

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50-670/S-015

50-693/S003

50-730/S005

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

NOV 8 2000

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA: 50-730, SEI-005 and SLR-006
Amendment SEI-005/BB (02/01/00)

Submission Date: January 13, 2000

Drug Product: Azithromycin 600 mg Tablets

Trade Name: ZITHROMAX® Tablets

Sponsor: Pfizer Central research
Groton, CT

Submission Type: Efficacy and Labeling Supplement – Azithromycin for Treatment of
MAC Opportunistic Infections

Review Category: 1S

OCPB Reviewer: Philip M. Colangelo, Pharm.D., Ph.D.

I. BACKGROUND / INTRODUCTION

This efficacy and labeling supplement to NDA 50-730 for azithromycin 600 mg tablets was submitted to allow use of ZITHROMAX for the *treatment* of disseminated *Mycobacterium avium Complex* (MAC) infections to be given in combination with ethambutol in HIV-infected patients (i.e., AIDS). In addition, the sponsor is also seeking an indication for ZITHROMAX tablets for the treatment of pulmonary MAC infections, in combination with other anti-mycobacterial drugs, in non-HIV infected patients. The proposed dosage regimen for both of these indications is one 600 mg tablet Q24 hours. The duration of therapy may continue indefinitely over the patient's lifespan.

Clinical data from a single pivotal, multi center Phase III study (#066-189), along with 5 additional supportive studies, were provided as part of **Item 8 (Clinical Data)** of this supplement to support the use of ZITHROMAX tablets for the treatment of disseminated *Mycobacterium avium Complex* (MAC) infections in HIV-infected patients. In addition, the sponsor has also provided publications and microbiologic results of clinical trials conducted by a single investigator (Dr. R. Wallace, University of Texas) to support the use of ZITHROMAX 600 mg/day for the treatment of pulmonary MAC infections in non-HIV patients.

The use of azithromycin 600 mg tablets was previously approved (June 12, 1996) under the original NDA 50-730 for the *prophylaxis/prevention* of MAC opportunistic infections in patients with advanced HIV infection at an oral dosage regimen of 1200 mg once weekly (2x600 mg ZITHROMAX tablets), given either alone or in combination with rifabutin.

In addition to the 600 mg tablets (NDA 50-730), this supplement also cross-references the labeling for azithromycin 250 mg capsules (NDA 50-670 approved November 1991) and azithromycin oral suspension (NDA 50-693 approved September 1994).

II. PROPOSED INDICATIONS / DOSAGE AND ADMINISTRATION

The proposed annotated labeling for azithromycin tablets, capsules, and oral suspension is provided with this review as Appendix 1. The following sections are excerpted from the proposed labeling; although not specifically stated, the duration of therapy may continue for the duration of the patient's life:

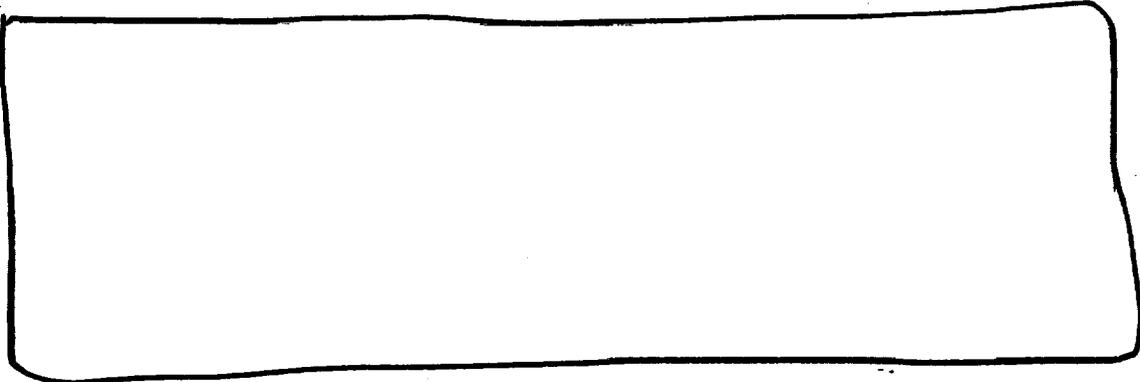
INDICATIONS:

Treatment of Disseminated *Mycobacterium avium* Complex (MAC) Disease
ZITHROMAX, taken in combination with ethambutol, is indicated for the treatment of disseminated MAC infections in persons with advanced HIV infection.



DOSAGE AND ADMINISTRATION:

Treatment of disseminated infection or pulmonary infections due to *Mycobacterium avium* complex



III. SUMMARY of NDA ITEM 6: HUMAN PHARMACOKINETICS (PK) and BIOAVAILABILITY (BA)

The following is a brief summary of the issues and findings from Item 6, addressed in a question-based review format. More detailed reviews of this information can be found in **APPENDIX 2: REVIEW OF HUMAN PHARMACOKINETICS AND BIOPHARMACEUTICS STUDIES FROM ITEM 6**, which is available upon request from the OCPB Reviewer, the OCPB Division of Pharmaceutical Evaluation 3 (DPE 3, HFD-880), or the Project Manager for the Division of Special Pathogen and Immunologic Drug Products (DSPIDP, HFD-590)

A. CLINICAL PHARMACOLOGY ISSUES

1. Dosage Regimen

- a.) Was a rationale for the proposed 600 mg Q24 hr dosage regimen of azithromycin tablets for treatment of disseminated MAC infections provided in the submission?

It appeared that sufficient evidence was provided to support the rationale for the proposed 600 mg Q24 hr regimen. Azithromycin was first recognized as a potential therapeutic option for treatment of disease due to *Mycobacterium avium* infection based on results from *in vitro* sensitivity testing and animal models of infection. The MIC₉₀ values from the sensitivity studies

ranged from [redacted] While such levels of drug are not obtainable in the serum at 600 mg Q24 hr, they can be achieved intracellularly, and specifically within the macrophage. Thus, the pharmacokinetic profile of azithromycin is such that drug levels within the macrophage typically equal or exceed these MIC values following repeated oral doses from 250 mg to 1200 mg (see Question 2 below for further details). For this reason, efficacy in animal models was explored and when animals were dosed at levels that mimicked human exposure, in vivo effects with azithromycin were found to be consistent with an anti-mycobacterial effect.

b.) Was a dose/exposure – response relationship explored with azithromycin?

There was some indirect evidence of a dose response with respect to both efficacy and safety/tolerability. Oral doses from 250 mg to 1200 mg were evaluated in the Phase II/III development program. Although a dose regimen of 500 mg Q24 hr, as azithromycin capsules, was first shown to have efficacy in the treatment of MAC in HIV infected patients (*Young et al. Lancet 1991; 338:1107-09*), a decision was made to develop a dosage form which could be used specifically for this indication. At the time there was only a capsule formulation available but work had been progressing on a tablet. The dosing strength of the tablet was increased to 600 mg, based on the tolerability of the 500 mg capsule dose and the potential utility of a larger dosage strength to maximize efficacy against this intracellular pathogen. The later Phase II/III trials demonstrated that a dosage regimen of 250 mg QD, as the tablet, was not as effective as the 600 mg QD tablet regimen. Furthermore, another study of patients with disseminated MAC infection showed that the 600 mg Q24 hr regimen was as effective as a regimen of 1200 mg QD (as 2x600 mg tablets), but was better tolerated than the 1200 mg regimen. Thus, the tablet dosage regimen of 600 mg Q24 hr was chosen.

There was no exploration of any potential relationships between plasma drug exposure with either efficacy or safety.

2. Have the pharmacokinetics (PK) of azithromycin been adequately characterized at the proposed oral tablet dosage regimen of 600 mg Q24 hr?

The PK of azithromycin was adequately characterized in one study of asymptomatic HIV-positive male subjects after once daily dosing with 250 mg or 600 mg tablet doses for 22 days. In addition, 4 drug-drug interaction studies were conducted with azithromycin and other drugs that may potentially be combined for either the prophylaxis/prevention of MAC or the treatment of MAC. In total, 5 PK studies were conducted by the sponsor and submitted for review as part of Item 6 of this NDA supplement. The table below provides a brief overview of these studies.

**APPEARS THIS WAY
ON ORIGINAL**

Overview of Clinical Pharmacokinetics Studies		
Study No.	Study Type	Description
066-077	Single and Multiple Dose PK Assessment of Azithromycin in Asymptomatic HIV-Positive Subjects	250 mg QD Azithromycin Tablet x 22 days (N=7); 600 mg QD Azithromycin Tablet x 22 days (N=7)
066-085	Interaction Study of Azithromycin and Indinavir in Healthy Subjects	Multiple Dose Indinavir 800 mg Q8 hr x 5 Days + Single Tablet Dose of Azithromycin 1200 mg (N=18) on Day 5 vs. Indinavir + Placebo (N=14)
066-086	Interaction Study of Azithromycin and Fluconazole in Healthy Subjects	Single Dose Fluconazole 800 mg Alone + Single Tablet Dose of Azithromycin 1200 mg (N=20)
066-088	Interaction Study of Azithromycin and Trimethoprim-Sulfamethoxazole in Healthy Subjects	TMP-SMZ Double-Strength Tablet QD x 7 Days + Single Tablet Dose of Azithromycin 1200 mg or Placebo on Day 7 (N=24)
066-094	Interaction Study of Azithromycin and Nelfinavir in Healthy Subjects	Nelfinavir 750 mg TID x 11 days + Single Tablet Dose of Azithromycin 1200 mg on Day 9; Azithromycin 1200 mg Single Dose Alone (N=12)

Two additional pieces of information were submitted by the sponsor as amendments to this current NDA supplement. One was the rationale for a proposed equivalent ZITHROMAX IV dose to that of the 600 mg tablets dose, based on the absolute bioavailability. The other was an extrapolation of the equivalent oral dose of azithromycin in pediatric patients, based on PK information in adults dosed at 600 mg. These items are reviewed in more detail below.

Azithromycin PK in Serum and in Leukocytes (Monocytes and Lymphocytes)

In Study 066-077, the PK of azithromycin was evaluated in serum and in peripheral leukocytes (i.e., buffy coat containing monocytes and lymphocytes) after single and repeated oral dosing with 250 mg QD and 600 mg QD for 22 days in 2 parallel groups of asymptomatic HIV-positive subjects (7 subjects per group). Since the 600 mg dose is the most clinically relevant, the PK parameters are summarized below for this dose.

Azithromycin PK Parameters in Serum and Leukocytes (Monocytes and Lymphocytes); Data Expressed as Mean ± SD, (%CV), [Range]

Parameter	Azithromycin in Serum 600 mg QD (N=7)		Azithromycin in Leukocytes 600 mg QD (N=7)	
	Day 1	Day 22	Day 1	Day 22
C _{max} (µg/mL)	0.329 ± 0.083 (25%) []	0.553 ± 0.097 (18%) []	----	252 ± 123 (49%) []
T _{max} (hr)	2.0 ± 1.0 (50%) []	2.1 ± 1.1 (52%) []	----	10.9 ± 3.0 (28%) []
C ₀ [*] (µg/mL)	0.039 ± 0.014 (36%) []	0.145 ± 0.037 (26%) []	----	146 ± 48 (33%) []
AUC(0-24) (µg·hr/mL)	2.37 ± 0.45 (19%) []	5.84 ± 1.46 (25%) []	----	4763 ± 2016 (42%) []
T _{1/2} (hr)	----	85 ± 7.9 (9%) []	----	91 ± 28 (31%) []
C _{max} Ratio Day 22/Day 1	1.73 ± 0.46 (27%) []		----	
AUC Ratio Day 22/Day 1	2.51 ± 0.53 (21%) []		----	

*Predose (Trough) Conc.; **Determined at 24 hr postdose on Day 2

**PK Comparison of Azithromycin in Leukocytes vs. Serum on Day 22;
Data Expressed as Mean ± SD, (%CV), (F. Co)**

Parameter	Day 22 Leukocytes/Serum Ratio* Azithromycin 600 mg QD
C _{max} (µg/mL)	456 ± 173 (38%) [redacted]
T _{max} * (hr)	8.7 ± 2.7 (31%) [redacted]
C ₀ (µg/mL)	955 ± 172 (18%) [redacted]
AUC(0-24) (µg·hr/mL)	816 ± 253 (31%) [redacted]
*Ratios for C _{max} , AUC, and C ₀ ; Difference (Leukocytes - Serum) for T _{max}	

The following conclusions regarding the PK of azithromycin after oral tablet doses of 600 mg QD for 22 days to asymptomatic HIV-positive subjects may be made:

- Steady state was attained in serum by Day 15.
- Accumulation of azithromycin in serum on Day 22 was substantial. The mean accumulation ratio, based on AUC(0-24), was ~2.5, which indicated that serum levels at steady state are approximately 2.5-times of those after single 600 mg doses.
- The concentrations of azithromycin in leukocytes following 22 days of once daily dosing with 600 mg greatly exceeded those in serum. After once-daily doses of 600 mg at steady state, maximum concentrations of azithromycin (C_{max}) in leukocytes are approximately 450-times higher than those in serum and the systemic exposure to azithromycin (AUC) in leukocytes was approximately 800-times higher than that in serum.
- After the 600 mg dose, the T_{1/2} of azithromycin in leukocytes (mean (range) 91 [redacted] hr) appeared to be slightly longer than that in serum (mean (range) 85 [redacted] hr).

3. Are there any significant PK and/or PD drug interactions with azithromycin at the clinically relevant dose?

As was indicated in the table above summarizing the PK studies included in this supplement, there were 4 azithromycin drug interaction studies conducted in healthy subjects. The choice of the 4 drugs (i.e., indinavir, fluconazole, trimethoprim-sulfamethoxazole, and nelfinavir) appeared to be based on potential concomitant administration with azithromycin for either the prophylaxis/prevention of MAC or for the treatment of MAC. The primary objective for each of these studies was to evaluate the effect(s) of azithromycin, given as a single 1200 mg oral dose (2x600 mg ZITHROMAX tablets), on the PK of the co-administered drug which was usually dosed to steady state. The secondary objective was to evaluate the effect(s) of the co-administered drug on the single dose PK of azithromycin. There were no studies to assess the potential for a PD interaction between azithromycin and any of the co-administered drugs.

It should be noted that single 1200 mg oral doses of azithromycin were given in all of these 4 interaction studies, rather than 600 mg tablet doses administered Q24 hr to steady state. However, the overall systemic exposure to azithromycin (i.e., C_{max} and AUC) after the single 1200 mg doses substantially exceeded that which was determined following repeated once daily tablet administration of 600 mg for 22 days (i.e., to steady state) in Study 066-077 (see above). For comparison, a summary of the PK parameters for azithromycin after single oral dose administration of 1200 mg *alone* is provided in the table below for the 4 drug interaction studies.

**Azithromycin PK Parameters Following a Single 1200 mg Tablet Dose when Given Alone;
Data Expressed as Mean ± SD, (%CV), [Range]**

Drug Interaction Study #	Cmax (µg/mL)	Tmax (hr)	AUC(0-last or 0-inf) (µg·hr/mL)
066-085 (N=13)	1.35 ± 0.38 (28%)	1.88 ± 0.69 (37%)	12.1 ± 2.4 (20%)
066-086 (N=18)	1.21 ± 0.39 (32%)	1.9 ± 0.6 (32%)	12.2 ± 2.8 (23%)
066-088 (N=12)	1.3 ± 0.3 (24%)	1.9 ± 0.3 (15%)	12.0 ± 3.5 (29%)
066-094 (N=12)	0.888 ± 0.487 (55%)	3.0 ± 0.85 (28%)	11.5 ± 3.6 (31%)

REVIEWER COMMENT:

Thus, the findings from these interaction studies using this single 1200 mg dose may be applied to the clinical setting where azithromycin is co-administered along with any of these other drugs for either the treatment (i.e., 600 mg QD) or prevention (i.e., 1200 mg/week) of MAC opportunistic infections.

The overall conclusion for all 4 interaction studies was that co-administration of a single 1200 mg tablet dose of azithromycin had no significant effect (i.e., statistically and/or clinically) on the pharmacokinetics of indinavir (CRIXIVAN® 800 mg Q8 hr x 5 days), fluconazole (DIFLUCAN® 800 mg x 1 dose), double-strength trimethoprim-sulfamethoxazole (SEPTRA-DS® x 7 days), or nelfinavir (VIRACEPT® 750 mg TID x 9 days). Also, co-administration of indinavir, fluconazole, or TMP-SMZ with azithromycin had no significant effect on the pharmacokinetics of azithromycin.

The only significant interaction was the effect of steady state administration of nelfinavir on the pharmacokinetics of azithromycin. Nelfinavir significantly increased the systemic availability (i.e., both AUC and Cmax) of azithromycin after the single 1200 mg tablet dose. The mean azithromycin AUC and Cmax values were approximately 2-times higher when given with nelfinavir and ranged up to approximately 4- and 5-times higher, respectively, compared to when azithromycin was given alone. The Kel and corresponding half-life of azithromycin, however, were not significantly altered by co-administration with nelfinavir. The PK data are shown in the table below.

Azithromycin PK Parameters after Single Dose Administration of 1200 mg Alone and When Co-Administered With Nelfinavir 750 mg TID for 9 Days (Study 066-094);

Data Expressed as Mean ± SD, (%CV), [Range]

	AZM* 1200 mg Alone (N=12)	AZM 1200mg + NLF* 750 mg TID (N=12)	Ratio or Difference**	90% Confidence Limits
Cmax (µg/mL)	0.888 ± 0.487 (55%)	2.10 ± 0.495 (24%)	2.37 ± 1.30 (55%)	1.77, 3.15
Tmax (hr)	3.0 ± 0.85 (28%)	2.3 ± 0.89 (39%)	-0.7 ± 1.50	-1.5, 0.1
AUC(0-inf) (µg·hr/mL)	11.5 ± 3.6 (31%)	24.5 ± 4.9 (20%)	2.12 ± 0.84 (30%)	1.80, 2.50
Kel (1/hr)	0.013 ± 0.019 (15%)	0.014 ± 0.016 (12%)	0.0007 ± 0.0025	Not Done
T½ (hr)	54.3 ± 7.9 (15%)	51.3 ± 6.2 (12%)	-3.1	-6.9, 0.8

*AZM = Azithromycin; NLF = Nelfinavir

**Ratio (AZM+NLF/AZM) for Cmax and AUC; Difference (AZM+NLF-AZM) for Tmax, Kel, and T½

There were no significant safety issues in this study even when subjects received both nelfinavir and azithromycin together.

REVIEWER COMMENTS:

The results suggested that the substantial increase in the systemic availability of azithromycin when given with nelfinavir might be due to an effect of nelfinavir on the oral bioavailability of azithromycin, rather than by inhibiting the elimination of azithromycin (i.e., inhibition of hepatic CYP3A4). The sponsor did not postulate on the mechanism of this effect. However, one potential mechanism of this effect on the oral bioavailability may possibly be inhibition of gut wall metabolism of azithromycin (i.e., inhibition of gut CYP3A4 rather than inhibition of hepatic CYP3A4) and/or inhibition of the protein efflux transporter, p-glycoprotein, by nelfinavir.

In the proposed labeling, no adjustment in the azithromycin dose is recommended. The label also recommends that the prescriber/clinician closely monitor patients for known side effects of azithromycin when azithromycin is given with nelfinavir.

The recommendation to closely monitor patients for known side effects of azithromycin when given with nelfinavir will be modified by the reviewing Medical Officer to specify the "known side effects" with azithromycin. Furthermore, an additional study should be performed to evaluate the effects of steady state nelfinavir on the steady state PK and safety of azithromycin after the 600 mg tablet dose.

Item 6 of this supplement also included the approved labeling for the non-nucleoside reverse transcriptase inhibitor, efavirenz (SUSTIVA® capsules), which provides evidence of no significant PK interaction between co-administered SUSTIVA® 400 mg x 7 days (*recommended adult dose is 600 mg*) and azithromycin as a single oral tablet dose of 600 mg. The SUSTIVA® label shows a 22% increase in mean C_{max} and no change in mean AUC of azithromycin, while azithromycin did not alter either the mean C_{max} or AUC of efavirenz. This information from the SUSTIVA® label was used to support a similar proposed change to the ZITHROMAX labeling. A letter from the manufacturer of SUSTIVA® (i.e., DuPont) authorizing use of this labeling information was included in this supplement.

REVIEWER COMMENT:

The use of this drug interaction information with azithromycin from the approved SUSTIVA® label is acceptable.

4. What is the equivalent IV dose of azithromycin to that of the 600 mg tablet dose?

This question arose from a concern by the sponsor that there may be some patients with disseminated MAC infections who cannot tolerate or may be unable to receive oral azithromycin. In such cases, if the clinician chooses to administer IV azithromycin to these patients, he/she needs to know what is the appropriate IV dose that will give similar systemic exposure as that of the 600 mg oral tablet dose. The sponsor proposed that the appropriate IV dose is 250 mg, based on what is known about the oral bioavailability of the tablet. At the request of the OCPB reviewer, the sponsor provided the following pharmacokinetic rationale for this proposed 250 mg IV dose as an amendment to this current NDA supplement.

Note, no PK study has been performed to directly assess the absolute bioavailability of a dose of one 600 mg ZITHROMAX tablet, nor are there any studies that evaluated the PK of the 250 mg IV dose of azithromycin.

Sponsor's PK Rationale for the Equivalent IV Dose of 250 mg:

- The mean absolute oral bioavailability of two 600 mg tablets (1200 mg) vs. a 1200 mg IV dose in HIV-infected subjects was ~34% (NDA 50-733 (Azithromycin IV), Study 066-062).

- Following oral administration of azithromycin at 600 mg (1x600 mg tablet) and 1200 mg (2x600 mg tablets) to HIV-infected patients, AUC and C_{max} were found to be directly dose proportional (NDA 50-730 (Azithromycin Tablets), Study 066-060).
- Thus, it may be concluded that the absolute oral bioavailability of one 600 mg tablet in HIV-infected patients would be approximately the same as that of 2x600 mg tablets, i.e., ~34%.
- Based on an average absolute oral bioavailability of the 600 mg tablets of ~34%, the equivalent IV dose is ~204 mg (i.e., 34% of 600 mg). Since the commercially available vials consist of 500 mg azithromycin, a dose of 250 mg would be more convenient and easier to administer. Clinically, a 250 mg IV dose should be similar to a 204 mg dose.

REVIEWER COMMENTS:

In the currently approved azithromycin IV label, the recommended IV dose for the treatment of adult patients with pneumonia or pelvic inflammatory disease is 500 mg IV Q24 hr for 1 to 2 days, with the switch to oral capsule therapy at 250 mg to 500 mg Q24 hrs for the remainder of the treatment duration. The absolute bioavailability of a single capsule dose of 500 mg was stated in the label to average 52% (vs. 500 mg IV over 3 hrs). The mean absolute bioavailability of a dose of two 600 mg tablets was also stated in the approved tablet, capsule, and oral suspension label to be 34% (CV 56%). Given that the absolute bioavailability of the 600 mg tablet is lower at 34%, then the 250 mg IV dose would be expected to produce adequate plasma exposure (i.e., AUC) to that of the tablet in the treatment of disseminated MAC.

However, in order to show additional proof of this concept, the sponsor should provide to the Agency for review, any observed (if available) values and/or simulated estimates of serum AUC and C_{max} for azithromycin with administration of the final proposed 250 mg IV dosage regimen for the treatment of disseminated MAC. Simulated estimates would be based on PK modeling from what is previously known about the PK of azithromycin after IV doses and may include consideration of other relevant factors such as the number of IV doses proposed for MAC treatment, loading dose administration, infusion time (i.e., 3 hr vs. 1 hr), etc. The ultimate goal of the modeling would be to provide more adequate labeling recommendations for the use of IV azithromycin in the treatment of disseminated MAC infections.

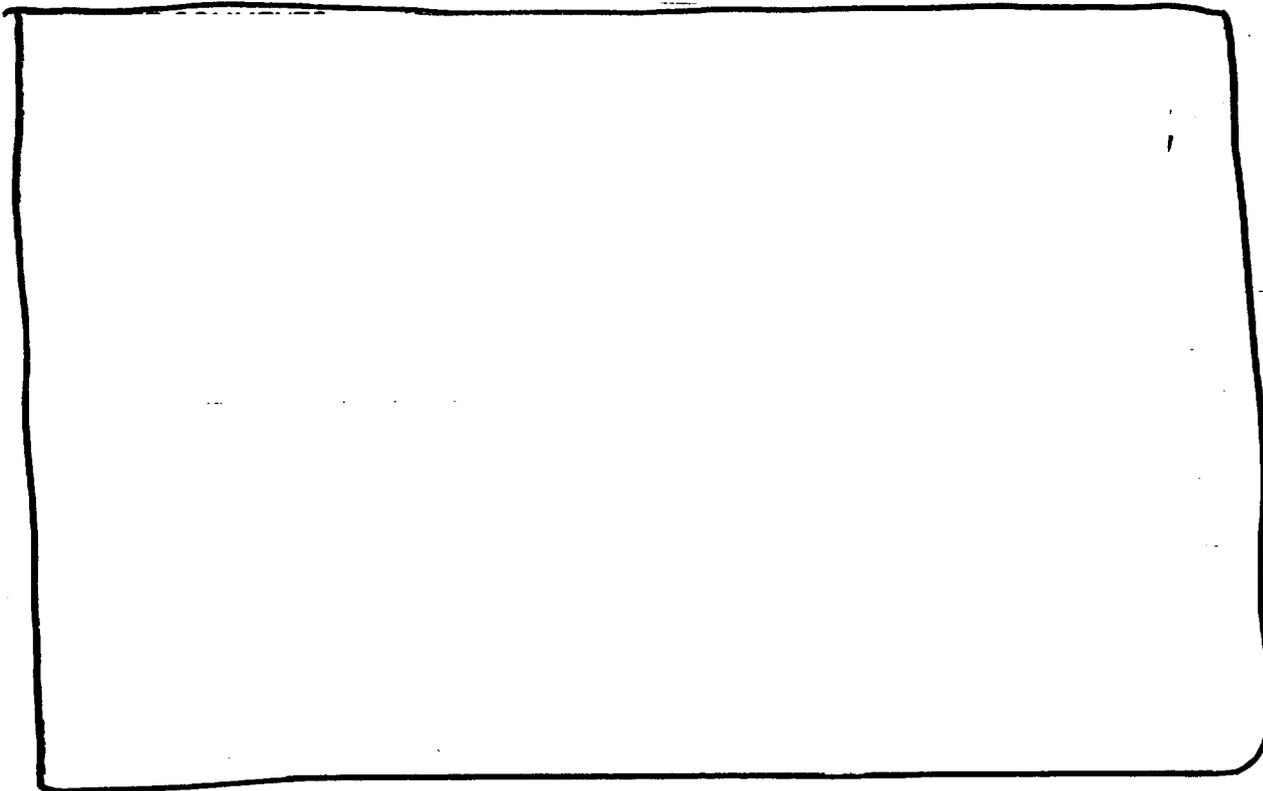
5. What is the equivalent oral azithromycin dose in HIV-infected pediatric patients to that of the 600 mg oral dose in HIV-infected adults for the treatment of disseminated MAC infections in children?

This question arose from the Review Division (HFD-590) in the context of a request by the Division for the sponsor to provide information on current or future plans for collecting data on pediatric use of azithromycin in MAC infections. The sponsor advised the Division that they are not seeking a claim for MAC treatment in children because of the rare incidence of disseminated MAC in children, and thus, resulting in an extremely difficult study to conduct. The Division agreed and suggested that the sponsor provide pharmacokinetic information for azithromycin in children (HIV-negative and/or HIV-infected) and relate this to the PK in adults (HIV-negative and/or HIV-infected) at oral doses of 600 mg. This information would serve to provide some prediction of a suitable dose in children.

The sponsor provided the response to this request by the Division as an amendment to this current NDA supplement. The basis of the PK information in pediatric patients was provided by the sponsor as a literature reference; Ngo LY, Yogev R, Danker WM, et al., *Pharmacokinetics of Azithromycin Administered Alone and with Atovaquone in Human Immunodeficiency Virus-Infected Children. Antimicrob Agents Chemother, 1999; 43(6): 1516-1519*. In this paper, PK data

was obtained from 8 HIV-infected children from 4 to 12 years of age following 5 mg/kg QD of azithromycin oral suspension for 10 days. The PK parameters obtained from these children were comparable to those that have been previously reported for non HIV infected children. This comparison was provided directly in this paper, which included the mean values \pm SD and the ranges of the PK parameters from two separate studies, one of acute otitis media (N=13) and the other of streptococcal pharyngitis (N=14) at the same oral suspension dose of 5 mg/kg. However, the age ranges of the non HIV-infected children in the comparison studies were not provided. **Nonetheless, the data provided in this comparison strongly suggested that the pharmacokinetics of azithromycin are similar between HIV-infected children and non HIV-infected children.**

The mean \pm SD (range) Cmax and AUC(0-24) values following 10 days of 5 mg/kg QD of azithromycin oral suspension (i.e., at steady state) for the 8 HIV-infected children in this paper were 0.230 ± 0.130 (0.048-0.447) $\mu\text{g/mL}$ and 2.33 ± 1.63 (0.70-5.56) $\mu\text{g}\cdot\text{hr/mL}$, respectively. The Day 8 Cmax and AUC(0-24) values following the once daily 600 mg tablet dose in adults in Study 066-077 of this NDA supplement were 0.528 ± 0.249 $\mu\text{g/mL}$ and 4.41 ± 1.46 $\mu\text{g}\cdot\text{hr/mL}$, respectively. Thus, the corresponding pediatric doses that would produce similar Cmax and AUC estimates as that in adults after the 600 mg tablet dose would be approximately 12 mg/kg (11.48 mg/kg) based on mean Cmax and approximately 10 mg/kg (9.46 mg/kg) based on mean AUC(0-24). **The sponsor indicated that while the safety assessment data in HIV-infected children treated for MAC infections is available only for a dose of 10 mg/kg, the sponsor recommends a dose of 12 mg/kg based on the pharmacokinetic data.**



IV. RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the information contained in Item 6 of this efficacy and labeling supplement to NDA 50-730 for azithromycin 600 mg tablets (SEI-005 and SLR-006, respectively) for the treatment of MAC infections and has found it to be acceptable. There are two comments to be conveyed to the sponsor and are provided below. The labeling comments have already been conveyed and incorporated by the sponsor into a more recent version (i.e., revision date: 09-Nov-2000).

V. GENERAL COMMENTS - NOT TO BE SENT TO SPONSOR

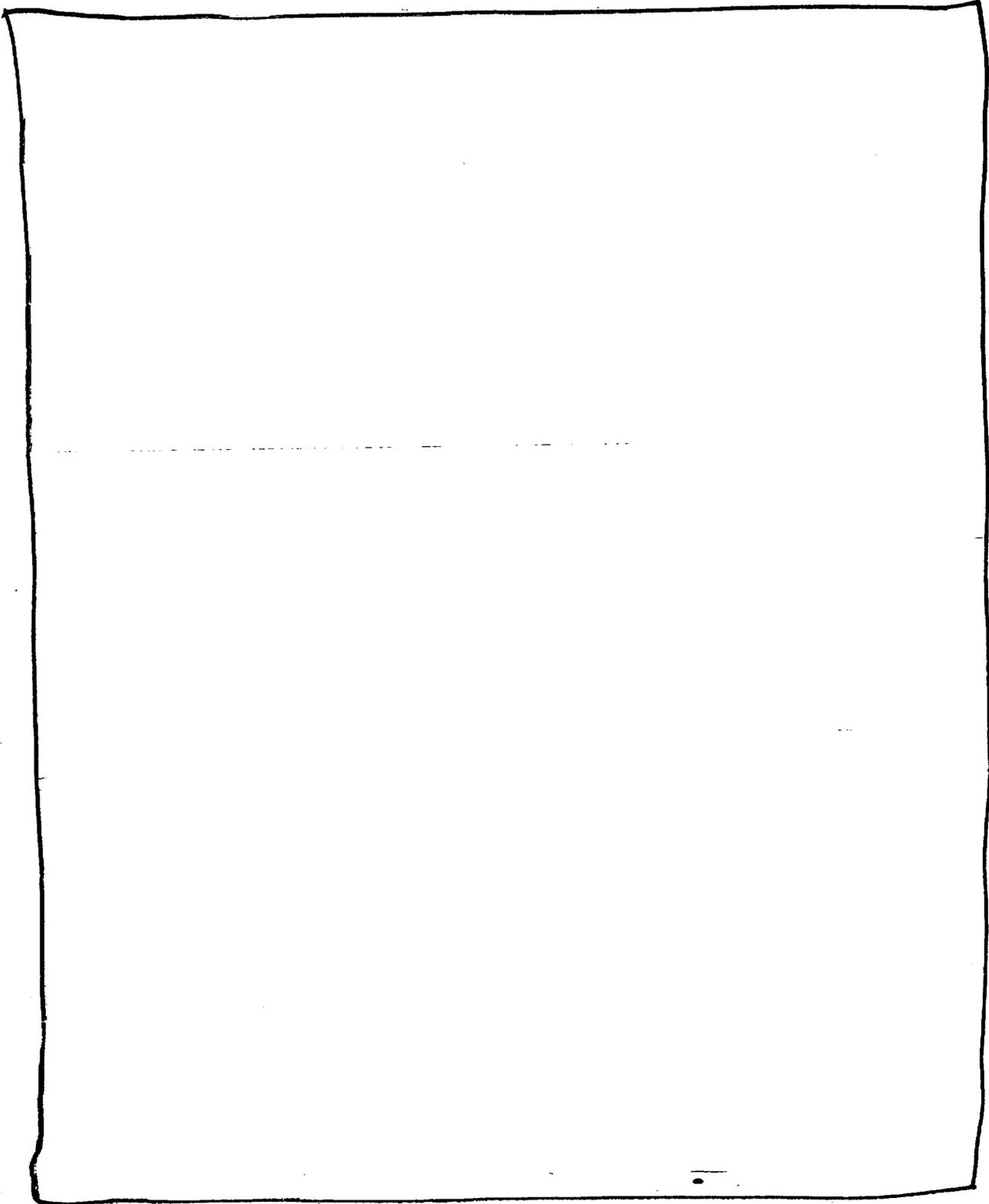
1. The existing labels for the co-administered drugs, particularly Nelfinavir and Indinavir, need to be revised/updated regarding the drug interaction information with azithromycin. This will be reviewed and implemented through Dr. Kellie Reynolds, OCPB TL in the Division of Anti-Viral Drug Products (DAVDP, HFD-530).
2. Regarding the recommendation of an appropriate dose for the treatment of MAC infections in pediatric patients, the sponsor submitted this as an amendment to this current NDA supplement (Submission Date February 1, 2000, Response to FDA Query #003). The sponsor's recommendation was based on the adult PK data from Study 066-077 of this current NDA supplement and from PK data from HIV-infected children aged 4 to 12 years following administration of azithromycin oral suspension at 5 mg/kg QD for 10 days (REF: *Antimicrob Agents Chemother*, 1999; 43(6): 1516-1519). The sponsor indicated that while the safety assessment data in HIV-infected children treated for MAC infections is available only for a dose of 10 mg/kg, a dose of 12 mg/kg was recommended, however, based on the pharmacokinetic data.

The OCPB reviewer agrees that the equivalent oral dose of azithromycin for children would be between 10 and 12 mg/kg, but only for children aged 4 to 12 years since there was no PK information provided for children less than 4 years of age. In addition, the OCPB reviewer believes that the reviewing Medical Officer will need to provide an evaluation of any safety information beyond the dose of 10 mg/kg, if it is available, to determine if the dose of 12 mg/kg may indeed be recommended for treatment of MAC infections in children.

VI. COMMENTS FOR THE SPONSOR

1. It is recommended that an additional drug interaction study be performed to evaluate the effects of steady state nelfinavir on the steady state PK and safety of azithromycin after the 600 mg tablet dose. This may be performed as a Phase 4 Study and the results from this study would provide additional labeling information and potentially more adequate recommendations for dose adjustment regarding this interaction in the context of treatment of HIV patients with disseminated MAC infections.
2. In order to demonstrate that an IV dose of 250 mg would provide similar systemic exposure to that of the tablet regimen of 600 mg Q24 hr for the treatment of disseminated MAC, it is recommended that the sponsor provide to the Agency for review any PK data (if available) or simulated PK data for azithromycin following administration of the proposed 250 mg IV dosage regimen. The simulated data would be based on PK modeling from what is already known after other IV doses and may incorporate consideration of other relevant factors such as the number of IV doses proposed for MAC treatment, loading dose administration, infusion time (i.e., 3 hr vs. 1 hr), etc. Simulated estimates of azithromycin AUC and C_{max} should be provided for the 250 mg IV dosage regimen. The ultimate goal of the modeling would be to

provide more adequate labeling recommendations for the use of IV azithromycin in the treatment of disseminated MAC infections.



3 page(s) of
revised draft labeling
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the review.

/S/

11/8/00

Philip M. Colangelo, Pharm.D., Ph.D.
Office Clinical Pharmacology/Biopharmaceutics,
Division of Pharmaceutical Evaluation 3

RD/FT signed by Funmi Ajayi, Ph.D (TL) /S/ 11/8/00
CP/B Briefing (11/2/00) Attendees: J. Lazor, A. Selen, F. Ajayi, K. Reynolds, D. Bashaw,
R. Patriak, J. Korvick, M. Cavaille-Coll,

cc:

Div. File (HFD-590): NDA 50-730, SEI-005 and SLR-006

HFD-590 (J. Korvick, MO)

HFD-590 (D. Willard, PM/CSO)

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HFD-205 (FOI)

HFD-880 (F. Ajayi)

26 page(s) of
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APPENDIX 2:
REVIEW OF
HUMAN PHARMACOKINETICS AND BIOAVAILABILITY STUDIES
FROM ITEM 6

II. CLINICAL PHARMACOLOGY - PHARMACOKINETICS STUDIES

1. PROTOCOL 066-077: PHASE I STUDY TO EVALUATE THE PHARMACOKINETIC PROPERTIES OF AZITHROMYCIN AFTER MULTIPLE ORAL DOSING OF THE TABLET FORMULATION IN ASYMPTOMATIC HIV-SEROPOSITIVE SUBJECTS

Study Dates: 05 Sept 1995 - 24 Nov 1995

sNDA Vol. 6, pp. 1-329

OBJECTIVES:

To assess the uptake of azithromycin in leukocytes (or WBCs) and to evaluate the pharmacokinetics of azithromycin after multiple oral doses of the tablet formulation in asymptomatic HIV-seropositive subjects.

FORMULATIONS/TREATMENTS:

Azithromycin 250 mg film-coated tablets (FID #YY-90-071; Lot #ED-G-063-391)
Azithromycin 600 mg film-coated tablets (FID #G00079AA; Lot #ED-G-047-393)

Both lots of these tablet strengths were not the market-image (or to-be-marketed) formulations.

SUBJECTS:

14 asymptomatic, HIV-seropositive (by both EIA and Western Blot analysis) male subjects; mean age 34.3 years (range: 26-46 years); mean weight 72.8 kg (range 57-93 kg). To be included in the study, subjects were to be off all prescription drug therapy (except contraceptives), OTC or recreational drugs for at least 2 weeks prior to participation in the study and off any investigational drug for at least 4 weeks. Subjects with active AIDS, and/or who have been treated with antiretroviral drugs or immunomodulators within 14 days before entry in the study, or those with CD4 T-lymphocyte count <200 cells/ μ l were to be excluded.

STUDY DESIGN and METHODS:

This was an open-label, randomized parallel-group study with the following 2 azithromycin treatment groups, with 7 subjects per group (described above):

- A: Azithromycin 250 mg tablet QD for 22 days (N = 7)
- B: Azithromycin 600 mg tablets QD for 22 days (N = 7)

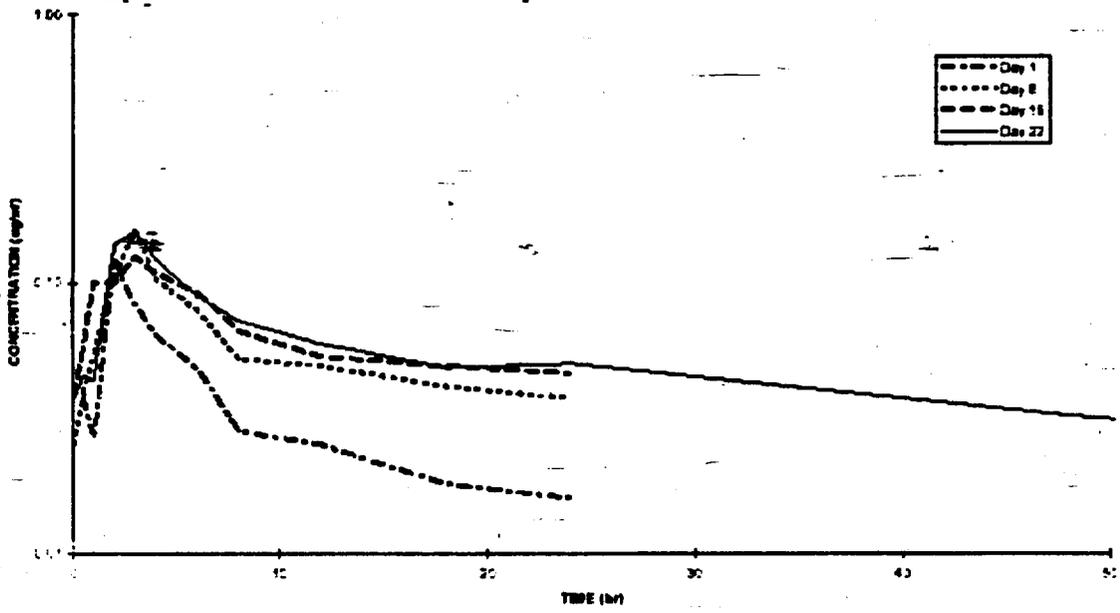
Study drug was administered at approximately 7:00 AM with 240 ml of water. All subjects were to fast overnight for at least 12 hours prior to dosing on Days 1, 8, 15, and 22 of the study, and they were to continue to fast for 4 hours following dosing.

Serum samples for determination of azithromycin concentrations were obtained just prior to each dose (0 hr), and at 0.5, 1, 2, 3, 4, 6, 8, 12, 18, and 24 hrs after dosing on Days 1, 8, 15, and 22. In addition, serum was obtained at 48, 72, 96, 120, 144, 168, 192, 216, and 240 hours postdose on Day 22. Samples for determination of azithromycin concentrations were obtained just prior to dosing (0 hr), and at 4 and 12 hours after dosing on Days 1, 8, 15, and 22. Additional samples were obtained at 24, 48, 72, 96, 144, 192, 240, 288, and 336 hours after dosing on Day 22.

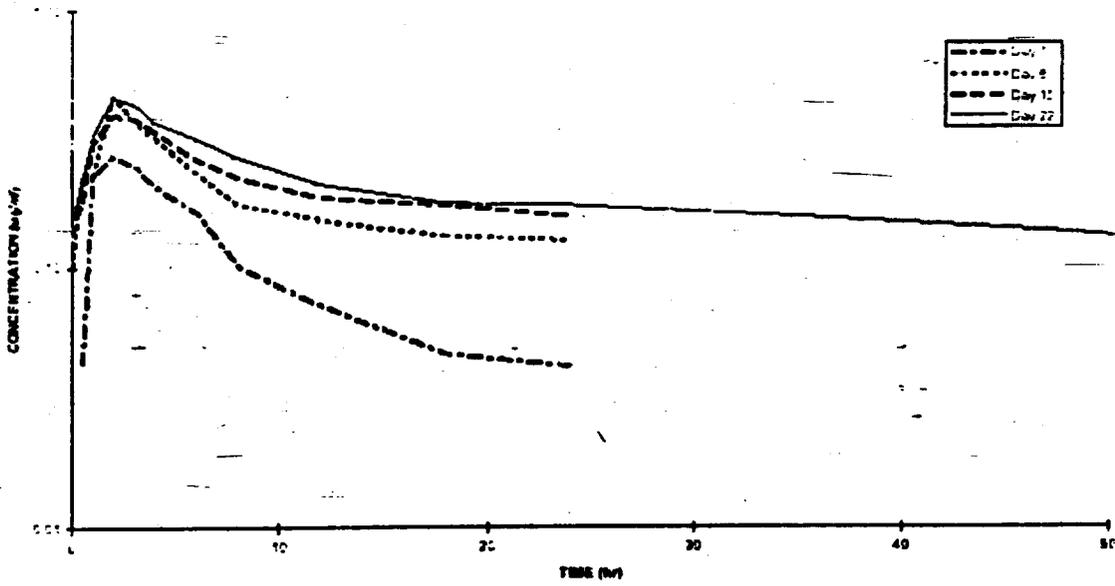
ANALYTICAL METHODS:

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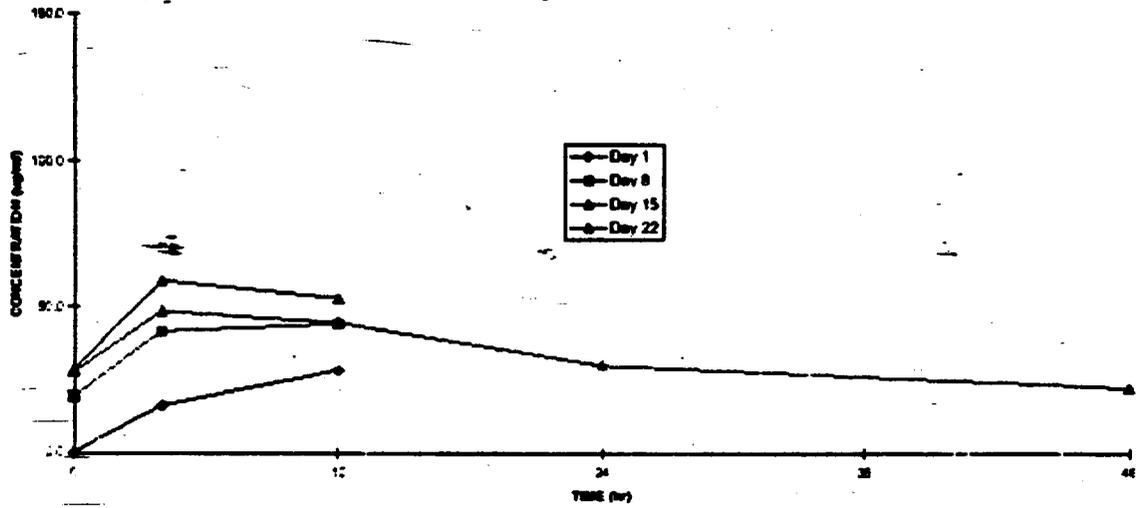
Mean Serum Concentrations of Azithromycin During a Regimen of Daily Administration of 250 mg Tablets to HIV-Seropositive Volunteers for 22 Days (Study 066-077-03g)



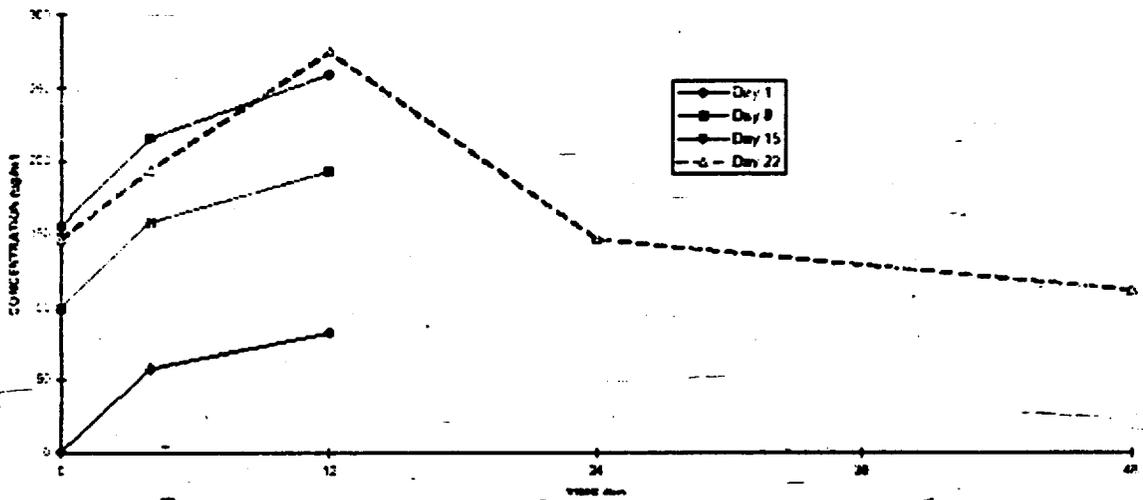
Mean Serum Concentrations of Azithromycin During a Regimen of Daily Administration of 600 mg Tablets to HIV-Seropositive Volunteers for 22 Days (Study 066-077-03g)



Mean Leukocyte (Monocytes and Lymphocytes) Concentrations of Azithromycin Following Daily Administration of 250 mg Tablets to HIV-Seropositive Volunteers for 22 Days



Mean Leukocyte (Monocytes and Lymphocytes) Concentrations of Azithromycin Following Daily Administration of 600 mg Tablets to HIV-Seropositive Volunteers for 22 Days



The PK parameters in serum and leukocytes are summarized in the tables below.

Azithromycin PK Parameters in Serum Expressed as Mean ± SD, (%CV), [Range]

Parameter	Azithromycin 250 mg QD (N=7)		Azithromycin 600 mg QD (N=7)	
	Day 1	Day 22	Day 1	Day 22
C _{max} (µg/mL)	0.107 ± 0.064 (60%)	0.187 ± 0.106 (57%)	0.329 ± 0.083 (25%)	0.553 ± 0.097 (18%)
T _{max} (hr)	3.9 ± 3.7 (95%)	2.7 ± 0.8 (30%)	2.0 ± 1.0 (50%)	2.1 ± 1.1 (52%)
C ₀ * (µg/mL)	0.016 ± 0.004 (25%)	0.033 ± 0.015 (46%)	0.039 ± 0.014 (36%)	0.145 ± 0.037 (26%)
AUC(0-24) (µg·hr/mL)	0.66 ± 0.33 (50%)	1.31 ± 0.74 (49%)	2.37 ± 0.45 (19%)	5.84 ± 1.46 (25%)
T _{1/2} (hr)		79, 113***	---	85 ± 7.9 (9%)
C _{max} Ratio Day 22/Day 1	1.97 ± 1.00 (51%)		1.73 ± 0.46 (27%)	
AUC Ratio Day 22/Day 1	2.59 ± 1.09 (42%)		2.51 ± 0.53 (21%)	

*Predose (Trough) Conc.
 **Determined at 24 hrs postdose on Day 2 (N=5)
 ***N=2

Azithromycin PK Parameters in Leukocytes (Monocytes and Lymphocytes) Expressed as Mean ± SD, (%CV), [Range]

Parameter	Azithromycin 250 mg QD (N=7)		Azithromycin 600 mg QD (N=7)	
	Day 1	Day 22	Day 1	Day 22
C _{max} (µg/mL)	---	42.4 ± 24.8 (58%)	---	252 ± 123 (49%)
T _{max} (hr)	---	6.9 ± 5.0 (72%)	---	10.9 ± 3.0 (28%)
C ₀ * (µg/mL)	---	27.4 ± 13.3 (49%)	---	146 ± 48 (33%)
AUC(0-24) (µg·hr/mL)	---	860 ± 438 (51%)	---	4763 ± 2016 (42%)
T _{1/2} (hr)	---	147 ± 49 (34%)	---	91 ± 28 (31%)

*Predose (Trough) Conc.

PK Comparison of Azithromycin in Leukocytes and Serum on Day 22 Expressed as Mean ± SD, (%CV), [Range]

Parameter	Day 22 Leukocytes/Serum Ratio Azithromycin 250 mg QD	Day 22 Leukocytes/Serum Ratio Azithromycin 600 mg QD
C _{max} (µg/mL)	227 ± 70.4 (31%)	456 ± 173 (38%)
T _{max} * (hr)	4.1 ± 5.4 (132%)	8.7 ± 2.7 (31%)
C ₀ (µg/mL)	773 ± 271 (35%)	955 ± 172 (18%)
AUC(0-24) (µg·hr/mL)	571 ± 91 (16%)	816 ± 253 (31%)

*Difference (Leukocytes - Serum)

The accumulation of azithromycin in serum was substantial after 22 days of QD administration of both 250 mg and 600 mg tablets. The mean accumulation ratio, based on AUC(0-24), was ~2.5 for both doses, which indicated that serum levels at steady state are approximately 2.5-times of those after single doses. Based on the statistical analyses of the mean ratios and 90% confidence intervals on the mean ratios for azithromycin trough levels (i.e., C_0) and AUC(0-24) in serum determined for Day 2 vs. 22, Day 8 vs. 22, and Day 15 vs. 22, steady state was attained in serum by Day 15 with both doses. The increases in mean C_{max} and AUC(0-24) values following both single and repeated QD administration of the 600 mg dose were not dose proportional to the mean C_{max} and AUC(0-24) values after the 250 mg dose. In general, these estimates were greater than dose proportional. The statistical analyses of the dose-normalized AUC(0-24) and C_{max} data for the 600 mg dose on Day 22 detected a statistically significant increase only in AUC(0-24) ($p=0.0401$), but not in C_{max} ($p=0.3696$), when compared to the 250 mg dose.

The concentrations of azithromycin in leukocytes following oral tablet doses of 250 mg and 600 mg greatly exceeded those in serum, as evidenced by the Day 22 leukocytes to serum ratios for C_{max} , C_0 , and AUC(0-24). These ratios suggested that after once-daily doses of 600 mg at steady state, maximum concentrations of azithromycin in leukocytes (i.e., C_{max}) are nearly 500-times higher than those in serum and systemic exposure to azithromycin in leukocytes (i.e., AUC(0-24)) was approximately 800-times higher than that in serum. It appeared that the mean $T_{1/2}$ of azithromycin in leukocytes was similar to that in serum after the 600 mg dose. The increases in the mean C_{max} and AUC(0-24) values in leukocytes on Day 22 after the 600 mg dose were substantially greater than dose proportional to the mean C_{max} and AUC(0-24) values after the 250 mg dose. Statistically significant differences were detected in the dose-normalized C_{max} and AUC(0-24) estimates in leukocytes for the 600 mg dose on Day 22, when compared to the 250 mg dose ($p=0.0059$ for AUC; $p=0.0083$ for C_{max}).

SAFETY/ADVERSE EVENTS:

There were no serious adverse events reported in this study and no subject discontinued the study because of an adverse event. Adverse events (not including intercurrent illnesses) were reported in 3 of 7 subjects (43%) receiving azithromycin 250 mg daily and 6 of 7 subjects (86%) receiving azithromycin 600 mg daily. The treatment-related adverse events involved the digestive system and body as a whole. Among the subjects receiving azithromycin 250 mg daily, there were 2 subjects with diarrhea, and 1 subject each with abdominal pain, flatulence, and rectal disorder. Among the subjects receiving azithromycin 600 mg daily, there were 4 subjects with diarrhea, and 1 subject each with abdominal pain, headache, moniliasis, flatulence, nausea, and rectal disorder. All events were mild or moderate in severity.

REVIEWER CONCLUSIONS:

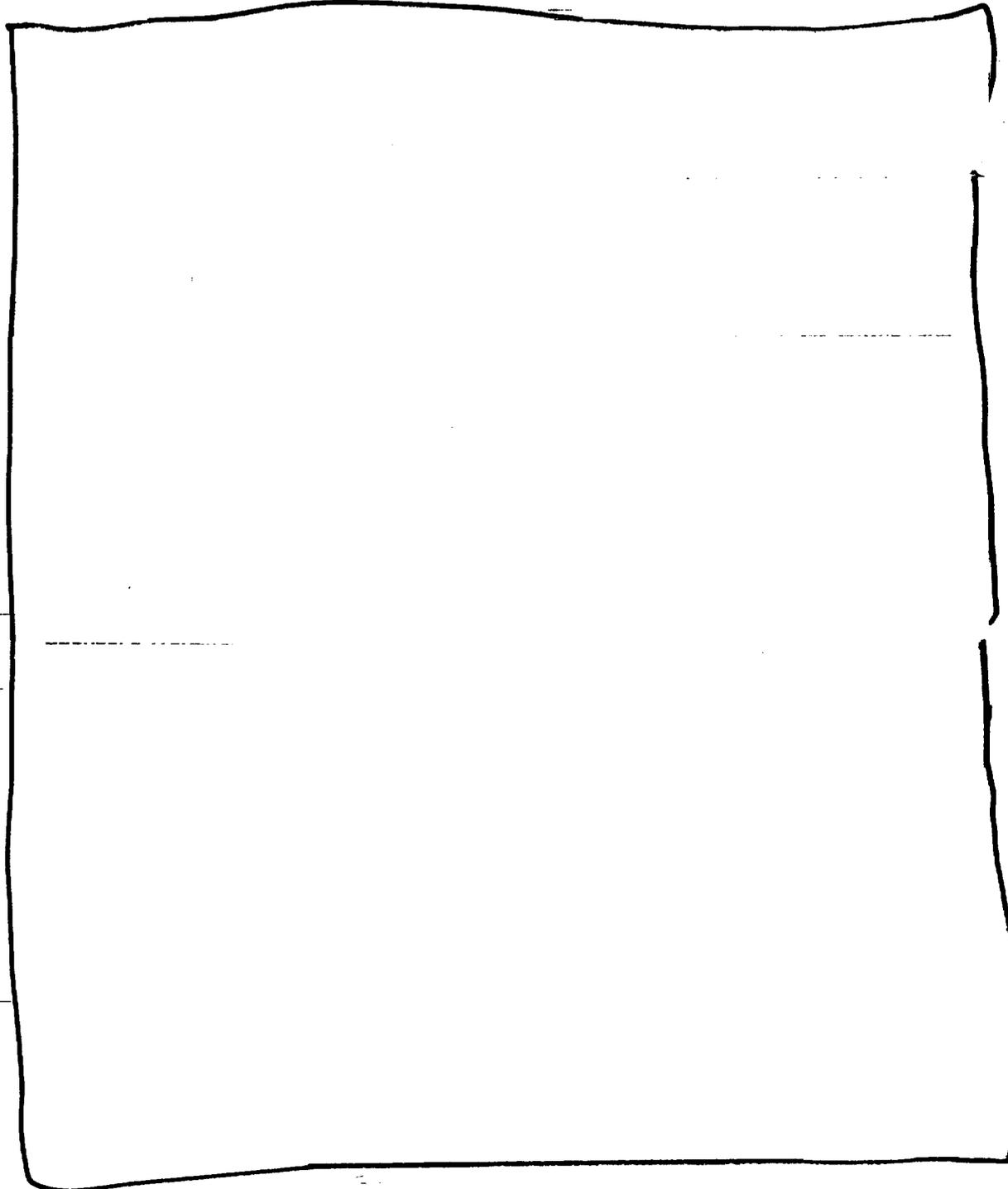
Following once-daily oral tablet administration of 250 mg and 600 mg of azithromycin to two parallel groups of asymptomatic HIV-seropositive subjects (N = 7 subjects/group) for a total of 22 days, the following conclusions regarding the PK of azithromycin may be made:

- Steady state was attained in serum by Day 15 with both doses.
- Accumulation of azithromycin in serum on Day 22 was substantial after both doses. The mean accumulation ratio, based on AUC(0-24), was ~2.5 for both doses, which indicated that serum levels steady state are approximately 2.5-times of those after single doses.
- The concentrations of azithromycin in leukocytes following 22 days of once-daily dosing with 250 mg and 600 mg greatly exceeded those in serum. After once-daily doses of 600 mg at steady state, maximum concentrations of azithromycin (C_{max}) in leukocytes are nearly 500-times higher than those in serum and the systemic exposure to azithromycin (AUC) in leukocytes was approximately 800-times higher than that in serum.

- After the 600 mg dose, the $T_{1/2}$ of azithromycin appeared to be similar in leukocytes (mean (range) 91 [] hr) and serum (mean (range) 85 [] hr).
- In general, the magnitude of the increases in C_{max} and $AUC(0-24)$ of azithromycin in both serum and leukocytes following the 600 mg dose were greater than dose-proportional to the 250 mg dose.

REVIEWER COMMENTS:

Reviewer agrees with the results from this study report and with the sponsor's conclusions.



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revised draft labeling
has been redacted
from this portion of
the review.

III. CLINICAL PHARMACOLOGY - DRUG-DRUG INTERACTION STUDIES

1. PROTOCOL 066-085: A STUDY TO ASSESS THE EFFECT OF A SINGLE 1200 MG DOSE OF AZITHROMYCIN ON THE PHARMACOKINETICS OF INDINAVIR

Study Dates: 16 October 1996 - 04 December 1996

sNDA Vol. 7, pp. 1-261

OBJECTIVES:

To assess the effect of a single 1200 mg oral dose of azithromycin on the pharmacokinetics of indinavir in healthy volunteers.

FORMULATIONS/TREATMENTS:

Azithromycin 600 mg tablet (FID#QC2099; Lot#ED-B-275-794)

Matching Placebo tablet (FID#G00770AA; Lot#ED-G-212-695)

Indinavir 400 mg Capsules (CRIXIVAN®)

SUBJECTS:

32 healthy male (N=22) and female (N=10) subjects; mean (range) age 26 (18-42) yr.; mean (range) weight 70 (55-87) kg.

STUDY DESIGN and METHODS:

Open-label, randomized, parallel-groups study design. Subjects were randomized to one of two treatment groups as follows:

Group A (N = 18; 13 males, 5 females) - Indinavir + azithromycin

Group B (N = 14; 9 males, 5 females) - Indinavir + placebo

All subjects received an 800 mg oral dose of indinavir as 2x400 mg CRIXIVAN® capsules Q8 hr for 4 days on Days 1 through 4 and two 800 mg doses at 8 hrs apart on Day 5 (total of 14 doses). One hour before the 13th dose (i.e., before the morning dose on Day 5), subjects randomized to Group A received a single 1200 mg oral dose of azithromycin as 2x600 mg ZITHROMAX® tablets and subjects randomized to Group B received a single dose of two matching placebo tablets.

All doses were administered with 240 ml of water. The morning doses of indinavir were administered after an overnight fast of at least 8 hours and a minimum of 1 hour before a light breakfast. A standard lunch could be taken 4 hours following the morning dose of indinavir; all other doses of indinavir were taken at least 1 hour before or 2 hours after a meal.

For assay of both indinavir and azithromycin, serum samples were obtained just prior to study drug (C hr) and at 15, 30, 45, 60, 75, 90 min, and 2, 3, 4, 5, 6, and 8 hrs after the morning dose on Days 4 and 5 of the study. Additional samples for assay of azithromycin were obtained at 12, 24, 48, 72, 96, and 120 hours following the morning dose of indinavir on Day 5.

ANALYTICAL METHODS:

DATA ANALYSIS:

The PK parameters for indinavir and azithromycin were determined using standard noncompartmental methods. Statistical analyses employed ANOVA of the natural log-transformed $AUC_{(last)}$ and C_{max} data and untransformed T_{max} and k_{el} data using an analysis of linear mixed-effect model containing subject as a random effect, and treatment group (azithromycin or placebo), day (Day 4 or 5), and the interaction between treatment group and day as fixed effects. The ESTIMATE statement of SAS was used to estimate the treatment effect (placebo or azithromycin) in each treatment group, as well as the difference between the two treatment effects (azithromycin minus placebo). The standard error for each estimate and a 90% confidence interval for each true difference were also calculated. For AUC and C_{max} , the antilog (exponent) of the differences and confidence intervals were taken to estimate the ratio for the treatment effect between Day 4 vs. Day 5 within each treatment group, the 90% confidence interval of the ratio, and the p-value. The ratio of the treatment effect between the two treatment groups (i.e., Day 5 azithromycin vs. placebo), the 90% confidence interval of the ratio, and the p-value were also calculated.

PK RESULTS:

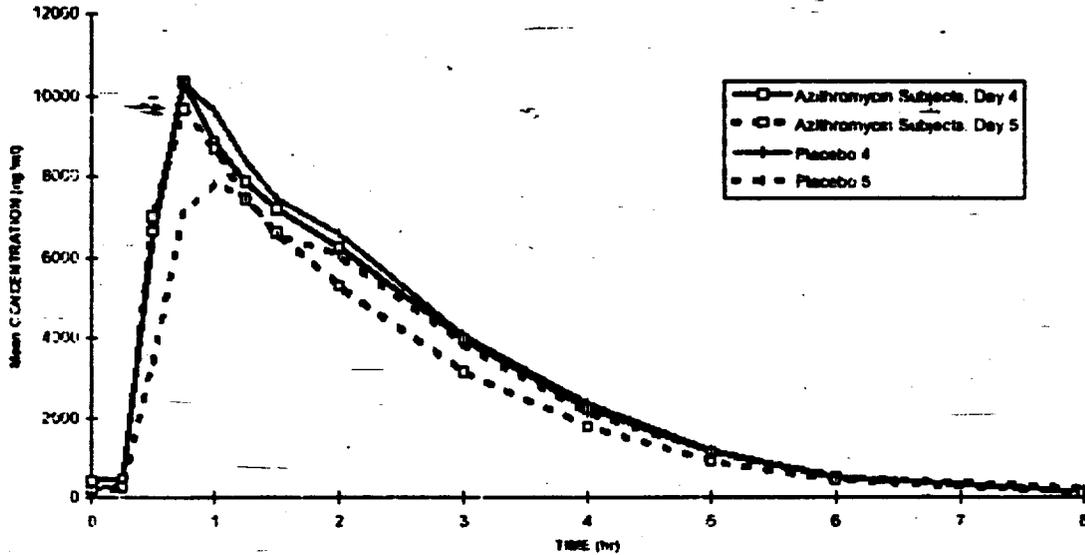
PK data was determined for all 32 subjects. However, the data for 5 of the 18 subjects in Group A (indinavir + azithromycin) were excluded from both the pharmacokinetic and statistical analyses due to emesis shortly after administration of study drug on Day 5. All 5 subjects vomited after receiving the morning dose of indinavir and 1 of the 5 also vomited after receiving the dose of azithromycin on Day 5. One of the 14 subjects in Group B (indinavir + placebo) was excluded from the PK analysis of k_{el} for indinavir due to a poorly-defined terminal phase on Day 5. In total, 27 subjects were included in the statistical analysis of PK parameters; 13 subjects received azithromycin (Group A) and 14 subjects received placebo (Group B).

Indinavir PK

The mean indinavir serum concentration-time profiles are shown in the figure below after administration of CRIVAN® capsules alone on Day 4 and with co-administration of either azithromycin or placebo on Day 5. As shown in this figure, there appeared to be a decrease in the mean serum concentrations of indinavir with placebo co-administration on Day 5 (Group B) from 1 to 4 hours postdose, and minimal or no apparent change (i.e., reduction) in indinavir levels with azithromycin co-administration on Day 5 (Group A).

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Mean Serum Indinavir Concentrations Following Oral Administration of 800 mg CRIVAN® Capsules Q8 HR Alone for 4 Days (Day 4) and With Co-Administration of Either Azithromycin Tablets 1200 mg on Day 5 (N=13) or Placebo Tablets on Day 5 (N=14) to Healthy Subjects



The PK parameters for indinavir are summarized in the following table.

Indinavir PK Parameters Following Oral Administration of 800 mg CRIVAN Capsules Q8 HR Alone for 4 Days (Day 4) and With Co-Administration of Azithromycin Tablets 1200 mg or Placebo Tablets on Day 5 to Healthy Subjects; Data Expressed as Mean ± SD, (%CV), [Range]

	GROUP A (N = 13)			GROUP B (N = 14)		
	Day 4 IND* Alone	Day 5 IND + AZM*	Day 5/Day 4 Ratio**	Day 4 IND Alone	Day 5 IND + PBO*	Day 5/Day 4 Ratio**
Cmax (ng/mL)	10300 ± 2140 (21%)	9889 ± 1780 (21%)	0.96 ± 0.22 (23%)	10600 ± 1820 (17%)	8520 ± 1980 (23%)	0.81 ± 0.20 (25%)
Tmax (hr)	0.79 ± 0.22 (28%)	0.71 ± 0.17 (24%)	-0.08 ± 0.28 (361%)	0.82 ± 0.18 (22%)	0.96 ± 0.38 (40%)	0.14 ± 0.40 (281%)
AUC(0-8) (ng·hr/mL)	23100 ± 7900 (34%)	20800 ± 5600 (27%)	0.90 ± 0.26 (29%)	24800 ± 4400 (18%)	21500 ± 3600 (17%)	0.87 ± 0.12 (13%)
T½*** (hr)	1.04	1.05	0.01	1.03	1.08	0.06

*IND = Indinavir; AZM = Azithromycin; PBO = Placebo
 **Day 5 - Day 4 Difference for Tmax and T½
 ***Mean T½ Values Expressed as Harmonic Mean (0.693/Mean Kel)

The statistical results for indinavir are summarized in the following table.

Indinavir PK Parameter	Treatment Day	Treatment Comparison	Ratio* (p-value)	90% Confidence Interval
AUC(0-8)	Day 5 vs. Day 4	IND+AZM vs. IND Alone	89.8% (0.094)	80.7%, 99.8%
	Day 5 vs. Day 4	IND+PBO vs. IND Alone	86.5% (0.023)	78.1%, 95.8%
	Day 5	IND+AZM vs. IND+PBO	103.7% (0.673)	89.6%, 120.2%
C _{max}	Day 5 vs. Day 4	IND+AZM vs. IND Alone	95.9% (0.543)	85.6%, 107.6%
	Day 5 vs. Day 4	IND+PBO vs. IND Alone	80.7% (0.003)	72.2%, 90.1%
	Day 5	IND+AZM vs. IND+PBO	118.9% (0.074)	101.5%, 139.4%
Difference* (p-value)				
T _{max}	Day 5 vs. Day 4	IND+AZM vs. IND Alone	-0.08 (0.432)	-0.24, 0.09
	Day 5 vs. Day 4	IND+PBO vs. IND Alone	0.14 (0.136)	-0.02, 0.30
	Day 5	IND+AZM vs. IND+PBO	-0.22 (0.113)	-0.45, 0.01
*Ratios or Differences Between the Adjusted Means IND = Indinavir; AZM = Azithromycin; PBO = Placebo				

The PK results and statistical analyses showed that the mean AUC(0-8), C_{max}, and T_{max} of indinavir were similar between Days 4 and 5 in the subjects receiving indinavir plus azithromycin. Although the data were not shown here, there was also no statistically significant difference detected in the mean Kel for indinavir, which was consistent with the similar mean T_{1/2} values determined on Days 4 and 5. Thus, there was no apparent interaction between a single 1200 mg dose of azithromycin and indinavir 800 mg Q8 hr given for 5 days.

There were statistically significant decreases in the mean indinavir C_{max} and AUC(0-8) estimates after co-administration with placebo from Day 4 to Day 5. The sponsor noted that these decreases were unexpected and unexplained.

In general, the PK parameters for indinavir determined in this present study on Days 4 and 5 for both azithromycin and placebo treatment groups were consistent with those reported in the approved product labeling for CRIXIVAN® capsules after steady state dosing with 800 mg Q8 hr.

Azithromycin PK

The PK parameters of azithromycin after a single 1200 mg oral tablet dose when co-administered with indinavir 800 mg Q8 hr for 5 days on Study Day 5 for the Group A subjects are provided in the table below.

Azithromycin PK Parameters	C _{max} (µg/mL)	T _{max} (hr)	AUC(0-last) (µg·hr/mL)
Mean ± SD (N=13)	1.35 ± 0.38	1.88 ± 0.69	12.1 ± 2.4
%CV	28%	37%	20%
Range			

These PK estimates for azithromycin are consistent with those reported after single 1200 mg oral tablet doses of azithromycin from the other PK studies in this current NDA supplement (i.e., Studies 066-086, 066-088, and 066-094).

SAFETY/ADVERSE EVENTS:

No subject discontinued from the study due to an adverse event and no serious adverse events were reported in this study.

Eight of the 32 (25%) subjects in the study experienced 14 treatment-emergent adverse events (not including intercurrent illnesses) while receiving indinavir alone. In 3 subjects, the events were severe. Twelve of the 18 (66.7%) subjects receiving azithromycin plus indinavir experienced 39 adverse events; in 6 subjects, the events were severe. The majority of events among subjects receiving the combination involved the digestive system and body as a whole. Six of 14 (42.9%) subjects receiving placebo plus indinavir experienced 10 adverse events, none of which were severe.

As might be expected, the incidence of gastrointestinal adverse events was highest among subjects receiving azithromycin plus indinavir; the events reported among these subjects included nausea (38.9%), vomiting (27.8%), diarrhea (22.2%), and dyspepsia (16.7%). Three cases of vomiting, two cases of nausea, and one case each of diarrhea and dyspepsia were rated severe by the investigator. In subjects receiving indinavir alone, the gastrointestinal adverse events included two cases of nausea (6.3%) and one case each of gastrointestinal disorder (3.1%) and eructation (3.1%). Severe adverse events among subjects receiving indinavir alone included one case each of pelvic pain, gastrointestinal disorder, and dizziness. Among subjects receiving azithromycin plus indinavir, all but one case each of headache and dyspepsia were deemed related to treatment by the investigator.

The incidence of clinically significant laboratory test abnormalities was higher in subjects receiving azithromycin plus indinavir (22%) than in those receiving placebo plus indinavir (7%), but none of the abnormalities was deemed to be clinically important.

REVIEWER CONCLUSIONS:

- There was no significant PK interaction detected between a single tablet dose of 1200 mg azithromycin when co-administered with multiple dose administration of indinavir capsules 800 mg Q8 hr for 5 days to healthy male and female subjects.
- Although only a single 1200 mg dose of azithromycin was given in this study, the overall systemic exposure to azithromycin in plasma (i.e., C_{max} and AUC) still exceeded that which was determined following repeated once daily tablet administration of 600 mg for 22 days (i.e., to steady state) in Study 066-077 of this NDA supplement. Thus, the finding of no interaction from this single dose study may also be applied to the clinical setting where it is deemed necessary to co-administer azithromycin 600 mg QD along with indinavir 800 mg Q8 hr for the treatment of MAC opportunistic infections in HIV-seropositive patients.

REVIEWER COMMENTS:

Reviewer agrees with the results from this study report and with the sponsor's conclusions.



2. PROTOCOL 066-086: A STUDY TO ASSESS THE EFFECT OF COADMINISTRATION OF A 1200 MG DOSE OF AZITHROMYCIN ON THE PHARMACOKINETICS OF FLUCONAZOLE

Study Dates: 12 February 1997 - 24 May 1997

sNDA Vol. 8, pp. 1-326

OBJECTIVES:

To assess the effect of a single 1200 mg oral dose of azithromycin on the pharmacokinetics of fluconazole in healthy subjects. Additionally, the effect of fluconazole 800 mg on the pharmacokinetics of azithromycin was evaluated in the same subjects.

FORMULATIONS/TREATMENTS:

Azithromycin 600 mg tablets (FID#QC2099; Lot#ED-B-275-794)

This was the marketed ZITHROMAX Tablet formulation

Fluconazole 200 mg tablets (FID#92720; Lot#54P011E)

SUBJECTS:

20 healthy male (N=7) and female (N=13) subjects; mean (range) age – males: 31 (19-41) yr., females: 31 (24-40) yr.; mean (range) weight – males: 77 (63-89) kg, females: 61 (49-73) kg

STUDY DESIGN and METHODS:

Open-label, randomized, three-way crossover, single dose study design. Subjects received the following single dose treatments, each separated by a 3-week (i.e., 21 days) washout period, on Study Days 1, 22, or 43:

Single Dose Fluconazole 800 mg Alone as 4 x 200 mg tablets

Single Dose Azithromycin 1200 mg Alone as 2 x 600 mg tablets

Co-Administration of Single Doses of Fluconazole 800 mg + Azithromycin 1200 mg

Study drugs were administered with 240 ml (8 oz.) of water in the morning following an overnight fast of at least 8 hours, and at least 1 hour before a light breakfast. A standard lunch was provided 4 hours following dosing. Serum samples for assay of fluconazole were obtained just prior to dosing (0 h), and at 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours following dosing. The same sampling scheme was followed for assay of azithromycin, except that the postdose blood draws also included two additional timepoints at 192 and 240 hours.

ANALYTICAL METHODS:

DATA ANALYSIS:

The PK parameters for fluconazole and azithromycin were determined using standard noncompartmental methods. The AUC(0-inf) was estimated for fluconazole, while the AUC(0-last), i.e., the AUC from 0 hours to the last time at which drug concentrations were measurable, was estimated for azithromycin.

The log-transformed AUC (AUC_{last} for azithromycin or AUC_{∞} for fluconazole) and C_{max} , and the untransformed T_{max} and k_{el} were analyzed for each drug separately using an ANOVA for cross over design. Mean effects were estimated using adjusted means (SAS LSMEANS) and the 90% confidence intervals were computed for the ratios of the AUCs and C_{max} , and the differences in T_{max} and k_{el} , for azithromycin or fluconazole administration alone vs. administration in

combination. Administration of azithromycin or fluconazole alone was the reference formulation. Estimates obtained for log-transformed variables were exponentiated to obtain geometric means or ratios on the regular scale. Statistical significance was assessed at the 5% level.

PK RESULTS:

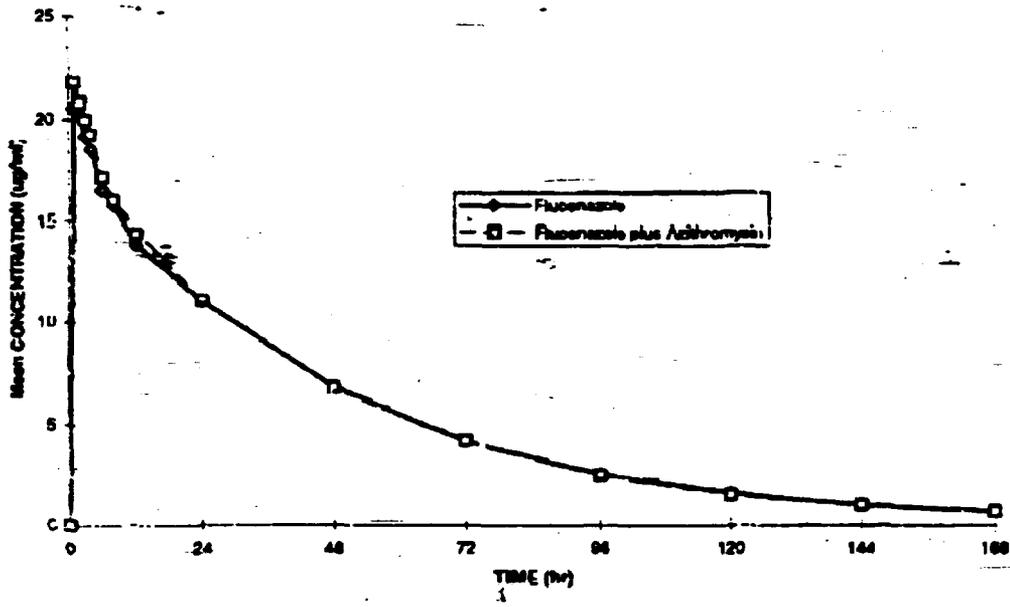
Complete PK data was obtained for 18 of the 20 subjects who were enrolled into the study. Two subjects discontinued after receiving only one arm of the assigned treatment sequence; **Subject 5990013** discontinued due to an intercurrent illness after the first arm (azithromycin plus fluconazole) and **Subject 5990011** withdrew consent after the first arm (fluconazole alone).

The mean fluconazole and azithromycin serum concentration-time profiles are illustrated in the figures below for the respective single dose administration alone and when co-administered with one another.

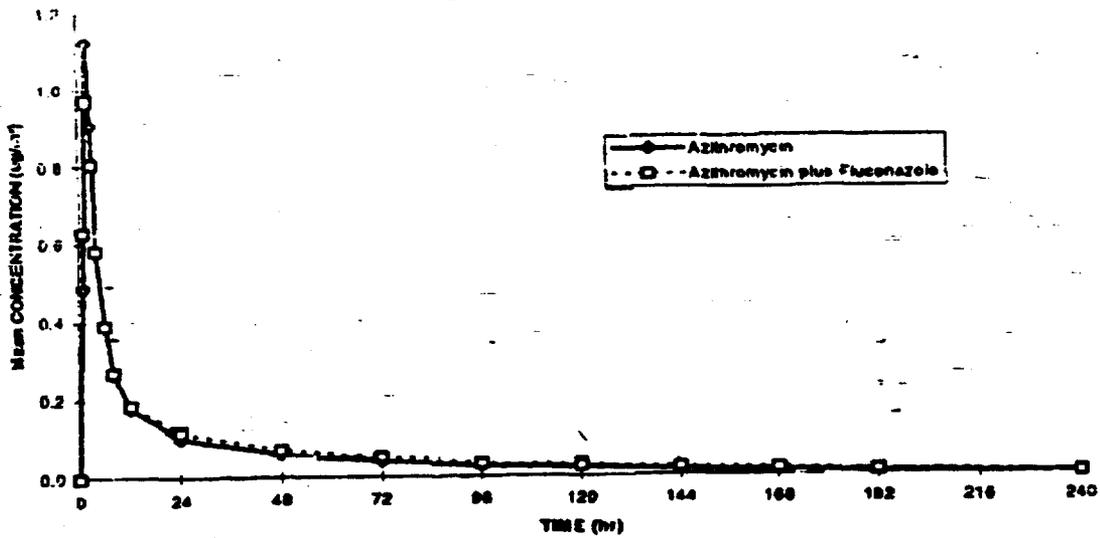
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Mean Concentrations of Fluconazole Following Oral Administration of 800 mg Fluconazole and 1200 mg Azithromycin to Healthy Volunteers (Azithromycin Protocol #086)



Mean Concentrations of Azithromycin Following Oral Administration of 1200 mg Azithromycin and 800 mg Fluconazole to Healthy Volunteers (Azithromycin Protocol #086)



The PK parameters for fluconazole and azithromycin are summarized in the tables below.

Fluconazole PK Parameters after Single Dose Administration of 800 mg Alone and When Co-Administered With Single Dose Azithromycin 1200 mg; Data Expressed as Mean \pm SD, (%CV), [Range]

	FCZ* 800 mg Alone (N=18)	FCZ 800 mg + AZM* 1200mg (N=18)	Ratio or Difference**
Cmax (μ g/mL)	21.2 \pm 4.0 (19%)	22.1 \pm 4.7 (21%)	1.04 \pm 0.6 (14%)
Tmax (hr)	1.4 \pm 0.6 (44%)	1.3 \pm 0.6 (45%)	-0.1 \pm 0.8
AUC(0-inf) (μ g \cdot hr/mL)	884 \pm 160 (18%)	893 \pm 168 (19%)	0.99 \pm 0.09 (9%)
Kel (1/hr)	0.022 \pm 0.005 (21%)	0.022 \pm 0.004 (20%)	0.000 \pm 0.002
T _{1/2} *** (hr)	43.2	43.2	Not Determined

*FCZ = Fluconazole; AZM = Azithromycin
 **Ratio for Cmax and AUC; Difference for Tmax and Kel
 ***Mean T_{1/2} Expressed as Harmonic Mean (0.693/mean Kel)

Azithromycin PK Parameters after Single Dose Administration of 1200 mg Alone and When Co-Administered With Single Dose Fluconazole 800 mg; Data Expressed as Mean \pm SD, (%CV), [Range]

	AZM* 1200 mg Alone (N=18)	AZM 1200mg + FCZ* 800 mg (N=18)	Ratio or Difference**
Cmax (μ g/mL)	1.21 \pm 0.39 (32%)	0.99 \pm 0.40 (41%)	0.82 \pm 0.41 (50%)
Tmax (hr)	1.9 \pm 0.6 (32%)	2.2 \pm 0.8 (36%)	0.3 \pm 0.8
AUC(0-last) (μ g \cdot hr/mL)	12.2 \pm 2.8 (23%)	13.1 \pm 5.1 (39%)	1.07 \pm 0.35 (33%)
Kel (1/hr)	0.013 \pm 0.003 (23%)	0.014 \pm 0.005 (34%)	0.0012 \pm 0.004
T _{1/2} *** (hr)	52.9	50.6	Not Determined

*AZM = Azithromycin; FCZ = Fluconazole
 **Ratio for Cmax and AUC; Difference for Tmax, Kel, and T_{1/2}
 *** Mean T_{1/2} Expressed as Harmonic Mean (0.693/mean Kel)

**APPEARS THIS WAY
ON ORIGINAL**

The statistical results are summarized in the tables below

Summary of Statistical Analyses of Fluconazole PK Parameters When Co-Administered with Azithromycin (FCZ + AZM) vs. Administration of Fluconazole Alone

PK Parameter	Comparison	Adj. Geometric Means	Ratio (p-value)	90% Confidence Limits
C _{max} (µg/mL)	FCZ + AZM vs. FCZ Alone	22.1 vs. 21.2	104.4% (0.230)	98.3%, 110.8%
AUC(0-inf) (µg·hr/mL)	FCZ + AZM vs. FCZ Alone	893 vs. 884	101.0% (0.645)	97.3%, 104.9%
		Adj. Arithmetic Means	Difference (p-value)	90% Confidence Limits
T _{max} (hr)	FCZ + AZM vs. FCZ Alone	1.28 vs. 1.39	-0.11 (0.601)	-0.476, 0.253
K _{el} (1/hr)	FCZ + AZM vs. FCZ Alone	0.0216 vs. 0.0216	0.0000 (0.976)	-0.0010, 0.0010

Summary of Statistical Analyses of Azithromycin PK Parameters When Co-Administered with Fluconazole (AZM + FCZ) vs. Administration of Azithromycin Alone

PK Parameter	Comparison	Adj. Geometric Means	Ratio (p-value)	90% Confidence Limits
C _{max} (µg/mL)	AZM + FCZ vs. AZM Alone	0.99 vs. 1.21	82.1% (0.127)	66.2%, 101.7%
AUC(0-last) (µg·hr/mL)	AZM + FCZ vs. AZM Alone	13.1 vs. 12.2	107.0% (0.388)	93.6%, 122.3%
		Adj. Arithmetic Means	Difference (p-value)	90% Confidence Limits
T _{max} (hr)	AZM + FCZ vs. AZM Alone	2.17 vs. 1.89	0.28 (0.152)	-0.045, 0.601
K _{el} (1/hr)	AZM + FCZ vs. AZM Alone	0.0135 vs. 0.0125	0.0010 (0.503)	-0.0018, 0.0038

The PK data and statistical results showed that there was no significant effect of co-administration of azithromycin on the pharmacokinetics of fluconazole. Similarly, co-administration of fluconazole had no significant effect on the AUC(0-last), T_{max}, and K_{el} of azithromycin. Azithromycin mean C_{max} was reduced by 18% when co-administered with fluconazole and the 90% confidence limits indicated a reduction as high as ~34% when given with fluconazole. The reduction in the mean C_{max} of azithromycin of 18% when co-administered with fluconazole failed to reach statistical significance (p = 0.127). Overall, the results indicated that there was no significant effect of co-administration of fluconazole on azithromycin pharmacokinetics.

SAFETY/ADVERSE EVENTS:

One subject discontinued from the study due to an intercurrent illness (acute pharyngitis). No serious adverse events were reported in this study.

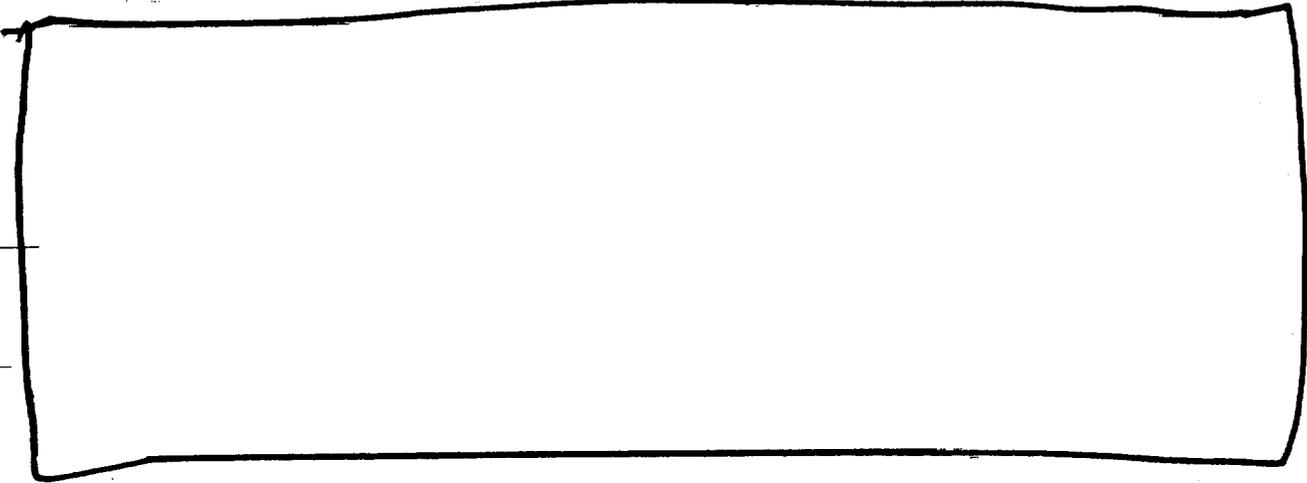
The majority of adverse events (not including intercurrent illnesses) occurred after the subjects received azithromycin alone or in combination with fluconazole. The frequency of adverse events was similar when the subjects received azithromycin alone (55.6%) or in combination with fluconazole (52.6%); however, only 1 of 19 subjects experienced an adverse event while receiving fluconazole alone (5.3%). The majority of adverse events affected the digestive system (nausea, diarrhea, flatulence, and dyspepsia) and the body as a whole (abdominal pain); other adverse events included dizziness, tremor, and vaginitis. All reported adverse events were mild in severity and deemed related to study drug by the investigator.

REVIEWER CONCLUSIONS:

- Single dose administration of 1200 mg azithromycin (2x600 mg ZITHROMAX tablets) had no significant effect on the pharmacokinetics of fluconazole following single dose tablet administration of 800 mg (4x200 mg) to healthy male and female subjects.
- Single dose administration of 800 mg fluconazole (4x200 mg) had no significant effect on the pharmacokinetics of azithromycin following single dose tablet administration of 1200 mg (2x600 mg ZITHROMAX tablets) to healthy male and female subjects.

REVIEWER COMMENTS:

Reviewer agrees with the results of this study report and with the sponsor's conclusions.



**APPEARS THIS WAY
ON ORIGINAL**

3. PROTOCOL 066-088: A STUDY TO ASSESS THE EFFECT OF A SINGLE 1200 MG DOSE OF AZITHROMYCIN ON THE PHARMACOKINETICS OF TRIMETHOPRIM-SULFAMETHOXAZOLE (TMP-SMZ)

Study Dates: 02 January 1997 - 24 January 1997

sNDA Vol. 9, pp. 1-308

OBJECTIVES:

To assess the effect of a single 1200 mg oral dose of azithromycin on the steady-state pharmacokinetics of orally administered double-strength TMP-SMZ (160 mg TMP + 800 mg SMZ) administered daily to healthy volunteers:

FORMULATIONS/TREATMENTS:

Azithromycin 600 mg tablets (FID#QC2099; Lot#N4270)

This was the marketed ZITHROMAX Tablet formulation

Placebo Tablets (FID#G00770AA; Lot#ED-G-212-695)

Trimethoprim-Sulfamethoxazole (TMP-SMZ) Double Strength (DS) Tablets - 160 mg TMP + 800 mg SMZ

SUBJECTS:

24 healthy male (N=11) and female (N=13) subjects; mean (range) age - males: 29 (22-40) yr., females: 30 (21-45) yr.; mean (range) weight - males: 78 (68-99) kg, females: 61 (49-75) kg

STUDY DESIGN and METHODS:

Open-label, randomized, two-way, parallel groups study design. The 24 subjects were randomized to one of two treatment groups (azithromycin vs. placebo), and all subjects received a total of 7 daily morning doses of TMP-SMZ, administered as one DS tablet (160 mg TMP + 800 mg SMZ) on Days 1 through 7 of the study. Immediately following the last TMP-SMZ dose on Day 7, 12 subjects in Group A received a single oral dose of 1200 mg azithromycin (2 x 600 mg tablets), and 12 subjects in Group B received two matching placebo tablets.

	Group A (N=12)	Group B (N=12)
Days 1 through 7: TMP-SMZ DS QD	YES	YES
Day 7: Azithromycin (AZM) 1200 mg	YES	NO
Day 7: Placebo (PBO)	NO	YES

Study drugs were administered with 240 ml (8 oz.) of water in the morning following an overnight fast of at least 8 hours, and at least 1 hour before a light breakfast. A standard lunch was provided 4 hours following dosing.

Plasma samples for analysis of TMP-SMZ were obtained just prior to dosing (0 hr), and at 1, 2, 3, 4, 5, 6, 8, 12, and 18 hours after dosing on Days 6 and 7 of the study. An additional sample for assay of TMP-SMZ was obtained 24 hours following TMP-SMZ dosing on Day 7. A trough blood sample was collected just prior to dosing on Day 5. Urine samples for analysis of TMP-SMZ were also collected from each subject prior to dosing on Day 1 and on Days 6 and 7 over the 24-hour period following TMP-SMZ dosing. Serum samples for the analysis of azithromycin were obtained just prior to dosing (0 hour), and at 1, 2, 3, 4, 5, 6, 8, 12, 18, 24, 48, 72, 96, and 120 hours following azithromycin dosing on Day 7.

ANALYTICAL METHODS:



[REDACTED]. The urine assay for both
TMP and SMZ was validated over the linear dynamic range from [REDACTED]

[REDACTED]
The validation and performance of both plasma and urine assays for TMP and SMZ during analyses of the study samples were acceptable. The validation and performance of the serum assay for azithromycin during study sample analysis were acceptable.

DATA ANALYSIS:

The PK parameters for TMP, SMZ, and azithromycin were determined using standard noncompartmental methods. PK parameter evaluations were performed on Days 6 and 7 for TMP and SMZ and on Day 7 for azithromycin. For TMP and SMZ, trough plasma levels on Days 5, 6, and 7 were evaluated to verify attainment of steady state. Urinary PK parameters evaluated for TMP and SMZ included the total amount of drug excreted in the urine (D_u) and renal clearance (CL_r), computed as $D_u/AUC_{(0-24)}$.

Statistical analyses included use of ANOVA and computation of 90% confidence intervals to test for treatment effects and mean effects for log-transformed AUC and C_{max} data (i.e., ratios) and for untransformed T_{max} , CL_r , and D_u data (i.e., differences) between Day 6 and Day 7 (i.e., TMP-SMZ + azithromycin vs. TMP-SMZ + placebo).

PK RESULTS:

PK data was obtained for all 24 subjects; 12 from Group A (TMP-SMZ + AZM) and 12 from Group B (TMP-SMZ + PBO).

Trimethoprim (TMP) PK

inspection of the pre-dose or trough TMP levels on Days 5, 6, and 7 and statistical analyses of these data showed that steady state was attained by Day 6 of once-daily dosing for all subjects. The mean TMP concentration-time profiles are shown in Figures 1 and 2 below for both treatment groups on Days 6 and 7.

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Figure 1: Mean Plasma Concentration (mcg/mL) of Trimethoprim Following Oral Administration of Trimethoprim-Sulfamethoxazole DS (160 mg TMP + 800 mg SMZ) QD alone for 6 days, and in combination with a single dose of Azithromycin 1200 mg on Day 7.

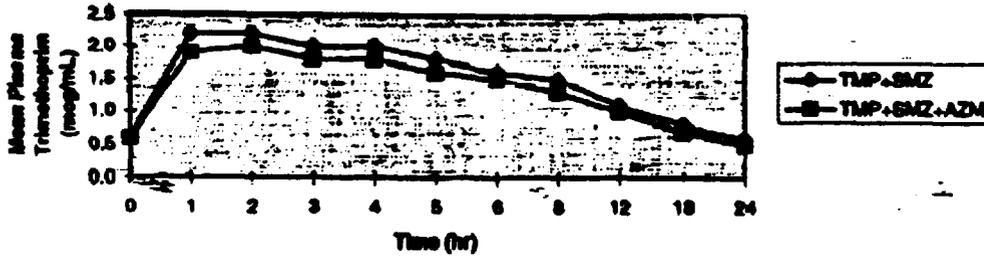
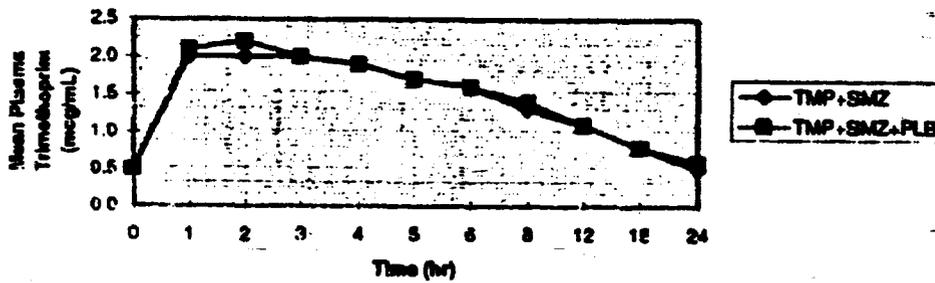


Figure 2: Mean Plasma Concentration of Trimethoprim (mcg/mL) Following Oral Administration of Trimethoprim-Sulfamethoxazole DS (160 mg TMP + 800 mg SMZ) QD alone for 6 Days, and in combination with a single dose of Placebo to match Azithromycin on Day 7.



**APPEARS THIS WAY
ON ORIGINAL**

The PK parameters for TMP are summarized in the table below.

Trimethoprim PK Parameters Following QD Administration of One TMP-SMZ DS Tablet Alone for 6 Days and With Single Dose Azithromycin 1200 mg or Matching Placebo Tablets on Day 7; Data Expressed as Mean \pm SD, (%CV), [Range]

PK Parameter	GROUP A (N=12)		GROUP B (N=12)	
	Day 6 TMP-SMZ* Alone	Day 7 TMP-SMZ + AZM*	Day 6 TMP-SMZ Alone	Day 7 TMP-SMZ + PBO*
Cmax (μ g/mL)	2.3 \pm 0.5 (21%)	2.0 \pm 0.5 (23%)	2.3 \pm 0.4 (18%)	2.3 \pm 0.5 (20%)
Tmax (hr)	1.6 \pm 1.0 (63%)	1.8 \pm 0.8 (50%)	1.8 \pm 0.9 (50%)	1.7 \pm 0.9 (53%)
AUC(0-24) (μ g·hr/mL)	29.4 \pm 6.5 (22%)	26.6 \pm 6.9 (26%)	27.7 \pm 5.5 (20%)	28.5 \pm 5.6 (20%)
CLr (mL/min)	47 \pm 13 (35%)	42 \pm 17 (41%)	51 \pm 22 (43%)	46 \pm 22 (47%)
Du (%)	49 \pm 13 (35%)	39 \pm 14 (36%)	49 \pm 12 (24%)	46 \pm 15 (32%)

*TMP-SMZ = Trimethoprim-Sulfamethoxazole Double Strength Tablet (160 mg TMP + 800 mg SMZ);
AZM = Azithromycin 1200 mg (2x600 mg Tablets); PBO = Matching Placebo Tablets to AZM

The statistical results for TMP are summarized in the table below.

Summary of Statistical Results for Trimethoprim

PK Parameter	Treatment Day	Treatment Group or Comparison	Adj. Geometric Means	Ratio	90% Confidence Limits	p-value
Cmax (μ g/mL)	Day 7 vs. Day 6	AZM	1.99 vs. 2.28	87.5%	79.9%, 95.8%	0.019
	Day 7 vs. Day 6	PBO	2.29 vs. 2.22	103.2%	94.2%, 113.0%	0.563
	Day 7	TMP-SMZ + AZM vs. TMP-SMZ + PBO		84.8%	74.6%, 96.5%	0.039
AUC(0-24) (μ g·hr/mL)	Day 7 vs. Day 6	AZM	25.8 vs. 28.8	89.5%	84.2%, 95.4%	0.007
	Day 7 vs. Day 6	PBO	27.9 vs. 27.1	102.9%	96.7%, 109.6%	0.436
	Day 7	TMP-SMZ + AZM vs. TMP-SMZ + PBO		87.1%	79.7%, 95.1%	0.014
			Adj. Arithmetic Means	Diff.	90% Confidence Limits	p-value
Tmax (hr)	Day 7 vs. Day 6	AZM	1.83 vs. 1.58	0.25	-0.46, 0.96	0.552
	Day 7 vs. Day 6	PBO	1.67 vs. 1.75	-0.08	-0.79, 0.63	0.842
	Day 7	TMP-SMZ + AZM vs. TMP-SMZ + PBO		0.33	-0.67, 1.34	0.575
CLr (mL/min)	Day 7 vs. Day 6	AZM	41.7 vs. 46.9	-5.14	-11.03, 0.74	0.147
	Day 7 vs. Day 6	PBO	45.7 vs. 50.7	-5.06	-10.94, 0.82	0.154
	Day 7	TMP-SMZ + AZM vs. TMP-SMZ + PBO		-0.09	-8.40, 8.23	0.986
Du(0-24) (mg)	Day 7 vs. Day 6	AZM	62.8 vs. 78.4	-15.56	-24.58, -6.54	0.007
	Day 7 vs. Day 6	PBO	74.1 vs. 79.3	-5.19	14.21, 3.83	0.334
	Day 7	TMP-SMZ + AZM vs. TMP-SMZ + PBO		-10.37	-23.13, 2.39	0.177

The PK data and the 90% confidence intervals from the statistical analyses indicated that co-administration of azithromycin had no significant effect on the PK of trimethoprim (TMP).

Sulfamethoxazole (SMZ) PK

Inspection of the pre-dose or trough SMZ levels on Days 5, 6, and 7 and statistical analyses of these data showed that steady state was attained by Day 6 of once-daily dosing for all subjects. The mean SMZ concentration-time profiles are shown in Figures 3 and 4 below for both treatment groups on Days 6 and 7.

Figure 3: Mean Plasma Concentration (mcg/mL) of Sulfamethoxazole Following Oral Administration of Trimethoprim-Sulfamethoxazole DS (160 mg TMP + 800 mg SMZ) QD alone for 6 days, and in combination with a single dose of Azithromycin 1200 mg on Day 7.

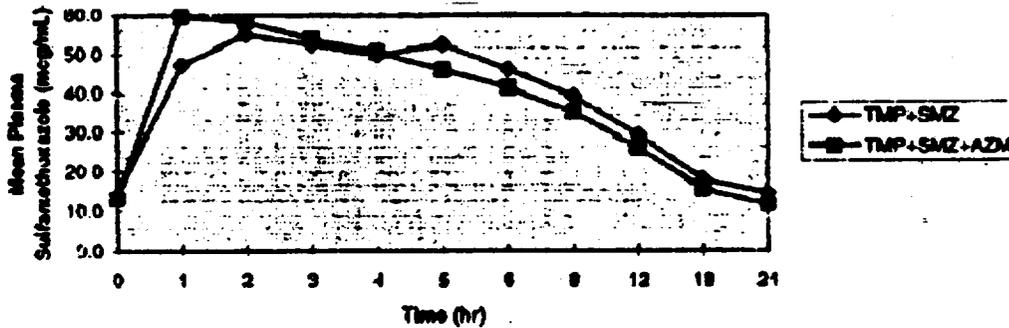
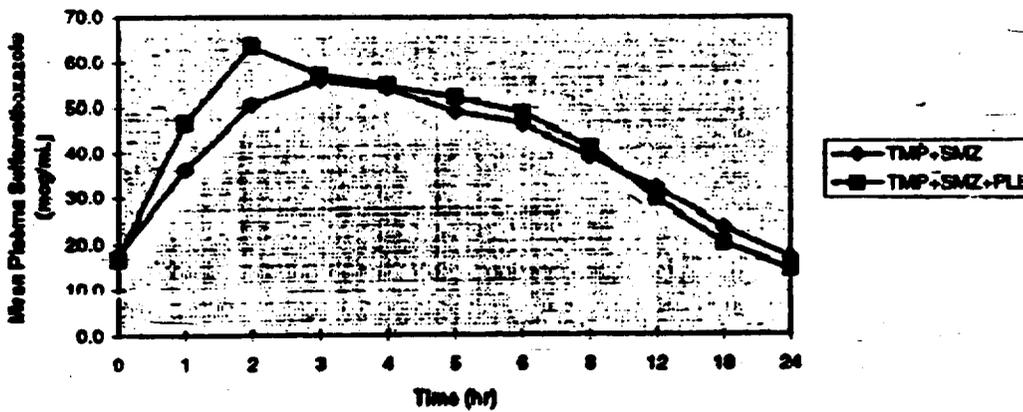


Figure 4: Mean Plasma Concentration of Sulfamethoxazole (mcg/mL) Following Oral Administration of Trimethoprim-Sulfamethoxazole DS (160 mg TMP+800 mg SMZ) QD alone for 6 days, and in combination with a single dose of Placebo to match Azithromycin on Day 7.



The PK parameters for SMZ are summarized in the table below.

Sulfamethoxazole PK Parameters Following QD Administration of One TMP-SMZ DS Tablet Alone for 6 Days and With Single Dose Azithromycin 1200 mg or Matching Placebo Tablets on Day 7; Data Expressed as Mean ± SD, (%CV), [Range]

PK Parameter	GROUP A (N=12)		GROUP B (N=12)	
	Day 6 TMP-SMZ* Alone	Day 7 TMP-SMZ + AZM*	Day 6 TMP-SMZ Alone	Day 7 TMP-SMZ + PBO*
C _{max} (µg/mL)	64.9 ± 12.8 (20%)	61.9 ± 7.6 (12%)	61.9 ± 11.5 (19%)	66.8 ± 13.3 (20%)
T _{max} (hr)	2.6 ± 1.8 (61%)	1.4 ± 0.5 (36%)	3.6 ± 2.8 (78%)	2.4 ± 1.1 (45%)
AUC(0-24) (µg·hr/mL)	747 ± 130 (17%)	702 ± 107 (15%)	795 ± 189 (24%)	791 ± 220 (28%)
CL _r (mL/min)	3.2 ± 1.3 (42%)	2.4 ± 1.2 (50%)	2.5 ± 1.1 (47%)	2.9 ± 1.5 (52%)
D _u (%)	17 ± 7.4 (43%)	12 ± 6.4 (44%)	14 ± 4.8 (35%)	16 ± 6.0 (38%)

*TMP-SMZ = Trimethoprim-Sulfamethoxazole Double Strength Tablet (160 mg TMP + 800 mg SMZ);
AZM = Azithromycin 1200 mg (2x600 mg Tablets); PBO = Matching Placebo Tablets to AZM

The statistical results for SMZ are summarized in the table below.

Summary of Statistical Results for Sulfamethoxazole

PK Parameter	Treatment Day	Treatment Group or Comparison	Adj. Geometric Means	Ratio	90% Confidence Limits	p-value
C _{max} (µg/mL)	Day 7 vs. Day 6	AZM	61.5 vs. 63.7	96.6%	87.6%, 106.6%	0.553
	Day 7 vs. Day 6	PBO	65.7 vs. 60.9	107.8%	97.8%, 118.9%	0.200
	Day 7	TMP-SMZ + AZM vs. TMP-SMZ + PBO		89.6%	78.0%, 102.9%	0.187
AUC(0-24) (µg·hr/mL)	Day 7 vs. Day 6	AZM	695 vs. 737	94.4%	89.3%, 99.7%	0.086
	Day 7 vs. Day 6	PBO	767 vs. 778	98.7%	93.4%, 104.3%	0.685
	Day 7	TMP-SMZ + AZM vs. TMP-SMZ + PBO		95.6%	88.4%, 103.4%	0.338
			Adj. Arithmetic Means	Diff.	90% Confidence Limits	p-value
T _{max} (hr)	Day 7 vs. Day 6	AZM	1.42 vs. 2.58	-1.17	-2.38, 0.04	0.112
	Day 7 vs. Day 6	PBO	2.42 vs. 3.58	-1.17	-2.38, 0.04	0.112
	Day 7	TMP-SMZ + AZM vs. TMP-SMZ + PBO		0.00	-1.71, 1.71	1.000
CL _r (mL/min)	Day 7 vs. Day 6	AZM	2.38 vs. 3.16	-0.78	-1.30, -0.26	0.017
	Day 7 vs. Day 6	PBO	2.81 vs. 2.46	0.35	-0.18, 0.87	0.268
	Day 7	TMP-SMZ + AZM vs. TMP-SMZ + PBO		-1.13	-1.86, -0.39	0.016
D _u (0-24) (mg)	Day 7 vs. Day 6	AZM	96.6 vs. 139.5	-42.91	-64.52, -21.30	0.003
	Day 7 vs. Day 6	PBO	122.0 vs. 110.5	11.51	-10.10, 33.12	0.370
	Day 7	TMP-SMZ + AZM vs. TMP-SMZ + PBO		-54.42	-84.97, -23.86	0.006

Although the CL_r and amount of SMZ excreted in the urine (i.e., D_u) appeared to be reduced with co-administration of azithromycin, there were no significant changes in the overall systemic exposure to SMZ. Thus, the PK data and the statistical analyses indicated that co-administration of azithromycin had no appreciable effect on the PK of sulfamethoxazole (SMZ).

Azithromycin (AZM) PK

The PK parameters for AZM following co-administration of a single 1200 mg oral dose (2x600 mg ZITHROMAX tablets) with double-strength TMP-SMZ on Day 7 are provided in the table below for the 12 Group A subjects.

Azithromycin PK Parameters	C _{max} (µg/mL)	T _{max} (hr)	AUC(0-120) (µg·hr/mL)	AUC(0-Inf) (µg·hr/mL)
Mean ± SD (N=12)	1.3 ± 0.3	1.9 ± 0.3	11.0 ± 3.2	12.0 ± 3.5
%CV	24%	15%	29%	29%
Range				

These PK parameters for azithromycin were consistent with those PK estimates reported in the other drug-drug interaction studies that employed the same 1200 mg oral tablet dose in this supplemental NDA. Thus, it appeared that co-administration with a once daily regimen of a single double-strength tablet of TMP-SMZ for 7 days had no significant effect on the PK of azithromycin.

SAFETY/ADVERSE EVENTS (AEs):

No subject discontinued from the study and no serious AEs were reported. Of the 12 subjects receiving azithromycin plus TMP-SMZ, 9 experienced a total of 20 AEs; of the 12 subjects receiving placebo plus TMP-SMZ, 2 experienced a total of 3 adverse events. The event in one of the subjects receiving placebo plus TMP-SMZ was non-treatment-emergent.

The majority of treatment-emergent AEs among the subjects receiving azithromycin plus TMP-SMZ involved the digestive system, and included nausea, diarrhea, and vomiting. The treatment-emergent AEs in the one subject receiving placebo plus TMP-SMZ included headache and tremor. All treatment-emergent AEs with the exception of leukorrhea, uterine spasm, back pain, and fever were deemed related to study treatment by the investigator. All events were mild or moderate in severity.

REVIEWER CONCLUSIONS:

- Single dose oral co-administration of 1200 mg azithromycin (2x600 mg ZITHROMAX tablets) with repeated QD administration of one trimethoprim-sulfamethoxazole double-strength tablet (160 mg TMP + 800 mg SMZ) for 7 days (i.e., at steady state) had no significant effect on the pharmacokinetics of either TMP or SMZ in healthy male and female subjects.
- Steady state administration of the double-strength TMP-SMZ tablet also had no significant effect on the PK of azithromycin after the single 1200 mg oral tablet dose in the same subjects.

REVIEWER COMMENTS:

Reviewer agrees with results of this study and with the sponsor's conclusions.



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

4. PROTOCOL 066-094: THE EFFECT OF AZITHROMYCIN ON THE PHARMACOKINETICS OF NELFINAVIR IN HEALTHY VOLUNTEERS

Study Dates: 15 December 1997 - 29 April 1998

sNDA Vol. 10, pp. 1-290

OBJECTIVES:

The primary objective was to assess the effect of azithromycin on the pharmacokinetics of nelfinavir at steady state. A secondary objective was to assess the effect of nelfinavir on the pharmacokinetics of azithromycin.

FORMULATIONS/TREATMENTS:

Azithromycin 600 mg tablets (FID # QC2499, Lot # N7112-G2)

This was the commercial ZITHROMAX tablet formulation.

Nelfinavir 250 mg tablets

SUBJECTS:

14 healthy male (N=6) and female (N=8) subjects; mean (range) age – males: 34.5 (24-43) yr., females: 35.9 (24-45) yr.; mean (range) weight – males: 76.2 (62-86) kg, females: 58.8 (49-70) kg

STUDY DESIGN and METHODS:

Open-label, randomized, two-treatment, parallel groups study design. Subjects were randomly assigned to one of the following 2 treatment regimens:

- (1) single dose azithromycin 1200 mg (2x600 mg ZITHROMAX tablets) followed by a sampling/washout period of at least 2 weeks; then nelfinavir 750 mg (3x250 mg VIRACEPT® tablets) TID x 11 days with a single 1200 mg dose of azithromycin on the 9th day of nelfinavir administration (N=6)
- (2) 750 mg nelfinavir TID x 11 days with a single 1200 mg dose of azithromycin on the 9th day of nelfinavir administration followed by a sampling/washout period of at least 3 weeks; then a single 1200 mg dose of azithromycin (N=8)

Azithromycin was administered with 120 ml of water immediately following a breakfast of cereal and/or toast with butter, jelly, and milk. Nelfinavir was administered with 120 ml of water at approximately 7:00am, 3:00pm, and 10:00pm with food as per label recommendations. On the 9th day, azithromycin was co-administered at the same time as the morning dose of nelfinavir. On days prior to morning sampling for nelfinavir, the evening dose was taken at 10:00pm with a light snack or 8-oz glass of milk. On sampling days, subjects were to fast for at least 8 hrs prior to consuming a standard breakfast. It was recommended that the subjects be given all other morning doses of nelfinavir with breakfast at the Clinical Research Facility. The afternoon and evening doses could be self-administered outside the Clinical Research Facility at the discretion of the investigator, but subjects were advised to take all doses of nelfinavir with food. On sampling days, all subjects were to refrain from lying down or drinking caffeinated beverages during the first 4 hrs after morning administration of nelfinavir. The next dose of nelfinavir was not administered until after the 8-hr PK sample was obtained.

PK Sampling for Nelfinavir (NLF) and M8 Metabolite: predose (0 hr), 1, 2, 3, 4, 5, 6, and 8 hrs after the morning dose of nelfinavir on Day 8 (i.e., alone) and Day 9 (i.e., with azithromycin) of nelfinavir administration. An additional sample was obtained just prior to the morning dose on Day 7 of nelfinavir administration.

PK Sampling for Azithromycin (AZM): predose (0 hr), 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144 and 168 hrs after administration of azithromycin.

ANALYTICAL METHODS:



DATA ANALYSIS:

The PK parameters for nelfinavir (NLF), M8 metabolite, and azithromycin (AZM) were determined using standard noncompartmental methods.

To statistically examine the effect of azithromycin on the PK of nelfinavir and its M8 metabolite, AUC_{0-8} , C_{max} , and T_{max} were evaluated on **Day 9 (NLF + AZM) vs. Day 8 (NLF alone)**. Natural log-transformed AUC and C_{max} and untransformed T_{max} were analyzed. For AUC and C_{max} , the anti-log (exponent) of the difference and the confidence limits were taken to estimate the ratio between the treatments and the corresponding 90% confidence intervals.

To examine whether concentrations of both NLF and the M8 metabolite were at steady state on **Days 8 and 9**, a fixed effects ANOVA allowing for variability due to study day and subject was run on the predose concentrations of NLF and the M8 metabolite.

To examine the effect of nelfinavir on the PK of azithromycin, natural log-transformed AUC and C_{max} and untransformed T_{max} and $T_{1/2}$ were analyzed using ANOVA. For AUC and C_{max} , the anti-log (exponent) of the difference and the confidence limits were taken to estimate the ratio between the treatments and the corresponding 90% confidence intervals.

PK RESULTS:

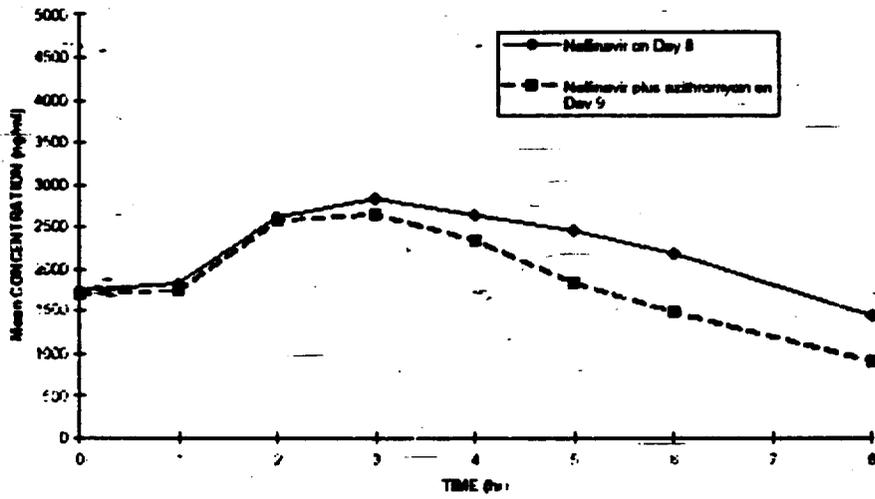
Complete PK data was obtained from 12 of the 14 subjects enrolled into the study. Two (2) subjects randomized to the 2nd treatment regimen were discontinued from the study while receiving nelfinavir, but prior to co-administration with azithromycin. Neither discontinuation was considered related to study drug treatment. The PK data from both treatment regimens were combined and statistically analyzed for the remaining 12 subjects, i.e., PK data for NLF and NLF + AZM, NLF M8 metabolite and M8 + AZM, and AZM.

Nelfinavir (NLF) and M8 Metabolite PK:

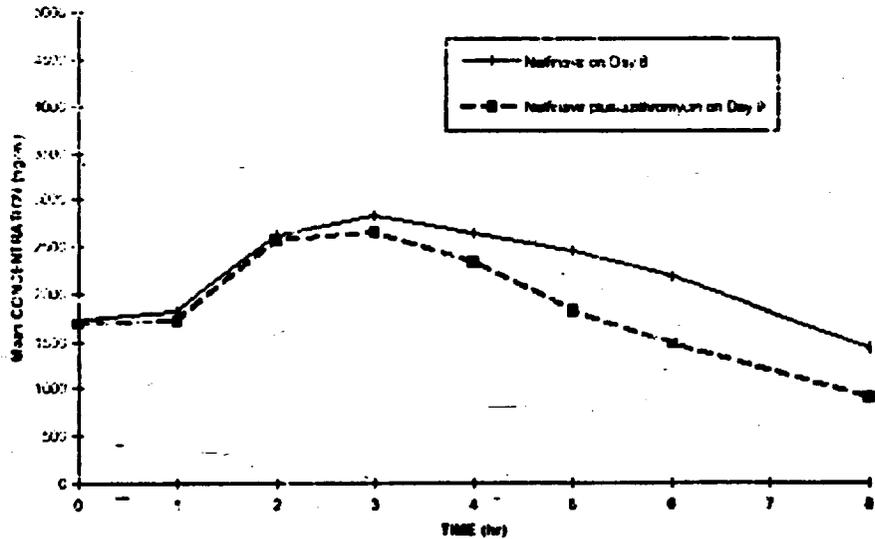
The mean NLF and M8-metabolite serum concentration-time profiles are shown in the figures below following NLF administration 750 mg TID on **Day 8 (alone) and Day 9 (+ AZM)**. There appeared to be some reduction in the mean serum concentrations of both NLF and M8 at the later timepoints from 4 to 8 hr after the nelfinavir dose when combined with AZM on **Day 9 vs. when given alone on Day 8**.

The mean \pm SD (%CV) pre-dose NLF levels on **Days 7, 8, and 9** were 2110 ± 964 ng/mL (46%), 1740 ± 712 ng/mL (41%), and 1700 ± 739 ng/mL (43%), respectively. Although these levels demonstrated a decreasing trend on **Days 8 and 9**, the statistical analyses showed no significant difference between the **Day 8 and Day 9** predose concentrations, which indicated that steady state was attained by **Day 8** for NLF. The same results were obtained for the pre-dose levels of the M8 metabolite, demonstrating that steady state was also attained by **Day 8** for M8.

Mean Concentrations of Nefinavir Following Oral Administration of 750 mg Nefinavir *t.i.d.* for 9 Days and a Single Dose of 1200 mg Azithromycin to Healthy Volunteers



Mean Concentrations of Nefinavir M8 Metabolite Following Oral Administration of 750 mg Nefinavir *t.i.d.* for 9 Days and a Single Dose of 1200 mg Azithromycin to Healthy Volunteers



The PK parameters for NLF and the M8 metabolite are summarized in the tables below.

Nelfinavir PK Parameters Following Oral Administration of 750 mg TID for 8 Days and in Combination with 1200 mg Oral Azithromycin on Day 9 to Healthy Subjects; Data Expressed as Mean \pm SD, (%CV), [Range]

NLF PK Parameters	Day 8 NLF* Alone (N=12)	Day 9 NLF + AZM* (N=12)	Day 9/Day 8 Ratio or D9-D8 Difference** (N=12)
Cmax (ng/mL)	3250 \pm 956 (29%)	2930 \pm 789 (27%)	0.90 \pm 0.20 (22%)
Tmax (hr)	3.2 \pm 0.9 (28%)	2.6 \pm 0.8 (31%)	-0.6 \pm 0.5
AUC(0-8) (ng \cdot hr/mL)	17200 \pm 5600 (33%)	14800 \pm 4290 (29%)	0.85 \pm 0.14 (16%)
*NLF = Nelfinavir; AZM = Azithromycin **Ratios for Cmax and AUC(0-8); Difference for Tmax			

Nelfinavir M8 Metabolite PK Parameters Following Oral Administration of 750 mg Nelfinavir TID for 8 Days and in Combination with 1200 mg Oral Azithromycin on Day 9 to Healthy Subjects; Data Expressed as Mean \pm SD, (%CV), [Range]

M8 PK Parameters	Day 8 NLF* Alone (N=12)	Day 9 NLF + AZM* (N=12)	Day 9/Day 8 Ratio or D9-D8 Difference** (N=12)
Cmax (ng/mL)	1240 \pm 325 (26%)	1140 \pm 346 (30%)	0.92 \pm 0.23 (25%)
Tmax (hr)	3.7 \pm 1.4 (38%)	3.1 \pm 1.4 (45%)	-0.6 \pm 1.7
AUC(0-8) (ng \cdot hr/mL)	8300 \pm 1850 (29%)	5270 \pm 1450 (28%)	0.64 \pm 0.21 (25%)
*NLF = Nelfinavir; AZM = Azithromycin **Ratios for Cmax and AUC(0-8); Difference for Tmax			

The statistical results for NLF and M8 metabolite are summarized in the tables below.

Summary of Statistical Analyses of Nelfinavir PK Parameters When Co-Administered with Azithromycin (NLF + AZM) on Day 9 vs. Administration of Nelfinavir Alone (NLF) on Day 8

NLF PK Parameter	Comparison				
		Adj. Geometric Means	Ratio	90% Confidence Limits	p-value
Cmax (ng/mL)	NLF + AZM vs. NLF	2928.58 vs. 3245.95	90%	- 81%, 101%	0.1326
AUC(0-8) (ng \cdot hr/mL)	NLF + AZM vs. NLF	14559.6 vs. 17183.2	85%	78%, 93%	0.0061
		Adj. Arithmetic Means	Difference	90% Confidence Limits	
Tmax (hr)	NLF + AZM vs. NLF	2.58 vs. 3.17	-0.6	-0.9, -0.3	0.0024

Summary of Statistical Analyses of Nelfinavir M8 Metabolite PK Parameters When Nelfinavir was Co-Administered with Azithromycin (NLF + AZM) on Day 9 vs. Administration of Nelfinavir Alone (NLF) on Day 8

M8 PK Parameter	Comparison	Adj. Geometric Means	Ratio	90% Confidence Limits	p-value
		C _{max} (ng/mL)	NLF + AZM vs. NLF	1139.5 vs. 1243.3	92%
AUC(0-8) (ng•hr/mL)	NLF + AZM vs. NLF	5270.9 vs. 6300.7	84%	74%, 95%	0.0287
		Adj. Arithmetic Means	Difference	90% Confidence Limits	
T _{max} (hr)	NLF + AZM vs. NLF	3.08 vs. 3.67	-0.6	-1.5, 0.3	0.2534

The results showed that mean NLF and M8 AUC values were slightly reduced ~15% and mean C_{max} values were also slightly reduced ~10% when co-administered with 1200 mg azithromycin. The range of individual AUC ratios indicated that the maximum reduction in AUC was 28% for NLF and was 36% for the M8 metabolite. For C_{max}, the range of individual C_{max} ratios indicated that the maximum reduction in C_{max} was 30% for both parent NLF and M8 metabolite.

Despite the relatively small changes in the mean AUC for NLF and M8, the statistical results (i.e., p-values) showed these reductions to be statistically significant. The lower bounds for the 90% confidence limits for NLF and M8 also fell slightly below the criteria that is considered by the Agency as equivalent (i.e., lower bound of 80%). The small changes in mean C_{max} for NLF and M8 were not statistically significant, as evidenced by both the p-values and 90% confidence limits.

REVIEWER NOTES/COMMENTS:

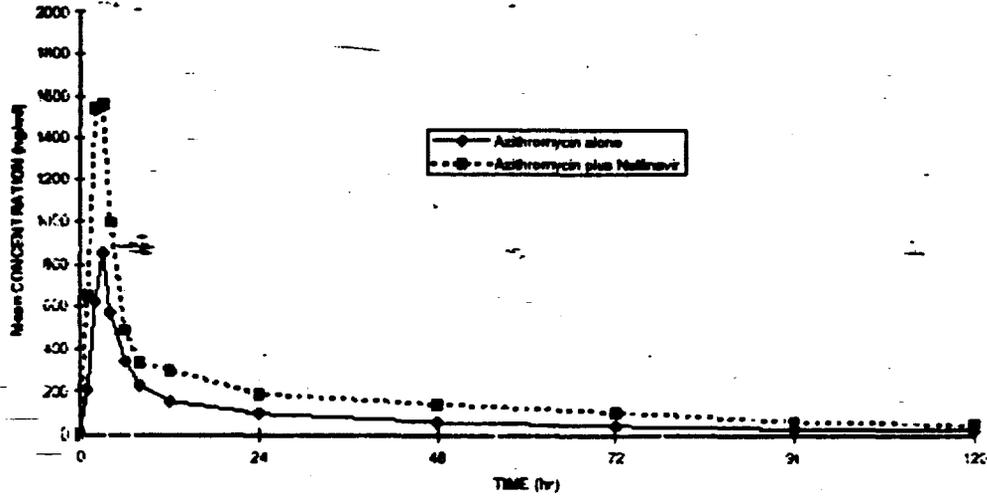
These changes in NLF and M8 metabolite AUC and C_{max} when co-administered with azithromycin would most likely not be clinically relevant. However, the changes should be noted in the proposed labeling for both azithromycin and nelfinavir.

The PK parameters for NLF and M8 from this present study were comparable to those previously reported in the PK studies from the nelfinavir NDA (20-778) after steady state oral dosing with 750 mg (as 3x250 mg tablets). This applies to the administration of NLF before AZM and with AZM in this present study.

Azithromycin (AZM) PK:

The mean azithromycin serum concentration-time profiles are shown in the figure below following AZM administration alone and with nelfinavir (NLF).

Mean Concentrations of Azithromycin Following Oral Administration of 1200 mg Azithromycin Alone and Following Administration of 750 mg Nelfinavir TID for 9 Days to Healthy Volunteers



Data truncated at 120 hr to improve visualization.

The PK parameters for azithromycin are provided in the table below.

Azithromycin PK Parameters after Single Dose Administration of 1200 mg Alone and When Co-Administered With Nelfinavir 750 mg TID for 9 Days; Data Expressed as Mean \pm SD, (%CV), [Range]

	AZM* 1200 mg Alone (N=12)	AZM 1200mg + NLF* 750 mg TID (N=12)	Ratio or Difference**
C _{max} (µg/mL)	0.888 \pm 0.487 (55%)	2.10 \pm 0.495 (24%)	2.37 \pm 1.30 (55%)
T _{max} (hr)	3.0 \pm 0.85 (28%)	2.3 \pm 0.89 (39%)	-0.7 \pm 1.50
AUC(0-inf) (µg·hr/mL)	11.5 \pm 3.6 (31%)	24.5 \pm 4.9 (20%)	2.12 \pm 0.64 (30%)
K _{el} (1/hr)	0.013 \pm 0.019 (15%)	0.014 \pm 0.016 (12%)	0.0007 \pm 0.0025
T _{1/2} (hr)	54.3 \pm 7.9 (15%)	51.3 \pm 6.2 (12%)	Not Reported

*AZM = Azithromycin; NLF = Nelfinavir
 **Ratio (AZM+NLF/AZM) for C_{max} and AUC; Difference (AZM+NLF-AZM) for T_{max} and K_{el}

The statistical results for AZM are summarized in the table below.

Summary of Statistical Analyses of Azithromycin (AZM) PK Parameters after Single Dose Administration of 1200 mg Alone and When Co-Administered With Nelfinavir (NLF) 750 mg TID for 9 Days

AZM PK Parameter	Comparison	Adj. Geometric Means	Ratio	90% Confidence Limits	p-value
Cmax (µg/ml)	AZM + NLF vs. AZM	2.099 vs. 0.889	236%	177%, 315%	0.0003
AUC(0-inf) (µg·hr/mL)	AZM + NLF vs. AZM	24.47 vs. 11.54	212%	180%, 250%	<0.0001
		Adj. Arithmetic Means	Difference	90% Confidence Limits	
Tmax (hr)	AZM + NLF vs. AZM	2.3 vs. 3.0	-0.7	-1.5, 0.1	0.1615
T½ (hr)	AZM + NLF vs. AZM	51.3 vs. 54.3	-3.1	-6.9, 0.8	0.1808

Co-administration of multiple doses of nelfinavir 750 mg TID for 9 days with a single dose of azithromycin significantly increased the mean Cmax and AUC(0-inf) of AZM. The mean azithromycin Cmax was 2.4-times higher when given with NLF, and the range of Cmax ratios indicated that the maximum increase in Cmax was 5-times of that when AZM was given alone. The mean AUC(0-inf) of AZM was also 2-times higher when given with NLF, and the range of individual AUC ratios indicated that the maximum increase in AUC was nearly 4-times of that when AZM was given alone. The increases in AZM Cmax and AUC were highly statistically significant. The Kel and corresponding half-life of azithromycin were not significantly altered by co-administration with nelfinavir.

These results suggested that the substantial increase in the systemic availability of azithromycin when given with nelfinavir might be due to an effect of nelfinavir on the oral bioavailability of AZM, rather than by inhibiting the elimination of AZM (i.e., inhibition of hepatic CYP3A4). The sponsor did not postulate on the mechanism of this effect.

REVIEWER NOTE:

The mechanism of the effect on the oral bioavailability may possibly be inhibition of gut metabolism of AZM (i.e., gut CYP3A4 rather than inhibition of hepatic CYP3A4) and/or inhibition of the protein efflux transporter, p-glycoprotein, by nelfinavir.

SAFETY/ADVERSE EVENTS (AEs):

One subject discontinued treatment with nelfinavir after eight days for moderate-viral enteritis; no serious AEs were reported.

The majority of AEs were reported for the NLF treatment group. Overall, 2, 5, and 7 subjects in the AZM, NLF+AZM, and NLF groups reported 3, 10, and 17 adverse events, respectively. All events with one exception, syncope in the AZM group, were treatment-emergent. Most subjects had treatment-emergent events associated with the digestive system (AZM 1, NLF+AZM 5, NLF 6), although some had events associated with the body as a whole (AZM 1, NLF+AZM 1, NLF 5) and skin and appendages (NLF+AZM 1, NLF 3)

All treatment-emergent digestive system events were mild, with the exception of one moderate enteritis with NLF. Other treatment-emergent adverse events reported were mild abdominal pain

(NLF+AZM 1), mild fever (AZM 1), mild or moderate headache (NLF 5), mild pruritus (NLF+AZM 1, NLF 1), and mild or moderate rash (NLF+AZM 1, NLF 3).

REVIEWER CONCLUSIONS:

- Co-administration of a single 1200 mg tablet dose of azithromycin (2x600 mg ZITHROMAX tablets) with multiple dose administration of nelfinavir 750 mg TID (3x250 mg VIRACEPT tablets) for 9 days (i.e., at steady state) reduced the mean steady state AUC values of nelfinavir and its major active M8 metabolite approximately 15% in healthy male and female subjects. The mean C_{max} values of nelfinavir and M8 were not altered by azithromycin co-administration. **The changes in NLF and M8 metabolite AUC and C_{max} when co-administered with azithromycin would most likely not be clinically relevant. However, these changes, especially in steady state AUC, should be noted in the proposed labeling for both azithromycin and nelfinavir.**
- Steady state tablet administration of nelfinavir at 750 mg TID for 9 days to the same healthy subjects significantly increased the systemic availability (i.e., both AUC and C_{max}) of azithromycin after the single 1200 mg tablet dose. The mean azithromycin AUC and C_{max} values were approximately 2-times higher when given with nelfinavir and ranged up to approximately 4- and 5-times higher, respectively, compared to when azithromycin was given alone. The K_{el} and corresponding half-life of azithromycin, however, were not significantly altered by co-administration with nelfinavir. **These results suggested that the substantial increase in the systemic availability of azithromycin when given with nelfinavir might be due to an effect of nelfinavir on the oral bioavailability of azithromycin, rather than by inhibiting the elimination of azithromycin (i.e., inhibition of hepatic CYP3A4). The sponsor did not postulate on the mechanism of this effect. However, the mechanism of the effect on the oral bioavailability may possibly be inhibition of gut wall metabolism of azithromycin (i.e., gut CYP3A4 rather than inhibition of hepatic CYP3A4) and/or inhibition of the protein efflux transporter, p-glycoprotein, by nelfinavir.**

REVIEWER COMMENTS:

Reviewer agrees with the results reported for this study and with the sponsor's conclusions.

