CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

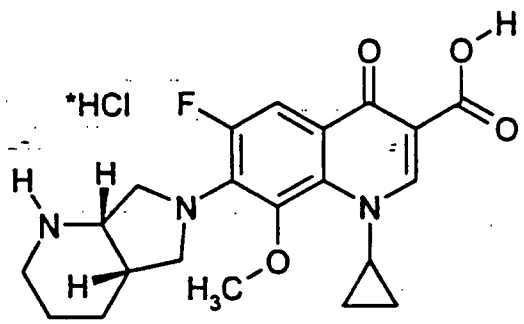
21-085

MEDICAL REVIEW

Medical Officer's Review of NDA 21-085
Indication: Acute Bacterial Exacerbation of Chronic Bronchitis

NDA Submission number:	21-085
Applicant:	Bayer Corporation
Address:	400 Morgan Lane West Haven, CT 06516
Contact person:	Deborah Church, MD Director, Medical Research Anti-Infectives
Date of Submission:	December 9, 1998
CDER stamp date:	December 10, 1998
Date submission received by reviewer:	February 28, 1999
Date Review Begun:	March 10, 1999
Date Review Completed:	November 12, 1999
Established name:	moxifloxacin
Proposed proprietary name	Avelox
Chemical name:	1-cyclopropyl-7-[(S,S)-2,8-diazabicyclo[4.3.0]non-8-yl]-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3-quinoline carboxylic acid

Chemical structure:



Molecular formula:	$C_{21}H_{24}FN_3O_4$ *HCl *H_2O
Molecular weight:	437.9
Pharmacologic category:	fluoroquinolone

Dosage form:	tablets
Route of administration:	oral
Strength	400mg

Proposed indications and usage:

Draft Labeling excerpt from the INDICATIONS AND USAGE section:

Avelox tablets are indicated for the treatment of adults (>18 years of age) with infections caused by susceptible strains of the designated microorganisms in the conditions listed below.

Acute Bacterial Exacerbation of Chronic Bronchitis caused *by Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Staphylococcus aureus*, or *Moraxella catarrhalis*

> **MO COMMENT: The three principle studies evaluating moxifloxacin for the treatment of acute bacterial exacerbations of chronic bronchitis (ABECB) were performed in patients with mild to moderate disease. "Severe" disease for the purposes of this study was defined by the investigator's assessment that parenteral therapy was necessary. However, individual cases were judged as mild, moderate or severe by the criteria of Anthonisen et al[1].**

Proposed Dosage and Administration:

Draft labeling from the DOSAGE AND ADMINSTRATION section:

Acute Bacterial Exacerbation of Chronic Bronchitis 400 mg x 5 days

Related Drugs:

Regulatory Background:

This drug would be the first quinolone to be labeled for ABECB with an indication for only 5 days of treatment. The only other antimicrobial with a 5 day indication for ABECB is cefdinir dosed at 300 mg PO BID. The following quinolones are indicated for oral treatment of ABECB

- Ciprofloxacin (Cipro) 500-750mg BID x 7 to 14 days.
- Ofloxacin (Floxin) 400mg BID x 10 days.

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[1] Anthonisen NR, Manfreda J, Warren CPW et al. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med 1987;106:196-204.

- Lomefloxacin (Maxaquin) 400mg qd x10 days.
- Levofloxacin (Levaquin) 500mg qd x 7 days.
- Sparfloxacin (Zagam) 400mg loading dose followed by 200mg qd for total treatment duration of 10 days.
- Grepafloxacin (Raxar) was indicated at 400 or 600mg qd x 10 days prior to its withdrawal by the applicant.
- Trovafloxacin (Trovan) dosing was 100mg qd x 7-10 days prior to withdrawal of the ABECB indication.

Except for cefdinir, all of the non-quinolone antimicrobials approved for ABECB are indicated for 7, 10, or 14 days of treatment. All the following are dosed orally with the exception of [redacted]

- Trimethoprim-sulfamethoxazole (Bactrim or Septra) one double strength tablet (160 mg/800mg) BID x 14 days
- Clarithromycin (Biaxin) 250-500 mg BID x 7-14 days
- Cefaclor (Ceclor) 500 mg q 12 hours x 7 days
- Ceftibuten (Cedax) 400 mg qd x 10 days
- Cefuroxime axetil (Ceftin) 250-500 mg BID x 10 days
- Cefprozil (Cefzil) 500 mg q 12 hours x 10 days
- Loracarbef (Lorabid) 400 mg q 12 hours x 7 days
- Cefdinir (Omnicef) 300 mg BID x 5 days
- Imipenem-cilastatin (Primaxin) 500-750 mg IM q 12 hours for at least two days after resolution of symptoms
- Cefixime (Suprax) 400 mg qd or 200 mg BID (duration not specified)
- Cefpodoxime (Vantin) 200 mg q 12 hours x 10 days

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CLINICAL STUDIES:

Introduction:
Table 1 shows the applicant's compilation of the clinical studies performed to support the indication of acute bacterial exacerbations of chronic bronchitis (ABECB). Three of these studies, D96-027; D96-022, and 0124 were considered pivotal. Study 0106 was a phase II dose ranging study that is considered supportive. This study enrolled a small number of patients and was terminated early. As this study did not reveal any additional findings other than those discussed in the three pivotal trials, study 106 will not be reviewed here.

Study No. D96-027

Prospective, randomized, double-blind, comparison of the safety and efficacy of BAY 12-8039 400 mg QD x 10 days versus 400 mg QD x 5 days versus clarithromycin 500 mg BID x 10 days for the treatment of patients with acute exacerbations of chronic bronchitis

Objective/Rationale

The aim of this study was to assess the efficacy and safety of 5 or 10 day regimens of moxifloxacin dosed at 400 mg QD, in comparison with an active control, clarithromycin, dosed at 500 mg BID for 10 days, in the treatment of patients with acute exacerbations of chronic bronchitis.

Design

This was a prospective, randomized, multi-center, double-blind, active controlled study conducted at 56 centers in the United States between November 26, 1996 to April 7, 1998. Patients were randomized to one of three study groups: 1) moxifloxacin at 400 mg PO daily for 5 days plus placebo, 2) moxifloxacin 400 mg PO daily for 10 days plus placebo, or 3) clarithromycin 500 mg PO twice daily for 10 days. Patients in the moxifloxacin 400 mg X 10 day regimen received one 400 mg tablet while patients in the 400 mg X 5 day regimen received two 200 mg tablets. In the 5 day regimen, active moxifloxacin was replaced by a placebo capsule on days 6-10. Patients in all three treatment groups took two capsules twice daily. Patients randomized to the comparator arm of the trial received two 250 mg tablets of clarithromycin PO twice daily for 10 days. Patients were evaluated 5 times over the course of the study including the entry, on therapy, end of therapy, and two post-therapy visits. The first post-therapy visit (post 1, day +7 to +17 after therapy) was considered the test of cure visit.

> **MO COMMENT: Clarithromycin is FDA approved for ABECB due to *Streptococcus pneumoniae* and *Moraxella catarrhalis* at 250 mg PO twice daily for 7 to 10 days. For *Haemophilus influenzae*, the approved dose of clarithromycin is 500mg PO twice daily for 7 to 10 days. All patients in this trial receiving clarithromycin took the higher dose regardless of the etiologic organism.**

TABLE 1 - TABLE OF STUDIES; INDICATION AECB

Protocol #/ Country	Status	Trial Design	Treatment/Dose	Duration of Treatment	# Patients Randomized /Treatment Arm (Total)	Age Range (Mean)	% M/F	% B/W/O
D96-027 US	Completed	controlled, double blind, parallel group, randomized Phase III	Moxifloxacin 400 mg QD x 5 days Moxifloxacin 400 mg QD x 10 days Clarithromycin 500 mg BID x 10 days	5 days 10 days 10 days	316 307 313 (936)	18-88 (57) 19-89 (56) 18-90 (56)	54/46 53/47 51/49	23/75/2 22/76/2 27/71/2
D96-022 US, CA	Completed	controlled, double blind, parallel group, randomized Phase III	Moxifloxacin 200 mg QD x 10 days Moxifloxacin 400 mg QD x 10 days Cefuroxime Axetil 500 mg BID x 10 days	10 days 10 days 10 days	223 225 234 (682)	18-93 (53) 19-88 (54) 18-86 (54)	45/55 50/50 51/49	22/76/2 26/72/2 23/75/2
0124 A, CH, D, E, F, GB, GR, NL	Completed	controlled, double blind, parallel group, randomized Phase III	Moxifloxacin 400 mg QD x 5 days Clarithromycin 500 mg BID x 7 days	5 days 7 days	376 373 (749)	18-95 (60) 22-90 (60)	59/41 58/42	0/78/22 0/78/22
#0106 D, GB, GR	Completed	controlled, double blind, parallel group, randomized Phase IIa	Moxifloxacin 200 mg QD x 6-14 days Moxifloxacin 400 mg QD x 6-14 days Cefixime 400 mg QD x 6-14 days	6-14 days 6-14 days 6-14 days	10 11 7 (28)	37-74 (60) 52-74 (64) 47-74 (63)	30/70 55/45 57/43	0/100/0 0/100/0 0/100/0

M/F = male/female; B/W/O = black, white, other; QD = once daily; BID = twice daily
A = Austria; CA = Canada; CH = Switzerland; D = Germany; E = Spain; F = France; GB = Great Britain; GR = Greece; NL = Netherlands; US = United States

The applicant calculated the sample size to establish equivalence between a given regimen of moxifloxacin (5 day or 10 day regimens) and clarithromycin 500 mg BID for 10 days using the 95% confidence interval to evaluate the difference in clinical response rates. Originally, the protocol specified that 849 patients (283 patients in each treatment arm) would be accrued. This projection was later revised upwards in response to a lower than expected numbers of microbiologically evaluable patients. By completion of the trial, 936 patients had been enrolled. The protocol specified that to test the null hypothesis of inequivalence, a two-sided 95% confidence interval for the weighted difference between treatment groups would be constructed, using Mantel-Haenszel weights (weighting by center). Equivalence was defined statistically as the lower limit of the two-sided 95% confidence interval for the difference between groups being greater than -15% if both success rates were between 90%-89%; the lower limit would need to be greater than -10% if the higher of the two success rates was greater than 90%.

MO COMMENT: This study represents one of the two types suggested in the 1992 Points to Consider (PTC) document for the evaluation of a drug in acute bacterial exacerbations of chronic bronchitis. It is a controlled, multi-center trial that attempts to establish equivalence to an approved product in which the primary endpoint is clinical effectiveness. The PTC document states that the analyses of the data should confirm the general correlation between clinical success and bacterial eradication in the evaluable population.

Protocol Overview

- **Population, procedures**

Patients enrolled were men or women 18 years of age or older, with acute, mild to moderate, bacterial exacerbations of chronic bronchitis. Chronic bronchitis was defined as the daily production of sputum on most days for at least 3 consecutive months for more than 2 consecutive years. An acute exacerbation was defined as

1. increased purulent/mucopurulent sputum AND
2. at least one of the following:
   a. increased cough, OR
   b. dyspnea, OR
   c. sputum volume OR
   d. presence of fever (oral temperature >100.4°F or >38°C) at the time of screening.

Patients with severe respiratory infections requiring parenteral antimicrobial therapy were not eligible for this study.

The severity of the exacerbation in the individual patient was graded according to the criteria of Anthonisen[2] as follows:

Type 1(severe): increased dyspnea, sputum volume and sputum purulence
Type 2(moderate): two of the three symptoms from Type 1
Type 3(mild) : one of the three symptoms from Type 1 along with at least one of the following:

[2] Anthonisen NR, Manfreda J, Warren CPW et al. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med 1987;106:196-204.

a. upper respiratory infection (sore throat, nasal discharge) within the past five days OR
b. fever without other cause OR
c. increased wheezing OR
d. increased cough OR
e. increase in respiratory rate or heart rate by 20% as compared with baseline.

MO COMMENT: Patients were analyzed for severity of their exacerbation in a post hoc fashion and were not stratified at enrollment. The severity criteria of Anthonisen et al have not been prospectively validated. Patients with type 1 exacerbations as defined in that study had lower clinical cure rates but were more likely to experience benefit from antimicrobial therapy compared to placebo than patients with type 2 or 3 exacerbations.

Eligible patients were evaluated five times over the course of the study according to the following schedule:

Pretreatment visit	baseline prior to therapy
During treatment visit	day 3 to 5 after initiation of therapy
End of therapy visit	day 2 to 4 after completion of therapy
POST I visit	day 7 to 17 after completing therapy (test of cure visit)
POST II visit	day 18 to 31 after completion of therapy

Clinical signs and symptoms were recorded at each visit. At the *pre-treatment visit*, medical history and physical examination were performed and the severity of the patient's exacerbation was graded. Patients satisfying the screening parameters were randomized to one of the three treatment arms. Blood and urine samples were collected for monitoring of safety laboratory parameters. Sputum samples were also collected at each visit as available and submitted to a local laboratory for Gram stain and culture. Electrocardiograms (ECGs) were collected at the pre-therapy and during therapy.

Patients were next seen during the treatment period at day 3 to 5 of therapy (*during treatment visit*) to determine clinical respiratory assessments and to perform a bacteriologic assessment of sputum, if available. If the patient did not show clinical improvement or worsened at this visit, study drug was discontinued, the patient was placed on alternative treatment and rated a clinical failure of therapy.

The third visit (*end of therapy visit*) was scheduled for two to four days after completion of drug or placebo (equivalent to 7 to 11 days after completing active medication in the group randomized to receive 5 days of moxifloxacin therapy). At the fourth visit (*POST I*), performed 7 to 17 days after completing study medication or placebo, the patient was evaluated for clinical efficacy. This post 1 visit was the test of cure visit. The final visit (*POST II*) was performed 18 to 31 days after completion of study medication or placebo.

MO COMMENT: The original scheduled follow-up times for the post 1 and post 2 visits were at day +7 to +14 and day +21 to +28. Prior to unblinding the post 1 follow-up window was expanded to +7 to +17 days and the post 2 window was expanded to +18 to +31 days in order to maximize the number of patients included in the analyses. The MO accepts these

changes. The half life of moxifloxacin is 12 hours, therefor a test of cure visit at least 7 days after therapy would ensure that drug has been cleared from the body.

- **Inclusion/Exclusion Criteria of Note**
- Inclusion criteria

a) Adult patients (18 years or older) with underlying chronic obstructive pulmonary disease (COPD) as defined by the daily production of sputum on most days for at least 3 consecutive months for more than 2 consecutive years who had an acute exacerbation of bronchitis clinically thought to be caused by a bacterial pathogen.

b) Only patients with mild to moderately severe respiratory tract infections (exacerbations) were entered.

c) Increases of bronchopulmonary symptoms and laboratory evidence of an acute lower respiratory tract infection documented the acute nature of the infection. Clinical symptoms of bronchopulmonary infection which were used for evaluation for study entry were:

d) Increased purulent/mucopurulent sputum AND at least one of the following:
1) increased cough
2) increased dyspnea
3) increase of sputum volume
4) presence of fever (oral temperature > 100.4°F or 38°C).

- Exclusion criteria

a) History of allergy to quinolone derivatives or macrolide derivatives

b) Pregnancy; women of childbearing potential in whom pregnancy could not be excluded by a negative pregnancy test and women using unreliable contraception; nursing mothers.

c) History of severe cardiac failure (class IV of the New York Heart Association [NYHA] classification).

d) Severe respiratory tract infections requiring parenteral antimicrobial therapy or mechanical ventilatory support.

e) Chest x-ray showing evidence of new bronchopulmonary infiltrates or lobar consolidation.

f) Significant liver impairment with baseline serum glutamic oxalacetic transaminase (SGOT) or serum glutamic pyruvic transaminase (SGPT) and/or total bilirubin > 3 times upper limit of normal.

g) Significant renal impairment, i.e., serum creatinine > 3.0 mg/dL (> 265 µmol/L) or creatinine clearance < 30 mL/min/1.73 m^2.

h) History of tendinopathy associated with fluoroquinolones.

i) Need for a concomitant antibacterial agent with a spectrum of activity similar to the study drugs.

j) Have received previous therapy with a systemic antibiotic for more than 24 hours prior to enrollment.

k) Need for terfenadine (Seldane®) or astemizole (Hismanal®) during the treatment period of this protocol. Study entry was allowed only if these H1-receptor antagonists (antihistamines) were discontinued prior to study drug therapy.

l) Diagnosis of a rapidly fatal underlying disease (death expected within 6 months).

m) Diagnosis of recent (less than 5 years) or unresolved lung or chest cavity malignancy, neutropenia (neutrophil count < 1000/mm^3), CD4 < 200/mm^3, active pulmonary tuberculosis, cystic fibrosis, or significant bronchiectasis. Human immunodeficiency virus (HIV) testing was not mandatory.

n) Previous participation in a BAY 12-8039 study.

o) Use of an investigational drug in the 30 days preceding enrollment.

p) Prolonged QTc intervals (inherited and sporadic syndromes of QTc prolongation)

q) Need for concomitant medication reported to increase the QTc interval, e.g., amiodarone, sotalol, disopyramide, quinidine, procainamide

MO COMMENT: Concomitant systemic steroid administration was not an exclusion criterion for this study. The numbers of patients on systemic steroids prior to enrolling in the trial and the numbers of patients started on steroids during the trial were equivalent across the groups (24%, 20% and 24% total prevalence of steroid usage in the moxifloxacin 5 day, 10 day, and clarithromycin groups, respectively). Patients were not stratified by steroid usage at entry into the trial.

Evaluability Criteria

1) The ***intention to treat population*** (ITT), referred to in this study as the "*valid for safety*" population, was defined as patients given any double-blind drug, regardless of duration.

MO COMMENT: A separate intention to treat analysis of patient outcomes was performed by the FDA biostatistical reviewer using the following criteria:

a) cures and improvements were combined as successes of treatment

b) failures and indeterminates were combined as treatment failures

c) patients who used alternative systemic antibiotics for any reason were treated as failures regardless of the actual clinical outcomes

d) patients lost to follow-up before the primary post 1 therapy visit were treated as failures

2) The ***clinically efficacy evaluable*** (CEE) and ***microbiologically and clinically efficacy evaluable*** (MCEE) populations were those patients that could be evaluated for both safety and efficacy. In

this study, these patients were referred to as "*valid for safety and efficacy.*" The MCEE population was defined as the subset of the CEE population with positive sputum cultures for a respiratory pathogen at baseline. An organism was coded as a pathogen, colonizer, or contaminant by the investigator. The applicant did not provided guidance in the protocol to clinicians on how to place organisms in these categories.

MO COMMENT: Although Gram's stains for each sputum sample were obtained and recorded, the protocol did not specify a Gram's stain positive for a predominant organism or an adequate Gram stain (>25 WBCs and <10 epithelial cells per high power field) was necessary for the patient to be considered evaluable in the MCEE population. A separate analysis of patients with adequate and inadequate sputa is presented in the efficacy section below.

3) For a course of therapy to be judged valid for the CEE or MCEE population for evaluating the efficacy of drug therapy, the following criteria were met:

a) acute exacerbation of chronic bronchitis must have been confirmed both by appropriate history of underlying disease and presentation with symptoms of acute infection

b) a chest x-ray was done pre-therapy to rule out pneumonia

c) sputum for culture was obtained pre therapy

d) the study drug must have been given for a minimum of 48 hours if a treatment result was a clinical failure, or for a minimum of 5 days if the result was a success

e) no other systemic antimicrobial agent could have been administered during the study period (through the POST II day +18 → +31 post-therapy evaluation) unless the patient was a treatment failure or relapse

f) adequate compliance with 80% or more of oral study medication administered must have been documented

g) an attempt must have been made to obtain sputum cultures at all follow-up visits (patients who could not produce sputum at follow-up would still be evaluable as long as this attempt was made)

h) no protocol violation influencing treatment efficacy may have occurred;

i) the random code was not broken

j) no essential data (i.e., primary efficacy variable) was missing or indeterminate which could not be recovered.

MO COMMENT: The MO accepted the applicant's inclusion and exclusion criteria to be in accordance with the criteria outlined in the "Draft guidance for industry: acute bacterial exacerbations of chronic bronchitis-developing antimicrobial drugs for treatment".

Endpoints (Clinical and Microbiologic)

According to the applicant, the primary endpoint ("test of cure" visit)for this study was the *clinical response* at the POST I follow-up visit (day +7 to +17). The secondary efficacy parameters were *bacteriologic response* at the during therapy, end of therapy, and POST II time points and the *clinical response* at the end of therapy and POST II time points

The following parameters were used to assess the *clinical response* of patients.

1. *auscultatory findings* e.g. rales, rhonchi, wheezing, and decreased breath sounds (present or absent)
2. *chest pain/discomfort*: greatly increased, slightly increased, or same as baseline
3. *cough frequency*: greatly increased, slightly increased, or same as baseline
4. *dyspnea*: greatly increased, slightly increased, or same as baseline
5. *fever*: >38 degrees C (oral)
6. *prolongation of expiratory phase*: present or absent
7. *sputum*: thickness/purulence (greatly increased, slightly increased, or same as baseline) and volume (greatly increased, slightly increased, or same as baseline)
8. *WBC*: >12,000 cells/mm3

MO COMMENT: In validating a 20% random sample of the patient database, the MO evaluated, in a blinded fashion, the response to therapy by examining the five main symptoms that were used to enroll patients in the trial, namely, 1) increased sputum production (necessary to be included in the trial) and 2)cough, 3)dyspnea, 4)sputum thickness/ purulence, and 5)fever (only one patient in this study was febrile). The MO agreed with the investigator's assessment of the patient as a clinical success if these particular symptoms were significantly improved from the pre-therapy visit, even if the symptoms did not return to the patient's pre-morbid baseline. If there was no change in any of these symptoms from the pre-therapy visit, the MO graded the patient as a clinical failure regardless of the investigator's assessment. A review of this 20% sample did not show any systematic errors and an analysis of the changes in outcome did not change the overall efficacy analysis. Therefore, the MO accepts the applicant's assessment of both evaluability and outcomes.

- **Clinical**

The *clinical response* of the patients to treatment in the CEE population was categorized by the applicant graded as follows:

1. Clinical cure: disappearance of acute signs and symptoms related to the infection (meaning complete return to a stable pre-exacerbation condition in chronic bronchitis) or sufficient improvement such that additional or alternative antimicrobial therapy was not required
2. Clinical improvement: reduction in severity and/or number of signs and symptoms of infection (This response was used only if applicable in patients requiring premature discontinuation of study medication).
3. Continued clinical cure: disappearance of acute signs and symptoms of infections or continued improvement where additional or alternative antimicrobial therapy was not required.

4. Clinical recurrence: reappearance of signs and symptoms of an acute exacerbation of bronchitis considered reported to an infectious (bacterial) process requiring reinstitution of antimicrobial therapy
5. Clinical failure: insufficient lessening of the signs and symptoms of infections such that additional or alternative antimicrobial therapy was required
6. Indeterminate: a clinical assessment was not possible for reasons documented in the case report form

For the various visits, the following clinical responses were considered possible:

End of therapy: clinical cure, improvement, clinical failure, indeterminate
Post 1 follow-up: (test of cure visit) clinical cure, continued clinical cure, clinical failure, clinical recurrence, indeterminate
Post 2 follow-up visit: continued clinical cure, clinical failure, clinical recurrence, indeterminate

MO COMMENT: One investigator graded a single patient's response at end of therapy in the moxifloxacin 10 day group as "continued clinical cure" and another patient in the moxifloxacin 5 day group was designated as "clinical recurrence" although these were not designated responses for that time point. The MO recategorized the first patient as a "clinical cure" and the second as a "clinical failure". In any case, these patients did not change the calculations for efficacy by the applicant.

The applicant defined a "clinical success" as any patient with a clinical response of "clinical cure" or "improved". The applicant also calculated an "overall response" category for the post 1 visit. This category used a denominator of all randomized patients who were evaluable at any time point during the study. In contrast, the post 1 follow-up success rates (the primary endpoint) only included patients in the denominator who were actually evaluated at the post 1 visit. Patients that were failures at the early follow-up (end of therapy) visit were considered failures at the post 1 follow-up time point as well (carried forward as failures).

MO COMMENT: For the purposes of study validation, the MO considered lack of improvement in any of the pre-therapy symptoms as a clinical failure, regardless of whether alternate antibiotic therapy was prescribed.

- **Microbiologic**

The ***microbiologic response*** to treatment was based on microbiologic evaluation of sputum cultures obtained before and after therapy. For infections caused by 2 or more pathogens, the response for each was determined as a separate episode of infection. The microbiologic responses at the *end of therapy* visit were graded as follows:

1. Eradication: initially causative organisms absent at the end of therapy.
2. Presumed eradication: no material to culture in a patient considered a clinical success
3. Eradication with relapse: original causative organisms absent at the end-of-therapy, but reappearance of the same organism at or before the follow-up visit.
4. Eradication with reinfection: causative organisms absent at the end of therapy, but reappearance of a different infecting organism at or before the follow-up visit. An infecting

organism was defined as an organism believed to be causing symptoms and requiring antimicrobial therapy

5. Persistence: initially causative organism present at the end of therapy.
6. Presumed persistence: no material to culture in a patient considered a clinical failure
7. Superinfection: presence of a new organism at the end of therapy visit judged to be causing an infectious process (associated with clinical signs) at the primary site of infection [respiratory tract] and requiring alternative antimicrobial therapy.
8. Indeterminate response: bacteriological response to the study drug was not evaluable for any reason (e.g., pre-treatment culture was negative, post-treatment culture not obtained when material was available).

For the various visits, the following microbiologic responses were utilized:

End of therapy:	eradication, presumed eradication, persistence, presumed persistence, superinfection, indeterminate
Post 1 visit:	(test of cure visit) eradication, presumed eradication, eradication with relapse, eradication with recurrence, persistence, presumed persistence
Post 2 visit:	eradication, presumed eradication, eradication with relapse, persistence, presumed persistence.

The applicant defined a "microbiologic success" as any patient with a microbiologic response of "eradicated" or presumed eradicated". Superinfections at the end of therapy visit, and eradications with recurrences and relapses at the follow-up visits were tabulated in a separate analysis.

MO COMMENT: The MO accepted the applicant's endpoint criteria to be in accordance with the criteria outlined in the "Draft guidance for industry: acute bacterial exacerbations of chronic bronchitis-developing antimicrobial drugs for treatment".

Statistical considerations

The applicant employed the recommendations of the 1992 Points to Consider document for determining statistical equivalence between moxifloxacin and the comparator drugs.

"The protocol specified that a two-sided 95% confidence interval for the weighted difference between treatment groups would be constructed, using Mantel-Haenszel weights (weighting by center). Success rates for both treatment groups were expected to be approximately 85%. Therefore, equivalence was defined statistically as the lower limit of the two-sided 95% confidence interval for the difference between groups being greater than -15%."

Results

Demographics, Evaluability

BAY 12 8039/D96-027
BRONCHITIS

TABLE 2
DEMOGRAPHIC DATA PER APPLICANT
POPULATION: ALL PATIENTS VALID FOR EFFICACY

			MOXIFLOXACIN 400MG X 5 (N=250)	MOXIFLOXACIN 400MG X 10 (N=256)	CLARITHROMYCIN (N=251)	TOTAL (N=757)
SEX (P=0.615)	MALE	N (%)	135 (54)	140 (55)	127 (51)	402 (53)
	FEMALE	N (%)	115 (46)	116 (45)	124 (49)	355 (47)
RACE (P=0.923)	CAUCASIAN	N (%)	189 (76)	192 (75)	178 (71)	559 (74)
	BLACK	N (%)	54 (22)	58 (23)	67 (27)	179 (24)
	ASIAN	N (%)	2 (<1)	2 (<1)	2 (<1)	6 (<1)
	AMERICAN INDIAN	N (%)	1 (<1)	1 (<1)		2 (<1)
	HISPANIC	N (%)	4 (2)	3 (1)	4 (2)	11 (1)
AGE AT ENROLLMENT (YRS) (P=0.397)		N	250	256	251	757
		MEAN	56.8	56.1	55.4	56.1
		STD	15.2	15.6	15.9	15.5
		MIN	19.0	18.0	18.0	18.0
		MEDIAN	57.0	59.0	56.0	58.0
		MAX	89.0	86.0	90.0	90.0
WEIGHT (KG) (P=0.911)		N	250	254	250	754
		MEAN	78.8	77.3	78.2	78.1
		STD	18.8	19.2	18.1	18.7
		MIN	44.1	38.6	36.4	36.4
		MEDIAN	76.4	73.8	76.4	75.0
		MAX	142.3	138.6	146.8	146.8
PATIENTS HOSPITALIZED		N (%)	10 (4)	13 (5)	16 (6)	39 (5)
INFECTION TYPE (P=0.488)	TYPE 1	N (%)	193 (77)	201 (79)	206 (82)	600 (79)
	TYPE 2	N (%)	55 (22)	54 (21)	42 (17)	151 (20)
	TYPE 3	N (%)	2 (<1)	1 (<1)	3 (1)	6 (<1)

P-VALUES FOR CATEGORICAL VARIABLES OBTAINED USING A CHI-SQUARE TEST.
P-VALUES FOR CONTINUOUS VARIABLES OBTAINED USING 1-WAY ANOVA.

- **Demographics**

Table 2 is the applicant's listing of the demographic characteristics of the patients in the CEE (valid for efficacy) population. The demographics in all enrolled patients were similar to those in the CEE population.

MO COMMENT: There were no statistically significant differences in demographics observed between study arms.

- **Evaluability**

The applicant's tabulation of the numbers of patients at each center that were randomized, and the numbers of patients per center in the ITT population (valid for safety), the CEE population (per protocol group), and the MCEE population (microbiologically valid) are presented in Appendix 1.

MO COMMENT: Center number 13 had the highest enrollment, accounting for 180/936 (19%) of the randomized patients, 150/757 (20%) of the CEE population (per protocol) and 132/420 (31%) of the MCEE (microbiologically valid) population. This is consistent with the recommendations of the 1992 Points to Consider document which states that no center should enroll more than 40% of the total patients in a multi-center trial.

Table 3 is the applicant's listing of the numbers of patients enrolled in the study, and the numbers of patients valid for the ITT (safety) and CEE (per protocol) analyses. This table also lists the reasons that patients were excluded from the various analyses.

MO COMMENT: The numbers of patients excluded from the study for various reasons was similar across the study arms. The 8 moxifloxacin patients lost to follow-up and excluded from the per protocol efficacy analysis included the 4 patients excluded from the ITT analysis, i.e. 4 patients were excluded because they never returned after enrollment, and 4 more were excluded subsequently after they took at least one dose of drug because did not return for follow-up.

MO COMMENT: The category of "essential data missing or invalid" was the single largest group of patients excluded from the per protocol efficacy analysis. The "essential data missing or invalid" group also included patients for whom a clinical assessment could not be made by the applicant at the post 1 visit due to an "indeterminate" assessment by the investigator. The MO reviewed these cases and found that these included patients who were coded as such for numerous reasons with no systematic error in the assessment of these patients. The number of disagreements with the applicant's assessments were few and did not change the overall efficacy analysis

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TABLE 3
PATIENT VALIDITY AND REASONS FOR EXCLUSIONS FROM ANALYSES PER APPLICANT
POPULATION: ALL RANDOMIZED PATIENTS

	MOXIFLOXACIN 400MG QD X 5	MOXIFLOXACIN 400MG QD X 10	CLARITHROMYCIN	TOTAL
PATIENTS RANDOMIZED	316	307	313	936
EXCLUDED FROM SAFETY (ITT) ANALYSIS	4	5	1	10
LOST TO FOLLOW-UP AFTER ENROLLMENT	4	5	1	10
VALID FOR SAFETY ANALYSIS = ITT	312 (99%)	302 (98%)	312 (100%)	926 (99%)
EXCLUDED FROM PER-PROTOCOL EFF ANALYSIS	66	51	62	179
VIOLATION OF INCLUSION/EXCLUSION CRITERIA	16	13	15	44
PREGNANT	0	1	1	2
NO PRE-THERAPY X-RAY	1	2	2	5
< REQUIRED CLINICAL SYMPTOMS FOR INCLUSION	7	8	6	21
ELEVATED LABORATORY VALUES	2	1	4	7
CHEST X-RAY WITH INFILTRATE	3	1	1	5
LUNG CANCER	3	0	1	4
RANDOM CODE BROKEN	1	0	0	1
NON-COMPLIANCE WITH STUDY DRUG	7	2	9	18
INSUFFICIENT DURATION OF THERAPY	8	10	11	29
VIOLATION OF TIME SCHEDULE	3	3	5	11
ESSENTIAL DATA MISSING OR INVALID	17	8	18	43
LOST TO FOLLOW-UP	8	8	2	18
USE OF PROHIBITED CONCOMITANT MEDICATION*	1	1	1	3
USE OF PROHIBITED POST-TREATMENT MEDICAT#	2	2	0	4
NO BASELINE CULTURE PERFORMED	3	4	1	8
IN PER-PROTOCOL EFFICACY (CEE) ANALYSIS	250 (79%)	256 (83%)	251 (80%)	757 (81%)
EXCLUDED FROM MCEE ANALYSIS	107	108	122	337
NO BASELINE PATHOGEN ISOLATED	107	108	122	337
MICROBIOLOGICALLY VALID (MCEE)	143 (45%)	148 (48%)	129 (41%)	420 (45%)

*prohibited concomitant medications were other antimicrobials, [redacted]astemizole; two patients received azithromycin and one received doxycycline for indications other than ABECB

#prohibited post-treatment medications were other antimicorbials, [redacted]astemizole; patients received Augmentin, levofloxacin and clarithromycin for indications other than lower respiratory tract infections

Efficacy

- **Clinical Efficacy**

According to the applicant, the primary outcome endpoint was the clinical outcome in the CEE (per protocol, valid for efficacy) population at the post 1 (+7 to +17 day) follow-up visit. Table 4 shows the applicant's tabulations of clinical efficacy at the end of therapy, and post 1 visits with an overall assessment of clinical efficacy in the per protocol population (valid for efficacy or CEE).

TABLE 4
SUMMARY OF CLINICAL RESPONSES AT END OF THERAPY, FOLLOWUP, AND OVERALL RESPONSE
POPULATION: PATIENTS VALID FOR EFFICACY (PER PROTOCOL)

		MOXIFLOXACIN X 5 DAYS		MOXIFLOXACIN X 10 DAYS		CLARITHROMYCIN	
		N=250	%	N=256	%	N=251	%
END OF THERAPY (DAY 0 - +6)	CLINICAL CURE	227	90.8	232	90.6	230	91.6
	IMPROVEMENT	1	0.4	1	0.4	1	0.4
	CLINICAL FAILURE	13	5.2	13	5.1	13	5.2
	INDETERMINATE	8	3.2	8	3.1	6	2.4
	CONTINUED CLINICAL CURE	0	0	1*	0.4	0	0
	CLINICAL RECURRENCE	1	0.4	1	0.4	1	0.4
POST 1 (DAY +7 - +17)	CLINICAL FAILURE	1	0.4	0	0	0	0
	INDETERMINATE	14	5.6	14	5.5	14	5.6
	CONTINUED CLINICAL CURE	222	88.8	234	91.4	224	89.2
	CLINICAL RECURRENCE	13	5.2	8	3.1	13	5.2
OVERALL RESPONSE	RESOLUTION	222	88.8	234	91.4	224	89.2
	CLINICAL FAILURE	28	11.2	22	8.6	27	10.8

*one patient was designated by the investigator as continued clinical cure at end of therapy although this was not an outcome option this visit

CLINICAL SUCCESS RATES			
END OF THERAPY	228/242 (94%)	234/248 (94%)	231/245 (94%)
POST 1	222/236 (94%)	234/242 (97%)	224/237 (95%)
OVERALL	222/250 (89%)	234/256 (91%)	224/251 (89%)

MO COMMENT: The end of therapy and post 1 follow-up clinical success rates use the numbers of patients who were evaluable at those particular visits only as the denominator. The overall success rates use the denominator of all patients randomized who were evaluable at any visit in the per protocol

analysis. This includes clinical failures at the end of therapy visit that were carried forward and included in the overall outcome as failures.

As shown in the following table, the center weighted 95% confidence interval around the difference in overall clinical efficacy rates for the per protocol population at the Post 1 visit between patients treated with moxifloxacin for 10 days (234/256, 91%) and clarithromycin (224/251, 89%) was (-2.7%, 7.2%). The center weighted 95% confidence interval around the difference in efficacy rates between patients treated with moxifloxacin for 5 days (222/250, 89%) and clarithromycin (224/251, 89%) was (-6.1%, 4.2%). The center weighted 95% confidence interval around the difference in efficacy rates between moxifloxacin treated patients for 5 days versus 10 days was (-7.4%, 2.7%). These rates demonstrate statistical similarity to an approved comparator as suggested in the 1992 Points to Consider document as the lower bound of the confidence intervals is less than 10% for all comparisons.

Table 5
Overall Clinical Success Rates at Post 1 Visit Per Applicant
Population: Per Protocol (Valid for Efficacy)

Study Group	Clinical Success Rates N(%)	95% Confidence Intervals*
Moxifloxacin 5 days	222/250 (89%)	(-6.1%, 4.2%)
Moxifloxacin 10 days	234/256 (91%)	(-2.7%, 7.2%)
Clarithromycin	224/251 (89%)	-

* the CI or each moxifloxacin group were calculated compared to the clarithromycin group

The following table demonstrates the intention-to-treat analysis of patients in the valid-for-safety-only population as performed by the FDA biostatistics reviewer. This calculation employed the criteria that a) cures and improvements were combined as successes of treatment; b) failures and indeterminates were combined and treated as failures; c) patients who used alternative systemic antibiotics for any reason were treated as failures regardless of the actual clinical outcomes; d) patients lost to follow-up before the primary post 1 therapy visit were treated as failures. The following table provides the efficacy rates in the intention-to-treat population at the post 2 (+18 to +31days) visit. The post 2 visit was chosen to give the most conservative estimate of efficacy.

Table 6
Clinical Success Rates at Post 2 Visit Per FDA Statistical Reviewer
Population : Intention to Treat (Valid for Safety)

Study Group	Clinical Success Rates N(%)#	95% Confidence Intervals*
Moxifloxacin 5 days	229/313 (73.2%)	(-3.6%, 12.9%)
Moxifloxacin 10 days	233/303 (76.9%)	(-7.5%, 9.3%)
Clarithromycin	219/303 (72.3%)	-

*the CI or each moxifloxacin group were calculated compared to the clarithromycin group

#denominators for this calculation are different than applicant's; see FDA biostatistics review

MO COMMENT: The intention to treat analysis confirms the results seen in the per protocol analysis and still results in confidence intervals with lower bounds less than –10% as suggested in the 1992 Point to Consider document.

One patient developed pneumonia in the 5 day moxifloxacin group on day 36 of the study. Two patients in the moxifloxacin 10 day group developed pneumonia on days 30 and 35 of study, respectively. No patients in the clarithromycin group developed pneumonia.

- **Special Populations**
- *Geriatric Populations: Efficacy*

The efficacy rates were similar across the three arms of the trials on various demographic groups (i.e. male vs female and various ethnic groups). The efficacy rates in patients older than age 65 treated with moxifloxacin for 5 or 10 days was lower than the rates of success with clarithromycin in this same population as demonstrated in the following table.

Table 7
Clinical Success Rates at Post 1 Visit in Patients by Age Group Per Applicant
Population: Patients Valid for Efficacy (Per Protocol)

D96-027	Moxifloxacin 400mgx5	Moxifloxacin 400mgx10	Clarithromycin	P-Value #
< 65	143/159 (90%)	159/169 (94%)	149/171 (87%)	0.425
65-74	51/56 (91%)	54/60 (90%)	43/46 (93%)	0.653
> 74	28/35 (80%)	21/27 (78%)	32/34 (94%)	0.082

#: P-Value for comparison of moxifloxacin 5 days and clarithromycin

- *Concomitant Steroid Use: Efficacy*

When systemic steroids were used concurrently, moxifloxacin dosed for 5 days had a lower efficacy rate than in patients treated with either 10 days of moxifloxacin or a 10 day course of clarithromycin. In all three study groups combined there were 171/757 (23%) patients in the per protocol valid for efficacy group treated with systemic steroids (either on steroids at the time of enrollment or placed on steroids during the study). The efficacy rate in the 5 day moxifloxacin group was 78% (47/60) in those patients receiving systemic steroids. The rates of success were 85% (47/55) for the 10 day moxifloxacin group and 91% (51/56) in the clarithromycin treated group.

Table 8
Clinical Efficacy in Patients Treated With and Without Systemic Steroids
CEE Population: Per Applicant

	Moxifloxacin 5 days	Moxifloxacin 10 days	Clarithromycin	P-Value #
Patients With Steroids	47/60 (78%)	47/55 (85%)	51/56 (91%)	0.058
Patients Without Steroids	175/190 (92%)	187/201 (93%)	173/195 (89%)	0.260
P-Value @	0.003	0.076	0.616	

#: P-Value for comparison of moxifloxacin 5 days and clarithromycin
@:P-Value for comparison of patients with and without steroids

MO COMMENT: The efficacy in this study of moxifloxacin dosed for 5 days in patients treated with systemic steroids appears less than that in systemic steroid treated patients in the 10 day moxifloxacin and clarithromycin groups. Patients were not stratified by steroid usage, however, and the subsequent studies in this review do not confirm these findings, showing similar efficacy between 5 days of moxifloxacin and comparators in steroid treated patients.

- *Clinical Response in Patients with Adequate Sputum Gram's Stains*

The clinical response of patients with adequate sputum Gram's stain (>25 WBCs and <10 epithelial cells per high power field) was compared to the clinical response in patients with inadequate Gram's stains.

Table 9
Clinical Response at Post 1 Visit by Gram's Stain Results
MCEE Population: Per Applicant

	Moxifloxacin 400 mg x 5 days		Moxifloxacin 400 mg x 10 days		Clarithromycin 500 mg BID x 10 days	
Gram Stain Missing	8/9	(89%)	8/9	(89%)	7/8	(88%)
WBC < 25, Epi <= 10	15/17	(88%)	17/20	(85%)	14/18	(78%)
WBC < 25, Epi > 10	5/8	(63%)	6/6	(100%)	2/2	(100%)
WBC >= 25, Epi <= 10	83/93	(89%)	75/84	(89%)	79/82	(96%)
WBC >= 25, Epi > 10	16/16	(100%)	28/29	(97%)	16/19	(84%)

MO COMMENT: With the exception of some groups in which there were small numbers of patients, the efficacy of moxifloxacin or the comparator is not dramatically different in patients with adequate versus inadequate sputa, or in patients in whom the Gram's stain was missing.

- **Microbiologic Efficacy**

Microbiologic efficacy was expressed as the proportion of the microbiologic and clinical efficacy evaluable population (MCEE) that was clinically cured at the post 1 (day +7 to +17) visit. The efficacy rates at the post 2 visit are not presented here. The post 2 efficacy rates were slightly lower but similar across all three groups to the post 1 efficacy rates.

TABLE 10
SUMMARY OF BACTERIOLOGICAL RESPONSES AT EOT AND POST 1 FOLLOWUP
PER APPLICANT
POPULATION: PATIENTS VALID FOR EFFICACY (PER PROTOCOL)

		MOXIFLOXACIN X 5 DAYS		MOXIFLOXACIN X 10 DAYS		CLARITHROMYC-IN	
		N=143	%	N=148	%	N=129	%
END OF THERAPY	ERADICATION	33	23	41	28	22	17
(DAY 0- +6)	PRESUMED ERADICATION	94	66	97	66	93	72
	PERSISTENCE	6	4	5	3	10	8
	INDETERMINATE	8	6	3	2	2	2
	PRESUMED PERSISTENCE	2	1	2	1	2	2
POST 1 VISIT	ERADICATION	23	16	23	16	11	9
(DAY +7- +17)	PRESUMED ERADICATION	104	73	112	76	99	77
	ERADICATION WITH RELAPSE	2	1	4	3	4	3
	PERSISTENCE AT EOT	6	4	5	3	10	8
	PRESUMED PERSISTENCE	8	6	4	3	5	4
MICROBIOLOGIC SUCCESS RATES							
END OF THERAPY		127/135 (94%)		138/145 (95%)		115/127 (91%)	
POST 1 VISIT		127/143 (89%)		135/148 (91%)		110/129 (85%)	

MO COMMENT: The end of therapy and post 1 visit follow-up visit microbiologic success rates use the numbers of patients who were clinically and microbiologically evaluable at those particular visits only as the denominator.

The following table enumerates the numbers of superinfections, reinfections, and relapsing organisms as defined in the protocol.

Table 11

Patients with Superinfecting, Reinfecting, and Relapsing Organisms at Post 1 Visit Per Applicant

MCEE Population

	Moxifloxacin 400 mg qd X 5 days # organisms	Moxifloxacin 400 mg qd X 10 days # organisms	Clarithromycin 500 mg bid X 10 days # organisms
Superinfecting	4	1	7
Reinfecting	4	6	5
Relapsing	3	4	5

Three of the four superinfections in the 5 day moxifloxacin group and three of the six reinfections in the moxifloxacin 10 day group were attributed to *Streptococcus pneumoniae*. Four of the seven superinfections in the clarithromycin group were attributed to *Haemophilus influenzae*.

The following table presents the center weighted 95% confidence interval around the difference in microbiologic efficacy rates between patients treated with moxifloxacin for 10 days (135/148, 91%) and clarithromycin (110/129, 85%) was (0.3%, 14.5%). The center weighted 95% confidence interval around the difference in efficacy rates between patients treated with moxifloxacin for 5 days (127/143, 89%) and clarithromycin was (-3.7%, 10.5%). The center weighted 95% confidence interval around the difference in efficacy rates between moxifloxacin-treated patients for 5 days versus 10 days was (-10.3%, 2.5%). These rates demonstrate statistical similarity to an approved comparator as suggested in the 1992 Points to Consider document as the lower bound of the confidence intervals is less than 15% for all comparisons.

Table 12
Microbiologic Success Rates at Post 1 Visit Per Applicant
Population: Per Protocol (Valid for Efficacy, MCEE)

Study Group	Clinical Success Rates N(%)	95% Confidence Intervals*
Moxifloxacin 5 days	127/143 (89%)	(-3.7%, 10.5%%)
Moxifloxacin 10 days	135/148 (91%)	(0.3%, 14.5%)
Clarithromycin	110/129 (85%)	-

*the CI or each moxifloxacin group were calculated compared to the clarithromycin group

MO COMMENT: The microbiologic success rates correlate with the clinical success rates and are similar between the three groups in the study.

The eradication rates per organisms for the major pathogens in ABECB sought in the label are presented in the following table.

Table 13

Eradication Rates* at Post 1 Follow-up Visit by Organism Per Applicant

MCEE Population

	Moxifloxacin 5 days # eradicated/ isolates (%)	Moxifloxacin 10 days # eradicated/ isolates (%)	Clarithromycin # eradicated/ isolates (%)
Haemophilus influenzae	33/37 (89%)	31/32 (97%)	31/41 (76%)
Moraxella catarrhalis	29/34 (85%)	26/27 (96%)	24/24(100%)
Streptococcus pneumoniae	16/16 (100%)	20/21 (95%)	21/23 (91%)
Klebsiella pneumoniae	17/20 (85%)	14/15 (93%)	10/11 (91%)
Staphylococcus aureus	15/16 (94%)	17/18 (94%)	7/8 (88%)
Haemophilus parainfluenzae	16/16 (100%)	21/21 (100%)	14/14 (100%)

*represents eradication plus presumed eradications

- *Microbiologic Efficacy in Patients with Adequate Sputa*

The bacteriologic response based on the presence or absence of an adequate sputum Gram's stain is presented in the following table.

Table 14

Bacteriologic Response at Post 1 Visit by Gram's Stain Results

MCEE Population: Per Applicant

	Moxifloxacin 400 mg x 5 days	**Moxifloxacin 400 mg x 10 days**	**Clarithromycin 500 mg BID x 10 days**
Gram Stain Missing	8/9 (89%)	8/9 (89%)	5/8 (63%)
WBC < 25, Epi <= 10	17/17 (100%)	18/20 (90%)	13/18 (72%)
WBC < 25, Epi> 10	5/8 (63%)	6/6 (100%)	2/2 (100%)
WBC >= 25, Epi <= 10	82/93 (88%)	75/84 (89%)	74/82 (90%)
WBC >= 25, Epi > 10	15/16 (94%)	28/29 (97%)	16/19 (84%)

MO COMMENT: In the MCEE population, eradication rates were similar across groups among patients who had adequate and inadequate Gram's stains considering the small numbers of patients in the groups with <25 WBCs

Study D96-027 is the only one of the three pivotal studies presented by the applicant with adequate numbers of patients in whom *S. aureus* was the causative pathogen. The following table is the applicant's analysis of clinical and bacteriologic efficacy in patients in whom *S. aureus* was the only pathogen isolated versus the clinical and bacteriologic efficacy in patients in whom *S. aureus* was one of many potential pathogens.

Table 15
Clinical and Bacteriologic Efficacy in Patients with *S. aureus* as a Sole Pathogen
MCEE Population: Per Applicant

	Moxifloxacin 400 mg x 5 days	Moxifloxacin 400 mg x 10 days	Clarithromycin 500 mg BID x 10 days
Bacteriological response	8/9 (89%)	12/13 (92%)	2/3 (67%)
Clinical response	8/9 (89%)	12/13 (92%)	2/3 (67%)

Table 16
Clinical and Bacteriologic Efficacy in Patients with *S. aureus* as One of Multiple Pathogens
MCEE Population: Per Applicant

	Moxifloxacin 400 mg x 5 days	Moxifloxacin 400 mg x 10 days	Clarithromycin 500 mg BID x 10 days
Bacteriological response	7/7 (100%)	5/5 (100%)	5/5 (100%)
Clinical response	7/7 (100%)	4/5 (80%)	4/5 (80%)

MO COMMENT: The clinical and bacteriologic efficacy of a 5 day course of moxifloxacin appeared similar to clarithromycin whether the S. aureus was a single isolate or one of many potential pathogens.

The bacteriologic response in patients in whom *S. aureus* was isolated was also evaluated based on the presence or absence of an adequate sputum Gram's stain as follows:

Table 17
Bacteriologic Efficacy by Gram's Stain in Patients with *S. aureus* as Causative Pathogen
MCEE Population: Per Applicant

	Moxifloxacin 400 mg x 5 days	Moxifloxacin 400 mg x 10 days	Clarithromycin 500 mg BID x 10 days
Gram stain missing	2/2 (100%)	1/1 (100%)	0/0
WBC < 25, Epi <= 10	0/0	6/6 (100%)	0/0
WBC < 25, Epi > 10	0/0	3/3 (100%)	0/0
WBC >= 25, Epi <= 10	12/13 (92%)	6/6 (100%)	3/3 (100%)
WBC >= 25, Epi > 10	1/1 (100%)	1/2 (50%)	4/5 (80%)

The clinical efficacy in patients in whom *S. aureus* was the causative pathogen was evaluated based on the presence or absence of an adequate sputum Gram's stain.

Table 18
Clinical Efficacy by Gram's Stain in Patients with *S. aureus* as Causative Pathogen
MCEE Population: Per Applicant

	Moxifloxacin 400 mg x 5 days	Moxifloxacin 400 mg x 10 days	Clarithromycin 500 mg BID x 10 days
Gram stain missing	2/2 (100%)	1/1 (100%)	0/0
WBC < 25, EPI < = 10	0/0	5/6 (83%)	0/0
WBC < 25, EPI > 10	0/0	3/3 (100%)	0/0
WBC > = 25, EPI < = 10	12/13 (92%)	6/6 (100%)	3/3 (100%)
WBC > = 25, EPI > 10	1/1 (100%)	1/2 (50%)	3/5 (60%)

eradicated/total isolates (%)

MO COMMENT: Most of the patients with *S. aureus* as a causative pathogen had at least the presence of an adequate number of WBCs in the sputum. The efficacy in the patients with >10 epithelial cells per high power field was not dramatically different from the efficacy in those patients in whom the Gram's stain demonstrated <10 epithelial cells per high power field.

There were only 7 patients in the moxifloxacin 5 day group, 11 in the moxifloxacin 10 day group, and one in the clarithromycin group in whom *Pseudomonas aeruginosa* was isolated as the causative pathogen. In the 5 day moxifloxacin group 1/7 (14%) patient was graded as an eradication, 3/7 (43%) were presumed eradicated and 3/7 (43%) were persistent. In the moxifloxacin 10 day group, 6/11 (55%) were presumed eradicated, 4/11(36%) were persistent, and 1/11(9%) was presumed persistent. The one patient in the clarithromycin group was graded as presumed eradicated.

The following in Table 18 describes the relationship between clinical success and microbiological outcome.

TABLE 19
SUMMARY OF BACTERIOLOGICAL RESPONSE AT POST 1 VISIT
BY OVERALL CLINICAL RESPONSE PER APPLICANT
POPULATION: PATIENTS VALID FOR EFFICACY

		CLINICAL SUCCESS	CLINICAL FAILURE
		N (%)	N (%)
MOXIFLOXACIN X 5 DAYS (N=143)	ERADICATION	20(14)	3 (2)
	PRESUMED ERADICATION	104 (73)	0 (0)
	ERADICATION WITH RELAPSE	0 (0)	2 (1)
	PERSISTENCE AT EOT	3 (2)	3 (2)
	PRESUMED PERSISTENCE	0 (0)	8 (6)
MOXIFLOXACIN X 10 DAYS (N=148)	ERADICATION	19 (13)	4 (3)
	PRESUMED ERADICATION	112 (76)	0 (0)
	ERADICATION WITH RELAPSE	2 (1)	2 (1)
	PERSISTENCE AT EOT	1(<1)	4 (3)
	PRESUMED PERSISTENCE	0	4 (3)
CLARITHROMYCIN (N=129)	ERADICATION	10 (8)	1 (<1)
	PRESUMED ERADICATION	99 (77)	0 (0)
	ERADICATION WITH RELAPSE	1 (<1)	3 (2)
	PERSISTENCE AT EOT	8 (6)	2 (1)
	PRESUMED PERSISTENCE	0 (0)	5 (4)

MO COMMENT: As noted in the table above, 124 of 127 patients (98%) in the moxifloxacin 5 day group who were graded as clinical successes had either eradication or presumed eradication of their organism. Of patients in whom sputum could be obtained at follow-up, 20 of 23 clinical successes had documented bacterial eradication. Only 3 of 16 (3 of 6 produeing sputum for culture) clinical failures in the moxifloxacin 5 day group had eradication of the causative pathogen. Another 3 of 127 (3 of 23 producing sputum for culture) patients had persistence of the infecting pathogen on follow-up culture but were graded as clinical successes. Similar numbers are noted above for the moxifloxacin 10 day group and the clarithromycin group. This conforms to the 1997 Guidance for Industry on ABECB, which recommends that studies demonstrate a general correlation between

clinical improvement and bacterial eradication (or suppression) in the clinically and microbiologically evaluable subset of patients.

Moxifloxacin at 400 mg orally for 5 days demonstrated clinical and bacteriologic efficacy in ABECB due to the organisms sought by the applicant in the draft label.

Safety

Total enrollment for this study was 936 patients. Of these, 316 were in the moxifloxacin 5 day arm, 307 were in the moxifloxacin 10 day arm, and 313 were in the clarithromycin arm. Ten patients were excluded from the valid for safety population (4 in the moxifloxacin 5 day, 5 in the moxifloxacin 10 day and 1 in the clarithromycin arms respectively). These patients were randomized but lost to follow-up prior to taking any medication. This resulted in a total safety database of 926 patients for this trial (312 in the moxifloxacin 5 day, 302 in the moxifloxacin 10 day, and 312 in the clarithromycin arms, respectively).

The following table summarizes the number of adverse events, drug-related events, and withdrawals from the study due to adverse related events in each treatment arm.

Table 20
Summary of Adverse Event Per Applicant
Population: Valid for Safety

	Moxifloxacin X 5 days (N=312) # patients (%)	Moxifloxacin X 10 days (N=302) # patients (%)	Clarithromycin X 10 days (N=312) # patients (%)
Any adverse event	131 (42%)	138 (46%)	149 (48%)
Any drug related AE	82 (26%)	91 (30%)	102 (33%)
Any serious AE	13 (4%)	15 (5%)	18 (6%)
Prematurely discontinued due to AE	13 (4%)	13 (4%)	21 (7%)

MO COMMENT: There were no significant differences between groups in total adverse events or drug-related adverse events.

The most common reason for discontinuation in the moxifloxacin 5 day group was nausea in 4 of the 13 patients (individual patients who discontinued therapy prematurely may have had multiple adverse events and the case report forms do not list the primary reason for discontinuation). Two patients had diarrhea and another had "loose stools". In the moxifloxacin 10 day group the most common reason for discontinuation was nervousness or dizziness (CNS side effects) in 6 of 13 and 4 patients with nausea and/or vomiting. Four patients in the clarithromycin group discontinued secondary to nausea and/or vomiting. Four more in the clarithromycin group discontinued due to nervousness or dizziness. There were no consistent patterns in serious adverse events in any group.

The following table delineates the numbers of patients with drug-related adverse events. According to the applicant, events were defined as drug-related if the investigator classified them as remotely, possibly, or probably related to drug, or if the investigator termed the relationship as not assessable.

Table 21
Incidence Rates of Drug-Related Adverse Events Occurring in at Least 2% of Any Treatment Group Per Applicant

Population: Valid for Safety

Adverse Event	BAY 12-8039 400 mg qd X 5 days (N=312) # patients (%)	BAY 12-8039 400 mg qd X 10 days (N=302) # patients (%)	Clarithromycin 500 mg bid X 10 days (N=312) # patients (%)
Headache	7 (2%)	7 (2%)	2 (<1%)
Asthenia	2 (<1%)	5 (2%)	3 (<1%)
Nausea	12 (4%)	23 (8%)	23 (7%)
Diarrhea	15 (5%)	18 (6%)	15 (5%)
Vomiting	3 (<1%)	8 (3%)	9 (3%)
Dyspepsia	7 (2%)	2 (<1%)	2 (<1%)
Flatulence	4 (1%)	2 (<1%)	5 (2%)
Dizziness	9 (3%)	14 (5%)	4 (1%)
Nervousness	2 (<1%)	4 (1%)	5 (2%)
Pruritus	3 (<1%)	2 (<1%)	5 (2%)
Taste perversion	6 (2%)	6 (2%)	26 (8%)

Overall, treatment-related adverse events were similar across the three treatment arms. There were more cases of dizziness in the moxifloxacin-treated patients than in the clarithromycin-treated group. The majority of the cases of dizziness were graded as mild. Of patients reporting dizziness only 1/9 in the 5 day moxifloxacin group and 1/14 in the moxifloxacin 10 day group were graded as severe. Of patients with any adverse event, two of four patients in the clarithromycin group reported severe dizziness. There were more cases of taste perversion in clarithromycin treated patients.

With regard to cardiovascular events, these were reported for 11 patients (4%) of the moxifloxacin 5 day group, 17 (6%) of the moxifloxacin 10 day group and 12 (4%) of the clarithromycin group. Of these, an abnormal ECG was reported for patient 912 (RMI) who was randomized to moxifloxacin for 5 days. The QT interval was prolonged from a baseline pre-therapy value of 0.4 sec to a during therapy value of 0.46 sec. There was no associated symptomatology and the patient was referred to her primary care physician for further evaluation. The investigator assessed the event as mild in severity and considered it possibly related to study drug administration. Study drug was not prematurely discontinued for this patient. The patient reported that on follow up with her primary care physician, further intervention was not considered necessary.

MO COMMENT: There were no reported cases of rash specifically associated with phototoxicity in the study database. Although moxifloxacin is known to prolong the QT interval, there were no cases of torsades de pointes or sudden death in this study. There were 3 cases of treatment emergent atrial fibrillation, all in moxifloxacin treated patients (2 in the 5 day arm and 1 in the 10 day arm). These

accounted for <1% of treated patients in these arms of the study. Patient 1508 was prematurely discontinued from the moxifloxacin 5 day arm with the onset of atrial fibrillation on day 2 of treatment. This patient was an 82 year old male with a prior history of congestive heart failure and hypertension. Patient 24 was a 72 year old female with a history of hypertension, cardiomegaly, and hypothyroidism who developed atrial fibrillation 3 weeks after completing study medication.

MO COMMENT: One patient discontinued therapy due to increased liver function tests. Patient 684 was a 34 year old female in the moxifloxacin 10 day arm of the study. She developed nausea after 6 doses of the drug and LFTs rose while the patient was on study drug (AST, twenty days prior to therapy was 58, three days into therapy was 163 and 22 days after start of therapy was 109 and ALT twenty days prior to therapy was 98, 3 days into therapy was 181 and 22 days into the study was 84). The patient was withdrawn from the study after 6 doses of study drug and LFTs returned to normal three weeks after cessation of therapy.

Deaths

There were two deaths during the study, one in the moxifloxacin 5 day arm and one in the clarithromycin arm.

Patient 548 was a 79-year-old male who died of a cardiac arrest 12 days after completing treatment with clarithromycin. This patient also had a prior history of bladder cell cancer. His chest x-ray was originally read as normal but was reread as consistent with a large mediastinal mass wrapped around the left main bronchus which was presumed to be a small cell neoplasm. He was withdrawn from the study and died suddenly at home of a presumed myocardial infarction.

Patient 994 was a 76 year old male with adenocarcinoma of the prostate who died of presumed acute pancreatitis 36 days after completing treatment with moxifloxacin. The pancreatitis was of unknown etiology and occurred after the patient had gone into renal failure at a nursing home. The diagnosis of pancreatitis was based on an elevated blood amylase level and there was no mention in the case report form of abdominal pain. As renal failure can result in elevated amylase levels in the absence of pancreatitis it is unclear whether this patient indeed had pancreatitis. The patient was treated with comfort measures only. No autopsy was performed. The investigator felt there was no relation of these events to study drug.

MO COMMENT: The MO reviewed these cases and found no relation to study drugs.

Clinical Laboratory Tests

Descriptive statistics for mean changes from baseline did not show much difference between treatment groups. The mean changes were extremely similar for the three groups for most of the laboratory variables analyzed. Other variables collected, such as minimum and maximum post-baseline values, also showed very similar results between groups.

Table 22
Incidence Rates of Laboratory Abnormalities Occurring at Any Time During the Study in at Least 5% of any Treatment Group Per Applicant

Lab Variable	BAY 12-8039 400 mg qd X 5 days	BAY 12-8039 400 mg qd X 10 days	Clarithromycin 500 mg bid X 10 days
High			
Hematocrit	8/284 (3%)	9/262 (3%)	15/269(6%)
MCH	12/277 (4%)	16/278 (6%)	5/270 (2%)
WBC	21/251 (8%)	12/237 (5%)	32/240 (13%)
Neutrophils (Bands)	1/5 (20%)	1/4 (25%)	1/5 (20%)
Neutrophils (segs)	33/239 (14%)	30/223 (13%)	36/233 (15%)
Neut (segs) absolute count	13/253 (5%)	15/239 (6%)	28/240 (12%)
Monocytes	9/295 (3%)	13/283 (5%)	13/291 (4%)
Eosinophils	25/281 (9%)	28/271 (10%)	18/279 (6%)
Platelets	15/296 (5%)	4/284 (1%)	9/294 (3%)
PT	30/261 (11%)	34/253 (13%)	23/266 (9%)
APTT	37/258 (14%)	33/243 (14%)	33/246 (13%)
Serum glucose	76/251 (30%)	54/246 (22%)	63/243 (26%)
Calcium	12/287 (4%)	11/274 (4%)	16/291 (5%)
Phosphorus, inorg	22/284 (8%)	18/277 (6%)	21/289 (7%)
Chloride	30/284 (11%)	37/283 (13%)	26/285 (9%)
Bicarbonate (HCO_3)	6/293 (2%)	14/278 (5%)	17/295 (6%)
C-reactive protein	21/180 (12%)	15/171 (9%)	17/168 (10%)
Cholesterol, total	43/164 (26%)	41/161 (25%)	26/158 (16%)
Triglycerides	47/244 (19%)	48/245 (20%)	40/229 (17%)
Theophylline	2/44 (5%)	1/49 (2%)	2/44 (5%)
Low			
Hematocrit	23/274 (8%)	19/272 (7%)	23/272 (8%)
Hemoglobin	25/274 (9%)	15/268 (6%)	28/269 (10%)
RBC	24/281 (9%)	21/274 (8%)	13/273 (5%)
MCHC	12/288 (4%)	14/273 (5%)	18/283 (6%)
WBC	9/298 (3%)	14/285 (5%)	9/294 (3%)
Neutrophils	8/298 (3%)	9/286 (3%)	15/295 (5%)
Lymphocytes	29/237 (12%)	28/221 (13%)	33/229 (14%)
Serum glucose	8/299 (3%)	14/289 (5%)	11/297 (4%)
Uric Acid	17/272 (6%)	20/254 (8%)	22/263 (8%)
Theophylline	10/39 (26%)	9/37 (24%)	6/34 (18%)
Urine Abnormalities*			
Appearance	55/209 (26%)	51/206 (25%)	53/215 (25%)
Protein, urine	42/222 (19%)	44/203 (22%)	47/222 (21%)
Ketones	12/282 (4%)	9/263 (3%)	18/271 (7%)
Blood, urine	15/271 (6%)	15/258 (6%)	23/270 (9%)
RBC, urine	14/275 (5%)	14/263 (5%)	19/272 (7%)
WBC, urine	12/276 (4%)	16/264 (6%)	13/274 (5%)

* Values were considered abnormal if the urine sample was not clear, yellow, free of glucose, protein, ketones, and occult blood, or if microscopic examination showed more than between 0 - 3 RBC/HPF or 0-5 WBC / HPF for male patients and 0 - 10 WBCs/HPF for female patients.

Several laboratory variables demonstrated differences between groups. The mean increase from pre-therapy to end of therapy in glucose was slightly higher in the two moxifloxacin groups (increase of 6.4 mg/dL in the moxifloxacin 5 day group and 4.4 mg/dL for the patients in the moxifloxacin 10 day group) than in the clarithromycin group (mean increase of 0.9 mg/dL). There were more abnormally high values in the clarithromycin group for hematocrit and absolute neutrophils. The clarithromycin group also had more patients with abnormal ketones and urine blood. The moxifloxacin groups had higher rates of abnormally high values for MCH, eosinophils, PT, chloride, and total cholesterol. The moxifloxacin groups also had more patients with abnormally low RBC.

MO COMMENT: A review of these laboratory changes by the MO did not reveal any changes that were considered clinically meaningful.

Medical Officer's Summary and Conclusions

Medical Officer's Summary

The MO agrees with the applicant that the treatment groups in this randomized trial were well matched with respect to demographics. The MO analyzed study drug clinical efficacy and found that moxifloxacin 400mg orally for 5 days was equivalent to both moxifloxacin 400mg for 10 days and the approved comparator drug, clarithromycin for 10 days (albeit at a higher dose for all patients), in overall clinical efficacy in ABECB. The clinical efficacy of both doses of moxifloxacin was also demonstrated in the subsets of patients in whom *Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae,* and *Moraxella catarrhalis* were the causative pathogens.

Clinical safety data suggests that dizziness is more common in moxifloxacin treated patients but does not appear to be treatment limiting. Nausea appeared more commonly in the 10 day moxifloxacin group than in the 5 day treatment group. There were no clinically significant differences in laboratory abnormalities between treatment groups. Ten days of treatment with moxifloxacin results in more side effects (dizziness and gastrointestinal disturbances) but did not clearly result in increased efficacy. Although the 10 day regimen of moxifloxacin appeared more clinically efficacious than 5 days of treatment in patients who received systemic steroid therapy, this was not a prospective analysis and was not confirmed in the subsequent studies to be discussed here.

Medical Officer's Conclusion

Moxifloxacin tablets at 400mg orally for 5 days is effective in the treatment of acute bacterial exacerbations of chronic bronchitis due to *Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae,* and *Moraxella catarrhalis.* Efficacy may be less in patients over the age of 65 or in patients receiving corticosteroid therapy.

Study No. D96-022

Prospective, randomized, double-blind comparison of the safety and efficacy of BAY 12-8039, 200mg once daily for 10 days versus BAY 12-8039, 400mg once daily for 10 Days versus cefuroxime axetil 500mg BID for 10 days for the treatment of patients with acute exacerbation of chronic bronchitis

Objectives

The trial was designed to compare the efficacy and safety of moxifloxacin 200 mg PO once a day for 10 days versus moxifloxacin 400 mg PO once a day for 10 days versus cefuroxime axetil 500 mg PO twice a day for 10 days for the treatment of adults with acute bacterial exacerbation of chronic bronchitis (ABECB). The primary efficacy objective of this study was to demonstrate equivalence in clinical resolution rates between moxifloxacin 200 mg daily or moxifloxacin 400 mg daily for 10 days and cefuroxime axetil 500 mg twice daily for 10 days

Design

This was a prospective, randomized, double-blind, controlled trial conducted at 53 centers in the United States and Canada between November 18, 1996 through June 4, 1998.

Eligible patients were randomly assigned to receive moxifloxacin 200mg once daily, moxifloxacin 400mg once daily, or cefuroxime axetil 500mg twice daily (BID). Each treatment regimen was to be administered for 10 days.

Patient visits to assess safety and efficacy were scheduled as in study D96-027, namely during therapy (days 3 to 5), at the end of therapy (0 to 6 days after the last dose of study drug), and at 2 follow-up visits (7-17 days and 18-31 days after the last dose of study drug)

Clinical effectiveness was evaluated on the basis of clinical response to study drug. Antimicrobial effectiveness was evaluated by means of clinical and bacteriological assessments before, during and after therapy (from sputum cultures). Blood and urine samples were collected for monitoring of safety laboratory parameters. Electrocardiograms (ECGs) were collected at the pre-therapy and during therapy time points.

MO COMMENT: Like study D96-027, this study is a controlled, multi-center trial that attempts to establish equivalence to an approved product in which the primary endpoint is clinical effectiveness. Analyses were conducted to confirm the general correlation between clinical success and bacterial eradication in the evaluable population.

Protocol Overview

- **Population, procedures**

Study D96-022 had the exact same design as study D96-027 (see above protocol overview). Study D96-022 differed from study D66-027 in the following ways:

1. Study D96-022 was conducted at sites in Canada as well as the United States.
2. The comparator used in study D96-022 was cefuroxime axetil.
3. All patients who received moxifloxacin in this study received the drug for 10 days.
4. Patients who received moxifloxacin received either 200mg or 400mg doses of the drug over the 10 day study period.

After the screening visit, patients were randomized to one of 3 treatment groups:1) moxifloxacin 200 mg once daily (one 200 mg capsule and one placebo capsule), 2) moxifloxacin 400mg once daily (one 400 mg capsule and one placebo capsule), 3) or cefuroxime axetil 500mg BID (two 250 mg capsules BID) in a 1:1:1 fashion.

MO COMMENT: Cefuroxime axetil is FDA-approved for the treatment of ABECB at 250 to 500mg PO BID for 10 days. All patients in this trial who received cefuroxime were treated with the higher dose.

To preserve blinding, patients randomized to treatment with moxifloxacin took 2 capsules BID. The odd doses consisted of an encapsulated tablet of moxifloxacin (either 200mg or 400mg) and a placebo capsule. The even doses consisted of 2 placebo capsules.

- **Inclusion/Exclusion Criteria of Note**

The inclusion and exclusion criteria for study D96-022 were identical to those in study D96-027.

MO COMMENT: As in trial D96-027, systemic steroid use was not an exclusion criterion in this trial. The numbers of patients on systemic steroids pre-randomization and the numbers of patients begun on steroids after randomization were equivalent across the three treatment arms. The overall prevalence of systemic steroid usage was 16%, 13% and 15% in the moxifloxacin 200mg, moxifloxacin 400mg, and cefuroxime arms. These numbers were slightly lower than those seen in trial D96-027.

MO COMMENT: The MO accepted the applicant's inclusion and exclusion criteria to be in accordance with the criteria outlined in the "Draft guidance for industry: acute bacterial exacerbations of chronic bronchitis-developing antimicrobial drugs for treatment".

Evaluability Criteria

The evaluability criteria in study D96-022 used to define the ***intention to treat*** population (valid for safety), the ***clinical efficacy evaluable*** population (CEE, valid for safety and efficacy), and the ***microbiologically and clinically evaluable*** populations (MCEE) were identical to those employed in study D96-027.

MO COMMENT: A separate intention-to-treat analysis was performed by the FDA biostatistical reviewer employing the same criteria as in study D96-027.

Endpoints (Clinical and Microbiologic)

The endpoints in trial D96-022 were identical to those on trial D96-027. According to the applicant, the primary endpoint was the clinical response at the 7- to 17-day follow-up time points (failures at end of therapy were carried forward). Secondary efficacy parameters included clinical response assessed at

each post-treatment time point including end of therapy, and 18 to 31 day follow-up and bacteriological responses assessed at each post-treatment time point.

Clinical and microbiologic outcomes were assigned in an identical manner to study D96-027. Again, adequate Gram's stains were not a requirement for evaluability in the MCEE population.

MO COMMENT: Given the similarity in trials D96-022 with trial D96-027, the MO reviewed a random 10% sample of patients for validation purposes. The same criteria were used by the MO, namely concentrating on the symptoms of 1) increased sputum production (necessary to be included in the trial) and 2) cough, 3)dyspnea, 4) sputum thickness/ purulence, and 5) fever. The MO agreed with investigator's assessment of the patient as a clinical success if these particular symptoms were improved from the pre-therapy visit, even if the symptoms were not back to the patient's pre-morbid baseline. If there was no change in any of these symptoms from the pre-therapy visit the MO graded the patient as a clinical failure regardless of the investigators assessment. A review of these patients showed no systematic errors and changes did not affect the overall efficacy analysis so the MO accepted the applicant's assessments of outcomes.

MO COMMENT: The MO accepted the applicant's endpoint criteria to be in accordance with the criteria outlined in the "Draft guidance for industry: acute bacterial exacerbations of chronic bronchitis-developing antimicrobial drugs for treatment".

Statistical Considerations

The applicant employed the recommendations of the 1992 Points to Consider document for determining statistical equivalence between the various doses of moxifloxacin and the comparator agent.

> "The protocol specified that to test this null hypothesis of inequivalence, a two-sided 95% confidence interval for the weighted difference between treatment groups would be constructed, using Mantel-Haenszel weights (weighting by center).. Success rates for all treatment groups were expected to be approximately 85%. Therefore, the experimental group would be shown to be equivalent to the control group if the lower limit of the two-sided 95% confidence interval for the difference between treatment groups was greater than -15%."

Study Results

Demographics, Evaluability

- **Demographics**

Table 23 is the applicant's listing of the demographic characteristics of the patients in the CEE (valid for efficacy) population. The demographics in the valid for safety population were quite similar.

MO COMMENT: There were no statistically significant differences in demographics observed between study arms. There was a trend toward lower weight among patients in the cefuroxime group.

Overall, the prevalence of prior medical conditions was very similar across the three groups for each of the most common conditions with these exceptions: more patients in the moxifloxacin 400 mg group had type II diabetes mellitus (11% versus 5% in the moxifloxacin 200 mg versus 6% in the cefuroxime axetil group); fewer patients in the moxifloxacin 200 mg group suffered from chronic ischemic heart disease (4% versus 7% in the BAY 12-8039 400 mg group versus 8% in the cefuroxime axetil group); more patients in the moxifloxacin 200 mg group had a history of peptic ulcer (6% versus 3% in each of the other two groups).

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BAY 12-8039/D96-022
BRONCHITIS

TABLE 23
DEMOGRAPHIC DATA PER APPLICANT

POPULATION: ALL PATIENTS VALID FOR EFFICACY (CEE POPULATION)

			BAY 12-8039 200MG (N=177)	BAY 12-8039 400MG (N=170)	CEFUROXIME AXETIL (N=185)	TOTAL (N=532)
SEX (P=0.405)	MALE	N (%)	79 (45)	85 (50)	95 (51)	259 (49)
	FEMALE	N (%)	98 (55)	85 (50)	90 (49)	273 (51)
RACE (P=0.779)	CAUCASIAN	N (%)	135 (76)	122 (72)	143 (77)	400 (75)
	BLACK	N (%)	39 (22)	44 (26)	40 (22)	123 (23)
	ASIAN	N (%)	1 (<1)	1 (<1)	1 (<1)	3 (<1)
	AMERICAN INDIAN	N (%)		1 (<1)	1 (<1)	2 (<1)
	HISPANIC	N (%)	2 (1)	1 (<1)		3 (<1)
	OTHER	N (%)		1 (<1)		1 (<1)
AGE AT ENROLLMENT (YRS) (P=0.911)		N	177	170	185	532
		MEAN	55.3	54.7	54.6	54.9
		STD	16.1	16.2	16.2	16.1
		MIN	18.0	19.0	18.0	18.0
		MEDIAN	57.0	56.0	55.0	56.0
		MAX	93.0	88.0	86.0	93.0
WEIGHT (KG) (P=0.060)		N	177	170	185	532
		MEAN	80.3	81.2	76.2	79.2
		STD	23.9	22.1	18.4	21.6
		MIN	38.6	42.3	41.8	38.6
		MEDIAN	75.5	77.0	72.7	75.0
		MAX	181.8	145.5	124.1	181.8
PATIENTS HOSPITALIZED		N (%)	6 (3)	6 (3)	9 (4)	21 (3)
INFECTION TYPE (P=0.325)	TYPE 1	N (%)	145 (65)	157 (70)	160 (68)	462 (68)
	TYPE 2	N (%)	72 (32)	64 (28)	73 (31)	209 (31)
	TYPE 3	N (%)	6 (3)	4 (2)	1 (<1)	11 (2)

P-VALUES FOR CATEGORICAL VARIABLES OBTAINED USING A CHI-SQUARE TEST.
P-VALUES FOR CONTINUOUS VARIABLES OBTAINED USING 1-WAY ANOVA.

- **Evaluability**

The applicant's tabulation of the numbers of patients at each center that were randomized, and the numbers of patients per center in the ITT population (valid for safety), the CEE population (per protocol group), and the MCEE population (microbiologically valid) are presented in Appendix 2.

> **MO COMMENT: Center 37 (the same principle investigator as site 13 in study D96-027) again had the highest enrollment in this study, accounting for 131/682 (19%) of randomized patients. 114/532 (21%) of the CEE population, and almost half, 112/235 (48%), of microbiologically evaluable patients.**

Table 23 shows the applicant's listing of the numbers of patients enrolled in the study, and the numbers of patients valid for the ITT (safety) and CEE (per protocol) analyses. This table also lists the reasons that patients were excluded from the various analyses.

> **MO COMMENT: The numbers of patients excluded from the study for various reasons was equivalent across the study arms. Unlike study D96-027, none of the randomized patients were excluded from the ITT (valid for safety) analysis. The most common reason for exclusion from the per protocol population was violation of the inclusion and exclusion criteria. There were far fewer patients in this trial in the "essential data missing or invalid" category than in study D96-027.**

BAY 12-8039/D96-022
BRONCHITIS

TABLE 23
PATIENT VALIDITY AND REASONS FOR EXCLUSIONS FROM ANALYSES PER APPLICANT
POPULATION: ALL RANDOMIZED PATIENTS

	MOXIFLOXACIN 200MG	MOXIFLOXACIN 400MG	CEFUROXIME AXETIL	TOTAL
PATIENTS RANDOMIZED	223	225	234	682
VALID FOR SAFETY ANALYSIS=ITT	223 (100%)	225 (100%)	234 (100%)	682 (100%)
EXCLUDED FROM PER-PROTOCOL EFF ANALYSIS	46	55	49	150
INCLUSION/EXCLUSION CRITERIA VIOLATION	17	16	12	45
PRE-THERAPY X-RAY OUTSIDE OF WINDOW	4	3	1	8
ELEVATED LABORATORY VALUES	3	2	1	6
NO PRE-THERAPY X-RAY	1	4	0	5
< REQUIRED CLINICAL SYMPTOMS FOR INC.	9	7	8	24
CHEST X-RAYS WITH INFILTRATE	0	0	1	1
SIGNIFICANT BRONCHIECTASIS	0	0	1	1
NON-COMPLIANCE WITH STUDY DRUG	6	5	2	13
INSUFFICIENT DURATION OF THERAPY	8	9	9	26
VIOLATION OF TIME SCHEDULE	3	3	2	8
ESSENTIAL DATA MISSING OR INVALID	4	9	12	25
LOST TO FOLLOW-UP	2	4	4	10
USE OF PROHIBITED CONCOMITANT MEDICATION	0	1	0	1
USE OF PROHIBITED POST-TX MEDICATION*	1	2	0	3
USE OF PROHIBITED PRE-TX MEDICATION#	1	1	0	
NO BASELINE CULTURE PERFORMED	4	5	8	17
IN PER-PROTOCOL EFFICACY ANALYSIS	177 (79%)	170 (76%)	185 (79%)	532 (78%)
EXCLUDED FROM MCEE ANALYSIS	100	97	100	297
NO BASELINE PATHOGEN ISOLATED	100	97	100	297
MICROBIOLOGICALLY VALID	77 (34%)	73 (32%)	85 (36%)	235 (34%)

*prohibited concomitant medications were astemizole, [redacted] other antimicrobials. All excluded patients received another antimicrobial for indications other than ABECB

#prohibited post-treatment medications were astemizole, [redacted] other antimicrobials. All patients excluded received another antimicrobial for indications other than lower respiratory tract infections

Efficacy

- **Clinical Efficacy**

The primary outcome endpoint was the clinical outcome in the CEE (per protocol, valid for efficacy) population at the post 1 (+7 to +17 day) follow-up visit. Table 18 shows the applicant's tabulations of clinical efficacy at the end of therapy, and post 1 visits with an overall assessment of clinical efficacy in the per protocol population (valid for efficacy).

TABLE 25
SUMMARY OF CLINICAL RESPONSES AT END OF THERAPY, FOLLOWUP, AND OVERALL RESPONSE PER APPLICANT
POPULATION: CEE PATIENTS (VALID FOR EFFICACY)

		MOXIFLOX. 200MG		MOXIFLOX. 400MG		CEFUROXIME AXETIL	
		N=177	%	N=170	%	N=185	%
END OF THERAPY (DAY 0 - +6)	CLINICAL CURE	160	90.4	154	90.6	161	87.0
	IMPROVEMENT	2	1.1	1	0.6	2	1.1
	CLINICAL RECURRENCE	1	0.6	1	0.6	1	0.5
	CLINICAL FAILURE	7	4.0	7	4.1	13	7.0
	INDETERMINATE	7	4.0	7	4.1	8	4.3
POST 1 (DAY +7 - +17)	CONTINUED CLINICAL CURE	160	90.4	154	90.6	160	86.5
	CLINICAL CURE	1	0.6	3	1.8	1	0.5
	CLINICAL RECURRENCE	7	4.0	5	2.9	9	4.9
	CLINICAL FAILURE	1	0.6	.	.	1	0.5
	INDETERMINATE	8	4.5	8	4.7	14	7.6
OVERALL RESPONSE	RESOLUTION	161	91.0	157	92.4	161	87.0
	CLINICAL FAILURE	16	9.0	13	7.6	24	13.0
CLINICAL SUCCESS RATES							
END OF THERAPY		162/170 (95%)		155/163 (95%)		163/177 (92%)	
POST 1 FOLLOW-UP		161/169 (95%)		157/162 (97%)		161/171 (94%)	
OVERALL		161/177 (91%)		157/170 (92.4%)		161/185 (87%)	

MO COMMENT: Again, the end of therapy and the post 1 (day +7 to +17 day) follow-up success rates use the numbers of patients who were evaluable at those visits only as the denominator. The overall success rates use the denominator of all patients randomized who were evaluable at any visit in the per protocol analysis. This includes clinical failures at the end of therapy visit that were carried forward and included in the overall outcome as failures.

The center-weighted 95% confidence interval around the difference in efficacy rates for the per protocol population between patients treated with moxifloxacin 400mg orally for 10 days (157/170, 92.4%) versus cefuroxime axetil for 10 days (161/185, 87%) was (-1.6%, 11.1%). The center-weighted 95% confidence interval around the difference in efficacy rates between patients treated with moxifloxacin 200mg orally for 10 days (161/177, 91%) versus cefuroxime axetil for 10 days was (-2.5%, 10.8%). The center-weighted 95% confidence interval around the difference in efficacy rates between patients treated with moxifloxacin 200mg for 10 days versus moxifloxacin 400mg for 10 days was (-7.3%, 4.7%). These rates meet the statistical requirement needed to demonstrate statistical similarity to an approved comparator as suggested in the 1992 Points to Consider document as the lower bound of the confidence intervals is less than 10% for all comparisons in trials in which the efficacy rates are ≥90%.

Table 26

Clinical Success Rates at Post 1 Visit Per Applicant

Population: Per Protocol (Valid for Efficacy)

Study Group	Clinical Success Rates N(%)*	95% Confidence Intervals*
Moxifloxacin 200mg x 10 days	161/177 (91%)	(-1.6%,11.1%)
Moxifloxacin 400mg x 10 days	157/170 (92.4%)	(-2.5%, 10.8%)
Cefuroxime axetil x 10 days	161/185 (87%)	-

* the CI or each moxifloxacin group were calculated compared to the clarithromycin group

An intention-to-treat analysis of patients in the valid-for-safety population was performed by the FDA biostatistics reviewer. This calculation employed the criteria that a) cures and improvements were combined as successes of treatment; b) failures and indeterminates were combined and treated as failures; c) patients who used alternative systemic antibiotics for any reason were treated as failures regardless of the actual clinical outcomes; d) patients lost to follow-up before the primary post 1 therapy visit were treated as failures. The following table provides the efficacy rates in the intention-to-treat population at the post 2 (+18 to +31days) visit. The post 2 visit was chosen to give the most conservative estimate of efficacy.

Table 27

Clinical Success Rates at Post 2 Visit Per FDA Biostatistics Reviewer

Population: Intention to Treat (Valid for Safety)

Study Group	Clinical Success Rates N(%)#	95% Confidence Intervals*
Moxifloxacin 200mg x 10 days	167/222 (75.2%)	(-9.4, 9.7)
Moxifloxacin 400mg x 10 days	168/221 (76.0%)	(-8.6, 10.4)
Cefuroxime axetil x 10 days	172/229 (75.1%)	-

* the CI or each moxifloxacin group were calculated compared to clarithromycin

#denominators for this calculation are different than applicant's; see FDA biostatistics review

No patient in the 200 mg moxifloxacin group developed pneumonia, while 2 patients (patients 339 and 349) in the moxifloxacin 400 mg group developed 3 episodes of pneumonia (patient 339 had recurrent pneumonia). Patient 349 developed pneumonia on day 5 of study but was non-complaint with study medication. Patient 339 was a 44 year old male with a history of sarcoidosis. His initial sputum isolate was *Pseudomonas aeruginosa* but this was eradicated by the end of therapy. He was graded a clinical failure on day 11 of study, admitted to the hospital and begun on single drug therapy with ceftazidime and discharged to home on oral ciprofloxacin, although the case report form states that his pneumonia was not resolved. The CRF does not state whether this refers to the infiltrate or clinical symptoms, but in any case the patient was readmitted on day 19 of study for intravenous treatment with tobramycin and ceftazidime for "recurrent pneumonia". The sputum on readmission grew normal oral flora. The CRF does not state if the patient was readmitted due to worsening symptoms or for failure of the infiltrate to resolve. The patient was deemed a clinical cure from pneumonia at the end of the second admission, 10 days after the readmission (day 29 of study). Two patients in the cefuroxime axetil group (patients 69 and 606) developed pneumonia on days 12 and 19 of the study.

- **Special Populations**

- *Geriatric Populations: Efficacy*

The efficacy of moxifloxacin 200mg for 10 days in patients greater than age 65 was less than that in the overall CEE population, but equivalent to the cefuroxime comparator in this trial (49/56 or 87.5% clinical successes in the moxifloxacin 200mg group and 49/57 or 86% in the cefuroxime group). The efficacy in patients over age 65 in the moxifloxacin 400mg group was higher than in either of the other arms with 45/47 or 95.7% of patients rated as clinical successes.

Table 28
Clinical Success Rates at Post 1 Visit in Patients by Age Group Per Applicant
Population: Patients Valid for Efficacy (Per Protocol)

D96-022	Moxifloxacin 200mg	Moxifloxacin 400mg	Cefuroxime axetil	P-Value #
< 65	110/119 (92%)	108/119 (91%)	108/124 (87%)	0.364
65-74	35/40 (88%)	29/30 (97%)	34/39 (87%)	0.166
> 74	16/18 (89%)	20/21 (95%)	19/22 (86%)	0.317

#: P-Value for comparison of moxifloxacin 400 mg and clarithromycin

- *Concomitant Steroid Use: Efficacy*

When systemic steroids were used concurrently, patients had success rates of 92% for the moxifloxacin 200 mg treatment group which was comparable with the overall clinical success rate of 91% for the patients in the same dose regimen group not receiving systemic steroid therapy. The respective success rates of 86% and 79% for the moxifloxacin 400 mg and cefuroxime axetil treatment group treated concomitantly with systemic steroids were in contrast to the respective rates of 93% and 89% for the patients who did not receive systemic steroids in each of these groups.

Table 29
Clinical Efficacy in Patients Treated With and Without Systemic Steroids
CEE Population: Per Applicant

D96-022	Moxifloxacin 200 mg	Moxifloxacin 400 mg	Cefuroxime axetil
Patients with Steroids	23/25 (92%)	18/21 (86%)	22/28 (79%)
Patients Without Steroids	138/152 (91%)	139/149 (93%)	139/157 (89%)

- *Clinical Response in Patients with Adequate Sputum Gram's Stains*

The clinical response of patients with adequate sputum Gram's stain (>25 WBCs and <10 epithelial cells per high power field) was compared to the clinical response in patients with inadequate Gram's stains.

Table 30
Clinical Response at Post 1 Visit by Gram's Stain Results
MCEE Population: Per Applicant

	Moxifloxacin 400 mg x 10 days	Cefuroxime 500 mg BID x 10 days
Gram Stain Missing	3/3 (100%)	3/4 (75%)
WBC < 25, Epi <= 10	8/9 (89%)	8/9 (89%)
WBC < 25, Epi > 10	4/4 (100%)	2/2 (100%)
WBC >= 25, Epi <= 10	35/38 (92%)	37/47 (79%)
WBC >= 25, Epi > 10	18/19 (95%)	23/23 (100%)

MO COMMENT: In the MCEE population, clinical sucess rates were similar across groups among patients who had adequate and inadequate Gram's stains considering the small numbers of patients in the groups with <25 WBCs

- **Microbiologic Efficacy**

Microbiologic efficacy was expressed as the proportion of the microbiologic and clinical efficacy evaluable population (MCEE) that was clinically cured at the post 1 (day +7 to +17) visit

TABLE 31
SUMMARY OF BACTERIOLOGICAL RESPONSES AT EOT AND POST 1 FOLLOWUP
PER APPLICANT
POPULATION: MCEE PATIENTS (VALID FOR EFFICACY)

		MOXIFLOXACIN 200MG		MOXIFLOXACIN 400MG		CEFUROXIME AXETIL	
		N=77	%	N=73	%	N=85	%
END OF THERAPY (DAY 0 - +6)	ERADICATION	13	17	12	16	14	16
	PRESUMED ERADICATION	58	75	56	77	60	71
	PERSISTENCE	4	5	1	1	6	7
	PRESUMED PERSISTENCE	.	.	1	1	2	2
	INDETERMINATE	2	3	3	4	3	4
POST 1 (DAY +7 - +17)	ERADICATION	10	13	8	11	6	7
	PRESUMED ERADICATION	62	81	59	81	66	78
	ERADICATION W/RELAPSE	1	1	3	4	.	.
	PERSISTENCE AT EOT	4	5	1	1	6	7
	PRESUMED PERSISTENCE	.	.	2	3	7	8
MICROBIOLOGIC SUCCESS RATES							
END OF THERAPY		71/77 (92%)		68/73 (93%)		74/85 (87%)	
POST 1 VISIT		72/77 (94%)		67/73 (92%)		72/85 (85%)	

The following table enumerates the numbers of superinfections, reinfections, and relapsing organisms as defined in the protocol.

TABLE 32
PATIENTS WITH SUPERINFECTING, REINFECTING, AND RELAPSING ORGANISMS

	BAY 12-8039 200 mg # organisms	BAY 12-8039 400 mg # organisms	Cefuroxime Axetil 500 mg BID # organisms
Superinfecting	1	4	10
Reinfecting	3	4	6
Relapsing	1	3	0

The single recurring organism in the moxifloxacin 200 mg group and one of the four moxifloxacin 400 mg reinfections were *Streptococcus pneumoniae*. *Haemophilus influenzae* or *H. parainfluenzae* accounted for three of the ten cefuroxime axetil superinfections and three of the six cefuroxime axetil reinfections.

In the following table, the 95% confidence interval around the difference in efficacy rates between

patients treated with moxifloxacin 400mg orally for 10 days versus cefuroxime axetil for 10 days was (-4.1%, 18.3%). The 95% confidence interval around the difference in efficacy rates between patients treated with moxifloxacin 200mg orally for 10 days versus cefuroxime axetil for 10 days was (-1.9%, 19.5%). The 95% confidence interval around the difference in efficacy rates between patients treated with moxifloxacin 200mg for 10 days versus moxifloxacin 400mg for 10 days was (-8.0, 11.4). Center weighting was not done on these intervals as there were too many centers in which patients were combined due to their enrolling too few microbiologically evaluable patients individually. These rates meet the statistical requirement needed to demonstrate statistical similarity to an approved comparator as suggested in the 1992 Points to Consider document as the lower bound of the confidence intervals is less than 10% for all comparisons in trials in which the efficacy rates are ≥90%.

Table 33

Microbiologic Success Rates at Post 1 Visit Per Applicant

Population: Per Protocol (Valid for Efficacy, MCEE)

Study Group	Clinical Success Rates N(%)*	95% Confidence Intervals*
Moxifloxacin 200mg x 10 days	72/77 (94%)	(-1.9%, 19.5%)
Moxifloxacin 400mg x 10 days	67/73 (92%)	(-4.1%, 18.3%)
Cefuroxime axetil x 10 days	72/85 (85%)	-

* the CI or each moxifloxacin group were calculated compared to the clarithromycin group

The eradication rates per organisms for the major pathogens in ABECB sought in the label are presented in the following table:

Table 34

Eradication Rates* at Follow-up by Organism Per Applicant

MCEE Population

	Moxifloxacin 200 mg # eradicated/ isolates (%)	Moxifloxacin 400 mg # eradicated/ isolates (%)	Cefuroxime Axetil 500 mg BID # eradicated/ isolates (%)
Staphylococcus aureus	7/7 (100)	8/9 (89)	8/9 (89)
Streptococcus pneumoniae	8/9 (89)	5/5 (100)	8/9 (89)
Klebsiella pneumoniae	9/11 (82)	10/11 (91)	16/16 (100)
Moraxella catarrhalis	10/10 (100)	7/8 (88)	7/10 (70)
Haemophilus influenzae	24/25 (96)	18/19 (95)	22/27 (81)
Haemophilus parainfluenzae	15/15 (100)	17/17 (100)	16/18 (89)

*eradication and presumed eradications

- *Microbiologic Efficacy in Patients with Adequate Sputa*

The bacteriologic response based on the presence or absence of an adequate sputum Gram's stain is presented in the following table.

Table 35
Bacteriologic Response at Post 1 Visit by Gram's Stain Results
MCEE Population: Per Applicant

	Moxifloxacin 400 mg x 10 days	**Cefuroxime 500 mg BID x 10 days**
Gram Stain Missing	3/3 (100%)	4/4 (100%)
WBC < 25, Epi<= 10	7/9 (78%)	6/9 (67%)
WBC < 25, Epi > 10	4/4 (100%)	2/2 (100%)
WBC >= 25, Epi <= 10	35/38 (92%)	38/47 (81%)
WBC >= 25, Epi > 10	18/19 (95%)	23/23 (100%)

MO COMMENT: In the MCEE population, eradication rates were similar across groups among patients who had adequate and inadequate Gram's stains.

There were 5 patients in the moxifloxacin 200 gm group, 6 in the moxifloxacin 400 mg group and 6 in the cefuroxime axetil group in whom *Pseudomonas aeruginosa* was the causative pathogen. In the 200 mg moxifloxacin group 4/5 were presumed eradicated and 1/5 was presumed persistent. In the moxifloxacin 400 mg group, 1/6 was eradicated, 3/6 were presumed eradicated, and 1/6 was persistent. In the cefuroxime axetil group, 5/6 were presumed eradicated and 1/6 was persistent.

Table 36 displays bacteriological response at follow-up by overall clinical response for the ITT (valid for safety) population. In general, patients with unfavorable bacteriological responses had unfavorable clinical responses and patients with favorable bacteriological responses had favorable clinical responses. By definition, all cases of presumed eradication correlated with resolution and all cases of presumed persistence correlated with failure. For bacteriological responses of eradication, 9/10 of moxifloxacin 200 mg patients had clinical resolution, as compared to 6/8 for moxifloxacin 400 mg patients and 5/6 of cefuroxime axetil patients. Persistence at the end of therapy was associated with clinical resolution in 2/4 of moxifloxacin 200 mg patients, none of moxifloxacin 400 mg patients, and 2/6 of cefuroxime axetil patients.