Study 154-125
Title: "A randomized, multicenter, double-blind comparative trial of trovafloxacin and oral ofloxacin plus clindamycin for the treatment of acute pelvic inflammatory disease (PID) in ambulatory subjects"

Objective
to compare the safety and compared efficacy of trovafloxacin and ofloxacin/clindamycin in the treatment of ambulatory subjects with acute PID.

STUDY DESIGN
In this double-blind, multicenter, comparative trial, patients with a clinical diagnosis of pelvic inflammatory disease, were treated with trovafloxacin or ofloxacin/clindamycin for 14 days on an outpatient basis. The following table summarizes the design of the trial:

Location	USA (55 sites), RSA (1 site)
Centers without enrollment	1 (US site)
Study dates	June 5, 1995-May 8, 1996
Amendment dates:	January 12, 1995, March 22, 1995 August 18, 1995
Patients	16 years and older
Study dose and duration	Trovafloxacin 200 mg qd for 14 days
Comparator	Ofloxacin 400 mg (2 capsules) bid for 14 days PLUS Clindamycin 450 mg (3 capsules) qid for 14 days
Blinding	third party blind; double dummy
Method of assignment	1:1 random assignment at each center
Primary efficacy variable	clinical outcome at visit 4
Safety variables	clinical signs and symptoms, laboratory results
Therapy evaluation, days (window):	
Baseline	1 (within 48 hours)
Visit 2	72 hours after initiation of treatment
End of treatment-EOT	14 (14-20)
End of study-EOS	4-6 weeks after study initiation
Number of subjects randomized	155 (trovafloxacin)/ 161 (Ofloxacin and clindamycin)

STUDY POPULATION

APPEARS THIS WAY ON ORIGINAL

Inclusion criteria
Medical officer's comments:
Criteria were the same as in study 122.

GRADING OF PID BY CLINICAL EXAMINATION

I. Uncomplicated: Limited to tube(s) and/or ovary(ies)
   A. Without pelvic peritonitis
   B. With pelvic peritonitis
II. Complicated: Inflammatory mass or abscess involving tube(s) and/or ovary(ies)
   A. Without pelvic peritonitis
   B. With pelvic peritonitis
III. Spread to structures beyond pelvis, i.e., ruptured tubo-ovarian abscess

NOTE: subjects with Grade II and III were excluded from the study.

Medical officer's comment:
As in study 122, patients with grade III PID were excluded; additionally, patients with grade II PID were also excluded.

Exclusion criteria

1. Inpatients.
2. Suspected tubo-ovarian abscess (TOA).
3. Severity of PID requiring hospitalization or parenteral therapy.

Medical officer's comments:
Criteria were the same as in study 122 with the exception of the additional exclusion criteria noted above.

SUBJECT EVALUATION VISITS

Visit 1 at day 1 (Baseline)

Within 24 hours prior to the start of therapy baseline visit assessments included:

a) collection of demographic information, concurrent disease, concomitant medication use
b) targeted physical examination, and vital signs (pulse, respiration, blood pressure, and body temperature)
c) for women of childbearing potential, a serum or urine gonadotropin pregnancy test.
d) a standard panel of blood and urine safety tests, a serologic test for syphilis (FTA or RPR).

In an attempt to standardize and semiquantitate clinical severity of PID and to assess clinical response to therapy, a Clinical Tenderness Score (CTS) was used (see study 122). Upon entry into the study, each subject had a determination made of the CTS (maximum CTS = 42), extent of fever, and white blood cell count. The subject's body temperature and CTS were also assessed at the follow-up visits two and four to six weeks following initiation of therapy.

Patients with adnexal masses were excluded from study 125.

Bacteriologic specimens should have been obtained within 24 hours prior to institution of therapy. They were obtained as outlined below or by the use of culdocentesis or endometrial biopsy, at the discretion of the investigator.

a) Culture by swab of the endocervix and rectum for *N. gonorrhoeae and of C. trachomatis* by culture or antigen detection from the endocervix.
b) At the discretion of the investigator, endometrial cultures could have been obtained. Endometrial material was obtained for anaerobic and facultative culture and for isolation of *N. gonorrhoeae. C. trachomatis* was sought by culture or antigen detection. All isolates of *C. trachomatis* were to be frozen at -70°C for possible later susceptibility testing.
c) All pathogenic isolates (except *C. trachomatis*) identified by the investigator were sent to a central laboratory for testing.

Visit 2 at 72 hours

Failure to demonstrate response at 72 hours after initiation of therapy (i.e., reduction in the CTS, and/or reduction in fever, and/or reduction in white blood cell count) constituted clinical failure. At any time, depending upon the clinical situation (e.g., deteriorating clinical condition), the investigator could remove the subject from treatment and initiate additional therapeutic measures. In such a case the subject was considered a clinical failure.

No bacteriological assessments were made.

Recording of vital signs, concomitant medication, study drug dosing, adverse events was done and repeat of the battery of blood and urine tests performed at baseline were repeated.

Visit 3 at 2 weeks (Days 14-20)

The subject's response to therapy was determined by repeating the following observations:

The CTS, extent of fever, and white blood cell count were assessed. Appropriate cultures, including endocervical, rectal, or endometrial (at the discretion of the investigator) specimens were assessed for *N. gonorrhoeae, C. trachomatis*, and anaerobic and aerobic bacteria.

Vital signs, concomitant medication, study drug dosing, adverse events were recorded and the battery of blood and urine tests performed at baseline was repeated. In addition, interval sexual history was obtained.

Visit 4 at 4-6 weeks (Days 28-42)
The tests and evaluations performed at visit 3 were repeated at visit 4. The battery of blood and urine tests performed at the first three visits were repeated at this visit only if clinically significant results were detected at visit 3. In addition, interval sexual history was obtained.

Visit 4 was the primary efficacy timepoint for overall clinical and bacteriological response.

Medical officer's comments:
The timing of the visits was the same as in study 122 but there were differences in the collection of bacteriologic specimens. See study 122 comments.

Susceptibility testing
Susceptibility to CP-99,219, ofloxacin, and clindamycin was determined by disk diffusion and minimum inhibitory concentrations (MICs) for all pathogenic isolates (except *C. trachomatis*), whether at baseline or at follow-up.
Criteria for determining susceptibility to the study drugs ("susceptibility breakpoints") are summarized below.

	Trovafloxacin		Ofloxacin		Clindamycin	
Criteria	MIC (µg/mL)	Zone Diameter (mm) (5 µg Disk)	MIC (µg/mL)	Zone Diameter (mm) (5 µg Disk)	MIC (µg/mL)	Zone Diameter (mm) (2 µg Disk)
Susceptible (For *N. gonorrhoeae*)	≤ 2	≥15	≤ 2 (≤ 0.25)	≥ 16 (≥ 31)	≤ 0.5	≥ 21
Intermediate (For *N. gonorrhoeae*)	4	11-14	4 (-)	13-15 (-)	1-2	15-20
Resistant (For *N. gonorrhoeae*)	≥8 (-)	≤ 10 (-)	≥ 8	≤ 12	≥4	≤ 14

Note: Trovafloxacin 5 µg disks were never approved for clinical trial use and were subsequently replaced with 10 µg disks. Results using the 10 µg disks were not available during the study report period.
(-) No intermediate or resistant strains of *N. gonorrhoeae* currently identified.

APPLICANT'S CRITERIA FOR EVALUABILITY
see study 122

Medical officer's (MO) evaluability criteria

A. The primary efficacy variable is clinical response at the 4-6 week visit.
Patients were non-evaluable clinically if:

- insufficient therapy ---MO accepted patients who received at least 10 days of the study drug unless they were clinical failures early in the course of treatment
- unprotected sexual contact during study
- no clinical assessment 2-4 weeks after completion of study therapy
- positive serologic test for syphilis (indeterminate status)
- patients who received antibiotics within 2 weeks prior to study initiation
- IUD in place >24 hours after initiation of study therapy
- missing data and data outside study windows
- no baseline clinical assessment
- incorrect baseline diagnosis
- concomitant antimicrobial therapy during study unrelated to PID

APPEARS THIS WAY ON ORIGINAL

B. Clinical failures will be those patients who:

- require surgery after 72 hours of study therapy
- patients who develop TOA while on therapy
- patients requiring hospitalization
- clinically cured but bacteriologic failure
- insufficient therapy with study drug due to poor clinical response
- required concomitant systemic antimicrobial therapy due to poor clinical response or persistent pathogen
- subjects who were given alternate treatment due to poor response to the study drug or persistent pathogen were considered evaluable

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C. Bacteriologically non evaluable:
The reviewer agrees with applicant's criteria.

Clinical and Microbiologic Endpoints
same criteria as in study 122

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Statistical considerations and Efficacy analyses
see study 122.

Criteria for Safety evaluation
same as for study 122; in addition the following criterion was added:

- Theophylline concentrations-since ofloxacin may raise theophylline levels, at the investigator's discretion, all subjects on concomitant theophylline should have theophylline levels monitored periodically at the local laboratory.

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SCHEDULE OF STUDY VISITS AND PROCEDURES

STUDY DAYS

	Baseline Day 1	Visit 2 72h	Visit 3 2 Weeks (Days 14-20)	Post-Therapy Visit 4 4-6 Weeks (Days 28-42)
Treatment	X		X	
Compliance Checks		X	X	X
Informed Consent	X			
Demographic Information	X			
Targeted Physical Examination	X			
Concomitant Medication	XX	X	X	
Vital Signs	XX	X	X	
Assessments				
Clinical	XX	X	X	
Culdocentesis	X[a]			
Endometrial Biopsy	X[a]		X[a]	X[a]
Laboratory				
1. Hematology	XX	X	X[b]	
2. Serum Chemistry	XX	X	X[b]	
3. Urinalysis	XX	X	X[b]	
4. Microbiology				
a. *N. gonorrhoeae* cultures	X	X	X	
b. *C. trachomatis* cultures or assays	X	X	X	
c. Anaerobic/aerobic cultures	X	X	X	
5. FTA or RPR	X			
6. Pregnancy Test	X			
Adverse Events	XX	X	X	

[a] Optional, and at investigator's discretion
[b] To be done only if there is/are significant abnormality(ies) at visit 3

[redacted]
APPEARS THIS WAY ON ORIGINAL

INVESTIGATORS AND STUDY SITES

COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
United States	5019	Nazir Memon, MD
	5112	Timothy Kotschwar, PharmD
	5165	Jane Schwebke, MD
	5166	Lorraine Dubouchet/ William McCormack, MD
	5202	Richard Beyerlein, MD
	5248	Carol Terregino, MD
	5601	James McGregor, MD
	5602	Stanley Gall, MD
	5604	James West, MD
	5609	Harvey Friedenson, MD
	5748	David Baker, MD
	5749	Gregory Fossum, MD
	5751	Abner Korn, MD
	5752	Maurizio Maccato, MD/ Charles Ericsson, MD
	5756	Kevin Huddleston, MD
	5757	James Van Hook, MD
	5758	Bernard Gonik, MD
	5759	Richard Sweet, MD
	5763	Rebecca Ryder, MD
	5764	Chong Chang, MD
	5765	Blane Crandall, MD
	5766	Sebastian Faro, MD
	5767	Javier Gutierrez, MD
	5768	Peter Marsh, MD
	5866	William Koltun, MD
	5872	George Wendel, Jr., MD
	5904	Richard Derman, MD
	5905	Harold Wittcoff, MD
	5906	Dean Coonrod, MD
	5907	Joseph Mortola, MD
	5908	Ronald Paul, MD
	5909	Elizabeth Trupin Campbell, MD
	5918	Roy Ducote, MD
	5919	Mickey Karram, MD
	5920	Harrihar Pershadsingh, MD
	6000	Lynn Borgatta, MD
	6001	David Campbell, MD
	6002	Luis Sanchez-Ramos, MD
	6003	John Larsen, MD
	6070	Stephen Kasparian, MD
	6109	Mark Martens, MD
	6145	Iris Reyes, MD
	6326	Clarence Alston, MD
	6327	Janice Bacon, MD
	6329	Clifford Callaway, MD
	6330	Jay Falk, MD
	6331	John McGee, MD
	6332	Vincent Pillari, MD
	6334	David Schreck, MD
	6377	Cheryl Walker, MD
	6378	Edward Zelnick, MD
	6390	Michael Margolis, MD
	6391	Howard Offenberg, MD

COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
	6407	Scott Boone, MD
	6408	Wynne Brown, MD
South Africa	6509	Barend Lindeque, MD

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RESULTS

PATIENT ENROLLLMENT AND DISPOSITION

Table 125.1 Applicant's clinically evaluable patients by center

		Trovafloxacin			oxacin/clindamycin		
center ID	total randomized	enrolled	evaluable	% evaluable	enrolled	evaluable	% evaluable
5019	0	0	0	0	0	0	0
5112	6	3	3	100	3	3	100
5165	18	9	6	67	9	4	44
5166	37	19	12	63	18	15	83
5248	8	4	0	0	4	1	25
5601	2	1	1	100	1	1	100
5602	6	2	2	100	4	1	25
5604	2	1	0	0	1	0	0
5609	3	1	0	0	2	1	50
5748	3	1	0	0	2	2	100
5751	4	2	1	50	2	1	50
5752	10	5	4	80	5	3	60
5756	7	3	2	67	4	2	50
5759	7	4	2	50	3	2	67
5763	3	2	0	0	1	1	100
5765	1	0	0	0	1	1	100
5768	5	3	3	100	2	1	50
5866	38	19	12	63	19	13	68
5872	3	1	0	0	2	0	0
5904	5	2	1	50	3	2	67
5905	3	2	0	0	1	0	0
5906	5	2	2	100	3	3	100
5908	21	10	9	90	11	7	64
5909	8	4	3	75	4	1	25
5919	2	1	0	0	0	0	0
5920	45	22	18	82	23	14	61
6000	3	1	1	100	2	1	50
6002	2	1	1	100	1	1	100
6109	10	4	2	50	6	5	83
6145	8	4	4	100	4	2	50
6327	3	1	0	0	2	1	50
6331	3	2	1	50	1	1	100
6332	2	2	0	0	0	0	0
6334	12	6	1	17	6	2	33
6377	2	1	0	0	1	0	0
6391	4	2	2	100	2	1	50
6407	5	2	2	100	3	1	33
6408	3	2	2	100	1	1	100
6509	7	3	3	100	4	2	50
Total	316	155	101	65.2	161	97	60.2

Medical officer's comments:
Sixty five per cent of the 155 randomized to the trovafloxacin arm and 60% of the 161 patients randomized to the ofloxacin/ clindamycin arm were clinically evaluable. Unlike the inpatient study, there was only 1 South African site, which accounted for a small number of evaluable patients. Six U.S. sites (5165, 5166, 5866, 5908, 5920, 6334) had more than 10 patients randomized into the study.

APPEARS THIS WAY ON ORIGINAL

Table 125.2 Summary of Subject Disposition

	Trovafloxacin		Ofloxacin/Clindamycin	
	Number and Percentage (%) of Subjects			
Randomized Subjects	155		161	
Randomized, Not Treated	6		5	
All Treated Subjects	149	(100%)	156	(100%)
Withdrawn from Treatment[a]	30	(20%)	47	(30%)
Completed Treatment	121	(81%)	109	(70%)
Withdrawn from Study	27	(18%)	31	(20%)
Withdrawn during Treatment	19	(13%)	24	(15%)
Withdrawn during Follow-Up	8	(5%)	7	(4%)
Completed Study	124	(83%)	126	(81%)
Completed Treatment and Study	111	(74%)	102	(65%)
Evaluated for Efficacy[b]				
Clinical Intent-to-Treat	152	(98%)	159	(99%)
Clinically Evaluable	101	(65%)	97	(60%)
Bacteriological Intent-to-Treat	40	(26%)	43	(27%)
Bacteriologically Evaluable	21	(14%)	27	(17%)
Assessed for Safety				
Adverse Events	149	(100%)	156	(100%)
Laboratory Tests	141	(95%)	140	(90%)

a Of the subjects withdrawn from treatment, 11 trovafloxacin and 23 ofloxacin/clindamycin subjects completed study.
b Based on number of randomized subjects.

Medical officer's comments:
There were 21/155 (14%) and 27/161(17%) bacteriologically evaluable patients, and 65% and 60% clinically evaluable patients in the trovafloxacin and ofloxacin/clindamycin groups, respectively.

APPEARS THIS WAY ON ORIGINAL

Table 125.3 Summary of Premature Discontinuations From Treatment (All Treated Subjects)

	Trovafloxacin (N=149)		Ofloxacin/Clindamycin (N=156)	
	Number and Percentage (%) of Subjects			
Total Discontinued	30	(20%)	47	(30%)
Discontinuations Related to Study Drug:	17	(11%)	24	(15%)
Adverse Event	17	(11%)	21	(13%)
Insufficient Response	0		3	(2%)
Discontinuations Unrelated to Study Drug:	13	(9%)	23	(15%)
Adverse Event	1	(<1%)	2	(1%)
Did not meet Randomization Criteria	1	(<1%)	0	
Laboratory Abnormality	0		1	(<1%)
Lost to Follow-up	8	(5%)	9	(6%)
Other	1	(<1%)	5	(3%)
Protocol Violation	1	(<1%)	1	(<1%)
Withdrawn Consent	1	(<1%)	5	(3%)

Medical officer's comments:
Although more patients were discontinued from the ofloxacin/clindamycin group overall, the number of discontinuations from adverse events and insufficient response (related to study drug) were the same in each arm.

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Table 125.4 Summary of patients disqualified from efficacy analysis

	Trovafloxacin 200 mg qd	Ofloxacin 400mg b. i. d./ Clindamycin 450mg q. i. d.
Clinically Not Evaluable Subjects	51	62
Randomized, Not Treated	5	4
No post- baseline clinical assessments	31	40
Insufficient Therapy	26	35
Concomitant Antibiotic Therapy	23	22
Intercurrent Illness	2	3
Others	0	1
Bacteriologically Not Evaluable Subjects	80	70
No baseline pathogen	76	69
No post- baseline cultures	76	67

Medical officer's comments:
After review of the case report forms for patients on concomitant therapy, and review of the applicant's failures and nonevaluable group, the reviewer accepted the applicant' s evaluable population.

DEMOGRAPHICS

Table 125.5 Demographic Characteristics of Randomized and Clinically Evaluable Subjects

	Trovafloxacin 200 mg	Ofloxacin 400mg b. i. d. / Clindamycin 450mg q. i. d.
Number of Subjects	149	156
Age (yr)		
16- 44	146(98%)	154(99%)
45- 64	3(2%)	2(1%)
Mean	26.7	26.7
Minimum	(b)(4)	
Maximum		
Race		
BLACK	75(50%)	69(44%)
HISPANIC	18(12%)	33(21%)
NATIVE AMERICAN	0	1(<1%)
ROMANIAN	0	1(<1%)
WHITE	56(38%)	52(33%)
Weight (kg)		
Mean	70.2	67.8
Minimum	(b)(4)	
Maximum		
Missing	1	0

Medical officer's comments:
The groups are comparable for race, weight and age.

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APPLICANT'S EFFICACY ANALYSIS

Table 125.6 Summary of Sponsor-Defined Clinical Response Rates at the End of Study Visit (Clinically Evaluable Subjects)

	Trovafloxacin (N=101)		Ofloxacin/Clindamycin (N=97)		95% CI
	Number and Percentage (%) of Subjects				
End of Study:					
Number of Subjects Assessed	101	(100%)	97	(100%)	
Cure	92	(91%)	89	(92%)	(-8.5, 7.1)
Failure	9	(9%)	8	(8%)	

CI=Confidence Interval

Medical officer's comments:
Statistical equivalence of the two treatment regimens was supported by the 95% confidence intervals for clinical cure rates at the end of study (trovafloxacin: 91%; ofloxacin/clindamycin: 92% [CI with continuity correction: (-9.5, 8.1)].

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Table 125.7 Summary of Clinical Cure Rates at the End of Study Visit For the Most Frequently Isolated Baseline Pathogens[a] (Clinically Evaluable Subjects)

	Trovafloxacin (N=101)	Ofloxacin/Clindamycin (N=97)
	Number of Subjects	
Pathogen	End of Study	
N. gonorrhoeae	12/12	8/8
C. trachomatis	11/12	14/14

a Includes ≥5 isolates of a given pathogen in any treatment; percents displayed only when denominator is ≥15. A subject could have had more than one pathogen isolated at baseline.

Medical officer's comments:
All the clinically evaluable patients with a baseline pathogen, with the exception of one patient in the trovafloxacin arm with *C. trachomatis,* were cured. This is contrast with the inpatient study in which there was a poor clinical response in the trovafloxacin arm for patients with *N. gonorrheae* (see table 122.8).

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Table 125.8 Summary of Bacteriologic Response rates at the EOS for Bacteriologically evaluable subjects (Table J in study report)

	Trovafloxacin n=21	Ofloxacin/clindamycin n=27
Satisfactory	21/21 (100%)	25/27 (93%)
Unsatisfactory	0	2 (7%)

Medical officer's comments:
Comparable percentages of satisfactory bacteriologic responses were seen in the two study groups.

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Table 125.9 Summary of the Differences Between Investigator-Defined and Sponsor Defined Clinical Responses at the End of Study (Clinically Evaluable Subjects)

Subject Number	Investigator Assessment	Sponsor Assessment	Reason
Trovafloxacin:			
5906-0024	Cure	Failure	Concomitant antibiotics for inadequate response (Day 28)
5920-0181	Not Assessable	Failure	Concomitant antibiotics for inadequate response (Day 17)
Ofloxacin/Clindamycin:			
5756-0103	Cure	Failure	Concomitant antibiotics for inadequate response (Day 3)
6109-0218	Not Assessable	Failure	Concomitant antibiotics for inadequate response (Day 4)

Medical officer's comment:
The case report forms for these patients were reviewed and the reviewer agrees with the sponsor's assessment in each case.

BEST POSSIBLE

BEST POSSIBLE

SAFETY

Table 125.10 Summary of the Most Commonly Reported Adverse Events[a,b] by Body System - All Causality (All Treated Subjects)

	Trovafloxacin (N=149)		Ofloxacin/Clindamycin (N=156)	
	Number and Percentage (%) of Subjects			
Number of Subjects With at Least One Adverse Event	114	(77%)	110	(71%)
BODY SYSTEM WHO Term				
CENTRAL AND PERIPHERAL NERVOUS	69	(46%)	24	(15%)
Dizziness	55	(37%)	10	(6%)
Headache	31	(21%)	12	(8%)
GASTROINTESTINAL	61	(41%)	80	(51%)
Abdominal Pain	12	(8%)	8	(5%)
Diarrhea	10	(7%)	34	(22%)
Dyspepsia	2	(1%)	8	(5%)
Nausea	36	(24%)	41	(26%)
Vomiting	16	(11%)	23	(15%)
REPRODUCTIVE	28	(19%)	34	(22%)
Vaginitis	19	(13%)	27	(17%)
SPECIAL SENSES	10	(7%)	21	(13%)
Taste Perversion	4	(3%)	21	(13%)

a ≥5 % of subjects in any treatment group.
b Includes data up to 7 days after last dose of active study medication
Ref.: Tables 6.2 and 6.4

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Table 125.11 Supplemental table of adverse events (provided by FDA statistician)

Safety	Trovafloxacin	ofloxacin/Clindamycin	Fisher's p value
Central and Peripheral nervous system	65 (43.6%)	24 (15.4%)	<0.001
Dizziness	55 (36.9%)	10 (6.4%)	<0.001
headache	31 (20.8%)	12 (7.7%)	0.002
Discontinuations due to an AE	19/149 (12.8%)	24/156 (15.4%)	0.622
Clinically significant lab abnormalities	44/141 (31.2%)	41/140 (29.3%)	0.795

Medical officer's comments:
The percentages of dizziness and headache were higher in the trovafloxacin than in the ofloxacin/clindamycin arm, and these differences were statistically significant.

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Laboratory Abnormalities
One subject in the ofloxacin/clindamycin group was discontinued from treatment due to laboratory abnormalities.

Two subjects (1%) in the trovafloxacin group and 2 subjects (1%) in the ofloxacin/clindamycin group had clinically significant elevations in aspartate aminotransferase (SGOT); one subject

(<1%) in the trovafloxacin group and two subjects (1%) in the ofloxacin/clindamycin group had clinically significant elevations in alanine aminotransferase (SGPT).

[redacted] APPEARS THIS WAY ON ORIGINAL

Conclusions

Trovafloxacin equivalent to ofloxacin/clindamycin in the treatment of pelvic inflammatory disease caused by *N. gonorrheae* or *C. trachomatis* in outpatient ambulatory patients.
However, alatrofloxacin/ trovafloxacin did not achieve equivalence with cefoxitin/doxycycline in hospitalized patients with PID caused by *N. gonorrheae* or *C. trachomatis* (insufficient number of subjects enrolled).

[redacted] APPEARS THIS WAY ON ORIGINAL

Recommendations

It is recommended that trovafloxacin be approved for the treatment of pelvic inflammatory disease caused by *N. gonorrheae* or *C. trachomatis* in ambulatory patients only.

[redacted] DRAFT LABELING

/s/ [redacted]

Mamodikoe K. Makhene, M.D.
Medical Reviewer, HFD-520

[redacted] APPEARS THIS WAY ON ORIGINAL

cc:

IND (b)(4) [redacted]
IND
NDA 20-759, 760
HFD-590/ Deputy Div Director/Albrecht
HFD-590/Medical TL/Leissa
HFD-344/DSI/Thomas
HFD-520/PharmTox/Ellis
HFD-520/Chemistry/Shetty
HFD-520/Microbiology/Altaie
HFD-590/Biopharm/Colangelo
HFD-590/CSO/Anderson
mkm/11/17/98
HFD-520/MO/MAKHENE

/s/ [redacted] 11/17/98
concurrence only:
HFD-590/Division Director/Goldberger

40J.

MEDICAL REVIEW OF NDA 20-759

NOV 19 1998

Applicant:
Pfizer Inc.
Central Research Division
Eastern Point Road
Groton, CT 06340
Contact person: Ronald Trust, Ph.D., M.B.A.

Submission/Review dates

Date of submission:	December 27, 1996
Date review begun:	February 24, 1997
First draft of review completed:	June 23, 1997
Second draft completed:	December 31, 1997
Date received from secondary reviewer:	October 21, 1998
Date review completed:	November 17, 1998

Related drugs
(b)(4) [redacted]

Currently approved indications: none

Material reviewed: Electronic submission

REGULATORY BACKGROUND

(b)(4) [redacted]

PROPOSED LABELLING

DRAFT LABELING [redacted]

AGENTS APPROVED FOR THE TREATMENT OF CHLAMYDIA URETHRITIS/CERVICITIS

Ofloxacin, Azithromycin and Grepafloxacin have been approved for the treatment of nongonococcal urethritis due to *Chlamydia trachomatis;* these products achieved eradication rates of 95% or better when compared with doxycycline in the treatment of non-gonococcal urethritis.

REGULATORY GUIDANCE

1. 1992 DAIDP Points to Consider

Establish equivalence or superiority to an approved product in one statistically adequate and well-controlled, multicenter trial in men, and one statistically adequate and well-controlled, multicenter trial in women.

2. IDSA/FDA Guidelines [Clin Infectious Dis 1992; 15(S1):131-9]

a) Subjects should be stratified for randomization according to gender if men and women are included in the same trial

b) Subjects (b)(4) can participate with the consent of a parent/guardian, or if they are considered emancipated minors according to local regulations.

c) A minimum of two centers with no single site contributing greater than 60% of the evaluable subjects should be involved. One hundred evaluable patients in each trial should be treated with the investigational drug and 100 with the control regimen; these numbers should be attained separately for men and women.

d) The presumptive enrollment of subjects on the basis of unprotected sexual contact with a documented case of *C. trachomatis* urogenital infection within the preceding 4 weeks is acceptable, but the isolation of *C. trachomatis* or documentation of chlamydial urethritis or cervicitis is necessary for continued participation in the study.

e) At least 3 follow-up visits should be scheduled:

- 2-4 days after completing multiple dose treatment
- 1-2 weeks after this visit
- 4-6 weeks after the treatment is complete to document the eradication of *C. trachomatis*. At least 60% of those who return for the visit at 2-3 weeks must return for the 4-6 week final visit.

f) The primary criteria for evaluability include:

- meeting of the case definition and the inclusion criteria
- the successful collection of specimens
- the completion of the treatment regimen (80% or greater compliance).

g) Eradication of *C. trachomatis* defines the primary outcome measure, microbiologic response and the overall cure. Unless the serotypes differ, isolation of *C. trachomatis* at any visit within the follow-up period represents persistence or reappearance of *C. trachomatis* infection.

APPEARS THIS WAY ON ORIGINAL

NON-CLINICAL STUDIES

(b)(4)

Animal Pharmacology/Toxicology

See Toxicology review by A. Ellis, Ph.D.

Microbiology

See Microbiology review by S. Altaie, Ph.D.

CLINICAL STUDIES

Human Pharmacokinetics/Pharmacodynamics

See full review by P. Colangelo, Ph.D.

Trovafloxacin's biologic half-life is approximately 9 to 11 hours. The mean bound fraction in plasma samples is approximately (b)(4) Steady state concentrations are achieved by the third daily dose. In adult subjects, the pharmacokinetics of trovafloxacin are not affected by age or gender. The peak blood level (Cmax) of trovafloxacin

at a 200 mg oral dose is 2.5 ug/mL and tissue/ serum concentration ratios in the cervix after single and multiple doses of trovafloxacin 200 mg were 0.5 ug/mL (3-29 hr postdose) and 0.6 ug/mL (3-16 hr postdose), respectively.

APPEARS THIS WAY ON ORIGINAL

Human Clinical Experience
The efficacy and safety of trovafloxacin for several indications were evaluated in 45 phase I studies and 31 phase II/III studies.

APPEARS THIS WAY ON ORIGINAL

INTRODUCTION TO CLINICAL TRIALS
The applicant submitted 2 pivotal clinical trials in support of this indication. The first was an unblinded, dose ranging study for the treatment of urogenital chlamydial infection with trovafloxacin. After completion of this study, the efficacy and safety of oral trovafloxacin 200 mg qd for 5 days in the treatment of uncomplicated chlamydial urethritis/ cervicitis was assessed in a randomized, double-blind, comparative trial, with the standard Center for Disease Control and Prevention (CDC) recommended doxycycline regimen as the comparator.

APPEARS THIS WAY ON ORIGINAL

Study 154-123
Title: "A double blind, randomized, comparative study of trovafloxacin in the treatment of uncomplicated chlamydial urethritis/cervicitis."

APPEARS THIS WAY ON ORIGINAL

Primary objective
To compare the safety and efficacy of trovafloxacin and doxycycline in the treatment of subjects with uncomplicated chlamydial urethritis/ cervicitis.

APPEARS THIS WAY ON ORIGINAL

Study design Summary

Location	multi-center, international
Total centers	41
Protocol amendments	January 12, 1995 and March 9, 1995
Study dates	27 March 1995-22 May 1996
Patient ages	16 years and older
Study dose and duration	Trovafloxacin 200-mg qd orally for 5 days
Concurrent control	Doxycycline 100 mg bid orally for 7 days
Blinding	third party blind
Method of assignment	1:1; stratification by gender
Efficacy variables	microbiologic, clinical
Safety variables	clinical signs and symptoms, laboratory results
Evaluation days (protocol window):	
Baseline	1 (within 48 hours before the start of therapy)
End of treatment-EOT	10 (9-11)
post	21 (19-23)
Test of cure (TOC) (end of study-EOS)	35 (31-39)
Number of subjects randomized	495 (trovafloxacin)/482 (doxycycline)

APPEARS THIS WAY ON ORIGINAL

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STUDY POPULATION (from the study protocol)
Approximately 500 subjects were to be enrolled in this study in order to obtain the desired 400 evaluable subjects, with 100 males and 100 females per treatment group. Each study site was to attempt to enroll at least 20 subjects.

Inclusion criteria

1. Outpatient men or women. Women of childbearing potential (i. e., not surgically sterile or < one year post-menopausal) must have had a negative urine or serum gonadotropin pregnancy test immediately prior to entry in the study, and must have used adequate contraception both during and for one month after the end of the study.
2. At least 16 years of age.
3. Males with presumptive chlamydial urethritis, defined as the presence of a

(b)(4)

[redacted]

Exclusion criteria

1. Pregnant women or nursing mothers.
2. History of hypersensitivity or intolerance to any quinolone or tetracycline
3. Inpatients.
4. Clinical evidence of gonococcal pharyngitis, proctitis, disseminated gonococcal infection, or the presence of any other infection at enrollment that may have required treatment with an antibiotic other than the study drug.
5. Treatment with any systemic antibiotic with potential anti-chlamydial activity within 72 hours prior to entry into the study (or up to two weeks or those with a positive culture or non culture test for chlamydia within two weeks prior to enrollment). Agents known to possess anti-chlamydial activity included: azithromycin, tetracycline, erythromycin, ofloxacin, ciprofloxacin, ampicillin, amoxicillin, sulfamethoxazole, clindamycin, rifampin, and rosaramycin.
6. Treatment with another investigational drug within 30 days prior to entry into the study.
7. Evidence of significant gastrointestinal or other conditions , which could affect drug absorption
8. Evidence or history of clinically significant hematologic, renal, or cardiovascular disease or immunologic compromise
9. History of epilepsy or seizures
10. Prior enrollment in this protocol
11. Subjects who for any reason in the opinion of the investigator, were not expected to comply with the requirements of this protocol.

[redacted]

APPEARS THIS WAY ON ORIGINAL

[redacted]

Medical reviewer's comments:
The reviewer agrees with the criteria chosen. Although the applicant did not exclude subjects with positive RPR or FTA at baseline, the reviewer excluded these patients.

[redacted]

APPEARS THIS WAY ON ORIGINAL

PROCEDURES (from applicant's submission)
Study medication was in the form of tablets and capsules, packaged in blister cards using a double-dummy technique to maintain blinding. The study drug administration schedule provided one of the following two doses of study drug:

trovafloxacin	200mg (2 tablets) daily as a single dose for 5 days
doxycycline	100 mg (1 capsule) bid for 7 days

Subjects began study drug medication with the morning dose (even if it was not morning), and completed a full day of medication on day 1.

Microbiologic measurements and Susceptibility testing

Susceptibility to trovafloxacin and doxycycline was determined by minimum inhibitory concentrations (MICs) for all isolates of *N. gonorrheae,* whether at baseline or at follow- up. For *C. trachomatis,* MICs were determined for two baseline isolates from each center and for all treatment failures. Susceptibility testing was subsequently performed at a central location. The criteria for determining susceptibility to the study drugs are summarized below:

CRITERIA	Trovafloxacin* MIC (ug/ml)	Doxycycline+ MIC (ug/ml)
SUSCEPTIBILITY	≤2	≤4
INTERMEDIATE	4	8
RESISTANT	≥8	≥16

APPEARS THIS WAY ON ORIGINAL

*Tentative criteria based on projections from pharmacokinetic data and *in vitro* susceptibility testing.

+NCCLS criteria.

APPEARS THIS WAY ON ORIGINAL

SUBJECT EVALUATION VISITS

Visit 1 at day 1 (Baseline)

This visit took place within 48 hours prior to the start of therapy.

APPEARS THIS WAY ON ORIGINAL

Visit 2 at day 10 (9- 11)

All subjects with culture confirmed chlamydial infection had urethral/cervical cultures for chlamydia repeated. In addition, follow-up cultures for *N. gonorrhoeae* were obtained in males or females with positive baseline cultures for *N. gonorrhoeae*, all females(endocervical culture) and any males with persistent, new, or recurrent clinical signs or symptoms of urethritis at this visit. The battery of blood and urine tests performed at baseline were repeated.

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Visit 3 at day 21 (19- 23)

Same as visit 2; in addition, the blood and urine tests performed at baseline were repeated at this visit only if clinically significant results were detected at visit 2.

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Visit 4 at day 35 (31- 39)

Visit 4 was the primary efficacy timepoint.

Same as visit 3; the blood and urine tests performed at baseline were repeated at this visit only if clinically significant results were detected at visit 3.

DRAFT LABELING

The sponsor-defined windows for evaluation were:

	protocol visit windows	applicant evaluable windows (post hoc)
Baseline	1 (within 48 hours)	
End of treatment	10	(b)(4)
post	21	
TOC (end of study)	35	

APPEARS THIS WAY ON ORIGI

The subjects were instructed not to donate blood during, and for 6 weeks following administration of study drug. Subjects were to abstain from sexual activity through the first follow-up visit. Thereafter, sexual intercourse with the use of a condom was permissible. (If unable to abstain from sexual activity until the first follow-up visit, the use of a condom was essential for the determination of evaluability).

APPEARS THIS WAY ON ORIGINAL

PROTOCOL OVERVIEW

SCHEDULE OF STUDY VISITS AND PROCEDURES (from the applicant's protocol)

	STUDY DAYS			
	Baseline Day, V1	V2	V3	V4
	1 2 3 4 5 6 7	(9- 11) [a] 10	(19- 23) 21	(31- 39) 35
Treatment	x----------x			
Compliance check		x		
History and Physical	x			
Assessments:				
Clinical	x	x	x	x
Laboratory				
1. ITA or RPR	x	x	abn[b]	abn[b]
2.Hematology	x	x	abn[b]	abn[b]
3. Serum Chemistry	x	x	abn[b]	abn[b]
4.Urinalysis	x			
5. Gram stain[c]	x			
6.Cultures for *C. trachomatis*	x	x	x	x
7.Cultures for *N. gonorrhoeae*	x	x	x	x
8.Pregnancy test[d]	x			
Adverse Events	x	x	x	

[a] window for follow-up visit
[b] Only for clinically significant abnormalities present at previous visit
[c] Where feasible (i.e. presence of urethral or cervical discharge)
[d] For women of childbearing potential
abn=abnormal

Medical reviewer's comments:
Safety evaluations were done up to visit 3 only indicating that adverse events occurring between visit 3 and the end of the study at visit 4 were likely missed.

Medical reviewer's comments:
The applicant's protocol windows and test-of-cure (TOC) visit at the end of study were consistent with the 1992 IDSA/FDA guidelines. The CDC guidelines [MMWR Sept 24, 1993; 42(RR-14):51] recommend that follow-up of patients treated for urogenital chlamydial infections be done at least 3 weeks after completion of treatment since the validity of testing done before 3 weeks after the completion of therapy has not been established. Based on this recommendation for the timing of the TOC visit, and the fact that few patients in the study had their TOC between days 28-31(lower limit of protocol vs. post hoc analysis windows), the reviewer accepted the applicant's evaluable windows for the analysis of the data.

APPEARS THIS WAY ON ORIGINAL

EVALUABILITY CRITERIA

Applicant's Criteria for Bacteriological Evaluability
Subjects were considered non-evaluable for bacteriological efficacy if any of the following was present:

1. a subject who did not have culture confirmation of *C. trachomatis* at baseline.
2. the baseline culture was done more than 2 calendar days prior to the first dose of study medication.
3. cultures were not obtained in the relevant time period after end of therapy, unless a previous post-baseline culture was positive.
4. a subject took an antibiotic with potential anti-chlamydial activity within 3 calendar days before Day 1 (excluded any antibiotic begun on Day 1).
5. a subject was prescribed a concomitant antibiotic (at any time before the end of study assessment) that was potentially effective against the condition under study. The use of concomitant antibiotic therapy due to insufficient therapeutic effect of the study medication was not a reason for exclusion from the bacteriologically evaluable subjects subset.
6. A subject who discontinued study medication, for any reason other than insufficient therapeutic effect, before the protocol-specific minimum requirement (4 days).
7. A subject who took study drug for at least the protocol-specific minimum requirement, but was less than 80% compliant with the study drug regimen.

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Medical reviewer's comments:
In addition to the applicant's criteria, the medical reviewer included the criteria outlined below:

- any patient with a positive culture at initial follow-up and within the 6 week follow-up period was bacteriologically evaluable and was considered to have persistent or recurrent infection
- any patient treated for an intercurrent illness with an antimicrobial agent with anti-chlamydial activity during the course of the study was considered an evaluable failure (differs from the applicant's criteria #5 above)
- any patient given concomitant antibiotic for continued clinical symptoms or positive culture was considered an evaluable failure
- patients treated for syphilis were bacteriologically evaluable as long as not treated with an antibiotic with potential anti-chlamydial activity
- patients with unprotected sexual contact during the study period were not evaluable

Applicant's Criteria for Clinical Evaluability

1. Subjects must have had at least one of the following clinical signs or symptoms recorded at the baseline visit:
   - urethral discharge
   - burning

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- painful urination
- cervical discharge
- cervical erythema
- cervical friability
- cervical edema
- cervical ectopy

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2. A subject who developed an intercurrent illness whose clinical course confounded the clinical evaluation of the disease or condition under investigation was not evaluable.

3. In order to be evaluable, a subject must have had an assessment in the end of study evaluable timepoint window, unless the investigator's clinical response was failure before the beginning of the End of Study window, or if a subject discontinued due to insufficient therapeutic effect before the End of Study visit.

Applicant's Criteria for Indeterminate Outcome

The following subjects were considered as having indeterminate outcomes and excluded from the evaluable visit 4 treatment analysis:

a. received less than four days of treatment unless discontinued prematurely for treatment failures.
b. inapplicable diagnosis (i. e., subject did not meet entry criteria for diagnosis of chlamydia)
c. received concomitant systemic antibiotic(s) (with potential anti-chlamydial activity) for intercurrent illness
d. no visit at evaluation timepoint unless subject was previously designated as a treatment failure
e. unprotected sexual contact during the study, prior to the follow- up assessments
f. asymptomatic subjects with positive cultures for chlamydia were clinically unevaluable but bacteriologically evaluable

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Medical reviewer's comments:
The reviewer agrees with the applicant's criteria except (c) as discussed in the medical officer comment of bacteriologic evaluability.

APPEARS THIS WAY ON ORIGINAL

CLINICAL AND MICROBIOLOGIC ENDPOINTS

Primary and Secondary Endpoints for Efficacy

The primary efficacy endpoint was bacteriological response at TOC visit.

The secondary efficacy endpoints were:

1. Clinical response at the end of study visit,
2. Pathogen outcome at each visit and pathogen eradication rates at the end of study visit.

Medical reviewer's comments:
Reviewer agrees with the choice of endpoints.

APPEARS THIS WAY ON ORIGINAL

Bacteriological Response

The bacteriological response was determined by the sponsor at visit 4, on the basis of bacterial culture findings compared to those at the pre-treatment assessment.

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Definitions of bacteriological response were as follows:

a. *Eradication:* C. *trachomatis* not present in any post-treatment culture from the same site
b. *Persistence*: Isolation of *C. trachomatis* in any post-treatment culture from the same site
c. *Recurrence*: Positive microbiologic culture at final follow-up visit

Medical reviewer's comments:
Reviewer agrees with definitions of bacteriologic response. Patients categorized with recurrence at the final follow-up visit must have had a negative microbiologic culture at Visit 2 or Visit 3.

Clinical Response
Clinical response, determined by the sponsor, was based on the evaluation at visit 4. The clinical response was based primarily on the global evaluations made by the investigator at the end of study visit who classified the clinical response of the subject as:

Cure: Complete resolution of signs and symptoms
Improvement: Incomplete resolution of signs and symptoms
Failure: No apparent response or progression of signs and symptoms

The occurrence of any of the following conditions was to supersede the investigator's assessment:

- If the investigator-defined clinical response was failure at any visit, then the sponsor-defined clinical response was failure at all subsequent visits.
- If a subject was given a concomitant antibiotic at any time for incomplete clinical response or failure, then the sponsor-defined clinical response was failure at that visit or the prior visit if within 1 day of the concomitant antibiotic dosing and all subsequent visits.

However, subjects who were given a concomitant antibiotic prior to the evaluation timepoint were classified as failure if the concomitant antibiotic was given for incomplete clinical response or failure.

Medical reviewer comments:
The reviewer accepted these definitions of clinical and bacteriologic responses.

SAFETY
Adverse events were monitored up to visit 3 and serious adverse events were monitored throughout the study and for 30 days after the last dose of the study drug. Events involving adverse drug reactions, illnesses with onset during the study, or exacerbations of pre-existing illnesses, and objective test findings (e.g., abnormal laboratory test results) that result in a change in study drug dosage were to be recorded and followed-up until resolved or stabilized.

Serious adverse events included any experience that suggested a significant hazard, such as events which were fatal, life threatening, resulted in permanent disability, required inpatient hospitalization or prolongation of a hospital stay, or involved cancer, a congenital anomaly, or drug overdose.

Clinical laboratory tests (hematology, biochemistry, and urinalysis) were performed at baseline and at visit 2. Additional tests were done at visit 3 and 4 if clinically indicated or if a clinically significant abnormality was present at visit 2 or 3.

STATISTICAL CONSIDERATIONS
Methods of analysis (from the protocol)
There were no planned interim analyses for this study. All statistical tests of significance were performed as two-sided tests (unless otherwise specified). No adjustments were made to significant levels for multiple endpoints for the same data. The Cochran-Mantel-Haenzel test controlling for center was used to compare the treatments for clinical and bacteriological response.

Also, 95% confidence intervals were produced for the difference between effects for cure and eradication rates. (For the confidence interval calculations, cure indicated cured or improved).

Baseline comparability of the treatment group was assessed for gender, age, race, and weight.

Clinical analyses were performed by comparing clinical outcomes at visit 4, based primarily on the global assessment made by the investigator. Subjects with no clinical information after baseline were considered as clinical treatment failure.

Bacteriological analyses was performed by comparing bacteriological outcomes at visit 4.

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PROTOCOL DEVIATIONS (from study report)
Significant deviations from protocol were noted for 19 subjects:

- 5 subjects became pregnant during the study and one subject was pregnant at baseline;
- 13 subjects were randomized into the incorrect strata: 12 females were intentionally assigned male randomization numbers due to shortages of female drug supply and one male was inadvertently randomized to a female randomization number);
- 2 subjects took only the tablet or capsule portion of their assigned study drug.

APPEARS THIS WAY ON ORIGINAL

RESULTS
Investigators and study sites

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PATIENT ENROLLMENT AND DISPOSITION

Table 123.1 Patients enrolled and bacteriologically evaluable by center (modified by reviewer from applicant's table 1.3)

		Trovafloxacin 200mg qd x 7 days			Doxycycline 100mg bid x 5 days		
center ID	randomized	enrolled	evaluable	% evaluable	enrolled	evaluable	% evaluable
5003	2	2	0	0	0	0	0
5012	95	47	25	53	48	26	54
5039	67	34	22	65	33	18	55
5068	39	20	12	60	19	10	53
5069	71	36	22	61	35	23	66
5078	3	2	0	0	1	0	0
5154	12	7	1	14	5	0	0
5162	27	13	8	62	14	3	21
5164	25	13	3	23	12	3	25
5166	156	78	45	58	78	39	50
5472	26	13	8	62	13	9	69
5473	12	6	2	33	6	2	33
5474	24	12	6	50	12	6	50
5506	46	24	11	46	22	10	45
5522	8	4	1	25	4	2	50
5649	8	5	4	80	3	1	33
5650	26	14	2	14	12	2	17
5680	26	12	6	50	14	7	50
5682	5	1	0	0	4	0	0
5683	13	6	4	67	7	2	29
5684	10	6	0	0	4	0	0
5685	24	11	4	36	13	8	62
5741	57	30	29	97	27	25	93
5762	9	5	1	20	4	1	25
5857	35	16	7	44	19	11	58
5858	20	10	5	50	10	7	70
5859	15	8	5	63	7	5	71
5989	25	13	10	77	12	8	75
6041	13	6	5	83	7	4	57
6109	16	8	3	38	8	5	63
6279	48	25	9	36	23	5	22
6282	3	2	2	100	1	1	100
6423	8	4	2	50	4	3	75
6449	3	2	1	50	1	0	0
total	977	495	265	54	482	246	51

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Medical reviewer's comments:
Patients appeared to have been randomized evenly between the two treatment groups at each of the centers. In total, 41 sites participated and enrolled subjects; there was no site without enrollment. Seven sites had enrollment of 20 or more subjects (per arm) and accounted for about 55% of the enrollments (per arm). At site 5741, greater than 90% of the randomized subjects were evaluable in both arms, while the other 6/7 sites had (b)(4) evaluable subjects from those randomized. There was an average of 6.5 subjects enrolled per site. Of the 977 randomized patients, 569 completed the treatment and study while 511 were evaluable bacteriologically based on the applicant's results.

Table 123.2 Discontinuations from Study---Treated Subjects (from applicant's table 4.3.2)

	Trovafloxacin 200 mg qd	Doxycycline 100 mg b. i. d.
Number of Treated Subjects	489(100%)	481(100%)
Discontinued Subjects	187(38%)	205(43%)
Related to Study Drug	3(< 1%)	2(< 1%)
ADVERSE EVENT	2(< 1%)	1(< 1%)
INSUFFICIENT RESPONSE	1(< 1%)	1(< 1%)
Not Related to Study Drug	184(38%)	203 (42%)
ADVERSE EVENT	0	1(< 1%)
DOES NOT MEET RANDOMIZATION CRITERIA	2(< 1%)	0
LOST TO FOLLOW- UP	41(8%)	44(9%)
OTHER	130(27%)	148(31%)
PROTOCOL VIOLATION	5(1%)	6(1%)
WITHDRAWN CONSENT	6(1%)	4(< 1%)

Percents are based on the number of treated subjects in each treatment group.

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Medical reviewer's comments:
The case report forms for subjects discontinued from the study were reviewed and the reviewer agrees with the applicant regarding their disposition.

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Table 123.3 Subject disposition for enrolled subjects (from applicant's table 1.1, 1.2.1, 1.2.2)

	Trovafloxacin 200 mg qd	Doxycycline 100 mg b.i.d.
Randomized	495	482
Treated	489	481
Withdrawn During Treatment	28	37
Completed Treatment	462	444
Withdrawn from study	187	205
Withdrawn During Treatment and Study	25	31
Withdrawn During Follow-up	162	174
Completed Study	303	276
Completed Treatment and Study	299	270
Negative Baseline Culture	163	181
Bacteriological Intent-to-Treat	332	301
Bacteriologically Evaluable	265	246
Clinically Evaluable	181	179
Analyzed for Safety (a)		
Adverse Events	489	481
Laboratory Data	366	381

(a) Based on number of treated subjects

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Medical Reviewer's comments:
The reviewer notes that in the trovafloxacin arm, 489 were treated and 462 completed treatment; therefore the number who withdrew during treatment is 27.

Table 123.4 Study Evaluation Groups--Randomized Male and Female Subjects (from applicant's tables 1.2.1, 1.2.2)

	Males		Females	
	Trovafloxacin	Doxycycline	Trovafloxacin	Doxycycline
All Randomized Subjects	203	203	292	279
All Treated Subjects	200	203	289	278
Negative Baseline Culture	77	80	86	101
Inappropriate Baseline Diagnosis	0	1	3	1
Subjects with No Baseline Clinical Signs and Symptoms	31	29	61	50
Bacteriological Intent-to-Treat	126	123	206	178
Bacteriologically Evaluable	100	102	165	144
Bacteriologically Not Evaluable	26	21	41	34
Randomized, Not Treated	2	0	1	0
No post- baseline cultures	19	21	36	30
Insufficient therapy	6	7	6	9
Concomitant antibiotics	6	2	11	6
Clinical Intent- to- Treat	95	93	142	127
Clinically Evaluable	72	79	109	100
Clinically Not Evaluable	28	23	56	44
No post- baseline clinical assessments	21	15	50	38
No baseline clinical signs and symptoms	26	21	51	41
Analyzed for Safety (a)				
Adverse Events	200	203	289	278
Laboratory Data	146	164	220	217

(a) Based on number of treated subjects

DEMOGRAPHICS

Table 123.5 Demographic Characteristics--Treated Subjects (applicant's Table 2.1.1)

	Trovafloxacin (200 mg)			Doxycycline (100 mg b.i.d.)		
	Male	Female	Total	Male	Female	Total
Number of Subjects	200	289	489	203	278	481
Age (yr)						
<16	0	0	0	0	1(<1%)	1(<1%)
16-44	194(97%)	285(99%)	479(98%)	198(98%)	272(98%)	470(98%)
45-64	6(3%)	4(1%)	10(2%)	5(2%)	5(2%)	10(2%)
Mean	27.4	23.5	25.1	26.4	24.2	25.1
Minimum	(b)(4)		(b)(4)		(b)(4)	
Maximum						
Race						
AMERICAN INDIAN/ALASKAN	1	0	1	0	0	0
ARABIAN	2(1%)	1(<1%)	3(<1%)	1(<1%)	0	1(<1%)
ASIAN	1(<1%)	2(<1%)	3(<1%)	1(<1%)	3(1%)	4(<1%)
BLACK	124(62%)	169(58%)	293(60%)	119(59%)	173(62%)	292(61%)
EAST INDIAN	0	0	0	1(<1%)	0	1(<1%)
HISPANIC	4(2%)	8(3%)	12(2%)	8(4%)	4(1%)	12(2%)
JAPANESE	1(<1%)	0	1	0	0	0
LATINO	0	0	0	0	1	1
MIXED (WHITE + ASIAN)	0	1	1	0	0	0
NATIVE AMERICAN	0	1(<1%)	1(<1%)	0	0	0
PALESTINIAN	0	1(<1%)	1(<1%)	0	0	0
PHILIPINO	0	0	0	0	1(<1%)	1(<1%)
WHITE	67(34%)	105(36%)	172(35%)	73(36%)	95(34%)	168(35%)
WHITE/HISPANIC	0	1(<1%)	1(<1%)	0	1(<1%)	1(<1%)
Weight (kg)						
Mean	78.3	66.9		78.4	66.1	
Minimum	(b)(4)			(b)(4)		
Maximum						

Medical reviewer's comments:
More women than men were treated in the study and less than 5% of the subjects were 45 years and older. Overall, the groups appeared comparable for age, race and weight.

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Table 123.6 Demographic Characteristics of Clinically Evaluable Subjects (modified by reviewer from applicant's table 2.1.2)

	Males		Females	
	Trovafloxacin	Doxycycline	Trovafloxacin	Doxycycline
Number of Subjects	100	102	165	144
Age (yrs)				
<16	0	0	0	1
16- 44	98	100	163	143
45- 64	2	2	2	0
Mean	26.6	25.5	22.7	23.0
Range	(b)(4)	(b)(4)	(b)(4)	(b)(4)
Race				
ARAB	1	0	1	0
ASIAN	0	1	0	2
BLACK	61	56	90	85
HISPANIC	0	5	4	2
PALESTINIAN	0	0	1	0
WHITE	38	40	68	55
WHITE/ HISPANIC	0	0	1	0
Weight (kg)				
Mean	78.4	79.1	66.3	66.3
Minimum	(b)(4)		(b)(4)	(b)(4)
Maximum				
Missing	0	0	1	0

There were no marked differences between subjects in the trovafloxacin and doxycycline groups with respect to medical history at baseline.