37.29)
Tmax (h) Median (Min, Max)	2.71	2.66	2.67
T-HALF (h) Mean (S.D.)	6.55 (2.03)	15.50 [c] (5.43)	18.13 [d] (6.21)

[a] Treatment: B = Atazanavir at 300 mg QD for 10 days (Days 1-10)

B + R = Co-administration of atazanavir at 300 mg QD and ritonavir at 100 mg QD for 10 days (Days 11-20).

[b] TAU = 24 h

[c] n = 25

[d] n = 26

Pharmacokinetic Parameter (Atazanavir)	Day 15/Day 10 Ratio Point Estimate	(90% C.I.)	Day 20/Day 10 Ratio Point Estimate	(90% C.I.)
Cmax (ng/mL)	1.96	(1.78, 2.16)	1.86	(1.69, 2.05)
AUCTAU (ng·h/mL) [a]	3.75	(3.48, 4.05)	3.38	(3.13, 3.65)

[a] TAU = 24 h

Compared to 400 mg atazanavir administered alone (Studies AI424040 and AI424076 Cmax = 4225 –5500 ng/mL, AUC = 23469 –33097 ng.h/mL), atazanavir Cmax and AUC increased by 17%-53% and 91%-170%, respectively, after administration of 300 mg atazanavir combined with 100 mg ritonavir.

Ritonavir

The following table summarizes the pharmacokinetic parameters of ritonavir.

Pharmacokinetic Parameter	Treatment B + R	
	Day 15 (n = 28)	Day 20 (n = 28)
Cmax (ng/mL) Geometric Mean (C.V.%)	2468.37 (24.42)	2386.24 (20.34)
AUC(TAU) (ng·h/mL)[b] Geometric Mean (C.V.%)	15760.14 (26.96)	14843.89 (21.77)
Tmax (h) Median (Min, Max)	4.16	3.17
T-HALF (h) Mean (S.D.)	4.46 (0.72)	5.13 (0.99)

[b] TAU = 24 h

Ritonavir pharmacokinetics following co-administration of 300 mg atazanavir were generally comparable to those observed previously with co-administration of 100 mg ritonavir and 400 mg atazanavir, thus suggesting that the pharmacokinetic effect of atazanavir, if any, is independent of the dose of atazanavir.

Pharmacodynamic Results:

Bilirubin

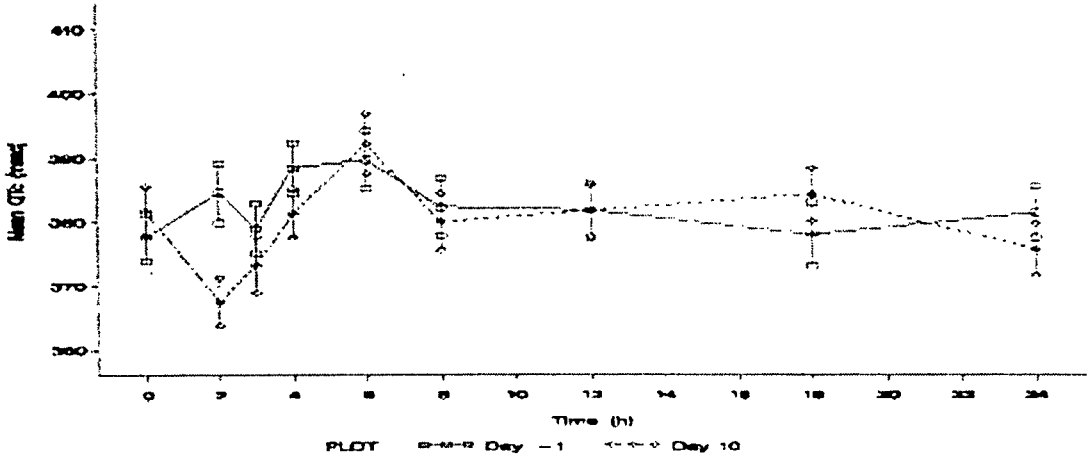
Twenty-nine of 30 (97%) subjects experienced elevated bilirubin levels. The elevations were observed in 19 subjects when atazanavir at 300 mg was administered alone and in 29 subjects when atazanavir at 300 mg with ritonavir at 100 mg were co-administered. The number of subjects who experienced Grades 3 and 4 bilirubin elevation is shown in the following table. All of the elevations reversed upon drug discontinuation at the study conclusion.

	Bilirubin elevation	
	Grade 3	Grade 4
	Count (%)	Count (%)
Atazanavir 300 mg	3 (10%)	2(6.7%)
Atazanavir/ritonavir 300/100 mg	17 (56.7%)	8 (26.7%)

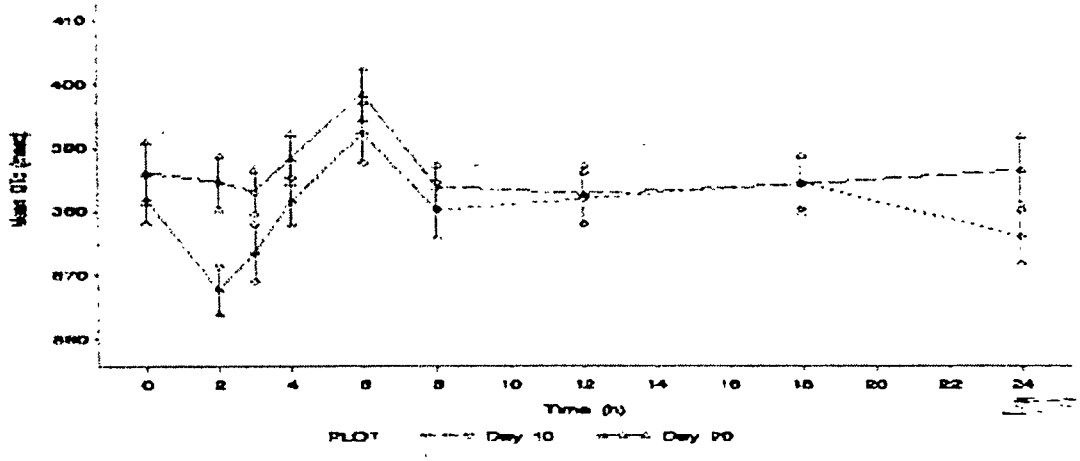
The results showed that atazanavir/ritonavir 300/100 mg increased the severity of bilirubin elevation as compared to atazanavir 300 mg, which might be mostly related to increased atazanavir concentrations in the presence of ritonavir.

QTc Interval

Plot of Mean QTc versus Time on Days -1 and 10



Plot of Mean QTc versus Time on Days 10 and 20



Counts of Subjects with different severity of QTc Changes from Baseline

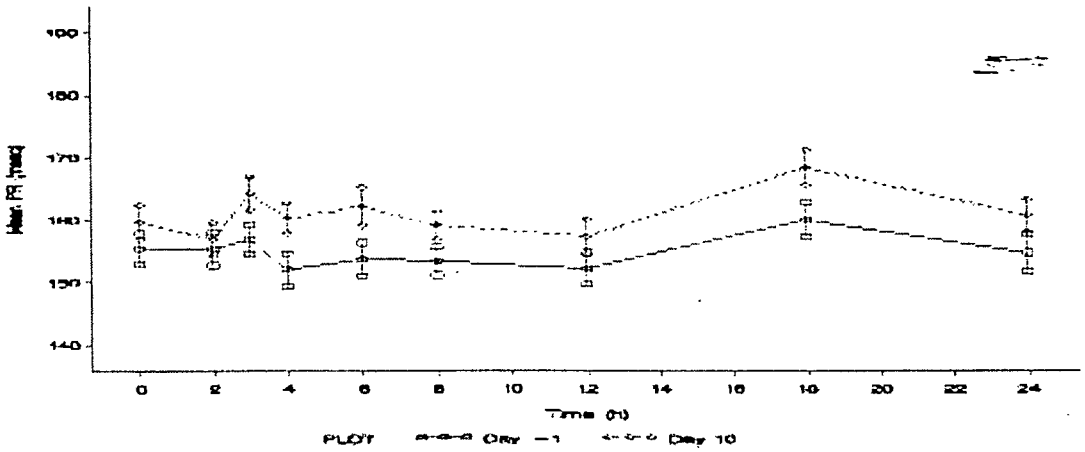
Study Day	Gender	QTc Changes from Baseline (msec)		
		< 30	30-60	> 60
		Count (%)	Count (%)	Count (%)
10	Male	15 (68%)	7 (32%)	0 (0%)
	Female	1 (13%)	7 (88%)	0 (0%)
15	Male	10 (48%)	8 (38%)	3 (14%)
	Female	2 (29%)	5 (71%)	0 (0%)
20	Male	10 (48%)	9 (43%)	2 (10%)
	Female	4 (57%)	2 (29%)	1 (14%)

The data showed that coadministration of atazanavir and ritonavir tends to increase the severity of QTc prolongation, as demonstrated by increased count of Δ QTc > 60 msec. However, the statistic significance is unknown, because the applicant used linear regression analysis which is considered not useful when there is a significant lag time between the occurrence of maximum QTcB prolongation and maximum plasma concentrations. In addition, Bazett's correction was used in the analysis. As we discussed in the QBR, Fridericia's correction may be more appropriate for atazanavir.

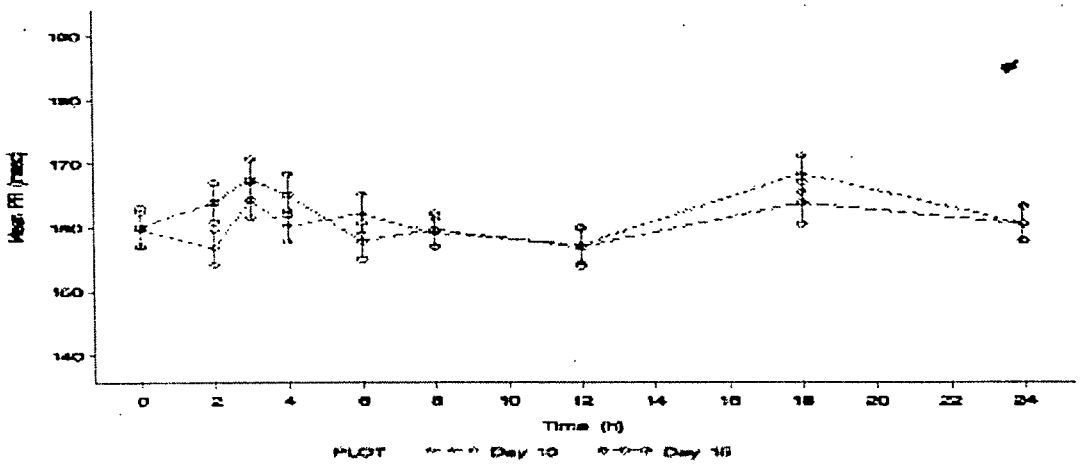
PR Interval

Five (5) subjects (3 males, 2 females) out of 30 (17%) had at least one ECG with PR > 200 msec. None of these prolonged PR intervals occurred during administration of atazanavir alone. In all cases but one, PR prolongation was mild (250 msec). One male subject (Subject 015) had a PR = 358 msec at 2 hours after dosing on Day 15; this subject had no other ECGs with a PR > 200 msec. The following figures show the plots of mean PR versus time on different days.

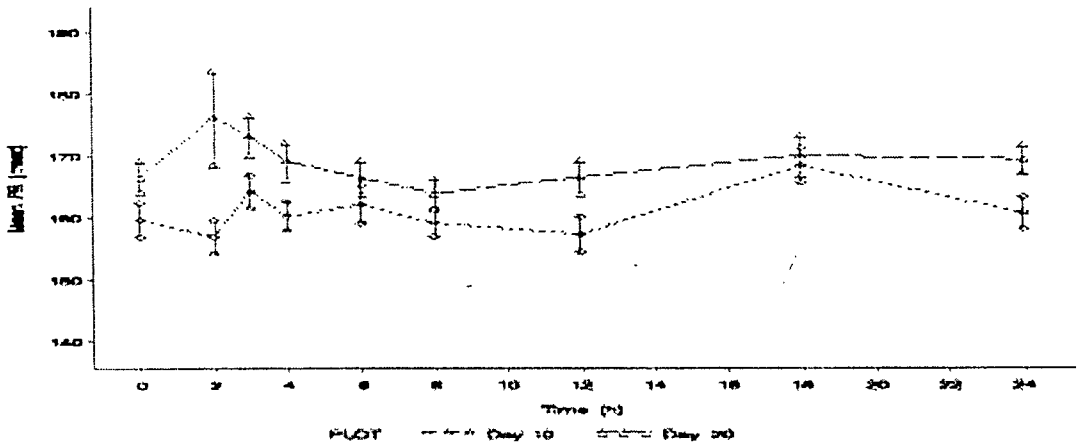
Plot of Mean PR versus Time on Days -1 and 10



Plot of Mean PR versus Time on Days 10 and 15



Plot of Mean PR versus Time on Days 10 and 20



The data showed that when atazanavir 300 mg was coadministered with ritonavir 100 mg, there was a tendency to increase PR intervals, as compared to atazanavir 300 mg alone.

Conclusion:

- Ritonavir increased the Cmax (80%) and AUC (228%) of atazanavir as compared to atazanavir alone, presumably due to CYP3A inhibition.
- Compared to 400 mg atazanavir alone, atazanavir Cmax and AUC increased by 24%-53% and 125%-170%, respectively, after administration of 300 mg atazanavir combined with 100 mg ritonavir.
- Ritonavir pharmacokinetics following co-administration of 300 mg atazanavir were generally comparable to those observed previously with co-administration of 100 mg

ritonavir and 400 mg atazanavir, thus suggesting that the pharmacokinetic effect of atazanavir, if any, is independent of the dose of atazanavir.

- Atazanavir/ritonavir 300/100 mg increased the severity of bilirubin elevation as compared to atazanavir 300 mg, which might be mostly related to increased atazanavir concentrations in the presence of ritonavir.
- The data showed that coadministration of atazanavir and ritonavir has a tendency to increase the severity of QTc prolongation. However, the statistical significance is unknown.
- When atazanavir 300 mg was coadministered with ritonavir 100 mg, there was a tendency to increase PR intervals, as compared to atazanavir 300 mg alone.

APPEARS THIS WAY
ON ORIGINAL

Pharmacokinetic Interaction Study to Evaluate the Pharmacokinetic Effect of Rifabutin on BMS-232632 with and without Ritonavir in Healthy Subjects (AI424021)

Background: BMS-232632 is a substrate and inhibitor of CYP3A while rifabutin is a known CYP3A substrate and inducer. Therefore, there is a potential for an increase in rifabutin exposure and decrease in BMS-232632 exposure upon concomitant administration of these two drugs. Ritonavir, at a dose of 500 mg BID, is already known to increase the exposure to rifabutin, presumably due to CYP3A inhibition. This observation suggests that the dose of rifabutin needs to be reduced for co-administration with BMS-232632 and ritonavir. A dosage reduction of rifabutin to half the standard dose of 300 mg is recommended for some marketed HIV protease inhibitors (indinavir, amprenavir, nelfinavir), which are also CYP3A inhibitors. A rifabutin dose of 150 mg was therefore chosen *a priori* for this study.

To counter the expected effect of rifabutin on BMS-232632, a higher dose of BMS-232632 (600 mg QD) and concomitant administration of BMS-232632 (400 mg) QD and ritonavir (100 mg) QD were studied in addition to BMS-232632 at 400 mg QD.

Objective: To evaluate the pharmacokinetic effect of rifabutin on BMS-232632 with and without ritonavir in healthy subjects.

Population: A total of 30 subjects (24 male and 6 female), aged from 20 to 43 years with an average of 32 years, participated in the study. Twenty-two (22) subjects completed the study.

Study Design: This was an open-label, randomized study in thirty (30) healthy subjects. Subjects were administered 400 mg of BMS-232632 QD for the first 14 days of the study. On Day 15, ten subjects each were randomly assigned to the following three regimens:

A: BMS-232632 at 400 mg QD and rifabutin at 150 mg QD for 14 days.
B: BMS-232632 at 600 mg QD and rifabutin at 150 mg QD for 14 days.
C: BMS-232632 at 400 mg QD, rifabutin at 150 mg QD and ritonavir at 100 mg QD for 14 days.

All doses were administered in the morning within 5 minutes after a light meal given as breakfast.

Formulation: BMS-232632 200 mg capsules (Batch #C99274). Mycobutin® (rifabutin) 150 mg capsules and Norvir® (ritonavir) 100 mg capsules (Lot#716922E21).

Pharmacokinetic Sampling: Blood samples for pharmacokinetic assessment were collected prior to dosing and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16 and 24 h after dosing on Days 7, 14, and 28. Additional blood samples for trough levels (Cmin) were obtained prior to the morning dose on Days 2, 4, 6, 11, 16, 19, 23 and 26.

Analytical Analysis: Plasma samples were assayed for BMS-232632, rifabutin, 25-O-desacetylrifabutin, and ritonavir concentrations by validated methods. The standard curve and QC data indicated that the plasma assay methods for BMS-232632, rifabutin, 25-O-desacetylrifabutin, and ritonavir were precise and accurate. See QBR for details.

Pharmacokinetic Results:

Summary statistics for BMS-232632 pharmacokinetic parameters are presented in the table below.

Regimen[a]	Study Day	n	Pharmacokinetic Parameter (BMS-232632)			
			Cmax (ng/mL) Geom. Mean (C.V.%)	AUC(TAU)[b] (ng·h/mL) Geom. Mean (C.V.%)	Tmax (h) Median (Min, Max)	T-HALF (h) Mean (S.D.)
All regimens pooled	7	30	3769.97 (28.17)	25070.31 (33.50)	2.25	9.83 (6.41)
	14	30	3629.55 (30.77)	22762.81 (34.70)	2.50	8.85 (5.08)
A	7	7	3390.76 (31.38)	23315.83 (42.14)	2.50	9.98 (8.76)
	14	7	3551.27 (36.18)	22107.25 (37.97)	3.00	7.91 (4.85)
	28	7	4770.30 (37.33)	25368.58 (32.21)	2.00	8.02 (4.01)
B	7	9	3623.46 (14.90)	24008.35 (30.89)	2.50	11.37 (8.51)
	14	9	3347.12 (21.05)	21099.22 (34.59)	2.50	10.83 (7.80)
	28	9	6833.05 (31.15)	44088.77 (30.61)	2.50	9.66 (3.93)
C	7	6	3915.53 (19.05)	26711.78 (33.63)	2.00	8.94 (1.89)
	14	6	3903.10 (19.70)	24851.84 (35.81)	2.50	8.05 (1.56)
	28	6	7062.67 (17.50)	72353.22 (25.73)	2.75	17.79 (6.68)

[a] All regimens pooled = BMS-232632 at 400mg QD for 14 days (Days 1-14).

A = BMS-232632 at 400 mg QD for 14 days (Days 1-14) followed by co-administration of BMS-232632 at 400 mg QD and rifabutin at 150 mg QD for 14 days (Days 15-28).

All regimens pooled = BMS-232632 at 400 mg QD for 14 days (Days 1-14).

B = BMS-232632 at 400 mg QD for 14 days (Days 1-14) followed by co-administration of BMS-232632 at 600 mg QD and rifabutin at 150 mg QD for 14 days (Days 15-28).

C = BMS-232632 at 400 mg QD for 14 days (Days 1-14) followed by co-administration of BMS-232632 at 400 mg QD, rifabutin at 150 mg QD and ritonavir at 100 mg QD for 14 days (Days 15-28).

[b] TAU = 24 h

The geometric means, ratios of the geometric means, and the 90% confidence intervals for the ratios of geometric means for Cmax and AUC(TAU) of BMS-232632 are presented below.

Pharmacokinetic Parameter (BMS-232632)	Regimen	Geometric Mean			Point Estimate (90% C.I.)	
		Day 7	Day 14	Day 28	Day 14/Day 7 Ratio	Day 28/Day 14 Ratio
Cmax (ng/mL)	A	3390.76	3551.27	4770.30	1.05 (0.89, 1.24)	1.34 (1.14, 1.59)
	B	3623.46	3347.12	6833.05	0.92 (0.80, 1.07)	2.04 (1.76, 2.37)
	C	3915.53	3903.10	7062.67	1.00 (0.83, 1.19)	1.81 (1.51, 2.17)
AUC(TAU)[b] (ng·h/mL)	A	23315.83	22107.25	25368.58	0.95 (0.81, 1.11)	1.15 (0.98, 1.34)
	B	24008.35	21099.22	44088.77	0.88 (0.76, 1.01)	2.09 (1.82, 2.40)
	C	26711.78	24851.84	72353.22	0.93 (0.78, 1.10)	2.91 (2.46, 3.45)

[b] TAU = 24 h

The data show that BMS-232632 exposure following co-administration of BMS-232632 at 400 mg QD and rifabutin at 150 mg QD for 14 days was similar to the exposure following administration of BMS-232632 at 400 mg QD alone for 14 days (Regimen A), while Cmax was increased by 34%. When rifabutin at 150 mg QD was co-administered with either BMS-232632 at 600 mg QD or BMS-232632 at 400 mg QD and ritonavir at 100 mg QD for 14 days, BMS-232632 exposure was 2- to 3-fold the exposure following administration of BMS-232632 at 400 mg QD alone for 14 days (Regimens B and C). The higher exposure following Regimen B compared to Regimen A is likely due to the higher dose of BMS-232632. The higher exposure following Regimen C compared to Regimen A appears to be due to the inhibition of CYP3A-mediated metabolism of BMS-232632 by co-administered ritonavir.

Rifabutin and 25-O-desacetylrifabutin

Summary statistics for rifabutin and 25-O-desacetylrifabutin pharmacokinetic parameters are presented in the table below.

Pharmacokinetic Parameter	Regimen		
	A (n = 7)	B (n = 9)	C (n = 6)
Rifabutin			
Cmax (ng/mL) Geometric Mean (CV%)	555.16 (20.99)	412.89 (23.34)	494.59 (22.42)
AUC(TAU)[b] (ng·h/mL) Geometric Mean (CV%)	7693.77 (20.34)	6291.70 (19.66)	7386.71 (19.48)
Tmax (h) Median (Min, Max)	3.00	3.00	4.00
25-O-desacetylrifabutin			
Cmax (ng/mL) Geometric Mean (CV%)	234.03 (16.10)	186.59 (21.72)	288.35 (10.06)
AUC(TAU) (ng·h/mL) Geometric Mean (CV%)	4376.40 (18.22)	3610.63 (21.85)	5658.71 16.82)
Tmax (h) Median (Min, Max)	5.00	5.00	7.50

The pharmacokinetics of rifabutin and its metabolite following 150 mg QD doses of rifabutin appeared similar across all regimens. However, the exposure produced by rifabutin at 150 mg QD in the presence of BMS-232632 (with or without ritonavir) was higher than that reported in the literature for the standard 300 mg QD doses of rifabutin suggesting that the 150 mg QD dose of rifabutin may need to be modified. Also see the review for Study AI424033, which addresses the effect of atazanavir on rifabutin pharmacokinetics. The applicant recommended a reduction in rifabutin dose up to 75% (eg, 150 mg every other day or 3 times per week), which is accepatable.

Ritonavir

Summary statistics for ritonavir pharmacokinetic parameters are presented in the table below.

Pharmacokinetic Parameter (Ritonavir)	Regimen [a] C (n = 6)
Cmax (ng/mL) Geometric Mean (C.V. %)	2264.61 (15.23)
AUC(TAU) [b] (ng·h/mL) Geometric Mean (C.V. %)	14261.15 (19.70)
Tmax (h) Median (Min, Max)	4.00
T-HALF (h) Mean (S.D.)	4.82 (0.42)

[a] C = BMS-232632 at 400 mg QD for 14 days (Days 1-14) followed by co-administration of BMS-232632 at 400 mg QD, rifabutin at 150 mg QD and ritonavir at 100 mg QD for 14 days (Days 15-28).

[b] TAU = 24 h

The ritonavir pharmacokinetic parameters were similar to those from historical data (i.e., AI424028).

Bilirubin

The following table shows the relationship between geometric means of BMS-232632 AUC(TAU) (± rifabutin) when coadministered with ritonavir and their corresponding mean (SD) total bilirubin values.

Study	Regimen	Baseline	AUC (TAU) BMS Alone	Total Bilirubin	AUC (TAU) BMS ± RIF + RTV	Total Bilirubin
AI424028 (n = 8)	BMS + RTV	0.61 (0.24)	26372.08	1.73 (0.98)	69578.30	4.16 (2.08)
AI424021 (n = 30)	BMS + RIF + RTV	0.54 (0.18)	22762.81	1.41 (0.82)	72353.22[a]	2.17 (0.88)[a]

[a] n = 6

The mean changes in total bilirubin values indicated that the addition of rifabutin reduced total bilirubin. The applicant suggested that rifabutin might induce UDPGT 1A1 enzyme production and facilitate elimination, as rifabutin is a non-specific inducer. One potential confounder is the balance of genotypes and if all genotypes respond to a presumptive inducer. The study showed that even "lower glucuronide producers" (i.e., 7/7 or

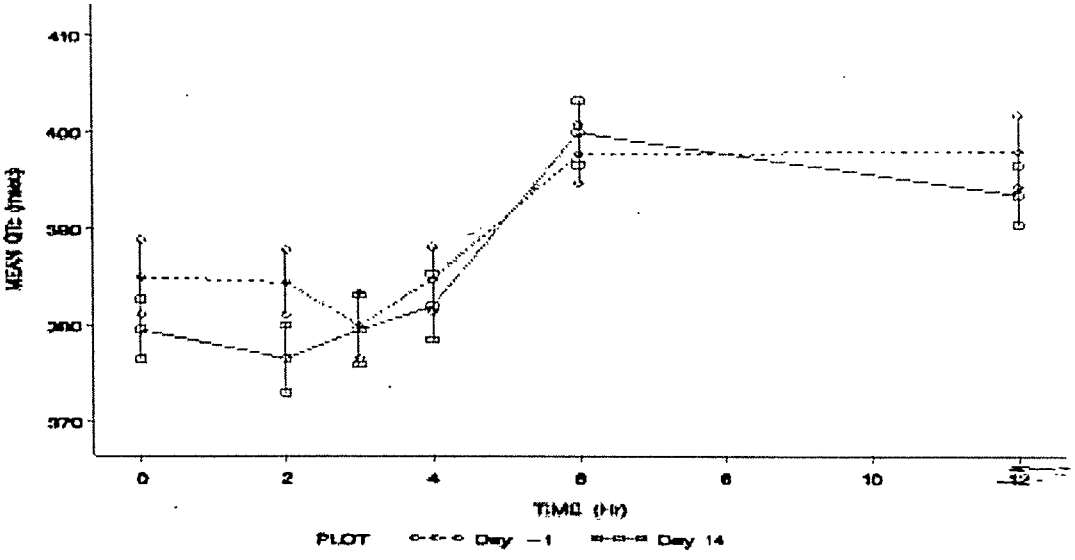
Gilbert™s syndrome subjects) could respond to an inducer, suggested by Subjects 018 and 025, each with a 7/7 genotype in this study.

Parameter	Baseline (Day -1)	Day 14	Day 28
Subject 018			
Total Bilirubin (mg/dL)	0.6	2.0	1.3
AUC(TAU) (ng·h/mL)	N/A	17268.13	28152.27
Subject 025			
Total Bilirubin (mg/dL)	0.4	2.9	0.9
AUC(TAU) (ng·h/mL)	N/A	29719.75	25814.59

The data show a substantial decline in total bilirubin values by Day 28 from those observed on Day 14. The total bilirubin values for Subjects 018 and 025 were 35% and 69% lower on Day 28 than on Day 14, although BMS-232632 AUC remained stable (Subject 025) or increased 60% (Subject 018). All other subjects had the similar trend. Therefore, rifabutin may induce UDPGT 1A1 enzyme production for any genotypes.

QTc (Bazett's correction)

Plot of Mean QTc versus Time on Days -1 and 14



The above plot shows that no clinically meaningful changes were apparent after BMS administration as compared to predose. No male subject had any QTc > 430 msec and no female subject had any QTc > 450 msec. There were no subjects with any change in QTc interval from baseline of > 60 msec. Nine (9) of 24 (38%) males and 1 of 6 (17%) females had at least one QTc change from baseline ≥ 30 msec (but ≤ 60 msec).

PR

First degree AV block (PR > 200 msec) was observed in one subject prior to any study drug administration, and developed in one ECG in 1 out of 24 male subjects (4%) and in two ECGs in 1 out of 6 female subjects (17%). The study results were similar to other studies.

Conclusion:

- BMS-232632 exposure following co-administration of BMS-232632 at 400 mg QD and rifabutin at 150 mg QD was similar to the exposure following administration of BMS-232632 400 mg QD alone, suggesting rifabutin may not have effect on pharmacokinetics of BMS-232632. The results are unexpected based on the known induction effect of rifabutin on CYP3A.
- BMS-232632 exposure following co-administration of rifabutin at 150 mg QD with either BMS-232632 at 600 mg QD or BMS-232632 at 400 mg QD and ritonavir at 100 mg QD was 2 to 3 fold higher than the exposure following administration of BMS-232632 400 mg QD alone.
- The pharmacokinetics of rifabutin and its metabolite following 150 mg QD doses of rifabutin appeared similar across all regimens. However, the exposure produced by rifabutin at 150 mg QD in the presence of BMS-232632 (with or without ritonavir) was higher than that reported in the literature 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 in rifabutin dose up to 75% (eg, 150 mg every other day or 3 times per week), which is acceptable.
- Rifabutin may induce UDPGT 1A1 enzyme production for any genotypes.
- No subjects had a QTc change from baseline > 60 msec. No male subject had a QTc > 450 msec and no female subjects had a QTc > 470 msec.

Interaction Study to Evaluate the Effect of BMS-232632 on the Steady-State Pharmacokinetics of Rifabutin in Healthy Subjects with and without Ritonavir (AI424033)

Objective:

- To assess the exposure of rifabutin when given at 150 mg once daily (QD) concomitantly with BMS-232632 at 600 mg QD for 10 days relative to the exposure of rifabutin when given at 300 mg QD for 10 days.
- To assess the exposure of rifabutin when given at 150 mg QD concomitantly with BMS-232632 at 400 mg QD and ritonavir 100 mg QD for 10 days relative to the exposure of rifabutin when given at 300 mg QD for 10 days.

Population: A total of 20 subjects participated in the study. Fifteen (15) subjects discontinued from the study. Six (6) subjects discontinued prior to randomization (received only rifabutin 300 mg), 5 subjects discontinued from Regimen A (BMS-232632 400 mg, ritonavir 100 mg and rifabutin 150 mg), and 4 subjects discontinued from Regimen B (BMS-232632 600 mg and rifabutin 150 mg).

Study Design: This was an open-label, randomized study in twenty healthy subjects. Twenty (20) subjects were administered 300 mg of rifabutin QD for the first 10 days of the study. On Day 11, subjects were randomly assigned to one of the two following regimens:

A: BMS-232632 at 600 mg QD and rifabutin at 150 mg QD for 10 days.
B: BMS-232632 at 400 mg QD, ritonavir at 100 mg QD and rifabutin at 150 mg QD for 10 days.

All doses were given in the A.M. within 5 minutes after a light meal.

Formulation: BMS-232632 200 mg capsules (Batch #C99331), Mycobutin® (rifabutin) 150 mg capsules (Lot #OGP031), and Norvir® (ritonavir) 100 mg capsules (Lot #716902E22).

Pharmacokinetic sampling: Blood samples were collected at the following time points:

Days 10 and 20: Prior to dosing and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hours after dosing;

Days 2, 4, 6, 8, 14, 16, and 18: Prior to dosing.

On Days 2 through 10, one blood sample was collected for rifabutin and 25-O-desacetylrifabutin analysis, while on Days 11 through 20, three blood samples were collected for analysis of rifabutin/25-O-desacetylrifabutin, BMS-232632 and ritonavir.

Analytical Analysis: Plasma samples were assayed for BMS-232632, rifabutin, 25-O-desacetylrifabutin, and ritonavir concentrations by validated [redacted] methods. The standard curve and QC data indicated that the plasma assay methods for BMS-232632, rifabutin, 25-O-desacetylrifabutin, and ritonavir were precise and accurate. See QBR for details.

Pharmacokinetic Results: The pharmacokinetic parameters of rifabutin, 25-O-desacetylrifabutin, BMS-232632, and ritonavir for the subjects who completed the study are summarized in the following table.

Pharmacokinetic Parameter	Regimen[a] A		Regimen[a] B	
	Day 10 (n = 3)	Day 20 (n = 3)	Day 10 (n = 2)	Day 20 (n = 2)
Rifabutin				
Cmax (ng/mL) Geometric Mean (C.V.%)	313.93 (47.14)	370.02 (39.46)	453.14 (44.34)	527.71 (24.75)
AUC(TAU) (ng·h/mL)[b] Geometric Mean (C.V.%)	2811.99 (35.85)	5897.58 (31.52)	4347.70 (15.10)	8502.44 (20.48)
Tmax (h) Median (Min, Max)	3.00	5.00	3.50 (3.00, 4.00)	4.50
25-O-desacetylrifabutin				
Cmax (ng/mL) Geometric Mean (C.V.%)	19.18 (36.76)	157.33 (26.77)	27.50 (55.56)	222.65 (25.75)
AUC(TAU) (ng·h/mL)[b] Geometric Mean (C.V.%)	138.15 (34.55)	3040.58 (21.06)	228.84 (26.32)	4486.15 (27.07)
Tmax (h) Median(Min, Max)	3.00	5.00	3.50 (3.00, 4.00)	4.50
BMS-232632				
Cmax (ng/mL) Geometric Mean (C.V.%)	N/A	7546.60 (16.70)	N/A	6258.18 (26.26)
AUC(TAU) (ng·h/mL)[b] Geometric Mean (C.V.%)	N/A	53092.40 (18.63)	N/A	67441.52 (38.56)
Tmax (h) Median (Min, Max)	N/A	2.50	N/A	2.00
T-HALF (h) Mean (S.D.)	N/A	7.21 (3.48)	N/A	15.10 (3.92)
Ritonavir				
Cmax (ng/mL) Geometric Mean (C.V.%)	N/A	N/A	N/A	1906.43 (21.37)
AUC(TAU) (ng·h/mL)[b] Geometric Mean (C.V.%)	N/A	N/A	N/A	12102.69 (39.74)
Tmax (h) Median (Min, Max)	N/A	N/A	N/A	5.00
T-HALF (h) Mean (S.D.)	N/A	N/A	N/A	4.20 (0.51)

[a] Regimen: A = Rifabutin at 300 mg QD for 10 days (Days 1-10), followed by co-administration of rifabutin at 150 mg QD, BMS-232632 at 600 mg QD for 10 days (Days 11-20).

B = Rifabutin at 300 mg QD for 10 days (Days 1-10), followed by co-administration of rifabutin at 150 mg QD, BMS-232632 at 400 mg QD, and ritonavir at 100 mg QD for 10 days (Days 11-20).

[b] TAU = 24 h

The geometric means, ratios of geometric means and 90% confidence intervals for the ratios of geometric means for Cmax and AUC(TAU) of rifabutin and 25-O-desacetylrifabutin are presented in the following table.

Pharmacokinetic Parameter	Regimen	Geometric Mean Day 10	Geometric Mean Day 20	Day 20/Day 10 Ratio Point Estimate (90% C.I.)
Rifabutin				
Cmax (ng/mL)	A	313.93	370.02	1.18 (0.94, 1.48)
	B	453.14	527.71	1.16 (0.88, 1.54)
AUC(TAU)(ng·h/mL)	A	2811.99	5897.58	2.10 (1.57, 2.79)
	B	4347.70	8502.44	1.96 (1.38, 2.78)
25-O-desacetylrifabutin				
Cmax (ng/mL)	A	19.18	157.33	8.20 (5.90, 11.40)
	B	27.50	222.65	8.10 (5.41, 12.11)
AUC(TAU)(ng·h/mL)	A	138.15	3040.58	22.01 (15.97, 30.34)
	B	228.84	4486.15	19.60 (13.23, 29.04)

Based on the results from the 3 subjects in Regimen A and 2 subjects in Regimen B who completed the study, the exposure to rifabutin after co-administration of 150 mg of rifabutin and 600 mg of BMS-232632 (Regimen A) or 400 mg of BMS-232632 and 100 mg of ritonavir (Regimen B) was approximately 2-fold higher than that following 300 mg of rifabutin alone. The higher rifabutin levels in the current study might partially result in higher levels of the metabolite 25-O-desacetylrifabutin, which is formed by cholinesterase-mediated metabolism of rifabutin. Similar increases in exposure to rifabutin and its metabolite were observed in Study AI424021. Overall, the data from the current and the previous study indicate that dose adjustment for rifabutin needs to be considered when being co-administered with BMS-232632. Typically, a rifabutin dose is reduced by half to 150 mg QD in the presence of an HIV PI. As the lowest dosing strength of rifabutin is 150 mg, any further reduction would come as a reduction in schedule frequency rather than further reduction in dose. The applicant recommended to reduce rifabutin dose up to 75% (eg, 150 mg every other day or 3 times per week), which is acceptable.

The exposure of BMS-232632 and ritonavir in this study are comparable to other studies with the same dose of BMS-232632 and ritonavir but without rifabutin, indicating rifabutin may not have clinically significant effect on BMS-232632 and ritonavir.

Conclusion:

- Co-administration of 150 mg QD rifabutin with 600 mg QD BMS-232632 (n = 3) or with 400 mg QD BMS-232632 and 100 mg QD ritonavir resulted in a 2-fold increase in rifabutin exposure and a 20-fold increase in 25-O-desacetylrifabutin exposure, respectively, as compared to the exposure following administration of 300 mg QD rifabutin alone.
- The addition of BMS-232632 (with or without ritonavir) increased rifabutin (and 25-O-desacetylrifabutin metabolite) exposures and may have contributed to the worsening of adverse events and discontinuation of several subjects during the combination regimen.
- The standard 300 mg dose of rifabutin should be reduced to 150 mg every other day or 3 times per week) when co-administered with BMS-232632.
- Rifabutin has no clinically significant effect on BMS-232632 and ritonavir exposure.

Safety and Pharmacokinetic Interaction Study of Atazanavir and Diltiazem in Healthy Subjects (AI424055)

Background: In Study AI424040, following multiple doses of atazanavir at 200 mg, 400 mg and 800 mg once-daily for 5 days, concentration-dependent effects were observed on the PR interval. Prolongations of the PR interval were most apparent at the 800 mg dose. Diltiazem, an L-type calcium channel blocker, prolongs the PR interval of the electrocardiogram by increasing the AV node refractory period in addition to decreasing AV node conduction velocity and SA node automaticity. Diltiazem might be therapeutically combined with atazanavir to treat hypertension in HIV-infected patients. The combination could potentially prolong the PR interval to a greater degree than either agent administered alone. In addition, since atazanavir and diltiazem are both substrates and inhibitors of CYP3A, there is a potential for a pharmacokinetic interaction between the drugs.

Objective: To assess the added effect of diltiazem, when co-administered with atazanavir, on the PR interval (specifically on the change from baseline PR Max to PR Max), as compared with the effect due to administration of atazanavir alone. To assess the pharmacokinetic interactions between atazanavir and diltiazem.

Population: Thirty (30) subjects participated in the study. Twenty-eight (28) subjects (18 males, 10 females) completed the study, and two (2) subjects discontinued from the study due to patient request.

Study Design: This was an open-label, non-randomized, multiple-dose study in healthy subjects. Subjects received atazanavir QD at 400 mg for 6 days (Days 1-6), followed by co-administration of atazanavir QD at 400 mg and diltiazem QD at 180 mg for 5 days (Days 7-11), then, after a washout period of 7 days (Days 12-18), subjects received diltiazem QD at 180 mg for 5 days (Days 19-23). All doses were given within 5 minutes after a standard light meal.

Formulation: Atazanavir (BMS-232632-05) 200 mg capsules (Batch #C99274); Cardizem CD® (diltiazem hydrochloride) 180 mg capsules (Lot #1034297).

Pharmacokinetic Sampling: Blood samples were collected prior to dosing and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 18 and 24 h after dosing on Days 6 (for atazanavir), 11 (for atazanavir and diltiazem/desacetyl-diltiazem) and 23 (for diltiazem/desacetyl-diltiazem). In addition, blood samples were collected prior to dosing on Days 2, 4, 9 and 21.

Analytical Analysis: Plasma samples were assayed for BMS-232632, diltiazem, and desacetyl-diltiazem concentrations by validated [redacted] methods. The standard curve and QC data indicated that the plasma assay methods for BMS-232632, diltiazem, and desacetyl-diltiazem were precise and accurate. See QBR for details.

Pharmacokinetic Results: The pharmacokinetic parameters of atazanavir, diltiazem and desacetyl-diltiazem are summarized in the table below.

Pharmacokinetic Parameter	Treatment[a]		
	B	B+D	D
	Day 6	Day 11	Day 23
Atazanavir (n = 30)			
Cmax (ng/mL) Geometric Mean (C.V.%)	5629.29 (25.66)	5826.64 (22.69)	--
AUC(TAU) (ng·h/mL)[b] Geometric Mean (C.V.%)	36228.37 (27.04)	36230.12 (27.31)	--
Tmax (h) Median (Min, Max)	2.50 (——)	2.18 (——)	--
T-HALF (h) Mean (S.D.)	7.14 (2.71)[c]	7.04 (2.65)[c]	--
Diltiazem (n = 28)			
Cmax (ng/mL) Geometric Mean (C.V.%)	--	199.37 (27.45)	100.73 (35.59)
AUC(TAU) (ng·h/mL)[b] Geometric Mean (C.V.%)	--	2987.21 (34.95)	1329.97 (40.27)
Tmax (h) Median (Min, Max)	--	6.17 (——)	6.17 (——)
Desacetyl-diltiazem (n = 28)			
Cmax (ng/mL) Geometric Mean (C.V.%)	--	22.51 (69.21)	8.27 (75.51)
AUC(TAU) (ng·h/mL)[b] Geometric Mean (C.V.%)	--	399.75 (69.85)	150.80 (71.07)
Tmax (h) Median (Min, Max)	--	5.25 (——)	9.09 (——)

[a] Treatment: B = Atazanavir at 400 mg QD for 6 days (Days 1-6)
B + D = Co-administration of atazanavir at 300 mg QD and diltiazem at 180 mg QD for 5 days (Days 7-11).
D = Administration of diltiazem at 180 mg QD for 5 days (Days 19-23).

[b] TAU = 24 h

[c] n = 29

The geometric means, ratio of geometric means and 90% confidence intervals (C.I.) for the ratios for atazanavir, diltiazem, and desacetyl-diltiazem are presented in the following table:

Pharmacokinetic	Geometric Mean			Point Estimate (90% C.I.)
Atazanavir				
	Day 6	Day 11	Day 23	Day 11/Day 6 Ratio
Cmax (ng/mL)	5629.29	5826.64	--	1.04 (0.96, 1.11)
AUC(TAU) (ng·h/mL)[a]	36228.37	36250.12	--	1.00 (0.95, 1.05)
Diltiazem				
	Day 6	Day 11	Day 23	Day 11/Day 23 Ratio
Cmax (ng/mL)	--	199.37	100.73	1.98 (1.78, 2.19)
AUC(TAU) (ng·h/mL)[a]	--	2987.21	1329.97	2.25 (2.09, 2.41)
Desacetyl-diltiazem				
	Day 6	Day 11	Day 23	Day 11/Day 23 Ratio
Cmax (ng/mL)	--	22.51	8.27	2.72 (2.44, 3.03)
AUC(TAU) (ng·h/mL)[a]	--	399.75	150.80	2.65 (2.45, 2.87)

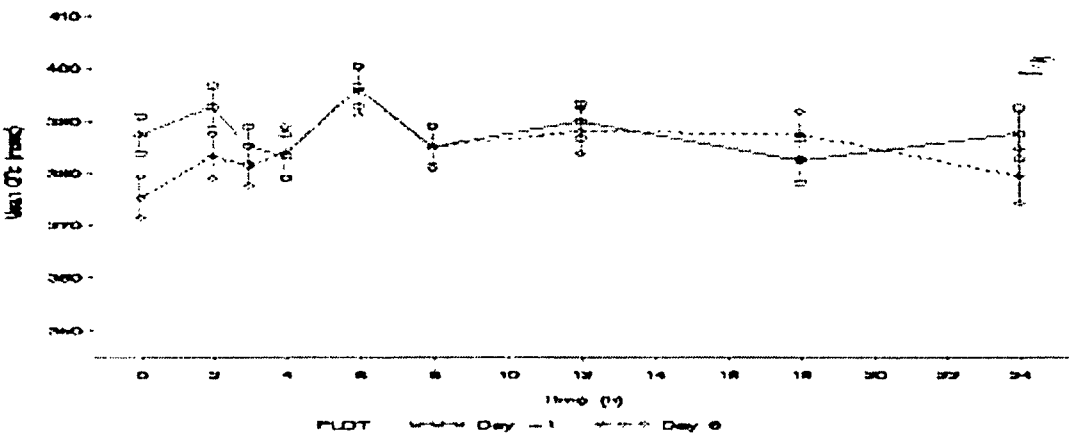
Treatment: Atazanavir at 400 mg QD for 6 days (Days 1-6) followed by co-administration of atazanavir at 400 mg QD and diltiazem at 180 mg QD for 5 days (Days 7-11). Washout of 7 days followed by administration of diltiazem at 180 mg QD for 5 days (Days 19-23)

[a] TAU = 24 h

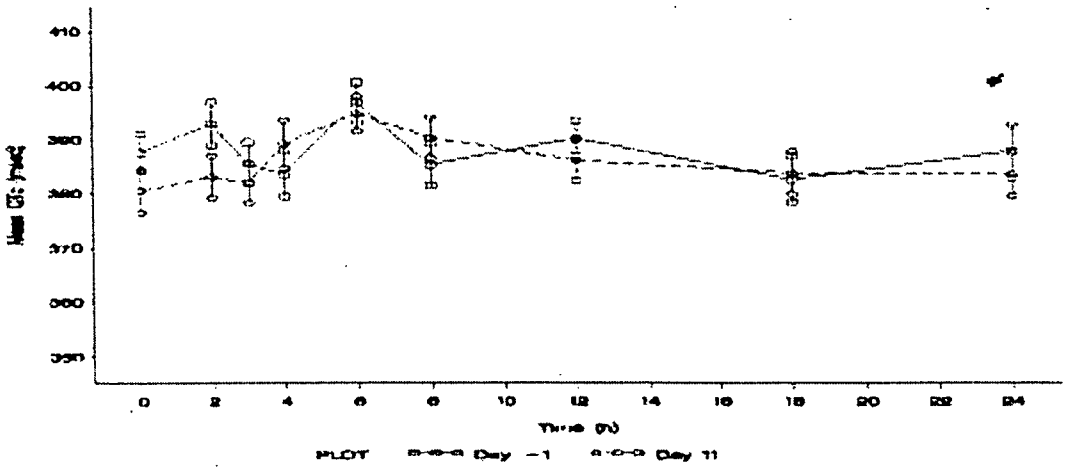
The results show that the pharmacokinetics of atazanavir were not affected by diltiazem. However, the Cmax and AUC of diltiazem and desacetyl-diltiazem were increased when diltiazem and atazanavir were administered simultaneously. The increase in diltiazem exposure may be due to the CYP3A-mediated inhibition by co-administered atazanavir. The fact that there was an increase in desacetyl-diltiazem exposure suggests that the metabolic pathway of its formation may not be mediated by CYP3A; in fact, there is evidence that CYP2D6 is involved in the metabolism of diltiazem.

QTcB

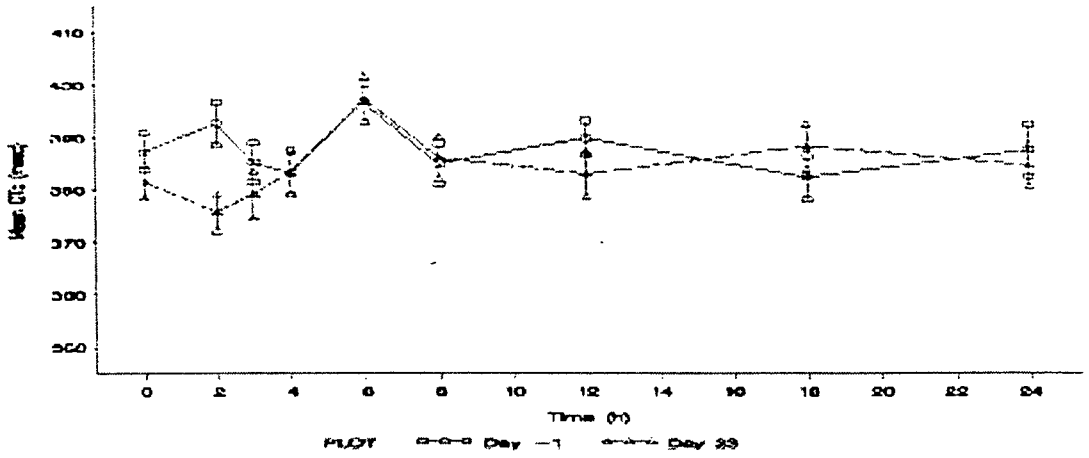
Plot of Mean QTcB versus Time on Days -1 and 6



Plot of Mean QTcB versus Time on Days -1 and 11



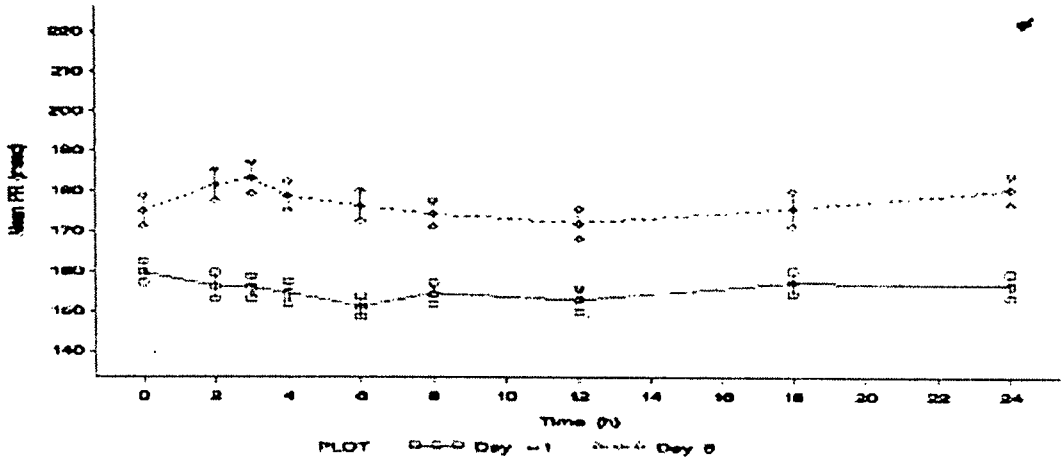
Plot of Mean QTc versus Time on Days -1 and 23



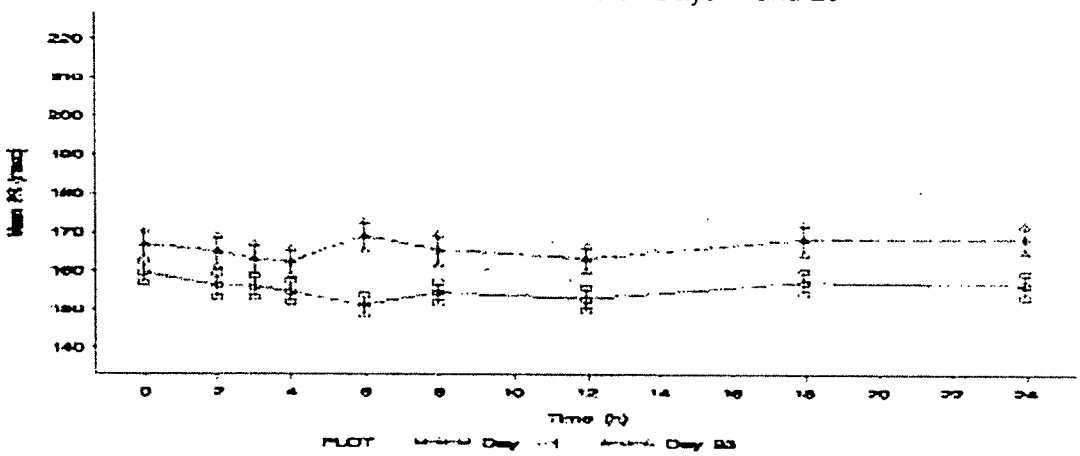
The above figures showed that atazanavir 400 mg ±diltiazem 180 mg once daily had no clinically significant effect on the QTc interval.

PR

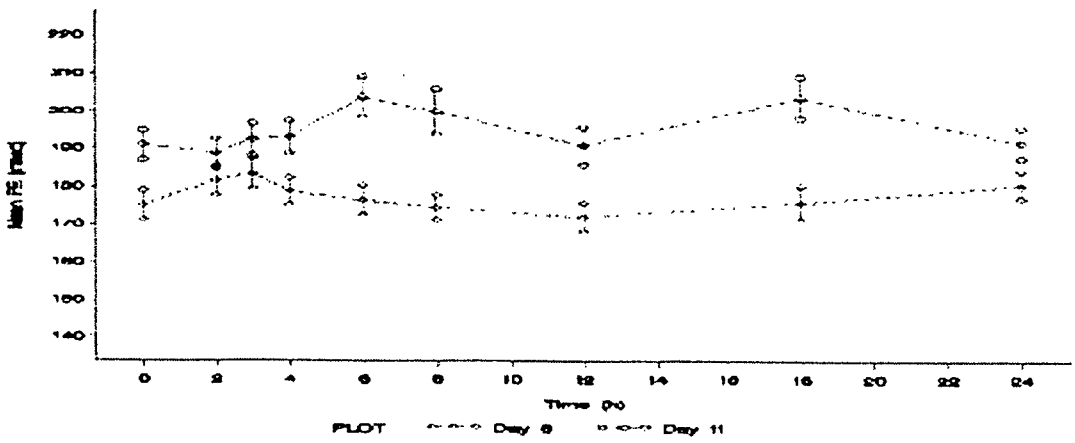
Plot of Mean PR versus Time on Days -1 and 6



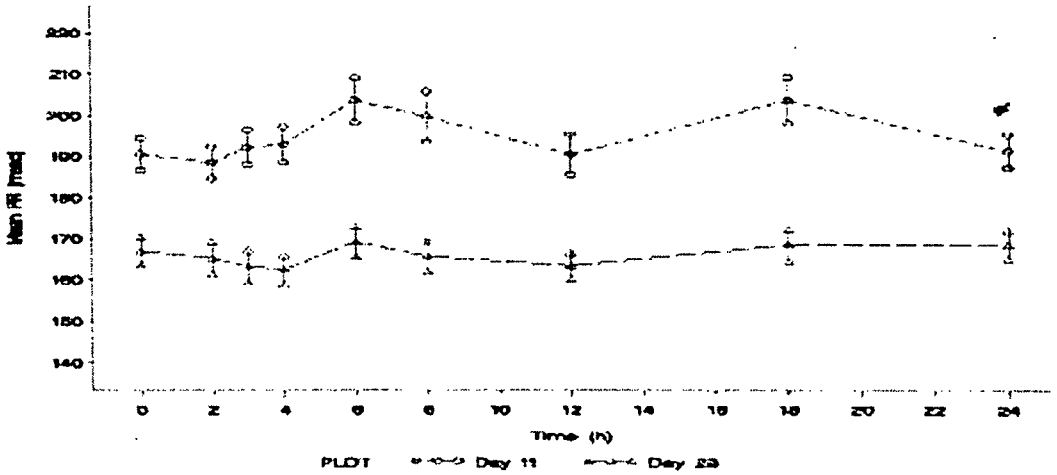
Plot of Mean PR versus Time on Days -1 and 23



Plot of Mean PR versus Time on Days 6 and 11



Plot of Mean PR versus Time on Days 11 and 23



The above plots show that atazanavir and diltiazem, when co-administered, had an additive effect on the PR interval, when compared to the effect due to administration of atazanavir or diltiazem alone. The following table summarizes count (%) of people with prolonged PR interval.

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

The data showed when atazanavir and diltiazem were co-administered, more severe PR prolongation was observed than with either drug alone. The applicant indicated isolated PR interval values of > 250 msec in otherwise healthy and asymptomatic individuals can be observed even when individuals are not on drug. The prolongations of the PR interval in this study were reversible and asymptomatic in all subjects and not considered important as an etiology of a clinically relevant proarrhythmic state.

The applicant suggested a dose reduction of diltiazem by 50%.

> *Reviewer's Comment: If atazanavir and diltiazem were co-administered in patients 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 19%-53% and 91%-170%, respectively, and thus increase the risk of PR prolongation further. Therefore, other than dose reduction, ECG monitoring is recommended.*

Conclusion:

- Atazanavir and diltiazem, when co-administered, had an added effect on the PR interval, when compared to the effect due to administration of atazanavir or diltiazem alone.
- Diltiazem at a dose of 180 mg daily, when co-administered with atazanavir at the 400 mg daily dose for 5 days, had no clinically significant added effect on the QTc interval, when compared to the effect due to administration of atazanavir at 400 mg alone.
- Co-administration of once daily doses of 400 mg of atazanavir and 180 mg of diltiazem had no effect on the pharmacokinetics of atazanavir.
- Co-administration of once daily doses of 400 mg of atazanavir and 180 mg of diltiazem resulted in a 2 to 3-fold increase in the AUC values of diltiazem and desacetyl-diltiazem, relative to the administration of diltiazem alone.
- Atazanavir may be co-administered without dose modification with diltiazem.
- Diltiazem may be co-administered with atazanavir, however, a dose reduction of diltiazem by 50% needs to be considered and ECG monitoring is recommended.

APPEARS THIS WAY
ON ORIGINAL

Safety and Pharmacokinetic Interaction Study of Atazanavir and Atenolol in Healthy Subjects (AI424057)

Objective: To assess the added effect of atenolol, when co-administered with atazanavir, on the PR interval (specifically on the change from baseline PR Max to PR Max), as compared with the effect due to administration of atazanavir alone. To assess the pharmacokinetic interactions between atazanavir and atenolol.

Population: Twenty subjects, age ranged from 21 to 50 years (mean = 36 years), participated in the study. Nineteen (19) subjects (11 males, 8 females) completed the study.

Study Design: This was an open-label, multiple-dose, non-randomized study. Subjects received atazanavir at 400 mg once-daily (QD) for 6 days (Days 1-6), then atazanavir at 400 mg QD co-administered with atenolol at 50 mg QD for 5 days (Days 7-11) followed by a 7-day washout period (Days 12-18) and finally atenolol at 50 mg QD for 5 days (Days 19-23). All doses of study drug were administered within 5 minutes of completion of a standard light meal.

Formulation: Atazanavir was supplied as 200 mg capsules (Batch # C99274). The investigator supplied the marketed drug Tenormin® (atenolol) as 50 mg tablets (Lot No. AAJ231).

Pharmacokinetic sampling: Blood samples were collected at the following time points:

Days 6, 11, and 23: Prior to dosing and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 18, and 24 h after dosing;

Days 2, 4, 9, and 21: Prior to dosing.

One blood sample was collected per timepoint on Days 2 to 6 for atazanavir analysis and on Days 19 to 23 for atenolol analysis. Two blood samples were collected at each sampling time on Days 7 to 11 for atazanavir and atenolol analysis.

Analytical Analysis: Plasma samples were assayed for BMS-232632 and atenolol concentrations by validated [redacted] methods. The standard curve and QC data indicated that the plasma assay methods for BMS-232632 and atenolol were precise and accurate. See QBR for details.

Pharmacokinetic/Pharmacodynamic Results: The pharmacokinetic parameters of atazanavir and atenolol are summarized in the table below.

Pharmacokinetic Parameter	Treatment[a]		
	B	B + A	A
	Day 6	Day 11	Day 23
Atazanavir (n = 19)			
Cmax (ng/mL)			
Geometric Mean (C.V.%)	5867.18 (31.08)	5855.32 (28.67)	--
AUC(TAU) (ng·h/mL)[b]			
Geometric Mean (C.V.%)	33792.07 (29.81)	31276.30 (33.21)	--
Tmax (h)			
Median (Min, Max)	2.67	3.17	--
T-HALF (h)			
Mean (S.D.)	7.71 (1.86)	7.06[c] (2.08)	--
Atenolol (n = 19)			
Cmax (ng/mL)			
Geometric Mean (C.V.%)	--	312.00 (31.63)	253.34 (21.92)
AUC(TAU) (ng·h/mL)[b]			
Geometric Mean (C.V.%)	--	2551.71 (31.07)	2042.70 (24.26)
Tmax (h)			
Median (Min, Max)	--	2.17	2.18
T-HALF (h)			
Mean (S.D.)	--	8.07 (2.00)	9.35 (2.28)

[a] Treatment: B = Atazanavir at 400 mg QD for 6 days (Days 1-6)
B + A = Co-administration of atazanavir at 400 mg QD and atenolol at 50 mg QD for 5 days (Days 7-11).
A = Atenolol at 50 mg QD for 5 days (Days 19-23)

[b] TAU = 24 h

[c] n = 18

The geometric means, ratio of geometric means, and 90% confidence intervals for the ratios of geometric means for atazanavir and atenolol are presented in the following table.

Pharmacokinetic Parameter	Geometric Mean		Point Estimate	(90% C.I.)
Atazanavir				
	Day 6	Day 11	Day 11/Day 6 Ratio	
Cmax (ng/mL)	5867.18	5855.32	1.00	(0.89, 1.12)
AUC(TAU) (ng·h/mL)[a]	33792.07	31276.30	0.93	(0.85, 1.01)
Atenolol				
	Day 11	Day 23	Day 11/Day 23 Ratio	
Cmax (ng/mL)	312.00	233.34	1.34	(1.26, 1.42)
AUC(TAU) (ng·h/mL)[a]	2551.71	2042.70	1.25	(1.16, 1.34)

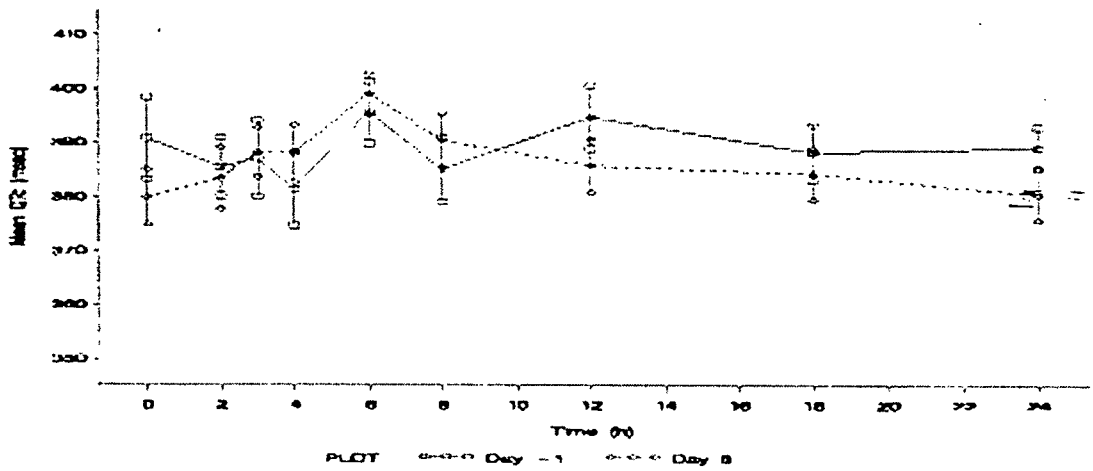
Treatment: Atazanavir at 400 mg QD for 6 days (Days 1-6) followed by co-administration of atazanavir at 300 mg QD and atenolol at 50 mg QD for 5 days (Days 7-11). Washout of 7 days (Days 12-18) followed by administration of atenolol at 50 mg QD for 5 days (Days 19-23)

[a] TAU = 24 h

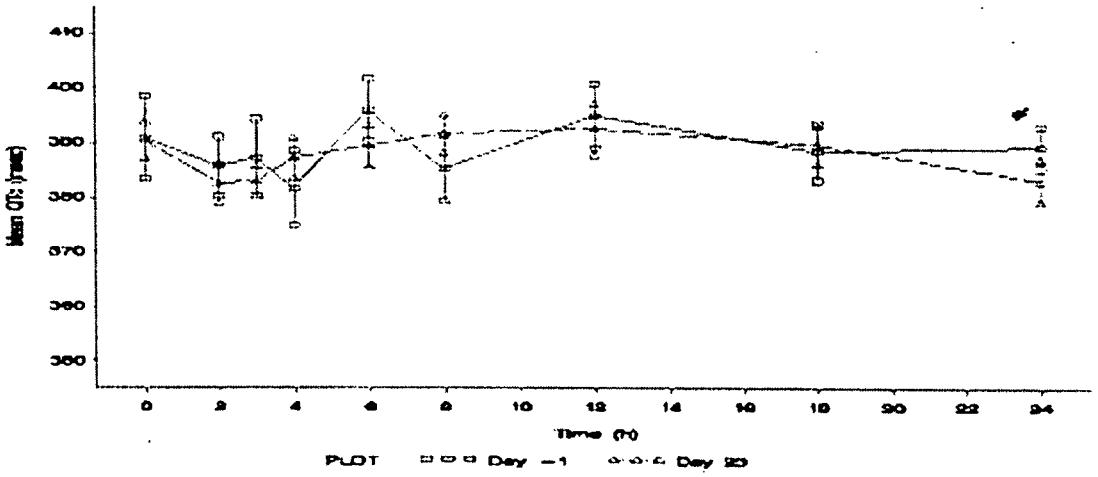
The geometric means for steady-state Cmax and AUC(TAU) of atazanavir after co-administration with atenolol were similar to those following atazanavir alone. The geometric means for Cmax and AUC(TAU) of atenolol after concomitant administration with atazanavir were 34% and 25% higher, respectively, compared to those following administration of atenolol alone. While atazanavir is a CYP3A inhibitor, it is not likely that the increase in atenolol exposure is due to a metabolic interaction as atenolol is minimally metabolized.

QTc

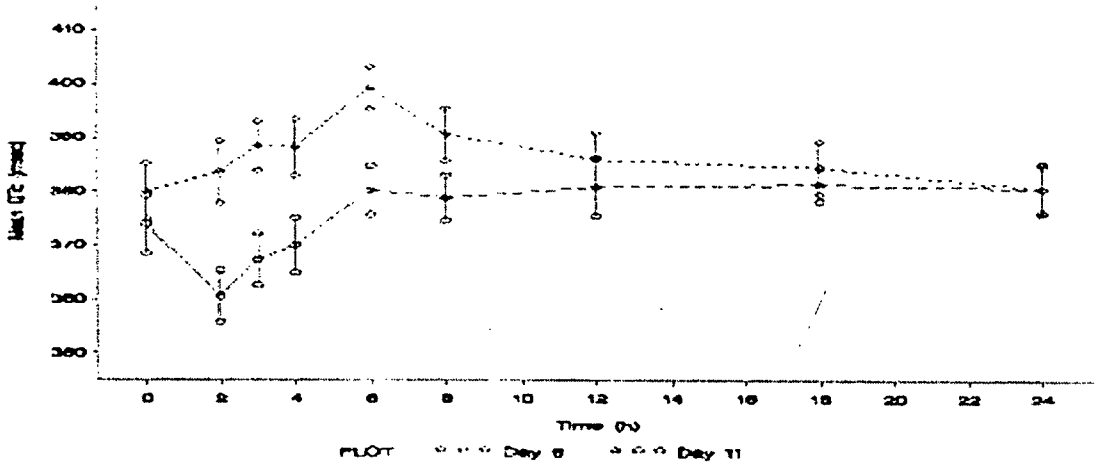
Plot of Mean QTc versus Time on Days -1 and 6



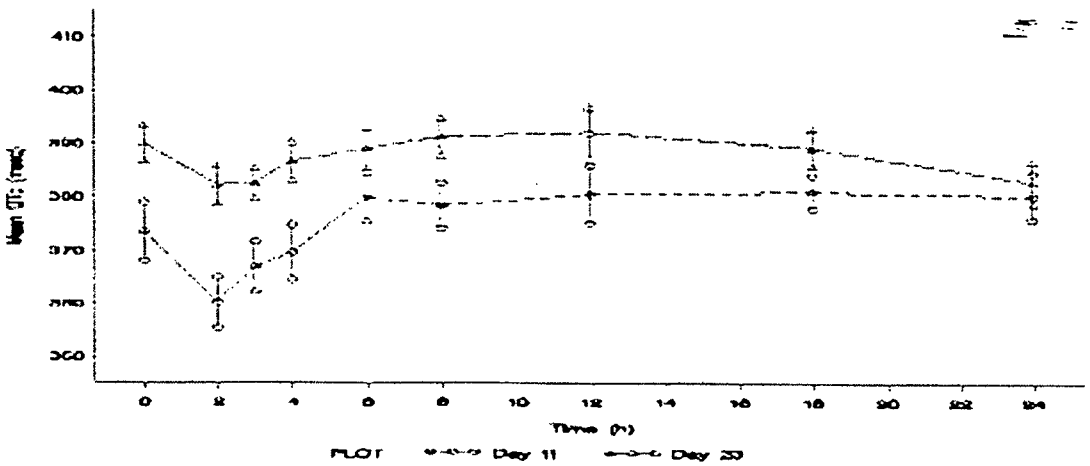
Plot of Mean QTc versus Time on Days -1 and 23



Plot of Mean QTc versus Time on Days 6 and 11



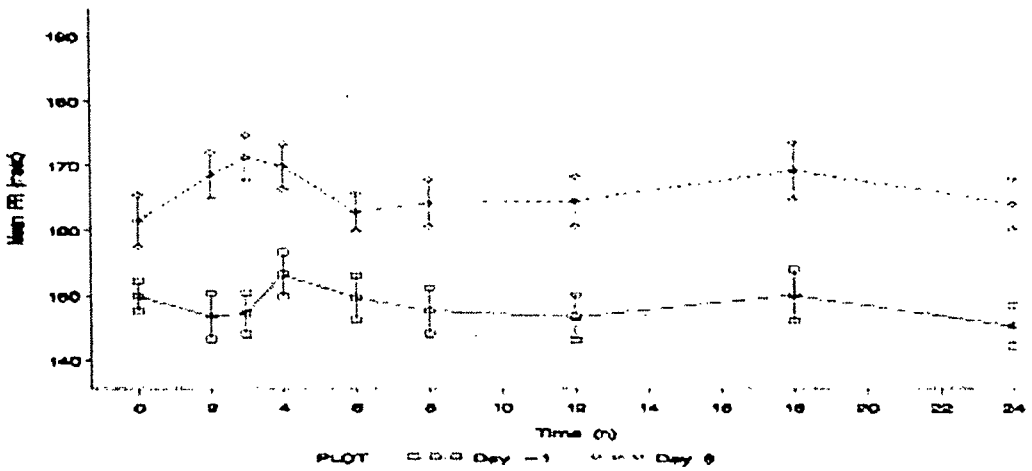
Plot of Mean QTc versus Time on Days 11 and 23



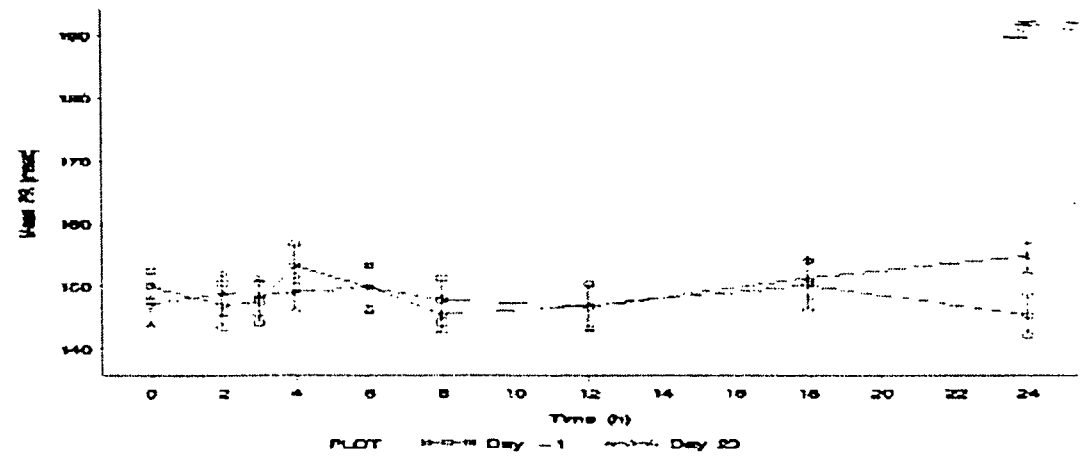
The results showed there was a decline of 7-25 msec in mean QTcB when subjects received atenolol and atazanavir concomitantly, while this decline was not observed with either drug alone. This suggested the possibility that combining the two drugs contributed to a decrease in QTcB. The change in QTc may have been explained if there was a difference in heart rate for the combination versus the other treatment periods. Atazanavir did not substantially change heart rate versus baseline. Atenolol, as a beta-adrenoceptor antagonist, decreased heart rate from baseline. However, the change in heart rate from baseline for the combination of atenolol and atazanavir was not substantially different from atenolol alone. Thus, the change in QTcB observed with the combination, versus either drug alone or baseline, did not appear to be a function of a difference in heart rate, beyond that of atenolol alone. Therefore, there may be unexplained mechanisms contributing to the observed phenomenon. After administration of any study drug, no male subject had any ECG with QTc > 430 msec and no female subject had any ECG with QTc > 450 msec.

PR

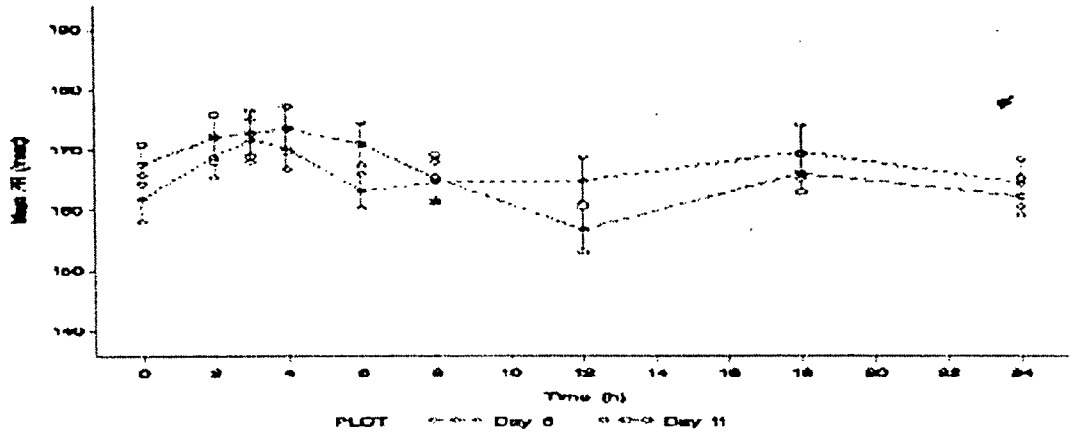
Plot of Mean PR versus Time on Days -1 and 6



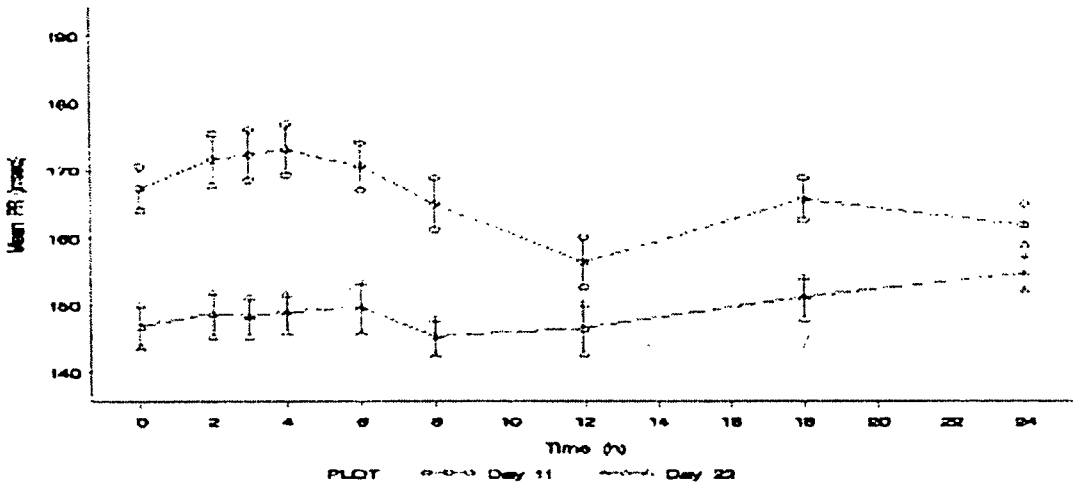
Plot of Mean PR versus Time on Days -1 and 23



Plot of Mean PR versus Time on Days 6 and 11



Plot of Mean PR versus Time on Days 11 and 23



The above figures showed that atenolol, when co-administered with atazanavir, has no added effect on the PR interval, when compared to the effect due to administration of atazanavir alone. One (1) subject (Subject 001, a male) out of 19 (5%) had at least one derived PR measure > 200 msec on Days 6 and 11. All other subjects had all derived PR measures ≤200 msec. In this study, there were no observations of second- or third-degree A-V block

Conclusion:

- Atenolol at the 50 mg once-daily dose for 5 days, when co-administered with atazanavir at the 400 mg once-daily dose for 5 days, had no clinically significant added effect on the PR interval, when compared to the effect due to administration of atazanavir at 400 mg alone.
- Combination of atenolol and atazanavir reduced QTc interval.
- Co-administration of once-daily doses of 50 mg of atenolol and 400 mg of atazanavir did not affect the pharmacokinetics of atazanavir.

- Co-administration of once-daily doses of 50 mg of atenolol and 400 mg of atazanavir resulted in a modest increase in Cmax and AUC of atenolol.

APPEARS THIS WAY
ON ORIGINAL

Safety and Pharmacokinetic Interaction Study of Atazanavir and Clarithromycin in Healthy Subjects (AI424058)

Background: Atazanavir and clarithromycin are both substrates and inhibitors of CYP3A. In Study AI424-040, following multiple doses of atazanavir at 200 mg, 400 mg, and 800 mg once-daily for 5 days, a mild concentration-dependent effect on the QTc interval was observed. Clarithromycin has been implicated in a reversible prolongation of the QTc interval and torsade de pointes. This study evaluated both pharmacokinetic and pharmacodynamic interactions between these two drugs.

Objective: To assess the added effect of clarithromycin, when co-administered with atazanavir, on the QTc interval (specifically on the change from baseline QTc Max to QTc Max), as compared with the effect due to administration of atazanavir alone. To assess the pharmacokinetic interactions between atazanavir and clarithromycin.

Population: Thirty (30) subjects, age ranged from 18 to 47 years (mean = 31 years), participated in the study. Twenty-one (21) subjects (13 males, 8 females) completed the study.

Study Design: This was an open-label, multiple-dose, non-randomized study. Subjects received atazanavir at 400 mg once daily (QD) for 6 days (Days 1-6), then atazanavir at 400 mg QD co-administered with clarithromycin 500 mg twice daily (BID) for 4 days (Days 7-10), followed by a washout period of 7 days (Days 11-17) and finally clarithromycin 500 mg BID for 4 days (Days 18-21). All doses were given within 5 minutes after a standard light meal.

Formulation: Atazanavir was supplied as 200 mg capsules (Batch # C99274). The investigator supplied the marketed Biaxin® 500 mg tablets (Lot # 73-420-AA-22).

Pharmacokinetic sampling: Blood samples were collected at the following time points: Days 6, 10, and 21: Prior to dosing and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 18, and 24 h after dosing;

Days 2, 4, 8, and 19: Prior to dosing.

One blood sample was collected per timepoint on Days 2 to 6 for atazanavir analysis and on Days 19 to 21 for clarithromycin/14-OH clarithromycin analysis. Two blood samples were collected at each sampling time on Days 7 to 10 for atazanavir and clarithromycin/14-OH clarithromycin analysis.

Analytical Analysis: Plasma samples were assayed for BMS-232632, clarithromycin, and 14-OH Clarithromycin concentrations by validated [redacted] methods. The standard curve and QC data indicated that the plasma assay methods for BMS-232632, clarithromycin, and 14-OH Clarithromycin were precise and accurate. See QBR for details.

Pharmacokinetic Results: The pharmacokinetic parameters of atazanavir, clarithromycin, and 14-OH clarithromycin are summarized in the table below.

Pharmacokinetic Parameter	Treatment[a]		
	B	B + C	C
	Day 6	Day 10	Day 21
Atazanavir (n = 29)			
Cmax (ng/mL) Geometric Mean (C.V.%)	5135.62 (33.17)	5420.97 (24.06)	--
AUC(TAU) (ng·h/mL)[b] Geometric Mean (C.V.%)	29493.64 (33.61)	37889.89 (26.37)	--
Tmax (h) Median (Min, Max)	3.17 [c]	2.17 [c]	--
T-HALF (h) Mean (S.D.)	8.21 (3.49)	13.06[c] (6.51)	--
Clarithromycin (n = 21)			
Cmax (ng/mL) Geometric Mean (C.V.%)	--	3574.96 (36.91)	2375.65 (45.73)
AUC(TAU) (ng·h/mL)[d] Geometric Mean (C.V.%)	--	34847.08 (35.22)	17916.62 (41.32)
Tmax (h) Median (Min, Max)	--	4.20 [e]	4.16 [f]
T-HALF (h) Mean (S.D.)	--	10.21[e] (2.38)	5.09[f] (1.16)
14-OH Clarithromycin (n = 21)			
Cmax (ng/mL) Geometric Mean (C.V.%)	--	209.72 (38.29)	736.83 (38.45)
AUC(TAU) (ng·h/mL)[d] Geometric Mean (C.V.%)	--	2044.59 (34.55)	6898.33 (32.74)
Tmax (h) Median (Min, Max)	--	1.50 [e]	4.16 [f]

[a] Treatment: B = Atazanavir at 400 mg QD for 6 days (Days 1-6)
B + C = Co-administration of atazanavir at 400 mg QD and clarithromycin at 500 mg BID for 4 days (Days 7-10).
C = Clarithromycin at 500 mg BID for 4 days (Days 18-21)

[b] TAU = 24 h

[c] n = 28

[d] TAU = 12 h

[e] n = 17

[f] n = 19

The geometric means, ratio of geometric means, and 90% confidence intervals for the ratios of geometric means for atazanavir, clarithromycin and 14-OH clarithromycin are presented in the following table.