

The mean (S.D.) values for changes in the 24-h urinary ratio of 6 - hydroxycortisol/cortisol on post-treatment days of measurement, each relative to baseline, are summarized in the following table. The 24-h urinary ratios of 6 $\beta$ -hydroxycortisol/cortisol after 800 mg QD administration of BMS-232632 did not increase relative to the baseline values on Day -1, indicating that a net induction of CYP3A4 enzymes, due to administration of BMS-232632 at 800 mg QD, did not occur. However, there was a consistent decrease in the ratios on each day of measurement, which suggests that BMS-232632 is an inhibitor of CYP3A4. In preclinical studies, BMS-232632 has been demonstrated to be an inhibitor of CYP3A4.

Cohort	Study Day	24-hour 6 $\beta$ -HC/C Ratio	Changes From Baseline
		Mean (S.D.)	Mean (S.D.)
Placebo (n = 2)	-1	8.74 (3.70)	n/a
	3	7.84 (3.29)	-0.90 (0.41)
	7	7.53 (2.19)	-1.20 (1.51)
	11	7.49 (3.30)	-1.24 (0.40)
	13	9.05 (1.23)	0.32 (2.47)
800 mg QD (n = 6)	-1	9.36 (4.50)	n/a
	3	3.69 (0.68)	-5.67 (4.37)
	7	3.34 (1.39)	-6.03 (3.55)
	11	3.90 (1.59)	-5.46 (3.67)
	13	4.12 (1.46)	-5.25 (3.69)

#### Conclusions:

- BMS-232632 was rapidly absorbed in the fasted state with a median Tmax of 0.88-2.0 hours. The mean half-life values after a single dose ranged from 2.26-6.33 hours. After dosing for 2 weeks, the mean half-life ranged between 4.95-5.70 hours.
- Steady-state for BMS-232632 appeared to have been achieved within 3-5 days after 200-800 mg QD or 100-200 BID daily doses.
- Urinary recovery of unchanged drug was low (7%). No conjugated metabolites (glucuronides, sulfates) were observed in the urine.
- Very low concentrations of BMS-421419, a metabolite with no anti-HIV activity, were observed in the plasma.
- The urinary 6-hydroxycortisol/cortisol ratios indicated that BMS-232632 has minimal potential to induce CYP3A4, when dosed once-daily for 14 days. However, the decrease in the ratios suggested that BMS-232632 is an inhibitor of CYP3A4.

Pilot Study of a High Fat Meal and Light Meal on the Bioavailability of BMS-232632 in Healthy Volunteers (Protocol AI424003)

**Objective:** To obtain a preliminary estimate of the effect of food on BMS-232632 in healthy subjects.

**Population:** 18 healthy male subjects, aged 18 to 50 years, were enrolled.

**Study Design:** This was an open-label, randomized, single dose, three-way crossover study. Subjects received a single 400 mg dose of BMS-232632 in three occasions in a randomized order: in the fasted state, within 5 minutes of a standard high-fat meal, and within 5 minutes of a light meal. There was at least a 7-day washout period between doses. The following tables listed calorie contents of the high fat meal and the light meal.

Calorie Content of High Fat Meal

Food Item	Calories	Fat (g)	Carbohydrates(g)	Protein(g)
2 eggs (fried in butter)	203	16.2	1.2	12.2
2 slices white bread toasted & buttered	128	1.8	23.4	4.2
1 teaspoonful butter	36	4.1	trace	0
1 tablespoon jelly	55	trace	14.1	trace
2 strips bacon	70	6.2	0.2	3.2
4 oz hash brown potatoes	72	0.1	16.4	1.8
8 oz of whole milk	157	8.9	11.4	8
<b>Total</b>	<b>721</b>	<b>37.3</b>	<b>66.7</b>	<b>29.4</b>
<b>% Total Calories</b>	<b>100</b>	<b>47.0</b>	<b>37.0</b>	<b>16.0</b>

Calorie Content of light Meal

Food Item	Calories	Fat(g)	Carbohydrates(g)	Protein(g)
2 slices white bread toasted	128	1.8	23.4	4.2
1 tablespoon low fat margarine	50	6.0	trace	trace
1 tablespoon jelly	55	trace	14.1	trace
5 oz orange juice	70	0.1	16.7	1.1
5 oz skimmed milk	70	0.25	7.4	5.3
<b>Total</b>	<b>357</b>	<b>8.2</b>	<b>61.6</b>	<b>12.6</b>
<b>% Total Calories</b>	<b>100</b>	<b>20.0</b>	<b>68.0</b>	<b>12.0</b>

**Formulation:** 200 mg capsules (Batch N98065). The formulation contains 0.2% w/w magnesium stearate as compared to 0.4% w/w magnesium stearate used in the to-be-marketed formulations

**Pharmacokinetic Sampling:** PK samples were collected prior to dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 36 and 48 hours after each dose.

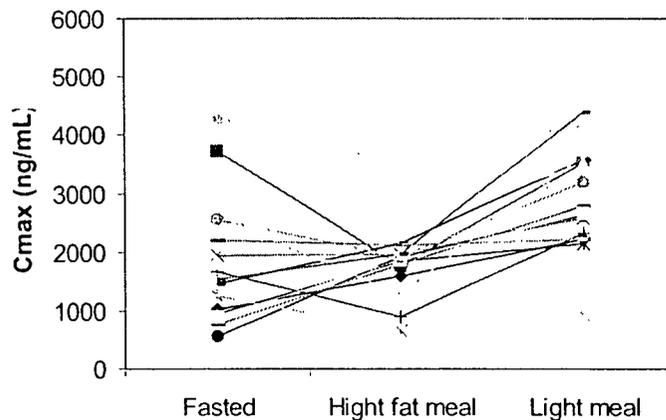
**Analytical Analysis:** Plasma samples were assayed for BMS-232632 concentrations by a validated method. The standard curve and QC data indicated that the plasma assay methods were precise and accurate. See QBR for details.

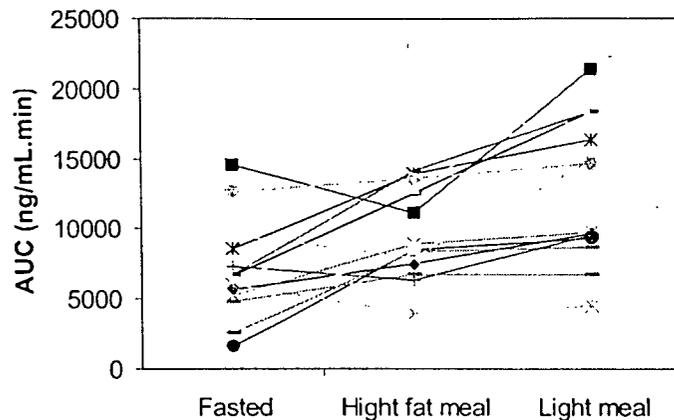
**Pharmacokinetic Results:** Summary statistics for the pharmacokinetic parameters of BMS-232632 following oral administration of a 400 mg dose of the capsule formulation in the fasted state and 5 minutes after a high fat or a light meal are shown in the following tables:

Pharmacokinetic Parameter	Fasted State (n=18)	High Fat Meal (n=18)	Light Meal (n=18)
C <sub>MAX</sub> (ng/mL) Mean (SD)	2188 (1452)	1904 (626)	2972 (858)
AUC(INF) (ng h/mL) Mean (SD)	9252 (6428)	10847 (4618)	13563 (4986)
T-HALF (h) Mean (SD)	6.75 (1.84)	6.60 (1.47)	6.91 (3.07)
T <sub>MAX</sub> (h) Mean (min, max)	1.50	3.00	2.00

Pharmacokinetic Parameter	Geometric Mean			Ratio (90% Confidence Interval)	
	Fasted	Light	Fat	Light/Fasted	Fat/Fasted
C <sub>MAX</sub> (ng/mL)	1794.6	2823.8	1795.0	1.57 (1.284, 1.928)	1.00 (0.816, 1.225)
AUC(INF) (ng.h/mL)	7391.6	12562.1	10000.2	1.70 (1.412, 2.045)	1.35 (1.124, 1.628)

The following figures show the individual stick plots of C<sub>max</sub> and AUC in the fasted state and 5 minutes after a high fat or a light-meal.



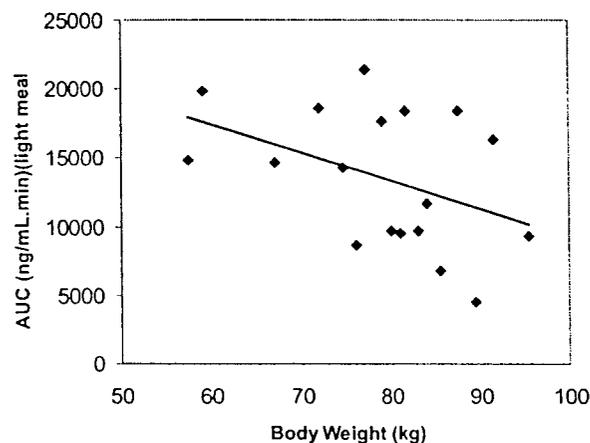


The data show that the light meal increased BMS-232632 bioavailability in most of the subjects, with average of 57% and 70% increase in C<sub>max</sub> and AUC, respectively. The high-fat meal had less effect as compared to light meal, with 35% increase in AUC but no change in C<sub>max</sub>. Variability was reduced when BMS-232632 was taken with food. BMS-232632 is a lipophilic drug, it is not clear why the high fat meal has less effect than light meal on the bioavailability of BMS-232632.

*Reviewer's Comment: Orange juice was used in the light meal. A study conducted by Japanese scientists (Takanaga, et. al., JPET 293:230-236, 2000) suggested that several polymethoxylated flavones isolated from orange juice are inhibitors of P-gp, although some other studies showed contradicting results. Atazanavir is a P-gp substrate. Therefore, it is possible that orange juice presented in the light meal increased the bioavailability of atazanavir.*

The coefficient of variation in the C<sub>max</sub> 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.

The data also show that exposure decreased with increased body weight. This is consistent with results observed in the study AI424-014.



Although there was a 12.5% increase in Cmax, and a 27.5% increase in AUC for White subjects (n = 6) compared to Black subjects (n = 9), there was no statistically significant difference between Black and White subjects.

**Conclusion:**

- Administration of a single dose of 400 mg of BMS-232632 with a meal high in calories and fat (721 kcal and 47% fat) had no effect on the Cmax of BMS-232632, but increased AUC by 35%.
- Administration of a single dose of 400 mg of BMS-232632 with a meal low in calories and fat (357 kcal and 20% fat) increased the Cmax and AUC of BMS-232632 by 57% and 70%, respectively.
- The variability of pharmacokinetic parameters decreased with food consumption.
- BMS-232632 exposure decreased with increased bodyweight.

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Open-Label, Randomized, Three-Way Crossover Study to Evaluate the  
Pharmacokinetics and Safety of BMS-232632 Administered with a Light Meal in  
Healthy Subjects (Protocol AI424-040)

**Objective:** The primary objective of this study was to assess the multiple-dose pharmacokinetics of BMS-232632 at the 200, 400 and 800 mg dose levels, when administered with a light meal.

**Population:** Twenty-four healthy subjects, aged 18 to 50 years, were enrolled. Twenty (20) completed the study. Four subjects discontinued prior to completion of the study; two for adverse events, and two for other reasons.

**Study Design:** This was an open-label, randomized, three-period, three-treatment, crossover study balanced for residuals. Subjects were randomized to receive three treatments (A, B, C), with no washout period, in one of six randomly assigned treatment sequences. Each of the three treatments consisted of 5 days of dosing for a total dosing period of 15 days. Treatments A, B, and C were as follows:

- (A) 200 mg BMS-232632 as 1x200 mg capsule QD for 5 days;
- (B) 400 mg BMS-232632 as 2x200 mg capsules QD for 5 days; and
- (C) 800 mg BMS-232632 as 4x200 mg capsules QD for 5 days.

All doses were given within 5 minutes after a light meal as shown in the following table.

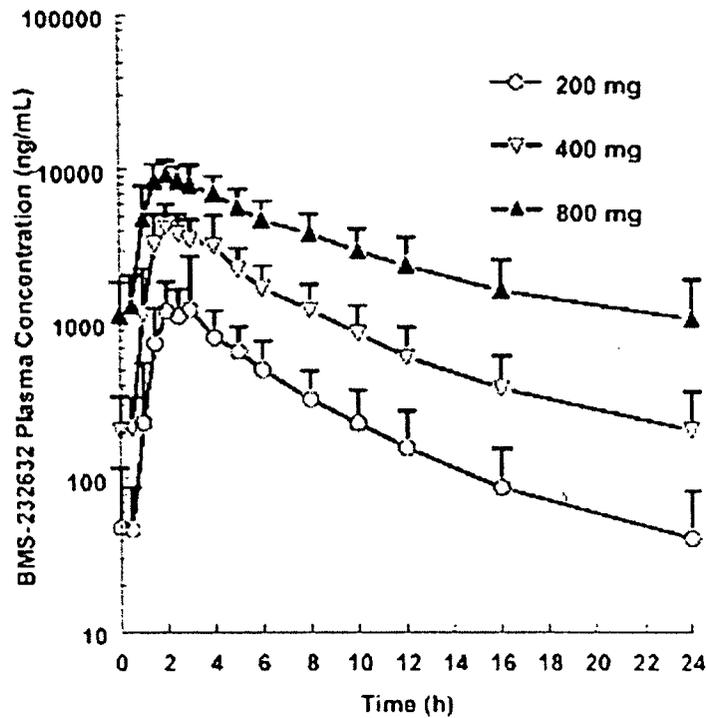
Food Item	Calories	Fat (g)	Carbohydrates (g)	Protein (g)
2 slices white bread toasted	128	1.8	23.4	4.2
1 teaspoonful low fat margarine	50	6.0	trace	0
1 tablespoon jelly	55	trace	14.1	trace
5 oz orange juice	70	0.1	16.4	1.1
5 oz of skim milk	70	0.3	7.4	5.3
Total	373	8.2	61.3	10.6
% Total Calories	100	20	68	12

**Formulation:** BMS-232632 200 mg to-be-marketed capsules (Batches N99274).

**PK/PD Sampling:** Plasma samples were obtained for pharmacokinetic assessment of BMS-232632 on Days 5, 10 and 15 prior to dosing, at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hours after dosing. In addition, plasma samples for trough concentrations were obtained in the morning prior to dosing on Days 2, 4, 6, 7, 9, 11, 12, 14 and 16. Blood samples for assessment of bilirubin were obtained at screening, on Day -3, at pre-dose on Day 5, 6, 10, 11, 15, 16, and at discharge. Genotyping samples (specifically identifying alleles 6 and 7 in the promoter region of the gene encoding uridinediphosphate-glucuronosyl transferase (UDP-GT) 1A1 isoform) were collected (the 6/6 allele pair is considered to be normal while 6/7 and 7/7 pairs result in deficient UGT1A1). Serial ECGs were obtained on Days 5, 10 and 15.

**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. See QBR for details.

**Pharmacokinetic Results:** The mean plasma concentration-time profiles and the mean pharmacokinetic parameters of BMS-232632 following BMS-232632 200 mg, 400 mg, and 800 mg QD regimens are shown in the following figure and table.



Pharmacokinetic Parameter	Dose		
	200 mg (n = 23)	400 mg (n = 22)	800 mg (n = 22)
C <sub>max</sub> (ng/mL) Geometric Mean (C.V. %)	1206.04 (94.16)	4224.97 (43.01)	9665.24 (23.55)
AUC <sub>0-24h</sub> (ng·h/mL) <sup>a</sup> Geometric Mean (C.V. %)	6110.98 (54.94)	23468.58 (42.11)	72338.29 (35.55)
T <sub>max</sub> (h) Median (Min, Max)	2.00	2.00	2.00
T-HALF (h) Mean (S.D.)	5.31 (1.39)	7.06 (2.09)	9.91 (6.14)

<sup>a</sup> TAU = 24 h

As dose increased in ratio 1 : 2 : 4, geometric mean of Cmax increased in ratio 1 : 3.5 : 8.0 and geometric mean of AUC(TAU) increased in ratio 1 : 3.8 : 11.8. These data suggest that Cmax and AUC(TAU) of BMS-232632 increase more than proportionally to dose. The intra-subject coefficient of variation for Cmax was calculated to be 58% and the intra-subject coefficient of variation for AUC(TAU) was 41%. The mean T-HALF tends to be increased with dose.

The inter-subject coefficient of variation for AUC observed in the current study with a light meal ranged between 36% and 55%, which is lower than the variability (51-71%) observed in the fasted state in study AI424-002 following 200-800 mg QD doses. This is consistent with results from study AI424-003 where a single dose of 400 mg of BMS-232632 administered to healthy subjects decreased the variability in exposure from 70% under fasted conditions to approximately 40% when BMS-232632 was given with a light meal.

**PK/PD Evaluation:**

Bilirubin

Individual bilirubin levels on Day -2 and pre-dose on Days 5, 6, 10, 11, 15 and 16 along with the corresponding genotype and BMS-232632 plasma trough concentrations are recorded. The data are summarized by dose level and study day (Day -2, last day before dosing for a given dose level, 24 h after last day of dosing for a given dose level) in the following table.

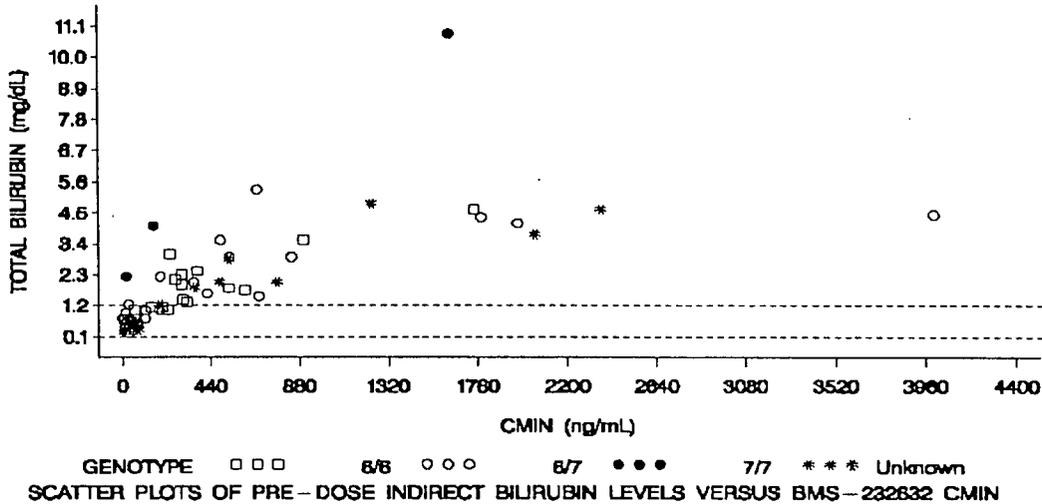
Dose	Study Day <sup>a</sup>	n	PK/PD Parameter		
			Total Bilirubin (mg/dL) Mean (S.D.)	Indirect Bilirubin (mg/dL) Mean (S.D.)	Cmin (ng/mL) Mean (S.D.)
	Day -2	24	0.49 (0.22)	0.39 (0.20) /	--
200 mg	Last Day	23	0.63 (0.50)	0.47 (0.45)	48.17 (70.63)
	24 h After Last Day	23	0.61 (0.42)	0.45 (0.38)	38.57 (38.55)
400 mg	Last Day	22	1.41 (0.93)	1.12 (0.82)	206.19 (134.52)
	24 h After Last Day	22	1.39 (0.90)	1.18 (0.88)	210.60 (171.03)
800 mg	Last Day	22	3.41 (1.71)	3.18 (1.71)	1138.03 (733.71)
	24 h After Last Day	22	3.50 (2.02)	3.23 (2.04)	1102.02 (921.91)

<sup>a</sup> Last Day = Pre-dose on last day of dosing (Day 5, 10 or 15) for each dose level; 24h after last Day = Pre-dose at 24 hours after last day of dosing (Day 6, 11 or 16) for each dose level;

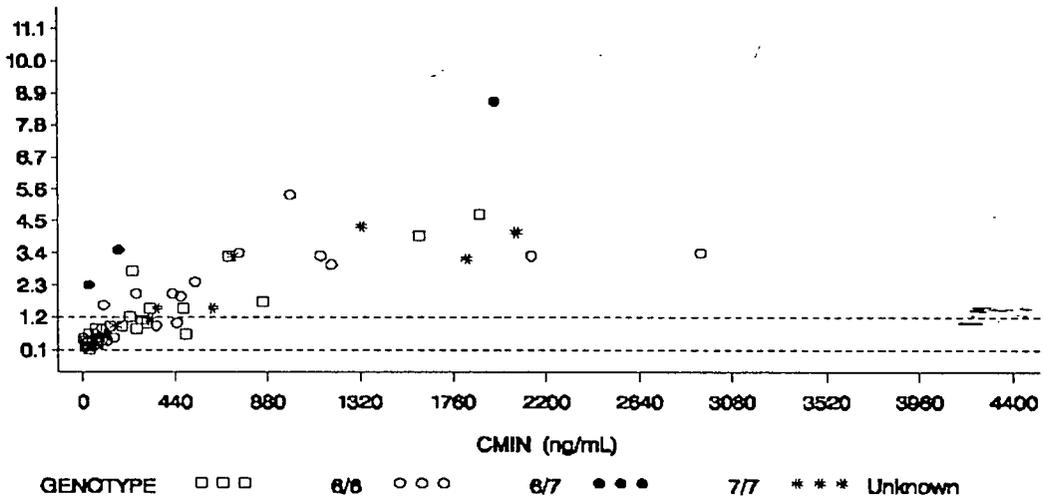
At baseline, no subject had bilirubin levels (total or indirect) outside the normal range of values (0.10 to 1.10 mg/dL). Most subjects had bilirubin levels greater than 1.10 mg/dL on at least one day after dosing started.

Scatter plots of bilirubin (both as total and indirect) versus BMS-232632 plasma trough concentrations are shown in the following figures. The scatter plots suggest that the bilirubin levels (both as total and indirect) tend to increase as plasma trough concentrations increase for all UDP-GT 1A1 genotypes. The 7/7 allele pair seemed to have a higher unconjugated (indirect) and total bilirubin elevation, but no statistical analysis was performed.

SCATTER PLOTS OF PRE-DOSE TOTAL BILIRUBIN LEVELS VERSUS BMS-232632 CMIN  
(24 HRS AFTER LAST DAY OF DOSING FOR EACH DOSE LEVEL)



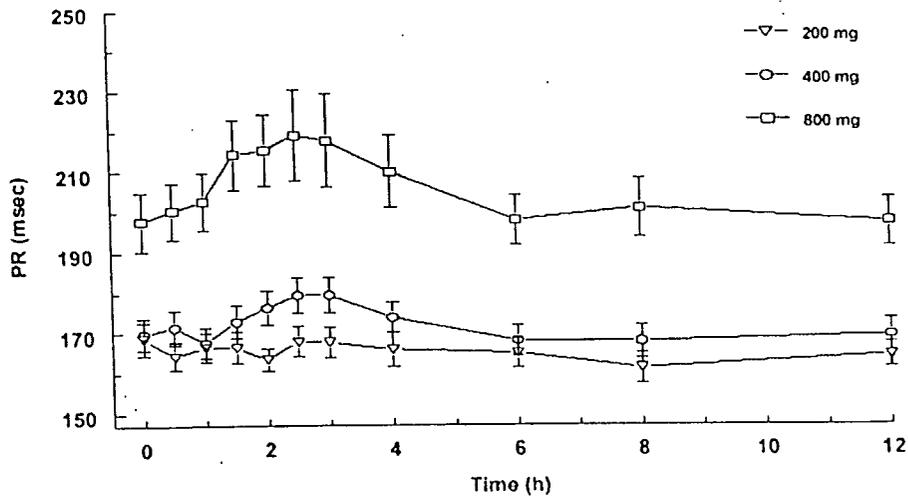
SCATTER PLOTS OF PRE-DOSE INDIRECT BILIRUBIN LEVELS VERSUS BMS-232632 CMIN  
(PRE-DOSE ON LAST DAY OF DOSING FOR EACH DOSE LEVEL)



Note: Horizontal lines represent the range of normal values



The following figure shows mean (SD) PR intervals plotted against time since last day of dosing for each dose.

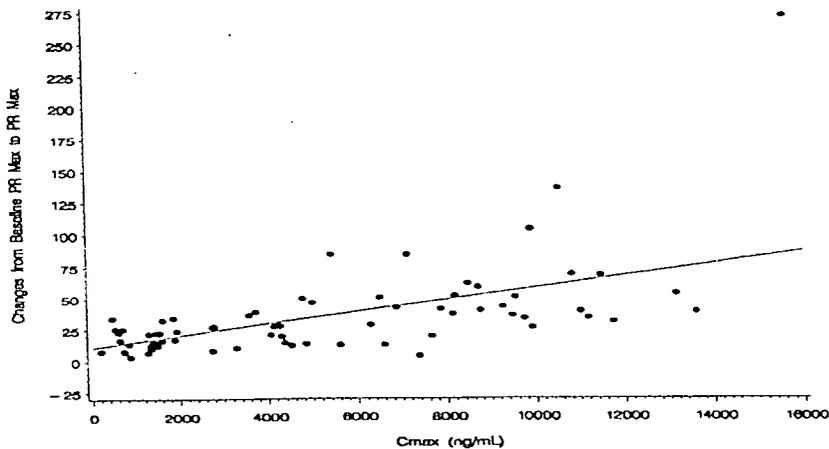


The following table summarizes the statistics for baseline PR Max and PR Max.

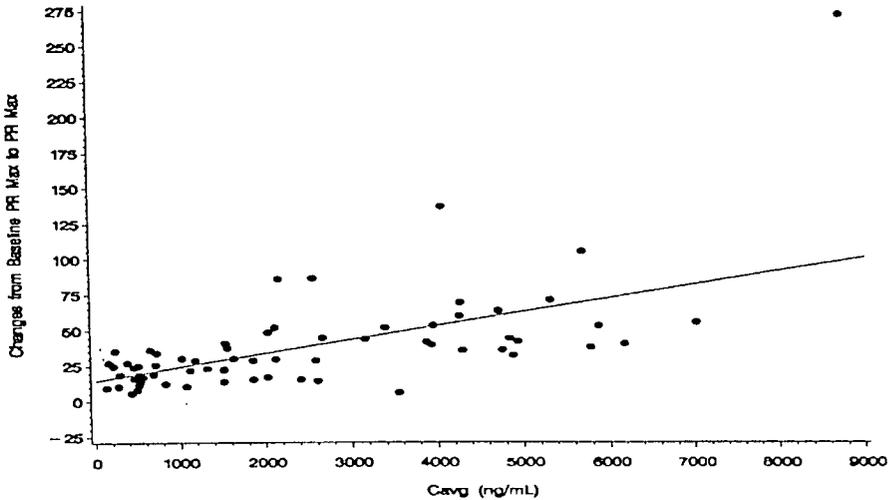
Dose	n	Baseline PR Max (msec) Mean (S.D.)	PR Max (msec) Mean (S.D.)
200 mg	23	158 (14)	177 (18)
400 mg	22	157 (16)	186 (21)
800 mg	22	159 (15)	225 (53)

The data show that mean PR baselines were very similar across dose levels, and mean PR measures (post-dose) increased with increasing dose.

The following figures show the scatter plots of PR changes from baseline versus C<sub>max</sub> and C<sub>avg</sub>, together with the corresponding fitted regression lines.



The data suggested BMS-232632 concentration-dependent prolongation of the PR interval of the ECG. Fifty-eight percent (58%) of the subjects developed first-degree AV blocks (PR > 200 msec) on at least one ECG at one or more dose levels. None of the subjects developed second- or third-degree AV block.

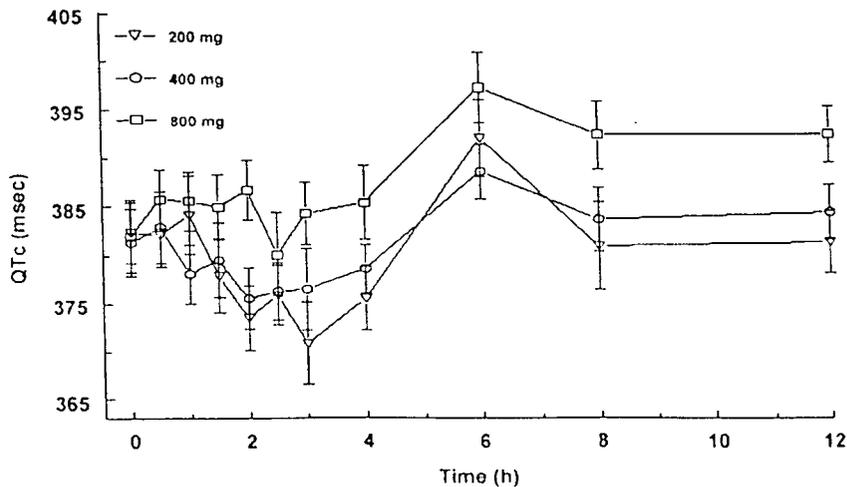


QT Prolongation

The following table lists subjects with borderline QTc (Bazett's correction) intervals as defined by CPMP guidelines as QTc interval of > 430 msec for males and > 450 msec for females. There were no subjects with QTc values of > 450 msec.

Dose	Subject	Gender	Study Day	Time After Dosing	QTc (msec)
200 mg	015	Male	15	6h	441
800 mg	011	Male	5	6h	442
			5	8h	432

The following figure shows mean QTc intervals plotted against time since dosing for each dose.

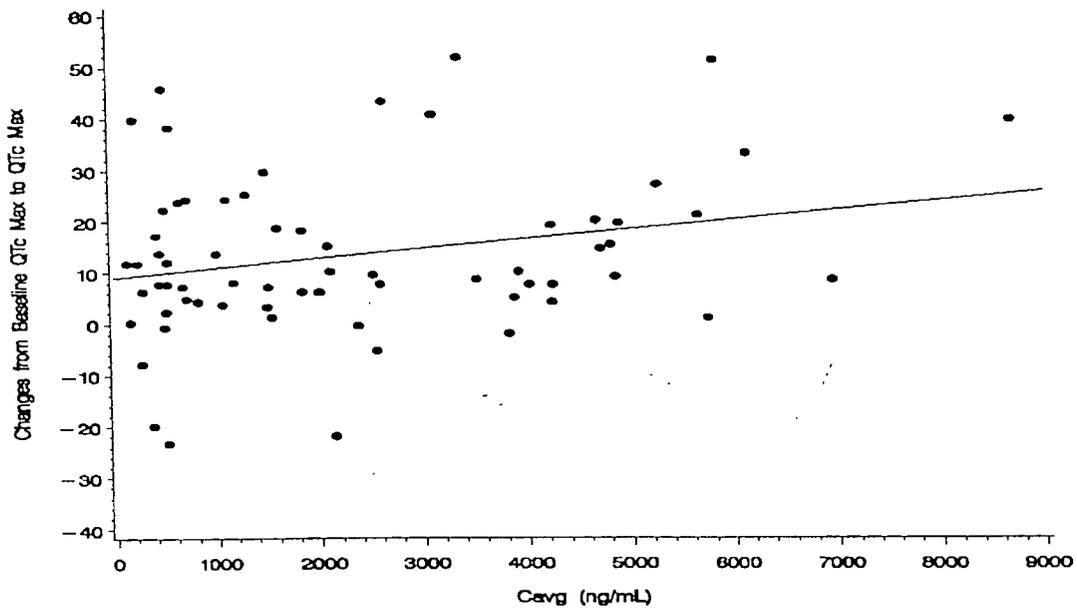


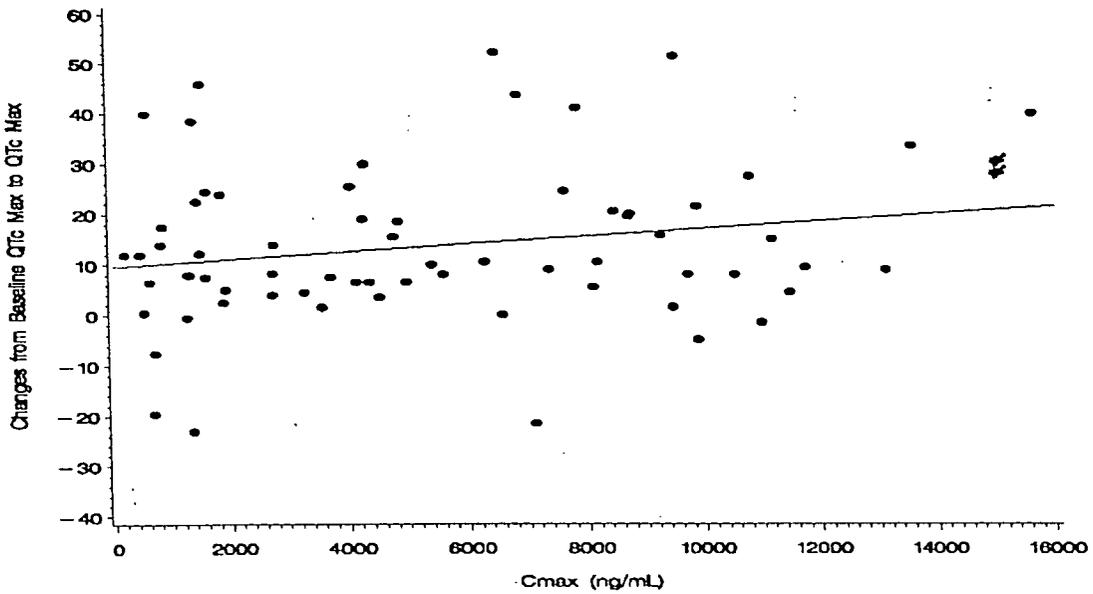
The following table summarizes the statistics for baseline QTc Max and QTc Max.

Dose	n	Baseline QTc Max (msec) Mean (S.D.)	QTc Max (msec) Mean (S.D.)
200 mg	23	388 (15)	400 (19)
400 mg	22	386 (20)	396 (14)
800 mg	22	386 (18)	405 (16)

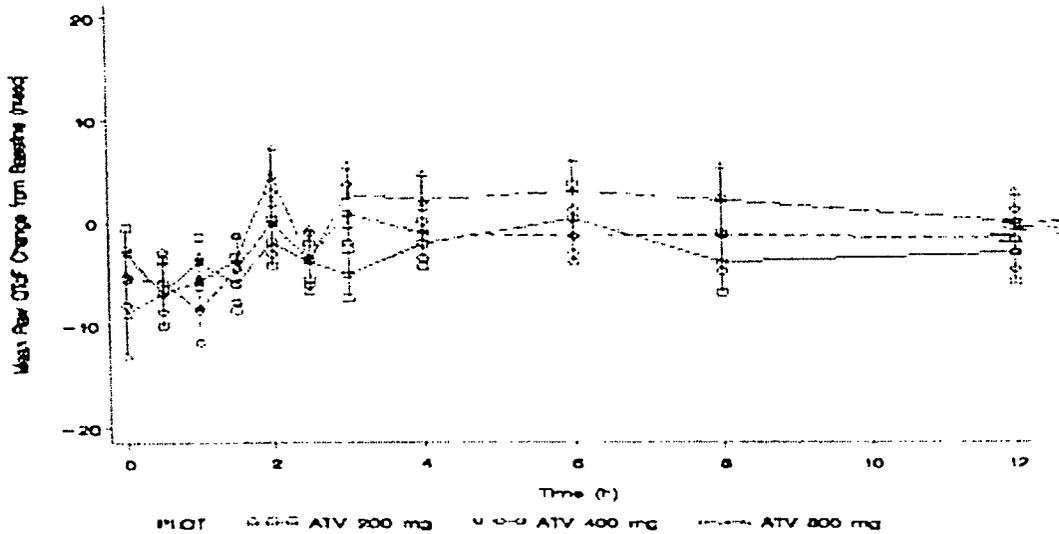
The data show that mean QTc baseline values were very similar across dose levels.

The following figures show the scatter plots of QTc Max changes from baseline versus Cmax and Cavg, together with the corresponding fitted regression lines. The data showed that  $\Delta$ QTc tended to increase with increased BMS-232632 concentration.





Reviewer's comment: The QT was corrected using Bazett's formula. As we discussed in Study A1424076, Fridericia's correction is more accurate, and dose-dependent QTc prolongation disappears with Fridericia's correction. We asked the applicant to reanalyze QT interval values using Fridericia's formula (QTcF) during the review cycle. The following figure shows plot of mean QTcF changes from baseline versus time since dosing on Day 5. The data show that the difference between 800 mg dose and 200 mg (or 400 mg) is not significant using Fridericia's correction. Since this study is not specifically designed for evaluation of QTc prolongation, please refer to the review for Study A1424076.



**Conclusions:**

- Once-daily doses of 200 mg, 400 mg, and 800 mg produced a greater than dose proportional increase in steady-state exposure to BMS-232632 in healthy subjects. For doses in ratios of 1 : 2 : 4, C<sub>max</sub> increased in ratios of 1 : 3.5 : 8.0 and AUC increased in ratios of 1 : 3.8 : 11.8.
- BMS-232632 was associated with dose- and concentration-dependent prolongations of the QTc interval of the ECG using Bazett's formula (QTcB). The dose-dependent QTcB prolongations were most apparent at the 800 mg dose. However, Bazett's correction tends to overestimate QTc with increased heart rate.
- BMS-232632 was associated with dose- and concentration-dependent prolongations of the PR interval of the ECG. The dose-dependent prolongations were most apparent at the 800 mg dose. Fifty-eight percent (58%) of the subjects developed first-degree AV blocks (PR > 200 msec) on at least one ECG at one or more dose levels. None of the subjects developed second- or third-degree AV block.
- Bilirubin levels (both as total and indirect) tended to increase as BMS-232632 plasma trough concentrations increased, and returned to baseline following discontinuation of BMS-232632.

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A Pilot Multiple Dose De-Escalation Study of the Safety, Tolerance and  
Pharmacokinetics of BMS-232632 in Previously Treated Healthy Subjects Who  
Developed Isolated Hyperbilirubinemia (Protocol AI424-011)

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**Objective:** To explore the relationship between elevation in total and unconjugated bilirubin and Cmin (trough) plasma levels of BMS-232632 in individuals who previously demonstrated a reversible rise in bilirubin with BMS-232632.

**Population:** Four white male healthy subjects, aged from 23 to 29 years, who previously developed isolated hyperbilirubinemia due to BMS-232632 exposure. Subjects who demonstrated a steady-state Cmin value of BMS-232632 in excess of 60 ng/mL (the adjusted-IC90) in Studies AI424002 and AI424012 were preferentially selected.

*Reviewer's Comment: The inclusion criteria preferentially select patients that had hyperbilirubinemia due to higher BMS-232632 exposure. Therefore, this study could not adequately address whether hyperbilirubinemia is associated with higher BMS-232632 exposure.*

**Study Design:** This was an open-label, non-randomized, multiple-dose de-escalation pilot study to explore the relationship between elevation in total and unconjugated bilirubin and Cmin (trough) plasma levels of BMS-232632. All subjects received a single oral dose of BMS-232632 daily for 12 consecutive days, administered on a de-escalating schedule, with 600 mg on Days 1 through 4, 400 mg on Days 5 through 8, and 200 mg on Days 9 through 12.

At the time of dosing, a light meal (as shown in the following table) was administered.

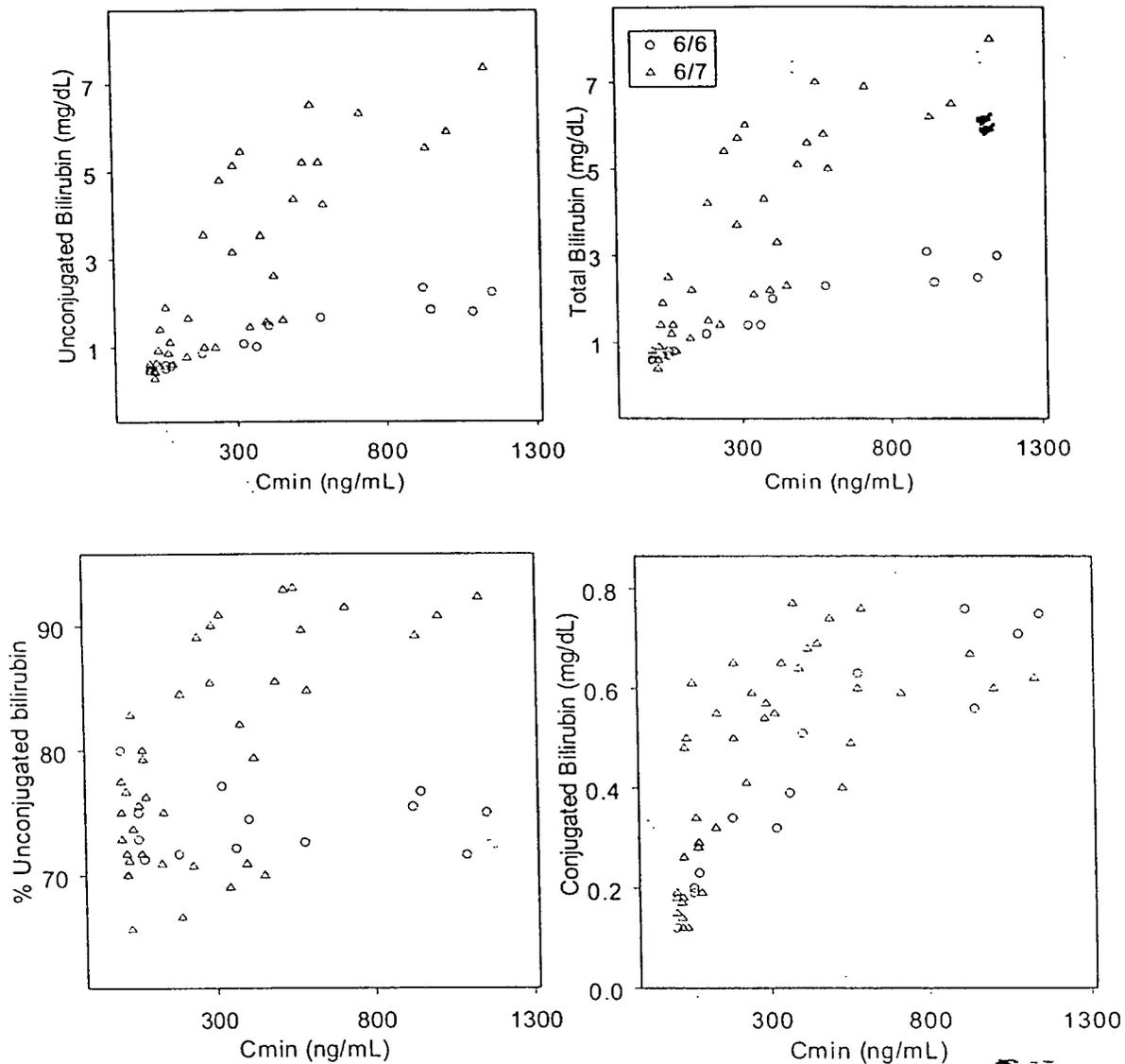
Food Item	Calories	Fat (g)	Carbohydrates (g)	Protein (g)
2 slices white bread toasted	128	1.8	23.4	4.2
1 teaspoonful low fat margarine	50	6.0	trace	0
1 tablespoon jelly	55	trace	14.1	trace
5 oz orange juice	70	0.1	16.4	1.1
5 oz of skim milk	70	0.25	7.4	5.3
Total	357	8.2	61.6	10.6
% Total Calories	100	20	68	12

**Formulation:** 200 mg BMS-232632 capsule (Batch N98065).

**Pharmacokinetic Sampling:** Blood samples for BMS-232632 PK analysis were collected prior to the morning dose from Days 1 to 13. Blood samples for measurement of bilirubin were collected at the same times as the pharmacokinetic samples and also on Study Days 14-16. Genotyping samples for UDP-GT 1A1 isoform were also collected.

**Analytical Analysis:** Plasma samples 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. See QBR for details.

**Pharmacokinetic Results:** The reviewer has analyzed the relationship among plasma trough concentrations, bilirubin levels (total bilirubin, unconjugated bilirubin, %unconjugated bilirubin), and UDP-GT 1A1 genotypes as shown in the following figures.



The data show that both unconjugated and conjugated bilirubin increase with increased concentration of BMS-232632. The magnitude of unconjugated bilirubin increase is higher in subjects with UDP-GT 1A1 genotype 6/7 as compared to genotype 6/6. Administration of BMS 232632 did not significantly affect % unconjugated bilirubin in the subject (only one subject) with genotype 6/6, but did increase % unconjugated bilirubin in the subjects with genotype 6/7 (n = 3) and reaches a plateau at Cmin of BMS 232632 above 500 ng/mL. The results suggested that BMS-232632 reduces bilirubin conjugation and reaches a plateau at higher concentration for genotype 6/7. As we discussed previously in Study AI424040 that either the bilirubin analysis method was not accurate or mechanisms other than UDP-GT inhibition may also contribute.

**Conclusions:**

1. BMS-232632 increases both unconjugated bilirubin and conjugated bilirubin.
2. BMS-232632 reduces bilirubin conjugation and reaches a plateau at higher concentration for genotype 6/7.
3. There was only one subject with genotype 6/6, and thus no conclusion can be made for this genotype.

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## Age and Gender Effects on the Single Dose Pharmacokinetics of BMS-232632 in Healthy Subjects (Protocol AI424-014)

**Objective:** To assess the effects of age and gender on the single-dose pharmacokinetics of BMS-232632.

**Population:** 60 healthy subjects, aged from 19 to 81 years.

**Study Design:** This was an open-label, non-randomized, parallel group, single-dose study. Subjects were assigned to one of four groups based on the subject's gender and age, as follows:

- Young females, aged from 18 to 40 years, with a body weight of  $\geq 40$  kg and a body mass index (BMI) of 18 to 30 kg/m<sup>2</sup>
- Elderly females, ages  $\geq 65$  years, with a body weight of  $\geq 40$  kg and a body mass index (BMI) of 18 to 30 kg/m<sup>2</sup>
- Young males, aged from 18 to 40 years, with a body weight of  $\geq 60$  kg and a body mass index (BMI) of 18 to 30 kg/m<sup>2</sup>
- Elderly males, ages  $\geq 65$  years, with a body weight of  $\geq 60$  kg and a body mass index (BMI) of 18 to 30 kg/m<sup>2</sup>

A single 400 mg oral dose of BMS-232632 was administered within 5 minutes after a light meal as shown in the following table.

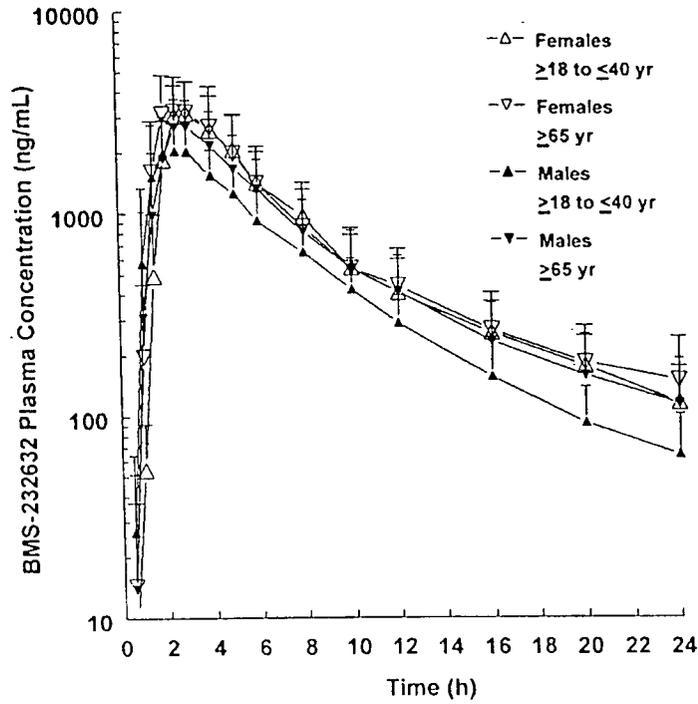
Food Item	Calories	Fat (g)	Carbohydrates (g)	Protein (g)
2 slices white bread toasted	128	1.8	23.4	4.2
1 teaspoonful low fat margarine	50	6.0	trace	0
1 tablespoon jelly	55	trace	14.1	trace
5 oz orange juice	70	0.1	16.4	1.1
5 oz of skim milk	70	0.3	7.4	5.3
Total	373	8.2	61.3	10.6
% Total Calories	100	20	68	12

**Formulation:** 200 mg BMS-232632 capsules (Batch C99274, the difference between this product and the to-be-marketed product is the size and color of the capsule shell).

**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, 20, and 24 hours after dosing on Day 1.

**Analytical Analysis:** Plasma samples were assayed for BMS-232632 concentrations by a validated  $\text{—}$  method. The standard curve and QC data indicated that the plasma assay method was precise and accurate. See QBR for details.

**Pharmacokinetic Results:** The mean plasma concentration-time profiles and the summary statistics for the pharmacokinetic parameters are shown in the following figure and tables.



Pharmacokinetic Parameter	Age/Gender Group			
	Young Females (n = 14) <sup>a</sup>	Elderly Females (n = 15)	Young Males (n = 15)	Elderly Males (n = 15)
C <sub>max</sub> (ng/mL) Geometric Mean (C.V.%)	3078.90 (41.89)	3696.25 (32.57)	2543.66 (28.18)	2900.90 (33.85)
AUC(INF) (ng·h/mL) Geometric Mean (C.V.%)	17330.81 (38.76)	18457.48 (44.48)	12843.58 (31.08)	16441.55 (40.43)
T <sub>max</sub> (h) Median (Min, Max)	2.50	2.50	2.00	2.50
T <sub>1/2</sub> (h) Mean (S.D.)	7.35 (2.44)	8.94 (3.39)	5.84 (1.32)	7.49 (2.45)

Pharmacokinetic Parameter	Gender		Age Group	
	Females (n = 29)	Male (n = 30)	Young (n = 29)	Elderly (n = 30)
C <sub>max</sub> (ng/mL) Geometric Mean (C.V.%)	3384.12 (37.60)	2716.42 (32.06)	2789.31 (38.59)	3274.51 (36.33)
AUC(INF) (ng·h/mL) Geometric Mean (C.V.%)	17904.71 (42.23)	14531.54 (39.82)	14842.56 (39.72)	17420.27 (43.37)
T <sub>max</sub> (h) Median (Min, Max)	2.50	2.25	2.50	2.50
T-HALF (h) Mean (S.D.)	8.18 (3.03)	6.67 (2.11)	6.57 (2.05)	8.22 (3.00)

Pharmacokinetic Parameter	Adjusted Geometric Means		Male/Female Ratio	
	Female	Male	Point Estimate	90% C.I.
C <sub>max</sub> (ng/mL)	3373.48	2716.42	0.805	(0.652, 0.994)
AUC(INF) (ng·h/mL)	17885.28	14531.54	0.812	(0.654, 1.010)
Pharmacokinetic Parameter	Adjusted Geometric Means		Elderly/Young Ratio	
	Young	Elderly	Point Estimate	90% C.I.
C <sub>max</sub> (ng/mL)	2798.51	3274.52	1.170	(0.948, 1.444)
AUC(INF) (ng·h/mL)	14919.44	17420.27	1.168	(0.939, 1.451)

The data show that female subjects have 20% higher BMS-232632 exposures compared to male subjects and elderly subjects have 17% higher exposures as compared to young subjects.

*Reviewer's comment: The reviewer reanalyzed the data based on 70 kg body weight. The gender difference disappeared, but elderly subjects still showed 16% higher exposures (AUC and C<sub>max</sub>) as compared to the young subjects.*

Pharmacokinetic Parameter (Geometric mean, normalized to 70 kg)	Gender		Age	
	Female	Male	Young	Elderly
C <sub>max</sub> (ng/mL)	3184.44	3116.72	2916.22	3393.41
AUC(INF) (ng·h/mL)	16848.22	16672.96	15517.87	18052.77

**Conclusions:**

1. Female subjects have 20% higher AUC and Cmax compared to male subjects due to lower body weight for the female subjects.
2. 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.

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Open-Label, Non-Randomized Study of the Single-Dose Pharmacokinetics of BMS-232632 in Subjects with Moderate to Severe Hepatic Impairment and in Matched Normal Healthy Subjects (A1424015)

**Objective:** To evaluate the influence of moderate to severe hepatic-impairment on the pharmacokinetics of a therapeutically relevant dose of BMS-232632 (400 mg).

**Population:** Thirty-three subjects were initially enrolled in the study, 32 (16 hepatically-impaired subjects [14 Child-Pugh Class B and 2 Child-Pugh Class C] and 16 matching control subjects) received study drug.

**Study Design:** This was a non-randomized, single-dose, open-label study. Healthy control subjects were matched to hepatically-impaired subjects with respect to age ( $\pm 5$  years), weight ( $\pm 10\%$ ), race, gender and smoking history. All subjects received a single 400 mg dose of BMS-232632 with a low-fat breakfast, as shown in the following table, on Day 1 of Study Period 1. The hepatically-impaired subjects returned to the study center for Study Period 2 (following a at least 7-day washout period) and received a single 200 mg dose of BMS-232632.

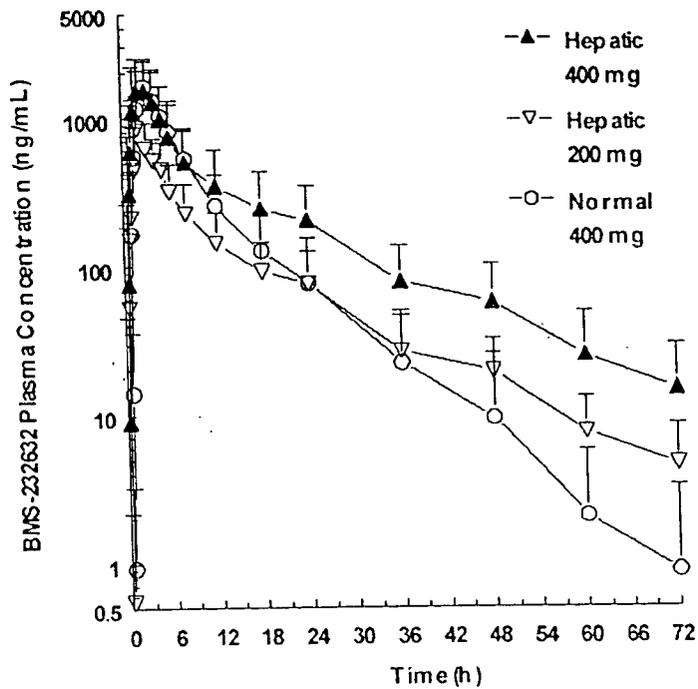
Food Item	Calories	Fat (g)	Carbohydrates (g)	Protein (g)
2 slices of toasted white bread	128	1.8	23.4	4.2
1 tablespoon of low-fat margarine	50	6.0	Trace	Trace
1 tablespoon of jam	55	Trace	14.1	Trace
150 mL of orange juice	70	0.1	16.7	1.1
150 mL of skim milk	70	0.25	7.4	5.3
Total	373	8.15	61.6	10.6
% Total Calories	100	20	68	12

**Formulation:** 200 mg capsule (Batch N98178). 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 pharmacokinetic assessment were collected prior to dosing and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 36, 48, 60 and 72 hours after dosing (Study Periods 1 and 2).

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

**Pharmacokinetic Results:** The mean plasma concentration-time profiles and the summary statistics for the pharmacokinetic parameters are shown in the following figure and tables.

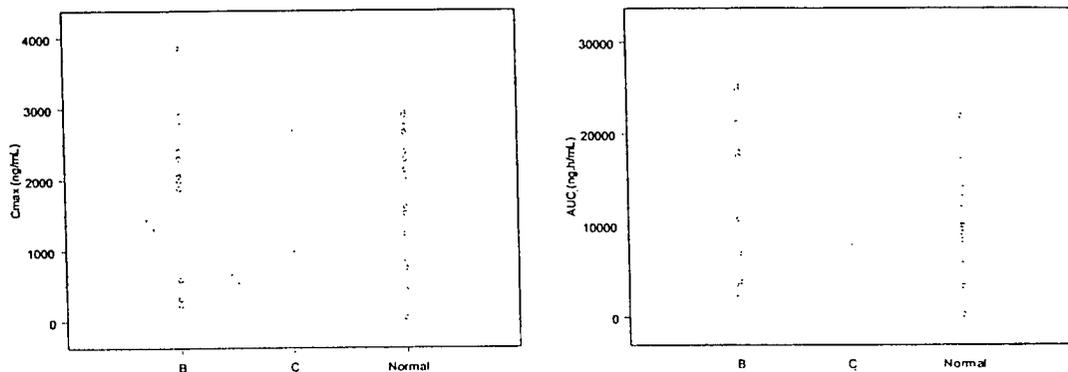


Pharmacokinetic Parameter	400 mg		200 mg
	Normal (N = 16)	Hepatic (N = 16)	Hepatic (N = 15)
C <sub>max</sub> (ng/mL) Geometric Mean (C.V.%)	1334.4 (51.2)	1391.0 (58.1)	826.7 (53.3)
AUC(INF) (ng·h/mL) Geometric Mean (C.V.%)	8071.1 (58.5)	11738.6 (62.6)	5548.2 (49.8)
T <sub>max</sub> (h) Median (Minimum, 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)

Pharmacokinetic Parameter	Group (400 mg)	Geometric Mean	Contrast	Ratio of Geometric Means Point Estimate (90% C.I.)
C <sub>max</sub> (ng/mL)	A B	1334.4 1391.0	B vs. A	1.04 (0.56, 1.93)
AUC(INF) (ng·h/mL)	A B	8071.1 11738.6	B vs. A	1.45 (0.80, 2.63)

The data show that the median  $T_{max}$  was 2.0 h for the hepatic-impairment group and 3.0 hours for the normal group. The mean  $T_{-HALF}$  was almost twice as long for the hepatic-impairment group (12.1 h after 400 mg and 11.6 h after 200 mg) as for the normal group (6.4 h).

The following figures show individual  $C_{max}$  and AUC separated by hepatic function (normal, Child-Pugh B and Child-Pugh C).



Neither  $C_{max}$  nor AUC(INF) satisfied the criteria for absence of effect of hepatic-impairment (90% CI within 80% to 125%). Although the geometric mean  $C_{max}$  was only 4% higher for the hepatic-impairment group than for the control group, the confidence interval (0.56, 1.93) was very wide. The results for AUC(INF) suggested a moderate increase (45%) in geometric mean with hepatic-impairment, but again the confidence interval (0.80, 2.63) was very wide. The results were similar if subjects with severe hepatic impairment were excluded.

Exposures from the 200 mg dose given to the hepatic-impairment group were substantially less than those from the 400 mg dose given to either the hepatic-impairment group or the control group. Within the hepatic impairment group, the geometric mean ratio of AUC(INF) and  $C_{max}$  for the 400 vs 200 mg doses was 2.1 and 1.7, respectively, which suggests that BMS-232632 exposure may be dose proportional in subjects with hepatic-impairment. Comparing the 200 mg dose in the hepatically-impaired group to the 400 mg dose in the control group, the ratios of the geometric means were 0.69 for AUC(INF) and 0.62 for  $C_{max}$ .

Following oral administration, BMS-232632 has similar half-lives after single dose and multiple 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, volume of distribution of BMS-232632 may not be changed after multiple dose administration. In conclusion, single dose could be used to predict pharmacokinetics of multiple dose for BMS-232632.

#### Conclusions:

1. Following a single 400 mg dose of BMS-232632, the geometric mean  $C_{max}$  and AUC(INF) in subjects with moderate to severe hepatic impairment were 4% and 45% greater, respectively, compared to normal subjects.

2. Compared to normal subjects who received a 400 mg dose, the geometric mean C<sub>max</sub> and AUC(INF) in subjects with moderate to severe hepatic impairment following a single 200-mg dose of BMS-232632 were 38% and 31% lower, respectively.
3. BMS-232632 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, BMS-232632 exposure may be dose proportional in subjects with hepatic impairment. Therefore, dose reduction to 300 mg may be considered for patients with moderate hepatic impairment.
4. Only 2 subjects with severe hepatic impairment were studied, so it is not possible to make a dose recommendation.
5. BMS-232632 exposure in subjects with mild hepatic impairment will likely be less than 45% higher than exposure in subjects with normal hepatic function. Based on available safety data, no dose adjustment is needed for subjects with mild hepatic impairment.

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Pharmacokinetics of BMS-232632 in HIV-infected patients in three Phase II studies  
(Protocols AI424007, AI424008, and AI424009)

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**Objective:** PK substudies were conducted in Protocols AI424007, AI424008, and AI424009. The purpose of this review is to compare the pharmacokinetics of BMS-232632 in HIV-infected patients (full PK profiles) and that in healthy subjects.

**Population:** HIV-infected patients. (AI424007, n = 30; AI424008, n = 25; AI424009, n=3).

**Study Design:** All three studies are Phase II trials in HIV-infected patients. BMS-232632 was compared to other PI or NNRTI, each in combination with two NRTIs. AI424007 was conducted under fasted conditions, while AI424008 was conducted with light meal, and AI424009 was conducted with a high fat meal. BMS-232632 plasma, CSF (AI424008 and AI424009), seminal fluid (AI424008) concentrations were determined. In AI424009, saquinavir plasma and CSF concentrations were also determined.

**Formulation:** BMS-232632 to-be-marketed capsules

AI424007: 100-mg (Batch N98177, C99193, N99028, N00097, N98178);  
200-mg (Batch N98178, C99274, C99331, N00104, C99179);  
AI424008: 200-mg (Batch N98178, C99179, C99274, C99331, N00024, N00102,  
N00103, 8MJC276, 8MBM117);  
AI424009: 200-mg (Batch N98178, C99274, C99331, 8MJC276, 8MBM117).

**Analytical Analysis:** Plasma, CSF, and seminal fluid samples were assayed for BMS-232632 and saquinavir concentrations by a validated \_\_\_\_\_ method. The standard curve and QC data indicated that the assay methods were precise and accurate. See QBR for details.

**Pharmacokinetic Results:**

*Plasma Pharmacokinetics:*

For AI424007, BMS-232632 was originally given under fasted conditions, and was amended to be given with food on January 7, 2000. Since this PK substudy was conducted from March 1999 to March 2001, it is not clear which subjects were given drug under fed conditions. The applicant did not specify if the substudy was conducted under fasted or fed conditions, but compared to PK results from this study to the PK from healthy subjects in a previous study. The following table summarizes the pharmacokinetic parameters of BMS-232632 in this study [Day 29 was in combination with ddl (separated from BMS-23263 by 1 hour) and d4T].

Pharmacokinetic Parameter	BMS-232632 Dose					
	200 mg (n = 6) <sup>a</sup>		400 mg (n = 10)		500 mg (n = 14)	
	Day 1 <sup>c</sup>	Day 29 <sup>c</sup>	Day 1 <sup>c</sup>	Day 29 <sup>c</sup>	Day 1 <sup>c</sup>	Day 29 <sup>c</sup>
C <sub>max</sub> (ng/mL) Geometric Mean (C.V. %)	344.46 (77.99)	323.56 (118.19)	763.63 (77.77)	2274.41 (46.70)	537.52 (98.02)	2499.13 (63.80)
AUC(INF) (ng·h/mL) Geometric Mean (C.V. %)	1601.94 (76.88)	n/a	4455.93 (110.09)	n/a	2828.37 (93.72)	n/a
AUC(TAU) (ng·h/mL) <sup>b</sup> Geometric Mean (C.V. %)	1541.94 (76.71)	1928.86 (116.95)	4054.83 (107.93)	12812.87 (45.66)	2733.37 (92.29)	12943.56 (69.14)
T <sub>max</sub> (h) Median (Min, Max)	1.50	2.00	1.25	1.50	1.00	1.00
T-HALF (h) Mean (S.D.)	4.76 (1.35)	4.78 (1.43)	6.75 (2.15)	6.10 (1.84)	4.78 (1.13)	5.63 (2.47)

<sup>a</sup> n = 5 for AUC(INF), AUC(TAU), and T-HALF on Day 1

<sup>b</sup> TAU = 24 h

<sup>c</sup> Day 1 = monotherapy; Day 29 = combination therapy

The data showed that BMS-232632 had high intersubject variability in HIV-infected subjects, which may partially due to difference in the food consumption. The high intersubject variability was also seen in healthy subjects under fasted conditions. The C<sub>max</sub> and AUC were 25% - 70% and 24%-64% lower, respectively, in HIV-infected subjects as compared to that in healthy subjects under fasted conditions (AI424002) for doses of 200 mg and 400 mg. However, the BMS-232632 exposure for the 500 mg dose in Study AI424002 was surprisingly lower than that for the 200 mg and 400 mg doses. Therefore, the BMS-232632 exposures in this study (HIV-infected subjects) at 500 mg were higher as compared to healthy subjects in Study AI424002. It is difficult to conclude if pharmacokinetics of BMS-232632 are comparable between healthy subjects and HIV-infected subjects due to food conditions and high variability. A greater than dose proportional increase in steady-state exposure was observed in HIV patients over the dose range of 200 mg to 400 mg, with the exposure at 500 mg being comparable to that at 400 mg.

The following table summarizes the pharmacokinetic parameters of BMS-232632 administered with a meal or snack (in combination with 3TC and d4T, AI424008).

Pharmacokinetic Parameter	400 mg BMS-232632		600 mg BMS-232632	
	Day 1 (n = 10)	Day 29 (n = 13)	Day 1 (n = 10)	Day 29 (n = 12)
Cmax (ng/mL)				
Geometric Mean (C.V. %)	1627.22 (57.58)	2297.65 (70.80)	3232.84 (45.05)	3848.43 (42.25)
AUC(INF) (ng·h/mL)				
Geometric Mean (C.V. %)	9170.49 (54.45)	n/a	21137.24 (52.61)	n/a
AUC(TAU) (ng·h/mL) <sup>a</sup>				
Geometric Mean (C.V. %)	8620.97 (52.80)	14873.76 (90.55)	19528.48 (49.48)	25124.94 (44.72)
Tmax (h)				
Median(Min, Max)	4.00	2.00	4.00	2.00
T-HALF (h)				
Mean (S.D.)	5.57 (1.64)	6.51 (2.57)	6.24 (2.45)	5.32 (1.55)

n/a = not applicable

<sup>a</sup> TAU = 24 h

The inter-subject variability, although still high, was lower in this study as compared to that in Study AI424007. On Day 1, Cmax and AUC increased about 100% under fed conditions as compared to that in Study AI424007 (400 mg doses). However, the differences almost disappeared at steady-state (Day 29), with AUC increased by only 16% and Cmax was comparable to that in Study AI424007. Since the PK in Study AI424007 may combine both fed and fasted data, it is difficult to compare these two studies.

Compared to healthy subjects, steady-state Cmax and AUC (24 h) in HIV-infected subjects were 46%-58% and 37%-55% lower, respectively, after 400 mg BMS-232632 QD (AI424040, AI424076); and single dose Cmax and AUC(INF) were 47% and 44% lower, respectively (AI424014).

When administered with a light meal, as dose increased from 400 mg to 600 mg (50% increase), Cmax and AUC increased 69% and 67%, respectively. The increases are similar to the magnitude seen in healthy subjects. The geometric means for the steady-state accumulation ratios ranged from 1.64 to 4.74, with a 3-fold accumulation at 400 mg.

In study AI424009, the study was conducted with a high-fat meal. The following table shows the pharmacokinetics of BMS-232632 in 3 subjects. BMS-232632 (400 mg QD) was administered with 1200 mg saquinavir QD plus two NRTIs.

Subject <sup>a</sup>	Cmax (ng/mL)		Tmax (h)		AUC(TAU) (ng·h/mL)		T-HALF (h)	
	Day 1	Day 29	Day 1	Day 29	Day 1	Day 29	Day 1	Day 29
Atazanavir								
AI424009-17-4	1928.57	7081.65	4.00	4.00	17848.36	94284.05	6.51	14.67
AI424009-17-78	442.10	832.55	6.00	4.00	3528.22	11248.81	4.37	6.30
AI424009-17-5	2946.84	4914.22	2.00	2.00	10162.77	27559.10	5.66	7.95

The first 2 subjects received BMS-232632 400 mg dose and the last subject received BMS-232632 600 mg dose. It is noted that there was about a 7- to 8- fold in BMS-

232632 exposure difference between the 2 subjects with 400 mg dose. The high variability and small number of subjects makes it difficult to come to any conclusions.

**CSF Penetration:**

AI424009: CSF samples were collected at Week 0 and 12 at least 3 hours or more after dosing with BMS-232632. No subject identifier or time of CSF sample collection was available. BMS-232632 was undetectable in the CSF of one subject; CSF concentration in the other two subjects was ~16 ng/mL at Week 12. The CSF concentrations were much lower than plasma trough concentrations of 103 – 2111 ng/mL.

AI424008: CSF samples were collected at Week 0, 12, 24, and 48 at least 3 hours or more after dosing with BMS-232632. CSF sampling is performed about the same time as plasma sampling. Ranges for the concentrations of BMS-232632 in plasma and cerebrospinal fluid (CSF) and for the CSF/plasma ratios on Week 12 are as follows:

BMS-232632 Dose	Study Week	Plasma Concentration (ng/mL)		CSF Concentration (ng/mL)		CSF/Plasma Ratio	
		n <sup>a</sup>	(Min, Max)	n <sup>a</sup>	(Min, Max)	n <sup>a</sup>	(Min, Max)
400 mg	Week 12	4		4		4	
600 mg	Week 12	3		6		3	

<sup>a</sup> n for ratios were different from n for concentrations if plasma and CSF concentrations were not available from the same subject

**Semen concentrations:**

Ranges for the concentrations of BMS-232632 in plasma and semen and for the semen/plasma ratios are as follows:

BMS-232632 Dose	Study Week	Plasma Concentration (ng/mL)		Semen Concentration (ng/mL)		Semen/Plasma Ratio	
		n <sup>a</sup>	(Min, Max)	n <sup>a</sup>	(Min, Max)	n <sup>a</sup>	(Min, Max)
400 mg	Week 12	5		5		5	
	Week 24	3		4		3	
	Week 48	1		2		1	
600 mg	Week 12	12		12		11	
	Week 24	10		9		8	
	Week 48	5		5		3	

<sup>a</sup> n for ratios were different from n for concentrations if plasma and semen concentrations were not available from the same subject

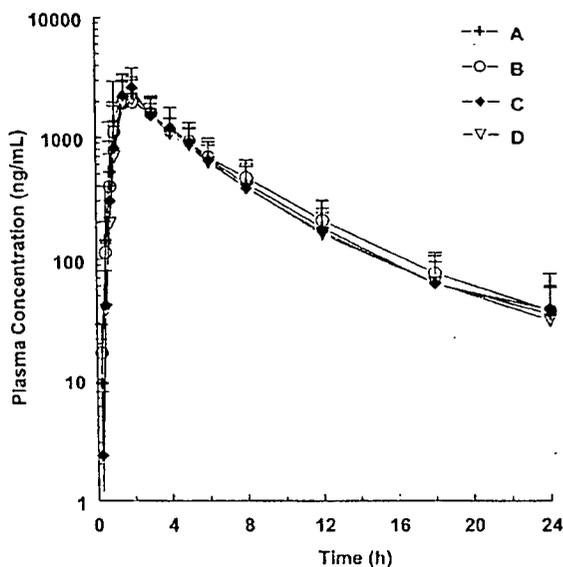
The data suggested that BMS-232632 is able to penetrate into the brain and testes.

**Conclusions:**

1. When administered with food, BMS-232632 exposures are about 50% lower (geometric mean) in HIV-infected subjects as compared to healthy subjects. It is not clear if the difference is due to non-standardized food used this Phase II study or disease state.
2. When administered under fed conditions, BMS-232632 exposures increased more than proportional with dose in HIV-infected subjects.
3. The geometric means for the steady-state accumulation ratios ranged from 1.64 to 4.74, with a 3-fold accumulation at 400 mg.
4. BMS-232632 is able to penetrate into the brain with CSF/plasma ratio ranging from \_\_\_\_\_
5. BMS-232632 is able to penetrate into the testes with seminal fluid/plasma ratio ranging from \_\_\_\_\_

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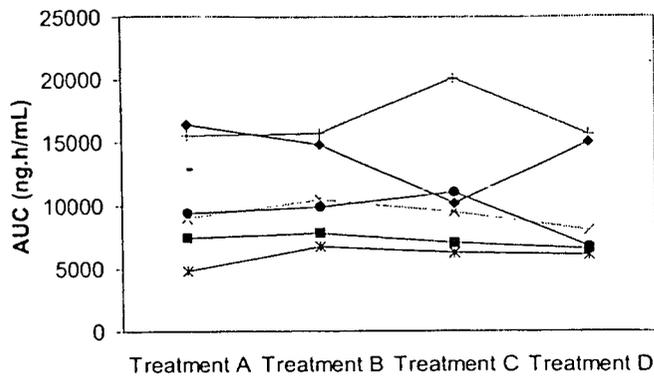
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Pharmacokinetic Parameter	Treatment <sup>a</sup>			
	A (n = 7) <sup>b</sup>	B (n = 7) <sup>b</sup>	C (n = 7) <sup>b</sup>	D (n = 7) <sup>b</sup>
C <sub>max</sub> (ng/mL)				
Geometric Mean	2244.19	2112.54	2912.09	2078.61
(C.V.%)	(55.03)	(31.71)	(34.36)	(41.95)
AUC(INF) (ng·h/mL)				
Geometric Mean	9932.67	10424.46	10114.80	9226.57
(C.V.%)	(39.65)	(30.70)	(42.19)	(41.50)
T <sub>max</sub> (h)				
Median	1.50	1.50	1.50	2.00
(Min, Max)				
T-half (h)				
Mean	4.48	4.68	5.05	4.90
(SD)	(0.78)	(0.60)	(1.61)	(0.94)

- a Treatment Codes:  
 A = 400 mg of BMS-232632 in \_\_\_\_\_ of oral powder formulation mixed with 4 oz of applesauce  
 B = 400 mg of BMS-232632 in \_\_\_\_\_ of oral powder formulation mixed with 50 mL of water  
 C = 400 mg of BMS-232632 (2 x 200 mg) in a capsule formulation  
 D = The contents of 2 x 200 mg BMS-232632 capsules mixed with 4 oz of applesauce
- b n = 7 as one subject dropped out of the study after Treatment Period 1 and therefore, the pharmacokinetic data for this subject are not included

The adjusted geometric means, ratio of geometric means, and 90% confidence intervals of the ratios are summarized in the following table for C<sub>max</sub> and AUC(INF).



According to the BA/BE Guidance, a BE study should typically be conducted under fasted conditions. Since this study is conducted under fed conditions, and is not powered to detect differences between            and capsules, we cannot conclude that the            and capsule are interchangeable.

**Conclusion:**

- Relative to the intact capsules, the AUC of BMS-232632 from the            formulation when administered with applesauce or water and from the contents of 2 x 200 mg capsules mixed with applesauce administered within 5 minutes of a light meal was 99.8%, 104.6%, and 91.7%, respectively.
- Relative to the intact capsule, the Cmax of BMS-232632 from the            formulation when administered with applesauce or water and from the contents of 2 x 200 mg capsules mixed with applesauce administered within 5 minutes of a light meal was 77.7%, 72.6%, and 71.7%, respectively.
- Since this study is conducted under fed conditions, and is not powered to detect differences between            and capsules, we cannot conclude that the            and capsule are interchangeable.

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- Pharmacokinetic and Safety Interaction Study of Didanosine, Stavudine and BMS-232632 in Healthy Subjects (Protocol A1424004)
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**Objective:** To determine if there is a drug-drug interaction between didanosine (ddl), stavudine (d4T) and BMS-232632 in Healthy Subjects

**Population:** 32 healthy male subjects were enrolled.

**Study Design:** This was an open-label, randomized, four-way crossover study. Subjects received the following regimens in a randomized order:

Treatment A: 400 mg BMS-232632

Treatment B: 200 mg ddl + 40 mg d4T

Treatment C: 200 mg ddl + 40 mg d4T + 400 mg BMS-232632

Treatment D: 200 mg ddl + 40 mg d4T followed one hour later by 400 mg BMS-232632

Study drug was administered after an 8-hour overnight fast. There was at least a 7-day washout period between doses.

**Formulation:** BMS-232632 200 mg capsules (Batch N98065), Videx ® 100 mg reduced mass tablets, Zerit ® 40 mg capsules

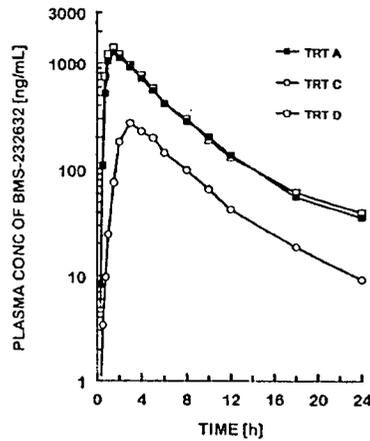
**Pharmacokinetic Sampling:** Subjects had blood samples for PK analysis collected at pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 18, and 24 hours after each dose of BMS-232632.

**Analytical Analysis:** BMS-232632 plasma concentrations were assayed by a validated method. Stavudine plasma concentrations were assayed by a validated method. Didanosine plasma concentrations were assayed by a validated method. The standard curve and QC data indicated that the plasma assay methods for BMS-232632 and ddl were precise and accurate, and the assay method for D4T was acceptable. See QBR for details.

#### **Pharmacokinetic Results:**

##### BMS-232632:

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



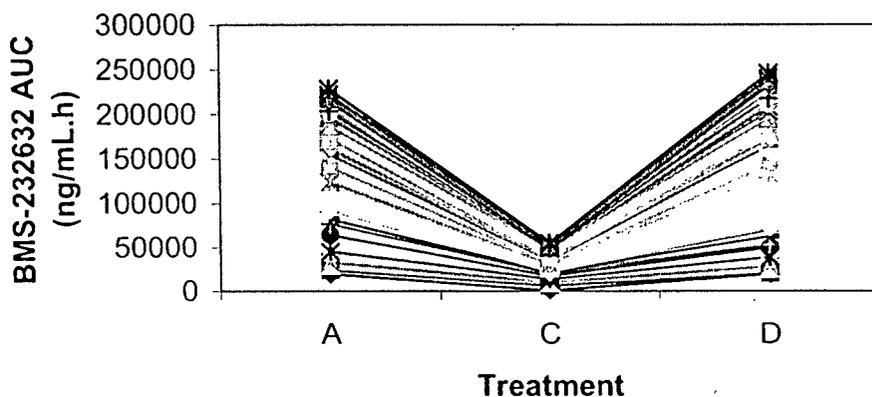
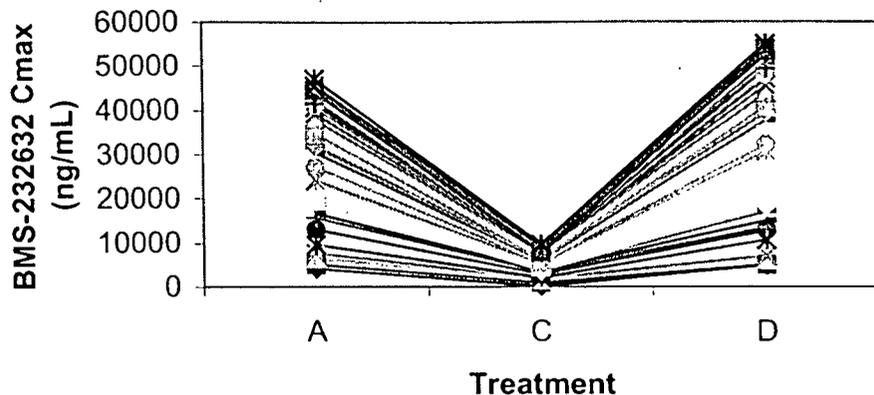
Pharmacokinetic Parameter	Treatment		
	A (n=32)	C (n=31)*	D (n=32)
C <sub>MAX</sub> (ng/mL)			
Mean	1471	309	1719
(SD)	(1185)	(406)	(1556)
AUC(INF) (ng·h/mL)			
Mean	7122	1786	7670
(SD)	(5995)	(2444)	(7328)
T-HALF (h)			
Mean	5.32	4.40	5.84
(SD)	(2.66)	(1.86)	(2.36)
T <sub>MAX</sub> (h)			
Median	1.50	3.00	1.25
(Min, Max)			

\* Subject 026 did not receive Treatment C

The geometric means, ratio of geometric means, and 90% confidence intervals of the ratios are summarized in the following table for C<sub>max</sub> and AUC(INF).

Pharmacokinetic Parameter	Treatment	Geometric Mean	Contrast	Ratios of Geo. Means Pt. Estimate (90% CI)
C <sub>MAX</sub> (ng/mL)	A	881.5		
	C	94.8	C vs. A	0.107 (0.064, 0.182)
	D	990.2	D vs. A	1.123 (0.670, 1.884)
AUC(INF) (ng·h/mL)	A	4515.7		
	C	586.6	C vs. A	0.130 (0.080, 0.212)
	D	4652.8	D vs. A	1.030 (0.637, 1.668)

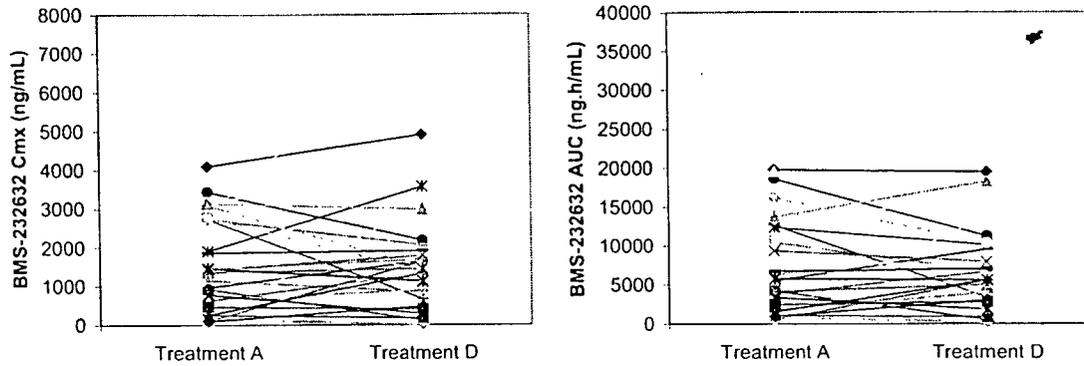
The following figures show the individual stick plots of C<sub>max</sub> and AUC for BMS-232632.



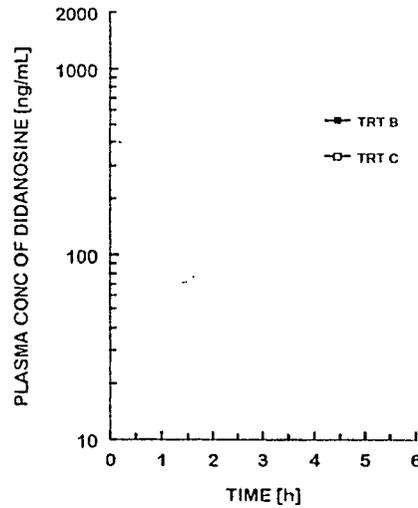
Simultaneous administration of BMS-232632, ddl and d4T (Treatment C) reduced BMS-232632 C<sub>max</sub> and AUC more than 80%. BMS-232632 (as the bisulfate salt) exhibits pH-dependent aqueous solubility, which decrease from 5.2 mg/mL at pH1.9 to 0.001 mg/mL at pH4.3. ddl is acid labile and its chewable/dispersible tablet is formulated with buffering agents. Therefore, the increase in gastric pH due to the presence of buffering agents in the ddl formulation probably reduced the solubility of BMS-232632 in the gastrointestinal fluid resulting in a decrease in the extent of absorption of BMS-232632. A similar effect has been reported for indinavir, when coadministered with ddl buffered formulation.

Administration of ddl plus d4T followed one hour later by BMS-232632 (Treatment D) had an indeterminate effect on BMS-232632 C<sub>max</sub> and AUC(INF) since 90% confidence intervals are outside the upper and lower boundaries of 80%-125% for both parameters, although point estimates show that there was no significant effect on C<sub>max</sub> or AUC. The following stick plot shows that there is great variability in the effect of ddl plus d4T on BMS-232632. Some subjects had more than a 10-fold increase in exposure, while others have a 3- to 4-fold decrease in exposures due to administration of ddl + d4T one hour before BMS-232632. It is not clear if these observations are due to intrasubject variability or other effects. BMS-232632 exposures in Treatment D were generally within the BMS-232632 exposure range in Treatment A. Therefore, BMS-232632 can be

administered one hour after the administration of didanosine reduced mass tablet and stavudine capsule to HIV-infected patients.



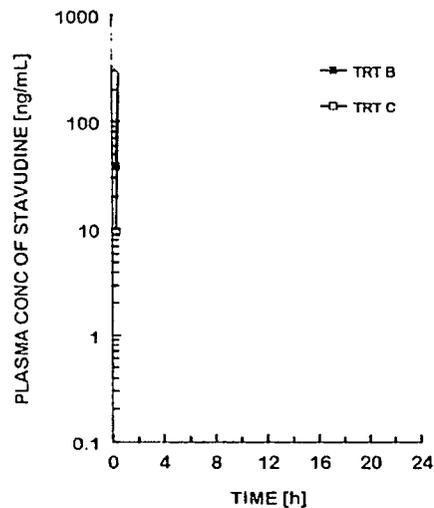
Didanosine: The following figure and tables show that BMS-232632 did not affect didanosine Cmax and AUC.



Pharmacokinetic Parameter (ddI)	Treatment	
	B (n=31)*	C (n=31)*
C <sub>MAX</sub> (ng/mL)		
Mean	942	856
(SD)	(379)	(319)
AUC(INF) (ng.h/mL)		
Mean	1480	1457
(SD)	(444)	(450)
T <sub>1/2</sub> (h)		
Mean	1.53	1.68
(SD)	(0.23)	(0.57)
T <sub>MAX</sub> (h)		
Median	0.50	0.50
(Min, Max)		

Pharmacokinetic Parameter (ddl)	Treatment	Geometric Mean	Contrast	Ratios of Geo. Means Pt. Estimate (90% CI)
C <sub>MAX</sub> (ng/mL)	B	874.1		
	C	808.8	C vs. B	0.925 (0.840, 1.020)
AUC(INF) (ng·h/mL)	B	1418.6		
	C	1394.2	C vs. B	0.983 (0.919, 1.052)

Stavudine: The following figure and tables show that BMS-232632 did not affect stavudine C<sub>max</sub> and AUC.



d4T Pharmacokinetic Parameter		B (n=31)*	C (n=31)*
C <sub>MAX</sub> (ng/mL)	Mean	596	643
	(SD)	(218)	(263)
AUC(INF) (ng·h/mL)	Mean	1553	1549
	(SD)	(235)	(265)
T-HALF (h)	Mean	2.40	2.50
	(SD)	(0.44)	(0.47)
T <sub>MAX</sub> (h)	Median (Min, Max)	0.75	0.75

Pharmacokinetic Parameter (d4T)	Treatment	Geometric Mean	Contrast	Ratios of Geo. Means Pt. Estimate (90% CI)
C <sub>MAX</sub> (ng/mL)	B	555.4	C vs. B	1.081 (0.955, 1.225)
	C	600.6		
AUC(INF) (ng·h/mL)	B	1523.4	C vs. B	1.002 (0.972, 1.033)
	C	1526.2		

**Conclusion:**

- BMS-232632 did not affect the pharmacokinetics of didanosine or stavudine when a 400 mg oral dose of BMS-232632 was coadministered with a 200 mg oral dose of didanosine reduced mass tablet and a 40 mg oral dose of stavudine capsule.
- Simultaneous administration of a 400 mg oral dose of BMS-232632 with a 200 mg dose of didanosine reduced mass tablet and 40 mg oral dose of stavudine resulted in > 80% lower BMS-232632 exposure.
- Administration of ddl plus d4T followed one hour later by BMS-232632 (Treatment D) had an indeterminate effect on BMS-232632 C<sub>max</sub> and AUC(INF) since 90% confidence intervals are outside the upper and lower boundaries of 80%-125% for both parameters, although point estimates show that there was no significant effect on C<sub>max</sub> or AUC.
- BMS-232632 can be administered one hour after the administration of didanosine reduced mass tablet and stavudine capsule to HIV-infected patients on combination therapy with these two drugs.

APPEARS TO BE  
ON 3/1/00

Open-Label, Pharmacokinetic Interaction Study of Lamivudine and Zidovudine  
(Combivir®) and BMS-232632 Administered with a Light Meal in Healthy Subjects  
(Protocol AI424027)

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**Objective:** To assess whether BMS-232632 when co-administered with Combivir® (150 mg lamivudine/300 mg zidovudine) has an effect on the steady-state pharmacokinetics of either zidovudine or lamivudine.

**Population:** Twenty (20) healthy subjects, aged 19 to 48 years, were enrolled in the study, 19 subject completed the study.

**Study Design:** This was an open-label, randomized study. All subjects were administered Combivir® BID for the first 6 days of the study, followed by Combivir® BID and BMS-232632 QD from Day 7 through Day 12. All doses were given in the morning within 5 minutes after a light meal given as breakfast.

**Formulation:** Combivir® (150 mg lamivudine and 300 mg zidovudine) tablet (Lot # OZP2002 expiration date November 2002); BMS-232632 200 mg capsules (Batch #C99274).

**Pharmacokinetic Sampling:** Blood samples for pharmacokinetic sampling were collected prior to dosing and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, and 12 hours after dosing on Days 6 and 12. Additional blood samples were collected at 16, 20, and 24 hours after dosing on Day 12. Trough levels (C<sub>min</sub>) were also obtained prior to the morning dose on Days 2, 4, 8, and 10.

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

**Pharmacokinetic Results:** Summary statistics for the pharmacokinetic parameters of lamivudine, zidovudine, zidovudine glucuronide, and BMS-232632 are presented in the table below.

Pharmacokinetic Parameter		Treatment <sup>a</sup>	
		Day 6	Day 12
<b>Lamivudine</b>			
C <sub>max</sub> (ng/mL)	Geometric Mean (%C.V.)	1578.35 (26.07)	1637.54 (24.45)
AUC(TAU) (ng·h/mL) <sup>b</sup>	Geometric Mean (%C.V.)	6135.94 (13.13)	6311.77 (16.05)
T <sub>max</sub> (h)	Median (Minimum, Maximum)	2.00	2.00
<b>Zidovudine</b>			
C <sub>max</sub> (ng/mL)	Geometric Mean (%C.V.)	1020.68 (39.15)	1067.49 (31.60)
AUC(TAU) (ng·h/mL) <sup>b</sup>	Geometric Mean (%C.V.)	1853.81 (18.63)	1942.35 (18.95)
T <sub>max</sub> (h)	Median (Minimum, Maximum)	1.50	1.50
<b>Zidovudine Glucuronide</b>			
C <sub>max</sub> (ng/mL)	Geometric Mean (%C.V.)	6135.60 (20.06)	5827.65 (22.51)
AUC(TAU) (ng·h/mL) <sup>b</sup>	Geometric Mean (%C.V.)	12365.70 (16.92)	12387.30 (18.37)
T <sub>max</sub> (h)	Median (Minimum, Maximum)	1.50	2.00
<b>BMS-232632</b>			
C <sub>max</sub> (ng/mL)	Geometric Mean (%C.V.)	--	4550.56 (26.06)
AUC(TAU) (ng·h/mL) <sup>b</sup>	Geometric Mean (%C.V.)	--	25078.59 (28.01)
T <sub>max</sub> (h)	Median (Minimum, Maximum)	--	2.00
t-1/2 <sub>ELF</sub> (h)	Mean (S.D.)	--	9.50 (4.37)

<sup>a</sup> Day 6: Administration of Combivir<sup>®</sup> (150 mg lamivudine + 300 mg zidovudine) BID; Day 12: Co-administration of Combivir<sup>®</sup> (150 mg lamivudine + 300 mg zidovudine) BID and 400 mg BMS-232632 QD

<sup>b</sup> TAU: 12 h for lamivudine, zidovudine, and zidovudine glucuronide and 24 h for BMS-232632

The geometric means, ratios of geometric means, and 90% confidence intervals for the ratios of geometric means for C<sub>max</sub> and AUC(TAU) of lamivudine, zidovudine, and zidovudine glucuronide are presented in the following table.

Pharmacokinetic Parameter	Geometric Means <sup>a</sup>		Ratio (90% Confidence Interval) Day 12/Day 6
	Day 6	Day 12	
Lamivudine			
C <sub>max</sub> (ng/mL)	1578.35	1637.54	1.038 (0.925, 1.163)
AUC(TAU) (ng·h/mL) <sup>b</sup>	6135.94	6311.77	1.029 (0.979, 1.081)
Zidovudine			
C <sub>max</sub> (ng/mL)	1020.68	1067.49	1.046 (0.884, 1.238)
AUC(TAU) (ng·h/mL) <sup>b</sup>	1853.81	1942.35	1.048 (0.964, 1.138)
Zidovudine Glucuronide			
C <sub>max</sub> (ng/mL)	6135.60	5827.65	0.950 (0.881, 1.024)
AUC(TAU) (ng·h/mL) <sup>b</sup>	12365.70	12387.30	1.002 (0.973, 1.031)

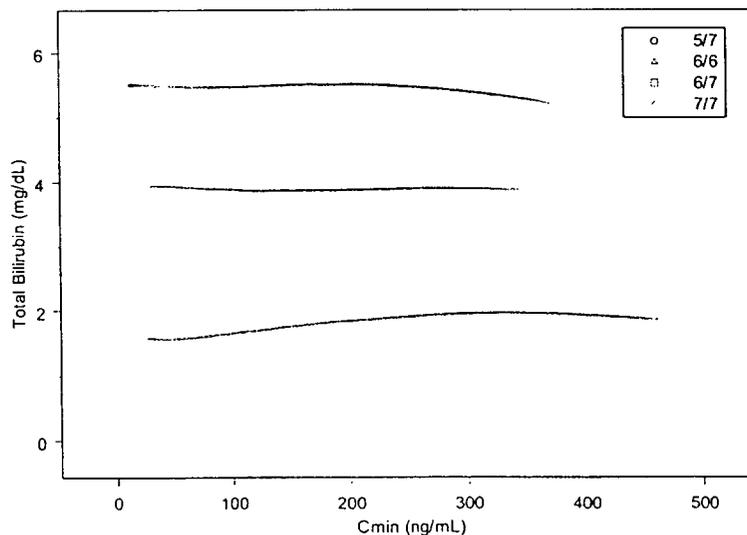
<sup>a</sup> Day 6: Administration of Combivir<sup>®</sup> (150 mg lamivudine + 300 mg zidovudine) BID;  
Day 12: Co-administration of Combivir<sup>®</sup> (150 mg lamivudine + 300 mg zidovudine) BID and 400 mg BMS-232632 QD

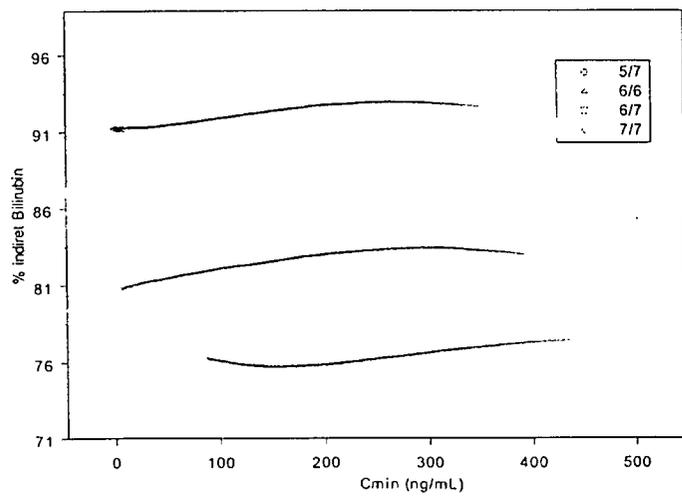
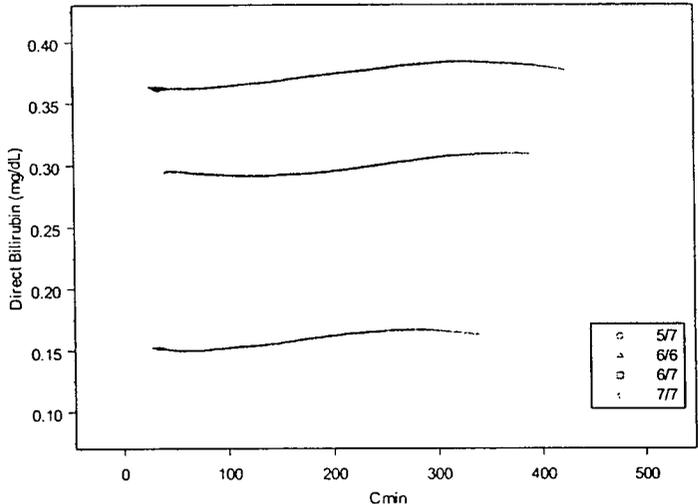
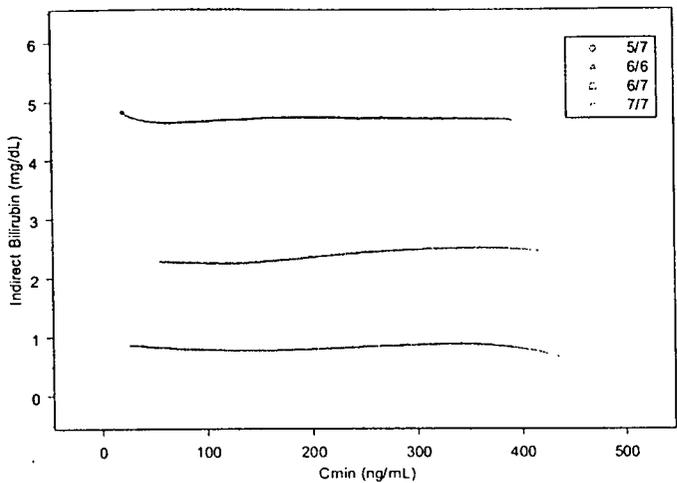
<sup>b</sup> TAU: 12 hours

Both C<sub>max</sub> and AUC(TAU) of lamivudine and zidovudine satisfied the criteria for concluding that BMS-232632 had no effect on the pharmacokinetics of lamivudine and zidovudine.

The atazanavir AUC values generated in this study are similar to the AUC values generated for atazanavir alone in other multiple dose studies in healthy subjects.

**Pharmacodynamic Results:** Serum bilirubin levels were determined. The following figures show C<sub>min</sub> vs. total bilirubin, indirect bilirubin, and % indirect bilirubin.





The study results are consistent with other studies, showing that both indirect and direct bilirubin had a tendency to increase with increased concentration of BMS-232632, and the magnitude of indirect bilirubin increase is higher in subjects with UDP-GT 1A1 genotype 6/7 as compared to genotype 6/6. Administration of BMS 232632 tended to increase % indirect bilirubin, especially in the subjects with genotype 6/7. Study AI424040 suggested bilirubin binding reached plateau at C<sub>min</sub> of BMS 232632 above 500 ng/mL. See the review for AI424040 for additional discussion.

**Conclusion:**

- BMS-232632 did not have an effect on the pharmacokinetics of lamivudine and zidovudine.
- The pharmacokinetics of zidovudine glucuronide were unaffected by the presence of BMS-232632.
- Comparison to previous data suggests that lamivudine and zidovudine did not affect the pharmacokinetics of BMS-232632.
- BMS-232632, lamivudine, and zidovudine may be co-administered without dose modification.
- When BMS-232632 is administered concomitantly with Combivir®, BMS-232632 tended to increase both indirect bilirubin and direct bilirubin, as observed when BMS-232632 was administered alone.
- The magnitude of the increase of indirect bilirubin by BMS-232632 and reduction of bilirubin conjugation were higher in subjects with UDP-GT 1A1 genotype 6/7 as compared to genotype 6/6.

APPEARS THIS WAY  
ON ORIGINAL

A Pilot Dose-Ranging Pharmacokinetic Interaction Study of BMS-232632 and Saquinavir (Protocol AI424012)

**Objective:** To determine the dosage(s) of saquinavir that, when combined with a fixed dose of BMS-232632, in healthy subjects would produce saquinavir trough levels in the range of those observed for a saquinavir/ritonavir combination (saquinavir C<sub>min</sub> = 600 ± 400 ng/mL).

**Population:** Twenty-four healthy white male subjects, age 18 to 50 years, with a body mass index of > 18 and < 30 kg/m<sup>2</sup>, a body weight > 60 kg, normal baseline serum creatinine and liver enzymes, and calculated creatinine clearance > 80 mL/min were enrolled.

**Study Design:** This was an open-label, randomized pilot study. Enrolled subjects received once daily oral doses of saquinavir as a single agent on Days 1 through 6 according to the treatment group randomization listed below, followed by the combination of once daily oral doses of saquinavir and 400 mg BMS-232632 on Days 7 through 13.

- 1) Saquinavir 800 mg QD
- 2) Saquinavir 1200 mg QD
- 3) Saquinavir 1600 mg QD

All doses of study drug were administered with a standard high fat breakfast shown in the following table.

Food Item	Calories	Fat (g)	Carbohydrates (g)	Protein (g)
2 eggs (fried in butter)	203	16.2	1.2	12.2
2 slices white bread toasted and buttered	128	1.8	23.4	4.2
1 teaspoonful butter	36	4.1	trace	0
1 tablespoon jelly	55	trace	14.1	trace
2 strips bacon	70	6.2	0.2	3.2
4 oz hash brown potatoes	72	0.1	16.4	1.8
8 oz of whole milk	157	8.9	11.4	8
Total	721	37.3	66.7	29.4
% Total Calories	100	47	37	16

**Formulation:** Saquinavir 200 mg soft gelatin capsules (Fortovase®, Batch 0200); BMS-232632 200 mg capsules (Batches N98178 and N98065).

**Pharmacokinetic Sampling:** On Days 2, 4, 5, 8, 10, and 12, plasma samples for morning pre-dose trough levels of saquinavir and BMS-232632 (only Days 8, 10, and 12) were obtained. Days 6 and 13 plasma samples were obtained at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 20, and 24 hours for pharmacokinetic assessment of saquinavir and BMS-232632 (Day 13). Blood samples for assessment of bilirubin (total and indirect) were obtained on Days 2, 4, 5, 8, 10, 12, and 14.

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

**Pharmacokinetic/Pharmacodynamic Results:**

Saquinavir

The steady-state pharmacokinetic parameters of saquinavir are summarized below:

Pharmacokinetic Parameter	Saquinavir Dose <sup>a</sup>					
	800 mg		1200 mg		1600 mg	
	Day 6 (n = 7)	Day 13 (n = 7)	Day 6 (n = 7)	Day 13 (n = 7)	Day 6 (n = 6)	Day 13 (n = 6)
C <sub>max</sub> (ng/mL)	580.41	3544.44	1007.90	4426.18	1353.39	6414.76
Geometric Mean (C.V. %)	(54.25)	(17.86)	(50.55)	(16.24)	(47.08)	(25.14)
AUC(TAU) (ng·h/mL)	1409.48	13270.92	3553.32	19520.95	3856.78	29211.55
Geometric Mean (C.V. %)	(63.05)	(32.79)	(36.21)	(17.62)	(38.35)	(35.08)
T <sub>max</sub> (h)	2.0	2.5	2.5	2.5	1.5	2.5
Median (Min, Max)						
T-HALF (h)	7.25	9.69	9.04	8.05	9.67	5.64
Mean (S.D.)	(1.55)	(5.45)	(1.51)	(2.14)	(1.77)	(0.89)

<sup>a</sup> Treatments: Day 6 = 800, 1200, or 1600 mg saquinavir QD administered alone  
 Day 13 = 800, 1200, or 1600 mg saquinavir QD co-administered with 400 mg BMS-232632 QD

The geometric means and 90% confidence intervals for the ratios of combination therapy to monotherapy for saquinavir C<sub>max</sub> and AUC(TAU) geometric means are provided in the table below:

Pharmacokinetic Parameter Day 13/Day 6 Ratio	Saquinavir Dose <sup>a</sup>		
	800 mg (n = 7)	1200 mg (n = 7)	1600 mg (n = 6)
C <sub>max</sub> (ng/mL)	6.11	4.39	4.74
Ratio of Geometric Means (90% C.I.)	(4.51, 8.27)	(3.24, 5.95)	(3.42, 6.58)
AUC(TAU) (ng·h/mL)	9.42	5.49	7.57
Ratio of Geometric Means (90% C.I.)	(6.93, 12.80)	(4.04, 7.47)	(5.44, 10.55)

<sup>a</sup> Treatments: Day 6 = 800, 1200, or 1600 mg saquinavir QD administered alone  
 Day 13 = 800, 1200, or 1600 mg saquinavir QD co-administered with 400 mg BMS-232632 QD

The data show that co-administration of BMS-232632 with 800 mg, 1200 mg, and 1600 mg of saquinavir increased the steady-state C<sub>max</sub> and AUC(TAU) of saquinavir. Furthermore, the increase in saquinavir exposure was dose-proportional. The intersubject variability for steady-state C<sub>max</sub> and AUC(TAU) values for saquinavir monotherapy were observed to be approximately 47-54% and 36-63%, respectively.

These were reduced to 16-25% (C<sub>max</sub>) and 18-35% [AUC(TAU)], respectively, after combination therapy. The half-life of saquinavir when administered alone was comparable to the values obtained when administered in combination with BMS-232632. The latter suggests that BMS-232632 did not change the terminal elimination of saquinavir; rather it increased the bioavailability of the compound.

*Reviewer's comment: The in vitro study using Caco-2 cells with P-gp substrate digoxin suggested that BMS-232632 is a weak inhibitor of P-gp with an IC<sub>50</sub> of 29 μM (20 μg/mL). Although the IC<sub>50</sub> is much higher than the observed BMS-232632 concentrations in this study, there could be substrate specific inhibition of P-gp. In addition in vitro-in vivo correlation for P-gp is not fully understood. This study showed BMS-232632 increased the bioavailability of saquinavir but did not alter disposition, which suggested that BMS-232632 inhibited either gut CYP3A4 or efflux transporter or both. As suggested by inhibition of P-gp in gut could increase drug's inhibition effect on gut CYP3A4. In contrast, inhibition of P-gp in liver could reduce the AUC of saquinavir. When this effect combines with the increase of AUC of saquinavir due to inhibition of CYP3A4 by BMS-232632, it could cancel out the effect of BMS-232632 on saquinavir elimination. Therefore, only the effect of BMS-232632 on the bioavailability of saquinavir was observed.*

Saquinavir coadministration with BMS-232632 resulted in lower steady-state trough concentrations of saquinavir in the study (mean C<sub>min</sub> = 128 ng/mL) than those reported following the coadministration of saquinavir (Fortovase®) with ritonavir (400/400 mg BID, mean C<sub>min</sub> is about 600 ng/mL). The combination of BMS-232632 and saquinavir 1200 mg QD produced daily exposures AUC<sub>24</sub> similar to the values produced by the standard therapeutic dosing of saquinavir at 1200 mg TID. However, the C<sub>max</sub> is about 79% higher than that for the standard dosing of saquinavir alone at 1200 mg TID. Coadministration of 400 mg ritonavir with 400 mg saquinavir (Fortovase®) BID is also used in the clinic although it is not approved. In this regimen, RTV increases SQV AUC and C<sub>max</sub> by 121% and 64% as compared to standard dosing of saquinavir alone at 1200 mg TID. Therefore, the C<sub>max</sub> for saquinavir coadministered with BMS-232632 is about 23% higher than that for 400 mg saquinavir combined with 400 mg RTV BID, with lowered AUC. It is not clear if the increased C<sub>max</sub> is clinically significant. Saquinavir/ BMS-232632 1200/400 mg QD are used in the ongoing Phase III clinical trial (AI424045). The preliminary data show that Saquinavir/ BMS-232632 combination regiment is not as effective as BMS-232632/ritonavir nor as Kaletra. Therefore, appropriate dosing recommendations for saquinavir/ritonavir combination, with respect to efficacy and safety, have not been established.

### BMS-232632

The steady-state pharmacokinetic parameters of BMS-232632 on Day 13 are listed in the following table. The pharmacokinetics of BMS-232632 appeared to be unchanged as saquinavir dose increased. The mean steady C<sub>max</sub> and AUC observed for BMS-232632 in the current study (C<sub>max</sub> = 4250-4582 ng/mL, AUC = 30351-31963 ng.h/mL, after high fat meal) were similar to the mean values in previously reported in healthy subjects after a light meal (C<sub>max</sub> = 4225-5500 ng/mL, AUC = 23469 –33100 ng.h/mL, Study AI424040 and AI424076). While Study AI424003 suggested that BMS-232632 exposure is lower after a high fat meal as compared to a light meal, AUC appeared to be 2-fold higher in this study than the AUC(INF) after single dose with a high fat meal (10847 ng.h/mL,

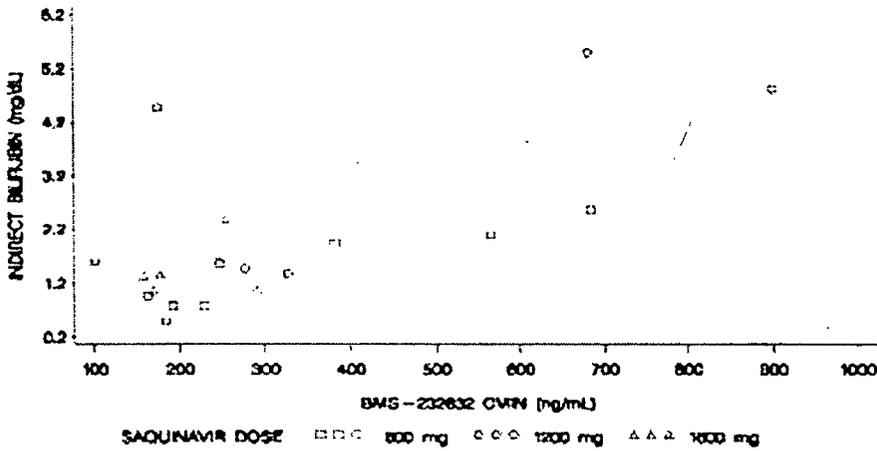
Study AI424003). Therefore, although the pharmacokinetics of BMS-232632 appeared to be unchanged over the different concomitantly administered doses of saquinavir, there are not enough data to conclude saquinavir does not affect the pharmacokinetics of BMS-232632.

Pharmacokinetic Parameter (BMS-232632)	Saquinavir Dose <sup>a</sup>		
	800 mg (n = 7)	1200 mg (n = 7)	1600 mg (n = 6)
C <sub>max</sub> (ng/mL)	4582.58	4411.06	4249.53
Geometric Mean (C.V. %)	(24.52)	(18.09)	(11.54)
AUC(TAU) (ng·h/mL)	31861.94	31962.58	30351.35
Geometric Mean (C.V. %)	(28.05)	(25.26)	(10.91)
T <sub>max</sub> (h)	3.00	4.00	3.00
Median (Min, Max)	-----		
T-HALF (h)	9.76	9.95	7.08
Mean (S.D.)	(4.13)	(2.37)	(3.25)

<sup>a</sup> Treatments: Day 13 = 800, 1200, or 1600 mg Saquinavir QD co-administered with 400 mg BMS-232632 QD

Bilirubin

SCATTER PLOT OF DAY 12 PRE-DOSE INDIRECT BILIRUBIN LEVELS VS DAY 12 BMS-232632 C<sub>MAX</sub>





The study showed that no apparent relationship at any dose level was observed between bilirubin levels (total and indirect) and saquinavir trough plasma concentrations on Day 5. Bilirubin levels (total and indirect) tended to increase with increasing trough plasma concentrations of BMS-232632 (in the presence of saquinavir) on Day 12.

**Conclusion:**

- Once-daily administration of BMS-232632 for 7 days with 800 mg, 1200 mg, and 1600 mg of saquinavir, resulted in a 6.1, 4.4, and 4.7 fold increase in the steady-state saquinavir C<sub>max</sub> and a 9.4, 5.5, and 7.6 fold increase in saquinavir AUC(TAU), as compared to saquinavir therapy alone.
- Saquinavir steady-state trough levels of 600 ± 400 ng/mL (as observed with saquinavir/ritonavir 400/400 mg combination) were not achieved at any of the saquinavir doses.
- Co-administration of BMS-232632 reduced the intersubject variability in steady-state saquinavir exposure by more than half.
- The pharmacokinetics of BMS-232632 appeared to be unchanged over the different concomitantly administered doses of saquinavir. However, the exposure of BMS-232632 in this study may be higher than that previously reported with a high fat meal.
- Coadministration of saquinavir at 1200 mg QD with BMS-232632 at 400 mg QD produced saquinavir exposures similar to published values for the approved saquinavir alone dosing regimen at 1200 mg TID.
- Coadministration of saquinavir at 1200 mg QD with BMS-232632 at 400 mg QD produced 79% higher C<sub>max</sub> than that for the standard dosing of saquinavir alone at 1200 mg TID, and 23% higher than that in 400 mg saquinavir combined with 400 mg RTV BID.
- No apparent relationship at any dose level was observed between bilirubin levels (total and indirect) and saquinavir trough plasma concentrations on Day 5.
- Bilirubin levels (total and indirect) tended to increase with increasing trough plasma concentrations of BMS-232632 (in the presence of saquinavir) on Day 12.

APPEARS THIS WAY  
ON ORIGINAL

An Evaluation of the Effect of Ketoconazole Upon the Steady-State Pharmacokinetics of  
BMS-232632 Administered with a Light Meal (Protocol AI424013)

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**Objective:** To determine the effect of ketoconazole upon the steady-state pharmacokinetics of BMS-232632 in the presence of a light meal.

**Population:** A total of 16 healthy subjects (12 males and 4 females) who met the inclusion/exclusion criteria participated in the study. The age ranged from 19 to 47 years with an average of 28 years.

**Study Design:** This was an open-label, non-randomized, single-sequence study. Subjects were administered 400 mg BMS-232632 once daily for six days followed by seven days of once daily ketoconazole (200 mg) co-administered with BMS-232632 (400 mg). All medications were given within 5 minutes of completion of a light meal.

**Formulation:** 200 mg BMS-232632 capsules (Batch N98178), and 200 mg Ketoconazole tablets (Batch 98P0579E).

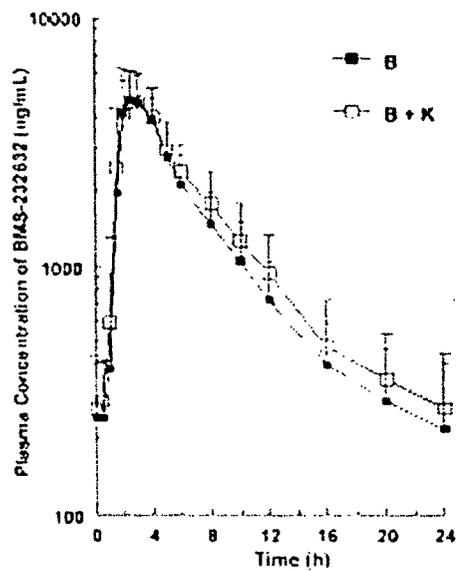
**Pharmacokinetic Sampling:** Blood samples were collected prior to dosing and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 20, and 24 h after dosing on Days 6 and 13 for measurement of BMS-232632 and ketoconazole (only Day 13). Blood samples were collected for trough (C<sub>min</sub>) levels for measurement of BMS-232632 on Days 1 (pre-dose), 3, 4, and 5 and for measurement of BMS-232632 and ketoconazole on Days 10, 11, and 12. Blood samples for bilirubin (total, direct and indirect) analysis were collected on Days 1, 3, 4, 5, 6, 7, 10, 11, 12, 13 and 14.

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

**Pharmacokinetic Results:**

BMS-232632

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



Pharmacokinetics of BMS-232632

Pharmacokinetic Parameter	Treatment <sup>a</sup>	
	B (Day 6) (n = 14)	B + K (Day 13) (n = 14)
C <sub>max</sub> (ng/mL)		
Geometric Mean (C.V. %)	5198.59 (25.59)	5145.81 (29.31)
AUC(TAU) (ng·h/mL) <sup>b</sup>		
Geometric Mean (C.V. %)	28132.00 (28.20)	31054.51 (27.88)
T <sub>max</sub> (h)		
Median (Min, Max)	2.50	2.25
T-1/2 (h)		
Mean (S.D.)	7.88 (2.94)	8.86 (3.58)

AI-24-013

Source: Supplemental Table S.11.3.1C

a Treatment codes:

B = BMS-232632 at 400 mg QD

B + K = Co-administration of BMS-232632 at 400 mg QD and ketoconazole at 200 mg QD

b TAU = 24 h

Statistical analyses of BMS-232632 C<sub>max</sub> and AUC(TAU) are summarized in the following table.

Pharmacokinetic Parameter	Geometric Means <sup>a</sup>		Ratio (90% Confidence Interval)	
	B (n = 14)	B + K (n = 14)	(B + K) / B	(0.889, 1.371)
C <sub>max</sub> (ng/mL)	5198.59	5145.81	0.990	(0.768, 1.276)
AUC(TAU) (ng·h/mL) <sup>b</sup>	28132.00	31054.51	1.104	(0.889, 1.371)

a Treatment codes:

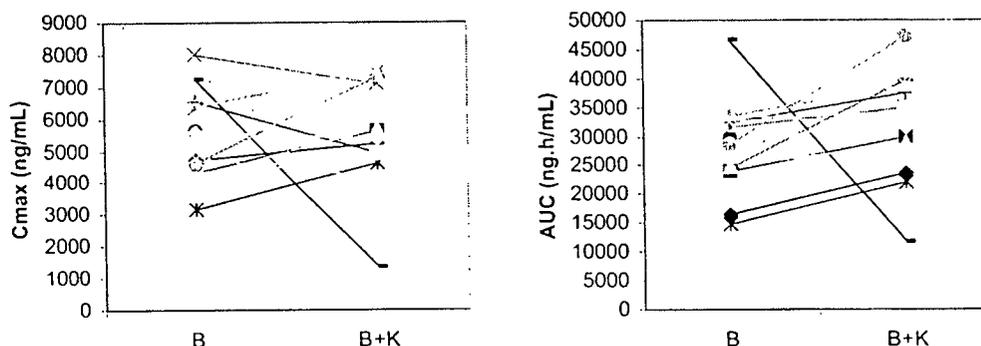
B = BMS-232632 at 400 mg QD

B + K = Co-administration of BMS-232632 at 400 mg QD and ketoconazole at 200 mg QD

b TAU = 24 h

The geometric means of Cmax and AUC for BMS-232632 alone are within the range of Cmax and AUC in healthy subjects. The geometric means for BMS-232632 Cmax and AUC(TAU) after co-administration of BMS-232632 and ketoconazole were 99.0% and 110.4%, respectively, of those after administration of BMS-232632 alone.

The following stick plot shows that there was one subject whose Cmax and AUC were reduced by 81%, 75%, respectively, when BMS-232632 was administered with ketoconazole. If this subject was excluded, ketoconazole will increase BMS-232632 Cmax and AUC by 13% and 24% respectively. Ketoconazole is a potent CYP3A4 inhibitor, and was expected to increase the exposure of BMS-232632. It is surprising to see there was not much effect of ketoconazole on the pharmacokinetics of BMS-232632. It is not known whether 400 mg of ketoconazole can affect the pharmacokinetics of BMS-232632.



### Ketoconazole

The steady-state plasma concentrations of ketoconazole following 200 mg once-daily doses coadministered with BMS-232632 (Cmax = 6.26 µg/mL, AUC = 52.82 µg.h/mL) appeared to be higher than those previously reported for ketoconazole alone (Cmax = 4.65-5.23 µg/mL, AUC = 24.14- 28.8 µg.h/mL). This difference from literature values could be attributed to the fact that previous studies were conducted in fasting conditions while a light meal was coadministered in the current study. There are reports indicating that food may enhance the absorption of ketoconazole following single doses. It is to be noted that ketoconazole exposure after once-daily doses of 200 mg in this study is comparable to that following a single dose of 400 mg with food (AUC = 59.2 µg.h/mL). Clinically, both 200 mg and 400 mg once-daily doses are fully approved for treatment of fungal infections; the 400 mg dose is typically employed in more serious or recalcitrant fungal infections. Therefore, ketoconazole dose would not need to be adjusted upon coadministration with BMS-232632.

### Bilirubin

Interestingly, 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.