Of note among line listings of clinically significant low values were hematocrit seen 31.2% and 10.1%, bicarbonate 24.2% and 15.0% of BAY 12-8039 and amoxicillin treatment groups, respectively.

> MO COMMENT: The significance of these differences is perhaps best understood in the context of the review of the safety database for the entire NDA. For further discussion, the reader is referred to the review of the Integrated Summary of Safety.

REVIEWER'S COMMENTS

This clinical trial of BAY 12-8039 400 mg daily for 10 days demonstrated clinical efficacy equivalent to that of high dose amoxicillin (1000 mg tid for 10 days) in the treatment of patients with community-acquired pneumonia. This study population, which was designed to enrich for patients infected with *S. pneumoniae*, provided data on over 300 hospitalized patients and provided blood culture data on all patients. Clinical efficacy for BAY 12-8039 was shown to be equivalent to that of high dose amoxicillin at both the EOT visit (applicant endpoint) and at the F/U visit (MO endpoint). Similarly, clinical efficacy for BAY 12-8039 was noted to be equivalent to that of amoxicillin in both ambulatory and hospitalized patients. Of note, however, was the decrease in efficacy rates for both treatment groups when cure rates for out-patients were compared with those for in-patients.

It is important to recognize that etiologic organisms of CAP may differ between these two patient populations, and that criteria for the admission to the hospital in the study under review may have differed substantially from current medical practice in the US. Surveillance data suggest that *S. pneumoniae* is probably a more common organism in CAP patients who are hospitalized compared with patients who are managed in an ambulatory setting. The predominant organism in ambulatory patients is more likely to be one that causes a self-limited disease, *Mycoplasma pneumoniae.* When the more serious manifestations of pneumococcal pneumonia were analyzed, it was not clear that BAY 12-8039 was clinically equivalent to high dose amoxicillin. Data from a small number of bacteremic patients did not demonstrate that BAY 12-8039 achieved a cure rate comparable to that of high dose amoxicillin. Similarly, data from a small number of patients infected with penicillin-resistant *S. pneumoniae* did not demonstrate that BAY 12-8039 achieved a cure rate comparable to that of high dose amoxicillin.

As was noted in study #D96026, gastrointestinal AEs were the most common AEs associated with treatment with moxifloxacin, and patients who were treated with moxifloxacin had a higher rate of low values for certain red blood cell indices. The review of safety data in this study also showed a higher rate of low serum bicarbonate values in patients treated with BAY 12-8039. The reports of cholestatic jaundice noted in three patients treated with BAY 12-8039 are perhaps best understood in the context of the Integrated Summary of Safety.

Study No. 0119

A multinational, multicentre, prospective, randomised, double-blind study to compare the efficacy and safety of two doses of BAY 12-8039 oral tablets to clarithromycin oral tablets in the treatment of patients with community acquired pneumonia

STUDY DESIGN

This equivalence study was conducted at 50 centers outside the United States from November 1996 to February 1998. The centers were located in Austria, Australia, Germany, Great Britain, Greece, Hong Kong, Israel, Indonesia, New Zealand, Norway, Philippines, South Africa, Sweden, Switzerland, and Taiwan. Moxifloxacin 400 mg daily for 10 days, moxifloxacin 200 mg daily for 10 days, and clarithromycin 500 mg daily for 10 days were compared in a 1:1:1 randomization for both efficacy and safety in the treatment of CAP. Clarithromycin 250 mg bid is approved for the treatment of CAP due to *S. pneumoniae, M. catarrhalis,* and *C. pneumoniae.* For additional discussion of this choice of comparator agent, the reader is referred to the MOR-CAP study no. D96026.

> MO COMMENT: The geographic regions included in this study provide an opportunity to evaluate the efficacy of both agents in developed and developing countries and in areas such as South Africa which have been shown to have high rates of penicillin-resistant pneumococcal isolates.

> MO COMMENT: This study enrolled both ambulatory and hospitalized patients with CAP. As noted in the introduction to the MO review of the CAP indication, the published literature suggests that etiologic agents may differ in these two populations as characterized in the US, Canada, and Western Europe. Atypical pathogens such as *M. pneumoniae* and *C. pneumoniae* account for a larger proportion of CAP in out-patients, while *S. pneumoniae* continues to be the most commonly isolated pathogen in in-patients with CAP.

Patients aged 18 years or older with signs and symptoms consistent with community acquired pneumonia were eligible for enrollment. Patients were treated as in-patients or out-patients at the discretion of the investigator. In order to be classified as having CAP, patients must have had evidence of all three of the following:

- Fever (core T $\geq$ 38.5° or oral T $\geq$ 38°C) and/or leukocytosis (WBC > 10, 000 or 15% bands)
- Radiologic evidence of an infiltrate consistent with pneumonia
- One or more of the following: productive cough, purulent sputum, dyspnea or tachypnea, rigors/chills, pleuritic chest pain, auscultatory findings such as rales/rhonchi indicating pulmonary consolidation

Exclusion criteria of note were patients with severe cardiac failure (NYHA Class IV), patients with severe respiratory tract infections requiring parenteral therapy or mechanical ventilatory support, patients with suspected aspiration pneumonia, patients hospitalized more than 48 hours, patients with significant liver impairment (SGOT, SGPT, and/or total bilirubin >3x upper limit of normal), patients with significant renal impairment (Cr >3.0 mg/dl or Cr clearance <30 cc/min), and patients with coexistent disease thought likely to affect the outcome of the study, including lung cancer, lung abscess, connective tissue disease affecting the lungs, empyema. A protocol amendment (dated 5/97) also excluded patients with prolonged QT interval on EKG or patients taking medication reported to increase the QT interval.

> MO COMMENT: Factors that determine whether or not a patient is to be hospitalized for a given illness can vary according to setting. Severity of illness, availability of resources, cultural perceptions of hospitalization, and local practice patterns can all affect whether a patient is managed in or out of the hospital. Because the decision to hospitalize was not standardized in this study, but rather left to the individual investigator, characteristics of the groups of ambulatory and hospitalized patients may vary widely and may only permit limited conclusions regarding these categories of CAP.

In addition to the clinical and radiologic evaluations described above, certain laboratory tests were performed prior to enrollment. Two aliquots of blood were taken for culture from each patient at enrollment. Specimens of sputum were obtained for gram stain and culture from all patients who were able to provide one. Transtracheal aspirates, bronchoscopic washings or brushings, and pleural fluid were also obtained when necessary for gram stain and culture. Serum samples were obtained for serologic testing for *Legionella pneumophila, Chlamydia pneumoniae, Chlamydia psittaci, and Coxiella burnetti.*. Routine hematology (complete blood count or CBC) serum chemistries, and urinalysis were also performed. ECGs were performed at enrollment and at specified time points during the treatment period for a small fraction of the patients enrolled. During the course of the study, any additional testing or use of therapeutic adjuncts including blood gas determination, CT scan, bronchoscopy, and supplemental oxygen administration were also recorded in the case report form.

> MO COMMENT: The sponsor reported that the performance of EKGs was instituted when this study was already underway. The EKG data on patients in study #0119 was not part of the study report, but summarized with EKG data from other clinical trials. The reader is referred to the MO Review of Safety for further information.

Once randomized and started on treatment, patients were instructed to return on Day 3-5 of treatment (During Therapy Visit), Day 3-5 post-treatment (End of Therapy Visit or

EOT), and Day 21-28 post-treatment (Follow-up Visit or F/U). Clinical, laboratory, and compliance assessments were made at these visits.

Patients were considered evaluable for efficacy analysis (per protocol population) if they met the clinical criteria for the diagnosis of CAP as noted above, if no other systemic antibacterial agents were administered concomitantly with the study drug (unless the patient were a treatment failure), if study drug were given for a minimum of 48 hours if the result of therapy were a failure, or a minimum of 5 days if the result were a success, if compliance with dosing were $\geq$ 80%, if there were no protocol violations which influenced treatment efficacy, if the random code were not broken, if there were no missing or 'indeterminate' essential data which could not be recovered.

The primary efficacy variable was the clinical cure in the per protocol population at the EOT Visit (3-5 days following the completion of therapy). To test the hypothesis that BAY 12-8039 was not less effective than control drug, the sponsor planned to calculate a two-sided 95% CI around the difference in the two efficacy rates. If the lower limit of this CI were > -15%, BAY 12-8039 was proven to be not less effective than controls, and subsequent hypotheses comparing the efficacy of BAY 12-8039 200 mg to control and to the 400 mg regimen were to be tested.

> MO COMMENT: The use of the EOT visit as the primary efficacy endpoint for this study is not consistent with FDA guidelines for CAP studies set forth in either the 1992 Points to Consider Document and the 1997 Draft Guidance for Industry. The applicant pointed out that this study, conducted outside the US, was undertaken using European regulatory guidelines that warranted that theTOC be assessed at this early post-treatment visit. The pharmacokinetics of moxifloxacin warrant some review when considering what can be learned from this visit. The t1/2 is approximately 12 hours at the end of a 10-day dosing regimen, at which time the plasma Cmax is 4.5mg/L (µg/ml). It has been shown that tissue concentrations can far exceed plasma levels. In the bronchial mucosa, Cmax has been shown to be ~1.7x plasma concentration; in the alveolar macrophages, Cmax has been shown to be ~18x plasma concentration. The MIC_{90} of moxifloxacin for *S. pneumoniae* strains isolated in the clinical studies of the NDA was 0.25 µg/ml. Three to five days following the completion of a 10-day course of therapy represents six to ten half-lives of drug. In the alveolar macrophage, moxifloxacin levels range from [redacted] µg/ml during this period. Patients with pneumococcal pneumonia who were evaluated during the 3-5 day interval following the completion of therapy would still have had drug levels above the MIC of the infecting organism in some tissue compartments of the lung, and late failures would not be included in this population. For this reason, the MO analysis also included an evaluation of clinical cure in the PP population at the F/U visit 21-28 days following the completion of therapy.

STUDY RESULTS

Demographics

There were 678 patients enrolled in this study; 224 were treated with BAY 12-8039 400 mg daily, 229 were treated with BAY 12-8039 200 mg daily, and 222 with clarithromycin 500 bid (three patients were withdrawn because they either did not receive study drug or had no post-baseline assessments). Demographic characteristics of patients in both treatment arms are presented in Table 1. The groups were well matched for gender, age, and weight.

Table 1. Demographic variables at enrollment by treatment group

	BAY 400 mg n= 224	BAY 200 mg n=229	Clarithromycin n=222
Sex – Male	137	142	138
Female	87	87	84
Age (Yrs), Mean	48.0	48.4	48.2
Weight (kg), Mean	67.8	67.3	68.0

MO COMMENT: Of the patients enrolled, 472/678 (69.6%) were hospitalized either 2 days prior to the start of therapy (n= 7), 1 day prior to the start of therapy (n=204) or the day therapy was initiated (n=261).

Evaluability and efficacy

Clinically evaluable population

Applicant assessment

Table 2 presents the applicant's analysis of clinical outcome in those patients who were clinically evaluable for efficacy analysis. As noted above, inclusion in this study population did not require that a microbiologic etiology of the patient's infection be identified.

Table 2. Clinical response in clinically evaluable population at 3-5 days post therapy (EOT)- applicant assessment.

	BAY 12-8039 400 mg q d x 10 d	**BAY 12-8039 200 mg q d x 10 d**	**Clarithromycin 500 bid x 10 d**
No. evaluable	177	180	174
No. cures	167	169	164
Efficacy rate	94.4%	93.9%	94.3%

The 95% CI around the difference in cure rates for the BAY 12-8039 400 mg group and the clarithromycin group was reported by the applicant as (-6.7, 4.1). The applicant's assessment of cure rates at the EOT visit meets the statistical requirement for

demonstrating equivalence with an approved comparator. As noted above, the pharmacokinetics of moxifloxacin suggest that at the EOT visit, a significant proportion of patients may have tissue levels of moxifloxacin above the MIC for *S. pneumoniae.* Thus assessment of cure rates at EOT may not provide information about late failures in pneumococcal pneumonia. The applicant also performed an analysis of clinical efficacy at F/U (day 21-28 following completion of therapy). These results are presented in Table 3 below.

Table 3. Clinical response in clinically evaluable population at 21-28 days post therapy (F/U)- applicant assessment

	BAY 12-8039 400 mg q d x 10 d	**BAY 12-8039 200 mg q d x 10 d**	**Clarithromycin 500 bid x 10 d**
No. evaluable	152	161	153
No. cures	141	146	141
Efficacy rate	92.8%	90.7%	92.2%

The 95% CI around the difference in cure rates for the BAY 12-8039 400 mg group and the clarithromycin group was reported by the applicant as (-8.6, 4.5). The applicant's assessment of cure rates at the EOT visit meets the statistical requirement for demonstrating equivalence with an approved comparator.

Clinically evaluable population
MO assessment
Clinical efficacy

Evaluability and efficacy in the clinically evaluable population were assessed by the MO using a sampling technique. A random sample of approximately 25% of the study population was generated. Individual CRTs and pertinent databases were reviewed by the MO for agreement between the MO and applicant regarding evaluability and outcome. The MO assessed patient evaluability and efficacy with the same general scheme as that used for study #D96026 (see MOR study #D96026).

Review of the sample as described above resulted in reclassification by the MO of four patients in the moxifloxacin 400 mg treatment group and one patient each in the moxifloxacin 200 mg and clarithromycin treatment groups. All of these patients were considered evaluable cures by the applicant; the MO reclassified them as unevaluable. Analysis of these changes demonstrated adequate agreement with the applicant's findings such that the MO accepted the applicant's assessments of evaluability and clinical outcome of the clinically evaluable population at the EOT and F/U visits. These data, presented above in Table 2, demonstrate a high efficacy rate for moxifloxacin in the treatment of CAP that is shown to be statistically equivalent to that of an approved comparator, clarithromycin, according to the prospectively determined criteria specified in the protocol. The lower bound of the 95% CI around the difference in point estimates of efficacy rates in both the EOT and F/U analyses is >-15%.

Microbiologically and clinically evaluable population
Clinical efficacy by infecting organism

Table 4 presents the applicant's assessment of clinical efficacy in microbiologically and clinically evaluable patients by infecting organism.

Table 4. **Clinical Resolution Rates of Proposed Dosing Regimen at the Test-of-Cure (EOT) Visit by Organism –Applicant analysis**

	BAY 12-8039 400 mg q D	Clarithromycin 500 mg bid
Streptococcus pneumoniae	15/16 (94%)	12/13 (92%)
Haemophilus influenzae	7/8 (88%)	5/10 (50%)
Mycoplasma pneumoniae	23/25 (92%)	30/32 (94%)
Chlamydia pneumoniae	20/20 (100%)	21/23 (91%)
Staphylococcus aureus	1/1 (100%)	2/2 (100%)
Moraxella catarrhalis	1/2 (50%)	3/3 (100%)
Klebsiella pneumoniae	1/2 (50%)	1/3 (33%)

Clinical efficacy of BAY 12-8039 400 mg daily in patients infected with *S. pneumoniae* was comparable to that observed for clarithromycin. Clinical efficacy of BAY 12-8039 400 mg daily in patients infected with *H. influenzae* was better than that observed for patients treated with clarithromycin. It should be noted once again that clarithromycin is not approved for treatment of CAP due to *H. influenzae.* Clinical efficacy rates observed for BAY 12-8039 400 mg daily in patients infected with the atypical pathogens *M. pneumoniae* and *C. pneumoniae* were comparable to the comparator and to what was observed for BAY 12-8039 in other studies. Study #0119 did not provide substantial additional data regarding clinical efficacy in CAP due to *S. aureus, K. pneumoniae,* or *M. catarrhalis.*

Clinical efficacy in patients with *S. pneumoniae* bacteremia

There were a total of 34 patients in study #0119 who were found to have *S. pneumoniae* growing in the blood. Table 5 presents the applicant's assessment of clinical efficacy in patients with pneumococcal bacteremia by treatment group, and demonstrates high efficacy rates that were comparable across treatment groups.

Table 5. Clinical efficacy in patients with pneumococcal bacteremia (F/U)-applicant analysis

	BAY 400 mg q d	BAY 200 mg q d	Clari 500 mg bid
No. pts	10	18	8
No. evaluable pts	5	12	5
No. cures (%)	5 (100.0)	12 (100.0)	5 (100.0)
Reasons for unevaluability			
Essential data missing	N=3 (#4, 931, 992)	N=0	N=0
Adverse event	N=1 (#31)	N=1 (#825)	N=2 (#2, 92)
Insuff therapeutic effect	N=1 (#63)	N=2 (#121, 650)	N=0
Non-compliance	N=0	N=2 (#901, 920)	N=1 (#525)
Consent withdrawn	N=0	N=1 (#167)	N=0
Total no. pts unevaluable	N=5	N=6	N=3

Of the 34 patients with pneumococcal bacteremia, the applicant found that 14 (41%) were unevaluable. Because a positive blood culture for *S. pneumoniae* in a patient with an infiltrate on chest x-ray represents the 'gold standard' for diagnosis of pneumococcal pneumonia, these patients represent an important population from which to gather data on drug efficacy in pneumococcal infection. It should also be noted that bacteremic patients may not be appropriate for oral antimicrobial therapy, and thus efficacy rates in this population may be an especially stringent analysis for the agents under study in #0119. Nonetheless, a comparison of efficacy rates across treatment groups can be informative, and the MO performed an independent analysis of these patients. This is presented in Table 6. below.

Table 6. Clinical efficacy in patients with pneumococcal bacteremia (F/U)- MO analysis

	BAY 400 mg q d	BAY 200 mg q d	Clari 500 mg bid
No. pts	10	18	8
No. evaluable pts	7	14	6
No. cures (%)	5 (71.4)	10 (71.4)	5 (83.3)
Reasons for unevaluability			
Essential data missing	N=2 (#931, 992)	N=0	N=0
Adverse event	N=0	N=1 (#825)	N=1 (#2)
Insuff therapeutic effect	N=0	N=0	N=0
Non-compliance	N=0	N=2 (#901, 920)	N=1 (#525)
Consent withdrawn	N=0	N=1 (#167)	N=0
Violation incl/excl criter	N=1 (#31)		
Total no. pts unevaluable	N=3	N=4	N=2

The MO review of the CRFs and pertinent databases for patients with pneumococcal bacteremia resulted in an increase in the number of evaluable patients. In the BAY 400 mg treatment group, there were two such patients. Patient # 4 was a 67 year old man who developed a right pleural effusion on day 4 of treatment. At that time, ampicillin and erythromycin were added to his regimen. In the setting of pneumococcal bacteremia, this

patient's clinical condition deteriorated and new antimicrobials were added to his regimen. He was considered a failure of therapy by the MO. Patient # 63 was also considered evaluable and a failure in the MO analysis. He was a 78 year old man whose clinical condition worsened on day 2 of therapy. In the BAY 200 treatment group there were also two such patients. Patient #121 was a 31 year old woman who discontinued study drug on day 6 for insufficient therapeutic effect; patient # 650 was a 77 year old woman who was considered to have an insufficient therapeutic effect on day 2. Both of these patients were considered failures by the MO. In the clarithromycin treatment group, patient # 92 was a 49 year old who developed hypoxia and died on day 2. The MO analysis regarded this patient as a failure of treatment.

The more stringent MO analysis of clinical efficacy rates in patients with pneumococcal bacteremia demonstrated lower rates for all three treatment groups. Such small numbers do not provide conclusive results. Rather they serve as a reminder that occasional pneumococcal pneumonia patients who are candidates for oral therapy can be bacteremic. As noted in study #0140, such patients treated with BAY 12-8039 do not achieve the same clinical success rates as non-bacteremic patients with this infection.

Safety

Extent of exposure

Of the 678 patients enrolled in the study, 675 received at least one dose of study medication and were available for follow-up and thus evaluable for safety. Safety data are presented below as adverse events or laboratory abnormalities.

Adverse events

Adverse event rates that occurred in at least 2% of any treatment group are presented in Table 7, and treatment-related adverse event rates that occurred in at least 1% of either treatment group are presented in Table 8.

Table 7. Incidence of adverse events occurring in at least 2% of any treatment group

Most frequently occurring adverse events (2% or more in any treatment group)									
Adverse Event	**Treatment group**								
COSTART Term	**200 mg BAY 12-8039 o.d.**			**400 mg BAY 12-8039 o.d.**			**500 mg Clarithromycin b.i.d.**		
	n	**(m)**	**%**	**n**	**(m)**	**%**	**n**	**(m)**	**%**
Total number of patients valid for safety	**229**	**(-)**	**-**	**224**	**(-)**	**-**	**222**	**(-)**	**-**
Total number of adverse events	**113**	**(210)**	**49.3**	**114**	**(244)**	**50.9**	**111**	**(214)**	**50.0**
Death	5	(-)	2.2	2	(-)	0.9	5	(-)	2.3
Diarrhoea	14	(15)	6.1	19	(20)	8.5	12	(12)	5.4
Liver function test abnormal	8	(9)	3.5	18	(18)	8.0	13	(15)	5.9
Nausea	9	(9)	3.9	10	(13)	4.5	13	(13)	5.9
Headache	4	(4)	1.7	10	(10)	4.5	9	(9)	4.1
Abdominal pain	10	(10)	4.4	8	(10)	3.6	4	(4)	1.8
Dizziness	8	(8)	3.5	8	(9)	3.6	3	(3)	1.4
Pneumonia	5	(5)	2.2	7	(8)	3.1	6	(7)	2.7
Herpes simplex	5	(5)	2.2	3	(3)	1.3	5	(5)	2.3
Taste perversion	3	(3)	1.3	2	(2)	0.9	8	(8)	3.6
Nausea and vomiting	3	(3)	1.3	5	(6)	2.2	5	(5)	2.3
Vomiting	3	(3)	1.3	5	(5)	2.2	4	(4)	1.8
Oral Moniliasis	7	(7)	3.1	2	(2)	0.9	2	(2)	0.9
Cough increased	5	(5)	2.2	2	(2)	0.9	2	(2)	0.9

Note: n = number of patients, (m) = number of mentions, % = percentage of patients.
Population: Safety/ITT population.

Table 8. Incidence of treatment-related adverse events occurring in at least 1% of any treatment group

Drug related adverse events by primary body system and treatment (1% or more in any treatment group)									
Body system	**Treatment group**								
	200 mg BAY 12-8039 o.d.			**400 mg BAY 12-8039 o.d.**			**500 mg Clarithromycin b.i.d.**		
	n	**(m)**	**%**	**n**	**(m)**	**%**	**n**	**(m)**	**%**
Digestive system	**42**	**(55)**	**18.3**	**57**	**(69)**	**25.4**	**46**	**(55)**	**20.7**
Diarrhoea	13	(14)	5.7	19	(20)	8.5	8	(8)	3.6
Liver function tests abnormal	8	(9)	3.5	16	(16)	7.1	13	(15)	5.9
Nausea	9	(9)	3.9	(9)	10	4.0	8	(8)	3.6
Nausea and vomiting	2	(2)	0.9	5	(6)	2.2	5	(5)	2.3
Vomiting	3	(3)	1.3	5	(5)	2.2	4	(4)	1.8
Oral moniliasis	6	(6)	2.6	2	(2)	0.9	2	(2)	0.9
Constipation	3	(3)	1.3	3	(3)	1.3	3	(3)	1.4
Body as a whole	**23**	**(24)**	**10.0**	**20**	**(28)**	**8.9**	**12**	**(14)**	**5.4**
Abdominal pain	9	(9)	3.9	8	(10)	3.6	3	(3)	1.4
Headache	4	(4)	1.7	7	(7)	3.1	4	(4)	1.8
Nervous system	**10**	**(11)**	**4.4**	**15**	**(17)**	**6.7**	**10**	**(11)**	**4.5**
Dizziness	1	(1)	0.4	2	(2)	0.9	1	(1)	0.5
Respiratory system	**6**	**(6)**	**2.6**	**6**	**(6)**	**2.7**	**12**	**(13)**	**5.4**
Pneumonia	2	(2)	0.9	3	(3)	1.3	1	(1)	0.5
Cardiovascular system	**6**	**(6)**	**2.6**	**8**	**(8)**	**3.6**	**3**	**(3)**	**1.4**
Special senses	**4**	**(4)**	**1.7**	**3**	**(3)**	**1.3**	**10**	**(10)**	**4.5**
Taste perversion	3	(3)	1.3	2	(2)	0.9	8	(8)	3.6
Skin and appendages	**7**	**(7)**	**3.1**	**1**	**(1)**	**0.4**	**7**	**(7)**	**3.2**
Hemic and lymphatic system	**6**	**(6)**	**2.6**	**2**	**(3)**	**0.9**	**3**	**(3)**	**1.4**

Note: n = number of patients, (m) = number of mentions, % = percentage of patients.

The most common drug-related adverse events in the BAY 12-8039 400 mg group were diarrhea (8.5%), liver function test abnormalities (7.1%), nausea (4%), abdominal pain (3.6%), headache (3.1%) and vomiting (2.2%). The most common drug-related adverse events in the clarithromycin group were liver function test abnormalities (5.9%), diarrhea (4.3%), taste perversion (3.6%), nausea (3.6%), and nausea and vomiting (2.3%) The incidence of liver function test abnormalities was higher in the BAY 400 mg treatment group (7.1%) than the BAY 200 mg treatment group (3.5%). However, review of the

incidence of clinically significant abnormalities in liver function tests (≥3x ULN) did not reveal a difference between these two treatement groups.

Deaths and serious adverse events

There were twelve deaths reported in this study. Five patients died in the moxifloxacin 200 mg treatment group, two in the moxifloxacin 400 mg treatment group, and five patients died in the clarithromycin treatment group.

> MO COMMENT: The MO reviewed the narratives of each of the above patients' deaths. Two of the patients in the moxofloxacin 200 mg group died following worsening of their infections, two others experienced cardiac arrest. One patient in the moxifloxacin 400 mg group had carcinoma of the esophagus and experienced cardiac arrest and apnea 3 days after the start of study medication. One patient in the clarithromycin group died from sepsis 1-2 days after stopping study medication. These deaths, possibly treatment related, are best viewed in the context of the review of the entire safety database. The reader is referred to the MOR of the Integrated Summary of Safety for further discussion.

A total of 29 patients were prematurely discontinued from study drug therapy due to adverse events, seven in the BAY 12-8039 200 mg treatment group, eleven in the BAY 400 mg treatment group and eleven in the clarithromycin treatment group. Reasons for discontinuations that were remotely, possibly, or probably related to study drug in the BAY 200 mg group included lack of drug effect, pancreatitis, pneumonia, atrial fibrillation, chills, cerebral infarct, and gastrointestinal hemorrhage. Such reasons in the BAY 400 mg treatment group included deep vein thrombosis, pleural effusion, atrial fibrillation, intestinal obstruction, cerebrovascular accident, diarrhea (2 patients), overdose, sepsis, pneumonia. Such reasons in the clarithromycin group included respiratory acidosis, cerebral infarct, respiratory disorded, and pleural effusion.

> MO COMMENT: A wide variety of events resulted in premature discontinuation of drug. There did not appear to be a trend among these findings.

Laboratory abnormalities

Clinically significant changes in laboratory values were observed for leukocytes, platelets, alkaline phosphatase, bicarbonate, glucose, and total protein. Review of the incidences of these abnormalities across treatment groups shows that they were similar, suggesting these clinically significant abnormalities resulted from the underlying disease process.

REVIEWER'S COMMENTS

This clinical trial of BAY 12-8039 400 mg daily for 10 days demonstrated clinical efficacy equivalent to that of clarithromycin 500 mg bid in the treatment of patients with community-acquired pneumonia. Clinical efficacy for BAY 12-8039 400 mg was shown to be equivalent to that of clarithromycin at both the EOT visit and at the F/U visit.

When bacteremic patients with pneumococcal pneumonia were analyzed, it was not clear that BAY 12-8039 400 mg was as efficacious as it was in all patients with CAP due to *S. pneumoniae*. Though the number of patients in this analysis was small, and bacteremic patients are generally not candidates for oral therapy, it is noteworthy that clinical efficacy in the population of patients with the most compelling data for pneumococcal infection was not as high as was observed in all patients thought to have this infection. As was noted in other studies of CAP, gastrointestinal AEs were the most common AEs associated with treatment with moxifloxacin.

APPEARS THIS WAY
ON ORIGINAL

STUDY NO. D96-025

Prospective, uncontrolled, non-blind multicenter clinical trial of the safety and efficacy of BAY 12-8039 400 mg once daily for 10 days in the treatment of patients with community acquired pneumonia

STUDY DESIGN

This open-label study was conducted in out-patients at 40 centers in the United States from December 1996 to May 1998. Patients aged 18 years or older with signs and symptoms consistent with bacterial pneumonia, as described for study # D96-026, were eligible for enrollment. As for study #D96-026, a protocol amendment was implemented before completion of the study to allow inclusion of patients who had CAP but did not have fever and/or leukocytosis. Exclusion criteria were the same as for the above-mentioned study, including a protocol amendment to exclude patients with prolongation of the QT interval of the EKG.

In addition to the clinical and radiologic evaluations, certain laboratory tests were performed prior to enrollment. These included sputum gram stain and bacterial culture, serology for *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* infections, throat and nasopharyngeal swabs for *Mycoplasma* and *Chlamydia* cultures (and in the case of *Mycoplasma*, throat swab for PCR also), sputum for *Mycoplasma* culture and PCR, and *Legionella pneumophila* culture, and urine for *Legionella* antigen assay. Routine hematology (complete blood count or CBC) serum chemistries, EKGs, and urinalyses were also performed.

Once randomized and started on treatment, patients were instructed to return on Day 3-5 of treatment (During Therapy Visit), Day 2-4 post-treatment (End of Therapy Visit or EOT), and Day 21-28 post-treatment (Follow-up Visit or F/U). Clinical, laboratory, and compliance assessments were made at these visits.

The applicant first determined that the primary efficacy endpoint for this study was to be clinical response at end of therapy (EOT). During the conduct of the study, draft FDA guidelines were released which specified that the primary time point for evaluating efficacy should be at least 5 elimination half-lives of the study drug or 7 days after the end of treatment, whichever was longer. A protocol amendment was implemented to change the primary efficacy endpoint to clinical response at follow-up (F/U), 21-28 days following the completion of therapy. Prior to unblinding, the window for this F/U visit was expanded to 14-35 days following the completion of therapy in order to maximize the number of evaluable patients. This modification was made following discussion with the review division, when it was also established that any failures at EOT would be 'carried forward' and included in the population of overall failures.

Patients were considered evaluable or valid for efficacy analysis if they met the clinical criteria for the diagnosis of CAP as noted above, if no other systemic antibacterial agents were administered concomitantly with the study drug, if study drug were given for a minimum of 48 hours if the result of therapy were a failure, or a minimum of 5 days if the result were a success, if compliance with dosing were $\geq$ 80%, if there were no protocol

violations which influenced treatment efficacy, if the random code were not broken, if there were no missing or 'indeterminate' essential data which could not be recovered.

> MO COMMENT: The applicant described the primary efficacy endpoint for this study as clinical outcome at the F/U visit in a clinically evaluable patient population. This is consistent with FDA guidelines for CAP studies set forth in both the 1992 Points to Consider Document and the 1997 Draft Guidance for Industry.

The applicant also performed a second efficacy analysis of patients who were both clinically and microbiologically evaluable. Clinical response and bacteriologic eradication rates were evaluated for this population.

> MO COMMENT: The MO analysis of patients who were clinically and microbiologically evaluable assessed clinical response in patients for whom a microbiologic etiology of CAP could be established using results of sputum gram stain, sputum culture, serology, and/or sputum or mucosal swab PCR.

STUDY RESULTS

Demographics

There were 254 patients enrolled in this study. Table 1 presents the demographics of this population.

Table 1. Demographic variables study population

	BAY 12-8039
Sex, % male	58%
Race, % caucasian	85%
Age at Enrollment (Yrs), Mean	49
Weight (kg), Mean	79
Cigarette smoker	53%
Mean # cigarettes smoked/day	21
Mean years of smoking	26

Evaluability and efficacy

Clinically evaluable population

Applicant assessment

Table 2 presents the applicant's analysis of clinical outcome at the F/U visit in those patients who were clinically evaluable for efficacy analysis. As noted above, inclusion in this study population did not require that a microbiologic etiology of the patient's infection be identified.

Table 2. Clinical response in clinically evaluable population - applicant assessment

	BAY 12-8039
End of Therapy	
Resolution	184/196 (93.9%)
Failure or Relapse	6/196(3.1%)
Indeterminate	6/196 (3.1%)
Follow-up	
Resolution	182/196 (92.9%)
Failure or Relapse	8/196(4.1%)
Indeterminate	6/196 (3.1%)
Overall* Resolution	182/196 (92.9%)
Failure	14/196 (7.1%)
* 95% Confidence Interval for overall success rates (88.1%, 95.9%)	

Clinically evaluable population
MO assessment

Evaluability and efficacy in the clinically evaluable population were assessed by the MO using a sampling technique. A random sample of ~20% of the study population was generated. Individual CRTs and pertinent databases for each of these patients were reviewed by the MO for agreement between the MO and applicant regarding evaluability and outcome. The MO assessed patient evaluability with the general scheme described for study #D96-026.

Review of the sample as described above resulted in the reclassification of one patient by the MO. The applicant scored patient #24008 as unevaluable, the MO reclassified this patient as an evaluable failure. Analysis of this reclassification suggested sufficient agreement with the applicant's findings such that the MO accepted the applicant's assessment of the primary efficacy endpoint, evaluability and clinical outcome of the clinically evaluable population at the TOC visit. These data, presented above in Table 2, demonstrate a high efficacy rate for moxifloxacin in the treatment of CAP that is comparable to what was observed in other CAP studies.

Microbiologically and clinically evaluable population
Applicant assessment

Table 3 presents the applicant's assessment of clinical efficacy in microbiologically and clinically evaluable patients by infecting organism.

Table 3. **Clinical Resolution Rates of Proposed Dosing Regimen at the Test-of-Cure Visit (F/U) by Organism**

	BAY 12-8039 400 mg q D
Streptococcus pneumoniae	13/14 (93%)
Haemophilus influenzae	11/13 (85%)
Mycoplasma pneumoniae	28/29 (97%)
Chlamydia pneumoniae	58/63 (92%)
Staphylococcus aureus	8/9 (89%)
Moraxella catarrhalis	4/4 (100%)
Klebsiella pneumoniae	4/4 (100%)

MO assessment
The applicant noted that a number of organisms may have been associated with a single case of pneumonia in an individual patient. As noted in the MOR of study # D96026, the review of clinical course, sputum gram stain, and sputum culture data did not support an etiologic diagnosis of *S. aureus* or *K. pneumoniae* in the small population of CAP patients thought possibly infected with those agents in that study. The study under review here presented a second study population that may provide information regarding the efficacy of moxifloxacin in these two serious infections. Table C. above states that there were nine patients considered by the applicant to be infected with *S. aureus* and four patients considered infected with *K. pneumoniae* who were evaluable for clinical outcome. Clinical presentation, sputum gram stains, and sputum culture results were individually reviewed for each of these patients. There were no blood culture results to review.

Of the four evaluable patients considered by the applicant to have CAP due to *K. pneumoniae*, three were afebrile with normal vital signs at presentation. All had purulent sputum specimens; two had gram negative rods seen on sputum gram stain, two had gram negative rods and gram positive cocci seen on sputum gram stain. For all four of these cases, there were three species considered 'infecting' microrganisms. All of these patients were considered infected with *K. pneumoniae*, *M. pneumoniae*, and *C. pneumoniae* based on the results of respiratory tract cultures. Two of the four patients from whom *K. pneumoniae* was isolated also provided upper respiratory tract specimens (specimens described by the applicant as 'upper respiratory' rather than 'respiratory') from which *K. pneumoniae* grew, thus introducing the possibility that this organism was an upper respiratory tract colonizer in these patients.

Of the nine evaluable patients considered by the applicant to have CAP due to *S. aureus*, five were afebrile with normal vital signs at presentation. For two of these nine patients, gram negative rods were the only organisms visualized on sputum gram stain, for two

others gram positive cocci and gram negative rods were visualized, and for the remaining five, gram positive cocci were the only organisms seen on gram stain. There were no data presented regarding the conformations of the cocci seen (eg. clusters, chains, pairs). For all nine of these patients, at least three species were considered 'infecting' organisms. All of these patients were considered infected with *S. aureus, M. pneumoniae,* and *C. pneumoniae* based on the results of respiratory tract cultures. All nine of these patients from whom *S. aureus* was isolated also provided upper respiratory tract specimens from which *S. aureus* grew, thus introducing the possibility that this organism was an upper respiratory tract colonizer in these patients.

While there can be a range of clinical presentations, sputum gram stain manifestations, and sputum culture results that are consistent with pneumonia due to *K. pneumoniae, S. aureus*, or any other etiologic agent, no single patient in the two subpopulations described above presented with clinical and microbiologic manifestations suggestive of either of these serious necrotizing infections. That all of these patients had multiple etiologic agents attributed to their presentations makes CAP due to one of these more rare organisms even less likely. This study did not provide adequate data to support an efficacy claim for moxifloxacin in the treatment of CAP due to *K. pneumoniae* or *S. aureus.*

SAFETY

Extent of exposure

All 254 patients enrolled in the study were evaluable for safety. The mean number of days of therapy was 9 days, and 89% of patients received treatment between 9 and 11 days.

Adverse events

Table 4 summarizes the types of adverse event data collected. Comparison of this table with that presented for the other out-patient study, #D96-026, shows that the rates of these events were comparable between the two studies except that in the present study, a higher proportion of patients discontinued study drug due to an adverse event (7% v. 3%)

Table 4. Summary of adverse events

	BAY 12-8039 400 mg (N=254)
Any Adverse Event	122 (48%)
Any Drug-Related Event	85 (33%)
Any Serious Event	14 (6%)
Discontinued due to AE	18 (7%)
Died	2 (1%)

Adverse event rates that occurred in at least 2% of either treatment group are presented in Table 5, and treatment-related adverse event rates that occurred in at least 2% of either treatment group are presented in Table 6.

Table 5. Incidence of adverse events occurring in at least 2% of patients

Adverse Event	BAY 12-8039 400 mg (N=254)
Any event	122 (48%)
Headache	12 (5%)
Abdominal pain	8 (3%)
Asthenia	5 (2%)
Chest pain	5 (2%)
Nausea	25 (10%)
Diarrhea	20 (8%)
Vomiting	10 (4%)
Dyspepsia	5 (2%)
Anorexia	4 (2%)
Dizziness	15 (6%)
Insomnia	10 (4%)
Asthma	6 (2%)
Pharyngitis	5 (2%)
Pneumonia	4 (2%)
Rhinitis	4 (2%)
Rash	4 (2%)

Table 6. Incidence of treatment-related adverse events occurring in at least 2% of patients

Adverse Event	BAY 12-8039 400 mg (N=254)	
Any event	85	(33%)
Headache	8	(3%)
Abdominal pain	4	(2%)
Nausea	22	(9%)
Diarrhea	16	(6%)
Vomiting	6	(2%)
Dizziness	10	(4%)
Insomnia	5	(2%)
Rash	4	(2%)

MO COMMENT: The MO reviewed the complete line listings for all adverse events and all treatment-related adverse events. In those listings, there was one additional adverse event that was clinically noteworthy, ventricular fibrillation and death that was not considered related to study medication. The MO reviewed the narrative for this patient, #25014, a 76 year old man with a complex history of cardiopulmonary disease who experienced a cerebrovascular accident after one day of study medication. Study drug was stopped at this point. Thirteen days later, the patient had an episode of ventricular fibrillation and died. The MO agreed that this arrhythmia was unrelated to study drug, and that there was a possible relationship between study drug and cerebrovascular accident.

The most common drug-related adverse events in this study were nausea, diarrhea and vomiting. Headache, dizziness and insomnia were also seen with relatively high frequency in this group. This profile of adverse events is similar to that reported in study #D96-026, the other US-based study of out-patients with CAP.

Deaths and serious adverse events

There were two deaths reported for this study. Patient #25014 is described above. Patient #13009 died of respiratory arrest four days after receiving one dose of moxifloxacin. This patient was a 68 year old man with a severe COPD exacerbation and was not evaluated for or enrolled in the study. He received one dose of moxifloxacin 400 mg by mistake because he was in the same hospital room as a patient who was enrolled in the study.

> MO COMMENT: The MO reviewed the narratives of each of the above patients' courses and concurs with the above conclusions.

A total of 18 patients were prematurely discontinued from study drug therapy due to adverse events. Three patients discontinued prematurely due to rash. No other event was associated with premature discontinuation more than twice. Other reasons for premature discontinuation were nausea, vomiting, diarrhea, congestive heart failure, asthma exacerbation, pulmonary embolism, dizziness, agitation, tremor/blurred vision/lightheadedness, anxiety attack, weight gain, respiratory failure, elevated liver function tests, cerebrovascular accident.

Serious adverse events

A total of 14 patients in this study experienced serious adverse events. In 4 cases the serious adverse events did not occur until after the end of study drug therapy. The majority of these events were respiratory, including four cases of pneumonia. Other serious AEs included elevated liver function tests, empyema, bilateral interstitial pneumonitis, and diabetic ketoacidosis.

> MO COMMENT: Review of the serious adverse events did not provide any additional information regarding the safety profile of BAY 12-8039 in the study under review. Worsening respiratory status was noted among a number of patients who prematurely discontinued study drug or who experienced a serious adverse event. Such events may provide more information about drug efficacy than safety.

Laboratory abnormalities

Table 7 presents incidence of high and low clinical chemistry and hematology parameters that occurred in at least 5% of patients. The denominators in this table refers to those patients with pre- and post- enrollment readings who did not have the abnormality pre-enrollment.

Table 7. Incidence Rates of Laboratory Abnormalities Occurring in at Least 5% of Patients

Lab Variable	BAY 12-8039 400 mg (N = 254)
High	
WBC	6/129 (5%)
Neutrophils (bands)	2/9 (22%)
Neutrophils (segs)	15/138 (11%)
Lymphocytes	18/247 (7%)
Monocytes	11/234 (5%)
Eosinophils	19/237 (8%)
Platelets	24/232 (10%)
PT	31/171 (18%)
PTT	17/194 (9%)
Serum glucose	36/204 (18%)
Calcium	12/234 (5%)
Phosphorus, inorg	19/237 (8%)
Potassium	11/243 (5%)
Chloride	21/244 (9%)
C-reactive protein	3/44 (7%)
SGPT/ALT	25/224 (11%)
GGT	12/202 (6%)
Cholesterol, total	59/170 (35%)
Triglycerides	68/214 (32%)
Low	
Hematocrit	24/196 (12%)
Hemoglobin	21/198 (11%)
RBC	15/129 (12%)
Lymphocytes	9/115 (8%)
Serum glucose	12/242 (5%)
Uric acid	18/195 (9%)

Without a comparator group in this study, the significance of these observations is unclear. A number of these findings are seen in acute infections such as pneumonia. It is noteworthy that depressed red blood cell indices were more common than other hematologic abnormalities, as was noted in study # D96-026.

REVIEWER'S COMMENTS

The clinical efficacy of BAY 12-8039 400 mg daily for 10 days observed in this study was comparable to what has been observed for this regimen in other studies of community-acquired pneumonia. This study did not provide sufficient to support a claim for clinical efficacy of moxifloxacin in the treatment of pneumonia due to *S. aureus* or *K. pneumoniae*. The adverse event and laboratory abnormality profile seen for moxifloxacin in this study was similar to what was reported from other studies.

APPEARS THIS WAY
ON ORIGINAL

STUDY NO. 0112

Prospective, randomised, double-blind, pilot study to investigate the safety and efficacy of two oral dosages of BAY 12-8039 vs amoxycillin in the treatment of patients with community acquired pneumonia

This phase II study was conducted at five centers in South Africa from July to December 1996. It enrolled 117 patients; 38 patients received moxifloxacin 200 mg daily, 40 patients received moxifloxacin 400 mg daily, and 39 patients received amoxicillin 500 mg tid. Patients were to receive study medication for a minimum of five days and a maximum of 14 days if the treatment were successful, and for a minimum of 2 days if the treatment failed. The primary efficacy endpoint was the clinical response at the end of therapy visit, 3-5 days following the completion of therapy.

One hundred four patients were evaluable for the per protocol analysis at the EOT visit. Cure rates observed for each treatment group were 29/33 (87.9%) for moxifloxacin 200 mg, 27/35 (77.1%) for moxifloxacin 400 mg, and 38/36 (77.8%) for amoxicillin 500 mg tid. The applicant concluded that the study was too small to provide conclusive results on the relative efficacy of the three treatments studied, but stated that the results suggested all three treatments have similar efficacy.

> MO COMMENT: Review of the total number of doses taken in each treatment group showed that patients received study drug for similar lengths of time across all three groups. The mean numbers of doses taken for each group were 19.7 for moxifloxacin 200 mg, 18.9 for moxifloxacin 400 mg, and 19.4 for amoxicillin.
>
> MO COMMENT: The endpoint established by the applicant was not the primary efficacy endpoint recommended by FDA in the 1997 Guidance Document, which suggests that the test-of-cure be assessed at the follow-up visit. In this study, that would be the visit 21-28 days following completion of therapy. As noted in the MOR of study # D96-026, the pharmacokinetics of moxifloxacin suggest that patients may still have clinically significant drug levels at 3-5 days following the completion of therapy. The applicant presented additional data regarding clinical efficacy in the per protocol population at follow-up. Cure rates for each treatment group were 18/33 (54.6%) for moxifloxacin 200 mg, 19/35 (54.3%) for moxifloxacin 400 mg, and 61/104 (66.7%) for amoxicillin 500 mg tid. As noted by the applicant, the study was too small to provide conclusive results regarding comparative efficacy, and did not reflect the efficacy rates of moxifloxacin demonstrated in larger clinical trials.
>
> MO COMMENT: The applicant included patients with missing results in the per protocol analysis discussed above. When clinical efficacy is assessed in the population of those patients who were either cured or failed therapy at F/U, efficacy rates were 18/23 (78.3%) for moxifloxacin 200 mg, 18/26 (73.1%) for moxifloxacin 400 mg, and 24/31 (77.4%) for amoxicillin.

MO COMMENT: The applicant described antimicrobial use in the per protocol population after the end of the study. Seven patients in the moxifloxacin 200 mg group (21.2%), four patients in the moxifloxacin 400 mg group (11.4%), and four patients in the amoxicillin group (11.1%) reported taking antimicrobials after the end of the study. There were no data provided regarding reasons for antimicrobial use or clinical status.

REVIEWER'S COMMENTS

This small study did not distinguish between the clinical efficacy of moxifloxacin 200 mg and moxifloxacin 400 mg for the treatment of community acquired pneumonia. It suggested that moxifloxacin may be similar to amoxicillin 500 mg tid in the treatment of this infection.

APPEARS THIS WAY
ON ORIGINAL

CONCLUSION TO MEDICAL OFFICER'S REVIEW OF CAP INDICATION FOR NDA 21-085

Moxifloxacin, an oral fluoroquinolone, has been shown to be safe and effective for the treatment of community acquired pneumonia of mild to moderate severity. Efficacy has been demonstrated in patients with CAP due to *S. pneumoniae, H. influenzae, M. catarrhalis, Mycoplasma pneumoniae,* and *Chlamydia pneumoniae.*

It should be recognized that in two studies (studies #0140 and #0119), data from a small number of patients who had CAP and pneumococcal bacteremia demonstrated lower efficacy rates (~70%) for moxifloxacin than either high dose amoxicillin or clarithromycin (100% or 83%, respectively). Similarly, these data demonstrated lower efficacy for moxifloxacin in treating pneumococcal pneumonia with bacteremia (~70%) than in treating non-bacteremic pneumococcal pneumonia (90-95%). For this reason, labeling should specify that moxifloxacin is indicated for the treatment of CAP of mild to moderate severity. Though a small population, such bacteremic patients represent the gold standard for the diagnosis of pneumococcal infection. The label should also include mention of these divergent results for bacteremic patients with *S. pneumoniae* in the CLINICAL STUDIES section.

Data from a small number of patients also demonstrated that moxifloxacin was not as effective as high-dose amoxicillin in the treatment of CAP due to strains of *S. pneumoniae* that were resistant to penicillin (MIC $\geq$ 2.0). The label should not include any statements in the INDICATIONS AND USAGE section suggesting efficacy in CAP due to PCN-R or PCN-I strains of *S. pneumoniae.* There were insufficient clinical and/or microbiologic data to support claims of efficacy in the treatment of CAP due to *K. pneumoniae* or *S. aureus.* These organisms should not be included in the CAP section of the INDICATIONS AND USAGE section.

I recommend approval of moxifloxacin for the treatment of community acquired pneumonia due to *S. pneumoniae, H. influenzae, M. catarrhalis, Mycoplasma pneumoniae,* and *Chlamydia pneumoniae.*

/S/

Andrea Meyerhoff MD MSc DTMH
Medical Officer/DSPIDP

CC: Original NDA 21-085
HFD-590
HFD-590/MO/Meyerhoff
HFD-590/Chem/Matecka
HFD-590/Micro/Dionne
HFD-590/Pharm/Ellis
HFD-590/Biopharm/Meyer
HFD-725/Biometrics/Shen
HFD-590/PM/Jensen

Concurrence only:
HFD-590/TmLdrMO/Hopkins
HFD-590/DivDir/Goldberger
HFD-104/OfficeDir/Kweder

/S/ 12/9/98

APPEARS THIS WAY
ON ORIGINAL

Bibliography

1. American Thoracic Society, Guidelines for the initial management of adults with community-acquired pneumonia: diagnosis, assessment of severity, and initial antimicrobial therapy. Am Rev Resp Dis; 148: 1418-1426, 1993.
2. Bartlett JG and Mundy LM, Community-acquired pneumonia. New Eng J Med; 333: 1618-24, 1995.
3. Bartlett JG et al, Community –acquired pnuemonia in adults: guidelines for management. Clin Infect Dis; 26:811-38, 1998.
4. Burman LA et al, Diagnosis of pneumonia by cultures, bacterial and viral antigen detection tests, and serology with special reference to antibodies to pneumococcal antigens. J Infect Dis; 163: 1087-93, 1990.
5. Chen DK et al, Decreased susceptibility of *Streptococcus pneumoniae* to fluoroquinolones in Canada. New Eng J Med; 341:233-9, 1999.
6. Fang GD et al, New and emerging etiologies for community acquired pneumonia with implications for therapy. Medicine; 69: 307-16, 1990.
7. Critchley I, et al, Activity of moxifloxacin against resistant and susceptible populations of *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis* isolated in the United States, Abstract presented at 39th ICAAC, September 26, 1999.
8. Grayston JT et al, A new *Chlamydia psittaci* strain, TWAR, isolated in acute respiratory tract infections. New Eng J Med; 315: 161-8, 1986.
9. Grayston JT et al, Evidence that *Chlamydia pneumoniae* causes pneumonia and bronchitis. J Infect Dis; 168: 1231-5, 1993.
10. Marrie TJ, et al, Ambulatory patients with community acquired pneumonia, the frequency of atypical agents and clinical course. Am J Med; 101: 508-515, 1996.
11. Marrie TJ, Community acquired pneumonia: epidemiology, etiology, and treatment. Infect Dis Clin N Amer; 12 (3) 723-740, 1998.
12. Michetti G et al, Community acquired pneumonia: is there a difference in etiology between hospitalized and out-patients (abstract). Minerva Med; 86: 341-51, 1995.
13. Musher DM and Spindel SJ, Community acquired pneumonia. Current Clin Topics Inf Dis; 16: 102-24, 1996.
14. Ostergaard L et al, Etiology of community acquired pneumonia. Chest; 104: 1400-07, 1993.
15. Thornsberry C et al, Longitudinal analysis of resistance among *Streptococcus pneumoniae* isolated from 100 geographically distributed institutions in the United States during the 1997-98 and 1998-99 respiratory seasons. Abstract presented at 39th ICAAC, September 27, 1999.
16. Uldum SA et al, Enzyme immunoassay for detection of immunoglobulin M (IgM) and IgG antibodies to *Mycoplasma pneumnoiae.* J Clin Micro; 30: 1198-1204, 1992.

Review of the Safety of Moxifloxacin hydrochloride

NDA 21-085
Title: Medical officer's review of NDA

Applicant identification

Bayer Corporation
400Morgan Lane
West Haven,
CT 065-4175
Phone: 203 812-2000

Submission/review dates
Date of submission: December 9, 1988
Date review completed: November 18, 1999

Medical reviewer: L Sacks

Drug identification:

Generic name: Moxifloxacin hydrochloride tablets
Trade name: AVELOX™ tablets
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 hydrochloride

Pharmacologic category: C-8methoxy-fluoroquinolone
Dosage form: tablet
Route of administration: oral

Table of contents

NDA 21-085
Safety review

This NDA review covers the worldwide safety experience with Moxifloxacin up until the data cutoff date of September 10, 1998. Included are all completed studies, and those patients from ongoing studies who were enrolled prior to May 31, 1998. Additional safety data until Dec 31 1998 is reviewed in the 4 month safety update.

Regulatory history: Since filing of the original moxifloxacin IND on December 22, 1995, interactions with the FDA included:
3 teleconferences in 1996 regarding dose selection.
A pre NDA meeting in February 1998 requesting studies in hairless mice for phototoxicity from UVA and UVB.
A meeting with the Cardio-renal division of the FDA in June 1998 addressed the prolongation of the QT interval by moxifloxacin and the potential risk for Torsade de Pointes.

Data Sources:

Safety data were obtained from 18 phase II and III studies for the claimed indications, three clinical studies for indications that were not claimed and 38 phase I clinical pharmacology studies
Safety results of the phase II and III clinical trials are discussed below. Safety results of the 38 phase I clinical pharmacology studies are discussed later.

Table 1 Clinical trials for claimed and unclaimed indications included
(number of patients on moxifloxacin given for each study)

Controlled US	Controlled non-US	Uncontrolled US
Sinusitis 267	Sinusitis 246	Sinusitis 372
Sinusitis 238	Sinusitis 244	
	Sinusitis 53	
AECB 623	AECB 376	
AECB 448	AECB 21	
CAP 237	CAP 454	CAP 254
	CAP 203	
	CAP 78	
Other 57	Other 218	
	Other 351	
Totals 2071	2536	626

A total of 5233 patients were allocated to receive Moxifloxacin in clinical trials listed above.

Patients were considered evaluable for safety if they had taken at least one dose of the study drug.
Of the 5233 patients enrolled, 267 participants in a sinusitis study were analyzed separately as the study was only completed later. Of the remaining 4966 patients 4926 were evaluable for safety. Forty were not evaluable for safety as they were not documented to have taken the medication (16 in US studies and 24 in foreign studies).
The table below illustrates the demographic characteristics of these patients

Table 2: Worldwide clinical studies- demographic data

		All BAY 12-8039 (N=4926) N (%)	Sinusitis BAY 12-8039 (N=1143) N (%)	AECB BAY 12-8039 (N=1457) N (%)	CAP BAY 12-8039 (N=1222) N (%)
Sex	Male	2347 (48)	473 (41)	771 (53)	718 (59)
	Female	2579 (52)	670 (59)	686 (47)	504 (41)
Race	Caucasian	3407 (69)	911 (80)	1110 (76)	778 (64)
	Black	770 (16)	48 (4)	235 (16)	281 (23)
	Asian	116 (2)	5 (<1)	7 (<1)	55 (5)
	Amer. Indian	7 (<1)	0	3 (<1)	2 (<1)
	Hispanic	103 (2)	35 (3)	15 (1)	37 (3)
	Other	225 (5)	0	3 (<1)	26 (2)
	Not Reported	255 (5)	143 (13)	84 (6)	0
	Missing	43 (<1)	0	0	43 (4)
Age*					
	18-64 years	3845 (78%)	1060 (93%)	940 (65%)	924 (76%)
	65-74 years	651 (13)	59 (5)	341 (23)	152 (12)
	> 74 years	426 (9)	22 (2)	176 (12)	145 (12)
Age (Years)	Mean	47.6	40.4	56.7	48.3
	Std	18.2	14.0	15.5	19.3
	Min	17.0	17.0	18.0	17.0
	Median	46.0	38.0	59.0	46.0
	Max	97.0	87.0	95.0	93.0

* Four patients were < 18 years for all indications. 2 of these were evaluable for safety in sinusitis indication, 1 of these was evaluable for safety in pneumonia indication.

Males and females were approximately equally represented. The majority of the patients were caucasian. The mean age was 47.6 years. The youngest population was found in the sinusitis studies and the oldest in the AECB studies. Approximately equal numbers of patients were studied at US and foreign sites.

Of the above 4926 evaluable patients treated with Moxifloxacin in the worldwide pool of phase III studies, 4301 were enrolled in controlled studies. Patients receiving control medications numbered 3415. Their demographic characteristics were very similar to patients treated with moxifloxacin (see below). The mean age of controls was 1.2 years younger than moxifloxacin treated patients.

Table 3: demographic features of participants in controlled studies worldwide

			BAY 12-8039 (N=4301) N (%)	CONTROL (N=3415) N (%)
SEX	MALE		2066 (48)	1571 (46)
	FEMALE		2235 (52)	1844 (54)
RACE	MISSING		43 (<1)	43 (1)
	CAUCASIAN		2883 (67)	2298 (67)
	BLACK		721 (17)	482 (14)
	ASIAN		111 (3)	92 (3)
	AMERICAN INDIAN		7 (<1)	4 (<1)
	HISPANIC		56 (1)	37 (1)
	OTHER		225 (5)	207 (6)
	NOT REPORTED		255 (6)	252 (7)
AGE*	18-64 YEARS		3306 (77)	2672 (78)
	65-74 YEARS		603 (14)	467 (14)
	> 74 YEARS		388 (9)	272 (8)
AGE (YEARS)		MEAN	48.1	46.9
		STD	18.4	18.3
		MIN	17.0	17.0
		MEDIAN	46.0	45.0
		MAX	97.0	95.0

* Four patients were < 18 years in each of the BAY 12-8039 and control groups.

Drug exposure:
In the worldwide pool of patients, 557 were treated with Moxifloxacin 200mg/day of which 556 were evaluable for safety. 4406 were treated with Moxifloxacin 400mg/day of which 4370 were evaluable for safety. Duration of treatment varied with the protocols, ranging between 5 and 14 days as shown below:

Table 4: Number of patients randomized to receive each dosing regimen with moxifloxacin

Treatment	Data Missing	Duration of Treatment (days) ≤4	5-8	9-12	>12
All Studies					
ALL BAY 12-8039	33	237	1294	2792	570
200 MG	2	32	80	416	26
400 MG	31	205	1214	2376	544
Controlled Studies					
ALL BAY 12-8039	32	214	921	2564	570
CONTROL	15	156	815	1896	533

Most patients received between 5 and 12 days of treatment with 400mg of Moxifloxacin a day.

Patients who received control medication:
3415 patients were treated with control drugs listed below:
Control drugs: cefuroxome axetil (most sinusitis studies)
clarithromycin (most CAP studies)
amoxacillin
[redacted]
metronidaxole,
TMP/SMX, ofloxacin, doxycycline, ciprofloxacin (UTI, PID)
In most cases, clarithromycin was given at doses of 500mg BID. (This is twice the dose recommended by the FDA for the treatment of pneumonia.)

MO comment: The comparative frequencies of adverse events for moxifloxacin and clarithromycin should be viewed in the light of the high doses of clarithromycin used. Lower rates of adverse events in comparator treated subjects might have been expected if the FDA recommended doses were used.

Outcomes:
The safety outcomes were reported as premature discontinuations, adverse events, serious adverse events, deaths, and laboratory abnormalities. Specific electrocardiographic outcomes are discussed later.

Premature discontinuations of treatment occurred in 557 of 4966 patients enrolled. Four of the 4966 patients were never randomized. Studies were completed by 89% of patients.

Table 5: Reasons given for premature discontinuation of drug

	All patients	200mg moxifloxacin	400mg moxifloxacin
Total number	4966	557	4409
Premature discontinuation	557 (11%)	90 (16%)	467 (11%)
Adverse event	208 (4%)	27 (5%)	181 (4%)
Non-compliance	47 (<1%)	11 (2%)	36 (<1%)
Consent withdrawn	42 (<1%)	6 (1%)	36 (<1%)
Insufficient therapeutic effect	74 (1%)	20 (4%)	54 (1%)
Lost to follow-up	129 (3%)	23 (4%)	106 (2%)
Death	6 (<1%)	1 (<1%)	5 (<1%)
Protocol violation	46 (<1%)	2 (<1%)	44 (<1%)
Resistant organism	2		2
Accidental dosing	1		1
Investigator request	2		2

Premature discontinuations were more common in patients treated on 200mg/day, mainly for reasons of an insufficient therapeutic effect or loss to follow-up. The six deaths reported here will be evaluated later with all study-related deaths.

Adverse events:

The Sponsor defined an adverse event (AE) as any undesirable experience occurring to a patient during a clinical study, whether or not considered related to the investigational product.

A serious adverse event (SAE) was an adverse event that was fatal, life-threatening, disabling or resulted in hospitalization, or prolonged hospitalization. Congenital anomalies and malignancy were also considered SAE's.

Medical officer's comment: The definition does not indicate that delayed drug related AE's occurring beyond the duration of a study are captured. Apart from the arthropathy seen in animals, most recognized adverse effects of quinolones are however not known to occur as delayed sequelae. Events unlikely to be identified under this definition included asymptomatic ECG changes which were addressed specifically in a modification of the study protocols and are discussed in a separate section.

The relationship of adverse events to the administration of medication was classified as "none", "remote", "possible", "probable", or "not assessable". This was a clinical decision by the investigator based on the time the drug was given and the time the event occurred, recovery on stopping the drug and recurrence on resumption, the presence of underlying conditions, the use of concomitant medication, known events associated with the class of drugs, other stresses or exposures experienced by the patient, and the pharmacokinetic behavior of the study drug.

Probable: followed a reasonable temporal sequence from drug administration, abated upon discontinuation of the drug (dechallenge), and could not be reasonably explained by known characteristics of the patient's clinical state.
Possible: followed a reasonable temporal sequence from drug administration, and could have been produced by the patient's clinical state or by other modes of therapy administered to the patient.
Remote: temporal association was such that the drug was not likely to have had any reasonable association with the observed event.
None: intercurrent conditions, illnesses, and injuries; events felt by the investigator to have had no relation to the study drug.
Not assessable: association with drug administration could not be determined.

The intensity of events was graded as mild (usually transient and not interfering with normal activities), moderate (causing sufficient discomfort to interfere with normal activities), or severe (incapacitating and interfering with normal activities).

Adverse events were followed a minimum of 7 days beyond the last dose of study drug. Adverse events were coded using COSTART terms and were considered drug related if the relationship to study drug was not equal to "none".

Presentation of AE data:
The worldwide phase III studies were presented as a single data pool and will be reviewed below. Other data sets to be reviewed separately include the incomplete sinusitis trial, the phase I/II study data pool and the data pool on ECG findings.

Summary of adverse events:
Overall, adverse events (including those considered drug related and not drug related) were reported by 46% of the 4926 patients treated with Moxifloxacin. (See table)

Similar event rates were reported for each of the indications ranging from 44% in the sinusitis AECB and [redacted] 49% in the CAP indication. The body system for which events were most commonly reported was the gastrointestinal system with event rates of 22% overall, ranging between 20% and for AECB) and 24% (for CAP). The most common individual adverse events were nausea (9%), diarrhea (7%) and headache (5%). Only nausea showed a dose response. Most events occurred in the first few days of dosing, and events emerging later in treatment were not evident in a follow-up of up to 49 days. 43 patients with a missing start date were not included in these figures and were separately presented. Among these patients, AE's of potential importance included photosensitivity in 1 and chest pain in 1, each treated with Moxifloxacin. No intervention was given for 60% of the adverse events. Remedial drugs were given for 27% of the AE's.

Events of unusual frequency:

Table 6: Incidence of AE's by body system occurring in more than 2% of patients

ADVERSE EVENT	ALL BAY 12-8039 (N=4926)	200 MG BAY 12-8039 (N=556)	400 MG BAY 12-8039 (N=4370)
ANY BODY SYSTEM			
ANY EVENT	2288 (46%)	248 (45%)	2040 (47%)
BODY AS A WHOLE			
ANY EVENT	781 (16%)	92 (17%)	689 (16%)
HEADACHE	245 (5%)	17 (3%)	228 (5%)
ABDOMINAL PAIN	152 (3%)	17 (3%)	135 (3%)
ASTHENIA	90 (2%)	6 (1%)	84 (2%)
CARDIOVASCULAR SYSTEM			
ANY EVENT	254 (5%)	24 (4%)	230 (5%)
DIGESTIVE SYSTEM			
ANY EVENT	1100 (22%)	103 (19%)	997 (23%)
NAUSEA	422 (9%)	20 (4%)	402 (9%)
DIARRHEA	359 (7%)	38 (7%)	321 (7%)
VOMITING	115 (2%)	7 (1%)	108 (2%)
DYSPEPSIA	81 (2%)	9 (2%)	72 (2%)
LIVER FUNCTION TESTS ABNORMAL	75 (2%)	11 (2%)	64 (1%)
ENDOCRINE SYSTEM			
ANY EVENT	18 (<1%)	2 (<1%)	16 (<1%)
HEMIC AND LYMPHATIC SYSTEM			
ANY EVENT	104 (2%)	11 (2%)	93 (2%)
METABOLIC AND NUTRITITIONAL DISORDER			
ANY EVENT	71 (1%)	8 (1%)	63 (1%)
MUSCULO-SKELETAL SYSTEM			
ANY EVENT	77 (2%)	5 (1%)	71 (2%)
NERVOUS SYSTEM			
ANY EVENT	432 (9%)	35 (6%)	397 (9%)
DIZZINESS	195 (4%)	15 (3%)	180 (4%)
RESPIRATORY SYSTEM			
ANY EVENT	420 (9%)	47 (8%)	373 (9%)
RHINITIS	83 (2%)	8 (1%)	75 (2%)
SKIN AND APPENDAGES			
ANY EVENT	207 (4%)	29 (5%)	178 (4%)
RASH	78 (2%)	13 (2%)	65 (1%)
SPECIAL SENSES			
ANY EVENT	132 (3%)	10 (2%)	122 (3%)
UROGENITAL SYSTEM			
ANY EVENT	205 (4%)	19 (3%)	186 (4%)

Treatment emergent adverse events in just the controlled studies were similar for Moxifloxacin and control drug treated patients. In these studies, adverse events were reported in 1978 of 4301 (46%) Moxifloxacin treated patients and in 1542 of 3415 (45%) patients treated with control drugs. Disparities in specific event rates for Moxifloxacin and controls included a greater frequency of headache, nausea, dizziness and "rhinitis" in Moxifloxacin treated patients. Taste perversion and "any urogenital events" were more frequent in patients on control medications (see table below).

Table 7: Adverse events occurring in more than 2% of participants in controlled studies. Rates for moxifloxacin and comparator drugs are shown.

ADVERSE EVENT	ALL BAY 12-8039 (N=4301)	CONTROL (N=3415)
ANY BODY SYSTEM		
ANY EVENT	1978 (46%)	1542 (45%)
BODY AS A WHOLE		
ANY EVENT	675 (16%)	492 (14%)
HEADACHE	196 (5%)	146 (4%)
ABDOMINAL PAIN	137 (3%)	98 (3%)
ASTHENIA	81 (2%)	56 (2%)
CARDIOVASCULAR SYSTEM		
ANY EVENT	191 (4%)	140 (4%)
DIGESTIVE SYSTEM		
ANY EVENT	953 (22%)	680 (20%)
NAUSEA	355 (8%)	240 (7%)
DIARRHEA	318 (7%)	198 (6%)
VOMITING	99 (2%)	80 (2%)
LIVER FUNCTION TESTS ABNORMAL	73 (2%)	69 (2%)
DYSPEPSIA	67 (2%)	52 (2%)
ENDOCRINE SYSTEM		
ANY EVENT	18 (<1%)	11 (<1%)
HEMIC AND LYMPHATIC SYSTEM		
ANY EVENT	98 (2%)	72 (2%)
METABOLIC AND NUTRITITIONAL DISORDER		
ANY EVENT	62 (1%)	49 (1%)
MUSCULO-SKELETAL SYSTEM		
ANY EVENT	72 (2%)	60 (2%)
NERVOUS SYSTEM		
ANY EVENT	354 (8%)	234 (7%)
DIZZINESS	166 (4%)	77 (2%)
RESPIRATORY SYSTEM		
ANY EVENT	357 (8%)	271 (8%)
RHINITIS	66 (2%)	40 (1%)
SKIN AND APPENDAGES		
ANY EVENT	189 (4%)	155 (5%)
RASH	71 (2%)	54 (2%)
SPECIAL SENSES		
ANY EVENT	113 (3%)	150 (4%)
TASTE PERVERSION	49 (1%)	90 (3%)
UROGENITAL SYSTEM		
ANY EVENT	187 (4%)	192 (6%)

Note: Incidence rate = # of events / # of patients, where: # of events = # of patients reporting the event with a start date during or after treatment.

Premature discontinuation of study drug due to adverse events occurred in 5% of patients treated with Moxifloxacin and 4% of controls. Nausea was the commonest reason for stopping the drug prematurely (38 cases among 4301 patients treated with Moxifloxacin 400mg QD). Other common reasons were dizziness (28 cases), diarrhea (25), rash (21), and vomiting (20).

Table 8: Premature discontinuations due to adverse events.

ADVERSE EVENT	ALL BAY 12-8039 (N=4926)		200 MG BAY 12-8039 (N=556)		400 MG BAY 12-8039 (N=4370)	
ANY BODY SYSTEM						
ANY EVENT	226	(5 %)	30	(5 %)	196	(4 %)
BODY AS A WHOLE						
ANY EVENT	64	(1 %)	12	(2 %)	52	(1 %)
ABDOMINAL PAIN	14	(< 1 %)	5	(< 1 %)	9	(< 1 %)
ALLERGIC REACTION	4	(< 1 %)	0	(0 %)	4	(< 1 %)
ASTHENIA	4	(< 1 %)	0	(0 %)	4	(< 1 %)
HEADACHE	13	(< 1 %)	1	(< 1 %)	12	(< 1 %)
CHEST PAIN	4	(< 1 %)	0	(0 %)	4	(< 1 %)
CARDIOVASCULAR SYSTEM						
ANY EVENT	17	(< 1 %)	0	(0 %)	17	(< 1 %)
DIGESTIVE SYSTEM						
ANY EVENT	97	(2 %)	12	(2 %)	85	(2 %)
DRY MOUTH	4	(< 1 %)	0	(0 %)	4	(< 1 %)
DIARRHEA	27	(< 1 %)	2	(< 1 %)	25	(< 1 %)
DYSPEPSIA	7	(< 1 %)	1	(< 1 %)	6	(< 1 %)
NAUSEA AND VOMITING	8	(< 1 %)	2	(< 1 %)	6	(< 1 %)
NAUSEA	41	(< 1 %)	3	(< 1 %)	38	(< 1 %)
VOMITING	21	(< 1 %)	2	(< 1 %)	19	(< 1 %)
LIVER FUNCTION TESTS ABNORMAL	6	(< 1 %)	1	(< 1 %)	5	(< 1 %)
ENDOCRINE SYSTEM						
ANY EVENT	1	(< 1 %)	0	(0 %)	1	(< 1 %)
HEMIC AND LYMPHATIC SYSTEM						
ANY EVENT	2	(< 1 %)	1	(< 1 %)	1	(< 1 %)
METABOLIC AND NUTRITITIONAL DISORDER						
ANY EVENT	3	(< 1 %)	0	(0 %)	3	(< 1 %)
MUSCULO-SKELETAL SYSTEM						
ANY EVENT	6	(< 1 %)	0	(0 %)	6	(< 1 %)
NERVOUS SYSTEM						
ANY EVENT	53	(1 %)	5	(< 1 %)	48	(1 %)
ANXIETY	4	(< 1 %)	0	(0 %)	4	(< 1 %)
DIZZINESS	32	(< 1 %)	4	(< 1 %)	28	(< 1 %)
VERTIGO	5	(< 1 %)	0	(0 %)	5	(< 1 %)
PARESTHESIA	4	(< 1 %)	1	(< 1 %)	3	(< 1 %)
RESPIRATORY SYSTEM						
ANY EVENT	33	(< 1 %)	6	(1 %)	27	(< 1 %)
ASTHMA	6	(< 1 %)	1	(< 1 %)	5	(< 1 %)
DYSPNEA	9	(< 1 %)	2	(< 1 %)	7	(< 1 %)
PNEUMONIA	8	(< 1 %)	0	(0 %)	8	(< 1 %)
SKIN AND APPENDAGES						
ANY EVENT	34	(< 1 %)	5	(< 1 %)	29	(< 1 %)
RASH	24	(< 1 %)	6	(1 %)	18	(< 1 %)
PRURITUS	7	(< 1 %)	0	(0 %)	7	(< 1 %)
SPECIAL SENSES						
ANY EVENT	8	(< 1 %)	0	(0 %)	8	(< 1 %)
UROGENITAL SYSTEM						
ANY EVENT	6	(< 1 %)	1	(< 1 %)	5	(< 1 %)

Note: Incidence rate = # of events / # of patients, where: of events = # of patients reporting the event with a start date during or after treatment.

Drug related adverse events

Drug related adverse events were reported by 32% of patients treated with Moxifloxacin in the world wide pool. Patients participating in CAP studies had the highest drug-related event rates (34%) and those in

AECB studies had lowest overall event rates (28%). The digestive system was the body system most commonly implicated with event rates ranging between 21% for CAP studies and 16% in AECB studies. Nausea and diarrhea were the commonest individual adverse events (8% and 6% of all drug-related adverse events respectively for Moxifloxacin treated patients.)
In just the controlled studies, drug related adverse events were more frequently reported in Moxifloxacin treated patients than control drug treated patients (32% vs 30%). Nausea, diarrhea and dizziness were the individual symptoms more commonly seen with Moxifloxacin than with comparator drugs. Taste perversion was more common in patients treated with control drugs.

Table 9: Drug-related adverse events occurring an at least 2% of patients in either treatment arm that differed in frequency between moxifloxacin and comparator treated patients:

	Moxifloxacin (n=4301)	Comparator (n=3415)
Any event	1377 (32%)	1020 (30%)
Nausea	324 (8%)	212 (6%)
Diarrhea	283 (7%)	171 (5%)
Dizziness	137 (3%)	54 (2%)
Taste perversion	44 (1%)	86 (3%)

Most events were reported in the first few days of dosing.

Medical officer's comment: The sponsor reported that nausea was the only AE noted to be dose-related. Small numbers of patients in the low dose (200mg/day) arm made this conclusion questionable. Certain rare AE's of significant concern appeared only in the 400mg/dy treatment arms.
In CAP studies, ventricular fibrillation was seen in 2/955 patients treated with 400mg/day and in 0/267 patients treated with 200mg/day. In the same group of studies, QT prolongation (reported as an adverse event) was seen in 2/955 patients on 400mg/day and 0/267 on 200mg/day. For all pooled studies, cardiovasular events were reported in 24/556 (4%) of patients receiving 200mg/day compared with 230/4370 (5%) of patients receiving 400mg/day (see table 6 above). While these observations may be confounded by the severity of the accompanying disease, larger numbers of patients would be required to clarify the relationship between rare adverse events and drug dosage.

Events of unusual severity

Deaths
US based studies reported "death" as the outcome of an adverse event. Foreign studies reported "death" as a reason for "end of study".
For all the studies in this application, a total of 39 deaths were reported among 8341 patients (0.45%) with valid safety data. Twenty-eight of these deaths occurred in studies for the CAP indication, where the sickest patients were encountered.
A total of 22 deaths occurred among the 4926 patients (0.45%) with valid safety data who were treated with moxifloxacin. Sixteen occurred among the 4370 patients (0.37%) treated with 400mg/day and 6 occurred in the 556 patients (1.1%) treated with 200mg/day.
Seventeen deaths occurred among the 3415 patients (0.5%) with valid safety data who received control medications. One of these deaths occurred on "day 41" and information was lacking on the circumstances surrounding this event.

Table 10: Deaths grouped by indication and study drug

Indication	Moxifloxacin 400mg	Moxifloxacin 200mg	Comparator
CAP	10	6	13
AECB	2	-	3
Other	2	-	1

Table 11:Summary of deaths in worldwide phase II/III trials

Study No. (Indication)	Patient No.	Age (Sex)	Duration of Therapy (in days)	Relative Day of Death[2]	Cause of Death
Bay 12-8039 200 mg QD					
112 (CAP)	72	23 (F)	8	+5	Cardio-Respiratory Arrest
119 (CAP)	89	75 (F)	9	+1	Sudden Death, Presumed Cardiac Event
119 (CAP)	228	78 (M)	3	3	Severe Sepsis
119 (CAP)	181	88 (F)	3	+4	Circulatory Failure and Renal Failure
119 (CAP)	765	81 (F)	10	+3	Pulmonary Embolism and Cardiac Arrest
119 (CAP)	548	45 (M)	11	+32	Cardiac Arrest
Bay 12-8039 400 mg QD					
112 (CAP)	67	25 (M)	2	+1	Respiratory Failure - Cardiorespiratory
119 (CAP)	36	75 (M)	9	+51	Laryngeal Carcinoma
119 (CAP)	26	73 (M)	4	+48	Respiratory Failure, Carcinoma Suspected
119 (CAP)	42	74 (M)	4	4	Cardiac Arrest
121 (UTI)	383	76 (M)	8	+19	Prostatic Carcinoma
[redacted]					
129 (CAP)	13009	68 (M)	2	+4	Respiratory Arrest
129 (CAP)	25014	76 (M)	2	+13	Ventricular Fibrillation
130 (CAP)	631	57 (F)	12	+13	Narcotic Sedative Overdose
[redacted]					
140 (CAP)	10399	72 (M)	9	+52	Ventricular Fibrillation
140 (CAP)	10524	87 (M)	11	11	Cor Pulmonale, Pulmonary Edema, Ventricular Thrombus
124 (AECB)	126	78 (F)	3	+1	Pneumonia
127 (AECB)	994	79 (M)	11	+36	Acute Pancreatitis
Clarithromycin 500 mg BID					
119 (CAP)	711	75 (F)	8	+2	Acute Renal Failure
119 (CAP)	827	77 (M)	11	+6	Multi-organ Failure
119 (CAP)	416	80 (M)	3	+5	Respiratory Failure
119 (CAP)	92	49 (F)	3	+3	Pneumonia with Abscess and Empyema
119 (CAP)	919	40 (M)	6	+1	Respiratory Failure
119 (CAP)	480	44 (M)	10	+41	Unknown
124 (AECB)	855	55 (M)	8	+16	Infiltrative Carcinoma of the Trachea, Massive Hemorrhage
124 (AECB)	176	72 (F)	2	+1	Myocardial Infarction
127 (AECB)	548	62 (M)	3	+13	Cardiac Arrest
130 (CAP)	958	44 (F)	11	+25	Cerebellar Tumor
Amoxicillin 500 mg TID					
112 (CAP)	41	47 (M)	5	+1	Septicemia
112 (CAP)	114	51 (M)	6	6	Klebsiella Pneumonia
Amoxicillin 1 gm TID					
140 (CAP)	10012	87 (M)	12	+9	High Probability of Pulmonary Embolism
140 (CAP)	10137	43 (M)	4	+3	Cardiac Arrhythmia
140 (CAP)	10486	42 (M)	4	+1	Cardiorespiratory Insufficiency
140 (CAP)	10242	64 (F)	2	+1	Secondary to Probable Pulmonary Embolism
Ofloxacin 200 mg BID					
121 (UTI)	213	63 (M)	15	+36	Respiratory Failure

[1] In addition to the 26 deaths reported in the data pool, one additional death (Patient 482) was reported in a patient who received clarithromycin in Study 0119 and died 41 days after completing treatment.
2 Relative day of therapy on which preceded by "+", relative days after end of therapy.
3 Internal study numbers to US-Studies. Study 127 is D96-027, Study 129 is D96-029 and Study 130 is D96-030.

Four deaths occurred while patients were still receiving study drug, one on moxifloxacin and three on comparator agents. Eight deaths occurred within one day of the last dose of study drug, 3 in patients treated with moxifloxacin and 5 in patients receiving control drugs.

Table 12: Time of death in relation to drug administration

	While on medication	Within 1 day of last dose	Within 2-7 days of last dose	>7 days after last dose
Moxi-floxacin	3	3	6	10
Comparator	1	5	5	5

See description of deaths in special cardiac summary, page 75.

Dropouts due to adverse events

Among 4926 patients treated with moxifloxacin worldwide, 226 (5%) discontinued treatment due to an adverse event, ranging from 3% in the sinusitis indication to 6% in the CAP indication. Six of the 226 patients discontinued prematurely because of death as described above. In 188 discontinuation was due to a drug related adverse event. Drug related adverse events most commonly resulting in drug discontinuation included nausea, dizziness, diarrhea, rash and vomiting.

Among 3415 control-drug treated patients, 153 (4%) discontinued prematurely for an adverse event. In 5 the event was death as described above. In 117 discontinuation was due to a drug related adverse event. The most common of these were nausea, diarrhea, abdominal pain vomiting and rash. The details of patients who discontinued treatment prematurely are shown below.

APPEARS THIS WAY
ON ORIGINAL

Table 13: Discontinuations due to drug related adverse events (worldwide database)

ADVERSE DRUG REACTION	Moxifloxacin (N=4301)		comparator (N=3415)	
ANY BODY SYSTEM				
ANY EVENT	171	(4 %)	117	(3 %)
BODY AS A WHOLE				
ANY EVENT	49	(1 %)	36	(1 %)
ABDOMINAL PAIN	12	(< 1 %)	16	(< 1 %)
ALLERGIC REACTION	4	(< 1 %)	3	(< 1 %)
ASTHENIA	4	(< 1 %)	3	(< 1 %)
HEADACHE	13	(< 1 %)	10	(< 1 %)
CHEST PAIN	1	(< 1 %)	4	(< 1 %)
CARDIOVASCULAR SYSTEM				
ANY EVENT	10	(< 1 %)	10	(< 1 %)
DIGESTIVE SYSTEM				
ANY EVENT	85	(2 %)	60	(2 %)
DIARRHEA	24	(< 1 %)	18	(< 1 %)
NAUSEA AND VOMITING	8	(< 1 %)	7	(< 1 %)
NAUSEA	38	(< 1 %)	25	(< 1 %)
VOMITING	20	(< 1 %)	14	(< 1 %)
LIVER FUNCTION TESTS ABNORMAL	4	(< 1 %)	4	(< 1 %)
HEMIC AND LYMPHATIC SYSTEM				
ANY EVENT	1	(< 1 %)	1	(< 1 %)
METABOLIC AND NUTRITITIONAL DISORDER				
ANY EVENT	2	(< 1 %)	2	(< 1 %)
MUSCULO-SKELETAL SYSTEM				
ANY EVENT	4	(< 1 %)	2	(< 1 %)
NERVOUS SYSTEM				
ANY EVENT	43	(< 1 %)	26	(< 1 %)
DIZZINESS	26	(< 1 %)	8	(< 1 %)
INSOMNIA	2	(< 1 %)	6	(< 1 %)
VERTIGO	4	(< 1 %)	3	(< 1 %)
RESPIRATORY SYSTEM				
ANY EVENT	16	(< 1 %)	6	(< 1 %)
DYSPNEA	5	(< 1 %)	2	(< 1 %)
PNEUMONIA	5	(< 1 %)	2	(< 1 %)
SKIN AND APPENDAGES				
ANY EVENT	26	(< 1 %)	22	(< 1 %)
RASH	18	(< 1 %)	12	(< 1 %)
URTICARIA	2	(< 1 %)	4	(< 1 %)
PRURITUS	7	(< 1 %)	8	(< 1 %)
SPECIAL SENSES				
ANY EVENT	5	(< 1 %)	4	(< 1 %)
UROGENITAL SYSTEM				
ANY EVENT	3	(< 1 %)	5	(< 1 %)

Note: Incidence rate = # of events / # of patients, where: # of events = # of patients reporting the event with a start date during or after treatment.

Discontinuations due to nausea occurred in .5% of patients treated with 200mg of Moxifloxacin a day compared with 0.9% in those treated with 400mg a day suggesting a dose related effect

Serious adverse events (SAE)

Serious adverse events were reported in 207/4926 (4%) of patients treated with Moxifloxacin and 103/3337 (4%) of patients treated with a comparator. Included were 21 patients treated with Moxifloxacin who died and 15 treated with a comparator who died. Pneumonia chest pain and dyspnea were the commonest serious adverse events reported in Moxifloxacin treated patients, and rates of SAE's were no different for patients treated with 400mg per day compared to those treated with 200mg per day.
The more common SAEs occurring in 4 or more patients treated with either Moxifloxacin or comparator drugs are shown below.

Table 14: Serious Adverse Events, occurring in at least 4 individuals.

ADVERSE EVENT	ALL BAY 12-9039 (N=4301)	CONTROL (N=3415)
ANY EVENT[2]		
BODY AS A WHOLE		
ABDOMINAL PAIN	3 (< 1 %)	6 (< 1 %)
ABSCESS	4 (< 1 %)	1 (< 1 %)
ACCIDENTAL INJURY	5 (< 1 %)	4 (< 1 %)
DEATH	4 (< 1 %)	4 (< 1 %)
INFECTION	5 (< 1 %)	6 (< 1 %)
NEOPLASM	1 (< 1 %)	4 (< 1 %)
SEPSIS	4 (< 1 %)	1 (< 1 %)
PELVIC PAIN	4 (< 1 %)	4 (< 1 %)
CHEST PAIN	14 (< 1 %)	1 (< 1 %)
SURGERY	10 (< 1 %)	1 (< 1 %)
	1 (< 1 %)	0 (0 %)
CARDIOVASCULAR SYSTEM		
ATRIAL FIBRILLATION	7 (< 1 %)	0 (0 %)
ENDOCRINE SYSTEM		
DIABETES MELLITUS	5 (< 1 %)	1 (< 1 %)
HEMIC AND LYMPHATIC SYSTEM		
LEUKOPENIA	2 (< 1 %)	4 (< 1 %)
RESPIRATORY SYSTEM		
ASTHMA	5 (< 1 %)	4 (< 1 %)
APNEA	5 (< 1 %)	6 (< 1 %)
DYSPNEA	13 (< 1 %)	5 (< 1 %)
BRONCHITIS	2 (< 1 %)	4 (< 1 %)
CARCINOMA OF LUNG	5 (< 1 %)	5 (< 1 %)
LUNG DISORDER	5 (< 1 %)	16 (< 1 %)
PNEUMONIA	21 (< 1 %)	14 (< 1 %)
PLEURAL EFFUSION	5 (< 1 %)	1 (< 1 %)
UROGENITAL SYSTEM		
SALPINGITIS	1 (< 1 %)	4 (< 1 %)
SURGERY	3 (< 1 %)	8 (< 1 %)

1 Incidence rate = # of events / # of patients, where: # of events = # of patients reporting the event with a start date during or after treatment.
2 Truncated to events with 4 or more patients in either all BAY 12-8039 or control.

MO comment: Chest pain and atrial fibrillation were more common in Moxifloxacin treated patients

Other events of unusual severity:
Table 15: Serious adverse events (extracted from table 27 (A3) of appendix 1)

Adverse event	Moxifloxacin 200mg (n=556)	200mg Control (n=555)	Moxifloxacin 400mg (n=3745)	400mg control (n=3415)
Allergic reaction	0	0	3	1
Carcinoma	1	0	0	0
Neoplasm	0	0	1	4
Death*	3	2	1	2
Arrhythmia	0	0	1	3
Extrasystoles	0	0	0	1
Heart arrest	2	0	1	0
Ventric fibrillation	0	0	1	0
Ventric tachy	0	0	0	1
Shock	0	0	3	0
Diabetes	1	0	4	1
Leukopenia	0	0	2	4
Hypoglycemia	0	0	0	1
Tenosinovitis	0	0	0	2
Coma	0	0	0	2
Hemiplegia	0	0	1	0
Asthma	1	0	5	4
Apnea	1	3	4	6
Dyspnea	1	3	9	5

Ca lung	0	3	5	5
Purpuric rash	0	0	1	0
Blindness	0	0	2	0
Acute renal failure	0	0	0	1

Clinical laboratory data:
In most studies, routine hematology, clinical chemistry and urinalysis tests were performed before and after treatment.
Tests required in most studies included:
Hemoglobin, hematocrit, red cell indices, white blood cell count (WBC) and differential, platelet count, prothrombin time (PT) and partial thromboplastin time (PTT), C reactive protein (CRP)
SGOT SGPT LDH alkaline phosphatase, total bilirubin serum creatinine, blood urea nitrogen (BUN), uric acid, sodium, potassium, chloride, amylase, gammaglutamyl transferase, inorganic phosphorus, total protein, albumin, calcium, glucose, serum bicarbonate, cholesterol, triglycerides.
Urinalysis included pH, ketones, protein, occult blood, glucose, and microscopy.

Analyses performed
A) percentage patients showing emergent clinically significant abnormalities.

Normal limits of laboratory tests were defined per protocol.
All laboratory abnormalities occurring more commonly in Moxifloxacin treated patients than comparator treated patients in the world wide data pool were identified as shown below.

Table 16: Treatment emergent, abnormally high laboratory values that were more common in moxifloxacin treated patients than comparator treated patients (from Appendix 1 table 21 A2) and values for additional selected tests of importance in quinolone safety (worldwide data pool of comparative studies)

Lab variable	All moxifloxacin		Control	
	Incidence rate	%	Incidence rate	%
MCH	72/1641	4	37/1146	3
Eosinophils	320/2865	11	219/2207	10
Eosinophils abs	81/654	12	36/510	7
Basophils abs	29/635	5	20/506	4
Platelets	352/3893	9	252/3069	8
PT	268/2187	12	121/1550	8
PT ratio	16/523	3	12/502	2
PTT	131/1121	12	90/918	10
Glucose fasting	11/61	18	11/69	16
Serum glucose	411/2051	20	300/1585	19
Potassium	228/3953	6	171/3126	5
Chloride	464/2824	16	260/2091	12
Creatinine	147/3782	4	94/2967	3
Urea	110/1905	6	81/1668	5
Globulin tot	3/20	15	2/19	11
SGOT	243/3663	7	239/2918	8
SGPT	320/3711	9	273/2919	9
Alk phos	132/3610	4	98/2875	3
Bilirubin tot	117/3793	3	69/2964	2
Bilirubin direct	30/278	11	20/241	8
Cholesterol	247/978	25	158/685	23

Incidence rate = # events/# at risk
events = # patients reporting the abnormality after treatment
at risk = # of patients with readings during and after the pretreatment visit who did not report the abnormality at the pretreatment visit.

MO comment: Values were similar for moxifloxacin and comparator treated patients. Tests of potential concern included prologed PT, hyperglycemia, elevated creatinine, elevations of transaminases and bilirubin particularly since the severity of the abnormality was not reflected in this analysis. Elevated eosinophil counts and chloride were more common in Moxifloxacin treated patients though the clinical significance of these abnormalities is not clear.

Table 17: Abnormally low laboratory values that were more common in moxifloxacin treated patients than comparator treated patients (from Appendix 1 table 21 A2) and values for additional selected tests of importance in quinolone safety (worldwide data pool of comparative studies)

Lab variable	All moxifloxacin		Control	
	Incidence rate	%	Incidence rate	%
Hematocrit	402/3394	12	293/2754	11
Hemoglobin	423/3266	13	296/2625	11
WBC	312/3962	8	224/3119	7
Neutrophils tot	110/1178	9	81/1040	8
Neutrophils abs	80/697	11	45/545	8
Lymphocytes	198/2550	9	149/1789	8
Eosinophils	61/404	15	50/358	14
Platelets	89/3857	2	53/3045	2
Serum glucose	129/2516	5	79/1945	4
Fasting glucose	7/85	8	11/79	14
Bicarbonate	198/2564	8	133/1893	7
Theophylline level	28/111	25	7/48	15

MO comment: Again, values were similar for moxifloxacin and comparator treated patients. Low values of potential concern included hypoglycemia, anemia, low neutrophil and platelet counts and low theophylline levels in patients receiving concurrent treatment, since the severity of these abnormalities was not reflected in this analysis.

Additionally the following occurred more frequently in moxifloxacin treated patients than comparator but the test result was only determined for small numbers of patients (<100)

Table 18: Abnormal results seen more frequently in Moxifloxacin than comparator treated patients for tests performed on small numbers of patients

	Decreases	
	Moxifloxacin	Control
"other WBC forms"	1/22 (5%)	0/22 (0%)
Glucose fasting	11/61 (18%)	11/69 (16%)
Ionized Ca	1/7 (14%)	0/9 (0%)
Albumin %	3/20 (15%)	2/19 (11%)
Globulin	3/15 (20%)	2/13 (15%)
	Increases	
Eosinophils abs	3/11 (27%)	1/12 (8%)
PO2	½	0/1
Bilirubin indirect	13/75 (17%)	11/84 (13%)

MO comment : Patient numbers in the above table were too small to allow conclusions on the relative frequency of each abnormality.

A second analysis was performed examining the change from baseline to the minimum and maximum recorded value for each patient (since many patients had more than one blood test in the course of treatment). The results are summarized below.

Table 19: Clinically significant laboratory abnormalities. Changes from baseline to maximum recorded value on treatment (from appendix 1 table 23 A2)

Lab Test	Moxifloxacin (n=4301)		Comparator (n=3415)	
	N	Mean Δ	N	Mean Δ
PT	2631	0.5	1874	0.4
PT ratio	62	0.1	60	0.1
INR	430	0	415	0.1
Glucose (unspecified) mg/dL	822	1.6	575	-1.0
Glucose (serum) mg/dL	2620	10	2051	9.1
Urea	2204	1.3	1893	1.9
Creatinine	4075	0	3205	0
SGOT U/L	4086	2.1	3232	3
SGPT U/L	4092	4.8	3236	6.3
Alk phos U/L	3999	3.6	3140	3.2
Bilirubin tot mg/dL	4028	0	3166	0
Eosinophils%	3140	1.1	2458	1.1
Platelets	4076	42.6	3230	43.3

MO comment: Mean changes from baseline were similar for Moxifloxacin and comparator. Greater mean increases were seen in PT, glucose and alkaline phosphatase for Moxifloxacin treated patients than for those treated with a comparator. The severity of the abnormalities in patients with elevated results is not reflected in this analysis.

Table 20: Clinically significant laboratory abnormalities. Mean changes from baseline to minimum recorded value on treatment (from appendix 1 table 23 A2)

Lab Test	Moxifloxacin (n=4301)		Comparator (n=3415)	
	N	Mean Δ	N	Mean Δ
Hematocrit %	4088	-1.5	3244	-1.2
Hemoglobin g/dL	4086	-0.4	3244	-0.4
WBC x10^9/L	4089	-2.5	3247	-2.5
Neutrophils %	1232	-9.5	1114	-8.5
Neutrophils (absolute count) x10^9/L	721	-4.7	569	-3.8
Platelets x10^9/L	4076	-2.5	3230	-0.1
Glucose unspecified mg/dL	822	-14.2	575	-12.8
Glucose fasting mg/dL	90	-17.9	90	-13.4
Glucose serum mg/dL	2620	-8.8	2051	-9.5
Potassium mmol/L	4076	-0.1	3220	-0.1

MO comment:
Most mean changes were not significantly different between Moxifloxacin- and comparator- treated patients. Notably the mean fall in fasting glucose among the 90 tested patients on Moxifloxacin was greater than the mean fall in comparator treated patients, and the mean decrease in platelets was greater in Moxifloxacin treated patients than in those treated with a comparator. The combination of decreases in hematocrit, neutrophil counts and platelet counts suggest a small possible suppressive effect on the bone marrow, though other explanations for these abnormalities are possible, including resolution of white cell counts following treatment of infection, decreasing platelet counts with infection related DIC, rehydration etc.

Notable deviations from baseline were a) a decrease in % and absolute neutrophil count, b) increase in absolute and % lymphocyte count, c) decrease in leukocytes, d)decrease in platelets, e) glucose decreases and increases, f) decreases in creatinine and g) increases in GGT.

In an attempt to quantify the severity of abnormalities among patients with reported abnormal results an analysis was performed to distinguish mild from severe abnormalities as shown below:

Table 21: Criteria for identifying patients with significantly abnormal laboratory results

LAB VARIABLE	CRITERION	BAY 12-8039 ALL	CONTROL
SGPT/ALT	> 1.5 * ULN	174/3934(4%)	163/3078(5%)
	> 3 * ULN	42/4056(1%)	32/3206(<1%)
SGOT/AST	> 1.5 * ULN	118/3897(3%)	107/3098(3%)
	> 3 * ULN	35/4043(<1%)	30/3193(<1%)
BILIRUBIN. TOTAL	> 1.5 * ULN	22/3942(<1%)	18/3105(<1%)
	> 3 * ULN	6/4023(<1%)	5/3155(<1%)
CREATININE	> 1.5 * ULN	20/4024(<1%)	10/3166(<1%)
	> 3 * ULN	4/4070(<1%)	0/3199(0%)
HEMOGLOBIN	< 75% LLN	32/3938(<1%)	17/3103(<1%)
PLATELETS	< 100 G/L	23/4031(<1%)	24/3199(<1%)
SERUM GLUCOSE	< 50 MG/DL	17/2613(<1%)	9/2047(<1%)
GLUCOSE. UNSPECIFIED	< 50 MG/DL	5/ 821(<1%)	2/ 574(<1%)

NOTES: INCIDENCE RATES = # OF EVENTS / # AT RISK, WHERE:
OF EVENTS = # OF PATIENTS REPORTING THE ABNORMALITY AFTER PRETREATMENT
AT RISK = # OF PATIENTS WITH READINGS DURING AND AFTER PRETREATMENT WHO DID NOT REPORT THE ABNORMALITY DURING PRETREATMENT

MO comment: Among the patients with established emergent abnormal laboratory tests, the frequency of more severe derangements was similar using Moxifloxacin or comparators. Abnormalities of liver function did not differ. Marked elevations of creatinine were more common in Moxifloxacin treated patients but only 4 such subjects were reported. Of the remaining investigations referred to in the table, hypoglycemia and significant anemia were more common in moxifloxacin treated patients.

Summary data on specific abnormalities:
Prolonged prothrombin time: A prolongation of prothrombin time was more common among moxifloxacin treated patients than controls and the mean increase in prothrombin time was greater in patients treated with Moxifloxacin than in those treated with controls. The maximum average increase in prothrombin time (+/- SD) was 0.5 (+-4.7) seconds for Moxifloxacin treated patients compared to 0.4 (+/-4.2) seconds for comparator treated patients. Forty-one patients treated with moxifloxacin had an adverse event of hemorrhage. Only one of these patients had a treatment-emergent elevation in PT of >=16 seconds and one had an abnormally high prothrombin time at baseline which had decreased but remained >=16s on treatment. Of the 41 adverse events reported as hemorrhage, 34 (83%) were related to sinus puncture.

Elevated chloride levels were more common in Moxifloxacin treated patients. The mean increase in chloride was 2.7 mmol/L (+/-4.3) compared with 2.3 mmol/L +/-4.5) for comparator treated patients. These isolated changes in chloride are of doubtful clinical significance.

Absolute neutropenia was more common in Moxifloxacin treated patients with a mean decrease of 4.7 (+/- 6.5) x 10^9/L compared to 3.8 (+/-5.5) x 10^9/L for patients treated with comparator drugs. The 10 patients

with the largest decreases in ANC were all participating in studies of CAP and the sponsor ascribed the severity of the neutropenias to the underlying disease. None of the patients had an ANC count below 1 Giga/L. Five other patients treated with moxifloxacin experienced ANCs of <1 Giga/L, similar to the rate in subjects treated with comparator drugs.

Anemia: Treatment emergent decreases in hematocrit, hemoglobin and RBC count were found in >=10% of moxifloxacin treated patients. Similar rates were found in patients treated with comparator drugs. Among the 10 patients with the greatest decreases in hematocrit, 9 were involved in CAP studies. The sponsor attributed these decreases to "comorbidity" including volume depletion.

Urinary abnormalities reported in the US safety data base included proteinuria in 17% of Moxifloxacin treated patients compared with 19% of controls and hematuria in 8% of Moxifloxacin treated patients versus 10% of controls.

A syndromic analysis was performed for patients with selected laboratory abnormalities to detect liver damage of the type reported with trovafloxacin, hemolytic syndrome of the type reported with [redacted] and other possible renal syndromes. Check marrow suppression.

Hepatitis- like reactions:
From the worldwide pool of controlled studies, a list was requested from the sponsor of patients with either AST>3xULN or ALT>3xULN or total bilirubin (BR)>1.5xULN.
Among 41 patients with a bilirubin level >1.5 x ULN, those developing a more than 2 fold increase in either AST, ALT or BR from the pre-treatment value were examined as shown below.

Table 22: Patients with clinically significant (> 2 fold) treatment emergent increases in either AST, ALT or BR

Drug	SGOT1	SGOT2	SGPT1	SGPT2	BILIRUBIN1	BILIRUBIN2	abnormality
Amox	23	36	11	17	0.8	2.4	b
Moxi 200	18	11	11	9	0.5	3.9	b
Moxi 200	33	41	12	16	0.8	3.5	b
Cefurox	18	21	11	13	0.1	2.4	b
moxi 400	9	16	34	29	1	2.6	b
moxi 400	14	16	11	11	0.7	3.9	b
moxi 400	19	35	15	25	0.9	1.9	b
moxi 400	20	17	14	10	0.6	2	b
moxi 400	22	24	17	19	0.5	2.1	b
cefurox	131	228	113	164	0.7	2.4	b
Cephalex/ metr	22	34	21	28	0.7	2.3	b
Clari	16	22	20	20	0.6	2.5	b
Clari	21	22	19	34	0.4	4.3	b
Clari	55	38	27	27	0.9	7	b
moxi 400	25	52	23	27	1.6	2	o
moxi 400	65	131	57	144	1.1	2	op
moxi 200	178	611	48	98	1	2.7	opb
moxi 400	5	20	11	32	1.2	2.4	opb
moxi 400	12	48	9	78	0.4	3.7	opb
Clari	26	98	20	65	0.6	2	opb
moxi 400	45	190	60	366	0.8	7.2	opb*
Clari	17	24	6	14	1.6	2.4	p

O=SGOT P=SGPT B=Bilirubin
1= pre-treatment value 2=maximum value after starting treatment

The most common pattern of abnormalities was an isolated >2 fold increase in total bilirubin (7 patients on Moxifloxacin, 7 on comparator agents.) A > 2 fold increase for all three tests was seen in 4 patients treated with Moxifloxacin and 1 treated with clarithromycin.
*The most marked changes were seen in this patient participating in a CAP study (study 121 #483).The outcome of this event and whether the study drug was discontinued were not recorded for this patient.
Similar analyses were performed on patients with any SGOT level > 3 x ULN and on patients with any SGPT level > 3x ULN as shown below.

Table 23: Characterization of liver function abnormalities in 77 patients with any SGPT > 3 x ULN

	Moxifloxacin	Comparators
>2 fold increase of SGOT	3	3
>2 fold increase of SGPT	4	0
>2 fold increase of Bilirubin	1	1
>2 fold increase of SGPT & bilirubin	1	0
>2 fold increase of SGOT & SGPT	20	20
>2 fold increase of SGOT, SGPT & Bilirubin	4*	2

* one of these patients with normal pretreatment transaminase levels and a missing pretreatment bilirubin developed a marked (> 2 fold) treatment emergent elevation of transaminases and a post treatment bilirubin of 5.2.
For the 66 patients with any SGOT level > 3 x ULN an analysis of liver function is shown below.

Table 24: Characterization of liver function abnormalities in 77 patients with any SGOT > 3 x ULN

	Moxifloxacin	Comparators
>2 fold increase of SGOT	8	3
>2 fold increase of SGPT	0	1
>2 fold increase of Bilirubin	0	0
>2 fold increase of SGPT & bilirubin	1	0
>2 fold increase of SGOT & SGPT	17	19
>2 fold increase of SGOT, SGPT & Bilirubin	3*	2

* one of these patients with normal pretreatment transaminase levels and a missing pretreatment bilirubin developed a marked treatment emergent elevation of transaminases and a post treatment bilirubin of 5.2. I have included this in the category of treatment emergent doubling of all three parameters.
Pre- and post-treatment transaminases and bilirubin are shown below for the patients with >2 fold treatment emergent increases of all three measurements

Pre- and post-treatment transaminases and bilirubin are shown below for the patients with >=2 fold treatment emergent increases of all three measurements

Table 25: Patients with a ≥2 fold increase in SGOT, SGPT and BR (where at least one transaminase result was >3ULN or BR was >1.5 ULN)

study	pat. ID	TREATMENT GROUP	SGOT1	SGOT2	SGPT1	SGPT2	BR1	BR2	OUTCOME
140	10716	Moxi 400mg O.D.	25	302	17	194		5.2	RESOLVED
118	504	Moxi 400mg O.D.	35	117	40	152	0.2	0.7	RESOLVED
119	118	Moxi 400mg O.D.	108	684	42	150	0.6	1.6	IMPROVED
121	483	Moxi 400mg O.D.	45	190	60	366	0.8	7.2	
122	3013	Cephalixin	26	109	18	135	0.54	1.12	RESOLVED
131	95	Cephalexin/metronidazole	63	191	59	179	0.4	0.8	
119	501	Clarithro	59	402	81	592	0.8	1.6	