

**Conclusions:****As per the Sponsor:**

The main portion of the sponsor's conclusion can be found at the conclusion of the sponsor's efficacy analysis. The sponsor concluded:  
(Copied from page 57 of the study report):

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Trovafloxacin 100 mg once daily for 7 days was statistically equivalent to clarithromycin 500 mg twice daily for 7 days for clinical success rates at the end of treatment and end of study in subjects with acute bacterial exacerbation of chronic bronchitis.

Pathogen eradication rates for *Haemophilus influenzae* at both the end of treatment and the end of study were higher in the trovafloxacin group compared to the clarithromycin group (end of treatment: 92% versus 75%, respectively; end of study: 92% versus 63%, respectively).

The overall incidence of all and treatment-related adverse events was lower among subjects in the trovafloxacin group as compared to subjects in the clarithromycin group (40% and 20% versus 51% and 38%, respectively). The percentage of subjects with adverse events leading to discontinuation was comparable between the two treatment groups (2% and 4%, respectively). Subjects in the trovafloxacin group had lower frequencies of gastrointestinal system (12% versus 24%) and special senses (5% versus 16%) adverse events and a higher frequency of central and peripheral nervous system (17% versus 12%) adverse events compared to subjects in the clarithromycin group. The frequency and type of clinically significant laboratory abnormalities were comparable between the two treatment groups.

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**Reviewer's Conclusions:**

In this pivotal study comparing trovafloxacin and clarithromycin in the treatment of AECB for 7 days, the sponsor was able to demonstrate equivalence of trovafloxacin to clarithromycin.

Amongst the FDA clinically evaluable population, the MO found that clinical response, (the primary efficacy variable), at the EOS, (the MO TOC), was 157/196 (80.1%) for the trovafloxacin-treated patients, and 129/176 (73.3%) for the clarithromycin-treated patients. Based on a 95% CI (EOS: Trovafloxacin versus Clarithromycin: - 2.3%, 15.9% ( $\Delta = 15$ ), trovafloxacin was equivalent to the comparator.

The clinical response at the EOT was 174/196 (88.8%) for the trovafloxacin-treated patients versus 148/176 (84.1%) for the clarithromycin-treated patients. A 95% CI also determined equivalence between the 2 arms at this earlier timepoint.

When patients receiving systemic steroids were excluded, the following results were obtained at the EOS: 137/164 (83.5%) trovafloxacin versus 108/136 (79.4%) clarithromycin. Based on a 95% CI (EOS: Trovafloxacin versus Clarithromycin: - 5.4%, 13.7% ( $\Delta = 15$ ), trovafloxacin was again equivalent to clarithromycin for the primary efficacy variable of clinical response.

The bacteriologic efficacy analysis yielded the following pathogen eradication rates:

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EOT: trovafloxacin 98/109 (90%) versus clarithromycin 76/87 (87.3%)  
EOS: trovafloxacin 94/111 (84.6%) versus clarithromycin 81/87 (83.5%)

If only the 3 main pathogens (*Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae*) were included, the overall pathogen eradication rates were:

EOT: trovafloxacin: 42/49 (85.7%) versus clarithromycin 40/45 (89%)  
EOS: trovafloxacin 42/49 (85.7%) versus clarithromycin 37/45 (82.2%)

Specific pathogen eradication rates for the three main pathogens, were as follows:

**Table 109.18**  
**Bacteriologic Eradication Rates (as per the MO)**

Pathogen	Trovafoxacin-100		Clarithromycin	
	EOT	EOS	EOT	EOS
<i>Haemophilus influenzae</i>	23/25 (92%)	22/25 (88%)	12/16 (100%)	10/16 (62.5%)
<i>Moraxella catarrhalis</i>	13/17 (88%)	13/17 (76.5%)	17/18 (94%)	16/18 (89%)
<i>Streptococcus pneumoniae</i>	6/7 (85.7%)	7/7 (100%)	11/11 (100%)	11/11 (100%)

Overall pathogen eradication rates at the EOS for the bacteriologically evaluable population minus the systemic steroid users were:

Trovafoxacin: 81/95 (85.2%)  
Clarithromycin: 61/71 (85.9%)

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Pathogen eradication rates at the EOS for the 3 main pathogens, excluding those patients on systemic steroids were:

Trovafoxacin:  
*Streptococcus pneumoniae*: 6/6 (100%)  
*Haemophilus influenzae*: 22/25 (88%)  
*Moraxella catarrhalis*: 11/14 (78.5%)

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Clarithromycin:  
*Streptococcus pneumoniae*: 9/9 (100%)  
*Haemophilus influenzae*: 8/12 (66.7%)  
*Moraxella catarrhalis*: 11/12 (91.7%)

These rates were the same as or very similar to those obtained when isolates from steroid users were included.

The MO concluded that the exclusion of this patient subgroup had no effect on either overall eradication rates or on eradication rates for the individual pathogens.

The MO determined that the sponsor's and MO's pathogen eradication rates were very similar for all subgroups. By the EOS, trovafoxacin had higher eradication rates (88% versus 63%), than did clarithromycin for *Haemophilus influenzae*.

The adverse events seen in this study, were similar to those noted in previous studies, with a lower overall incidence of adverse events in the trovafoxacin-treated patients (42/210: 20%) as compared to the clarithromycin-treated patients (76/200: 38%)

The most common complaints were from the gastrointestinal tract, with 5% (11/210) of trovafoxacin patients having nausea that was treatment related. As seen previously, there were also complaints of dizziness and headache. In this trial, 6/210 (3%) of the episodes of dizziness and 7/210 (3%) of the episodes of headache were determined to be treatment-related.

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There were no significant laboratory abnormalities.

In conclusion, trovafoxacin appeared safe and effective in the treatment of AECB caused by the three main pathogens and was equivalent to the approved comparator, clarithromycin.

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Based on the above, trovafloxacin 100 mg PO for 7 days was equivalent to clarithromycin in the treatment of AECB caused by *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*.

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**Study 154-141**

**TITLE:**

**A RANDOMIZED, DOUBLE BLIND, MULTICENTER TRIAL COMPARING 7 DAYS OF ORAL THERAPY WITH TROVAFLOXACIN (100 MG DAILY) AND CIPROFLOXACIN (500 MG BID) FOR THE TREATMENT OF ACUTE EXACERBATION OF CHRONIC BRONCHITIS.**

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**Study Dates:** December 21, 1994 - September 21, 1995

**Objective:** The objective of this study was to compare the safety and efficacy of trovafloxacin with ciprofloxacin in the treatment of subjects with acute exacerbation of chronic bronchitis.

**List of Principal Investigators:**

COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
United States	5015	Sanford Chodosh, MD
	5017	John Gezon, MD
	5078	C. Andrew Deabate, MD
	5096	Jeffrey Adelglass, MD
	5144	Kirk Jacobson, MD
	5145	Stephen Kraus, MD
	5147	Alex Pareigis, MD
	5148	Stan Parman, MD
	5149	Gary Ruoff, MD
	5150	Irwin Spim, MD
	5151	Keith Vanzandt, MD
	5152	Lawrence Alwine, DO
	5153	Spencer Coleman, MD
	5154	John Estess, MD
	5156	Andrew Hughes, MD
	5157	Mark Lamos, MD
5159	Onelio Perdomo, MD	
5160	Thomas Saddoris, II, MD	
5161	Sandra Willsie, DO	
5210	Thomas Nolen, MD	
6579	William Gray, MD	
Costa Rica	5034	Guillermo Rodriguez Gomez, MD

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**Study Design:** Study 154-141 was a Phase III, randomized, double-blind, double-dummy, comparative, multicenter trial of trovafloxacin (100 mg daily as a single dose in the morning), versus ciprofloxacin (500 mg twice daily), administered orally for 7 days for the treatment of AECB.

**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
Study day:	Day 1	Day 4	Day 8	Day 28
Allowable Window:	-48 hours	Day 3-5	Day 7-9	Day 25-31
Treatment Period	Day 1 to Day 7			
Follow-up period	Day 8 to Day 31			
Informed consent	X			
Demographic Information	X			
Physical Examination	X			
Concomitant Medication	X	X	X	X
Vital Signs	X	X	X	X
Dosing Record			X	
Clinical Signs & Symptoms	X	X	X	X
Chest X-ray	X			
Microbiology				
Sputum Gm stain	X	X	X	X
culture & sensitivity	X	X	X	X
serology	X			X
Safety laboratory tests				
hematology	X		X	abn
biochemistry	X		X	abn
urinalysis	X		X	abn
Pregnancy test*	X			
Adverse events				
routine events		X	X	X
serious adverse events		X	X	X
Investigator's evaluation				
clinical		X	X	X

abn= abnormal at previous visit or clinically significant adverse event

\*to be done by local site for women of child bearing potential

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

At the baseline visit (V1, Day 1), all subjects had to have a clinical picture characterized by the following criteria:

- Clinical signs and symptoms of chronic bronchitis defined by the presence of cough, dyspnea, lung sounds (rales and rhonchi), 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 exacerbation, including increased dyspnea and increased sputum volume and 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 pneumonia on chest x-ray.

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Those patients who met the above definition and who gave informed consent were eligible for randomization, if they fulfilled the inclusion and exclusion criteria. Baseline visit assessments also included collection of demographic information, concurrent disease, medical history and 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, 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 not randomized and no further evaluation was performed. Hematology, serum chemistry, and urinalysis determinations were performed and serum was obtained at baseline for the determination of antibodies to *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*.

Susceptibility to the study drugs, trovafloxacin and ciprofloxacin, was determined from bacterial isolates grown from adequate sputum specimens. Randomization was permitted prior to the availability of the baseline culture and sensitivity report. However, if no pathogen was detected on baseline culture, the 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 4) and 3 (V3: Day 8; EOT), a determination of clinical efficacy was performed. These determinations included clinical assessments of signs and symptoms of AECB and adequate sputum samples for culture and sensitivity to assess bacteriological response to study therapy. Safety was assessed through the recording of concomitant medication, vital signs, study drug dosing, and adverse events. At Visit 3, hematology, chemistry, and urinalysis tests were performed.

At Visit 4 (V4: Day 28; EOS), efficacy and safety observations were again performed as in V2 and V3 with the exception of the laboratory analyses which were only performed if a clinically significant abnormality was present at V3 (Day 8) or if the subject was experiencing a clinically significant adverse event. Final serology was performed at this visit and the investigator provided a final evaluation of clinical response.

**Compliance:**

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

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**Concomitant Illnesses and 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.

The concomitant use of systemic corticosteroids was allowed in the form of 10 mg of prednisone or less daily. 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.

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**Discontinuation of Study Therapy:**

Discontinuations were allowed at the discretion of the investigator only if the patient showed no signs of clinical improvement or worsening before the EOT (V3).

Additionally, patients could discontinue therapy if they developed an adverse event or a clinically significant laboratory abnormality.

The reason for discontinuation was recorded on the CRF and the patient followed through the EOS, if possible. The investigator made a final evaluation at the time of discontinuation.

**Protocol Amendments:**

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This protocol was amended once on October 13, 1994, as detailed below:

- Study drug administration for ciprofloxacin was changed from one 500 mg capsule twice daily to two 250 mg capsules twice daily. This was done in order to increase the number of placebo tablets to 2, in order to accommodate the double-dummy study design.
- Monitoring procedures for subjects who took theophylline during the study were specified.

**Precautions:**

Because ciprofloxacin can affect theophylline levels, all subjects on concomitant theophylline had serum levels monitored periodically at a local laboratory.

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**Study Population:**

Approximately 250 subjects with acute exacerbation of chronic bronchitis were expected to be randomized to one of the treatment groups. Each study site attempted to enrol at least 10 patients.

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**Inclusion and Exclusion Criteria:**

***Medical Officer's Comment:** Overall, the MO agreed with the inclusion and exclusion criteria which were the same as those in study 154-109. Therefore, all the MO's comments are unchanged.*

**Randomization and Blinding:**

Study numbers were sequentially assigned to the patients by the investigator as they were determined to be eligible for treatment. The study number was entered onto the patient's CRF and the patient received

study medication with the corresponding number. Study medication was blinded by a double-dummy technique.

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**Dosage Form and Administration:**

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

	<u>AM Administration</u>	<u>PM Administration</u>
Trovafloracin (100 mg/d)	2-placebo for Ciprofloracin 1-Trovafloracin x 100 mg	2-placebo for Ciprofloracin
Ciprofloracin (1,000 mg/d)	2-Ciprofloracin 250 mg 1-placebo for Trovafloracin	2-Ciprofloracin 250 mg

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The blister cards contained sufficient supplies for a 7 day course of treatment, and were given to the subjects at V1. Subjects began study drug medication with the morning dose (even if it was not the morning) and completed a full day of medication on Day 1. The subjects were informed that compliance with taking all tablets as instructed was imperative.

Note: The concomitant use of systemic corticosteroids was allowed in patients receiving chronic, low dose oral steroids (10 mg prednisone daily or less).

To ensure adequate records of disposition of unused supplies at the study site and to facilitate the final drug accountability process a Drug Inventory Record was maintained by the investigator.

**Compliance:**

Patients were informed that compliance with taking all tablets as instructed was imperative. Outpatients were asked to bring all unused medication and empty containers to the first follow-up visit. All doses taken were charted in the case report form.

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**Microbiologic Methods:**

Bacteriologic response was assessed at V3 (EOT) and V4 (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 11 of the study report)

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Criteria	Trovafoxacin*		Ciprofloxacin+	
	Zone size(mm) 5µg disc	MIC µg/ml	Zone Size(mm) 5 µg disc	MIC µg/ml
Susceptible	≥15	≤2	≥21	≤1
Intermediate	11-14	4	16-20	—
Resistant	≤10	≥8	≤15	≥4

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#### Clinical Response:

Clinical response was determined by the sponsor and evaluated at the EOT: V3 (Day 8), and at the EOS: V4 (Day 28), or at the time of discontinuation from the study. Clinical response was primarily based on the global assessment of the clinical presentation of the subject at the evaluation time point.

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

*Medical Officer's Comment: For the MO's comment on both clinical and bacteriologic response, see the MOR of study 154-101. The MO points out that in this study as in study 154-109, the determination of clinical response was made by the sponsor and not by the investigator (154-101). The sponsor's TOC visit was the EOT but as noted previously, assessments could be made at either visit. Therefore, the sponsor's population was not static but contained patients with an assessment at either visit and not necessarily both.*

#### Safety Assessments:

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#### 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 V1 and at V2, V3 (EOT), and V4 (EOS).

#### Clinical Laboratory Tests:

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

#### 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:**

Primary efficacy endpoints were:

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- Sponsor-defined subject clinical response at the EOT and;
- Pathogen eradication rates at the EOT.

Secondary efficacy endpoints were:

- Pathogen eradication rates at the EOS;
- Investigator-defined subject clinical response at the EOT, and sponsor-defined and investigator-defined subject clinical response at the EOS.

**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. This study is the same as study 154-109 and the MO's management of the data was unchanged.*

**Definitions of Response:**

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

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**Interim Analyses:**

No interim analyses were performed.

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**Demographics:**

As per the sponsor, 256 patients were randomized and treated (131 subjects to receive trovafloxacin (51.2%), and 125 to receive ciprofloxacin (48.8%)).

Of the treated patients, 235 completed treatment (121/131 (92.3%) trovafloxacin-treated patients and 114/125 (91.2%) ciprofloxacin-treated patients). 21 patients were withdrawn from treatment, (10 trovafloxacin, and 11 ciprofloxacin), but 10 of these completed the study. In addition to these 11 (7 trovafloxacin and 4 ciprofloxacin patients) withdrawn during the treatment, an additional 1 trovafloxacin and 1 ciprofloxacin patient were withdrawn during follow-up, thus 13 patients were withdrawn from the study (8 trovafloxacin and 5 ciprofloxacin).

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

**Table 141.1**  
**Subject Disposition, All Enrolled Patients (As per the Sponsor)**

		Trovafloxacin 100 mg	Ciprofloxacin 500 mg bid
Subjects with Signed Consent	261		
Withdrawn Prior to Randomization	5		
Randomized		131	125
Randomized, But Not Treated		0	0
All Treated Subjects		131 (100%)	125 (100%)
Withdrawn During Treatment		10 ( 8%)	11 ( 9%)
Completed Treatment		121 (92%)	114 (91%)
Withdrawn During Follow-up		1 ( <1%)	1 (<1%)
Completed Study		123 (94%)	120 (96%)
Completed Treatment and Study		120 (92%)	113 (90%)
Withdrawn During Treatment and Study		7 ( 5%)	4 (3%)

*Medical Officer’s Comment:* A comparable number of patients was withdrawn from both arms.

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 141.2**  
**Number of Subjects Enrolled By Center: All Randomized Patients (As per the Sponsor)**

Center	Total Randomized N = 256 (100%)		Trovafloxacin		Ciprofloxacin	
			Randomized and Treated N = 131	100%	Randomized and Treated N = 125	100 %
5015	26	10.1	13	9.9	13	10.4
5017	7	2.7	3	2.3	4	3.2
5034	19	7.4	9	6.9	10	8.0
5078	47	18.3	24	18.3	23	18.4
5096	3	1.1	2	1.5	1	0.8
5144	7	2.7	3	2.3	4	3.2
5145	11	4.2	5	3.8	6	4.8
5149	5	1.9	3	2.3	2	1.6
5150	5	1.9	2	1.5	3	2.4
5151	3	1.1	2	1.5	1	0.8
5152	4	1.5	2	1.5	2	1.6
5153	13	5.0	7	5.3	6	4.8
5154	4	1.5	2	1.5	2	1.6
5156	54	21.0	28	21.3	26	20.8
5157	1	0.3	1	0.7	0	-
5159	7	2.7	4	3.0	3	2.4
5160	27	10.5	13	9.9	14	11.2
5161	3	1.1	2	1.5	1	0.8
5210	10	3.9	6	4.5	4	3.2

*Medical Officer’s Comment:* There were 19 centers, all of which enrolled patients. There was 1 center (5156) with > 20% of the patients. Additionally center 5078 had approximately 18%. Therefore these 2 centers enrolled 39.3% of the patients.

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

**Table 141.3**  
**Study Evaluation Groups/All Randomized Patients as per the Sponsor (Modified by MO)**

	Trovafloxacin	Ciprofloxacin
	100 mg	500 mg bid
All Randomized Subjects	131 (100%)	125 (100%)
All Treated Subjects	131 (100%)	125 (100%)
Subjects with Inappropriate Baseline Diagnosis	6 (5%)	4 (3%)
Clinically Intent-to-Treat Subjects	125 (95%)	121 (97%)
Clinically Evaluable Subjects	116 (89%)	115 (92%)
Clinically evaluable with baseline pathogen	63 (48%)	71 (57%)
Clinically Not Evaluable Subjects	9 (7%)	6 (5%)
Insufficient Therapy	7 (5%)	5 (4%)
No post-baseline clinical assessment	5 (4%)	5 (4%)
Prior Antibiotic therapy	1 (<1%)	1 (<1%)
Concomitant Antibiotic therapy	3 (2%)	0
No post-baseline clinical assessment in evaluable analysis window	5 (4%)	5 (4%)
Clinically evaluable at EOS	110 (84%)	102 (82%)
Clinically evaluable at EOS with baseline pathogen	59 (45%)	65 (52%)
Bacteriologically Evaluable Subjects	60 (46%)	69 (55%)
Bacteriologically Not Evaluable Subjects	56 (43%)	46 (37%)
No Baseline Pathogen	52 (40%)	44 (35%)
Baseline culture Outside Window	1 (<1%)	0
No post-baseline cultures	3 (2%)	2 (2%)
Bacteriologically Evaluable at EOS	55 (42%)	61 (49%)
Analyzed for Safety		
Adverse Events	131 (100%)	125 (100%)
Laboratory Data	124 (95%)	118 (94%)

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

**Medical Officer's Comment:** 21 of the randomized and treated subjects were not clinically evaluable, (11/131 11.9%) trovafloxacin-treated subjects and 10/125 (8%) ciprofloxacin-treated subjects).

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 10/131 (8%) trovafloxacin-treated patients who discontinued therapy. 3 of these patients continued the study and were clinically evaluable. The remaining 7 did not complete the study and were not evaluable.

On the ciprofloxacin arm, 11/125 (9%) patients discontinued treatment. 7 of these patients continued the study and 6 of these patients were clinically evaluable. The remaining 4 did not complete the study and were not evaluable.

All patients who discontinued treatment were reviewed (see below):

Trovafloxacin (N = 10):

- #50340411: 47 YO was lost to follow-up after 1 day of therapy. The patient discontinued both the study and treatment. This patient had Haemophilus influenzae in the initial sputum culture and was not clinically or bacteriologically evaluable at either timepoint. Reviewer agreed because the patient did not receive an adequate course of therapy. \*

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- #50340415: 85 YO withdrawn from treatment on day 5 because of insufficient response. This patient completed the study and was clinically and bacteriologically evaluable. *Haemophilus influenzae* was isolated in the initial sputum as well as in the EOT and EOS specimens. The patient was classified as a failure with persistence and received amoxicillin therapy. Reviewer agreed.
- #50780224: 40 YO was lost to follow-up after 1 day of therapy. The patient discontinued both the study and treatment. The patient was neither clinically nor bacteriologically evaluable. Reviewer agreed. \*
- #50780229: 44 YO was lost to follow-up after 1 day of therapy. The patient discontinued both the study and treatment. The patient was neither clinically nor bacteriologically evaluable. Reviewer agreed. \*
- #50780232: 40 YO was lost to follow-up after 1 day of therapy. The patient discontinued both the study and treatment. The patient was neither clinically nor bacteriologically evaluable. Reviewer agreed. \*
- #50780250: 40 YO was lost to follow-up after 1 day of therapy. The patient discontinued both the study and treatment. The patient was neither clinically nor bacteriologically evaluable. Reviewer agreed. \*
- #51530035: 63 YO withdrawn from treatment on day 2 for multiple adverse events including theophylline toxicity, nausea, hypochloremic acidosis, and respiratory failure. The patient did not complete the study and was hospitalized and treated with a number of intravenous antimicrobials active against the initial isolate, *Moraxella catarrhalis*. This patient was neither clinically nor bacteriologically evaluable. Reviewer agreed because the patient did not receive the minimum number of doses to be considered an evaluable failure. \*
- #51530204: 67 YO withdrawn from treatment on day 3 because of an adverse event. The patient completed the study and was clinically and bacteriologically evaluable. *Escherichia coli* and *Klebsiella pneumoniae* were isolated from the initial specimen and were presumed eradicated at the EOT and EOS. The patient was classified as a clinical cure. Reviewer disagreed because although the patient did not receive an alternative antimicrobial, she did not receive the minimum duration of therapy necessary to be evaluable as a cure.
- #51560214: 70 YO withdrawn on day 4 because she withdrew consent despite an initial improvement. The patient did not complete the study and was not bacteriologically evaluable but was clinically evaluable as per the sponsor as an improvement. The patient had *Staphylococcus aureus* and *Streptococcus pneumoniae* at baseline and at day 4 and received Cefprozil®. This patient was excluded from the Reviewer's analysis because she had no EOS visit, although she was included in the sponsor's analysis as an improvement.
- #52100181: 50 YO withdrawn from treatment after 2 days of therapy because of chest tightness and blurry vision. The patient continued the study but was neither clinically nor bacteriologically evaluable. Reviewer agreed because the patient did not receive the minimum number of doses to be considered evaluable. \*

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Ciprofloxacin (N=11):

- #50150143: 64 YO withdrawn from treatment on day 6 because of adverse events including shakiness, lightheadedness, and anxiety. The patient completed the study and was clinically and bacteriologically evaluable as an improvement with eradication of the baseline pathogen, *Xanthomonas maltophilia*. Reviewer agreed.

- #50170072: 66 YO withdrawn from treatment on day 1 because of adverse events including nausea, vomiting, and hives. The patient completed the study but was neither clinically nor bacteriologically evaluable. Reviewer agreed. \*
- #50780231: 40 YO was lost to follow-up after 1 day of therapy. The patient discontinued both the study and treatment. The patient was neither clinically nor bacteriologically evaluable. Reviewer agreed. \*
- #50780286: 47 YO withdrawn on day 5 because of an increase in LFTs. The patient completed the study and was clinically but not bacteriologically evaluable. No baseline pathogen was isolated. Reviewer agreed.
- #51440068: 74 YO withdrawn from treatment on day 1 because of an adverse event (bitter taste in mouth). The patient did not complete the study and was neither clinically nor bacteriologically evaluable. Reviewer agreed. \*
- #51450094: 62 YO withdrawn from treatment on day 4 because of an adverse event, (diarrhea). The patient completed the study and was clinically and bacteriologically evaluable. This patient was categorized as an improvement at the EOT and a relapse at the EOS. Initial sputum isolate was *Klebsiella pneumoniae*, eradicated at the EOT but recultured at the EOS. The patient was treated with Bactrim® from study days 10- 24. Reviewer agreed.
- #51560076: 84 YO withdrawn from treatment on day 7 because of an adverse event (diverticulitis). The patient completed the study and was clinically but not bacteriologically evaluable. Reviewer agreed.
- #51560159: 70 YO withdrawn from treatment on day 1 because of an adverse event, (nausea and vomiting). The patient did not complete the study and was neither clinically or bacteriologically evaluable. Reviewer agreed. \*
- #51560169: 50 YO withdrawn from treatment and the study on day 1 because he withdrew consent. The patient did not complete the study and was neither clinically or bacteriologically evaluable. Reviewer agreed. \*
- #51560216: 83 YO withdrawn on day 3 because of adverse events including dizziness, insomnia and shaking. The patient completed the study and was carried forward as an evaluable cure because she did not receive any alternative antimicrobial therapy. This patient had *Staphylococcus aureus* isolated at baseline which was presumed eradicated. Reviewer disagreed and excluded this patient from the FDA evaluable population because the patient did not receive the minimum duration of therapy necessary to be classified as a cure.
- #51610090: 48 YO withdrawn from treatment on day 7 because of insufficient response. The patient completed the study and was clinically and bacteriologically evaluable. The patient was classified as an evaluable failure with presumed persistence of the baseline pathogen, *Chlamydia pneumoniae*. Bactrim® r/x was prescribed from day 7 – 21. Reviewer agreed.

Although the 10 trovafloxacin and 11 ciprofloxacin patients listed above, represent discontinuations from therapy or the study, only those patients with a \* are those patients who were excluded from the sponsor's clinical efficacy analysis (trovafloxacin (7) and ciprofloxacin (5)). An additional 8 trovafloxacin-treated patients and 5 ciprofloxacin-treated patients were clinically unevaluable as per the sponsor. The most common reason for exclusion was inappropriate baseline diagnosis, (6 trovafloxacin, and 4 ciprofloxacin). This determination was made based on the patients' response to a questionnaire

regarding the existence of symptoms of AECEB as outlined in the inclusion criteria. If the patient answered no to any question, the sponsor automatically excluded them. This was done retrospectively and in most cases the patients received 7 days of therapy and would have been classified as cures.

All clinically unevaluable patients (as per the sponsor), not listed above, are reviewed below:

*Trovafloxacin (N = 8)*

- #50150118: Inappropriate baseline diagnosis: *Haemophilus influenzae* isolated at baseline. Reviewer agreed.
- #50150119: Inappropriate baseline diagnosis: *Haemophilus influenzae* isolated at baseline. Reviewer agreed.
- #50170071: Inappropriate baseline diagnosis: *Haemophilus influenzae* and *Streptococcus pneumoniae* isolated at baseline and eradicated at EOT and EOS. Reviewer agreed.
- #50340414: Prior antibiotic therapy: Bactrim® up until day -1. *Streptococcus pneumoniae* isolated at baseline and at the EOS. Would have been a clinical cure with persistence at the EOS. Reviewer agreed.
- #51490101: Inappropriate baseline diagnosis: *Streptococcus pneumoniae* isolated at baseline. Reviewer agreed.
- #51560172: Inappropriate baseline diagnosis: *Haemophilus influenzae* at baseline. Classified as a clinical cure with presumed eradication at the EOS. Reviewer agreed.
- #51600173: Inappropriate baseline diagnosis: sputum culture performed 72 hours prior to baseline assessment. Reviewer agreed.
- #51600207: Concomitant antimicrobial therapy: ciprofloxacin days 4 – 14 for a sinus headache. All sputum specimens were inadequate.

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*Ciprofloxacin (N =5):*

- #50150012: Inappropriate baseline diagnosis: *Moraxella catarrhalis* isolated at baseline. Reviewer agreed.
- #50170188: Prior antimicrobial therapy: Doxycycline from day - 11 to start. Reviewer agreed.
- #51440066: Inappropriate baseline diagnosis: *Haemophilus influenzae* isolated at baseline but no Gram stain. Reviewer agreed.
- #51560180: Inappropriate baseline diagnosis: *Haemophilus influenzae* at baseline which was eradicated but patient developed a septic arthritis on day 4 and received intravenous cefazolin. Reviewer agreed.
- #51590024: Inappropriate baseline diagnosis: Inadequate sputum production at all timepoints. Reviewer agreed.

Based on the above listings, and in conjunction with the study report, the MO found that the sponsor's clinically evaluable trovafloxacin population consisted of 116 patients and the ciprofloxacin of 115. The bacteriologically evaluable population consisted of 60 trovafloxacin and 69 ciprofloxacin patients. The

*most common reason for exclusion from the bacteriologically evaluable population was “no baseline pathogen” in 52 trovafloxacin and 44 ciprofloxacin patients. Other reasons included “baseline culture outside of window” and “no post-baseline cultures.”*

*The sponsor provided the Reviewer with a listing of patients that were clinically evaluable as per the sponsor but who had no EOS evaluation. This listing included the following patients:*

*Trovafloxacin (N = 6):*

- #50340405: *Cure at EOT.*
- #50780235: *Cure at EOT.*
- #50780253: *Cure at EOT.*
- #51440065: *Improvement at EOT.*
- #51560214: *Improvement at EOT.*
- #51560111: *Improvement at EOT.*

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*Ciprofloxacin (N =13)*

- #50340404: *Cure at EOT.*
- #50340412: *Improvement at EOT*
- #50780252: *Cure at EOT.*
- #50780256: *Cure at EOT.*
- #50780286: *Improvement at EOT.*
- #50780310: *Cure at EOT.*
- #50780311: *Cure at EOT.*
- #51520002: *Cure at EOT*
- #51520003: *Improvement at EOT.*
- #51540039: *Improvement at EOT.*
- # 51560076: *Improvement at EOT.*
- #51600124: *Improvement at EOT.*
- #51600176: *Improvement at EOT.*

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*The MO excluded all of the above patients who did not have an EOS visit because the MO TOC was applied to the EOS. The above listing excluded failures, which were always carried forward.*

**Baseline Characteristics:**

The 2 groups were comparable in terms of age, race, weight, sex, and smoking history. The distribution of smokers was similar between the trovafloxacin and ciprofloxacin groups (33% and 43% ex-smokers, 16% and 15% non-smokers, and 51% and 42% smokers, respectively.)

76 of the trovafloxacin patients were male with a mean age of 58.2 and 62% were white.  
55 of the trovafloxacin patients were women with a mean age of 57.5 and 76% were white.

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77 of the ciprofloxacin patients were male with a mean age of 58.5 and 60% were white.  
48 of the ciprofloxacin patients were women with a mean age of 58.2 and 75% were white.

The median duration since the onset of the underlying primary diagnosis of CB was not provided.

The median duration since the onset of the present episode was 6 days for both treatment groups

The respective means were 9.8 days for the trovafloxacin patients and 8.2 days for the ciprofloxacin patients.

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**Duration of Treatment:**

The median duration of treatment was 7 days for subjects in the both treatment groups.

**Concomitant Medications:**

The majority of patients were on concomitant medications during therapy. The most commonly used medications were bronchodilators (98 and 106 patients per arm respectively) (b)(4)

Systemic steroids were taken by 42 (21%), of the trovafloxacin-treated patients and 49 (28%), of the ciprofloxacin-treated patients. However, based on line listings provided by the sponsor, the MO found that 15/116 (13%), of the clinically evaluable (as per the sponsor), trovafloxacin patients and 18 (15.6%), of the clinically evaluable ciprofloxacin patients were on systemic steroids.

**Medical Officer's Comment:** *The MO did not exclude patients taking steroids in studies 154-101 and 154-109, but instead, provided separate analyses of clinical and bacteriological response with and without these patients in the MO's efficacy analyses. The MO elected to do the same for this study. The rationale was that there was no major difference in efficacy with or without these patients. The MO found that 34 of the sponsor's clinically evaluable trovafloxacin patients and 42 ciprofloxacin patients received systemic steroids.*

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**Concomitant Antimicrobials:**

Of the treated patients, 22 trovafloxacin-treated patients and 26 ciprofloxacin-treated patients received concomitant antimicrobials for the following reasons:

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(Copied from page 29 of the study report)

During the study, 22 trovafloxacin and 26 ciprofloxacin subjects received antibiotics other than study drug for the following reasons: inadequate response (14 subjects in each group), side effects (2 subjects in each group), as prior or concomitant medications (trovafloxacin, 2), and other reasons (trovafloxacin 4; ciprofloxacin, 10). All subjects with an appropriate baseline diagnosis who received concomitant medication for inadequate response were evaluable; all other subjects who received concomitant antibiotics were considered to be clinically not evaluable

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

- inadequate response: 14 trovafloxacin and 14 ciprofloxacin (all carried forward as evaluable failures)
- other reasons: 8 trovafloxacin and 12 ciprofloxacin patients.

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The other category was compromised of the following patients:

Trovafloxacin (N = 8):

- #50150080: Other/relapse: ampicillin day 29, classified as a failure. Reviewer agreed.
- #51530035: Other/early discontinuation because of adverse events day 2 (see above). Reviewer agreed.
- #51560168: Other/exacerbation of COPD on days 22 and 26. Patient was treated with cefotaxime and cephalexin. Carried forward as a failure. Reviewer agreed.
- #51560214: Other/withdrew consent: Cefprozil® day 4. Patient would have been excluded from MO analysis because of a missing EOS visit.
- #51600111: Other/sinusitis: amoxicillin day 21. Classified as a cure per the sponsor but patient would have been excluded from MO analysis because of a missing EOS visit.
- #51600175: Other/sinusitis: ciprofloxacin day 25. Classified as a cure per the sponsor. Reviewer disagreed and patient was included in the MO's analysis as an evaluable failure at the EOS.
- #51600207: Other/sinusitis: ciprofloxacin day 3. Reviewer agreed to exclusion because of apparent misdiagnosis and inadequate sputum samples (see above).
- #52100181: Other/adverse events: day 12. Reviewer agreed.

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Ciprofloxacin (N= 12):

- #50170072: Other/adverse event: azithromycin day 4, sponsor unevaluable because of inappropriate baseline diagnosis. Reviewer agreed.
- #50340412: Other/surgical prophylaxis: cephalexin and gentamicin days 11-16 and 19 - 25. Classified as an improvement at EOT. The patient was excluded from the MO evaluable population because there was no EOS visit.
- #50780286: Other/elevated LFTs day 6. Classified as an improvement at the EOT. The patient was excluded from the MO's evaluable population because of a missing EOS visit.
- #51450094: Other/adverse events, Bactrim® days 10 - 24. Classified as a failure. Reviewer agreed.
- #51520002: Other/sinusitis: Ceclor® day 8, classified as a cure. The patient was excluded from the MO's evaluable population because of a missing EOS visit.
- #51520003: Other/surgical prophylaxis: vancomycin and cefazolin days 7 - 14, classified as a cure. The patient was excluded from the MO's evaluable population because of a missing EOS visit.
- #51560076: Other/diverticulitis: ciprofloxacin days 5 - 16, classified as a cure. Reviewer agreed but the patient was excluded from the MO population because there was no EOS visit.

- #51560165: Other/pharyngitis: Ceclor®, erythromycin day 14, classified as a failure. Reviewer agreed.
- #51560180: Other/septic arthritis (see above): sponsor and Reviewer unevaluable.
- #51560210: Other/rhinitis: Cefuroxime® day 25. Classified as a cure by the sponsor. Reviewer disagreed and reclassified as a failure at the EOS.
- #51600124: Other/lung abscess: amoxicillin and Cefixime® days 12 –32. Sponsor classified as improved. The patient was excluded from the MO's evaluable population because of a missing EOS visit.
- #51600176: Other/patient took doxycycline on her own from days 13 –36, sponsor classified as improved. The patient was excluded from the MO's evaluable population because of a missing EOS visit.

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**Protocol Deviations:**

(Copied from page 29 of the study report)

Deviations from protocol were noted for 23 subjects, one of whom had more than one deviation, during the study. These deviations were categorized as follows:

- Inclusion criteria deviations included subjects <40 years of age (3 subjects), subjects with an inappropriate diagnosis due to insufficient symptoms or inappropriate sputum histology (10 subjects), and a subject for whom a Gram stain was not performed (1 subject);
- Other (study procedure) deviations included randomized out of order (8 subjects) and baseline physiological examination performed outside of the 48-hour window prior to treatment initiation (1 subject);
- Deviations that involved taking medications in amounts greater than specified by protocol (prednisone >10 mg/day) (1 subject).

Subjects with an inappropriate baseline diagnosis were not included in the clinical and bacteriological intent-to-treat and evaluable analyses. All other deviations did not effect evaluability. Subjects with protocol deviations are listed in the following table.

<b>Table A. Summary of Protocol Deviations</b>	
<b>(All Randomized Subjects)</b>	
Inclusion	5015-0012; 5015-0118; 5015-0119; 5017-0071; 5078-0222; 5144-0066; 5149-0101; 5152-0004; 5156-0172; 5156-0180; 5159-0024; 5160-0124; 5160-0173
Other (randomized out of order or baseline visit outside window)	5017-0188; 5078-0326; 5160-0109; 5160-0111; 5160-0121; 5160-0176; 5160-0191; 5160-0207; 5160-0227
Taking Medications Not Specified by Protocol or Taking an Allowed Medication in Amounts Greater Than Specified by Protocol	5154-0040

**Medical Officer's Comment:** *The MO reviewed all deviations and agreed with the sponsor's judgement. Notable was the exclusion of the patient on higher systemic steroid doses than those allowed for in the protocol as compared to study 154-109 where such patients were included.*

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

- *Patients receiving steroid therapy (trovafloxacin: 14 sponsor-evaluable (12 FDA-evaluable), and ciprofloxacin: 18 sponsor-evaluable (15 FDA-evaluable), should be evaluated in a separate analysis in order to ascertain if their inclusion in the evaluable population affected outcome.*
- *Patients who received concomitant antimicrobials (2 patients, 1 each arm), should be carried forward as failures.*
- *Patients who did not have an EOS visit (19), should be excluded from the MO evaluable population.*
- *Patients who did not receive the previously specified minimum duration of therapy to be evaluable as cures should be excluded. (2 from MO review)*

*Overall, there was concordance between the MO and the sponsor in terms of outcome assessments and evaluability.*

**Sponsor's Efficacy Analysis:**

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ON ORIGINAL**

**Sponsor-Defined Clinical Response:**

**Table 141.4**  
**Sponsor-Defined Clinical Response/Clinically Evaluable Population at EOT and EOS: (Modified by MO from Sponsor Table 5.1.1)**

Timepoint	Trovafloxacin N= 131	Ciprofloxacin N = 125
Number of patients evaluated at EOT	116 (100%)	115 (100%)
Cure	47 (41%)	47 (41%)
Improvement	64 (55%)	59 (51%)
Failure	5 (4%)	9 (8%)
<b>Success (Cure + Improvement)</b>	<b>111 (96%)</b>	<b>106 (92%)</b>
Number of patients evaluated at EOS	110(100%)	102 (100%)
Cure	87 (79%)	62 (61%)
Improvement	8 (7%)	19 (19%)
Failure	5 (5%)	9 (9%)
Relapse	10 (9%)	12 (12%)
<b>Success (Cure + Improvement)</b>	<b>95 (86%)</b>	<b>81 (79%)</b>

The sponsor provided the following 95% CIs, without continuity correction factor:

EOT: Trovafloxacin versus Ciprofloxacin: - 2.6%, 9.7% ( $\Delta = 10$ )

EOS: Trovafloxacin versus Ciprofloxacin: - 3.2%, 17.1% ( $\Delta = 15$ )

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The sponsor stated that (copied from page 32 of the study report):

Comparisons (95% confidence intervals) of the difference between the two treatment groups in sponsor-defined clinical success rates (cure + improvement) at the end of treatment and at the

end of study supported equivalence of the two treatments. At the end of study, the distribution of clinical cure, improvement, failure, and relapse (trovafloxacin, 79%, 7%, 5%, and 9%, respectively; ciprofloxacin, 61%, 19%, 9%, and 12%, respectively) showed a statistically significant ( $p=0.005$ ) advantage for trovafloxacin.  
(Mandel-Haentzel-Cochran)

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Medical Officer's Comment:

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 versus Ciprofloxacin: - 3.5%, 10.5% ( $\Delta = 10$ ):

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EOS: Trovafloxacin versus Ciprofloxacin: -4.1%, 18.0% ( $\Delta = 15$ )

Based on the FDA analysis, there was therapeutic equivalence between both arms at the EOT and the EOS with trovafloxacin numerically superior to ciprofloxacin at both timepoints.

As per the sponsor, for the clinical ITT population, the success rates were 114/125 (91%) for the trovafloxacin-treated patients and 107/121 (88%) for the ciprofloxacin-treated patients at the EOT (CI: - 4.8%, 10.3%). The respective values at the EOS were 104/125 (83%) and 95/121 (79%): 95% CI for this analysis: - 5.1, 14.5%. The sponsor stated that this analysis also showed equivalence between the 2 treatment arms, with a statistically significant advantage for trovafloxacin ( $p = 0.035$ ) at the EOS.

The sponsor stated that the clinical failure rate was 9% and 12% per arm respectively, at the EOT. At the EOS, 8% and 10% of patients were relapses. Thus as per the MO calculations, the failure rate was 21/125 (17%) on the trovafloxacin arm and 26/121 (22%) on the ciprofloxacin arm, when failures and relapses were added together, (see introduction re definitions).

The clinically evaluable subjects with an outcome of failure at the EOT (5 trovafloxacin and 9 ciprofloxacin) or relapse at the EOS (10 trovafloxacin and 12 ciprofloxacin) and a baseline pathogen (EOT 4 per arm respectively, and EOS 8 and 9 respectively), are listed below:  
(Outcomes are for EOS only and include patients classified as relapses by the sponsor)

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Trovafloxacin (N = 12):

- #50150080: Failure: *Haemophilus influenzae* at baseline, eradicated. Also had *Streptococcus pneumoniae* which was persistent.
- #50170070: Failure: *Chlamydia pneumoniae* titer positive. Classified as presumed persistent.
- #50340415: Failure: *Haemophilus influenzae* at baseline which was presumed persistent.
- #51560114: Failure: *Staphylococcus aureus* at baseline which was presumed persistent.
- #50150009: Relapse: *Staphylococcus aureus* at baseline which was eradicated.
- #50150011: Relapse: *Moraxella catarrhalis* at baseline which was persistent.
- #50150079: Relapse: *Streptococcus pyogenes* at baseline which was presumed persistent.
- #50150144: Relapse: *Pseudomonas aeruginosa* at baseline which was persistent. Also had *Mycoplasma pneumoniae* which was presumed persistent.

- #51560074: Relapse: *Moraxella catarrhalis* at baseline which was presumed persistent.
- #51560177: Relapse: *Haemophilus influenzae* at baseline which was persistent.
- #51600123: Relapse: *Pseudomonas aeruginosa* at baseline which was presumed persistent.
- #52100182: Relapse: *Haemophilus influenzae* at baseline which was eradicated.

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Ciprofloxacin (N = 13):

- #50150120: Failure: *Haemophilus influenzae* and *Moraxella catarrhalis* at baseline. Both eradicated
- #50170185: Failure: *Haemophilus influenzae* and *Staphylococcus aureus* at baseline which were presumed persistent.
- #51500031: Failure: *Haemophilus parainfluenzae* at baseline which was presumed persistent
- #51610090: Failure: *Mycoplasma pneumoniae* at baseline which was presumed persistent.
- #50150077: Relapse: *Haemophilus influenzae* at baseline which was eradicated. Also had *Streptococcus pneumoniae* which was persistent.
- #50150117: Relapse: *Moraxella catarrhalis* at baseline which was presumed persistent.
- #50150142: Relapse: *Streptococcus pneumoniae* at baseline which was eradicated.
- #50150147: Relapse: *Haemophilus influenzae* at baseline which was persistent.
- #50780251: Relapse: *Haemophilus parainfluenzae* and *Streptococcus pneumoniae* at baseline were eradicated.
- #51450094: Relapse: *Klebsiella pneumoniae* at baseline which was presumed persistent.
- #51560088: Relapse: *Moraxella catarrhalis* at baseline which was presumed persistent.
- #516001091: Relapse: *Pseudomonas aeruginosa* at baseline which was persistent.
- #521000058: Relapse: *Haemophilus influenzae* at baseline which was persistent.

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**Medical Officer's Comment:** The MO elected to present only those failures and relapses with a baseline pathogen. Overall, the MO did not disagree with the sponsor's determination of outcome. The MO, however, reclassified those patients classified as relapses, into failures.

The most common pathogen associated with failure on the trovafloxacin arm was *Haemophilus influenzae* followed by *Moraxella catarrhalis*, and *Pseudomonas aeruginosa*. On the ciprofloxacin arm, the most common pathogen associated with failure was *Haemophilus influenzae*.

None of the bacterial isolates associated with failure were resistant or developed resistance to either study drug (as per the sponsor).

Clinical response rates for both clinically and bacteriologically evaluable patients can be seen below:

**Table 141.5**  
**Sponsor-Defined Clinical Response/Clinically and Bacteriologically Evaluable Population at EOT and EOS: (Modified by MO from Sponsor Table 5.1.3)**

Timepoint	Trovafloxacin N= 60	Ciprofloxacin N = 69
Number of patients evaluated at EOT	60 (100%)	69 (100%)
Cure	29 (48%)	35 (51%)
Improvement	27 (45%)	30 (43%)
Failure	4 (7%)	4 (6%)
<b>Success (Cure + Improvement)</b>	<b>56 (93%)</b>	<b>65 (94%)</b>
Number of patients evaluated at EOS	57(100%)	64 (100%)
Cure	44 (77%)	41 (64%)
Improvement	1 (2%)	10 (16%)
Failure	4 (7%)	4 (6%)
Relapse	8 (14%)	9 (14%)
<b>Success (Cure + Improvement)</b>	<b>45 (79%)</b>	<b>51 (72%)</b>

The sponsor provided the following 95% CIs, without continuity correction factor:

EOT: Trovafloxacin versus Ciprofloxacin: - 9.3%, 7.5% ( $\Delta = 10$ )

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ON ORIGINAL

EOS: Trovafloxacin versus Ciprofloxacin: - 15.2%, 13.7% ( $\Delta = 20$ )

*Medical Officer's Comment: Trovafloxacin appeared numerically superior to ciprofloxacin at the MO TOC, the EOS. However, there was no significant difference between the results of this population (clinically and bacteriologically evaluable), and the clinically evaluable population. The FDA-generated 95% CIs (with continuity correction factor) for the above were:*

EOT: Trovafloxacin versus Ciprofloxacin: - 10.8%, 9.1% ( $\Delta = 10$ )

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EOS: Trovafloxacin versus Ciprofloxacin: - 16.9%, 15.4% ( $\Delta = 20$ )

*Thus, the 2 agents were marginally equivalent at the EOT, but equivalence was demonstrated at the MO TOC, the EOS.*

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**Clinical Response by Baseline Pathogen:**

**Table 141.6**  
**Sponsor-Defined Clinical Response by Baseline Pathogen at the EOT and EOS (Clinically evaluable Population: Modified 5.3 by MO)**

Pathogen		Trovafloracin			Ciprofloxacin		
		N	No. Cured	%	N	No. Cured	%
<i>Haemophilus influenzae</i>	EOT	17	15	88	20	18	90
	EOS	16	12	75	19	14	74
<i>Moraxella catarrhalis</i>	EOT	13	13	100	13	12	92
	EOS	13	11	85	12	9	75
<i>Streptococcus pneumoniae</i>	EOT	5	4	80	9	9	100
	EOS	4	3	75	8	5	63
<i>Haemophilus parahaemolyticus</i>	EOT	3	3	100	6	6	100
	EOS	2	2	100	6	6	100
<i>Haemophilus parainfluenzae</i>	EOT	7	7	100	12	11	92
	EOS	6	6	100	10	8	80
<i>Klebsiella pneumoniae</i>	EOT	4	4	100	5	5	100
	EOS	4	4	100	5	4	80
<i>Pseudomonas aeruginosa</i>	EOT	3	3	100	6	6	100
	EOS	3	1	33	5	4	80
<i>Mycoplasma pneumoniae</i>	EOT	2	2	100	1	0	0
	EOS	2	1	50	1	0	0
<i>Chlamydia pneumoniae</i>	EOT	6	5	83	3	3	100
	EOS	6	5	83	3	3	100
<i>Neisseria meningitidis</i>	EOT	-	-	-	2	2	100
	EOS	-	-	-	1	1	100
<i>Pasteurella multocida</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
<i>Pseudomonas fluorescens</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
<i>Staphylococcus aureus</i>	EOT	13	12	92	10	9	90
	EOS	11	9	82	9	8	89
<i>Streptococcus pyogenes</i>	EOT	1	1	100	1	1	100
	EOS	1	0	0	1	1	100
<i>Xanthomonas maltophilia</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
<b>Total</b>	EOT	<b>74</b>	<b>69</b>	<b>93.2</b>	<b>91</b>	<b>85</b>	<b>93.4</b>
	EOS	<b>68</b>	<b>54</b>	<b>79.4</b>	<b>83</b>	<b>66</b>	<b>79.5</b>

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Copied below from page 40 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) were similar ( $\leq 10$  percentage-point difference) in both treatment groups at the end of treatment and at the end of study.

**Medical Officer's Comment:** *The clinical response by baseline pathogen was proportionately the same for the trovafloxacin-treated patients as compared to the ciprofloxacin-treated patients at both the EOT and EOS. Confidence intervals were not generated for this variable because this table was baseline*

pathogen and not patient driven, thus there were patients with more than 1 baseline pathogen. This decision was made in consultation with Dr. Nancy Silliman, FDA statistician.

For the 3 main pathogens most commonly associated with AECB and for which the sponsor is requesting approval, the MO appended a portion of the above table, below:

**Table 141.7**  
**Sponsor-Defined Clinical Response by Baseline Pathogen at the EOT and EOS (Clinically evaluable Population/Main Pathogens Only: Modified 5.3 by MO)**

Pathogen		Trovafoxacin			Ciprofloxacin		
		N	No. Cured	%	N	No. Cured	%
<i>Haemophilus influenzae</i>	EOT	17	15	88	20	18	90
	EOS	16	12	75	19	14	74
<i>Moraxella catarrhalis</i>	EOT	13	13	100	13	12	92
	EOS	13	11	85	12	9	75
<i>Streptococcus pneumoniae</i>	EOT	5	4	80	9	9	100
	EOS	4	3	75	8	5	63

Again, CIs were not applied but it appeared that trovafoxacin was equivalent to ciprofloxacin in eradicating *Haemophilus influenzae* at the EOS, and numerically slightly superior versus the other 2 main pathogens. The total cure/eradication rates for the 3 main pathogens were:

Trovafoxacin EOT: 32/35 (91.4 %) and EOS: 26/33 (78.7%)  
 Ciprofloxacin EOT: 39/42 (92.8%) and EOS: 28/39 (71.7%)

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Thus the response for both agents for this variable match the clinical response for all evaluable patients.

**Signs and Symptoms:**  
 (Copied from page 42 of the study report)

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The percentage of clinically evaluable subjects with moderate or severe signs and symptoms of acute bacterial exacerbation of chronic bronchitis at baseline was comparable between the two treatment groups and was as follows: dyspnea (trovafoxacin: 65%; ciprofloxacin: 66%), cough (trovafoxacin: 96%; ciprofloxacin: 97%), lung sounds (trovafoxacin: 78%; ciprofloxacin: 77%), and increased sputum volume (trovafoxacin: 96%; ciprofloxacin: 95%).

In both treatment groups, the percentage of subjects with signs and symptoms of infection decreased from baseline to the end of treatment and further decreases were observed at the end of study. In general, among the subjects who continued to display these signs or symptoms, the severity was decreased. Similar trends were observed among clinically intent-to-treat subjects. A summary of the percentage of subjects with clinical signs and symptoms of acute bacterial exacerbation of chronic bronchitis at baseline, end of treatment and end of study is presented in the following table.

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<b>Table B. Summary of Clinical Signs and Symptoms</b>						
	<b>Trovafloxacin 200 mg</b>			<b>Ciprofloxacin 500 mg BID</b>		
	<b>Baseline (N=114)</b>	<b>EOT (N=116)</b>	<b>EOS (N=112)</b>	<b>Baseline (N=114)</b>	<b>EOT (N=115)</b>	<b>EOS (N=110)</b>
<b>Sign/Symptom<sup>a</sup></b>	<b>Percentage of Clinically Evaluable Subjects With Clinical Signs and Symptoms</b>					
Dyspnea	99%	39%	26%	98%	44%	29%
Cough	100%	78%	50%	100%	78%	59%
Lung Sounds	94%	34%	20%	96%	37%	26%
ISV	100%	42%	22%	100%	50%	35%
	<b>Baseline (N=124)</b>	<b>EOT (N=120)</b>	<b>EOS (N=116)</b>	<b>Baseline (N=121)</b>	<b>EOT (N=117)</b>	<b>EOS (N=115)</b>
<b>Sign/Symptom<sup>a</sup></b>	<b>Percentage of Clinically Intent-to-Treat Subjects With Clinical Signs and Symptoms</b>					
Dyspnea	99%	40%	26%	98%	45%	30%
Cough	100%	78%	51%	100%	79%	58%
Lung Sounds	94%	37%	21%	95%	38%	25%
ISV	100%	42%	23%	100%	51%	36%
EOT=End of Treatment; EOS=End of Study; ISV=Increased Sputum Volume						
a Not all subjects were evaluated for all signs/symptoms at all timepoints						
Ref.: Tables 5.8.1 and 5.8.2						

**Medical Officer's Comment:** *The MO agreed with the sponsor's analysis and verified from the CRFs, that there was indeed a decrease in signs and symptoms as described above.*

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**Bacteriologic 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:

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**Table 141.8**  
**Sponsor-Defined Pathogen Eradication Rates at the EOT and EOS (Bacteriologically evaluable Population: Modified 5.4.1 by MO)**

Pathogen		Trovafloracin			Ciprofloxacin		
		N	No. Erad.	%	N	No. Erad.	%
<i>Haemophilus influenzae</i>	EOT	16	15	94	19	18	95
	EOS	15	13	87	16	13	81
<i>Moraxella catarrhalis</i>	EOT	12	12	100	12	12	100
	EOS	12	10	83	12	9	75
<i>Streptococcus pneumoniae</i>	EOT	3	2	67	9	8	89
	EOS	3	2	67	8	7	88
<i>Haemophilus parahaemolyticus</i>	EOT	3	3	100	6	6	100
	EOS	2	2	100	6	6	100
<i>Haemophilus parainfluenzae</i>	EOT	7	7	100	12	11	92
	EOS	6	6	100	10	9	90
<i>Klebsiella pneumoniae</i>	EOT	3	2	67	5	5	100
	EOS	3	3	100	5	4	80
<i>Pseudomonas aeruginosa</i>	EOT	2	1	50	6	5	83
	EOS	2	0	0	5	4	80
<i>Mycoplasma pneumoniae</i>	EOT	2	2	100	1	0	0
	EOS	2	1	50	1	0	0
<i>Chlamydia pneumoniae</i>	EOT	6	5	83	3	3	100
	EOS	6	5	83	3	3	100
<i>Neisseria meningitidis</i>	EOT	-	-	-	2	2	100
	EOS	-	-	-	1	1	100
<i>Pasteurella multocida</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
<i>Pseudomonas fluorescens</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
<i>Staphylococcus aureus</i>	EOT	12	11	92	9	8	89
	EOS	11	10	91	8	7	88
<i>Streptococcus pyogenes</i>	EOT	1	1	100	1	1	100
	EOS	1	0	0	1	1	100
<i>Xanthomonas maltophilia</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	-	-	-
<b>Total</b>	<b>EOT</b>	<b>67</b>	<b>61</b>	<b>91</b>	<b>88</b>	<b>82</b>	<b>93.1</b>
	<b>EOS</b>	<b>63</b>	<b>52</b>	<b>82.5</b>	<b>78</b>	<b>66</b>	<b>84.6</b>

The sponsor's text has been copied from page 43 of the study report below:

Among bacteriologically evaluable subjects with the most frequently isolated baseline pathogens, sponsor-defined pathogen eradication rates were similar ( $\leq 10$  percentage-point difference) in both treatment groups at the end of treatment and at the end of study.

**Medical Officer's Comment:** As can be appreciated from the sponsor's text, an overall eradication rate was not provided in the study report. Based on the MO's analysis, the 2 agents were numerically comparable at the EOT and EOS, with ciprofloxacin being slightly numerically superior. For the 3 main pathogens however, there was a slight numerical difference in favor of trovafloxacin (EOS).

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The pathogen eradication rates for the 3 main pathogens only were:

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Trovafloxacin EOT: 29/31 (93.5%) and EOS: 25/30 (83.3%)  
Ciprofloxacin EOT: 38/40 (95%) and EOS: 29/36 (80.5%)

Based on the above, ciprofloxacin was slightly numerically inferior to trovafloxacin at the EOS with regards to overall bacteriological eradication rate versus the 3 main pathogens associated with AECB. CIs were not applied as discussed previously.

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**Superinfecting Pathogens and Colonizing Organisms:**  
(Copied from page 44 of the study report)

Superinfecting organisms were not isolated from any subject in the trovafloxacin or ciprofloxacin treatment groups. Colonizing organisms were isolated from 4 subjects (3%) in the trovafloxacin group and from 2 subjects (2%) in the ciprofloxacin group.

Medical Officer's Comment: The MO agreed with the sponsor's determination in all cases after review of the PIDs.

**Cross-tabulation of Sponsor-Defined Clinical Response and Pathogen Outcome:**

The sponsor provided only a cross tabulation for the EOT and not the EOS. 6 patients, (3 trovafloxacin and 3 ciprofloxacin), had clinical responses inconsistent with pathogen outcome. The sponsor's table C has been copied from page 46 of the study report, below and modified to reflect the MO's determination of clinical and bacteriological outcome at the EOS:

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Table 141.9

**Cross-Tabulation of Clinical and Bacteriological Response at the EOT (as per the Sponsor) and the EOS (as per the MO)**

Table C. Summary of Discrepancies Between Sponsor-Defined Clinical Response and Pathogen Outcome at the End of Treatment (Bacteriologically Evaluable Subjects)					
Subject Number	Baseline Pathogen	Clinical Response		Pathogen Bacteriological Response	
<b>Trovafloxacin 100 mg</b>					
5045-0080	<i>Haemophilus influenzae</i> <i>Streptococcus pneumoniae</i>	Failure	Failure	Eradicated	Eradicated
5145-0017	<i>Klebsiella pneumoniae</i>	Improvement	Cure	Persistent	Pres.pers.
5160-0123	<i>Pseudomonas aeruginosa</i>	Improvement	Failure	Persistent	Persistent
<b>Ciprofloxacin 500 mg BID</b>					
5015-0077	<i>Streptococcus pneumoniae</i>	Cure	Failure	Persistent	Persistent
5015-0120	<i>Haemophilus influenzae</i> <i>Moraxella catarrhalis</i>	Failure	Failure	Eradicated	Eradicated
5160-0191	<i>Pseudomonas aeruginosa</i>	Improvement	Failure	Persistent	Persistent
Ref.: Table 6.7.1 and Appendix I, Table 8					

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Medical Officer's Comment:

Inconsistency between clinical and bacteriologic outcome persisted in 2 of the original 3 trovafloxacin patients, one a clinical cure with presumed persistence of the baseline pathogen, *Klebsiella pneumoniae*, and the other was a clinical failure with documented eradication of one of the baseline pathogens, *Haemophilus influenzae*, but with persistence of the other, *Streptococcus pneumoniae*.