CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-711/S-009
50-710/S-011

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

NDA#	50-670/S-018, 50-693/S-006, 50-710/S-011,.50-711/S-009, 50-730/S-008, 50-733/S-007
PRODUCT	Azithromycin (Zithromax®)
FORMULATIONS	250 mg capsules, 1 g sachets, powder for oral suspension, 250 mg tablets, 600 mg tablets, powder for injection
SUBMISSION DATE	February 7, 2001
SUBMISSION TYPE	Labeling Supplement
SPONSOR	Pfizer, Inc.
REVIEWER	Charles R. Bonapace, Pharm.D.
ACTING TEAM LEADER	Sue-Chih Lee, Ph.D.

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

SYNOPSIS

The sponsor submitted a labeling supplement for NDAs 50-670, 50-693, 50-710, 50-711, 50-730, and 50-733 to address the effect of renal impairment and hepatic impairment on the pharmacokinetics of azithromycin as well as the results of drug interaction studies of azithromycin co-administered with oral theophylline, oral midazolam, atorvastatin, cetirizine, sildenafil, and carbamazepine.

The administration of a single 1,000 mg dose of azithromycin to subjects with GFR ≤80 to ≥10 mL/min resulted in an increase in the C_{max} and AUC_{0-120} of 4.8% and 4.2%, respectively. The C_{max} and AUC_{0-120} increased 60.0% and 34.7%, respectively in subjects with GFR <10 mL/min.

Azithromycin pharmacokinetics were determined in subjects with hepatic impairment following the administration of a single 500 mg dose of azithromycin. However, due to questionable analytical data and missing plasma and urine data, the study is not acceptable.

Co-administration of azithromycin (500 mg PO × 1 day, then 250 mg PO × 4 days) to subjects at theophylline steady-state (300 mg PO BID) resulted in an increase in the theophylline mean C_{max} and AUC_{0-12} values approximately 8% compared to baseline after administering azithromycin for 5 days. There appeared to be no difference in the incidence of adverse events between subjects receiving theophylline co-administered with azithromycin or placebo.

Pretreatment with azithromycin (500 mg PO QD × 3 days) or erythromycin (500 mg PO TID × 5 days) followed by a single 15 mg dose of oral midazolam increased midazolam plasma concentrations and exposure. Following erythromycin pretreatment, the midazolam mean C_{max} and $AUC_{0-\infty}$ increased by 171% and 281%, respectively whereas the midazolam mean C_{max} and $AUC_{0-\infty}$ increased by 29% and 27%, respectively following azithromycin pretreatment. Pharmacodynamic measurements demonstrated that erythromycin significantly increased the sedation caused by midazolam, whereas no statistically significant changes were detected with azithromycin.

Co-administration of azithromycin (500 mg PO QD × 3 days) or clarithromycin (500 mg PO BID × 3 days) and atorvastatin (10 mg PO QD) to subjects at steady-state for atorvastatin altered the atorvastatin pharmacokinetics. Clarithromycin increased the atorvastatin mean C_{max} and AUC_{0-24} by 55.7% and 90.4%, respectively whereas azithromycin decreased the atorvastatin mean C_{max} by 15.5% and increased the atorvastatin mean AUC_{0-24} by 2.4%. The changes following co-administration with azithromycin

were similar to placebo, although there was a large degree of inter-subject variability. The incidence of side effects between subjects receiving azithromycin or placebo were similar.

Co-administration of cetirizine (20 mg PO QD) at steady-state and azithromycin (500 mg PO × 1 day, then 250 mg PO × 4 days) increased the cetirizine mean C_{max} and AUC_{0-24} by 3.2% and 1.9%, respectively. The addition of azithromycin to cetirizine treatment appears to have no additional effect on QTc changes.

Co-administration of a single 100 mg dose of oral sildenafil following azithromycin 500 mg PO QD × 3 days increased the sildenafil mean C_{max} by 15.7% whereas it decreased the sildenafil mean $AUC_{0-\infty}$ by 7.1%. There was a large degree of inter-subject variability in the azithromycin and placebo groups. The incidence of treatment related adverse events was similar when sildenafil was administered with azithromycin or placebo.

Co-administration of carbamazepine 200 mg PO Q12h at steady-state with azithromycin (500 mg PO × 3 days) decreased the carbamazepine mean C_{max} and AUC_{0-12} by 3.6% and 4.0%. Subjects receiving carbamazepine + azithromycin were associated with a similar incidence of adverse events compared to subjects receiving carbamazepine + placebo.

Co-administration of a single 0.125 mg dose of oral triazolam and azithromycin (500 mg PO on day 1, then 250 mg on day 2) increased the triazolam mean C_{max} and $AUC_{0-\infty}$ by 5.6% and 1.8%, respectively. The apparent oral clearance of triazolam was unchanged. Pharmacodynamic measurements demonstrated that there were no statistically significant changes when triazolam was administered with azithromycin.

Cross-reference from NDA 21-363: Co-administration of desloratadine 5 mg PO QD at steady-state and azithromycin (500 mg PO on day 1, then 250 mg/day for 4 days) increased the desloratadine mean C_{max} and AUC_{0-24} by 19% and 8%, respectively. The mean C_{max} and AUC_{0-24} of 3-OH-desloratadine were increased by 14% and 3%, respectively. No significant changes in ECG parameters were observed for the comparison of desloratadine alone or in combination with azithromycin.

LABELING RECOMMENDATIONS:

The administration of sildenafil following azithromycin 500 mg PO QD × 3 days increased the sildenafil mean C_{max} by 15.7% whereas it decreased the sildenafil mean $AUC_{0-\infty}$ by 7.1%. Although azithromycin increased the peak sildenafil plasma concentrations, the data were highly variable and no dosage adjustment of sildenafil is warranted in patients receiving azithromycin.

No dosage adjustment of carbamazepine, triazolam, or desloratadine is warranted when co-administered with azithromycin.

COMMENTS:

1. The hepatic impairment study (AZM-I-90-001) is unacceptable due to the limited number of subjects evaluated for pharmacokinetic and safety data, the degree of inter-subject variability, missing plasma and urine concentrations, and questionable validation of the azithromycin serum assay for the quantitation of plasma samples. The label should reflect this finding.

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RECOMMENDATIONS:

The sponsor's proposed label is not acceptable from a clinical pharmacology and biopharmaceutics point of view. The sponsor should revise their label as recommended.

Please forward comments #1-4 to the sponsor and the reviewing medical officer.

Charles R. Bonapace, Pharm.D.
Office of Clinical Pharmacology/Biopharmaceutics
Division of Pharmaceutical Evaluation III

RD/FT Initialed by Sue-Chih Lee, Ph.D., Acting Team Leader_____

cc:
Division File: NDAs 50-670, 50-693, 50-710, 50-711, 50-730, 50-733
HFD-520 (CSO/Milstein)
HFD-880 (Division File, Lazor, Lee, Bonapace)
CDR (Clin. Pharm./Biopharm.)

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Study AZM-NY-90-008: An Open Study to Evaluate the Pharmacokinetics of Azithromycin When Administered to Subjects With Varying Degrees of Renal Impairment

Date: July 5, 1991 to March 17, 1992
Clinical Site: [redacted]

Analytical Site: Not stated

OBJECTIVES:
To determine the pharmacokinetics and safety of azithromycin when administered to subjects with varying degrees of renal impairment.

FORMULATION:
Azithromycin 250 mg capsules (Lot No. ED-G251-890, FID No. YY-89-051)

STUDY DESIGN:
An open-label, single-dose, multi-center pharmacokinetic study of oral azithromycin 1 gram (4 x 250 mg capsules) administered to fasted male and female adult subjects one hour before a standardized meal with normal renal function (Glomerular Filtration Rate [GFR] >80 mL/min, Group I), mild/moderate renal impairment (GFR ≤80 to ≥10 mL/min, Group II), or severe renal impairment (GFR <10 mL/min, Group III). Subjects in Group III undergoing hemodialysis were administered the dose of azithromycin after hemodialysis was completed. The GFR in subjects with normal renal function was estimated from creatinine clearance based on a 24-hour urine collection, whereas the Cr^{51}-EDTA clearance was used to estimate GFR in subjects with renal impairment. Subjects received azithromycin after an overnight fast of at least 8 hours.

Blood samples were collected for 120 hours at the following times: predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 24, 48, 72, 96, and 120 hrs following administration.

Urine samples were collected for 72 hours at the following intervals: 0 to 2, 2 to 4, 4 to 8, 8 to 24, 24 to 48, and 48 to 72 hrs following administration.

[redacted]

High performance liquid chromatography with [redacted] (HPLC) [redacted]

Criterion	Plasma	Comments
Concentration range	[redacted]	Satisfactory
LLOQ		Satisfactory
Linearity	R^2 ≥0.999	Satisfactory
Accuracy	97.6% to 98.0%	Satisfactory
Precision (% CV)	6.1% to 7.6%	Satisfactory
Specificity	Satisfactory	Satisfactory
Stability	Long-term -20°C, short-term at RT, post-preparation stability	Satisfactory

AZITHROMYCIN URINE ASSAY METHODOLOGY:
High performance liquid chromatography with electrochemical detection (HPLC/EC)

Criterion	Urine	Comments
Concentration range	[redacted]	Satisfactory
LLOQ	[redacted]	Satisfactory
Linearity	$R^2 \geq 0.999$	Satisfactory
Accuracy	100.5% to 109.3%	Satisfactory
Precision (% CV)	4.2% to 9.1%	Satisfactory
Specificity	Satisfactory	Satisfactory
Stability	Long-term -20°C, short-term at RT, post-preparation stability	Satisfactory

DATA ANALYSIS:
The maximum observed plasma concentration (C_{max}) was estimated directly from the observed plasma concentration-time data. T_{max} was defined as the time corresponding to the occurrence of C_{max}. The terminal phase elimination rate constant (k_{el}) was estimated using linear least squares regression analysis of the azithromycin plasma concentration-time data obtained during the terminal log-linear phase. The area under the serum concentration time curve from 0-120 hours (AUC_{0-120}) was estimated using the linear trapezoidal approximation. The amount of unchanged azithromycin excreted in urine over 72 hours (Xu_{0-72}) was calculated from urine concentrations and urine volume. The renal clearance (CL_R) was calculated as the ratio of Xu_{0-72}/plasma AUC_{0-72}.

STATISTICAL ANALYSIS:
Pharmacokinetic parameters (log-transformed AUC_{0-120}, log-transformed C_{max}, T_{max}, and CL_R) were compared using a one-way ANOVA with 95% confidence intervals. Also, 95% confidence intervals on the ratios of the geometric means of AUC_{0-120} and C_{max} were calculated by back-transforming the confidence intervals of the differences in $\log_{10}(AUC_{0-120})$ and $\log_{10}(C_{max})$, respectively. A correlation analysis of AUC_{0-120}, C_{max}, and CL_R with GFR was performed using Pearson's product-moment correlations.

The reviewer compared the geometric mean ratios and 90% confidence intervals of C_{max} and AUC_{0-120} using the PROC GLM of SAS version 6.12. These results were compared to those calculated by the sponsor.

RESULTS:
One subject in Group III vomited after receiving the azithromycin dose and was excluded from the pharmacokinetic analysis. The demographics of the remaining 42 subjects are shown in Table 1 below.

Table 1. Mean (SD) demographic data for all subjects by renal function

Renal function	Group	N	Gender	Age (years)	Height (cm)	Weight (kg)	GFR (mL/min)
Normal renal function	I	12	6M/6F	27.3 (5.4)	174.0 (9.2)	66.8 (11.2)	101.0 (20.1)
Mild/moderate renal impairment	II	12	7M/5F	54.2 (15.8)	166.5 (9.4)	75.0 (13.9)	27.8 (20.7)
Severe renal impairment (w/o dialysis)	III	18	12M/6F	58.7 (17.2)	169.5 (8.5)	66.8 (12.4)	3.1 (2.1)

Subjects in Group I ranged in age from 21 to 36 years, Group II ranged from 25 to 79 years, and Group III ranged from 21 to 85 years.

The azithromycin plasma concentration-time profiles for each subject are shown in Figure 1. Plasma concentrations are shown for only 24 hours to emphasize differences immediately following administration. The azithromycin concentrations from subjects with normal renal function (Group I) were similar to subjects with mild/moderate renal impairment (Group II). However, subjects with severe renal impairment (Group III) were associated with greater plasma concentrations than either Group I or Group II. These findings are also illustrated in the mean concentration-time profiles shown in Figure 2.

The pharmacokinetic parameters for each group are shown in Table 2. The sponsor reported that inadequate plasma samples were obtained to estimate the terminal elimination phase. Thus, the $AUC_{0\text{-}120}$ is reported rather than the AUC from time zero to infinity ($AUC_{0\text{-}\infty}$).

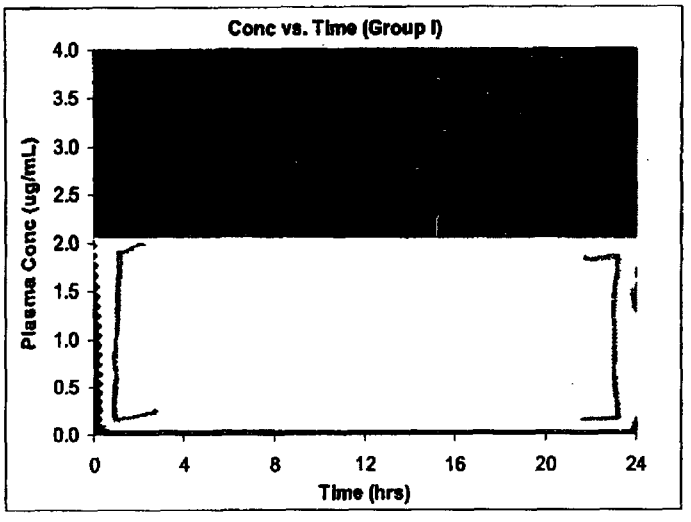
Table 2. Arithmetic mean (SD) pharmacokinetic parameters for azithromycin by renal function group following a single 1 gram dose

Renal function	C_{max} (µg/mL)	$AUC_{0\text{-}120}$ (µg*hr/mL)	T_{max} (hrs)	CL_R (mL/min)	$Xu_{0\text{-}72}$ (mg)	$Xu_{0\text{-}72}$ (% dose)
Normal renal function	1.05 (0.48)	9.36 (2.88)	1.7 (0.6)	153 (33)	72.6 (23.3)	7.3 (2.3)
Mild/moderate renal impairment	1.10 (0.47)	9.75 (2.97)	1.9 (0.7)	64 (37)	23.8 (7.0)	2.6 (1.2)
Severe renal impairment (w/o hemodialysis)	1.68 (0.75)	12.61 (5.33)	1.7 (0.6)	13 (7)	7.5 (5.0)	0.8 (0.5)

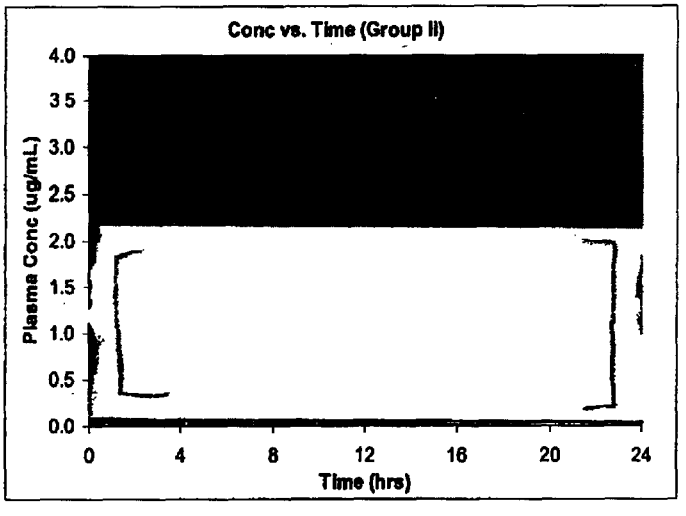
The mean C_{max} and $AUC_{0\text{-}120}$ increased modestly between Group I and II (4.8% and 4.2%, respectively), whereas Group III was associated with greater increases for both parameters (60% and 35%, respectively). Although azithromycin is eliminated primarily through non-renal mechanisms (7.3% of the administered dose was excreted unchanged in the urine of subjects with normal renal function), CL_R and $Xu_{0\text{-}72}$ progressively decreased as renal function declined. The CL_R decreased by 58% in subjects with mild/moderate renal impairment and 92% in subjects with severe renal impairment compared to subjects with normal renal function. Similar decreases were noted with the fraction of azithromycin excreted unchanged in urine.

The geometric mean ratios (Group II/Group I & Group III/Group I) and 90% confidence intervals for various pharmacokinetic parameters are illustrated in Table 3. The 90% confidence intervals for C_{max} and $AUC_{0\text{-}120}$ fell outside of the 0.80 to 1.25 boundaries in subjects with mild/moderate and severe renal impairment.

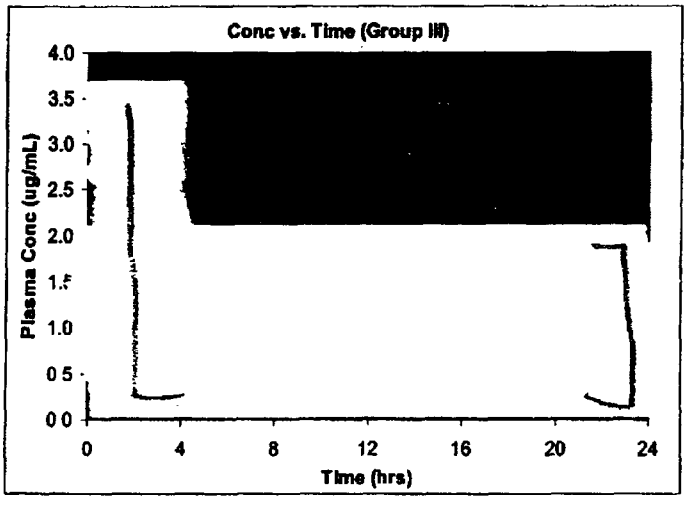
Figure 1. Individual azithromycin plasma concentration-time profiles following a single 1 gram oral dose to subjects with varying degrees of renal impairment



Group I: Normal renal function (GRF >80 mL/min)

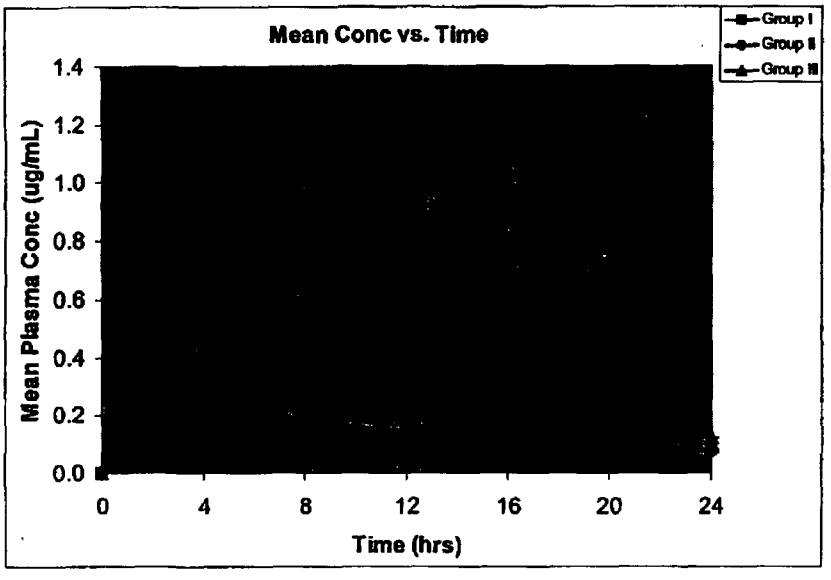


Group II: Mild/Moderate renal impairment (GRF ≤80 to ≥10 mL/min)



Group III: Severe renal impairment (GRF <10 mL/min)

Figure 2. Mean azithromycin plasma concentration-time profiles following a single 1 gram oral dose to subjects with varying degrees of renal impairment



Group I, GFR >80 mL/min; Group II, GFR ≤80 to ≥10 mL/min; Group III, GFR <10 mL/min

Table 3. Geometric mean ratios (renal impairment/normal renal function) and 90% CIs for pharmacokinetic parameters

Parameter		Mild/Moderate renal impairment	Severe renal impairment
C_{max}	GMR 90% CI	1.05 (0.77 to 1.45)	1.59 (1.17 to 2.39)
AUC_{0-120}	GMR 90% CI	1.04 (0.82 to 1.32)	1.30 (1.02 to 1.85)

The sponsor did not assess the impact of renal function on the protein binding of azithromycin. The protein binding of azithromycin ranges from 51% (at 0.02 µg/mL) to 7% (2 µg/mL) in healthy volunteers. Changes in the protein binding of azithromycin in subjects with impaired renal function are unlikely to significantly impact the unbound fraction.

The effect of hemodialysis on the clearance of azithromycin was not evaluated in subjects receiving hemodialysis (n=3). Thus, the effect of hemodialysis on the clearance of azithromycin is unknown.

REVIEWER'S COMMENT:

A non-compartmental analysis was performed by the reviewer using WinNonlin to estimate the $AUC_{0-\infty}$, plasma clearance (CL_T/F), apparent volume of distribution (Vss/F), and half-life. These parameters are shown in Table 4. The terminal elimination rate constant was unable to be estimated for one subject in the mild/moderate and one subject in the severe renal impairment group.

The relationship between GFR and various pharmacokinetic parameters was strongest with renal clearance (r^2 =0.8892) and cumulative urinary excretion (r^2 =0.7802). C_{max}, CL/F, AUC_{0-120}, and $AUC_{0-\infty}$ were not as strongly associated with GFR (r^2 ≤0.1420).

Table 4. Arithmetic mean (SD) pharmacokinetic parameters for azithromycin by renal function group following a single 1 gram dose (calculated by reviewer)

Renal function	$AUC_{0-\infty}$ (μg*hr/mL)	CL_T/F (L/hr)	Vss/F (L/kg)	Half-life (hrs)
Normal renal function	10.53 (3.31)	102.6 (27.2)	120.2 (40.7)	55.2 (17.6)
Mild/moderate renal impairment	11.75 (4.02)	95.8 (38.4)	145.5 (66.3)	77.8 (25.5)
Severe renal impairment (w/o hemodialysis)	16.05 (6.93)	72.5 (27.6)	103.5 (50.4)	66.9 (22.7)

The $AUC_{0-\infty}$ and CL_T/F were similar between Group I and Group II, whereas Group III was associated with a decreased plasma clearance and increased $AUC_{0-\infty}$. In general, the half-life was prolonged among subjects with renal impairment.

In addition, the reviewer also assessed the impact of renal impairment on pharmacokinetic parameters using the following ranges of GFR: >80 mL/min, 80 to 30 mL/min, <30 to 10 mL/min, and <10 mL/min. Three subjects had a GFR that was within 80 mL/min to 30 mL/min (40, 64, and 71 mL/min). The geometric mean ratios (renal impairment/normal renal function) are shown in Table 5. A GFR >80 mL/min was defined as normal renal function.

Table 5. Geometric mean ratios (renal impairment/normal renal function) for selected pharmacokinetic parameters

		GFR (mL/min)	
Parameter	80 to 30 mL/min (n=3)	<30 to 10 mL/min (n=9)	<10 mL/min (n=19)
C_{max}	0.951	1.085	1.593
AUC_{0-120}	0.896	1.080	1.302
CL_R	.688	.324	.071
Xu_{0-72}	.391	.315	.086

The C_{max} and AUC_{0-120} geometric mean ratios from subjects with GFR 80 to 30 ml/min and <30 to 10 mL/min are similar. Thus, the sponsor's analysis of combining subjects with a GFR ≤80 and ≥10 mL/min is acceptable.

SAFETY:
Three of 12 subjects in Group I and one of 12 subjects in Group II experienced adverse events, whereas eight of 19 subjects in Group III experienced adverse events. Some subjects reported more than one adverse event. The breakdown of adverse events by category is shown below in Table 6:

Table 6. Incidence of adverse events based on renal function

Adverse event	Group I (n=12)	Group II (n=12)	Group III (n=19)
Central/peripheral nervous system			
Mild	0	1	2
Moderate	1	0	0
Severe	0	0	0
Autonomic nervous system			
Mild	0	0	0
Moderate	0	0	1
Severe	0	0	0
Gastrointestinal			
Mild	2	3	8
Moderate	0	0	2
Severe	0	0	1
Cardiovascular			
Mild	0	0	1
Moderate	0	0	0
Severe	0	0	0
General - Asthenia			
Mild	0	0	1
Moderate	0	0	0
Severe	0	0	0

Due to the limited number of subjects and the lack of a comparator, it is unknown whether the increased incidence of gastrointestinal adverse events in Group III is attributed to the presence of the underlying disease state (severe renal impairment) and/or increased plasma concentrations of azithromycin.

CONCLUSIONS:

The C_{max} and $AUC_{0-\infty}$ increased 4.5% and 2.8% in subjects with mild/moderate renal impairment, whereas they increased 60.0% and 49.3% in subjects with severe renal impairment.

CL_R and Xu_{0-72} were associated with GFR (r^2=0.8892 and r^2=0.7802, respectively).

Based on the modest changes with C_{max} and $AUC_{0-\infty}$, no dosage adjustment is recommended for subjects with mild/moderate renal impairment (GFR ≤80 and ≥10 mL/min) or severe renal impairment (GFR <10 mL/min).

COMMENTS:

The large increase in C_{max} and AUC_{0-120} between subjects in Group II and Group III was associated with a small decrease in the amount of total azithromycin excreted unchanged in urine (2.6% for Group II vs. 0.8% for Group III). The 53% increase in C_{max} and 29% increase in AUC_{0-120} are likely due to other causes rather than not excreting 1.8% of the total dose in the urine.

An increase in adverse events were noted in subjects with severe renal impairment. However, due to the limited number of subjects with adverse events and the lack of a control group (to identify adverse events related to the disease state), the reviewer is unable to conclude that subjects with severe renal impairment have a greater incidence of adverse events due to azithromycin compared to subjects with normal renal function. The reviewing medical officer should be consulted on the safety of administering azithromycin in subjects with severe renal impairment (GFR <10 mL/min).

Accurate determinations of GFR can be calculated with inulin clearance or radio-labeled markers such as I^{125}-iothalamate or Cr^{51}-EDTA in patients whom creatinine is not likely a reliable indicator. However, these methods require pre-existing renal function in order to calculate the GFR. The sponsor has not provided a rationale for use of Cr^{51}-EDTA in subjects with severe renal impairment.

Study AZM-I-90-001: An Open, Non-Comparative Study on the Safety, Toleration, and Pharmacokinetics of Azithromycin in Adult Subjects With Hepatic Insufficiency Following Oral Administration of a Single Dose

Date: October 12, 1990 to December 12, 1991
Clinical Site: [ ]

Analytical Site: Not stated

OBJECTIVES:
To assess the toleration, safety, and pharmacokinetics of azithromycin following oral administration to adult subjects with hepatic insufficiency.

FORMULATION:
Azithromycin 250 mg capsules (Lot No. ED-G-001-190, FID No. YY-89-051 and Lot No. 810-24, FID No. YY-87-018). The two formulations were shown to be bioequivalent in study 066-025.

STUDY DESIGN:
An open-label, single-dose, pharmacokinetic study of oral azithromycin 500 mg (2 × 250 mg capsules) administered to male and female adult subjects at least two hours before or one hour after a standardized meal with normal hepatic function (Group I), mild hepatic impairment (Group II), or moderate hepatic impairment (Group III). Subjects received 150 mL of water with the azithromycin dose. Subjects were assigned to one of the three groups based on Child-Pugh classification (Group II, Child-Pugh Class A; Group III, Child-Pugh Class B).

Blood samples were collected for 192 hours at the following times: predose, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, and 192 hrs following administration.

Urine samples were collected for 192 hours at the following intervals: 0 to 4, 4 to 8, 8 to 12, 12 to 16, 16 to 20, 20 to 24, 24 to 28, 28 to 32, 32 to 36, 36 to 40, 40 to 44, 44 to 48, 48 to 60, 60 to 72, 72 to 84, 84 to 96, 96 to 120, 120 to 144, 144 to 168, and 168 to 192 hrs following administration.

[ ]

Criterion	Serum - low curve	Serum - high curve	Comments
Concentration range	[ ]		Satisfactory
LLOQ			Satisfactory
Linearity	R^2=0.997	R^2=0.999	Satisfactory
Accuracy	110.8%	101.0%	Satisfactory
Precision (% CV)	8.1%	4.2%	Satisfactory

AZITHROMYCIN URINE ASSAY METHODOLOGY:
Liquid chromatography with [redacted]

Criterion	Urine - low curve	Urine - high curve	Comments
Concentration range	[redacted]		Satisfactory
LLOQ			Satisfactory
Linearity	R^2=0.999	R^2=0.999	Satisfactory
Accuracy	96.8%	99.6%	Satisfactory
Precision (% CV)	2.9%	1.7%	Satisfactory

DATA ANALYSIS:
The maximum observed plasma concentration (C_{max}) was estimated directly from the observed plasma concentration-time data. T_{max} was defined as the time corresponding to the occurrence of C_{max}. The terminal phase elimination rate constant, k_{el}, was estimated using linear least squares regression analysis of the azithromycin plasma concentration-time data obtained during the terminal log-linear phase. The area under the serum concentration time curve from 0 to 72 hours (AUC_{0-72}) was estimated using the linear trapezoidal approximation. The amount of unchanged azithromycin excreted in urine over 72 hours (Xu_{0-72}) was calculated from urine concentrations and urine volume. The renal clearance (CL_R) was calculated as the ratio of Xu_{0-72}/plasma AUC_{0-72}.

STATISTICAL ANALYSIS:
Pharmacokinetic parameters ($\log_{10} AUC_{0-72}$, $\log_{10} C_{max}$, T_{max}, and CL_R) were compared using a one-way ANOVA with 95% confidence intervals. Also, 95% confidence intervals on the ratios of the geometric means of AUC_{0-72} and C_{max} were calculated by back-transforming the confidence intervals of the differences in $\log_{10}(AUC_{0-72})$ and $\log_{10}(C_{max})$, respectively.

The reviewer compared the geometric mean ratios and 90% confidence intervals of C_{max} and AUC_{0-72} using the PROC GLM of SAS version 6.12 These results were compared to those calculated by the sponsor.

APPEARS THIS WAY
ON ORIGINAL

RESULTS:
The demographics of the 22 subjects are shown in Table 1.

Table 1. Mean (SD) demographic data for all subjects by hepatic function

Hepatic function	Group	N	Gender	Age (years)	Height (cm)	Weight (kg)
Normal hepatic function	I	6	4M/2F	33.2 (5.7)	172.5 (8.7)	68.1 (14.7)
Mild hepatic impairment	II	10	5M/5F	59.9 (6.2)	161.8 (7.3)	67.5 (6.0)
Moderate hepatic impairment	III	6	4M/2F	60.0 (9.7)	166.8 (8.0)	77.3 (12.0)

Subjects in Group I ranged in age from 27 to 43 years, Group II ranged from 50 to 73 years, and Group III ranged from 44 to 69 years.

The individual azithromycin plasma concentration-time profiles for all subjects are shown in Figure 1. Plasma concentrations are shown for only 24 hours. Plasma concentrations were not reported for several time points (and appear as a concentration of zero on the plot) either because no sample was obtained, poor chromatography, or insufficient sample volume was available to quantitate the concentration.

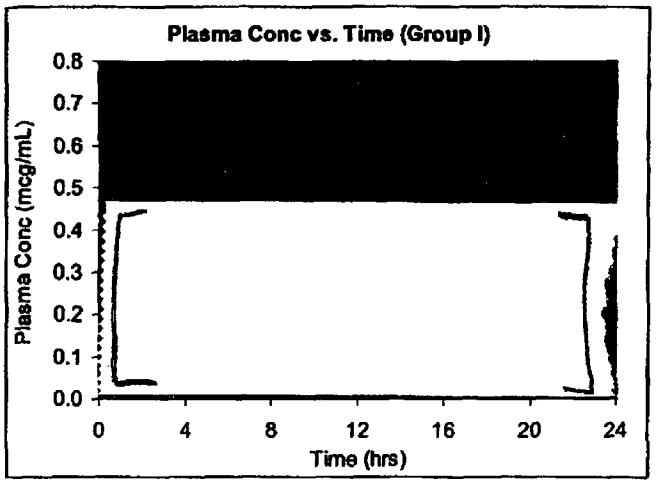
Azithromycin plasma concentrations from subjects with mild and moderate hepatic impairment (Groups II and III) were greater than plasma concentrations from subjects with normal hepatic function (Group I) as shown in Figure 1. The mean concentration-time profiles shown in Figure 2 demonstrate that plasma concentrations of azithromycin increased with declining hepatic function.

The pharmacokinetic parameters for each group of subjects are shown in Table 2. The sponsor stated that inadequate plasma samples were obtained to estimate the terminal elimination phase. Thus, the $AUC_{0\text{-}72}$ is reported rather than the AUC from time zero to infinity ($AUC_{0\text{-}\infty}$). The sponsor was unable to provide plasma concentrations for every sample collected for two subjects in Group I, five subjects from Group II, and two subjects from Group III. Reasons consisted of poor chromatography, insufficient sample volume, or the lack of a sample collected. In addition, the sponsor calculated the renal clearance (CL_R) from 0-72 hrs in subjects who were missing one or more collection intervals of urine data or were missing sufficient plasma concentration data to prevent calculation of the $AUC_{0\text{-}72}$.

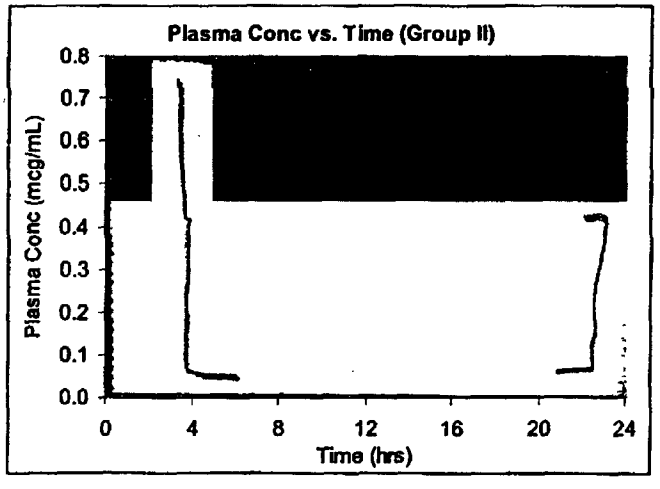
Table 2. Mean (SD) pharmacokinetic parameters by hepatic function provided by sponsor

Hepatic function	C_{max} (µg/mL)	T_{max} (hrs)	$AUC_{0\text{-}72}$ (µg*hr/mL)	CL_R (mL/min)	$Xu_{0\text{-}72}$ (mg)	$Xu_{0\text{-}72}$ (% dose)
Normal hepatic function (n=6)	0.26 (0.13)	3.3 (1.5)	2.52 (0.88)	162 (69)	21.7 (5.2)	4.3 (1.0)
Mild hepatic impairment (n=10)	0.32 (0.18)	2.8 (0.6)	2.45 (1.01)	197 (92)	26.6 (15.3)	5.3 (3.1)
Moderate hepatic impairment (n=6)	0.32 (0.20)	3.0 (1.8)	2.33 (1.09)	255 (192)	23.9 (15.5)	4.8 (3.1)

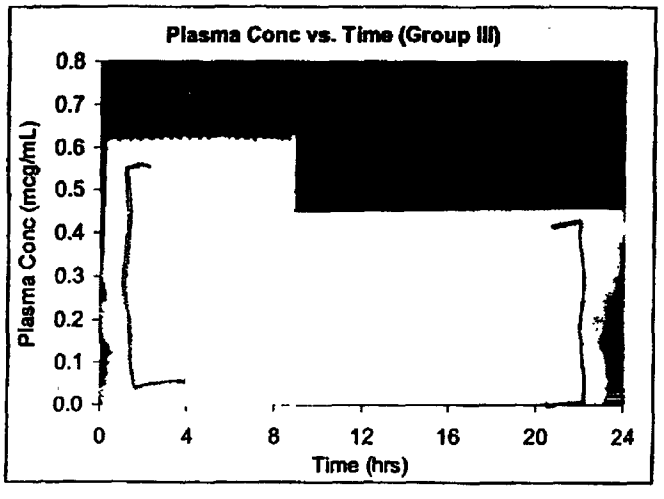
Figure 1. Individual azithromycin plasma concentration-time profiles following a single 500 mg oral dose to subjects with normal hepatic impairment, mild hepatic impairment (Child-Pugh Class A), and moderate hepatic impairment (Child-Pugh Class B)



Group I: Normal hepatic function

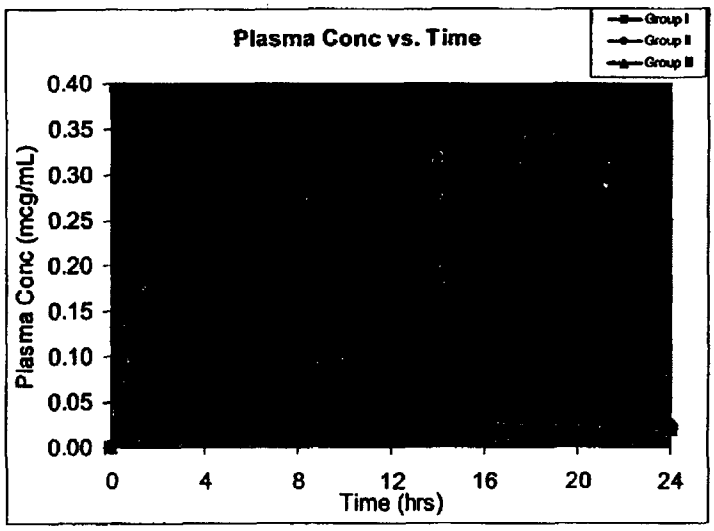


Group II: Mild hepatic impairment (Child-Pugh Class A)



Group III: Moderate hepatic impairment (Child-Pugh Class B)

Figure 2. Mean azithromycin plasma concentration-time profiles following a single 500 mg oral dose to subjects with varying degrees of hepatic impairment



The C_{max} was greater for subjects with mild and moderate hepatic impairment compared to subjects with normal hepatic function, although the increased concentrations were not reflected in the AUC_{0-72}. Thus, the AUC_{0-72} was greater in subjects with normal hepatic function compared to subjects with hepatic impairment. The renal clearance increased progressively with increasing severity of hepatic impairment and was most likely the result of renal compensation. The percentage of the dose excreted unchanged in the urine (Xu_{0-72}) was greater for subjects with hepatic impairment.

The reviewer is unable to explain the decreasing AUC_{0-72} with increasing hepatic impairment, although it may be due to the large degree of variability with azithromycin concentrations (intra-subject and inter-subject) as well as missing data. To assess the impact of including subjects with missing plasma and/or urine data, the reviewer calculated the pharmacokinetic parameter estimates for subjects who had no missing data. The results are shown in Table 3.

Table 3. Mean (SD) pharmacokinetic parameters* by hepatic function calculated by the reviewer

Hepatic function	C_{max} (µg/mL)	T_{max} (hrs)	AUC_{0-72} (µg*hr/mL)	CL_R (mL/min)	Xu_{0-72} (mg)	Xu_{0-72} (% dose)
Normal hepatic function	0.27 (0.15)	2.8 (1.0)	2.92 (1.00)	142 (71)	21.7 (5.2)	4.3 (1.0)
Mild hepatic impairment	0.32 (0.18)	2.8 (0.6)	2.77 (0.73)	214 (66)	31.4 (13.3)	6.3 (2.7)
Moderate hepatic impairment	0.42 (0.14)	2.0 (0.8)	2.82 (0.65)	194 (34)	24.4 (14.7)	4.9 (2.9)

*subjects with missing data were excluded from analysis

The results from the above analysis are similar to the sponsor's analysis and also demonstrate that the AUC_{0-72} was less in subjects with hepatic impairment. Consistent with Figure 2, the mean C_{max} increased with hepatic impairment. The renal clearance and Xu_{0-72} were greater in subjects with hepatic impairment compared to subjects with normal hepatic function.

To assess differences in the plasma clearance and the AUC zero to infinity ($AUC_{0-\infty}$), the reviewer also performed a noncompartmental analysis using WinNonlin to estimate differences between half-life, plasma clearance (CL_T), volume of distribution (Vss), and $AUC_{0-\infty}$. Three subjects from Group I, five subjects from Group II, and two subjects from Group III were excluded due to the inability to estimate the terminal elimination phase. The resulting pharmacokinetic parameters are shown in Table 4.

Table 4. Mean (SD) Pharmacokinetic parameters by hepatic function calculated by the reviewer

Hepatic function	$AUC_{0-\infty}$ (µg*hr/mL)	CL_T/F (L/hr)	Vss (L/kg)	Half-life (hrs)
Normal hepatic function (n=3)	3.58 (0.86)	146 (39)	184 (58)	54 (21)
Mild hepatic impairment (n=5)	3.88 (0.97)	138 (46)	238 (118)	79 (20)
Moderate hepatic impairment (n=4)	4.72 (0.29)	106 (6.6)	204 (98)	106 (44)

Although few subjects were included in the analysis, the plasma clearance decreased progressively with declining hepatic function, resulting in an increase of the $AUC_{0-\infty}$. An increase in the half-life of azithromycin was associated with increasing hepatic impairment. The geometric mean ratios (GMR) for pharmacokinetic parameters are listed in Table 5. The 90% confidence intervals for the geometric mean ratios (hepatic impairment/normal hepatic function) and are not reported due to the limited sample size.

Table 5. Geometric mean ratios (hepatic impairment/normal hepatic function) for pharmacokinetic parameters (calculated by the reviewer)

Parameter	Mild hepatic impairment	Moderate hepatic impairment
C_{max}	1.148	1.667
$AUC_{0-\infty}$	1.071	1.344
CL_T/F	0.934	0.744
CL_R	1.559	1.469
Vss	1.236	1.076
Xu_{0-72}	1.323	0.982

SAFETY:

Three of six subjects in Group I, one of 10 subjects in Group II, and none of six subjects in Group III experienced treatment related adverse events, of which all the adverse events were related to the gastrointestinal system. The breakdown of gastrointestinal adverse events by severity are shown below:

Table 6. Incidence of treatment-related adverse events based on hepatic function

Adverse event	Group I (n=6)	Group II (n=10)	Group III (n=6)
Gastrointestinal - Abdominal pain			
Mild	3	0	0
Moderate	0	1	0
Severe	0	0	0

Hepatic impairment did not appear to be related to the incidence of adverse events, although there were a limited number of subjects in the study. None of the subjects experienced progression of their liver disease based on signs/symptoms of hepatic impairment and laboratory test results.

CONCLUSIONS:
Due to the limited number of subjects evaluated for pharmacokinetic and safety data, the degree of inter-subject variability, missing plasma and urine concentrations, and questionable validation of the azithromycin serum assay to quantitate plasma samples, insufficient evidence exists to recommend a dosage adjustment for the administration of azithromycin in subjects with hepatic impairment.

COMMENTS:
Although the sponsor experienced poor chromatography with several subjects, the azithromycin assay has been validated based on accuracy and precision. However, the sponsor appears to have used an azithromycin assay validated with serum to quantitate azithromycin concentrations obtained from plasma. No data were submitted demonstrating that azithromycin in plasma can be accurately quantitated using an assay validated with serum and that plasma from subjects with hepatic impairment will not interfere with the accurate quantitation of azithromycin using HPLC.

Even though blood samples were obtained for 192 hrs, the sponsor calculated the AUC_{0-72} for each subject. The concentration of azithromycin was below the LOQ in plasma by 72 hrs in four subjects. The reviewer calculated the $AUC_{0-\infty}$ for subjects with adequate plasma concentration-time data (blood samples were obtained over 192 hrs following dosing).

Study 066-228: A Double Blind, Placebo Controlled, Parallel Group Study to Investigate the Effect of Orally Administered Azithromycin on the Plasma Concentration Profile of Theophylline

Date: August 12, 1991
Clinical Site:
Analytical Site:

OBJECTIVES:
To study the effect of azithromycin administered as a 5-day regimen on oral theophylline pharmacokinetics dosed to steady-state.

FORMULATION:
Azithromycin 250 mg capsules (Lot #ED-G-001-190, Pfizer, UK)
Uniphyllin 300 mg sustained-release tablets (Lot #00122, [illegible] and Lot #829-46, Pfizer, UK)
Azithromycin placebo capsules (Lot #ED-G-192-887, Pfizer, UK)

STUDY DESIGN:
A multiple-dose, double-blind, placebo-controlled, randomized, parallel-group design pharmacokinetic interaction study involving 16 healthy adult male volunteers. Subjects received extended-release theophylline 300 mg BID on days 1-15 and either azithromycin 500 mg PO in the morning on day 6, then azithromycin 250 mg PO QD in the morning on days 7-10 or matching placebo. Breakfast was consumed immediately following the morning theophylline dose, whereas the evening dose was administered 2.5 hrs after the start of dinner.

Blood samples for theophylline concentration determination were collected on days 5, 10, and 15 at 0 (predose), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hrs after the morning theophylline administration. In addition, pre-theophylline dosing samples were obtained on days 3, 4, 8, 9, 13, and 14.

Criterion	Plasma	Comments
Concentration range	[illegible]	Satisfactory
LLOQ	[illegible]	Satisfactory
Linearity	$R^2 \geq 0.9998$	Satisfactory
Accuracy	100.5%	Satisfactory
Precision (% CV)	2.2% to 3.5%	Satisfactory
Specificity	Satisfactory	Satisfactory
Stability	Freeze-thaw, long term (-20°C), short term (+4°C and +22°C)	Satisfactory

DATA ANALYSIS:
Steady-state pharmacokinetic parameter estimates were determined for theophylline during a 12-hr interval on days 5, 10, and 15 for the maximum observed plasma concentration (C_{max}), the time to achieve the maximum concentration (T_{max}), and the area under the plasma concentration time curve from 0 to 12 hours (AUC_{0-12}) estimated using the

STATISTICAL ANALYSIS:
For each subject, the change from day 5 to day 10 and day 5 to day 15 were calculated for each un-transformed parameter. All day 5 parameters were obtained at baseline (prior to azithromycin or placebo administration).

To study the effect of azithromycin on theophylline plasma concentration the differences for the azithromycin group were compared with the differences of the placebo group, using the two sample t-test.

The reviewer calculated the geometric mean ratio (GMR) and 90% confidence interval (CI) for theophylline log-transformed C_{max} and AUC_{0-12} values using the PROC GLM of SAS version 6.12. The GMR was calculated for day 10/day 5 and day 15/day 5 for both C_{max} and AUC_{0-12}.

RESULTS:
The demographics of the 16 subjects are shown in Table 1. Age, weight, and height were similar among subjects in the azithromycin and placebo groups.

Table 1. Mean (SD) subjects demographics

Treatment Group	Age (yrs)	Height (cm)	Weight (kg)
Azithromycin Group (N=8)	24.4 (3.8)	183.1 (7.9)	77.3 (5.3)
Placebo Group (N=8)	28.4 (10.0)	183.9 (3.2)	73.5 (8.4)

The theophylline plasma concentration-time profiles for theophylline with azithromycin and placebo on days 5, 10, and 15 are shown in Figures 1-3. Theophylline concentrations were similar among all subjects and did not appear to be dependent on whether subjects received azithromycin or placebo.

Figure 1. Theophylline plasma concentration-time profiles after the morning dose on day 5 for the placebo and azithromycin groups

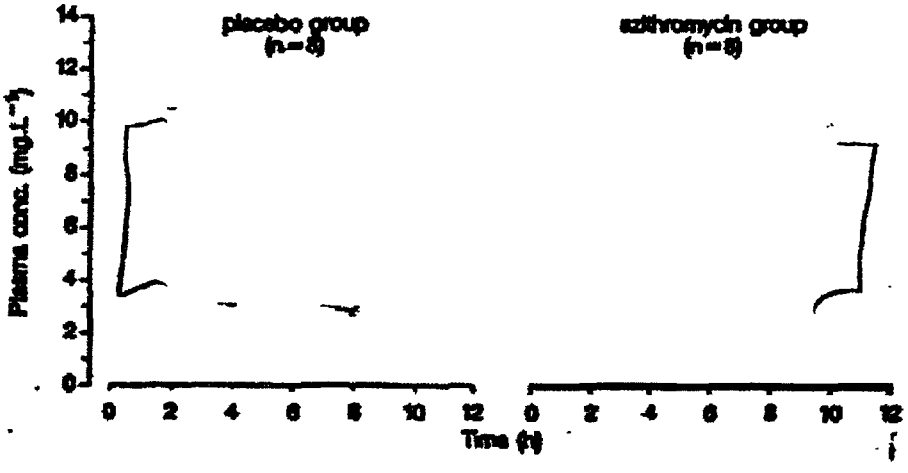


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Figure 2. Theophylline plasma concentration-time profiles after the morning dose on day 10 for the placebo and azithromycin groups

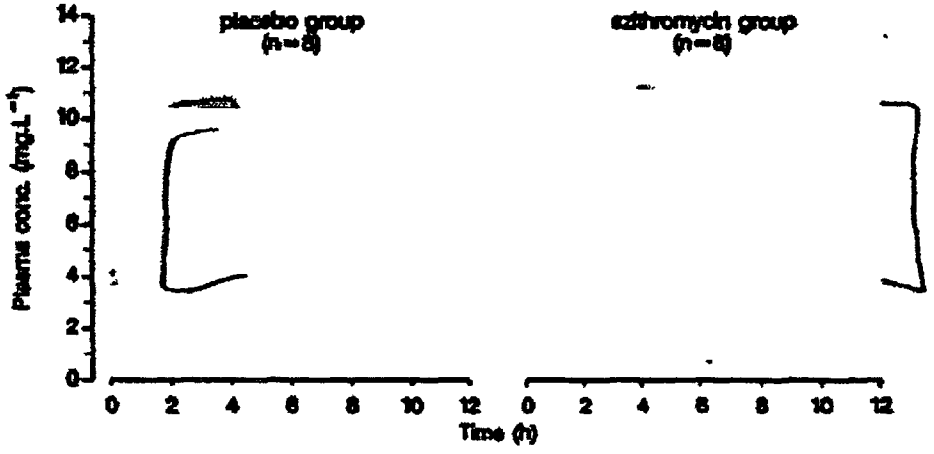
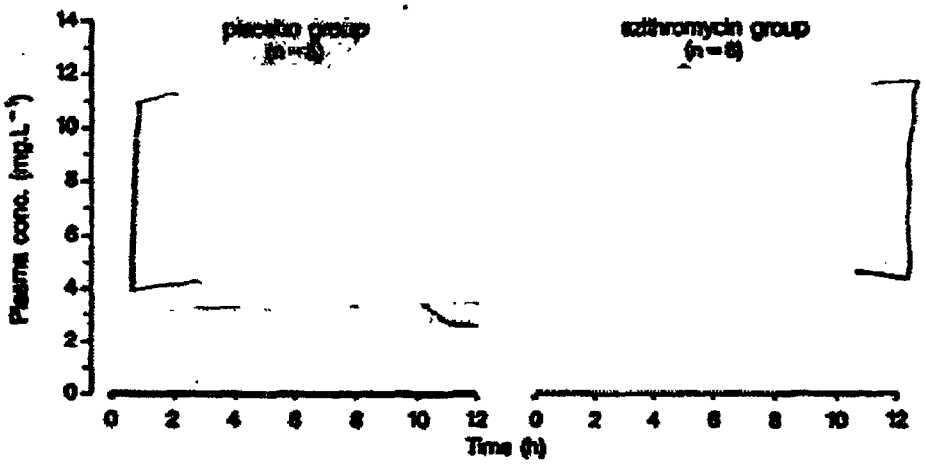


Figure 3. Theophylline plasma concentration-time profiles after the morning dose on day 15 for the placebo and azithromycin groups



Mean (SD) theophylline pharmacokinetic parameters obtained over 12 hrs after the morning dose on days 5, 10, and 15 are shown in Table 2. The theophylline C_{max} and AUC_{0-12} increased 8.4% and 7.2%, respectively, between day 5 (baseline) and day 10 in subjects receiving azithromycin. Theophylline concentrations remained elevated on day 15 compared to day 5 (baseline). However, theophylline concentrations in subjects receiving placebo remained essentially unchanged over the course of the study. The theophylline C_{max} and AUC_{0-12} decreased by 3.4% and 4.4%, respectively between day 5 and day 10 in subjects receiving placebo.

Table 2. Mean (SD) parameter estimates for theophylline administered with azithromycin or placebo

	Azithromycin Group			Placebo Group		
Treatment Day	**Cmax (µg/mL)**	**T_{max} (hrs)**	**AUC_{0-12} (µg*hr/mL)**	**Cmax (µg/mL)**	**T_{max} (hrs)**	**AUC_{0-12} (µg*hr/mL)**
Day 5	8.64 (1.59)	5.6 (2.7)	82.0 (17.8)	8.66 (1.48)	3.8 (2.7)	78.8 (17.2)
Day 10	9.38 (1.62)	4.5 (1.5)	87.9 (15.3)	8.36 (1.97)	4.4 (2.3)	75.3 (16.0)
Day 15	9.51 (1.86)	5.5 (2.4)	89.9 (17.7)	8.61 (1.78)	4.4 (3.2)	76.6 (16.6)

The reviewer calculated the geometric mean ratio (GMR) and 90% confidence intervals for the log-transformed C_{max} and AUC_{0-12} values in subjects receiving azithromycin and placebo between day 10 & day 5 and day 15 & day 5 (Table 3). The GMRs of day 10/day 5 for the azithromycin group were 1.085 and 1.080 for C_{max} and AUC_{0-12}, respectively. The 90% CIs exceeded 1.25 for both parameters. Five days after the last dose of azithromycin was administered, the day 15/day 5GMRs were 1.10 for both parameters although the 90% CIs exceeded 1.25. Thus, co-administration of azithromycin resulted in an increase in the C_{max} and AUC_{0-12} of theophylline that remained elevated five days after the last dose of azithromycin.

The C_{max} and AUC_{0-12} GMRs for day 10/day 5 and day 15/day 5 for subjects receiving placebo were approximately 1.00. There was no trend for increasing theophylline concentrations between day 5 and day 15 in subjects receiving placebo. However, the 90% CIs included values less than 0.80 for all parameters except the C_{max} for day 15/day 5.

The individual subject and mean C_{max} and AUC_{0-12} values on days 5, 10, and 15 are demonstrated in the stick plots in Figures 4-5. The inter-subject variability was similar between the azithromycin and placebo groups.

Table 3. Geometric mean ratios (90% confidence intervals) for day 10/day 5 and day 15/day 5 for azithromycin and placebo groups

	Azithromycin Group		Placebo Group	
Treatment Day	**Cmax**	**AUC_{0-12}**	**Cmax**	**AUC_{0-12}**
Day 10/Day 5	1.085 (0.915 to 1.286)	1.080 (0.888 to 1.312)	0.954 (0.768 to 1.186)	0.957 (0.762 to 1.203)
Day 15/Day 5	1.096 (0.914 to 1.314)	1.099 (0.889 to 1.358)	0.988 (0.808 to 1.208)	0.973 (0.771 to 1.228)

Figure 4. Stick plots of individual (●) and mean (■) theophylline C_{max} values from subjects in the azithromycin and placebo groups

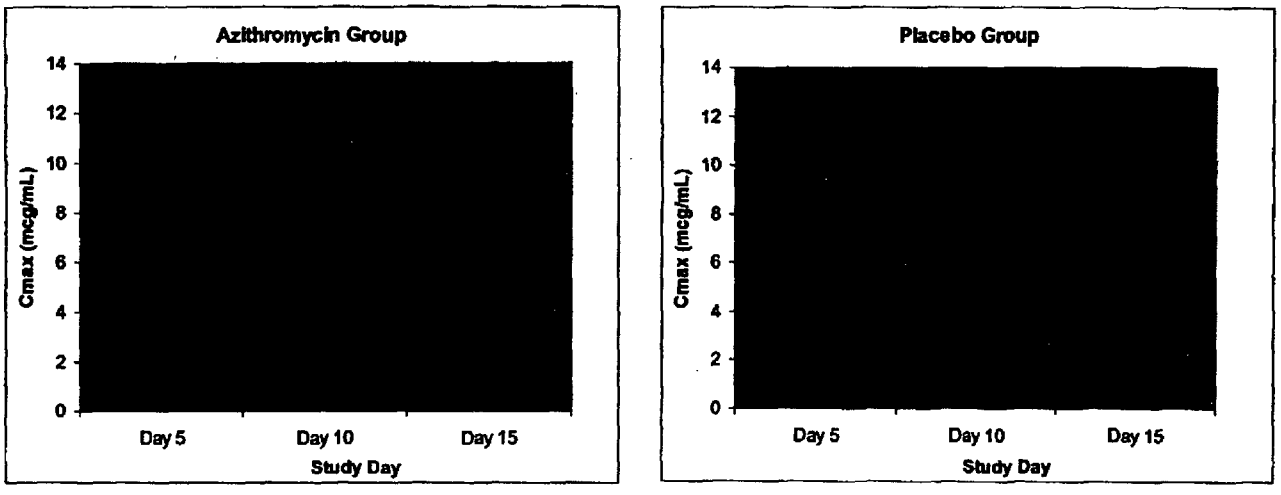
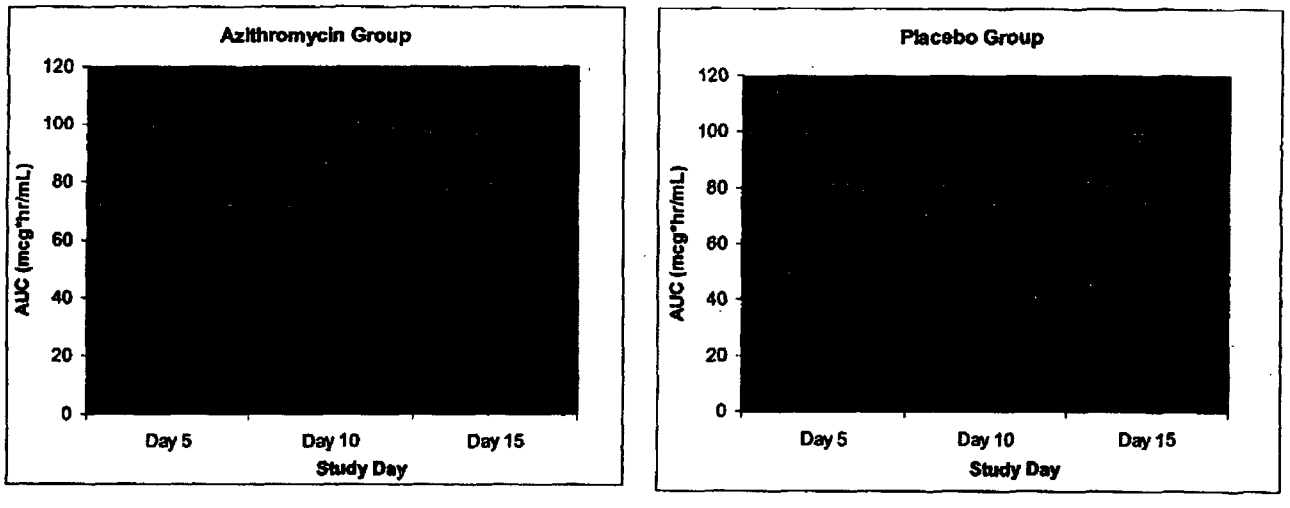


Figure 5. Stick plots of individual (●) and mean (■) theophylline AUC_{0-12} values from subjects in the azithromycin and placebo groups



SAFETY:

None of the subjects discontinued the study for any reason. The incidence of the most common adverse events by treatment is shown the table below.

Table 4. Incidence of adverse events by treatment group

Adverse Event	Azithromycin Group (n=8)	Placebo Group (n=8)
CNS		
Headache	38% (3/8)	50% (4/8)
Tremor	25% (2/8)	13% (1/8)
Restlessness	13% (1/8)	0% (0/8)
Dizziness	0% (0/8)	25% (2/8)
Sleepiness	13% (1/8)	13% (1/8)
Cardiovascular		
Palpitations	25% (2/8)	13% (1/8)
Gastrointestinal		
Nausea	25% (2/8)	13% (1/8)
Vomiting	0% (0/8)	13% (1/8)
Abdominal cramps/pain	25% (2/8)	0% (0/8)

There were no subjects with theophylline concentrations above the therapeutic range of 15 μg/mL

CONCLUSIONS:
Co-administration of azithromycin with theophylline increased the theophylline C_{max} and AUC_{0-12} values approximately 8% compared to baseline after administering azithromycin for 5 days. Theophylline C_{max} and AUC_{0-12} values increased 10% compared to baseline five days after stopping the administration of azithromycin.

There appeared to be no difference in the incidence of adverse events between subjects receiving theophylline co-administered with azithromycin or placebo.

No dosage adjustment of theophylline is necessary for patients administered azithromycin.

COMMENTS:
Although changes in theophylline C_{max} and AUC_{0-12} when co-administered with azithromycin may have been clinically irrelevant in healthy volunteers, this may not be true of all patients receiving theophylline. The change in theophylline concentrations may become clinically relevant in patients with theophylline concentrations near the upper limit of normal who may develop adverse reactions when theophylline concentrations are further increased. Thus, health care providers should be made aware that azithromycin may cause a modest increase in theophylline concentrations necessitating more frequent monitoring of theophylline plasma concentrations.

Although the study was a parallel-design, the reviewer analyzed the data as a one-sequence cross-over design (without sequence and period effects) to calculate a GMR and 90% CI. The reviewer felt this was acceptable since each treatment group (placebo or azithromycin) could be compared to itself and act as its own control. This method of analysis assesses a treatment effect but does not allow for the assessment of sequence and period effects.

Azithromycin concentrations were not quantitated in this study. Thus, the effect of theophylline on the pharmacokinetics of azithromycin, if any, has not been determined.

Study AZM-MACK-94-004: Open, Three-way Crossover Study of the Single dose Pharmacokinetics and Pharmacodynamics of Midazolam in Healthy Volunteers: With and Without Multiple Dose Pretreatment with Erythromycin and Azithromycin

Date: March 17 to August 29 1994
Clinical Site:
Analytical Site:

OBJECTIVES:
To characterize the effect of pretreatment with erythromycin and azithromycin on the pharmacokinetics and pharmacodynamics of midazolam in healthy subjects.

FORMULATION:
Azithromycin 250 mg capsules (Lot No. P-2705-07-001, Pfizer, UK)
Erythromycin 500 mg film tablets, (Erythrocin 500 Neo, Lot No. 80053 VA, Abbott)
Midazolam 7.5 mg tablets (Dormicum, Lot No. 08041, Roche)

STUDY DESIGN:
A single-center, single-dose, randomized, open label, three-way crossover study to investigate the impact of pretreatment with erythromycin or azithromycin on the pharmacokinetics and pharmacodynamics of midazolam. The study involved 4 male and 8 female healthy adult volunteers who received the following regimens: erythromycin 500 mg PO TID for 5 days, azithromycin 500 mg QD for 3 days, and no pretreatment (control). On day 5 of erythromycin treatment or day 3 of azithromycin treatment, subjects received a single oral dose of midazolam 15 mg at 1.5 hrs after the last morning antibiotic dose. Erythromycin and azithromycin were administered prior to a meal with 100 mL of water. The washout period between treatments was at least 4 weeks.

Blood samples for midazolam concentration were collected at time 0 (predose) and 0.5, 1, 2, 3, 4, 5, 6, 8, 12, and 24 hrs after the morning midazolam administration.

Baseline measurements for psychometric tests were performed approximately 1 hr prior to midazolam administration and at 1, 2, 4, 8, and 12 hrs after midazolam dosing to determine the pharmacodynamic activity. The pharmacodynamic activity of midazolam was measured by duration of sleep, the digit symbol substitution test (DSST), the critical flicker test (CFFT), and visual analog scales (VAS) for subjective alertness.

Criterion	Plasma	Comments
Concentration range	[redacted]	Satisfactory
LLOQ	[redacted]	Satisfactory
Linearity	$R^2 \geq 0.9927$	Satisfactory
Accuracy	97.0% to 103.5%	Satisfactory
Precision (% CV)	2.7% to 12.9%	Satisfactory
Specificity	Satisfactory	Satisfactory
Stability	Satisfactory	Satisfactory

DATA ANALYSIS:
The maximum observed plasma concentration (C_{max}) and the time to achieve the maximum concentration (T_{max}) were read directly from the individual plasma concentration-time profiles. The terminal elimination rate constant (K_{el}) was calculated using least squares regression analysis on the plasma concentration-time data obtained during the terminal log-linear elimination phase. The area under the concentration-time curve ($AUC_{0-\infty}$) was estimated using the linear trapezoidal method from time zero to the last time with a quantified concentration, adding the last quantified concentration/K_{el} for the residual area. The half-life was calculated from K_{el} as Ln 2/K_{el}.

The pharmacodynamic activity of midazolam was measured by duration of sleep, the digit symbol substitution test (DSST), the critical flicker test (CFFT), and with visual analog scales (VAS) for subjective alertness. In the DSST, the number of symbols correctly assigned during 90 seconds was recorded. In the 100 mm VAS, the subjects had to rate their actual feelings in terms of a single dimension with the extremes alert and drowsy. In the CFFT, the maximum frequency of flickering was determined at which the subject could detect the flickering of a red light (frequencies ranged from 25 to 55 min^{-1}).

STATISTICAL ANALYSIS:
Analysis of variance was performed with midazolam pharmacokinetic parameters ($AUC_{0-\infty}$, C_{max}, and K_{el}) and for the pharmacodynamic parameters. Log-transformed values were used for $AUC_{0-\infty}$ and C_{max}.

The reviewer calculated the geometric mean ratio (GMR) and 90% confidence interval for log-transformed C_{max} and $AUC_{0-\infty}$ values using the General Linear Models Procedure of SAS version 6.12. The GMR was calculated for erythromycin/control and azithromycin/control for both C_{max} and $AUC_{0-\infty}$.

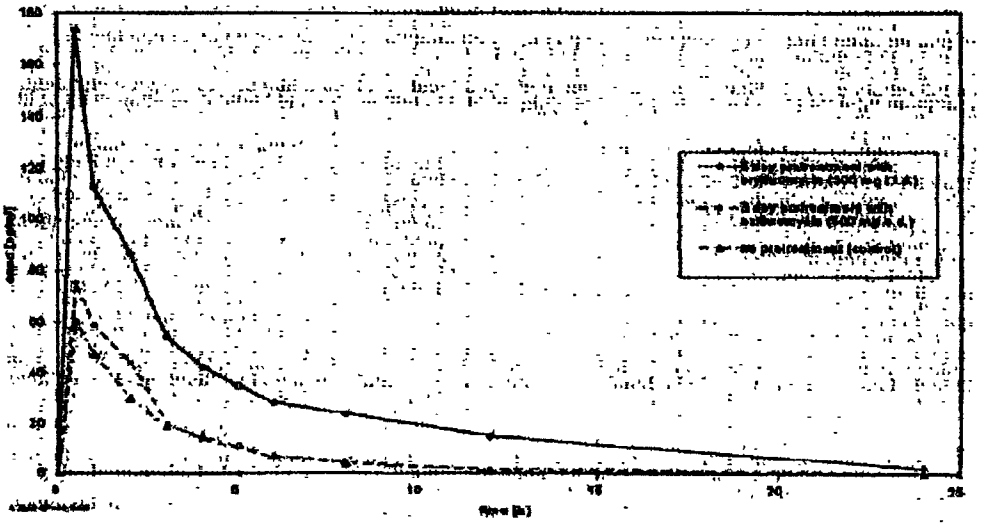
RESULTS:
The mean (SD) age, weight, and height are shown in Table 1. In general, male subjects were older, taller, and heavier than female subjects.

Table 1. Mean (SD) age, weight, and height of all subjects

Subjects	Age (yrs)	Weight (kg)	Height (cm)
All (n=12)	38.0 (8.3)	67.3 (13.7)	168.8 (6.8)
Male (n=4)	46.0 (6.2)	80.3 (14.8)	172.3 (9.5)
Female (n=8)	34.0 (6.1)	60.9 (7.6)	167.0 (4.9)

The plasma concentration-time profiles of midazolam administered with erythromycin, azithromycin, and no pretreatment (control) are shown in Figure 1. Midazolam plasma concentrations were greatest following pretreatment of erythromycin. Midazolam plasma concentrations were increased when co-administered with azithromycin compared to no pretreatment, although the extent of the increase was less than compared to erythromycin.

Figure 1. Midazolam plasma concentration-time profiles after administration of erythromycin, azithromycin, and no pretreatment



The pharmacokinetic parameters of midazolam were altered when subjects received pretreatment of erythromycin or azithromycin (Table 2). The C_{max} and $AUC_{0-\infty}$ increased approximately 171% and 281% with erythromycin and 29% and 27% with azithromycin, respectively. In addition, the half-life of midazolam increased approximately 100% and 48% following pretreatment with erythromycin and azithromycin, respectively, compared to control.

The influence of erythromycin and azithromycin pretreatment on the C_{max} and $AUC_{0-\infty}$ of midazolam is shown in Figure 2. The stick plots demonstrate that erythromycin had a greater effect on C_{max} and $AUC_{0-\infty}$ compare to azithromycin, although azithromycin exerted an effect compared to control.

Table 2. Mean (SD) pharmacokinetic parameters for midazolam after pretreatment with erythromycin, azithromycin, or control (no pretreatment)

Treatment	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng*hr/mL)	T_{max} (hrs)	Half-life (hrs)
Erythromycin	182.3 (79.2)	662.7 (265.1)	0.63 (0.43)	5.37 (1.48)
Azithromycin	86.7 (43.2)	220.0 (105.8)	0.83 (0.58)	3.96 (2.43)
Control	67.2 (39.5)	173.8 (85.4)	1.08 (1.31)	2.68 (1.13)

The midazolam geometric mean ratios and 90% confidence intervals for C_{max} and $AUC_{0-\infty}$ exceeded 1.25 following pretreatment with erythromycin and azithromycin (Table 3). Erythromycin and azithromycin significantly altered the pharmacokinetics of midazolam.

Figure 2. Stick plots demonstrating individual (●) and mean (■) midazolam C_{max} and AUC with pretreatment of erythromycin, azithromycin, or no pretreatment (control)

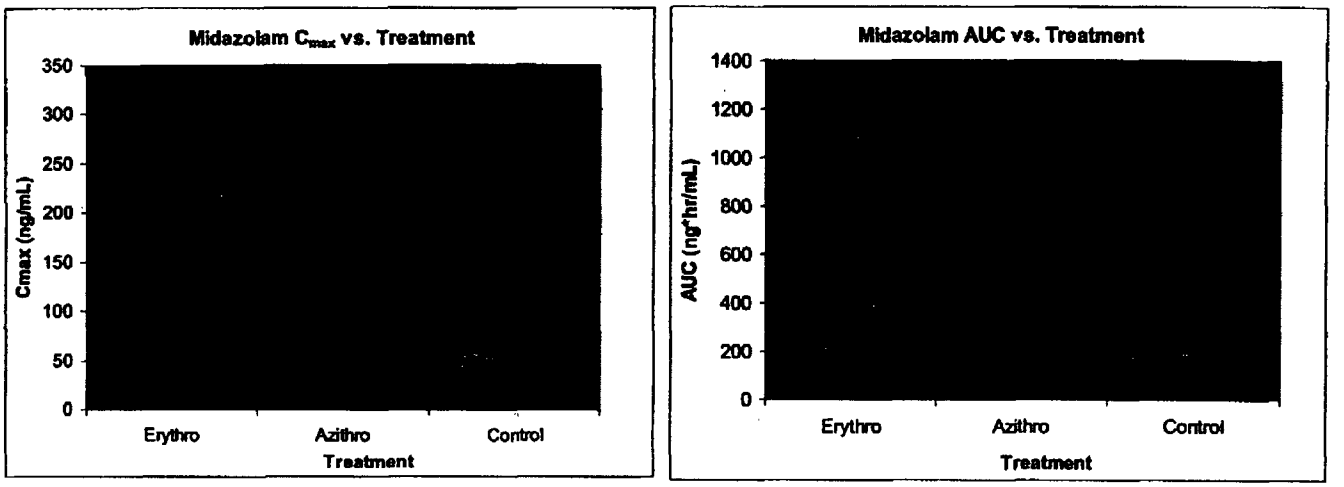


Table 3. Midazolam geometric mean ratios (90% confidence intervals) for erythromycin/control and azithromycin/control

Treatment	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng*hr/mL)
Erythromycin	2.777	3.918
Azithromycin	1.270	1.256

The reviewer also assessed the effect of gender on the interaction between pretreatment with erythromycin or azithromycin and midazolam C_{max} and $AUC_{0-\infty}$. Female subjects were generally associated with a greater geometric mean ratio for C_{max} and $AUC_{0-\infty}$ than male subjects. One should bear in mind, however, that the sample size for male subjects was small (n=4).

Table 4. Midazolam geometric mean ratios for erythromycin/control and azithromycin/control based on gender

	Geometric Mean Ratios	
Group	**C_{max} (ng/mL)**	**$AUC_{0-\infty}$ (ng*hr/mL)**
Erythromycin/Control		
All subjects (n=12)	2.777	3.918
Male (n=4)	2.109	2.793
Female (n=8)	3.187	4.640
Azithromycin/Control		
All subjects (n=12)	1.270	1.256
Male (n=4)	1.285	1.121
Female (n=8)	1.263	1.329

Erythromycin pretreatment significantly increased the duration of sleep relative to azithromycin and to control (Table 5). The results of the digit symbol substitution test, critical flicker fusion test, and visual analog scales were significantly less with erythromycin pretreatment than with azithromycin pretreatment

or control. The difference between the azithromycin pretreatment and control groups were not significant in any test.

Table 5. Mean (SD) midazolam pharmacodynamics for erythromycin, azithromycin, and control

Treatment	Duration of Sleep (min)	DSST (No.)	CFFT (min^{-1})	VAS (mm)
Control	125 (76)	39.7 (11.5)	35.3 (2.0)	19.4 (17.0)
Erythromycin	196 (115)	19.5 (12.1)	32.2 (4.5)	10.8 (11.7)
Azithromycin	113 (77)	37.0 (14.4)	35.4 (2.5)	25.4 (16.9)

DSST -digit symbol substitution test
CFFT - critical flicker fusion test
VAS - visual analog scales

CONCLUSIONS:
Pretreatment with erythromycin increased the C_{max} and $AUC_{0-\infty}$ of midazolam by 171% and 281%, respectively. Pretreatment with azithromycin increased the C_{max} and $AUC_{0-\infty}$ of midazolam by 29% and 27%, respectively.

Pharmacodynamic measurements demonstrated that erythromycin significantly increased the sedation caused by midazolam, whereas no statistically significant changes were detected with azithromycin.

No midazolam dosage adjustment is necessary in patients who are currently receiving azithromycin.

COMMENTS:
Since pharmacodynamic measurements demonstrated a statistically significant increase in sedation with erythromycin pretreatment but not azithromycin, the sponsor stated that midazolam can be safely administered to patients being treated with azithromycin but not erythromycin. The reviewer agrees with the findings.

Statistically significant ($p \leq 0.007$) sequence and subject (sequence) effects were observed for $AUC_{0-\infty}$ but not C_{max} in this open label three-way crossover study. Since the washout period between treatment groups was at least four weeks, the sequence of drug administration may have unexpectedly impacted the $AUC_{0-\infty}$ of midazolam.

Azithromycin concentrations were not quantitated in this study. Thus, the effect midazolam on the pharmacokinetics of azithromycin, if any, has not been determined.

Study 066-092: The Effect of Azithromycin or Clarithromycin on the Pharmacokinetics of Atorvastatin in Healthy Subjects

Date: July 16, 1997 to August 11, 1997
Clinical Site:
Analytical Site:

OBJECTIVES:
To determine the potential pharmacokinetic interaction of concurrent administration of atorvastatin and azithromycin or clarithromycin in healthy male and female subjects.

FORMULATION:
Atorvastatin 10 mg tablets (Lot No. CG-0281096-G2, Warner-Lambert)
Azithromycin 250 mg tablets (FID No. G00267AA, Lot No. ED-G-120-494)
Clarithromycin 500 mg tablets, (FID No. G00475AA-G, Lot No. ED-G-159-497)
Placebo tablets, (FID No. G00461AA, Lot No. ED-G-210-695)

STUDY DESIGN:
A single-center, randomized, open label, three-treatment arm, parallel-group study in healthy male and female volunteers. Subjects were randomized to receive one of the following three regimens: atorvastatin 10 mg QAM on days 1-5, then atorvastatin 10 mg QAM co-administered with azithromycin 500 mg QAM on days 6-8 (Group A); atorvastatin 10 mg QAM on days 1-5, then atorvastatin 10 mg QAM co-administered with clarithromycin 500 mg BID on days 6-8 (Group B); atorvastatin 10 mg QAM on days 1-5, then atorvastatin 10 mg QAM co-administered with placebo QAM on days 6-8 (Group C).

Blood samples for determination of atorvastatin equivalents (concentration of parent compound and active metabolites) were collected pre-dose (time 0) and at 0.5, 1, 2, 3, 4, 6, 9, 12, 16, and 24 hrs post-dose on days 5 and 8.

Criterion	Plasma	Comments
Concentration range	[redacted]	Satisfactory
LLOQ		Satisfactory
Accuracy	90.3% to 106.2%	Satisfactory
Precision (% CV)	2.9% to 8.6%	Satisfactory
Specificity	Satisfactory	Satisfactory

DATA ANALYSIS:
The maximum observed plasma concentration (C_{max}), the time to reach the maximum observed plasma concentration (T_{max}), and the area under the plasma drug concentration-time curve from time 0 to 24 hrs (AUC_{0-24}) were calculated for atorvastatin on days 5 and 8. The AUC_{0-24} was calculated using the linear trapezoidal rule.

STATISTICAL ANALYSIS:
The natural-logarithmically-transformed atorvastatin AUC_{0-24} and C_{max} and the untransformed T_{max} on days 5 and 8 were analyzed using an analysis of variance model with terms for day, treatment group, day-by-treatment group interaction, and subject-within-treatment group.

The reviewer calculated the geometric mean ratio and 90% confidence intervals for atorvastatin log-transformed C_{max} and AUC_{0-24} values between day 5 and day 8 for subjects receiving atorvastatin and either azithromycin, clarithromycin, or placebo using the General Linear Models Procedure of SAS, Version 6.12. The geometric mean ratio was calculated as day 8/day 5 for both C_{max} and AUC_{0-24}.

RESULTS:
One subject in the placebo group discontinued after only one day of atorvastatin treatment (reason not stated). The mean (SD) age, weight, and height of the remaining 36 subjects are shown in Table 1. Age, weight, and height were similar among the three treatment groups.

Table 1. Mean (SD) age, weight, and height of all subjects

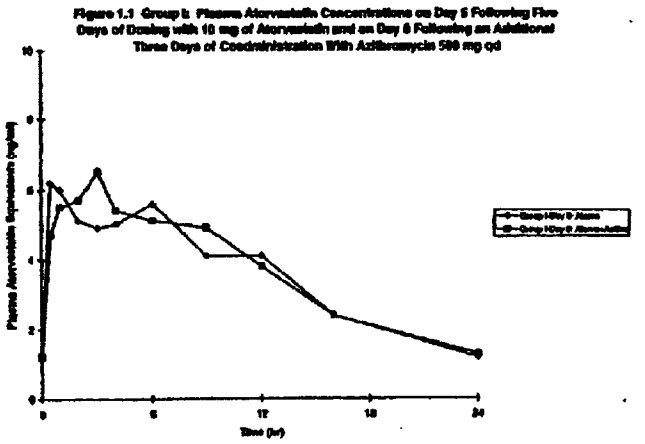
Study Group	Age (yrs)	Weight (kg)	Height (cm)
Azithromycin (n=12)			
All	31.4 (8.7)	76.6 (11.8)	174.2 (8.3)
Male (n=8)	30.9 (8.4)	80.1 (9.9)	178.4 (6.7)
Female (n=4)	32.5 (10.5)	69.8 (13.5)	165.8 (3.0)
Clarithromycin (n=12)			
All	31.6 (8.1)	72.8 (8.0)	170.8 (9.0)
Male (n=4)	29.5 (9.0)	81.2 (6.4)	180.8 (4.3)
Female (n=8)	32.6 (7.9)	68.7 (4.8)	165.9 (5.9)
Placebo (n=12)			
All	27.6 (7.3)	70.7 (11.3)	172.5 (7.8)
Male (n=5)	30.6 (9.0)	81.3 (2.3)	179.2 (5.6)
Female (n=7)	25.4 (5.4)	63.2 (8.5)	167.7 (5.1)

The mean atorvastatin plasma concentration-time profiles for subjects receiving atorvastatin and either azithromycin, clarithromycin, or placebo on day 5 and day 8 are shown in Figure 1. Atorvastatin plasma concentrations were similar between day 5 and day 8 for subjects receiving azithromycin and placebo, although day 5 and day 8 atorvastatin plasma concentrations were lower for subjects receiving azithromycin compared to clarithromycin or placebo. Atorvastatin plasma concentrations were increased following administration of clarithromycin 500 mg BID for 3 days.

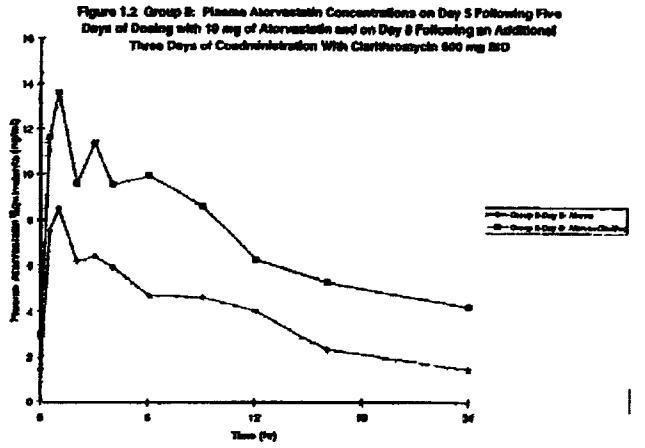
The pharmacokinetic parameters of atorvastatin on day 5 and day 8 in subjects receiving azithromycin, clarithromycin, or placebo are shown in Table 2a. Although the atorvastatin AUC_{0-24} increased 2.4% following the administration of azithromycin, the C_{max} decreased by more than 15%. In contrast, the C_{max} and AUC_{0-24} of atorvastatin increased by 55.9% and 90.4%, respectively following the administration of clarithromycin. However, the atorvastatin C_{max} decreased by more than 20% following the administration of placebo. The atorvastatin AUC_{0-24} in this group remained essentially unchanged.

The sponsor provided no explanation for the decrease in atorvastatin C_{max} following the administration of azithromycin or placebo. However, the atorvastatin plasma concentration-time profiles demonstrated that one subject in the clarithromycin group and two subjects in the placebo group had atorvastatin plasma concentrations that were several-fold greater than other subjects prior to and after receiving clarithromycin. In order to determine the impact of these subject, the reviewer calculated the pharmacokinetic parameters of atorvastatin on day 5 and day 8 with these subjects excluded (Table 2b). The atorvastatin C_{max} was still less on day 8 than day 5 for the placebo group.

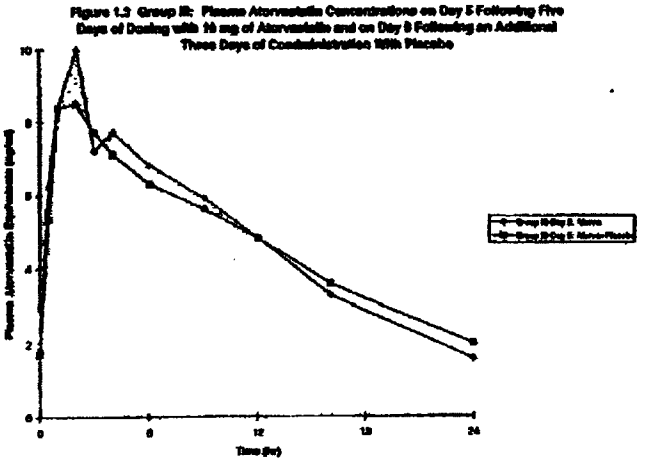
Figure 1. Day 5 and day 8 atorvastatin plasma concentration-time profiles for subjects receiving azithromycin, clarithromycin, or placebo



Atorvastatin + azithromycin



Atorvastatin + clarithromycin



Atorvastatin + placebo

Table 2a. Mean (SD) day 5 and day 8 pharmacokinetic parameters for atorvastatin with azithromycin, clarithromycin, or placebo

	Azithromycin (n=12)		Clarithromycin (n=12)		Placebo (n=12)	
Treatment	Day 5	Day 8	Day 5	Day 8	Day 5	Day 8
AUC_{0-24} (ng*hr/mL)	85.4 (19.9)	87.5 (26.9)	90.7 (44.3)	172.7 (108.7)	116.7 (54.1)	115.2 (43.3)
C_{max} (ng/mL)	8.4 (2.5)	7.1 (2.6)	9.7 (8.7)	15.1 (11.1)	13.4 (9.9)	10.6 (5.0)
T_{max} (hrs)	2.8 (3.5)	3.0 (2.4)	1.9 (1.7)	1.5 (1.0)	1.9 (1.4)	1.7 (1.1)

Table 2b. Mean (SD) day 5 and day 8 pharmacokinetic parameters for atorvastatin with azithromycin, clarithromycin (excluding subject #23), or placebo (excluding subjects #17 and #22)

	Azithromycin (n=12)		Clarithromycin (n=11)		Placebo (n=10)	
Treatment	Day 5	Day 8	Day 5	Day 8	Day 5	Day 8
AUC_{0-24} (ng*hr/mL)	85.4 (19.9)	87.5 (26.9)	79.6 (23.0)	144.3 (48.7)	89.7 (37.3)	103.0 (35.2)
C_{max} (ng/mL)	8 4 (2.5)	7.1 (2.6)	7.3 (2.1)	12.3 (5.9)	9.7 (3.8)	9.0 (3.6)

The geometric mean ratios and 90% confidence intervals for atorvastatin C_{max} and AUC_{0-24} are shown in Table 3. The 90% confidence intervals for atorvastatin C_{max} from the azithromycin group were less than 0.80 and within 0.80 to 1.25 for C_{max} and AUC_{0-24}, respectively. In contrast, the 90% confidence intervals for atorvastatin C_{max} from the clarithromycin group exceeded 1.25 for C_{max} and AUC_{0-24}, respectively. The 90% confidence intervals for atorvastatin C_{max} from the placebo group were less than 0.80 and greater than 1.25 for C_{max} and AUC_{0-24}, respectively

Table 3. Atorvastatin geometric mean ratios (90% confidence intervals) for day 8/day 5 for subjects receiving azithromycin, clarithromycin, and placebo

Treatment	C_{max}	AUC_{0-24}
Azithromycin	0.827 (0.633 to 1.082)	1.006 (0.813 to 1.246)
Clarithromycin	1.555 (1.005 to 2.408)	1.818 (1.293 to 2.558)
Placebo	0.879 (0.566 to 1.364)	1.024 (0.729 to 1.437)

Stick plots demonstrating individual and mean C_{max} and AUC_{0-24} values are shown in Figure 2. The inter-subject variability was less in the azithromycin group than either the clarithromycin or placebo groups.

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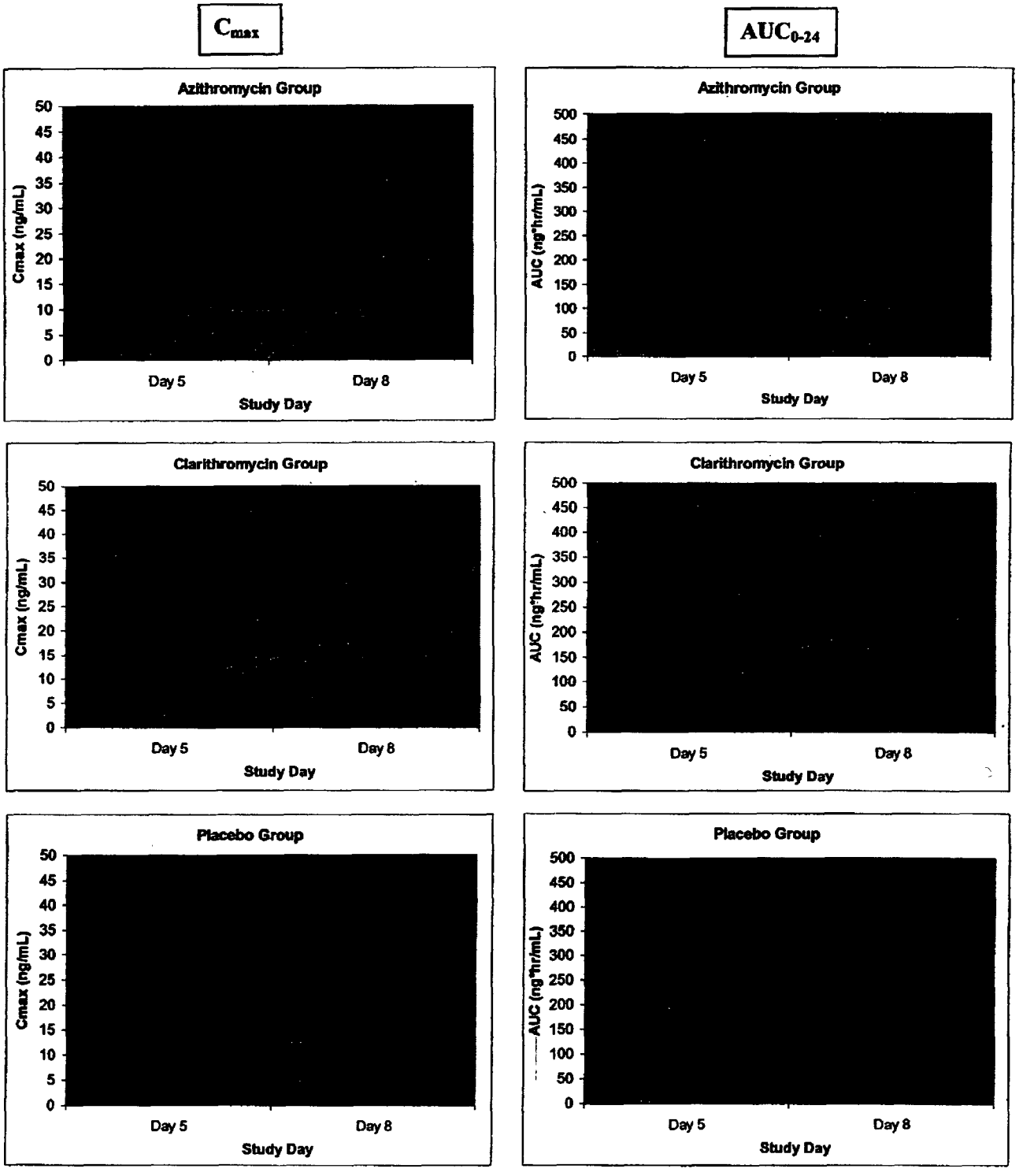
Figure 2. Stick plots of individual (●) and mean (■) atorvastatin C_{max} and AUC_{0-24} values on day 5 and day 8 from subjects in the azithromycin, clarithromycin, and placebo groups



SAFETY:
No subjects discontinued the study for safety-related reasons. The overall incidence of side effects (all causality) was higher for subjects receiving atorvastatin/clarithromycin (58%) than atorvastatin/ azithromycin (33%) and atorvastatin/placebo (25%) as shown in Table 4.

Table 4. Incidence of adverse events for each treatment group

Category	Atorvastatin/ Azithromycin	Atorvastatin/ Clarithromycin	Atorvastatin/ Placebo
Adverse events: All causality	4/12 (33%)	7/12 (58%)	3/12 (25%)
Adverse events: Treatment-related	4/12 (33%)	7/12 (58%)	3/12 (25%)
Intercurrent illnesses	1/12 (8%)	3/12 (33%)	3/12 (25%)

CONCLUSIONS:
The atorvastatin mean C_{max} decreased by 15.5% whereas the AUC_{0-24} increased by 2.4% following the administration of azithromycin.

The overall incidence of side effects between subjects receiving atorvastatin/azithromycin and atorvastatin/placebo were similar.

No adjustment in atorvastatin dosage is recommended for patients receiving co-administration of atorvastatin and azithromycin.

COMMENTS:
The day 8/day 5 90% confidence interval for the atorvastatin C_{max} and AUC_{0-24} geometric mean ratio exceeded the 0.80 to 1.25 range (on both sides) for the placebo group. Since the confidence interval included a value of 1.00, the significance of this finding is unknown and may be due to excessive inter-subject variability as well as the study design. The modest changes in atorvastatin C_{max} and AUC_{0-24} with the azithromycin group are probably not clinically relevant.

Although the study was a parallel design, the reviewer analyzed the data as a one-sequence cross-over design (without sequence and period effects) to calculate a geometric mean ratio and 90% confidence interval. This was performed since the subjects in each treatment group could be compared to themselves and act as their own control. This method of analysis assesses a treatment effect but does not allow for the assessment of sequence and period effects.

Azithromycin concentrations were not quantitated in this study. Thus, the effect of atorvastatin on the pharmacokinetics of azithromycin, if any, has not been evaluated.

Study 93CK16-0624: A Multiple Dose Study to Evaluate the Pharmacokinetic and/or ECG Effects on Concomitant Administration of a Course of Azithromycin Therapy With Cetirizine

Date: August 24, 1993 to October 2, 1993
Clinical Site:
Analytical Site: [ ]

OBJECTIVES:
To determine whether cetirizine, in the presence of azithromycin, induces a prolongation of the QT interval and to determine whether there are pharmacokinetic interactions between cetirizine and azithromycin.

FORMULATION:
Azithromycin 250 mg capsules (Lot No. C2150, Pfizer, US)
Placebo azithromycin capsules (Lot No. C1225, Pfizer, US)
Cetirizine 10 mg tablets, (Lot No. C0385, UCB, Belgium,)
Placebo cetirizine tablets, (Lot No. C0378, UCB, Belgium)

STUDY DESIGN:
A single-center, randomized, open label, multiple-dose, parallel-group study in 42 healthy young male volunteers. Subjects were randomized to receive one of the three regimens in the table below during an 11-day period of drug administration.

Study Day	Group A	Group B	Group C
Day 1	Placebo cetirizine QD	Placebo cetirizine QD	Placebo cetirizine QD
Days 2-6	Cetirizine 2 × 10 mg PO QD	Cetirizine 2 × 10 mg PO QD	Placebo cetirizine QD
Day 7	Azithromycin 2 × 250 mg PO QD Cetirizine 2 × 10 mg PO QD	Placebo azithromycin QD Cetirizine 2 × 10 mg PO QD	Placebo azithromycin QD Placebo cetirizine QD
Days 8-11	Azithromycin 250 mg PO QD Cetirizine 2 × 10 mg PO QD	Placebo azithromycin QD Cetirizine 2 × 10 mg PO QD	Placebo azithromycin QD Placebo cetirizine QD

Study drugs were administered at approximately 7 AM each morning with 180 mL of water.

ECGs obtained were 12-leads with a 15 second 3 lead (I, II, and precordial lead with the longest mean QT) rhythm strip. ECGs were recorded on days 1, 6, and 11 immediately prior to dosing and at 1, 2, 3, 4, 6, 8, 10, 12, and 16 hrs post-dose. ECGs were also recorded prior to dosing, 1 hr, and 24 hrs post-dose on days 2 and 7, and 24 hrs after the day 11 dose (morning of Day 12). All ECGs were read by a consultant cardiologist who was blinded to the treatment and time of recording. A QT correction (QTc) was subsequently computed by Hodges' formula.

Potential subjects with a prolonged QT interval (>400 msec for QTc) or any other clinically significant abnormality on a screening ECG, or any clinically significant laboratory abnormality were disqualified.

Blood samples for determination of cetirizine concentration were collected immediately prior to dosing and at 1, 2, 3, 4, 6, 8, 10, 12, and 16 hrs post-dose on day 6 and 11. Blood samples were obtained pre-dose and 1 hr post-dose on days 1, 2, 7, and 24 hrs post-dose on days 2 and 7. A final blood sample was obtained 24 hrs after the day 11 dose (morning of day 12).

Blood samples for determination of azithromycin concentration were collected predose (time 0) and at 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hrs post-dose on day 11.

Criterion	Plasma	Comments
Concentration range	[redacted]	Satisfactory
LLOQ	[redacted]	Satisfactory
Linearity	$R^2 \geq 0.9994$	Satisfactory
Accuracy	99.4% to 102.9%	Satisfactory
Precision (% CV)	2.4% to 3.5%	Satisfactory
Specificity	Satisfactory	Satisfactory
Stability	Long term at -20°C	Satisfactory

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Criterion	Plasma	Comments
Concentration range	[redacted]	Satisfactory
LLOQ	[redacted]	Satisfactory
Linearity	$R^2 \geq 0.9984$	Satisfactory
Accuracy	94.2% to 100.7%	Satisfactory
Precision (% CV(	5.5% to 7.3%	Satisfactory
Specificity	Satisfactory	Satisfactory
Stability	Freeze-thaw, extract stability, long term at -70°C, short term at RT and 5°C, whole blood	Satisfactory

DATA ANALYSIS:

The maximum observed plasma concentration (C_{max}), the time to reach the maximum observed plasma concentration (T_{max}), and the area under the plasma drug concentration-time curve through 24 hrs post-dosing (AUC_{0-24}) were calculated for cetirizine on Days 6 and 11 for subjects in Groups A and B. The disposition half-life ($t_{1/2}$), was computed as 0.693 divided by the disposition rate constant, β. The disposition rate constant was determined from the slope of the least squares regression line fitted to the terminal portion of the log-linear concentration-time curve. These parameters, excluding $t_{1/2}$, were also calculated for azithromycin on Day 11 for subjects in Group A.

The C_{max} and AUC_{0-24} was calculated for azithromycin on day 11 for subjects in Group A.

For study days 6 and 11, the following variables were computed for changes from baseline (at corresponding times the ECG was obtained) in the ECG QT intervals, using Hodges' correction (Hodges' QTc = QT + 1.75*((60/RR)-60)): AVGCHG (mean of the 11 ECG changes over hour 0 to 24), AUCCHG (area under the changes curve from hour 0 to 24 calculated by the trapezoidal rule), MAXCHG (maximum of the 11 changes (sign included) over hour 0 to 24), and HR2CHG (change at hr 2 only). These ECG parameters were analyzed comparatively among treatments using analysis of variance procedures appropriate to a repeated measured model.

STATISTICAL ANALYSIS:

The reviewer calculated the geometric mean ratio (GMR) and 90% confidence interval for log-transformed C_{max} and $AUC_{0-\infty}$ values using the General Linear Models Procedure of SAS version 6.12. The GMR was calculated for cetirizine alone/cetirizine + azithromycin and cetirizine alone/cetirizine + placebo for both C_{max} and $AUC_{0-\infty}$.

RESULTS:
The mean (SD) age, weight, and height are shown in Table 1. Age, weight, and height were similar among the three treatment groups.

Table 1. Mean (SD) age, weight, and height of all subjects

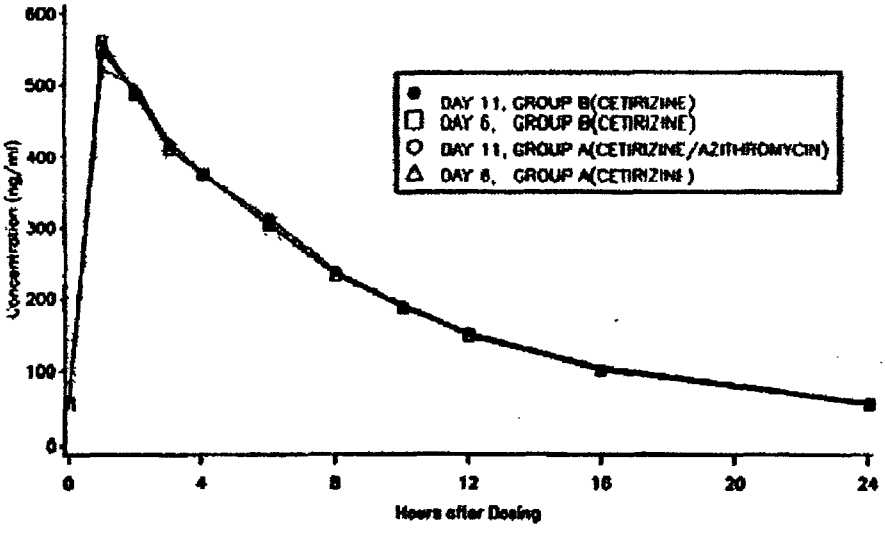
Study Group	Age (yrs)	Weight (lbs)	Height (in)
Group A (n=14)	28.2 (5.7)	165.1 (14.6)	71.2 (2.3)
Group B (n=14)	26.1 (6.5)	164.3 (24.0)	70.8 (4.3)
Group C (n=14)	26.7 (6.3)	170.1 (13.2)	72.5 (1.8)

Group A = Cetirizine + azithromycin
Group B = Cetirizine + placebo
Group C = Placebo alone

The mean (SD) azithromycin C_{max} and AUC_{0-24} were 0.22 (0.08) µg/mL and 1.41 (0.44) µg*hr/mL, respectively. The mean (SD) T_{max} was 2.79(0.43) hrs. These values were comparable to published values of azithromycin following administration of the 5-day regimen.

The mean cetirizine plasma concentration-time profiles for Groups A and B are shown in Figure 1. The plasma profiles were similar between day 6 and day 11 for both Group A and Group B.

Figure 1. Day 6 and Day 11 cetirizine plasma concentration-time profiles for Group A and Group B



The pharmacokinetic parameters of cetirizine from days 6 and 11 were similar whether subjects received azithromycin or placebo on days 7 to 11 (Table 2). The C_{max} and AUC_{0-24} increased approximately 3.2% and 1.9% with administration of azithromycin and 0.8% and 1.9% with administration of placebo, respectively. The mean difference (day 6 vs. day 11) of all other pharmacokinetic parameters (except T_{max}) was less than 3%.

Table 2. Mean (SD) day 6 and day 11 pharmacokinetic parameters for cetirizine from Group A and Group B

	Group A (n=14)		Group B (n=14)	
Treatment	**Day 6**	**Day 11**	**Day 6**	**Day 11**
AUC_{0-24} (ng*hr/mL)	4,756 (705)	4,847 (774)	4,760 (676)	4,848 (733)
C_{max} (ng/mL)	554 (81)	572 (91)	562 (80.7)	567 (96.9)
T_{max} (hrs)	1.14 (0.36)	1.14 (0.36)	1.21 (0.43)	1.29 (0.47)
CL/F (L/hr)	71.5 (10.7)	70.4 (11.5)	71.3 (9.8)	70.2 (10.6)
Vd/F (L)	48.9 (5.5)	49.0 (5.6)	48.4 (5.2)	49.6 (7.1)
$T_{1/2}$ (hrs)	7.97 (0.83)	8.13 (0.92)	7.95 (1.16)	8.23 (1.03)

The geometric mean ratios and 90% confidence intervals for cetirizine C_{max} and AUC_{0-24} are shown in Table 3. The 90% confidence intervals were all within the 0.80 to 1.25 interval and no statistically significant pharmacokinetic drug interaction was observed between cetirizine and azithromycin.

Table 3. Cetirizine geometric mean ratios (90% confidence intervals) for day 11/day 6 from Group A and Group B

Treatment	C_{max}	AUC_{0-24}
Group A	1.029 (0.927 to 1.142)	1.017 (0.917 to 1.129)
Group B	1.003 (0.901 to 1.116)	1.017 (0.922 to 1.122)

Stick plots demonstrating individual C_{max} and AUC_{0-12} values are shown in Figures 1-2. The degree of inter-subject variability was similar between the cetirizine + azithromycin group and cetirizine + placebo group.

Figure 2. Stick plots of individual (●) and mean (■) cetirizine C_{max} values on day 6 and day 11 for Group A and Group B

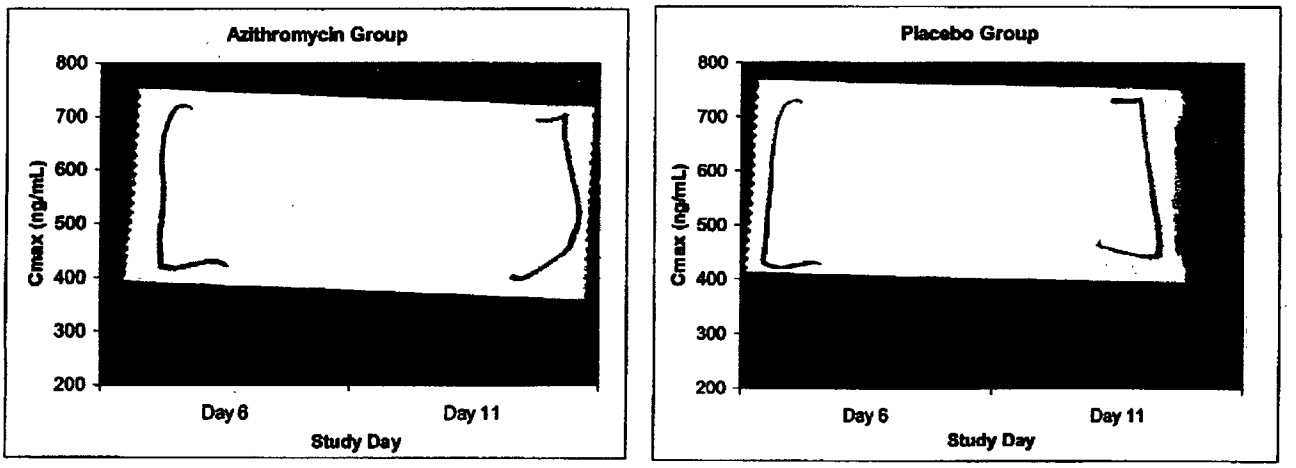
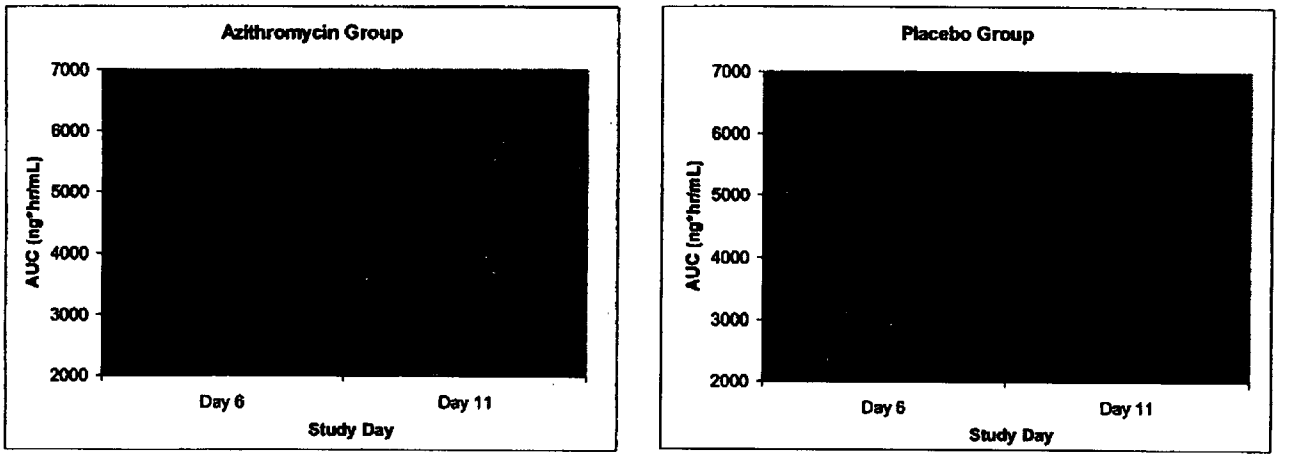


Figure 3. Stick plots of individual (●) and mean (■) cetirizine AUC_{0-12} values on day 6 and day 11 for Group A and Group B



All three treatment groups (Groups A, B, and C) showed small mean increases from baseline after 5 and 10 doses of cetirizine with respect to each of the four derived QTc variables (with the exception of day 6 HR2CHG for the cetirizine + placebo group, Table 4). Differences among treatment groups were not statistically significant for any analysis.

Table 4. Summary of ECG parameters from baseline Hodges' QTc

	Placebo	Cetirizine + Placebo	Cetirizine + Azithromycin	p-value
Baseline AVGQTc	409	404	410	
Day 6	1.62	0.69	0.27	0.829
Day 11	1.33	2.01	2.41	0.903
Δ Day 6 to Day 11	-0.29	1.32	2.14	0.327
Baseline AUCQTc	9834	9716	9837	
Day 6	47.6	21.4	5.5	0.702
Day 11	14.2	36.0	28.9	0.917
Δ Day 6 to Day 11	-33.4	14.6	23.4	0.376
Day 6	23.21	17.36	21.36	0.284
Day 11	25.00	24.14	21.79	0.799
Δ Day 6 to Day 11	1.79	6.79	0.43	0.247
Baseline QTc	408	403	411	
Day 6	6.79	-0.29	1.79	0.500
Day 11	3.57	0.36	2.21	0.911
Δ Day 6 to Day 11	-3.21	0.64	0.43	0.702

AVGCHG - mean of the 11 ECG changes over hour 0 to 24
AUCCHG - area under the change curve from hour 0 to 24 calculated by the trapezoidal rule
MAXCHG - maximum of the 11 changes (sign included) over hour 0 to 24
HR2CHG - change at hour 2 only

At study day 11, the mean AVGCHG of 2.41 msec for cetirizine + azithromycin, 2.01 msec for cetirizine alone, and 1.33 msec for placebo were not significantly different among the treatments.

Individual subject day 11 AVGCHG values ranged from -18.82 to 13.00 msec for cetirizine + azithromycin, -4.09 to 6.55 msec for cetirizine alone, and -9.64 to 17.82 msec for placebo. Thus, the range in individual subject day 11 AVGCHG values were similar between cetirizine + azithromycin and placebo treatment groups and both were greater than the range of cetirizine alone.

The results for AUCCHG, MAXCHG, and HR2CHG demonstrate that a 5-day regimen of azithromycin added to cetirizine therapy does not significantly affect QTc.

CONCLUSIONS:
The mean cetirizine C_{max} and AUC_{0-24} increased 3.2% and 1.9%, respectively, when co-administered with azithromycin. The 90% confidence interval of the C_{max} and AUC_{0-24} geometric mean ratio was 0.927 to 1.142 and 0.917 to 1.129, respectively.

The addition of azithromycin to cetirizine treatment appears to have no additional effect on QTc changes.

No dosage adjustment of cetirizine is warranted when azithromycin is co-administered with cetirizine.

COMMENTS:
The sponsor calculated the change in QTc for each subject on day 6 and day 11 using the baseline ECG recording (day 1) that corresponded to the time of the day 6 and day 11 ECG recording. This method is more informative than using a single baseline ECG recording on day 1 since it takes diurnal variability into account.

The sponsor failed to investigate the relationship between cetirizine concentration and change in QTc. However, since there was not a significant alteration of cetirizine pharmacokinetics when it was co-administered with azithromycin and no significant change in QTc with cetirizine alone or cetirizine + placebo compared to placebo, assessment of this relationship may be unnecessary.

Although the study was a parallel-design, the reviewer analyzed the data as a one-sequence cross-over design (without sequence and period effects) to calculate a geometric mean ratio and 90% CI. The reviewer felt this was acceptable since each treatment group (cetirizine + azithromycin or cetirizine + placebo) could be compared to itself and act as its own control. Although this method of analysis assesses a treatment effect, it does not allow for the assessment of sequence and period effects.

Study 148-238: An Open, Randomised, Placebo Controlled, Parallel Group Study to Investigate the Effects of Azithromycin (500 mg OD × 3 Days) on the Pharmacokinetics of a Single 100 mg Dose of Sildenafil

Date: November 25, 1997 to February 5, 1998
Clinical Site:
Analytical Site:

BACKGROUND:
The metabolism of sildenafil *in vitro* is dependent on cytochrome P450 enzymes. A major route of metabolism is N-demethylation to UK-103,320, the formation of which is mediated by a high affinity, low capacity enzyme (CYP 2C9) and a low affinity, high capacity enzyme (CYP 3A4). The relative contribution of these enzymes to the metabolism of sildenafil depends upon the concentration of the drug in the liver. During the absorption phase, when hepatic portal vein drug concentrations are high, CYP 3A4 is likely to be the predominant route of metabolism. However, during the post-absorption phase, CYP 2C9 may be predominant.

Erythromycin at steady state (500 mg PO BID for 5 days) has previously been shown to increase the systemic exposure of sildenafil by 182% (Viagra label, 1/2000). Azithromycin does not appear to be an inhibitor of CYP 3A4 and may be an alternative to erythromycin in patients receiving sildenafil.

OBJECTIVES:
To investigate the effects of multiple doses of azithromycin (500 mg once daily for three days) on the pharmacokinetics of a single 100 mg dose of sildenafil and to evaluate the safety and toleration of sildenafil co-administered with azithromycin.

FORMULATION:
Sildenafil 100 mg tablets (FID No. S00502AA, Lot No. 4469-115)
Azithromycin 250 mg tablets (FID No. G00267AA, Lot No. 97D0S016)
Placebo tablets (FID No. G00501AA, Lot No. 97D0S017)

STUDY DESIGN:
A single-center, randomized, open label, placebo-controlled, parallel-group study of a single oral dose of sildenafil co-administered with multiple doses of azithromycin. Twenty-four healthy male volunteers received a single 100 mg dose of sildenafil on day 1 and were then randomized to receive either azithromycin 500 mg (2 × 250 mg) or placebo once daily for three days, with a further single dose of sildenafil 100 mg administered on day 4 one hr after dosing with azithromycin or placebo. Sildenafil was administered on day 1 three hrs after a standard light breakfast with 240 mL of water. Azithromycin or placebo was administered two hrs after a standard light breakfast with 240 mL of water on days 2-4.

Blood samples for determination of sildenafil and metabolite (UK-103,320) concentrations were collected on days 1 and 4 at pre-dose (time 0) and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, and 24 hrs post sildenafil dosing.

Criterion	Plasma	Comments
Concentration range	[redacted]	Satisfactory
LLOQ	[redacted]	Satisfactory
Linearity	R^2 ≥0.9993	Satisfactory
Accuracy	95.8% to 98.7%	Satisfactory
Precision (% CV)	2.3% to 7.7%	Satisfactory
Specificity	Satisfactory	Satisfactory

Criterion	Plasma	Comments
Concentration range	[redacted]	Satisfactory
LLOQ	[redacted]	Satisfactory
Linearity	R^2 ≥0.9985	Satisfactory
Accuracy	92.5% to 98.3%	Satisfactory
Precision (% CV)	2.6% to 4.5%	Satisfactory
Specificity	Satisfactory	Satisfactory

DATA ANALYSIS:

The maximum observed plasma concentration (C_{max}) and the time to reach the maximum observed plasma concentration (T_{max}) were taken directly from the concentration-time data. The area under the plasma concentration-time curve from time 0 to the last quantifiable concentration (AUC_{0-t}) was calculated for sildenafil on days 1 and 4 using the linear trapezoidal method. The terminal elimination phase rate constant (K_{el}) was calculated by linear regression of the log-linear plasma concentration-time curve. The area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$) was calculated from the AUC_{0-t} and the last quantifiable concentration extrapolated to infinity (C_{last}/K_{el}). The apparent terminal elimination half-life ($t_{1/2}$) was calculated as $\ln(2)/K_{el}$.

STATISTICAL ANALYSIS:

AUC, C_{max} (both natural log-transformed), K_{el}, and T_{max} for both sildenafil and UK-103,320 were subjected to an analysis of variance appropriate to the study design. The two treatment groups were compared by estimating the difference between day 1 and day 4 values for the two groups, together with the corresponding standard error and 95% confidence interval.

The reviewer calculated the geometric mean ratio and 90% confidence intervals for sildenafil log-transformed C_{max} and $AUC_{0-\infty}$ values between day 1 and day 4 for subjects receiving either azithromycin or placebo using the General Linear Models Procedure of SAS, Version 6.12.

RESULTS:

The mean (SD) demographics are shown in Table 1. Age, weight, and height were similar among the two treatment groups. Approximately one-third of subjects in each group were current smokers (≤10 cigarettes/day) and most subjects were current drinkers (≤28 units/week).

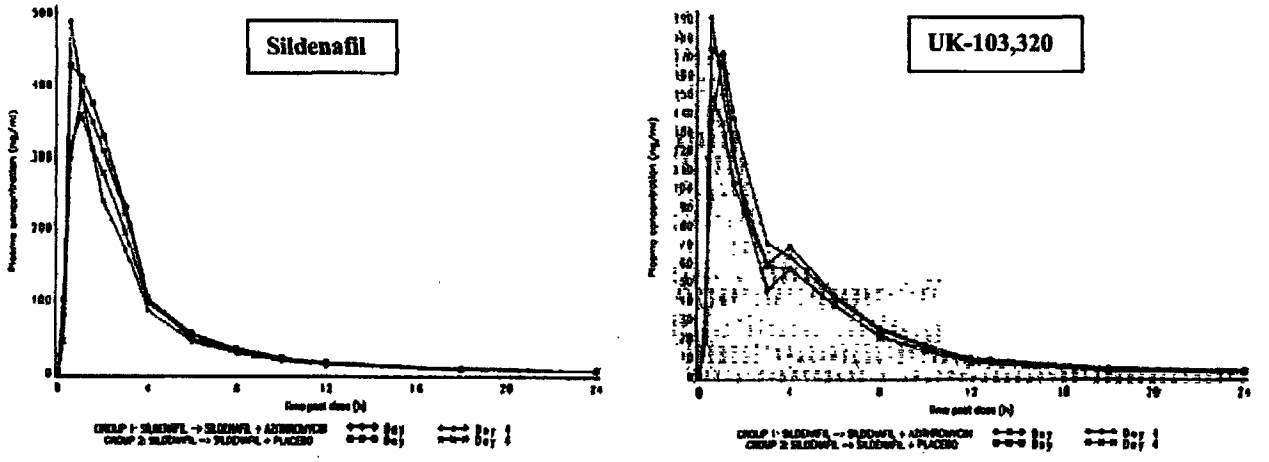
Table 1. Mean (SD) demographics of all subjects

	Azithromycin (n=12)	Placebo (n=12)
Age (yrs)	23.6 (3.9)	22.3 (2.1)
Weight (kg)	71.0 (7.1)	71.2 (9.7)
Height (cm)	178.9 (7.2)	174.3 (6.2)
Smoking history (%)[a]		
non-smoker	33%	33%
ex-smoker	33%	25%
current smoker	33%	42%
Drinking history		
current drinker	100%	92%
units/week[b]	11.8 (7.8)	10.3 (8.4)

a-inclusion criteria allowed smokers who smoke up to 10 cigarettes per day to be enrolled
b-1 unit = 285 mL of beer, 25 mL of spirits, or 1 glass of wine

The mean sildenafil and UK-103,320 plasma concentration-time profiles on days 1 and 4 for subjects receiving sildenafil and either azithromycin or placebo are shown in Figure 1. Although the mean concentration-time profiles were similar between the treatment groups, the mean peak sildenafil plasma concentrations were greater on day 4 than day 1 for the azithromycin group and day 1 than day 4 for the placebo group, respectively. A similar relationship was observed for mean UK-103,320 plasma concentrations.

Figure 1. Day 1 and day 4 sildenafil and UK-103,320 plasma concentration-time profiles for subjects receiving azithromycin or placebo



The pharmacokinetic parameters of sildenafil on day 1 and day 4 in subjects receiving azithromycin or placebo are shown in Table 2a. Following the administration of azithromycin, the sildenafil C_{max} increased by 15.7% whereas the $AUC_{0-\infty}$ decreased by 7.1%. In contrast, the sildenafil C_{max} and $AUC_{0-\infty}$ decreased by 17.0% and 13.5%, respectively when administered with placebo. The mean T_{max} in the azithromycin group decreased from 1.15 hrs (day 1) to 0.79 hrs (day 4) and may have contributed to the increase in C_{max}. There was no change in T_{max} among the placebo group.

The pharmacokinetic parameters of UK-103,320 on day 1 and day 4 in subjects receiving azithromycin or placebo are shown in Table 2b. Following the administration of azithromycin, the UK-103,320 C_{max}

increased by 13.3% whereas the $AUC_{0-\infty}$ decreased by 4.9%. Similar to sildenafil, the UK-103,320 C_{max} and $AUC_{0-\infty}$ decreased by 9.4% and 11.2%, respectively when administered with placebo.

Table 2a. Mean (SD) day 1 and day 4 pharmacokinetic parameters for sildenafil with azithromycin or placebo

	Azithromycin (n=12)		Placebo (n=12)	
Treatment	**Day 1**	**Day 4**	**Day 1**	**Day 4**
AUC_{0-t} (ng*hr/mL)	1,345 (315)	1,248 (315)	1,475 (475)	1,275 (381)
$AUC_{0-\infty}$ (ng*hr/mL)	1,359 (313)	1,262 (318)	1,489 (476)	1,288 (382)
C_{max} (ng/mL)	485 (187)	561 (170)	504 (226)	418 (120)
T_{max} (hrs)	1.15 (0.77)	0.79 (0.50)	0.96 (0.54)	0.96 (0.50)
$T_{1/2}$ (hrs)[a]	4.53	4.50	4.53	4.29

a - harmonic mean

Table 2b. Mean (SD) day 1 and day 4 pharmacokinetic parameters for UK-103,320 with azithromycin or placebo

	Azithromycin (n=12)		Placebo (n=12)	
Treatment	**Day 1**	**Day 4**	**Day 1**	**Day 4**
AUC_{0-t} (ng*hr/mL)	674 (223)	651 (190)	605 (232)	543 (146)
$AUC_{0-\infty}$ (ng*hr/mL)	698 (231)	663 (194)	622 (239)	552 (146)
C_{max} (ng/mL)	209 (75)	236 (35)	204 (117)	185 (83)
T_{max} (hrs)	1.04 (0.50)	0.79 (0.50)	0.88 (0.38)	0.88 (0.43)
$T_{1/2}$ (hrs)[a]	6.38	4.59	6.44	4.57

a - harmonic mean

The geometric mean ratios (day 4/day 1) and 90% confidence intervals for sildenafil and UK-103,320 C_{max} and $AUC_{0-\infty}$ are shown in Tables 3a and 3b. The 90% confidence intervals for sildenafil C_{max} was outside of the 0.80 to 1.25 range for the azithromycin group at the upper end (exceed 1.25) and the placebo group at the lower end (less than 0.80). The 90% confidence interval for sildenafil $AUC_{0-\infty}$ was less than the 0.80 to 1.25 range for the azithromycin and placebo groups. The results were similar with UK-103,320 for both groups as compared to sildenafil.

Table 3a. Sildenafil geometric mean ratios (90% confidence intervals) for day 4/day 1 in subjects receiving azithromycin or placebo

Treatment	C_{max}	$AUC_{0-\infty}$
Azithromycin	1.162 (0.860 to 1.569)	0.916 (0.750 to 1.118)
Placebo	0.877 (0.664 to 1.159)	0.872 (0.702 to 1.085)

Table 3b. UK-103,320 geometric mean ratios (90% confidence intervals) for day 4/day 1 in subjects receiving azithromycin or placebo

Treatment	C_{max}	$AUC_{0-\infty}$
Azithromycin	1.204 (0.955 to 1.519)	0.961 (0.768 to 1.202)
Placebo	0.946 (0.683 to 1.310)	0.917 (0.735 to 1.144)

The individual and mean C_{max} and AUC values of sildenafil are shown in the stick plots below (Figures 2-3). The azithromycin group was associated with more inter-subject variability than the placebo group as well as more subjects having a greater C_{max} on day 4 than day 1 compared to the placebo group. The $AUC_{0-\infty}$ values were similar between the two groups.

Figure 2. Stick plots of individual (●) and mean (■) C_{max} values for sildenafil from subjects in the azithromycin and placebo groups

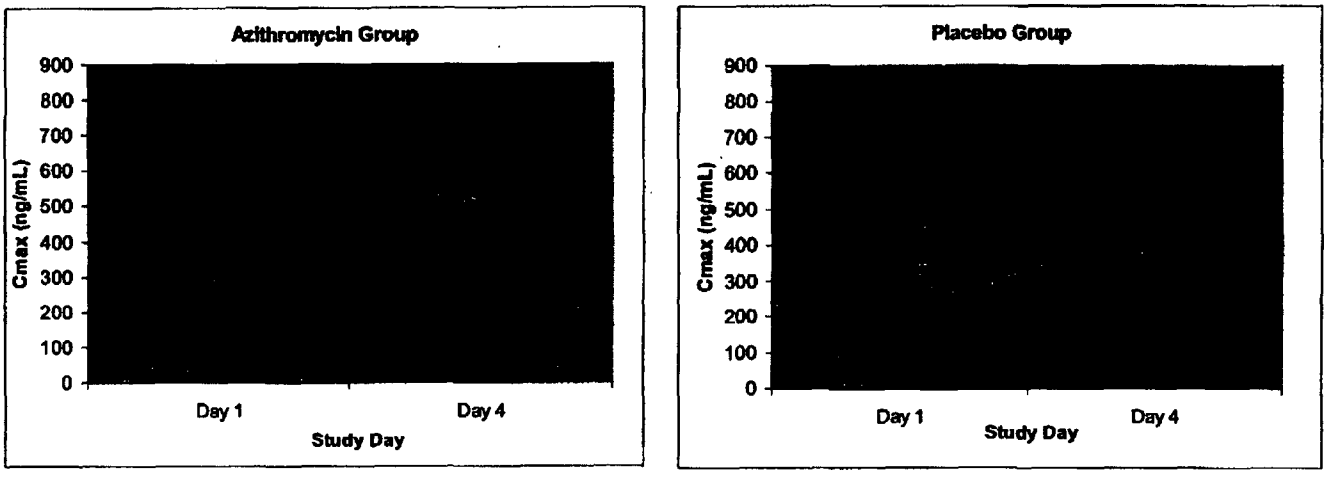
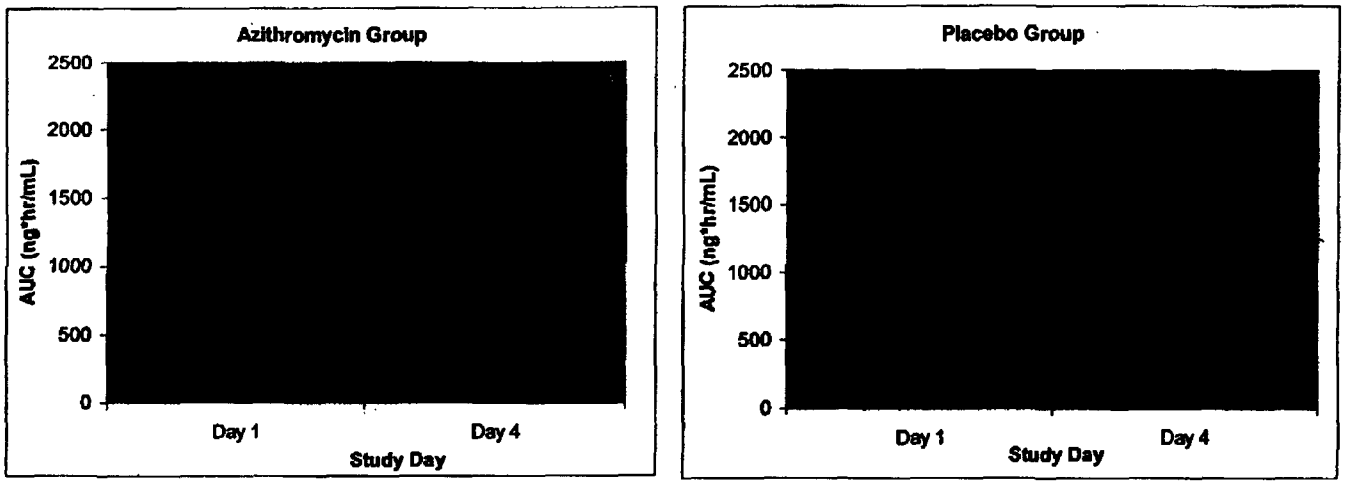


Figure 3. Stick plots of individual (●) and mean (■) $AUC_{0-\infty}$ values for sildenafil from subjects in the azithromycin and placebo groups



SAFETY:

There were no discontinuations due to adverse events. Although the incidence of treatment related adverse events was greater in the azithromycin group following administration of sildenafil alone (day 1), the incidence was similar when sildenafil was administered with azithromycin or placebo (day 4).

Table 4. Subjects with adverse events by treatment group and treatment period

	Sildenafil + Azithromycin (n=12)			Sildenafil + Placebo (n=12)		
Treatment Emergent Adverse Events	**Sildenafil**	**Atorvastatin**	**Sildenafil + Azithromycin**	**Sildenafil**	**Placebo**	**Sildenafil + Placebo**
All Causality	11 (92%)	4 (33%)	8 (67%)	8 (67%)	4 (33%)	7 (58%)
Treatment Related						
Mild to moderate	10 (83%)	1 (8%)	7 (58%)	7 (67%)	3 (25%)	6 (50%)
Severe	0	0	0	1 (8%)	0	0

CONCLUSIONS:
The administration of sildenafil following azithromycin 500 mg QD × 3 days increased the mean sildenafil C_{max} by 15.7%.

The overall number of subjects reporting adverse events was similar in both treatment groups and the majority of these were mild to moderate.

Although azithromycin increased sildenafil and UK-103,320 plasma concentrations, the data were highly variable and no dosage adjustment of sildenafil is warranted in patients receiving azithromycin.

COMMENTS:
The day 4/day 1 90% confidence interval for the sildenafil C_{max} geometric mean ratio exceeded 1.25 and the 90% confidence interval for the sildenafil $AUC_{0-\infty}$ geometric mean ratio was less than 0.80 for the azithromycin group. The 90% confidence intervals for the sildenafil C_{max} and $AUC_{0-\infty}$ geometric mean ratio was less than 0.80 for the placebo group. The high degree of inter-subject variability and parallel-group design complicate the interpretation of the data. The reason for the observed decrease in C_{max} and AUC for the placebo group is unknown and may be attributed in part to the study design. However, the modest increase in sildenafil C_{max} when co-administered with azithromycin is unlikely to be clinically relevant.

Although subjects with a history of smoking and drinking were enrolled in the study, it is unlikely that this impacted the study results. Tobacco products may lead to an induction of CYP1A2 and ethanol is substrate for CYP 2E1, but sildenafil is primarily metabolized by CYP3A4 and to a lesser extent CYP2C9. Thus, it is unlikely that the observed results are due to the subject's smoking and drinking history.

Although the study was a parallel design, the reviewer analyzed the data as a one-sequence cross-over design (without sequence and period effects) to calculate a geometric mean ratio and 90% confidence interval. This was performed since the subjects in each treatment group could be compared to themselves and act as their own control. This method of analysis assesses a treatment effect but does not allow for the assessment of sequence and period effects.

Azithromycin concentrations were not quantitated in this study. Thus, the effect of sildenafil on the pharmacokinetics of azithromycin, if any, has not been evaluated.

Study 066-221: A Double Blind, Placebo Controlled, Parallel Group Study to Investigate the Effect of Orally Administered Azithromycin on the Plasma Concentration Profile of Carbamazepine and its Epoxide Metabolite in Healthy Volunteers

Date: August 6, 1990 to September 14, 1990
Clinical Site:
Analytical Site:

BACKGROUND:
Previous pharmacokinetic studies have indicated that erythromycin inhibits the hepatic metabolism of carbamazepine, causing decreased clearance with the attendant risk of drug accumulation with repeated dosing.

OBJECTIVE:
To investigate the effects of oral azithromycin (500 mg daily for 3 days) on the pharmacokinetics of carbamazepine and carbamazepine-10,11-epoxide.

FORMULATION:
Carbamazepine 200 mg tablets (Lot No. N524, Geigy)
Azithromycin 250 mg capsules (FID No. YY-89-05, Lot No. 817-50)
Azithromycin matching placebo capsules (FID No. BD-87-026, Lot No. 680-23)

STUDY DESIGN:
A single-center, double-blind, placebo-controlled, parallel-group study to investigate the effects of oral azithromycin on the pharmacokinetics of carbamazepine and its metabolite carbamazepine-10,11-epoxide. Fourteen healthy male volunteers were enrolled to receive oral carbamazepine 200 mg PO QD on days 1 and 2, then carbamazepine 200 mg PO Q12h on days 3 to 20 while receiving either oral azithromycin 500 mg (2 × 250 mg capsules) or placebo once daily for days 16 to 18. Azithromycin was administered two hrs prior to the morning dose of carbamazepine. The morning dose of carbamazepine was to be taken with 240 mL of water after an overnight fast and immediately before a standard light breakfast, whereas the evening dose was administered at least 2 hrs after a meal.

Blood samples for determination of carbamazepine and metabolite (carbamazepine-10,11-epoxide) concentrations were collected prior to the morning dose of carbamazepine on days 13 to 20 and was also performed 12 hrs after the final dose on day 21. On days 15 and 18, additional blood samples were collected over a 12 hr period following the morning dose at the following times: 1, 2, 3, 4, 6, 8, 10, and 12 hrs after the morning dose.

CARBAMAZEPINE PLASMA ASSAY METHODOLOGY:
High performance liquid chromatography with UV detection (HPLC-UV)

Criterion	Plasma	Comments
Concentration range	[ ]	Satisfactory
LLOQ		Satisfactory
Linearity		Satisfactory
Accuracy	101.2% to 104.3%	Satisfactory
Precision (% CV)	2.3% to 4.8%	Satisfactory
Specificity	Satisfactory	Satisfactory
Stability	Freeze-thaw, long term at -20°C	Satisfactory

Criterion	Plasma	Comments
Concentration range	[redacted]	Satisfactory
LLOQ	[redacted]	Satisfactory
Linearity	R^2 ≥0.9935	Satisfactory
Accuracy	97.7% to 100.4%	Satisfactory
Precision (% CV)	2.4% to 6.6%	Satisfactory
Specificity	Satisfactory	Satisfactory
Stability	Freeze-thaw, long term at -20°C	Satisfactory

DATA ANALYSIS:
The pharmacokinetic parameters of carbamazepine and carbamazepine-10,11-epoxide were calculated on day 15 (baseline) and day 18. The maximum observed plasma concentration (C_{max}) and the time to reach the maximum observed plasma concentration (T_{max}) were taken directly from the concentration-time data. The area under the plasma concentration-time curve from time 0 to 12 hrs (AUC_{0-12}) was calculated using the linear trapezoidal method.

STATISTICAL ANALYSIS:
The day 15 pharmacokinetic parameters were subtracted from the day 18 pharmacokinetic parameters and analyzed using the two-sample t-test.

The reviewer calculated the geometric mean ratio and 90% confidence intervals for carbamazepine and carbamazepine-10,11-epoxide log-transformed C_{max} and AUC_{0-12} values between day 15 and day 18 for subjects receiving carbamazepine and either azithromycin or placebo using the General Linear Models Procedure of SAS, Version 6.12.

RESULTS:
One subject withdrew for personal reasons after receiving carbamazepine for 11 days and has been evaluated for all causality safety only. The mean (SD) demographics for the remaining 13 subjects are shown in Table 1. Age, weight, and height were similar among the two treatment groups. The majority of subjects in each group were current smokers (≤5 cigarettes/day) and most subjects were current drinkers (≤14 units/week).

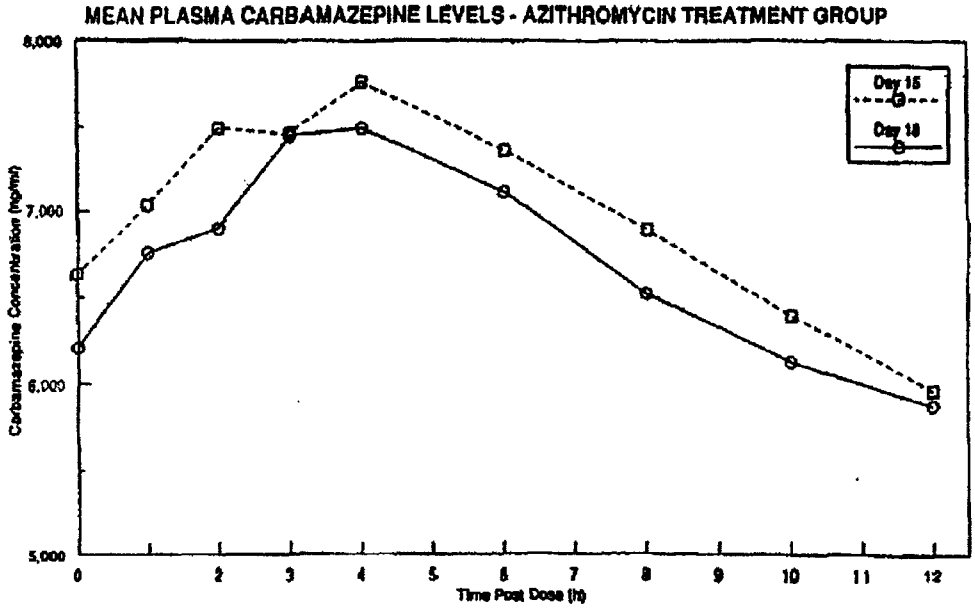
Table 1. Mean (SD) demographics of all subjects

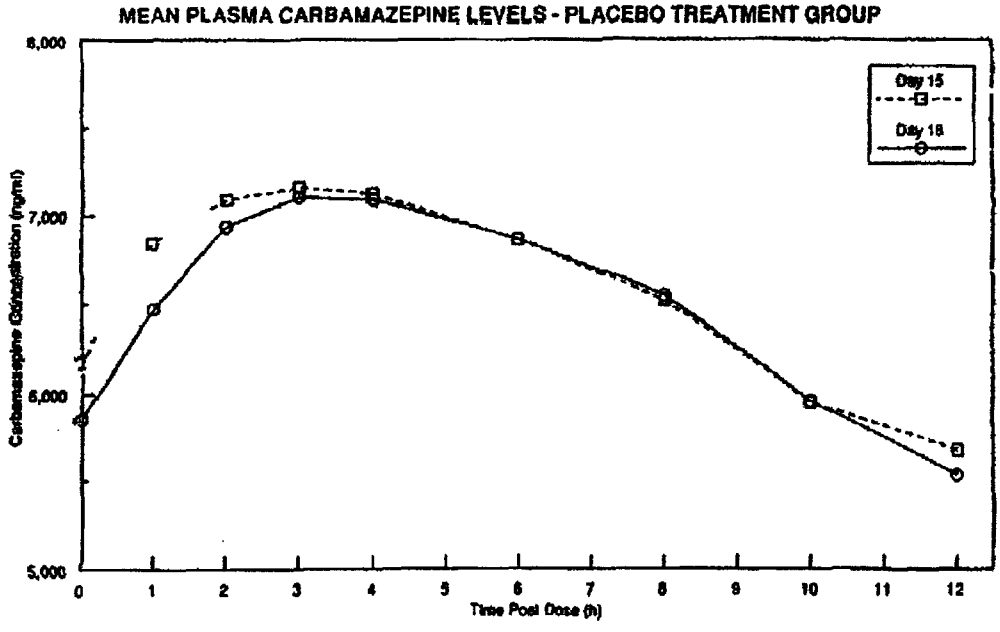
	Azithromycin (n=7)	Placebo (n=6)
Age (yrs)	29.9 (6.0)	29.0 (7.3)
Weight (kg)	69.6 (6.3)	66.5 (4.7)
Height (cm)	173.4 (4.1)	174.2 (5.2)
Smoking history (%)		
non-smoker	14%	17%
ex-smoker	29%	0%
current smoker[a]	57%	83%
Drinking history		
current drinker	86%	100%
units/week[b]	10.0 (1.3)	13.3 (1.0)

a-inclusion criteria allowed smokers who smoke up to 5 cigarettes per day to be enrolled
b-1 unit = 1/2 pint of beer, 1 glass of wine, or 1 measure of spirits

The mean carbamazepine and carbamazepine-10,11-epoxide plasma concentration-time profiles on days 15 and 18 for subjects receiving carbamazepine and either azithromycin or placebo are shown in Figure 1.

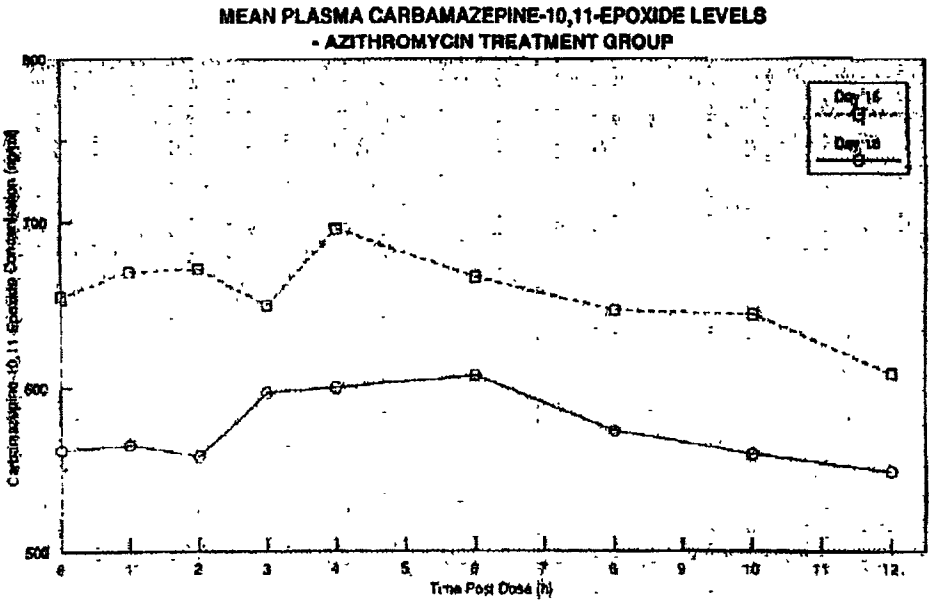
Figure 1. Day 15 and day 18 mean carbamazepine plasma concentration-time profiles for the azithromycin and placebo groups

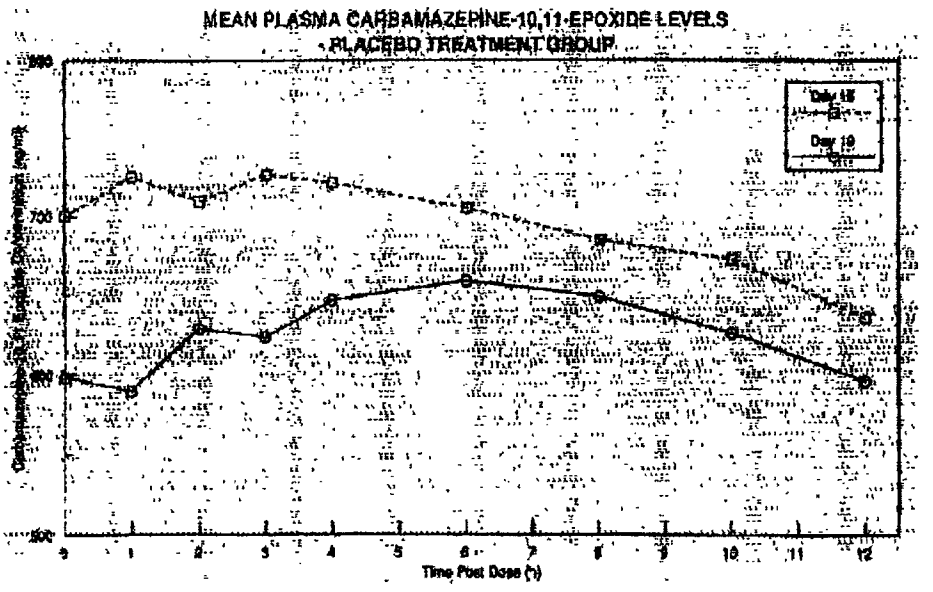




The mean carbamazepine plasma concentrations were consistently greater on day 15 than day 18 for the azithromycin group, whereas carbamazepine plasma concentrations where greater initially for day 15 than day 18 for the placebo group. Carbamazepine plasma concentrations were similar after approximately 4 hrs following the carbamazepine dosage administration.

Figure 2. Day 15 and day 18 mean carbamazepine-10,11-epoxide plasma concentration-time profiles for the azithromycin and placebo groups





The mean carbamazepine-10,11-epoxide plasma concentrations were greater on day15 than day 18 for both the azithromycin group and placebo groups. Mean carbamazepine-10,11-epoxide plasma concentrations were greater when carbamazepine was administered with azithromycin than placebo.

The mean pharmacokinetic parameters of carbamazepine on day 15 and day 18 for subjects receiving azithromycin or placebo are shown in Table 2a. Following the administration of azithromycin, the carbamazepine C_{max} and AUC_{0-12} decreased by 3.6% and 4.0%, respectively. Although the carbamazepine C_{max} and AUC_{0-12} decreased following the administration of placebo, they decreased by only 0.2% and 1.1%, respectively. The mean T_{max} increased in both the azithromycin and placebo groups and may have contributed to the decrease in C_{max}.

Table 2a. Mean (SD) day 15 and day 18 pharmacokinetic parameters for carbamazepine with azithromycin or placebo

	Azithromycin (n=7)		Placebo (n=6)	
Treatment	**Day 15**	**Day 18**	**Day 15**	**Day 18**
AUC_{0-12} (ng*hr/mL)	84,160 (8,235)	80,793 (5915)	79,151 (15,822)	78,311 (14,085)
C_{max} (ng/mL)	7,873 (811)	7,589 (506)	7,312 (1,369)	7,300 (1,169)
T_{max} (hrs)	3.4 (0.8)	4.0 (1.0)	2.7 (2.1)	3.2 (1.2)

The mean pharmacokinetic parameters of carbamazepine-10,11-epoxide on day 15 and day 18 in subjects receiving azithromycin or placebo are shown in Table 2b. Following the administration of azithromycin and placebo, the carbamazepine-10,11-epoxide C_{max} and AUC_{0-12} decreased by 12.9% and 12.2% in the azithromycin group and 8.9% and 9.3% in the placebo group, respectively.

Table 2b. Mean (SD) day 15 and day 18 pharmacokinetic parameters for carbamazepine-10,11-epoxide with azithromycin or placebo

	Azithromycin (n=7)		Placebo (n=6)	
Treatment	**Day 15**	**Day 18**	**Day 15**	**Day 18**
AUC_{0-12} (ng*hr/mL)	7,884 (1,533)	6,923 (1,359)	8,350 (1,239)	7,570 (1,457)
C_{max} (ng/mL)	715 (163)	623 (123)	747 (105)	680 (134)
T_{max} (hrs)	4.7 (3.2)	4.6 (1.4)	2.2 (1.3)	5.2 (1.8)

The geometric mean ratios (day 18/day 15) and 90% confidence intervals for carbamazepine and carbamazepine-10,11-epoxide C_{max} and AUC_{0-12} are shown in Tables 3a and 3b. The 90% confidence intervals for carbamazepine C_{max} and AUC_{0-12} geometric mean ratios for the azithromycin group were within the 0.80 to 1.25 range. The 90% confidence interval for carbamazepine AUC_{0-12} geometric mean ratio when administered with placebo exceeded the 0.80 to 1.25 range on both sides, although the geometric mean ratio was approximately 1.00.

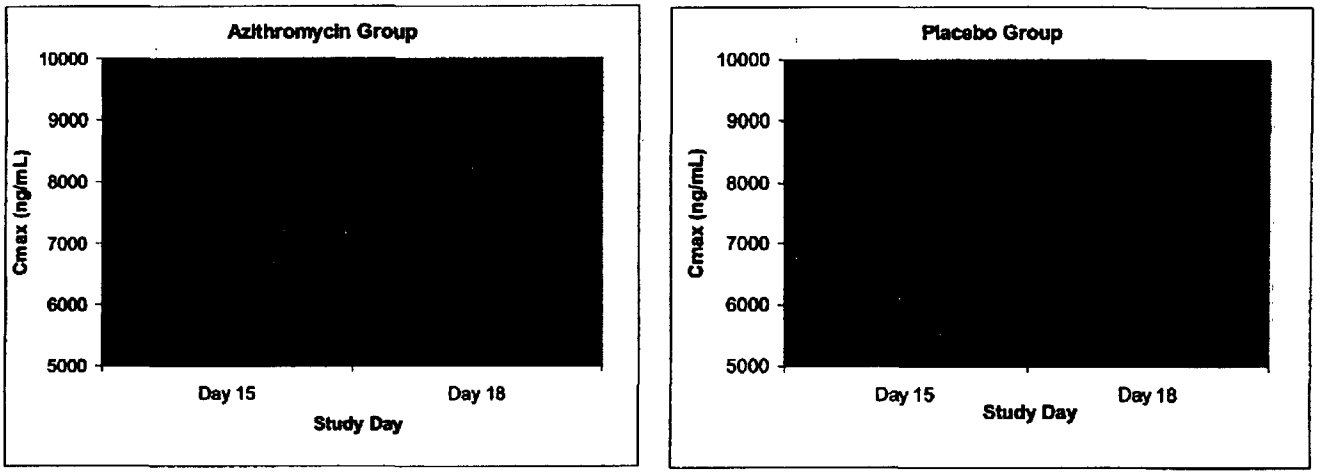
Table 3a. Carbamazepine geometric mean ratios (90% confidence interval) for day 18/day 15 in subjects receiving azithromycin or placebo

Treatment Group	C_{max}	AUC_{0-12}
Azithromycin (n=7)	0.967 (0.879 to 1.062)	0.962 (0.876 to 1.055)
Placebo (n=6)	1.002 (0.804 to 1.249)	0.993 (0.779 to 1.266)

Table 3b. Carbamazepine-10,11-epoxide geometric mean ratios (90% confidence interval) for day 18/day 15 in subjects receiving azithromycin or placebo

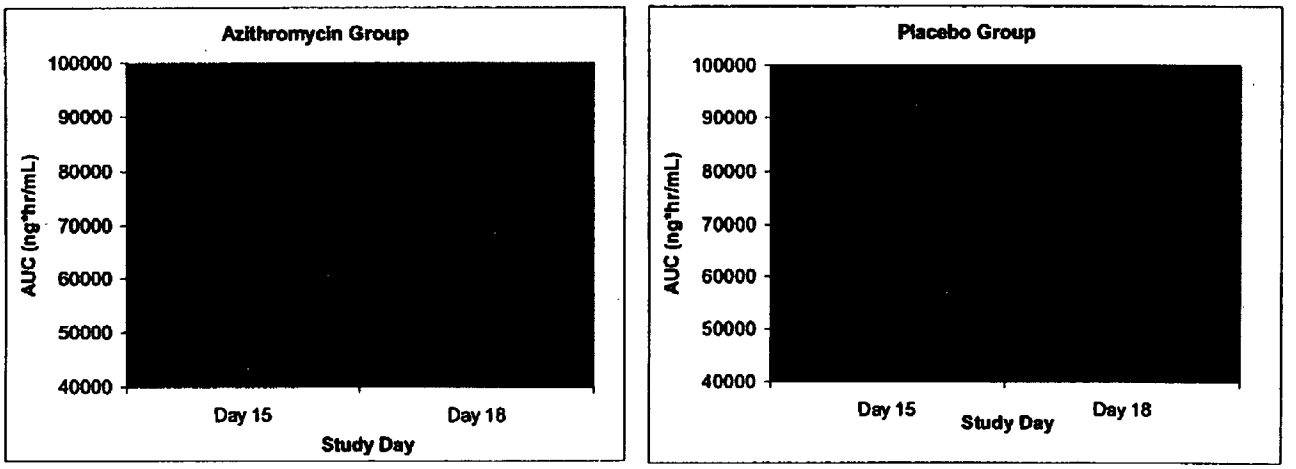
Treatment Group	C_{max}	AUC_{0-12}
Azithromycin (n=7)	0.876 (0.687 to 1.118)	0.877 (0.702 to 1.097)
Placebo (n=6)	0.904 (0.731 to 1.118)	0.901 (0.729 to 1.113)

Figure 3. Stick plots demonstrating day 15 and day 18 of individual (●) and mean (■) carbamazepine C_{max} values for the azithromycin (n=7) and placebo groups (n=6)



Note: subject #9 in the placebo group has C_{max} values similar to the mean.

Figure 34. Stick plots demonstrating day 15 and day 18 of individual (●) and mean (■) carbamazepine AUC_{0-12} values for the azithromycin (n=7) and placebo groups (n=6)



Note: subjects #1 and #12 in the azithromycin group and subject #9 in the placebo group have AUC_{0-12} values similar to the mean.

SAFETY:
There were no discontinuations due to adverse events. The incidence of all treatment related adverse events was similar between the azithromycin and placebo groups as shown in Table 4.

Table 4. Subjects with treatment related adverse events by treatment group

	Carbamazepine + Azithromycin (n=7)	Carbamazepine + Placebo (n=6)
Number of patients		
Evaluable	7	6
With side effects	3 (43%)	2 (33%)
Skin/appendages		
Mild	1	0
Moderate	0	0
Severe	0	0
Gastrointestinal		
Mild	2	2
Moderate	0	1
Severe	0	0
General		
Mild	0	1
Moderate	0	0
Severe	0	0

CONCLUSIONS:
The mean carbamazepine C_{max} and AUC_{0-12} decreased by 3.6% and 4.0%, respectively when co-administered with azithromycin.

Subjects receiving carbamazepine and azithromycin were associated with a similar incidence of adverse events than subjects receiving carbamazepine and placebo.

Unlike erythromycin, the administration of azithromycin for 3 days to subjects receiving carbamazepine was not associated with increased carbamazepine concentrations and is unlikely to result in carbamazepine accumulation. No carbamazepine dosage adjustment is warranted when carbamazepine is co-administered with azithromycin.

COMMENTS:
Carbamazepine has the potential to induce its own metabolism with prolonged administration. Auto-induction is typically completed after 3-5 weeks of a fixed dosing regimen and may or may not have been completed in subjects in the study. This may partially explain the decreased plasma concentrations of carbamazepine on day 18 compared to day 15.

Although the study was a parallel design, the reviewer analyzed the data as a one-sequence cross-over design (without sequence and period effects) to calculate a geometric mean ratio and 90% confidence interval. This was performed since the subjects in each treatment group could be compared to themselves and act as their own control. This method of analysis assesses a treatment effect but does not allow for the assessment of sequence or period effects.

Azithromycin concentrations were not quantitated in this study. Thus, the effect of carbamazepine on the pharmacokinetics of azithromycin, if any, has not been evaluated.

Inhibition of Triazolam by Macrolide Antimicrobial Agents: In Vitro Correlates and Dynamic Consequences

Greenblatt DJ, Von Moltke LL, Harmatz JS, et al. Clinical Pharmacology and Therapeutics. 1998;64:278-285.

The authors performed an *in vitro* and in vivo drug metabolism study to assess the interaction between triazolam and macrolide antibiotics (troleandomycin [*in vitro* only], erythromycin, clarithromycin, and azithromycin). Microsomal preparations from 4 different livers were used for the *in vitro* study. Ascending concentrations (0 to 250 μmol/L) of each macrolide were preincubated for 20 minutes at 37°C prior to transfer to tubes containing 250 μmol/L triazolam. Rates of formation of α-hydroxytriazolam and 4-hydroxytriazolam in reaction mixtures with inhibitor were reported as a percentage ratio relative to control velocity without inhibitor.

The clinical study was a double-blind, randomized, five-way crossover design study of twelve healthy volunteers to assess the interaction between triazolam and azithromycin, erythromycin, and clarithromycin. Regimens were separated by at least 7 days and are shown in the table below:

	Day 1		Day 2		
Regimen	**8 AM**	**4 PM**	**8 AM**	**9 AM**	**5 PM**
A	Placebo	Placebo	Placebo	Placebo	Placebo
B	Placebo	Placebo	Placebo	Triazolam 0.125 mg	Placebo
C	Azithromycin 500 mg	Placebo	Azithromycin 250 mg	Triazolam 0.125 mg	Placebo
D	Erythromycin 500 mg	Erythromycin 500 mg	Erythromycin 500 mg	Triazolam 0.125 mg	Erythromycin 500 mg
E	Clarithromycin 500 mg	Clarithromycin 500 mg	Clarithromycin 500 mg	Triazolam 0.125 mg	Clarithromycin 500 mg

The pharmacodynamic effects of triazolam were recorded using an electroencephalogram, subjects' self rating of sedative effects and mood state, the digit symbol substitution test (DSST), and acquisition and recall of information.

RESULTS:

Using *in vitro* methods, troleandomycin was the most potent inhibitor of triazolam metabolism to α-hydroxytriazolam and 4-hydroxytriazolam (mean IC_{50} 3.9 and 3.3 μmol/L, respectively), followed by erythromycin (mean IC_{50} 33.0 and 27.3 μmol/L, respectively), clarithromycin (mean IC_{50} 31.4 and 25.2 μmol/L, respectively), and then azithromycin (less than 20% inhibition at 250 μmol/L).

Co-administration of triazolam and azithromycin increased the triazolam mean C_{max} and $AUC_{0-\infty}$ by 5.6% and 1.8%, respectively. The apparent oral clearance of triazolam was essentially unchanged (413 mL/min with placebo vs. 416 ml/min with azithromycin). The effects of triazolam plus placebo and triazolam plus azithromycin were similar on EEG β-amplitude, whereas erythromycin and clarithromycin enhanced the effect of triazolam. Triazolam co-administered with azithromycin was significantly different than erythromycin and clarithromycin on the DSST score, observer-rated sedation, and speed of subject thinking. Triazolam co-administered with azithromycin or erythromycin was significantly different than clarithromycin on the self-rated sedation and subject reporting of fatigue.

COMMENTS:
The results of the *in vitro* drug metabolism study are supported by the clinical drug interaction study. Based on the modest changes in triazolam pharmacokinetics when triazolam is co-administered with azithromycin and lack of pharmacodynamic effects, no dosage adjustment of triazolam is necessary when co-administered with azithromycin.

The drug interaction between triazolam and erythromycin, clarithromycin, and azithromycin was assessed on the second day of macrolide therapy. Although this does not represent steady-state macrolide concentrations, it may be a better predictor of a drug interaction between triazolam and macrolides than a single-dose study.

NDA 21-363 Clarinex® (desloratadine) 5 mg tablets, approved December 21, 2001.

The reviewer cross-referenced the approved label for NDA 21-363 describing the interaction between desloratadine 5 mg PO QD at steady-state and azithromycin 500 mg PO on day 1, then 250 mg PO QD for 4 days in healthy male and female volunteers. The point estimate and 90% confidence intervals are shown in Tables 1 and 2 below. No statistically significant changes in the ECG parameters were observed for the comparison of desloratadine alone or in combination with azithromycin. Although azithromycin administration caused changes in the C_{max} and AUC of desloratadine and desloratadine administration caused changes in the C_{max} and AUC of azithromycin, no dose adjustments are recommended.

Table 1. Point estimates and 90% confidence intervals for the log-transformed C_{max} and AUC_{0-24} values of desloratadine and 3-OH desloratadine with and without azithromycin.

	Desloratadine (with/without azithromycin)			
	Desloratadine		3-OH Desloratadine	
Parameter	Point Estimate	90% CI	Point Estimate	90% CI
C^{max}	1.15	0.95 to 1.44	1.15	0.98 to 1.36
AUC_{0-24}	1.00	0.82 to 1.34	1.04	0.88 to 1.22

Table 2. Point estimates and 90% confidence intervals for the log-transformed C_{max} and AUC_{0-24} values of azithromycin with and without desloratadine.

	Azithromycin (with/without desloratadine)	
Parameter	Point Estimate	90% CI
C_{max}	1.31	0.92 to 1.87
AUC_{0-24}	1.12	0.83 to 1.53

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