

outcome is correlated with AUC/MIC values  $\geq 125$  and  $C_{max}/MIC$  values  $\geq 10$ . As can be seen from the table, these targets are reached at steady-state for the organisms that will be treated that have the highest MICs for moxifloxacin.

**Table 55 - Following Single and Multiple Doses of 400 mg Once Daily**

Variable	Day 1	Day 10
AUC (mg×hr/L)	30.2	48.0
$C_{max}$ (mg/L)	3.36	4.52
$t_{1/2}$ (hr)	9.3	12.0
$C_{min}$ (mg/L)	0.52	0.94
AUC ( <i>S. pneumoniae</i> )*	120.8	192
AUC ( <i>S. aureus</i> )**	241.6	384
$C_{max}/MIC$ ( <i>S. pneumoniae</i> )*	13.4	18.1
$C_{max}/MIC$ ( <i>S. aureus</i> )**	28	36.2

\*  $MIC_{90} = 0.25 \mu\text{g/mL}$

\*\*  $MIC_{90} = 0.12 \mu\text{g/mL}$

TABLE 56 shows some sample tissue concentration data following administration of 400 mg of moxifloxacin. Moxifloxacin concentrates, as do most other fluoroquinolones, in respiratory tract tissue. Concentrations in most skin tissue, however, are less than in plasma.

**Table 56 – Tissue and plasma concentrations of moxifloxacin at 3 hours post-dose**

Tissue	Tissue conc. ( $\mu\text{g/g}$ )	Plasma conc. ( $\mu\text{g/mL}$ )
Bronchial mucosa	5.4	
Alveolar macrophages	56.7	
Maxillary sinus	7.5	
Skin blister fluid	2.6	
Saliva	1.7	
Subcutaneous tissue	0.9	
Skeletal muscle	0.9	
Epithelial lining fluid	20.7	

## ANIMAL PROPHYLATIC AND THERAPEUTIC STUDIES

The in vivo efficacy of moxifloxacin in the therapy of various animal models of human disease has been compared to antimicrobial agents currently used as standard therapy in these human infections. Usually, moxifloxacin dosages were selected to reflect serum levels achieved in humans after oral administration of 400 mg of moxifloxacin (standard human dose). Experimental dosages of comparative agents were also chosen to produce serum levels in animals similar to those seen in humans.

### MOUSE PROTECTION STUDIES

*Staphylococcus aureus* and *Streptococcus pyogenes* were used to evaluate the efficacy of moxifloxacin in preventing death in a murine intraperitoneal infection model (75). A single dose of 5, 10, 20, 40, or 80 mg/kg body weight of moxifloxacin was administered either orally or subcutaneously in each group of ten mice. The mice were challenged intraperitoneally with  $1.53 \times 10^8$  cfu/mouse in the *Staphylococcus aureus* group and with  $1.14 \times 10^3$  cfu/mouse in the *Streptococcus pyogenes* group. Sparfloxacin and ciprofloxacin were used as comparators. Moxifloxacin effected a survival rate of 100% at 20 mg/kg subcutaneously, while 80 mg/kg was needed for the same response in mice treated with ciprofloxacin or sparfloxacin. Moxifloxacin was better than ciprofloxacin against *Streptococcus pyogenes*; however, 80 mg/kg of either sparfloxacin or moxifloxacin subcutaneously was needed for 100% survival. At 80 mg/kg ciprofloxacin effected only 60% survival. Similar results were seen for moxifloxacin and sparfloxacin when 80 mg/kg oral doses were given. Ciprofloxacin had little effect at 80 mg/kg orally.

To evaluate efficacy against gram-negative bacteria, groups of ten mice were infected intraperitoneally with  $1.7 \times 10^7$  cfu/mouse of either *Escherichia coli* or *Klebsiella pneumoniae* (75). Moxifloxacin, sparfloxacin, or ciprofloxacin were administered in doses of 0.06 to 5.0 mg/kg subcutaneously or orally. When administered subcutaneously, 0.25 mg/kg of ciprofloxacin effected 100% survival, while 0.5 mg/kg subcutaneously of moxifloxacin or sparfloxacin gave the same results. After oral administration, 100% survival was obtained with 1.0 mg/kg moxifloxacin or sparfloxacin and with 0.5 mg/kg ciprofloxacin.

These data show the moxifloxacin is slightly inferior to ciprofloxacin against gram-negative bacteria, but superior against gram-positive bacteria in mouse protection studies.

## EXPERIMENTAL PNEUMONIA

An immunocompetent mouse model of pneumonia was used to assess the clearance of a strain of penicillin-resistant *Streptococcus pneumoniae* (102, 35). Therapy was initiated four hours after the lungs of the mice were intratracheally inoculated with  $3 \times 10^7$  cfu/mL of pneumococci. The mice were treated with moxifloxacin, 100 mg/kg orally; trovafloxacin, 15 mg/kg, orally; sparfloxacin, 50 mg/kg, orally; levofloxacin, 50 mg/kg, orally; ciprofloxacin, 100 mg/kg orally; amoxicillin, 20 mg/kg orally; or vancomycin, 20 mg/kg, intraperitoneally. The drugs were given every six hours for four doses, the animals were killed, and cfu/g were obtained from cultured homogenized lung tissue. Moxifloxacin, trovafloxacin, and vancomycin were equally effective in reducing the lung load to a median  $\log_{10}$  cfu/g lung tissue of 0.5. Moxifloxacin, trovafloxacin, and vancomycin were significantly more effective than amoxicillin, ciprofloxacin, levofloxacin, and sparfloxacin, which were similar in activity and reduced the lung load to a median  $\log_{10}$  cfu/g of 3.9-5.9. Moxifloxacin was the most effective agent in sterilizing 11/15 lungs followed by trovafloxacin at 8/15, and vancomycin at 4/14 lungs.

Infection in another murine pneumonia model was established with a penicillin-susceptible strain of *Streptococcus pneumoniae* (138). The mice were inoculated intranasally with approximately  $10^7$  cfu/mL. Groups of mice were treated with 10 mg/kg, 30 mg/kg, or 90 mg/kg of either moxifloxacin or penicillin. Preliminary data suggested that moxifloxacin was as effective as penicillin.

Mixed infection was evaluated in a rat pneumonia model (75). Baby rats were challenged intratracheally with  $1 \times 10^7$  cfu's of *Streptococcus pneumoniae* plus  $4 \times 10^7$  cfu's of *Haemophilus influenzae*. Oral treatment with 2.5, 10, or 50 mg/kg sparfloxacin, ciprofloxacin, or moxifloxacin was administered at one and four hours after infection. Data from groups of five animals showed that 2.5 mg/kg sparfloxacin or ciprofloxacin reduced the cfu's of *Haemophilus influenzae* by 8  $\log_{10}$  compared to controls, while 10 mg/kg were needed for similar results with moxifloxacin. All three quinolones were ineffective at doses up to 10 mg/kg against *Streptococcus pneumoniae*. Sparfloxacin was more active than ciprofloxacin at 50 mg/kg in reducing cfu of *Streptococcus pneumoniae* by approximately 4  $\log_{10}$ , while moxifloxacin had practically no effect in this model at this dose. The authors attributed the differences among the quinolones in this model to the differences in the pharmacokinetics in baby rats compared with the pharmacokinetics in the adult animal. Serum and tissue levels were eightfold higher in sparfloxacin treated animals compared to the levels obtained in either ciprofloxacin or moxifloxacin treated animals.

Vesga et al. (110) evaluated the efficacy of moxifloxacin against *Klebsiella pneumoniae* in a neutropenic mouse model. The mice were infected by exposure to an aerosol that delivered an inoculum of  $9.32 \log_{10}$  cfu/mL. Fourteen hours after infection, moxifloxacin was administered subcutaneously with total daily doses ranging in fourfold increments from 0.586 to 2400 mg/kg given in 1, 2, 4, or 8 doses over a 24-hour period.

The pharmacokinetic/pharmacodynamic parameter that correlated best with therapeutic efficacy was the 24-hour AUC/MIC ( $R^2 = 93.9\%$ ) compared with  $C_{max}/MIC$  ( $R^2=81.5\%$ ) or Time above MIC ( $R^2 = 71.7\%$ ).

The *in vivo* efficacy of moxifloxacin for pneumonia caused by *Mycoplasma pneumoniae* was evaluated in a guinea pig model of infection (139). The guinea pigs were infected intranasally with  $1 \times 10^8$  cfu. Moxifloxacin was administered subcutaneously twice a day for seven days to groups of eight guinea pigs each. The doses used were 1 mg/kg, 3 mg/kg, or 10 mg/kg. Colony counts of *Mycoplasma pneumoniae* were performed ten days post infection by intratracheally washing the lungs of the guinea pigs after sacrifice and culturing the lung wash fluid. The cfu/mL of  $10^5$  obtained from the 1 mg/kg treated groups were comparable to untreated controls. A slight decrease in cfu was seen in those animals treated with 3 mg/kg. Cultures of lung fluid wash from animals treated with 10 mg/kg moxifloxacin were either negative or had 10 cfu/mL when animals had been infected with subtype 1 bacteria. The cfu/mL obtained from subtype 2 infected animals were  $10^2$  to  $10^3$ . Moxifloxacin at 10 mg/kg is effective in reducing cfu/mL for both subtypes of *Mycoplasma pneumoniae*, but has greater efficacy against subtype 1 in this model.

### **THIGH MUSCLE INFECTIONS**

Groups of five female mice were rendered neutropenic by treating with cyclophosphamide prior to infection. Infection was accomplished by injecting  $1.55 \times 10^5$  cfu of *Enterococcus faecalis* into the thigh muscles (75). Oral administration of 10, 20, 40, or 80 mg/kg of moxifloxacin, sparfloxacin, or ciprofloxacin resulted in dose dependent reduction in cfu's. Sparfloxacin and moxifloxacin gave similar results at all concentrations. The 80 mg/kg dose for both drugs achieved a 3  $\log_{10}$  reduction in cfu's of *E. faecalis*. Ciprofloxacin had no effect at any dose in this model.

Vesga et al. (110) evaluated the pharmacokinetic parameters and therapeutic efficacy of moxifloxacin against penicillin-susceptible and penicillin-resistant *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Escherichia coli*, and *Klebsiella pneumoniae* in normal and neutropenic mouse thigh models. The MICs of the test organisms were 0.015-0.25  $\mu\text{g/mL}$ . Thigh muscles were injected with  $7.77 \log_{10}$  cfu/mL two hours prior to the initiation of treatment. To determine the effect of static doses after various dosing intervals and therapeutic efficacy, moxifloxacin was administered subcutaneously with total daily doses ranging in fourfold increments from 0.586 to 2400 mg/kg given in 1, 2, 4, or 8 doses over a 24 hour period. The static dose for time intervals q3h, q6h, q12h, or q24h were similar for all of the time intervals and all organisms in neutropenic mice, which suggests the feasibility of once daily dosing. The static doses were similar at 24 hours for the q12h dosing interval for both neutropenic and normal mice infected with *Klebsiella pneumoniae*. This indicates that neutrophils had no effect on the activity of moxifloxacin. However, at 24 hours and the same dosing

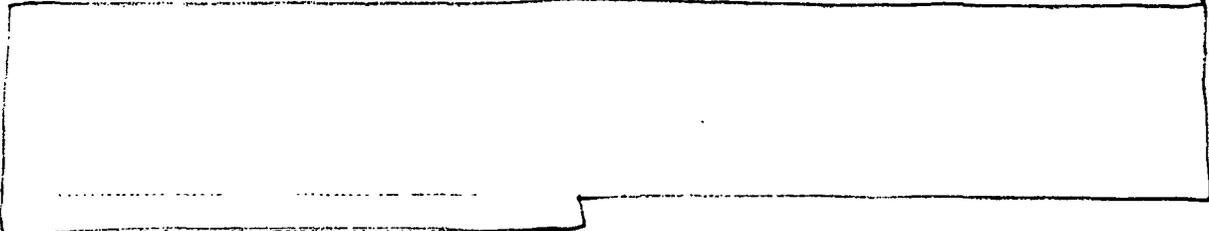
interval in mice infected with *S. pneumoniae*, the static dose was 57.6 mg/kg/24h in the neutropenic mice, but only 17.1 mg/kg/24h for the normal mice. The therapeutic efficacy of moxifloxacin correlated best with AUC/MIC compared with  $C_{max}/MIC$  or Time above MIC.

#### POUCH MODEL

A rat pouch model of infection with a ciprofloxacin susceptible strain of *Staphylococcus aureus* was used to evaluate the effect of moxifloxacin on slowly growing or stationary phase organisms (75). An oral dose of 20 mg/kg of moxifloxacin produced an approximate  $1.5 \log_{10}$  reduction of cfu's. Sparfloxacin at this same dosage did not produce any decrease in cfu's. At 80 mg/kg, moxifloxacin effected a  $2.5 \log_{10}$  reduction in cfu's, while sparfloxacin at this dose had little effect. The concentration of moxifloxacin in the pouch was several fold lower than the concentration of sparfloxacin, but moxifloxacin worked much better.

Further studies in the granuloma pouch model in rats evaluated a ciprofloxacin susceptible strain of *Staphylococcus aureus* (QSSA); a ciprofloxacin resistant, [redacted] resistant strain of *Staphylococcus aureus* (QMRSA); and a strain of *Streptococcus pneumoniae* (140, 141). Once daily doses of 100 mg/kg moxifloxacin, which achieved concentrations in the pouch that simulated those seen in human serum after a 400 mg oral dose, were administered orally. Treatment started either one hour or 24 hours after infecting the animals. A suboptimal dose of 50 mg/kg moxifloxacin was administered orally for six days after infection with a one-step or multiple-step mutant of each organism. Samples of the pouch exudates were withdrawn daily and cultured on drug free agar and agar containing 2 x MIC or 4 x MIC moxifloxacin in order to determine the extent of emergence of resistance during optimal and suboptimal therapies. A reduction of approximately  $7 \log_{10}$  cfu/mL was achieved in *Streptococcus pneumoniae* after optimal treatment (100 mg/kg, 1 hour after infection) at one day, followed by the optimally treated QSSA after 3 days. The suboptimal initiation of therapy resulted in much slower reductions in cfu/mL for *Streptococcus pneumoniae*. A  $7 \log_{10}$  reduction took six days (instead of 1 day). QSSA was reduced by  $3 \log_{10}$  after six days. No emergence of resistance was seen for either organism regardless of treatment. The results for the QMRSA strain were similar to those for the ciprofloxacin susceptible strain. The suboptimal treatment of 50 mg/kg resulted in a reduction in cfu/mL of approximately  $4 \log_{10}$  after 8 days for *Staphylococcus aureus* and  $6 \log_{10}$  for *Streptococcus pneumoniae*. There was little reduction in cfu/mL for the multiple-step mutants of either organism, but there was no emergence of resistance.

*This page of the document  
contains confidential  
information that will not  
be included in the  
redacted portion of the  
document for the public to  
obtain.*



### MENINGITIS

A comparison of moxifloxacin and ceftriaxone in the therapy of experimental meningitis caused by a strain of penicillin susceptible *Streptococcus pneumoniae* was performed in a rabbit model (144,145,146). In addition to evaluating efficacy, the modulation of the inflammatory host response and the effect of coadministration of dexamethasone were measured. Therapy was started 12 hours after rabbits had been inoculated intracisternally with  $10^6$  cfu of *Streptococcus pneumoniae*. Ten rabbits received 10 mg/kg/h moxifloxacin iv for 12 hours and six rabbits received the same dose, but were administered 1.0 mg/kg dexamethasone 15 minutes prior to receiving the antibiotic. Another six rabbits received 2.5 mg/kg/h iv moxifloxacin and 4 rabbits received 20 mg/kg/h iv moxifloxacin. Ten rabbits were administered 10 mg/kg/h iv ceftriaxone after receiving an initial bolus of 20 mg/kg iv. The bactericidal activity of moxifloxacin at 10 mg/kg/h was almost the same as the bactericidal activity of 10 mg/kg/h ceftriaxone ( $-0.32 \pm 0.14$  versus  $-0.39 \pm 0.11$   $\Delta\log$  cfu/mL/h). The bactericidal activity of 2.5 mg/kg/h moxifloxacin ( $-0.19 \pm 0.06$   $\Delta\log$  cfu/mL/h) was substantially less than that of moxifloxacin at 10 mg/kg/h. The bactericidal activity of 20 mg/kg/h moxifloxacin ( $-0.31 \pm 0.10$   $\Delta\log$  cfu/mL/h) was similar to 10 mg/kg/h moxifloxacin. The addition of dexamethasone to the 10 mg/kg/h moxifloxacin regime slightly reduced bactericidal activity ( $-0.25 \pm 0.06$   $\Delta\log$  cfu/mL/h). Dexamethasone did not effect the penetration of moxifloxacin into CSF in contrast to the 30-50% reduction in penetration into CSF when coadministered with ceftriaxone. The inflammatory host response was delayed about 3 hours in the moxifloxacin treated animals.

Ostergaard et al. (147, 148) evaluated moxifloxacin against penicillin resistant and penicillin susceptible *Streptococcus pneumoniae* in experimental meningitis in rabbits. The efficacy of moxifloxacin was compared with that of ceftriaxone and vancomycin. Rabbits were challenged intracisternally with 0.2 mL of  $1 \times 10^6$  to  $2 \times 10^6$  cfu/mL of *Streptococcus pneumoniae*. Approximately 10 hours after inoculation, the group of rabbits infected with the penicillin resistant isolate was given two doses of moxifloxacin 40 mg/kg iv, five hours apart; two doses of moxifloxacin 20 mg/kg iv, five hours apart; one dose of ceftriaxone 125 mg/kg iv; or 2 doses of vancomycin 20 mg/kg iv, five hours apart. The rabbits infected with the penicillin susceptible isolate were given two doses of moxifloxacin 40 mg/kg. Ten hours post treatment the  $\log_{10}$  cfu/mL in CSF was below the detection level for all treatment groups. However, at three hours

## CLINICAL EFFICACY (CLINICAL MICROBIOLOGY)

### ISOLATES/RELEVANCE TO APPROVED INDICATIONS

The sponsor has presented several Phase III studies for each indication that they seek. A satisfactory response indicates that the pathogen was eradicated or presumed eradicated at the test of cure visit.

#### Acute Sinusitis

The sponsor is requesting an indication of acute sinusitis caused by *Streptococcus pneumoniae* (including penicillin-susceptible, intermediate, or resistant strains), *Haemophilus influenzae*, or *Moraxella catarrhalis*.

A total of six studies were conducted. One study, D96-023, an antral tap study for collecting isolates, was completed as a 7-day treatment regimen. [REDACTED]

Four trials (100107, 0161, 0116, D96-024) were controlled trials and were considered pivotal along with uncontrolled trial, D96-023. One small study (0109) was a supportive study. Five of the six studies (100107, 0161, 0116, D96-023, D96-024) included a moxifloxacin dosing regimen consistent with the proposed labeling of 400 mg once daily for 7 to 10 days; one Phase IIa study (0109) had a dosing regimen of 7 to 14 days. Four of the six studies (100107, 0161, 0116, D96-024) were randomized, multicenter, parallel-group, active controlled, and double blind. The other two (D96-023 and 0109) were open label studies, with D96-023 being uncontrolled and 0109 using an active control. Three of these studies (0161, 0116, and D96-023) isolated pathogens. Cefuroxime axetil was used as the control agent in the five Phase III trials and clarithromycin was used in the Phase IIa study.

In Study D96-023, all pathogens were collected by needle aspirate. In studies 0161 and 0116, the pathogens were collected by needle aspirate, endoscopic cannulation, and swab. TABLE 57 shows the eradication rates for the three common pathogens.

TABLE 57  
Pathogen Eradication Rates for Sinusitis

Study Number	Moxifloxacin 400 mg x 7 days	Moxifloxacin 400 mg x 10 days	Cefuroxime axetil 250 mg BID x 10 days
<b><i>Streptococcus pneumoniae</i></b>			
#0161	na	36/38 (95%)	32/32 (100%)
#0116	38/39 (97%)	na	45/48 (94%)
D96-023	29/30 (97%)	na	na
Combined	67/69 (97%)	36/38 (95%)	77/80 (96%)
<b><i>Haemophilus influenzae</i></b>			
#0161	na	17/17 (100%)	15/16 (94%)
#0116	28/29 (97%)	na	30/35 (86%)
D96-023	24/30 (80%)	na	na
Combined	52/59 (88%)	17/17 (100%)	45/51 (88%)
<b><i>Moraxella catarrhalis</i></b>			
#0161	na	10/10 (100%)	5/5 (100%)
#0116	14/14 (100%)	na	8/9 (89%)
D96-023	15/18 (83%)	na	na
Combined	29/32 (91%)	10/10 (100%)	13/14 (93%)

In general the eradication rates with moxifloxacin were comparable to eradication rates with cefuroxime axetil.

Six strains of *Streptococcus pneumoniae* were resistant (MICs 2-4 µg/mL) to penicillin. These isolates were in study D96-023 (patients 2009, 2013, 3008, 7014, 7017, 23024). All of these isolates were eradicated.

#### Acute Bacterial Exacerbation of Chronic Bronchitis (AECB)

The sponsor is requesting an indication of acute bacterial exacerbations of chronic bronchitis (AECB) caused by *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Moraxella catarrhalis*, or *Klebsiella pneumoniae*.

A total of four studies were conducted. Two of the four studies (D96-027 and 0124) included a moxifloxacin dosing regimen consistent with the proposed labeling (400 mg x 5 days). All four studies were randomized, multicenter, parallel group, active controlled, and double blind. Three of the four studies (D96-027, 0124, and D96-022) were Phase III trials and were considered pivotal. Study 0106 was a pilot Phase IIa study. Cefuroxime axetil was the comparator in study D96-022 and clarithromycin was the comparator in studies D96-027 and 0124. TABLE 58 shows the eradication rates in the two studies that included a 5 day regime. There was one penicillin-resistant (MIC = 2 µg/mL) isolate in study D96-027 (patient 1128) that was eradicated.

TABLE 58  
Pathogen Eradication Rates AECB Studies

Study Number	Moxifloxacin 400 mg x 5 day	Clarithromycin 500 mg BID
<b><i>Haemophilus influenzae</i></b>		
D96-027	33/37 (89%)	31/41 (76%)
#0124	40/44 (91%)	23/43 (53%)
Combined	73/81 (90%)	54/84 (64%)
<b><i>Haemophilus parainfluenzae</i></b>		
D96-027	16/16 (100%)	14/14 (100%)
#0124	5/9 (56%)	4/4 (100%)
Combined	21/25 (84%)	18/18 (100%)
<b><i>Streptococcus pneumoniae</i></b>		
D96-027	16/16 (100%)	21/23 (91%)
#0124	32/38 (84%)	35/36 (97%)
Combined	48/54 (89%)	56/59 (95%)
<b><i>Staphylococcus aureus</i></b>		
D96-027	15/16 (94%)	7/8 (88%)
#0124	1/1 (100%)	9/11 (82%)
Combined	16/17 (94%)	16/19 (84%)
<b><i>Moraxella catarrhalis</i></b>		
D96-027	29/34 (85%)	24/24 (100%)
#0124	14/16 (87%)	23/24 (96%)
Combined	43/50 (86%)	47/48 (98%)
<b><i>Klebsiella pneumoniae</i></b>		
D96-027	17/20 (85%)	10/11 (91%)
#0124	0	0
Combined	17/20 (85%)	10/11 (91%)

It appears that moxifloxacin was more effective than clarithromycin against *Haemophilus influenzae* and *Staphylococcus aureus*, although study #0124 had only one isolate of *Staphylococcus aureus* in the moxifloxacin group. Clarithromycin appears to be more effective against *Moraxella catarrhalis*. The data also suggest that clarithromycin is more effective than moxifloxacin against *Haemophilus parainfluenzae* and *Streptococcus pneumoniae* in study #0124, but this observation is not confirmed in study D96-027. The number of *Haemophilus parainfluenzae* isolates in study #0124 was small.

### Community Acquired Pneumonia (CAP)

The sponsor is requesting an indication of community-acquired pneumonia (CAP) caused by *Streptococcus pneumoniae* (including penicillin-susceptible, [redacted] strains), *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, or *Moraxella catarrhalis*.

A total of five studies were conducted. Four of the studies (D96-026, 0119, 0140, and 0112) were randomized, multicenter, parallel group, active controlled, and double blind. Study 0112 was a pilot Phase II trial. Studies D96-026, D96-025, 0119, and 0140 were Phase III pivotal studies. Study D96-025 was an open label, prospective study. Clarithromycin was used as a comparator in studies D96-026 and #0119. Amoxicillin was used as a comparator in study #0140. Studies D96-025 and D96-026 were United States studies and included special diagnostic methods for culture of atypical pathogens in addition to serological testing for these organisms. Study #0140 included countries with a high resistant rate of *Streptococcus pneumoniae*. TABLE 59 shows the eradication rates in these studies.

It appears that moxifloxacin is more effective against *Haemophilus influenzae* in all three pivotal studies than the control regimen. The eradication rates for *H. influenzae* were less in study #0119 than in studies D96-026 and 0140 for both treatment groups. The eradication rates for *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae* were equivalent for moxifloxacin and the controls. For the less frequent pathogens; *Staphylococcus aureus*, *Moraxella catarrhalis*, and *Klebsiella pneumoniae*, the small number of isolates for each regimen limit comparisons.

Most of the *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* isolates were detected by serology. In study D96-026 there were 11 *Mycoplasma pneumoniae* in the moxifloxacin treated group detected by culture and all were eradicated. There were seven isolates detected by culture in the control group and all were eradicated. In study D96-025 there were 22 *Mycoplasma pneumoniae* isolates cultured and 21 (95%) were eradicated. In study D96-026 there were three isolates of *Chlamydia pneumoniae* detected by culture in the moxifloxacin group and one (33%) was eradicated. Four of four isolates cultured in the control group were eradicated. In study D96-025, four (67%) of six isolates cultured in the moxifloxacin group were eradicated.

For three of the four pivotal studies (D96-026, D96-025, and 0140) the penicillin sensitivity of *Streptococcus pneumoniae* was determined. Study 0140 had 41 patients with penicillin-susceptible isolates, 25 patients with penicillin-intermediate isolates, and six patients with penicillin-resistant (MIC  $\geq 2$   $\mu\text{g/mL}$ ) isolates. The other two studies combined had three patients with penicillin-resistant isolates (two in the moxifloxacin group) and six penicillin-intermediate isolates. In the moxifloxacin treated group the eradication rate for penicillin-resistant *S. pneumoniae* was 4/6 (67%). The eradication rate for penicillin-resistant *S. pneumoniae* in the control group was 3/3 (100%). The small number of isolates limits comparison between groups. For penicillin-intermediate isolates the eradication rates were 18/19 (95%) for moxifloxacin and 8/12 (67%) for the controls.

TABLE 59  
Pathogen Eradication Rates in CAP Studies

Study Number	Moxifloxacin	Control Regimen
<b><i>Streptococcus pneumoniae</i></b>		
D96-026	17/17 (100%)	18/19 (95%)
D96-025	13/14 (93%)	—
#0119	14/16 (88%)	12/13 (92%)
#0140	34/41 (83%)	35/42 (83%)
Combined	78/88 (89%)	65/74 (88%)
<b><i>Haemophilus influenzae</i></b>		
D96-026	22/23 (96%)	14/16 (88%)
D96-025	11/13 (85%)	—
#0119	6/8 (75%)	5/10 (50%)
#0140	8/8 (100%)	13/17 (76%)
Combined	47/52 (90%)	32/43 (74%)
<b><i>Mycoplasma pneumoniae</i></b>		
D96-026	23/24 (96%)	20/20 (100%)
D96-025	27/29 (93%)	—
#0119	22/24 (92%)	30/32 (94%)
#0140	6/6 (100%)	11/12 (92%)
Combined	78/83 (94%)	61/64 (95%)
<b><i>Chlamydia pneumoniae</i></b>		
D96-026	42/45 (93%)	43/44 (98%)
D96-025	56/63 (89%)	—
#0119	19/19 (100%)	21/23 (91%)
#0140	4/5 (80%)	1/1 (100%)
Combined	121/132 (92%)	65/68 (96%)
<b><i>Staphylococcus aureus</i></b>		
D96-026	5/5 (100%)	5/5 (100%)
D96-025	8/9 (89%)	—
#0119	1/1 (100%)	2/2 (100%)
#0140	3/3 (100%)	2/3 (67%)
Combined	17/18 (94%)	9/10 (90%)
<b><i>Moraxella catarrhalis</i></b>		
D96-026	6/7 (86%)	2/2 (100%)
D96-025	4/4 (100%)	—
#0119	1/2 (50%)	3/3 (100%)
#0140	1/1 (100%)	1/2 (50%)
Combined	12/14 (86%)	6/7 (86%)
<b><i>Klebsiella pneumoniae</i></b>		
D96-026	6/6 (100%)	5/5 (100%)
D96-025	4/4 (100%)	—
#0119	1/2 (50%)	1/3 (33%)
#140	2/3 (67%)	2/2 (100%)
Combined	13/15 (87%)	8/10 (80%)

*This page of the document  
contains confidential  
information that will not  
be included in the  
redacted portion of the  
document for the public to  
obtain.*

## DISK CONTENT STUDIES

The disk potency of other quinolones is either 5 or 10 µg depending on the diffusion characteristics of the drug. Both a 5-µg and 10-µg disk were evaluated in preliminary tests. The 5-µg disk produced sufficiently large and easy to read zones in the critical interval of MIC breakpoints of 1.0 or 2.0 µg/mL; the zone sizes corresponding to a resistant breakpoint of 4.0 or 8.0 µg/mL were large enough to minimize errors that may occur in reading small zone sizes; and the zone diameters were large enough to discriminate between MIC breakpoints for resistant and susceptible. The 10-µg disk, which produced larger zone diameters, offered no advantages over the 5-µg disk. NCCLS document M-23 states that "The ideal disk is one that provides zone diameters greater than 15 mm and less than 45 mm for most susceptible strains but only small zone diameters of inhibition with resistant strains. However, susceptible breakpoints should, ideally, be between 15 and 24 mm". The 5-µg disk appears to produce zone diameters close to this ideal.

The two- to fourfold higher *in vitro* activity against gram-positives compared to ciprofloxacin, and levofloxacin, as well as diminished activity against *Pseudomonas aeruginosa*, indicate that moxifloxacin needs a separate diffusion disk. Zone sizes produced by moxifloxacin were compared with zone sizes produced by either ciprofloxacin or levofloxacin disks during the course of the study to determine tentative interpretive criteria for nonfastidious bacteria comprised of 520 isolates representing 33 species (150). Regression plots comparing moxifloxacin with ciprofloxacin or moxifloxacin with levofloxacin demonstrated that the activities of ciprofloxacin and levofloxacin differed considerably and a moxifloxacin disk was needed.

## MIC BROTH/AGAR DILUTION COMPARISONS

Macrobroth dilution, microbroth dilution, and agar dilution susceptibility test methods were compared against representative isolates to determine if the test methods were interchangeable (34). Good correlation among MICs was obtained between all three methods for all organisms. MICs were either the same or within a twofold dilution of each other for all isolates tested.

Barry and Brown (151) tested ATCC quality control strains by both agar dilution and broth microdilution methods against moxifloxacin, ciprofloxacin, and ofloxacin. They concluded that the agar and broth dilution test results were essentially identical when testing these three fluoroquinolones.

pages have been removed here because they contain confidential information that will not be included in the redacted portion of the document for the public to obtain.

## QUALITY CONTROL STUDIES (MIC AND DISK DIFFUSION)

Two collaborative studies were performed in order to establish the quality control limits for the standard susceptibility test assay strains *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 25923 (disk) or ATCC 29213 (MIC), *Pseudomonas aeruginosa* ATCC 27853, *Haemophilus influenzae* ATCC 49247, *Streptococcus pneumoniae* ATCC 49619, and *Enterococcus faecalis* ATCC 29212 (broth only). Ten clinical microbiology laboratories participated under the direction of [REDACTED]. All laboratories performed susceptibility tests by disk diffusion or broth microdilution according to NCCLS guidelines.

### 5- $\mu$ g MOXIFLOXACIN DISK QUALITY CONTROL STUDIES

Brown, Barry and Fuchs (152) oversaw a collaborative study in November, 1997. Each of ten laboratories performed susceptibility tests on ten separate days using two different lots of 5- $\mu$ g moxifloxacin disks, one made by [REDACTED]. Each laboratory was provided a common lot of Mueller-Hinton agar, Mueller-Hinton agar containing 5% sheep blood, and HTM agar in order to determine the effects of medium on zone diameters produced with the 5- $\mu$ g moxifloxacin disk and the standard test organisms. The use of a common lot also demonstrates interlaboratory differences in performing the test. In addition, each laboratory received one of five unique lots of each type of medium. On each day, each control strain was inoculated onto the medium appropriate for that strain. Two moxifloxacin disks were applied to each medium; therefore, a total of 400 zone diameters were generated. Ciprofloxacin disks were used as the control for all organisms except *Streptococcus pneumoniae*; ofloxacin disks were used for this organism.

The mean zone sizes for the two different lots of disks varied from 31.3 to 31.6 mm for *E. coli*, 20.8 to 20.8 mm for *P. aeruginosa*, 31.3 to 31.7 mm for *S. aureus*, 27.7 to 28.1 mm for *S. pneumoniae*, and from 34.2 to 34.6 mm for *H. influenzae*. This shows that both lots of disk were equivalent.

The common lot produced almost identical mean zone sizes for the two lots of disks for each of the control strains. For each of the ATCC strains, the zone diameters obtained on the common lot and unique lots were similar within the respective laboratories, which indicated that there were no essential differences among the various media used. Interlaboratory zone sizes, with rare exception, also were similar among the laboratories. The zone sizes for *Pseudomonas aeruginosa* and moxifloxacin tended to be smaller for one laboratory (Laboratory 1) using an unique lot. For the control quinolones and all of the test strains, only one zone diameter did not fall within QC limits. The results of tests can be seen in TABLE 61.

TABLE 61  
Moxifloxacin Disk Quality Control Data  
Zone Diameter in mm, surrounding 5- $\mu$ g Moxifloxacin Disk

Organism	Median	Mean	Range	$\frac{1}{2}$ MR <sup>a</sup>	$\pm 2SD^b$
<i>E. coli</i> ATCC 25922	31	31.5			2.94
<i>P. aeruginosa</i> ATCC 27853	21	20.8			2.78
<i>S. aureus</i> ATCC 25923	32	31.5			2.60
<i>S. pneumoniae</i> ATCC 49619	28	27.9			2.94
<i>H. influenzae</i> ATCC 49247	34	34.4			2.90

<sup>b</sup>  $\pm 2SD = \pm 2$  standard deviations.

For *E. coli* ATCC 25922, the mean  $\pm$  2 SD rounded out would be 28-35 mm, the median  $\pm$  1/2 MR is [redacted]. The authors proposed a range of [redacted]. This includes 98.7 % of the data (Figure 1). A range of [redacted] was accepted by NCCLS in January, 1999. There are very few zones at 27 mm.

For *P. aeruginosa* ATCC 27853, the mean  $\pm$  2 SD rounded out would be [redacted]. This range includes only 92.3% of the data, however, which is below the 95% that NCCLS recommends. The authors proposed a range of [redacted]. This includes 96.8% of the data (Figure 2). A range of [redacted] was accepted by NCCLS in January, 1999.

For *S. aureus* ATCC 25923, the mean  $\pm$  2 SD rounded out would be 28-35 mm, the median  $\pm$  1/2 MR is [redacted]. The authors proposed a range of [redacted]. This includes 98.3% of the data (Figure 3). A range of [redacted] was accepted by NCCLS in January, 1999.

For *S. pneumoniae* ATCC 49619, the mean  $\pm$  2 SD rounded out would be 24-31mm, the median  $\pm$  1/2 MR is [redacted]. The authors proposed a range of [redacted]. This range includes 98.5% of the data (Figure 4). A range of [redacted] was accepted by NCCLS in January, 1999.

For *H. influenzae* ATCC 49247, the mean  $\pm$  2 SD rounded out would be 31-38 mm, the median  $\pm$  1/2 MR is [redacted]. The authors proposed a range of [redacted]. This range includes 98.7% of the data (Figure 5). A range of [redacted] was accepted by NCCLS in January, 1999.

The following disk diffusion quality control limits were approved by NCCLS for the 5- $\mu$ g moxifloxacin disk.

ORGANISM	MOXIFLOXACIN ZONE DIAMETER (mm)
<i>Escherichia coli</i> ATCC 25922	[redacted]
<i>Pseudomonas aeruginosa</i> ATCC 27853	[redacted]
<i>Staphylococcus aureus</i> ATCC 25923	[redacted]
<i>Streptococcus pneumoniae</i> ATCC 49619	[redacted]
<i>Haemophilus influenzae</i> ATCC 49247	[redacted]

The limits for *Pseudomonas aeruginosa* will not be included in the label since moxifloxacin does not have an indication for this organism and the zone diameter limits for this organism extend into the non-susceptible range. The limits for *E. coli* and *S. aureus* will be included (even though moxifloxacin has no indication for *E. coli*) since at least two quality control organisms should be used for non-fastidious organisms. In order to be consistent with NCCLS their QC ranges should be used in labeling if acceptable to FDA. NCCLS QC limits are acceptable and will be placed in the label except for *Pseudomonas aeruginosa* as noted above.

3 pages have been removed here because they contain confidential information that will not be included in the redacted portion of the document for the public to obtain.

### MIC QUALITY CONTROL STUDIES

To determine the range of MICs that should be expected for susceptibility test of the ATCC quality control strains, six lots of cation-adjusted Mueller-Hinton broth from \_\_\_\_\_ were prepared in microdilution trays containing serially diluted moxifloxacin. Barry and Brown (151) conducted this study in February, 1997. Ciprofloxacin and ofloxacin were used as control drugs. For testing *Streptococcus pneumoniae* ATCC 49619, the trays were supplemented with lysed horse blood and HTM supplements were added for testing *Haemophilus influenzae* ATCC 49247. Only five lots were used for evaluating *Streptococcus pneumoniae* and *Haemophilus influenzae* and only ofloxacin was used as the control for these two organisms. Over ten separate days, each lot was tested with the ATCC strains of *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Enterococcus faecalis* to give 60 tests per lot per laboratory for a total of 600 tests. Similarly, five lots were tested with the ATCC strains of *Streptococcus pneumoniae* and *Haemophilus influenzae* to yield 500 test results per organism. Colony counts were performed to check the inoculum.

For all test organisms except *Streptococcus pneumoniae*, interlaboratory MICs were in good agreement for the proposed QC limit for each organism. The different lots of media generally did not produce discrepant MICs for any of the test strains except *Streptococcus pneumoniae*. Lot 4-Laboratory 7 accounted for the majority of out-of-range MICs for *Streptococcus pneumoniae*. The proposed limits are defined as the mode  $\pm$  one doubling dilution. If the mode is between two dilutions, then a 4-dilution range is proposed. The results of this study are presented in TABLE 62.

APPEARS THIS WAY  
ON ORIGINAL

TABLE 62  
Quality Control Data, Moxifloxacin MICs

Control Strain	MIC Values and No. Times Each Reported						
<i>E. coli</i> ATCC 25922	0.008	0.015	0.03	0.06	0.125	[REDACTED]	
<i>S. aureus</i> ATCC 29213	0.008	0.015	0.03	0.06	0.125	0.25	[REDACTED]
<i>E. faecalis</i> ATCC 29212	0.03	0.06	0.12	0.25	0.5	1.0	[REDACTED]
<i>P. aeruginosa</i> ATCC 27853	0.5	1.0	2.0	4.0	8.0	[REDACTED]	
<i>H. influenzae</i> ATCC 49247	0.008	0.015	0.03	0.06	0.12	0.25	0.5
<i>S. pneumoniae</i> ATCC 49619	0.015	0.03	0.06	0.12	0.25	0.5	1 16

\* Brackets enclose proposed ranges

The authors proposed the limits indicated by brackets in TABLE 61. These limits included 100% of the data for *E. coli* ATCC 25922 (Figure 6), 100% of the data for *P. aeruginosa* ATCC 27853 (Figure 7), 98.8% of the data for *E. faecalis* ATCC 29212 (Figure 8), 99.2% of the data for *S. aureus* ATCC 29213 (Figure 9), 97.0% of the data for *S. pneumoniae* (Figure 10), and 99.4% of the data for *H. influenzae* (Figure 11).

APPEARS THIS WAY  
ON ORIGINAL

3 pages have been removed here because they contain confidential information that will not be included in the redacted portion of the document for the public to obtain.

### STREPTOCOCCUS SPECIES INCLUDING STREPTOCOCCUS PNEUMONIAE

Two studies were performed at different times. The first study (32) included only *Streptococcus pneumoniae* and did not include any strains with high level resistance to ciprofloxacin. The second study (153) evaluated *Streptococcus* species including *Streptococcus pneumoniae* and included strains that had intermediate and high level resistance to ciprofloxacin.

In the first study, a total of 301 strains of *Streptococcus pneumoniae* were tested by both disk diffusion and broth microdilution methods. Of these strains, 134 were penicillin-susceptible, 106 were penicillin-intermediate, and 61 were penicillin-resistant. *Streptococcus pneumoniae* ATCC 49619 was tested each day for quality control. Ciprofloxacin, levofloxacin, and ofloxacin were included as control drugs.

Results of broth tests showed that the range of MICs for moxifloxacin was [redacted] Moxifloxacin was fourfold more active than ciprofloxacin and levofloxacin and eightfold more active than ofloxacin. The range of zone diameters for moxifloxacin was [redacted] The strain with a MIC of 0.5 µg/mL had a zone diameter of 29 mm. Figure 12 shows the scattergram of zone diameter versus MICs. Based on the unimodal population distribution of the MICs and lack of resistant strains, an arbitrary breakpoint of ≥22 mm for susceptible was proposed. This fits the model of using one dilution greater than the highest MIC value for 99% of the population and 3 mm smaller than the smallest zone diameter for 99% of the population. There were five strains with a zone diameter of [redacted]

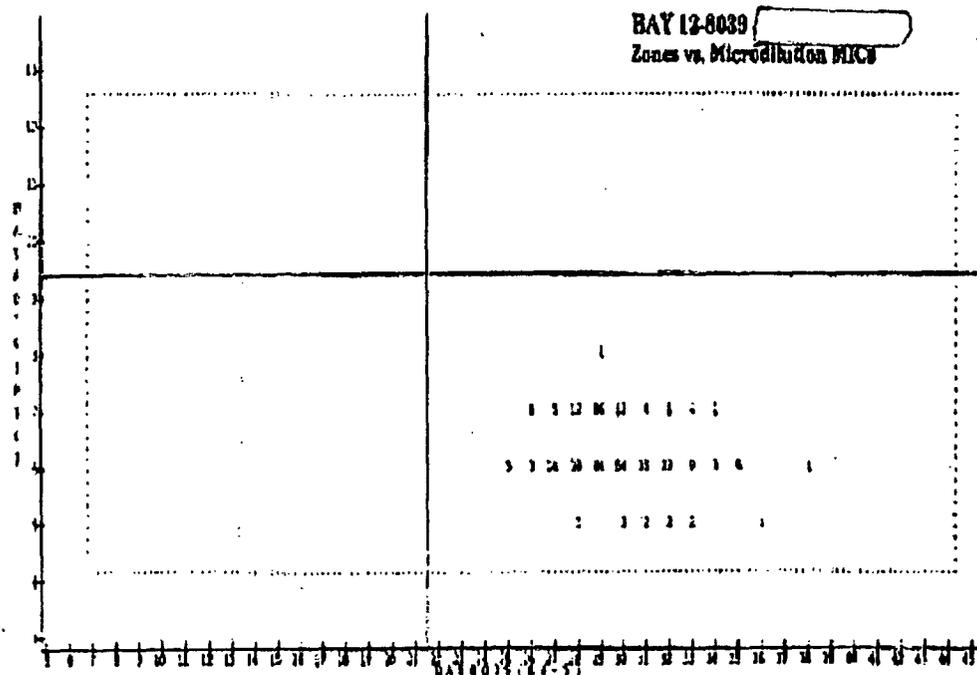
In the second study, four laboratories evaluated disk diffusion susceptibility tests against 495 strains of streptococci (153). Each laboratory tested 122-125 clinical strains of streptococci from their respective stock collection. The study was under the direction of [redacted] The other sites were [redacted]

[redacted] A preliminary study was performed that ensured that the data from the four sites were consistent among the sites and could be pooled. All laboratories used a common lot of broth microdilution panels and susceptibility disks. Each laboratory tested their own set of challenge strains in order to test as many different species of streptococci as possible. In addition, each laboratory tested the quinolone-resistant strains in their collection. TABLE 63 lists the distribution of organisms tested by each site.

TABLE 64 provides the frequency distribution of MICs for β-hemolytic streptococci, [redacted] *Streptococcus pneumoniae*. The study strains included 42 ciprofloxacin-intermediate (MIC 4-8 µg/mL) and 21 strains with high level resistance to ciprofloxacin (MIC ≥ 16 µg/mL). Fourteen strains of *Streptococcus pneumoniae* had intermediate resistance to ciprofloxacin and 17 strains had high level resistance to ciprofloxacin. Of these 31 *Streptococcus pneumoniae* strains, 4 strains had moxifloxacin MICs of 4 µg/mL.

Data Analysis - Regression(s) defined by [redacted]  
Page 2 Printed on 20-FEB-97 at 15:50:23 for study 1337  
Plot: 1 X: BAY8039(KB-5) Y: BAY0039(MIC)

FIGURE 2



Axis	Expr	Spec	Min	Max	Scale	Coeff	Intercept	R
X	BAY8039(KB-5)	3611	301	7	44	0.25	-0.0333	
Y	BAY0039(MIC)		5	10	0.20		7.1627	-0.1380

Log2 -0.00 Scale: 0( 0.5) 1( 0.25) 4( 0.125) 5( 0.0625)  
( End of Report )

FIGURE 12. STREPTOCOCCUS PNEUMONIAE

*This page of the document  
contains confidential  
information that will not  
be included in the  
redacted portion of the  
document for the public to  
obtain.*

TABLE 64

Overall Distribution of Streptococcal MICs

	Number of strains with the following MICs ( $\mu\text{g/ml}$ )									
	0.06	0.12	0.25	0.5	1.0	2.0	4.0	8.0	16	>16
<b>Beta Hemolytic (144)</b>										
Bay 12-8039	3	69	44	6	0	0	1			
Ciprofloxacin		1	11	106	19	6	0	0	1	
Ofloxacin				4	80	53	6	0	1	
<b>Viridans Group (241)</b>										
Bay 12-8039	6	104	112	17	0	0	2			
Ciprofloxacin			2	36	98	74	22	6	2	1
Ofloxacin				5	40	131	60	3	1	1
<b><i>S. pneumoniae</i> (110)</b>										
Bay 12-8039	12	67	3	5	4	15	4			
Ciprofloxacin			3	21	50	5	7	7	8	9
Ofloxacin				1	29	50	5	2	14	9
<b>All Streptococci (495)</b>										
Bay 12-8039	21	260	159	28	4	15	7			
Ciprofloxacin		1	16	163	167	85	29	13	11	10
Ofloxacin				10	149	234	71	5	16	10

APPEARS THIS WAY  
ON ORIGINAL

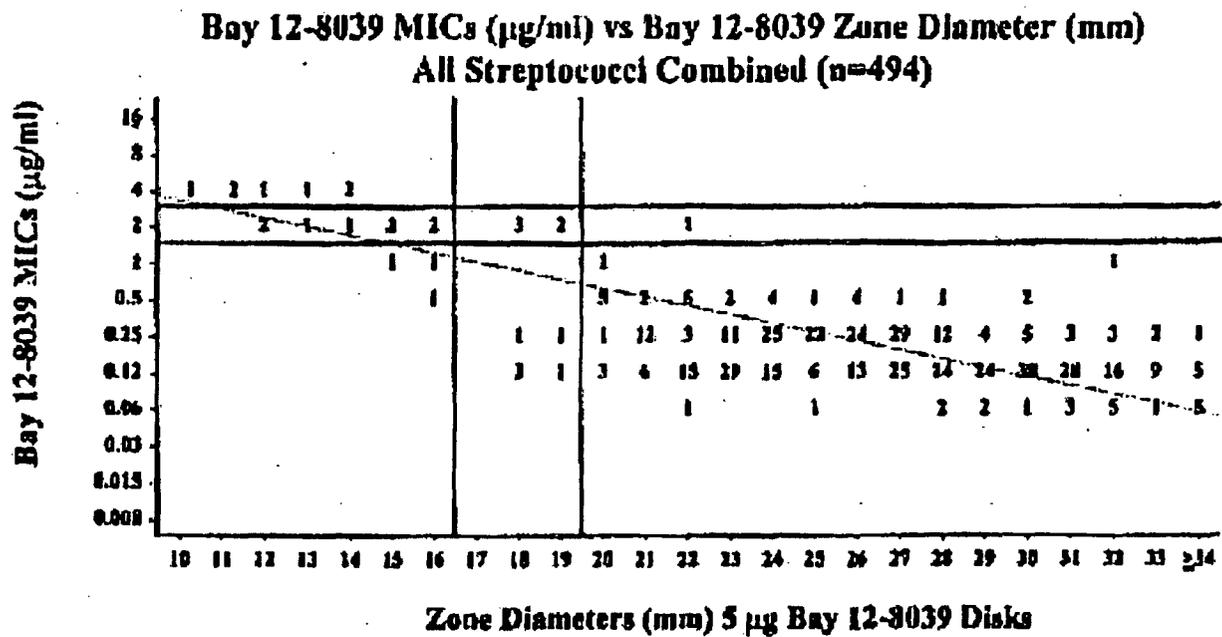
The scattergram comparing the MIC and zone diameters of all 495 streptococcal strains is shown in Figure 13A. The scattergrams for the individual groups of streptococci are presented in Figure 14 (*Streptococcus pneumoniae*), Figure 15 ( $\beta$ -hemolytic), and Figure 16 (viridans group). Even including the 63 ciprofloxacin-resistant/intermediate strains, the population distribution was still unimodal for moxifloxacin for each group and for all streptococci combined. Since there was essentially no difference in population distribution among the three groups, criteria were applied for all streptococci including *Streptococcus pneumoniae*. The provisional breakpoints, pending clinical data were Susceptible  $\geq 20$  mm (MIC  $\leq 1.0$   $\mu\text{g/mL}$ ), Intermediate 17-19 mm (MIC 2.0  $\mu\text{g/mL}$ ), and Resistant  $\leq 16$  mm ( $\geq 4.0$   $\mu\text{g/mL}$ ). These criteria resulted in no very major errors, 3 (0.6%) major errors, and 16 (3.2 %) minor errors.

An alternative way to evaluate the data for streptococci is shown in Figure 13B. A distinct bimodal population is seen when ciprofloxacin-resistant strains are tested. This bimodality is particularly discernible by disk diffusion. The organisms with zone diameters  $\geq 18$  mm are in one population, while organisms with zones  $\leq 16$  mm are in the other, less susceptible population. A MIC breakpoint of  $\leq 1.0$   $\mu\text{g/mL}$  and a zone  $\geq 18$  mm for susceptible and a MIC of  $\geq 4.0$   $\mu\text{g/mL}$  and zone  $\leq 14$  mm for resistant distinguishes the two populations of organisms. This gives us the traditional 3 mm intermediate zone. If  $\leq 15$  mm is chosen for the resistant breakpoint then only a 2 mm intermediate zone results. There are no very major or major errors and the minor error rate is 1.8%. If a zone of 15 mm was chosen as the resistant breakpoint there would be one major error. These alternative breakpoints also allow the streptococci having MICs of  $\leq 0.25$   $\mu\text{g/mL}$  to be categorized as susceptible, rather than intermediate as they would be if breakpoints of Susceptible  $\geq 20$  mm and Resistant  $\leq 16$  mm were used.

It appears that the following are the most appropriate breakpoints for streptococci including *Streptococcus pneumoniae*:

	<u>MIC (<math>\mu\text{g/mL}</math>)</u>	<u>Zone Diameter (mm)</u>
Susceptible	$\leq 1.0$	$\geq 18$
Intermediate	2.0	15-17
Resistant	$\geq 4.0$	$\leq 14$

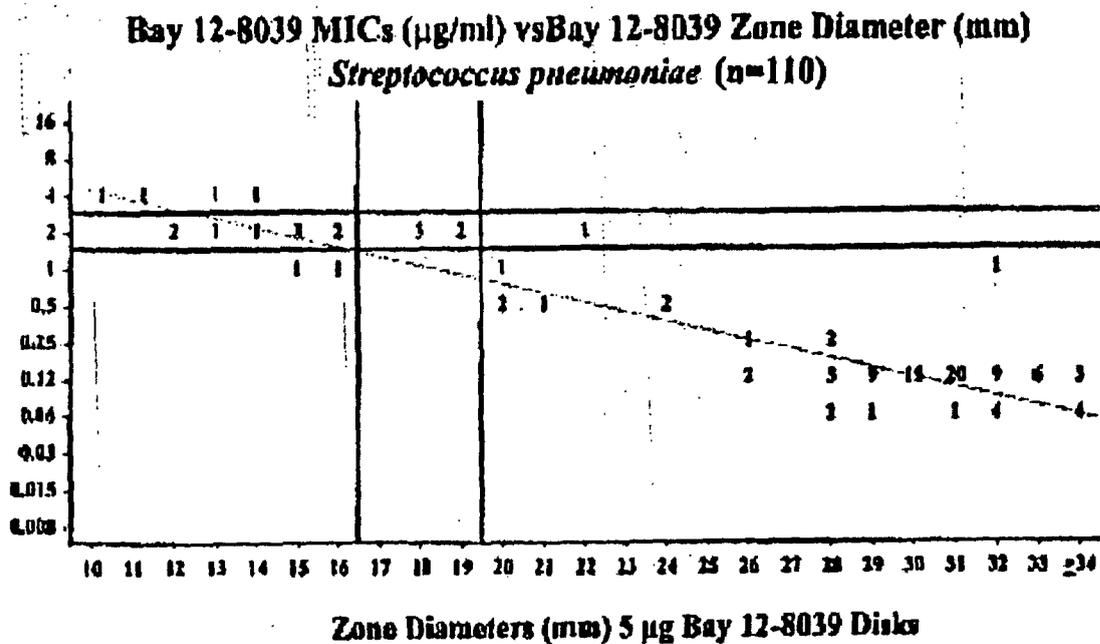
The final breakpoints will be decided when zone diameters in the clinical trials are compared to bacteriological and clinical outcomes and discussed in this review under the section titled "Correlation of Test Results with Outcome Statistics".



Slope -0.074      Intercept 2.250      r -0.597

FIGURE 13A. CMI BREAKPOINTS

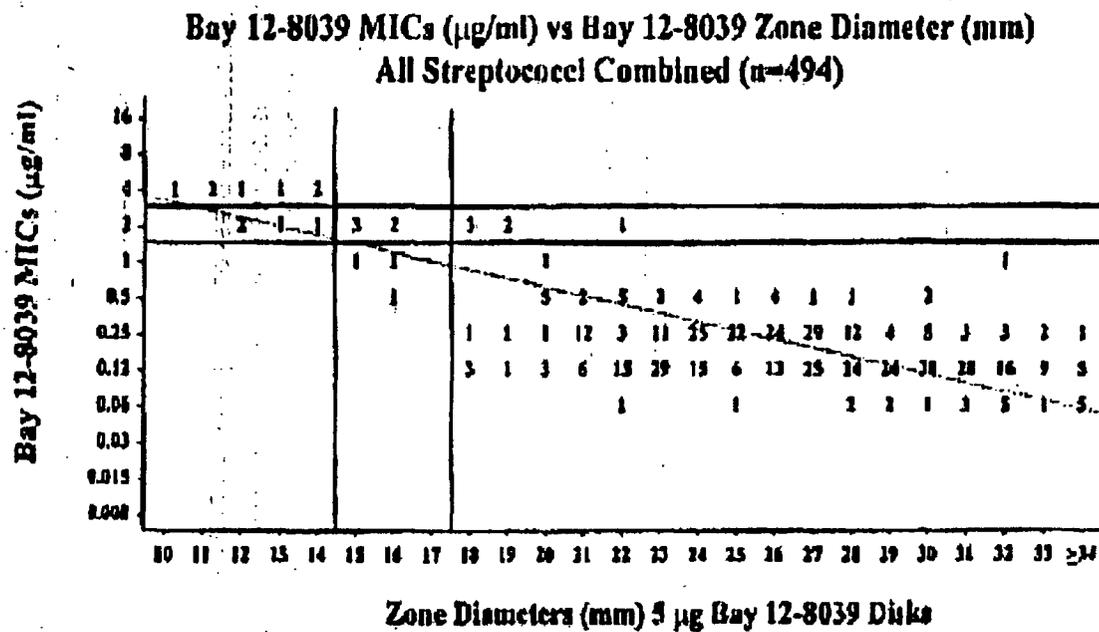
Bay 12-8039 MICs (µg/ml) vs Bay 12-8039 Zone Diameter (mm)



Slope -0.124      Intercept 3.950      r -0.875

FIGURE 14

2 pages have been removed here because they contain confidential information that will not be included in the redacted portion of the document for the public to obtain.



Slope -0.074      Intercept 1.283      r -0.597

FIGURE 13B. ALTERNATIVE BREAKPOINTS

**HAEMOPHILUS INFLEUNZAE STUDIES**

A total of 253 strains of *Haemophilus influenzae* including 141  $\beta$ -lactamase positive strains and 112  $\beta$ -lactamase negative strains were evaluated by Fuchs, Barry, and Brown (154). Ciprofloxacin and levofloxacin were included as control drugs. The QC strain *Haemophilus influenzae* ATCC 49747 was tested against all drugs to ascertain that values fell within the expected QC limits.

All of the strains were highly susceptible to moxifloxacin, as well as to ciprofloxacin and levofloxacin. The range of MICs for moxifloxacin was [redacted] which was twofold higher than the range for ciprofloxacin and levofloxacin. The zone diameters ranged from [redacted] with the majority of zone diameters ranging from [redacted]. The scattergram for zone diameter versus MICs is shown in Figure 17. All three quinolones exhibited an unimodal population. The authors proposed breakpoints of MIC  $\leq 1.0 \mu\text{g/mL}$  and zone  $\geq 22 \text{ mm}$  for the susceptible category. If we, however, use the technique of one dilution greater than the highest MIC value for 99% of the population the susceptible breakpoint should be  $\leq 0.25 \mu\text{g/mL}$  and 3 mm less than the smallest zone diameter for 99% of the population would be  $\geq 28 \text{ mm}$ . Since no resistant strains were detected only a susceptible breakpoint is appropriate.

It appears that the following are the most appropriate breakpoints for *Haemophilus influenzae*:

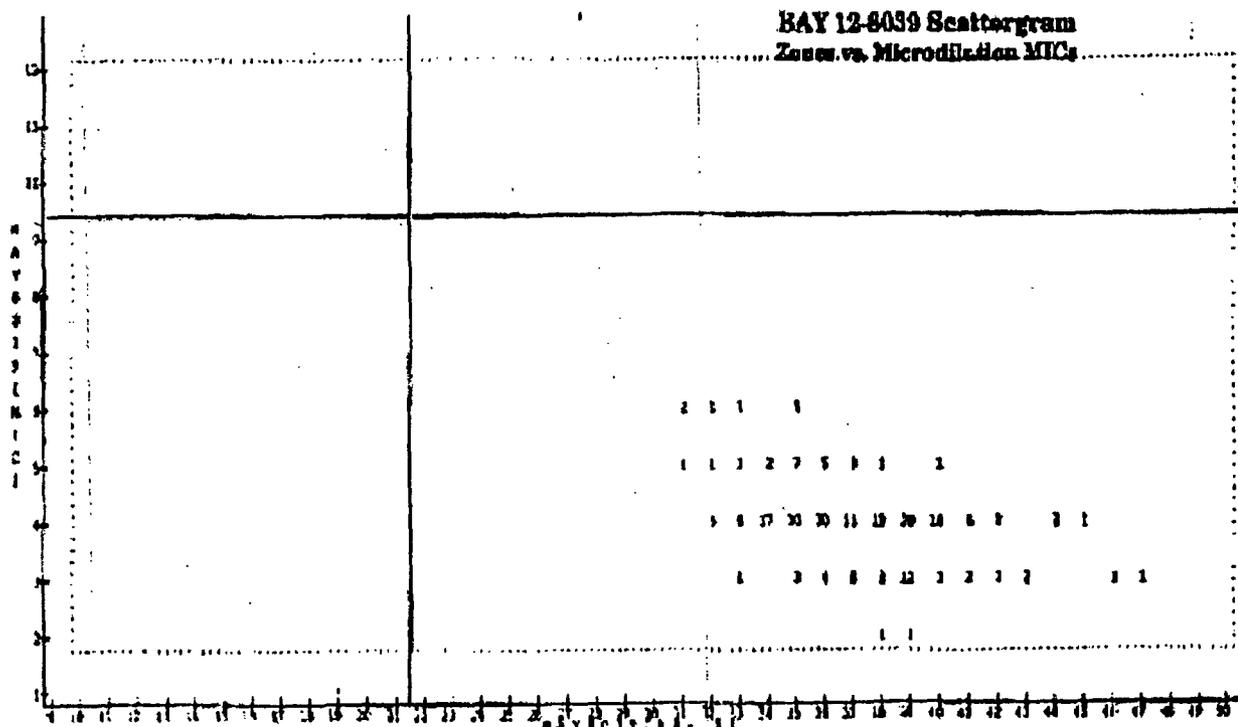
	MIC ( $\mu\text{g/mL}$ )	Zone Diameter (mm)
Susceptible	$\leq 0.25$	$\geq 28$

The final breakpoints will be decided when zone diameters in the clinical trials are compared to bacteriological and clinical outcomes and discussed in this review under the section titled "Correlation of Test Results with Outcome Statistics".

**APPEARS THIS WAY  
ON ORIGINAL**

Data Analysis - Regression(s) defined by SCATTERGRAM  
Page 1 Printed on 27-FEB-97 at 10:47:02 for study 8520  
Plot: 1 X: BAY8019 (KB- 5) Y: BAY8019 (MIC)

FIGURE 1



Axis Group	Open	Min	Max	Scale	Coeff	Intercept	R
X BAY8019(KB- 5)	2551 2523	10.	50.	0.25	-0.1004		
Y BAY8019(MIC)		2.	12.	0.20	1.6628	-0.4313	
LOG2 -9. (0 Scale)	6 ( 0.125)	5 ( 0.0625)	4 ( 0.03125)	3 ( 0.015625)	2 ( 0.0078125)		

{ End of Report }

FIGURE 17. HAEMOPHILUS INFLUENZAE

**NONFASTIDIOUS ORGANISMS**

For the determination of interpretive criteria for nonfastidious bacteria Fuchs, Barry, and Brown (150) evaluated 520 clinical isolates comprised of 34 species. These strains included genera of the family Enterobacteriaceae, nonfermentative genera, *Moraxella catarrhalis*, staphylococci, enterococci, *Listeria monocytogenes*, *Corynebacterium jeikeium*, and 75 strains of streptococci including *Streptococcus pneumoniae*. Quality control strains were tested and ciprofloxacin and levofloxacin were used as control drugs.

Susceptibility tests by broth microdilution demonstrated that moxifloxacin was usually two- to fourfold more active than ciprofloxacin and levofloxacin against the gram-positive bacteria. Ciprofloxacin, the most active quinolone against the gram-negative bacteria, was generally fourfold more active than levofloxacin. Moxifloxacin was usually twofold less active than ciprofloxacin.

Figure 18A shows the scattergram of MICs versus zone diameters. From these data and a MIC of  $\leq 1.0$   $\mu\text{g/mL}$  for susceptible and  $\geq 4.0$   $\mu\text{g/mL}$  for resistant, a zone diameter of  $\geq 22$  mm for susceptible and  $\leq 18$  mm for resistant was proposed. The interpretive error rates were 1% very major, 0.6% major, and 5.6% minor. An alternative proposal uses a MIC of  $\leq 2.0$   $\mu\text{g/mL}$  for susceptible and  $\geq 8.0$   $\mu\text{g/mL}$  for resistant (Figure 18B). With these MIC breakpoints a 3 mm decrease in zone diameters to  $\geq 19$  mm for susceptible and  $\leq 15$  mm for resistant seem appropriate. With these criteria there were only 3.6% resistant strains.

It appears that the following are the most appropriate breakpoints for nonfastidious bacteria:

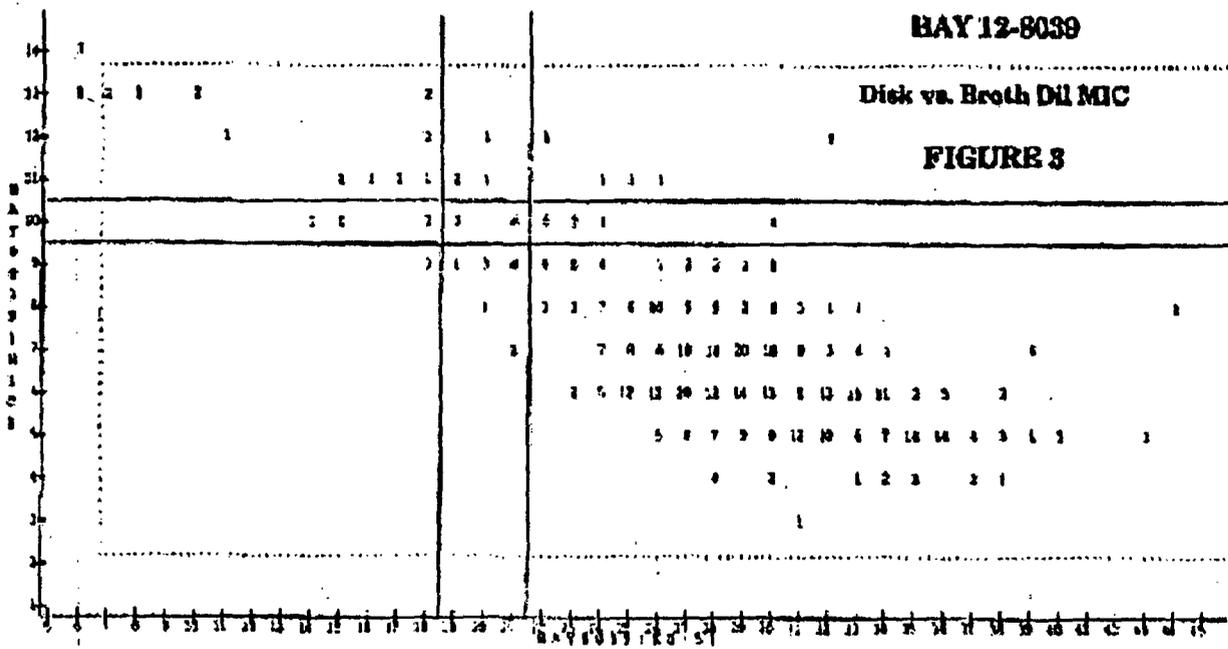
	<u>MIC (<math>\mu\text{g/mL}</math>)</u>	<u>Zone Diameter (mm)</u>
Susceptible	$\leq 1.0$	$\geq 22$
Intermediate	2.0	19-21
Resistant	$\geq 4.0$	$\leq 18$

or

	<u>MIC (<math>\mu\text{g/mL}</math>)</u>	<u>Zone Diameter (mm)</u>
Susceptible	$\leq 2.0$	$\geq 19$
Intermediate	2.0	16-18
Resistant	$\geq 4.0$	$\leq 15$

The final breakpoints will be decided when zone diameters in the clinical trials are compared to bacteriological and clinical outcomes and discussed in this review under the section titled "Correlation of Test Results with Outcome Statistics".

Data Analysis - Regression(s) defined by SCATTERGRAM  
Page 1 Printed on 13-FEB-97 at 17:20:02 for study 1334  
Plot: 1 X: BAY8039(KB-5) Y: BAY8039(MEC)



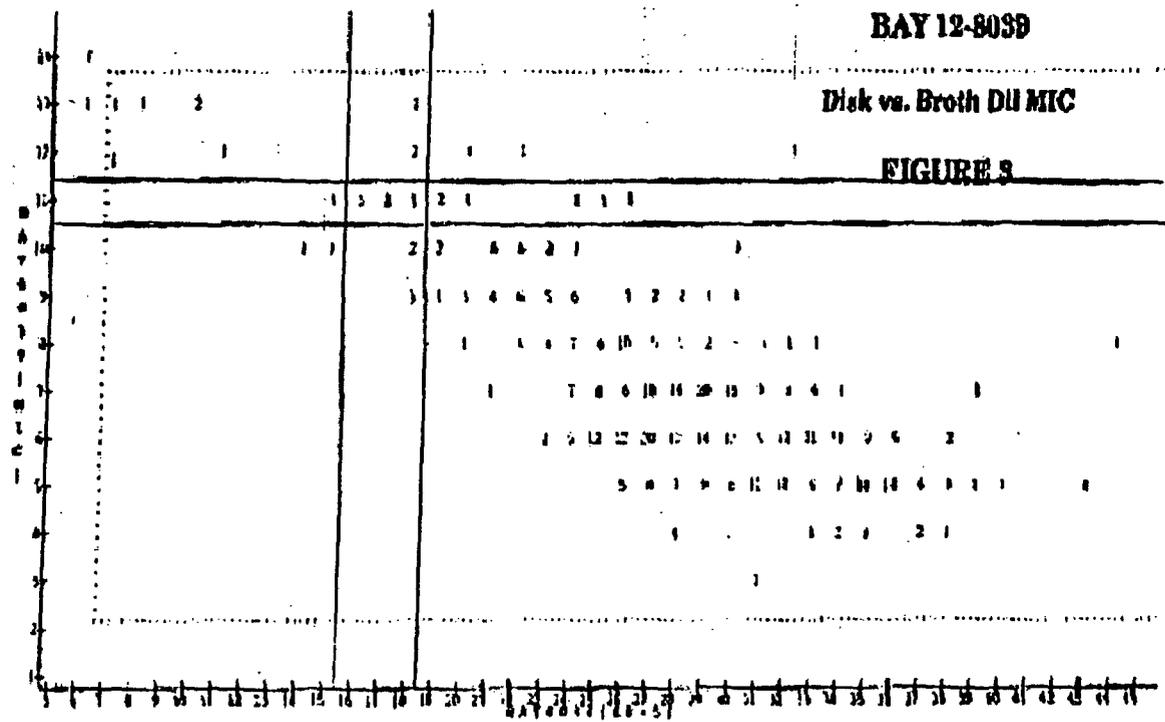
Axis	Drug	Optc	Min	Max	Scale	Coeff	Intercept	R
X	BAY8039(KB-5)	512 (520)	7	60	0.25	-0.2593		
Y	BAY8039(MEC)		3	16	0.25		14.1302	-0.7349

LOC2 +9.20 Scale: 14( 32.0) 13( 16.0) 12( 8.0) 11( 4.0) 10( 2.0) 9( 1.0)  
8( 0.5) 7( 0.25) 6( 0.125) 5( 0.0625) 4( 0.03125)  
3( 0.015625)

( End of Report )

FIGURE 18A NONFASTIDIOUS AEROBIC BACTERIA

Data Analysis - Regression(s) defined by SCATTERGRAM  
 Page 2 Printed on 13-FEB-97 at 17:10:02 for study P334  
 Plot: 1 - X: BAY8039 (RB-5) Y: BAY8039 (MIC)



Axis	Drug	Units	Min	Max	Scale	Coeff	Intercept	R
X	BAY8039 (RB-5)	µg/ml	7.5	60.0	0.25	-0.2593	14.1302	-0.7345
Y	BAY8039 (MIC)	µg/ml	0.25	14.0	0.25			

LOG2 +9.00 Scale:	14 ( 32.0)	13 ( 16.0)	12 ( 8.0)	11 ( 4.0)	10 ( 2.0)	9 ( 1.0)
µg ( 0.5)	7 ( 0.25)	6 ( 0.125)	5 ( 0.0625)	4 ( 0.03125)		
µg ( 0.015625)						

( End of Report )

FIGURE 18B NONFASTIDIOUS AEROBIC BACTERIA

## BACTERIOLOGICAL EFFICACY

### CORRELATION OF TEST RESULTS WITH OUTCOME STATISTICS

Clinical trials were conducted for the treatment of respiratory tract infections [redacted]. The respiratory tract infections included sinusitis, acute exacerbations of chronic bronchitis, and community acquired pneumonia.

During each Phase III clinical study with moxifloxacin, the susceptibility of the causative organisms was tested at the clinical trial site by the E-test according to the manufacturer's instructions and by the disk diffusion test as outlined in NCCLS guidelines.

Clinical isolates were sent to the microbiology laboratory at Bayer Corporation, Pharmaceutical Division for confirmation of each organism's identity and for susceptibility testing by both the disk diffusion test and the broth microdilution test. While every effort was made to test all causative organisms isolated during the clinical trials, some organisms were not viable when received. Quality control stains were included in each day's testing. NCCLS methods were used for all testing.

Cultures and serology for *Mycoplasma pneumoniae* were performed at the [redacted]. Cultures for *Chlamydia pneumoniae* were performed at [redacted].

[redacted] while serology tests for *Chlamydia pneumoniae* were performed at [redacted]. The Urine Antigen test for detection of *Legionella pneumophila* was performed by [redacted].

[redacted] Results of serological testing will not be discussed in this section. These tests are not used to determine breakpoints. These organisms do not have established breakpoints.

Discrepancies in identification of an isolate between the trial site and the Bayer microbiology laboratory were submitted to the reference laboratory [redacted].

[redacted] In addition, all isolates of *Streptococcus pneumoniae* were submitted to [redacted] for further confirmation of identification and for repeat microdilution susceptibility testing for both moxifloxacin and penicillin. If test results from [redacted] and Bayer were within one doubling dilution of each other, the Bayer test results were used in the analyses. In the interest of obviating any bias, [redacted] results were used to determine penicillin susceptibility of *Streptococcus pneumoniae* isolates.

The Bayer microbiology laboratory tested 526 targeted key pathogens isolated from 458 microbiologically valid patients. The number of patients per indication and the corresponding number of isolates (# patients/# isolates) were sinusitis, 74/76; AECB, 239/294; community acquired pneumonia (CAP), [redacted]. With the exception of AECB, most patients had only one causative organism.

The clinical responses for the causative organisms that were tested by Bayer microbiology laboratory were grouped by indication and represent USA isolates only. TABLES 65-68 summarize the clinical response for each organism by indication for the USA studies. TABLES 69-72 show the bacteriological response for each organism by indication. Since in most cases the clinical response drove the bacteriological response (i. e. most studies reported bacteriological response as presumed eradicated or presumed persisted), the clinical response and bacteriological response are well coordinated.

Eight strains of *Streptococcus pneumoniae* were resistant to penicillin (MICs 2.0 to 4.0 µg/mL). Two strains were isolated from the community acquired pneumonia studies (D96-025, patient 4006; D90-026, patient 248) and six strains were isolated during the sinusitis study (D96-023, patients 2009, 2013, 3008, 7014, 7017, 23024). The Test-of-Cure clinical response for all eight strains was resolution. These eight strains plus 13/15 intermediate strains were eradicated at the Test-of-Cure visit.

Table 65 - CLINICAL RESPONSE / SINUSITIS (D96-023)

Organism	End of Therapy (%)		Test-of-Cure (%)	
	Resolve	Fail	Resolve	Fail
<i>S. pneumoniae</i>	28 (97)	1 (3)	28 (97)	1 (3)
<i>H. influenzae</i>	27 (96)	1 (4)	22 (79)	6 (21)
<i>M. catarrhalis</i>	17 (94)	1 (6)	16 (84)	3 (17)

APPEARS THIS WAY  
ON ORIGINAL

Table 66 - CLINICAL RESPONSE / AECB (D96-022, D96-027))

Organism	End of Therapy (%)				Test-of-Cure (%)	
	Cure	Fail	Recur/Relapse	Ind	Resolve	Fail
<i>S. pneumoniae</i>	25 (96)	1 (4)	0	0	24 (92)	2 (8)
<i>H. influenzae</i>	70 (93)	3 (4)	0	2 (3)	69 (92)	6 (8)
<i>H. parainfluenzae</i>	33 (97)	0	0	1 (3)	33 (97)	1 (3)
<i>M. catarrhalis</i>	50 (88)	4 (7)	1 (2)	2 (4)	50 (88)	7 (12)
<i>S. aureus</i>	38 (95)	0	0	2 (5)	38 (95)	2 (5)
<i>K. pneumoniae</i>	38 (93)	1 (2)	0	2 (5)	37 (90)	4 (10)

Table 67 - CLINICAL RESPONSE / PNEUMONIA (D96-025, D96-026))

Organism	End of Therapy (%)				Test-of-Cure (%)	
	Cure	Fail	Recur/Relapse	Ind	Resolve	Fail
<i>S. pneumoniae</i>	20 (87)	0	0	3 (13)	22 (96)	1 (4)
<i>H. influenzae</i>	23 (85)	1 (4)	1 (4)	2 (7)	24 (89)	3 (11)
<i>H. parainfluenzae</i>	3	0	0	0	3	0
<i>M. catarrhalis</i>	10 (91)	0	0	1 (9)	10 (91)	1 (9)
<i>S. aureus</i>	12 (92)	0	0	1 (8)	13 (100)	0
<i>K. pneumoniae</i>	7	0	0	0	7	0

APPEARS THIS WAY  
ON ORIGINAL

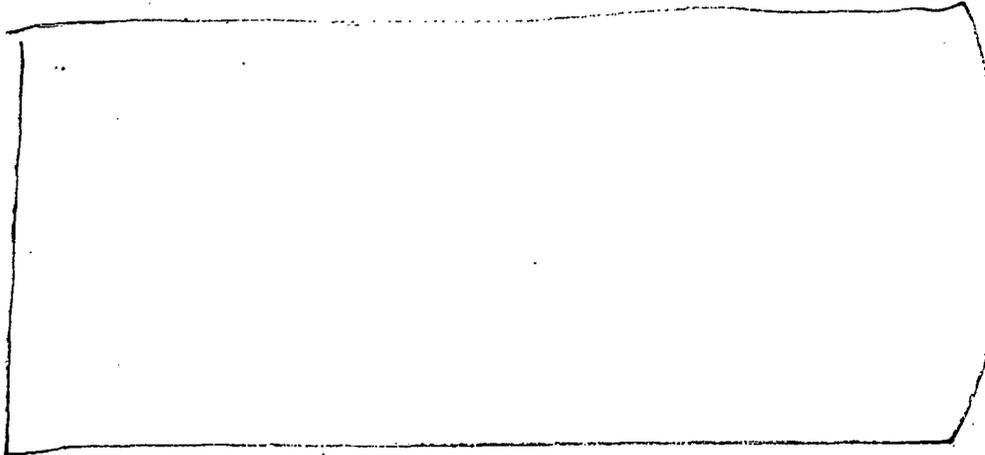


Table 69 - BACTERIOLOGIC RESPONSE / SINUSITIS (D96-023)

Organism	End of Therapy (%)				Test-of-Cure (%)		
	Erad	Presume Erad	Presume Persist	Ind	Erad	Presume Erad	Presume Persist
<i>S. pneumoniae</i>	1 (4)	27 (96)	0	0	0	27 (96)	1 (4)
<i>H. influenzae</i>	1 (4)	26 (96)	0	0	0	21 (78)	6 (22)
<i>M. catarrhalis</i>	0	16 (89)	1 (5.5)	1 (5.5)	0	15 (83)	3 (17)

APPEARS THIS WAY  
ON ORIGINAL

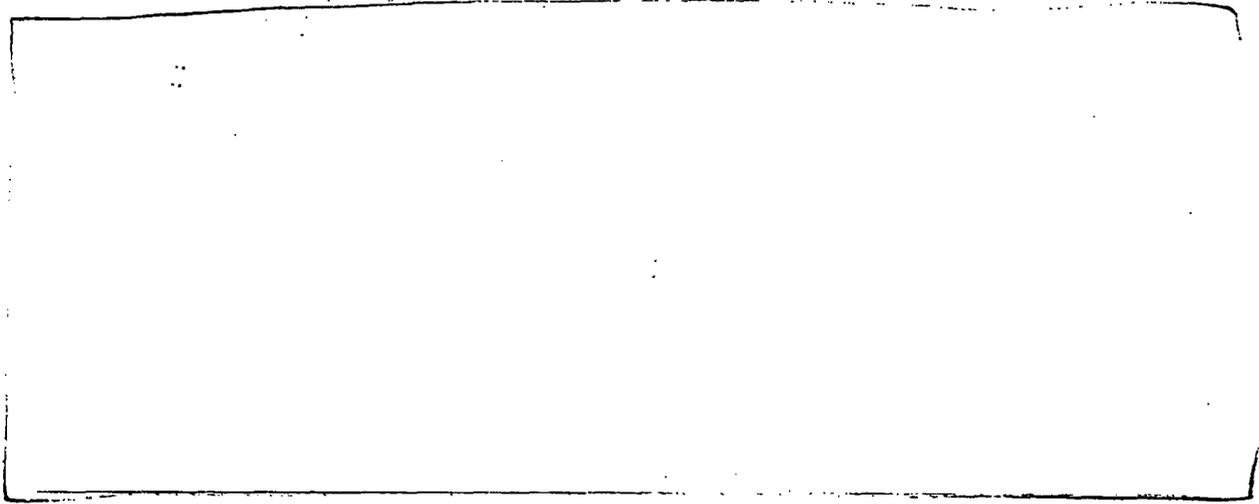
Table 70 - BACTERIOLOGIC RESPONSE / A/CB (D96-022, D96-027)

Organism	End of Therapy (%)					Test-of-Cure (%)			
	Erad	Pres Erad	Persist	Pres Persist	Ind	Erad	Pres Erad	Persist	Pres Persist
<i>S. pneumoniae</i>	6 (23)	20 (77)	0	0	0	3 (11)	22 (85)	1 (4) <sup>a</sup>	0
<i>H. influenzae</i>	18 (24)	55 (73)	0	0	2 (3)	13 (17)	57 (76)	2 (3) <sup>a</sup>	3 (4)
<i>H. parainfluenzae</i>	6 (16)	30 (81)	0	0	1 (3)	3 (8)	34 (92)	0	0
<i>M. catarrhalis</i>	28 (49)	27 (47)	0	0	2 (5)	13 (23)	38 (67)	1 (2) <sup>a</sup>	5 (9)
<i>S. aureus</i>	9 (23)	29 (73)	0	0	2 (4)	6 (15)	31 (78)	2 (5) <sup>a</sup>	1 (2)
<i>K. pneumoniae</i>	2 (5)	35 (85)	1 (2)	1 (2)	2 (5)	4 (10)	34 (83)	1 (2)	2 (5)

<sup>a</sup>Eradication with recurrence

Table 71 - BACTERIOLOGIC RESPONSE / PNEUMONIA (D96-025, D96-026)

Organism	End of Therapy (%)			Test-of-Cure (%)			
	Erad	Presume Erad	Ind	Erad	Presume Erad	End Recur	Presume Persist
<i>S. pneumoniae</i>	3 (13)	17 (74)	3 (13)	2 (9)	20 (87)	0	1 (4)
<i>H. influenzae</i>	6 (22)	19 (70)	2 (7)	1 (4)	23 (85)	1 (4)	2 (7)
<i>H. parainfluenzae</i>	1	2	0	0	3	0	0
<i>M. catarrhalis</i>	1 (9)	9 (82)	1 (9)	0	10 (91)	0	1 (9)
<i>S. aureus</i>	1 (8)	11 (84)	1 (8)	1 (8)	12 (92)	0	0
<i>K. pneumoniae</i>	1	6	0	0	7	0	0



The bacteriological and clinical responses for *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* are presented in TABLE 73. All of the strains of *Mycoplasma pneumoniae* were eradicated and there were no clinical failures. Six of ten *Chlamydia pneumoniae* isolates were eradicated. The MICs of *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* were 0.008-0.06 µg/mL and 0.5-1.0 µg/mL, respectively. Four of seven *Chlamydia pneumoniae* isolates with MICs of 0.5 µg/mL were eradicated as were two of the three isolates with MICs of 1.0 µg/mL.

Table 73 - BACTERIOLOGIC AND CLINICAL RESPONSE / ATYPICALS FROM PNEUMONIA STUDIES (D96-025, D96-026)

Organism	End of Therapy (%)		Test-of-Cure	
	Erad/Cure (%)	Persist/Fail (%)	Erad/Cure	Persist/Fail
<i>M. pneumoniae</i>	15/15 (100)	0	15/15 (100)	0
<i>C. pneumoniae</i>	6/9 (90)	4/1 (10)	6/9 (90)	4/1 (10)

APPEARS THIS WAY  
ON ORIGINAL

**MIC BREAKPOINTS**

**NON-FASTIDIOUS ORGANISMS**

TABLE 74 shows the relationship between MICs and pathogen bacteriological response for non-fastidious organisms treated with moxifloxacin. Some organisms that are not indicated have been included since they tended to have higher MIC values in many cases which might help divide the population into susceptible and resistant based on MICs and related bacteriological outcome.

**APPEARS THIS WAY  
ON ORIGINAL**

**APPEARS THIS WAY  
ON ORIGINAL**

TABLE 74  
Relationship between Moxifloxacin MICs and Bacteriological Outcome at Test-of -Cure

Baseline Pathogen	MIC ( $\mu\text{g/mL}$ )	# Isolates	# Eradicated (%)	# Persisted (%)
<i>S. aureus</i>	0.03	26	25 (96)	1 (4)
	0.06	67	61 (92)	6 (8)
	0.125	18	17 (94)	1 (6)
	0.25	1	1 (100)	0
	2	2	2 (100)	0
	4	1	1 (100)	0
<i>K. pneumoniae</i>	0.06	3	3 (100)	0
	0.125	25	24 (96)	1 (4)
	0.25	12	11 (92)	1 (8)
	0.5	6	5 (83)	1 (17)
	2	1	1 (100)	0
	4	1	1 (100)	0
<i>Serratia marcescens</i>	0.125	1	1 (100)	0
	0.25	1	1 (100)	0
	0.5	2	2 (100)	0
	8	1	0	1 (100)
<i>Citrobacter freundii</i>	0.06	1	1 (100)	0
	0.125	1	1 (100)	0
	0.25	1	1 (100)	0
	1	2	2 (100)	0
	4	1	1 (100)	0
<i>Pseudomonas aeruginosa</i>	0.5	1	1 (100)	0
	1	9	5 (56)	4 (44)
	2	5	3 (60)	2 (40)
	4	2	2 (100)	0
	8	5	4 (80)	1 (20)
	16	2	0	2 (100)
<i>Stenotrophomonas maltophilia</i>	0.25	1	1 (100)	0
	0.5	2	2 (100)	0
	1	3	3 (100)	0
<i>Moraxella catarrhalis</i>	2	1	1 (100)	0
	0.03	3	3 (100)	0
	0.06	30	26 (87)	4 (13)
	0.125	33	30 (91)	3 (9)
	0.25	2	2 (100)	0

The above TABLE shows that most isolates had MICs of  $\leq 0.25 \mu\text{g/mL}$ . There were several isolates at  $\geq 2 \mu\text{g/mL}$ . Except for isolates of *Pseudomonas aeruginosa* and one *Serratia marcescens* isolate (with an MIC of  $8 \mu\text{g/mL}$ ), all isolates with a MIC of  $\geq 2 \mu\text{g/mL}$  were eradicated. *Pseudomonas aeruginosa* isolates with MICs of 1 or  $2 \mu\text{g/mL}$  were eradicated at a rate of about 50%, but isolates with MICs of  $4 \mu\text{g/mL}$  were all eradicated and isolates of *Pseudomonas aeruginosa* with MICs of  $8 \mu\text{g/mL}$  were eradicated at an 80% rate. The two *Pseudomonas aeruginosa* isolates with a MIC of