Safety Review:

25/142 (18%) trovafloxacin subjects and 9/133 (7%) ofloxacin subjects discontinued therapy because of an adverse event. 20 of the discontinuations on the trovafloxacin arm and 8 on the ofloxacin arm were determined to be related to the study drug. The remainder were discontinued because of adverse events that were attributed to other causes.

The most common adverse events leading to discontinuation on the trovafloxacin arm were related to the central nervous and peripheral nervous systems, with 14/142 subjects or 10% discontinued because of one or more of the following: headache (7), dizziness (12), and confusion (1).

On the ofloxacin arm the system most affected was the gastrointestinal, with 5/133 (4%) of subjects discontinued because of one or more of the following: nausea (3), diarrhea (2), and abdominal pain (2).

There were 4 trovafloxacin and 2 ofloxacin subjects who were temporarily discontinued from therapy due to adverse events. These patients are listed below:

Trovafloxacin (N = 4):

- #56480206: viral infection day 8, unrelated to study drug.
- #56660377: back pain secondary to an injury on day 6, resolved on day 13.
- #61030290: facial rash day 18, related to study drug, resolved on day 20.
- #63730284: dizziness day 3, associated with nausea, sweating, blurry vision, and nervousness. All were thought to be study drug related and resolved on day 8.

Ofloxacin (N = 2):

- #5660218: severe chest pain day 2, unrelated to the study drug. Event resolved.
- #56690053: moderate diarrhea day 3, related to the study drug, resolved the same day.

Copied from the Esub and modified by the MO are the Sponsor's Tables 6.1 and 6.2, Summary of Adverse Events by Body System: All Causality and Table 6.3, Summary of Adverse Events by Body System, Treatment-Related.

Table 119.15
Adverse Events, All Treated Patients (Modified Sponsor Table 6.1)

	Trovafloxacin	Ofloxacin
Number of Subjects Treated	142 (100%)	133 (100%)
Subject-Days of Exposure	1468	5214
Subjects With At Least One Event	114 (80%)	95 (71%)
Number of Adverse Events	238	193
Subjects with Serious Adverse Events	2 (1%)	3 (2%)
Subjects with Severe Adverse Events	13 (9%)	9 (7%)
Subjects Discontinued Due to Adverse Events	24 (17%)	9 (7%)
Subjects with Dose Reductions or Temporary Discontinuations due to Adverse Events	4 (3%)	2 (2%)
Subjects Discontinued Due to Objective Test Findings	5 (4%)	0
Subjects with Dose Reductions or Temporary Discontinuations due to Objective Test Findings	0	0

2 trovafloxacin patients and 3 ofloxacin patients had serious AEs, and 13 and 9 per arm respectively had severe AEs.

Table 119.16
Adverse Events by Body System, All Causality (Modified Table of Sponsor Table 6.2)

	Trovafloxacin		Ofloxacin	
NUMBER OF SUBJECTS:				
Evaluable for Adverse Events	142	(100%)	133	(100%)
Subjects With At Least One Event	114	(80%)	90	(45%)
Subjects Discontinued due to Adverse Event	24	(17%)	9	(7%)
ADVERSE EVENTS BY BODY SYSTEM:				
Appl./ Inj./ incision/ Insertion Site	0	-	1	(< 1%)
Autonomic Nervous	8	(6%)	6	(5%)
Cardiovascular	6	(4%)	9	(7%)
Centr. & Periph. Nerv.	66	(46%)	21	(16%)
Gastrointestinal	51	(36%)	41	(24%)
General	20	(14%)	20	(9%)
Hematopoietic	0	-	2	(2%)
Musculoskeletal	5	(4%)	8	(2%)
Neoplasms	1	(< 1%)	0	-
Other Adverse Events	3	(2%)	3	(2%)
Psychiatric	17	(12%)	28	(21%)
Reproductive	3	(2%)	1	(< 1%)
Respiratory	8	(6%)	19	(14%)
Skin/ Appendages	10	(7%)	3	(2%)
Special Senses	6	(4%)	8	(6%)
Urinary System	3	(2%)	2	(2%)

Table 119.17
Adverse Events by Body system: Treatment-Related (Modified Sponsor Table 6.3).

	Trovafloxacin		Ofloxacin	
NUMBER OF SUBJECTS:				
Evaluable for Adverse Events	142	(100%)	133	(100%)
Subjects With At Least One Event	61	(43%)	39	(29%)
Subjects Discontinued due to Adverse Event	20	(14%)	8	(6%)
ADVERSE EVENTS BY BODY SYSTEM:				
Autonomic Nervous	4	(3%)	1	(< 1%)
Cardiovascular	1	(< 1%)	0	-
Centr. & Periph. Nerv.	40	(28%)	9	(7%)
Gastrointestinal	28	(20%)	23	(17%)
General	4	(3%)	4	(3%)
Psychiatric	7	(5%)	15	(11%)
Skin/ Appendages	7	(5%)	1	(< 1%)
Special Senses	4	(3%)	4	(3%)

Overall and as noted in previous trials, the most frequent AEs were from the CNS and GI systems. The % of nervous system AEs is approximately four times as high for the trovafloxacin patients as compared to the ofloxacin, as opposed to the GI-related AEs where there was a similar number between the arms in this trial. The further breakdown of these events can be found on the MO's Table 119.17.

Table 119.17
Most Common AEs/Treatment-related/All Treated Patients (as per the MO)

	Trovafloxacin N = 61		Ofloxacin N = 39	
Nervous System	40	(28%)	9	(7%)
Headache	18	13	4	3
Dizziness	32	23	5	3
GI System	28	20	23	17
Nausea	15	11	9	7
Constipation	6	4	4	3
Dyspepsia	2	1	4	3
Diarrhea	2	1	7	5
Abdominal Pain	1	< 1	4	3

Other events of note included a rash, maculopapular, in 7 (7%) trovafloxacin-treated patients and 1 (< 1%) ofloxacin-treated patient, abnormal vision in 2 (1%) trovafloxacin-treated patients and 3 (2%) ofloxacin-treated patients, and insomnia in 1(< 1%) trovafloxacin-treated patient and 11 (8%) ofloxacin-treated patients.

The AE profile in this trial was similar to that seen in the previously reviewed indications and no deaths were reported.

Listed below are the severe adverse events that were considered treatment-related:

Trovafloxacin (7 patients:9 events):

- #60360161: 42 YO dizziness, vertigo, vomiting (all severe) as well as flushing at day 2, discontinued.
- #63730336: 40 YO with dizziness on the first day of therapy that resolved and the patient completed therapy.
- #50050441: 58 YO with headache and toothache, discontinued on day 26.
- #60360388: 61 YO with headache and nausea (moderate) on day 2, discontinued.
- #60360397: 42 YO with headache and anxiety from day 1, discontinued R/x on day 9.
- #61050393: 70 YO with headache on day 3, discontinued from R/x.
- #61050267: 72 YO with maculopapular rash day 34, which was after active therapy had been discontinued.

Ofloxacin (4):

- #56610403: abdominal pain
- #63730334: 36 YO with sever diarrhea, day 2, resolved day 5, therapy was continued. Also had other GI complaints of a mild nature.
- #56610436: 56 YO with dyspepsia starting on day 2 of therapy through day 49. Also had intermittent headache and insomnia of mild severity, evaluable patient.
- #56310066: 63 YO with allergic reaction manifested as a macular/pap rash and itching day 10, discontinued..

Clinical Laboratory Abnormalities:

The sponsor submitted tables 4.1, 4.2, 6.1, and 3.3, which contained listings of patients who discontinued therapy because of laboratory abnormalities.

5 trovafloxacin-treated subjects were discontinued due to increased LFTs that were considered treatment-related by the investigator: (copied from the study report, pages 58 and 59):

#56670045: 71 YO with a history of arthritis, received trovafloxacin for 28 days followed by placebo. This subject developed liver function test abnormalities on Day 34 and was discontinued from treatment. The subject's LDH value, which was within the normal range at baseline, increased to above the normal range on Day 34, returned to within the normal range on Day 49 and remained within the normal range until Day 64, after which it was not re-measured. The subject's SGOT and SGPT values, which were within the normal range at baseline, increased to above the normal range on Day 34 and remained elevated until Day 146, when they both returned to within the normal range

	LDH (U/L)	SGOT (U/L)	SGPT (U/L)		LDH (U/L)	SGOT (U/L)	SGPT (U/L)
Baseline				Day 64			
Day 3				Day 70			
Day 17				Day 77			
Day 34				Day 83			
Day 41				Day 90			
Day 44				Day 97			
Day 49				Day 112			
Day 56				Day 146			
Normal Range				Normal Range			

#56690233: 94 YO with a history of hypertension, received trovafloxacin for 29 days followed by placebo. This subject developed liver function test abnormalities on Day 35 and was discontinued from treatment on Day 36. The subject's SGOT and SGPT values, which were within the normal range at baseline, increased to above the normal range on Day 35 and remained elevated until Day 105 and Day 160, respectively.

	SGOT (U/L)	SGPT (U/L)		SGOT (U/L)	SGPT (U/L)
Baseline			Day 48		
Day 3			Day 55		
Day 8			Day 76		
Day 20			Day 84		
Day 35			Day 105		
Day 42			Day 160		
Normal Range			Normal Range		

#60370101: 50 YO with a history of hypertension, received trovafloxacin for 28 days followed by placebo. This subject developed liver function test abnormalities on Day 5 with an SGPT level that increased from within the normal range at baseline to above the normal range. On Day 34, the subject's SGOT increased from normal at baseline to above the normal range and the subject was discontinued from treatment. Although resolving, the subject's SGOT and SGPT values remained above the normal range at his final laboratory evaluation (Day 65).

	SGOT (U/L)	SGPT (U/L)		SGOT (U/L)	SGPT (U/L)
Baseline			Day 37		
Day 5			Day 41		
Day 21			Day 55		
Day 34			Day 65		
Normal Range			Normal Range		

#61050034: 67 YO with a history of insomnia, received trovafloxacin for 28 days followed by placebo. The subject's SGOT and SGPT values increased from within the normal range at baseline to above the normal range on Day 35 when he was discontinued from treatment. Although resolving, the subject's SGOT and SGPT levels remained above the normal range at his final laboratory evaluation (Day 90).

	SGOT (U/L)	SGPT (U/L)		SGOT (U/L)	SGPT (U/L)
Baseline			Day 49		
Day 5			Day 56		
Day 21			Day 63		
Day 35			Day 70		
Day 37			Day 77		
Day 41			Day 90		
Normal Range			Normal Range		

#61050035: 44 YO received trovafloxacin for 28 days followed by placebo. The subject's SGOT and SGPT values increased from within the normal range at baseline to above the normal range on Day 33, when the subject was discontinued from treatment. The subject's SGOT value remained above the normal range until Day 52 and his SGPT value remained above the normal range until Day 63.

	SGOT (U/L)	SGPT (U/L)		SGOT (U/L)	SGPT (U/L)
Baseline			Day 38		
Day 3			Day 45		
Day 18			Day 52		
Day 33			Day 63		
Normal Range			Normal Range		

None of the subjects in the ofloxacin group was discontinued from treatment due to abnormal laboratory test results.

In addition to the above, the sponsor provided a separate listing of patients with elevated LFTs where the investigator did not consider the abnormalities related to the study drug. This listing consisted of 14 trovafloxacin and 1 ofloxacin patient. 4 of the patients listed above were included in this second listing as well as an additional 10 trovafloxacin patients (9 with LFTs ≥ 3 x normal and 1 with ≥ 2 x normal) and 1 ofloxacin patient. Summaries of these patients are provided below (copied from Appendix 1 of the study report):

Trovafloxacin (N = 10)

#50140269:

This 73-year-old male entered the study on November 1, 1995 and received 36 days of study drug (28 days active then placebo). The subject's SGPT and SGOT values began rising on Day 36. The subject considered himself a clinical failure and with the approval of the site, discontinued his medication that day. The subject's SGPT and SGOT levels peaked on Day 50 reaching respectively and remained above the normal range. On Day 40 the subject had a positive CMV test by IgG antibodies.

Hepatitis B surface antigen: negative
Hepatitis A IgM antibody: negative
CMV IgM
CMV IgG:

The subject was prescribed 30 days' worth of ofloxacin on Day 36. Concurrent medications taken by the subject included Motrin and aspirin for arthritis, Alupent and Beconase for emphysema, and Cardura for benign prostatic hypertrophy. He had no history of related liver function problems. He had no history of alcohol abuse. He was asymptomatic.

The investigator did not believe that the elevated LFT values were clinically significant, nor did the investigator attribute these levels to any particular causality. At the subject's last visit on Day 76, LFT values had not yet returned to normal. At that time, the investigator determined that the subject would no longer be seen in connection with the study.

A summary of the subject's results follows:

Visit	SGPT	SGOT
Day 1		
Day 5		
Day 19		
Day 36		
Day 40		
Day 50		
Day 71		
Day 76		
Normal Ranges		

#56300355:

This 50-year-old male entered the study on December 11, 1995 and received 33 days of study drug (28 days active then placebo) was temporarily discontinued for nine days. The subject's SGPT and SGOT values began rising on Day 33, and peaked on Day 48, respectively. The subject completed study drug on Day 42.

Concomitant medications included Tagamet from Day 64 until Day 78 for hyperacidity; Vasotec from 01/--/87 to Day 92 for hypertension; Procardia from Day 92 to present for hypertension; Xanax from Day 92 to present for anxiety; Tenorim from 01/--/87 to present for prostatitis symptoms; Prozac from Day 44 to Day 49 for depression; Phygeum and Saw Palmetto during March 1996 for prostate enlargement. The subject had no history of related liver function problems. He claimed to have consumed more alcohol than "normal" on Day 46, but otherwise described himself as a moderate drinker. He was asymptomatic.
The investigator attributed the LFT abnormalities to the study medication. The subject's SGPT/SGOT values returned to normal as of Day 147.

A summary of the subject's results follows:

Visit	SGPT	SGOT
Screening		
Day 5		
Day 22		
Day 33		
Day 47		
Day 48		
Day 54		
Day 64		
Day 78		
Day 92		
Day 147		
Normal Range		

#56480205:

This 65-year-old male entered the study on December 7, 1995 and received 31 days of study drug (28 days active then placebo). SGPT and SGOT values began rising on Day 35 and peaked on Day 49 respectively. The subject completed the study drug dosing on Day 42.

Concomitant medication during study drug dosing included Vasotec for hypertension, potassium supplement, multivitamin, Vitamin C, Vitamin B complex, Vitamin E, Prozac for depression and Cardura for benign prostatic hypertrophy. He had no history of related liver function problems nor any history of alcohol abuse. He was asymptomatic.

The investigator believed the study drug may have caused elevated LFTs. The subject's SGPT and SGOT values returned to normal.

A summary of the subject's results follows:

Visit	SGPT	SGOT
Screening		
Day 4		
Day 23		
Day 35		
Day 49		
Day 59		
Day 80		
Normal Range		

#56610401:

This 51-year-old male entered the study on January 3, 1996 and received 41 days of study drug (28 days active then placebo). SGPT and SGOT values began rising on Day 41, and peaked on Day 48, with values The subject completed study medication.

The subject was not on any concomitant medication. He was asymptomatic. He had no history of alcohol or substance abuse.

The investigator attributed the elevated LFT values to the study medication. The subject's values were returning to normal when he was released from being seen for any further follow-up.
A summary of the subject's results follows:

Visit	SGPT	SGOT
Screening		
Day 5		
Day 19		
Day 41		
Day 48		
Day 78		
Day 89		
Day 105		
Normal Range		

56660257

This 73-year-old male entered the study on October 19, 1995 and received study drug for 24 days. SGPT and SGOT values began rising on Day 25, and peaked on Day 41, reaching , respectively. The subject discontinued study medication on his own on Day 24 because he believed it was making him constipated. On Day 41 the subject had a positive CMV test by IgG antibodies.

Hepatitis B surface antigen: negative Hepatitis A IgM antibody: negative
CMV IgM CMV IgG

No concomitant medication was taken during the time of study dosing. On Day 46 the subject was prescribed tetracycline for an ENT problem. The investigator switched the subject to Macrobid on Day 50 because he believed the tetracycline was affecting liver function values. The subject had no history of related liver function problems. He described himself as a moderate to heavy drinker and stated that he had been drinking the week prior to the Day 41 labs. He was asymptomatic.

The investigator attributed the elevated LFTs to a combination of excessive alcohol consumption, study drug dosing, and tetracycline dosing. At the last visit on Day 75 the subject's LFT values had almost returned to normal when he refused to be seen for any further follow-up.

A summary of the subject's results follows:

Visit	SGPT	SGOT
Screening		
Day 9		
Day 25		
Day 37		
Day 41		
Day 46		
Day 60		
Day 75		
Normal Ranges		

56660321:

This 56-year-old male entered the study on November 24, 1995 and received 42 days of study drug (28 days active then placebo). SGPT and SGOT values began rising on Day 36 and peaked on Day 44, respectively. The subject completed study drug treatment on Day 42. On Day 39 the subject had a positive CMV test by IgG antibodies.

Hepatitis B surface antigen: negative
Hepatitis A IgM antibody: negative
CMV IgM
CMV IgG

The subject indicated that he did consume alcohol over the Christmas holiday vacation (the site inferred from the subject's statements that he may have over-indulged). Concomitant medication included Centrum vitamins only. He had a history of low back pain. He was asymptomatic.

The subject's LFT values returned to normal. The investigator determined causality as the study drug in conjunction with the subject's diet. The subject was eating fish between five and six times per week. The investigator believed that the toxins in the fish may have been preventing the LFT values from returning to normal. The investigator believed his assumption was confirmed as the subject stopped eating fish altogether and his LFT values began decreasing shortly thereafter. A summary of the subject's SGPT and SGOT results follows:

Visit	SGPT	SGOT
Screening		
Day 4		
Day 18		
Day 36		
Day 39		
Day 44		
Day 50		
Day 58		
Day 71		
Day 81		
Day 93		
Day 106		
Day 121		
Normal Ranges		

56690054:

This 77-year-old male entered the study on September 7, 1995 and received 42 days of study drug (28 days active then placebo). SGPT and SGOT values began rising on Day 37 and peaked on Day 51
respectively. The subject completed study drug on Day 42.

Hepatitis B surface antigen: negative Hepatitis A IgM antibody: negative

The subject's medical history included hypothyroidism and stomach ulcers. Concomitant medications included levothyroxine (since 1958) and ranitidine (since 1991). He had no history of alcohol abuse. The subject was asymptomatic.

The investigator attributed the elevated LFT values to the study drug. The SGPT and SGOT values returned to "normal."
A summary of the subject's results follows

Visit	SGPT	SGOT
Screening		
Day 6		
Day 22		
Day 37		
Day 51		
Day 66		
Day 80		
Day 87		
Normal Ranges		

* noted as not clinically significant, per Investigator

#56690234:

This 82-year-old male entered the study on October 25, 1995 and received 17 days of study drug. SGPT and SGOT levels began rising at Day 35 and peaked on Day 42 (12/6/95), , respectively. The subject was advised to discontinue his study medication on Day 17.

The subject visited the emergency room on Day 17 complaining of left arm pain and numbness. His medical history included congestive heart failure, angina, GI disorders, back pain, hypertension, and hiatal hernia. The ER physician discontinued the study medication on Day 17. Concomitant medications included Darvocet-N, nitroglycerin, Sectral, Dyazide, isosorbide, Mylanta, ibuprofen and Benadryl. The subject was prescribed Keflex on Day 27 for a genital rash. At Day 50, the subject was asymptomatic and feeling better than at previous visits. He had no history of alcohol abuse, nor any history of related liver function problems.
The investigator believed the study medication was most likely the cause of the elevated LFTs. The subject's SGPT and SGOT levels returned to normal.

A summary of the subject's results follows:

Visit	SGPT	SGOT
Screening		
Day 5		
Day 21		
Day 35		
Day 42		
Day 49		
Day 57		
Day 77		
Normal Ranges		

#58460426:

This 61-year-old male entered the study on January 31, 1996. SGPT and SGOT values began rising on Day 33, and peaked on Day 50, respectively. The subject completed study drug on Day 42 (28 days active then placebo).

The subject's medical history included hypertension. Concomitant medications included Hytrin from 12/09/95 to 02/07/96 (Day 1); Procardia from 12/--/95 to present for hypertension; and Cozaar from 12/--/95 to present for hypertension. He denied any history of alcohol or substance abuse. He was asymptomatic.

The investigator attributed the elevated LFT values to the study medication. The subject's SGPT and SGOT values returned to normal.

A summary of the subject's results follows:

Visit	SGPT	SGOT
Screening	Not Done	Not Done
Day 3		
Day 20		
Day 33		
Day 50		
Day 75		
Normal Ranges		

Primary Care Lab

Visit	SGPT	SGOT
Day 123		
Normal Ranges		

#60360386:

This 68-year-old male entered the study on December 8, 1995 and received study drug for 42 days (28 days active then placebo). SGPT, SGOT, LDH and total bilirubin values began rising on Day 28, with SGPT, SGOT and LDH peaking the same Day, respectively. The subject's total bilirubin level peaked on Day 46, He completed study drug dosing on Day 42. On Day 46 the subject had a positive CMV test by IgG antibodies.

Hepatitis B surface antigen: negative Hepatitis A IgM antibody: negative
CMV IgM CMV Ig

Concomitant medications included water-soluble vitamins (e.g., beta-carotene and B-complex vitamins), and 50 micrograms of selenium. He had no history of alcohol abuse. The subject was asymptomatic.

The investigator attributed the causality of the elevated LFTs to the study medication. The subject's SGPT, SGOT and LDH levels returned to normal. Total bilirubin value was still above the upper limit of normal (0.2-1.2 mg/dL) at the subject's last visit; however this result was below the subject's screening visit value.

A summary of the subject's results follows:

Visit	SGPT	SGOT	LDH	Total bilirubin
Screening				
Day 4				
Day 18				
Day 28				
Day 46				
Day 50				
Day 57				
Normal Ranges				

Ofloxacin (N = 1)

#56660218:

This 44-year-old male entered the study on October 6, 1995 and received 42 days of study drug. SGPT and SGOT values began rising on Day 50, and peaked on Day 57 , respectively. The subject completed study drug on Day 42. On Day 73 the subject had a positive CMV test by IgG antibodies.

Hepatitis B surface antigen: negative
Hepatitis A IgM antibody: negative
CMV IgM
CMV IgG

The subject was hospitalized on Day 3 (10/12/95) for tightness in his chest, and was discharged on Day 4. The final diagnosis was "Chest pain with questionable etiology - (a) could be angina; (b) could be sternum tenderness due to the need for his sternal rewiring." The subject had a history of coronary artery disease and bypass surgery (1993).

Concomitant medications included ibuprofen (since 1989, for pain), aspirin (since 1993, for coronary artery disease prophylaxis), Hytrin (since 10/04/95, for benign prostatic hypertrophy), Lisinopril (since 10/13/95, possibly for hypertension), Nicotine Transdermal (since 10/13/95, for assistance in smoking cessation) and Lortab (from 11/14/95 - 11/17/95 for back pain). The investigator suspected that the subject had taken excessive Lortab, based on statements made by the subject. The subject was a suspected substance abuser, specifically of marijuana.

The investigator attributed the elevated LFTs to excessive Lortab use. The subject's SGPT and SGOT values returned to normal.

A summary of the subject's results follows:

Visit	SGPT	SGOT
Screening		
Day 4		
Day 18		
Day 36		
Day 50		
Day 57		
Day 64		
Day 73		
Day 81		
Normal Ranges		

Medical Officer's Comment: *Despite the fact that the investigators did not consider the LFT abnormalities in the 10 patients listed above as attributable to trovafloxacin, the MO determined that the pattern of the abnormalities was consistent with that of the previously listed 5 patients in whom they were attributable to the study drug, both in terms of the timing of the events as well as the duration (approximately 3 – 4 weeks of trovafloxacin usually without an associated increase in bilirubin and with apparent resolution after 6 – 10 weeks off therapy). Therefore, the MO determined that the true incidence of LFT abnormalities (≥ 3 x normal), attributable to the study drug was 14/140 (10%), and only ≥ 2 x normal in 1/140 (0.7%) as compared to 1/132 (0.8%) on the ofloxacin arm. (Total ≥ 2 x normal = 15/140).*

In addition to the above, there were 2 trovafloxacin patients, (# 56620077, #63140192), with increased creatinine (1%) as compared to 0 ofloxacin patients, . which subsequently resolved).

The MO did not consider any of the other laboratory abnormalities found as clinically significant.

Conclusions:

As per the Sponsor: (copied from page 63 of the study report and modified by the MO in Times New Roman font):

Trovafloxacin 200 mg QD administered for 28 days was statistically equivalent to ofloxacin 300 mg BID administered for 42 days for sponsor-defined clinical success rates one week post-therapy (101/113 (89%) trovafloxacin versus 96/11 (86%) ofloxacin).

Sponsor-defined subject bacteriological eradication rates one week post-therapy were comparable between both regimens (89/98 (91%) trovafloxacin versus 94/98 (96%) ofloxacin).
The analyses of pathogen eradication rates were similar between the treatment groups for 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), *Staphylococcus epidermidis* (24/33 (73%) trovafloxacin versus 22/34 (65%) ofloxacin), and Coagulase-negative *Staphylococcus* (28/28 trovafloxacin versus 33/33 ofloxacin).

Both treatments were well tolerated, with similar percentages of subjects reporting adverse events. The most frequently reported treatment-related adverse events are those commonly associated with quinolone therapy including dizziness (23%), headache (13%), and nausea (11%) for subjects in the trovafloxacin group and insomnia (8%) and nausea (7%) for subjects in the ofloxacin group. Twenty of 142 subjects (14%) in the trovafloxacin group and eight of 133 subjects (6%) in the ofloxacin group were discontinued from treatment due to treatment-related adverse events. Four trovafloxacin subjects and three ofloxacin subjects reported serious adverse events, none of which was considered treatment-related. No deaths were reported.

A trend was observed for liver enzyme elevations after 3 to 4 weeks of trovafloxacin therapy, suggesting that subjects receiving prolonged treatment (≥21 days) may need to have periodic assessment of hepatic function.

Reviewer's Conclusion:

The MO determined that there were 68 patients clinically and bacteriologically evaluable on the trovafloxacin arm as compared to 58 on the ofloxacin arm. These numbers represented a significant decrease from the sponsor's evaluable population. This decrease was due to the application of strict criteria in order to ensure that the sponsor's evaluable population was indeed a "true prostatitis" population. Additionally, the MO wanted to ensure that a fair comparison was made between the 2 study arms. The longer duration of ofloxacin therapy and the different intervals for assessing the patients, as designed and implemented by the sponsor, did not adequately ensure this.

The MO ascertained, prior to the institution of the review, that this trial was designed and implemented in a manner very similar to that utilized for the approval of other quinolone products for this indication and that the protocol was designed in conjunction with the PTC document as well as IDSA guidance.

The MO and the sponsor differed as to the classification of the patients into a specific disease entity. Although the PTC document refers only to "bacterial prostatitis", the antimicrobial agent most recently approved for this indication, ciprofloxacin, was granted the indication as "chronic bacterial prostatitis." Because of the similarities in the populations studied, and after extensive review of the medical literature, the MO concluded that the population in this trial did indeed suffer from what could be termed as a "chronic bacterial prostatitis." This conclusion was not only based on the clinical picture but also on the bacteriology submitted.

In this submission, a significant number of patients presented with coagulase-negative staphylococci as their primary pathogen. The MO did not find evidence in the literature to support the sponsor's contention that all of the isolates submitted were true pathogens and therefore, sought to establish criteria which would

justify the inclusion of some of these organisms in the analyses. The MO did accept that chronic bacterial prostatitis may be associated with increased numbers of these isolates as compared to the more common *Escherichia coli* or *Enterococcus faecalis*, however, in the absence of literature verification and in the face of regulatory precedence wherein all submissions in the last 5 years have excluded this organism, the MO elected to accept only those that met the strict MO criteria.

Clinical efficacy, at the TOC, which was also the primary efficacy variable was 62/68 (91.1%) for the trovafloxacin-treated patients as compared to 51/58 (87.9%) for the ofloxacin-treated patients. The 95 % CI was –9.1%, 15.6%, thus establishing the clinical equivalence of the 2 agents.

Bacteriologic equivalence was not obtained with bacteriologic efficacy rates at the TOC by patient of 57/58 (83.8%) trovafloxacin compared to 52/58 (89.6%) ofloxacin. At the EOS which was only utilized in order to assess recurrence, the bacteriologic efficacy rates were 38/54 (70.4%) trovafloxacin versus 38/35 ofloxacin (80%). These overall EOS rates were comparable to those of previously approved quinolones. Specifically, ofloxacin (75%), norfloxacin (80%), ciprofloxacin (83.6%), and temofloxacin (97.2%).

The analyses of pathogen eradication rates also revealed higher ofloxacin eradication rates of: 60/71 (84.5%) trovafloxacin verus 56/62 (90.3%) ofloxacin (95% CI with CCF:
–18.5%, 6.9%, ($\Delta = 10$), thus equivalence was not established.

The eradication rate for *Escherichia coli* was 12/13 (92.3%) trovafloxacin versus 16/16 (100%) ofloxacin.

The eradication rate for *Enterococcus faecalis* (11/14 (78.6%) trovafloxacin versus 11/14 (78.6%) ofloxacin) was equal to that of ofloxacin, but ofloxacin was not approved for this isolate. Only carbenicillin has been approved for this organism

Although not statistically significant, trovafloxacin and ofloxacin appear numerically comparable for these traditional pathogens.

A stated above, the MO's evaluability criteria excluded most of the coagulase-negative staphylococcal isolates. The MO disagrees with the sponsor's claim of superiority of trovafloxacin versus ofloxacin for this unspeciated (by the sponsor), category of organisms. As no approvals have been granted previously for any speciated coagulase-negative staphylococci, the MO recommended approval only for *Staphylococcus epidermidis.* For trovafloxacin versus the other requested organisms, not only was the number of isolates too small to be granted an indication but also "superiority, as claimed by the sponsor" could not be established. Specifically, the eradication rates for the speciated requested pathogens were: *Staphylococcus haemolyticus* (4/6 (66.7%) trovafloxacin versus 8/8 (100%) ofloxacin), *Staphylococcus epidermidis* (8/10 (80%) trovafloxacin versus 5/6 (83.3%) ofloxacin, thus revealing numerical superiority of ofloxacin. Coagulase-negative staphylococci were not accepted by the MO for review unless speciated, therefore the sponsor's request to include this category of organisms was rejected.

A review of previous approvals, (see introduction), revealed that approvals have been issued in the past with similar numbers of bacterial isolates. Specifically, norfloxacin was approved with 15 isolates of *Escherichia coli* per arm, and temofloxacin was approved for *Enterococcus faecalis* with 16 isolates on the temofloxacin arm.

Alternatively, and applicable to this trial, no agent has been approved for prostatitis caused by a bacterial isolate that represented less than 10% of the evaluable pathogens.

Based on the above, the Reviewer recommends approval for the indication of prostatitis, expressed as "chronic bacterial prostatitis" due to *Escherichia coli Enterococcus faecalis,* and *Staphylococcus epidermidis."*

From a safety standpoint, the MO found, as did the sponsor that, 14/140 (10%) of treated patients developed increased transaminases to ≥ 3x normal after approximately 3 to 4 weeks of therapy. Additionally, 15/140 (10.7%) of patients developed an increase of transaminases to ≥ 2 x normal. These abnormalities were not

associated in all cases, with clinical complaints or with concomitant increases in alkaline phosphatase, bilirubin, or GGT. The LFT abnormalities resolved after therapy with trovafloxacin was discontinued over the course of 6 – 10 weeks.

Other adverse events included headache (13%), dizziness (23%), and nausea (7%) and were consistent with those reported in the previously reviewed trials of urinary tract infections.

Recommended Regulatory Action:

The following statement can be added to the labeling:

;es:

/S/ 12.18.97
Regina Alivisatos, MD
Medical Officer, DSPIDPs

Orig. NDA #20-759
Orig. NDA #20-760
HFD-590
HFD-590/Div. Dir./MGoldberg /S/ 6
HFD-590/Dep. Dir./RAlbrecht
HFD-590/MTL/BLeissa /S/ 12/18/97
HFD-590/MO/RAlivisatos
HFD-590/CSO/PFogarty
HFD-725/Biostat/Silliman
HFD-344/Thomas

Acute Exacerbation of Chronic Bronchitis:

The **proposed indication** as it will appear in the labeling if approved is:

Acute bacterial exacerbations of chronic bronchitis caused by *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*.

The **proposed dose** is 100 mg PO daily for 7 – 10 days.

In support of this indication, the sponsor submitted three double-blind, comparative trials of the efficacy and safety of trovafloxacin at the proposed dose compared to ofloxacin 400 mg PO BID for 10 days (study 154-101), clarithromycin 250 mg PO BID for 7 days (study 154-109), and ciprofloxacin 500 mg PO BID for 7 days (study 154-141).

The MO located other documents within the electronic submission related to the pharmacokinetics and microbiological properties of trovafloxacin and the requested indication. These were summarized in the MOR.

Oral Antimicrobial Agents Currently Approved for this Indication:

Ofloxacin: (*Haemophilus influenzae* and *Streptococcus pneumoniae*)
Ciprofloxacin: (LRTI: *Haemophilus influenzae, Streptococcus pneumoniae*, and *Moraxella catarrhalis*)
Ceftin®: (*Haemophilus influenzae, Streptococcus pneumoniae*, and *Haemophilus parainfluenzae*)
Cefzil®: (*Haemophilus influenzae, Streptococcus pneumoniae*, and *Moraxella catarrhalis*)
Biaxin®: (*Haemophilus influenzae, Streptococcus pneumoniae*, and *Moraxella catarrhalis*)
Bactrim DS®: (*Haemophilus influenzae* and *Streptococcus pneumoniae*)
Septra®: (*Haemophilus influenzae* and *Streptococcus pneumoniae*)
Cedex®: (*Haemophilus influenzae, Streptococcus pneumoniae*, and *Moraxella catarrhalis*)
Lorabid®: (*Haemophilus influenzae, Streptococcus pneumoniae*, and *Moraxella catarrhalis*)
Maxaquin®: (*Haemophilus influenzae* and *Moraxella catarrhalis*)
Spectobid®: (LRTI: *Haemophilus influenzae, Streptococcus pneumoniae*, beta hemolytic streptococci, and non-penicillinase producing staphylococci)
Suprax®: (*Haemophilus influenzae, Streptococcus pneumoniae*, and *Moraxella catarrhalis*)
Vantin®: (*Haemophilus influenzae, Streptococcus pneumoniae*, and *Moraxella catarrhalis*)
Sparfloxacin: (*Streptococcus pneumoniae, Staphylococcus aureus, Enterobacter cloace, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis*, and *Chlamydia pneumoniae*)
Levofloxacin: (*Staphylococcus aureus, Streptococcus pneumoniae Haemophilus influenzae, Haemophilus parainfluenzae*, and *Moraxella catarrhalis)*
Grepafloxacin: (*Haemophilus influenzae, Streptococcus pneumoniae*, and *Moraxella catarrhalis*)

Abbreviations used in this section:

Ofloxacin = Floxin®, Oflox
URTI = upper respiratory tract infection
LRTI = lower respiratory tract infection
URT = upper respiratory tract
LRT = lower respiratory tract
AECB = acute exacerbation of chronic bronchitis
CB = chronic bronchitis
AB = acute bronchitis
COPD = chronic obstructive pulmonary disease
Biaxin = clarithromycin
Cipro = ciprofloxacin
Trovafloxacin = trovafloxacin

V1 = visit one or baseline visit on study day 1
V2 = visit 2, window: study days 3 –5
V3 = visit 3
V4 = visit 4
V5 = visit 5
EOT = End of Therapy
EOS = End of Study
TOC = Test of Cure
AE = Adverse Event
PTC = Points-to-Consider
ELF = epithelial lining cells
MSSA = methicillin-sensitive *Staphylococcus aureus*
MRSA = methicillin-resistant *Staphylococcus aureus*
PMN = polymorphonuclear
AC = advisory committee
AE = adverse event
UTI = urinary tract infection

Materials Reviewed for this Indication:

Electronic submission/December 29, 1996
Fax/July 28, 1997 containing data related to study 101
Fax/July 31, 1997 containing tables related to studies 101, 109, and 141

Background:

Chronic bronchitis is a clinical diagnosis, loosely applied to patients who cough up sputum on most days, during at least three consecutive months for more than 2 successive years. 3 factors that contribute to CB are cigarette smoking, infection, and inhalation of fumes in the workplace. This disease affects about of the adult population and is more common in men than in women as well as in the > 40 years of age group.

Objective findings of a superimposed acute infection are not always obvious. Patients complain of increased sputum production as well as a change in the color and consistency of the sputum. Purulent sputum may or may not be evidence for an AECB. Other symptoms include increasing cough and dyspnea but most patients do not have systemic findings of an acute infectious process (chills and fever).

The evaluation of sputum samples is helpful in establishing the diagnosis. The presence of eosinophils is presumptive evidence of a noninfectious process and the presence of many epithelial cells would indicate a poor specimen. Routinely a gram stain of sputum of patients with CB shows a mixture of gram-positive and gram-negative flora, consistent with contamination by normal oral flora or with tracheal colonization with *Haemophilus influenzae, Streptococcus pneumoniae*, and *Moraxella catarrhalis*. This colonization can occur in up to of patients. Usually the colonizing isolates are unencapsulated. These organisms can persist in sputum during quiescence.

The following statements can be made:

- Chronic colonization of the airways and sputum with unencapsulated strains of *Haemophilus influenzae* and pneumococci occurs in at least 50% of the affected CB population.
- Many physicians usually attribute an AECB to one or the other organism. *Moraxella catarrhalis* can also be found in up to 17% of the cases.
- Other bacteria such as hemolytic species of streptococci, *Staphylococcus aureus*, and gram-negative enteric bacilli are infrequent causes of AECB

- *Mycoplasma pneumoniae* infections can be responsible for some AECB, although sporadic
- Viruses are frequent causes of AECB, occurring in up tc of cases
- Standard chest radiographic films serve the purpose of excluding other diseases such as pneumonia and because they do not confirm the diagnosis of AECB, they are not a useful tool with which to follow patients.

In terms of management of AECB, prophylactic antimicrobial therapy has been found to decrease the number of exacerbations in those who experience more than 4 episodes a year. Additionally, it is generally accepted in clinical practice that the treatment of an AECB with a 7 – 10 day course of antimicrobial therapy decreases the duration of the episode and the incidence of respiratory decompensation associated with it. The mainstays of treatment include antimicrobials effective against the 3 main pathogens. Steroids are also often used in those case where patients do not respond to improved pulmonary toilet and antimicrobials.

Mandell, Douglas, and Bennett's principles and Practice of Infectious Diseases, Fourth edition, pages 608 - 612.

The FDA PTC document suggests that 2 trials are necessary in order to attain approval for the indication of AECB. One should be a statistically adequate and well-controlled trial establishing equivalence or superiority to an approved product. In this trial, patients should be clinically and microbiologically evaluable.

The second study, in which clinical effectiveness should be used as the primary endpoint, does not require that each patient be bacteriologically evaluable. Rather 2 groups of patients should be analyzed; those who were clinically evaluable and a subset of this group who were clinically and microbiologically evaluable.

Although the PTC document states that only *Haemophilus influenzae, Streptococcus pneumoniae,* and *Moraxella catarrhalis* should be listed as pathogens, recent regulatory precedence with sparfloxacin indicates the change in approach recently instituted by the Division as regards to bacterial pathogens.

Current IDSA Guidelines for the evaluation of anti-infective drug products, Vol. 15, suppl. 1, Nov. 1992, pages S77 – S80, suggest the following:

The minimal diagnostic criteria permitting the inclusion of patients in clinical trials are:

- the presence of the underlying diagnosis of CB, defined as the presence of a chronic cough for > 2 consecutive years and on most days for 3 consecutive months, and
- the presence of evidence of an acute exacerbation as indicated by the combination of increased cough and/or dyspnea, increased sputum volume or purulence
- the presence of a negative chest radiograph to rule out pneumonia
- the production of purulent sputum defined as the presence on gram stain of > 25 PMN leukocytes and < 10 squamous epithelial cells per low-power magnification, with a predominant bacterial morphology.

In addition to the above, the trial should include only adult patients (≥ 18), who are able to give informed consent. The use of steroids is not necessarily grounds for exclusion. Patients suffering from cystic fibrosis should be excluded.

The duration of treatment should be 7 – 10 days and patients who worsen or who do not improve after 3- 5 days should be removed from the study and classified as clinical failures. The addition of an antimicrobial that is not a study drug should also result in the designation of clinical failure.

The clinical response should be classified as clinical cure, clinical improvement, clinical failure, and indeterminate. Patients should be evaluated at 3 – 5 days after the initiation of therapy and weekly thereafter.

The definitions of clinical response are as follows:

- Clinical cure: the resolution of acute signs and symptoms to a baseline level of dyspnea, cough, sputum production, and , if elevated at enrollment, resolution of fever.
- Clinical improvement: the subjective improvement in dyspnea with reduction in cough, a quantified reduction in 24-hour volume or purulence of sputum and a return of the temperature to normal if initally elevated.
- Clinical failure: the lack of any resolution in the signs and symptoms of the disease.
- Indeterminate: must be substantiated by stated reasons.

The definitions of microbiologic response include:

- Eradication
- Persistence
- Relapse
- Reinfection
- Superinfection.

Clinical and microbiologic reassessment should be done within 48 hours, 7 – 14 days, and 21 – 28 days after completion of therapy.

The current guidance for evaluability criteria of the DAIDP recently addressed the issue of AECB. Amongst the points that were stressed, were:

- The differentiation of an AECB as opposed to a SBIAC (subacute bacterial infection of acute bronchitis), in other words, a true bacterial infection in a population of CB patients from a viral, atypical, or bacterial infection in a population of patients with AB.
- The exclusion of patients on steroid therapy
- The prerequisite of , of therapy for evaluability
- The "optional" EOT visit, as this visit cannot be used as the TOC
- The "required" TOC visit at 1 – 2 weeks after completion of therapy
- Clinical outcome as the primary efficacy variable
- The preference of the division to avoid the category of "improved"
- The addition of the microbiologic response categories of "presumed eradication" and "presumed persistence" and the elimination of the category of "relapse," while maintaining the categories of "superinfection, reinfection, and colonization."

The DAIDP advisory committee agreed to all of the above.

Medical Officer's Comment: *The MO determined that there was concurrence from all sources as to the criteria utilized in the diagnosis of an AECB as well as in the design and implementation of clinical trials to assess the efficacy and safety of new agents for this entity.*

The MO adhered to these criteria and made the following determinations with regards to evaluabilty criteria:

- *The diagnosis of an underlying CB with an acute exacerbation must be well established.*

The sponsor adequately provided this information. A review of the CRFs revealed that the investigators not only had to verify the presence of increased cough, sputum production, increased purulence, dyspnea, and in study 101 only, the presence of fever, but additionally had to obtain a chest radiograph to exclude an underlying pneumonia as well as a sputum culture to assess not only for purulence but also for a predominant organism.

Additionally, the investigator was able to provide in written form, the duration of the underlying CB as well as the duration of the current episode of AECB.

- *The MO carried forward any patient who received any additional antimicrobial during the study as an evaluable failure. Failure was determined after 2 full days of therapy. This was consistent with the protocol design wherein the investigators were able to determine failure on the second day of therapy.*

- *The MO did not consider evaluable those patients who received an alternative antimicrobial within 72 hours of the start of the study, unless the prerequisite clinical and microbiologic criteria were present (that is the isolation of a predominate pathogen on culture in association with the clinical picture of AECB).*

- *The MO excluded patients on steroid therapy or provided separate analyses of clinical response if they were not excluded.*

- *The MO adhered to the categories of clinical and microbiologic assessment as described above in the IDSA Guidelines with the modifications of the advisory committee. This included the use of the primary efficacy variable of clinical response as a determinate of microbiologic outcome. That is, a patient who was cured was assumed to have "eradication/presumed eradication" of the primary pathogen or alternatively, a patient who failed was assumed to have "persistence/presumed persistence" of the primary pathogen.*

- *The MO assessed cure and improvement together in order to provided a dichotomous "cure/fail" analysis.*

- *The MO determined that the TOC should be applied to the EOS visit. This determination differed from that of the sponsor where the primary efficacy variable, clinical response, was applied to the EOT. The logical continuation of this argument was that a patient who was not seen at the later follow-up visit was not evaluable. If, however, the sponsor excluded a patient because they were not seen at the EOT but were seen at the later visit, the MO determined that this patient was evaluable. All failures were carried forward.*

- *Patients were eligible for classification as clinical cures if they received between 80 – 120 % of the study drug or between 5 – 8 days and 10 – 12 days of therapy for the 7 day pivotal studies.*

- *The windows of evaluability provided for by the sponsor were not changed for the EOS as the MO TOC was at the EOS (or 1 – 2 weeks after the EOT), and therefore sufficiently far out from therapy that the presence of active drug or post-drug effect could be excluded.*

The MO reviewed the sponsor's evaluability criteria and general approach in this introduction. Although study 101 was a phase II study as opposed to 109 and 141 which were phase III studies, there were minor differences between them only and these were pointed out in this section. Subsequent to the introduction, each study was reviewed separately and the MO referred back to this introductory section.

Microbiology:

In support of the effectiveness of trovafloxacin against the requested pathogens, the sponsor submitted, (microbiology section of the electronic submission), the results of microbiology studies of trovafloxacin versus the requested pathogens. These MIC-90 results are summarized below:

Streptococcus pneumoniae: 0.06 – 0.25 mcg/mL
Penicillin-resistant pneumococci:
Moraxella catarrhalis:
Haemophilus influenzae.

Pharmacokinetics:

The sponsor provided 2 studies assessing the penetration of orally administered trovafloxacin into the bronchial tree (study 154-016: an open study to assess concentrations of trovafloxacin in bronchial washings and serum after administration of a single dose to subjects undergoing bronchoscopy and 154-020: an open study to assess the concentration of trovafloxacin in bronchial mucosa, epithelial lining fluid, and alveolar macrophages compared to that of serum after administration of single and multiple oral 200 mgm doses to subjects undergoing fiber-optic bronchoscopy). The pharmacokinetics reviewer reviewed these studies, however, for the purposes of this review, they are briefly reviewed here.

Study 154-020:

This open, multiple group study assessed the penetration of orally administered trovafloxacin into bronchial mucosa, epithelial lining fluid, and alveolar macrophages obtained by bronchial lavage during bronchoscopy at 6, 12, and 24 hours after the administration of a single dose of 200 mg trovafloxacin, and 6 hours after the fourth and final dose of a multiple dose regimen of trovafloxacin 200 mg. Nineteen subjects, (15 male and 4 female), ranging in age , participated in the single dose arm and 9 subjects, (7 male and 2 female), ranging in age , participated in the multidose arm of the study. Among those subjects in the single dose arm, trovafloxacin was administered 6 hours prior to scheduled bronchoscopy in six subjects, 12 hours prior to scheduled bronchoscopy in six subjects, and 24 hours prior to scheduled bronchoscopy in seven subjects. All nine subjects in the multidose arm received their final dose of trovafloxacin 6 hours prior to the scheduled bronchoscopy.

Trovafloxacin concentrations were determined in bronchial mucosal tissue, epithelial lining fluid, and macrophages. Serum concentrations of trovafloxacin were also determined for the calculation of the tissue/serum drug concentration ratio. Seventeen of the 19 subjects in the single dose arm and all nine of the subjects in the multiple dose arm were included in the pharmacokinetic analysis (i.e., had trovafloxacin concentrations determined for serum and at least one of the three tissue samples).

After single doses of trovafloxacin, the mean bronchial mucosal tissue to serum concentration ratios were 1.1 and 1.2 at 6 and 12 hours, respectively.

The mean ELF to serum concentration ratio was 2.3 at 6 hours after dosing and was maintained at 2.2 at 24 hours after dosing. The mean macrophage to serum concentration ratios were 13.3 and 16.3 at 6 and 12 hours after dosing, respectively, and reached 22.4 at 24 hours after dosing.

Multiple dose administration of trovafloxacin resulted in a similar mean mucosal tissue to serum concentration ratio (1.1) and even greater ELF to serum and macrophage to serum ratios (5.8 and 24.1, respectively) when compared to single dosing.

Study 154-016:

This open study assessed the penetration of trovafloxacin into bronchial mucous and bronchial epithelial cells and macrophages obtained by bronchial lavage during bronchoscopy. Twenty-six subjects, (17 female and 9 male), ranging in age entered and completed this study. Bronchial tissues and fluids were collected by bronchial lavage 4 to 6 hours or 18 to 24 hours after the administration of a single dose of 200 mg trovafloxacin.

Trovafloxacin concentrations were determined in bronchial mucous, broncho-alveolar epithelial cells, macrophages, and supernatant of lavage fluid. Serum concentrations of trovafloxacin during bronchoscopy were also determined for the calculation of the tissue/serum drug concentration ratio.

At 4 to 6 hours after the administration of 200 mg trovafloxacin, the mean serum concentration of trovafloxacin was 2.2 μg/mL, while the corresponding mean concentration in epithelial cells/macrophages (cells) was 5.7 μg/g (cells/serum ratio: 2.9). At 18 to 24 hours postdose, the mean serum trovafloxacin concentration was 1.0 μg/mL, while the mean trovafloxacin concentration in the bronchial epithelial cells and macrophages was 6.1 μg/g (cells/serum ratio: 7.3).

The penetration of trovafloxacin into human bronchial tissues was also studied. Following a single 200 mg dose the mean concentrations of trovafloxacin 1-6 h post dose were 2.2 mcg/mL in plasma and 6.1 mcg/mL in cells obtained by broncheolar lavage. At 18-24 h after dosing, mean trovafloxacin concentrations were 1.1 μg/mL and 5.2 mcg/g in serum and cells, respectively.

In another study, nine patients given once daily 200 mg doses of trovafloxacin for four days were evaluated for drug levels in lung tissue. Six hours after the last dose, trovafloxacin levels in serum, alveolar macrophages, epithelial lining fluid, and broncheolar mucosa were 1.5, 34.3, 10.2, and 1.7 mcg/mL, respectively.

The results of these studies are provided below (copied from the electronic submission):

154-016	26	Bronchial epithelial cells/macrophages	2.9 (4-6 hr postdose) 7.3 (18-24 hr postdose)
154-020	5	Lung mucosa (single dose)	1.1 (6 hr postdose)
	9	Lung mucosa (multiple dose)	1.1 (6 hr postdose)
154-020	5	Lung epithelial lining fluid (single dose)	2.3 (6 hr postdose)
	7	Lung epithelial lining fluid (multiple dose)	5.8 (6 hr postdose)
154-020	5	Alveolar macrophages (single dose)	13.3 (6 hr postdose)
	8	Alveolar macrophages (multiple dose)	24.1 (6 hr postdose)

Medical Officer's Comment: *These results indicated that trovafloxacin was well distributed to bronchial mucosal tissue, ELF and macrophages following single and multiple 200 mg doses. In addition, the concentrations obtained were well above the MIC-90s of pathogens commonly responsible for respiratory infections (Streptococcus pneumoniae, Moraxella catarrhalis,* and *Haemophilus influenzae).*

General Approach to Evaluation:

Copied below from page 9 of section H.3.A, is the sponsor's table of the studies performed in support of this indication:

Acute Bacterial Exacerbations of Chronic Bronchitis					
154-101	100 mg QD (10 days) 300 mg QD (10 days)	74 76	Ofloxacin 400 mg BID (10 days)	73	Phase II DB
154-109	100 mg QD (7 days)	210	Clarithromycin 500 mg BID (7 days)	200	Phase III DB
154-141	100 mg QD (7 days)	131	Ciprofloxacin 500 mg BID (7 days)	125	Phase III DB

Medical Officer's Comment: *Although all studies were comparative, double blinded studies, study 154-101 differed from the others in that it was a Phase II dose-ranging study. This study was included in the submission in order to increase the number of organisms.*

Definitions:

As per the sponsor, AECB was defined as follows (copied from page 12 of section H.3.A):

clinical signs and symptoms of chronic bronchitis defined by the presence of cough, dyspnea, lung sounds, (rales and rhonchi; all protocols except 154-101) and excessive secretion of mucus, (subjects were to have coughed up sputum on most days during three consecutive months for two or more successive years.

signs and symptoms characteristic of acute bacterial exacerbations, including increased dyspnea, increased sputum volume and purulence;

presence of purulent sputum defined by Gram stain showing >25 polymorphonuclear leukocytes and <10 squamous epithelial cells per low-power magnification field [10X];

absence of pneumonia on chest x-ray and absence of cystic fibrosis.

Subjects had to be over 40 years of age (to select subjects with true chronic bronchitis), except in protocol 154-101 where subjects could be enrolled. Subjects with unstable pulmonary disease were excluded from all studies.

Medical Officer's Comment: *The MO agreed with this definition.*

Systemic Antibiotic Usage (copied from page 13 of section H.3.A):

Prior systemic antibiotic usage for more than 24 hours within 72 hours of baseline was prohibited unless there was documented evidence of bacterial resistance or clinical failure. Subjects with infections that may have required treatment with an antibiotic other than study drug were also excluded.

Medical Officer's Comment: *The MO agreed with this definition.*

Data Analysis:

Copied below from page 14, section H.3.A, are the sponsor's definitions of subject subsets:

- **All Randomized (Double-Blind Studies) or Enrolled (Non-Randomized Open Studies) Subjects**
  The all randomized or enrolled subjects subsets included all subjects who were randomized or enrolled to a treatment group, regardless of whether or not a particular subject received any study medication.

- **All Treated Subjects**
  The all treated subjects subset included all subjects who received one or more doses of study medication (active double-blind study medication for the double-blind studies).

- **Clinical Intent-to-Treat Subjects**
  The clinical intent-to-treat subjects subset included those subjects in the all randomized or enrolled subjects subset who had a baseline diagnosis of the disease or condition under investigation determined by protocol specific inclusion and exclusion criteria (not applicable to protocol 154-101, which had a check box on the case report form for underlying disease rather than inclusion/exclusion criteria). Some subjects in this subset may never have received any study medication.

- **Clinically Evaluable Subjects**
  The clinically evaluable subjects subset included all subjects in the clinical intent-to-treat subjects subset who received study medication, unless any one or more of the criteria for non-evaluability applied.

- **Bacteriological Intent-to-Treat Subjects**
  The bacteriological intent-to-treat subjects subset included those subjects in the clinical intent-to-treat subjects subset with at least one pathogen identified at baseline. Some subjects in this subset may never have received any study medication.

- **Bacteriologically Evaluable Subjects**
  The bacteriologically evaluable subjects subset included all subjects in the clinically evaluable subjects subset, unless one or more of the criteria for non-evaluability applied.

***Medical Officer's Comment**: The MO's evaluable population was compromised of a subset of the sponsor's clinically evaluable subset.*

Evaluability Criteria (copied from pages 15- 16 of section H.3.A):

Clinical:

If any of the following were present, the subject was considered non-evaluable for clinical efficacy:

- insufficient therapy (subject discontinued study medication, for any reason other than insufficient therapeutic effect, before the protocol specific minimum requirement);
- non compliance with study drug regimen (phase II, study 101 only);
- prior antibiotic usage (for >24 hours within 3 days before Day 1 of the study);
- use of a concomitant antibiotic, given for intercurrent illness or adverse event, that was potentially effective against the condition under study (unless given for insufficient response);
- or intercurrent illness that could confound clinical evaluation of the condition under study.

Subjects in the Phase II protocol (154-101), were also non-evaluable for clinical efficacy if they were lost to follow-up (i.e., completed protocol specific minimum of study treatment but failed to return for the end of treatment or end of study visits). However, subjects who discontinued for lack of efficacy or subjects who were clinical failures at the end of treatment visit and failed to return for the end of study visit were evaluable.

Subjects in Phase III studies were also non-evaluable for clinical efficacy if the following applied:

- no post-baseline assessment in the evaluable analysis window, unless the investigator's clinical response was failure before the beginning of the end of treatment window,
- or the subject was given an antibiotic for insufficient response at any time during the study.

For Phase II and Phase III studies, a subject was included in the analysis at the end of study assessment if the subject:

was clinically evaluable at the end of treatment visit, and

was not given any antibiotics for intercurrent illness before the assessment at the end of study visit (unless given for insufficient response), and

had a clinical assessment in the appropriate window or was given an antibiotic for insufficient response at any time during the study,

or the subject was:

clinically evaluable at the end of treatment visit, and

the sponsor-defined clinical response was failure or relapse at end of treatment.

Medical Officer's Comment: The MO agreed with the sponsor's evaluability criteria. All failures were carried forward and the EOS visit was necessary to apply the TOC. The MO did not consider the EOT visit necessary. During the review of study 154-101, the MO found several instances of patients who because of an adverse event, were discontinued from the study drug at day 2 or 3. These patients were routinely treated with an alternative antimicrobial but not classified as failures or carried forward as such. The MO determined that these patients had to be evaluated on a case-by-case basis.

Bacteriological:

For subjects with no baseline atypical pathogen, and protocol 154-101, if any of the following were present the subject was considered non-evaluable for bacteriological efficacy:

- no baseline pathogen or baseline culture outside baseline visit window (>2 days before the first dose of study medication).
- no post-baseline culture, except in the instance of no suitable culture material due to clinical cure or improvement based on the investigator-defined clinical response,
- or the subject was given an antibiotic for insufficient response or the investigator's clinical response was failure (at any time up to and including the last day of the evaluable end of study analysis window.
- Subjects with a serologically defined baseline atypical pathogen, except in protocol 154-101, were bacteriologically evaluable if they were clinically evaluable.

For all protocols and for subjects with no baseline atypical pathogens and protocol 154-101, bacteriologically evaluable subjects were excluded from the analysis at the end of study visit if:

they were excluded from the clinical analysis at the end of study visit, or

they did not have a culture result in the end of study window, unless given an antibiotic for inadequate response or the investigator's clinical response was failure any time during the study, up to and including the last day of the end of study analysis window.

Subjects in protocols with a serologically defined baseline atypical pathogen, except protocol 154-101, were included in the bacteriological analysis at end of study if they were included in the clinical analysis at end of study.

***Medical Officer's Comment**: The MO agreed with these criteria. The MO's bacteriologically evaluable population was a subset of the clinically evaluable. As the MO TOC was applied to the EOS visit, the presence of a culture result in the EOS window was necessary within the context of making a presumptive versus a definite determination of outcome. However, as stated above, as the main determinant of efficacy is clinical, the MO accepted a presumptive determination in correlation with the clinical.*

Primary and Secondary Endpoints for Efficacy (copied from page 16 of section H.3.A):

The primary efficacy endpoints were:

Sponsor-defined subject clinical response at the end of treatment visit;

Pathogen eradication rates at the end of treatment visit.

Secondary efficacy endpoints were:

Pathogen eradication rates at the end of study visit;

Investigator-defined subject clinical response at the end of treatment visit, and sponsor-defined and investigator-defined subject clinical response at the end of study visit.

***Medical Officer's Comment**: As stated previously, in accordance with regulatory precedence as well as the DAIDP's guidance document and the AC recommendations, the MO elected to assess outcome, clinical and bacteriological, at the EOS as opposed to the EOT visit. Any patient without an EOS visit was not considered evaluable and any patient excluded by the sponsor because they did not have an EOT visit but did have an EOS visit was considered evaluable. Additionally, if there was no bacteriologic response documented at the EOS, the EOT response was carried forward from the EOT to the EOS by the MO as a presumptive response.*

Definitions of Response (copied from pages 17,18, and 19 of section H.3.A.A):

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 the end of treatment and end of study visits.

The investigator classified the clinical response of the subject as cure (resolution of all signs and symptoms of the disease under study to the level that existed before baseline), improvement (incomplete resolution of signs and symptoms), or failure (lack of resolution of any of the signs and symptoms of infection).

The occurrence of the following conditions superseded the investigator's assessment:

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 visits.

Failure. If a subject was given a concomitant antibiotic for insufficient clinical response or failure then the sponsor-defined subject clinical response was failure at that visit and at all subsequent visits.

Failure: If a subject had no post-baseline assessment, that subject was classified as a clinical failure at both the end of treatment and end of study visits (ITT only).

Relapse:

If a subject was a clinical cure or improvement at the end of treatment visit, and was assessed by the investigator to be a failure at a subsequent visit, then that subject was classified as a clinical relapse at the end of study visit.

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

Medical Officer's Comment: *As the MO determined outcome at the EOS as opposed to the EOT, patients would be unable to be classified as "relapses" in the MO's analysis. The MO provided a detailed analysis of all of the sponsor's patients who were classified as either "failures" or "relapses."*

For the analysis of the Clinically Intent-to-Treat Subject subset, a 'last observation carried forward' strategy will be used for subjects who are lost to follow-up before the End of Study visit. If, for any reason, no clinical assessment was made at the End of Treatment visit, but an assessment was made at the End of Study visit, the End of Treatment assessment will be treated as missing data.

Sponsor-Defined Pathogen Outcome

For both evaluable and intent-to-treat subjects, the sponsor classified each baseline organism as a pathogen or as a non-pathogen. Each baseline organism classified as a 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 for the end of treatment and end of study visits. If multiple visits occurred in the end of treatment analysis window, the last outcome assigned to each baseline pathogen was used. If multiple visits occurred in the end of study window, the worst case outcome was used. Selection of the worst case outcome followed the order persistence or relapse, presumed persistence, presumptive eradication, eradication.

The sponsor-defined pathogen outcomes were defined as follows:

1. Eradication: Baseline pathogen absent from a culture from the same site. 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.

2. Presumptive eradication: Absence of adequate culture material for evaluation and the sponsor-defined subject clinical response was cure or improvement.

3. Persistence: Baseline pathogen present in a culture sample from the same site (or any relevant site, including blood). 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.

4. Presumed Persistence:

Use of concomitant antibiotic therapy due to insufficient response, not starting on the same day, 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 visits, regardless of subsequent culture results. If the subject was lost to follow-up, the presumed persistence was carried forward to subsequent implied visits. Absence of microbiological data was either no visit in the window or culture not done at all visits in the window.

No culture was obtained (either not done or absence of adequate culturable material) 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 either the end of treatment or end of study visits were assigned the outcome of presumed persistence if the pathogen was persistent at any previous visit.

5. Relapse: The original baseline pathogen was present at the end of study visit in a culture from the same site after the end of treatment culture was negative.

Organisms not present at baseline were classified as superinfection or colonization, defined as follows:

6. Superinfection: A pathogen, other than one identified at baseline, that is identified at any post-baseline time in culture material obtained from the site of infection consistent with the disease under study, and associated with emergence or worsening of clinical and laboratory evidence of infection.

7. Colonization: Any organism, other than one identified at baseline, that is identified at any post-baseline time in culture material obtained from the site of infection consistent with the disease under study, and not associated with signs or symptoms of active infections.

Each atypical pathogen, identified by serology test, was assigned a sponsor-defined pathogen outcome as follows:

1. Presumed persistence: A positive antigen or antibody titer rise for atypical pathogens but no positive culture at baseline, and sponsor-defined subject clinical response was failure.

2. Presumed eradication: A positive antigen or antibody titer rise for atypical pathogens but no positive culture at baseline, and the sponsor-defined subject clinical response was cure or improvement.

Medical Officer's Comment: *The MO agreed with the sponsor's definitions of bacteriologic outcome for those cases where the change in the TOC did not affect the response. For the purposes of this review, the MO elected to evaluate only the 3 requested pathogens.*

Evaluability Windows:

The sponsor, as in previously reviewed indications, for the purposes of their analyses, did not adhere to the by-protocol specified windows. Specifically in study 101, the sponsor applied the EOT window to study days 9 – 15 and the EOS to study days 21 – 35. For the pivotal studies, 109 and 141, the EOT window was applied from study days 3 – 18 and the EOS from study days 19 – 40.

On July 24, 1997, the sponsor was queried as to the meaning of these windows from the standpoint of evaluable cures and failures and the minimum duration of therapy necessary for either. The sponsor

responded that in their analyses, a failure could have been classified as such from the second day of therapy onwards and was always carried forward.

The minimum duration of therapy necessary to be classified as a cure was changed to 3 days (42.8% of a 7-day regimen).

The MO elected not to accept this minimum duration with regards to "cures" but instead required a minimum duration of 5 days of therapy. Therefore for the MO's analyses, the EOT visit was applied for study 101, anywhere from study days 6 – 13 for those patients who received 7 days of therapy or from days 9 – 15 for those patients who received 10 days of therapy. The EOS window was maintained unchanged.

For the pivotal studies 109 and 141, the EOT window for cure was changed to study days 5 – 18 and the EOS (MO TOC window), was maintained at days 19 – 40.

In the MO's analysis as in the sponsor's, failures were carried forward from day 2 of therapy.