TABLE 36
SUMMARY OF BACTERIOLOGICAL RESPONSE AT FOLLOWUP
BY OVERALL CLINICAL RESPONSE PER APPLICANT
POPULATION: ITT PATIENTS (VALID FOR EFFICACY)

		CLINICAL SUCCESS	CLINICAL FAILURE
		N (%)	N (%)
MOXIFLOXACIN 200MG (N=77)	ERADICATION	9 (12)	1 (1)
	PRESUMED ERADICATION	62 (80)	0 (0)
	ERADICATION W/RELAPSE	0 (0)	1 (1)
	PERSISTENCE AT EOT	2 (3)	2 (3)
MOXIFLOXACIN 400MG (N=73)	ERADICATION	6 (8)	2 (3)
	PRESUMED ERADICATION	59 (81)	0 (0)
	ERADICATION W/RELAPSE	3 (4)	0 (0)
	PERSISTENCE AT EOT	0 (0)	1 (1)
	PRESUMED PERSISTENCE	0 (0)	2 (3)
CEFUROXIME AXETIL (N=85)	ERADICATION	5 (6)	1 (1)
	PRESUMED ERADICATION	66 (78)	0 (0)
	PERSISTENCE AT EOT	2 (2)	4 (5)
	PRESUMED PERSISTENCE	0 (0)	7 (8)

MO COMMENT: The results above conform 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 dosed at either 200mg or 400mg orally for 10 days demonstrated clinical and bacteriological efficacy due to organisms sought by the applicant in the draft label.

Safety

All but one of 682 randomized patients had documentation of receipt of at least two capsules of study medication and were therefore included in the valid for safety population. The one patient who was lost to follow-up without information of whether she received any study medication (patient number 2016)

reported an adverse event and was included in the valid for safety population for this reason. The distribution of the patients considered valid for safety was therefore the same as for all randomized patients; 223 in the moxifloxacin 200 mg group, 225 in the moxifloxacin 400 mg group and 234 in the cefuroxime axetil group.

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

TABLE 37
SUMMARY OF ADVERSE EVENTS PER APPLICANT
POPULATION: VALID FOR SAFETY

	BAY 12-8039 200 mg (N=223) #patients (%)	BAY 12-8039 400 mg (N=225) # patients (%)	Cefuroxime Axetil 500 mg BID (N=234) # patients (%)
Died	0	0	0
Any adverse event	100 (45)	102 (45)	111 (47)
Any drug related AE	55(25)	66 (29)	64 (27)
Any serious AE	5 (2)	6 (3)	8 (3)
Prematurely discontinued due to AE	11 (5)	9 (4)	9 (4)

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

The following table delineates the numbers of patients with drug related adverse events. 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 38
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 200 mg (N=223) #patients (%)	BAY 12-8039 400 mg (N=225) # patients (%)	Cefuroxime Axetil 500 mg BID (N=234) # patients (%)
Headache	4 (2)	5 (2)	7 (3)
Abdominal pain	5 (2)	3 (1)	5 (2)
Diarrhea	17 (8)	17 (8)	13 (6)
Nausea	6 (3)	17 (8)	11 (5)
Dyspepsia	6 (3)	3 (1)	6 (3)
Dry mouth	2(<1)	5 (2)	1 (<1)
Constipation	2 (<1)	5 (2)	1 (<1)
Flatulence	1 (<1)	6 (3)	1 (<1)
Vomiting	2 (<1)	5 (2)	3 (1)
Dizziness	7 (3)	8 (4)	6 (3)
Insomnia	1 (<1)	4 (2)	3 (1)
Rash	6 (3)	2 (<1)	2 (<1)
Taste perversion	1 (<1)	2 (<1)	5 (2)
Vaginal moniliasis	3 (1)	1 (<1)	6 (3)

Overall, the incidence rates of all adverse events were very similar across the three treatment groups for most body systems and individual events. The body system most commonly affected by adverse events in all treatment groups was the digestive system (experienced by 25% of moxifloxacin 400 mg patients and 20% of patients in the moxifloxacin 200mg and cefuroxime axetil treatment groups). The higher incidence of reporting of these events by the moxifloxacin 400 mg-treated patients was primarily due to more of these patients experiencing nausea, flatulence or constipation. In the moxifloxacin 400 mg-treated patients 23% of patients who discontinued study medication treatment prematurely due to nausea was identical to the 23% adverse event related discontinuation rate for patients who reported nausea in the cefuroxime axetil group, and lower than the adverse event related discontinuation rate of 29% amongst moxifloxacin 200 mg-treated patients who reported nausea. None of the patients in the 200 mg moxifloxacin group and only one of the patients in the moxifloxacin 400 mg group had nausea that was considered severe. Diarrhea was more common in the moxifloxacin groups than in the cefuroxime axetil group, but did not seem to be dose-related. None of the cases of diarrhea in any group were considered severe. There were a higher percentage of cefuroxime axetil-treated patients with symptoms of taste perversion, or vaginal moniliasis than in moxifloxacin groups. There were no consistent patterns among the patients with serious adverse events in any patient group.

MO COMMENT: There were no rashes due to phototoxicity reported in the database. There were no episodes of atrial fibrillation reported and no cases of torsades de pointes or sudden death. The one case of elevated liver enzymes (to 100% of baseline) was in a patient in the cefuroxime arm of the trial.

Deaths

There were no deaths in this trial.

Clinical Laboratory Tests

Descriptive statistics for mean changes from baseline did not show much difference between treatment groups. Minimum and maximum post-baseline values also showed very similar results between groups. Rates for specific abnormalities were generally similar across groups with several exceptions. High and low abnormalities of serum glucose were most common in the moxifloxacin 400 mg group, but notably there were more diabetics in this group than in the other two treatment groups. Prothrombin time prolongation, low hematocrit, or low hemoglobin was present in more moxifloxacin 400 mg-treated patients, but this did not result in any reports of abnormal bleeding.

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Table 39

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

Lab Variable	BAY 12-8039 200 mg # incidences/ # patients (%)	BAY 12-8039 400 mg # incidences/ # patients (%)	Cefuroxime Axetil 500 mg BID # incidences/ # patients (%)
High			
MCH	9/192 (5)	11/186 (6)	7/200 (4)
WBC	15/190 (8)	10/170 (6)	16/191 (8)
Neutrophils (segs)	21/185 (11)	14/181 (8)	21/189 (11)
Neut (segs) absolute count	16/191 (8)	9/176 (5)	14/198 (7)
Monocytes	5/212 (2)	9/202 (4)	12/214 (6)
Eosinophils	14/198 (7)	21/190 (11)	11/206 (5)
PT	20/178 (11)	29/182 (16)	16/182 (9)
APTT	18/179 (10)	21/182 (12)	17/184 (9)
Serum glucose	23/185 (12)	40/177 (23)	35/189 (19)
Phosphorus, inorg	15/204 (7)	13/202 (6)	21/207 (10)
Chloride	20/207 (10)	28/207 (14)	16/208 (8)
Bicarbonate (HCO3)	8/209 (4)	5/201 (2)	10/215 (5)
C-reactive protein	12/150 (8)	22/137 (16)	16/147 (11)
SGPT/ALT	6/205 (3)	9/202 (4)	13/208 (6)
GGT	0/174 (0)	7/175 (4)	10/182 (5)
Cholesterol, total	39/115 (34)	23/106 (22)	30/108 (28)
Triglycerides	33/170 (19)	36/166 (22)	32/170 (19)
Low			
Hematocrit	14/199 (7)	18/196 (9)	12/201 (6)
Hemoglobin	10/193 (5)	19/192 (10)	13/200 (7)
RBC	14/200 (7)	13/191 (7)	15/203 (7)
MCHC	11/201 (5)	10/193 (5)	11/209 (5)
Lymphocytes	20/181 (11)	14/174 (8)	17/183 (9)
Serum glucose	7/211 (3)	10/206 (5)	4/212 (2)
Uric acid	9/189 (5)	11/187 (6)	15/190 (8)
BUN	11/210 (5)	5/202 (2)	10/213 (5)
Amylase	3/209 (1)	9/200 (5)	7/207 (3)
Theophylline	5/ 11 (45)	3/ 18 (17)	0/ 7 (0)
Urine Abnormalities*			
Appearance, urine	27/142 (19)	28/147 (19)	58/176 (33)
Protein, urine	34/163 (21)	21/160 (13)	34/179 (19)
Ketones	7/201 (3)	10/197 (5)	11/205 (5)
Blood, urine	21/193 (11)	9/182 (5)	13/195 (7)
RBC, urine	16/195 (8)	9/183 (5)	13/197 (7)
WBC, urine	14/195 (7)	7/187 (4)	10/204 (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.

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

Medical Officer's Summary/Conclusions

Medical Officer's Summary

The MO agrees 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 200mg orally or 400mg orally dosed for 10 days were equivalent to the approved comparator drug, cefuroxime axetil at 500mg BID for 10 days, in overall clinical efficacy in ABECB. The two doses of moxifloxacin were also equivalent to each other in efficacy. The clinical efficacy of both doses of moxifloxacin was alsc 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.

The efficacy rate in patients over age 65 in the 200mg moxifloxacin group was lower than the overall efficacy rate but as equivalent to that in the cefuroxime group. The efficacy in the 400mg moxifloxacin group in patients over age 65 was actually higher than the overall efficacy. Patients receiving concomitant corticosteroids had efficacy rates lower than the overall study population but were equivalent between the study arms.

Clinical safety data suggest that nausea and diarrhea were more common in moxifloxacin-treated patients but does not appear to be treatment limiting. There were no clinically significant differences in laboratory abnormalities between treatment groups.

Medical Officer's Conclusion

Moxifloxacin tablets at 200mg or 400mg orally for 10 days is effective in the treatment of mild to moderate acute bacterial exacerbations of chronic bronchitis due to *Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae,* and *Moraxella catarrhalis.*

Study No. 0124

A multi-national, multi-center, double-blind study of BAY 12-8039 oral tablets compared to clarithromycin oral tablets in the treatment of acute exacerbations of chronic bronchitis

Objectives

This trial was designed to compare the efficacy and safety of moxifloxacin 400 mg PO once a day for 5 days versus clarithromycin 500 mg PO, BID for 7 days for the treatment of acute exacerbation of chronic bronchitis (AECB). The primary efficacy objective of this study was to demonstrate equivalence in clinical resolution rates between moxifloxacin 400 mg daily for 5 days and clarithromycin 500 mg twice daily for 7 days.

Design

This was a prospective, randomized, double-blinded, multi-center, multi-national study conducted from November 22, 1996 through June 8, 1997. A total of 85 clinical centers enrolled patients into the study. Study centers (with numbers of sites in parentheses) were located in the following 8 countries: Austria (2), France (26), Germany (13), Greece (3), Netherlands (6), Spain (4), Switzerland (1), and United Kingdom (30).

Patients were randomized to one of two study groups in a 1:1 fashion: 1) moxifloxacin 400mg PO once daily for 5 days plus placebo, or 2) clarithromycin 500mg PO BiD for 7 days. Patients randomized to moxifloxacin received 1 active drug capsule and 1 placebo capsule in the morning and 2 placebo capsules in the evening for 5 days, and 2 placebo capsules each in the morning and the evening for another 2 days. Patients in the clarithromycin arm received two clarithromycin 250 mg encapsulated tablets (i.e. 500 mg), administered orally twice daily. Each patient received study medication (active plus placebo capsules) for a total of 7 days. . Patients were evaluated at baseline and immediately following (day 7), at 1 week (day 14) and 3-4 weeks (day 28-35) after completion of therapy. In the Netherlands, Spain and Greece, local laboratories were used. In Germany, Austria, Switzerland, the United Kingdom and France, central laboratory facilities were utilized.

MO COMMENT: Clarithromycin is FDA-approved for ABECB due to *Streptococcus pneumoniae* and *Moraxella catarrhalis* at 250mg 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 the clarithromycin arm of this trial received the higher dose of clarithromycin regardless of the etiologic organism.

Protocol Overview

- **Population, procedures**

Patients enrolled were adult patients aged 18 years or older with underlying chronic bronchitis as defined by a cough productive of sputum, for at least three consecutive months, for more than two consecutive years.

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

"Pretreatment visit"	baseline prior to therapy, actual window from day –3 (inclusive) to start of drug therapy
"Day 7 visit"	end of therapy, no window applicable
"Day 14 visit"	first follow-up visit, corresponds to +7 days after end of therapy; actual window from +5 days to +12 days after the end of therapy (both days inclusive)
"Day 28-35 visit"	second follow-up visit, +21 to +28 days after end of therapy

Efficacy was evaluated by means of clinical assessments before and after therapy. Patients' respiratory function (FEV_1) was measured at all assessment visits. Sputum sampling (for Gram staining, culture and susceptibility testing of any isolated bacterial organism) was attempted at all visits even if patients were asymptomatic, in order to assess bacteriological efficacy. Safety of drug treatment was monitored by careful clinical observation of adverse events from the start of treatment (day 1) until the day 14 visit. All adverse events were to be followed until resolved. Serious adverse events were monitored until the day 28-35 visit. Serum biochemistry and haematology tests and urinalysis were to be performed before and immediately after treatment (day 7). In case of abnormalities, these were to be followed up at the next patient visits (day 14 and day 28-35) until normalised. Patients at study centers in France also had ECGs performed at baseline before administration of study drug and repeated at day 5 during therapy approximately 1.5 to 2.0 hours following the dose of drug.

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

In order to be eligible for study entry, patients had to present with symptoms of an acute exacerbation of their underlying chronic bronchitis defined by at least 2 of the following 3 signs/symptoms indicative of ABECB:

1. Purulent/mucopurulent sputum.
2. Increased dyspnea.
3. Increased sputum volume

The above criteria limited enrollment to only patients with moderate to severe ABECB according to the Anthonisen criteria (Anthonisen type 1 or 2, see definitions in trial D96-027 above[3]). However, patients ill enough to require parenteral therapy were not enrolled.

  - **Exclusion criteria**

a) History of allergy to carboxyquinolone derivatives (e.g. ciprofloxacin, ofloxacin, norfloxacin or nalidixic acid) or macrolides.

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

b) Pregnant or lactating women, or women using unreliable contraception. A urine pregnancy test was to be performed on all women of childbearing potential prior to enrolment into the study and was to be confirmed by a serum test.
c) History of severe cardiac failure (class IV of the NYHA classification).
d) Severe respiratory tract infection requiring parenteral antimicrobial therapy or mechanical ventilatory support.
e) Clinical diagnosis of pneumonia (radiographic diagnosis not mandatory since not standard practice in this setting)
f) Known significant liver impairment with baseline ALT or AST and/or total bilirubin greater than three times the upper limit of normal.
g) Known significant renal impairment with baseline serum creatinine greater than 3.0 mg/dl (> 265 µmol/L) or creatinine clearance <30 ml/min/1.73 m^2.
h) Previous history of tendinopathy associated with fluoroquinolones.
i) Requirement for a systemic concomitant antibacterial agent.
j) Previous therapy with an effective systemic antibiotic within 48 hours of screening.
k) Neutropenia (neutrophil count less than 1000/mm^3) due to malignancy or chemotherapy.
l) Patients known to have AIDS (CD4 count less than 200/mm^3); however, HIV testing was not required for this study.
m) Active pulmonary tuberculosis, cystic fibrosis, or significant bronchiectasis
n) Patients who had previously been enrolled into this study.
o) Patients who had participated in a clinical trial 3 months before enrollment into this study.

MO COMMENT: The inclusion criteria in this trial were not as strict as in trials D96-027 and D96-022 in that fewer symptoms were required for inclusion. The exclusion criteria in this trial are similar to those employed in the other two trials. The major differences are that there was no requirement for an initial chest x-ray in this trial to rule out pneumonia and patients were allowed to receive up to 48 hours of prior antimicrobial therapy as opposed to a maximum of 24 hours of prior therapy in the previous trials. Patient 126 in the moxifloxacin group was diagnosed with pneumonia after one day of therapy. This patient died one day later (day 2 of study).

MO COMMENT: Concomitant systemic steroid administration was not an exclusion criterion in this trial. In the moxifloxacin group 160/322 (50%) evaluable patients in the CEE population received concomitant steroids. In the clarithromycin group, 128/327 (39%) evaluable patients in the CEE population were treated with steroids. The rate of steroid usage in this trial was higher than in trials D96-027 and D96-022. This may reflect differences in medical practice between the U.S and non-U.S. sites.

Evaluability Criteria

1) The ***intention-to-treat population*** (ITT) included patients who were randomised and received at least 1 dose of study drug. The ITT population equalled the population valid for the safety analysis.

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

e) cures and improvements were combined as successes of treatment

f) failures and indeterminates were combined and treated as failures

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

h) 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. The MCEE population was defined as the subset of the CEE population with positive sputum cultures for a respiratory pathogen at baseline. To be microbiologically evaluable a patient must have had at least 1 causative organism identified in an appropriate pre-treatment culture and an appropriate post-treatment bacteriological evaluation (i.e. positive or negative culture or "no material to culture") was available.

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

a) The diagnosis of ABECB was to be fully documented.

b) The study drug was to be administered for a minimum of 3 full days (in case of clinical failure) or 5 full days (in case of clinical success).

c) No other systemic antibacterial agent was to be administered concomitantly with the study drug unless the patient was a treatment failure.

d) Documented compliance with ≥80% of study medication administered.

e) No protocol violations influencing study drug treatment efficacy.

f) The random code was not broken.

g) No essential data (e.g. primary efficacy variable) missing or "indeterminate" which could not be recovered

MO COMMENT: The MO accepts the applicant's inclusion, exclusion and evaluability 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)

- **Clinical**

The primary efficacy parameter was the clinical response at day 14 in patients with acute exacerbations of chronic bronchitis. Secondary efficacy parameters were: 1) bacteriological response at end of treatment (day 7), day 14 and at day 28-35, 2) clinical response at day 7 and day 28-35, 3) clinical response at day 7, day 14 and day 28-35 in patients with bacteriologically proven ABECB at the start of the study, and 4) safety in terms of adverse events (including laboratory abnormalities).

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

1. Sputum Quality
    a. Sputum color: rust, white, yellow, or green
    b. Sputum purulence: clear, mucoid, mucopurulent, frankly purulent
2. Symptomatology (compared to the patient's baseline prior to the acute exacerbation and graded as same, slightly increased, or greatly increased)
    a. wheezes
    b. dyspnea
    c. cough
    d. auscultatory findings: rales and/or rhonchi (graded as present or absent)

The ***clinical response*** of the patients to treatment was categorized as:

1. Clinical cure: Resolution of clinical signs and symptoms related to the infection, not requiring any further antibiotic therapy.
2. Clinical improvement: Subjective improvement in signs and symptoms, with reduction of cough, sputum volume or return of the temperature to normal (if the patient was initially febrile), not requiring any further antibiotic therapy.
3. Clinical failure: Failure to respond to the study antibiotic, requiring a modification in antibiotic therapy or resulting in death from the primary diagnosis.
   was not possible for any reason
4. Clinical relapse: Initial resolution or partial resolution of clinical signs and symptoms within the study drug treatment period, but with subsequent recurrence of the clinical condition, requiring further antibiotic therapy within 21-28 days after the end of therapy.
5. Indeterminate: Patients in whom clinical evaluation was not possible for any reason.

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

Day 7: Cure, improvement, failure, or indeterminate.
Day 14: (primary efficacy timepoint) Cure, relapse, failure, or indeterminate.
Day 28-35: Cure, relapse, failure, or indeterminate.

MO COMMENT: Note that a response of "improvement" was not a possible choice at the primary endpoint.

- **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 following microbiologic responses were possible:

1. Eradication: Original causative pathogen(s) were not present in the following specimen to a positive culture.
2. Presumed eradication: Because of clinical improvement, the patient was unable to produce a sputum sample for investigation.
3. Persistence: Re-isolation/identification of one or more of the original causative organisms.
4. Presumed persistence: The patient was assessed to be a clinical failure, but was unable to produce sputum for culture. This criterion was not part of the original study protocol, but was added later, being applicable for the bacteriological evaluation of all BAY 12-8039 phase III clinical studies.
5. Recurrence: Initial eradication of the causative organism with re-isolation of the same organism during the follow-up period.
6. Superinfection: Patients in whom a new pathogen was isolated during treatment (i.e. causative pathogen not eradicated at the time the superinfecting organism is detected)
7. Reinfection: Eradication of the original causative pathogen with subsequent isolation of 1 or more new pathogen(s).
8. Indeterminate: Microbiological evaluation not possible for any reason including all patients who had a negative pre-treatment sputum culture, or who had other relevant data missing.

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

Day 7: Eradication, presumed eradication, persistence, superinfection, or indeterminate.
Day 14: (primary efficacy timepoint) Eradication, presumed eradication, persistence, recurrence, reinfection, or indeterminate.
Day 28-35: Eradication, presumed eradication, persistence, recurrence, reinfection, or indeterminate.

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 equivalence between the various doses of moxifloxacin and the comparator agent. In addition to an overall efficacy and per center analysis, the applicant also analyzed results by geographic region to account for different standards of care throughout Europe. Three geographic regions were designated: 1) Great Britain (30 centers), 2) Middle Europe (22 centers; by country: Austria (2 centers), Germany (13 centers), The Netherlands (6 centers) and Switzerland (1 center)) and 3) France/ South Europe (33 centers, by country: France (26 centers), Greece (3 centers), and Spain (4 centers)).

"...Based on a failure rate of 10% in the control group, an equivalence (clinically relevant) delta of 10% (in accordance with the FDA "points to consider", number 2, 26 October 1992), α = 2.5% (one-sided), β = 10% (obtained at a failure rate of 10% in the BAY 12-8039 group)" was employed. "Centres were to be clustered by geographical region (e.g. country) so that the ratio between smallest and largest region was not more than 1:2 (before unblinding the study). Statistical analyses were to be adjusted to these clusters of centres (geographic region)".

Study Results
Demographics, Evaluability

- **Demographics**

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 3.

> **MO COMMENT: Patients were evenly distributed across centers and geographic areas. Center number 195 in The Netherlands had the highest enrollment, but still only accounted for 31/750 (4.1%) of enrolled patients, 30/649 (4.6%) of the per protocol population and 19/229 (8.3%) of the microbiologically valid patients. There were 294 patients in the Great Britain, 206 patients in the Middle Europe, and 250 patients in the France/South Europe regions. This is well within 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 40 is the applicant's listing of the demographic characteristics of the patients in the CEE (valid for efficacy) population.

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

- **Evaluability**

> **MO COMMENT: The MO analyzed (in a blinded fashion) a 10% random sample of the patients from a list generated by the biostatistics reviewer. The MO found no systematic errors in the database. Therefore, the MO has accepted the applicant's assessments of evaluability and outcomes.**

A tabulation of the numbers of patients composing the various populations in the trial is found in the last line of Appendix 3 and is summarized here. There were a total of 750 patients enrolled in the trial. One patient was not randomized, leaving a total number of randomized patients of 749 (376 in the moxifloxacin arm and 373 in the clarithromycin arm). A total of 4 patients, 2 in each arm, were immediately lost to follow-up and did not take any doses of study medication. These patients were excluded from the ITT analysis. This left a total ITT (valid for safety) population of 745 (374 in the moxifloxacin arm and 371 in the clarithromycin group). In addition to the above-mentioned patients,

TABLE 40 :
CATEGORICAL DEMOGRAPHIC AND MEDICAL CHARACTERISTICS

POPULATION: ALL PATIENTS VALID PER PROTOCOL PER APPLICANT

		MOXIFLOXACIN 400 MG (N=322)		CLARITHROMYCIN 1000 MG (N=327)		ALL TREATMENT GROUPS COMBINED (N=649)		P-VALUE OF CHECK OF HOMOGENEITY
		N	%	N	%	N	%	
SEX	MALE	191	59.3	191	58.4	382	58.9	0.856275614
	FEMALE	131	40.7	136	41.6	267	41.1	
FEMALES - LACTATING	NO	131	40.7	136	41.6	267	41.1	
FEMALES - BIRTH CONTROL ADEQUATE	NOT REPORTED	131	40.7	136	41.6	267	41.1	
RACE	NOT REPORTED	76	23.6	69	21.1	145	22.3	
	CAUCASIAN	245	76.1	256	78.3	501	77.2	
	ORIENTAL	1	0.3	2	0.6	3	0.5	
HOSPITALIZED PRE THERAPY	NO	315	97.8	316	96.6	631	97.2	
	YES	7	2.2	11	3.4	18	2.8	
WARD	NOT REPORTED	4	1.2	5	1.5	9	1.4	
	GENERAL MEDICAL	3	0.9	6	1.8	9	1.4	

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TABLE 40 (CONTINUED): DEMOGRAPHICS - AGE(YEARS) AND WEIGHT (KG)

		MOXIFLOXACIN 400 MG (N=322)		CLARITHROMYCIN 1000 MG (N=327)		ALL TREATMENT GROUPS COMBINED (N=649)		P-VALUE OF CHECK OF HOMOGENEITY
		N	%	N	%	N	%	
AGE (YEARS)	<18							0.9156
	18 - <30	10	3.1	8	2.4	18	2.8	
	30 - <40	17	5.3	18	5.5	35	5.4	
	40 - <50	39	12.1	43	13.1	82	12.6	
	50 - <60	72	22.4	77	23.5	149	23.0	
	60 - <70	101	31.4	90	27.5	191	29.4	
	>=70	83	25.8	91	27.8	174	26.8	
	N	322		327		649		
	MEAN	60		60.2		60.1		0.9572
	STD	13.99		13.46		13.72		(0.8363)
	MINIMUM	18		22		18		
	LOWER QUARTIL	52		52		52		
	MEDIAN	61		61		61		
	UPPER QUARTIL	70		70		70		
	MAXIMUM	95		90		95		
WEIGHT(KG)	NOT REPORTED	3	0.9	3	0.9	6	0.9	
	<= 50	13	4.0	26	8.0	39	6.0	0.1519
	> 50 - <= 70	145	45.0	129	39.4	274	42.2	
	> 70 - <=100	149	46.3	155	47.4	304	46.8	
	>100	12	3.7	14	4.3	26	4.0	
	N	319		324		643		
	MEAN	73.01		72.44		72.72		0.6843
	STD	15.56		15.8		15.67		(0.7309)
	MINIMUM	37		38		37		
	LOWER QUARTIL	62		62		62		
	MEDIAN	71		72		71		
	UPPER QUARTIL	83		83		83		
	MAXIMUM	130		128		130		

There were an additional 96 patients considered invalid for efficacy in the per protocol analysis (52 in the moxifloxacin arm and 44 in the clarithromycin group). Including the patients not valid for ITT as noted above, this resulted in 54 total invalid patients for the CEE population in the moxifloxacin group, 46 invalid patients for the CEE population in the clarithromycin group, and one non-randomized person. A tabulation of the reasons for these patients' exclusion from the per protocol (CEE) analysis is presented in Table 41. The MCEE subset consisted of 115 patients in the moxifloxacin group and 114 patients in the clarithromycin group.

MO COMMENT: The most common reason for exclusion was insufficient duration of therapy. The second most common reason was "essential data missing or invalid". As in study D96-027, this category included patients seen outside the specified time windows and patients for whom data was not recorded.

Efficacy

- **Clinical Efficacy**

The primary endpoint was the clinical outcome in the CEE population (per protocol, valid for efficacy) population at the day 14 (+7 days after therapy) follow-up visit. Table 40 shows the applicant's tabulations of clinical efficacy at the end of therapy (the primary endpoint for European submissions), the day 14 visit and the day 28-35 visit (21-28 days post therapy). Two analyses are presented for the second follow-up visit. In the first case, only patients actually seen at this visit are counted. In the second analysis, all patient including those who were considered failures at the day 14 visit are counted.

The calculated 95 % confidence interval for the difference of the clinical success rates at day 14 for all regions (moxifloxacin minus clarithromycin) was (-3.9%, 5.8.%).

TABLE 41
REASONS FOR EXCLUSION FROM VALID PER PROTOCOL ANALYSIS (PATIENT INVALIDITY) PER APPLICANT

POPULATION: ALL PATIENTS ENROLLED

	MOXIFLOXACIN 400 MG (N=376)		CLARITHROMYCIN 1000 MG (N=373)		NOT RANDOMIZED (N=1)		ALL TREATMENT GROUPS COMBINED (N=750)		P-VALUE OF CHECK OF HOMOGENEITY
	N	%	N	%	N	%	N	%	
TOTAL PATIENTS INVALID FOR EFFICACY	54	14.4	46	12.3	1	100.0	101	13.5	0.424835564
VIOLATION OF IN / EXCLUSION CRITERIA	5	1.3	8	2.1			13	1.7	
RANDOM CODE BROKEN	1	0.3	2	0.5			3	0.4	
NOT TREATED WITH STUDY DRUG	2	0.5	2	0.5	1	100.0	5	0.7	
NON-COMPLIANCE WITH STUDY DRUG	1	0.3	1	0.3			2	0.3	
INSUFFICIENT DURATION OF THERAPY	24	6.4	14	3.8			38	5.1	
VIOLATION OF TIME SCHEDULE	7	1.9	11	2.9			18	2.4	
ESSENTIAL DATA MISSING OR INVALID	17	4.5	11	2.9			28	3.7	
USE OF PROHIBITED POST-TREATMENT MEDICATION			1	0.3			1	0.1	

NOTE: A PATIENT MAY HAVE MORE THAN ONE REASON FOR EXCLUSION THEREFOR SUM OF PATIENTS IN COLUMNS ARE GREATER THAN TOTAL

TABLE 42
SUMMARY OF CLINICAL RESPONSES AT END OF THERAPY
AND AT FOLLOW-UP PER APPLICANT

ALL PATIENTS VALID PER PROTOCOL

CLINICAL EVALUATION		MOXIFLOXACIN 400 MG (N=322)		CLARITHROMYCIN 1000 MG (N=327)	
		N	%	N	%
DAY 7 (END OF THERAPY)	CLINICAL CURE	142	44.10	162	49.54
	IMPROVEMENT	162	50.31	145	44.34
	CLINICAL FAILURE	17	5.28	17	5.20
	INDETERMINATE	1	0.31	3	0.92
7 DAYS POST THERAPY (DAY 14) 1)	CLINICAL CURE	287	89.13	289	88.38
	CLINICAL FAILURE / RELAPSE	35	10.87	38	11.62
21-28 DAYS POST THERAPY 2)	CLINICAL CURE	256	89.20	257	88.93
	CLINICAL RECURRENCE / RELAPSE	23	8.01	26	9.00
	INDETERMINATE	7	2.44	4	1.38
	MISSING	1	0.35	2	0.69
21-28 DAYS POST THERAPY 3)	CLINICAL CURE	271	81.87	270	79.88
	CLINICAL FAILURE / RELAPSE	60	18.13	68	20.12

1) CLINICAL FAILURES AT DAY 7 (END OF THERAPY) ARE ALSO COUNTED AS CLINICAL FAILURES AT DAY 14 (7 DAYS POST THERAPY)
2) BASED ON PATIENTS WITH CLINICAL CURE AT DAY 14 (7 DAYS POST THERAPY)
3) CLINICAL FAILURES AT DAY 14 CARRIED FORWARD FOR FOLLOW-UP

An intention-to-treat analysis of patients in the valid-for-safety only 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.

Table 43

Clinical Success Rates at Day 28-35 Visit Per FDA Biostatistics Reviewer

Population : Intention to Treat (Valid for Safety)

Study Group	Clinical Success Rates N(%)#	95% Confidence Intervals
Moxifloxacin	287/371 (77.4%)	(-5.6, 7.1)
Clarithromycin	281/367 (76.6%)	-

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

MO COMMENT: The ITT analysis confirmed the equivalent efficacy results seen in the per protocol analysis.

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

The clinical success rate in the moxifloxacin treatment group was 169/191 (88%) in patients aged less than 65 years compared to 81/90 (90%) in patients age 65-74 years and 37/41 (90%) in patients greater than age 74. In the clarithromycin treatment group the success rate was 169/192 (88 %) in patients aged less than 65 years, 85/93 (91 %) in patients age 65-74 years, and 35/42 (83%) in patients over age 74.

Table 44
Clinical Efficacy by Age Groups
CEE Population: Per Applicant

0124	**Moxifloxacin 400mg**	**Clarithromycin**	**P-Value**
< 65	169/191 (88%)	169/192 (88%)	0.889
65-74	81/90 (90%)	85/93 (91%)	0.745
> 74	37/41 (90%)	35/42 (83%)	0.353
P-Value	0.902	0.389	

MO COMMENT: Unlike studies D96-022 and D96-027, the efficacy of moxifloxacin was similar in the older population compared to younger patients in the CEE population.

- *Concomitant Steroid Use: Efficacy*

The clinical success rate in the moxifloxacin treatment group was 140/160 (88%) in patients with concomitant systemic steroid medication compared to 147/162 (91%) in patients without concomitant steroid medication. In the clarithromycin treatment group the success rate was 105/128 (82%) in patients with concomitant systemic steroid medication and 184/199 (92%) in patients without concomitant systemic steroid medication. A tendency towards an increased clinical failure rate could be seen in the sub-group of patients receiving concomitant systemic steroids in both treatment groups. However, in this sub-group analysis the Middle Europe and France/South Europe regions drove the results (especially for the clarithromycin treatment group). The success rates for clarithromycin were 79.5 % and 69 % in the sub-group of patients with concomitant systemic steroids in these regions, respectively, but the success rate was 97.6 % in Great Britain in systemic steroid treated patients.

Table 45
Clinical Efficacy in Patients Treated With and Without Systemic Steroids
CEE Population: Per Applicant

0124	**Moxifloxacin 5 days**	**Clarithromycin**	**P-Value #**
Patients With Steroids	140/160 (88%)	105/128 (82%)	0.196
Patients Without Steroids	147/162 (91%)	184/199 (92%)	0.556
P-Value @	0.350	0.004	

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

MO COMMENT: This trial included the greatest percentage of patients treated with concomitant systemic steroids. Patients who are in need of steroid therapy may be sicker so it is not surprising that the efficacy rate in this subgroup would be lower. However, in this trial, unlike trial D96-027, the results were comparable across treatment arms. Moxifloxacin does appear to be effective when dosed for 5 days in steroid treated patients. There does not appear to be an explanation for the wide variation in cure rates from region to region 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 46
Clinical Response at Post 1 Visit by Gram's Stain Results
MCEE Population: Per Applicant

	Moxifloxacin 400 mg x 5 days	Clarithromycin 500 mg BID x 7 days
Gram Stain Missing	15/18 (83%)	21/22 (95%)
WBC <= 25, Epi < 10	23/26 (88%)	14/16 (88%)
WBC <= 25, Epi >= 10	2/3 (67%)	5/6 (83%)
WBC > 25, Epi < 10	42/48 (88%)	40/51 (78%)
WBC > 25, Epi >= 10	16/20 (80%)	17/19 (89%)

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

- *Effect of Treatment on FEV1*

This trial measured the forced expiratory volume in 1 second (FEV1) on patients pre-therapy, end of therapy and the two follow-up visits. . The data are presented in the following table.

Table 47
FEV_1 assessment after study drug therapy per applicant

FEV_1 assessment (% of normal value) and patient rates						
	Day 7		Day 14		Follow-up (day 28-35)	
FEV_1 (% of normal value)	MOX[1]	CLA[2]	MOX	CLA	MOX	CLA
≤ 25 %	7.5 %	8.0 %	7.5 %	7.3 %	3.7 %	3.4 %
> 25 ≤ 50 %	30.4 %	26.6 %	26.4 %	24.8 %	15.8 %	18.0 %
> 50 ≤ 75 %	33.9 %	31.8 %	35.1 %	33.6 %	28.0 %	26.9 %
> 75 %	24.5 %	31.2 %	25.5 %	30.9 %	24.8 %	24.2 %
Missing data	3.7 %	2.4 %	5.6 %	3.4 %	27.6 %	27.5 %

Footnote:
1) MOX = BAY 12-8039
2) CLA = Clarithromycin

MO COMMENT: Although the clinical efficacy as far as decrease or resolution of symptoms was demonstrated for both moxifloxacin and clarithromycin in this trial, there was very little effect seen on FEV1 with either drug relative to baseline measurements. This was a secondary endpoint for this trial and follow-up times may be rather short in this trial to see a difference in this parameter.

- **Microbiologic Efficacy**

Microbiologic efficacy was expressed as the proportion of the microbiologic and clinical efficacy evaluable population (MCEE) that was clinically cured at the day 14 (first follow-up, +7 days after therapy) visit. The rates of clinical cures, and failures/ relapses are presented in Table 45.

Table 48
Bacteriological responses by patient at day 14 (7 days post therapy) per applicant

Bacteriological response	Moxifloxacin (N = 115)		Clarithromycin (N = 114)	
	N	%	N	%
Bacteriological success	**89**	**77.4 %**	**71**	**62.3 %**
Eradication	41	35.7 %	27	23.7 %
Presumed eradication	48	41.7 %	44	38.6 %
Bacteriological failure	**26**	**22.6 %**	**43**	**37.7 %**
Eradication with superinfection /reinfection [1)]	5	4.3 %	10	8.8 %
Eradication with recurrence [2)]	9	7.8 %	8	7.0 %
Persistence [3)]	5	4.3 %	23	20.2 %
Presumed persistence	7	6.1 %	2	1.8 %

Footnote:
1) Superinfections at day 7 are also counted
2) Recurrence overwrites superinfection or reinfection
3) Including persistence with superinfection/reinfection; persistence at any time is counted

MO COMMENT: There was a greater persistence of organisms in the clarithromycin group compared to the moxifloxacin group. The majority of this difference was accounted for by the greater eradication rate of moxifloxacin for *H. influenzae*. The clinical success rate in these patients, however, was similar in both the moxifloxacin and clarithromycin treated groups.

The calculated 95 % confidence interval for the differences of bacteriological success rates by patient at day 14 (moxifloxacin minus clarithromycin) was (3.6 %, 26.9 %). The bacteriologic success rates were consistent in two of the three regions. In Middle Europe, 29/37 patients (78%) were bacteriological successes in the moxifloxacin group and 19/37 (51 %) in the clarithromycin group. In Great Britain 40/48 patients (83 %) were bacteriological successes in the moxifloxacin group and 33/51 (65 %) in the clarithromycin group. Only in the region of France/South Europe was the bacteriological success rate in favor of clarithromycin with 20/30 patients (67 %) bacteriological successes in the moxifloxacin group and 19/26 patients (73 %) in the clarithromycin group.

TABLE 49
CLINICAL RESPONSE CROSSED WITH BACTERIOLOGICAL RESPONSE AT DAY 14

POPULATION: ALL PATIENTS VALID PER PROTOCOL
SUBGROUP: ONLY MICROBIOLOGICALLY VALID PATIENTS
REGION: ALL REGIONS

TREATMENT GROUP: MOXIFLOXACIN 400 MG (N=115)

	BACTERIOLOGICAL RESPONSE AT DAY 14						
	ERADICATION	PRESUMED ERADICATION	ERADICATION WITH SUPERINFECTION/REINFECTION 3)	ERADICATION WITH RECURRENCE	PERSISTENCE 2)	PRESUMED PERSISTENCE	NO CAUSATIVE ORGANISM PRE THERAPY
	NUMBER	NUMBER	NUMBER	NUMBER	NUMBER	NUMBER	NUMBER
CLINICAL EVALUATION AT DAY 14							
CLINICAL CURE	37	48	2	7	4		
CLINICAL FAILURE 1)	1				1	3	
CLINICAL RELAPSE	3		3	2		4	
INDETERMINATE / MISSING							

TREATMENT GROUP: CLARITHROMYCIN 1000 MG (N=114)

	BACTERIOLOGICAL RESPONSE AT DAY 14						
	ERADICATION	PRESUMED ERADICATION	ERADICATION WITH SUPERINFECTION/REINFECTION 3)	ERADICATION WITH RECURRENCE	PERSISTENCE 2)	PRESUMED PERSISTENCE	NO CAUSATIVE ORGANISM PRE THERAPY
	NUMBER	NUMBER	NUMBER	NUMBER	NUMBER	NUMBER	NUMBER
CLINICAL EVALUATION AT DAY 14							
CLINICAL CURE	26	44	5	7	15		
CLINICAL FAILURE 1)	1				4		
CLINICAL RELAPSE			5	1	4	2	
INDETERMINATE / MISSING							

Table 49 demonstrates the clinical outcomes in patients in the MCEE population by bacteriologic response.

MO COMMENT: These results conform 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.

- *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 50
Bacteriologic Response at Post 1 Visit by Gram's Stain Results
MCEE Population: Per Applicant

	Moxifloxacin 400 mg x 5 days	**Clarithromycin 500 mg BID x 7 days**
Gram Stain Missing	13/18 (72%)	15/22 (68%)
WBC <= 25, Epi < 10	21/26 (81%)	13/16 (81%)
WBC <= 25, Epi >= 10	3/3 (100%)	5/6 (83%)
WBC > 25, Epi < 10	44/48 (92%)	34/51 (67%)
WBC > 25, Epi >= 10	13/20 (65%)	14/19 (74%)

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

The eradication rates per organism at the primary endpoint (day 14 visit) for the major pathogens in ABECB sought in the label are presented in the following table:

Table 51

Bacteriological response by organism group and bacterial species at study day 14

Organism (group)	Treat-ment group	Bacteriological success [1]		Bacteriological failure [2]	
		Number / total number of organism(s)	(%)	Number / total number of organism(s)	(%)
All groups	MOX [3]	111 / 134	(82.8 %)	23 / 134	(17.2 %)
	CLA [4]	106 / 139	(76.3 %)	33 / 139	(23.7 %)
Gram-positive aerobic	MOX	35 / 41	(85.4 %)	6 / 41	(14.6 %)
	CLA	45 / 48	(93.8 %)	3 / 48	(6.3 %)
Staphylococcus aureus	MOX	1 / 1	(100 %)	0 / 1	(0 %)
	CLA	9 / 11	(81.8 %)	2 / 11	(18.2 %)
Streptococcus pneumoniae	MOX	32 / 38	(84.2 %)	6 / 38	(15.8 %)
	CLA	35 / 36	(97.2 %)	1 / 36	(2.8 %)
Gram-negative aerobic	MOX	76 / 93	(81.7 %)	17 / 93	(18.3 %)
	CLA	61 / 91	(67.0 %)	30 / 91	(33.0 %)
Haemophilus influenzae	MOX	40 / 44	(90.9 %)	4 / 44	(9.1 %)
	CLA	23 / 43	(53.5 %)	20 / 43	(46.5 %)
Haemophilus parainfluenzae	MOX	5 / 9	(55.6 %)	4 / 9	(44.4 %)
	CLA	4 / 4	(100 %)	0 / 4	(0 %)
Moraxella catarrhalis	MOX	14 / 16	(87.5 %)	2 / 16	(12.5 %)
	CLA	23 / 24	(95.8 %)	1 / 24	(4.2 %)

Footnote:
1) Defined as bacteriological response "eradication" or "presumed eradication"
2) Defined as bacteriological response "persistence" or "presumed persistence" or "eradication with recurrence"
3) MOX = Moxifloxacin
4) CLA = Clarithromycin

MO COMMENT: As in trials D96-027 and D96-022, moxifloxacin performed better than the comparator agents against *H. influenzae*. Unlike the other two trials, however, moxifloxacin performed less well against *H. parainfluenzae* in this trial than the comparator, although the numbers of isolates were small. There were no isolates of *Klebsiella pneumoniae* recovered from patients in this trial in either group and only one patient in the moxifloxacin group had *S. aureus* as th the causative pathogen. The bacterial eradication rate of *S. pneumoniae* was lower for moxifloxacin in this trial than the other two trials. Of the 6 bacteriological failures for the pneumococcus in the moxifloxacin arm, 3 of the patients (patients 29, 174 and 383) were clinical cures, 2 were clinical relapses (patients 277 and 526) and one was a frank clinical failure at the end of therapy visit on day 7 (patient 121).

Moxifloxacin dosed at 400mg for 5 days demonstrated equivalent clinical and bacteriologic efficacy to clarithromycin at 500mg BID for 7 days in ABECB due to the *S. pneumoniae, H influenzae, H.*

parainfluenzae and *M. catarrhalis* as sought in the draft label. There were no cases with *Klebsiella pneumoniae* as the causative pathogen and there were too few patients with *S. aureus* to draw conclusions relative to these organisms.

Safety

Of the 750 patients enrolled into the study, 745 patients received at least 1 dose of study medication and were thus valid for the safety analysis (the safety population equals the intention-to-treat population). Adverse events were reported in 165/374 (44.1 %) in the moxifloxacin treatment group and in 172 /371 (46.4 %) in the clarithromycin treatment group. Drug-related adverse events (defined as events with any other relationship to study drug than "none") were reported in 107 patients (28.6 %) in the moxifloxacin treatment group and in 100 patients (27.0 %) in the clarithromycin treatment group. Table 52 presents a summary of the number of adverse events, drug-related events, withdrawals from the study and deaths due to adverse related events in each treatment arm.

MO COMMENT: There were no significant differences between groups in terms of total adverse events or drug related adverse events. There were slightly more patients in the moxifloxacin arm who discontinued therapy due to adverse events. The MO review of these cases revealed that the most common reasons for discontinuation in the moxifloxacin group were nausea (6 cases) and dizziness or vertigo (6 cases). Some of these patients experienced more than one of these symptoms. This was compared with 2 patients in the clarithromycin group who were discontinued due to nausea and 3 for dizziness or vertigo.

TABLE 52
OVERVIEW OF EVENTS AND SURVIVAL OF PATIENTS
POPULATION: ALL PATIENTS VALID FOR ITT / SAFETY ANALYSIS

REGION: ALL REGIONS

		TREATMENT GROUP			
		MOXIFLOXACIN 400 MG (N=374)		CLARITHROMYCIN 1000 MG (N=371)	
		N	%	N	%
IS THE PATIENT STILL ALIVE AT THE END OF STUDY?	NO	1	0.3	2	0.5
	YES	372	99.5	369	99.5
	NOT REPORTED	1	0.3		
ADVERSE EVENTS (BY PATIENT)	NO	209	55.9	199	53.6
	YES	165	44.1	172	46.4
	NOT REPORTED				
DRUG-RELATED ADVERSE EVENTS (BY PATIENT)	NO	267	71.4	271	73.0
	YES	107	28.6	100	27.0
	NOT REPORTED				
SERIOUS OR LIFE THREATENING ADVERSE EVENTS (BY PATIENT)	NO	360	96.3	360	97.0
	YES	14	3.7	11	3.0
	NOT REPORTED				
PREMATURE TERMINATION DUE TO ADVERSE EVENTS (BY PATIENT)	NO	348	93.0	356	96.0
	YES	26	7.0	15	4.0
	NOT REPORTED				
HOSPITALIZATION OR PROLONGED HOSPITALIZATION DUE TO ADVERSE EVENTS (BY PATIENT)	NO	361	96.5	363	97.8
	YES	13	3.5	8	2.2
	NOT REPORTED				

Table 53 lists the drug related adverse events by body system. Overall, treatment related adverse events were similar across the two study arms. There were more case of nausea (21 cases vs 16 cases), nausea and vomiting (5 vs.2), vomiting alone (3 vs 1) and dizziness (14 vs 4) in the moxifloxacin-treated patients than in those who received clarithromycin. There was more cases of taste perversion (14 vs 0) in clarithromycin-treated persons. One case of arrythmia considered remotely related to study drug treatment occurred in the moxifloxacin group. The symptoms started 19 days after the end of study medication, and the patient had a history of cardiac arrhythmias (patient number 457). Two patients in the moxifloxacin group experienced atrial fibrillation.

MO COMMENT: There were no reported cases of phototoxic rashes in the database for this trial.

Deaths

There were three deaths in the study, one in the moxifloxacin arm and one in the clarithromycin arm. In the moxifloxacin treatment group, patient number 126 died 1 day after stopping study medication. The investigator reported pneumonia as the cause of death. The relationship of the pneumonia to study drug therapy was graded as "probable" by the investigator. This 78-old female patient was suffering from chronic bronchitis for 16 years and had 3 exacerbations of chronic bronchitis in the year preceding the study. Upon study entry, the patient was febrile but did not receive a chest x-ray (N.B. chest x rays were not required for enrollment in this study). After 1 day of moxifloxacin therapy, study medication was stopped after a diagnosis of pneumonia. The patient died 1 day later, with no details on further medications. No culture data was available. It is probable that the pneumonia had already developed before the start of study medication.

In the clarithromycin treatment group, patient number 176 died at the first day of study medication from a myocardial infarction. This patient had a long-lasting history of essential hypertension and hypertensive heart disease, and the event was classified as remotely related to study drug treatment by the investigator. Patient number 855 died 16 days after the stop of study medication from a sudden massive haemorrhage from a tracheal tumour; the event was not considered related to study medication by the investigator.

MO COMMENT: The MO reviewed these cases and found no clear causal association with the study drugs.

TABLE 53
INCIDENCE RATES OF DRUG-RELATED ADVERSE EVENTS BY BODY SYSTEM AND TREATMENT

POPULATION: ALL PATIENTS VALID FOR ITT / SAFETY ANALYSIS PER APPLICANT

REGION: ALL REGIONS

		TREATMENT GROUP			
		MOXIFLOXACIN 400 MG (N=374)		CLARITHROMYCIN 1000 MG (N=371)	
		N	%	N	%
ANY BODY SYSTEM	ANY EVENT	107/374	28.6	100/371	27.0
BODY AS A WHOLE	ANY EVENT	30/374	8.0	24/371	6.5
	ABDOMINAL PAIN	12/374	3.2	10/371	2.7
	AGGRAVATION REACTION	2/374	0.5		
	ASTHENIA	3/374	0.8	2/371	0.5
	BACK PAIN	1/374	0.3		
	CHEST PAIN	1/374	0.3		
	FEVER			1/371	0.3
	HAND PAIN	1/374	0.3		
	HEADACHE	12/374	3.2	12/371	3.2
	INFECTION FUNGAL			1/371	0.3
	LEG PAIN	1/374	0.3		
	PAIN	2/374	0.5		
CARDIOVASCULAR SYSTEM	ANY EVENT	7/374	1.9	11/371	3.0
	ARRHYTHMIA	1/374	0.3		
	AV BLOCK			1/371	0.3
	BRADYCARDIA			1/371	0.3
	ELECTROCARDIOGRAM ABNORMAL			1/371	0.3
	HEART BLOCK			1/371	0.3
	HEART FAILURE	1/374	0.3		

(CONTINUED)

NOTES: INCIDENCE RATE = NO. OF EVENTS / NO. AT RISK, WHERE:
NO. OF EVENTS = NO. OF PATIENTS REPORTING A DRUG-RELATED EVENT
NO. AT RISK = ALL PATIENTS VALID FOR SAFETY

TABLE 53 (CONTINUED)
INCIDENCE RATES OF DRUG-RELATED ADVERSE EVENTS BY BODY SYSTEM AND TREATMENT

POPULATION: ALL PATIENTS VALID FOR ITT / SAFETY ANALYSIS PER APPLICANT

REGION: ALL REGIONS

		TREATMENT GROUP			
		MOXIFLOXACIN 400 MG (N=374)		CLARITHROMYCIN 1000 MG (N=371)	
		N	%	N	%
CARDIOVASCULAR SYSTEM	HYPERTENSION	1/374	0.3	1/371	0.3
	HYPOTENSION			1/371	0.3
	MIGRAINE	1/374	0.3		
	MYOCARDIAL INFARCT			1/371	0.3
	PALPITATION	1/374	0.3	2/371	0.5
	PERIPHERAL EDEMA			1/371	0.3
	SUPRAVENTRICULAR EXTRASYSTOLES	1/374	0.3		
	SYNCOPE	1/374	0.3		
	TACHYCARDIA			1/371	0.3
	VASODILATATION			1/371	0.3
DIGESTIVE SYSTEM	ANY EVENT	54/374	14.4	51/371	13.7
	ANOREXIA			1/371	0.3
	APHTHOUS STOMATITIS	1/374	0.3		
	CONSTIPATION	2/374	0.5	1/371	0.3
	DIARRHEA	14/374	3.7	16/371	4.3
	DRY MOUTH	1/374	0.3	2/371	0.5
	DYSPEPSIA	2/374	0.5	7/371	1.9
	DYSPHAGIA	1/374	0.3	1/371	0.3
	ERUCTATION			1/371	0.3
	FLATULENCE	2/374	0.5	3/371	0.8

(CONTINUED)

NOTES: INCIDENCE RATE = NO. OF EVENTS / NO. AT RISK, WHERE;
NO. OF EVENTS = NO. OF PATIENTS REPORTING A DRUG-RELATED EVENT
NO. AT RISK = ALL PATIENTS VALID FOR SAFETY

TABLE 53 (CONTINUED)
INCIDENCE RATES OF DRUG-RELATED ADVERSE EVENTS BY BODY SYSTEM AND TREATMENT

POPULATION: ALL PATIENTS VALID FOR ITT / SAFETY ANALYSIS PER APPLICANT

REGION: ALL REGIONS

		TREATMENT GROUP			
		MOXIFLOXACIN 400 MG (N=374)		CLARITHROMYCIN 1000 MG (N=371)	
		N	%	N	%
DIGESTIVE SYSTEM	GLOSSITIS	1/374	0.3	1/371	0.3
	INCREASED SALIVATION			1/371	0.3
	JAUNDICE			1/371	0.3
	LIVER FUNCTION TESTS ABNORMAL	3/374	0.8	3/371	0.8
	MOUTH ULCERATION	1/374	0.3		
	NAUSEA	21/374	5.6	16/371	4.3
	NAUSEA AND VOMITING	5/374	1.3	2/371	0.5
	ORAL MONILIASIS	2/374	0.5	2/371	0.5
	PERIODONTAL ABSCESS	1/374	0.3		
	STOMATITIS	2/374	0.5		
	VOMITING	3/374	0.8	1/371	0.3
METABOLIC AND NUTRITIONAL D.	ANY EVENT	1/374	0.3		
	NPN INCREASED	1/374	0.3		
MUSCULO-SKELETAL SYSTEM	ANY EVENT	4/374	1.1	1/371	0.3
	ARTHROSIS	1/374	0.3		
	BONE PAIN	1/374	0.3		
	LEG CRAMPS	1/374	0.3	1/371	0.3
	MYALGIA	1/374	0.3		
	TENDON DISORDER	1/374	0.3		
NERVOUS SYSTEM	ANY EVENT	18/374	4.8	10/371	2.7

(CONTINUED)

NOTES: INCIDENCE RATE = NO. OF EVENTS / NO. AT RISK, WHERE:
NO. OF EVENTS = NO. OF PATIENTS REPORTING A DRUG-RELATED EVENT
NO. AT RISK = ALL PATIENTS VALID FOR SAFETY

TABLE 53 (CONTINUED)
INCIDENCE RATES OF DRUG-RELATED ADVERSE EVENTS BY BODY SYSTEM AND TREATMENT

POPULATION: ALL PATIENTS VALID FOR ITT / SAFETY ANALYSIS PER APPLICANT

REGION: ALL REGIONS

		TREATMENT GROUP			
		MOXIFLOXACIN 400 MG (N=374)		CLARITHROMYCIN 1000 MG (N=371)	
		N	%	N	%
NERVOUS SYSTEM	ANXIETY			1/371	0.3
	APHASIA	1/374	0.3		
	CONFUSION	1/374	0.3		
	DEPERSONALIZATION			1/371	0.3
	DIZZINESS	14/374	3.7	4/371	1.1
	HYPERTONIA	1/374	0.3	1/371	0.3
	NERVOUSNESS	1/374	0.3	1/371	0.3
	TREMOR	1/374	0.3		
	VERTIGO	2/374	0.5	2/371	0.5
RESPIRATORY SYSTEM	ANY EVENT	13/374	3.5	8/371	2.2
	ASTHMA	3/374	0.8	2/371	0.5
	BRONCHITIS	4/374	1.1	2/371	0.5
	BRONCHOSTENOSIS			1/371	0.3
	COUGH INCREASED	3/374	0.8		
	DYSPNEA			3/371	0.8
	LUNG DISORDER	1/374	0.3	1/371	0.3
	PNEUMONIA	2/374	0.5		
	RHINITIS	1/374	0.3	1/371	0.3
SKIN AND APPENDAGES	ANY EVENT	10/374	2.7	6/371	1.6
	ACNE	1/374	0.3		

(CONTINUED)

NOTES: INCIDENCE RATE = NO. OF EVENTS / NO. AT RISK, WHERE:
NO. OF EVENTS = NO. OF PATIENTS REPORTING A DRUG-RELATED EVENT
NO. AT RISK = ALL PATIENTS VALID FOR SAFETY

TABLE 53 (CONTINUED)
INCIDENCE RATES OF DRUG-RELATED ADVERSE EVENTS BY BODY SYSTEM AND TREATMENT

POPULATION: ALL PATIENTS VALID FOR ITT / SAFETY ANALYSIS PER APPLICANT

REGION: ALL REGIONS

		TREATMENT GROUP			
		MOXIFLOXACIN 400 MG (N=374)		CLARITHROMYCIN 1000 MG (N=371)	
		N	%	N	%
SKIN AND APPENDAGES	HERPES ZOSTER	1/374	0.3		
	PRURITUS	2/374	0.5	3/371	0.8
	RASH	2/374	0.5	4/371	1.1
	SEBORRHEA	1/374	0.3		
	SWEATING	1/374	0.3	1/371	0.3
	URTICARIA	2/374	0.5		
SPECIAL SENSES	ANY EVENT	2/374	0.5	15/371	4.0
	ABNORMAL VISION	1/374	0.3		
	TASTE LOSS			1/371	0.3
	TASTE PERVERSION			14/371	3.8
	TINNITUS	1/374	0.3		
UROGENITAL SYSTEM	ANY EVENT	2/374	0.5	8/371	2.2
	CRYSTALLURIA			4/371	1.1
	KIDNEY FUNCTION ABNORMAL			1/371	0.3
	POLYURIA			1/371	0.3
	URATE CRYSTALLURIA	1/374	0.3		
	URINARY TRACT DISORDER			2/371	0.5
	VAGINAL HEMORRHAGE			1/371	0.3
	VAGINAL MONILIASIS	1/374	0.3		

NOTES: INCIDENCE RATE = NO. OF EVENTS / NO. AT RISK, WHERE:
NO. OF EVENTS = NO. OF PATIENTS REPORTING A DRUG-RELATED EVENT
NO. AT RISK = ALL PATIENTS VALID FOR SAFETY

Clinical Laboratory Tests

Table 52 shows descriptive statistics for mean changes from baseline in clinical laboratory tests. These did not show much difference between treatment groups. The most common change was in platelets. Thirty-four (34) patients (9.0 %) in the moxifloxacin and 32 patients (8.6 %) in the clarithromycin treatment group had a significant change of platelets.

The rate of increase of PTT during therapy was slightly higher in the moxifloxacin group (20 %) than in the clarithromycin group (9 %). The PT ratio decrease rate during therapy was slightly higher in the moxifloxacin group (29 %) than in the clarithromycin group (18 %). There were no episodes of bleeding associated with these changes. Amylase increases during therapy were observed at a rate of 4 % in the moxifloxacin group and 14 % in the clarithromycin group. No patients experienced pancreatitis.

In patients with changes in liver function tests, three patients (0.8 %) in the moxifloxacin and 3 patients (0.8 %) in the clarithromycin treatment group had a significant change of AST, 6 patients (1.6 %) in the moxifloxacin and 7 patients (1.8 %) in the clarithromycin treatment group had a significant change of ALT. Seven patients in the moxifloxacin (1.8 %) and 3 patients (0.8 %) in the clarithromycin treatment group had a significant change of alkaline phosphatase. No patient experienced an increase in serum bilirubin that was considered clinically significant by the investigator. Nine of 341 (3%) patients in the moxifloxacin group and 8/342 (2%) of patients in the clarithromycin arm had bilirubin elevations during study that were above pre-therapy baseline that were considered minor.

MO COMMENT: MO review of the elevations in liver transaminases and bilrubin showed that these were all less than three times the upper limit of normal

TABLE 54
INCIDENCE RATES OF HIGH LABORATORY ABNORMALITIES PER APPLICANT

ALL PATIENTS VALID FOR ITT / SAFETY ANALYSIS

LABORATORY VARIABLE		BAY 12 - 8039 400 MG (N=374)	CLARITHROMYCIN 1000 MG (N=371)
HEMATOLOGY	HEMATOCRIT (%)	14 /312 (4%)	15 /317 (5%)
	HEMOGLOBIN (G/DL)	2 /339 (1%)	3 /341 (1%)
	ERYTHROCYTES (T/L)	12 /321 (4%)	9 /325 (3%)
	MCV (FL)	8 / 46 (17%)	7 / 48 (15%)
	MCH (PG)	0 / 66 (0%)	0 / 62 (0%)
	MCHC (G/DL)	0 / 68 (0%)	0 / 63 (0%)
	LEUCOCYTES (G/L)	33 /244 (14%)	34 /251 (14%)
	NEUTROPHILS (%)	19 /245 (8%)	24 /245 (10%)
	NEUTROPHILS (BANDS) (%)	0 / 40 (0%)	0 / 42 (0%)
	NEUTROPHILS (SEGS) (%)	3 / 29 (10%)	6 / 36 (17%)
	LYMPHOCYTES (%)	11 /337 (3%)	15 /339 (4%)
	MONOCYTES (%)	10 /309 (3%)	14 /312 (4%)
	EOSINOPHILS (%)	14 /322 (4%)	6 /310 (2%)
	BASOPHILS (%)	25 /315 (8%)	18 /292 (6%)
	PLATELETS (G/L)	27 /321 (8%)	29 /323 (9%)
	PT TIME (SEC)	2 / 29 (7%)	0 / 30 (0%)
	PT RATIO (NONE)	0 / 79 (0%)	0 / 77 (0%)
	PT INR (NONE)	0 / 13 (0%)	0 / 18 (0%)
	PTT TIME (SEC)	15 / 76 (20%)	7 / 74 (9%)

TABLE 54 CONTINUED
INCIDENCE RATES OF HIGH LABORATORY ABNORMALITIES PER APPLICANT

ALL PATIENTS VALID FOR ITT / SAFETY ANALYSIS

LABORATORY VARIABLE		BAY 12 - 8039 400 MG (N=374)	CLARITHROMYCIN 1000 MG (N=37)
CLINICAL CHEMISTRY	GLUCOSE (MG/DL)	15 / 73 (21%)	16 / 79 (20%)
	URIC ACID (MG/DL)	6 /109 (6%)	7 / 94 (7%)
	CALCIUM (MG/DL)	0 /106 (0%)	0 /100 (0%)
	PHOSPHORUS (MG/DL)	5 / 94 (5%)	7 / 91 (8%)
	SODIUM (MMOL/L)	4 /348 (1%)	4 /344 (1%)
	POTASSIUM (MMOL/L)	14 /330 (4%)	12 /336 (4%)
	CHLORIDE (MMOL/L)	3 / 12 (25%)	2 / 13 (15%)
	BICARBONATE (MMOL/L)	2 / 11 (18%)	3 / 11 (27%)
	CREATININE (MG/DL)	12 /324 (4%)	12 /323 (4%)
	B U N (MG/DL)	0 / 22 (0%)	2 / 20 (10%)
	UREA (MG/DL)	26 /321 (8%)	25 /316 (8%)
	PROTEIN (G/DL)	2 /113 (2%)	3 /104 (3%)
	ALBUMIN (G/DL)	0 /115 (0%)	2 /106 (2%)
	C-REACTIVE PROTEIN (MG/DL)	5 / 32 (16%)	1 / 23 (4%)
	SGOT / AST (U/L)	15 /318 (5%)	11 /320 (3%)
	SGPT / ALT (U/L)	21 /312 (7%)	14 /324 (4%)
CLINICAL CHEMISTRY	GAMMA GT (U/L)	4 / 38 (11%)	1 / 32 (3%)
	L D H (U/L)	10 / 85 (12%)	14 / 86 (16%)
	ALKALINE PHOSPHATASE (U/L)	11 /308 (4%)	14 /300 (5%)
	BILIRUBIN (TOTAL) (MG/DL)	9 /341 (3%)	8 /342 (2%)
	BILIRUBIN (DIRECT) (MG/DL)	0 / 3 (0%)	0 / 2 (0%)
	BILIRUBIN (INDIRECT) (MG/DL)	0 / 2 (0%)	1 / 2 (50%)
	AMYLASE (U/L)	4 / 93 (4%)	12 / 87 (14%)

TABLE 54 CONTINUED
INCIDENCE RATES OF LOW LABORATORY ABNORMALITIES PER APPLICANT

ALL PATIENTS VALID FOR ITT / SAFETY ANALYSIS

LABORATORY VARIABLE		BAY 12 - 8039 400 MG (N=374)	CLARITHROMYCIN 1000 MG (N=371)
HEMATOLOGY	HEMATOCRIT (%)	10 /333 (3%)	5 /327 (2%)
	HEMOGLOBIN (G/DL)	10 /325 (3%)	10 /318 (3%)
	ERYTHROCYTES (T/L)	6 /330 (2%)	5 /326 (2%)
	MCV (FL)	0 / 68 (0%)	0 / 62 (0%)
	MCH (PG)	6 / 60 (10%)	6 / 53 (11%)
	MCHC (G/DL)	11 / 16 (69%)	14 / 19 (74%)
	LEUCOCYTES (G/L)	5 /346 (1%)	8 /340 (2%)
	NEUTROPHILS (%)	9 /316 (3%)	15 /308 (5%)
	NEUTROPHILS (BANDS) (%)	3 / 31 (10%)	4 / 36 (11%)
	NEUTROPHILS (SEGS) (%)	1 / 51 (2%)	1 / 47 (2%)
	LYMPHOCYTES (%)	27 /234 (12%)	27 /241 (11%)
	MONOCYTES (%)	3 /341 (1%)	1 /336 (0%)
	EOSINOPHILS (%)	13 /258 (5%)	16 /254 (6%)
	BASOPHILS (%)	2 /334 (1%)	6 /327 (2%)
	PLATELETS (G/L)	4 /342 (1%)	5 /336 (1%)
	PT TIME (SEC)	2 / 31 (6%)	2 / 32 (6%)
HEMATOLOGY	PT RATIO (NONE)	15 / 52 (29%)	8 / 44 (18%)
	PT INR (NONE)	0 / 15 (0%)	0 / 18 (0%)
	PTT TIME (SEC)	2 /104 (2%)	6 /101 (6%)

TABLE 5(CONTINUED
INCIDENCE RATES OF LOW LABORATORY ABNORMALITIES PER APPLICANT

ALL PATIENTS VALID FOR ITT / SAFETY ANALYSIS

LABORATORY VARIABLE		BAY 12 - 8039 400 MG (N=374)	CLARITHROMYCIN 1000 MG (N=371)
HEMATOLOGY	HEMATOCRIT (%)	10 /333 (3%)	5 /327 (2%)
	HEMOGLOBIN (G/DL)	10 /325 (3%)	10 /318 (3%)
	ERYTHROCYTES (T/L)	6 /330 (2%)	5 /326 (2%)
	MCV (FL)	0 / 68 (0%)	0 / 62 (0%)
	MCH (PG)	6 / 60 (10%)	6 / 53 (11%)
	MCHC (G/DL)	11 / 16 (69%)	14 / 19 (74%)
	LEUCOCYTES (G/L)	5 /346 (1%)	8 /340 (2%)
	NEUTROPHILS (%)	9 /316 (3%)	15 /308 (5%)
	NEUTROPHILS (BANDS) (%)	3 / 31 (10%)	4 / 36 (11%)
	NEUTROPHILS (SEGS) (%)	1 / 51 (2%)	1 / 47 (2%)
	LYMPHOCYTES (%)	27 /234 (12%)	27 /241 (11%)
	MONOCYTES (%)	3 /341 (1%)	1 /336 (0%)
	EOSINOPHILS (%)	13 /258 (5%)	16 /254 (6%)
	BASOPHILS (%)	2 /334 (1%)	6 /327 (2%)
	PLATELETS (G/L)	4 /342 (1%)	5 /336 (1%)
	PT TIME (SEC)	2 / 31 (6%)	2 / 32 (6%)
HEMATOLOGY	PT RATIO (NONE)	15 / 52 (29%)	8 / 44 (18%)
	PT INR (NONE)	0 / 15 (0%)	0 / 18 (0%)
	PTT TIME (SEC)	2 /104 (2%)	6 /101 (6%)

TABLE 54 CONTINUED
INCIDENCE RATES OF LOW LABORATORY ABNORMALITIES PER APPLICANT

ALL PATIENTS VALID FOR ITT / SAFETY ANALYSIS

LABORATORY VARIABLE		BAY 12 - 8039 400 MG (N=374)	CLARITHROMYCIN 1000 MG (N=371)
CLINICAL CHEMISTRY	GLUCOSE (MG/DL)	1 /115 (1%)	3 /115 (3%)
	URIC ACID (MG/DL)	2 /114 (2%)	1 /107 (1%)
	CALCIUM (MG/DL)	4 /105 (4%)	2 / 98 (2%)
	PHOSPHORUS (MG/DL)	11 / 94 (12%)	6 / 89 (7%)
	SODIUM (MMOL/L)	6 /347 (2%)	5 /337 (1%)
	POTASSIUM (MMOL/L)	18 /332 (5%)	13 /333 (4%)
	CHLORIDE (MMOL/L)	3 / 12 (25%)	1 / 6 (17%)
	BICARBONATE (MMOL/L)	0 / 18 (0%)	0 / 18 (0%)
	CREATININE (MG/DL)	7 /341 (2%)	5 /345 (1%)
	B U N (MG/DL)	0 / 23 (0%)	0 / 23 (0%)
	UREA (MG/DL)	7 /344 (2%)	1 /338 (0%)
	PROTEIN (G/DL)	5 /115 (4%)	1 /110 (1%)
	ALBUMIN (G/DL)	4 /117 (3%)	2 /105 (2%)
	C-REACTIVE PROTEIN (MG/DL)	0 / 90 (0%)	0 / 85 (0%)
	SGOT / AST (U/L)	15 /317 (5%)	15 /311 (5%)
	SGPT / ALT (U/L)	5 /350 (1%)	3 /350 (1%)
CLINICAL CHEMISTRY	GAMMA GT (U/L)	0 / 38 (0%)	0 / 35 (0%)
	L D H (U/L)	2 /114 (2%)	1 /110 (1%)
	ALKALINE PHOSPHATASE (U/L)	0 /351 (0%)	3 /349 (1%)
	BILIRUBIN (TOTAL) (MG/DL)	5 /349 (1%)	1 /341 (0%)
	BILIRUBIN (DIRECT) (MG/DL)	0 / 5 (0%)	0 / 4 (0%)
	BILIRUBIN (INDIRECT) (MG/DL)	0 / 2 (0%)	0 / 2 (0%)
	AMYLASE (U/L)	0 / 99 (0%)	0 / 94 (0%)

Medical Officer's Summary/Conclusions for Study 0124

Medical Officer's Summary

The MO agrees 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 the approved comparator drug, clarithromycin at 500mg BID for 7 days, 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, Haemophilus influenzae, Haemophilus parainfluenzae,* and *Moraxella catarrhalis* were the causative pathogens. There was inadequate data in patients with *Staphylococcus aureus* or *Klebsiella pneumoniae* as the causative pathogen to evaluate efficacy in these subsets of patients.

Clinical safety data suggest that dizziness, nausea, and vomiting are more common in moxifloxacin treated patients but does not appear to be treatment limiting. There were no clinically significant differences in laboratory abnormalities between treatment groups.

Medical Officer's Conclusions

Moxifloxacin tablets at 400mg orally for 5 days is effective in the treatment of acute bacterial exacerbations of chronic bronchitis due to *Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae,* and *Moraxella catarrhalis.* The bacteriologic success rate with *S. pneumoniae* was lower in this trial (84.2%) than in the previous two trials, but the absolute number of failures (6) was low. In addition, three of the six bacteriologic failures in this subset were clinical cures. In this trial, efficacy in both groups was actually slightly greater in patients over age 60 than in those younger than age 60. Efficacy in patients receiving concomitant systemic corticosteroids was less than that in the overall study population and in those not receiving steroids but was equivalent between study arms.

Medical Officer's Conclusions for Acute Bacterial Exacerbations of Chronic Bronchitis

Summary

The clinical efficacy of moxifloxacin at 400mg PO once daily for 5 days in ABECB was demonstrated in a randomized, blinded, active controlled trial in the United States (D96-027) in which the overall clinical efficacy of moxifloxacin was shown to be equivalent to a longer course of moxifloxacin at 400mg daily for 10 days, or an approved comparator, clarithromycin, dosed at 500mg PO twice daily for 10 days. The conclusions of this trial were supported by the results of a second, blinded, active-controlled trial performed in Europe (0124) in which the clinical efficacy rates of moxifloxacin 400mg PO daily for 5 days were shown to be reproducible and equivalent to a 7 day course of clarithromycin dosed at 500mg PO BID for 7 days. The bacteriologic success rate (eradications and presumed eradications) for *S. pneumoniae* in the European trial 0124 was lower than that observed in U.S. trial D96-027 (84.2% versus 100%, respectively) but the absolute number of failures in trial 0124 was low (6) and three of the six bacteriologic failures were clinical successes.

The U.S. trial demonstrated the clinical efficacy of moxifloxacin at 400mg PO daily for 5 days in patients in whom *Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis,* and *Klebsiella pneumoniae* were isolated as the causative pathogen. These results were reproducible in the European trial for 4 of the six organisms, but there were too few patients in this trial in whom *S aureus* (N=1) or *K. pneumoniae* (N=0) were isolated

to draw conclusions. The bacteriologic results in both trials were driven by the better efficacy of moxifloxacin over clarithromycin in the eradication of *H. influenzae*. There were adequate numbers of patients in trial D96-027 to support the efficacy of a 5 day course of moxifloxacin for *S. aureus* and *K. pneumoniae*. An analysis of patients in whom *S. aureus* was the sole pathogen and patients with *S. aureus* who had adequate sputum Gram's stains revealed similar results to the comparator groups.

In the U.S. trial (D96-027), the efficacy of a 5-day course of moxifloxacin in steroid-treated patients appeared to be lower than the efficacy of the approved comparator in this same population, although this difference did not reach statistical significance as defined by $p \leq 0.05$. However, in the European trial (0124) in which a larger number of patients were treated with steroids, the efficacy rate in the 5 day moxifloxacin group was equivalent to the comparator, although lower than the efficacy in the overall study population.

Similarly, in the U.S. trial (D96-027) the efficacy of a 5-day course of moxifloxacin in patients over age 65 appeared to be lower than that in the comparator group. The European trial (0124), however, actually showed better efficacy of both moxifloxacin and the comparator agent in patients over age 65 compared with those aged less than 65 years.

In both trials, more patients receiving moxifloxacin experienced mild to moderate gastrointestinal side effects such as nausea and vomiting compared to comparators. In the second U.S. trial (D96-022) more patients in the moxifloxacin arm also experienced diarrhea than patients who received cefuroxime, although the rate of diarrhea was equivalent to clarithromycin in the other two trials. The rate of dizziness also appears to be greater for moxifloxacin-treated patients than in those who received comparator agents. The rate of dizziness appears more common in patients who receive a 10-day course of moxifloxacin versus a 5-day course of the drug. Taste perversion was less common in the moxifloxacin groups.

Recommendation

Moxifloxacin 400mg PO daily for 5 days should be approved for the treatment of acute exacerbations of chronic bronchitis caused by *Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis*, and *Klebsiella pneumoniae.*

/S/

John H. Powers, M.D.
Medical Officer (HFD-590)

CC: Powers/MO/HFD590
Leissa/TL/HFD590 BL 12/17/99
Hopkins/TL/HFD590
Jensen/PM/HFD590
Meyerhoff/MO/HFD590
Sacks/MO/HFD590
Navarro/MO/HFD590
Dionne/Micro/HFD590
Shen/Stats/HFD590

Concurrence only:
DivDir/Goldberger
ODE4Dir/Kweder

Appendices

BAY 12-8039/D96-027
BRONCHITIS

APPENDIX 1
STUDY PERIODS AND SAMPLE SIZES BY CENTER PER APPLICANT

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS RANDOMIZED	VALID FOR SAFETY	PER PROTOCOL	MICROBIO. VALID	COMPLETED STUDY
1	Chodosh	04DEC96	08MAR98	BAY 12-8039 400MG X 5	13	13	12	11	13
				BAY 12-8039 400MG X 10	12	12	12	10	12
				CLARITHROMYCIN	12	12	9	9	10
				TOTAL	37	37	33	30	35
2	Littlejohn	03DEC96	26FEB98	BAY 12-8039 400MG X 5	4	4	2	1	4
				BAY 12-8039 400MG X 10	4	4	4	2	4
				CLARITHROMYCIN	6	6	5	1	6
				TOTAL	14	14	11	4	14
3	Abrahams	12DEC96	23JAN98	BAY 12-8039 400MG X 5	5	5	4	4	4
				BAY 12-8039 400MG X 10	6	6	6	4	5
				CLARITHROMYCIN	5	5	3	1	3
				TOTAL	16	16	13	9	12
4	Berger	09JAN97	05MAR98	BAY 12-8039 400MG X 5	7	7	4	2	6
				BAY 12-8039 400MG X 10	7	7	6	2	7
				CLARITHROMYCIN	7	7	5	0	7
				TOTAL	21	21	15	4	20
5	Broughton	03DEC96	16APR97	BAY 12-8039 400MG X 5	3	3	3	1	3
				BAY 12-8039 400MG X 10	4	4	3	2	3
				CLARITHROMYCIN	4	4	3	0	3
				TOTAL	11	11	9	3	9
6	Pearl	05DEC96	04OCT97	BAY 12-8039 400MG X 5	5	5	5	2	5
				BAY 12-8039 400MG X 10	3	3	3	0	3
				CLARITHROMYCIN	4	4	2	1	3
				TOTAL	12	12	10	3	11
7	Repsher	17DEC96	18JAN98	BAY 12-8039 400MG X 5	4	4	4	2	4
				BAY 12-8039 400MG X 10	4	4	4	2	4
				CLARITHROMYCIN	5	5	4	4	5
				TOTAL	13	13	12	8	13
8	Schear	21NOV96	24DEC96	BAY 12-8039 400MG X 5	5	4	2	1	4
				BAY 12-8039 400MG X 10	5	4	2	0	3
				CLARITHROMYCIN	4	4	1	0	1
				TOTAL	14	12	5	1	8

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APPENDIX 1 (CONTINUED)
STUDY PERIODS AND SAMPLE SIZES BY CENTER PER APPLICANT

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS RANDOM-IZED	VALID FOR SAFETY	PER PROTOCOL	MICROBIO. VALID	COMPLETED STUDY
9	Simon	25NOV96	26APR97	BAY 12-8039 400MG X 5	14	14	9	3	12
				BAY 12-8039 400MG X 10	14	14	12	4	12
				CLARITHROMYCIN	14	14	14	3	11
				TOTAL	42	42	35	10	35
10	Willsie	17JAN97	19JUN97	BAY 12-8039 400MG X 5	3	3	3	0	3
				BAY 12-8039 400MG X 10	3	3	3	2	3
				CLARITHROMYCIN	4	4	4	0	4
				TOTAL	10	10	10	2	10
11	Baz	27NOV96	04MAR98	BAY 12-8039 400MG X 5	12	12	12	5	11
				BAY 12-8039 400MG X 10	12	12	11	6	11
				CLARITHROMYCIN	12	12	11	3	12
				TOTAL	36	36	34	14	34
12	Bowman	03JAN97	28NOV97	BAY 12-8039 400MG X 5	4	4	4	0	4
				BAY 12-8039 400MG X 10	2	2	2	1	2
				CLARITHROMYCIN	4	4	4	3	4
				TOTAL	10	10	10	4	10
13	DeAbate	22NOV96	29JUN97	BAY 12-8039 400MG X 5	60	57	48	43	52
				BAY 12-8039 400MG X 10	60	56	47	42	50
				CLARITHROMYCIN	60	59	55	47	58
				TOTAL	180	172	150	132	160
14	Dewan	16DEC96	07MAR98	BAY 12-8039 400MG X 5	18	18	14	4	15
				BAY 12-8039 400MG X 10	18	18	14	7	17
				CLARITHROMYCIN	16	16	13	5	15
				TOTAL	52	52	41	16	47
15	Kreitzer	03JAN97	09NOV97	BAY 12-8039 400MG X 5	6	6	6	2	6
				BAY 12-8039 400MG X 10	6	6	4	2	4
				CLARITHROMYCIN	7	7	6	2	6
				TOTAL	19	19	16	6	16
16	Castle	02DEC96	28JAN98	BAY 12-8039 400MG X 5	4	4	4	1	4
				BAY 12-8039 400MG X 10	5	5	5	3	4
				CLARITHROMYCIN	5	5	5	3	4
				TOTAL	14	14	14	7	12

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APPENDIX 1 (CONTINUED)
STUDY PERIODS AND SAMPLE SIZES BY CENTER PER APPLCANT

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS RANDOMIZED	VALID FOR SAFETY	PER PROTOCOL	MICROBIO. VALID	COMPLETED STUDY
17	Folds	23JAN97	01FEB97	BAY 12-8039 400MG X 5	0	0	0	0	0
				BAY 12-8039 400MG X 10	0	0	0	0	0
				CLARITHROMYCIN	1	1	1	0	1
				TOTAL	1	1	1	0	1
18	Laviolette	22NOV96	27MAR97	BAY 12-8039 400MG X 5	4	4	3	1	3
				BAY 12-8039 400MG X 10	4	4	3	1	4
				CLARITHROMYCIN	4	4	3	0	4
				TOTAL	12	12	9	2	11
19	Muramoto	27NOV96	26SEP97	BAY 12-8039 400MG X 5	4	4	3	1	3
				BAY 12-8039 400MG X 10	4	4	2	0	4
				CLARITHROMYCIN	5	5	4	1	4
				TOTAL	13	13	9	2	11
20	Miller	20JAN97	20NOV97	BAY 12-8039 400MG X 5	2	2	2	1	1
				BAY 12-8039 400MG X 10	2	2	2	1	2
				CLARITHROMYCIN	2	2	0	0	1
				TOTAL	6	6	4	2	4
21	Moore	03FEB97	27MAR97	BAY 12-8039 400MG X 5	0	0	0	0	0
				BAY 12-8039 400MG X 10	1	1	1	1	1
				CLARITHROMYCIN	1	1	1	0	1
				TOTAL	2	2	2	1	2
22	Wray	22JAN97	20FEB97	BAY 12-8039 400MG X 5	1	1	0	0	0
				BAY 12-8039 400MG X 10	0	0	0	0	0
				CLARITHROMYCIN	2	2	1	1	2
				TOTAL	3	3	1	1	2
23	Fino	27NOV96	08APR97	BAY 12-8039 400MG X 5	6	6	4	2	6
				BAY 12-8039 400MG X 10	4	4	3	2	4
				CLARITHROMYCIN	4	4	4	2	4
				TOTAL	14	14	11	6	14
25	Whitlock	15JAN97	29MAR97	BAY 12-8039 400MG X 5	2	2	0	0	1
				BAY 12-8039 400MG X 10	4	4	3	1	4
				CLARITHROMYCIN	3	3	2	1	2
				TOTAL	9	9	5	2	7

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APPENDIX 1 (CONTINUED)
STUDY PERIODS AND SAMPLE SIZES BY CENTER PER APPLICANT

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS RANDOMIZED	VALID FOR SAFETY	PER PROTOCOL	MICROBIO. VALID	COMPLETED STUDY
26	Aldrich	20DEC96	09MAR98	BAY 12-8039 400MG X 5	13	13	13	10	13
				BAY 12-8039 400MG X 10	12	12	12	8	12
				CLARITHROMYCIN	13	13	13	10	12
				TOTAL	38	38	38	28	37
27	Haberman	03FEB97	13FEB97	BAY 12-8039 400MG X 5	1	1	0	0	1
				BAY 12-8039 400MG X 10	0	0	0	0	0
				CLARITHROMYCIN	0	0	0	0	0
				TOTAL	1	1	0	0	1
28	Storrow	07FEB97	24DEC97	BAY 12-8039 400MG X 5	3	3	3	1	3
				BAY 12-8039 400MG X 10	4	4	3	1	3
				CLARITHROMYCIN	4	4	4	0	4
				TOTAL	11	11	10	2	10
29	Atwater	28JAN97	30APR97	BAY 12-8039 400MG X 5	2	2	1	0	1
				BAY 12-8039 400MG X 10	3	3	2	1	3
				CLARITHROMYCIN	2	2	1	0	1
				TOTAL	7	7	4	1	5
31	Collins	03JAN97	15MAR97	BAY 12-8039 400MG X 5	4	4	2	1	4
				BAY 12-8039 400MG X 10	4	4	2	0	4
				CLARITHROMYCIN	4	4	2	1	3
				TOTAL	12	12	6	2	11
32	Nolen	23DEC96	16FEB97	BAY 12-8039 400MG X 5	1	1	0	0	0
				BAY 12-8039 400MG X 10	0	0	0	0	0
				CLARITHROMYCIN	1	1	1	0	1
				TOTAL	2	2	1	0	1
33	Samuels	18DEC96	07MAR98	BAY 12-8039 400MG X 5	3	3	2	2	2
				BAY 12-8039 400MG X 10	3	3	3	2	3
				CLARITHROMYCIN	5	5	4	2	5
				TOTAL	11	11	9	6	10
34	Bruya	03DEC96	03MAR98	BAY 12-8039 400MG X 5	18	18	16	6	17
				BAY 12-8039 400MG X 10	18	18	16	5	15
				CLARITHROMYCIN	17	17	12	2	13
				TOTAL	53	53	44	13	45

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APPENDIX 1 (CONTINUED)
STUDY PERIODS AND SAMPLE SIZES BY CENTER PER APPLICANT

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS RANDOMIZED	VALID FOR SAFETY	PER PROTOCOL	MICROBIO. VALID	COMPLETED STUDY
35	Casale	10DEC96	04MAY97	BAY 12-8039 400MG X 5	3	3	2	0	3
				BAY 12-8039 400MG X 10	3	3	2	0	3
				CLARITHROMYCIN	2	2	2	0	2
				TOTAL	8	8	6	0	8
36	Gower	05DEC96	24FEB97	BAY 12-8039 400MG X 5	2	2	1	0	2
				BAY 12-8039 400MG X 10	0	0	0	0	0
				CLARITHROMYCIN	1	1	0	0	0
				TOTAL	3	3	1	0	2
37	Krainson	27JAN97	23AUG97	BAY 12-8039 400MG X 5	6	6	4	2	5
				BAY 12-8039 400MG X 10	5	5	4	3	5
				CLARITHROMYCIN	5	5	3	0	4
				TOTAL	16	16	11	5	14
38	Ruoff	27JAN97	25JAN98	BAY 12-8039 400MG X 5	8	8	5	1	7
				BAY 12-8039 400MG X 10	9	9	5	2	9
				CLARITHROMYCIN	8	8	5	2	8
				TOTAL	25	25	15	5	24
39	Jimenez	27FEB97	16APR97	BAY 12-8039 400MG X 5	0	0	0	0	0
				BAY 12-8039 400MG X 10	1	1	0	0	0
				CLARITHROMYCIN	1	1	0	0	1
				TOTAL	2	2	0	0	1
40	Pace	22FEB97	17FEB98	BAY 12-8039 400MG X 5	1	1	0	0	0
				BAY 12-8039 400MG X 10	3	3	3	0	3
				CLARITHROMYCIN	1	1	0	0	0
				TOTAL	5	5	3	0	3
41	Siegel	14JAN97	20DEC97	BAY 12-8039 400MG X 5	5	5	4	2	4
				BAY 12-8039 400MG X 10	5	5	4	1	5
				CLARITHROMYCIN	5	5	2	1	5
				TOTAL	15	15	10	4	14
43	Bode	29JAN97	20MAR97	BAY 12-8039 400MG X 5	2	2	2	1	2
				BAY 12-8039 400MG X 10	1	1	1	0	1
				CLARITHROMYCIN	3	3	3	2	2
				TOTAL	6	6	6	3	5