Study 154-101

TITLE:

A RANDOMIZED, DOUBLE BLIND, MULTICENTER TRIAL COMPARING 10 DAYS OF ORAL THERAPY WITH TROVAFLOXACIN (TROVAFLOXACIN) (100 MG OR 300 MG DAILY) OR OFLOXACIN (800 MG DAILY) FOR THE TREATMENT OF ACUTE EXACERBATION OF CHRONIC BRONCHITIS.

Study dates: November 24, 1993 – July 11, 1994

Objective: The objective of this Phase II study was to compare the safety and efficacy of 2 doses of trovafloxacin and ofloxacin in the treatment of subjects with AECB,

List of Principal Investigators:

COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
United States	5004	Harold Schnaper, M.D.
	5015	Sanford Chodosh, M.D.
	5016	H. Charles Miller, M.D.
	5017	John Gezon, M.D.
	5018	George Bell, M.D.
	5019	Nazir Memon, M.D.
	5021	Steven Pace, M.D.
	5022	Lee Payne, M.D.
	5023	Warren Whitlock, M.D.
	5026	Mark Peacock, M.D.
	5033	Thomas Parker, M.D.
	5045	Lawrence Repsher, M.D.
	5047	Roger Menendez, M.D.
	5048	Daniel Gremillion, M.D.
	5050	Charles VanHook, M.D.
	5051	Robin Miller, M.D.
	5052	Madeleine Neems, M.D.
	5053	F. Stephen Herrington, M.D.
	5054	Steven Becker, M.D.
	5055	Pasquale Dilorenzo, M.D.
	5056	Stuart Topkis, D.O.
	5057	Jack Tomlinson, M.D.
	5058	Stephen Kreitzer, M.D.
	5059	Narayan Krishnamurthy, M.D.
	5060	Anjuli Nayak, M.D.
	5061	Michael Kalafer, M.D.
	5066	Robert Pieroni, M.D.
Costa Rica	5034	Guillermo Rodriguez, M.D.

Study Design: Study 154-101 was a Phase II, randomized, double-blind, double-dummy, comparative, multicenter trial of trovafloxacin (100 mg or 300 mg daily as a single dose in the morning), versus ofloxacin (400 mg in the morning and evening), administered orally for 10 days for the treatment of acute exacerbation of chronic bronchitis.

Efficacy was evaluated through clinical assessments of signs and symptoms of AECB. Safety was assessed throughout the study by recording concomitant medication, vital signs, study drug dosing, adverse events, and laboratory evaluations. In addition, serum trough concentrations of study drug were also determined.

Protocol Overview:

Copied below from the electronic submission, appendix A of the study report is the sponsor's schedule of visits and procedures:

Schedule Of Study Visits and Procedures

Visit Number:	1	2	3	4	5
Study Day:	Day 1	Day 6	Day 11	Day 18	Day 25
Allowable Window:	Day 1	Day 4-8	Day 9-13	Day 14-22	Day 23-27
Treatment Period:	Day 1 to Day 11				
Follow-up Period:			Day 12 to Day 25		
Informed Consent	X				
Demographic Information	X				
Medical History	X				
Physical Examination	X				
Concomitant Medication	X	X	X	X	X
Vital Signs	X	X	X	X	X
Dosing Record			X		
Adverse Experiences		X	X	X	X
Clinical Signs and Symptoms[1]	X	X	X	X	X
Chest x-ray[2]	X				
Microbiology					
sputum gram stain[3]	X	X	X	X	X
culture & sensitivity[4]	X*	X	X	X	X
serology[5]	X				X
Safety Laboratory					
ESR, PT, APTT[6]	X	X	X	abn	abn
CBC + chemistry[7]	X	X	X	abn	abn
urinalysis[5]	X	X	X	abn	abn
Serum Drug Level		X			
Pregnancy Test[8]	X				
Investigator's Clinical Evaluation			x		x

1. includes assessment of sputum volume and degree of sputum purulence
2. should be repeated after baseline only if clinically indicated
3. to be done by local site
4. to be done initially by the local laboratory with pure culture sent to the central laboratory for reanalysis and storage
5. to be done by central laboratory
6. to be done by the local laboratory
7. to be done by central laboratory and includes CBC with differential and platelet count, ALT, AST, AP, GGT, serum total protein and albumin, serum bilirubin, LDH, BUN, serum creatinine, serum calcium and phosphorus, electrolytes, blood glucose, uric acid, serum cholesterol and triglycerides
8. to be done by local site for women of childbearing potential only

* only on isolates obtained from adequate sputum based on Gram stain results (other subjects are to be excluded)

abn only for clinically significant abnormalities persisting at Visit 3

As noted from the above schedule, all baseline evaluations were performed within 48 hours prior to the start of therapy.

At the baseline assessment (Visit 1, Day 1), all subjects had to have a clinical picture characterized by all of the criteria defined below:

Clinical signs and symptoms of chronic bronchitis defined by cough 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 exacerbation, including increased cough or dyspnea, increased sputum volume, or increased sputum purulence.
- Purulent sputum was to be present and defined by Gram stain showing >25 polymorphonuclear leukocytes and <10 squamous epithelial cells per low-power magnification field (LPF) [10X].
- The absence of acute infiltrate on chest x-ray.

Those patients who met the above definition and who gave informed consent were eligible for randomization, if they also fulfilled the inclusion and exclusion criteria. Baseline assessments included the collection of demographic information, medical history, physical examination, concomitant medication use, and vital signs (pulse, respiration, blood pressure, and body temperature).

The clinical assessment of signs and symptoms of AECB included sputum characteristics, cough, dyspnea, chills/rigors, constitutional symptoms, lung sounds, and chest x-ray (unless one had been taken within 48 hours of the baseline assessment).

Macroscopic sputum examination (i.e., color, consistency, and volume), followed by Gram stain and microscopic examination (i.e., polymorphonuclear cells per LPF, squamous epithelial cells per LPF) of sputum were performed. Subjects with inadequate sputum specimens were excluded from randomization. Any intercurrent illness was to be appropriately recorded on the CRF.

Susceptibility to the study drugs, trovafloxacin and ofloxacin, was determined for all causative organisms isolated from adequate sputum specimens. In addition, hematology, coagulation, serum chemistry, and urinalysis determinations, and *Legionella pneumophilia, Chlamydia pneumoniae,* and *Mycoplasma pneumoniae* serologies were performed. Randomization was permitted prior to the availability of the baseline culture and sensitivity report. If no pathogen was detected on baseline culture, continuation of the study drug was at the discretion of the investigator. If a pathogen was resistant to study medication, study treatment could continue at the investigator's discretion, only if there was evidence of clinical improvement.

At Visits 2 (V2: Day 6), and 3 (V3: Day 11: EOT), a determination of efficacy was made. These determinations included clinical assessments of signs and symptoms of AECB, excluding chest x-ray, to assess response to study therapy. Safety was also assessed at these timepoints, by the recording of concomitant medication, vital signs, study drug dosing, adverse events, and laboratory evaluations. Serum trough study drug concentrations were also determined at Visit 2. If no clinical improvement had occurred by Visit 2, study drug was discontinued and the patient started on an appropriate alternative antimicrobial. All discontinued patients were followed through the EOS, when possible. The investigators provided an evaluation of clinical response, (the primary efficacy variable), at V3.

At Visits 4 and 5 (V4: Day 18 and V5: Day 25, respectively, 7 and 14 days after completion of study therapy), efficacy and safety observations were again performed as at V2 with the exception of the

laboratory analyses which were only performed if a clinically significant abnormality was present at V3 (Day 11). At V5 (Day 25), final serologies were performed and the investigators provided a final evaluation of clinical response.

Compliance:

This study was conducted in compliance with local or central Institutional Review Board (IRB) and informed consent regulations.

Protocol Amendments:

This protocol was amended once, in December 1994, to reflect:

- the addition of pharmacokinetic data from study 154-004, "Phase I Study Comparing the Apparent Bioavailability of Solid Dosage Formulation of TROVAFLOXACIN in a Fed and Fasted State, Relative to the Solution in Healthy Male Subjects", regarding the effect of food intake on C_{max} and T_{max} to the introduction of the protocol. Subsequent to this amendment, dosing with meals was no longer prohibited.

- that sensitivity testing at the local laboratory was only to be performed on sputum specimens from some centers rather than at all centers.

- the addition of monitoring procedures for subjects who were taking theophylline or warfarin during the study.

Concomitant Medications:

The investigator documented all concomitant medication usage at each visit. This included any therapeutic interventions. No other antimicrobials were allowed. If another antimicrobial was used, the patient was classified as a treatment failure.

Patients taking theophylline had levels monitored at each study visit. Subjects receiving warfarin had prothrombin time monitored at each study visit. Dose adjustments for theophylline or warfarin were made as clinically appropriate. The concomitant use of systemic corticosteroids was allowed. The use of other (non-anti-infective) medications was limited to those essential to the care of the subject. The use of any other investigational drug was prohibited. Mineral supplements, vitamins with iron or minerals, calcium-, aluminum-, or magnesium-based antacids were not to be taken within (before or after) two hours of dosing.

Discontinuation of Therapy:

Discontinuation of therapy was allowed, at the discretion of the investigator:

- in the event of *in vitro* resistance to a study drug, only if there were no signs of clinical improvement by V2
- In the event of a serious or severe adverse event, limiting side effects or significant laboratory abnormalities

All discontinuations were recorded on the CRF and alternative therapy was instituted. If possible, these patients were followed through the EOS.

Precautions:

Subjects were advised to avoid direct or indirect sunlight and artificial ultraviolet light during treatment and for several days thereafter. In addition, subjects were instructed to discontinue study therapy at the first sign or symptom of phototoxicity reaction such as a sensation of skin burning, redness, swelling, blisters, rash, itching, or dermatitis. Subjects were instructed not to donate blood during and for 6 weeks following administration of study drug.

Study Population:

Approximately 200 subjects with acute exacerbation of chronic bronchitis were expected to be randomized to one of three treatment groups. One hundred fifty (150) of these subjects were expected to be clinically evaluable.

Inclusion and Exclusion Criteria:
(Copied from pages 3 and 4 of the original protocol)

A. Inclusions:

1. Age at baseline.
2. Outpatient men or women. Women of childbearing potential (i.e., not surgically sterile or ≤ one year post-menopausal) must have a negative urine gonadotrophin pregnancy test immediately prior to entry in the study and must use adequate contraception both during and for one month after the end of the study.
3. Clinically documented acute exacerbation of chronic bronchitis as defined below.
4. Written informed consent must be obtained.

Medical Officer's Comment: *The definition of AECB was provided in the study overview and is in accordance with the generally accepted definition.*

B. Exclusions:

1. Pregnant women or nursing mothers.
2. Known hypersensitivity or intolerance to any quinolone antibiotics.
3. Subjects who are currently hospitalized for any reason.
4. Treatment with any other systemic antibiotic for 24 hours or longer within 72 hours prior to the baseline visit.
5. Subjects with unstable pulmonary disease, cystic fibrosis, or evidence of pneumonia on chest radiography.
6. Subjects with infections that may require treatment with an antibiotic other than the study drugs.
7. Subjects with significant gastrointestinal or other conditions which may affect study drug absorption.
8. Subjects with evidence or history of significant hematological, renal or cardiovascular disease or immunologic compromise (i.e. neutropenia, ARC/AIDS, non-skin cancers or malignant melanoma).
9. Subjects with any significant neurologic disease including all forms of epilepsy or any other condition that increases the risk of seizure (e.g. significant head injury, intracranial hemorrhage).
10. Treatment with another investigational drug within four weeks prior to the baseline visit.
11. Prior enrollment in this protocol.
12. Evidence of drug or alcohol abuse or dependence.

Medical Officer's Comment: *The MO agreed with the standard exclusion criteria.*

Randomization and Blinding:

The investigator sequentially assigned study numbers to the subjects as they were determined to be eligible for treatment. The study number was entered onto the subject's case report form and the subject received study medication with the corresponding number.

Dosage Form and Administration:

Study drug was in the form of tablets and was packaged in blister cards using a double dummy technique to maintain blinding. The study drug administration schedule provided one of the following three doses of study drug, dependent on the random assignment:

Trovafloxacin: 100 mg daily as a single active dose in the morning.

Trovafloxacin: 300 mg daily as a single active dose in the morning.

Ofloxacin: 800 mg daily in two equally divided doses (morning, evening).

The blister cards contained sufficient supplies for a 10 day course of treatment, along with an extra day of medication, should it be needed.

In order to maintain blinding, subjects were instructed to take the following tablets during each day of the 10 days of treatment:

	AM Administration	PM Administration
Trovafloxacin (100 mg/d)	1-placebo for ofloxacin 1-Trovafloxacin x 100 mg 2-Trovafloxacin placebo	1-placebo for ofloxacin
Trovafloxacin (300 mg/d)	1-placebo for ofloxacin 3-Trovafloxacin x 100 mg	1-placebo for ofloxacin
Ofloxacin (800 mg/d)	1-ofloxacin x 400 mg 3-Trovafloxacin placebo	1-ofloxacin x 400 mg

The blister card with the randomization number corresponding to that assigned to the subject was given to the subject at V1. Subjects were instructed to begin study drug medication with the morning dose (even if it was not the morning) and to complete a full day of medication on Day 1. They were also informed that compliance with taking all tablets as instructed was imperative. The investigator reviewed the following with the subjects:

- blister card labeling, clearly indicating those to be used for morning administration and evening administration
- morning and evening dosing was to be approximately 12 hours apart
- mineral supplements, vitamins with iron or minerals, calcium-, aluminum-, or magnesium based antacids were not be taken within (before or after) two hours of dosing.
- not to take their study medication for day 6, (V2) until the visit was completed, because a serum trough level was determined at that visit.

Indices of Compliance

Subjects were informed that compliance with taking all tablets and capsules as instructed was imperative and were asked to bring all unused medication to visits 2 and 3, and again (or empty packs) to visits 4 and 5. All doses taken were recorded in the case report form.

Microbiologic Methods:

Bacteriologic response was assessed at V3 (EOT) and V5 (EOS). Only those sputum specimens that were adequate, as defined previously, were cultured. If there was no obtainable "adequate" specimen, at the EOT or EOS, and the patient was cured or improved, a presumptive assignment of eradication was made.

All specimens were initially sent to the local laboratory for culture. Isolates considered significant were sent to the central laboratory where susceptibility testing was performed. Local susceptibility data was used only if the central laboratory's data was missing.

Criteria for determining susceptibility to the study drugs are summarized below:
(Copied from page 17 of the study report)

Criteria	Trovafloxacin MIC (µg/mL)	Ofloxacin MIC (µg/mL)	Zone Diameter (mm) (5 µg Disk)
Susceptible	≤ 2	≤ 2	≥ 16
Intermediate	4	4	13-15
Resistant	≥8	≥8	≤ 12

MIC for trovafloxacin were tentative criteria based on projections from pharmacokinetic data and *in vitro* susceptibility testing. MIC and Zone diameter (mm) for 5 µg disk for ofloxacin were based on NCCLS criteria.

Legionella pneumophilia, Chlamydia pneumoniae, and *Mycoplasma pneumoniae* serology were performed at baseline (Day 1) and at Visit 5 (Day 25). A four-fold increase in titer was considered positive for the presence of the organism.

Medical Officer's Comment: *This methodology was standard thoughout the NDA.*

Clinical Response:

Clinical response was determined by the investigator and evaluated at the EOT: V3 (Day 11) and at the EOS: V5 (Day 25), or at the time of discontinuation from study. Clinical response was primarily based on the global assessment of the clinical presentation of the subject at the evaluation time point.

Clinical assessment was based upon resolution or improvement of clinical laboratory signs of infection such as defervescence, disappearance or decreased purulent sputum production, changes in dyspnea and cough, and stabilization in general physical condition. Supporting data to evaluate clinical response was to include reduction in leukocytosis. Clinical response was to be classified as cure, improvement, failure, or indeterminate, as defined in the introduction of the MOR.

Subjects were assessed for signs and symptoms, as detailed below, and these assessments were recorded on the CRF.

1. Sputum was obtained at baseline (V1) and at every visit thereafter. Macro and micro evaluations were performed.

2. Chest x-ray was obtained at baseline (V1) and at any other time point deemed necessary by the investigator.

3. Cough, dyspnea, chills/rigors, constitutional symptoms, and lung sounds were each assessed at baseline (V1) and at every visit thereafter and rated on a scale of 0 to 3 as follows: 0 = absent, 1 = mild, 2 = moderate, and 3 = severe.

Medical Officer's Comment: *This method of evaluation of clinical response was standard thoughout the indication of AECB. The only difference in this study is that chills and fever were recorded and graded. A sum of the symptom ratings was not provided.*

Bacteriologic Response

Bacteriological response was determined by the sponsor and evaluated at the EOT (V3) and at the EOS (V5), or at the time of discontinuation from the study. Bacteriologic response was classified by the sponsor as indeterminate (unevaluable), eradication, presumptive eradication, persistence, relapse, superinfection, colonization, eradication with reinfection, or presumed persistence, as defined in the introduction of the MOR.

Medical Officer's Comment: *As noted above, clinical response, the primary efficacy variable, was determined by the investigator and bacteriologic response by the sponsor. Assessments were made both at the EOT and the EOS, when possible.*

Safety Assessments:

Adverse Events:

An adverse event was defined as a sign or symptom, illness, or significant objective test abnormality. All observed or volunteered adverse events and intercurrent illnesses that occurred during the clinical trial regardless of treatment group or suspected causal relationship to study drug were recorded on the adverse event page of the CRF. Following resolution of the adverse event or at the EOS, the investigator's judgment of causality of the adverse event was recorded.

Adverse events were classified as serious if they were fatal; life threatening; resulted in permanent disability; required inpatient hospitalization or prolongation of hospital stay; or involved congenital anomaly, cancer, or drug overdose. Any other adverse experience considered by the investigator to be serious was also reported to the sponsor project clinician immediately by telephone. In the case of death, a summary of available autopsy findings was submitted as soon as possible to the sponsor.

In addition, physical examination was performed at baseline (V1). Concomitant medication use and vital signs (blood pressure, pulse rate, body temperature, and respiratory rate) were evaluated at the V1 and at V2, V3 (EOT), V4, and V5 (EOS).

Clinical Laboratory Tests:

Hematology, coagulation, serum chemistry, and urinalysis determinations were performed at baseline (V1), and at V2 and V3. At V4 and V5, hematology, coagulation, serum chemistry, and urinalysis were only performed if a clinically significant abnormality was present at V3.

Study Monitoring

The sponsor appointed monitor monitored the study routinely through site visits. In addition, CROs (Contract Research Organizations), monitored designated sites under the supervision of the sponsor.

Data Analysis:

See the introduction to the MOR for a review of the sponsor's subsets and their definitions.

Clinical Evaluability Criteria:

See the introduction to the MOR for a review of the sponsor's criteria.

Criteria for Bacteriological Evaluability:

See the introduction of a review of the sponsor's criteria.

Primary and Secondary Endpoints for Efficacy:

In this study, the primary efficacy endpoint was the sponsor-defined clinical response at the EOT.

Medical Officer's Comment: *As stated in the introduction, the MO applied the TOC to the later EOS visit, therefore the primary endpoint for the MO's analysis was clinical response at that timepoint.*

Secondary efficacy endpoints were:

- Pathogen eradication rates at the EOT and at the EOS
- Investigator-defined clinical response at the EOT and the EOS.

Medical Officer's Comment*: The MO determined that in the MO analysis, the secondary endpoints would be applied to the EOS. However, if there was a patient with a bacteriologic response at the EOT of eradication and no response at the EOS, the MO elected to carry this response forward as a "presumed eradication." Failures/persistences were always carried forward in both the sponsor's and the MO's analyses.*

Definitions of Response:

Please refer to the introduction of the MOR for the sponsor's definitions.

Interim Analyses:

2 planned and 2 unplanned analyses were performed during the course of this study. These were performed for administrative reasons. The data was not unblinded and no modifications were made.

Demographics:

As per the sponsor, 223 patients were randomized to treatment (74 subjects to receive trovafloxacin 100 mg (33.1%), 76 to receive trovafloxacin 300 mg (34%), and 73 to receive ofloxacin (32.7%)). 221 of the randomized patients received study drug (73 trovafloxacin-100, 75 trovafloxacin-300, and all of the 73 randomized ofloxacin patients). 2 randomized subjects, one from each trovafloxacin arm did not receive therapy (see below).

Of the treated groups, 187 completed treatment (67/73 (92%) trovafloxacin-100 patients, 56/75 (75%) trovafloxacin-300 patients, and 64/73 (88%) ofloxacin patients).

The MO has recreated sponsor's Table 1.1, the Disposition of Enrolled subjects.

Table 101.1
Subject Disposition, All Enrolled Patients (As per the Sponsor)

		Trovafloxacin 100 mg	Trovafloxacin 300 mg	Ofloxacin 400 mg bid
Subjects with Signed Consent	229			
Withdrawn Prior to Randomization	0			
Randomized		74	76	73
Randomized, But Not Treated		1	1	0
All Treated Subjects		73 (100%)	75 (100%)	73 (100%)
Withdrawn During Treatment		6 (8%)	19 (25%)	9 (12%)
Completed Treatment		67 (92%)	56 (75%)	64 (88%)
Withdrawn During Follow- up		1 (1%)	1 (1%)	1 (1%)
Completed Study		66 (90%)	55 (73%)	63 (86%)
Completed Treatment and Study		66 (90%)	55 (73%)	63 (86%)
Withdrawn During Treatment and Study		7 (10%)	20 (27%)	10 (14%)

Medical Officer's Comment: *There was a higher dropout rate from the trovafloxacin-300 arm as compared to the lower dose trovafloxacin and ofloxacin arms. As can be seen below, there were 19 patients who discontinued therapy because of adverse events (related to study drug), on the trovafloxacin-300 arm as compared to 4 on the trovafloxacin-100 arm and 6 on the ofloxacin arm.*

Additionally, there were 2 patients, who were randomized but did not receive study medication:

Trovafloxacin-100:

- *#50210313: withdrew consent at screening visit, normal flora in sputum culture.*

Trovafloxacin-300:

- *#50220057: Streptococcus pneumoniae, withdrawn because of protocol violation.*

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

Table 101.2
Number of Subjects Enrolled By Center: All Randomized Patients (As per the Sponsor, Modified by MO)

			Trovafloxacin 100 mg				Trovafloxacin 300 mg				Ofloxacin 400 mg b. i. d.			
Center	Total Randomized N =223	(100%)	Randomized N = 74	(100%)	Treated N= 73	(100%)	Randomized N = 76	(100%)	Treated N= 75	(100%)	Randomized N = 73	(100%)	Treated N= 75	(100%)
5015	18	8.1	6	8.1	6	8.2	6	7.9	6	8	6	8.2	6	8.2
5016	1	0.4	0	0	0	0	1	1.3	1	1.3	0	0	0	0
5017	8	3.5	3	4.0	3	4.1	3	3.9	3	3.9	2	2.7	2	2.7
5018	16	7.0	5	6.7	5	6.8	5	6.8	5	6.6	6	8.2	6	8.2
5019	8	3.5	3	4.0	3	4.1	3	3.9	3	3.9	2	2.7	2	2.7
5021	13	5.8	5	6.7	4	5.8	4	5.3	4	5.3	4	5.4	4	5.4
5022	11	4.9	4	5.4	4	5.8	3	3.9	2	2.6	4	5.4	4	5.4
5023	4	1.8	1	1.3	1	1.3	1	1.3	1	1.3	2	2.7	2	2.7
5026	3	1.3	0	0	0	0	2	2.6	2	2.6	1	1.3	1	1.3
5033	4	1.8	0	0	0	0	2	2.6	2	2.6	2	2.7	2	2.7
5034	66	29.5	22	29.7	22	30.1	22	28.9	22	29.3	22	30.1	22	30.1
5047	4	1.8	1	1.3	1	1.3	2	2.6	2	2.6	1	1.3	1	1.3
5048	2	0.8	1	1.3	1	1.3	1	1.3	1	1.3	0	0	0	0
5051	4	1.8	1	1.3	1	1.3	1	1.3	1	1.3	2	2.7	2	2.7
5053	1	0.4	0	0	0	0	0	0	0	0	1	1.3	1	1.3
5054	1	0.4	0	0	0	0	0	0	0	0	1	1.3	1	1.3
5055	23	10.3	8	10.8	8	11	8	10.5	8	10.6	7	9.6	7	9.6
5056	4	1.8	2	2.7	2	2.7	1	1.3	1	1.3	1	1.3	1	1.3
5057	12	5.4	4	5.4	4	5.8	4	5.3	4	5.3	4	5.4	4	5.4
5058	5	2.5	2	2.7	2	2.7	2	2.6	2	2.6	1	1.3	1	1.3
5059	5	2.5	2	2.7	2	2.7	2	2.6	2	2.6	1	1.3	1	1.3
5060	10	5.0	4	5.4	4	5.8	3	3.9	3	3.9	3	4.1	3	4.1

Medical Officer's Comment: *There were 22 centers, all of which were in the US with the exception of #5034. This center, which enrolled and treated approximately 30% of the patients, was located in Costa Rica. The MO evaluated the patients from this center separately in order to ascertain the advisability of pooling the data. The MO found no specific inconsistencies in the recordation of the data from this center and agreed with the classification of clinical and bacteriological efficacy from this center. However, the DSI investigator, Dr. Thomas, on a site visit found many recording abnormalities which were of concern and partially unresolved.*

Amongst the irregularities were:

- *The lack of CxRs for review because of the recycling policy at the hospitals where this investigator enrolled patients.*
- *On those X/R reports that were available, there was no signature.*
- *All gram stains performed at the site were sent for a second opinion. Neither the original gram stains nor the second opinions were available for review.*

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

Table 101.3
Study Evaluation Groups/All Randomized Patients as per the Sponsor (Modified by MO)

	Trovafloxacin 100 mg	Trovafloxacin 100 mg bid	Ofloxacin 400 mg bid
All Randomized Subjects	74 (100%)	76 (100%)	73 (100%)
All Treated Subjects	73 (99%)	75 (99%)	73 (100%)
Subjects with Inappropriate Baseline Diagnosis	0	0	0
Clinically Intent- to- Treat Subjects	74 (100%)	76 (100%)	73 (100%)
Clinically Evaluable Subjects	65 (88%)	58 (76%)	62 (85%)
Clinically Not Evaluable Subjects	9 (12%)	18 (24%)	11 (15%)
Randomized, Not Treated	1 (1%)	1 (1%)	0
Insufficient Therapy	4 (5%)	14 (18%)	7 (10%)
Non-compliance	0	0	1 (1%)
Prior Antibiotic therapy	3 (4%)	2 (3%)	1 (1%)
Concomitant Antibiotic therapy	2 (3%)	3 (4%)	0
Lost to Follow- up	1 (1%)	1 (1%)	2 (3%)
Clinically evaluable at EOS	64 (86%)	55 (72%)	61 (84%)
Subjects with Negative baseline Culture	41 (55%)	43 (57%)	43 (59%)
Bacteriologically Intent- to- Treat Subjects	33 (45%)	33 (43%)	30 (41%)
Bacteriologically Evaluable Subjects	25 (34%)	19 (25%)	21 (29%)
Bacteriologically Not Evaluable Subjects	49 (66%)	57 (75%)	52 (71%)
Randomized, Not treated	1 (1%)	1 (1%)	0
No Baseline Pathogen	39 (53%)	43 (57%)	42 (58%)
Baseline culture Outside Window	1 (1%)	0	1 (1%)
Not assessable at EOT	17 (23%)	25 (33%)	24 (33%)
Not Clinically Evaluable	2 (3%)	2 (3%)	2 (3%)
Bacteriologically Evaluable at EOS	24 (32%)	15 (20%)	20 (27%)
Analyzed for Safety			
Adverse Events	73 (99%)	75 (99%)	73 (100%)
Laboratory Data	72 (99%)	72 (96%)	69 (95%)

* Subjects may have had more than one reason to have been unevaluable

Medical Officer's Comment: *38 of the randomized subjects were not clinically evaluable (9/74 (12%) trovafloxacin-100, 18/76 (24%) trovafloxacin-300, and 11/73 (15%) ofloxacin).*

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 6/73(8%) trovafloxacin-100 treated patients who discontinued therapy and who did not complete the study, as compared to 20/75 (26.6%) trovafloxacin-300 treated patients and 9/73 (12%) ofloxacin-treated patients.

Additionally, there was 1 trovafloxacin-100 patient (#50190006) who completed treatment but who was lost to follow-up. This patient received 11 days of therapy, was followed up until day 27, and was excluded from the analyses because he did not have a follow-up visit. The investigator classified this patient as non-assessable. In the sponsor's ITT analysis, this patient was classified as a failure. Haemophilus parainfluenzae was the initial isolate, and this patient would have been evaluable as a failure as per the MO.

There was a similar patient on the trovafloxacin-300 arm, (#50150063), who received 10 days of therapy and was excluded on day 13 for insufficient response. This patient had Streptococcus pneumoniae in the initial isolate, no follow-up cultures were obtained, and the patient was included in the clinical and bacteriological efficacy analyses as a "failure/eradication." This patient was evaluable as a failure as per the Reviewer.

There was also 1 patient (#50340035), on the ofloxacin arm, who completed therapy but not the study. This patient received 11 days of therapy. The initial sputum isolate was Haemophilus influenzae. The

patient was withdrawn for severe dizziness and was classified as not assessable by the investigator and as a failure by the sponsor. This patient was not included in the evaluable analyses but only in the ITT. This patient was evaluable as a failure as per the Reviewer.

The patients who were clinically unevaluable by arm follow:

Trovafloxacin-100 (N = 9):

- *#50170125: Prior antibiotic therapy. Patient had received Biaxin® up until 48 hours prior to the start of the study. Pseudomonas aeruginosa was isolated from his sputum and he received 11 days of therapy with an initial response of improvement, which was changed to failure at the EOS. This patient was unevaluable as per the MO's criteria.*
- *#50180248: Insufficient therapy. Discontinued on day 2 because of an AE. Reviewer agreed.*
- *#50190006: Lost to follow-up: this patient received 11 days of therapy but did not have an EOS visit. Reviewer agreed.*
- *#50120313: Randomized, not treated. Reviewer agreed.*
- *#50220055: Insufficient therapy: Discontinued on day 2 because she did not meet randomization criteria. Reviewer agreed.*
- *#50480164: Prior antibiotic therapy. Received amoxicillin up until day –2. Reviewer agreed.*
- *#50560176: Insufficient Therapy: Discontinued after 4 days because of an AE. Patient could have been a "cure" but did not receive an adequate course as per the sponsor. Reviewer agreed.*
- *#50600297: Insufficient therapy: Discontinued after 2 days because of an AE. Reviewer agreed.*
- *#50600376: Prior antibiotic therapy: Received amoxicillin up until day –2. Reviewer agreed.*

Thus there were 74 patients initally, 1 was excluded prior to randomization and 8 during the study. Thus the clinically evaluable population as per the sponsor was 65 at the EOT. One additional patient was excluded at the EOS: #50590263. Therefore there were 64 clinically evaluable patients at the EOS. The bacteriologically evaluable population at the EOT was and at the EOS 1ll patients excluded from this group had no baseline pathogen.

Trovafloxacin-300 (N = 18):

- *#50160013: Insufficient therapy: Excluded on day 1 because of an AE. Reviewer agreed.*
- *#50180089: Insufficient therapy. Excluded on day 1 because of an AE. Reviewer agreed.*
- *#50180250: Prior antibiotic therapy. Received Augmentin® up until day –2. Reviewer agreed.*
- *#50190003: Lost to follow-up: Patient did not return after 7 days. The sponsor did not assess the patient. The sponsor classified this patient as a "failure" in the ITT. Reviewer agreed.*
- *#50190004: Insufficient therapy: Excluded on day 3 because of an AE. Reviewer agreed because the patient did not receive an alternative antimicrobial.*
- *#50220057: Randomized, not treated. Reviewer agreed.*
- *#50230037: Insufficient therapy. Excluded on day 2 because of an AE. Reviewer agreed*

- *#50340280: Insufficient therapy. Excluded on day 5 because of an AE. Classified as a "cure" and no further antimicrobial therapy was given. Reviewer agreed*
- *#50340371: Insufficient therapy. Excluded on day 4 because of an AE. Classified as a "cure" and no further antimicrobial therapy was given. Reviewer agreed*
- *#50470134: Insufficient therapy. Excluded on day 1 because of an AE. Reviewer agreed*
- *#50510218: Prior antibiotic therapy. Received Biaxin® up until study start. Reviewer agreed.*
- *#50550174: Insufficient therapy. Excluded on day 2 because of an AE. Reviewer agreed*
- *#50550216: Insufficient therapy. Excluded on day 4 because of an AE. Classified as a "cure" and no further antimicrobial therapy was given. Reviewer agreed.*
- *#50570200: Insufficient therapy. Excluded on day 1 because of an AE. Reviewer agreed*
- *#50570253: Insufficient therapy. Excluded on day 4 because of an AE. Classified as a "cure" and no further antimicrobial therapy was given. Reviewer agreed*
- *#50580207: Insufficient therapy. Excluded on day 1 because of an AE. Reviewer agreed*
- *#50590261: Insufficient therapy. Excluded on day 4 because of an AE. Classified as a "cure" and no further antimicrobial therapy was given. Reviewer agreed*
- *#50600300: Insufficient therapy. Excluded on day 2 because of an AE. Reviewer agreed*

Thus of the initial 76 patients, 1 was excluded prior to randomization. Of the 75 randomized, 17 were excluded during the study, leaving 58 clinically evaluable at the EOT. An additional 3 patients did not follow-up at the EOS, (#50180090, #50330110, #60600296), thus leaving 55 clinically evaluable patients at that timepoint. There were 19 subjects bacteriologically evaluable at the EOT and 15 at the EOS. All patient excluded from this subgroup had no baseline pathogen.

Ofloxacin (N = 11)

- *#50170124: Lost to follow-up. Did not return after day 1. Reviewer agreed.*
- *#50180247: Insufficient therapy. Excluded on day 2 because of an AE. Reviewer agreed*
- *#50210097: Insufficient therapy. Excluded on day 2 because of an AE. Reviewer agreed*
- *#50210100: Insufficient therapy. Excluded on day 2 because of an AE. Reviewer agreed*
- *#50220051: Insufficient therapy. Excluded on day 3 because of an AE. Reviewer agreed because the patient did not receive an alternative antimicrobial.*
- *#50230039: Insufficient therapy. Excluded on day 3 because of an AE. Reviewer agreed because the patient did not receive an alternative antimicrobial.*
- *#50330112: Prior antibiotic therapy. Ceftin® until day –2. Reviewer agreed.*
- *#50340282: Insufficient therapy. Excluded on day 4 because of an AE. Classified as a "cure" and no further antimicrobial therapy was given. Reviewer agreed*

- *#50340335: Lost to follow-up. See above. Reviewer agreed.*

- *#50540187: Lost to follow-up. Did not return after 8 days. Reviewer agreed.*

- *#50570203: Non-compliant. Patient stopped therapy for 2 days. Reviewer agreed that patient did not receive the by-protocol specified minimum amount of therapy.*

Thus of the initial 72 ofloxacin patients, 11 were excluded and 62 were clinically evaluable at the EOT. One additional patient was excluded at the EOS (#60600374). Thus, 61 were clinically evaluable at the EOS. 21 patients were bacteriologically evaluable at the EOT and 20 at the EOS. All excluded patients had no baseline pathogen.

In addition to the above, the MO requested that the sponsor provide a listing of patients who were included in the sponsor's clinically evaluable population and who had either no EOS or no EOT visit. In this study as well as in previously reviewed studies for other requested indications, the sponsor's population has not been the same at these timepoints. These differences do not occur because the patients are lost to follow-up but because of an either/or approach that the sponsor applied to their analyses. Specifically for this study, there were 5 patients who did not have an EOS visit and who were excluded from the MO evaluable population:

Trovafloxacin-100 (N = 1)

- *#50590263: cure at the EOT (this patient however, was reevaluated by the MO and carried forward as an evaluable failure).*

Trovafloxacin-300 (N = 3)

- *#50180090: improvement at EOT*
- *#50330110: improvement at EOT*
- *#50600296: cure at EOT*

Ofloxacin (N=1)

- *#50600374: cure at EOT*

Additionally, there were 13 patients in the sponsor's clinically evaluable population who had an EOS visit but not an EOT visit. These patients were included in the MO's analysis as well as the sponsor's. The MO included them because the MO's TOC was applied to the EOS. The sponsor included them because their TOC was applied both to the EOT and the EOS.

These patients are listed below by treatment arm:

Trovafloxacin-100 (N = 4)

- *#50570257: cure at EOS*
- *#50510219: failure at EOS*
- *#50340362: cure at EOS*
- *#50340238: cure at EOS*

Trovafloxacin-300 (N = 5)

- *#50170128: cure at EOS*
- *#50210099: cure at EOS*
- *#50340236: cure at EOS*
- *#50340363: cure at EOS*

- *#50550212: cure at EOS*

Ofloxacin (N = 4)

- *#50340305: cure at EOS*
- *#50340327: cure at EOS*
- *#50340356: cure at EOS*
- *#50570255: improvement at EOS*

As stated previously, the MO's TOC was applied to the EOS and therefore the MO's clinically evaluable population was that which was analyzed at that timepoint. The MO also presented efficacy analyses at the EOT but the FDA patient population was compromised of significantly fewer patients.

Baseline Characteristics:

The 3 groups were comparable in terms of age, race, weight, sex, and smoking history. The distribution of smokers was approximately for all groups, for non-smokers, it was , and for ex-smokers, it was

The mean age of the patients was 50 and > 95% were white.

The median duration since the onset of the underlying primary diagnosis of CB was 7 years for the trovafloxacin-100 group, 6 years for the trovafloxacin-300 group, and 7 years for the ofloxacin group.

The respective means were 10.8, 9, and 10.4 years.

The median duration since the onset of the present episode was 7 days for the trovafloxacin-100 group, 7 days for the trovafloxacin-300 group, and 6 days for the ofloxacin group.

The respective means were 14.1, 17.9, and 10 days per arm.

Duration of Treatment:

The median duration of treatment was 10 days for subjects in the 3 treatment groups.

Concomitant Medications:

The majority of patients were on concomitant medications during therapy. The most commonly used medications were bronchodilators

Steroids were taken by 18 (25%) of the trovafloxacin-100 patients, 14 (19%) of the trovafloxacin-300 patients, and 18 (25%) of the ofloxacin patients.

Medical Officer's Comment: *The MO did not exclude patients taking steroids in this pilot study but did provide separate analyses of clinical and bacteriological response with and without these patients in the MO's efficacy analysis.*

Concomitant Antimicrobials:

Of the clinically evaluable patients, 7 trovafloxacin-100 patients, 5 trovafloxacin-300 patients, and 2 ofloxacin patients received concomitant antimicrobials for the following reasons:

(This information was located in sponsor's table 2.4, appendix 1).

- inadequate response: 5 trovafloxacin-100, 1 trovafloxacin-300, and 2 ofloxacin (all carried forward as evaluable failures)
- discontinued early due to adverse events: 1 trovafloxacin-300 patient
- other or no reason: 1 trovafloxacin-100, 3 trovafloxacin-300 and 0 ofloxacin patients.

The other category was compromised of the following patients:

Trovafloxacin-100 (N = 1):

- #50590263: Exacerbation of bronchitis. This patient was clinically evaluable but not bacteriologically evaluable (no baseline pathogen). The patient received 10 days of therapy and was classified as a "cure" by both the investigator and the sponsor. The patient received Bactrim® starting on day 17. A repeat sputum culture at the EOT and EOS were negative. At the EOS, the sponsor classified this patient as an "improvement." The Reviewer disagreed and determined that this patient should have been included in the analyses as an evaluable failure.

Trovafloxacin-300 (N = 3):

- #50170122: Sinus infection. This patient was clinically evaluable but not bacteriologically evaluable (no baseline pathogen). The patient received 11 days of therapy and was classified as a "cure" by both the investigator and the sponsor. The patient received amoxicillin starting on day 17. A repeat sputum culture at the EOT and EOS were negative. At the EOS, the sponsor classified this patient as a "cure." The Reviewer disagreed and determined that this patient should have been excluded from the analyses.

- #50180090: UTI. This patients was clinically evaluable and bacteriologically evaluable (*Moraxella catarrhalis*). The patient received 10 days of therapy and was classified as an "improvement" by both the investigator and the sponsor. The patient received Bactrim® for 5 days on days 20-25. A repeat sputum culture at the EOT and EOS was negative. At the EOS, the sponsor classified this patient as a "cure." The Reviewer disagreed and determined that this patient should have been excluded from the analyses.

- #50210107: New episode of bronchitis. This patient was clinically evaluable but not bacteriologically evaluable. The patient received 10 days of therapy and was classified as a "cure" by both the investigator and the sponsor. The patient received Bactrim® starting on day 24. A repeat sputum culture at the EOT and EOS was negative. At the EOS, the sponsor classified this patient as an "improvement." The Reviewer disagreed and determined that this patient should have been included in the analyses as an "evaluable failure."

The Reviewer requested that these patients be either excluded from the FDA evaluable population or carried forward as failures. Although the patients were not classified as "failures," the MO determined that the addition of the other antimicrobial agents before the EOS and also for "other" respiratory indications, when applicable", was not appropriate.

Protocol Deviations:

There were 16 subjects in whom deviations occurred.

The inclusion criteria violations included subjects who exceeded the age limits, had pneumonia on CxR, and unacceptable sputum samples.

There was one violation of the exclusion criteria where a patient who had received chemotherapy was included.

There was 1 patient who took 2 tablets a day for 3 days instead of 1.

Medical Officer's Comment: *The sponsor provided a list of patients but did not state if there were excluded from the analyses. The MO queried the sponsor as to the disposition of these patients on July 27, 1997. The sponsor's representative responded that 4 of these patients were evaluable:*

- *#50150069: > 73 years of age. Reviewer agreed.*
- *#50590259: Bacteriologically and clinically evaluable on the trovafloxacin-100 arm. Classified as a clinical cure with relapse at EOS. Reviewer included patient as a failure with persistence of the baseline pathogen, Haemophilus influenzae.*
- *#50590260: > 73 YO Clinically evaluable only, as a cure on the ofloxacin arm. Reviewer agreed.*
- *#50600295: Clinically evaluable only, as a cure on the ofloxacin arm. Reviewer agreed.*

Medical Officer's Comment: *Based on the above demographic information, the MO determined that:*

- *Patients receiving steroid therapy should be evaluated in a separate analysis.*
- *Patients who received antimicrobials for an AECB (2) should be included in the analyses as "evaluable failures"*
- *Patients who received antimicrobials for other well-documented infections (2) should be excluded from the MO evaluable population.*
- *Patients who did not have an EOS visit (5), should be excluded from the MO evaluable population.*

Sponsor's Efficacy Analysis:

Sponsor-Defined Clinical Response:

Table 101.4

Sponsor-Defined Clinical Response/Clinically Evaluable Population at EOT and EOS: (Modified by MO from Sponsor Table 5.1.1)

Timepoint	Trovafloxacin-100 N= 65	Trovafloxacin-300 N = 58	Ofloxacin N =62
Number of patients evaluated at EOT	N = 61 (100%)	N = 53 (100%)	N = 58 (100%)
Cure	43 (70%)	34 (64%)	39 (67%)
Improvement	16 (26%)	18 (34%)	17 (29%)
Failure	2 (3%)	1 (2%)	2 (3%)
Success (Cure + Improvement)	**59 (97%)**	**52 (98%)**	**56 (97%)**
Number of patients evaluated at EOS	N = 64 (100%)	N = 65 (100%)	N = 61 (100%)
Cure	55 (86%)	47 (85%)	50 (82%)
Improvement	3 (5%)	7 (13%)	7 (11%)
Failure	3 (5%)	1 (2%)	2 (3%)
Relapse	3 (5%)	0	2 (3%)
Success (Cure + Improvement)	58 (91%)	54 (98%)	57 (93%)

The sponsor provided the following 95% CIs, without continuity correction factor ($\Delta = 10$):

EOT: Trovafloxacin-100 versus Trovafloxacin-300: -7.2%, 4.4% ($\Delta = 10$):
Trovafloxacin-100 versus Ofloxacin: - 6.3%, 6.7% ($\Delta = 10$)
Trovafloxacin-300 versus Ofloxacin: - 4.4%, 7.5% ($\Delta = 10$)

EOS: Trovafloxacin-100 versus Trovafloxacin-300: -15.5%, 0.4% ($\Delta = 10$)
Trovafloxacin-100 versus Ofloxacin: - 12.3%, 6.6% ($\Delta = 10$)
Trovafloxacin-300 versus Ofloxacin: - 2.4%, 11.9% ($\Delta = 10$)

The sponsor stated that (copied from page 28 of the study report):

Pairwise comparisons (95% confidence intervals) of the difference between treatment groups in sponsor-defined clinical success rates (cure + improvement) at the end of treatment and at the second follow-up evaluation showed that the three treatments were similar. Because this study was not powered to fall within the confidence limits for equivalence, no definitive conclusions regarding equivalency of the three treatments could be drawn.

Medical Officer's Comment: *The MO agreed that the results of all 3 arms were numerically comparable at both timepoints and that the 95% CI was met for all 3 arms at the EOT but not at the EOS as per the sponsor's analysis.*

The MO requested that the FDA statistical reviewer, Dr. Silliman, provide a 95% CI with continuity correction factor for the above. The results were as follows:

EOT: Trovafloxacin-100 versus Trovafloxacin-300: - 8.9%, 6.1% (Δ = 10):
Trovafloxacin-100 versus Ofloxacin: - 8.0%, 8.3% (Δ = 10)
Trovafloxacin-300 versus Ofloxacin: - 6.2%, 9.3% (Δ = 10)

EOS: Trovafloxacin-100 versus Trovafloxacin-300: -17.1%, 1.5% (Δ = 10)
Trovafloxacin-100 versus Ofloxacin: - 13.9%, 8.2% (Δ = 10)
Trovafloxacin-300 versus Ofloxacin: - 3.5%, 13.5% (Δ = 10)

Based on the FDA analysis, there was therapeutic equivalence between all 3 arms at the EOT only. At the EOS, the FDA TOC, therapeutic equivalence was achieved only for the trovafloxacin-300 arm versus ofloxacin, but not for the trovafloxacin-100 arm versus ofloxacin or versus trovafloxacin-300.

Similar but slightly lower efficacy was seen for the clinical ITT population, with success rates of 63/69 (91%) trovafloxacin-100, 60/70 (86%) trovafloxacin-300, and 59/69 (86%) ofloxacin at the EOT. The respective values at the EOS were 63/74 (85%), 66/76 (87%), and 61/73 (84%). The sponsor did not provide a 95% CI for this analysis.

Clinical Response by Baseline Pathogen:

Table 101.5
Sponsor-Defined Clinical Response by Baseline Pathogen at the EOT and EOS (Clinically evaluable Population: Modified 5.3 by MO)

		Trovafloxacin-100			Trovafloxacin-300			Ofloxacin		
Pathogen		N	No. Cured	%	N	No. Cured	%	N	No. Cured	%
Haemophilus influenzae	EOT	12	12	100	7	7	100	6	6	100
	EOS	13	6	46.1	9	9	100	6	4	66.6
Moraxella catarrhalis	EOT	6	6	100	3	3	100	9	9	100
	EOS	6	5	83.3	2	2	100	9	9	100
Streptococcus pneumoniae	EOT	3	3	100	4	3	75	3	3	100
	EOS	3	2	66.6	5	4	80	3	3	100
Haemophilus parahemolyticus	EOT	2	2	100	1	1	100	-	-	-
	EOS	2	2	100	1	1	100	-	-	-
Haemophilus parainfluenzae	EOT	2	2	100	4	4	100	3	3	100
	EOS	2	2	100	4	4	100	3	3	100
Klebsiella pneumoniae	EOT	3	3	100	-	-	-	-	-	-
	EOS	4	4	100	-	-	-	-	-	-
Pseudomonas aeruginosa	EOT	1	1	100	1	1	100	3	2	66.6
	EOS	1	1	100	1	1	100	3	2	66.6
Haemophilus hemolyticus	EOT	-	-	-	1	1	100	-	-	-
	EOS	-	-	-	1	1	100	-	-	-
Mycoplasma pneumoniae	EOT	-	-	-	1	1	100	-	-	-
	EOS	-	-	-	1	1	100	-	-	-
Chlamydia pneumoniae	EOT	3	3	100	2	2	100	3	3	100
	EOS	4	3	75	2	2	100	3	3	100
Beta-hemolytic *streptococcus*	EOT	-	-	-	1	1	100	-	-	-
	EOS	-	-	-	1	1	100	-	-	-
Total	**EOT**	**32**	**32**	**100**	**25**	**25**	**100**	**27**	**26**	**96.2**
	EOS	**35**	**25**	**71.4**	**27**	**26**	**96.2**	**27**	**24**	**88.8**

Copied below from page 29 of the study report is the sponsor's text:

Among clinically evaluable subjects with the most frequently isolated baseline pathogens, sponsor-defined clinical success rates (cure + improvement) at the end of treatment were 100% in all three treatment groups with two exceptions. One of four subjects in the trovafloxacin 300 mg group with *Streptococcus pneumoniae* isolated at baseline and one of three subjects in the ofloxacin group with *Pseudomonas aeruginosa* isolated at baseline were clinical failures.

The two subjects who were clinical failures at end of treatment were failures at the second follow-up evaluation. In addition, three subjects in the trovafloxacin 100 mg group with baseline isolates of *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae* and two subjects in the ofloxacin group with baseline isolates of *Haemophilus influenzae* were clinical successes at end of treatment and clinical relapses at follow-up. One subject in the trovafloxacin 100 mg group with a positive titer for *Chlamydia pneumoniae* at baseline was not assessed at end of treatment and was designated a clinical failure at follow-up.

Medical Officer's Comment: *The MO agreed with the sponsor's analysis and determined that all 3 treatment groups appeared numerically comparable at the EOT but not at the EOS, where trovafloxacin-300 appeared superior to both comparators and trovafloxacin-100 was inferior to both comparators when total clinical response rates by pathogen were compared. A 95% CI was not applied because of the small numbers of isolates.*

For the 3 primary pathogens, the clinical response rates were the same at the EOT for Haemophilus influenzae and Moraxella catarrhalis. The clinical response rate for the trovafloxacin-300 arm for patients with Streptococcus pneumoniae was 75% compared to 100% for the 2 comparator arms at the EOT.

At the EOS however, only the trovafloxacin-300 arm maintained 100% efficacy against Haemophilus influenzae, and once again, trovafloxacin-100 appeared to be inferior to ofloxacin. The response rates were also lower for trovafloxacin-100 compared to the other 2 arms in patients with Moraxella catarrhalis and Streptococcus pneumoniae at this timepoint.

A review of Table 16, appendix V and the PID's of the "failures/relapses," revealed the following:

Trovafloxacin-100 (N = 3):

- *#50150070: Moraxella catarrhalis: improvement/relapse. This patient initally had Moraxella catarrhalis which was eradicated. The patient relapsed and a sputum specimen at the EOS revealed Haemophilus influenzae. The patient was treated with Bactrim®.*

- *#50580205: Streptococcus pneumoniae: cure/relapse. This patient was a clinical cure at the EOT with eradication of the baseline pathogen. At the EOS the patient was classified as a relapse with growth of Escherichia coli. (Day 18 had Streptococcus pneumoniae). Patient was treated with Cefuroxime®.*

- *#50580208: Haemophilus influenzae: improvement/relapse. This patient initally was classified as a clinical cure with eradication of the baseline pathogen. On day 25, the patient had clinically relapsed with Haemophilus influenzae again isolated. The patient was treated with Bactrim®*

Trovafloxacin-300 (N = 1):

- *#50150063: Streptococcus pneumoniae: failure/failure. This patient clinically failed despite eradication at the EOT of the baseline pathogen. The patient received ampicillin on day 13 until the EOS.*

Ofloxacin (N = 2):

- *#50230038: Pseudomonas aeruginosa: failure/failure. This patient was a clinical failure with persistence of the baseline pathogen. From days 11- 25, the patients received Bactrim® and then was changed to Augmentin® on day 25 for an unspecified duration.*

- *#50260025: Haemophilus influenzae: cure/relapse. This patient was a clinical cure with eradication of the baseline pathogen at the EOT. At the EOS, the patient relapsed and Moraxella catarrhalis was cultured. The patient was treated with Augmentin®.*

Bacteriological Response:

Sponsor-Defined Pathogen Eradication Rates at EOT and EOS can be seen in Sponsor's Table 5.4.1, copied and modified by the MO:

Table 101.6

Sponsor-Defined Pathogen Eradication Rates/Bacteriologically Evaluable Population: (Modified from Sponsor Table 5.4.1)

Pathogen		Trovafloxacin-100			Trovafloxacin-300			Ofloxacin		
		N	No. Erad.	%	N	No. Erad.	%	N	No. Erad.	%
Haemophilus influenzae	EOT	12	12	100	7	7	100	5	5	100
	EOS	12	10	83	9	9	100	6	5	66.6
Moraxella catarrhalis	EOT	6	6	100	4	3	75	9	9	100
	EOS	5	5	100	4	3	75	10	10	100
Streptococcus pneumoniae	EOT	3	3	100	5	5	100	3	3	100
	EOS	3	2	66.6	5	5	100	3	3	100
Haemophilus parahemolyticus	EOT	2	2	100	1	1	100	-	-	-
	EOS	2	2	100	1	1	100	-	-	-
Haemophilus parainfluenzae	EOT	2	2	100	4	4	100	4	4	100
	EOS	2	2	100	3	3	100	4	4	100
Klebsiella pneumoniae	EOT	3	3	100	-	-	-	-	-	-
	EOS	3	3	100	-	-	-	-	-	-
Pseudomonas aeruginosa	EOT	1	1	100	1	1	100	3	2	66.6
	EOS	1	0	0	1	1	100	3	2	66.6
Haemophilus hemolyticus	EOT	-	-	-	1	1	100	-	-	-
	EOS	-	-	-	1	1	100	-	-	-
Beta-hemolytic *streptococcus*	EOT	-	-	-	1	1	100	-	-	-
	EOS	-	-	-	1	1	100	-	-	-
Total	**EOT**	**29**	**28**	**96.5**	**24**	**23**	**95.8**	**24**	**23**	**95.8**
	EOS	**28**	**24**	**85.7**	**25**	**24**	**96**	**26**	**24**	**92.3**

The sponsor's comment has been copied from page 32 of the study report:

At the end of treatment, a sponsor-defined pathogen outcome of persistence was observed for one subject in the ofloxacin group with *Pseudomonas aeruginosa* isolated at baseline (Subject number 50230038). At baseline, this isolate of *Pseudomonas aeruginosa* was found to be of intermediate susceptibility to trovafloxacin (MIC = 4 mcg/mL) and resistant to ofloxacin (MIC = 16 mcg/mL; disk zone = 7 mm); at the end of treatment, the recovered pathogen was susceptible to trovafloxacin (MIC = 1 mcg/mL) and resistant to ofloxacin (MIC = 8 mcg/mL; disk zone = 10 mm).

At the second follow-up visit, sponsor-defined pathogen outcomes of relapse were observed for three subjects in the trovafloxacin 100 mg group, two with *Haemophilus influenzae* isolated at baseline and one with *Pseudomonas aeruginosa* isolated at baseline. Persistence was observed for one subject in the trovafloxacin-100 mg group with *Streptococcus pneumoniae* isolated at baseline. None of these four pathogens developed resistance to trovafloxacin during the course of the study. No bacteriologic relapses or persistence were observed in the trovafloxacin 300 mg and ofloxacin groups.

Medical Officer's Comment: *The MO agreed with the sponsor's determination of pathogen outcome in all cases after review of the PIDs. Overall, the 3 treatment arms were numerically comparable at the EOT but trovafloxacin-300 appeared numerically superior to the 2 comparator arms at the EOS, and trovafloxacin-100 was inferior to both comparators at this timepoint.*

Pathogen eradication rates for Haemophilus influenzae, were similar at the EOT but trovafloxacin-300 was numerically superior to both comparators at the EOS and trovafloxacin-100 was numerically superior to ofloxacin.

The numbers of Moraxella catarrhalis and Streptococcus pneumoniae isolates were too small to be able to make any valid comparisons.

Superinfecting Pathogens:

One bacteriologically evaluable subject in the trovafloxacin-100 mg group (Subject number 5058-0205) developed a superinfection (sputum: Escherichia *coli*). There were no superinfections observed in the trovafloxacin-300 mg and ofloxacin groups. Colonizing organisms were isolated from three subjects (12%) in the trovafloxacin 100-mg group, one subject (5%) in the trovafloxacin-300 mg group, and two subjects (10%) in the ofloxacin group.

Medical Officer's Comment: ***The*** *MO reviewed Table 5.6, a table of superinfecting and colonizing organisms as well as the PIDs for these patients and Table 18 appendix V and found the following:*

Trovafloxacin-100 (N = 4):

- *#50150070: Haemophilus influenzae at day 25. Classified as a colonizing organism. Patient had normal flora in the baseline and EOT specimens. The patient relapsed and a sputum specimen at the EOS revealed Haemophilus influenzae. The patient was treated with Bactrim®. The MO determined that this patient was a failure with a superinfecting organism.*

- *#50220058: Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter calcoaceticus v. lwoffi at day 25. Classified as "colonizing organisms." Patient had normal flora in the baseline and EOT specimens. This patient was classified as a clinical improvement at the EOT and a "cure" at the EOS. Reviewer agreed.*

- *#50580205: Escherichia coli day 25. Classified as a superinfecting pathogen. Streptococcus pneumoniae found at baseline, eradicated. This patient was a clinical cure at the EOT with eradication of the baseline pathogen. At the EOS the patient was classified as a relapse with growth of Escherichia coli. (Day 18 had Streptococcus pneumoniae). Patient was treated with Cefuroxime®. Reviewer agreed.*

- *#50580208: Klebsiella pneumoniae at day 18. Classified as a colonizing organism. Haemophilus influenzae also found at day 25 and at baseline. This patient initially was classified as a clinical cure with eradication of the baseline pathogen. On day 25, the patient had clinically relapsed with Haemophilus influenzae again isolated. The patient was treated with Bactrim®. Reviewer agreed.*

Trovafloxacin-300 (N = 1):

- *#50600373: Enterobacter aerogenes isolated at day 25 and classified as a colonizing organism. Patient had normal flora in the baseline and EOT specimens. Reviewer agreed.*

Ofloxacin (N = 2):

- *#50180092: Moraxella catarrhalis and Streptococcus pneumoniae day 25. Classified as colonizing organisms. This patient was initally classified as a clinical cure with eradication of the baseline pathogen, Haemophilus influenzae. No further therapy was prescribed. Reviewer agreed with designation of organisms as colonizers.*

- *#50580206: Haemophilus parahemolyticus day 25. Classified as a colonizing organism Patient had Pseudomonas aeruginosa in the baseline specimen which was eradicated. This patient was classified as a clinical improvement at the EOT and clinical cure at the EOS. Reviewer agreed.*

Medical Officer's Comment: *Overall, the MO agreed with the sponsor's determinations with the exception of 1 patient on the trovafloxacin-100 arm. This patient would have been classified as a failure/superinfection by the MO.*

Bacteriological ITT Subjects:

The sponsor stated that (copied from page 43 for the study report):

Results differed from those obtained in the bacteriologically evaluable population due to the inclusion of additional intent-to-treat subjects who were not included in the analysis of bacteriologically evaluable subjects. Additional bacteriological failures (persistent, presumed persistent, and relapse) observed in the intent-to-treat analysis were as follows:

One subject in the trovafloxacin 300 mg group had a pathogen outcome of presumed persistent for one isolate of *Moraxella catarrhalis* at the end of treatment. At the second follow- up evaluation, five subjects (2 trovafloxacin 100 mg; 1 trovafloxacin 300 mg; 2 ofloxacin) had pathogen outcomes of presumed persistent (*Moraxella catarrhalis*, one isolate) or persistent (*Streptococcus pneumoniae*, one isolate; *Pseudomonas aeruginosa*, two isolates; and *Haemophilus influenzae*, two isolates). None of these pathogens, for which susceptibility testing was done, developed resistance to trovafloxacin during the course of the study.

Medical Officer's Comment*: The MO did not incorporate all of the ITT subjects into the document because these patients were not bacteriologically evaluable as per the MO.*

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 EOT (TOC) analysis in 1 trovafloxacin-300 and 1 ofloxacin patient.

Specifically:

Trovafloxacin-300 patient 50150063 was a clinical failure with bacteriologic persistence of the baseline pathogen (*Streptococcus pneumoniae*). The MO agreed with this determination. This patient was reviewed above in the clinical failures section.

Ofloxacin patient #50230038 was a clinical cure with bacteriologic persistence of the baseline pathogen, *Pseudomonas aeruginosa*. This isolate was of intermediate sensitivity to trovafloxacin and resistant to ofloxacin

Medical Officer's Comment: *The MO reviewed the sponsor's tables 5.7.1 and 5.7.2 and agreed with the presentation of the data.*

Signs and Symptoms:
(Copied from the study report, page 34)

Among the clinically evaluable subjects, the number of subjects with dyspnea, cough, or DAAF (diffuse abnormal auscultatory findings) decreased from baseline to the end of treatment in all three treatment groups. Further decreases were observed at the second follow-up visit. Among the subjects who continued to display these signs or symptoms, the severity was decreased. Similar results were observed for the clinical intent-to-treat subjects.

Medical Officer's Comment: *The MO reviewed the sponsor's tables and agreed with their conclusion.*

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

Two hundred twenty-three (223) subjects with acute exacerbation of chronic bronchitis were randomized to treatment with trovafloxacin 100 mg once daily, trovafloxacin 300 mg once daily, or ofloxacin 400 mg twice daily for 10 days.

The three treatment groups were comparable with respect to demographic characteristics at baseline, medical history, and prior and concomitant medications.

One hundred eighty-five (185) subjects were clinically evaluable (65, trovafloxacin 100 mg; 58, trovafloxacin 300 mg; and 62, ofloxacin) and 65 subjects were bacteriologically evaluable (25, trovafloxacin 100 mg; 19, trovafloxacin 300 mg; and 21, ofloxacin). All treated subjects were included in analysis of safety.

Pairwise comparisons (95% confidence intervals) of the difference between treatment groups in sponsor-defined clinical success rates (cure + improvement) at the end of treatment and at the second follow-up evaluation showed that the three treatment groups were similar for both evaluable and intent-to-treat subjects. Clinically evaluable: trovafloxacin-100: EOT: 59/61(97%); EOS: 58/64 (91%), trovafloxacin-300: EOT: 52/53 (98%); EOS: 54/55 (98%); ofloxacin EOT: 56/58 (97%); EOS 57/61 (93%).

At the second follow-up evaluation among clinically evaluable subjects, clinical relapses were observed for three subjects in the trovafloxacin 100 mg group with *Moraxella catarrhalis, Streptococcus pneumoniae, or Haemophilus influenzae* isolated at baseline and two subjects in the ofloxacin group with *Haemophilus influenzae* isolated at baseline. No subjects in the trovafloxacin 300 mg group were designated as a clinical relapse at the second follow-up evaluation.

Sponsor-defined pathogen eradication rates were comparable among the three treatment groups at the end of treatment. A sponsor-defined pathogen outcome of persistence was observed for only one subject in the ofloxacin group with *Pseudomonas aeruginosa* isolated at baseline.

EOT Trovafloxacin-100:
Haemophilus influenzae: 12/12 (100%)
Moraxella catarrhalis: 6/6 (100%)
Streptococcus pneumoniae: 3/3 (100%)

EOS Trovafloxacin-100:
Haemophilus influenzae: 10/12 (80%)
Moraxella catarrhalis: 5/5 (100%)
Streptococcus pneumoniae: 2/3 (67%)

EOT Trovafloxacin-300:
Haemophilus influenzae: 6/6 (100%)
Moraxella catarrhalis: 3/3 (100%)
Streptococcus pneumoniae: 4/4 (100%)

EOS Trovafloxacin-300:
Haemophilus influenzae: 5/5 (100%)
Moraxella catarrhalis: 2/2 (100%)
Streptococcus pneumoniae: 3/3 (67%)

EOT Ofloxacin:
Haemophilus influenzae: 5/5 (100%)
Moraxella catarrhalis: 8/8 (100%)
Streptococcus pneumoniae: 3/3 (100%)

EOS Ofloxacin:
Haemophilus influenzae: 5/5 (100%)
Moraxella catarrhalis: 8/8 (100%)
Streptococcus pneumoniae: 3/3 (100%)

At the second follow-up visit, sponsor-defined pathogen outcomes of relapse were observed for three subjects in the trovafloxacin 100 mg group, two with *Haemophilus influenzae* isolated at baseline and one with *Pseudomonas aeruginosa* isolated at baseline. Persistence was observed for one subject in the trovafloxacin 100 mg group with *Streptococcus pneumoniae* isolated at baseline. None of these four pathogens developed resistance to trovafloxacin during the course of the study. No bacteriologic relapses or persistence were observed in the trovafloxacin 300 mg and ofloxacin groups.

Trovafloxacin 100 mg or 300 mg and ofloxacin 400 mg BID were similar with respect to clinical response rates at the end of treatment and at the second follow-up evaluation for both intent-to-treat and evaluable subjects. Pathogen eradication rates were comparable among the three treatment groups at the end of treatment. At the second follow-up evaluation, bacteriologic relapses were observed in four subjects in the trovafloxacin 100 mg group.

Because of the small number of bacteriologically evaluable subjects in this treatment group (N=24), no definitive conclusions could be drawn.