CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 050670/S008

Trade Name ZITHROMAX CAPSULES 250mg

Generic Name Azithromycin

Sponsor Pfizer, Inc.

NDA 50-670/S-008

NOV 22 1996

Pfizer Incorporated
Attention: Robert B. Clark
Senior Associate Director
Regulatory Affairs Division
235 East 42nd Street
New York, NY 10017-5755

Dear Mr. Clark :

Please refer to your December 12, 1994 supplemental new drug application submitted under section 507 of the Federal Food, Drug, and Cosmetic Act for Zithromax (azithromycin) Capsules 250mg.

We also acknowledge receipt of your amendments dated January 11, 1996, and August 22, 1996, in response to our approvable letter dated December 13, 1995.

We have completed the review of this supplemental application and the draft package insert and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the draft printed labeling submitted on August 22, 1996. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on August 22, 1996.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDA 50-670/S-008. Approval of this FPL is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print.

Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please call Mr. Jose R. Cintron, R.Ph., M.A., Project Manager, at (301) 827-2125.

Sincerely,

David W. Feigal, Jr., M.D., M.P.H.
Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:
Original NDA 50-670

HFD-520/Div. file
HFD-2/MLumpkin
HF-2/Medwatch (with labeling)
HFD-92 (with labeling)
HFD-40/DDMAC (with labeling)
HFD-104/D.Feigal
HFZ-400
HFD-426/TLBIOPHARM/FPelsor
HFD-426/BIOPHARM/HSun
HFD-520/LGirardi 11/8/96
HFD-520/TLPHARM/ROsterberg
HFD-520/PHARM/MAdeyemo
HFD-520/ATL/BDunn
HFD-520/CHEM/JTimper
HFD-520/TLMICRO/AShledon
HFD-520/MICRO/HSilver
HFD-520/PMS/JCintron
HFD-613 (with labeling)
HFD-735/(with labeling) - for all NDAs and supplements for adverse reaction changes.
DISTRICT OFFICE

Concurrence Only
HFD-520/Act.Div.Director/DFeigal
HFD-520/TL/MAlbuerne 11/15/96
HFD-/CPMS/JBona 11/4/96

drafted: jrc/September 20, 1996/
r/d Initials:
final:

APPROVAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-670/S-008

DEC 13 1995

Pfizer Incorporated
Attention: Robert B. Clark
Senior Associate Director
Regulatory Affairs Division
235 East 42nd Street
New York, NY 10017-5755

Dear Mr. Clark:

Please refer to your December 13, 1994 supplemental new drug application submitted under section 507 of the Federal Food, Drug, and Cosmetic Act for Zithromax®(azithromycin)Capsules, 250mg.

We also acknowledge receipt of your amendment dated May 16, 1995.

The supplemental application provides for the treatment of urethritis and cervicitis due to *Neisseria gonorrhoeae and* the treatment of Chancroid in males due to *Haemophilus ducreyi*.

We have completed the review of this supplemental application as submitted with draft labeling. We find that adequate information has been presented for the indications of urethritis and cervicitis due to *Neisseria gonorrhoeae* and Chancroid in males due to *Haemophilus ducreyi*. However, there were inadequate data to support the indication for

Before this supplement may be approved for the above stated indications, however, it will be necessary for you to revise the labeling to be in conformity to that in NDA 50-710, azithromycin for oral suspension, approved on October 19, 1995.

Please submit sixteen copies of the printed labeling, ten of which are individually mounted on heavy weight paper or similar material. If additional information relating to the safety or effectiveness of this drug becomes available, revision of that final printed labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product.

All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and
Communications, HFD-240
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action, FDA may take action to withdraw the application.

Under section 736(a)(1)(B)(ii) of the Prescription Drug User Fee Act of 1992, this letter triggers the remaining 50% of the fee assessed for this supplemental application. You will receive an invoice for the amount due within the next month. Payment will be due within 30 days of the date of the invoice.

This change may not be implemented until you have been notified in writing that this supplemental application is approved.

Should you have any questions, please contact Ms. Frances LeSane, Project Manager, at 301-827-2125.

Sincerely yours,

Mary Farning, M.D., Ph.D., FACP
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:
Original NDA 50-670/S-008
HFD-520/Div. File
HFD-2/Lumpkin
HFC-130/JAllen
HFD-520/MO/PBais
HFD-520/SPHARM/ROsterberg
HFD-520/PHARM/MAdeyemo
HFD-520/SCHEM/SRoy
HFD-520/CHEM/JTimper
HFD-520/SMICRO/ASheldon
HFD-520/MICRO/HSilver
HFD-426/SBIOPHARM/FPelsor
HFD-426/BIOPHARM/HSun
HFD-713/SSTAT/RHarkins
HFD-713/STAT/AChakvaraty
HFD-520/PMS/JCintron
HFD-520/PMS/FVLeSane/12/2/95/12-8-95/12-13-95 FVL 12-13-95

Concurrence Only:
HFD-520/Div.Dir/MFanning MF 12/13/95
HFD-520/SMO/MAlbuerne MSA 12/13/95
HFD-520/SPMS/JBona 12/13/95

APPROVABLE

PROJECT MANAGER'S REVIEW OF LABELING

APPLICANT:	Pzifer Inc 235 East 42nd Street New York, NY 10017-5755
DATE OF SUBMISSION:	August 22, 1996
DATE OF REVIEW:	October 17, 1996
NAME OF DRUG:	Zithromax® (azithromycin) Capsules
DESCRIPTION OF SUBMISSION:	On December 15, 1995, an approvable letter was issued for the indications of urethritis and cervciitis due to *Neisseria gonorrhoeae* and the treatment of Chancroid in males due to *Haemophilus ducreyi.*

The final printed draft labeling was revised as follows:

2 Pages
deleted
Labeling Revisions

RECOMMENDATION: An approval letter should be issued informing the applicant that the final draft labeling dated August 22, 1996 (70-5179-00-4, NDA 50-670/S-008 is approved. I have reviewed the submitted label in accordance with our December 13, 1995 approvable letter, and it is acceptable.

Jose R. Cintron, R.Ph., M.A.
Project Manager

Dr. Luigi Girardi, MD
Medical Officer

cc:
Original NDA 50-670

HFD-520/Div. files
HFD-520/PM/JCintron
HFD-520/ MO/L Girardi

Concurrence Only
HFD-520/Act.Div.Director/DFeigal
HFD-520/TL/MAlbuerne
HFD-/SPMS/JBona

approvable letter, and it is acceptable.

Jose R. Cintron, R.Ph., M.A.
Project Manager

Dr. Luigi Girardi, MD
Medical Officer

MEDICAL OFFICER'S REVIEW OF SUPPLEMENTAL NDA 50-670/SE1-008

SPONSOR: PFIZER CENTRAL RESEARCH
MEDICAL RESEARCH LABORATORY
EASTERN POINT ROAD
GROTON, CT 06340

DATE OF SUBMISSION:	DECEMBER 12, 1994
DATE RECEIVED BY AGENCY:	DECEMBER 13, 1994
DATE OF ASSIGNMENT TO M.O.:	JANUARY 24, 1995
DATE INITIAL REVIEW STARTED:	MARCH 13, 1995
DATE OF FINAL REVIEW:	DECEMBER 13, 1995

DRUG TRADE NAME: ZITHROMAX® CAPSULES

GENERIC NAME: Azithromycin

DRUG CLASS: Macrolide

SUB-CLASS: Azalide

CHEMICAL NAME: (2R,3S,4R,5R,8R,12S,13S,14R)-13-(2,6-dideoxy-3-C-methyl-3-O-methyl-a-L-ribo-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-b-D-xylo-hexopyranosyl]-1-oxa-6-azacyclopentadecan-15-one.

CHEMICAL FORMULA: $C_{38}H_{72}N_2O_{12}2H_2O$

MOLECULAR WEIGHT: 785.0.

MATERIAL SUBMITTED: In this NDA a total of 66 volumes were submitted with data to support the efficacy and safety of azithromycin for the treatment of urethritis and cervicitis due to *Neisseria gonorrhoeae,* non-gonococcal urethritis in men due to and genital ulcer disease in men due to *Haemophilus ducreyi* (chancroid).

BACKGROUND: Azithromycin is approved for 5-day treatment of adults for pharyngitis/tonsillitis, lower respiratory tract infection, skin and skin structure infections caused by susceptible organisms. It has also been approved in a single 1 gram dose for the treatment of urethritis/cervicitis due to *C. trachomatis.*

Urethritis and cervicitis due to *N. gonorrhoeae* Protocols:

PROTOCOL: 066-130

PROTOCOL TITLE: A multicenter open comparative trial of Azithromycin (CP-62,993) and Ceftriaxone in patients with uncomplicated gonococcal urethritis/cervicitis.

STUDY OBJECTIVE: To compare the efficacy and safety of single doses of azithromycin (2 g oral) and ceftriaxone (250 mg intramuscular) in the treatment of acute gonococcal urethritis and/or cervicitis in both male and female population.

STUDY PERIOD: July 1990 to August 1994

STUDY SUMMARY: This multicenter, open-label study was a randomized comparison of single doses of azithromycin (2 g oral) and ceftriaxone (250 mg intramuscular) in patients with acute gonococceal urethritis and/or cervicitis. All infections were to be confirmed by culture of *Neisseria gonorrhoeae.* The study was performed at 10 centers in the United States. The study population consisted of male and female patients 16 years or older who had presumptive diagnoses of gonococcal urethritis and/or cervicitis, defined as the presence of a urethral/cervical discharge which on Gram stain showed intracellular Gram-negative diplococci. A total of 727 patients were randomized into the study, with 484 randomized to azithromycin and 243 to ceftriaxone. Prior to admission, each patient was to provide written, informed consent. The study had IRB approval. Urethral and/or cervical samples were to be obtained for Gram staining for gonococcal infection to indicate eligibility for study entry prior to availability of culture results. Each patient was to have a physical examination performed, and blood and urine specimens were to be obtained for a panel of routine safety tests. Predose urethral, cervical, pharyngeal, and rectal specimens were to be obtained on the same day as dosing for *N. gonorrhoeae* culture.

Patients with culture-confirmed gonococcal infection at any site were to be reevaluated clinically and bacteriologically at the visits week 1 after dosing and, following a request from FDA (October 11, 1990 protocol amendment), at visit week 2. Follow-up cultures were to be obtained from urethra and other sites culture-positive at baseline. Patients were to be instructed not to donate blood and to abstain from sexual relations while in the study.

ENROLLMENT CRITERIA:

Inclusion criteria:

- At least 16 years of age.

- Outpatients.

- Males with presumptive gonococcal urethritis, defined as the presence of a urethral discharge which on Gram stain showed intracellular Gram-negative diplococci.

- Women with presumptive gonococcal urethritis and/or cervicitis, defined as a urethral or cervical discharge which on Gram stain showed intercellular Gram-negative diplococci. Women of childbearing potential must have had a negative serum gonadotropin pregnancy test prior to entry into the study and must have been using adequate contraception both during and for 3 months after the end of the study.

- The investigator was to obtain informed written consent from each patient prior to inclusion in the study. In States where the legal age of consent for medical procedures is 21, patients below the age of 21 had to have, in addition to the above consent, written permission and informed consent from a parent or guardian.

Exclusion criteria:

- Pregnant or lactating women.

- Evidence or history of significant hematologic, renal, hepatic or cardiac diseases.

- History of allergy or hypersensitivity to erythromycin, ceftriaxone, or any other betalactam antibiotics.

- Clinical evidence of gonococcal pharyngitis, proctitis, disseminated gonococcal infection, or the presence

of any other infection at enrollment that might require treatment with an antibiotic other than the study drugs.

- Subjects who, for any reason judged by the investigator, might not be expected to comply with the requirements of the protocol.

- Treatment with another investigational drug within the 30 days prior to entry into the study.

- Treatment with any systemic antibiotic within the 72 hours prior to entry into the study.

- Patients with ulcers, gastrectomy, or other conditions affecting drug absorption.

- Donation of blood or blood components while receiving experimental drug.

CONCOMITANT MEDICATIONS:

During the study the patient may not have been treated with another antibiotic. Additional antibiotic therapy before the appropriate follow-up culture(s) had been performed would render the patient nonevaluable for efficacy for subsequent visits.

Patients found to have a positive serologic test for syphilis at entry were to be evaluated and receive appropriate treatment. If additional antiinfective medication was required during the study, the patient was to be discontinued from the study and the appropriate therapy instituted.

The use of other (nonantiinfective) medications were to be limited to those essential for the care of the patient. All concomitant medications were to be recorded. The use of any other investigational drug was to be prohibited.

INTERCURRENT ILLNESS:

Any intercurrent illness was to be appropriately recorded in the case report form.

PRECAUTIONS:

Patients were to be instructed not to donate blood and to abstain from sexual activity during the study.

DRUG ADMINISTRATION:

The investigator was provided with a randomization schedule consisting of a list of sequential numbers. Patients were randomly allocated in a 2:1 ratio to receive one of the following dosing regimens:

1. Azithromycin, 2 g (8-250 mg capsules) as a single dose.
2. Ceftriaxone, 250 mg as a single intramuscular dose.

Study drug was to be administered in an open fashion. Azithromycin was to be administered at least one hour before or 2 hours following meals. Study drug was to be administered in the clinic under direct supervision.

DRUG SUPPLIES:

Azithromycin was supplied in an amount sufficient to complete 40 evaluable patients. Ceftriaxone, sufficient to complete 20 evaluable patients, was supplied by the investigator.

DRUG STORAGE AND ACCOUNTABILITY:

1. Azithromycin capsules were to be stored under refrigeration.

2. The investigator was responsible for recording the receipt and usage of all drugs supplied, and for ensuring the supervision of the storage and allocation of these supplies. At completion or termination of the study, all unused drug supplies were to be returned to Pfizer Central Research.

CRITERIA FOR EVALUATION FOR EFFICACY:

Symptoms of cervicitis or urethritis (e.g., discharge, burning, and painful urination), together with any additional volunteered symptoms and signs, were to be recorded at baseline. Symptoms present at entry were to be assessed at the follow-up visits as absent, improved, no change, or worse. At the follow-up visits, patients were to be questioned concerning interval sexual exposure. At the end of the study, the patient's clinical response was to be classified as cured, improved, or failed.

Each pathogen cultured was defined as being either resistant or susceptible to azithromycin or ceftriaxone. The susceptibility of *N. gonorrhoeae* was classified according to its MIC and/or zone of inhibition. The cutoff points used to define resistance were:

	MIC(mcg/mL)	ZONE(mm)
Azithromycin	≥ 8	≤ 13*
Ceftriaxone	≥ 64	≤ 13

* 15 mcg azithromycin disks

LABORATORY PARAMETERS:

The following safety tests were to be performed within 24 hours before study entry, and at visit weeks 1 and 2:

Hematology:

CBC including differential and platelet counts, ESR, prothrombin time, and APTT.

Chemistry:

GGT, AST, ALT, alkaline phosphatase, total protein and albumin, serum bilirubin, LDH, BUN, serum creatinine, serum calcium and phosphorus, electrolytes, blood glucose (fasting when feasible), uric acid, serum cholesterol and triglycerides.

Urinalysis.

Pregnancy tests (for women of childbearing age), tests for HBsAg, and tests for syphilis (FTA or R.P.R.) were to be performed only at study entry. Patients with a positive syphilis test were to be evaluated and receive appropriate treatment. If this involved antiinfective medication other than the randomly assigned study drug, the patient was to be discontinued from the study.

Gram stain of urethral and/or cervical exudates were examined at entry. Swab specimens were cultured for *N. gonorrhoeae* (urethra, rectum, pharynx, and cervix in females) at entry and for any culture positive

site(s) at the follow-up visits. Disk susceptibility or MIC values were to be determined for all isolates. Patients with persistent symptoms at the one-week follow-up visit were also to be cultured for *C. trachomatis, and M. hominis*, at the discretion of the investigator (urethral and/or cervical cultures only). Susceptibility testing for these isolates was not required).

RESULTS:

CENTER	INVESTIGATORS
509	HUGH HUNTER HANDSFIELD, M.D.
526	JAMES McCARTY, M.D.
554	NORMAN GARRISON, Jr., M.D.
589	JOHN MILLS, M.D.
712	DAVID MARTIN, M.D.
736	JANET ARNO, M.D.
742	JOHN DOUGLAS, M.D.
757	ZIAD DALU, M.D.
773	BRANT VINER, M.D.
792	DAVID SCHLOSSBERG, M.D.

NUMBER OF PATIENTS ENROLLED BY CENTER:

Table-1

CENTER	AZITHROMYCIN		CEFTRIAXONE	
	ASSIGNED	RECEIVED TX	ASSIGNED	RECEIVED TX
509	32	32	16	16
526	55	55	27	27
554	40	40	20	20
589	34	34	18	18
712	31	31	16	16
738	25	25	12	12
742	34	33	16	16
757	161	161	79	79
773	35	35	18	18
792	37	37	21	21
TOTAL	484	483	243	243

DEMOGRAPHICS AND COMPARABILITY OF ENROLLED (ALL) PATIENT POPULATION BY SPONSOR
Table-2

VARIABLE	AZITHROMYCIN			CEFTRIAXONE		
SEX	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL
NUMBER	301	182	483	154	89	243
RACE						
WHITE	30	17	47(9.7)	22	13	35(14.4)
BLACK	215	156	371(76.8)	110	72	182(74.9)
ORIENTAL	0	1	1(0.2)	0	1	1(0.4)
AMERICAN INDIAN	2	2	4(0.8)	0	0	0
OTHER	2	0	2(0.4)	0	0	0
HISPANIC	52	6	58(12)	21	3	24(9.9)
ASIAN	0	0	0	1	0	1(0.4)
AGE (MEAN)	27.6	24.2	26.3	27.1	24.0	25.9
WEIGHT(kg, MEAN)	77.6	67.7		78.0	64.6	

(Numbers in the parentheses are the percentages)

DEMOGRAPHICS AND COMPARABILITY OF EVALUABLE PATIENT POPULATION BY SPONSOR'S DATA (Week-1):
Table-3

VARIABLE	AZITHROMYCIN			CEFTRIAXONE		
SEX	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL
NUMBER	235	138	373	112	64	176
RACE						
WHITE	25	12	37(9.9)	18	8	26(14.8)
BLACK	169	120	289(77.5)	77	52	129(73.3)
ORIENTAL	0	0	0	0	1	1 (0.6)
AMERICAN INDIAN	1	2	3 (0.8)	0	0	
OTHER	2	0	2 (0.5)	0	0	
HISPANIC	38	4	42(11.3)	16	3	19(10.8)
ASIAN	0	0	0	1	0	1(0.6)
AGE (MEAN)	27.8	24.5	26.6	27.5	23.7	26.1
WEIGHT(kg, MEAN)	76.2	67.5		78.2	67.5	

(Numbers in the parentheses are the percentages)

NUMBER OF EVALUABLE PATIENTS FOR EFFICACY BY THE SPONSOR :

There were 549 evaluable patients in the study, 373 in the azithromycin group and 176 in the ceftriaxone group. 235 were male and 138 were female in the azithromycin group and 112 were male and 64 were female in the ceftriaxone group.

DEMOGRAPHICS AND COMPARABILITY OF EVALUABLE PATIENT POPULATION BY MEDICAL OFFICER'S DATA:

Table-4

VARIABLE	AZITHROMYCIN			CEFTRIAXONE		
SEX	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL
NUMBER	229	129	358	109	61	170
RACE						
WHITE	25	11	36(10)	17	7	24(14.1)
BLACK	164	114	278(77.6)	77	48	125(73.5)
ORIENTAL	0	0		0	1	1 (0.6)
AMERICAN INDIAN	1	1	2(0.5)	0	0	
OTHER	1	0	1(0.5)	0	0	
HISPANIC	37	4	41(11.5)	16	3	19(11)
ASIAN	0	0		1	0	1(0.6)
AGE (MEAN)	27.7	24.4	26.05	26.9	24.1	25.5
WEIGHT(kg, MEAN)	76.9	67.3		78.1	67.1	
ACCOMPANYING DISEASES YES	19/229	29/129	48/358(13.4)	12/109(11)	14/61(22.9)	26/170 (15.3)
NO	210/229	100/129	310/358(86.5)	97/109(89)	47/61(77)	144/170 (84.7)

(Numbers in the parentheses are the percentages)

MEDICAL OFFICER'S DATA:

According to the medical officer a total of 528 patients were evaluable, 358 in the azithromycin group and 170 in the ceftriaxone group. 229 were male and 129 were female in the azithromycin group, and 109 were male and 61 were female in the ceftriaxone group.

REASONS FOR UNEVALUABILITY AS PER M.O.:

Table-5

	AZITHROMYCIN		CEFTRIAXONE	
SEX	MALE	FEMALE	MALE	FEMALE
CONCOMITANT ANTIMICROBIAL	0	5/129(3.9)	0	2/61(3.3)
ASYMPTOMATIC	1/229(0.4)	0	1/109(0.9)	0
NO BASELINE PATHOGEN IN C/U	4/229(1.7)	5/129(3.9)	1/109(0.9)	2/61(3.3)
TOTAL	5/229(2.2)	10/129(7.8)	2/109(1.8)	4/61(6.6)

(Numbers in the parentheses are the percentages)

In the azithromycin group 1 male patient was asymptomatic (no urethral discharge) and 4 male patients did not have baseline pathogen; 5 female patients received concomitant antimicrobial and 5 female patients did not have baseline pathogen.

In the ceftriaxone group, one male patient was asymptomatic and one did not have a baseline pathogen; two female patients were receiving concomitant antibiotic and two did not have a baseline pathogen.

 # OF INFECTIONS IN EACH ORGAN SYSTEM IN BOTH MALE AND FEMALE ACCORDING TO THE SPONSOR:

Table-6

ORGAN	AZITHROMYCIN		TOTAL	CEFTRIAXONE		TOTAL
	MALE	FEMALE		MALE	FEMALE	
URETHRA	230	23	253	111	15	126
CERVIX	0	131	131	0	59	59
RECTUM	5	24	29	3	9	12
PHARYNX	13	7	20	6	6	12
TOTAL	248	185	433	120	89	209

 # OF INFECTIONS IN EACH ORGAN SYSTEM IN BOTH MALE AND FEMALE ACCORDING TO MEDICAL OFFICER'S DATA:

Table-7

ORGAN	AZITHROMYCIN			CEFTRIAXONE		
	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL
URETHRA	226	20	246	109	13	122
CERVIX	0	125	125	0	59	59
RECTUM	5	23	28	3	8	11
PHARYNX	8	7	15	5	5	10
TOTAL	239	175	414	117	85	202

BETA-LACTAMASE PRODUCTION:

Beta-lactamase positive----36
Beta-lactamase negative---279
Beta-lactamase not done--58

 # OF ERADICATIONS AT WEEK 1 - DATA FROM THE SPONSOR:

Table-8

ORGAN	AZITHROMYCIN		CEFTRIAXONE	
	MALE	FEMALE	MALE	FEMALE
URETHRA	229/230(99.6)	23/23 (100)	110/111(99.1)	14/15(93.3)
CERVIX	0	127/131(96.9)	0	57/59(96.6)
RECTUM	4/5 (80.0)	24/24 (100)	3/3 (100)	9/9 (100)
PHARYNX	13/13 (100)	7/7 (100)	6/6 (100)	6/6 (100)

(NUMBERS IN THE PARENTHESES ARE THE PERCENTAGES)

Urethra:

229/230 (99.6%) male patients and 23/23 (100%) female patients had eradications during the first week follow-up in the azithromycin group as compare to 110/111 (99.1%) male patients and 14/15 (93.3%) female patients in the ceftriaxone group.

Cervix:
127/131 (96.9%) female patients had eradication in the azithromycin group as compared to 57/59 (96.6%) female patients in the ceftriaxone group.
Rectum:
4/5 (80%) male and 24/24 (100%) female patients had eradications in the azithromycin group as compared to 3/3 (100%) male and 9/9 (100%) female patients in the ceftriaxone group.
Pharynx:
13/13 (100%) male and 7/7 (100%) female patients had eradications in the azithromycin group as compared to 6/6 (100%) male and 6/6 (100%) female patients in the ceftriaxone group.

 # OF ERADICATIONS AT WEEK -1, DATA FROM M.O.:
Table-9

ORGAN	AZITHROMYCIN		CEFTRIAXONE	
	MALE	FEMALE	MALE	FEMALE
URETHRA	223/226(98.7)	20/20 (100)	107/109(98.2)	13/13 (100)
CERVIX	0	123/125(98.4)	0	57/59(96.6)
RECTUM	4/5 (80.0)	23/23 (100)	3/3 (100)	8/8 (100)
PHARYNX	7/8 (87.5)	7/7 (100)	5/5 (100)	5/5 (100)

(NUMBERS IN THE PARENTHESES ARE THE PERCENTAGES)

Comment: Medical officer's results were comparable to the sponsor's for the eradication of organisms from all sites for the first week follow-up.

 # OF ERADICATIONS AT WEEK 2 - DATE FROM THE SPONSOR:
Table-10

ORGAN	AZITHROMYCIN		CEFTRIAXONE	
	MALE	FEMALE	MALE	FEMALE
URETHRA	102/102 (100)	15/15 (100)	38/41 (92.7)	7/8 (87.5)
CERVIX	0	101/103(98.1)	0	36/37 (97.3)
RECTUM	1/1 (100)	18/18 (100)	2/2 (100)	3/4 (75.0)
PHARYNX	6/6 (100)	5/5 (100)	2/3 (66.7)	3/3 (100)

(NUMBERS IN THE PARENTHESES ARE THE PERCENTAGES)

Urethra:
102/102 (100%) follow-up male patients and 15/15 (100%) female patients had eradications during the second week in the azithromycin group as compared to 38/41(92.7%) male patients and 7/8 (87.5%) female patients in the ceftriaxone group.
Cervix:
101/103 (98.1%) female patients had eradication in the azithromycin group as compared to 36/37 (97.3%) female patients in the ceftriaxone group.
Rectum:
1/1 (100%) male and 18/18 (100%) female patients had eradications in the azithromycin group as compared 2/2 (100%) male and 3/4 (75%) female patients in the ceftriaxone group.
Pharynx:
6/6 (100%) male and 5/5 (100%) female patients had eradications in the azithromycin group as compared to 2/3 (66.7%%) male and 3/3 (100%) female patients in the ceftriaxone group.

 # OF ERADICATIONS AT WEEK 2 - DATA FROM M.O.:

TABLE-11

ORGAN	AZITHROMYCIN		CEFTRIAXONE	
	MALE	FEMALE	MALE	FEMALE
URETHRA	99/99(100)	12/12 (100)	37/41 (90.2)	6/7(85.7)
CERVIX	0	93/95(97.9)	0	31/33(92.9)
RECTUM	1/1 (100)	16/17(94)	2/2 (100)	3/4 (75)
PHARYNX	5/5(100)	5/5 (100)	2/3 (66.7)	3/3 (100)

(NUMBERS IN THE PARENTHESES ARE THE PERCENTAGES)

Comment: Medical officer's results were comparable to the sponsor's for the eradication of organisms from all sites for the second week follow-up.

CLINICAL EVALUATION AT WEEK 1 - DATA FROM THE SPONSOR:

TABLE-12

CLINICAL RESPONSE	AZITHROMYCIN		CEFTRIAXONE	
	MALE	FEMALE	MALE	FEMALE
CURED	209/235(88.9)	91/122 (74.6)	85/109 (78.0)	43/58 (74.1)
IMPROVED	26/235 (11.1)	24/122 (19.7)	20/109 (18.3)	12/58 (20.7)
FAILED	0/235 (0)	7/122 (5.7)	4/109 (3.7)	3/58 (5.2)
TOTAL	235/235(100)	122/122(100)	109/109 (100)	58/58 (100)

(NUMBERS IN THE PARENTHESES ARE THE PERCENTAGES)

In the azithromycin group, 209/235 (88.9%) male and 91/122 (74.6%) female patients were cured, 26/235 (11.1%) male and 24/122 (19.7%) female patients were improved and 7/122 (5.7%) female patients failed. In the ceftriaxone group, 85/109 (78%) male and 43/58 (74.1%) female patients were cured, 20/109 (18.3%) male and 12/58 (20.7%) female patients were improved and 4/109 (3.7%) male and 3/58 (5.2%) female patients failed.

CLINICAL EVALUATION AT WEEK 2 - DATA FROM THE SPONSOR:

TABLE-13

CLINICAL RESPONSE	AZITHROMYCIN		CEFTRIAXONE	
	MALE	FEMALE	MALE	FEMALE
CURED	99/105 (94.3)	82/99 (82.8)	36 /41 (87.8)	31/37 (83.8)
IMPROVED	2/105 (1.9)	2/99 (2.0)	0/41 (0)	0/37 (0)
FAILED	4/105 (3.8)	15/99 (15.2)	5/41 (12.2)	6/37 (16.2)
TOTAL	105/105 (100)	99/99 (100)	41/41 (100)	37/37 (100)

(NUMBERS IN THE PARENTHESES ARE THE PERCENTAGES)

In the azithromycin group, 99/105 (94.3%) male and 82/99 (82.8%) female patients were cured, 2/105 (1.9%) male and 2/99(2%) female patients were improved and 4/105 (3.8%) male and 15/99 (15.2%) female patients were failures. In the ceftriaxone group, 36/41 (87.8%) male and 31/37 (83.8%) female patients were cured and 5/41 (12.2%) male and 6/37 (16.2%) female patients were failures. –

CLINICAL EVALUATION AT WEEK 1 - DATA FROM THE M.O.:
TABLE-14

CLINICAL RESPONSE	AZITHROMYCIN		CEFTRIAXONE	
	MALE	FEMALE	MALE	FEMALE
CURED	208/233(89.3)	89/120(74.2)	85/109 (78.0)	43/59(72.9)
IMPROVED	25/233(10.7)	23/120(19.2)	19/109 (17.4)	13/59(22)
FAILED	0/233 (0)	8/120 (6.7)	5/109 (4.6)	3/59 (5.1)
TOTAL	233/233(100)	120/120(100)	109/109 (100)	59/59 (100)

(NUMBERS IN THE PARENTHESES ARE THE PERCENTAGES)

CLINICAL EVALUATION AT WEEK 2 - DATA FROM THE M.O.:
TABLE-15

CLINICAL RESPONSE	AZITHROMYCIN		CEFTRIAXONE	
	MALE	FEMALE	MALE	FEMALE
CURED	97/104(93.3)	82/98(83.7)	36/40(90)	31/35(88.6)
IMPROVED	1/104(1)	3/98(3.1)	1/40 (2.5)	1/35 (2.8)
FAILED	6/104 (5.8)	13/98(13.3)	3/40 (7.5)	3/35(8.6)
TOTAL	104/104(100)	98/98(100)	40/40(100)	35/35(100)

(NUMBERS IN THE PARENTHESES ARE THE PERCENTAGES)

SAFETY EVALUATION: CLINICAL ADVERSE EVENTS:

All patients who received study medication and returned for a follow-up were included in the safety evaluation. A detailed description of each adverse event was provided on the case report form, including the time of onset, duration of the reaction and whether or not any corrective measures were instituted. The reactions were graded on a qualitative scale as mild, moderate, severe, or not specified. For all events, the relationship to the treatment was determined by the investigator using the following terms: probable. possible, remote, or none.

POPULATION:

There were 726 patients included in the evaluation for safety (483 in the azithromycin group and 243 in the ceftriaxone group). 159/483 (32.9%) patients in the azithromycin group and 19/243 (7.8%) in the ceftriaxone group experienced an adverse event. On the whole the rate of occurrence of adverse events was higher in the azithromycin group as compared to the ceftriaxone group.

DEATHS:

There was one reported death in the ceftriaxone group secondary to stab wound to the groin area.

SEVERE:

14/235 (5.9%) events were severe in intensity in the azithromycin group and none in the ceftriaxone group. These were nausea (7), vomiting (3), abdominal pain (2), and diarrhea (2).

ANALYSIS OF ADVERSE EVENTS BY TYPE AND BODY SYSTEM:

The most commonly occurring events in the azithromycin group were gastrointestinally related (90.2%) followed by central nervous (3.4%) and reproductive (vaginitis-1.7%). The most commonly occurring adverse events in the ceftriaxone group were related to the injection site (33.3%), then myalgia (23.8%) and gastrointestinal (23.8%).

INCIDENCE OF SIDE EFFECTS BY BODY SYSTEM RELATED TO THE STUDY DRUG: (SPONSOR'S DATA)
TABLE-16

NUMBER OF PATIENTS	AZITHROMYCIN	CEFTRIAXONE
EVALUABLE	483	243
WITH SIDE EFFECTS	160 (33.1)	20 (8.2)
WITHDRAWN WITH SIDE EFFECTS	0	0
ORGAN SYSTEM SIDE EFFECTS		
Skin/Appendages	3 (1.3)	1 (4.8)
Musculoskeletal	0 (0)	5 (23.8)
Nervous system	8 (3.4)	0 (0)
Autonomic Nervous	1 (0.4)	1 (4.8)
Psychiatric	0 (0)	1 (4.8)
Gastrointestinal	212 (90.2)	5 (23.8)
Metabolic/Nutritional	1 (0.4)	0 (0)
Appl./Inj. Site	0 (0)	7 (33.3)
Special Senses	1 (0.4)	0 (0)
Cardiovascular	1 (0.4)	0 (0)
Hematopoietic	1 (0.4)	0 (0)
Reproductive	4 (1.7)	0 (0)
General	3 (1.3)	1 (4.8)
TOTAL	235 (48.6)	21 (8.6)

(Numbers in the parentheses are the percentages

INTENSITY OF ADVERSE EVENTS RELATED TO THE STUDY DRUG: (SPONSOR'S DATA)
TABLE-17

INTENSITY	AZITHROMYCIN	CEFTRIAXONE
# OF PATIENTS EXPOSED	483	243
MILD	167 (71.1)	16 (76.2)
MODERATE	53 (22.5)	5 (23.8)
SEVERE	14 (5.9)	0
NOT SUSPECTED	1 (0.4)	0
TOTAL # OF ADVERSE EVENTS	235 (48.6)	21 (8.6)

SEVERITY OF TREATMENT-RELATED SIDE EFFECTS: (SPONSOR'S DATA)
TABLE-18

SEVERITY OF SIDE EFFECTS				
ORGAN SYSTEM SIDE EFFECT	AZITHROMYCIN # =483		CEFTRIAXONE N = 243	
	# OF PATIENTS	1 2 3 NS	# OF PATIENTS	1 2 3 NS
ORGAN SYSTEM SIDE EFFECTS				
Skin/Appendages	1	1 0 0 0	0	0 0 0 0
Pruritus	2	1 1 0 0	0	0 0 0 0
Rash				
Musculoskeletal				
Myalgia	0	0 0 0 0	5	5 0 0 0
Nervous system				
Dizziness	6	6 0 0 0	0	0 0 0 0
Headache	1	1 0 0 0	0	0 0 0 0
Autonomic Nervous				
Sweating Increased	1	1 0 0 0	1	1 0 0 0
Psychiatric				
Somnolence	0	0 0 0 0	1	1 0 0 0
Gastrointestinal				
Loose stools	1	1 0 0 0	0	0 0 0 0
Vomiting	30	15 12 3 0	0	0 0 0 0
Abdominal Pain	30	18 10 2 0	0	0 0 0 0
Dyspepsia	6	6 0 0 0	0	0 0 0 0
Nausea	86	63 15 7 1	1	0 1 0 0
Diarrhea	59	45 12 2 0	4	4 0 0 0
Appl./Inj. Site				
Appl./Inj. Site Pain	0	0 0 0 0	7	4 3 0 0
Special Senses				
Vision Abnormal	1	1 0 0 0	0	0 0 0 0
Hematopoietic				
Purpura	1	1 0 0 0	0	0 0 0 0
Reproductive				
Vaginitis	4	2 2 0 0	0	0 0 0 0
General				
Back Pain	1	1 0 0 0	0	0 0 0 0
Fever	1	1 0 0 0	0	0 0 0 0
Malaise	1	1 0 0 0	0	0 0 0 0
Infection Fungal	0	0 0 0 0	1	0 1 0 0

(Numbers in the parentheses are the percentages)

LAB TEST ABNORMALITIES - MAY BE RELATED TO THE TREATMENT:
TABLE-19

LAB. TEST	AZITHROMYCIN N=425	CEFTRIAXONE N=210
HEMOGLOBIN	1 (.2)	0
RED BLOOD CELL	1 (.2)	0
WBC	10 (2.4)	2 (.95)
NEUTROPHILS	24 (5.6)	6 (2.85)
LYMPHOCYTES	1 (.2)	1 (.5)
BASOPHIL	0	1 (.5)
TOTAL BILIRUBIN	7 (1.6)	1 (.5)
SGOT	7 (1.6)	5 (2.4)
SGPT	5 (1.2)	3 (1.4)
GGT	2 (.5)	1 (.5)
LDH	1 (.2)	0
POTASSIUM	1 (.2)	1 (.5)
GLUC F	1 (.2)	0
GLUCOSE RANDOM	1 (.2)	0
I. PHOS	0	1 (.5)
TOTAL	64/425 30.5	22/210 (10.5)

(Numbers in the parentheses are the percentages)

The majority of the azithromycin patients (96.2%) with treatment-related side effects had at least one gastrointestinal side effect as compared to about a quarter (26.3%) of the ceftriaxone patients. Most common side effects were vomiting, abdominal pain, nausea and diarrhea. The majority of the gastrointestinal side effects resolved on the day of dosing. Six azithromycin patients experienced mild dizziness. Five azithromycin patients discontinued from the study due to treatment related side effects which included vomiting alone or with nausea. In the ceftriaxone group, mild to moderate injection site pain occurred in 7 of 19 patients with treatment related side effects and mild myalgia reflecting injection site tenderness or soreness occurred in 5 patients. Fourteen gastrointestinal side effects in the azithromycin group were severe.

Fifty-three (12.5%) of 425 azithromycin-treated patients and 18 (8.6%) of 210 ceftriaxone-treated patients developed one or more clinically significant, possibly treatment-related laboratory test abnormalities. Of these, one or more liver function test abnormalities occurred in a total of 18 (4.2%) of 425 azithromycin patients and a total of 8 (3.8%) of 210 ceftriaxone patients. A total of 24 (5.6%) azithromycin patients exhibited decreased neutrophils and/or decreased WBC as compared to 4 (1.9%) ceftriaxone patients with decreased neutrophils.

Serious adverse events considered by the investigator to be unrelated to the treatment were reported for 2 patients in each group. Of these, one ceftriaxone patient with stab wounds died.

SUMMARY:

In study protocol 066-130, a single oral 2-g dose of azithromycin was compared to a 250-mg intramuscular injection of ceftriaxone for the treatment of gonococcal urethritis/cervicitis, an open label comparative study conducted in the United States. Analyses were performed based on assessments of bacteriological and clinical response at visit week-1 (4-10 days after dosing) and week-2 (11-19 days after dosing) for patients meeting evaluability criteria. The analysis of bacteriological response was done by site of infection (cervix, urethra, rectum, and pharynx). *N. gonorrhoeae* present at the baseline was either classified as eradicated or persistent.

Bacteriological response: (Data from Sponsor)

At visit week-1, the eradication rate from the cervix was 127/131 (96.9%) in the azithromycin group as compared to 57/59 (96.6%) in the ceftriaxone group. At week-2, the eradication rate from the cervix was

101/103 (98.1%) in the azithromycin group as compared to 36/37 (97.3%) in the ceftriaxone group.

The eradication rate from the urethra was 229/230 (99.6%) in males and 23/23 (100%) in females in the azithromycin group as compared to 110/111 (98.1%) in males and 14/15 (99.3%) in females in the ceftriaxone group. However, at week-2, the eradication rate from the urethra was 102/102 in males and 15/15 (100%) in females in the azithromycin group as compared to 38/41(92.7%) in males and 7/7 (87.5%) in females in the ceftriaxone group.

Clinical response:

At week-1, 209/235 (88.9%) male and 91/122 (74.6%) female patients were cured, 26/235 (11.1%) male and 24/122 (19.7%) females were improved and 7/122 (5.7%) female patients were failures in the azithromycin group. 85/109 (78%) male and 43/58 (74.1%) female patients were cured, 20/109 (18.3%) male and 12/58 (20.7%) females were improved and 4/109 (3.7%) male and 3/58 (5.2%) female patients were failures in the ceftriaxone group.

At week-2, 99/105 (94.3%) male and 82/99 (82.8%) female patients were cured, 2/105 (1.9%) male and 2/99(2%) female patients were improved and 4/105 (3.8%) male and 15/99 (15.2%) female patients were failures in the azithromycin group. 36/41 (87.8%)male and 31/37 (83.8%) female patients were cured and 5/41 (12.2%) male and 6/37 (16.2%) female patients were failures in the ceftriaxone group.

Comment: Medical officer's data was comparable to the sponsor's data for the bacteriological and clinical responses from all sites for week-1 and week-2 post-treatment follow-up.

The majority of the azithromycin patients (96.2%) had at least one gastrointestinal side effect as compared to a quarter (26.3%) of the ceftriaxone patients. Most common side effects were vomiting, abdominal pain, nausea and diarrhea. The majority of the side effects resolved on the day of dosing. Six azithromycin patients experienced mild dizziness. Five azithromycin patients discontinued therapy due to treatment related side effects. In the ceftriaxone group, mild to moderate injection site pain occurred in 7 of 19 patients with treatment related side effects, and mild myalgia, reflecting injection site tenderness or soreness, occurred in 5 patients. Fourteen azithromycin side effects in the azithromycin group were severe.

Fifty-three (12.5%) of 425 azithromycin-treated patients and 18 (8.6%) of 210 ceftriaxone-treated patients developed one or more clinically significant, possibly treatment-related laboratory test abnormalities. Of these, one or more liver function test abnormalities occurred in a total of 18 (4.2%) of 425 azithromycin patients and a total of 8 (3.8%) of 210 ceftriaxone patients. A total of 24 (5.6%) azithromycin patients exhibited decreased neutrophils and/or decreased WBC as compared to 4 (1.9%) ceftriaxone patients with decreased neutrophils.

Serious adverse events unrelated to the treatment were reported for 2 patients in each group. Of these, one ceftriaxone patient with stab wounds died.

CONCLUSIONS: From these data, the following summary statements can be made:

A single 2-g oral dose of Azithromycin appears to be as effective as a 250 mg intramuscular dose of ceftriaxone in the treatment of uncomplicated gonococcal urethritis in male and urethritis/cervicitis in female adult patients.

There are not enough data for proctitis and pharyngitis secondary to the *N. gonorrhoeae* to grant an approval.

The incidence of gastrointestinally related side effects were more frequent in the azithromycin treated patients, while infection site pain and myalgia were the most common side effects associated with the

intramuscular injection of ceftriaxone.

PROTOCOL 066-114:

PROTOCOL TITLE: A multicenter Open Comparative Trial of Azithromycin (CP-62,993) and Ceftriaxone in Patients with Uncomplicated Gonococcal Urethritis in males.

STUDY OBJECTIVE: To compare the efficacy and safety of single doses of azithromycin (2 g oral) and ceftriaxone (250 mg i.m.) in the treatment of acute gonococcal urethritis in male population and to compare efficacy and safety of single doses of azithromycin (1 g oral) and doxycycline (100 mg bid for seven days) for the treatment of *C. trachomatis* urethritis in male population.

STUDY SUMMARY: This open randomized study of the treatment of gonococcal urethritis was to have occurred in two phases. In phase one of the study, 100 male patients with presumptive diagnosis of gonococcal urethritis were to be randomly assigned to treatment with azithromycin or ceftriaxone. A second phase was to compare azithromycin and doxycycline in the treatment of those patients initially treated with ceftriaxone and found to be coinfected with *N. gonorrhoeae* and *C. trachomatis*. Originally planned to include 100 patients, this study was terminated after the enrollment of 58 patients due to the initiation of a larger multicenter study (Protocol 066-130: A Multicenter Open Comparative Trial of Azithromycin (CP-62,993) and Ceftriaxone in Patients with Uncomplicated Gonococcal Urethritis/Cervicitis).

This study was carried out at one center only and had IRB approval. The study population consisted of male patients, 18 years or older who had presumptive diagnosis of gonococcal urethritis, defined as the presence of a urethral discharge which on Gram stain showed intracellular Gram-negative diplococci. In addition, a specimen was to be obtained for the fluorescein conjugated antibody test or enzyme immunoassay for *C. trachomatis*.

Patients were initially assigned in a 1:1 ratio in blocks of 12 to treatment with a single 1-g oral dose of azithromycin or a single 250-mg i.m. dose of ceftriaxone. The dose of azithromycin was increased to 2-g, since failure rate was higher with the 1-g dose. Also the ratio of assignment of patients to treatment with azithromycin or ceftriaxone was changed from 1:1 to 2:1 in blocks of 12. Chlamydia-positive, ceftriaxone-treated patients were subsequently to be similarly rerandomized in a 1:1 ratio to treatment with azithromycin or doxycycline.

Prior to admission to the study, each patient was to provide written informed consent, undergo a physical examination, and blood and urine specimens were to be obtained for baseline laboratory evaluation. Laboratory safety tests were to be repeated 2 weeks after treatment. At entry into the study, swab specimens from the urethra, pharynx, and rectum were to be obtained for *N. gonorrhoeae* (all sites), and *C. trachomatis* (urethra only). Patients with cultured confirmed gonococcal infection of any site were to return 1, 2, and 4 weeks after treatment for follow-up cultures of the urethra and any other site that was culture-positive for *N.gonorrhoeae* at study entry. Patients were to be instructed not to donate blood and to abstain from sexual relations while in the study.

ENROLLMENT CRITERIA:

Inclusion criteria:

1. Male outpatients, 18 years of age or older.

2. Patients with presumptive gonococcal urethritis, defined as the presence of a urethral discharge which on Gram stain showed intracellular Gram negative diplococci.

Exclusion criteria:

1. Women.

2. Patients with significant hematological, renal, hepatic, or cardiac disease.

3. Patients with a history of allergy or hypersensitivity to erythromycin, doxycycline, or ceftriaxone, or any other beta-lactam antibiotic.

4. Patients with clinical evidence of gonococcal pharyngitis, proctitis, disseminated gonococcal infection, or the presence of any other infection at enrollment that may require treatment with an antibiotic other than the study drugs.

5. Patients known to have abused alcohol, drugs, or who for any other reason may not be expected to comply with the requirements of the protocol.

6. Patients who had received any investigational drug in the 30 days prior to entry into the study.

7. Patients who had received any systemic antibiotic in the 72 hours before entry into the study.

EFFICACY:

Bacteriological response was to be evaluated separately for *N. gonorrhoeae* and *C. trachomatis.* Bacteriological response for *N. gonorrhoeae* was to be classified as "eradication" if this pathogen was absent in the post-treatment culture and "persistence" if *N. gonorrhoeae* was isolated from the post-treatment culture. If *N. gonorrhoeae* was absent from the 1-week culture but isolated from the 2- or 4-week culture, the response was to be classified as "eradication with recurrence". Recurrence was to be considered to represent relapse of the original infection unless the patient had sexual contact in the interim or there was laboratory evidence that the strain isolated after treatment was different from that isolated at baseline, in which cases it was to be reinfection.

Bacteriological response for *C. trchomatis* was to be classified as "eradication" if *C. trachomatis* was not present in either the 2-week or 4-week post-treatment culture and as "persistence" if the pathogen was present. A patient withdrawn from the study because of inadequate response was to have an appropriate culture performed to document that treatment failure was due to persistence of the original causative organism.

For clinical evaluation of efficacy, symptoms of urethritis (discharge, burning, and painful urination) together with any additional volunteered symptoms and signs were to be recorded at baseline. Symptoms present at baseline were to be clinically reevaluated at the 1-, 2-, and 4-week follow-up visits. The complete resolution of signs and symptoms of infection was to be recorded as "cured", incomplete resolution of signs and symptoms was to be recorded as "improved", and persistence or progression of signs and symptoms was to be recorded as "failed". At every visit, patients were to be questioned concerning sexual exposure in the interim.

PHARMACOKINETICS:

Blood, sufficient to provide a 5 mL serum sample, was to be drawn from those patients assigned to azithromycin treatment at 2 hours following drug administration, as well as at the 1-, 2-, and 4-week visits. After clotting, serum was to be separated from whole blood, frozen at -20 degree C, and forwarded on dry ice to the sponsor for assay. Urine specimens of at least 20 mL were to be obtained at the 1-, 2-, and 4-week visits, similarly frozen and forwarded to the sponsor. Prostatic fluid, obtained by prostatic massage 24, 48, 72, 120, or 168 hours after azithromycin administration, was also to be forwarded to the sponsor to

be assayed for azithromycin content.

SAFETY:

All side effects, either reported by the patient or observed by the investigator, were to be recorded at each clinic visit with information on their severity (mild, moderate, severe), time of onset, duration, any treatment required, and the investigator's assessment of their possible relationship to the study drug. Any serious adverse experience after drug administration was to be immediately reported to the sponsor.

LABORATORY TESTS:

The following laboratory safety tests were to be performed for all patients within the 24 hours before entry into the study and again two weeks after treatment. Patients who were to be rerandomized in the second phase of the study were to have laboratory safety tests repeated at that time and at two weeks after completion of their treatment.

Hematology:

Hgb, WBC (total and differential)

Serum Chemistry:

SGOT, SGPT, GGT, alkaline phosphatase, bilirubin, BUN, creatinine.

Urinalysis

Serum tests for syphilis (FTA or RPR) and HBsAg were to be performed at study entry only.

To monitor the possible occurance of phospholipidosis, a further 5 mL blood was to be drawn from azithromycin-treated patients at the same time of their prostatic massage and from ceftriaxone-treated patients (as control) at their first follow-up visit. These samples were to be shipped to the sponsor for electron microscopic examination of blood lymphocytes for the presence of lamellated cytoplasmic inclusion bodies.

CONCOMITANT MEDICATIONS:

During the study the patient was not to be treated with another antibiotic. Additional antibiotic therapy before the appropriate follow-up culture(s) had been performed would render the patient nonevaluable for efficacy for subsequent visits.

Patients found to have a positive serologic test for syphilis at entry were to be evaluated and receive appropriate treatment. If additional antiinfective medication was required during the study, the patient was to be discontinued from the study and the appropriate therapy instituted.

The use of other (nonantiinfective) medications was to be limited to those essential for the care of the patient. All concomitant medications were to be recorded. The use of any other investigational drug was prohibited.

INTERCURRENT ILLNESSES:

Any intercurrent illness was to be appropriately recorded in the case report form.

PRECAUTIONS:

Patients were to be instructed not to donate blood and to abstain from sexual activity during the study.

INVESTIGATOR: H. H. Handsfield, M.D.
Seattle, WA.

DRUG STORAGE AND ACCOUNTABILITY:

1. Azithromycin capsules were to be stored under refrigeration.

2. The investigator was responsible for recording the receipt and usage of all drugs supplied, and/or ensuring the supervision of the storage and allocation of these supplies. At completion or termination of the study, all unused drug supplies were to be returned to Pfizer Central Research.

RESULTS:

SPONSOR'S DATA:

Table-1

		AZI. 2gm	CEF.
Randomized to treat.			
Phase 1		0	9
Phase 2		27	13
Received treat.	27	22	
Discontinued treat.		0	0
Completed treat.		27	22
Returned for 30-day visit		8	8
Efficacy evaluation			
Bacteriological			
week-1		21	16
week-2		12	10
Clinically evaluable			
week-1		21	16
week-2		12	10
Safety analysis			
Side effects		27	22
Lab. Tests		21	15

COMMENT: Although patients were enrolled in a 1-g azithromycin arm, the M.O. will not review the data for this arm because of lack of efficacy of this dose (rate of eradication of *N. gonorrhoeae* was not adequate).

DEMOGRAPHICS AND COMPARABILITY OF EVALUABLE PATIENT POPULATION BY THE SPONSOR:
TABLE-2

SEX			AZI	CEF
MALE	AGE	MEAN	31.0	29.0
	HEIGHT	MEAN	179.0	179.6
	WEIGHT	MEAN	76.7	76.5
	RACE	TOTAL #	27	22
	Black		22 (81.5)	19 (86.4)
	Hispanic		2 (7.4)	1 (4.5)
	White		3 (11)	2 (9.1)
CONCOMITANT THERAPY	NO		15 (55.5)	13 (59)
	YES		12 (44.4)	9 (41)
CONCOMITANT DISEASES	NO		19 (70.4)	17 (77.3)
	YES		8 (29.6)	5 (22.7)
	UNKNOWN		0	0

(Numbers in the parentheses are the percentages)

DURATION OF PRESENT EPISODE OF GONOCOCCAL URETHRITIS (Data from the sponsor)
TABLE-3

DISTRIBUTION	AZITHROMYCIN		CEFTRIAXONE	
	NUMBER	%	NUMBER	%
< = 2 DAYS	13	48	8	36.4
3-5 DAYS	10	3.7	8	36.4
> 5 DAYS	4	14.8	4	18.2
MISSING	0		2	9.1

RESULTS/BACTERIOLOGY: The Post-Therapy Evaluation. (week-1 or 5-11 days) SPONSOR'S DATA:
TABLE-4

	AZITHROMYCIN	CEFTRIAXONE
TOTAL PATIENTS	27	22
ERAD.	21/21 (100)	16/16 (100)
PERSIST	0	0
NOT ASSESSED/CONCOMITANT ANTIBIOTIC	6 (22)	6 (27.3)

(NUMBERS IN THE PARENTHESES ARE THE PERCENTAGES)

RESULTS/BACTERIOLOGY: The Post-treatment Evaluation (week-2 or 12-20 days) SPONSOR'S DATA:
TABLE-5

TOTAL PATIENTS	AZITHROMYCIN	CEFTRIAXONE
	21	16
ERAD.	12/12 (100)	10/10 (100)
PERSIST	0	0
NOT ASSESSED/CONCOMITANT ANTIBIOTIC	7/2	5/1

(NUMBERS IN THE PARENTHESES ARE THE PERCENTAGES)

The rate of eradication of *N. gonorrhoeae* from the urethra was 100% for patients in both treatment groups at both week-1 and week-2 follow-up.

RESULTS/CLINICAL: The Post-Therapy Evaluation (week-1) SPONSOR'S DATA:
TABLE-6

	AZITHROMYCIN	CEFTRIAXONE
CURED	17/21 (81)	15/16 (93.8)
IMPROVED	4/21 (19)	1/16 (6.2)
FAILURE	0	0
NOT ASSESSED/CONCOMITANT ANTIBIOTICS	6	6

(NUMBERS IN THE PARENTHESES ARE THE PERCENTAGES)

Clinical cure rates at week-1 for the azithromycin group were 17/21 (81%) as compared to 15/16 (94%) for the ceftriaxone group. The improvement rates were 4/21 (19%) in the azithromycin group as compared to 1/16 (6.2%) in the ceftriaxone group. There were no failures in either group.

RESULTS/CLINICAL: The Post-Therapy Evaluation (week-2) SPONSOR'S DATA:
TABLE-7

	AZITHROMYCIN	CEFTRIAXONE
CURED	10/12 (83.3)	7/10 (70)
IMPROVED	0	1/10 (10)
FAILURE	2/12 (16.7)	2/10(20)
TOTAL	12/12(100)	10/10(100)

(NUMBERS IN THE PARENTHESES ARE THE PERCENTAGES)

Clinical cure rates at week-2 for the azithromycin group were 10/12 (83.3%) as compared to 7/10 (70%) for the ceftriaxone group. The improvement rate was 1/10 (10%) in the ceftriaxone group. The failure rate was 2/12 (16.7%) in the azithromycin group as compared to 2/10 (20%) in the ceftriaxone group.

Two patients in the azithromycin group and one in the ceftriaxone group were infected with both *C. trachomatous* and *N. gonorrhoeaea* at baseline. At week-1 evaluation, *C. trachomatis* was eradicated in the two patients in the azithromycin group but persisted in the patient in the ceftriaxone group. This patient was treated with doxycycline as per protocol.

SAFETY:

Twelve of 27 patients treated with 2 g azithromycin had treatment-related side effects which involved the gastrointestinal tract (11), nervous system (1) and psychiatric system (1). Adverse events related to the gastrointestinal tract included vomiting (1), abdominal pain (4), nausea (4), and diarrhea (4). All treatment related adverse events were mild in severity except three patients in the azithromycin group who experienced moderate gastrointestinal side effects.

Two patients treated with ceftriaxone experienced a mild injection site reaction.

Clinically significant, possibly treatment-related laboratory abnormalities developed in three patients treated with 2 g azithromycin. One had low WBC and neutrophil counts, one had elevated levels of SGPT, SGOT, and GGT, and one had both decreased WBC and elevated SGPT and SGOT.

One patient treated with ceftriaxone had elevated SGPT.

SUMMARY:

This open randomized study was conducted to compare the efficacy and the safety of azithromycin and ceftriaxone in the treatment of gonococcal urethritis and to compare the efficacy and safety of azithromycin and doxycycline in the treatment of chlamydial urethritis in the male patients. Originally planned to include 100 patients, this study was terminated after the enrollment of 58 patients due to the inititiation of a larger multicenter study (Protocol 066-130). The medical officer opted to review patients treated with 2-g dose of azithromycin and 250-mg dose of ceftriaxone as a comparator in this study.

The rate of eradication of *N. gonorrhoeae* from the urethra was 100% of patients treated with azithromycin and ceftriaxone at both week-1 and week-2.

Clinical cure rates at week-1 for the azithromycin group were 17/21 (81%) as compared to 15/16 (93.8%) for the ceftriaxone group. The improvement rates were 4/21 (19%) in the azithromycin group as compared to 1/16 (6.2%) in the ceftriaxone group. There were no failures in either group.

Clinical cure rates at week-2 for the azithromycin group were 10/12 (83.3%) as compared to 7/10 (70%) for the ceftriaxone group. The improvement rate was 1/10 (10%) in the ceftriaxone group. The failure rate was 2/12 (16.7%) in the azithromycin group as compared to 2/10 (20%) in the ceftriaxone group.

Twelve of 27 patients treated with 2 g azithromycin had treatment-related side effects which involved the gastrointestinal tract (11), nervous system (1) and psychiatric system (1). Adverse events related to the gastrointestinal tract included vomiting (1), abdominal pain (4), nausea (4), and diarrhea (4). All treatment related adverse events were mild in severity except three patients in the azithromycin group who experienced moderate gastrointestinal side effects.

Two patients treated with ceftriaxone experienced a mild injection site reaction.

Clinically significant, possibly treatment-related laboratory abnormalities developed in three patients treated with 2 g azithromycin. One had low WBC and neutrophil counts, one had elevated levels of SGPT, SGOT, and GGT, and one had both decreased WBC and elevated SGPT and SGOT.

One patient treated with ceftriaxone had elevated SGPT.

PROTOCOL-066-124

PURPOSE OF STUDY:

The primary objective of this study was to assess the efficacy and safety of single oral doses of 2-grams and 4-grams of azithromycin in the treatment of gonococcal urethritis and/or cervicitis. In addition, the pharmacokinetics profiles of these doses were to be determined.

STUDY DESIGN AND PROCEDURES:

This was an open label noncomparative study of the efficacy and safety of single 2-gram and 4-gram doses of azithromycin in the treatment of gonococcal urethritis and/or cervicitis. Azithromycin was administered as 250 mg capsules. The study was to be conducted in two phases, beginning with the 2-gram dose and progressing to the 4-gram dose after assessment of the 2-gram dosing results. In the first phase, 20 patients (10 at each of two centers) with a presumptive diagnosis of gonococcal urethritis/cervicitis were to be treated with a single 2-gram oral dose of azithromycin. Following favorable assessment of safety in these patients, 20 similar patients were to be treated with a single 4-gram oral dose of azithromycin. All patients with culture-confirmed gonococcal infection were to return 1,2, and 4 weeks after azithromycin treatment for clinical and bacteriological evaluation. The pharmacokinetics profile of these azithromycin doses were to be assessed at 2 hours and 1, 2, and 4 weeks after treatment. The study had IRB approval.

PATIENT SELECTION CRITERIA

Inclusion Criteria:

- At least 16 years of age.

- Outpatients.

- Males with presumptive gonococcal urethritis, defined as the presence of a urethral discharge which on Gram stain showed intracellular Gram-negative diplococci.

- Women with presumptive gonococcal urethritis and/or cervicitis, defined as a urethral or cervical discharge which on Gram stain showed intercellular Gram-negative diplococci. Women of childbearing potential must have had a negative serum gonadotropin pregnancy test prior to entry into the study and must have been using adequate contraception both during and for 3 months after the end of the study.

Exclusion Criteria:

- Pregnant or lactating women.

- Evidence or history of significant hematologic, renal, hepatic or cardiac diseases.

- History of allergy or hypersensitivity to erythromycin, ceftriaxone, or any other betalactam antibiotics.

- Clinical evidence of gonococcal pharyngitis, proctitis, disseminated gonococcal infection, or the presence of any other infection at enrollment that might require treatment with an antibiotic other than the study drugs.

- Subjects who, for any reason judged by the investigator, might not be expected to comply with the requirements of the protocol.

- Treatment with another investigational drug within the 30 days prior to entry into the study.

- Treatment with any systemic antibiotic within the 72 hours prior to entry into the study.

- Patients with ulcers, gastrectomy, or other conditions affecting drug absorption.

- Donation of blood or blood components while receiving experimental drug.

CLINICAL OBSERVATIONS AND LABORATORY MEASUREMENT:

Efficacy:

Bacteriological response was to be based on the presence or absence of *N. gonorrhoeae*. Gram stain of urethral and/or cervical exudate was to be examined at entry. Swab specimens from urethra, pharynx, rectum (and cervix for females) were to be cultured for *N. gonorrhoeae* at entry as well as at the scheduled follow-up visits. Disk susceptibility or MIC were to be determined for all isolates.

Bacteriological response were to be classified as "eradication" if *N. gonorrhoeae* was absent from the posttreatment culture and "persistence" if *N. gonorrhoeae* was isolated from the posttreatment culture. If *N. gonorrhoeae* was isolated from the 2- or 4-week culture after being absent form 1-week culture, the response was to be "eradication with recurrence". Recurrence was to be considered to represent relapse of original infection unless the patient had sexual contact in the interim of there was laboratory evidence that the strain isolated after treatment was different from that isolated at baseline, in which cases recurrence was to be considered to be infection.

A patient withdrawn because of inadequate response was to have appropriate culture performed to document that treatment failure was due to persistence of the original causative pathogen.

For clinical evaluation of efficacy, symptoms of urethritis (discharge, burning, and painful urination) together with any volunteered symptoms and signs were to be recorded at baseline. Symptoms present at entry were to be assessed at each follow-up visit as absent, improved (diminished), no change, or worse. At each evaluation the patient's clinical response was to be classified by the investigators as "cured" if there was complete resolution of signs and symptoms, "improved" if there was incomplete resolution of signs and symptoms, and failed if there was no apparent response or progression of signs and symptoms. Patients were to be questioned concerning sexual exposure between follow-up visits.

PHARMACOKINETICS:

Blood, sufficient to provide a 5 mL serum sample, was to be drawn from those patients assigned to azithromycin treatment at 2 hours following drug administration, as well as at the 1-, 2-, and 4-week visits. Serum was to be separated from whole blood and frozen at -20 degree C. Urine specimens were to be obtained at the 1-, 2-, and 4-week visits, similarly frozen. All samples were to be shipped on dry ice to the sponsor to be assayed for azithromycin concentration by HPLC-EC. The limits of quantification for the assay were 0.01 to 1.00 mcg/ml in serum and 0.2 to 1.00 mcg/ml in urine. Serum samples with apparent concentrations above 1.00 mcg/ml were diluted with human serum and reassayed.

SAFETY:

Side Effects

All side effects, either reported by the patient or observed by the investigator, were to be recorded at each clinic visit with information on their severity (mild, moderate, severe), time of onset, duration, any treatment required, and the investigator's assessment of their possible relationship to the study drug. Any serious

adverse experience after drug administration was to be immediately reported to the sponsor.

Laboratory Tests

The following laboratory safety tests were to be performed for all patients within the 24 hours before entry into the study and at each follow-up visit:

Hematology

CBC (including differential and platelet counts), ESR, prothrombin time, and activated partial prothrombin time

Serum Chemistry

GGT, SGOT, SGPT, alkaline phosphatase, total protein and albumin, serum bilirubin, LDH, BUN, serum creatinine, serum calcium, serum phosphorus, electrolytes, blood glucose (fasting when feasible), uric acid, serum cholesterol, and serum glycerides.

Urinalysis

Serum tests for syphilis (FTA or RPR) and HbsAg were to be performed at study entry only.

DRUG ADMINISTRATION:

Azithromycin was administered in the clinic under direct observation at the patient's baseline visit. Patients received 2 g azithromycin (8 x 250 mg capsules) as a single oral dose. Azithromycin was taken with 240 ml water at least one hour before or two hours following a meal.

RESULTS:

NUMBER OF PATIENTS ENROLLED BY CENTER AND INVESTIGATOR:
TABLE-1

CENTER	TREATMENT GROUP		
	AZITHROMYCIN		
	PRINCIPAL INVESTIGATORS	ASSIGNED	RECEIVED TREATMENT
736	JANET ARNO, M.D.	17 (63)	17 (63)
742	JOHN DOUGLAS, M.D.	10 (37)	10 (37)
TOTAL		27 (100)	27 (100)

(NUMBERS IN THE PARENTHESES ARE THE PERCENTAGES)

PATIENT EVALUATION GROUPS:
TABLE-2

	Azithromycin 2 g
Received treatment	27
Completed treatment	27
Discontinued treatment	0
Bacteriologically evaluable	
Week-1	21
Week-2	15
Clinically evaluable	
Week-1	21
Week-2	15
Evaluated for pharmacokinetics	27
Evaluated for safety	
Side effects	27
Laboratory tests	26

***COMMENT: No patient received 4-g azithromycin.**

EVALUABLE PATIENT ANALYSIS:
TABLE-3

Eradication, *N. gonorrhoeae*	**Azithromycin 2 gm**
Week-1	21/21
Week-2	15/15
Clinically Cured/Improoved	
Week-1	20/21
Week-2	15/15

PHARMACOKINETICS

Mean Serum Concentration (mcg/ml)	
2 hours (N=27)	1.404
Week-1 (N=26)	0.036
Week-2 (N=22)	0.005

SAFETY

Patients with treatment-related side effects:	20/27
Gastrointestinal side effects:	20/27
Clinically significant laboratory test abnormalities:	4/26

DEMOGRAPHIC DATA OF ALL PATIENTS: SPONSOR'S DATA
TABLE-3

PATIENT AGE,WEIGHT, SEX AND RACE			
	AZITHROMYCIN		
	MALE	FEMALE	TOTAL
NUMBER OF PATIENTS	24(88.9)	3(11.1)	27
AGE CATEGORY			
<15	0	0	0
15-44	24	3	27
>-45	0	0	0
MEAN AGE	25.4	21.3	24.9
MEAN WEIGHT (Kg)	74.1	56.7	
WHITE	1	0	1 (3.7)
BLACK	22	3	25(92.6)
HISPANIC	1	0	1 (3.7)

(NUMBERS IN THE PARENTHESES ARE THE PERCENTAGES)

DEMOGRAPHIC DATA OF EVALUABLE PATIENTS: SPONSOR'S DATA
TABLE-4

PATIENT AGE,WEIGHT, SEX AND RACE			
	AZITHROMYCIN		
	MALE	FEMALE	TOTAL
NUMBER OF PATIENTS	20(95.2)	1(4.8)	21/21(100)
AGE CATEGORY			
<15	0	0	0
15-44	20	1	21
>-45	0	0	0
MEAN AGE	25.3	21.0	25.0
MEAN WEIGHT (Kg)	73.9	54.4	
WHITE	1	0	1 (4.8)
BLACK	18	1	19(90.5)
HISPANIC	1	0	1 (4.8)

(NUMBERS IN THE PARENTHESES ARE THE PERCENTAGES)

NUMBER OF EVALUABLE PATIENTS FOR EFFICACY BY THE SPONSOR :

There were 21 evaluable patients in the study, 20 were male and 1 was female. 1 (4.8%) was white, 19 (90.5%) were black, and 1 (4.8%) was hispanic. The mean age was for male patients was 25.3 years and female patients was 21.0 years. The mean weight for male patients was 73.9 Kg and for female patients was 54.4 Kg.

PRIMARY DIAGNOSIS - ALL PATIENTS
TABLE-5

	TREATMENT GROUP	
	AZITHROMYCIN	
	SEX	
	FEMALE	MALE
	#	#
PRIMARY DIAGNOSIS		
URETHRITIS	0	24(88.9)
CERVICITIS	3 (11.1)	0
ALL	3 (11.1)	24(88.9)

(NUMBERS IN THE PARENTHESES ARE THE PERCENTAGES)

N. gonorrhoeae was isolated from urethra or cervix in 27 patients. One patient was also infected in the pharynx.

PRIMARY DIAGNOSIS - EVALUABLE PATIENTS AT WEEK-1
TABLE-6

	TREATMENT GROUP	
	AZITHROMYCIN	
	SEX	
	FEMALE	MALE
	#	#
PRIMARY DIAGNOSIS		
URETHRITIS	0	20 (95.2)
CERVICITIS	1(4.8)	0
ALL	1 (4.8)	20 (85.2)

(NUMBERS IN THE PARENTHESES ARE THE PERCENTAGES)

REASONS FOR NON-EVALUABILITY
TABLE-7

	TREATMENT GROUP	
	AZITHROMYCIN	
	#	
WEEK	REASON	
1	NO ASSESSMENT IN THE WINDOW	2
	NO BASELINE PATHOGEN	1
	HAD CONCOMITANT ANTIBACTERIAL TREATMENT	2
	HAD SEX WITHOUT CONDOM	1
	TOTAL UNEVALUABLE	6
2	REASON	
	NO ASSESSMENT IN THE WINDOW	6
	NO BASELINE PATHOGEN	1
	HAD CONCOMITANT ANTIBACTERIAL TREATMENT	4
	UNEVALUABLE AT WEEK-1	1
	TOTAL UNEVALUABLE	12

During week-1, 2 patients had no assessment, 1 patient did not have a baseline pathogen; 2 patients received concomitant antimicrobial treatment, and 1 patient had sex without condom.

During week-2, 6 patients had no assessment, 1 patient did not have a baseline pathogen; 4 patients received concomitant antimicrobial treatment, and 1 patient was unevaluable.

BACTERIOLOGICAL ERADICATION: WEEK-1 AND WEEK-2
TABLE-8

WEEK		TREATMENT GROUP: AZITHROMYCIN	
	SEX	ERADICATED	TOTAL
1	FEMALE	1	1
	MALE	20	20
	ALL	21	21
2	SEX		
	FEMALE	0	0
	MALE	15	15
	ALL	15	15

(NUMBERS IN THE PARENTHESES ARE THE PERCENTAGES)

20/20 (100%) male patients and 1/1 (100%) of female patients had eradication during first week. 15/15 (100%) male patients had eradication during second week.

RESULTS/CLINICAL: The Post-Therapy Evaluation:
TABLE-9

		TREATMENT GROUP: AZITHROMYCIN			
		CLINICAL RESPONSE			ALL
WEEK	SEX	CURED	IMPROVED	FAILED	
		#	#	#	#
1	FEMALE	0	0	1(100)	1/1(100)
	MALE	18(90)	2(10)	0	20/20(100)
	ALL	18(85.7)	2(9.5)	1(4.8)	21/21(100)
2	SEX				
	FEMALE	0	0	0	0
	MALE	15(100)	0	0	15/15(100)
	ALL	15(100)	0	0	15/15(100)

(NUMBERS IN THE PARENTHESES ARE THE PERCENTAGES)

20 male and 1 female were included in the week-1 evaluation. 18/20 (90%) male patients were cured and 2/20 (10%) were improved. 1/1 (100%) female patients failed.

At the week-2 evaluation, all 15 evaluable patients (100%) were considered cured. Two patients who were clinically improved at week-1 were assessed as cured at their week-2 visit.

INCIDENCE OF TREATMENT-RELATED SIDE EFFECTS: SPONSOR'S DATA
TABLE-10

INCIDENCE OF SIDE EFFECTS	
NUMBER OF PATIENTS:	AZITHROMYCIN
EVALUABLE	27
WITH SIDE EFFECTS	20(74.1)
WITHDRAWN WITH SIDE EFFECTS	0
SIDE EFFECTS BY ORGAN SYSTEM	
Centr. & Periph. Nerv. System	1(4.3)
Psychiatric	1(4.3)
Gastrointestinal	20(86.9)
General	1(4.3)
TOTAL	23

(NUMBERS IN THE PARENTHESES ARE THE PERCENTAGES)

SEVERITY OF TREATMENT-RELATED SIDE EFFECTS
TABLE-11

SEVERITY OF SIDE EFFECTS		
ORGAN SYSTEM Side Effects	AZITHROMYCIN	
	# OF PATIENTS	1 2 3 NS
Centr. & Periph. Nerv. System		
Headache	1	1 0 0 0
Psychiatric		
Somnolence	1	0 1 0 0
Gastrointestinal		
Vomiting	5	4 1 0 0
Abdominal Pain	2	2 0 0 0
Nausea	8	7 1 0 0
Diarrhea	10	8 2 0 0
General		
Back Pain	1	1 0 0 0

(NUMBERS IN THE PARENTHESES ARE THE PERCENTAGES)

LAB TEST ABNORMALITIES - MAY BE RELATED TO THE TREATMENT:
TABLE-12

LAB. TEST	AZITHROMYCIN
	N =26
WBC	1 (3.8)
NEUTROPHILS	2 (7.7)
LYMPHOCYTES	1 (3.8)
SGOT	1 (3.8)
SGPT	1 (3.8)
TOTAL	6/26

(NUMBERS IN THE PARENTHESES ARE THE PERCENTAGES)

Twenty of 27 evaluable patients reported one or more treatment-related side effects. The most common occurring events were gastrointestinally related (86.9%), then central nervous system, psychiatric, and general. The side effects associated with the gastrointestinal tract included vomiting 5/20, abdominal pain 2/20, nausea 8/20, and diarrhea 10/20. Other reported side effects included headache, somnolence, and back pain. Five side effects were considered to be moderately severe and the rest were mild. All side

effects were resolved within one day and all were limited to the day of dosing with the exception of two patients who experienced somnolence and back pain, respectively, on the day following medication.

Clinically significant, possibly treatment-related laboratory abnormalities developed in 4 patients. Three of these patients had reduced hematological values and one patient had elevated liver enzymes (SGOT and SGPT). No serious adverse events were reported in this study. Due to the side effects profile of patients dosed with 2-gram azithromycin, even though side effects were all assessed to be mild or moderate in severity, it was decided not to proceed with 4-gram dosing segment of the protocol.

SUMMARY AND CONCLUSION:

Twenty seven patients, 24 male and 3 female with presumptive gonococcal urethritis/cervicitis were treated with a single 2-gm oral dose of azithromycin. *N. gonorrhoeae* was isolated from the urethera or cervix in 26 patients. One patient was also infected in the pharynx. Analysis was performed based on assessment of bacteriological and clinical response at visit week-1 (5-11 days after dosing) and week-2 (12-20 days after dosing) for patients meeting evaluability criteria. The analysis of bacteriological response was classified as eradicated or persistent.

Bacteriological response (data form Sponsor):

20 male and 1 female patients were included in the week-1 evaluation. 18/20 (90%) male patients were cured and 2/20 (10%) were improved. 1/1 (100%) female patient failed.

At the week-2 evaluation, all 15 evaluable patients (100%) were considered cured. Two patients who were clinically improved at week-1 were assessed as cured at their week-2 visit.

Clinical responses of 21 patients evaluated at week-1 amounted to 18 cured, 2 improved, and 1 failed. The failed clinical response was recorded for the single female patient. This patient was coinfected with *C.trachomatis* at baseline, was treated with doxycycline at week-1, and withdrawn from efficacy analysis. At week-2 all 15 patients were considered cured.

High serum concentrations of azithromycin were detected two hours following a single 2-gm oral dose of the drug. One week after the dose, drug was detected in serum and urine from all patients. After four weeks drug could not be detected in serum from any of 22 patients examined and was detectable in urine from less than half of these patients.

Side effects possibly or probably related to treatment were reported for 20 of 27 evaluable patients. The most common occurring events were gastrointestinally related, then central nervous system, psychiatric, and general. Side effects were most frequently associated with the gastrointestinal tract, including vomiting, abdominal pain, nausea, and diarrhea. Five side effects were considered to be moderately severe and the rest were mild. All side effects were resolved within one day and all were limited to the day of dosing with the exception of two patients who experienced somnolence and back pain, respectively, on the day following medication.

Clinically significant, possibly treatment-related laboratory abnormalities developed in 4 patients. Three of these patients had reduced hematological values and one patient had elevated liver enzymes (SGOT and SGPT). No serious adverse events were reported in this study. Due to the side effects profile of patients dosed with 2-gram azithromycin, even though side effects were all assessed to be mild or moderate in severity, it was decided not to proceed with 4-gram dosing segment of the protocol.

The small number of female patients enrolled in the study precludes any conclusion concerning azithromycin efficacy in the treatment of cervicitis. However this study does show that azithromycin, as a single 2-gm oral dose, is effective in the treatment of urethritis caused by *N. gonorrhoeae.*

Genital Ulcer Disease In Men Due To *Haemophilus ducreyi* Protocols:

BACK GROUND:

In 1985, CDC recommended the use of either erythromycin 500 mg four times a day, orally, for seven days or ceftriaxone 250 mg, intramuscularly, once for the treatment of chancroid. These regimens have been proven to be effective inside and outside of the United States. No known strains of *H. ducreyi* isolated in the United States have been resistant to either drug, although strains resistant to erythromycin have been documented in Singapore.

Since azithromycin has been shown to be efficacious as a single oral dose against *Chlamydia trachomatis* and has in vitro activity against *H.ducreyi* , azithromycin is felt to have the potential of being a highly effective agent for the treatment of chancroid. In support of this claim, several studies have been submitted by the sponsor.

PROTOCOL 066-120: (U.S. STUDY)

This open-label study was designed to compare the efficacy and safety of a single dose of azithromycin (1 g-orally) with those of ceftriaxone (250-mg im) in the treatment of chancroid due to *Haemophilus ducreyi.*

STUDY PERIOD:

February 1990 to February 1992

PRINCIPAL INVESTIGATORS:

William M. McCormick, M.D., Chief, Infectious Diseases Division, Department of Medicine, Downstate Medical Center, Brooklyn, N.Y.

David H. Martin, M.D., Chief, Section of Infectious Diseases, LSH Medical School;

George D. Wendel, Jr., M.D., Associate Professor, Dept. of Obstetrics and gynecology, University of Texas, Southwestern Medical school, Dallas, TX;

Susie J. Sargent,M.D., Associate Professor of Medicine, Dept. of Medicine, Division of Infectious Diseases, The University of Tennessee, Minneapolis.

STUDY SUMMARY:

This was a multicenter, open-label randomized comparison of a single dose of azithromycin (1-g orally) vs ceftriaxone (250-mg intramuscularly) in patients with a clinical diagnosis of chancroid at baseline. Patients whose baseline cultures failed to confirm infection or for whom the *H. ducreyi* isolate proved not susceptible to the assigned study drug were still to be followed for clinical ulcer response until clinical signs and symptoms resolved.

Prior to admission, each patient was to

- provide a written consent

- have a medical history taken

- have a physical examination performed

- have a blood and urine specimens obtained for a panel of routine safety tests

- genital/perianal ulcer specimens obtained and/or inguinal/femoral bubo aspirates were to be obtained for *H. ducreyi* culture

- susceptibility testing was to be done on all isolates (to be performed at the study sites)

Patients were to receive a single 1 g dose of azithromycin or a single 250 mg dose of commercial ceftriaxone (ceftriaxone was provided by the investigator). Azithromycin capsules were provided by the sponsor and were to be taken orally at least one hour before or two hours after a meal. Ceftriaxone was to be reconstituted with normal sterile saline for injection into the deltoid muscle.

Investigators were to receive a list of sequential patient numbers to which treatment regimens were randomly allocated in a ratio of 1:1 in blocks of 10. Patients entering the study were then to be assigned numbers in sequence.

The study was monitored by the sponsor routinely either by visits or by phone.

ENROLLMENT CRITERIA:

The study was to enroll up to 200 patients ($\leq$ 75/center) with clinically- and culture-documented chancroid.

Inclusion Criteria:

- Female or male inpatients/outpatients at least 16 years of age with one or more painful genital or perianal lesions without a history of preceding blisters, typical of herpes simplex.

- Women of childbearing potential who had a negative serum gonadotropin pregnancy test, and who were using adequate contraception during the study and agreed to continue to do so for 3 months after the study.

- Patients with a negative dark-field examination of the genital ulcer for *Treponema pallidum* and negative stat rapid plasma reagin test (RPR), unless patient had known antecedent RPR positivity.

- Patients who provided written informed consent; in States where the laws applied, additional written informed consent was to be obtained from the parent or the guardian of a patient less than 21 years old.

Exclusion Criteria:

- Pregnant or lactating females.

- Patients with a history of genital herpes, known human immunodeficiency virus (HIV) seropositivity, or with symptoms compatible with Acquired Immune Deficiency Syndrome (AIDS) or AIDS-related complex (ARC).

- Patients treated with any other antimicrobial within 7 days before enrollment, or with another investigational drug within the 4 weeks before enrollment.

- Patients with known hypersensitivity or intolerance to penicillin or macrolide or cephalosporin antibiotics.

- Patients with active peptic ulcer disease, gastrectomy, or other conditions affecting drug absorption, and patients with evidence or history of significant hematologic, renal, hepatic or cardiac disease, or with a positive HBsAG test.

- Patients known to abuse alcohol or drugs, and who for any other reason might be expected to be noncompliant with protocol requirements.

CONCOMITANT THERAPY:

During the study, patients were not to be treated with another antibiotic (unless a patient was felt to be an objective failure on study day 7). If a patient required another drug prior to study day 7, the patient was to be discontinued from the study and appropriate alternate therapy instituted.

The use of other medications should have been limited to those essential for the care of the patient. All concomitant medications were recorded. The use of any other investigational drug was prohibited.

INTERCURRENT ILLNESSES:

Any intercurrent illness was to be documented on the case report form.

CRITERIA FOR WITHDRAWAL FROM STUDY:

Patients withdrawn from the study because of side effects, significant laboratory abnormalities, inadequate response to the study medication, or for any other reason, circumstances and data surrounding these events were to be recorded on the case report form. A patient withdrawn because of an inadequate response must have had an appropriate culture performed to document that treatment failure was due to a persistence of the original organism. A patient withdrawn because of side effects or laboratory abnormalities were to be followed until all untoward events returned to normal. The frequency of follow-up visits was to be determined by the investigator.

DRUG STORAGE AND ACCOUNTABILITY:

The investigator was responsible for the receipt, usage and return (of unused drugs and supplies) of all the drugs and supplies.

CLINICAL OBSERVATIONS AND LABORATORY MEASUREMENTS:

A. EFFICACY

At study entry, patients were to have a clinical diagnosis of chancroid, considering one or more of the following:

1. one or more painful genital or perianal ulcers,
2. tender inguinal or femoral nodes enlarged to more than 1 cm (buboes) and unilateral or bilateral lymphadenopathy.

At the baseline visit, genital/perianal ulcer specimens and/or inguinal/femoral bubo aspirates were to be obtained for *H. ducreyi* culture. Susceptibility testing was to be done on all isolates and was to be performed at the study sites.

During the follow-up visits, the following assessments were to be made:

1. Assessment of the number, size, and tenderness of the ulcer(s). The degree of tenderness was to be

evaluated and scored as follows: able to squeeze without pain (0), able to squeeze but with pain (1+), barely able to touch (2+), and unable to touch (3+).

Clinical efficacy was to be based on ulcer tenderness and size. A decrease in tenderness was called a subjective ulcer response and a decrease in size an objective ulcer response.

2. Inguinal and femoral nodes were to be evaluated as follows: not palpable, shotty, large and firm, or large and fluctuant. Nodal tenderness was to be assessed as present or absent.

Patients were to be assessed for efficacy as follows:

Visit Day 7: Patients were to be reevaluated clinically based on the subjective and objective ulcer responses. In all cases, except for clinical cure (ulcer completely healed and without culturable material), *H. ducreyi* culture was to be repeated.

Visit Day 14: Clinical assessments of ulcer response were also to be made at day 14, unless patients were clinically cured at day 7, in which case they were not required to return for follow-up.

Visit Day 21: Clinical assessments of ulcer response were also to be made at day 21 if patients were not clinically cured at day 14. Patients not completely healed by day 21 were to be considered treatment failure and were to undergo evaluation and treatment as deemed appropriate by the investigator.

DEFINITION FOR OVERALL CLINICAL OUTCOMES:

Cured: Clinical signs/symptoms of infection resolved during the study with complete resolution by day 14

Improved: Clinical signs/symptoms subsided during the study but with incomplete resolution at day 14

Failed: No apparent objective response to therapy at day 7, or no apparent subjective or objective response at day 14

Patients withdrawn from the study due to lack of study drug efficacy were to have cultures for confirmation of *H. ducreyi* infection. All isolates were to be tested for susceptibility to the study drugs.

BACTERIOLOGICAL RESPONSE:

Eradication - Elimination of initial causative pathogen at day 7.

Persistence - Presence of initial causative pathogen at day 7 in a satisfactory culture specimen.

Relapse - Evidence of recurrence of infection with the initial causative pathogen after an apparent cure at day 7. This definition was applied to relapse occurring in the post-therapy follow-up period.

SUSCEPTIBILITY:

Susceptibility to the study drugs, azithromycin and ceftriaxone was determined for all *H. ducreyi* isolates using the Kirby- Bauer method. Zones of inhibition and/or MIC's for both study drugs were recorded on the case report forms for all isolates.

Criteria for determining susceptibility to the study drugs are listed below:

	AZITHROMYCIN		CEFTRIAXONE	
CRITERIA	MIC	ZONE SIZE	MIC	ZONE SIZE
SUSCEPTIBLE	≤ 2	≥ 18	≤ 16	≥ 18
INTERMEDIATE	4	14-17	32	14-17
RESISTANT	≥ 8	≤ 13	≥ 64	≤ 13

SAFETY ASSESSMENT:

Side effects:

All side effects, either reported by the patient or observed by the investigator, were to be recorded with information on their severity, date of onset, duration, and any treatment required. The possible relationship to study drug of all volunteered or observed side effects was to be assessed by the investigator.

All deaths, serious adverse experiences and study drug discontinuations due to an adverse experience or intercurrent illness, which occurred during the study or post-therapy period, regardless of treatment group or relationship to drug were to be reported immediately by telephone to the Pfizer project clinician.

A serious adverse experience included, but was not necessarily restricted to, events which were:

- Fatal
- Life-threatening or potentially life-threatening
- Permanently disabling
- Required inpatient hospitalization
- A congenital anomaly, cancer, or the result of overdose

LABORATORY PARAMETERS:

The following clinical laboratory tests were to be performed at baseline and on each follow-up visit: CBC with differential and platelet counts, ESR, prothrombin time, APTT, GGT, ALT and AST, alkaline phosphate, total protein and albumin, serum bilirubin, LDH, BUN, serum creatinine, serum calcium and phosphorus, electrolytes, blood glucose (fasting when feasible), uric acid, serum cholesterol and triglycerides, and urinanalysis. Pregnancy test, HBsAG, and HIV serology were to be obtained at the baseline.

Moderate and marked liver function abnormalities were defined as follows:

	ALT/AST	ALKALINE PHOSPHATASE	TOTAL BILIRUBIN
MODERATE	≥1.5 ULN	≥1.2 ULN	≥1.5 ULN
MARKED	≥3 ULN	≥1.5 ULN	≥2 ULN

where ULN was defined as upper limit of normal if the pretreatment baseline was normal, or pretreatment baseline if it was abnormal.

Moderately abnormal liver function tests were to be repeated within 3 to 7 days. If they were confirmed, then they were to be repeated on a weekly basis until they were resolved.

Patients with marked liver function abnormalities were to discontinue treatment immediately, and the Pfizer Project Clinician to be notified . The abnormal tests should have been repeated within 48 hours, and then at 3 to 7-day intervals until they resolved. In consultation with Pfizer Project Clinician, additional evaluations were to be arranged for the patients with marked lab. abnormalities that persisted after the study drug treatment was stopped. The additional evaluations may have included GI consultation and additional laboratory tests (e.g., HBV, HAV, or CMV serology; CPK; reticulocyte count).

PATIENT EVALUATION GROUPS: Sponsor's Data -
Table - 1

	AZITHROMYCIN	CEFTRIAXONE
Randomized to treatment	99	98
Received treatment	99	98
Discontinued treatment	0	0
Completed study	74	73
Efficacy evaluation:		
Bacteriological Response @ day 7	32	29
Ulcer Response	86	82
Safety Analysis:		
Side effects	99	98
Laboratory Tests	84	81

NUMBERS OF PATIENTS ENROLLED BY EACH CENTER:
TABLE - 2

CENTER	TREATMENT GROUP			
	AZITHROMYCIN		CEFTRIAXONE	
	RANDOMIZED	RECEIVED TREATMENT	RANDOMIZED	RECEIVED TREATMENT
694	3 (3)	3 (3)	4 (4.1)	4 (4.1)
*712	74 (74.7)	74 (74.7)	70 (71.4)	70 (71.4)
755	5 (5.1)	5 (5.1)	5 (5.1)	5 (5.1)
770	17 (17.2)	17 (17.2)	19 (19.4)	19 (19.4)
TOTAL	99 (100)	99 (100)	98 (100)	98 (100)

(Numbers in the parentheses are the percentages)

***COMMENT: Center number 712 enrolled 144 (73%) of the total 197 patients in both groups (azithromycin and ceftriaxone).**

According to the protocol no more than 75 patients were to be enrolled per center and this is a deviation from the protocol.

DEMOGRAPHIC DATA OF ALL TREATED PATIENTS : SPONSOR'S DATA -
TABLE - 3

SEX	TREATMENT GROUP					
	AZITHROMYCIN			CEFTRIAXONE		
	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL
# OF PATIENTS	92(92.9)	7 (7.1)	99(100)	91 (92.8)	7 (7.1)	98(100)
AGE CATEGORY						
<15	0 0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
15-44	82(82.8)	7 (7.1)	89(89.9)	88 (89.8)	7 (7.1)	95 (96.9)
45-64	9 (.1)	0 (0)	9 (9.1)	3 (3.1)	0 (0)	3 (3.1)
>=65	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
MEAN AGE	29.1	23.4	28.7	28.4	21.9	27.9
MEAN WEIGHT (KG)	77.8	58.6	68.2	75.2	65.3	70.3
RACE						
WHITE	2 (2)	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)
BLACK	90 (90.9)	7 (7.1)	97 (98)	91 (92.8)	7 (7.1)	98 (100)

(Numbers in the parentheses are the percentages)

One -hundred-ninety-seven patients were recruited for this study, 99 for the azithromycin group and 98 for the ceftriaxone group.

In the azithromycin group, 92 (92.9%) were male and 7 (7.1%) were female as compared to the ceftriaxone group where 91 (92.8%) were male and 7 (7.1%) were female patients. Mean age was 28.7 years in the azithromycin group and 27.9 years in the ceftriaxone group. Average weight was 68.2 kg in the azithromycin group and 70.3 kg in the ceftriaxone group.

Two (2%) were white and 97 (98%) were black in the azithromycin group and all (100%) were black in the ceftriaxone group.

REASONS FOR BACTERIOLOGICAL UNEVALUABILITY: Data by the sponsor
TABLE - 5

REASON	TREATMENT GROUP	
	AZITHROMYCIN	CEFTRIAXONE
	NUMBER	NUMBER
No assessment in the window	6	8
No baseline pathogen	61	61
*Concomitant antibiotics/Previous Antibiotic	7	9
Total	67	69

(Numbers in the parentheses are the percentages)

Six (6.1%) patients in the azithromycin group had no assessment during scheduled visits as compared to 8(8.2%) in the ceftriaxone group.

Sixty-one (61.6%) patients enrolled in the azithromycin group did not have baseline pathogen as compared to 61(62.2%) in the ceftriaxone group.

COMMENT: Patients treated with antibiotics concomitantly or within 7 days prior to starting therapy are already counted under no assessment and no baseline pathogen groups.

DEMOGRAPHIC DATA OF BACTERIOLOGICALLY EVALUABLE PATIENTS:
TABLE - 6

	TREATMENT GROUP					
	AZITHROMYCIN			CEFTRIAXONE		
	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL
# OF PATIENTS	29 (90.6)	3 (9.4)	32 (100)	29 (100)	0 (0)	29 (100)
AGE CATEGORY						
< 15	0 (0)	0 (0)	0 (0)	0 (0)	0	0 (0)
15-44	25 (78.1)	3 (9.4)	27 (78.1)	27 (93.1)	0	27 (93.1)
45-64	3 (9.4)	0 (0)	3 (9.4)	2 (6.9)	0	2 (6.9)
>=65	1 (3.1)	0 (0)	1 (3.1)	0 (0)	0	0 (0)
MEAN AGE	32.4	24.0	31.6	31.2	0	31.2
MEAN WEIGHT (KG)	75.5	56.4		74.0	0	74.0
RACE						
BLACK	29 (90.6)	3 (9.4)	32 (100)	29 (100)	0	29 (100)

(Numbers in the parentheses are the percentages)

Twenty-nine (90.6%) of 32 bacteriologically evaluable patients were male and 3 (9.4%) were female in the azithromycin group and 29 (100%) were male in the ceftriaxone group. Mean age was 31.6 years in the azithromycin group and 31.2 years in the ceftriaxone group. Average weight was 66 kg and 74 kg in the azithromycin and ceftriaxone group, respectively.

One- hundred percent of evaluable patients were black in both the azithromycin and ceftriaxone group.

DATA OF CONCURRENT DISEASES AT THE BASELINE: DATA BY THE SPONSOR
TABLE -6

DISEASES	AZITHROMYCIN	CEFTRIAXONE
HERPES SIMPLEX	2	3
SYPHILIS	3	4
GONORRHOEA	1	2
TRICHOMONIASIS	3	1
HEPATITIS B	1	0
HIV (AIDS AND ARC) -	No data was provided in this study by the sponsor.	
TOTAL	10/99 (10.1)	10/98 (10.2)

BACTERIOLOGICAL RESPONSE AT DAY 7 OF EVALUABLE PATIENTS: Data by the sponsor and medical officer
TABLE - 7

	TREATMENT GROUP			
	AZITHROMYCIN		CEFTRIAXONE	
	ERAD.	PERSIST.	ERAD.	PERSIST.
SEX				
FEMALE	3	0 (0)	0(0)	0 (0)
MALE	28 (96.6)	1 (3.4)	29(100)	0 (0)
TOTAL	31/32(96.9)	1/32(3.1)	29(100)	0 (0)

(Numbers in the parentheses are the percentages)

At visit day 7 post-treatment, the *H. ducreyi* eradication was 31/32 (96.9%) in the azithromycin group and 29/29 (100%) male patients in the ceftriaxone group. Only one patient was a bacteriological failure in the azithromycin group. The bacteriologic eradication in male patients in the azithromycin group was 28/29 (96.6%).

RECURRENCE RATE: Data by the sponsor and medical officer

Table - 8

SEX	TREATMENT GROUP			
	AZITHROMYCIN		CEFTRIAXONE	
	RECURRENT	TOTAL	RECURRENT	TOTAL
FEMALE	0	1	0	0
MALE	0	9	0	12
TOTAL	0	10	0	12

Ten azithromycin and twelve ceftriaxone patients were evaluated at visit day 14 (10-16 days after dosing) as they returned for routine follow-up visit. These patients showed *H. ducreyi* eradication at visit day 7 and at visit day 14. (As per discussion with the sponsor, these patients were not symptomatic on visit day 14).

ULCER RESPONSE AT DAY 7- Sponsor's Data

TABLE - 9

	TREATMENT GROUP					
	AZITHROMYCIN			CEFTRIAXONE		
	SEX			SEX		
	FEMALE	MALE	TOTAL	FEMALE	MALE	TOTAL
ULCER RESPONSE						
HEALED	1 (20)	41 (56.2)	42 (53.8)	3 (50)	29 (42.6)	32 (43.2)
IMPROVED	4 (80)	26 (35.6)	31 (38.5)	2 (33.3)	35 (51.5)	37 (50.0)
UNCHANGED OR WORSE	0	6 (8.2)	6 (7.7)	1 (16.7)	4 (5.9)	5 (6.8)
TOTAL	5 (100)	73 (100)	78 (100)	6 (100)	68 (100)	74 (100)

(Numbers in the parentheses are the percentages)

COMMENT: Includes all patients who were clinically assessed at day 7. Patients who were given non-study antibiotic for chancroid at or before day 7, or who withdrew previously for failure were assigned the 'unchanged or worse' categorization.

ULCER RESPONSE AT DAY 7 - PATIENTS BOTH ULCER-RESPONSE-ASSESSABLE (AT DAY 7) AND BACTERIOLOGICALLY EVALUABLE AT DAY 7: Sponsor's Data

TABLE - 10

ULCER RESPONSE	TREATMENT GROUP					
	AZITHROMYCIN			CEFTRIAXONE		
	SEX			SEX		
	FEMALE	MALE	TOTAL	FEMALE	MALE	TOTAL
HEALED	1 (33.3)	21(72.4)	22(68.8)	0 (0)	15(51.7)	15 (51.7)
IMPROVED	2 (66.7)	8 (27.6)	10(31.3)	0 (0)	14(48.3)	14 (48.3)
TOTAL	3 (100)	29(100)	32(100)	0 (0)	29(100)	29 (100)

(Numbers in the parentheses are the percentage

In the azithromycin group at visit day 7, 1/3 female patients and 21/29 (72.4%) male patients were considered healed. Two out of three female patients and 8/29 (27.6%) male patients were considered improved.

In the ceftriaxone group at visit day 7, 15/29 (51.7%) were considered healed and 14/29 (48.3%) were improved. There were no female patients to be assessed.

ULCER RESPONSE AT DAY 14 - PATIENTS BOTH ULCER-RESPONSE-ASSESSABLE (AT DAY 14) AND BACTERIOLOGICALLY EVALUABLE AT DAY 7: Sponsor's Data

TABLE - 11

ULCER RESPONSE	TREATMENT GROUP				
	AZITHROMYCIN			CEFTRIAXONE	
	SEX			SEX	
	FEMALE	MALE	TOTAL	MALE	TOTAL
HEALED	1(50.0)	10(37.0)	11(37.9)	9(33.3)	9(33.3)
HEALED LAST PRIOR VISIT	1(50.0)	17(63.0)	18(62.1)	15(55.6)	15(55.6)
IMPROVED	0	0	0	3(11.1)	3(11.1)
TOTAL	2(100.0)	27(100.0)	29(100.0)	27(100.0)	27(100.0)

(NUMBERS IN THE PARENTHESES ARE THE PERCENTAGES)

ULCER RESPONSE AT DAY 21 - PATIENTS BOTH ULCER-RESPONSE-ASSESSABLE (AT DAY 21) AND BACTERIOLOGICALLY EVALUABLE AT DAY 7: Sponsor's Data

TABLE - 12

ULCER RESPONSE	TREATMENT GROUP				
	AZITHROMYCIN			CEFTRIAXONE	
	SEX			SEX	
	FEMALE	MALE	TOTAL	MALE	TOTAL
HEALED	1(33.3)	2(6.9)	3(9.4)	3(11.1)	3(11.1)
HEALED LAST PRIOR VISIT	2(66.7)	27(93.1)	29(90.6)	22(81.5)	22(81.5)
IMPROVED	0	0	0	2(7.4)	2(7.4)
TOTAL	3(100.0)	29(100.0)	32(100.0)	27(100.0)	27(100.0)

(NUMBERS IN THE PARENTHESES ARE THE PERCENTAGES)

BACTERIOLOGICAL RESPONSE AT DAY 7 OF EVALUABLE PATIENTS BY HIV STATUS: Sponsor's Data

TABLE - 13

		TREATMENT GROUP			
		AZITHROMYCIN		CEFTRIAXONE	
		ERAD.	TOTAL	ERAD.	TOTAL
HIV STATUS	ALL	29(90.6)	30(93.6)	28(96.5)	28 (96.5)
NEG					
POS	SEX	1	1	0	0
	MALE				
	TOTAL	1 (3.1)	1 (3.1)	0	0
NOT DONE	SEX	1 (3.1)	1	1	1
	MALE				
	TOTAL	31(96.9)	32 (100)	29 (100)	29 (100)

(Numbers in the parentheses are the percentages)

Only one evaluable patient was HIV positive in this study. Based on these data no conclusion can be derived on the effect of azithromycin in healing ulcers caused by *H. ducreyi* in HIV infected patients.

SAFETY EVALUATION: Clinical Adverse Events

All patients who received study medication were included in the safety evaluation. Side effects which occurred during or within 35 days of dosing were tabulated by their severity (the reactions were graded on a qualitative scale as mild, moderate, severe, and not significant), organ system, and by the investigator's assessment of their relationship to study drug therapy.

The procedures for classifying laboratory abnormalities as treatment-related or unrelated to treatment was assigned a category. For each patient, changes in any of the laboratory test between baseline and 35 days after dosing which were defined as abnormal were reviewed by the sponsor and their possible

relationship to the study drug therapy was evaluated. The abnormalities were categorized by the sponsor as transient and unrelated to the study drug, due to laboratory error, due to concurrent or intercurrent diseases, due to concomitant therapies, clinically insignificant, or as related to treatment.

All illnesses that occurred within 35 days after dosing were tabulated. Assessments of their casual relationship to study drug therapy were neither provided by the investigator nor made by the sponsor.

DEATHS:

There were no deaths during this study.

DISCONTINUATIONS:

There was no patient discontinued in this study.

SEVERE/LIFE THREATENING EVENTS:

One patient in the azithromycin group exhibited an exacerbation of a pruritic rash on the upper body, treatment related lose stools, and vomiting. The rash was described as 1-2 mm papules and pustules, and it healed without concomitant therapy in few weeks. In the ceftriaxone group, out of 8 cases of injection site pain or stiffness only one case was considered severe . This patient also experienced mild facial rash and moderate thirst which was attributed to the treatment.

INCIDENCE OF THE ADVERSE EVENTS: Sponsor's Data

TABLE - 13

INCIDENCE OF ADVERSE EVENTS		
NUMBER OF PATIENTS	AZITHROMYCIN	CEFTRIAXONE
Evaluable	99	98
With Adverse Events	19 (19.2)	10 (10.2)
Withdrawn with Adverse Events	0	0
ADVERSE EVENTS BY BODY SYSTEM		
Skin/Appendages	1 (1)	1 (1)
Psychiatric	1 (1)	0
Gastrointestinal	17 (17.1)	0
Metabolic/Nutritional	0	1 (1)
Appl./Incision Site	0	8 (8.2)

(Numbers in the parentheses are the percentages)

Nineteen patients (19.2%) in the azithromycin group and 10 patients (10.2%) in the ceftriaxone group suffered at least one adverse event. In the azithromycin group, 17/99 (17%) patients had gastrointestinally related adverse events as compared to none in the ceftriaxone group. 8/98 (8.2%) had injection site related adverse events in the ceftriaxone group.

In the azithromycin group, the most frequently occurring gastrointestinal adverse events were nausea, vomiting, and diarrhea. Most of the adverse events were mild to moderate in severity. Only one severe treatment related adverse event occurred in each treatment group (rash in one azithromycin patient and injection site pain and stiffness in one ceftriaxone patient).

SEVERITY OF THE ADVERSE EVENTS: Sponsor's Data

TABLE -14

SEVERITY OF THE ADVERSE EVENTS									
ORGAN SYSTEM	AZITHROMYCIN					CEFTRIAXONE				
	Number of Patients	1	2	3	NS	Number of Patients	1	2	3	NS
Skin/Appendages										
Rash	1 (1)	0	0	1	0	1 (1)	1	0	0	0
Psychiatric										
Somnolence	1 (1)	1	0	0	0	0	0	0	0	0
Gastrointestinal										
Stools Loose	7 (7.1)	6	1	0	0	0	0	0	0	0
Vomiting	5 (5.1)	5	0	0	0	0	0	0	0	0
Abdominal	1 (1)	1	0	0	0	0	0	0	0	0
Dyspepsia	2 (2)	2	0	0	0	0	0	0	0	0
Nausea	9 (9.1)	8	1	0	0	0	0	0	0	0
Metabolic/Nutritional										
Thirst	0	0	0	0	0	1 (1)	0	1	0	0
Appl./Inj./Insertion Site										
Site Pain	0	0	0	0	0	7 (7.1)	2	4	1	0
Device Complication	0	0	0	0	0	1 (1)	1	0	0	0

(Numbers in the parentheses are the percentages)

DATA OF ABNORMAL LABORATORY VALUES:

TABLE - 15

LABORATORY VALUES	AZITHROMYCIN	CEFTRIAXONE
NUMBER OF PATIENTS	84	81
HEMOGLOBIN	0	1 (1.2)
HEMATOCRIT	0	1 (1.2)
RBC	1 (1.2)	1 (1.2)
WBC	3 (3.6)	1 (1.2)
NEUTROPHILS	7 (8.3)	1 (1.2)
EOSINOPHIL	0	1 (1.2)
BASOPHIL	0	2 (2.5)
MONOCYTES	1 (1.2)	1 (1.2)
TOTAL BILIRUBIN	3 (3.6)	4 (4.9)
SGOT	1 (1.2)	5 (6.2)
SGPT	5 (5.9)	3 (3.7)
GGT	1 (1.2)	0
LDH	0	3 (3.7)
URIC ACID	0	2 (2.5)
I PHOS	1 (1.2)	0
TOTAL # OF ABNL. LAB. VALUES	23	26
TOTAL # OF PATIENTS WITH ABNL LABS.	18/84 (21.4)	17/81 (21.0)

(Numbers in the parentheses are the percentages)

Following a single 1 g dose of azithromycin, 18 of 84 (21.4%) patients developed one or more clinically significant treatment related laboratory abnormality. Eight (9.5%) patients had liver function abnormalities, 8 (9.5%) had hematologic abnormalities.

Following a single 250-mg im dose of ceftriaxone, 17 of 81 (21.0%) developed one or more clinically significant treatment related laboratory abnormality. Eleven of 17 (64.7%) patients developed liver function abnormalities, and 6 of 17 (35.3%) exhibited hematologic abnormalities.

SEVERITY OF THE ADVERSE EVENTS: Sponsor's Data

TABLE -14

SEVERITY OF THE ADVERSE EVENTS									
ORGAN SYSTEM	AZITHROMYCIN					CEFTRIAXONE				
	Number of Patients	1	2	3	NS	Number of Patients	1	2	3	NS
Skin/Appendages										
Rash	1 (1)	0	0	1	0	1 (1)	1	0	0	0
Psychiatric										
Somnolence	1 (1)	1	0	0	0	0	0	0	0	0
Gastrointestinal										
Stools Loose	7 (7.1)	6	1	0	0	0	0	0	0	0
Vomiting	5 (5.1)	5	0	0	0	0	0	0	0	0
Abdominal	1 (1)	1	0	0	0	0	0	0	0	0
Dyspepsia	2 (2)	2	0	0	0	0	0	0	0	0
Nausea	9 (9.1)	8	1	0	0	0	0	0	0	0
Metabolic/Nutritional										
Thirst	0	0	0	0	0	1 (1)	0	1	0	0
Appl./Inj./Insertion Site										
Site Pain	0	0	0	0	0	7 (7.1)	2	4	1	0
Device Complication	0	0	0	0	0	1 (1)	1	0	0	0

(Numbers in the parentheses are the percentages)

DATA OF ABNORMAL LABORATORY VALUES:

TABLE - 15

LABORATORY VALUES	AZITHROMYCIN	CEFTRIAXONE
NUMBER OF PATIENTS	84	81
HEMOGLOBIN	0	1 (1.2)
HEMATOCRIT	0	1 (1.2)
RBC	1 (1.2)	1 (1.2)
WBC	3 (3.6)	1 (1.2)
NEUTROPHILS	7 (8.3)	1 (1.2)
EOSINOPHIL	0	1 (1.2)
BASOPHIL	0	2 (2.5)
MONOCYTES	1 (1.2)	1 (1.2)
TOTAL BILIRUBIN	3 (3.6)	4 (4.9)
SGOT	1 (1.2)	5 (6.2)
SGPT	5 (5.9)	3 (3.7)
GGT	1 (1.2)	0
LDH	0	3 (3.7)
URIC ACID	0	2 (2.5)
I PHOS	1 (1.2)	0
TOTAL # OF ABNL. LAB. VALUES	23	26
TOTAL # OF PATIENTS WITH ABNL LABS.	18/84 (21.4)	17/81 (21.0)

(Numbers in the parentheses are the percentages)

Following a single 1 g dose of azithromycin, 18 of 84 (21.4%) patients developed one or more clinically significant treatment related laboratory abnormality. Eight (9.5%) patients had liver function abnormalities, 8 (9.5%) had hematologic abnormalities.

Following a single 250-mg im dose of ceftriaxone, 17 of 81 (21.0%) developed one or more clinically significant treatment related laboratory abnormality. Eleven of 17 (64.7%) patients developed liver function abnormalities, and 6 of 17 (35.3%) exhibited hematologic abnormalities.

PROTOCOL 066-328 (FRANCE)

PROTOCOL TITLE: An open, pilot study to assess the efficacy, toleration and safety of azithromycin in the treatment of chancroid caused by *Haemophilus ducreyi.*

STUDY PERIOD: June 1989 to February 1990

INVESTIGATORS:

Professor P.Morel and Professor Y. Perol
Hospital Saint Louis
2, Place du Docteur A. Fournier
75475 Paris Cedex 10

CENTER NUMBER: 137

STUDY DESIGN:

In this open-label single dose study, patients with clinical and bacteriological evidence of chancroid caused by *Haemophilus ducreyi* were treated with a single 1 g dose of azithromycin and were to be followed up with clinical and bacteriological assessments at days 3, 7, 14 and 21 (only if improved but not healed at day 14) after dosing (day 0). Side effects inquiry were conducted at each post-therapy visit and laboratory safety tests were performed at baseline and at day-3 and 14 post-treatment visits.

All patients were required to give written informed consent, provide blood and urine samples for a battery of standard tests and to undergo a full medical examination. Microbiological and clinical assessments were to be performed before commencing therapy. The protocol was reviewed and approved by the hospital ethics committee. Investigators were required to contact the sponsor immediately by telephone in the event of a significant adverse experience. Monitoring visits were conducted periodically during the study by the sponsor.

26 patients were randomized to enroll into the study at center 137. All of them received treatment and were eligible for safety.

ENROLLMENT CRITERIA:

Inclusion Criteria:

- Female or male inpatients/outpatients at least 16 years of age with one or more painful genital or perianal lesions without a history of preceding blisters, typical of herpes simplex.

- Women of childbearing potential who had a negative serum gonadotropin pregnancy test, and who were using adequate contraception during the study and agreed to continue to do so for 3 months after the study.

- Patients with a negative dark-field examination of the genital ulcer for *Treponema pallidum* and negative stat rapid plasma reagin test (RPR), unless patient had known antecedent RPR positivity.

Exclusion Criteria:

- Pregnant or lactating females.

- Patients with a history of genital herpes, known human immunodeficiency virus (HIV) seropositivity, or with symptoms compatible with Acquired Immune Deficiency Syndrome (AIDS) or AIDS-related complex (ARC).

- Patients treated with any other antimicrobial within 7 days before enrollment, or with another investigational drug within the 4 weeks before enrollment.

- Patients with known hypersensitivity or intolerance to penicillin or macrolide or cephalosporin antibiotics.

- Patients with active peptic ulcer disease, gastrectomy, or other conditions affecting drug absorption, and patients with evidence or history of significant hematologic, renal, hepatic or cardiac disease, or with a positive HBsAG test.

- Patients known to abuse alcohol or drugs, and who for any other reason might be expected to be noncompliant with protocol requirements.

CONCOMITANT THERAPY:

During the study the patient may not have been treated with another antibiotic (unless a patient was felt to be an objective failure on study day 7). If patient did require another drug prior to study day 7, the patient was to be discontinued from the study and appropriate alternate therapy to be instituted.

The use of other medications should have been limited to those absolutely essential for the care of the patient. All concomitant medications were recorded. The use of any other investigational drug was prohibited.

INTERCURRENT ILLNESSES:

Any intercurrent illness was to be documented on the case report form.

DRUG SUPPLIES:

Azithromycin was provided by the sponsor.

PRECAUTIONS:

Patients were instructed not to donate blood and to abstain from sexual activity during the study period.

BACTERIOLOGICAL RESPONSE:

This was derived from the bacteriology assessment at each visit. It was classified as eradicated, presumed eradicated or persisted. A pathogen was presumed to be eradicated when there was no material to culture because either all the lesions were dried up or healed.

CLINICAL RESPONSE:

The clinical response in patients was classified as cured or failure at each visit. Clinical cure was defined as complete disappearance of all lesions.

SAFETY ASSESSMENT:
Side effects:

Patients were evaluated by the clinician and were instructed to immediately contact the clinician if any suspected side effects were noted. The duration and severity, and possible relationship to study drug of all volunteered or observed side effects were to be recorded.

All deaths, serious adverse experiences and study drug discontinuations due to adverse experience or intercurrent illness, which occurred during the study or post-therapy period, regardless of treatment group or relationship to drug were to be reported immediately by telephone to the Pfizer project Clinician.

A serious adverse experience included, but was not necessarily restricted to, events which were:
- Fatal
- Life-threatening or potentially life-threatening
- Permanently disabling
- An event requiring inpatient hospitalization
- A congenital anomaly, cancer, or the result of overdose

DEMOGRAPHIC DATA - ALL PATIENTS
TABLE -1

SEX	AZITHROMYCIN		
	MALE	FEMALE	TOTAL
# OF PATIENTS	26	0	26
AGE			
<15	0	0	0
15-44	20 (76.9)	0	20 (76.9)
45-64	5 (19.2)	0	5 (19.2)
>=65	1 (3.8)	0	1 (3.8)
MEAN AGE	37.0	0	37.0
MEAN WEIGHT	73.0	0	73.0
RACE			
White	11 (42.3)	0	11 (42.3)
Black	15 (57.7)	0	15 (57.7)

(Numbers in the parentheses are the percentages)

Twenty-six patients were enrolled into the study and all were male. Forty-two percent were white and 57.7% were black. Average weight was 73 kg and average age was 37 years.

REASONS FOR UNEVALUABILITY: As assessed on day 7.
TABLE -2

REASONS	TREATMENT GROUP
	AZITHROMYCIN
	NUMBER
No Assessment in the Window	0
No Baseline Pathogen	1 (3.8)
Positive for Syphilis	6 (23.1)
Total	7 (26.9)

(Numbers in the parentheses are the percentages)

Seven (26.9%) patients were considered unevaluable; one (3.8%) patient had no baseline pathogen and 6 (28.1%) patients tested positive for syphilis.

BACTERIOLOGICAL ASSESSMENT: SPONSOR'S DATA:

TABLE -3

ERAD.	DAY 3	DAY 7	DAY 14	DAY 21
	4 (22.2)	2 (10.5)	0 (0)	0 (0)
PRESUMED ERAD.	14 (77.8)	17(89.5)	16100)	5 (100)
PERSISTENCE	0 (0)	0 (0)	0 (0)	0 (0)
TOTAL	18 (100)	19(100)	16(100)	5 (100)

(Numbers in the parentheses are the percentages)

The bacteriological evaluations were done at days 3, 7, 14 and 21. On visit day 3, 4 patients (22.2%) were bacteriologically eradicated and 14 patients (77.8%) were considered presumed eradicated, since there was no material to be cultured from the lesions.

On visit day 7, 2 patients (10.5%) were eradicated and 17 patients (89.5%) were considered presumed eradicated. Sixteen patients (100%) were considered presumed eradicated on day 14 visit and 5 patients (100%) were considered presumed eradicated on day 21 visit.

BACTERIOLOGICAL ASSESSMENT: MEDICAL OFFICER'S DATA:

TABLE -4

ERAD.	DAY 3	DAY 7	DAY 14	DAY 21
	4 (21.1)	2 (10.5)	0 (0)	0 (0)
PRESUMED ERAD.	14(73.7)	17(89.5)	16(84.2)	5 (26.1)
*NOT EVALUABLE	1 (5.3)	0 (0)	3 (15.8)	14(73.7)
PERSISTENCE	0 (0)	0 (0)	0 (0)	0 (0)
TOTAL	18(100)	19(100)	19 (100)	19 (100)

(Numbers in the parentheses are the percentages)

***COMMENT: Under "not evaluable" , these patients did not show up for the visit in that window period. There is no difference in the data between the sponsor and the medical officer except for the explanation of "non-evaluable" patients and the differences in the percentages secondary to these patients.**

CLINICAL ASSESSMENT OF PATIENT OUTCOME: SPONSOR'S DATA:
TABLE -5

CLINICAL CURE	DAY 3	DAY 7	DAY 14	DAY 21
	N	N	N	N
Yes	0(0)	4(21.1)	13(81.3)	6(100)
No	18(100)	15(78.9)	3(18.8)	0 (0)
Total	18(100)	19(100)	16(100)	6(100)

(Numbers in the parentheses are the percentages)

Of 19 patients, 18 patients attended the clinic on day 3 and clinical cure was not seen in any one of the 18 patients who attended the day 3 visit. Clinical cure was seen in 4/19 patients (21.1%) who attended day 7 visit, in 13/16 patients (81.3%) who attended the day 14 visit and in 6/6 patients (100%) who attended the day 21 visit. Seventeen of 19 (89.5%) evaluable patients were clinically cured on their last visit on day 21. Two patients failed to return for follow-up visits after day 7. These patients did show improvement in their symptoms but were not considered clinically cured on day 7.

SAFETY:

ADVERSE EVENTS:

There were no adverse events reported.

LABORATORY TESTS ABNORMALITIES:
TABLE -7

LABORATORY VALUES	AZITHROMYCIN
# OF PATIENTS	26
Total Bilirubin Sodium Chloride Calcium	1 (3.8) 1 (3.8) 1 (3.8) 1 (3.8)
Total # of Abnormal Labs	4 (15.4)
Total # of Patients with Abnormal Labs	3 (11.5)

(Numbers in the parentheses are the percentages)

Three (11.5%) patients had clinically significant, treatment related laboratory test abnormalities. These include elevation of the bilirubin in one patient on post-treatment days 4 and 14; increase in sodium and decrease in chloride in one patient on post-treatment days 4 and 14; and decreased calcium level in one patient on post-treatment days 4 and 14.

PROTOCOL AZM-NY-90-007 (NON-U.S. KENYA)

TITLE:

Single dose Azithromycin for the Treatment of Chancroid: A randomized Comparison with 250 mg of Ceftriaxone I.M.

PRINCIPAL INVESTIGATOR:

Alan Ronald, M.D.

CO-INVESTIGATORS:

Mark W. Tyndall, M.D.
Elizabeth Agoki
Francis A. Plummer, M.D.
William Malisa, MB.Ch.B.
J.O. Ndinya-Achola, MB.Ch.B.

STUDY SITE:

WHO Collaborating Center for Research and Training in Sexually Transmitted Diseases
Department of Medical Microbiology
University of Nairobi
Nairobi, Kenya.

STUDY PERIOD:

April 1991 to July 1991.

OBJECTIVE:

The objective of the study was to compare the clinical and microbiological effectiveness and safety of a single 1 g oral dose of azithromycin versus a single 250 mg dose of Ceftriaxone administered intramuscularly for the treatment of Chancroid.

STUDY DESCRIPTION:

This study was an open, parallel design, comparative study. The details of the study, including potential side effects of the study drug, were to be fully explained to each patient. Informed consent was to be obtained from each patient prior to enrollment into the study as well as each patient's HIV status. Before administration of the first dose of study drug, a complete medical history was to be taken, and a physical examination performed.

Patients were to be evaluated before the first dose of study drug (Day 1) on day 3-5, on day 8-10 and on day 14 $\pm$ 2. All patients were to return on the 28th day for a repeat HIV test. At each evaluation, signs and symptoms of the infection were to be assessed and graded. Microbiological examination and laboratory tests were to be performed. Patients were to be considered evaluable for microbiological

DURATION:

The total observation period for data collection was to be approximately 4-5 weeks.

METHODS OF SUBJECT ASSIGNMENTS:

For this study a 2:1 randomization of azithromycin/ceftriaxone was to be used.

ENROLLMENT CRITERIA:

Inclusion criteria:

- Male and female outpatients between the ages of 18 and 60 years who present with a genital ulcer typical of chancroid. An ulcerative lesion was defined as a lesion with no intact covering epithelium present and with a diameter of more than 2 mm.

- A dark-field examination of the genital ulcer must have been negative for *T. pallidum*.

- Patients who gave informed consent in accordance with the provisions of the pertinent excerpt from the Declaration of Hong Kong 1989.

Exclusion criteria:

- Treatment with another antimicrobial for the present infection within two weeks prior to enrollment into the study, unless there was documented failure of the other antimicrobial.

- Previous treatment with azithromycin or ceftriaxone whether treatment was completed or prematurely discontinued.

- Terminal illness or other condition that precluded completion and evaluation of study therapy.

- Known hypersensitivity to macrolides or to beta-lactam antibiotics.

- Treatment with any investigational drug within one month prior to enrollment into the study.

- Pregnancy, lactation or in women of child bearing potential, lack of use of adequate contraception.

- Infections requiring treatment with another antimicrobial agent in addition to the study drug.

- Concurrent treatment with ergotamine or carbamazepine or digitalis glycosides.

- Evidence or history of chronic diarrheal diseases or any other gastrointestinal condition that could affect study drug absorption.

- A suspicion that the subject would not return for follow-up visits.

- Clinical evidence of primary or secondary syphilis. (A positive dark-field examination of the lesion)

- Clinical or microbiological evidence of Herpes simplex.

PROCEDURES AND MEASUREMENTS:

Assessment at baseline:

- Obtain written or oral informed consent form from the patient.
- Obtain the patient's medical history and perform a physical examination.
- Dark field examination.
- Smear for Gram stain.
- Smear for Giemsa stain.
- Swab for culture for *H. ducreyi* on selective media.
- *Herpes simplex* virus culture.
- Chlamydia culture.
- Randomize the patient to a regimen according to his/her HIV status.
- Obtain blood and urine samples and perform the following laboratory tests:

a. Hematology
   Erythrocyte count
   Platelet count
   Leukocyte with differential
   Hgb/Hct

b. Clinical Chemistry
   SGOT
   SEPT
   Alkaline phosphatase
   BUN
   Bilirubin

c. Urinalysis
   Protein
   Glucose

CONCOMITANT ILLNESS AND MEDICATIONS:

At each visit, the investigator was to obtain any information about concomitant illness and medications for their treatment. The diagnoses and dates of onset and remission of all illnesses, as well as the name, daily dosage taken, and dates and reasons for administration of all medications, whether physician-prescribed or not, were to be included, if applicable.

MONITORING OF STUDY:

Periodically, a representative of the Sponsor was to visit or communicate with the investigator to assess the progress of the study and adherence to the protocol.

The investigator was to maintain source documents such as laboratory reports, X-rays, ECG's, any consultation reports, complete history and physical examinations, etc. for possible review by the Sponsor.

RECORDING OF THE DATA:

The investigator was to ensure that all data from subject's visits were to be entered promptly in accordance with specific instructions accompanying the Case Report Form and/or diary supplied by the

Sponsor. An explanation for the omission of any required data was to appear on the appropriate page. The signature of the investigator or his/her appropriate designee was to appear on each page of the CRF.

LABORATORY FINDINGS:

All results outside the normal values for the laboratory in which the tests were to be performed were to be identified and, if possible, explained by the investigator. When appropriate, repeat measurements were to be made to differentiate between possible laboratory error and an abnormality of clinical significance. All patients demonstrating clinically meaningful abnormalities or changes in laboratory parameters were to be monitored until the condition returned to pre-study status or restoration of any problem was achieved.

PRECAUTIONS:

Patients were instructed to abstain from sexual activity until the end of a study or, if not feasible, to use a condom each time.

EFFICACY:

Clinical effectiveness:

Cure: Disappearance of all baseline signs and symptoms relevant to infection. Disappearance of the ulcer and any associated lymphadenopathy. Time (in days) to healing were to be recorded.

Improvement: Marked improvement or significant change in baseline signs and symptoms.

Failure: No change or worsening in signs and symptoms and reinfection unlikely.

Relapse: Partial or complete disappearance of baseline signs and symptoms on visit 3 follow-up, but worsening or reappearance of signs and symptoms on visit 4.

Unevaluable: No evaluation of the clinical response can be made. Reasons include failure to return for follow-up; concomitant antibacterial therapy; failure to adhere to dosing scheme, etc.

Microbiological assessment:

Eradication: Eradication of the baseline pathogen (*H. ducreyi*).

Eradication with Recurrence (visit 3&4): Eradication of baseline pathogen (*H. ducreyi*) on visit 3 follow-up, but culturing of baseline pathogen on visit 4.

Persistence: Presence of baseline pathogen (*H. ducreyi*) during therapy and/or immediately after termination of therapy.

Unevaluable: No evaluation of the microbiological response can be made. Reasons include no follow-up culture; inadequate culture source; concomitant antibacterial therapy; failure to adhere to dosing scheme, etc.

CRITERIA FOR WITHDRAWAL FROM STUDY:

- At the request of the subject.

- If the investigator considered that a patient's health would be compromised due to adverse experience or concomitant illness that developed after entering the study.

- If a subject was recognized after entry to be uncooperative or a consistent violator of protocol requirements.

For any patient who discontinued therapy before the study was completed, the investigator was to:

- Complete the case report including any summary sheet, indicating the date of and explanation for the early discontinuation of medication.

- Whenever feasible, complete all scheduled examinations for the final study visit either at the time medication was discontinued or, preferably, at a scheduled visit one or two weeks later.

- Arrange for alternative medical care of the discontinued subject and record on the appropriate case report form pages any follow-up of subjects discontinued for adverse experiences.

DRUG ADMINISTRATION:

Patients were to be assigned to each drug group according to a predetermined randomized allocation schedule provided by Pfizer International. Patients assigned to azithromycin were to take orally a single 1 g dose, and those assigned to ceftriaxone were to receive a single 500 mg intramuscular injection. Replacement of patients lost to follow-up was to be done via the Randomization code.

SAFETY:

Side effects:

Patients were to be evaluated by the clinician and were to be instructed to immediately contact the clinician if any suspected side effects were noted. The duration and severity, and possible relationship to study drug of all volunteered or observed side effects were to be recorded.

All deaths, serious adverse experiences and study drug discontinuations due to adverse experience or intercurrent illness, which occurred during the study or post-therapy period, regardless of treatment group or relationship to drug were to be reported immediately by telephone to the Pfizer project Clinician.

A serious adverse experience included, but was not necessarily restricted to, events which were:

- Fatal
- Life-threatening or potentially life-threatening
- Permanently disabling
- An event requiring inpatient hospitalization
- A congenital anomaly, cancer, or the result of overdose

PROTOCOL DEVIATIONS:

The objective of this study was to evaluate the efficacy of a single-dose of azithromycin (1-g orally) versus ceftriaxone (250-mg im) for the treatment of chancroid in men (investigator chose to use erythromycin 500 mg four times a day for 7 days instead of ceftriaxone as the comparative agent. His recent experience in Kenya found a significant failure rate in HIV positive patients treated with ceftriaxone). This was a randomized, prospective, observer-blinded, parallel-treatment study. At baseline genital ulcers were measured and assessed for cultures. Sera were collected for syphilis and HIV testing. Patients were randomized to receive azithromycin or erythromycin in a 2:1 ratio. Patients were asked to return for follow-up on days 7, 14, and 21. They were questioned about genital ulcer symptoms; genital examination was repeated and persisting ulcers were measured and recultured. The response of the treatment was evaluated without knowledge of the treatment received or the HIV-1 serologic status by the observer.

The original protocol was the same as the rest of the protocols used in other studies conducted for *H. ducreyi* but, for a number of reasons, including information concerning the efficacy of ceftriaxone in the treatment of chancroid in HIV infected patients and the level of resources available to the investigator, the investigator made a variety of modifications to the study design. These modifications resulted in significant deviations from the protocol. These deviations are as follows:

1 . Use of Erythromycin as the comparative agent instead of Ceftriaxone

2. Patients were seen at days 7,14 and 21.

3. Repeat HIV testing was not done at day 28 but rather at the discretion of the investigator.

4. Females were not enrolled in the study.

5. Dark-field examination of the genital ulcer was not done.

6. No screening for clinical or microbiological evidence of Herpes simplex was performed.

7. Chlamydia cultures were not performed.

8. The laboratory and urine testing was not performed as part of the study. Patients may have had laboratory testing performed as part of routine medical care but these results were not collected on the case report form.

9. Patients were not randomized by HIV status.

10. The primary Clinical Effectiveness was based on the epithelialization of the genital ulcer. A secondary analysis of the data described the resolution of symptoms, defined as resolved, improved, same or worse.

11. Microbiological Assessment: A formal evaluation of eradication with recurrence was not performed.

12. Although Pfizer is not aware of any serious adverse events, there was no mechanism in place for immediate reporting of Serious Adverse Events to Pfizer.

13. Pfizer representative did not monitor the performance of this study. The data were recorded on the investigator designed case report forms and not on CRF's supplied by the sponsor. After the study was completed, the investigator's case report forms were supplied to Pfizer who analyzed the data as

presented. No attempt was made to validate information on the CRF's with source documents.

14. Case report forms were not supplied to Pfizer on a routine basis, rather they were requested by the Sponsor after publication of the data by the investigator.

PRIMARY EFFICACY RESPONSE:

a. Microbiological Response

Criteria for the assessment of microbiological response were as follow:

- a baseline culture positive for growth of *H. ducreyi*,
- the patient returned to have a culture performed at day 7 visit

Response assessed as follows:

Eradication: Culture done at day 7 was negative for growth; if the ulcer did not yield any culturable material, the organism was considered eradicated.

Persistence: Culture of the ulcer grew *H. ducreyi*

b. Clinical Response

An evaluable patient analysis of the clinical response was performed at day 14. Criteria for inclusion in this analysis were as follows:

- a baseline culture positive for *H. ducreyi*

- a negative serologic exam (RPR) for syphilis at baseline (if no test was performed, the patient was excluded)

- the patient did not receive antibiotic potentially effective against *H. ducreyi* prior to the visit; if antibiotic was given at a time when the ulcer had not epithelialized, the clinical response was carried forward as failed; if the ulcer had already healed, the patient was excluded from the analysis. Antibiotics considered as active against *H. ducreyi* were: ciprofloxacin, erythromycin, penicillin, minocycline, azithromycin.

- the patient returned for the day 14 visit; if there was no day 14 visit but the ulcer had previously epithelialized, a clinical response of cure was carried forward.

- the window for the day 14 visit was $\pm$ 2 days, except if the patient was previously cured.

Clinical response was assessed as:

Cure: Epithelialization of the ulcer by day 14

Failure: Ulcer had not epithelialized by day 14.

In this study, 207 patients received either azithromycin or erythromycin but only 191 case report forms were submitted to the sponsor. 132 patients received azithromycin and 59 received erythromycin. Of the 191 patients, 23 were lost to follow up. One-hundred-forty-three met the study inclusion criteria of a positive *H. ducreyi* culture at baseline, 93 in the azithromycin group and 50 in the erythromycin group.

DEMOGRAPHIC DATA: Data from the Sponsor

Table -1

SEX	TREATMENT GROUP	
	AZITHROMYCIN	ERYTHROMYCIN
	MALE	MALE
# of Patients	132	59
Mean Age	26.5	26.6
*Mean Weight	0	0
*Race	-	-
HIV	39 + (30) 93 - (70)	19 + (32) 40 - (68)
RPR	14 + (11) 112- (85) *6 (4)	3 + (5) 52-(88) *4 (7)
Circumcised Yes No	 95 ((72) 37 (28)	 45 (76) 14 (24)
Duration of the ulcer < 1 week 1-2 weeks 2-3 weeks 3-4 weeks > 4 weeks	 20 (15) 44 (33) 32 (24) 11 (8) 25 (19)	 9 (15) 17 (29) 23(39) 3 (5) 7 (12)
Ulcer size ≤ 10 mm >10 mm	 113 (86) 19 (14)	 50 (85) 9 (15)
Ulcer HD Culture Positive Negative Unavailable	 93 (70) 39 (30) 0 (0)	 50 (85) 7 (12) 2 (3)

(Numbers in the parentheses are the percentages)

*COMMENT: There are no data for the weight or race. The results for 6 patients in the azithromycin group and 4 patients in the erythromycin group were not reported.

The mean age was 26.5 years in the azithromycin group and 26.6 years in the erythromycin group. Eighty-six percent of patients had ulcers ≤ 10 mm in diameter in the azithromycin group and 85% in the erythromycin group.

Ninety-three percent of 132 patients (72%) were culture positive for *H. ducreyi* in the azithromycin group; 14 of 132 patients (11%) had positive RPR, and 39 of 132 patients (30%) were HIV positive at baseline in the azythromycin group.

Fifty of 59 patients (85%) had positive cultures for *H. ducreyi* in the erythromycin group; 3 of 59 patients (5%) had a positive RPM and 19 of 59 patients (32%) were HIV positive at baseline in the erythromycin group. There seems to be significant difference between erythromycin and azithromycin in the number of patients positive for *H. ducreyi* at the baseline.

BACTERIOLOGICAL ERADICATION AT DAY 7 POST-TREATMENT: SPONSOR'S DATA
TABLE -2

ALL PATIENTS	AZITHROMYCIN		ERYTHROMYCIN	
	ERADICATION	PERSISTENT	ERADICATION	PERSISTENT
	72 (92)	6 (8)	37 (88)	5 (12)
HIV+	22 (92)	2 (8)	11 (73)	4 (27)
HIV-	50 (93)	4 (7)	26 (96)	1 (4)

(Numbers in the parentheses are the percentages)

Ninety-two percent of the patients with a positive baseline culture for *H. ducreyi* were eradicated in the azithromycin group as compare to 88% in the erythromycin group. Among the subset of patients with Positive HIV serology at baseline, 92% of patients in the azithromycin group were eradicated as compare to 73% patients in the erythromycin group. Patients who were negative for HIV at the baseline, 93% were eradicated in the azithromycin group as compare to 96% in the erythromycin group.

Eight percent of patients who were HIV positive had persistent organisms in the azithromycin group, as compare to 7% who were HIV negative. 27% of patients who were HIV positive had persistent organism in the erythromycin group as compare to 4% who were HIV negative.

CLINICAL RESPONSE AT DAY 14 - SPONSOR'S DATA
TABLE -3

ALL PATIENTS	AZITHROMYCIN		ERYTHROMYCIN	
	CURE	FAILURE	CURE	FAILURE
	44 (83)	9 (17)	32 (91)	3 (9)
HIV +	12 (75)	4 (25)	11 (85)	2 (15)
HIV -	32 (86)	5 (14)	21 (95)	1 (5)

(Numbers in the parentheses are the percentages)

The clinical response analysis was performed at day 14. The assessment of the cure was based solely on the status of epithelialization of the ulcer.

Eighty-three percent of patients had clinical cure in the azithromycin group as compare to 91% in the erythromycin group. 75% of HIV positive patients were clinically cured in the azithromycin group as compare to 85% in the erythromycin group. 86% of HIV negative patients had clinical cure in the azythromycin group as compare to 95% of patients in the erythromycin group.

SAFETY:

No clinical or laboratory data were submitted for the safety analysis in this review. There has been some mention of events possibly related to azithromycin, these include rash (4), pruritus (3), dysuria (2), vomiting (1), and cough (1). Those possibly related to erythromycin include dysuria (2).

The article published by the investigator reporting the results of this study indicates mild episodes of nausea occurred in the erythromycin treated patients.

PROTOCOL: L-0196

TITLE:

"Azithromycin in the Treatment of Nongonococcal Urethritis: A Multicenter, Double-Blind, Double-Dummy Study Employing Doxycycline as a comparative Agent."

STUDY OBJECTIVE:

To compare the efficacy and safety of azithromycin and doxycycline as the treatment of nongonococcal urethritis in males.

STUDY PERIOD:

January 1992 to February 1993

STUDY DESIGN:

This was a multicenter, randomized (2:1; azithromycin:doxycycline), double-blind, double-dummy, comparative and parallel-group study conducted in the United States. Participants in this study were patients with acute nongonococcal urethritis (i.e., $\leq$ 14 days of signs and symptoms). At the baseline visit, all patients were required to have a Gram-stain of urethral smear with $\geq$ 5 PMNL/field. All patients were to have cultures tested at baseline for *C. trachomatis, N.gonorrhoeae, M. hominis,* Patients with positive cultures for gonorrhoea and/or syphilis were to be to discontinued from the study but evaluated and treated with appropriate therapy. All other patients with or without positive cultures were to be followed. Patients were randomly assigned in a 2:1 fashion to therapy with a single 1-g oral dose of azithromycin or oral doxycycline, 100 mg b.i.d. for seven days, respectively, each with placebo for the alternate drug. Evaluations were to be done at baseline and one and four weeks following completion of treatment. Laboratory safety profiles were also to be obtained at these times.

ENROLLMENT CRITERIA:

Approximately 60 patients were to be enrolled at each of up to 11 centers. Only males were eligible for enrollment.

INFORMED CONSENT:

The risks and benefits of participating in the study were to be explained to the patients by the investigator prior to the entry into the study. The written informed consent was to be obtained by the investigator from the patient and the form was to be retained by the investigator.

INSTITUTIONAL REVIEW:

The investigator was to obtain written approval from the institutional review board for the study protocol, informed consent form, and any change in the protocol or informed consent form.

PATIENT SELECTION CRITERIA:

Inclusion Criteria:

- At least 18 years of age.

- Outpatients.

- Sexually active males with presumptive symptomatic acute Nongonococcal urethritis, defined as the presence of a urethral discharge and/or dysuria, with $\geq$ 5 PMNL/OIF of Gram-stained urethral smear. There should be no visible Gram-negative intracellular diplococci. Signs and symptoms of infection should be acute (present for $\leq$ 14 days).

Exclusion Criteria:

- Presence of Gram-negative intracellular diplococci on the urethral smear and positive culture for *N.gonorrhoea.*

- Evidence or history of significant hematologic, renal, hepatic or cardiac disease.

- Evidence of any urological anatomic abnormality.

- Known HIV seropositivity or known Acquired Immunodeficiency Syndrome (AIDS) or AIDS Related Complex (ARC)

- Treatment of episodes of urethritis within two months prior to entry into the study.

- History of allergy or hypersensitivity to erythromycin or doxycycline.

- Presence of any other infection at enrollment that required treatment with any antibiotic other than the study drugs.

- Patients who for any reason, in the opinion of the investigator, might not be expected to comply with the requirements of the protocol.

- Treatment with another investigational drug within the 30 days prior to entry into the study.

- Treatment with any systemic antibiotic within two weeks prior to entry into the study

- Patients with peptic ulcers, gastrectomy, or other conditions affecting drug absorption.

CONCOMITANT THERAPY:

During the study, the patient was not to be treated with another antibiotic (unless the patient's course of treatment required such anti-infective). If a patient did require another drug prior to completion of the study, the study drug was to be stopped and appropriate alternate therapy initiated.

The use of other medications (non-infective) was to be limited to those essential for the care of the patients. All concomitant medications were to be recorded in the case report form. The use of any other investigational drug was to be prohibited.

METHODS OF SUBJECT ASSIGNMENTS:

The investigators were provided with a randomization schedule prepared by Pfizer, Inc. consisting of a list of sequential numbers to which the study drug regimens were randomly allocated in a 2:1 fashion. The investigator was to assign a study number sequentially to patients as they were determined eligible for entry into the study.

OBSERVATION AND MEASUREMENTS:

Baseline visit -Day 1:

1. Medical History and Physical Exam

2. Urethral swab specimen for Gram stain and Cultures

3. First 10-20 mL of a urine specimen for cultures for *C. trachomatis,* and *M. hominis*

4. Susceptibility Testing

5. Written Informed Consent

6. Laboratory Analysis to include:

   - CBC with Differential and Platelet counts
   - Serum chemistry panel with liver function tests
   - Urinalysis
   - RPR or VDRL

7. Dispensing of double-blind medication in blister cards, with first dose administered in the clinic

8. Counseling

POST-TREATMENT PROCEDURES:

a. 5-9 days (one week) post-treatment visit:

- Assessment of signs and symptoms
- Assessment of Drug compliance
- A genital exam
- Repeat Gram Stain of urethral smear for PMNL
- Repeat cultures (urethral and urine)
- Repeat all laboratory tests
- Adverse events review
- Assessment of bacteriological and clinical efficacy

b. 25-31 days (four week) post-treatment visit:
- Same as above

INTERCURRENT ILLNESSES:
Any intercurrent illness was to be documented in the case report form.

CRITERIA FOR WITHDRAWAL FROM THE STUDY:

- Serious or severe adverse event

- Treatment failure

- Investigator's opinion that treatment with another antibiotic was indicated.

Reasons for withdrawal were to be clearly documented in the case report form.

Patients with persistent symptoms and $\geq$ 5 PMNL/OIF, or patients with persistent urethral discharge 5-9 days following treatment were to be withdrawn from the study.

DRUG ADMINISTRATION:

Patients were assigned to either azithromycin 1-g oral (four 250 mg capsules) as a single dose or doxycycline, 100 mg b.i.d. for seven days. The first study medication was administered in the clinic. Study drug was dispensed in blister cards at the baseline visit. The study drug was blinded in a double-dummy manner.

Table-1 presents the medication schedule:
TABLE -1

Days(S)	DOSE	AZITHROMYCIN	AZI. PLACEBO	DOXYCYCLINE	DOXY. PLACEBO
Azithromycin-Treated Patients(1 GM oral, as a single dose)					
1	1	4	-	-	1
	2	-	-	-	1
2-7	1	-	-	-	1
	2	-	-	-	1
Doxycycline-Treated Patients (100 mg b.i.d. x 7 days)					
1	1	-	4	1	-
	2	-	-	1	-
2-7	1	-	-	1	-
	2	-	-	1	-

DRUG SUPPLIES:

Both drugs were provided by Pfizer Inc. The study drugs were blinded in a "double-dummy" manner. There were identical appearing placebos for both azithromycin and doxycycline capsules.

PRECAUTIONS:

Patients were to be instructed not to donate blood and to abstain from sexual activity during the study.

PATIENT EVALUABILITY:

EVALUABLE PATIENT ANALYSIS:

The evaluable patient analysis was conducted on all patients who received a dose of medication, and who were compliant with the protocol requirements, including the individually scheduled visits outlined by the protocol. Patients were to be excluded from the evaluable patient group based on the criteria listed below:

Patients who met any of the following criteria were unevaluable for any bacteriologic or clinical efficacy analysis:

- Chronic NGU (symptoms present > 14 days at baseline)

- Asymptomatic at baseline

- Concomitant gonorrhea or syphilis

- Did not return for any follow-up visits

- Concurrent antibiotics received before the appropriate follow-up assessments had been done

- Poor compliance with the study medication. To be considered evaluable for efficacy, a patient must have been treated for at least five days, with at least 75% of the prescribed medication received.

- Unprotected sex after baseline visit and before the first follow-up

- Discontinued because of an adverse event or other reason

BACTERIOLOGIC RESPONSE:

To be bacteriologically evaluable, an appropriate pathogen must have been isolated at baseline and a follow-up culture must have been done at either week-two (1-week post therapy) or week-five (4-week post therapy). For the analysis of general bacteriologic response, patients without a week-two visit were unevaluable. Similarly, patients for whom the baseline pathogen was eradicated at week-two but who did not return for a week-five visit were also unevaluable for the analysis of general bacteriologic response.

Eradication - elimination of the initial causative pathogen at both the week-two and week-five visits

Persistence - persistence of initial causative pathogen at either the first follow-up visit or at both follow-up visits

Eradications with recurrence - elimination of the initial causative pathogen at the week-two visit, with recurrence at the week-five visit

CLINICAL RESPONSE:

Cure -

One-week post-treatment visit:

- Complete resolution of signs and symptoms of infection, and ≤4 PMNL/OIF on urethral smear Gram stain at 1-week post-treatment visit.

4-week post-treatment visit:

- Complete resolution of signs and symptoms of infection and ≤4 PMNL/OIF on uretheral smear Gram stain at the 1-week and 4-week post-treatment visit.

- Persistent symptoms alone at 5-week (with no discharge and ≤4 PMNL)

Failure

One-week post-treatment visit:

- Persistent symptoms and ≥5 PMNL (regardless of urethral discharge) or persistent urethral discharge alone (regardless of symptoms or PMNL).

4-week post-treatment visit:

- ≥5 PMNL alone (regardless of symptoms or discharge) or persistent urethral discharge alone (regardless of symptoms or PMNL)

ANTIBIOTIC SUSCEPTIBILITY TESTING:

Of those isolates which could be recovered, the MIC for azithromycin was from mcg/mL and for doxycycline isolates MIC's ranged from mcg/mL.

SAFETY:

All patients who took at least one dose of the study medication were included in the analysis of adverse events. Patients who received treatment and had one follow-up laboratory assessment were included in the analysis of laboratory safety data.

Adverse Events:

At each visit, patients were to be interviewed by the responsible physician to elicit any adverse events. Also, they were to report to the physician if any adverse events were noted. The symptoms, duration, severity, and possible relationship to study drug were to be recorded in the case report form.

LABORATORY PARAMETERS:

The following clinical laboratory tests were to be performed at 1 and 4 week following completion of therapy:

- CBC with Differential and platelets

- Serum chemistry panel with Liver function tests

- Urinanalysis

- Rapid plasma reagin (RPR) or Venereal Disease Research Laboratory (VDRL) test for syphilis at baseline only)

Marked and moderate liver function abnormalities were defined as follows:

	AST/ALT	ALKALINE PHOSPHATASE	TOTAL BILIRUBIN
Moderate	> 1.5 X ULN	>1.2 X ULN	> 1.5 X ULN
Marked	> 3 X ULN	> 1.5 X ULN	> 2 X ULN

ULN was defined as upper limit of normal if the pretreatment baseline was normal, or the pretreatment baseline if it was abnormal.

PATIENT DISPOSITION:

Four-hundred-fifty-two patients were enrolled at 11 centers, 301 in the azithromycin group and 151 in the doxycycline group.

PATIENT ACCOUNTABILITY BY SITE:

Table-1

Site	Patients Enrolled	Patients Discontinued Treatment Prematurely	Patients Completed
0061	23	3	20
0062	82	16	66
0063	21	6	15
0064	43	3	40
0065	68	10	58
0066	42	10	32
0067	28	3	25
0068	43	8	35
0069	21	2	19
0070	19	4	15
0080	62	9	53
Total	452	74	378

DEMOGRAPHIC DATA: Accumulative demographic data for **all patients** were provided by the sponsor, and is presented in the table-2:

Table-2

VARIABLE	AZITHROMYCIN	DOXYCYCLINE
SEX	MALE	MALE
NUMBER	301	151
RACE WHITE	62 (20.6)	31 (20.5)
BLACK	232(77.1)	115(76.2)
HISPANIC	5 (1.7)	3 (2)
ASIAN	2 (0.7)	1 (0.7)
MIXED	0	1 (0.7)
AGE (mean)	26.1	26.6
WEIGHT(kg, MEAN)	78.3	78.6

(Numbers in the parentheses are the percentages)

DEMOGRAPHIC DATA: Accumulative demographic data for the **evaluable patients** infected with the three organisms *C. trachomatis*, and *M. hominis)* was provided by the sponsor in this study and is presented in the table-3:

Table -3

VARIABLE	AZITHROMYCIN	DOXYCYCLINE
SEX	MALE	MALE
NUMBER	229	117
RACE WHITE	54 (23.6)	27 (23.1)
BLACK	169(73.8)	87 (74.3)
HISPANIC	4 (1.7)	3 (2.7)
ASIAN	2 (0.9)	0
AGE (mean)	25.9	26.7
WEIGHT(kg, MEAN)	78.2	78.3

(Numbers in the parentheses are the percentages)

OVERALL BACTERIOLOGICAL RESPONSE OF EVALUABLE PATIENTS WITH ALONE OR WITH MIXED INFECTIONS - SPONSOR'S DATA

TABLE-4

Bacteriological response (Sponsor's data):

Response	Azithromycin		Doxycycline	
	Week-2	week-5	week-2	week-5
Eradication	63/84(75%)	31/58(53.4%)	19/31(61.3%)	14/24(58.3%)

Of 115 bacteriologically evaluable patients from whom was isolated at baseline, negative culture results were noted at week-2 for 63 of 84 azithromycin (75%) patients and 19 of 31 doxycycline (61%) patients.

Eradication was noted at week-5 in 31 of 58 azithromycin (53.4%) and in 14 of 24 doxycycline (58.3%) patients.

eradication rates based on last evaluable cultures were 53/86 (62%) for azithromycin and 18/32 (56%) for doxycycline.

Overall bacteriological response for in 62 evaluable azithromycin patients was eradication in 29 patients (47%), persistence in 21 patients (34%), and eradication with recurrence in 12 patients (19%).

Overall bacteriological response for in 27 evaluable doxycycline patients was eradication in 12 patients (44.4%), persistence in 12 patients (44.4%), and eradication with recurrence in 3 patients (11.1%).

Susceptibility of Clinical Isolates of

The mean inhibitory concentration for azithromycin ranged from mcg/mL; those for doxycycline ranged from mcg/mL.

CLINICAL RESPONSE OF CLINICALLY EVALUABLE PATIENTS -Sponsor' data for week-2

TABLE -5

RESPONSE	AZITHROMYCIN	DOXYCYCLINE
WEEK	WEEK-2	WEEK-2
Cure	67/84(80)	23/31(74)
Failure	5/84 (5.9)	4/31 (12.9)
Cannot Assess	12/84(14.3)	4/31 (12.9)
TOTAL	84/84(100)	31/31 (100)

(Numbers in the parentheses are the percentages)

At week-2 visit, 67/84 (80%) azithromycin patients were cured as were 23/31 (74%) doxycycline patients. Five of eighty-four (5.9%) azithromycin patients were failures as were 4/31 (12.9%) doxycycline patients. Twelve of eighty-four (14.3%) azithromycin patients were not assessable and 4/31 (12.9%) doxycycline patients were also not assessable.

CLINICAL RESPONSE OF CLINICALLY EVALUABLE PATIENTS -Sponsor' data for week-5 and last evaluation

TABLE-6

RESPONSE	AZITHROMYCIN		DOXYCYCLINE	
WEEK	WEEK-5	*LAST EVALUATION	WEEK-5	LAST EVALUATION
CURE	49/56(87.5)	69/84(82.1)	20/23(90)	22/31(71)
FAILURE	7/56 (12.5)	12/84(14.3)	3/23 (13)	7/31 (22.5)
CANNOT ASSESS		3/84 (3.6)		2/31 (6.5)
TOTAL	56/56(100)	84/84(100)	23/23(100)	31/31(100)

(Numbers in the parentheses are the percentages)

*For Last Evaluation, Cure equals Presumed Cure at week-2 or Cure at Week-5.

At week-5, 49/56 (88%) azithromycin patients were cured; 20/23 (90%) doxycycline patients were cured.

At last evaluation, the cure rate in the azithromycin group was 82% (69/84) and 71% (22/31 in the doxycycline group.

SAFETY EVALUATION:

All patients with *M. hominis,* and/or *C. trachomatis* who took at least one dose of the study medications were included in the analysis of adverse events. Adverse events of any causality were reported for 74 (25%) azithromycin and 45 (30%) of doxycycline patients.

Adverse events were classified by body system, were graded on a qualitative scale as mild, moderate, or severe, and by the investigator's assessment of their relationship to study drug therapy.

INCIDENCE OF ADVERSE EVENTS - ALL CASUALTIES

TABLE -7

INCIDENCE OF ADVERSE EVENTS		
NUMBER OF PATIENTS	AZITHROMYCIN	DOXYCYCLINE
Evaluable	301	151
With Adverse Events	74 (24.6)	45 (29.8)
Discontinued Treatment With Adverse Event	1 (0.3)	4 (2.6)
Withdrawn From Study With Adverse Event	1 (0.3)	0
ADVERSE EVENTS BY ORGAN SYSTEM:		
Skin/Appendages	5 (1.7)	7 (2.3)
Musculoskeletal	1 (0.3)	0
Centr. & Periph. Nerv. System	8 (2.7)	5 (3.3)
Psychiatric	5 (1.7)	0
Gastrointestinal	57 (18.9)	40(26.5)
Respiratory System	3 (1)	1 (0.7)
Urinary System	1 (0.3)	1 (0.7)
Cardiovascular	1 (0.3)	0
General	2 (0.7)	1 (0.7)

(Numbers in the parentheses are the percentages)

The adverse events of the gastrointestinal system accounted for the largest incidence of adverse events: 57 (18.9%) azithromycin patients and 40 (26.5%) doxycycline patients. Nausea, diarrhea, and abdominal pain were the most frequent gastrointestinal system events. The central nervous system were second highest, occurring in 8 azithromycin (2%) and 5 doxycycline (3%) patients. Headache and dizziness were the most frequent central nervous system events in both groups.

SEVERITY OF THE ADVERSE EVENTS: DATA BY THE SPONSOR

TABLE -8

SEVERITY OF THE ADVERSE EVENTS					
ORGAN SYSTEM	AZITHROMYCIN		DOXYCYCLINE		
	# of patients	1 2 3 NS	# of patients	1 2 3 NS	
Skin/Appendages					
Pruritis	1 (0.3)	1 0 0 0	1 (0.7)	1 0 0 0	
Rash	3 (1)	2 1 0 0	5 (3.3)	5 0 0 0	
Skin Ulceration	0	0 0 0 0	1 (0.7)	1 0 0 0	
Skin Dry	1 (0.3)	1 0 0 0	0	0 0 0 0	
Musculoskeltal					
Arthralgia	1 (0.3)	0 0 1 0	0	0 0 0 0	
Centr. & Periph. Nerv.					
Dizziness	3 (1)	1 1 1 0	3 (2)	3 0 0 0	
Headache	6 (2)	4 2 0 0	2 (1.3)	2 0 0 0	
Psychiatric					
Insomnia	1 (0.3)	1 1 0 0	0	0 0 0 0	
Somnolence	4 (1.3)	4 0 0 0	0	0 0 0 0	
Gastrointestinal					
Constipation	1 (0.3)	0 0 1 0	0	0 0 0 0	
Stools Loose	6 (2)	6 0 0 0	2 (1.3)	2 0 0 0	
Vomiting	1 (0.3)	1 0 0 0	4 (2.6)	1 3 0 0	
Abdominal Pain	12 (4)	6 5 1 0	5 (3.3)	5 0 0 0	
Dyspepsia	3 (1)	2 1 0 0	4 (1.3)	2 0 2 0	
Flatulance	4 (1.3)	3 1 0 0	1 (0.7)	0 0 1 0	
Nausea	22(7.3)	16 5 1 0	21(13.9)	17 4 0 0	
Diarrhea	19(6.3)	13 5 1 0	6 (4)	5 1 0 0	
Esophagitis	0	0 0 0 0	4 (1.3)	0 3 1 0	
Diseases of esophagitis	0	0 0 0 0	1 (0.7)	1 0 0 0	
Respiratory System					
Epistaxis	1 (0.3)	1 0 0 0	0	0 0 0 0	
Rhinitis	1 (0.3)	0 1 0 0	0	0 0 0 0	
Sinusitis	0	0 0 0 0	1 (0.7)	0 1 0 0	
Dyspnea	1 (0.3)	0 1 0 0	0	0 0 0 0	
Urinary System					
Micturation	0	0 0 0 0	1 (0.7)	1 0 0 0	
Polyuria	1 (0.3)	1 0 0 0	0	0 0 0 0	
Cardiovascular					
Chest Pain	1 (0.3)	1 0 0 0	0	0 0 0 0	
General					
Back Pain		0 0 0 0	1 (0.7)	1 0 0 0	
Fever		1 0 0 0	0	0 0 0 0	
Pain		0 0 1 0	0	0 0 0 0	
Rigors		1 0 0 0	0	0 0 0 0	

The severity of the adverse events was determined by the investigator. Seven severe adverse events were reported for four patients in the azithromycin group; these were arthralgia, dizziness, constipation, abdominal pain, nausea, diarrhea, and pain. Four severe adverse events were reported in the doxycycline group; these were dyspepsia, flatulence, and esophagitis.

One patient from the azithromycin group withdrew from the study secondary to the adverse event (nausea and diarrhea). Four patients from the doxycycline group withdrew from the study secondary to treatment related or possibly related adverse events. These events were severe esophagitis, severe dyspepsia, moderate nausea, and mild nausea. Since these patients received enough study medication, they were included in the efficacy analysis.

DATA OF ABNORMAL LABORATORY VALUES:

TABLE -9

LABORATORY VALUES	AZITHROMYCIN	DOXYCYCLINE
NUMBER OF PATIENTS	264	134
HEMATOLOGIC		0
Haemoglobin	1	0
Hematocrit	1	0
RBC	1	0
WBC	3	5
Neutrophils	9	0
Neutrophils, Bands	1	5
Eosinophil	1	3
Lymphocytes	6	2
Atypical Lymphocytes	13	2
Platelets	0	
HEPATIC		
SGOT	10	8
SGPT	7	7
LDH	0	3
Bilirubin, Total	3	4
Bilirubin, Direct	1	1
I. Phos	1	4
Glucose	0	1
Uric Acid	0	0
Protein, Total Serum	0	1
TOTAL # OF ABNL. LAB. VALUES	56	46
Total # of Patients With Abnl. Labs.	40/264 (15%)	29/134 (22%)

(numbers in the parentheses are the percentages)

The relationship of the laboratory abnormalities to the study medications were determined by the sponsor under blinded conditions. Two hundred and sixty-four azithromycin patients and 134 doxycycline patients were included in the analysis of laboratory tests. Forty azithromycin patients (15%) and 29 doxycycline patients (22%) had clinically significant treatment-related and possibly treatment-related laboratory abnormalities.

Eighteen (7%) azithromycin and 14 (10%) doxycycline patients were reported to have clinically significant, treatment-related liver function abnormalities. Three azithromycin and four doxycycline patients were noted to have markedly abnormal liver function tests, and the rest were considered to have moderate abnormalities. The incidence of these results is greater than the incidence rates of 1 to 2% presented in the package insert for azithromycin.

CONCLUSION:

In this study the overall bacteriological eradication rate of in the azithromycin group was 46.8%. This is a very low bacteriological eradication rate to recommend approval for this indication.

ANALYSIS OF THE OTHER STUDIES FOR :(101, 107 A, 114, 119, 125, 130, 135, 137, 301, 305, 319)

Data from 11 studies were analyzed. The 11 studies used in these analyses were treatment studies of sexually transmitted diseases which contained *N. gonorrhoea, C. trachomatous, and M. hominis* culture data.

The copies of reports for studies 101,107 A,119, 125, 301, and 305 were not submitted with this supplement and no reports are available for studies 135 and 137. The data from the studies 130 and 114 are provided in this submission in support of the claim for gonococcal urethritis/cervicitis.

Pursuant to the 11 studies conducted, the sponsor inferred that the patients, who had positive cultures for U. urealyticum and N. gonorrhoea at the baseline from urethera, cervix, rectum and pharynx were identified. The bacteriological response was determined based upon:

- follow-up cultures
- adjusting for presumed use of concomitant antibiotics
- withdrawl of patients from the study due to persistance of infection.

Since no data were submitted for these studies, there was no assessment made by the medical officer.

CONCLUSIONS AND RECOMMENDATIONS:

Urethritis and Cerviciris due to N. gonoerhoea:

Three U.S. studies were conducted:

Study 066-130 (pivotal study) was a multicenter, well-controlled study comparing the efficacy and safety of azithromycin, a single 2-gram oral dose vs. ceftriaxone, a single 250-mg intramuscular dose. Results of this study showed that one week post-treatment *N. gonorrhoeae* was eradicated from the urethra in 223/226 (99%) male patients and in 20/20 (100%) female patients, and from the cervix in 123/125 (98%) female patients. At 2-weeks post-treatment, *N. gonorrhoeae* remained eradicated from the urethra in 99/99 (100%) male patients and 12/12 (100%) female patients, and from the cervix in 93/95 (98%) female patients.

These results showed that azithromycin, 2-gram single oral dose, was as effective as ceftriaxone, 250-mg single intramuscular dose.

Studies 066-114 and 066-124 were smaller supportive studies. Study 066-114 enrolled only male patients. Results showed 100% eradication rate from the urethra at both week-1 (21/21)and week-2 (12/12) post-treatment evaluations. Study 066-124 had mostly male patients. Results showed 100% eradication rate from the urethra at both week-1 (20/20) and week-2 (15/15) post-treatment evaluations.

Adverse events were significantly higher in the azithromycin-treated patients than in the ceftraixone-treated patients. These were mostly related to the gastrointestinal tract and resolved within one day of drug administration.

It has been an established policy in the DAIDP that effectiveness in the treatment of uncomplicated gonococcal urethritis and cervicitis should be established by either two open trials - one trial for each gender - or one trial enrolling adequate number of both men and women. At least 100 men and 100 women should be evaluable. Bacterial eradication rate should be the primary effectiveness endpoint, and at least 95% bacterial eradication rate should be achieved.

It is, therefore, concluded that the data provided in this application demonstrate the efficacy and safety of a single 2-gram oral dose of azithromycin in the treatment of uncomplicated urethritis and cervicitis due to *N. gonorrhoeae.*

Approval of this indication is recommended.

Genital ulcer disease in men due to Haemophilis ducreyi (Chancroid):

Three studies were conducted in support of this indication: one in the U.S., one in France, and one in Kenya. The U.S. study (protocol 066-120) was an open, multicenter, randomized, comparative study of the efficacy and safety of a single 1.0-gram oral dose of azithromycin vs. a single 250-mg intramuscular dose of ceftriaxone.

Results of this study showed that one week post-treatment *H. ducreyi* was eradiacted in 28/29 (97%) male patients in the azithromycin group and in 29/29 (100%) male patients in the ceftriaxone group.

The ulcer response in this evaluable population was healed in 21/29 (72%) and improved in 8/29 (28%) male patients in the azithromycin group as compared to 15/29 (52%) healed and 14/29 (48%) improved in the ceftriaxone group.

The French study (protocol 066-328) was an open-label, non-comparative study of the safety and efficacy of a single 1.0-gram oral dose of azithromycin.

Results showed that 3 days post-treatment, 18/18 (100%) patients had eradication or presumed eradication of *H. ducreyi;* 7 days post-treatment, 19/19 (100%) patients had eradication or presumed eradication; 14 days post-treatment 16/16 (100%) patients had presumed eradication, and 21 days post-treatment 5/5 patients had presumed eradication. On day 3 post-treatment, no patient experienced a clinical cure; on day 7 post-treatment, 4/19 (21%) patients were cured; on day 14 post-treatment13/16 (81%) were cured, and on day 21, 6/6 (100%) patients were cured.

The Kenya study (protocol AZM-NY-90-007) was an open, comparative study of the efficacy and safety of a single 1.0-gram oral dose of azithromycin vs. erythromycin 500 mg four times a day for 7 days. Bacteriologic response at day 7 post-treatment showed eradication of *H. ducreyi* in 72/78 (92%) patients in the azithromycin group and in 37/42 (88%) patients in the erythromycin group.

Clinical response assessed on day 14 post-treatment was cure in 83% of the patients in the azithromycin group and in 91% of the patients in the erythromycin group.

COMMENTS:

The U.S. and the French studies are considered to be the pivotal studies, and the Kenya study is considered to be supportive.

All three studies showed an eradiaction rate of *H. ducreyi* over 95%.

Azithromycin has excellent *in vitro* activity. MIC_{90} values of 0.03 mcg/mL or below have been reported. The highest observed MIC value in the clinical trials was 0.06 mcg/mL. Tissue levels of azithromycin in cervical mucus, prostatic tissue, falopian tubes, ovaries, uterus, and seminal fluid reach levels between 2.6 and 5.69 mcg/mL after doses of 500 mg or 1 gram. These concentrations are well above the MIC_{90} values in most studies for *H. ducreyi.*

Azithromycin is more active *in vitro* than erythromycin.

The only presently approved drug in the U.S. for the treatment of chancroid is tetracycline. According to W. Lee Hand (Mandell, Douglas and Bennett *Principles and Practice of Infectious Diseases*) "many strains of *H. ducreyi* (99% in Thailand) are resistant to tetracycline, which should no longer be used for the treatment of Chancroid." He also states that "Recent evidence linking genital ulcer disease (especially Chancroid) to an increase in hetrosexual transmission of human immunodeficiency virus (HIV-1) infection greatly increases the known impact of Chancroid."

The failure rate of ceftriaxone 250 mg I.M. in the treatment of Chancroid is very high in men with concurrent HIV-1 infection.

Although the number of patients treated in the two pivotal studies may appear to be small relative to the higher number required for approval of uncomplicated gonorrhea, it should be noted that according to CDC, in 1990, Chancroid was reported in 4212 (1.7/100,000 persons) patients in the U.S., in 1992, 1885 (0.7/100,000 persons) cases were reported, and in 1994, 773 (0.3/100,000 persons) cases were reported. Therfore, it would be practically impossible to conduct studies of Chancroid in the U.S. as large as those that are conducted for uncomplicated gonorrhea.

In conclusion, azithromycin has been shown to be safe and effective in the treatment of Chancroid in men and approval of this indication is recommended.

Non-gonococcal urethritis in men due to

A multicenter double-blind, double-dummy study was conducted in the U.S. to compare the efficacy and safety of azithromycin versus doxycycline in the treatment of non-gonococcal urethritis in males due to Results of this study showed an overall bacteriologic response of eradication in 29/62 patients (47%), eradication with recurrence in 12/62 (19%), and persistence in 21/62 patients (34%), in the azithromycin group.

Comparable results were seen in the doxycycline group.

Because of the low bacteriologic eradication rate observed in this study, it is recommended that this indication not be approved.

Pammi T. Bais,M.D.
Medical Officer, FDA

CONCURRENCE ONLY:
HFD-520/Director/MFanning 6/12/96
HFD-520/DeputyDir/LGavrilovich
HFD-520/TLMO/MAlbuerne 2/1/96 5/22/96

cc. Orig NDA 50-670/S-008
HFD-520/MO/PBais
HFD-520/Pharm/MAdeyemo
HFD-520/Chem/JTimper
HFD-520/Micro/PDionne
HFD-880/BIOPHARM/HSun
HFD-713/STAT/AChakvaraty
HFD-520/PM/FLeSane
HFD-520/PM/JCintron

JAN 3 1996

NDA. 50,670
SE1 (008)

SUBMISSION DATE: Dec. 12, 94

Azithromycin Capsule
SPONSOR: Pfizer Central Research.
Eastern Point Road
Groton, CT 06340

TYPE OF SUBMISSION: Supplemental NDA

REVIEWER: HE SUN, Ph.D.

CLINICAL PHARMACOLOGY BIOPHARMACEUTICS REVIEW

NDA 50,670

I. SYNOPSIS

Summaries of pharmacokinetic and biopharmaceutic characteristics of azithromycin, two published papers, and four study reports were submitted to support the addition of new efficacy claims for treatment of STD. Extending the duration of oral administration of azithromycin 2000 mg over a 3.5 hour interval compared to administration as a 2000 mg all at once resulted in lower and later C_{max} but the same AUC (Study #066-047). The median concentration of azithromycin found in cervical mucus was, even on day 14-16, significantly greater ($p< 0.0002$) than the plasma concentration on day 2, well above the MIC_{90} found in other studies (Study AZM-NY-92-012). Study #066-124 is a efficacy study of 2 gm for *N. gonorrhoeae*. Results show that high serum concentrations of azithromycin (mean 1.40 mcg/ml; N=27) were observed 2 hours following a single 2 gm oral dose of the drug. All other studies submitted herein had been reviewed and accepted in previous reviews (NDA 50,670; NDA 50,710; NDA 50,711 and IND and support the new dose size.

II. RECOMMENDATION

Studies #066-047, #066-124, and AZM-NY-92-012 of NDA 50,670 are acceptable for meeting the requirements of 21 CFR 320.21 and the Clinical Pharmacology labeling requirements under 21 CFR 201.57. Overall, the applicant's conclusions about these studies are supported by the results provided. Please convey specific comments to the sponsor.

TABLE OF CONTENTS:

III. BACKGROUND

Five azithromycin oral formulations were submitted by the sponsor to date: The oral capsule (NDA 50,670, approved on Nov. 1, 1991); the 1 gram single dose Packet (NDA 50,693, approved on Sept. 28, 1994), the pediatric suspension formulation (NDA 50, 711), the IV formulation (IND and a tablet formulation (NDA 50,710). The present Supplemental New Drug Application is intended to support the addition of new efficacy claims to the azithromycin product labeling for treatment of STD (sexually transmitted disease). The doses to be employed for the treatment of these indications involve either a single 1 gram or 2 gram dose (using either 1 gram single dose packet, capsules or tablets). The currently approved labeling for azithromycin provides for the administration of a maximal single daily dose of 1 gram. In the treatment of gonorrhea, a 2 gram single dose is being proposed.

Information relevant to the pharmacokinetics, bioequivalence, and tissue distribution of azithromycin is compiled in the present NDA. The absence of an effect of food on the bioavailability of the 1 gram packet and tablet dosage forms of azithromycin was reviewed (NDA 50,670 and NDA 50,710, Dr. Sun). Study #066-056 was reviewed in IND report (Dr. Sun's review). All other studies presented in this section have appeared in previous NDA submissions and accepted (See Dr. Sun's reviews). Therefore, only three new studies will be reviewed herein.

IV. DRUG FORMULATION

No new dosage forms are presented for consideration in this NDA. It is anticipated that the 1 gram packet, 250 mg present commercial capsule, or the new 250 mg tablet formulation of azithromycin will be used.

V. SUMMARY OF STUDIES

Study 066-047: A pilot study to compare the gastrointestinal effects of oral azithromycin when given as a single dose and over a defined period of time in parallel groups of healthy volunteers.

To assess gastrointestinal symptomatology following azithromycin administration as either a single oral dose of 2 grams or as 2 grams given orally over a 3.5 hour period (250 mg every 30 minutes)

compared to a control group given placebo, a single-center, double-blind, randomized, placebo controlled, parallel study in healthy male volunteers was conducted. Blood samples were collected up to 240 hours after the start of dosing for determination of serum azithromycin concentrations. Visual analog scales rating gastrointestinal complaints were completed in conjunction with pharmacokinetic blood sampling.

Results show that extending the duration of oral administration of azithromycin 2000 mg over a 3.5 hour interval compared to administration all at once resulted in lower and later C_{max}. There were no differences noted between the two administration regimens with respect to total drug exposure (AUC), laboratory abnormalities, side effects or subject assessment of gastrointestinal effects.

Study AZM-NY-92-012. An open study of the kinetics and efficacy of azithromycin given as a single dose in the treatment of Chlamydia cervicitis in women.

This study was a single center, open study designed to determine the kinetics, efficacy and tolerability of a single oral 1.0 g dose of azithromycin in the treatment of women with Chlamydia cervicitis. The efficacy variables were signs and symptoms of cervicitis and frequency of negative Chlamydia cultures. The kinetic variables were the concentration of azithromycin in mucus and plasma.

The median concentration of azithromycin found in cervical mucus was, even on day 14-16, significantly greater ($p< 0.0002$) than the plasma concentration on day 2, well above the MIC_{90} found in other studies, and did support the clinical and microbiological results found in this study.

Study 066-124: An open trial of azithromycin in patients with uncomplicated gonococcal urethritis/cervicitis.

This was an open, two-center study of the efficacy and safety of single 2 gram and 4 gram doses of azithromycin in the treatment of gonococcal urethritis and/or cervicitis. Patients with culture-confirmed gonococcal infection returned 1, 2, and 4 weeks after azithromycin treatment for clinical and bacteriological evaluation. The pharmacokinetic profiles of these azithromycin doses were assessed at 2 hours and 1, 2, and 4 weeks after treatment.

High serum concentrations of azithromycin (mean 1.40 mcg/ml; N=27) were observed 2 hours following a single 2 gm oral dose of the drug. The concentrations were greater than those usually observed two hours following single 500 mg doses (0.35 mcg/ml; Studies 066-006, 066-025, 066-042). One week after the dose, drug was detected in serum and urine from all patients (N=26). After four weeks drug could not be detected in serum from any of the 22 patients examined and was detectable in urine from less than half of these patients. Side effects involved the gastrointestinal tract and included vomiting, abdominal pain, nausea, and diarrhea. All gastrointestinal side effects began and resolved on the day of dosing. Due to the side effect profile of patients dosed with 2 gm azithromycin, even though side effects were all assessed to be mild or moderate in severity, it was decided not to proceed with the 4 gm dosing segment of the protocol.

VI. SPECIFIC COMMENTS

1. The sponsor state that three formulations, the capsule, the tablet and the 1 gram packet, will be used. In review of the past submissions, as demonstrated at lower dose size, these formulations are bioequivalent under fasting conditions, and the food effect on capsule is different than that on tablet and 1 gram packet. Therefore, in the revised drug label which may include the new indication and recommend higher dose size, the sponsor should provide instructions for using the capsule formulation (at this dose size) regarding food intake.

2. The results of study AZM-NY-92-012 is supportive to the indication. The median concentration of azithromycin found in cervical mucus was, even on day 14-16, significantly greater ($p < 0.0002$) than the plasma concentration on day 2, well above the MIC_{90} found in other studies.

1/3/95

He Sun, Ph.D.
Division of Pharmaceutical Evaluation III

RD/FT Initialed by Frank Pelsor, Pharm. D.

cc: NDA 50,670, HFD-520 (Clinical, ~~LeSane~~ Cintron), HFD-880 (Fleischer, Pelsor, Sun), HFD-860 (Malinowski), Chron, Drug, HFD-19(FOI), HFD-340 (Viswanathan).

APPENDIXES

APPENDIX I.

TITLE A pilot study to compare gastrointestinal effects of oral azithromycin when given as a singles dose and over a defined period of time to parallel groups of healthy volunteers.

STUDY NO. 066-047

INVESTIGATOR & LOCATION

PURPOSE OF STUDY

The purpose of this study was to assess gastrointestinal symptomatology following azithromycin administration as either a single oral dose of 2 grams or as 2 grams given orally over a 3.5 hour period (250 mg every 30 minutes) compared to a control group given placebo.

FORMULATION

Azithromycin, FID# YY-89-054, 250mg capsules.

STUDY DESIGN AND PROCEDURES

This was a single-center, double-blind, randomized, placebo controlled, parallel study in healthy male volunteers. All subjects received a combination of azithromycin and placebo capsules. Eight capsules were administered at time 0 followed by one capsule every 30 minutes for 3.5 hours. Subjects were fasted for 12 hours prior to and for 4.5 hours following the start of dosing. Blood samples were collected immediately prior to (0 time) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16, 24, 48, 72, 96, 144, 192 and 240 hours after the start of dosing for determination of serum azithromycin concentrations. Samples from the 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16 and 24 hour times were also used for determining serum motilin concentrations. Visual analog scales rating gastrointestinal complaints were completed in conjunction with pharmacokinetic blood sampling.

a. Evaluation Groups

	Group 1	Group 2	Placebo
Entered study	15	14	16
Completed study	15	14	16
Assessed for pharmacokinetics;	15	14	0
Assessed for side effects	15	14	16
Assessed for laboratory tests	15	14	16

Group 1 received 2000 mg azithromycin all at once. Group 2 received 2000 mg azithromycin as 250 mg every 30 minutes for 3.5 hours.

b. Subjects

Forty-five healthy male volunteers entered and completed the study. Subjects ranged in age from 19 to 44 years (mean 28.5 years) and in weight from 60.1 to 86.2 kg (mean 75.7 kg). Forty subjects were white, four were black and 1 was Latin American. –

ASSAY

HPLC with electrochemical detection

Specificity:	Satisfactory.	Chromatogram submitted.
Sensitivity:	Satisfactory.	0.00966 ug/ml.
Accuracy:	Satisfactory.	errors < 7.8% except for 0.00966 ug/ml which is -13.1%
Linearity:	Satisfactory.	0.00966 - 0.466 ug/ml, r = 0.99957
Precision(intra):	Satisfactory.	CV=2.0% - 9.0%.
Precision(inter):	Satisfactory.	CV=2.4% - 6.0%.

DATA ANALYSIS

$AUC_{0\text{-}inf}$, C_{max}, T_{max} were calculated. Motilin concentration-time curves were plotted. Visual analog scale scores were plotted and summarized.

RESULTS

1. Pharmacokinetics - means (standard deviations)

	Group 1	Group 2
AUC_{inf} (ug*hr/ml)	21.7 (6.1)	21.3 (6.0)
C_{max} (ug/ml)	1.69 (0.53)	1.13 (0.28)
T_{max} (hr)	1.3 (0.6)	4.4 (1.4)

Serum concentration-time profile following oral administration of a single 2 gram dose and eight 250 mg doses q 0.5 hours are shown in Figure 1 and 2. Mean data are platted in Figure 3.

2. Side Effect scores

	Group 1	Group 2	Placebo
Treatment-related side effects	8/15 (0)	8/14 (0)	1/16 (0)
Treatment-related laboratory test abnormalities	2/15 (0)	1/14 (0)	1/16 (0)

3. Pharmacodynamics

Graphs of serum motilin concentrations over time showed no apparent differences between any of the three treatment groups (Figure 4). Visual analog scale scores for gastrointestinal complaints

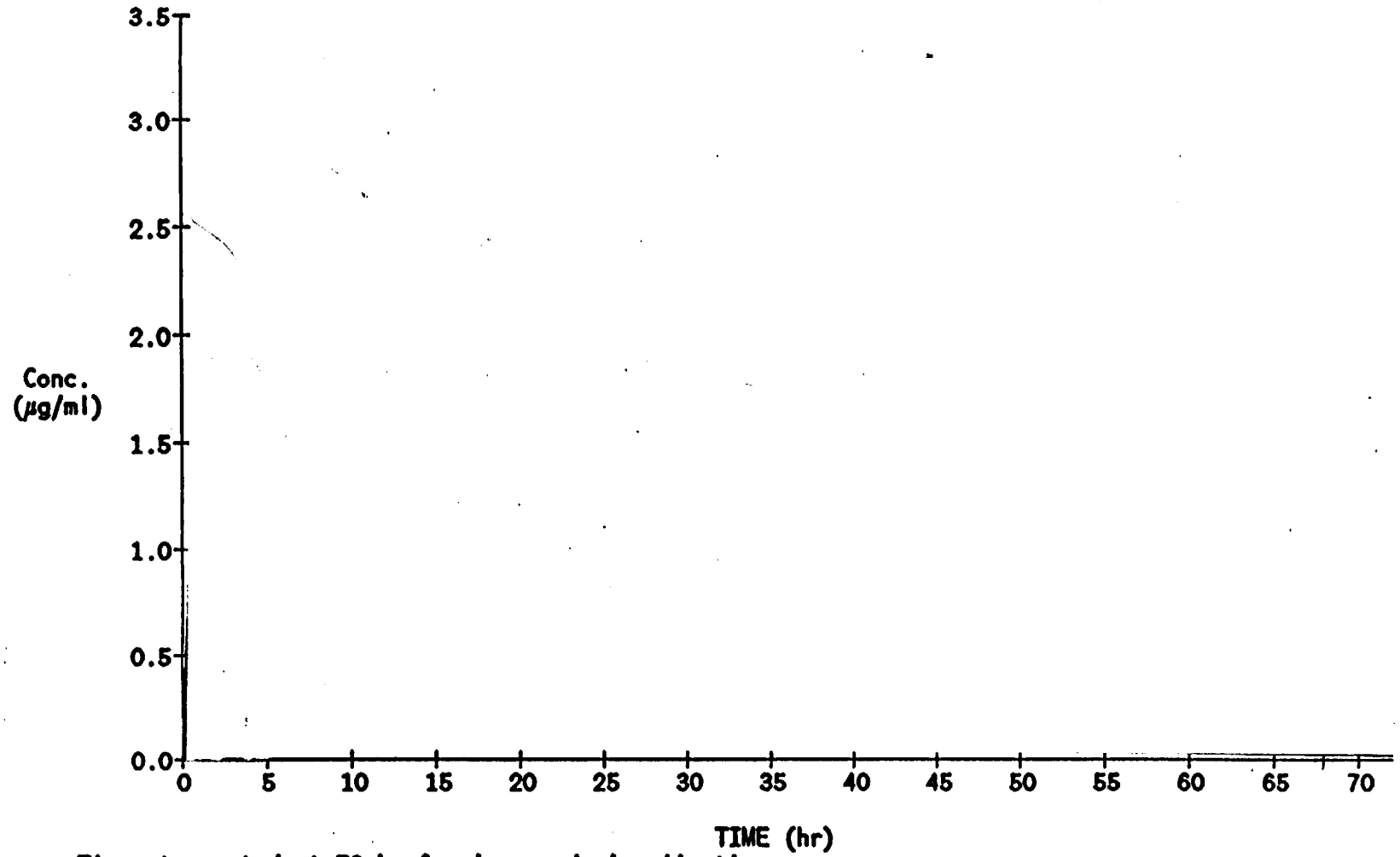
indicated that subjects receiving azithromycin experienced abdominal pain, nausea, butterflies, urgency to defecate, abdominal cramping and burping/belching slightly more often than placebo-treated subjects (Figure 5). There were no consistent differences between the two azithromycin groups.

4. Conclusions

Total drug exposure as assessed by AUC was similar in both azithromycin treated groups. C_{max} was slightly lower and occurred later following the extended administration regimen. Visual analog scores indicated that the gastrointestinal effects of abdominal pain, nausea, butterflies, urgency to defecate, abdominal cramping and burping/belching were more prevalent in the azithromycin treated subjects. However, the gastrointestinal effects following oral administration of azithromycin 2000 mg over an extended 3.5 hour duration did not differ from those observed following azithromycin 2000 mg administered as a single-dose.

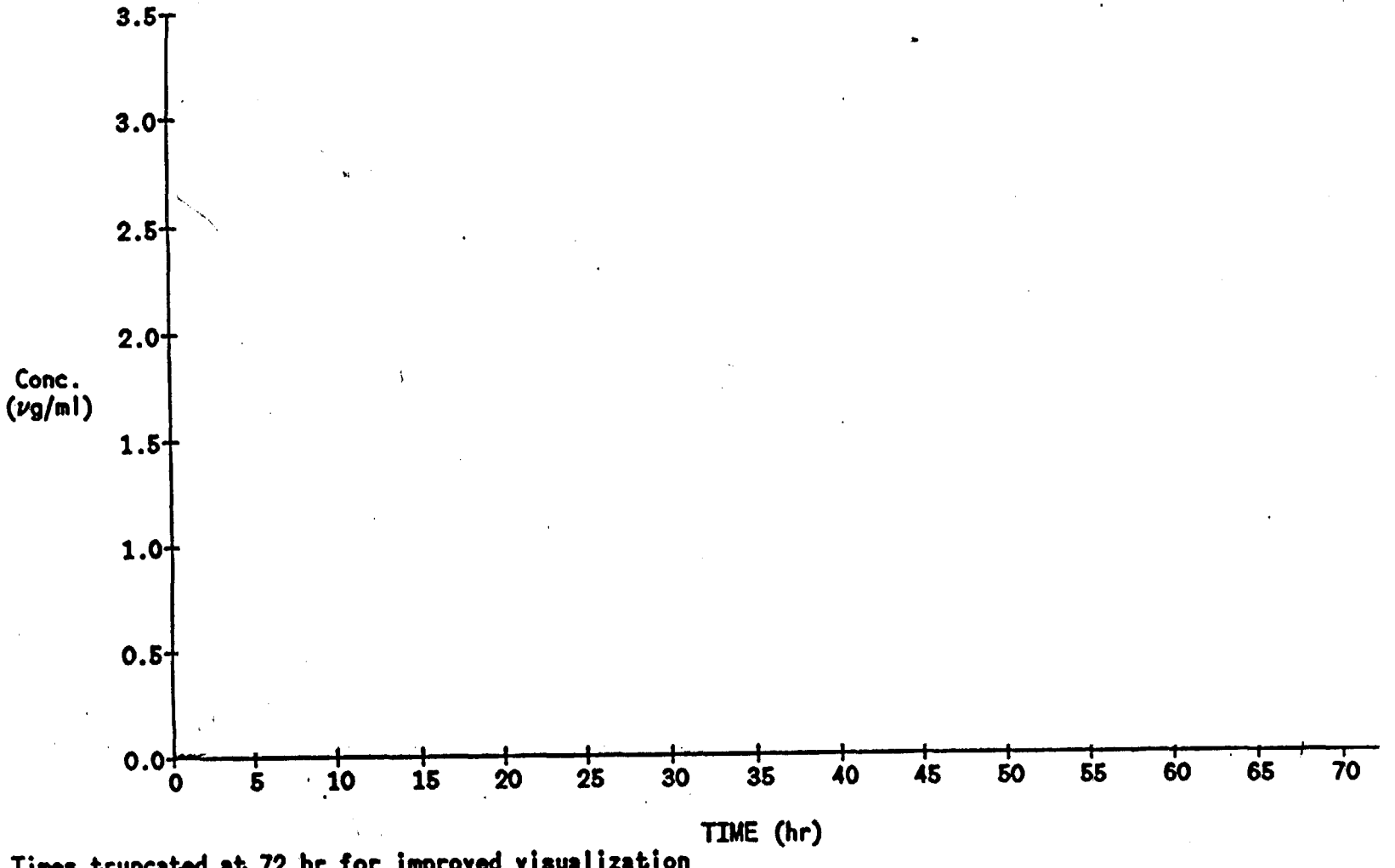
No subject was discontinued from the study.

Figure 1. Serum Concentrations of Azithromycin Following Oral Administration of a Single 2 gram Dose to 15 Healthy Volunteers (Clinical Study #066-047-54C, Dr. Levy)



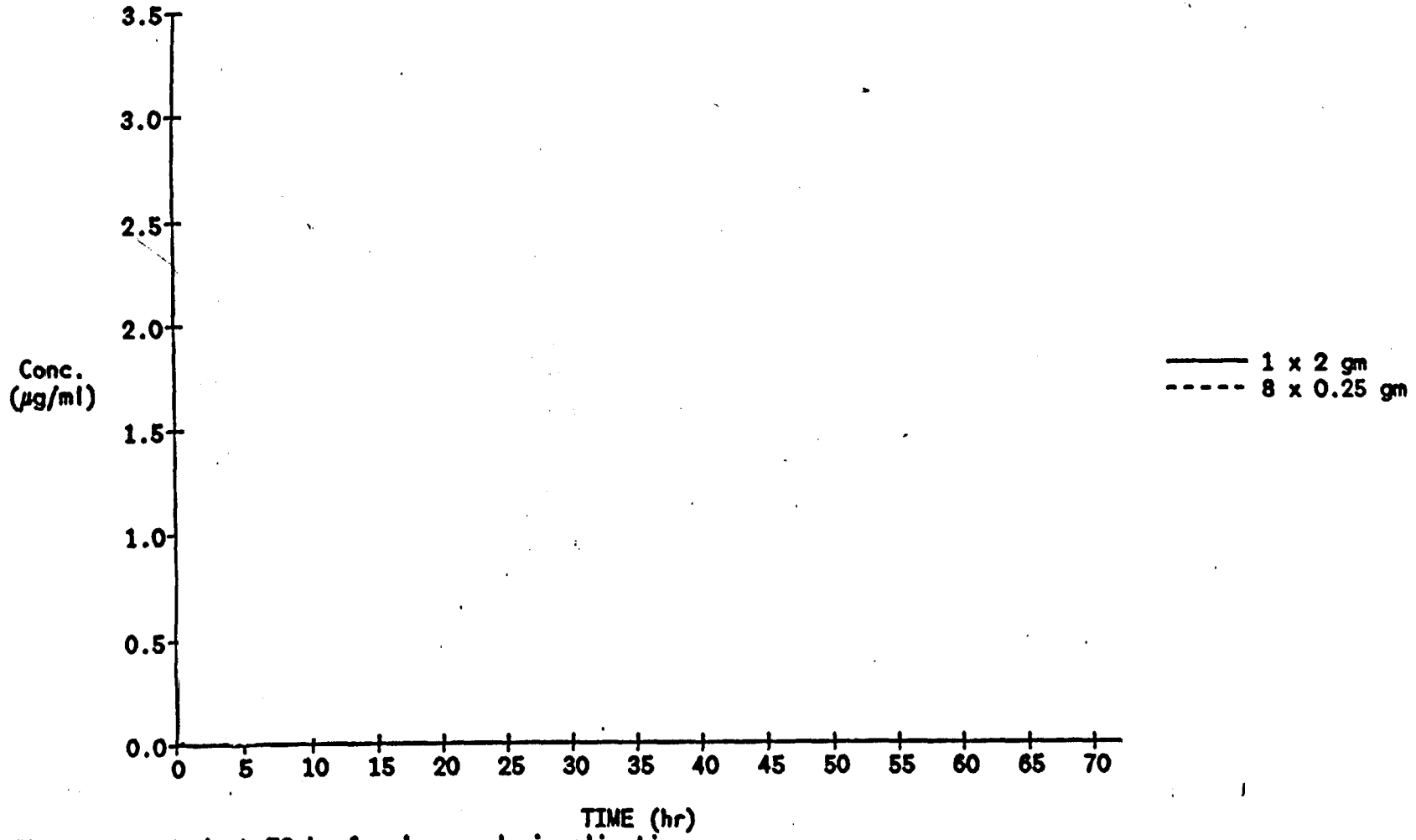
Times truncated at 72 hr for improved visualization.

Figure 2: Serum Concentrations of Azithromycin Following Oral Administration of Eight 250 mg Doses, q. 0.5 h, to 14 Healthy Volunteers (Clinical Study #066-047-54C, Dr. Levy)



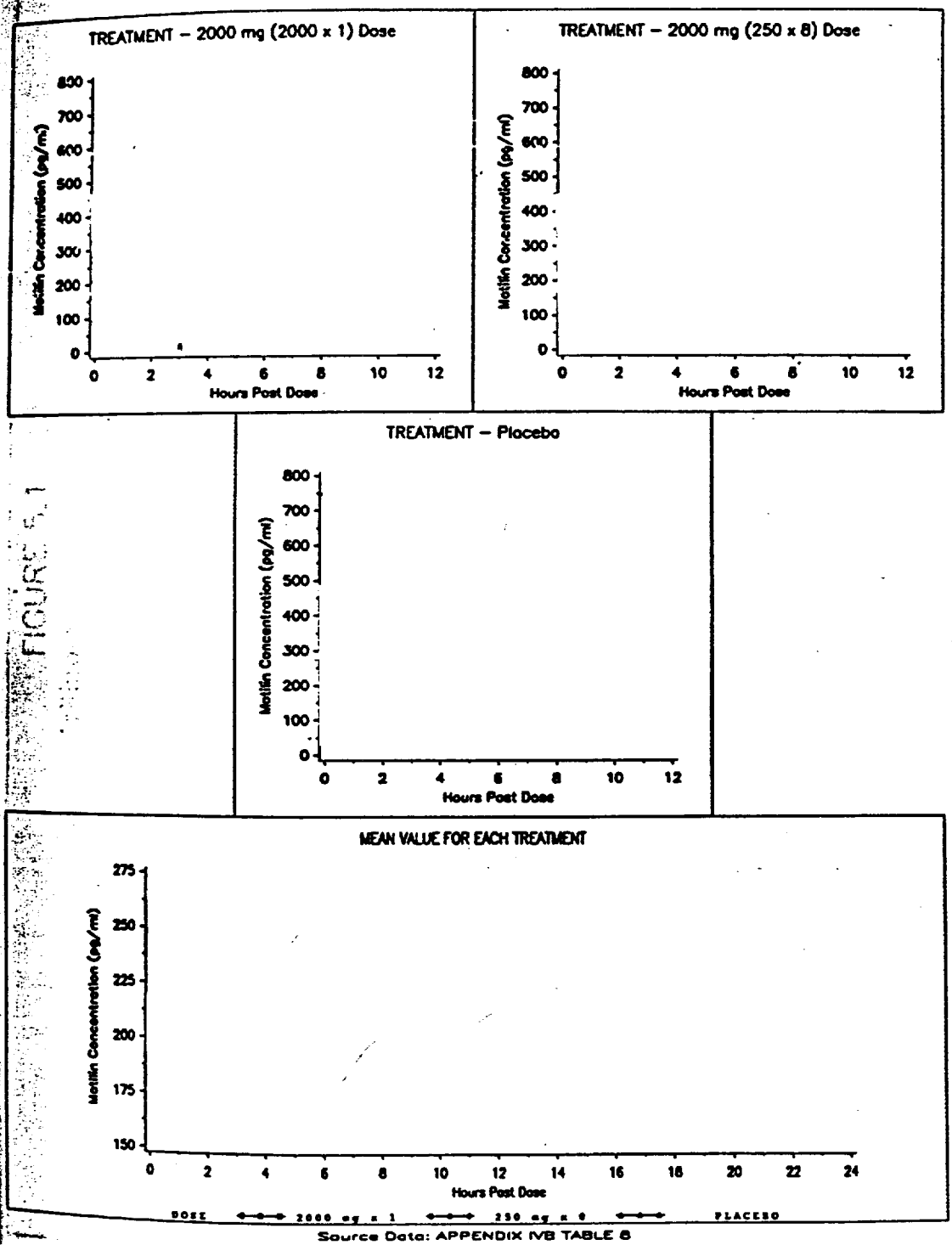
Times truncated at 72 hr for improved visualization

Figure 3. Mean Serum Concentrations of Azithromycin Following Oral Administration of a Single 2 gram Dose or Eight 250 mg Doses, q. 0.5h, to Healthy Volunteers (Clinical Study #066-047-54C, Dr. Levy)



Times truncated at 72 hr for improved visualization

FIGURE 4
Azithromycin Protocol 047
Motiiin Concentrations vs Time



Source Data: APPENDIX IVB TABLE 8
Source Data: APPENDIX IIIB TABLE 2

FIGURE 5.1
Azithromycin Protocol 047
Percentage of Nonzero Visual Analog Scale Scores (Abdominal Pain) vs Time

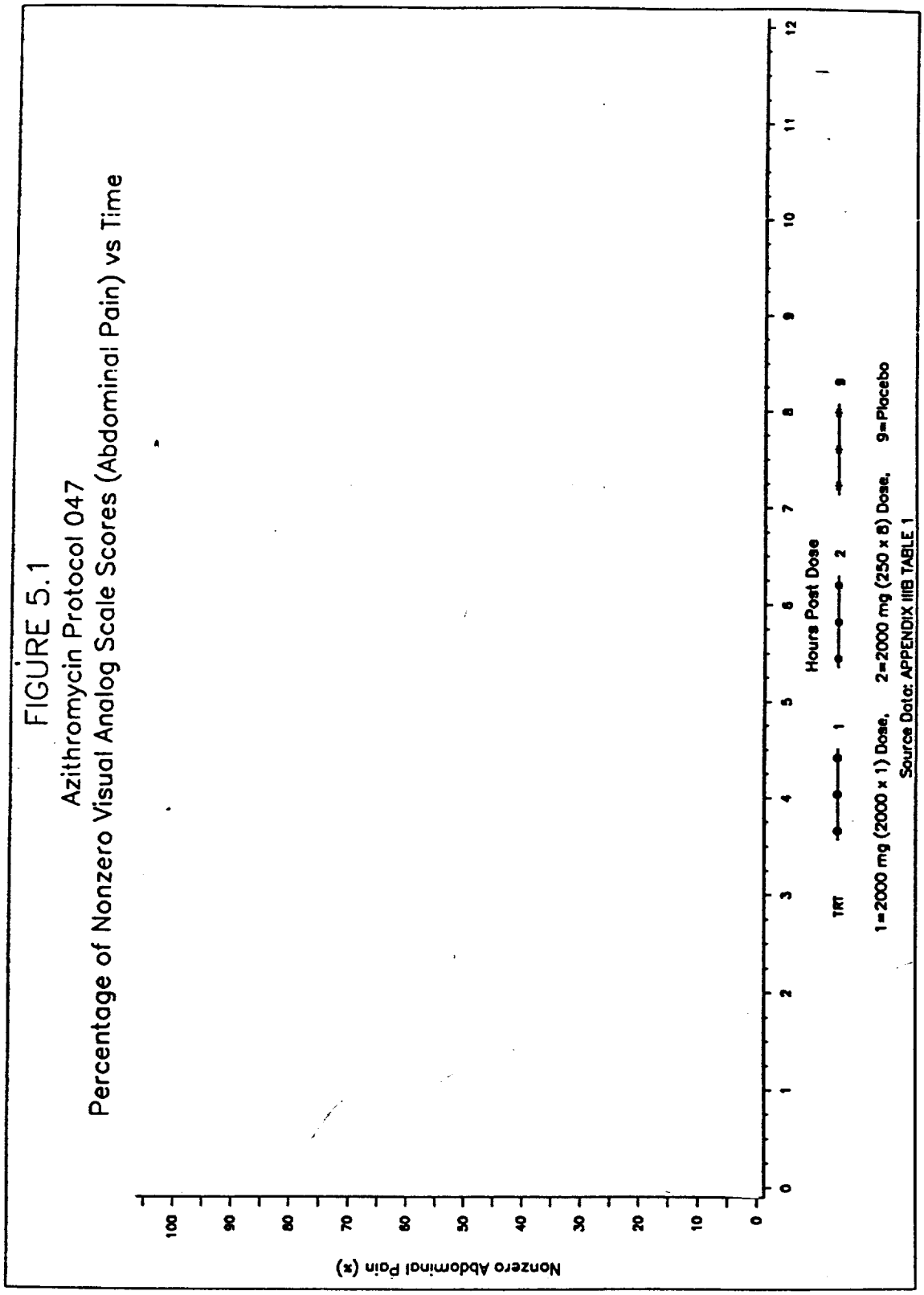


FIGURE 5.2
Azithromycin Protocol 047
Percentage of Nonzero Visual Analog Scale Scores (Nausea) vs Time

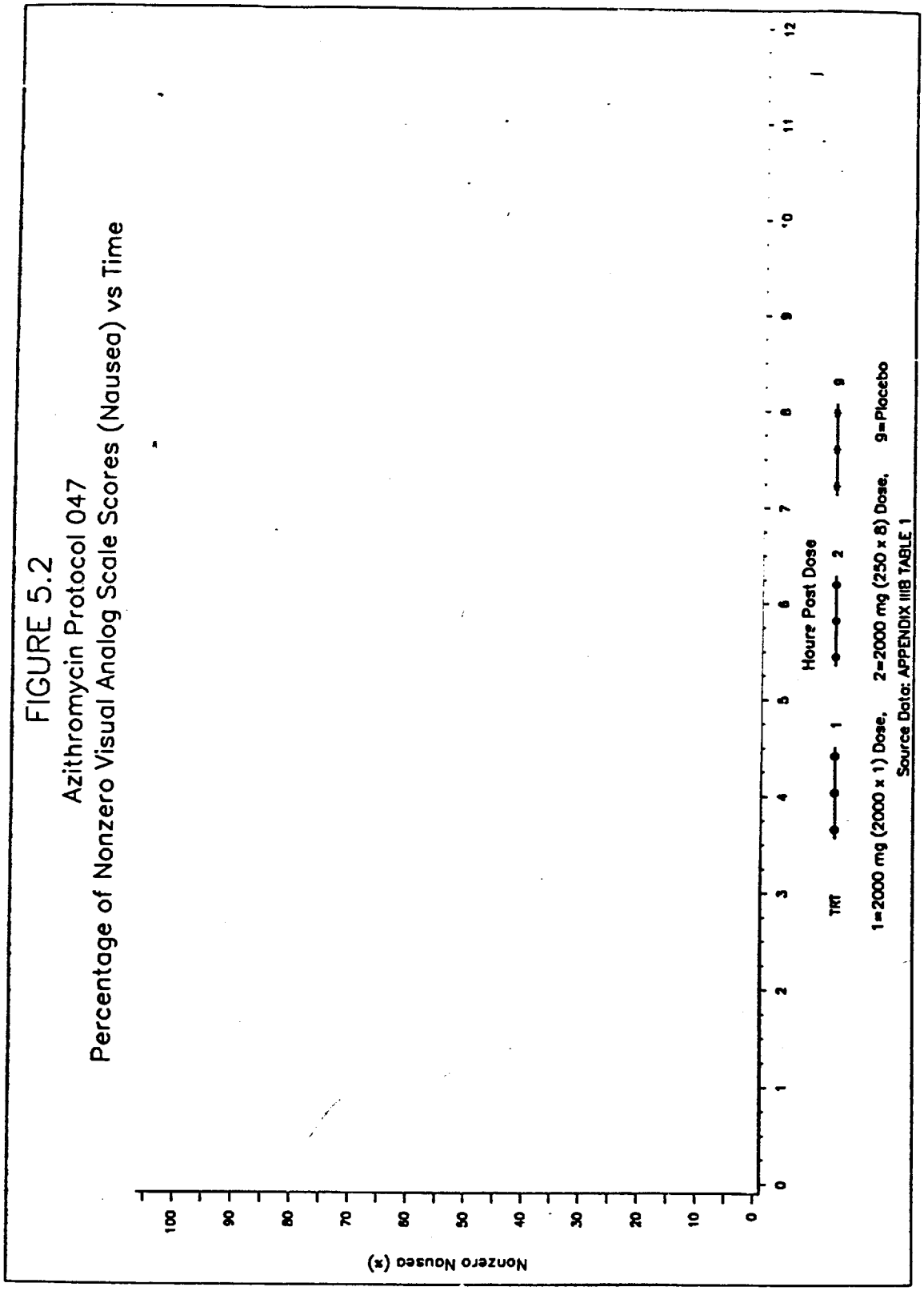
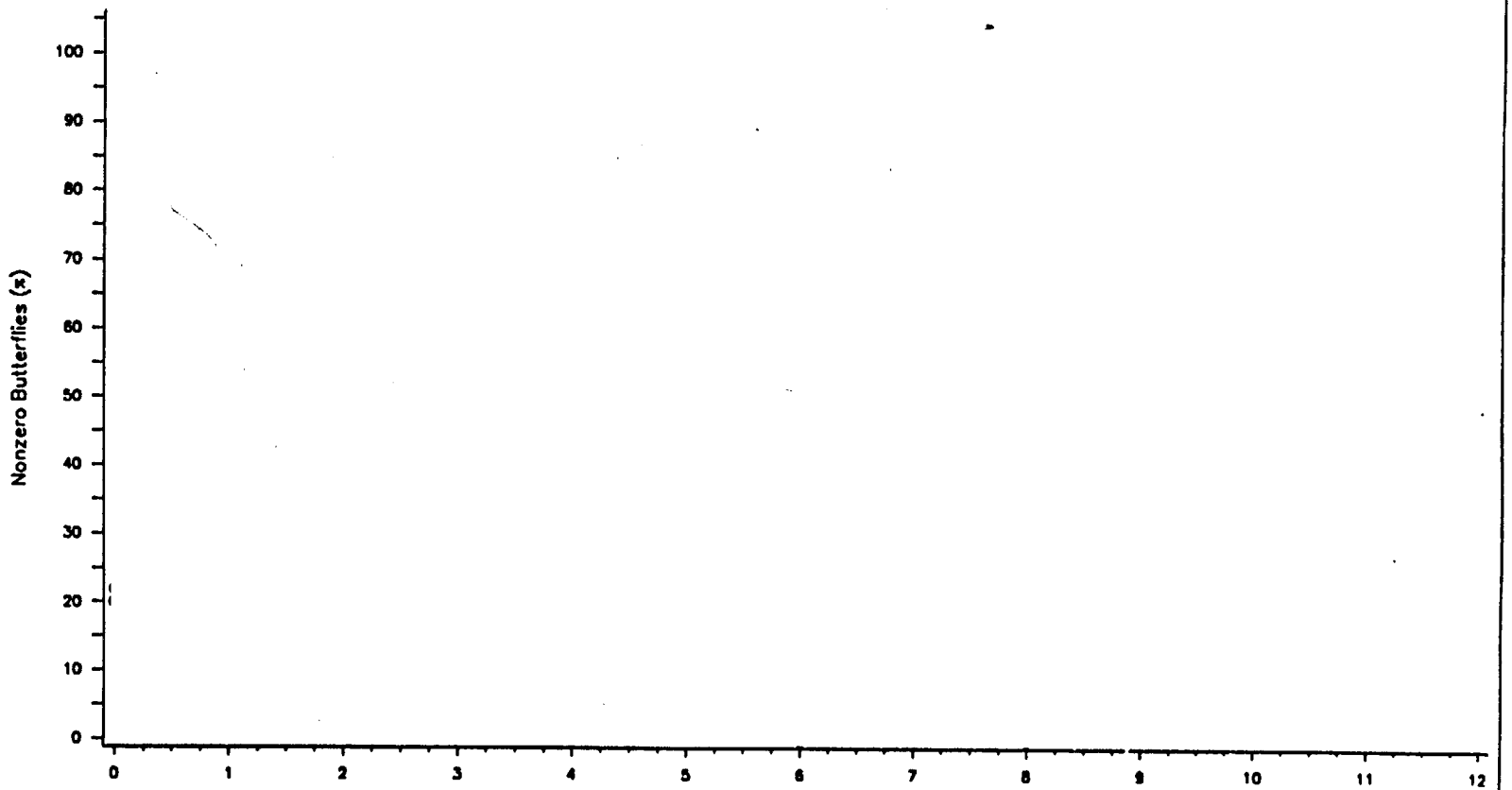


FIGURE 5.3

Azithromycin Protocol 047

Percentage of Nonzero Visual Analog Scale Scores (Butterflies) vs Time



1=2000 mg (2000 x 1) Dose, 2=2000 mg (250 x 8) Dose, 9=Placebo

Source Data: APPENDIX IIIB TABLE 1

FIGURE 5.4
Azithromycin Protocol 047
Percentage of Nonzero Visual Analog Scale Scores (Urgency to Defecate) vs Time

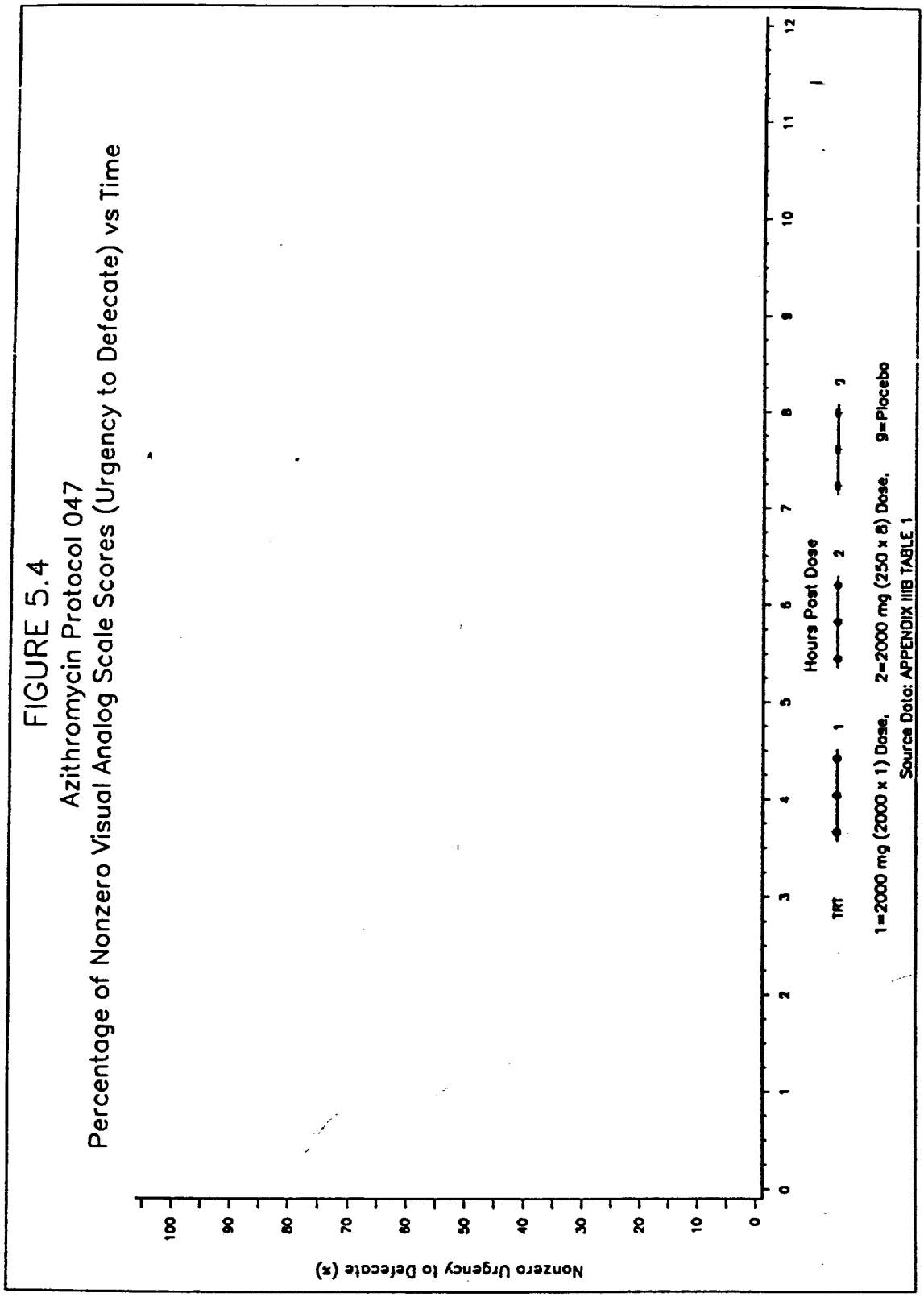
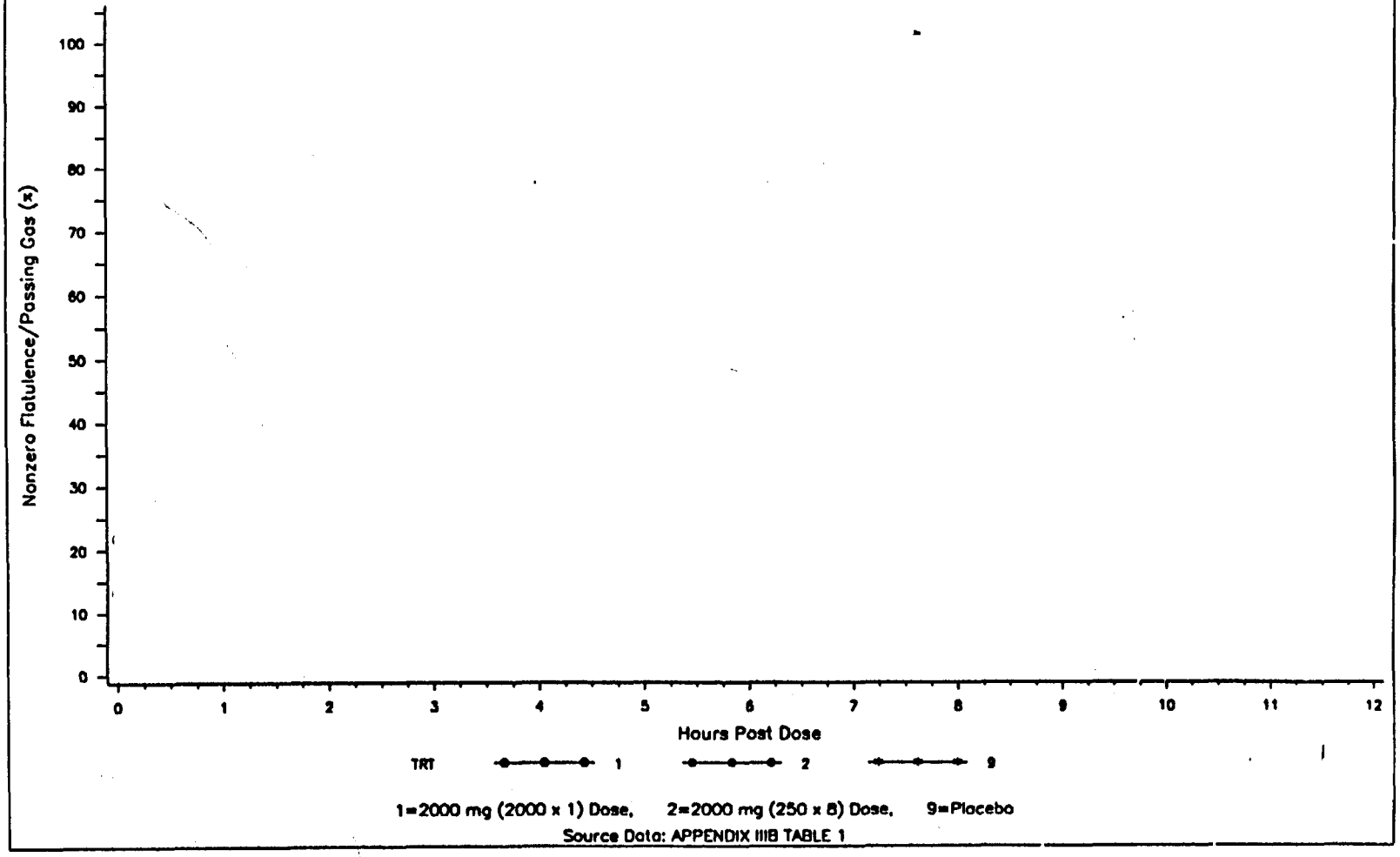


FIGURE 5.5

Azithromycin Protocol 047

Percentage of Nonzero Visual Analog Scale Scores (Flatulence/Passing Gas) vs Time



1=2000 mg (2000 x 1) Dose, 2=2000 mg (250 x 8) Dose, 9=Placebo

Source Data: APPENDIX IIIB TABLE 1

FIGURE 5.6
Azithromycin Protocol 047
Percentage of Nonzero Visual Analog Scale Scores (Regurgitation) vs Time

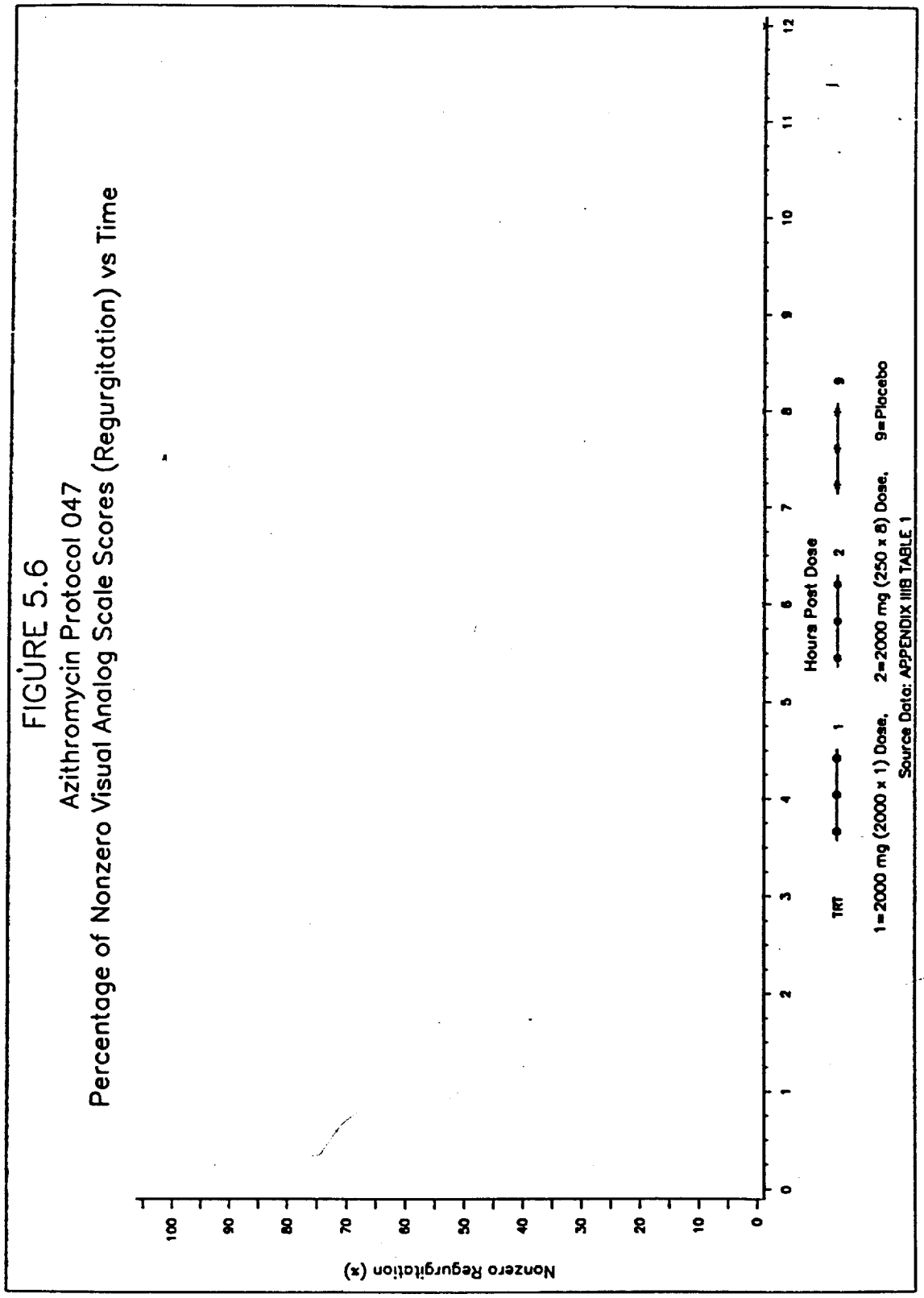
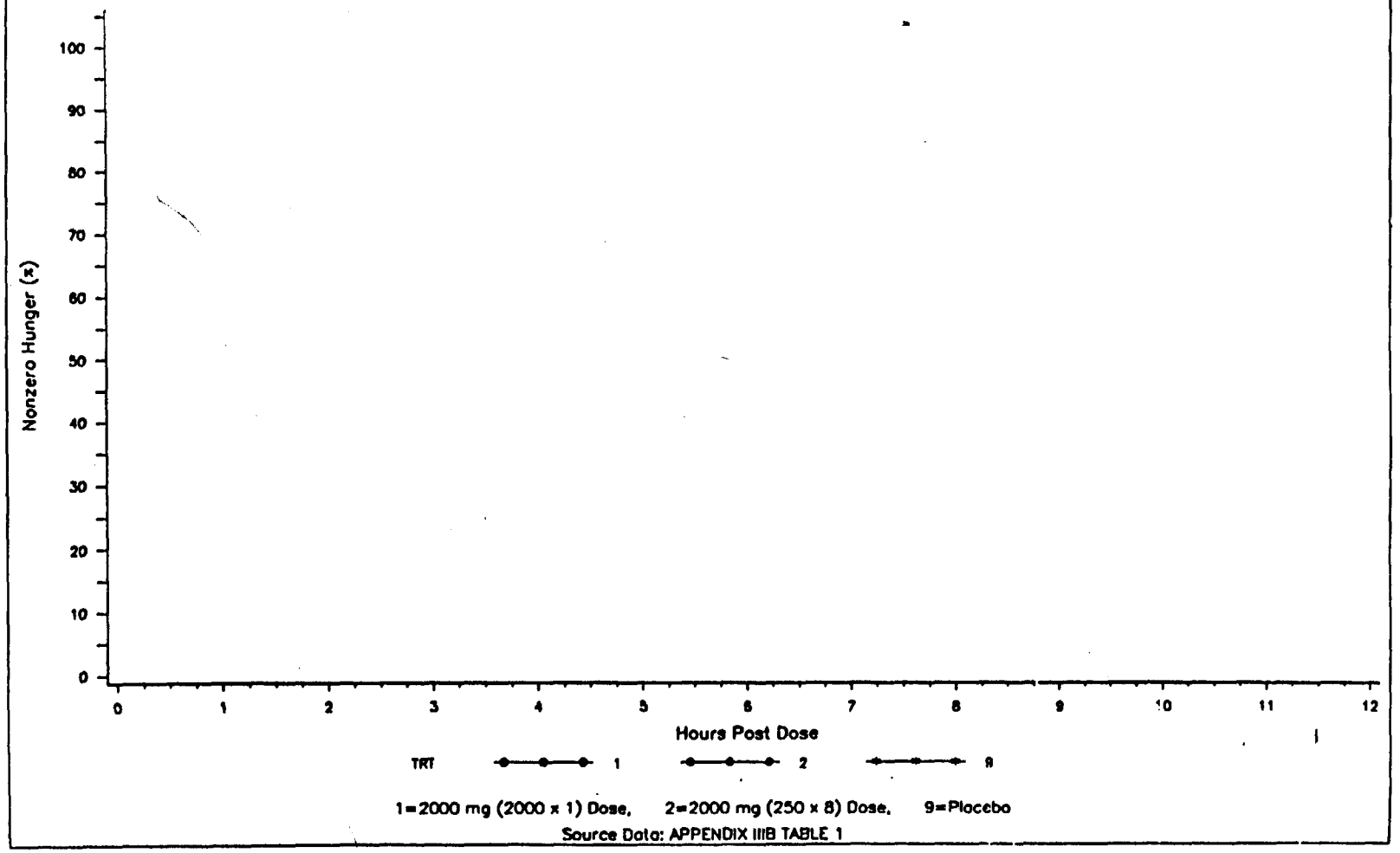


FIGURE 5.7

Azithromycin Protocol 047

Percentage of Nonzero Visual Analog Scale Scores (Hunger) vs Time



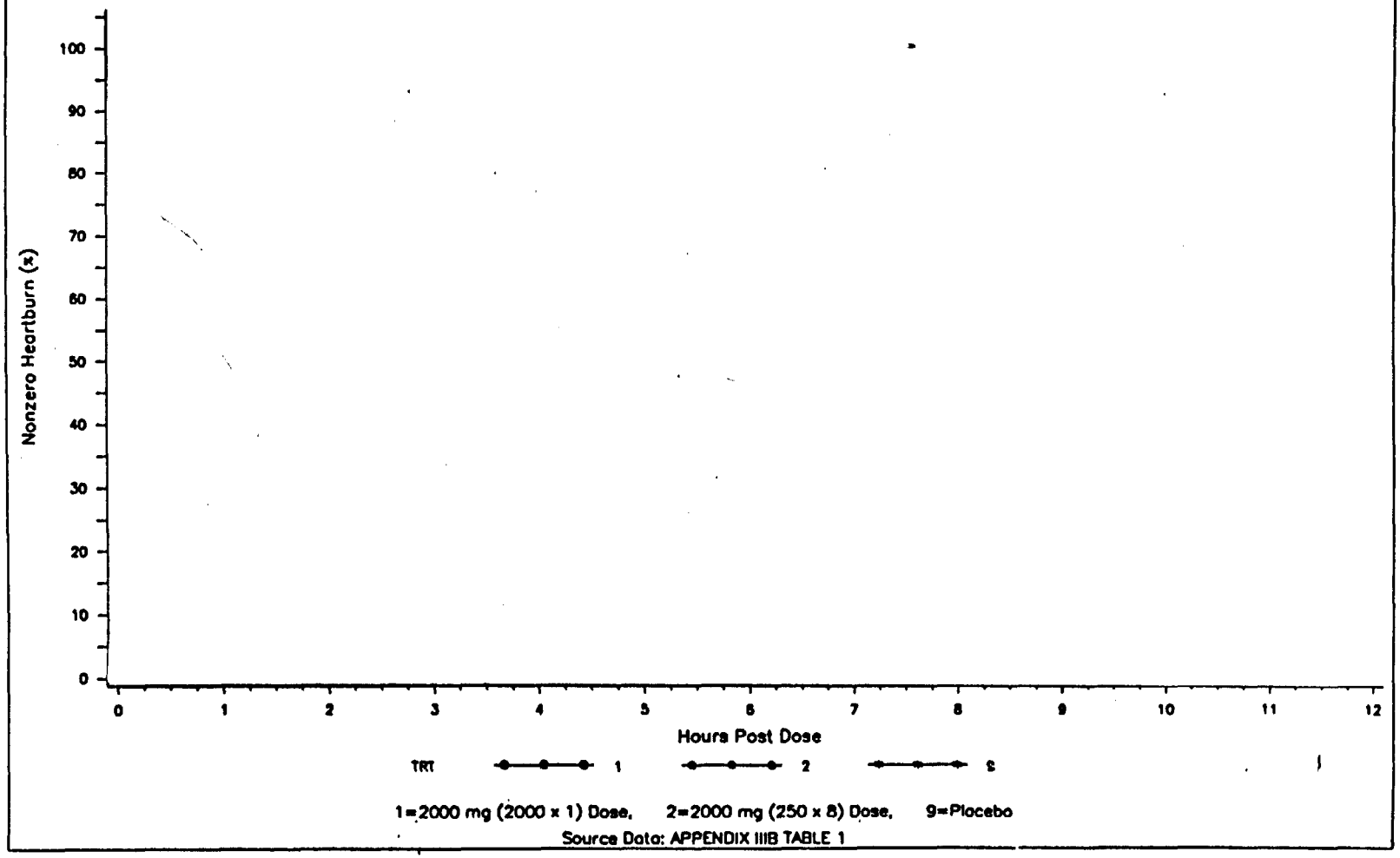
1=2000 mg (2000 x 1) Dose, 2=2000 mg (250 x 8) Dose, 9=Placebo

Source Data: APPENDIX IIIB TABLE 1

FIGURE 5.8

Azithromycin Protocol 047

Percentage of Nonzero Visual Analog Scale Scores (Heartburn) vs Time

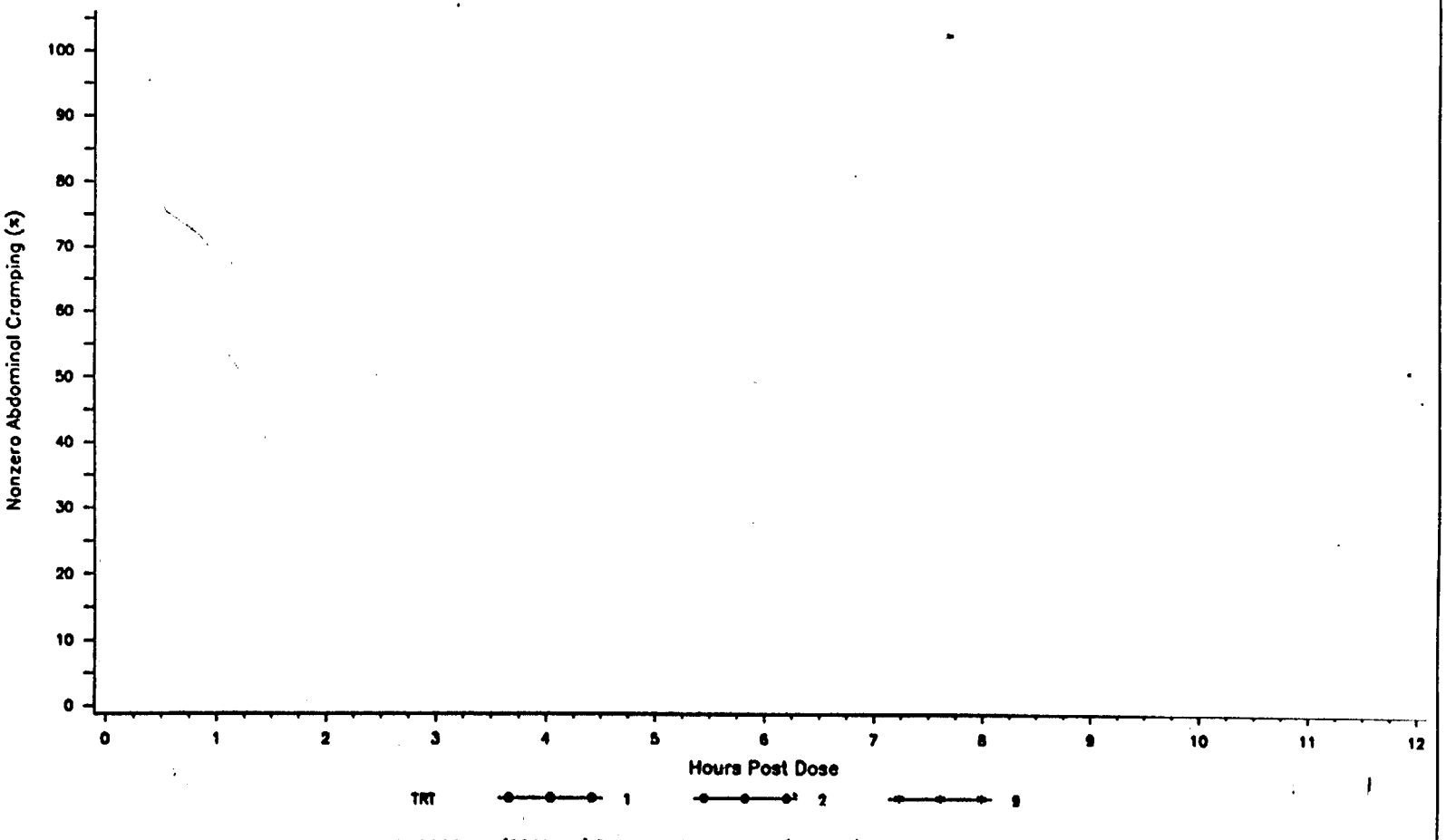


Source Data: APPENDIX IIIB TABLE 1

FIGURE 5.9

Azithromycin Protocol 047

Percentage of Nonzero Visual Analog Scale Scores (Abdominal Cramping) vs Time



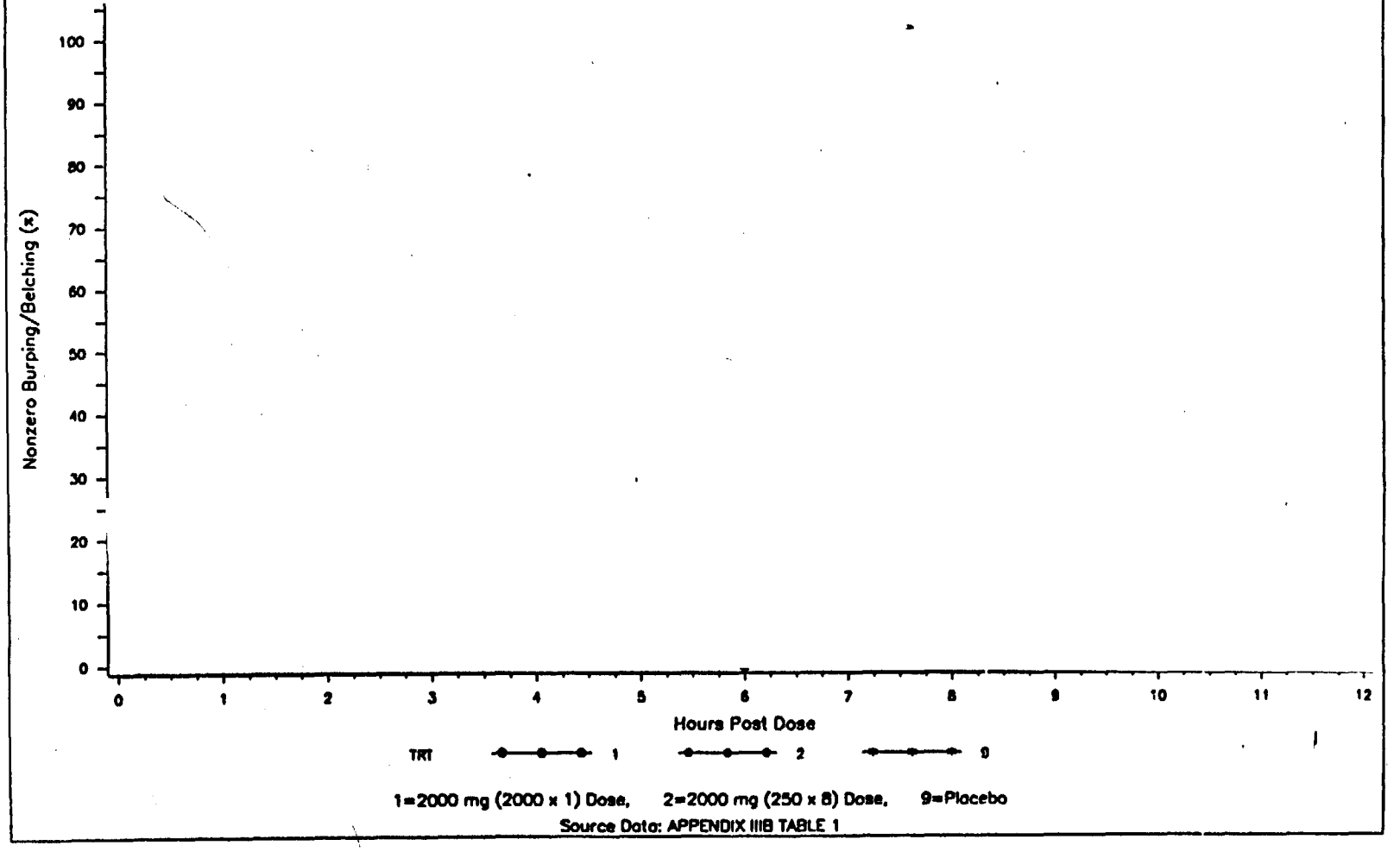
1=2000 mg (2000 x 1) Dose, 2=2000 mg (250 x 8) Dose, 9=Placebo

Source Data: APPENDIX IIIB TABLE 1

FIGURE 5.10

Azithromycin Protocol 047

Percentage of Nonzero Visual Analog Scale Scores (Burping/Belching) vs Time



Source Data: APPENDIX IIIB TABLE 1

APPENDIX II.

TITLE An open study of the kinetics and efficacy of azithromycin given as a single dose in the treatment of Chlamydia cervicitis in women.

STUDY NO. AZM-NY-92-012

INVESTIGATOR & LOCATION

PURPOSE OF STUDY

The purpose of this study was to determine the kinetics of a single oral 1 gram dose of azithromycin in cervical mucus and plasma, and to evaluate the clinical and microbiological efficacy and tolerance of a single oral 1 gram dose of azithromycin in the treatment of women with Chlamydia cervicitis.

FORMULATION

Commercial Capsules

STUDY DESIGN AND PROCEDURES

This study was a single center, open, non-comparative study in outpatients designed to determine the kinetics, efficacy and tolerability of a single oral 1.0 g dose of azithromycin in the treatment of women with Chlamydia cervicitis. Twenty women (mean age was 21 years (range 18-27)) with Chlamydia trachomatis, isolated within 1 week prior to enrollment in the study, were included. The patients were evaluated before treatment with azithromycin (day 1), day 2, 7-9, and 14-16, respectively. At each visit, blood and cervical mucus samples were obtained for determination of azithromycin concentration, and on days 1, 7-9, and 14-16, a Chlamydia culture was carried out. The clinical and microbiological efficacy was evaluated on day 7-9 and 14-16, respectively. On days 2, 7-9. and 14-16, an evaluation of tolerability was made.

ASSAY

HPLC with electrochemical detection

Specificity:	Satisfactory.	Chromatogram submitted.
Sensitivity:	Satisfactory.	0.02 for plasma and 0.01 for cervical mucus.
Accuracy:	Satisfactory.	errors < -7.6% for plasma and <-11.4% for cervical mucus at the lowest detection limits.
Linearity:	Satisfactory.	0.02-0.5 ug/ml for plasma and 0.01-0.5 ug/ml for cervical mucus.

Precision(intra): Satisfactory. CV=5% at 0.04 ug/ml and 2.3% at 0.4 ug/ml for plasma.
CV=4.4% at 0.04 ug/ml and 1.5% at 0.4 ug/ml for cervical mucus.
Precision(inter): Satisfactory. CV<5.0% for plasma and <-3.1% for cervical mucus.

DATA ANALYSIS

The efficacy variables were signs and symptoms of cervicitis and frequency of negative Chlamydia cultures. The kinetic variables were the concentration of azithromycin in mucus and plasma.

RESULTS

1. Pharmacokinetics - means (range).

	DAY 2	DAY 7-9	DAY 14-16
Mucus ug/ml	2.67[1] (0.57-9.51)	1.285[1,2] (0.39-5.65)	0.433[1,3] (0.07-1.06)
Plasma ug/ml	0.077 (0.024-0.126)	BLQ	BLQ

[1] $p < 0.0002$ compared to plasma on day 2.
[2] $p = 0.0013$ compared to mucus on day 2.
[3] $p = 0.002$ compared to mucus on day 7-9.

BLQ = Below Limit of Quantification (< 0.02 ug/ml).

3. Conclusions

The plasma concentration of azithromycin which was above the limit of quantification, was below MIC_{90} for Chlamydia in all samples. The median concentration of azithromycin found in cervical mucus was, even on day 14-16, significantly greater ($p < 0.0002$) than the plasma concentration on day 2, well above the MIC_{90} found in other studies, and did support the clinical and microbiological results found in this study.

APPENDIX III.

TITLE	An open trial of azithromycin in patients with uncomplicated gonococcal urethritis/cervicitis
STUDY NO.	#066-124
INVESTIGATOR &LOCATION	

PURPOSE OF STUDY

The purpose of this study was to assess the efficacy and safety of single oral doses of 2 grams and 4 grams of azithromycin in the treatment of gonococcal urethritis and/or cervicitis. In addition, the pharmacokinetic profile of these doses will be determined.

FORMULATION

Azithromycin, FID#YY-87-018, 250mg capsules

STUDY DESIGN AND PROCEDURES

This was an open two-center study of the efficacy and safety of single 2 gram and 4 gram doses of azithromycin in the treatment of gonococcal urethritis and/or cervicitis. The study was conducted in two phases, beginning with the 2 gram dose and progressing to the 4 gram dose after assessment of 2 gram dosing results. Patients with culture-confirmed gonococcal infection returned 1, 2, and 4 weeks after azithromycin treatment for clinical and bacteriological evaluation. The pharmacokinetic profiles of these azithromycin doses were to be assessed at 2 hours and 1, 2, and 4 weeks after treatment.

Patients statistics:

Azithromycin 2 gm[1] (FID #YY-87-018)	
Received treatment	27
Completed treatment	27
Discontinued treatment	0
Bacteriologically evaluable	
Week 1	21
Week 2	15
Clinically evaluable	
Week 1	21
Week 2	15
Evaluated for pharmacokinetics	27
Evaluated for safety	
Side effects	27
Laboratory tests	26

[1] No patients received 4 gm azithromycin due to the observations in 2 gram dose study.

ASSAY

HPLC with electrochemical detection.

Specificity: Satisfactory. Chromatogram submitted.
Sensitivity: Satisfactory. 0.01 ug/ml in serum and 0.2 ug/ml in urine.
Accuracy: Satisfactory. errors < 7.8%.
Linearity: Satisfactory. 0.01-1.0 ug/ml in serum and 0.2-100 ug/ml in urine, r = 0.99957.
Precision(intra): Satisfactory. CV=2.0% - 9.0%.
Precision(inter): Satisfactory. CV=2.4% - 6.0%.

DATA ANALYSIS

$AUC_{0\text{-inf}}$, C_{max}, T_{max} were calculated.

RESULTS

1. Pharmacokinetics - means (standard deviations)

	Serum (ug/ml)	Urine (ug/ml)
2 hours (N=27)	1.404 (0.743)	
Week 1 (N=26)	0.036 (0.018)	7.05 (5.42)
Week 2 (N=22)	0.005 (0.008)	1.82 (1.89)
Week 4 (N=22)		0.23 (0.40)

2. Side Effect scores

Treatment-related side effects	20/27
Treatment-related laboratory test abnormalities	4/26
Gastrointestinal side effects	20/27

3. Conclusions

High serum concentrations of azithromycin (mean 1.40 mcg/ml; N=27) were observed 2 hours following a single 2 gm oral dose of the drug. The concentrations were greater than those usually observed two hours following single 500 mg doses (0.35 mcg/ml; Studies 066-006, 066-025, 066-042). One week after the dose, drug was detected in serum and urine from all patients (N=26). After four weeks drug could not be detected in serum from any of the 22 patients examined and was detectable in urine from less than half of these patients.

Due to the side effect profile of patients dosed with 2 gm azithromycin, even though side effects were all assessed to be mild or moderate in severity, it was decided not to proceed with the 4 gm dosing segment of the protocol.

Statistical Review and Evaluation

NDA#:	50-670; SE1-008
Applicant:	Pfizer Central Research, Groton, CT 06340
Name of Drug:	Azithromycin
Documents Reviewed:	Volume 1 of 66
Indication:	Uncomplicated gonococcal urethritis and/or cervicitis Nongonococcal urethritis Chancroid
Type of Review:	Clinical/Statistical
Medical Input:	Dr. Pammi Bais, HFD-520

A. INTRODUCTION

This supplementary NDA has three indications.

a) Gonococcal urethritis and/or cervicitis (gonorrhea) -- Results from three U.S. trials (Protocols 066-130, 066-114 and 066-124) were submitted, two of them were comparative.
b) Nongonococcal urethritis -- Results from one U.S. comparative study (Protocol L-0196) were submitted.
c) Chancroid -- Results from three studies (Protocols 066-120, 066-328 and NY-90-007) were submitted, one of which (NY 90-007) was a foreign study.

Since all the protocols were for single dose therapies of Azithromycin in treatment of STDs, the statistical review will be limited to the following:

- Adequate representation of gender
- Adequate representation of each center in the studies
- Cure rates in excess of 95% for the treatment and comparator arms
- Cure rates in excess of 95% for each body site, if available
- Centerwise cure rates, if available.

The efficacy analyses will be based on the Medical Officer's database where available. The primary efficacy variables, are as determined by the Reviewing Medical Officer.

B. EFFICACY EVALUATION

Indication: Gonococcal urethritis and/or cervicitis (gonorrhea)

Gender Representation:
Table 1: Gender Summary

Protocol	Male	Female
066-130	229	129
066-114	49	---
066-124	27 (gender information not available)	

It is seen that there is an adequate representation of each gender in protocol 130. Protocol 114 was designed to enroll males only, and no gender information is available in protocol 124, which was a non-comparative open-label study.

Center Representation:
Center information was available in Protocol 066-130 only. It seems that there is adequate representation from each center (> 10 patients /arm). Center 757 enrolled 161 patients out of 484 (33%) in the Azithromycin arm and 79 out of 243 (32%) in the comparator arm.

Cure Rate Analysis:

Patients were seen at the end of Week 1 and for follow-up, at the end of Week 2.The cure rate summary for eradications in Week 1 on Protocol 130 is given in Table 2.

Table 2: Eradication summary at Week 1 (Protocol 130)

Organ	Azithromycin		Ceftriaxone	
	Male	Female	Male	Female
Urethra	223/226 (98.7%)	20/20 (100%)	107/109 (98.2%)	13/13 (100%)
Cervix	0	123/125 (98.4%)	0	57/59 (96.6%)
Rectum	4/5 (80%)	23/23 (100%)	3/3 (100%)	8/8 (100%)
Fharynx	7/8 (87.5%)	7/7 (100%)	5/5 (100%)	5/5 (100%)

It is seen that all sites, except rectum and pharynx for males on Azithromycin meet the 95% cure rate criteria.

The cure rate summary for eradications at the end of Week 2 on Protocol 130 is given in Table 3.

Table 3: Eradication summary at Week 2 (Protocol 130)

Organ	Azithromycin		Ceftriaxone	
	Male	Female	Male	Female
Urethra	99/99 (100%)	12/12 (100%)	37/41 (90.2%)	6/7 (85.7%)
Cervix	0	93/95 (97.9%)	0	31/33 (92.9%)
Rectum	1/1 (100%)	16/17 (94%)	2/2 (100%)	3/4 (75%)
Pharynx	5/5 (100%)	5/5 (100%)	2/3 (66.7%)	3/3 (100%)

It is seen that all sites on Azithromycin, except rectum for females meet 95% cure rate criteria. The comparator drug, Ceftriaxone, on the other hand, meets the 95% criteria only for rectum site on males and pharynx on females. The sample sizes are too small to draw any robust conclusion.

In Protocol 066-114, cure rates by location were not available for the Medical Officer database. For the sponsor's database, there is 100% eradication on both treatment arms for Week 1 and Week 2 visits. The clinical cure rates on Azithromycin are 81% and 83.3% for Weeks 1 and 2 as compared to 93.8% and 70% on Ceftriaxone respectively.

Protocol 066-124 was an open label, noncomparative study that was analyzed for safety only.

Indication: Chancroid

Protocols 066-120 and 066-328 will be discussed. Protocol NY-90-007 was a non US study, and will not be reviewed as a part of the statistical analysis.

Gender Representation:

On Protocol 066-120, only 7 out of 99 (7%) patients on Azithromycin and 7 out of 98 (7%) on Ceftriaxone were female. There were no female patients enrolled in Protocol 066-328.

Center Representation:

Center number 712 has 144 out of 197 (73.1%) of the total patients. According to the protocol, no centers should have enrolled more than 75 patients. According to the IDSA Guidelines, no center should contribute more than 50% of the patient population.

No centerwise information was available on Protocol 066-328.

Cure Rate Analysis:

The rate of ulcer healing, primary efficacy variable in Protocol 066-120, is summarized in Table 4.

Table 4: Ulcer Healing Summary (Protocol 066-120)

Days	Azithromycin			Ceftriaxone		
	Cure	Improve	Total	Cure	Improve	Total
Day 7	18 (100%)	0	18	14 (93.3%)	1 (6.7%)	15
Day 14	11 (100%)	0	11	8 (88.9%)	1 (11.1%)	9
Day 21	3 (100%)	0	3	3 (60%)	2 (40%)	5
Total	32 (100%)	0	32	25 (86.2%)	4 (13.8%)	29

It is seen that Azithromycin cures 100% of the ulcers from 7 day onwards. It seems to have a better cure profile than Ceftriaxone.

For Protocol 066-328, the bacteriologic and clinical outcomes are reported, but no ulcer healing information was analyzed. This protocol was an open label,

noncomparative study. The bacteriologic eradication summary is provided in Table 5.

Table 5: Bacteriologic Eradication Summary (Protocol 066-328)

Criteria	Day 3	Day 7	Day 14	Day 21
Eradication	4 (21.1%)	2 (10.5%)	0	0
Presumed Eradication	14 (73.7%)	17 (89.5%)	16 (84.2%)	5 (26.1%)
Not Evaluable	1 (5.3%)	0	3 (15.8%)	14 (73.7%)
Total	19	19	19	19

It is seen that none of the eradication rates meet the 95% cure rate criteria. Similar profile is seen in the clinical assessment, summarized in Table 6.

Table 6: Clinical Assessment Summary (Protocol 066-328)

Criteria	Day 3	Day 7	Day 14	Day 21
Cured	0	4 (21.1%)	13 (81.3%)	6 (35.2%)
Not cured	18	15 (57.7%)	5 (19.2%)	2 (11.7%)
Total	19	19	17	17

It is seen that the clinical cures do not meet the 95% cure criteria, which is consistent with Table 5. However, there seems to be some accounting problem in the MO database on this particular tabulation. The number of patients cure and not cured do not add up to the total number of evaluable patients on Day 3 and 14. On Day 21, 11 patients were lost to follow-up. If they are taken into account, the total number of patients on Day 21 seems to be inconsistent too.

Cure rates by center were not available.

Indication: Nongonococcal Urethritis

There was one clinical trial, Study L0196 reported on this indication.

Gender Representation:
This indication precludes enrollment of females.

Center Representation:

There was no centerwise data reported in the analysis.
Cure Rate Analysis:

Bacteriologic eradication was noted in 29/62 (46.8%) of Azithromycin and 14/24 (58%) of Doxycycline patients at Week 5. Persistence was noted in 21/62 (33.9%) of Azithromycin and 12/27 (44.4%) of Doxycycline patients.

Clinical response was observed at Week 2 when 33/45 (73.3%) of the Azithromycin and 13/17 (76.5%) of the Doxycycline patients were cured.

It is seen that none of the clinical or bacteriologic cure rates meet the 95% cure rate criteria.

B. SAFETY EVALUATION

No statistical review of safety data was deemed to be needed.

C. CONCLUSIONS (That May Be Conveyed To The Sponsor):

Gonorrhea: On Protocol 066-130, all sites, except rectum and pharynx for males on Azithromycin meet the 95% cure rate criteria at Week 1 with respect to bacteriologic eradication. At Week 2, all sites on Azithromycin, except rectum for females meet 95% cure rate criteria (Tables 2 and 3). However, the sample sizes are too small to draw any robust conclusion. On Protocol 066-114, clinical cure rates on Azithromycin are 81% and 83.3% for Weeks 1 and 2 as compared to 93.8% and 70% on Ceftriaxone respectively. Thus, there is only one study that statistically supports the claim for gonorrhea.

Azithromycin fails to establish 95% cure rate criteria in both clinical and bacteriologic cures in indications for chancroid and nongonococcal urethritis (Tables 5 and 6).

Ralph Harkins, Ph.D. for
Alaka G. Chakravarty, Ph.D.
Biomedical Statistician, Biometrics IV

Daphne Lin, Ph.D. 12/12/95
Concur: Daphne Lin, Ph.D.
Acting Team Leader, Biometrics IV

Ralph Harkins, Ph.D. 12/12/95
Ralph Harkins, Ph.D.
Acting Division Director, Biometrics IV

cc:
Archival: NDA 50-670; SE1-008
HFD-520
HFD-520/Ms. LeSane
HFD-520/Dr. Fanning
✓HFD-520/Dr. Albuerne
HFD-520/Dr. Bais
HFD-701/Dr. Anello
HFD-725/Dr. Harkins
HFD-725/Dr. Lin
HFD-713/Dr. Chakravarty
HFD-344/Dr. Thomas
Chron.

This review contains 7 pages.

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MAR 24 1995

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

Microbiological Clinical Review of Efficacy Supplement

NDA #: 50-670 **MICRO.REVIW #:** 1 **REVIEW DATE:** 02-FEB-95

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SUPPLEMENT/SEI-008	12-DEC-94	15-DEC-94	16-DEC-94

NAME & ADDRESS OF APPLICANT: PFIZER CENTRAL RESEARCH
Eastern Point Road
Groton, CT 06340

Contact Person: Charles A. Ritrovato, Pharm.D.
Associate Director II
Regulatory Affairs Liaison
(203)441-6899

DRUG PRODUCT NAME

Proprietary:	Zithromax®
Nonproprietary/USAN:	Azithromycin Inhalation
Code Names/#'s:	CP-62,993;XZ-450
Chemical Type/ Therapeutic Class:	Azalide antibiotic

ANDA Suitability Petition/DESI/Patent Status:
N/A [if applicable]

PHARMACOLOGICAL CATEGORY/INDICATION: macrolide antibiotic/treatment of gonorrhea, chancroid, and non-gonococcal urethritis

DOSAGE FORM:	Single Dose Packet
STRENGTHS:	1 gm;2 gm
ROUTE OF ADMINISTRATION:	ORAL
DISPENSED:	__X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

CHEMICAL NAME: (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-13-[(2,6-dideoxy-3-C-methyl-3-O-methyl-a-L-ribo-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-tridexoy-3-(dimethylamino)-b-D-xylo-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

Molecular Formula: $C_{38}H_{72}N_2O_{12}$

Molecular Weight: 749.0

TISSUE DISTRIBUTION

The following information is a synopsis of data that the sponsor has submitted and does not represent a true analysis of the data which will be reviewed by biopharm.

Study AZM-NY-92-012 examined the concentration of azithromycin in cervical mucus following a single one gram dose. Samples were obtained from 20 women on day 2, days 7-9 and days 14-16 for assay. Mean plasma concentrations were 0.71 μg/mL on day 2 and below detectable levels (0.02 μg/mL) at the other test points. Mean cervical mucus concentrations were 2.67 μg/mL on day 2, 1.29 μg/mL on days 7 to 9, and 0.43 μg/mL on days 14-16.

Study #066-001 assessed the concentration of azithromycin in tissues of patients undergoing prostatectomy or other urological procedures following oral administration of 500 mg of azithromycin as two 250 mg capsules q.12h. Between 12 and 137 hours after the second dose, prostate and other tissue samples were taken during surgery from 34 patients. The mean concentration in prostate tissue between 12 and 17.5 hours after the second dose was 2.2 μg/g (range μg/g). Azithromycin was still found in prostate of two patients approximately 137 hours after the last dose at a concentration of μg/g.

Study #066-004 examined the concentrations of azithromycin in prostatic tissue from 23 elderly patients following oral administration of two 250 mg capsules given 12 hours apart. Tissue samples and plasma were collected between 11 hours and 4.5 days after the second dose. The mean concentration of azithromycin in prostatic tissue collected approximately 14 hours after the second dose was 2.8 μg/g (range μg/g). Azithromycin was still detectable in the prostate of six patients 3.5 days after the last dose, with a mean concentration of 1.3 μg/g.

Study #066-005 examined azithromycin concentrations in gynecological tissues from seven patients undergoing elective gynecological and surgical procedures following oral administration of a single dose of 500 mg azithromycin. Between 14 and 19 hours after the dose tissue samples, serum, and peritoneal fluid were collected. Azithromycin concentrations in gynecological tissues approximately 17 hours after a 500 mg dose ranged from μg/g. Concentrations were similar in fallopian tube, ovary, uterus, and cervix, with means ranging from 2.7 to 3.5 μg/g. Similar concentrations were also found in single samples of fibroid tissue (2.2 μg/g) and peritoneal adhesion tissue (4.0 μg/g). The mean azithromycin concentration in peritoneal fluid was 0.078 μg/mL and in serum was 0.036 μg/mL.

In study #066-208 samples of gynecological tissue (uterus or cervix-uteri in 18/19 samples, 1 fallopian tube), plasma, peritoneal fluid, and urine were collected from 19 surgical patients approximately 24, 48, 72 or 96 hours after oral administration of a single 500 mg dose of azithromycin. Mean tissue concentrations in gynecological tissues were 1.44, 1.08, 0.85, and 0.78 μg/g at approximately 24, 52, 72, and 97 hours postdose. Plasma concentrations were ≤0.04 μg/mL. Mean peritoneal fluid concentration were 0.13, 0.15, <0.02 and 0.07 μg/mL at the same time points.

Lebel (1) examined the concentrations of azithromycin in human prostatic fluid and ejaculate. Two groups of 18 and 20 healthy males received a single oral dose of 1000 mg. In group 1, plasma and urine samples were collected up to 72 hours, other fluids up to 48 hours. In group 2, samples were collected up to 7 days after dosing. In group 1 subjects did not void urine until 4 hours after administration and prostatic fluid was collected at 8 hours. In group 2 subjects did not void urine until 8 hours after dosing and prostatic fluid was collected at 4 hours. Mean pharmacokinetic parameters in plasma were approximately: C_{max}= 1.04 μg/mL in Group 1, 0.84 μg/mL in Group 2; half-life 38.6 hours in Group 1 and 34.5 hours in Group 2. Plasma concentrations declined to approximately 0.044 μg/mL at 48 hours. Mean prostatic fluid concentrations were approximately 5.7 μg/mL at 4 hours, and 1.8 μg/mL at 48 hours in Group 1; 4.9 μg/mL at 8 hours, 5.7 μg/mL at 24 hours, and 2.1 μg/mL at 48 hours in Group 2. Seminal fluid concentrations reached C_{max} of approximately 2.4 μg/mL at 24 hours in Group 1 and 3.3 μg/mL at 8 hours in Group 2. Seminal fluid concentrations declined slowly with concentrations of approximately 1.9 and 0.43 μg/mL remaining at 48 and 168 hours in Group 1 and 1.4 and 0.34 μg/mL at 48 and 168 hours in Group 2.

AZITHROMYCIN *IN-VITRO* ACTIVITY

ACTIVITY AGAINST *NEISSERIA GONORRHOEAE*

This submission contains reports on the activity of azithromycin against *Neisseria gonorrhoeae*.

The Centers for Disease Control (2) have published a study in which the MIC_{100} for azithromycin was 0.25 μg/mL compared to an MIC_{90} for penicillin, tetracycline and erythromycin of 16, 16, and 1.0 μg/mL, respectively. In a study in France (3) the MIC_{90} was 0.25 μg/mL. An MIC_{90} of 0.5 μg/mL was reported in a study from South Africa (3). The Table below gives a summary of the studies included in this submission:

TABLE 1
Azithromycin Activity against *Neisseria gonorrhoeae*

Investigator	Country	# Tested	Method	MIC_{50}	MIC_{90}
Rice (2)	USA	69	GC(10^4)	0.06	0.25
		11 resistant to PE,TC		0.06	0.25
Lefevre (3)	France	20 β-lac$^+$	MHA(10^4)	0.06	0.25
		40 β-lac$^-$		0,016	0.25
Ison (4)	South Africa	164 β-lac$^-$	DST (10^4)	0.12	0.5
		28 β-lac$^+$		0.25	0.5
Barry (5)	USA	50 (25 β-lac$^+$)	MHB (10^5)	0.12	0.25
Fernandes (6)	USA	10	Agar dilution	0.03	0.03
Hardy (7)	USA	15	Agar dilution	0.03	0.06
Neu (8)	USA	10	Choc MHA(10^5)	0.06	0.5
Slaney (9)	Canada	100 Winnapeg 200 Kenya (100 β-lac$^+$)	CG (10^4)	0.25	0.5

Only the Center for Disease Control study (Rice) used the current NCCLS methodology for testing susceptiblity of *Neisseria gonorrhoeae*, the other studies support the MIC values found by in this study.

ACTIVITY AGAINST *HAEMOPHILUS DUCREYI*

Recent reports demonstrate that azithromycin has good activity against *Haemophilus ducreyi*. All reported MIC_{90} values are 0.03 μg/mL or below. The table below gives a summary of recent reports included in this submission.

TABLE 2
Azithromycin Activity against *Haemophilus ducreyi*

Investigator	Country	# Tested	Method	MIC_{50}	MIC_{90}
Motley (10)	USA	27 No plasmid	GC(10^4)	≤0.008	0.016
		8 3.2 MDalton plasmid		≤0.008	≤0.008
		59 5.7 MDalton β-lac⁻ plasmid		0.016	0.016
Aldridge (11)	USA	100 β-lac+	GC (10^5)	≤0.06	≤0.06
Knapp (12)	USA	29 Thailand 25 San Francisco	GC (10^4)	0.03	0.03
Jones (13)	UK	46	Agar Dilution	≤0.03	≤0.03
Slaney (9)	Canada	100 Kenya (β-lac +)	GC(10^5)	0.0018	0.003

ACTIVITY AGAINST

This submission includes many papers that studied the *in vitro* activity of azithromycin against

The MIC_{90} values in these studies ranged from μg/mL. In some studies some isolates had MICs as high as 128 μg/mL. Broth microdilution was used in most of these studies. U9 broth or Shepard's broth supplement with horse serum, yeast extract, or peptone and urea was used. The pH of the media was around 5 to 6 in most cases. The inoculum was approximately 10^4 to 10^5 cfu/mL. The following table gives a summary of the papers included in this submission.

TABLE 3
Azithromycin Activity against

Investigator	Country	# Tested	Method	MIC_{50}	MIC_{90}
Renaudin (14)	France	65	U9C broth 20% horse serum 0.08% urea	1.0	2.0
Ferreruela (15)	Spain	50	U9 broth	2.0	4.0
Aviles (16)	Mexico	200	U-agar 20 % peptone	1.0	8.0
Renaudin (17)	France	26	microdilution	2.0	4.0
Rumpianesi (18)	Italy	40	PPLO 20% horse serum 10% yeast extract	1.0	2.0
Felmingham (19)	UK	20	microdilution 20% horse serum Urea	0.25	1.0
Bauriaud (20)	France	40	Shepard horse serum + urea	2.0	2.0
Rylander (21)	Sweden	30	Agar dilution Shepard +horse serum +yeast extract	0.25	0.5
		33	Broth dilution BHI + PPLO + yeast extract + phenol red + urea pH 5.6	0.032	0.064
Lefevre (3)	France	40	Shepard broth	2.0	2.0

CORRELATION OF *IN VITRO* CLINICAL LABORATORY RESULTS WITH CLINICAL AND BACTERIOLOGICAL RESPONSE

An agar diffusion or minimal inhibitory concentration susceptibility determination was performed on baseline cultures of *N. gonorrhoeae* in studies 066-114, 066-124, and 066-130 and *H. ducreyi* in studies 066-120 and 066-328. The susceptibility determinations were performed according to NCCLS specifications.

The first 10-20 mL of a urine specimen in study L-0196 was collected and cultured Some of the positive cultures were frozen (-70°C) for later susceptibility testing. MIC determinations on the isolates were performed at the on all available isolates after completion of the study. Many isolates were lost after storage, shipment and thawing.

NEISSERIA GONORRHOEAE SUSCEPTIBILITY TESTING

The highest MIC values observed in the clinical trials were 0.5 µg/mL (7 occurrences out of 226) and 0.25 µg/mL (69 occurrences). Among those bacteriologically evaluable subjects treated with azithromycin with an MIC recorded, only one subject was culture positive (persistent) at either day 7 or day 14. This isolate had an MIC of 0.015 µg/mL and persisted on day 7. The subject was not evaluated bacteriologically at day 14, or clinically at day 7 or 14. There were 61 occurrences of a zone of <30 mm, and 20 occurrences of a zone of ≤ 25 mm among the 538 zone determinations. Zone sizes ranged from 15 to 52 mm. In the azithromycin treated patients there was forty isolates with zone sizes <30 mm and 13 with zones ≤25 mm and all these strains were eradicated at day 7 and remained eradicated at day 14. In all bacteriologically evaluable patients treated with azithromycin, there were 5 occurrences of a site giving persistence at day 7. Three of the persistent isolates had a zone size of 37 mm, one had a zone of 36 mm, one had a one of 33 mm. The smallest zone diameter in the azithromycin treated patients was 19 mm.

HAEMOPHILUS DUCREYI SUSCEPTIBILITY TESTING

The highest observed MIC value in the clinical trails was 0.06 µg/mL (1 of 22 strains). The lowest zone diameter seen was 22 mm (1 of 74 strains). Among subjects treated with azithromycin and having a baseline susceptibility determination performed on the strain, only one subject was persistent at day 7. This isolate gave a zone of 47 mm and had a satisfactory clinical response at day 7.

SUSCEPTIBILITY TESTING

There were only 35 baseline strains available for MIC determinations. The MICs ranged from µg/mL with an $MIC_{50/90}$ of 2.0/4.0 µg/mL. The number of isolates available for comparison with bacteriological and clinical response was small. Only 13 treated with azithromycin and six treated with doxycycline for bacteriological response. At the two week visit 75% of the azithromycin treated patients were culture negative. Susceptibility testing of patient isolates are not routinely performed.

Based on the data collected in these clinical trails, all *H. ducreyi* and *N. gonorrhoeae* having MIC values of ≤0.06 µg/mL and ≤0.5 µg/mL, respectively are susceptible to azithromycin using the 1 g and 2 g doses in these studies. Strains with higher MIC values were not detected. The limited amount of data available for does not permit a conclusion to be made relating MICs to eradication and clinical outcome. The MICs for are considerably higher than for the other two organisms in this submission and may be above the achievable tissue levels for the drug.

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CONCLUSIONS & RECOMMENDATIONS:

Studies have been performed that show that the level of drug in cervical mucus, prostatic tissue, fallopian tubes, ovaries, uterus, and seminal fluid reaches a peak level between 2.6 and 5.69 μg/mL. These concentrations were usually achieved with a dose of 500 milligrams or 1 gram, which is equal to or less that the doses being proposed in this supplement (1 gram for *H. ducreyi* and 2 grams for gonorrhea). Concentrations, up to 2 weeks after the final dose, are approximately 0.4 μg/mL (when a one gram dose was used). These concentrations are well above the MIC_{90} values in most studies for *Haemophilus ducreyi* of 0.03 μg/mL or lower. The peak levels obtained in most tissue is also 4 to 5 times the highest MIC_{90} value obtained in studies against *Neisseria gonorrhoeae*. The level after 2 weeks is close to the MIC_{90} value for this organism, but most of the tissue level studies were performed with a 500 milligram dose and a 2 gram dose will be used for this indication. The tissue levels obtained may be below the MIC_{90} value for that is obtained in many studies. From the microbiological only viewpoint it appears that the drug may not work for this organism.

In the clinical trials the highest MIC value obtained for *Neisseria gonorrhoeae* was 0.5 µg/mL. All isolates were eradicated, except for one with an MIC of 0.015 µg/mL. MIC values ranged from µg/mL (most between 0.03 and 0.25 µg/mL). Zone sizes ranged from 15mm to 52 mm (most between 30 and 42 mm). There were five persistent isolates that had zone diameters determined for them. These five isolates had zones between 33 and 37 mm. At the present time it appears that there are no resistant *Neisseria gonorrhoeae* isolates and susceptibility testing is not recommended.

The highest MIC observed in the clinical trials for *Haemophilus ducreyi* was 0.06 µg/mL. The smallest zone size was 22 mm. There was only one persistent isolate and it had a zone size of 47 mm. All *Haemophilus ducreyi* isolates should be considered susceptible. No susceptibility testing should be performed.

There were very few isolates that had an MIC determined for them in the study. There does appear to be some failures since only 75% of the azithromycin patients were culture negative at the two week visit. From the limited amount of susceptibility data submitted it can not be determined what the MIC values were for the isolates that were not eradicated.

FROM THE MICROBIOLOGICAL VIEWPOINT THIS SUPPLEMENT SHOULD BE APPROVED FOR *HAEMOPHILUS DUCREYI* AND FOR *NEISSERIA GONORRHOEAE*.

Peter a. Dionne

PETER A. DIONNE,
Review Microbiologist

cc: Orig. NDA 50-670
HFD-502
HFD-520/Division File
HFD-520/MICRO/Dionne
HFD-520/MO/Moledina
HFD-520/Pharm/Adeyemo
HFD-520/Chem/Shetty
HFD-520/CSO/Lesane

Concurrence Only:
HFD-520/ActingDIR/LGavrilovich
HFD-520/SMicro/ATSheldon
RD init 3/10/95 ATS
FIN 3/23/95 ATS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date DEC 19 1994

NDA No 50-670

Charles A. Ritrovato, Pharm.D.
Pfizer Inc.
Eastern Point Road
Groton, CT 06340

Attention: Charles A. Ritrovato, Pharm.D.

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Zithromax Oral

NDA Number: 50-670

Supplement Number: S-008

Date of Supplement: December 12, 1994

Date of Receipt: December 15, 1994

Unless we find the application not acceptable for filing, the filing date will be 60 days from the receipt date above.

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Attention: Document Control, Room 12B-30
5600 Fishers Lane
Rockville, MD 20857

Sincerely yours,

for

Supervisory Consumer Safety Officer
Division of Anti-Infective Drug Products
Center for Drug Evaluation and Research

FORM FDA 3217d (12/91)

701

MEMORANDUM OF TELECON

DATE: January 19, 1996

APPLICATION NUMBER: 50-670/S-008; ZITHROMAX Capsules

BETWEEN:

Name: Bob Clark and Dr. Scott Hopkins
Phone: 212-573-3412
Representing: PFIZER

AND

Name: Mercedes Albuerne, M.D.
Name: Frances LeSane
Division of Anti-Infective Drug Products, HFD-520

SUBJECT: Request for Information Chancroid indication

This call was made to request more information on the indication for *chancroid* in males due to *Haemophilus* ducreyi.
Please submit the following:

1. Validation for the study in Kenya, indicate the investigator.
2. Check on the investigator's documentation for the study since the submission contains a draft.
   - list clinic location, documentation
   - Data confirmation - patient reports, how recorded, when were they turned in

3. Send us as much information as you can for justification for indication.

PFIZER note that the investigator was Dr. Ronald from Montreal, they also said they would find out as much information and they could and, send it in to the supplemental application for our review. After which they would send draft labeling.

Frances LeSane
Project Manager

cc: Original 50-670/S-008
HFD-520/Div. File
HFD-520/PMS/FLeSane
HFD-520/MO/PBais

TELECON

Eastern Point Road
Groton, CT 06340
Tel 203 441 4100

Central Research

December 12, 1994

Department of Clinical Research

Lillian Gavrilovich, M.D., Acting Director
Division of Anti-Infective Drug Products
Center for Drug Evaluation and Research HFD #520
Office of Drug Evaluation II
ATT: DOCUMENT CONTROL ROOM #12B-30
5600 Fishers Lane
Rockville, MD 20857

Dear Doctor Gavrilovich:

RE: NDA-50-670 - ZITHROMAX® Oral, Azalide Antibiotic

Pursuant to Paragraph 507 of the Federal Food, Drug, and Cosmetic Act, and Paragraph 314.1 of the Code of Federal Regulations, Title 21, we are submitting for priority review, a Supplemental New Drug Application to support additional indications for azithromycin in the treatment of sexually transmitted diseases (STDs). We believe that the data presented in this Efficacy Supplement to NDA-50-670 substantiate the safety and effectiveness of a single 2 gram dose of azithromycin for the treatment of gonorrhea, and of a single 1 gram dose for the treatment of chancroid and non-gonococcal urethritis U.S. studies of azithromycin in the treatment of sexually transmitted diseases were conducted under IND

The availability of single dose therapy marked a major advance in the treatment of sexually transmitted diseases, as non-compliance with multiple dose regimens often resulted in continued transmission of disease and long term medical sequelae. A single IM injection, in past times with benzathine penicillin and now with ceftriaxone, became popular as a treatment modality because compliance was assured. However, as the importance of concurrent treatment for chlamydia infection was recognized, the addition of a seven day regimen of doxycycline again raised the issue of non-compliance. Because azithromycin can be employed as a single agent for the treatment of STDs which currently require multi-drug therapy, it effectively eliminates issues associated with non-compliance, and the additive toxicities of multi-drug regimens. Azithromycin retains the advantage of single dose therapy, but in comparison to ceftriaxone, offers a broader spectrum of activity against sexually transmitted pathogens and adds the convenience of oral administration. In light of these advances offered by azithromycin, the Applicant request that this Efficacy Supplement to NDA-50-670 be designated for priority review.

Azithromycin previously received marketing approval in the U.S. on November 1, 1991 (NDA-50-670) as a capsule dosage form for the treatment of respiratory tract, skin and skin structure infections, and *Chlamydia trachomatis* genitourinary infections in patients 16 years of age and older. On September 28, 1994, azithromycin also received marketing approval as a single dose packet (1 g), an alternative dosage form for the treatment of non-gonoccocal

urethritis and cervicitis due to *Chlamydia trachomatis* (NDA-50-693). The chemistry, manufacturing and control data, samples, methods validation package, and labeling contained in both NDA-50-670 and NDA-50-693 are directly applicable to the current Application and are incorporated by cross-reference. Nonclinical pharmacology and toxicology data contained in NDA-50-670 is also incorporated into the current Application by cross-reference.

Data from four multicenter and two single center clinical trials presented in this NDA Supplement comprise the primary evidence to support the effectiveness and safety of azithromycin in the treatment of patients with the sexually transmitted diseases of gonorrhea (three trials), chancroid (two trials) or non-gonococcal urethritis (one trial).

Of the three U.S. studies in the treatment of gonorrhea, two were open label, randomized, comparative trials of azithromycin versus ceftriaxone (study #130 and #114) and one was an open label, noncomparative trial (study #124). In these studies, the efficacy of azithromycin as a single oral 2 gram dose for the treatment of gonococcal urethritis/cervicitis was assessed. The results of the three studies support the conclusion that azithromycin is effective as a single dose treatment of acute gonococcal urethritis/cervicitis. In addition to the three studies referenced above, the results of two non-U.S. studies (#305 and #319) of azithromycin in the treatment of gonorrhea are presented in this Application and provide additional safety data for this indication.

In support of the chancroid indication, two open label azithromycin trials were conducted; one was comparative, azithromycin versus ceftriaxone (study #120 conducted in the U.S.), and one was noncomparative (study #328 conducted in France). When administered as a single 1 gram oral dose in these studies, azithromycin was demonstrated to be effective in the treatment of chancroid caused by *H. ducreyi.* In addition, the results of study #AZM-NY-90-007, an observer blinded, comparative study conducted in Kenya, provide additional efficacy data of azithromycin in the treatment of chancroid.

One double blind, comparative study (#L-0196) supports the claim that azithromycin is bacteriologically and clinically efficacious in the treatment of non gonococcal urethritis This study demonstrates that a single 1 gram dose of azithromycin is as safe and effective as a 7-day twice daily course of doxycycline therapy.

Data obtained from patients in clinical trials for STD indications, other than those described above, are presented in this Application as they provide pertinent safety information.

Safety data are presented for all subjects enrolled in planned single 1 or 2 gram oral dose studies and for subjects enrolled in STD studies employing other dosage regimens. Serious adverse events, from clinical trials and spontaneous reports, are provided for all subjects fitting this definition.

In addition to the safety information presented in this Application, an IND Safety Report involving a patient who received a single 1 gram dose of azithromycin has been recently submitted to relevant azithromycin INDs and pending NDAs on file with the Division. This case involved an event characterized as nonviral acute hepatitis in a 25 year old male patient being treated for nongonococcal urethritis in Canadian study #AZM-CDM-93-001. Although this case meets the safety definition used in the preparation of this NDA Supplement, it was entered into

the safety database after the cutoff date of May 1, 1994. A description of this case can be found in our submission of November 23, 1994 to IND (serial number 061).

The location of the various sections of this NDA, number of volumes being submitted, and other explanatory notes are listed in Attachment I of this letter.

In accordance with the requirements of the Generic Drug Enforcement Act of 1992, and in connection with this application, to the best of its knowledge, Pfizer Inc did not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act.

Please be advised that the applicable user fee for this submission has been remitted in accordance with the Prescription Drug User Fee Act of 1992 and that Form FDA 3397 is enclosed as required. The User Fee I.D. number for this NDA Supplement is 2696. We believe this Application to be complete for review by the Division and look forward to a response within 180 days of receipt.

Should you have any questions regarding the content or organization of this submission, please contact Dr. Charles A. Ritrovato at (203) 441-6899.

Sincerely yours,

Charles A. Ritrovato, Pharm.D.
Associate Director II
Regulatory Affairs - Liaison

Dilip J. Mehta, M.D., Ph.D.
Vice President
Department of Clinical Research

mgd/mfb
Enclosures
Copy No.
Serial No.

ORIGINAL

Regulatory Affairs Division
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 3412 Fax 212 573 1563

S-008
SUPPLEMENT

Note
- P. Lynn
1/29/96

Robert B. Clark
Senior Associate Director

January 5, 1996

Mary Fanning, M.D., Ph.D., Director
Division of Anti-Infective Drug Products (HFD-520)
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration
5200 Fishers Lane
Rockville, Maryland 20857

RE: NDA 50-670/S-008
ZITHROMAX® (azithromycin) Capsules

Dear Dr. Fanning:

Reference is made to our approvable supplemental New Drug Application for ZITHROMAX® (azithromycin), NDA 50-670/S-008. This supplemental application was approvable for the indications of urethritis and cervicitis due to *Neisseria gonorrhoeae* and Chancroid in males due to *Haemophilus ducreyi*. The Division of Anti-Infective Drug Products issued an approvable letter to Pfizer for this supplemental NDA on December 13, 1995.

Please be advised that we intend to amend this approvable application in the near future.

Sincerely,

Robert B. Clark

CONFIDENTIAL/TRADE SECRET INFORMATION
SUBJECT TO 18-USC-1905 AND TO WHICH ALL
CLAIMS OF PRIVILEGE AND CONFIDENTIALITY
ARE ASSERTED IN BOTH STATUTORY AND
COMMON LAW.

ORIGINAL

Regulatory Affairs Division
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 3412 Fax 212 573 1563

AL

S-008

Robert B. Clark
Senior Associate Director

August 22, 1996

REVIEWS COMPLETE

SUBMISSION:

David Feigal, Jr., M.D., M.P.H., Acting Director
Division of Anti-Infective Drug Products (HFD-520)
Document Control Room 12B-30
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 50-670/S-008
ZITHROMAX® (azithromycin) Capsules
Treatment of Sexually Transmitted Diseases

Dear Dr. Feigal:

Reference is made to our approved New Drug Application for ZITHROMAX® (azithromycin) Capsules NDA 50-670 as well as our pending supplement filed on December 12, 1994 to provide data in support of the use of azithromycin for the treatment of urethritis and cervicitis due to *Neisseria gonorrhoeae* and Chancroid in males due to *Haemophilus ducreyi.* We also refer to the division's December 13, 1995 approvable letter for this supplement, which noted that the submission was approvable for the treatment of urethritis and cervicitis due to *Neisseria gonorrhoeae* and Chancroid in males due to *Haemophilus ducreyi.*

Attached please find the draft package insert containing the additions relevant to these indications. Please note that this insert also includes a "Post-Marketing Experience" section for adverse events as well as other minor editorial changes made for consistency with the recently approved labeling for NDA 50-730: Zithromax Tablets (600 mg) for MAC Prophylaxis (approved by HFD-530). Questions on the attached should be directed to the undersigned. Please include this information in the subject file.

Sincerely,

Robert B. Clark

cc: Ms. Frances LeSane, Project Manager (HFD-520)
Mr. Jose Cintron, Project Manager (HFD-520)

DUPLICATE

Regulatory Affairs Division
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 3412 Fax 212 573 1563

Fanning
FYI
Jane
S-008
SUPPL NEW CORRESP

Robert B. Clark
Senior Associate Director

May 2, 1996

Mary Fanning, M.D., Ph.D., Director
Division of Anti-Infective
Drug Products (HFD-520)
Attention: Document Control Room 12B-30
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RE: Zithromax (azithromycin) Capsules NDA 50-670
Supplement S-008: Treatment of Sexually Transmitted Diseases

Dear Dr. Fanning:

Reference is made to our approved New Drug Application for Zithromax (azithromycin) Capsules NDA 50-670 as well as our pending supplemental new drug application (S-008) submitted on December 12, 1994. This supplemental application provided data in support of the use of azithromycin for the treatment of urethritis and cervicitis due to *Neisseria gonorrhoeae* and Chancroid in males due to *Haemophilus ducreyi*. We also refer to the division's December 13, 1995 approvable letter for this supplement, which noted that the submission was approvable for treatment of urethritis and cervicitis due to *Neisseria gonorrhoeae* and Chancroid in males due to *Haemophilus ducreyi*. In response to the division's approvable letter, Pfizer submitted a final safety update on January 11, 1996.

During a teleconference held on January 19, 1996 between representatives from Pfizer and Dr. Albeurne, Dr. Bais and Ms. LeSane of HFD-520, the division requested additional information regarding the conduct of protocol AZM-NY-90-007, entitled; "Azithromycin in the Treatment of Chancroid; a Randomized Comparison with Erythromycin" conducted in Kenya by Dr. Alan Ronald. This letter represents a summary of our efforts regarding this request.

To address Dr. Albeurne's request, on April 1, 1996 Pfizer performed an on-site verification at the "SPECIAL TREATMENT CLINIC" (a WHO collaborative Center for Research and Training in Sexually Transmitted Diseases), Department Of Medical Microbiology, University Of Nairobi, Nairobi, Kenya. The Pfizer clinician met with two of the physicians who participated in the study, Professor Ndinya Achola (Head of the STD/HIV/AIDS Research Unit) and Dr. Francis Plummer.

During this site visit, discussions with the investigators and other support personnel confirmed that the clinic is an active study site and that this trial took place, as described in the New Drug Application supplement. The Pfizer physician who visited the site obtained a working copy of a Clinic Register (dated "up to April 1991"). Forty (40) patient names on the register up to that period matched 40 patient initials, clinic numbers and CRF study numbers from the study files.

Neither the complete Clinic Register nor the actual patient cards could be obtained and evaluated against the entire study population. However, based on this site visit, we confirm that azithromycin protocol AZM-NY-90-007 was conducted at the "Special Treatment Clinic" in Nairobi, Kenya and along with the other study results contained in the supplement, support the approval of azithromycin in the treatment of chancroid due to *Haemophilus ducreyi.*

Following the division's review of this information and concurrence with our conclusion, sixteen copies of final printed labeling for this product will be submitted to HFD-520.

Please include this information in the above file.

Sincerely,

Robert B Clark

Robert B. Clark

desk copy: Dr. Mercedes Albeurne (HFD-520)
Dr. Pammi Bais (HFD-520)
Ms. Frances LeSane (HFD-520)

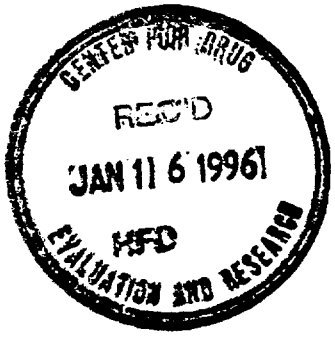
ORIGINAL

NDA SUPPL AMEND
SEI-008 (SLL)

Regulatory Affairs Division
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 3412 Fax 212 573 1563

Robert B. Clark
Senior Associate Director

January 11, 1996



Mary Fanning, M.D., Ph.D., Director
Division of Anti-Infective Drug Products (HFD-520)
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 50-670/S-008
ZITHROMAX® (azithromycin) Capsules

Dear Dr. Fanning:

Reference is made to our approvable supplemental New Drug Application for ZITHROMAX® (azithromycin), NDA 50-670/S-008. This supplemental application was approvable for the indications of urethritis and cervicitis due to *Neisseria gonorrhoeae* and Chancroid in males due to *Haemophilus ducreyi*. The Division of Anti-Infective Drug Products issued an approvable letter to Pfizer for this supplemental NDA on December 13, 1995.

Attached please find a final safety update which provides a listing of clinical trial serious adverse events (SAEs) and spontaneously-reported SAEs from our safety database pertinent to this supplemental application. The safety definition included any subject receiving a planned 1 or 2 gram single oral dose of azithromycin and any subject enrolled in a STD study receiving any dosage regimen. During the incremental reporting period of March 1, 1995 through November 30, 1995, one clinical trial SAE and three spontaneously-reported SAEs were entered into the database. A 29 year-old male subject enrolled in a study (AZM-CDN-93-001) conducted in Canada suffered pneumothorax and lacerations of the head from a physical assault 17 days after receiving 7 days of treatment with blinded therapy; the events resolved (see Table 1, attached). The spontaneously-reported SAEs in patients receiving azithromycin included hemorrhagic gastritis, drowsiness, and nausea in a 27 year-old female patient in Spain; an allergic reaction in a 36 year-old male patient in South Africa; and shock and loss of consciousness in a patient in Germany (see Table 2, attached). There were no deaths entered into the database during this reporting period.

The data contained herein support the overall findings of the original NDA supplement and the Four-Month Safety Update.

Copies of final printed labeling for this supplemental NDA will be submitted in the near future. Please note that as directed in the division's December 13, 1995 approvable letter, this revised labeling has been revised to be in conformity to that in NDA 50-710, azithromycin for oral suspension for pediatric use.

If there are questions on the attached, please direct them to the undersigned at (212) 573-3412.

Sincerely,

Robert B. Clark

CONFIDENTIAL/TRADE SECRET INFORMATION
SUBJECT TO 18-USC-1905 AND TO WHICH ALL
CLAIMS OF PRIVILEGE AND CONFIDENTIALITY
ARE ASSERTED IN BOTH STATUTORY AND
COMMON LAW.

DUPLICATE

Regulatory Affairs Division
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 3412 Fax 212 573 1563

Franier FYI Jane

S 008
SUPPL NEW CORRESP

Robert B. Clark
Senior Associate Director

May 2, 1996

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Mary Fanning, M.D., Ph.D., Director
Division of Anti-Infective
Drug Products (HFD-520)
Attention: Document Control Room 12B-30
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RE: Zithromax (azithromycin) Capsules NDA 50-670
Supplement S-008: Treatment of Sexually Transmitted Diseases

Dear Dr. Fanning:

Reference is made to our approved New Drug Application for Zithromax (azithromycin) Capsules NDA 50-670 as well as our pending supplemental new drug application (S-008) submitted on December 12, 1994. This supplemental application provided data in support of the use of azithromycin for the treatment of urethritis and cervicitis due to *Neisseria gonorrhoeae* and Chancroid in males due to *Haemophilus ducreyi*. We also refer to the division's December 13, 1995 approvable letter for this supplement, which noted that the submission was approvable for treatment of urethritis and cervicitis due to *Neisseria gonorrhoeae* and Chancroid in males due to *Haemophilus ducreyi*. In response to the division's approvable letter, Pfizer submitted a final safety update on January 11, 1996.

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Neither the complete Clinic Register nor the actual patient cards could be obtained and evaluated against the entire study population. However, based on this site visit, we confirm that azithromycin protocol AZM-NY-90-007 was conducted at the "Special Treatment Clinic" in Nairobi, Kenya and along with the other study results contained in the supplement, support the approval of azithromycin in the treatment of chancroid due to *Haemophilus ducreyi.*

Following the division's review of this information and concurrence with our conclusion, sixteen copies of final printed labeling for this product will be submitted to HFD-520.

Please include this information in the above file.

Sincerely,

Robert B Clark

Robert B. Clark

desk copy: Dr. Mercedes Albeurne (HFD-520)
Dr. Pammi Bais (HFD-520)
Ms. Frances LeSane (HFD-520)

021-003

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: June 30, 1992
See OMB Statement on Page 3.

FOR FDA USE ONLY	
DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314)*.

NAME OF APPLICANT	DATE OF SUBMISSION
Pfizer Central Research, Medical Research Laboratory	December 12, 1994
ADDRESS *(Number, Street, City, State and Zip Code)*	TELEPHONE NO *(Include Area Code)*
Eastern Point Road Groton, CT 06340	(203)441-6899
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued) NDA 50-670

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*	PROPRIETARY NAME *(If any)*
Azithromycin	Zithromax®

CODE NAME *(If any)*	CHEMICAL NAME
Pfizer Code CP-62,993 Pliva Code XZ-450	9-Deoxo-9a-aza-9a-methyl-9a-homoerythromycin A-(USAN 3)

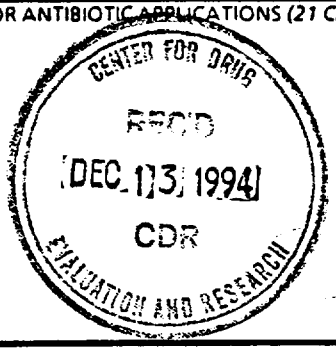
DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
Single Dose Packet	Oral	1g 2g

PROPOSED INDICATIONS FOR USE

Azalide Antibiotic

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21CFR 314 420)* REFERRED TO IN THIS APPLICATION:

MF522
NDA-50-670
NDA-50-693
IND-
IND-



INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☒ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

STATUS OF APPLICATION *(Check one)*

☐ PRESUBMISSION ☐ ORIGINAL APPLICATION ☐ AN AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☒ SUPPLEMENTAL APPLICATION

PROPOSED MARKETING STATUS *(Check one)*

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☐ APPLICATION FOR AN OVER - THE - COUNTER PRODUCT *(OTC)*

CONTENTS OF APPLICATION	
This application contains the following items: *(Check all that apply)*	
X	1. Index
X	2. Summary (21 CFR 314.50 (c))
	3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d) (1))
	4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)
	b. Methods Validation Package (21 CFR 314.50 (e) (2) (i))
	c. Labeling (21 CFR 314.50 (e) (2) (ii))
X	i. draft labeling *(4 copies)*
	ii. final printed labeling (12 copies)
	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))
X	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))
X	7. Microbiology section (21 CFR 314.50 (d) (4))
X	8. Clinical data section (21 CFR 314.50 (d) (5))
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))
X	10. Statistical section (21 CFR 314.50 (d) (6))
	11. Case report tabulations (21 CFR 314.50 (f) (1))
X	12. Case reports forms (21 CFR 314.50 (f) (1))
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. OTHER *(Specify)*

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211
2. Labeling regulations in 21 CFR 201
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
Charles A. Ritrovato, Pharm. D. Associate Director II, Regulatory Affairs, Liaison		12/12/94

ADDRESS *(Street, City, State, Zip Code)*	TELEPHONE NO. *(Include Area Code)*
Eastern Point Road Groton, CT 06340	(203)441-6899

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)