Primary and Secondary Endpoints for Efficacy:

The sponsor provided the text for both their initial analysis as well as for that which was developed later, that is that of a staggered analysis. Therefore, although V4 is not mentioned, the primary efficacy endpoint was sponsor-defined clinical response at V4 for the trovafloxacin-treated patients and V5 for the ofloxacin-treated patients.

Copied below, from page 28 of the study report are the secondary efficacy endpoints:

> Sponsor-defined subject clinical response three to six weeks post-therapy in the new analyses; Visit 4 and end-of-study per the protocol.
>
> Investigator-defined subject clinical response one week post-therapy in the new analyses; Visits 4, 5, and end-of-study per the protocol.
>
> Sponsor-defined subject bacteriological response one week post-therapy in the new analyses; Visits 4, 5, and end-of-study per the protocol.
>
> Sponsor-defined organism outcome one week post-therapy in the new analyses; Visits 4, 5, and end-of-study per the protocol.

Medical Officer's Comment: *The MO agreed with these endpoints (although they were not strictly adhered to in the sponsor's analysis), and their definitions as provided below:*

Sponsor-Defined Subject Clinical Response:

For both evaluable and intent-to-treat subjects, sponsor-defined subject clinical response was based primarily on the global evaluations made by the investigator at Visits 4 and 5 and the end of study visit. The occurrence of any of the following conditions were to supersede the investigator's assessment.

1. Failure: If the investigator-defined subject clinical response was failure at any visit, then the sponsor-defined subject clinical response was failure at all subsequent assessments.

2. Failure: If a subject was given a concomitant antibiotic for insufficient clinical response during double-blind therapy plus one day then the sponsor-defined subject clinical response was failure at the end of treatment and all subsequent assessments. If a subject was given a concomitant antibiotic for insufficient clinical response at any time before the assessment plus one day the sponsor-defined clinical response was failure at that assessment and all subsequent assessments. If a subject did not have an assessment in a particular window and was given and antibiotic for insufficient response in that assessment window then the sponsor-defined clinical response was failure at that timepoint and all subsequent assessments.

3. Failure: If a subject had no post-baseline assessment, then the sponsor-defined clinical response was failure at all visits (Intent-to-Treat Analysis only).

4. Recurrence:

   If a subject was a clinical cure or improvement at Visit 5 and was assessed by the investigator to be a failure at the end of study, then that subject was classified as a clinical recurrence at the end of study.

   If a subject was a clinical cure or improvement at Visit 5, but required additional antibiotic therapy for the primary disease before the end of study, then the subject was classified as a clinical recurrence at the end of study.

For the analysis of the clinical intent-to-treat subject subset, a "last observation carried forward" strategy was used for subjects who were lost to follow-up before the end of study. If, for any reason, no clinical assessment was made at Visit 4, but an assessment was made at Visit 5, then the Visit 4 assessment was treated as missing data.

CIs (95%) for differences in clinical success (cure + improvement) rates between treatments were calculated using the normal approximation method as the primary means to compare treatment groups. The Cochran-Mantel-Haenszel test controlling for centers was also done. Centers with less than five observations in either or both treatment groups were pooled for the purposes of the analysis.

Medical Officer's Comment: *The MO agreed with the sponsor's proposed definitions and points out that ultimate clinical assessments of cure were made by the investigators but that the sponsor's determination superseded that of the investigators' in the cases of failures that were not carried forward.*

Sponsor-Defined Subject Bacteriological Outcome (copied from page 29 of the study report):

The sponsor-defined subject bacteriological assessment was defined as follows:

1. Complete Eradication: Eradication of all initial pathogens.
2. Partial Eradication: Eradication of at least one, but not all initial pathogens.
3. Complete Persistence: Persistence of all initial pathogens.
4. Recurrent Infection: Appearance of one or more of the initial baseline pathogens, eradicated at Visit 5, but with recurrence of the eradicated pathogen(s) at the end of study.

CIs (95%) for differences in subject bacteriological eradication (complete + partial) rates between treatments were calculated using the normal approximation method as the primary means to compare treatment groups. The Cochran-Mantel-Haenszel test controlling for centers was also done. Centers with less than five observations in either or both treatment groups were pooled for the purposes of the analysis.

Medical Officer's Comment: *Once again the sponsor did not refer to V4 in the above statement. The MO agreed with these definitions but repeats that only Gram (-) isolates or Enterococcus faecalis were considered evaluable pathogens. All coagulase (-) gram (+) isolates were considered evaluable only if they were the sole organism isolated and met the aforementioned criteria.*

Sponsor-Defined Pathogen Outcome (copied from pages 29 –31 of the study report):

For both evaluable and intent-to-treat subjects, the sponsor classified each baseline organism as a pathogen or as a non-pathogen. Each baseline pathogen was assigned a sponsor-defined pathogen outcome. Multiple baseline pathogens identified in culture samples from the same subject were assigned separate outcomes. Baseline pathogens were assigned a separate outcome at Visits 4 and 5 and the end of study.

1. Eradication: Baseline pathogen was absent from a culture from VB_3 and EPS. Or, absent only from EPS or VB_3 if the baseline pathogen was identified in EPS or VB_3 only, respectively. If the subject was started on a concomitant antibiotic for insufficient response on the same day or up to 3 days after this negative culture, the eradication was carried forward to all subsequent visits, regardless of subsequent culture results. If the subject was lost to follow-up, the eradication was carried forward to subsequent implied visits. (clinical failure but bacteriologic eradication)

   Presumed Eradication: No culture results (i.e., not done), and subject was clinically cured or improved.

Persistence: Baseline organism is present in EPS. Or, the baseline organism was present in VB_3 if the baseline pathogen was identified in VB_3. If the subject was started on a concomitant antibiotic for insufficient response on the same day or up to 3 days after this positive culture, the persistence was carried forward to all subsequent visits, regardless of subsequent culture results. (Clinical failure and bacteriologic persistence). If the subject was lost to follow-up, persistence was carried forward to subsequent implied visits.

2. Presumed Persistence:

   Use of concomitant antibiotic therapy due to insufficient response, not starting on the same day as, or within 3 days after, a positive or negative culture, in the absence of prior microbiological data in the same evaluable analysis window resulted in a sponsor-defined pathogen outcome of presumed persistence at that visit and all subsequent implied visits, regardless of subsequent culture results. If the subject was lost to follow-up then the presumed persistence was carried forward to subsequent implied visits. Absence of microbiological data was defined as either no visit in the window or culture not done (results from VB_3 or EPS were missing) at all visits in the window.

   Culture was not done (results from VB_3 or EPS were missing) and the sponsor-defined subject clinical response was failure.

   The baseline pathogens of subjects who were lost to follow-up (i.e., no visit) at Visits 4, 5 or the end of study were assigned the outcome presumed persistence if the organism was persistent at any previous visit.

3. Recurrence: The original baseline pathogen was present at end of study after a previous post-baseline culture was negative at Visit 5 (applicable at end of study only).

In addition, organisms not present at baseline were classified as follows:

1. Superinfection: A pathogen, other than one identified at baseline, that was identified at any post-baseline time in culture material obtained from the site of infection and associated with emergence or worsening of clinical evidence of infection.

2. Colonization: Any organism, other than one identified at baseline, that was identified at any post-baseline time in culture material obtained from the site of infection and not associated with signs or symptoms of active infection.

CIs (95%) for differences in pathogen eradication rates between treatments were calculated using the normal approximation method as the primary means to compare treatment groups. The Cochran-Mantel-Haenszel test controlling for centers was also done. Centers with less than five observations in either or both treatment groups were pooled for the purposes of the analysis.

Medical Officer's Comment: *Although the MO agreed with the general proposal/definitions of the sponsor, the MO was unclear as the meaning of the underlined statements and requested clarification from the sponsor on June 17. 1997. The sponsor responded that the intent of the statements was to reflect the timing of when a response was carried forward. The MO has added the potential responses in Times New Roman font.*

If a patient was a clinical cure with documented bacteriologic eradication and was given an antibiotic for insufficient response within 3 days of a visit, they were classified as a clinical failure with bacteriologic eradication since this would have been the last culture obtained. If this occurred 4 days after the visit then the patient was classified as a clinical cure with bacteriologic failure or recurrence depending on the timepoint.

At this point the MO determined that a change in the evaluable windows was necessary (See above). The MO presented the sponsor's analysis as is and for the MOR (utilizing the MO-defined timepoints) determined that:

- *If a trovafloxacin patient was seen twice within the context of V4 with the initial assessment being a clinical cure and the second, a clinical failure, then the failure would be the assigned assessment for this patient. In this case a V6 visit to assess for recurrence was not necessary.*

- *If a trovafloxacin-treated patient was a clinical cure at V4, then a determination for relapse/recurrence was made at V6*

- *If an ofloxacin-treated patient was a clinical cure at V5, then a determination of relapse/recurrence was made at V6.*

- *If an ofloxacin-treated patient was seen twice within V5, initially as a cure and then as a failure, the assessment for V5 was failure and the patient was not re-evaluated for recurrence at V6.*

- *Pathogens were assessed for eradication, presumed eradication, persistence, presumed persistence, recurrence, superinfection, and colonization as defined by the sponsor within the context of the MO's windows of evaluability and the MO's criteria of acceptable pathogens.*

- *The MO accepted, after review of the patient profiles and verification of the accuracy of the data, the sponsor's determination of clinical and bacteriologic efficacy. Overall, the sponsor's determinations were more conservative than those of the investigators'.*

Based on the above, the MO requested, on June 18, 1997, that the sponsor provide a reanalysis of the data utilizing the MO's evaluabilty criteria.

Demographics:

As per the sponsor, 660 subjects signed consent. 385 subjects were withdrawn prior to randomization because they did not meet entry criteria. Thus 142 subjects were randomized, to receive trovafloxacin and 135 to receive ofloxacin. All 142 randomized trovafloxacin patients received treatment as compared to 133 of the randomized ofloxacin patients. 2 randomized subjects from the ofloxacin arm did not receive therapy (see below).

Of the treated groups, 128 trovafloxacin patients and 123 ofloxacin patients completed the study and 105 trovafloxacin and 118 ofloxacin completed treatment. 37 trovafloxacin patrients or 26% as compared to 15 or 11% of the ofloxacin patients were withdrawn during treatment. An additional 7 (5%) patients on the trovafloxacin arm and 2 (2%) patients on the ofloxacin arm were withdrawn during follow-up, thus 98 (69%) trovafloxacin and 116 (87%) ofloxacin patients completed the study and treatment. 7 (5%) trovafloxacin and 8 (6%) ofloxacin patients were withdrawn from treatment and from the study.

The MO recreated the Sponsor's Table of the Disposition of Enrolled subjects (119.1)

Table 119.1
Subject Disposition, All Enrolled Patients (As per the Sponsor)

		Trovafloxacin		Ofloxacin	
		N	%	N	%
Subjects with Signed Consent	660				
Withdrawn Prior to Randomization	385				
Randomized		142	100	135	100
Randomized, But Not Treated		0	0	2	
All Treated Subjects		142	100	133	100
Withdrawn During Treatment		37	26	15	11
Completed Treatment		105	74	118	89
Withdrawn During Follow- up		7	5	2	2
Completed Study		128	90	123	92
Completed Treatment and Study		98	69	116	87
Withdrawn During Treatment and Study		7	5	8	6

Copied and modified below is the Sponsor's Table 1.3 from the Esub, which depicts the number of subjects randomized and treated by center.

Table 119.2
Number of Subjects Enrolled By Center: All Randomized Patients (As per the Sponsor, Modified by MO)

Center	Total Randomized N = 277 (100%)		Trovafloxacin				Ofloxacin			
			Randomized		Treated		Randomized		Treated	
			N = 142	100%	N = 142	100%	N = 135	100%	N = 133	100%
5005	18	6.4	9	6.3	9	6.3	9	6.6	9	6.7
5014	8	2.8	4	2.8	4	2.8	4	2.9	4	3.0
5630	12	4.3	6	4.2	6	4.2	6	4.4	6	4.5
5631	3	1.0	1	0.7	1	0.7	2	1.4	2	1.5
5642	8	2.8	4	2.8	4	2.8	4	2.9	4	3.0
5645	7	2.5	3	2.1	3	2.1	4	2.9	4	3.0
5647	9	3.2	5	3.5	5	3.5	4	2.9	4	3.0
5648	6	2.1	4	2.8	4	2.8	2	1.4	2	1.5
5655	2	0.7	1	0.7	1	0.7	1	0.7	1	0.7
5657	11	3.9	6	4.2	6	4.2	5	3.7	5	3.7
5661	14	5.0	7	4.9	7	4.9	7	5.1	7	5.2
5662	1	0.4	1	0.7	1	0.7	0	0	0	0
5666	32	11.5	16	11.2	16	11.2	16	11.8	16	12.0
5667	4	1.4	2	1.4	2	1.4	2	1.4	2	1.5
5668	3	1.0	2	1.4	2	1.4	1	0.7	1	0.7
5669	17	6.1	9	6.3	9	6.3	8	5.9	8	6.0
5827	1	0.4	1	0.7	1	0.7	0	0	0	0
5836	7	2.5	4	2.8	4	2.8	3	2.2	3	2.2
5846	7	2.5	4	2.8	4	2.8	3	2.2	3	2.2
6029	5	1.8	3	2.1	3	2.1	2	1.4	2	1.5
6031	9	3.2	5	3.5	5	3.5	4	2.9	4	3.0
6032	1	0.4	0	0	0	0	1	0.7	1	0.7
6035	1	0.4	0	0	0	0	1	0.7	1	0.7
6036	9	3.2	5	3.5	5	3.5	4	2.9	4	3.0
6037	4	1.4	2	1.4	2	1.4	2	1.4	1	0.7
6082	3	1.0	2	1.4	2	1.4	1	0.7	1	0.7
6083	1	0.4	0	0	0	0	1	0.7	1	0.7
6085	2	0.7	1	0.7	1	0.7	1	0.7	1	0.7
6086	6	2.1	4	2.8	4	2.8	2	1.4	2	1.5
6102	3	1.0	1	0.7	1	0.7	2	1.4	2	1.5
6103	6	2.1	3	2.1	3	2.1	3	2.2	3	2.2
6104	3	1.0	2	1.4	2	1.4	1	0.7	1	0.7
6105	14	5.0	7	4.9	7	4.9	7	5.1	7	5.2
6128	3	1.0	1	0.7	1	0.7	2	1.4	2	1.5
6129	2	0.7	0	0	0	0	2	1.4	2	1.5
6130	6	2.1	3	2.1	3	2.1	3	2.2	3	2.2
6146	1	0.4	1	0.7	1	0.7	0	0	0	0
6314	8	2.8	4	2.8	4	2.8	4	2.9	3	2.2
6315	1	0.4	1	0.7	1	0.7	0	0	0	0
6316	5	1.8	2	1.4	2	1.4	3	2.2	3	2.2
6318	2	0.7	1	0.7	1	0.7	1	0.7	1	0.7
6335	2	0.7	0	0	0	0	2	1.4	2	1.5
6371	1	0.4	0	0	0	0	1	0.7	1	0.7
6373	9	3.2	5	3.5	5	3.5	4	2.9	4	3.0

Medical Officer's Comment: From *Table 119.2 it appears as if the patients were randomized equally between treatment arms and centers. Center 5666 (Dr. John Tuttle/US) had the greatest number of patients overall, compromising approximately 11- 12% of the patients per arm. Centers 6031, 6032, 6083, 6129, 6335, and 6371 had no patients on trovafloxacin. Centers 5662, 5827, 6146, and 6135 had no patients on ofloxacin.*

Copied and modified below is the sponsor's table of all randomized patients and the study evaluation groups:

Table 119.3
Study Evaluation Groups/All Randomized Patients as per the Sponsor (Modified by MO)

Table A. Summary of Subject Disposition				
	Trovafloxacin		**Ofloxacin**	
	Number and Percentage (%) of Subjects			
Randomized Subjects	142		135	
Randomized, Not Treated	0		2	
All Treated Subjects	142	(100%)	133	(100%)
Withdrawn from Treatment[a]	37	(26%)	15	(11%)
Completed Treatment	105	(74%)	118	(89%)
Withdrawn from Study	14	(10%)	10	(8%)
Withdrawn during Treatment	7	(5%)	8	(6%)
Withdrawn during Follow-Up	7	(5%)	2	(2%)
Completed Study	128	(90%)	123	(92%)
Completed Treatment and Study	98	(69%)	116	(87%)
Evaluated for Efficacy (Original Analyses)				
Clinical Intent-to-Treat	141	(>99%)	135	(100%)
Clinically Evaluable at Visits 4 and 5	108	(76%)	111	(82%)
Clinically Evaluable at End of Study	100	(70%)	103	(76%)
Bacteriological Intent-to-Treat	136	(96%)	128	(95%)
Bacteriologically Evaluable at Visits 4 and 5	92	(65%)	98	(73%)
Bacteriologically Evaluable at End of Study	86	(61%)	92	(68%)
Evaluated for Efficacy (Additional Analyses)				
Clinical Intent-to-Treat one week post-therapy	134	(94%)	129	(97%)
Clinically Evaluable one week post-therapy	113	(80%)	111	(83%)
Clinical Intent-to-Treat three to six weeks post-therapy	132	(93%)	135	(100%)
Clinically Evaluable three to six weeks post-therapy	107	(75%)	103	(77%)
Bacteriological Intent-to-Treat one week post-therapy	128	(90%)	118	(89%)
Bacteriologically Evaluable one week post-therapy	98	(69%)	98	(74%)
Assessed for Safety				
Adverse Events	142	(100%)	133	(99%)
Laboratory Tests	140	(99%)	132	(99%)

a Of the subjects withdrawn from treatment, 30 trovafloxacin and seven ofloxacin completed study.
Ref.: Tables 1.1 and 1.2

Medical Officer's Comment: *Please note that although the sponsor states that 142 patients were randomized to trovafloxacin, only 141 were included in their ITT and evaluable analyses. One patient, # 56420197, was randomized but then found to have been inappropriately diagnosed and excluded. This patient had prostatodynia as opposed to prostatitis and received 5 days of therapy before discontinuing therapy because of dizziness.. The sponsor's tables and percentages in this section of the study report did not reflect this patient's exclusion.*

The 2 ofloxacin patients who were randomized but not treated were #60370104 (27 yo, withdrew consent prior to R/x), and #63140359 (21 YO, lost to follow-up after randomization but prior to R/x, patient had Staphylococcus aureus in amounts that would not have met MO or sponsor evaluability criteria).

In addition, the sponsor provided 2 separate efficacy analyses . The second analysis was performed to assess response in relation to time off therapy as opposed to the initial analysis where the trovafloxacin patients were evaluated at both V4 and V5. The reviewer agreed with the revised approach and presented this analysis. The sponsor's evaluable population in table 119.3 is the "Evaluated for Efficacy (Additional analysis) population."

All further numerical references are based on these figures.

Medical Officer's Comment: *The MO chose to provide a simplification of this table below:*

ALL RANDOMIZED
N = 277
Trovafloxacin = 142 Ofloxacin = 135
↓
Clinical Intent-to Treat
N = 263
Trovafloxacin = 134 Ofloxacin = 129
↓ ↓
Clinically Evaluable
N = 224
Trovafloxacin = 113 Ofloxacin = 111
↓
Bacteriologically Evaluable
N = 196
Trovafloxacin = 98 Ofloxacin = 98

Bacteriological Intent-to Treat
N = 246
Trovafloxacin = 128 Ofloxacin = 118

From this diagram, the reader can appreciate that the bacteriologically-evaluable population was a subset of the clinically-evaluable population and the bacteriological ITT population, which were both subsets of the clinical ITT population. There were a total of 37/142 (26%) trovafloxacin-treated patients who discontinued therapy as compared to 15/133 (11%) ofloxacin-treated patients.

Of the 37 trovafloxacin patients, 26/142 (26%) discontinued for reasons associated with the study drug including:

- Adverse event: 20/142 (14%)
- Insufficient response or failure 2/142 (1%)
- Laboratory abnormality: 4/142 (3%)

The additional 11/142 (8%) of trovafloxacin-treated patients who discontinued therapy, were classified as discontinuations unrelated to the study drug and included:

- Adverse event: 5/142 (4%)
- Laboratory abnormality 1/142 (< 1%)
- Lost to follow-up: 1/142 (<1%)
- Other: 1/142 (<1%)
- Protocol violation: 2/142 (1%)

- Withdrew consent 1/142 (<1%)

Of the 15/133 (11%) ofloxacin patients, 10/133 (8%) discontinued for reasons associated with the study drug including:

- Adverse event: 8/133 (6%)
- Insufficient response or failure 2/133 (2%)
- Laboratory abnormality: 0

The additional 5/133 (4%) of ofloxacin-treated patients who discontinued therapy, were classified as discontinuations unrelated to the study drug and included:

- Adverse event: 1/133 (<1%)
- Did not meet randomization criteria: 1/133 (< 1%)
- Laboratory abnormality: 0
- Lost to follow-up: 1/133 (<1%)
- Other: 0
- Protocol Violation: 1/133 (<1%)
- Withdrew consent 1/133 (<1%)

Of these 37 and 15 patients per arm, respectively, 14/142 (10%) of the trovafloxacin patients and 10/133 (8%) of the ofloxacin patients were discontinued from the study. 7 of the trovafloxacin patients were withdrawn during treatment and 7 during follow-up as compared to 8 and 2 ofloxacin patients.

As noted by the MO, not all patients who were discontinued from either treatment or study or both were either clinically or bacteriologically unevaluable. The MO has reviewed the sponsor's tables 4.3.1 and 4.3.2 which were compromised of line listings and divided up the patients in the following manner:

Trovafloxacin:
Discontinued from treatment and clinically and bacteriologically unevaluable (n = 27):

- #50050441: 58 YO discontinued after 26 days because of a toothache. The patient was placed on Pen VK®. The patient had *Enterococcus faecalis* and *Escherichia coli* in appropriate amounts and would have been an evaluable cure. The exclusion was based on the sponsor's rule to exclude all patients who received another antimicrobial unless they were a failure. Reviewer agreed.

- #50140085: 70 YO discontinued after 1 day because of dizziness. Reviewer agreed. Patient did not receive minimum duration necessary to be evaluable.

- #50140086: 69 YO discontinued after 2 days because of dizziness. Reviewer agreed. Patient did not receive minimum duration necessary to be evaluable.

- #56470228: 62 YO discontinued after 13 days because of dizziness and rash. Reviewer agreed. This patient had eradication of a *Staphylococcus aureus* but did not receive the minimum duration of 21 days to be an evaluable cure.

- #56480206: 63 YO discontinued after 6 days because of a viral syndrome. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.

- #56480409: 31 YO discontinued after 10 days because of a rash. Reviewer agreed. Patient did not have meet reviewer criteria of bacteriologic evaluability.

- #56480210: 34 YO discontinued after 8 days because of an error with randomization. Reviewer agreed, patient did not meet reviewer criteria of bacteriologic evaluability.

- #56550185: 81 YO discontinued after 4 days because of headache. Repeat culture was not done and no further R/x was given. Reviewer agreed.
- #56570037: 47 YO discontinued on day 18 because of dizziness. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.
- #56610060: 73 YO discontinued after 1 day because of headache. Reviewer agreed. Patient did not receive the minimum duration necessary to be evaluable.
- #56610404: 71 YO discontinued after 1 day because a lymphoma was diagnosed. Reviewer agreed. Patient did not receive the minimum duration necessary to be evaluable.
- #56660147: 41 YO discontinued after 2 days because of headache. Reviewer agreed. Patient did not receive the minimum duration necessary to be evaluable.
- #56660220: 50 YO discontinued after 14 days because of GI distress. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.
- #56660257: 73 YO discontinued after 23 days because of constipation. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.
- #56690234: 82 YO discontinued after 17 days because of GI distress. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.
- #60290118: 47 YO discontinued after 8 days because of dizziness. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.
- #60360161: 42 YO discontinued after 2 days because of flushing. Reviewer agreed. Patient did not receive the minimum duration necessary to be evaluable.
- #60360397:42 YO discontinued after 9 days because of dizziness. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.
- #60850142: 59 YO discontinued after 4 days because of dizziness. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.
- #60860293: 56 YO discontinued after 2 days Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.
- #61030082: 35 YO discontinued after 3 days because of dizziness. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.
- #61030084: 50 YO discontinued after 3 days Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.
- #61050393: 70 YO discontinued after 3 days because of dizziness. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.
- #63140191: 53 YO lost to follow-up after 28 days. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.
- #63140360: 39 YO discontinued after 15 days. Protocol violation, D/x: nonbacterial prostatitis. Reviewer agreed.

- #63730284: 54 YO discontinued after 12 days because of blurry vision. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.

- #61460177: 66 YO discontinued after 28 days because of a protocol violation (patient stopped capsules). *Escherichia coli* isolated in equivalent amounts in EPS, VB1, and VB2 specimens.
- Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.

Discontinued from treatment but clinically and bacteriologically evaluable (n = 9):

- #50050008: 43 YO discontinued after 28 days because of insufficient response. Evaluable failure.

- #50140269: 73 YO discontinued after 28 days because of insufficient response. Evaluable failure

- #56570341: 59 YO discontinued after 28 days because of diarrhea. Evaluable cure per sponsor but patient does not meet reviewer criteria of evaluability.

- #56670045: 71 YO discontinued after 28 days because of lab abnormalities. Evaluable cure.

- #56690233: 94 YO discontinued after 28 days because of lab abnormalities. Evaluable cure per sponsor but patient did not meet reviewer criteria of evaluability.

- #60370101: 59 YO discontinued after 28 days because of lab abnormalities. Evaluable improvement per sponsor but patient did not meet reviewer criteria of evaluability.

- #61050034: 67 YO discontinued after 28 days because of lab abnormalities. Evaluable cure per sponsor but patient did not meet reviewer criteria of evaluability.

- #61050035: 44 YO discontinued after 28 days because of lab abnormalities. Evaluable cure.

- #61050267: 72 YO discontinued after 28 days because of a rash. Evaluable cure.

One additional patient #56660378 (not included in list), completed therapy but was clinically and bacteriologically unevaluable because he received erythromycin from day 19 – 30 for a sinus infection. The Reviewer agreed with this determination and additionally, this patient did not have meet the reviewer's criteria of bacteriologic evaluability.

Similar categories for the ofloxacin arm are:

Ofloxacin (N= 15):
Discontinued from treatment and clinically and bacteriologically unevaluable (n = 13)

- #50050301: 70 YO withdrew consent after 20 days of therapy, no follow-up cultures, and mixed specimen. Reviewer agreed that patient was not evaluable as per sponsor criteria.

- #56310066: 63 YO discontinued after 10 days because of a rash. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.

- #56480208: 43 YO discontinued after 2 days because of headache. Reviewer agreed. Patient did not receive minimum duration necessary to be evaluable.

- #56550186: 73 YO discontinued after 2 days because of diarrhea. Reviewer agreed. Patient did not receive minimum duration necessary to be evaluable.

- #56570314: 55 YO discontinued after 7 days because of insomnia. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.

- #56610403: 46 YO discontinued after 4 days because of cramps. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.

- #58360138: 65 YO discontinued after 7 days because of abdominal pain. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.

- #60310223: 43 YO discontinued after 1 day because of flushing. Reviewer agreed. Patient did not receive minimum duration necessary to be evaluable.

- #60850141: 66 YO discontinued after 31 days because of an URI. Patient did not meet reviewer criteria of evaluability. The sponsor excluded him because he received Biaxin® for 10 days.

- #61030081: 53 YO discontinued after 3 days because of blurry vision. Reviewer agreed. Patient did not receive minimum duration necessary to be evaluable.

- #61040029: 57 YO discontinued after 11 days because of a protocol violation. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.

- #61290090: 80 YO discontinued after 3 days because of randomization violation. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.

- #63140358: 29 YO lost to follow-up after 27 days. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.

Discontinued from treatment but clinically and bacteriologically evaluable (n = 2):

- #60290120: Insufficient response after 38 days of therapy, evaluable failure carried forward.

- #63730283: Insufficient response after 4 weeks of therapy, evaluable failure carried forward.

In addition to the 27 trovafloxacin-treated patients and the 13 ofloxacin-treated patients listed above, the sponsor appeared to have excluded an additional 16 trovafloxacin and 22 ofloxacin patients from the bacteriologically-evaluable populations. 1 additional trovafloxacin and 9 ofloxacin patients were also clinically unevaluable.

The Reviewer was unable to identify the patients excluded from the analyses based on the information provided in the sponsor's line listings and tables 4.3.1 and 4.3.2., and requested that the sponsor provide the PIDs on June 24, 1997. Provided by the sponsor on June 26, 1997, via FAX, were 16 pages of additional line listings which revealed the following:

Trovafloxacin: Clinically evaluable but bacteriologically unevaluable (N=15):

- #56300020
- #56300413
- #56300414
- #58460128
- #61040030
- #56690298
- #58270181
- #58360140
- #58460426
- #63140192
- #63140357

- #63150229
- #63160203
- #63730335
- #63730437

Ofloxacin: Clinically evaluable but bacteriologically unevaluable (N = 13):

- #56300354
- #56420199
- #56480207
- #56610434
- #56610446
- #56670046
- #56690370
- #60290119
- #60320069
- #60830165
- #63140189
- #63160202
- #63160204

Ofloxacin: Excluded from clinical ITT and all further analyses (N= 6):

- #50050304: 22 YO excluded after 42 days of R/x. Did not meet sponsor or reviewer criteria of evaluability.
- #56300353: 62 YO excluded after 42 days of R/x. Did not meet sponsor or reviewer criteria of evaluability.
- #56420062: 81 YO excluded after 51 days of R/x. Did not meet sponsor or reviewer criteria of evaluability.
- #56660322: 48 YO excluded after 43 days of R/x. Did not meet sponsor or reviewer criteria of evaluability.
- #58460427: 30 YO excluded after 42 days of R/x. Did not meet sponsor or reviewer criteria of evaluability.
- #61020074: 47 YO excluded after a full course because he did not meet sponsor or reviewer criteria of evaluability.

Additional ofloxacin patients excluded from analyses, both clinical and bacteriological, found from line listings by reviewer (N= 3):

- #56690236: 67 YO excluded after 43 days of therapy because he received a 10 day course of Amoxicillin for a sore throat. Reviewer agreed. Patient did not have meet reviewer criteria of bacteriologic evaluability.
- #56690299: 40 YO excluded after a full course because he received 1 day of intravenous ceftriaxone peri-operatively. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.
- #61050036: 42 YO excluded after a full course of R/x because he received 24 hours of achromycin for surgical prophylaxis. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.

Medical Officer's Comment: *For the trovafloxacin arm, the MO in subtracting the 27 clinically and bacteriologically unevaluable patients in addition to the one additional patient found in the line listings that was clinically and bacteriologically unevaluable, was able to obtain the sponsor's clinically-evaluable population. Further subtraction of the 15 bacteriologically unevaluable patients (113 – 15 = 98), gave the sponsor's bacteriologically-evaluable population.*

For the ofloxacin-treated patients, the MO subtracted the 2 patients who were randomized but not treated from 135 to reach 133. From these patients, an additional 6 were excluded from the clinical ITT population, and thus all further analyses, leaving 127. From 127, the 16 clinically and bacteriologically unevaluable patients were subtracted, leaving 111, the sponsor's clinically-evaluable population. If the 13 bacteriologically unevaluable only patients were subtracted from this, 98 patients or the sponsor's bacteriologically-evaluable population remained.

Baseline Characteristics:

All treated subjects were male, mean age of 52 for the trovafloxacin patients and 51.7 for the ofloxacin patients. The median duration since the onset of symptoms was 25 days for the trovafloxacin patients and 22.5 days for the ofloxacin. There were no marked differences between the populations in terms of underlying disease.

Medical Officer's Comment: *As stated in the introduction, the investigators were confused as to the meaning of the "duration of illness." Responses included the duration of the present episode while others provided the duration of the underlying diagnosis of prostatitis, thus rendering it impossible based on this parameter alone, to delineate whether the populations analyzed had acute prostatitis or acute exacerbations of chronic prostatitis.*

Concomitant Medications:

The majority of treated patients in both groups received concomitant medications during therapy (77% trovafloxacin and 73% ofloxacin). The most commonly used medications were anti-hypertensives and drugs for the treatment of arthritic conditions.

Concomitant Antimicrobials:

35 trovafloxacin and 14 ofloxacin patients received antimicrobials for the following reasons:

- Inadequate response: 10 trovafloxacin and 3 ofloxacin (all carried forward as evaluable failures)
- Discontinued early due to adverse events: 14 trovafloxacin and 4 ofloxacin
- Other or no reason: 11 trovafloxacin and 7 ofloxacin.

These patients were not listed again as they were already included in the listings of unevaluable patients. The MO agreed with the sponsor's determinations. Patients discontinued for other reasons were usually suffering from an unrelated infection, such as a URI . These patients received antimicrobials, which would not have been expected to have an effect on a prostatitis, and would have been evaluable cures if they had not been excluded.

Protocol Deviations:

There were 2 deviations on the ofloxacin arm.

- #56470225 had a cracked capsule. The site was unblinded but the subject remained blinded.
- #61040029 unblinded himself and the site by cracking a capsule to see which drug he was receiving.

Sponsor's Efficacy Analysis:

Sponsor-Defined Clinical Response:

Table 119.4

Sponsor-Defined Clinical Response/Clinically Evaluable Population at One-week Post-therapy: (Modified from Sponsor Table 5.1.1a)

	Trovafloxacin	Ofloxacin	p value*	95% CI	
Total Number of Subjects	116	111			
One week post R/x analysis V4 versus V5					
Number of Assessed Subjects	113 (100%)	111 (100%)			
Cure	28 (25%)	42 (38%)	0.020		
Improvement	73 (65%)	54 (49%)			
Failure	12 (11%)	15 (14%)			
Success (Cure + Improvement)	101 (89%)	96 (86%)	0.448	(-5.6%	11.4%)

* p-value = Cochran-Mantel-Haenszel Test includes adjusting for center effect.

Medical Officer's Comment: *At the EOT (sponsor's TOC), the two arms appeared equivalent (Δ = 15). Ofloxacin was numerically superior to trovafloxacin in terms of overall cure versus improvement only, at this timepoint. The MO applied a 95% CI with continuity correction factor to this analysis and found the following: -6.5%, 2.3% (Δ = 15). The MO agreed with the sponsor's determination of equivalence as it applied to the sponsor's evaluable population for the primary efficacy variable.*

Table 119.5

Sponsor-Defined Clinical Response/Clinically Evaluable Population at V6: (Modified from Sponsor Table 5.1.1b)

	Trovafloxacin	Ofloxacin	p value*	95% CI	
Total Number of Subjects	107	111			
Three to Six week post R/x analysis (V6)					
Number of Assessed Subjects	107 (100%)	103 (100%)			
Cure	54 (50%)	71 (69%)	<.001		
Improvement	20 (19%)	0 (0%)			
Failure	33 (31%)	32 (31%)			
Success (Cure + Improvement)	74 (69%)	71 (69%)	0.864	(-12.3%	12.7%)

* p-value = Cochran-Mantel-Haenszel Test includes adjusting for center effect.

Medical Officer's Comment: *At the V6 assessment or the late follow-up, which included only those patients who were cured or improved at V4 and V5, the 2 agents appeared equivalent (Δ = 20). Interestingly, once again ofloxacin was numerically superior to trovafloxacin in terms of complete cure versus improvement only. The MO applied a 95% CI with continuity correction factor to this analysis and found the following: -13.2%, 13.6% (Δ = 20). The MO agreed with the sponsor's determination of equivalence as it applied to the sponsor's evaluable population.*

The following results were seen in the ITT analyses: success at EOT: 85% (114/134) trovafloxacin-treated patients versus 79% (102/129) ofloxacin-treated patients (95% CI –3.3%, 15.3% (Δ = 15). Thus indicating equivalence between the 2 regimens. In this analysis the apparent numerical superiority of ofloxacin was again apparent in terms of cure (ofloxacin 46/129 (36%), trovafloxacin 33/114 (25%), versus improvement (ofloxacin 56/129 (43%) versus trovafloxacin 81/114 (60%). There were 20/114 (15%) failures on the trovafloxacin arm as compared to 27/129 (21%) on the ofloxacin arm.

At V6, the overall success rate was 89/132 (67%) trovafloxacin versus 89/135 (66%) ofloxacin (95% CI

–9.8%, 12.8% (Δ = 20). These results mirrored those of the evaluable population, with 46/135 (34%) failures and 3/135 (2%) improvements on the ofloxacin arm compared to 43/132 (33%) failures and 24/132 18%) improvements on the trovafloxacin arm.

The sponsor and the investigators differed in their determination of response in 6 trovafloxacin patients and 18 ofloxacin patients at V6. There were no differences between them at V4 for the trovafloxacin patients and 3 differences for the ofloxacin patients at V5. In all cases, these were patients who were carried forward by the sponsor as failures as opposed to improvements by the investigator.

Because the Points-to-Consider guidance document provides that the prostatitis indication be studied as a clinical/microbiological study, that is that patients must be both clinically and microbiologically evaluable in order to be assessed, the MO provided the sponsor's analysis for this subgroup of patients below:

Table 119.6

Sponsor-Defined Clinical Response/Clinically and Bacteriologically Evaluable Population at EOT: (Modified from Sponsor Table 5.1.3a)

	Trovafloxacin	Ofloxacin	p value*	95% CI	
Total Number of Subjects	100	98			
One week post R/x analysis (V4, V5)					
Number of Assessed Subjects	98 (100%)	98 (100%)			
Cure	26 (27%)	38 (39%)	0.491		
Improvement	62 (63%)	47 (48%)			
Failure	10 (10%)	13 (13%)			
Success (Cure + Improvement)	88 (90%)	85 (87%)	0.043	(- 5.9%	12.1%)

* p-value = Cochran-Mantel-Haenszel Test includes adjusting for center effect.

Medical Officer's Comment: *This analysis essentially mirrored the previous analyses and supported the claim of equivalence of the 2 regimens. No V6 analysis was provided for this subgroup. The MO applied a 95% CI with continuity correction factor to this analysis and found the following: -7.0%, 13.0% (Δ = 10). The MO agreed with the sponsor's determination of equivalence as it applied to the sponsor's evaluable population.*

Bacteriological Response:

Sponsor-Defined Bacteriologic Response for Bacteriologically Evaluable Subjects at EOT can be seen in Sponsor's Table 5.3.1a, copied and modified by the MO:

Table 119.7
Sponsor-Defined Bacteriological Response/Bacteriologically Evaluable Population (Modified from Sponsor Table 5.3.1a)

	Trovafloxacin	Ofloxacin	p-value*	95% CI	
Total Number of Subjects	100	98			
One week post R/x (V4 versus V5)					
Number of Assessed Subjects	98 (100%)	98 (100%)			
Complete Eradication	77(77%)	80 (82%)	0.172	(- 12.0%	-1.8%)
Partial Eradication	12 (23%)	14 (14%)			
Complete Persistence	9	4 (4%)			
Eradication (Complete and Partial)	89 (91%)	94 (96%)	0.072		

- p-value = Cochran-Mantel-Haenszel Test includes adjusting for center effect.

Medical Officer's Comment: *The complete eradication rate was numerically superior for the ofloxacin arm. The 95% CI with continuity correction factor performed by the MO was –13.05%, 2.85% (Δ = 10), indicating that trovafloxacin was not equivalent to ofloxacin for this subpopulation.*

Below is the sponsor-defined pathogen eradication rate at one week post-therapy for all bacteriologically evaluable subjects. The sponsor stated that (copied from page 44 of the study report):

"Among bacteriologically evaluable subjects, both treatment regimens were 100% effective in eradicating Coagulase-negative *staphylococcus* one week post-therapy. Pathogen eradication rates for other frequently isolated pathogens, including *Escherichia coli* (trovafloxacin: 95%, 19/20; ofloxacin: 100% 18/18), *Enterococcus faecalis* (trovafloxacin: 82%, 14/17; ofloxacin: 83% 15/18), *Staphylococcus haemolyticus* (trovafloxacin: 74%, 14/19; ofloxacin: 86% 18/21), and *Staphylococcus epidermidis* (trovafloxacin: 73%, 24/33; ofloxacin: 65%, 22/34), were comparable between trovafloxacin- and ofloxacin-treated subjects. Pathogen eradication rates for other frequently isolated baseline pathogens were generally similar between the two treatment groups."

The MO created a table of all baseline pathogens and their eradication rates below.

Table 119.8

Sponsor-Defined Pathogen Eradication Rates/ All Bacteriologically Evaluable Patients at EOT (As per the sponsor)

Pathogen	Trovafloxacin n/N	%	Ofloxacin n/N	%
Escherichia coli	13/ 14	(93%)	18/ 18	(100%)
Enterococcus spp.	12/ 12	(100%)	18/ 18	(100%)
Enterococcus faecalis	14/ 17	(82%)	15/ 18	(83%)
Enterobacter spp.	1/ 1	(100%)	3/ 3	(100%)
Pseudomonas aeruginosa	1/ 2	(50%)	1/2	(50%)
Enterobacter aerogenes	4/4	(100%)	1/1	(100%)
Proteus mirabilis	1/1	(100%)	1/ 1	(100%)
Enterobacter cloace	1/1	(100%)	3/3	(100%)
Klebsiella pneumoniae	4/6	(67%)	1/1	(100%)
Pseudomonas spp.	1/1	(100%)	-	-
Pseudomonas maltophilia	1/1	(100%)	-	-
Proteus spp.	1/1	(100%)	-	-
Staphylococcus saprophyticus	2/2	(100%)	2/2	(100%)
Acinetobacter baumanii	1/1	(100%)	-	-
Acinetobacter calcoaceticus	1/1	(100%)	-	-
Acinetobacter anitratus	1/1	(100%)	-	-
Acinetobacter lwoffi	1/1	(100%)	-	-
Citrobacter spp.	-	-	1/1	(100%)
Citrobacter amalonaticus	1/1	(100%)	-	-
Citrobacter diversus	1/1	(100%)	1/ 1	(100%)
Citrobacter freundii	2/2	(100%)	1/1	(100%)
Serratia liquefaciens	1/1	(100%)	-	-
Staphylococcus spp.	11/11	(100%)	8/8	(100%)
Satphylococcus aureus	4/4	(100%)	2/2	(100%)
Staphylococcus epidermidis	24/33	(73%)	22/34	(65%)
Satphylococcus haemolyticus	14/19	(74%)	18/21	(86%)
Staphylococcus hominis	4/4	(100%)	6/6	(100%)
Staphylococcus simulans	2/2	(100%)	3/3	(100%)
Coagulase (-) staphylococci	28/28	(100%)	33/33	(100%)
Streptococcus spp.	3/3	(100%)	3/3	(100%)
Streptococcus agalactiae	5/6	(83%)	4/4	(100%)
Streptococcus anginosus	3/3	(100%)	2/2	(100%)
Streptococcus bovis	-	-	1/1	(100%)
Streptococcus mitis	5/6	(100%)	6/6	(100%)
Streptococcus salivarius	1/1	(100%)	2/2	(100%)
Streptococcus sanguis I	1/1	(100%)	-	-
Streptococcus sanguis II	3/3	(100%)	2/2	(100%)
Beta streptococcus Group B	-	-	1/1	(100%)
Beta hemolytic streptococcus Gp B	-	-	1/1	(100%)
TOTAL	**174/197**	**(88.3%)**	**174/194**	**(89.6%)**

Medical Officer's Comment: *Trovafloxacin and ofloxacin were comparable in terms of overall bacterial eradication rates. The sponsor did not provide a total eradication rate and this number was derived from the line listings.*

Of note, was the large number of Gram (+) pathogens (non- enterococcal) in the sponsor's analysis as compared to what is generally expected from a population of patients with prostatitis. As discussed in the introduction, the validity of including these organisms in the analysis was questionable.

The MO's initial impression that the patient population was more consistent with a population of patients with chronic disease as opposed to acute prostatitis could be considered validated by the bacteriology of this submission if one is prepared to accept the argument that these organisms are indeed responsible for acute exacerbations of chronic prostatitis. As stated previously, the sponsor did not apply a strict definition of acute versus chronic prostatitis and has been unable to provide the data which would enable a differentiation of patients based on diagnostic criteria alone. Additionally, although the protocol specified that in order for an isolate to be considered an evaluable pathogen, it had to be present in the EPS or VB3 specimen in an amount at least 10-fold that isolated in VB1 or VB2, this was not done and a rule of "greater than" was applied. The MO was unable to ascertain if these organisms represented urethral commensuals or true pathogens based on the information as currently provided. This issue was dealt with in the MO's analysis, wherein the MO's evaluability criteria were applied.

The sponsor provided a 95% CI for Enterococcus faecalis of –26.0%, 24.0%. The MO did not provide a CI for any isolate as the numbers were too small for the results to have had any validity.

Superinfecting Pathogens:

The sponsor stated that (copied from page 45 of the study report):

Thirteen (13) superinfecting pathogens were isolated from 25 subjects (18%) in the trovafloxacin group, and 10 superinfecting pathogens were isolated from 24 subjects (18%) in the ofloxacin group. The most common superinfecting pathogens isolated from subjects in the trovafloxacin group were *Staphylococcus epidermidis* (8 subjects), *Enterococcus faecalis* (5 subjects) and *Staphylococcus haemolyticus* (5 subjects); the most common superinfecting pathogens isolated from subjects in the ofloxacin group were *Enterococcus faecalis* (9 subjects) and *Staphylococcus epidermidis* (9 subjects).

Medical Officer's Comment: *The MO reviewed the sponsor's table 5.7 of superinfecting pathogens and found the following:*

For trovafloxacin-treated subjects the most common superinfecting pathogens were Escherichia coli (2), Enterococcus faecalis (5), Pseudomonas aeruginosa (1), Klebsiella pneumoniae (1), Staphylococcus spp. *(1), Staphylococcus epidermidis (8), Staphylococcus haemolyticus (5), Staphylococcus hominis (1), Streptococcus* spp. *(2). Streptococcus agalactiae (2), Streptococcus anginosus (3), Streptococcus mitis (3), and Streptococcus salivarius (1).*

The respective numbers for the ofloxacin arm were 0, 9, 0,0, 3, 9,3, 4, 0, 2, 0, 2, and 1. In addition there was 1 Stomatococcus spp. *and 1 Serratia marcescens*

No conclusions could be drawn from this information other than that both treatment groups had a large number of Gram (+) isolates which met the sponsor's definition of superinfecting pathogens.

Bacteriological ITT Subjects:

The sponsor stated that (copied from page 45 of the study report):

"Sponsor-defined bacteriological eradication rates (complete + partial) one week post-therapy were comparable between the treatment groups for bacteriological intent-to-treat subjects (trovafloxacin: 91%, 117/128; ofloxacin: 94%, 111/118 [CI: -9.1, 3.8])."

"Among bacteriological intent-to-treat subjects, eradication rates of frequently isolated pathogens were generally similar between the treatment groups."

Medical Officer's Comment: *The MO elected not to present the sponsor's full analysis and tables for the ITT population. The results were very similar to those of the evaluable population and the pathogens again included a large number of possible contaminants as opposed to true pathogens.*

Subjects with a Sponsor-Defined Clinical Response of Failure and/or a Bacteriological Response of Persistence One Week Post-Therapy and Subjects with a Sponsor-Defined Clinical Response of Recurrence Three to Six Weeks Post-Therapy (sponsor's analysis, modified by MO in Times New Roman):

Clinical Failure:

Twelve (12) evaluable trovafloxacin subjects and 15 evaluable ofloxacin subjects were clinical failures one week post-therapy. Two (2) of the 12 clinical failures in the trovafloxacin group, (#50140269, #5005008), and two of the 15 clinical failures in the ofloxacin group, (#60290120, #63730283), were discontinued from treatment due to insufficient response after being treated for 28 days (both trovafloxacin subjects), and 38 or 27 days (two ofloxacin subjects). No subject in either treatment group was hospitalized due to worsening of condition. Of the subjects who were clinical failures one week post-therapy, four (4) of the 12 trovafloxacin subjects, (same as above and #56420061, #56680050), and two of the 15 ofloxacin subjects, (same as above), received additional antibiotics for insufficient response.

Of the subjects designated as clinical failures one week post-therapy, one subject in the trovafloxacin group had repeat cultures that showed persistence of *Staphylococcus epidermidis,* one subject showed persistence of *Enterococcus faecalis* and one subject had presumed persistence of *Escherichia coli.* Six of 15 subjects in the ofloxacin group had repeat cultures that showed persistence of *Staphylococcus epidermidis, Enterococcus faecalis* and/or *Streptococcus anginosus* one week post-therapy.

Clinical Recurrence. Seven (7) trovafloxacin subjects and four ofloxacin subjects were clinical recurrences at three to six weeks post-therapy; none was discontinued from treatment due to insufficient response. Of the subjects who were clinical recurrences, two (2) of the 7 trovafloxacin subjects and none of the 4 ofloxacin subjects received additional antibiotics for insufficient response.

Of the subjects designated as clinical recurrences at the end of study, two of seven subjects in the trovafloxacin group had repeat cultures that showed persistence of *Enterococcus faecalis,* one subject showed persistence of *Klebsiella pneumoniae*, and one subject had recurrence of *Staphylococcus epidermidis.* Six of 15 subjects in the ofloxacin group had repeat cultures that showed persistence of *Staphylococcus epidermidis, Enterococcus faecalis* and/or *Streptococcus anginosus* one week post-therapy.

Subject Bacteriological Response and Pathogen Outcome of Persistence: Nine (9) trovafloxacin and four (4) ofloxacin bacteriologically evaluable subjects had sponsor-defined subject bacteriological responses of complete persistence one week post-therapy.

Eight (8) of the nine trovafloxacin subjects with a sponsor-defined subject bacteriological response of complete persistence had repeat cultures that showed persistence of *Klebsiella pneumoniae, Enterococcus faecalis, Staphylococcus haemolyticus, Staphylococcus epidermidis* and/or *Streptococcus mitis* one week post-therapy. The remaining trovafloxacin subject with a

sponsor-defined subject bacteriological response of complete persistence had a pathogen outcome of presumed persistence for baseline isolate *Escherichia coli* one week post-therapy.

All four ofloxacin subjects with a sponsor-defined subject bacteriological response of complete persistence had repeat cultures that showed persistence of baseline isolates *Staphylococcus epidermidis* and/or *Enterococcus faecalis* one week post-therapy.

Of the subjects with an unfavorable clinical or bacteriological response, who had baseline pathogens with susceptibility testing performed both prior to and following treatment, one subject in the trovafloxacin group had baseline isolates of *Staphylococcus epidermidis* that were susceptible to trovafloxacin (MIC = ≤ 2) at baseline and were resistant to trovafloxacin (MIC = ≥8) at the end of study, and two subjects in the ofloxacin group had baseline isolates of *Staphylococcus epidermidis* that were susceptible to ofloxacin (MIC = ≤ 2) at baseline and became resistant to ofloxacin (MIC = ≥8) by the end of study.

Cross Tabulation of Sponsor-Defined Clinical Response and Sponsor-Defined Bacteriological Response and Pathogen Outcome:

As per the sponsor, there was an inconsistent response at the 1 week post-therapy (TOC) analysis in 15 trovafloxacin and 8 ofloxacin patients. On the trovafloxacin arm there were 7 patients who were clinical failures with bacteriological eradication and 8 were clinical cures with bacteriological persistence. The respective numbers on the ofloxacin arm were 7 and 1. A review of the line listings and table 5.9.1a revealed that these inconsistencies were associated with the following pathogens (patients had more than 1 baseline pathogen):

Trovafloxacin:

Enterococcus spp.: 2 clinical failures with eradication.
Enterococcus faecalis: 2 clinical cures with persistence and 2 clinical failures with eradication.
Pseudomonas aeruginosa: 1 clinical cure with bacteriological persistence and one clinical failure with eradication.
Staphylococcus saprophyticus: 1 clinical failure with eradication.
Citrobacter freundii: 1 clinical failure with eradication.
Staphylococcus spp: I clinical failure with eradication.
Klebsiella pneumoniae: 2 clinical cures with persistence and 2 clinical failures with eradication.
Staphylococcus aureus: 1 clinical failure with eradication.
Staphylococcus epidermidis: 1 clinical failure with eradication and 8 clinical cures with persistence.
Staphylococcus haemolyticus: 3 clinical failures with eradication and 5 clinical cures with persistence.
Coagulase-negative *staphylococci*: 3 clinical failure with eradication.
Streptococcus spp.: 1 clinical failure with eradication.
Streptococcus agalactiae: 1 clinical cure with persistence.
Streptococcus mitis: 2 clinical failures with eradication and 1 clinical cure with persistence.

Ofloxacin:

Escherichia coli: 1 clinical failure with eradication.
Enterococcus faecalis: 1 clinical cure with persistence and 2 failures with eradication.
Enterococcus spp.: 1 clinical failure with eradication.
Pseudomonas aeruginosa: 1 clinical cure with bacteriological persistence.
Staphylococcus spp.: 2 clinical failure with eradication.
Enterobacter spp: 1 clinical failure with eradication.
Klebsiella pneumoniae: 2 clinical failures with eradication.
Staphylococcus epidermidis: 2 clinical failures with eradication and 8 clinical cures with persistence.
Staphylococcus haemolyticus: 2 clinical failures with eradication and 3 clinical cures with persistence.
Coagulase-negative staphylococci: 2 clinical failures with eradication.
Staphylococcus hominis: 1 clinical failure with eradication.

Streptococcus agalactiae: 2 clinical failures with eradication.
Streptococcus mitis: 1 clinical failure with eradication.

Sponsor's Conclusion: (Copied from the Esub and modified by the MO (in Times New Roman font), to reflect the numerators and denominators):

One hundred forty-two (142) subjects were randomized to receive trovafloxacin and 135 subjects were randomized to receive ofloxacin. The two treatment groups were generally comparable with respect to demographic characteristics at baseline, medical history, and prior and concomitant medications.

Among clinically evaluable and clinical intent-to-treat subjects, comparisons (95% CIs) of the difference between the two treatment groups in sponsor-defined clinical success rates (cure + improvement) supported equivalence of the two treatment regimens one week post-therapy (101/113 (89%) trovafloxacin clinically evaluable versus 96/11 (86%) ofloxacin clinically evaluable), suggesting that the additional two weeks of ofloxacin therapy was of no clinical benefit.

Among bacteriologically evaluable and bacteriological intent-to-treat subjects, sponsor-defined subject bacteriological eradication rates (complete + partial) one week post-therapy were comparable between the treatment groups (89/98 (91%) trovafloxacin bacteriologically evaluable versus 94/98 (96%) ofloxacin bacteriologically evaluable).

Among bacteriologically evaluable subjects, both treatment regimens were 100% effective in eradicating Coagulase-negative *Staphylococcus* one week post-therapy (28/28 trovafloxacin versus 33/33 ofloxacin). Pathogen eradication rates for other frequently isolated pathogens, including *Escherichia coli* (13/14 (93%) trovafloxacin versus 18/18 (100%) ofloxacin, *Enterococcus faecalis* (14/17 (82%) trovafloxacin versus 15/18 (83%) ofloxacin), *Staphylococcus haemolyticus* (14/19 (74%) trovafloxacin versus 18/21 (86%) ofloxacin), and *Staphylococcus epidermidis* (24/33 (73%) trovafloxacin versus 22/34 (65%) ofloxacin) were comparable between the two treatment groups.

Medical Officer's Comment: *The MO agreed with the sponsor's conclusion that trovafloxacin appeared to be numerically comparable to ofloxacin in terms of clinical success and bacteriologic eradication rates as it pertained to the sponsor's evaluable population. The MO also agreed with the sponsor's claim of equivalence with regards to Escherichia coli and Enterococcus faecalis. The MO, however, did not agree with the sponsor's claim in regards to the coagulase-negative staphylococci. The MO recognized the eradication of these organisms but was unclear as to their significance as pathogens.*

Medical Officer's Efficacy Analysis:

On July 11, 1997, the sponsor faxed partial tables and listings for the MO evaluable population, in accordance with the evaluability criteria discussed above.

Table 119.9
Evaluable Population (as per the MO)

MO's Evaluable Population		
Reason for exclusion	**Trovafloxacin**	**Ofloxacin**
	N= 277	
Total Randomized	142	135
Number Treated	142	133
Excluded from Clinical Analysis by Sponsor (Table 119. 3)	29	22
Excluded from Bacteriological analysis by Sponsor	44	35
Clinically Evaluable by Sponsor	113	111
Bacteriologically Evaluable by Sponsor	98	98
Additional Patients Excluded by MO	30	40
Total MO Evaluable at EOT/TOC	**68 (67)***	**58**

*no. in parentheses refers to final evaluable no. of patients as determined by the MO subsequent to the drafting of table 119.9. This second determination was made based on a second review of 2 patients with initial cultures that reveled mixed microbial flora and who were determined to be "partial cures" by the applicant. However, for purposes of consistency between the tables, both totals of evaluable trovafloxacin patients have been provided in table 119.9 and 119.14.

The MO's population was significantly smaller than that of the sponsor (68 trovafloxacin and 58 ofloxacin patients at the TOC/V4: trovafloxacin, and V5: ofloxacin). The MO excluded an additional 30 patients from the sponsor's trovafloxacin bacteriologically evaluable population and 40 from the ofloxacin. Additionally, those sponsor clinically evaluable patients, who were not evaluable bacteriologically, were not evaluable as per the MO. The MO's population was both clinically and microbiologically evaluable. A by-center breakdown is presented below:

Table 119.10
Evaluable Population by Center/Sponsor/MO

			Trovafloxacin				Ofloxacin			
Center	Total Randomized N = 277 (100%)		Sponsor Evaluable N = 142	100%	MO Evaluable N = 68	100%	Sponsor Evaluable N = 133	100%	MO Evaluable N = 58	100%
5005	18	6.4	9	6.3	7	10.3	9	6.7	6	10.3
5014	8	2.8	4	2.8	2	2.9	4	3.0	4	6.9
5630	12	4.3	6	4.2	2	2.9	6	4.5	4	6.9
5631	3	1.0	1	0.7	1	1.5	2	1.5	0	-
5642	8	2.8	4	2.8	1	1.5	4	3.0	2	3.4
5645	7	2.5	3	2.1	2	2.9	4	3.0	4	6.9
5647	9	3.2	5	3.5	1	1.5	4	3.0	1	1.7
5648	6	2.1	4	2.8	0	-	2	1.5	0	-
5655	2	0.7	1	0.7	0	-	1	0.7	0	-
5657	11	3.9	6	4.2	2	2.9	5	3.7	1	1.7
5661	14	5.0	7	4.9	4	5.9	7	5.2	2	3.4
5662	1	0.4	1	0.7	1	1.5	0	0	0	-
5666	32	11.5	16	11.2	9	13.2	16	12.0	9	15.5
5667	4	1.4	2	1.4	2	2.9	2	1.5	1	1.7
5668	3	1.0	2	1.4	2	2.9	1	0.7	0	-
5669	17	6.1	9	6.3	5	7.4	8	6.0	3	5.2
5827	1	0.4	1	0.7	0	-	0	0	0	-
5836	7	2.5	4	2.8	3	4.4	3	2.2	1	1.7
5846	7	2.5	4	2.8	2	2.9	3	2.2	1	1.7
6029	5	1.8	3	2.1	2	2.9	2	1.5	1	1.7
6031	9	3.2	5	3.5	2	2.9	4	3.0	1	1.7
6032	1	0.4	0	0	0	-	1	0.7	0	-
6035	1	0.4	0	0	0	-	1	0.7	0	-
6036	9	3.2	5	3.5	0	-	4	3.0	2	3.4
6037	4	1.4	2	1.4	2	2.9	1	0.7	1	1.7
6082	3	1.0	2	1.4	1	1.5	1	0.7	1	1.7
6083	1	0.4	0	0	0	-	1	0.7	0	-
6085	2	0.7	1	0.7	0	-	1	0.7	0	-
6086	6	2.1	4	2.8	1	1.5	2	1.5	2	3.4
6102	3	1.0	1	0.7	0	-	2	1.5	0	-
6103	6	2.1	3	2.1	1	1.5	3	2.2	0	-
6104	3	1.0	2	1.4	0	-	1	0.7	0	-
6105	14	5.0	7	4.9	6	8.8	7	5.2	4	6.9
6128	3	1.0	1	0.7	1	1.5	2	1.5	1	1.7
6129	2	0.7	0	0	0	-	2	1.5	0	-
6130	6	2.1	3	2.1	3	4.4	3	2.2	1	1.7
6146	1	0.4	1	0.7	0	-	0	0	0	-
6314	8	2.8	4	2.8	1	1.5	3	2.2	1	1.7
6315	1	0.4	1	0.7	0	-	0	0	0	-
6316	5	1.8	2	1.4	0	-	3	2.2	0	-
6318	2	0.7	1	0.7	1	1.5	1	0.7	0	-
6335	2	0.7	0	0	0	-	2	1.5	1	1.7
6371	1	0.4	0	0	0	-	1	0.7	1	1.7
6373	9	3.2	5	3.5	1	1.5	4	3.0	2	3.4

As in the sponsor's population, the majority of patients came from center #5666.

The demographic characteristics of the MO evaluable population can be seen in Table 119.11.

Table 119.11
Demographic Characteristics of the FDA Evaluable Population:

Characteristics		Trovafloxacin N = 68	Ofloxacin N = 58
Age (years)	16 -44	21	24
	45.- 64	32	26
	≥ 65	15	8
Mean		52.3	49.4
Race:	Asian	1	0
	Black	5	6
	White	60	50
	Hispanic	2	2
	Nat Am.	0	0
Body weight (kg) mean		86	87.4

The patients on both arms were comparable in terms of age, weight, and race.

EFFICACY:

Table 119.12
Bacteriologic Efficacy by Patient (as per the MO)

Timepoint	Trovafloxacin N	Trovafloxacin No. Erad.	Trovafloxacin %	Ofloxacin N	Ofloxacin No. Erad.	Ofloxacin %
EOT	**68**	**57**	**83.8**	**58**	**52**	**89.6**
EOS	**54**	**38**	**70.4**	**35**	**28**	**80.0**

This table applied to complete eradication of the baseline pathogen only. A 95% CI with continuity correction factor (EOT), was: Trovafloxacin versus Ofloxacin: –19.1%, 7.5 % (Δ =15). Thus, equivalence was not established. The sponsor also supplied a table for complete and partial eradication of the baseline pathogens (EOT), where the respective eradication rates were: trovafloxacin 58/68 (85.3%) versus ofloxacin 53/58 (91.3%), 95% CI with continuity correction factor: -18.8%, 6.6%, (Δ = 10). Equivalence was again not established although, the numerical differences were very small.

At the EOS, the 95% CI with continuity correction factor was – 30%, 10.7% (Δ = 20). Once again, equivalence was not established. The sponsor also provided an analysis of bacteriologic response at the EOS , which included complete and partial eradication. In that analysis, the trovafloxacin eradication rate was 40/54 (74.1%), versus 29/35 (82.9%) ofloxacin. The 95% CI with continuity correction factor was – 28.2%, 10.6% (Δ = 20). Thus equivalence was not established.

A by-pathogen analysis is presented below:

Table 119.13
Bacteriologic Efficacy by Pathogen at EOT: (All MO Evaluable Patients)

	Trovafloxacin			Ofloxacin		
Pathogen	N	No. Erad	%	N	No. Erad	%
Escherichia coli	13	12	92.3	16	16	100
Enterococcus faecalis	14	11	78.6	14	11	78.6
Enterococcus spp.	2	2	100	-	-	-
Klebsiella pneumoniae	6	4	66.7	1	1	100
Proteus mirabilis	1	1	100	1	1	100
Enterobacter aerogenes	4	4	100	-	-	-
Enterobacter cloace	1	1	100	3	3	100
Citrobacter diversus	-	-	-	1	1	100
Pseudomonas aeruginosa	2	1	50	2	1	50
Pseudomonas maltophilia	1	1	100	-	-	-
Staphylococcus aureus	1	1	100	1	1	100
Staphylococcus epidermidis	10	8	80	6	5	83.3
Staphylococcus saprophyticus	2	2	100	2	2	100
Staphylococcus haemolyticus	6	4	66.7	8	8	100
Staphylococcus hominis	2	2	100	2	2	100
Staphylococcus simulans	1	1	100	-	-	-
Staphylococcus spp.	2	2	100	-	-	-
Streptococcus anginosus	-	-	-	1	0	0
Streptococcus bovis	-	-	-	1	1	100
Streptococcus mitis	-	-	-	1	1	100
Streptococcus salivarius	1	1	100	-	-	-
Streptococcus sanguis I	1	1	100	-	-	-
Streptococcus sanguis II	1	1	100	1	1	100
Streptococcus spp.	-	-	-	1	1	100
Total	**71**	**60**	**84.5**	**62**	**56**	**90.3**

A CI was not performed for this analysis as a patient could have had more than one bacterial isolate.

For *Escherichia coli* and *Enterococcus faecalis*, the additive eradication rates were: 23/27 (85.1%) trovafloxacin versus 27/30 (90%) ofloxacin. A CI was not applied but the 2 agents appeared numerically comparable for these traditional pathogens. The MO's evaluability criteria excluded most of the Coagulase-negative staphylococcal isolates. However, the MO would contest the sponsor's claim of superiority of trovafloxacin versus ofloxacin for these organisms. As no approvals have been granted previously for coagulase-negative staphylococci, the MO does not recommend approval for trovafloxacin either as not only is the number of isolates too small to be granted an indication but superiority could not be established.

Table 119.14
Clinical Efficacy (MO Bacteriologically Evaluable Population)

	Trovafloxacin			Ofloxacin		
Timepoint	N	No. Cured	%	N	No. Cured	%
EOT	**68**	**62**	**91.1**	**58**	**52 (51)***	**89.7 (87.9)***
EOS	**56**	**37**	**66.1**	**39**	**23**	**59**

*no. in parentheses refers to final no. of evaluable patients/see table 119.9

The 95% CI: - 10.4%, 13.5% (with CCF), applied by the MO at the EOT, did not establish the equivalence of trovafloxacin versus ofloxacin ($\Delta = 10$) for the primary efficacy variable. The EOS 95% CI was - 14.9, 29% ($\Delta = 20$).

However, the revised outcomes (in parentheses), did establish equivalence with a lower bound of the 95% CI with continuity correction factor of 9.1%, (see discussion below).

There were 6 patients on each arm (6/68 (8.8%), trovafloxacin versus 7/58 (12%) ofloxacin) who were clinical failures associated with persistence of the baseline pathogen.

Therefore the 2 agents were clinically equivalent (primary efficacy variable), but bacteriologic equivalence (secondary efficacy variable), was not established. The 2 agents appeared to be numerically comparable for the primary pathogens associated with acute or acute exacerbations of chronic prostatitis, that is *Escherichia coli* and *Enterococcus faecalis.*

Cross Tabulation of Clinical and Bacteriological Efficacy at the EOT for FDA Evaluable Population:

From the line listings provided by the sponsor, the MO found that of the 68 evaluable trovafloxacin patients, 53/68 or 77.9 % of the patients were clinical successes with complete eradication, 0/68 clinical successes had only partial eradication and 9/68 (13.2%) clinical successes had inconsistent results with bacteriologic failure. Additionally there were 4/68 (5.9%) clinical failures associated with complete eradication, 1 clinical failure with partial eradication (1/68 (1.5%) and 1/68 (1.5%) clinical failure with persistence of the baseline pathogen. Therefore, on the trovafloxacin arm, there were 14 patients with inconsistent results between clinical success and bacteriological eradication.

On the ofloxacin arm, there were 49/58 (84.4%) clinical successes with complete eradication, 1/58 (1.7%) with clinical success and partial eradication and 2/58 (3.4%) clinical success with bacteriologic persistence. Additionally, there were 2/58 (3.4%) clinical failures with complete eradication, 0/58 clinical failures with partial eradication and 3/58 (5.2%) clinical failures with persistence. Therefore, there were 4 patients with inconsistent results and an additional 1 with partially inconsistent results on the ofloxacin arm.

Because the CIs for clinical success and bacteriologic eradication between the 2 arms were very close (lower bound: - 10.4%) for clinical response), the MO determined that this difference was negligible. The MO elected to evaluate those patients with partial eradication separately, in order to assess the value of retaining them in the analysis. These patients with partial eradication were reviewed below:

Trovafloxacin:

- #56690297: 66 YO with multiple organisms isolated in baseline culture (primary pathogen was Enterococcus spp.). This organism was persistent at days 35 and 64. It was the MO's determination that this patient was a clinical failure with complete persistence.

The patient had already been counted as a clinical failure (primary efficacy variable).

Ofloxacin:

- #58360286: 76 YO with 3 baseline pathogens: *Escherichia coli, Pseudomonas aeruginosa,* and *Staphylococcus epidermidis. Escherichia coli* was completely eradicated at day 57 but there were 1000 colonies each of *Pseudomonas aeruginosa* and *Staphylococcus epidermidis.* This patient was classified as a clinical success with partial eradication by the sponsor and as a "relapse" by the investigator. The MO determined that this patient should be a clinical failure with partial persistence.

This change in outcome, changed the clinical efficacy to trovafloxacin 62/68 (91.2%) versus ofloxacin 51/58 (87.9%): 95% CI with continuity correction factor: –9.1%, 15.6% ($\Delta = 10$).

Although the Reviewer recognized that outcome could potentially change on other patients, if a case-by case review was performed, the MO also determined that trovafloxacin and ofloxacin were equivalent. The difference of 1 patient on the 95% CI associated with the primary efficacy variable, although critical, was in this case negligible, in that the sponsor's results were very close to the Δ of 10, thus not justifying a redetermination of outcome in every patient.

Recurrences:

The sponsor provided a table of clinical recurrences by arm. There were 9 recurrences on the trovafloxacin arm and 10 on the ofloxacin. These cases with their causative pathogens, are listed below:

Trovafloxacin (N = 9):

- 56300018: *Enterococcus faecalis/Staphylococcus aureus.*
- 56300355: *Escherichia coli.*
- 56570315: *Staphylococcus epidermidis*
- 58360287: *Staphylococcus epidermidis*
- 60310224: *Staphylococcus epidermidis*
- 61050330: *Klebsiella pneumoniae*
- 61280123: *Enterococcus faecalis*
- 61300109: *Staphylococcus epidermidis*
- 63730281: coagulase-negative staphylococcus

Ofloxacin (N = 10):

- 50050006: Coagulase-negative staphylococcus
- 56300017: *Escherichia coli, Klebsiella pneumoniae*
- 56300019: *Escherichia coli*
- 56420198: *Staphylococcus epidermidis*
- 56450327: *Escherichia coli*
- 56660042: Coagulase-negative staphylococcus
- 56660146: *Staphylococcus haemolyticus*
- 56690235: *Staphylococcus haemolyticus*
- 58360286:Reclassified as failure (see above).
- 60370103: *Staphylococcus aureus*

The MO agreed with the sponsor's determination of recurrence on all patients with the exception of 1 patient on the ofloxacin arm who should have been classified as a failure at the TOC.

The only trend noted by the MO was that 5/9 cases of recurrence on each arm were associated with coagulase-negative staphylococci.

Overall, the MO determined that 8/9 trovafloxacin recurrences and 8/9 ofloxacin recurrences were seen in patients who had improved at the TOC.