

TABLE 44  
Number of Patients with Key Pathogens (Bacteriology PP Follow-Up Population)

| Pre-Therapy Pathogen     | Treatment Group                     |        |  |        |
|--------------------------|-------------------------------------|--------|--|--------|
|                          | Gemifloxacin<br>320 mg od<br>N = 64 |        | Ceftriaxone 2g iv od/<br>Cefuroxime 500 mg bid<br>N = 63 |        |
|                          | n                                   | (%)*   | n  | (%)*   |
| <i>S. pneumoniae</i>     | 20                                  | (31.3) | 19   | (30.2) |
| <i>M. pneumoniae</i>     | 19                                  | (29.7) | 15   | (23.8) |
| <i>C. pneumoniae</i>     | 13                                  | (20.3) | 15   | (23.8) |
| <i>H. influenzae</i>     | 7                                   | (10.9) | 12   | (19.0) |
| <i>H. parainfluenzae</i> | 8                                   | (12.5) | 4  | (6.3)  |
| <i>L. pneumoniae</i>     | 3                                   | (4.7)  | 1  | (1.6)  |

\* Percentages are based on the total number of patients; some patients may have more than one pathogen

The number of patients with key pathogens isolated from blood in the bacteriology ITT and bacteriology PP follow-up populations, respectively are shown in TABLE 45. The most prevalent blood-borne pathogen in the bacteriology ITT population was *Streptococcus pneumoniae* which was identified in the blood of 15/88 (17.0%) patients in the gemifloxacin treatment group and 9/82 (11.0%) of patients in the ceftriaxone/cefuroxime treatment group. In the bacteriology PP population at follow-up, *S. pneumoniae* was isolated from the blood of 12/64 (18.8%) patients in the gemifloxacin treatment group and 5/63 (7.9%) patients in the ceftriaxone/cefuroxime treatment group.

*Acinetobacter calcoaceticus* was the second most common pathogen identified from the blood. All the patients with this pathogen were from one center in the Philippines. Other screening sample sources from these patients did not yield *Acinetobacter calcoaceticus*. All of these patients were clinical successes at end of therapy even though bacteriological persistence was noted in one of the patients in the gemifloxacin treatment group and two of the patients in the ceftriaxone/cefuroxime treatment group for the bacteriological ITT population. *A. calcoaceticus* was not identified in the blood of these patients at the end of therapy visit; the outcome of persistence was either due to a colonizing pathogen or in the case of the gemifloxacin patient, due to *A. calcoaceticus* identified from the sputum.

TABLE 45  
Number of Patients with Key Pathogens at Screening from Blood

| Pre-Therapy Pathogen        | Treatment Group                     |        |  |        |
|-----------------------------|-------------------------------------|--------|--|--------|
|                             | Gemifloxacin<br>320 mg od<br>N = 88 |        | Ceftriaxone 2g iv od/<br>Cefuroxime 500 mg bid<br>N = 82 |        |
|                             | n                                   | (%)*   | n  | (%)*   |
| Bacteriology ITT Population |                                     |        |  |        |
| <i>S. pneumoniae</i>        | 15                                  | (17.0) | 9  | (11.0) |
| <i>A. calcoaceticus</i>     | 2                                   | (2.3)  | 5  | (6.1)  |
| Bacteriology PP Follow-Up   |                                     |        |  |        |
| <i>S. pneumoniae</i>        | 12                                  | (18.8) | 5  | (7.9)  |
| <i>A. calcoaceticus</i>     | 2                                   | (3.1)  | 3  | (4.8)  |

\* Percentages are based on the total number of patients; some patients may have more than one pathogen

The number of atypical pathogens and the method of identification at screening are summarized in TABLE 46 for the Bacteriology ITT and Bacteriology PP follow-up populations. In the gemifloxacin treatment group the most prevalent atypical pathogen was *Mycoplasma pneumoniae* (26/88; 29.5%), followed by *Chlamydia pneumoniae* (19/88; 21.6%). In the ceftriaxone/cefuroxime treatment group; *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* were isolated from 18/82 (22%) and 16/82 (19.5%) patients, respectively.

TABLE 46  
Number of Atypical Pathogens Identified at Screening

| Pre-Therapy Pathogen                 | Treatment Group           |        |  |        |
|--------------------------------------|---------------------------|--------|--|--------|
|                                      | Gemifloxacin<br>320 mg od |        | Ceftriaxone 2g iv od/<br>Cefuroxime 500 mg bid |        |
|                                      | n                         | (%)    | n  | (%)    |
| Bacteriology ITT Population          | N = 88                    |        | N = 82   |        |
| <i>M. pneumoniae</i> : Serology      | 26                        | (29.5) | 16   | (19.5) |
| <i>C. pneumoniae</i> : Serology      | 19                        | (21.6) | 18   | (22.0) |
| <i>L. pneumoniae</i> : Serology      | 1                         | (1.1)  | 0  |        |
| <i>L. pneumoniae</i> : Urine Antigen | 5                         | (5.7)  | 4  | (4.9)  |
| <i>C. psittaci</i> : Serology        | 0                         |        | 1  | (1.2)  |
| Bacteriology PP Follow-Up            | N = 64                    |        | N = 63   |        |
| <i>M. pneumoniae</i> : Serology      | 19                        | (29.7) | 15   | (23.8) |
| <i>C. pneumoniae</i> : Serology      | 13                        | (20.3) | 15   | (23.8) |
| <i>L. pneumoniae</i> : Serology      | 0                         |        | 0  |        |
| <i>L. pneumoniae</i> : Urine Antigen | 3                         | (4.7)  | 1  | (1.6)  |
| <i>C. psittaci</i> : Serology        | 0                         |        | 1  | (1.6)  |

Note: The total will not necessarily be the total of the methods used for each pathogen as the diagnosis may have been made by more than one method.

TABLE 47 shows the bacteriological response at the end of therapy for both the intent-to-treat (ITT) and the per protocol (PP) populations. TABLE 48 shows the same information at the follow-up visit.

TABLE 47  
Bacteriological Response Rates at End of Therapy

| Success Rate   | Gemifloxacin n/N (%) | Ceftriaxone/Cefuroxime n/N (%) |
|----------------|----------------------|--------------------------------|
| ITT Population | 76/88 (86.4%)        | 70/82 (85.4%)                  |
| PP Population  | 65/67 (97.0%)        | 60/65 (92.3)                   |

TABLE 48  
Bacteriological Response Rates at Follow-Up

| Success Rate   | Gemifloxacin n/N (%) | Ceftriaxone/Cefuroxime n/N (%) |
|----------------|----------------------|--------------------------------|
| ITT Population | 67/88 (76.1%)        | 65/82 (79.3%)                  |
| PP Population  | 58/64 (90.6%)        | 55/63 (87.3%)                  |

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The per pathogen bacteriological outcome for the key pathogens for the Bacteriology PP end of therapy population are shown in TABLE 49. There were no marked differences between treatment groups in the proportion of eradication/presumed eradications at end of therapy. Approximately 95% of the initial pathogens were either eradicated or presumed eradicated. TABLE 50 shows the same data for the Bacteriology ITT population at the end of therapy.

**TABLE 49  
Bacteriological Outcome at End of Therapy (Bacteriology PP Population)**

| Initial Pathogen         | Bacteriological Outcome | Treatment Group                     |         |  |         |
|--------------------------|-------------------------|-------------------------------------|---------|--|---------|
|                          |                         | Gemifloxacin<br>320 mg od<br>N = 67 |         | Ceftriaxone 2g iv od/<br>Cefuroxime 500 mg bid<br>N = 65 |         |
|                          |                         | n*                                  | (%)     | n*   | (%)     |
| All Pathogens            | (n)**                   | 94                                  |         | 91   |         |
|                          | Presumed Eradication    | 89                                  | (94.7)  | 81   | (89.0)  |
|                          | Eradication             | 2                                   | (2.1)   | 4  | (4.4)   |
|                          | Presumed Persistence    | 3                                   | (3.2)   | 4  | (4.4)   |
| <i>M. pneumoniae</i>     | (n)**                   | 21                                  |         | 15   |         |
|                          | Presumed Eradication    | 21                                  | (100.0) | 14   | (93.3)  |
|                          | Presumed Persistence    | 0                                   |         | 1  | (6.7)   |
| <i>S. pneumoniae</i>     | (n)**                   | 20                                  |         | 19   |         |
|                          | Presumed Eradication    | 19                                  | (95.0)  | 17   | (89.5)  |
|                          | Presumed Persistence    | 1                                   | (5.0)   | 1  | (5.3)   |
| <i>C. pneumoniae</i>     | (n)**                   | 14                                  |         | 15   |         |
|                          | Presumed Eradication    | 14                                  | (100.0) | 14   | (93.3)  |
|                          | Presumed Persistence    | 0                                   |         | 1  | (6.7)   |
| <i>H. influenzae</i>     | (n)**                   | 7                                   |         | 13   |         |
|                          | Presumed Eradication    | 5                                   | (71.4)  | 10   | (76.9)  |
|                          | Eradication             | 1                                   | (14.3)  | 2  | (15.4)  |
| <i>H. parainfluenzae</i> | (n)**                   | 9                                   |         | 4  |         |
|                          | Presumed Eradication    | 9                                   | (100.0) | 4  | (100.0) |
|                          | Presumed Persistence    | 1                                   | (14.3)  | 1  | (7.7)   |
| <i>L. pneumoniae</i>     | (n)**                   | 5                                   |         | 1  |         |
|                          | Presumed Eradication    | 5                                   | (100.0) | 1  | (100.0) |

\* Number (%) of pathogens with specified outcome. Percentages are calculated from the total number of patients with each initial pathogen.

\*\* Number of pathogens

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TABLE 50  
Bacteriological Outcome at End of Therapy (Bacteriology ITT Population)

| Initial Pathogen         | Bacteriological Outcome | Treatment Group                     |        |  |         |
|--------------------------|-------------------------|-------------------------------------|--------|--|---------|
|                          |                         | Gemifloxacin<br>320 mg od<br>N = 88 |        | Ceftriaxone 2g iv od/<br>Cefuroxime 500 mg bid<br>N = 82 |         |
|                          |                         | n*                                  | (%)    | n*   | (%)     |
| All Pathogens            | (n)**                   | 127                                 |        | 115  |         |
|                          | Presumed Eradication    | 98                                  | (77.2) | 94   | (81.7)  |
|                          | Eradication             | 9                                   | (7.1)  | 5  | (4.3)   |
|                          | Presumed Persistence    | 7                                   | (5.5)  | 5  | (4.3)   |
|                          | Persistence             | 2                                   | (1.6)  | 4  | (3.5)   |
|                          | Unable to Determine     | 11                                  | (8.7)  | 7  | (6.1)   |
| <i>M. pneumoniae</i>     | (n)**                   | 26                                  |        | 16   |         |
|                          | Presumed Eradication    | 24                                  | (92.3) | 15   | (93.8)  |
|                          | Presumed Persistence    | 0                                   |        | 1  | (6.3)   |
|                          | Unable to Determine     | 2                                   | (7.7)  | 0  |         |
| <i>S. pneumoniae</i>     | (n)**                   | 26                                  |        | 25   |         |
|                          | Presumed Eradication    | 22                                  | (84.6) | 20   | (80.0)  |
|                          | Eradication             | 0                                   |        | 2  | (8.0)   |
|                          | Presumed Persistence    | 3                                   | (11.5) | 1  | (4.0)   |
|                          | Unable to Determine     | 1                                   | (3.8)  | 2  | (8.0)   |
| <i>C. pneumoniae</i>     | (n)**                   | 19                                  |        | 18   |         |
|                          | Presumed Eradication    | 16                                  | (84.2) | 16   | (88.9)  |
|                          | Presumed Persistence    | 1                                   | (5.3)  | 2  | (11.1)  |
|                          | Unable to Determine     | 2                                   | (10.5) | 0  |         |
| <i>H. influenzae</i>     | (n)**                   | 10                                  |        | 15   |         |
|                          | Presumed Eradication    | 6                                   | (60.0) | 11   | (73.3)  |
|                          | Eradication             | 2                                   | (20.0) | 2  | (13.3)  |
|                          | Presumed Persistence    | 1                                   | (10.0) | 1  | (6.7)   |
|                          | Unable to Determine     | 1                                   | (10.0) | 1  | (6.7)   |
| <i>H. parainfluenzae</i> | (n)**                   | 10                                  |        | 4  |         |
|                          | Presumed Eradication    | 9                                   | (90.0) | 4  | (100.0) |
|                          | Unable to Determine     | 1                                   | (10.0) | 0  |         |
| <i>L. pneumoniae</i>     | (n)**                   | 6                                   |        | 4  |         |
|                          | Presumed Eradication    | 5                                   | (83.3) | 3  | (75.0)  |
|                          | Unable to Determine     | 1                                   | (16.7) | 1  | (25.0)  |

\* Number (%) of pathogens with specified outcome. Percentages are calculated from the total number of patients with each initial pathogen.

\*\* Number of pathogens

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The per pathogen bacteriological outcome at follow-up for all initial pathogens combined and for key pathogens associated with CAP that were eradicated/presumed eradicated at the end of therapy for the Bacteriology PP follow-up population are shown in TABLE 51. There were no marked differences between treatment groups in the proportions of eradications/presumed eradications at follow-up. Approximately 90% overall of key initial pathogens were either eradicated or presumed eradicated at follow-up in the Bacteriology PP population. TABLE 52 shows the same data for the Bacteriology ITT population at follow-up.

TABLE 51  
Bacteriological Outcome at Follow-Up (Bacteriology PP Population)

| Initial Pathogen***      | Bacteriological Outcome | Treatment Group                     |         |  |         |
|--------------------------|-------------------------|-------------------------------------|---------|--|---------|
|                          |                         | Gemifloxacin<br>320 mg od<br>N = 67 |         | Ceftriaxone 2g iv od/<br>Cefuroxime 500 mg bid<br>N = 65 |         |
|                          |                         | n*                                  | (%)     | n*   | (%)     |
| All Pathogens            | (n)**                   | 87                                  |         | 89   |         |
|                          | Presumed Eradication    | 76                                  | (87.4)  | 76   | (85.4)  |
|                          | Eradication             | 4                                   | (4.6)   | 4  | (4.5)   |
|                          | Presumed Recurrence     | 4                                   | (4.6)   | 2  | (2.2)   |
|                          | Recurrence              | 0                                   |         | 1  | (1.2)   |
|                          | Missing+                | 3                                   | (3.4)   | 6  | (6.7)   |
| <i>S. pneumoniae</i>     | (n)**                   | 20                                  |         | 19   |         |
|                          | Presumed Eradication    | 18                                  | (90.0)  | 17   | (89.5)  |
|                          | Presumed Recurrence     | 1                                   | (5.0)   | 1  | (5.3)   |
|                          | Missing+                | 1                                   | (5.0)   | 1  | (5.3)   |
| <i>M. pneumoniae</i>     | (n)**                   | 19                                  |         | 15   |         |
|                          | Presumed Eradication    | 19                                  | (100.0) | 14   | (93.3)  |
|                          | Missing+                | 0                                   |         | 1  | (6.7)   |
| <i>C. pneumoniae</i>     | (n)**                   | 13                                  |         | 15   |         |
|                          | Presumed Eradication    | 12                                  | (92.3)  | 14   | (93.3)  |
|                          | Presumed Recurrence     | 1                                   | (7.7)   | 0  |         |
|                          | Missing+                | 0                                   |         | 1  | (6.7)   |
| <i>H. influenzae</i>     | (n)**                   | 7                                   |         | 12   |         |
|                          | Presumed Eradication    | 5                                   | (71.4)  | 9  | (75.0)  |
|                          | Eradication             | 1                                   | (14.3)  | 1  | (8.3)   |
|                          | Presumed Recurrence     | 0                                   |         | 1  | (8.3)   |
|                          | Missing+                | 1                                   | (14.3)  | 1  | (8.3)   |
| <i>H. parainfluenzae</i> | (n)**                   | 8                                   |         | 4  |         |
|                          | Presumed Eradication    | 8                                   | (100.0) | 4  | (100.0) |
| <i>L. pneumoniae</i>     | (n)**                   | 3                                   |         | 1  |         |
|                          | Presumed Eradication    | 3                                   | (100.0) | 1  | (100.0) |

\* Number (%) of pathogens with specified outcome. Percentages are calculated from the total number of patients with each initial pathogen.

\*\* Number of pathogens;

\*\*\* Only those pathogens that were eradicated or presumed eradicated at end of therapy have an initial pathogen outcome at follow-up

+ An outcome of missing indicates that the patient had a bacteriological response of failure (i.e., a bacteriological outcome of persistence, presumed persistence or superinfection) at end of therapy visit.

TABLE 52  
Bacteriological Outcome at Follow-Up (Bacteriology ITT Population)

| Initial Pathogen***      | Bacteriological Outcome | Treatment Group                     |        |  |         |
|--------------------------|-------------------------|-------------------------------------|--------|--|---------|
|                          |                         | Gemifloxacin<br>320 mg od<br>N = 88 |        | Ceftriaxone 2g iv od/<br>Cefuroxime 500 mg bid<br>N = 82 |         |
|                          |                         | n*                                  | (%)    | n*   | (%)     |
| All Pathogens            | (n)**                   | 127                                 |        | 115  |         |
|                          | Presumed Eradication    | 87                                  | (68.5) | 89   | (77.4)  |
|                          | Eradication             | 6                                   | (4.7)  | 5  | (4.3)   |
|                          | Presumed Recurrence     | 8                                   | (6.3)  | 3  | (2.6)   |
|                          | Recurrence              | 1                                   | (0.9)  | 1  | (0.9)   |
|                          | Unable to Determine     | 5                                   | (3.9)  | 1  | (0.9)   |
|                          | Missing+                | 20                                  | (15.7) | 16   | (13.9)  |
| <i>M. pneumoniae</i>     | (n)**                   | 26                                  |        | 16   |         |
|                          | Presumed Eradication    | 22                                  | (84.6) | 15   | (93.8)  |
|                          | Unable to Determine     | 2                                   | (7.7)  | 0  |         |
|                          | Missing+                | 2                                   | (7.7)  | 1  | (6.3)   |
| <i>S. pneumoniae</i>     | (n)**                   | 26                                  |        | 25   |         |
|                          | Presumed Eradication    | 21                                  | (80.8) | 20   | (80.0)  |
|                          | Presumed Recurrence     | 1                                   | (3.8)  | 2  | (8.0)   |
|                          | Missing+                | 4                                   | (15.4) | 3  | (12.0)  |
| <i>C. pneumoniae</i>     | (n)**                   | 19                                  |        | 18   |         |
|                          | Presumed Eradication    | 15                                  | (78.9) | 16   | (88.9)  |
|                          | Presumed Recurrence     | 1                                   | (5.3)  | 0  |         |
|                          | Missing+                | 3                                   | (15.8) | 2  | (11.1)  |
| <i>H. influenzae</i>     | (n)**                   | 10                                  |        | 15   |         |
|                          | Presumed Eradication    | 6                                   | (60.0) | 10   | (66.7)  |
|                          | Eradication             | 1                                   | (10.0) | 1  | (6.7)   |
|                          | Presumed Recurrence     | 1                                   | (10.0) | 1  | (6.7)   |
|                          | Unable to Determine     | 0                                   |        | 1  | (6.7)   |
|                          | Missing+                | 2                                   | (20.0) | 2  | (13.3)  |
| <i>H. parainfluenzae</i> | (n)**                   | 10                                  |        | 4  |         |
|                          | Presumed Eradication    | 8                                   | (80.0) | 4  | (100.0) |
|                          | Unable to Determine     | 1                                   | (10.0) | 0  |         |
|                          | Missing+                | 1                                   | (10.0) | 0  |         |
| <i>L. pneumoniae</i>     | (n)**                   | 6                                   |        | 4  |         |
|                          | Presumed Eradication    | 3                                   | (50.0) | 3  | (75.0)  |
|                          | Unable to Determine     | 2                                   | (33.3) | 0  |         |
|                          | Missing+                | 1                                   | (16.7) | 1  | (25.0)  |

\* Number (%) of pathogens with specified outcome. Percentages are calculated from the total number of patients with each initial pathogen.

\*\* Number of pathogens

\*\*\* Only those pathogens that were eradicated or presumed eradicated at end of therapy have an initial pathogen outcome at follow-up

+ An outcome of missing indicates that the patient had a bacteriological response of failure (i.e., a bacteriological outcome of persistence, presumed persistence or superinfection) at end of therapy visit.

TABLE 53 shows gemifloxacin susceptibility for the key pathogens in the Bacteriology PP follow-up population. Virtually all of the initial pathogens isolated in this study exhibited very low gemifloxacin MICs at screening. Although there were very few pathogens at each of the gemifloxacin MICs, there was no increase in the percentage of bacteriological failures with increasing gemifloxacin MIC.

TABLE 53  
Bacteriological Successes at Follow-Up by Screening Pathogen  
Susceptibility (MIC) to Gemifloxacin for Key Pathogens  
(Bacteriology PP Follow-Up Population)

| Key Pathogen<br>Gemifloxacin MIC (µg/mL) | n/N*  | Treatment Group           |         |
|--|-------|---------------------------|---------|
|  |       | Gemifloxacin<br>320 mg od | (%)     |
| <i>S. pneumoniae</i>                     |       | N = 24                    |         |
| 0.015                                    | 9/9   |                           | (100.0) |
| 0.03                                     | 13/14 |                           | (92.9)  |
| Missing**                                | 1/1   |                           | (100.0) |
| All                                      | 23/24 |                           | (95.8)  |
| <i>H. parainfluenzae</i>                 |       | N = 9                     |         |
| ≤ 0.001                                  | 1/1   |                           | (100.0) |
| 0.004                                    | 2/2   |                           | (100.0) |
| 0.008                                    | 1/1   |                           | (100.0) |
| 0.015                                    | 2/2   |                           | (100.0) |
| 0.03                                     | 1/1   |                           | (100.0) |
| 0.06                                     | 1/1   |                           | (100.0) |
| Missing**                                | 1/1   |                           | (100.0) |
| All                                      | 9/9   |                           | (100.0) |
| <i>H. influenzae</i>                     |       | N = 7                     |         |
| ≤ 0.001                                  | 1/1   |                           | (100.0) |
| 0.002                                    | 4/5   |                           | (80.0)  |
| 0.004                                    | 1/1   |                           | (100.0) |
| All                                      | 6/7   |                           | (85.7)  |

\* n/N = number of successes/number of isolates of a pathogen with the specified gemifloxacin Mic. Percentages are calculated from the total number of patients with each MIC value.

\*\* MIC testing was not done at screening ...

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Penicillin-Resistant *Streptococcus pneumoniae* (PRSP)

Only three patients yielded a sample positive for penicillin-resistant *Streptococcus pneumoniae* (PRSP). All three patients were in the Bacteriology PP follow-up population and were a clinical and bacteriological success at follow-up with a pathogen outcome of presumed eradication.

Two isolates of PRSP were isolated from the sputum of patient 185.153.29538 randomized to the gemifloxacin treatment group. Both of these isolates had gemifloxacin MICs of 0.015 µg/mL, penicillin MICs = 2 µg/mL, and were resistant to cefuroxime (MIC = 4 µg/mL), clarithromycin (MIC = 32 µg/mL; ≥32 µg/mL), erythromycin (MIC >16 µg/mL), and trimethoprim/sulfamethoxazole (MIC = 8 µg/mL; 4 µg/mL). Both isolates were of intermediate susceptibility to ceftriaxone (MIC = 1 µg/mL) and amoxicillin/clavulanate (MIC = 1 µg/mL). This patient also had *M. pneumoniae* isolated at screening.

In the ceftriaxone/cefuroxime treatment group, patient 185.305.29814 had an isolate of PRSP isolated from a respiratory sample. This isolate had a gemifloxacin MIC of 0.015 µg/mL, a penicillin MIC = 2 µg/mL, and was resistant to amoxicillin/clavulanate (MIC = 2 µg/mL), ceftriaxone (MIC = 2 µg/mL), cefuroxime (MIC = 16 µg/mL), clarithromycin (MIC = 4 µg/mL), erythromycin (MIC = 8 µg/mL) and trimethoprim/sulfamethoxazole (MIC = 4 µg/mL). This patient did not receive a macrolide concomitant with study medication.

Also in the comparator treatment group, Patient 185.351.29734 had an isolate from the sputum at screening. This isolate had a gemifloxacin MIC of 0.015 µg/mL and penicillin MIC of 2 µg/mL. It was resistant to amoxicillin/clavulanate (MIC = 2 µg/mL), cefuroxime (MIC = 8 µg/mL), clarithromycin (MIC = 1 µg/mL), erythromycin (MIC = 2 µg/mL) and trimethoprim/sulfamethoxazole (MIC = 4 µg/mL). This isolate was intermediate to ceftriaxone (MIC = 1 µg/mL). This patient received two days iv followed by three days oral azithromycin therapy concomitant with study treatment.

Macrolide-Resistant *Streptococcus pneumoniae*

There were eight *Streptococcus pneumoniae* isolates that were resistant to both clarithromycin and erythromycin. These isolates were from six patients, three in each treatment group. They were all clinical and bacteriological successes.

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STUDY 287

This was an open label, non-comparative study to assess the efficacy and safety of oral gemifloxacin 320 mg, once daily for 7 days, for the treatment of community-acquired pneumonia (CAP) of suspected pneumococcal origin in countries with a high prevalence of drug-resistant respiratory pathogens. The study was carried out in 28 centers in nine countries.

The primary objective of the study was to evaluate the bacteriological efficacy of oral gemifloxacin in the treatment of CAP of suspected pneumococcal origin. The secondary objectives were to evaluate the clinical efficacy of gemifloxacin in the treatment of CAP of suspected pneumococcal origin and to evaluate the clinical and bacteriological efficacy of gemifloxacin in the treatment of penicillin-resistant pneumococcal.

Only those CAP patients with suspected *S. pneumoniae* infection (identified based on a positive pneumococcal urine antigen test and/or a confirmed positive Gram stain for diplococci resembling *S. pneumoniae*) received treatment with gemifloxacin. The first dose of medication was given in the clinic or hospital at the end of the screening visit (Visit 1, Day 0). Patients were assessed on three further occasions over a total duration of approximately five weeks (Visit 2, Day 3-5; Visit 3; 2-4 days post-therapy; Visit 4, 21-28 days post-therapy) to evaluate their clinical and bacteriological response to treatment. The study was designed to enroll at least 16 patients with CAP and a documented penicillin-resistant *S. pneumoniae* (PRSP) isolate at screening. The interim analysis submitted was conducted after seven such patients had been enrolled.

The primary efficacy parameter was bacteriological response at follow-up (Visit 4; 21-28 days post-therapy) for the Bacteriology ITT population. Secondary efficacy parameters included bacteriological response at end-of-therapy (Visit 3; 2-4 days post-therapy); clinical response at end of therapy and follow-up; radiological response at end of therapy and follow-up; and combined clinical/radiological response at end of therapy and follow-up. Clinical and bacteriological parameters were evaluated for the subset of patients with CAP due to *Streptococcus pneumoniae*, particularly PRSP.

A total of 188 enrolled patients were included in the interim analysis presented in this submission. Of these patients, 186 received at least one dose of study medication and comprised the intent-to-treat (ITT) and safety population. Two patients withdrew before receiving study medication. TABLE 54 shows the patient disposition for this study.

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TABLE 54  
Patient Disposition (All Enrolled Patients)

| Population                      | Gemifloxacin 320 mg od |  |
|---------------------------------|------------------------|--|
|                                 | n                      |  |
| Enrolled                        | 188                    |  |
| Received Study Medication (ITT) | 186                    |  |
| Completed Study                 | 156                    |  |
| Clinical PP End of Therapy      | 156                    |  |
| Clinical PP Follow-Up           | 147                    |  |
| Bacteriology ITT                | 94                     |  |
| Bacteriology PP End of Therapy  | 82                     |  |
| Bacteriology PP at Follow-Up    | 80                     |  |

In samples from all sources, 94 (50.5%) of patients had at least one pathogen. Of these, 79 patients had one pathogen, 13 had two pathogens, and two had three pathogens. TABLE 55 shows the number of pathogens identified per patient at the screening visit.

TABLE 55  
Number of Pathogens Identified Per Patient at Screening

|  | Gemifloxacin 320 mg od<br>N = 186 |        |
|--|-----------------------------------|--------|
|  | n                                 | (%)    |
| No. of Patients Sampled*                     | 186                               | (100)  |
| No. of Patients with at Least One Pathogen** | 94                                | (50.5) |
| Number of Pathogens                          |                                   |        |
| 0  | 89                                | (47.8) |
| 1  | 79                                | (42.5) |
| 2  | 13                                | (7.0)  |
| 3  | 2                                 | (1.1)  |
| Unknown***                                   | 3                                 | (1.6)  |

\* These patients constituted the ITT population

\*\* These patients constituted the Bacteriology ITT population

\*\*\* No evaluable samples taken

TABLE 56 shows the distribution of key pathogens associated with CAP identified at screening in the Bacteriology ITT and Bacteriology PP populations.

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TABLE 56  
Number (%) of Key Pathogens Screening

| Pre-Therapy Pathogen             | Gemifloxacin 320 mg od |        |
|----------------------------------|------------------------|--------|
|                                  | n                      | (%)    |
| <b>Bacteriology ITT</b>          |                        |        |
|                                  | <b>N = 94</b>          |        |
| <i>S. pneumoniae</i>             | 51                     | (54.3) |
| <i>H. influenzae</i>             | 15                     | (16.0) |
| <i>K. pneumoniae</i>             | 15                     | (16.0) |
| <i>S. aureus</i>                 | 8                      | (8.5)  |
| <i>P. aeruginosa</i>             | 5                      | (5.3)  |
| <b>Bacteriology PP Follow-Up</b> |                        |        |
|                                  | <b>N = 80</b>          |        |
| <i>S. pneumoniae</i>             | 44                     | (55.0) |
| <i>H. influenzae</i>             | 13                     | (16.3) |
| <i>K. pneumoniae</i>             | 13                     | (16.3) |
| <i>S. aureus</i>                 | 7                      | (8.8)  |
| <i>P. aeruginosa</i>             | 4                      | (5.0)  |

TABLE 57 shows the pathogens isolated pre-therapy from blood in both the Bacteriology ITT and Bacteriology PP populations. *Streptococcus pneumoniae* was the most often found organism.

TABLE 57  
Number (%) of Patients with Key Pathogens Isolated from Blood Cultures

| Pre-Therapy Pathogen             | Gemifloxacin 320 mg od |       |
|----------------------------------|------------------------|-------|
|                                  | n                      | (%)   |
| <b>Bacteriology ITT</b>          |                        |       |
|                                  | <b>N = 94</b>          |       |
| <i>S. pneumoniae</i>             | 7                      | (7.4) |
| <i>Burkholderia cepacia</i>      | 1                      | (1.1) |
| <b>Bacteriology PP Follow-Up</b> |                        |       |
|                                  | <b>N = 80</b>          |       |
| <i>S. pneumoniae</i>             | 6                      | (7.5) |
| <i>Burkholderia cepacia</i>      | 1                      | (1.3) |

Susceptibility testing was performed at screening. A total of 54 isolates of *Streptococcus pneumoniae* were tested. Gemifloxacin MIC values ranged from 0.008 to 0.06 µg/mL with a MIC<sub>90</sub> value of 0.03 µg/mL. Levofloxacin MIC values ranged from 0.25 to 1.0 µg/mL with a MIC<sub>90</sub> value of 1.0 µg/mL. Moxifloxacin MIC values ranged from 0.03 to 0.25 µg/mL with a MIC<sub>90</sub> value of 0.25 µg/mL. There were seven penicillin-resistant isolates of *S. pneumoniae*, 18 isolates resistant to clarithromycin, 17 resistant to erythromycin, and 12 resistant to trimethoprim/sulfamethoxazole. There were three isolates with ciprofloxacin MICs of 4 µg/mL. Gemifloxacin MICs for these three isolates were 0.015 to 0.06 µg/mL.

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TABLE 58 shows the bacteriological response at follow-up in the Bacteriology ITT population and Bacteriology per Protocol (PP) populations. This TABLE also shows the results for penicillin-resistant *S. pneumoniae*.

**TABLE 58**  
Per Patient Bacteriological Response at Follow-Up

| <i>Population</i>            | <i>Gemifloxacin 320 mg od</i> |               |
|------------------------------|-------------------------------|---------------|
| <i>Bacteriology ITT</i>      |                               |               |
|                              |                               | <i>N = 94</i> |
| Success, n (%)               | 79                            | (84.0)        |
| Failure, n (%)               | 15                            | (16.0)        |
| <i>Bacteriology PP</i>       |                               |               |
|                              |                               | <i>N = 80</i> |
| Success, n (%)               | 72                            | (90.0)        |
| Failure, n (%)               | 8                             | (10.0)        |
| <i>PRSP Bacteriology ITT</i> |                               |               |
|                              |                               | <i>N = 7</i>  |
| Success, n (%)               | 6                             | (85.7)        |
| Failure, n (%)               | 1                             | (14.3)        |
| <i>PRSP Bacteriology PP</i>  |                               |               |
|                              |                               | <i>N = 6</i>  |
| Success, n (%)               | 6                             | (100.0)       |
| Failure, n (%)               | 0                             | ---           |

TABLE 59 shows the clinical response at follow-up for each of these same populations.

**TABLE 59**  
Clinical Response Rates at Follow-Up

| <i>Population</i>            | <i>Gemifloxacin 320 mg od</i> |                |
|------------------------------|-------------------------------|----------------|
| <i>ITT</i>                   |                               |                |
|                              |                               | <i>N = 186</i> |
| Success, n (%)               | 146                           | (78.5)         |
| Failure, n (%)               | 40                            | (21.5)         |
| <i>Clinical PP</i>           |                               |                |
|                              |                               | <i>N = 147</i> |
| Success, n (%)               | 132                           | (89.8)         |
| Failure, n (%)               | 15                            | (10.2)         |
| <i>PRSP Bacteriology ITT</i> |                               |                |
|                              |                               | <i>N = 7</i>   |
| Success, n (%)               | 6                             | (85.7)         |
| Failure, n (%)               | 1                             | (14.3)         |
| <i>PRSP Bacteriology PP</i>  |                               |                |
|                              |                               | <i>N = 6</i>   |
| Success, n (%)               | 6                             | (100.0)        |
| Failure, n (%)               | 0                             | ---            |

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The per pathogen bacteriological outcomes at follow-up are summarized in TABLE 60 for all initial pathogens combined and for individual pathogens associated with CAP which were isolated from five or more patients. Approximately 83% of patients in the Bacteriology ITT population and 88% in the Bacteriology PP population had outcomes of either eradication or presumed eradication. Documented or presumed bacteriological recurrence at follow-up did not occur for any patient in the study. All bacteriological failures occurred at the end of therapy visit.

TABLE 60  
Bacteriological Outcome at Follow-Up

| Initial Pathogen     | Bacteriological Outcome   | Gemifloxacin 320 mg od     |        |                           |        |
|----------------------|---------------------------|----------------------------|--------|---------------------------|--------|
|                      |                           | Bacteriology ITT<br>N = 94 |        | Bacteriology PP<br>N = 80 |        |
|                      | (n)**                     | n*                         | (%)    | n*                        | (%)    |
| All Pathogens        | (n)**                     | 111                        |        | 95                        |        |
|                      | Eradication               | 3                          | (2.7)  | 2                         | (2.1)  |
|                      | Presumed Eradication      | 89                         | (80.2) | 82                        | (86.3) |
|                      | Unable to Determine       | 2                          | (1.8)  | 0                         |        |
|                      | Not done (Failure at EOT) | 17                         | (15.3) | 11                        | (11.6) |
| <i>S. pneumoniae</i> | (n)**                     | 51                         |        | 44                        |        |
|                      | Eradication               | 3                          | (5.9)  | 2                         | (4.5)  |
|                      | Presumed Eradication      | 39                         | (76.5) | 37                        | (84.1) |
|                      | Unable to Determine       | 1                          | (2.0)  | 0                         |        |
|                      | Not done (Failure at EOT) | 8                          | (15.7) | 5                         | (11.4) |
| PRSP                 | (n)**                     | 7                          |        | 6                         |        |
|                      | Eradication               | 1                          | (14.3) | 1                         | (16.7) |
|                      | Presumed Eradication      | 5                          | (71.4) | 5                         | (83.3) |
|                      | Not done (Failure at EOT) | 1                          | (14.3) | 0                         |        |
| <i>H. influenzae</i> | (n)**                     | 15                         |        | 13                        |        |
|                      | Presumed Eradication      | 13                         | (86.7) | 12                        | (92.3) |
|                      | Not done (Failure at EOT) | 2                          | (13.3) | 1                         | (7.7)  |
| <i>K. pneumoniae</i> | (n)**                     | 15                         |        | 13                        |        |
|                      | Presumed Eradication      | 15                         | (100)  | 13                        | (100)  |
| <i>S. aureus</i>     | (n)**                     | 8                          |        | 7                         |        |
|                      | Presumed Eradication      | 5                          | (62.5) | 5                         | (71.4) |
|                      | Not done (Failure at EOT) | 3                          | (37.5) | 2                         | (28.6) |
| <i>P. aeruginosa</i> | (n)**                     | 5                          |        | 4                         |        |
|                      | Presumed Eradication      | 4                          | (80.0) | 3                         | (75.0) |
|                      | Not done (Failure at EOT) | 1                          | (20.0) | 1                         | (25.0) |

\* Number (%) of pathogens with specified outcome. Percentages are calculated from the total number of patients with each initial pathogen.

\*\* Number of pathogens for "All pathogens" category; number of patients with pathogen for individual pathogens.

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The per pathogen bacteriological outcomes at end of therapy visit resembled results for the follow-up visit. Overall bacteriological eradication/presumed eradication rates for gemifloxacin treated patients were 84.7% in the Bacteriology ITT population and 88.9% in the Bacteriology PP population. Eradication/presumed eradication rates for *S. pneumoniae* and *H. influenzae* were similar to the overall rates. These data are summarized in TABLE 61.

TABLE 61  
Bacteriological Outcome at End of Therapy

| Initial Pathogen     | Bacteriological Outcome | Gemifloxacin 320 mg od     |        |                           |        |
|----------------------|-------------------------|----------------------------|--------|---------------------------|--------|
|                      |                         | Bacteriology ITT<br>N = 94 |        | Bacteriology PP<br>N = 82 |        |
|                      | (n)**                   | n*                         | (%)    | n*                        | (%)    |
| All Pathogens        | (n)**                   | 111                        |        | 99                        |        |
|                      | Eradication             | 4                          | (3.6)  | 3                         | (3.0)  |
|                      | Presumed Eradication    | 90                         | (81.1) | 85                        | (85.9) |
|                      | Presumed Persistence    | 12                         | (10.8) | 11                        | (11.1) |
|                      | Unable to Determine     | 5                          | (4.5)  | 0                         |        |
| <i>S. pneumoniae</i> | (n)**                   | 51                         |        | 46                        |        |
|                      | Eradication             | 2                          | (3.9)  | 1                         | (2.2)  |
|                      | Presumed Eradication    | 41                         | (80.4) | 40                        | (87.0) |
|                      | Presumed Persistence    | 6                          | (11.8) | 5                         | (10.9) |
|                      | Unable to Determine     | 2                          | (3.9)  | 0                         |        |
| PRSP                 | (n)**                   | 7                          |        | 6                         |        |
|                      | Eradication             | 1                          | (14.3) | 1                         | (16.7) |
|                      | Presumed Eradication    | 5                          | (71.4) | 5                         | (83.3) |
|                      | Presumed Persistence    | 1                          | (14.3) | 0                         |        |
| <i>H. influenzae</i> | (n)**                   | 15                         |        | 13                        |        |
|                      | Presumed Eradication    | 13                         | (86.7) | 12                        | (92.3) |
|                      | Presumed Persistence    | 1                          | (6.7)  | 1                         | (7.7)  |
|                      | Unable to Determine     | 1                          | (6.7)  | 0                         |        |
| <i>K. pneumoniae</i> | (n)**                   | 15                         |        | 14                        |        |
|                      | Eradication             | 1                          | (6.7)  | 1                         | (7.1)  |
|                      | Presumed Eradication    | 14                         | (93.3) | 13                        | (92.9) |
| <i>S. aureus</i>     | (n)**                   | 8                          |        | 7                         |        |
|                      | Presumed Eradication    | 5                          | (62.5) | 5                         | (71.4) |
|                      | Presumed Persistence    | 2                          | (25.0) | 2                         | (28.6) |
|                      | Unable to Determine     | 1                          | (12.5) | 0                         |        |
| <i>P. aeruginosa</i> | (n)**                   | 5                          |        | 4                         |        |
|                      | Eradication             | 1                          | (20.0) | 1                         | (25.0) |
|                      | Presumed Eradication    | 3                          | (60.0) | 2                         | (50.0) |
|                      | Presumed Persistence    | 1                          | (20.0) | 1                         | (25.0) |

\* Number (%) of pathogens with specified outcome. Percentages are calculated from the total number of patients with each initial pathogen.

\*\* Number of pathogens.

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TABLE 62 shows the gemifloxacin MIC values for pathogens from patients who were bacteriological failures. Except for an isolate of *P. aeruginosa*, *S. aureus*, and one *B. cepacia* isolate all failures had low gemifloxacin MICs.

TABLE 62  
Patients with Bacteriological Response of Failure

| Patient ID    | Bact. Response<br>--EOT<br>--FU | Pathogen(s)          | Bact. Outcome<br>--EOT<br>--FU              | Screening<br>Gemifloxacin<br>MIC (µg/mL) |
|---------------|---------------------------------|----------------------|---|--|
| 287.005.49830 | Failure<br>Failure              | <i>S. pneumoniae</i> | Unable to determine<br>Not done             | 0.015                                    |
| 287.005.49976 | Failure<br>Failure              | <i>S. pneumoniae</i> | Unable to determine<br>Not done             | 0.03                                     |
| 287.009.49981 | Failure<br>Failure              | <i>E. coli</i>       | Presumed persistence<br>Presumed failure    | 0.008                                    |
|               |                                 | <i>P. aeruginosa</i> | Presumed persistence<br>Presumed failure    | 0.12                                     |
|               |                                 | MRSA                 | Presumed persistence<br>Presumed failure    | 0.008                                    |
| 287.009.49984 | Failure<br>Failure              | <i>S. aureus</i>     | Presumed persistence<br>Presumed failure    | 0.15                                     |
|               |                                 | <i>S. pneumoniae</i> | Presumed persistence<br>Presumed failure    | 0.03                                     |
| 287.023.60084 | Failure<br>Failure              | <i>B. cepacia</i>    | Presumed persistence<br>Presumed failure    | 1.0                                      |
| 287.041.49797 | Failure<br>Failure              | <i>H. influenzae</i> | Presumed persistence<br>Presumed failure    | 0.002                                    |
| 287.042.49742 | Success<br>Failure              | <i>S. marcescens</i> | Presumed eradication<br>Unable to determine | 0.06                                     |
|               |                                 | <i>S. pneumoniae</i> | Presumed eradication<br>Unable to determine | 0.015                                    |
| 287.051.60059 | Failure<br>Failure              | <i>S. aureus</i>     | Unable to determine<br>Not done             | 0.015                                    |

EOT = end of therapy; FU = follow-up

MRSA = methicillin-resistant *Staphylococcus aureus*

TABLE 63 shows the bacteriological response rate for patient who had *Streptococcus pneumoniae* isolated at screening. In general, bacteriological success rates for patients with *S. pneumoniae* were similar to the overall bacteriological success rates for all pathogens.

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TABLE 63  
Bacteriological Response for Patients with CAP due to *S. pneumoniae*

| <i>S. pneumoniae</i>  | Gemifloxacin 320 mg od |                 |
|-----------------------|------------------------|-----------------|
|                       | Bacteriology ITT       | Bacteriology PP |
| <b>End of Therapy</b> | <b>N = 51</b>          | <b>N = 46</b>   |
| Success, n (%)        | 48 (84.3)              | 41 (89.1)       |
| Failure, n (%)        | 8 (15.7)               | 5 (10.9)        |
| <b>Follow-up</b>      | <b>N = 51</b>          | <b>N = 44</b>   |
| Success, n (%)        | 42 (82.4)              | 39 (88.6)       |
| Failure, n (%)        | 9 (17.6)               | 5 (11.4)        |

Penicillin-Resistant *Streptococcus pneumoniae*

Bacteriological response by *S. pneumoniae* susceptibility to penicillin is presented in TABLE 64. Most strains of penicillin-resistant *S. pneumoniae* were bacteriological successes.

TABLE 64  
Bacteriological Success Rate at Follow-up  
*Streptococcus pneumoniae* by Penicillin-Susceptibility

| Susceptibility | Gemifloxacin 320 mg od      |        |                            |         |
|----------------|-----------------------------|--------|----------------------------|---------|
|                | Bacteriology ITT<br>N* = 51 |        | Bacteriology PP<br>N* = 44 |         |
|                | n/N**                       | (%)    | n/N**                      | (%)     |
| Susceptible    | 29/34                       | (85.3) | 27/31                      | (87.1)  |
| Intermediate   | 9/13                        | (69.2) | 8/10                       | (80.0)  |
| Resistant      | 6/7                         | (85.7) | 6/6                        | (100.0) |

\* N = number of patient with *S. pneumoniae*

\*\* n/N = number of successes/number of isolates with specified susceptibility

Macrolide-Resistant *Streptococcus pneumoniae*

Bacteriological response by *S. pneumoniae* susceptibility to clarithromycin or erythromycin is presented in TABLE 65. *Streptococcus pneumoniae* that was resistant to clarithromycin and erythromycin was isolated from 17 patients in the Bacteriology ITT population. The eradication/presumed eradication rate from macrolide-resistant *S. pneumoniae* in the Bacteriology PP population was 86.7%. Bacteriological success in the Bacteriology ITT population was somewhat lower for erythromycin-resistant (76.5%) and clarithromycin-resistant (72.2%) isolates. At follow-up, the macrolide-resistant pathogens were eradicated in two patients and presumed to be eradicated in an additional 11 patients, for a total eradication rate of 76.5%. The lower success rate in the ITT population is due in part to the inclusion of patients with outcomes of "unable to determine" as failures.

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TABLE 65  
Bacteriological Success Rate at Follow-up  
*Streptococcus pneumoniae* by Macrolide-Susceptibility

|                |                | Gemifloxacin 320 mg od      |        |                            |        |
|----------------|----------------|-----------------------------|--------|----------------------------|--------|
|                |                | Bacteriology ITT<br>N* = 51 |        | Bacteriology PP<br>N* = 44 |        |
|                | Susceptibility | n/N**                       | (%)    | n/N**                      | (%)    |
| Erythromycin   | Susceptible    | 31/37                       | (83.8) | 38/32                      | (87.5) |
|                | Resistant      | 13/17                       | (76.5) | 13/15                      | (86.7) |
| Clarithromycin | Susceptible    | 31/36                       | (86.1) | 28/32                      | (87.5) |
|                | Resistant      | 13/18                       | (72.2) | 13/15                      | (86.7) |

\* N = number of patient with *S. pneumoniae*

\*\* n/N = number of successes/number of isolates with specified susceptibility

TABLE 66 shows the bacteriological outcome for the *Streptococcus pneumoniae* isolates based on their gemifloxacin MIC values at screening. All isolates had gemifloxacin MICs of  $\leq 0.06$   $\mu\text{g/mL}$ .

TABLE 66  
Bacteriological Success Rate at Follow-up  
*Streptococcus pneumoniae* by Gemifloxacin MIC Value

|                  |  | Gemifloxacin 320 mg od      |         |                            |         |
|------------------|--|-----------------------------|---------|----------------------------|---------|
|                  |  | Bacteriology ITT<br>N* = 51 |         | Bacteriology PP<br>N* = 44 |         |
| Gemifloxacin MIC |  | n/N**                       | (%)     | n/N**                      | (%)     |
| ALL              |  | 44/54                       | (81.5)  | 41/47                      | (87.2)  |
| 0.008            |  | 12/15                       | (80.0)  | 12/15                      | (80.0)  |
| 0.015            |  | 23/28                       | (82.1)  | 20/22                      | (90.9)  |
| 0.03             |  | 8/10                        | (80.0)  | 8/9                        | (88.9)  |
| 0.06             |  | 1/1                         | (100.0) | 1/1                        | (100.0) |

\* N = number of patient with *S. pneumoniae*

\*\* n/N = number of successes/number of isolates with specified MIC

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Peter A. Dionne  
Microbiologist HFD-590

**CONCURRENCES:**

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**NDA 21-158**

**FACTIVE<sup>®</sup> (gemifloxacin mesylate) 320mg Tablets**

**Action Date: December 15, 2000**

TL: Leissa

MO: Powers, Alivisatos, Cox

CHM: M. Sloan

PCL: Ellis

MIC: Dionne

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BPH: Colangelo

STT: Higgins, Dixon, Silliman

RPM: Kimzey

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HFD-590/L.Kimzey

JUN 30 2000

**MICROBIOLOGY REVIEW**  
**DIVISION OF SPECIAL PATHOGENS AND IMMUNOLOGIC DRUG PRODUCTS**  
**(HFD-590)**

**NDA #:** #21-158

**REVIEWER:** Peter A. Dionne  
**CORRESPONDENCE DATE:** 15-DEC-99  
**CDER DATE:** 16-DEC-99  
**REVIEW ASSIGN DATE:** 03-JAN-00  
**REVIEW COMPLETE DATE:** 15-MAR-00

**SPONSOR:** SmithKline Beecham Pharmaceuticals  
One Franklin Plaza, P.O. Box 7929  
Philadelphia, PA 19101-7929

**CONTACT PERSON:** Edward M. Yuhas, Ph.D.  
Associate Director U. S. Regulatory Affairs  
Phone Number: (215) 751-3468

**SUBMISSION REVIEWED:** Original NDA Submission

**DRUG CATEGORY:** Antimicrobial: Fluoroquinolone

**INDICATIONS:** Community Acquired Pneumonia (CAP), Acute Exacerbations of  
Chronic Bronchitis (AECB), \_\_\_\_\_

**DOSAGE FORM:** Tablet--320 mg/tablet

**DRUG PRODUCT NAME**

**PROPRIETARY:**

FACTIVE™

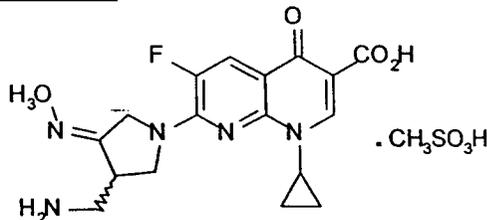
**NONPROPRIETARY/USAN:** Gemifloxacin mesylate tablet

**CODE:**

SB-265805-S; LB20304a

**CHEMICAL NAME:** (±)-7-[3-(aminomethyl)-4-oxo-1-pyrrolidinyl]-1-cyclopropyl-  
6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic  
acid, 7<sup>4</sup>-(Z)-(O-methyloxime), monomethanesulfonate.

**STRUCTURAL FORMULA:**



**Molecular Formula:** C<sub>18</sub>H<sub>20</sub>FN<sub>5</sub>O<sub>4</sub>•CH<sub>4</sub>O<sub>3</sub>S

**Molecular Weight:** 485.49.

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SUPPORTING DOCUMENTS: \_\_\_\_\_

REMARKS/COMMENTS:

This application is for a new fluoroquinolone, gemifloxacin. The applicant wishes approval for community acquired pneumonia, acute exacerbation of chronic bronchitis,

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CONCLUSIONS & RECOMMENDATIONS:

The application is approvable from the microbiological viewpoint under section 505(b) of the Act when changes are made to the MICROBIOLOGY subsection of the package insert. The changes needed should be sent to the sponsor. These revisions are listed under Recommendations at the end of this review on pages 231-240.

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### EXECUTIVE SUMMARY

Most of the older fluoroquinolones such as ciprofloxacin have excellent *in vitro* activity against gram-negative aerobic bacteria. They have limited or no activity, however, against gram-positive aerobic bacteria or anaerobes. Recent efforts have been directed toward the synthesis of quinolone compounds that provide improved activity against gram-positive organisms, while retaining gram-negative activity.

Gemifloxacin has a novel 3-aminomethyl-4-syn-methoxyimino-1-pyrrolidinyl substituent at the C7 position of the 6-fluoro-1, 8-naphyridone ring. This substituent appears to enhance the antipneumococcal activity of gemifloxacin compared to other fluoroquinolones. Gemifloxacin's *in vitro* MIC values against *Streptococcus pneumoniae* are 4-8 times lower than those of trovafloxacin and moxifloxacin and over 32 times lower than the MIC values for ciprofloxacin and levofloxacin. Unfortunately, at the proposed human dose the AUC value for gemifloxacin is only about one-fourth that of most of the other fluoroquinolones. A 4-fold lower MIC value is, therefore, basically equivalent to that of trovafloxacin or moxifloxacin. These lower MIC values for gemifloxacin are seen with most gram-positive bacteria. The difference between gemifloxacin and other fluoroquinolones against these gram-positive species, however, is not as great as that seen with *Streptococcus pneumoniae*. The MIC values for gemifloxacin are usually equivalent of one dilution lower than those seen with trovafloxacin and 2- to 4-fold less than those seen with moxifloxacin. Gemifloxacin MICs are usually about 16 times less than those seen with ciprofloxacin.

Against most gram-negative bacteria, gemifloxacin MICs are usually 2-fold greater than those seen with ciprofloxacin and equivalent to those for most of the other comparator fluoroquinolones. Since gemifloxacin, however, will have a susceptible breakpoint that is 4 to 8 times lower than that for most other fluoroquinolones, many of the gram-negative species will have MIC<sub>90</sub> values at or greater than the susceptible breakpoint. This means that during treatment there may be isolates that have MIC values above achievable serum or tissue levels of the drug. This may lead to the growth of these resistant isolates.

Against anaerobes gemifloxacin MIC values are generally worst than those of trovafloxacin and 2 to 4 times less than those of ciprofloxacin or levofloxacin. It has borderline activity against *Peptostreptococcus* species and *Fusobacterium nucleatum* but poor activity against most other species. TABLE A shows MIC<sub>90</sub> values for gemifloxacin against some common pathogens. Based on the preclinical and clinical data provided in this NDA the susceptible breakpoint for gemifloxacin for enterobacteriaceae was set at  $\leq 0.25 \mu\text{g/mL}$ . The susceptible breakpoint for staphylococci, *Streptococcus pneumoniae*, and *Haemophilus* species was set at  $0.12 \mu\text{g/mL}$ .

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TABLE A  
Gemifloxacin *in vitro* Activity

| PATHOGEN   | MIC <sub>90</sub> (µg/mL)* |
|--|----------------------------|
| <i>Staphylococcus aureus</i> (methicillin-susceptible) | 0.06                       |
| <i>Staphylococcus aureus</i> (methicillin-resistant)   | ≥8.0                       |
| <i>Staphylococcus epidermidis</i>                      | 1.0                        |
| <i>Staphylococcus saprophyticus</i>                    | 0.03                       |
| <i>Streptococcus pneumoniae</i>                        | 0.03                       |
| <i>Streptococcus pyogenes</i>                          | 0.03                       |
| Viridans Group <i>Streptococci</i>                     | 0.06                       |
| <i>Streptococcus agalactiae</i>                        | 0.06                       |
| <i>Enterococcus faecalis</i>                           | 4.0                        |
| <i>Acinetobacter</i> species                           | ≥8.0                       |
| <i>Escherichia coli</i>                                | 0.25                       |
| <i>Klebsiella pneumoniae</i>                           | 0.5                        |
| <i>Klebsiella oxytoca</i>                              | 0.12                       |
| <i>Enterobacter cloacae</i>                            | 0.25                       |
| <i>Enterobacter aerogenes</i>                          | ≥8.0                       |
| <i>Proteus mirabilis</i>                               | 4.0                        |
| <i>Proteus vulgaris</i>                                | 0.25                       |
| <i>Citrobacter freundii</i>                            | 2.0                        |
| <i>Morganella morganii</i>                             | 0.25                       |
| <i>Serratia marcescens</i>                             | 1-4                        |
| <i>Pseudomonas aeruginosa</i>                          | ≥8.0                       |
| <i>Haemophilus influenzae</i>                          | 0.03                       |
| <i>Haemophilus parainfluenzae</i>                      | 0.06                       |
| <i>Moraxella catarrhalis</i>                           | 0.015                      |
| <i>Bacteroides fragilis</i>                            | 2-4                        |
| <i>Clostridium</i> species                             | 0.06->16                   |
| <i>Prevotella</i> species                              | 0.5-16                     |
| <i>Peptostreptococcus</i> species                      | 0.03-4.0                   |
| <i>Fusobacterium nucleatum</i>                         | 0.25-2.0                   |
| <i>Legionella pneumoniae</i>                           | 0.015                      |
| <i>Mycoplasma pneumoniae</i>                           | 0.12                       |
| <i>Chlamydia pneumoniae</i>                            | 0.25                       |
| <i>Mycobacterium tuberculosis</i>                      | 64.0                       |

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TABLE B gives a summary of gemifloxacin's *in vitro* activity compared to other fluoroquinolones. It must be remembered that gemifloxacin's susceptible breakpoint is 4-8 fold lower than that of most of the comparator quinolones.

TABLE B

*In vitro* Activity of Gemifloxacin compared to other Fluoroquinolones (MIC<sub>90</sub>s µg/mL)

| Organism                            | GEMI  | CIPRO    | LEVO  | TROV   | GREP  | OFL  |
|-------------------------------------|-------|----------|-------|--------|-------|------|
| <i>Streptococcus pneumoniae</i>     | 0.03  | 2.0      | 1.0   | 0.25   | 0.25  | 2.0  |
| <i>Streptococcus pyogenes</i>       | 0.03  | 1.0      | 1.0   | 0.12   | 0.5   | 2.0  |
| <i>Streptococcus agalactiae</i>     | 0.06  | 1.0      | 1.0   | 0.25   | 0.5   | 2.0  |
| Viridans Group streptococci         | 0.06  | ≥4.0     | 1.0   | 0.25   | 0.5   | 4.0  |
| <i>Staphylococcus aureus</i> (MS)   | 0.06  | 1.0      | 0.5   | 0.12   | 0.12  | 1.0  |
| <i>Staphylococcus aureus</i> (MR)   | ≥8.0  | ≥4.0     | ≥8.0  | 4.0    | ≥32   | ≥8.0 |
| <i>Staphylococcus epidermidis</i>   | 1.0   | ≥4.0     | ≥8.0  | 4.0    | ≥32   | ≥8.0 |
| <i>Staphylococcus saprophyticus</i> | 0.03  | 1.0      | 0.5   | 0.12   | 0.12  | 1.0  |
| <i>Acinetobacter</i> species        | ≥8.0  | ≥4.0     | ≥8.0  | ≥8.0   | 8.0   | ≥8.0 |
| <i>Enterococcus faecalis</i>        | 4.0   | ≥4.0     | ≥8.0  | ≥8.0   | ≥32   | ≥8.0 |
| <i>Haemophilus influenzae</i>       | 0.03  | 0.03     | 0.03  | 0.03   | 0.015 | 0.12 |
| <i>Haemophilus parainfluenzae</i>   | 0.06  | 0.06     | 0.06  | 0.12   | 0.12  | 0.25 |
| <i>Moraxella catarrhalis</i>        | 0.015 | 0.06     | 0.06  | 0.03   | 0.015 | 0.12 |
| <i>Escherichia coli</i>             | 0.25  | 0.5      | 0.5   | 0.5    | 0.5   | 1.0  |
| <i>Klebsiella pneumoniae</i>        | 0.5   | 1.0      | 1.0   | 1.0    | 1.0   | 4.0  |
| <i>Klebsiella oxytoca</i>           | 0.12  | 0.25     | 0.25  | 0.12   | 0.12  | 0.5  |
| <i>Enterobacter aerogenes</i>       | ≥8.0  | ≥4.0     | ≥8.0  | ≥8.0   | ≥32   | ≥8.0 |
| <i>Enterobacter cloacae</i>         | 0.25  | 0.5      | 0.5   | 1.0    | 0.5   | 2.0  |
| <i>Morganella morganii</i>          | 0.25  | 0.25     | 0.5   | 1.0    | 0.5   | 1.0  |
| <i>Serratia marcescens</i>          | 1-4   | 0.5-4    | 0.5   | 2->16  | ---   | ---  |
| <i>Citrobacter freundii</i>         | 2.0   | 2.0      | 2.0   | 4.0    | 2.0   | 4.0  |
| <i>Proteus mirabilis</i>            | 4.0   | 1.0      | 1.0   | ≥8.0   | 16.0  | 4.0  |
| <i>Proteus vulgaris</i>             | 0.25  | 0.06     | 0.06  | 0.5    | 0.5   | 0.25 |
| <i>Morganella morganii</i>          | 0.25  | 0.25     | 0.5   | 1.0    | 0.5   | 1.0  |
| <i>Pseudomonas aeruginosa</i>       | ≥8.0  | ≥4.0     | ≥8.0  | ≥8.0   | ≥32   | ≥8.0 |
| <i>Bacteroides fragilis</i>         | 2.0   | 16.0     | 4.0   | 1.0    | ---   | 2.0  |
| <i>Fusobacterium nucleatum</i>      | 0.25  | 4.0      | 0.5   | 1.0    | ---   | 2.0  |
| <i>Prevotella</i> species           | 2.0   | 16.0     | 1.0   | 1.0    | ---   | 8.0  |
| <i>Clostridium</i> species          | 2.0   | ---      | >16.0 | 8.0    | ---   | ---  |
| <i>Peptostreptococcus</i> species   | 0.25  | 4.0      | 4.0   | 0.5    | ---   | 8.0  |
| <i>Chlamydia pneumoniae</i>         | 0.25  | 0.25-0.5 | 1.0   | 1.0    | ---   | ---  |
| <i>Mycoplasma pneumoniae</i>        | 0.12  | ---      | 0.5   | 0.25   | ---   | ---  |
| <i>Legionella pneumophila</i>       | 0.015 | 0.03     | 0.015 | ≤0.004 | ---   | ---  |

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TABLE C  
Efficacy of gemifloxacin against respiratory tract infections in rats

| <i>S. pneumoniae</i>             | MIC (µg/mL) | Bacterial counts in Lungs 17 h post-therapy<br>(log <sub>10</sub> cfu/lungs) |                      |
|----------------------------------|-------------|--|----------------------|
|                                  |             | Non-treated  | Gemifloxacin-treated |
| 1629 (pen-S)                     | ≤ 0.03      | 6.8 ± 1.2  | <1.7                 |
| 10127 (pen-S)                    | ≤ 0.03      | 6.4 ± 1.9  | 1.9 ± 0.5            |
| L11259 (pen-S)                   | ≤ 0.03      | 8.0 ± 0.8  | <1.7                 |
| 406081 (macrolide-R)             | ≤ 0.03      | 5.0 ± 0.9  | 2.2 ± 0.6            |
| N1387 (macrolide-R)              | ≤ 0.03      | 5.1 ± 1.0  | 2.5 ± 1.1            |
| 404053 (pen-R)                   | ≤ 0.03      | 5.8 ± 1.4  | 1.8 ± 0.2            |
| 205118 (pen-R)                   | ≤ 0.03      | 6.3 ± 0.6  | 3.6 ± 0.19           |
| 305313 (cipro-R)*                | 0.125       | 7.1 ± 1.4  | 2.1 ± 0.14           |
| 622286 (cipro-R)*                | 0.125       | 6.4 ± 1.3  | 2.4 ± 1.1            |
| PT9424123 *                      | 0.25        | 8.1 ± 0.8  | 4.42 ± 0.7           |
| 402123*                          | 0.25        | 8.3 ± 0.8  | 5.7 ± 0.9            |
| 509063                           | 0.25        | 6.2 ± 1.6  | 3.5 ± 1.1            |
| 214152                           | 0.5         | 6.6 ± 1.6  | 3.8 ± 1.4            |
| <i>H. influenzae</i>             |             |  |                      |
| H128 (BLA+)                      | ≤ 0.008     | 4.3 ± 1.2  | ≤ 1.7                |
| Chesterfield (BLNAR)             | ≤ 0.008     | 4.94 ± 1.06  | ≤ 1.7                |
| LA85021 (BLA+)                   | ≤ 0.008     | 6.9 ± 0.9  | ≤ 1.7                |
| H143*<br>(Cipro MIC = 1.0 µg/mL) | ≤ 0.125     | 6.0 ± 1.2  | ≤ 1.7                |

\* dosing twice daily commencing 1 hour post-infection

Gemifloxacin was also shown to reduce bacterial counts in experimental surgical wound infections in rats caused by *S. pyogenes*, *S. aureus*, or *S. epidermidis*. Treatment usually commenced one hour post-infection. Effectiveness was shown in models of urinary tract infections caused by *P. aeruginosa*, *P. mirabilis*, and *E. coli*.

During the clinical trials there were 219 patients who were treated with gemifloxacin or comparator which had isolates showing an apparent increase in MIC of 4-fold between initial screening and end of therapy or post-therapy visits, or a decrease in disk zone diameter of 6 mm or more. Isolates from 55 of these patients were in the comparator group. Isolates or complete retest data was not available for 74 patients. Of the 90 patients still left, 63 of the 90 patients had MIC or disk changes that were not between screening and end of therapy or post-therapy. Isolates from 20 of the remaining 27 patients demonstrated an increase in MIC of < 4-fold or a decrease in disk diameter < 6 mm to gemifloxacin upon retest. Further testing of the remaining 7 patients showed screening and post-therapy isolates that they were not the same species or strains. Only one patient (using the sponsor's criteria) had screening and end of therapy or post-therapy isolates that were identified as the same. It should be noticed that 74

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patients had isolates that were lost and that another 63 patients had isolates that did increase although they were not between the required visits. In reviewing other fluoroquinolones this number of increased MIC or decrease in zone diameters is very unusual. There are usually only a few patients with this large an increase in MIC values. There were, however, more patients in this NDA than are usually seen and the percentage of patients with increases in MICs was not that unusual (1%) and the control arms had approximately the same percentage of patients with MIC increases.

Plasma binding of gemifloxacin is about 70% and is independent of concentration. The majority of the oral dose (61%) is excreted in the feces and urinary excretion accounts for 36% of the oral dose. The absolute oral bioavailability was 71%. The terminal phase half-life is approximately 5 to 9 hours. Gemifloxacin is a racemic mixture and the enantiomers have similar microbiological activity. The mean AUC was 8.36  $\mu\text{g}\cdot\text{h}/\text{mL}$ . The mean  $C_{\text{max}}$  was 1.6  $\mu\text{g}/\text{mL}$ .

**PRECLINICAL EFFICACY (IN VITRO)**

**MECHANISM OF ACTION**

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The bacterial chromosome is a circular molecule of double-stranded DNA that is much longer than the bacterial cell itself. The linear length of the chromosome is condensed through the process of positive and negative supercoiling. Topoisomerases are enzymes that maintain the proper state of supercoiling of DNA at replicating and nonreplicating sites of the double-stranded DNA molecule.

There are two types of topoisomerases, I and II, which are characterized by reactions involving single- or double-stranded breaks in DNA, respectively. DNA gyrase is a type II enzyme. Gyrase consists of two subunits, GyrA and GyrB, encoded by the *gyrA* and *gyrB* genes. The active enzyme is an  $A_2B_2$  complex. The GyrA subunit is responsible for breakage and reunion of DNA and is the target of quinolones. The GyrB subunit is involved in the ATP activated passage of one DNA segment through the double-stranded break. Gyrase binds to DNA and a segment of approximately 130 base pairs (130 bp) is wrapped around the protein. This wrapped DNA is cleaved in both strands, with a 4-base stagger between break sites, which results in the formation of DNA-protein covalent bonds between the GyrA subunits and the 5'-phosphates on the DNA molecule. Another segment of DNA is passed through this double-stranded break which may then be resealed. The quinolone drugs interrupt this process at the DNA breakage-reunion step.

In the beginning it was shown that nalidixic acid was an inhibitor of bacterial DNA replication. Prior to the discovery of DNA gyrase, a number of possible targets were found not to be inhibited by nalidixic acid. Following the isolation of gyrase from *Escherichia coli* by Gellert (1) it was shown that its supercoiling activity could be inhibited by oxolinic acid (2,3). Moreover, gyrase extracted from a nalidixic acid-resistant mutant was found to be resistant to oxolinic acid. Since then a large number of quinolone-

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resistant mutations have been mapped to the gyrase genes, principally to *gyrA* (4,5,6). This lead to the belief that gyrase was the principal target of quinolones.

Recently the existence of a second target, DNA topoisomerase IV, has been established. Like gyrase, topoisomerase IV is a bacterial type II DNA topoisomerase. It cannot supercoil DNA, however (7). Topoisomerase IV carries out the ATP-dependent relaxation of DNA and has been found to be a more potent decatenase than DNA gyrase (8). This enzyme is composed of two subunits, which in *E. coli* are encoded by the *parC* and *parE* genes. The *parC* gene encodes the ParC subunit (equivalent to GyrA) and the *parE* gene encodes the ParE subunit (equivalent to GyrB). Originally it was thought that *E. coli* DNA topoisomerase IV was not readily inhibited by the fluoroquinolones, since 30 times more drug was required to inhibit topoisomerase IV mediated relaxation than to inhibit relaxation by DNA gyrase (9). It has now been shown (8) that fluoroquinolones may have significant activity against topoisomerase IV mediated decatenation of DNA.

Ferrero (10) demonstrated using resistant isolates that topoisomerase IV is a primary target of fluoroquinolones in *Staphylococcus aureus*. Isolates with high levels of resistance were found to have mutations in both *gyrA* and *grlA* (equivalent to *parC* in *E. coli*). Clinical isolates with low level resistance were found to have mutations in only *grlA*. Fluoroquinolone resistant isolates of *Neisseria gonorrhoeae* also have mutations in both *gyrA* and *parC* genes. However, low level resistance is associated with mutations in *gyrA* (11). Analysis of quinolone resistance in *E. coli* (12,13) revealed that topoisomerase IV is likely a secondary target. These studies were unable to detect resistance associated with ParC alone. These data lead to the conclusion that quinolones primary target is gyrase in gram-negative bacteria and topoisomerase IV in gram-positive bacteria. Sparfloxacin, however, may target gyrase in *Streptococcus pneumoniae*. This may indicate that the structure of the drug molecule and not the type of bacteria may determine the primary cellular target. Some newer fluoroquinolones, however, seem to have less preference for one target over the other. This suggests that mutations in both gyrase and topoisomerase IV genes would be necessary for resistance. This double mutation would be a rare event.

The precise lethal events affected by quinolones is not known. It appears quinolones stabilize the gyrase-DNA complex. This prevents DNA synthesis and cell growth. DNA with double-stranded breaks is eventually released from these complexes and this leads to cell death. A cascade of physiological events results from the formation of these quinolone-DNA-DNA gyrase complexes including loss of supercoiling, filamentation of the bacterial cells, inhibition of DNA segregation, induction of the SOS response, and antagonism of RNA and protein synthesis at high concentrations.

A cooperative quinolone-DNA-binding model has been proposed for the interaction of quinolones with gyrase and DNA by Shen (14). DNA gyrase binds to relaxed DNA and cleaves both strands with a 4-bp stagger in the presence of ATP. Quinolones then bind to the exposed single-stranded regions via hydrogen bonding between donors from the single-stranded DNA and the carbonyl and carboxyl groups common to all quinolones. Four or more drug molecules may bond to the same region with quinolone rings stacked one over the other. Tail to tail hydrophobic interactions between the N-1 substituents of drugs may occur. Another model suggests that Mg<sup>++</sup>

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acts as a bridge between the phosphate groups of DNA and the carbonyl and carboxyl moieties of quinolones. The drugs are thought to be stabilized through stacking interactions between a DNA base in a single-stranded region and the quinolone planar ring system (15).

The mechanism of cell killing is still not fully understood. The fact that quinolones completely inhibit gyrase-catalyzed supercoiling *in vitro* suggest that this is how they act *in vivo*. However, observations suggest this is not the case. Hane and Wood (16) showed that in partial diploids the *nalA<sup>S</sup>* allele is dominant over *nalA<sup>R</sup>*. The *nalA* gene was later shown to be the gene encoding the A subunit of DNA gyrase (*gyrA*). If quinolones simply inhibited DNA supercoiling *in vivo* the wild-type gene should not be dominant. It has also been shown that the amount of quinolone drug required to inhibit supercoiling *in vivo* exceeds that required to inhibit bacterial growth (2). Domagala (17) compared the concentrations of drug needed to inhibit supercoiling *in vitro* by *E. coli* gyrase with MICs for a range of quinolones and found MICs to be lower by factors ranging from 40 to 300. It has also been shown that other reactions of gyrase, such as DNA relaxation and decatenation, are as sensitive to quinolones as DNA supercoiling (18).

It has been suggested that quinolones convert DNA gyrase into a poison. The poison was thought to be a complex between gyrase and DNA. Snyder and Drlica (19) showed that inhibition of DNA synthesis correlated with the formation of blocked replication fork movement. Sensitive alleles are dominant because the resistant gene product will not prevent the drug binding the sensitive protein and forming a poison. The amount of drug-enzyme complex required to kill the cell could represent only a small fraction of the total gyrase in the cell and thus have very little impact on the overall supercoiling activity.

It is still not known how this ternary complex (gyrase-drug-DNA) leads to cell death. It has been shown that quinolones are inhibitors of DNA replication. It has also been shown that the activity of most quinolones is bactericidal at low concentrations and bacteriostatic at higher concentrations. These observations correlate with inhibition of DNA synthesis at low concentrations and inhibition of RNA and protein synthesis at high concentrations. It has been suggested that the "poison" is a ternary complex that blocks the passage of polymerases.

Fluoroquinolones are thought to possess up to four mechanisms of cell killing (21, 22). Mechanism A (common to all quinolones) requires RNA and protein synthesis and is only effective against dividing bacteria; mechanism B does not require RNA and protein synthesis and can act on bacteria unable to multiply; mechanism C requires RNA and protein synthesis but does not require cell division. Mechanism B<sub>1</sub> is the most recently discovered mechanism of action. This mechanism does not require protein of RNA synthesis, but is lost against non-dividing bacteria. It is postulated that mechanism A is related to the blocking of replication by the gyrase-quinolone complex on DNA, mechanism B (chloramphenicol insensitive) is correlated with dissociation of the gyrase subunits which constrain the ternary complex, and mechanism C is correlated with trapping of topoisomerase IV complexes on DNA. Mechanism A is the sole mechanism of action of older quinolones such as nalidixic acid. Mechanism B is shown by many

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modern fluoroquinolones (FQs) against *E. coli*, but this does not guarantee that this mechanism will be present against other bacteria. Ciprofloxacin does not possess mechanisms B against *S. aureus*, whereas levofloxacin does possess this mechanism. Against *S. pneumoniae* only sitafloxacin appears to have mechanism B. Mechanism C has only been seen with enoxacin and norfloxacin. Mechanism B<sub>1</sub> has been seen with clinafloxacin against *E. coli* and staphylococci and with sitafloxacin and trovafloxacin against *E. faecalis*.

The inhibition of bacterial type II topoisomerases by gemifloxacin and comparator fluoroquinolones isolated from *S. pneumoniae*, *S. aureus*, and *E. coli* has been investigated and the IC<sub>50</sub> values determined. The results of these studies are summarized in TABLE 1.

TABLE 1  
Inhibition of Type II Topoisomerases by gemifloxacin and comparators

| Reference | Organism                       | MIC (µg/mL) |      |       | DNAG IC <sub>50</sub> (µg/mL) |         |         | TOPO IV IC <sub>50</sub> (µg/mL) |      |       |
|-----------|--------------------------------|-------------|------|-------|-------------------------------|---------|---------|----------------------------------|------|-------|
|           |                                | Cipro       | Gemi | Trova | Cipro                         | Gemi    | Trova   | Cipro                            | Gemi | Trova |
| (23)      | <i>S. pneumoniae</i><br>C3LN4  | 2           | 0.06 | 0.06  | 59.2                          | 47.5    | 44.0    | 6.4                              | 1.4  | 3.7   |
| (23)      | <i>S. pneumoniae</i><br>50226  | 32          | 0.5  | 2.0   | 142.9                         | 88.0    | 61.9    | 16.1                             | 3.1  | 11.0  |
| (23)      | <i>S. pneumoniae</i><br>503244 | 64          | 0.5  | 8.0   | 160.3                         | 92.8    | 92.3    | 43.4                             | 7.9  | 11.1  |
| (24) (25) | <i>E. coli</i>                 | ---         | ---  | ---   | 0.5 µM                        | 0.27 µM | 0.31 µM | 3.7                              | 2.0  | ---   |
| (25)      | <i>S. aureus</i>               | ---         | ---  | ---   | 35 µM                         | 2.1 µM  | 6.8 µM  | ---                              | ---  | ---   |

Morrissey and George (23) purified DNA gyrase and TOPO IV from a fluoroquinolone-susceptible (FQ-S) *S. pneumoniae* strain (C3LN4) and two clinical isolates of *S. pneumoniae* with MICs to ciprofloxacin of 32 and 64 µg/mL (50226 and 503244). Inhibition of DNA gyrase supercoiling and TOPO IV decatenation was determined for gemifloxacin, trovafloxacin, levofloxacin, ciprofloxacin, moxifloxacin, and grepafloxacin to allow the calculation of IC<sub>50</sub> values (the concentration of FQ required to inhibit enzyme activity by 50%). Pneumococcal TOPO IV was found to be considerably more sensitive to all the FQs tested than was DNA gyrase. This indicates that in *S. pneumoniae*, TOPO IV is the primary target for most FQs. TOPO IV was 34-fold more sensitive to gemifloxacin than DNA gyrase. Gemifloxacin was the most potent inhibitor of TOPO IV, with an IC<sub>50</sub> value of 1.4 µg/mL for the FQ-S strain (other FQs ranged from 3.5-6.4 µg/mL). By contrast, all the FQs possessed similar activity against pneumococcal DNA gyrase from the FQ-S strain (IC<sub>50</sub> values of 42.8-59.2 µg/mL). IC<sub>50</sub> values against both TOPO IV and DNA gyrase isolated from FQ-resistant (FQ-R) strains were higher (TOPO IV IC<sub>50</sub> values ranged from 3.1-18.0 µg/mL and DNA gyrase IC<sub>50</sub> values ranged from 61.9-142.9 µg/mL for a strain with ciprofloxacin MIC of 32 µg/mL). Ability to inhibit TOPO IV showed good correlation with FQ susceptibility (MIC) and was, therefore, a better indicator of FQ MIC than was inhibition of DNA gyrase. Gemifloxacin had the lowest IC<sub>50</sub> values even against the FQ-R strains although trovafloxacin IC<sub>50</sub>

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values were only slightly greater and appeared to not increase as much for the strain with ciprofloxacin MIC of 64 µg/mL.

Wilding and Gwynn (24) investigated the 50% inhibition of *E. coli* TOPO IV decatenation activity by gemifloxacin and ciprofloxacin using an agarose gel-based assay system. The IC<sub>50</sub> values for gemifloxacin and ciprofloxacin were 2.0 ± 0.1 µg/mL and 3.7 ± 0.1 µg/mL, respectively. This indicates that gemifloxacin inhibited *E. coli* TOPO IV decatenation activity as well as ciprofloxacin. The primary target for these drugs in this species, however, is DNA gyrase.

Erskine studied the inhibition of *S. aureus* and *E. coli* DNA gyrase by gemifloxacin and three FQ comparators (25). Gemifloxacin was found to be the most potent inhibitor of *E. coli* DNA gyrase with an IC<sub>50</sub> value of 0.27 µM. Trovafloxacin exhibited similar activity (IC<sub>50</sub> = 0.31 µM), which was more active than ciprofloxacin (IC<sub>50</sub> value of 0.5 µM) and sparfloxacin (IC<sub>50</sub> value of 0.7 µM). Against *S. aureus* DNA gyrase, gemifloxacin was the most potent inhibitor (IC<sub>50</sub> = 2.1 µM), followed by trovafloxacin, sparfloxacin, and ciprofloxacin (IC<sub>50</sub> = 6.8 µM, 17 µM, and 35 µM, respectively). Despite having the highest IC<sub>50</sub> value against *E. coli* DNA gyrase, ciprofloxacin generally is the most active FQ against this species. Since TOPO IV is usually the primary target for FQs in *S. aureus* it would have been more interesting to have performed this experiment against *S. aureus* TOPO IV.

Selectivity for DNA gyrase over related mammalian enzyme topoisomerase II (TOPO II) is desirable for antibacterial therapy. Kim et al (26) showed that gemifloxacin was approximately 8-fold more potent than ciprofloxacin at inhibiting the supercoiling activity of DNA gyrase from *M. luteus*. Gemifloxacin did not induce human TOPO II-associated DNA cleavage even at a concentration of 10 mg/mL (10,000 µg/mL), while ciprofloxacin induced DNA cleavage at 1 mg/mL (1,000 µg/mL).

The bactericidal activities of gemifloxacin against *E. coli* KL16, *S. aureus* E3T and *S. pneumoniae* C3LN4 were evaluated (27). Gemifloxacin produced a characteristic bi-phasic dose-response curve in nutrient broth with all three species. This is typical of the FQs. The optimum bactericidal concentrations (OBC) for gemifloxacin against *E. coli* KL16, *S. aureus* E3T, and *S. pneumoniae* C3LN4 were 1.0, 0.5, and 0.5 µg/mL, respectively. Gemifloxacin has a lower OBC than either trovafloxacin or sitafloxacin against *S. aureus*. The bactericidal activity of gemifloxacin at the OBC against *S. aureus* E3T in nutrient broth was greater than that observed with other tested FQs.

Against *S. aureus* E3T, the most potent bactericidal activity was observed in nutrient broth. Reduced kill was observed when chloramphenicol was added or when experiments were carried out in phosphate-buffered saline (PBS) against non-multiplying bacteria. Good bactericidal activity was, however, maintained against *S. aureus* E3T under both conditions i.e., against both staphylococci unable to undergo protein synthesis or multiplication. Gemifloxacin appears to possess bactericidal mechanisms A and B against *S. aureus* E3T.

Addition of chloramphenicol to nutrient broth reduced the bactericidal activity of gemifloxacin against *E. coli* KL16, although gemifloxacin remained bactericidal under these conditions. In PBS, the bactericidal activity of gemifloxacin against *E. coli* KL16

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was considerably reduced. This implies that gemifloxacin can kill bacteria devoid of protein synthesis, but not bacteria completely incapable of multiplication. Against *E. coli* KL16 gemifloxacin possesses bactericidal mechanisms A and B<sub>1</sub>.

Against *S. pneumoniae* C3LN4 the bactericidal activity of gemifloxacin in nutrient broth (supplemented with laked horse blood) was lower than that observed against either *E. coli* KL16 or *S. aureus* E3T. Little or no activity was retained when chloramphenicol was added or when experiments were performed in PBS (supplemented with horse serum). Against *S. pneumoniae* C3LN4 gemifloxacin possesses only bactericidal mechanism A.

The significance of these mechanisms has not been fully elucidated, but mechanisms C and possibly B and B<sub>1</sub> may be beneficial *in vivo*, where organisms are often metabolizing and multiplying slowly or not at all.

## IN VITRO ACTIVITY OF ENANTIOMERS, ISOMERS, SALT FORMS AND METABOLITES

### SALT FORMS

The mesylate salt of gemifloxacin is what is used routinely in laboratory standard material and dosing formulations. A study (76) compared the antimicrobial activities of the mesylate and citrate salts with that of the free base by determining MICs against 27 Gram-positive and Gram-negative strains. The *in vitro* antibacterial activities of the three forms were identical.

### ISOMERS

The oximino group of gemifloxacin can exist in two forms (E or Z configuration). For thermodynamic reasons and from the experimental results of chemical transformation, it was found that gemifloxacin exists mainly in the Z-form. The comparative *in vitro* antibacterial activities of the Z-form and its partially resolved E-isomer (mixture of 80% E and 20% Z) were evaluated against 27 standard strains (77). Against most strains tested, the mixture showed approximately one quarter the activity of the Z-form. This indicates that the relative activity ratio of the E-form to the Z-form is about 0.06 (activity of the 80% E-form and 20% Z-form mixture =  $0.8 (0.06) + 0.2 (1.0) = 0.25$ ). These results indicate that the antibacterial activity of the E-form is about 6% of the Z-form (gemifloxacin). The geometric conformation of the methyloxime group in gemifloxacin is very important for its activity.

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### ENANTIOMERS

Gemifloxacin is a 50-50 racemic mixture of two optically active enantiomers. The activity of the partially resolved enantiomers has been compared with that of the racemate in three studies.

In an *in vitro* study, the antibacterial activities of the partially resolved mixtures ( $\pm$  ratios of 83/17 and 13/87) and the racemate ( $\pm$  ratio of 50/50) were identical against a panel of 27 Gram-positive and Gram-negative isolates (78).

In another study (79), the same partially resolved mixtures were used (50/50, 83/17, and 13/87) and no statistical difference was seen between any of these three mixtures against 82 clinical isolates.

Pure (>97%) enantiomers were tested against 95 Gram-positive and Gram-negative clinical isolates (80). The potency of the enantiomers differed by approximately 0.2 log<sub>2</sub> from each other and by 1.0 log<sub>2</sub> from the racemate. While these differences are statistically significant, they represent less than a one dilution difference between compounds and this is within the error of the assay. It can be assumed that the enantiomers are equipotent.

### METABOLITES

All fluoroquinolones undergo some metabolism in man and animals. Three of the major metabolites of gemifloxacin (i. e, the N-acetyl, O-desmethyl, and hydroxymethyl derivatives) have been synthesized. The antibacterial activity of these three compounds has been compared to that of gemifloxacin (81) against 25 Gram-positive and Gram-negative isolates including six ATCC QC organisms. All three metabolites were significantly less active than gemifloxacin. The O-desmethyl and hydroxymethyl metabolites were, on average, 16-fold less active than gemifloxacin and the N-acetyl metabolite was at least 128-fold less active than gemifloxacin.

## ANTIMICROBIAL SPECTRUM OF ACTIVITY

This section focuses on the *in vitro* activity of gemifloxacin against a broad range of organisms. The data presented are from two types of studies. The first referred to, as "*in vitro* profile studies" were conducted by investigators both within and external to SmithKline Beecham. They are based on collections of isolates, usually in limited numbers, and often containing well-characterized isolates.

The other type of study presented are large, national and international surveillance studies. A major global study, **The Global Gemifloxacin surveillance Study**, was conducted in over 17 countries and includes data on approximately 25,000 recently collected clinical isolates (1997-1999), both fastidious and non-fastidious (28). The data are presented for North America (US and Canada), Europe, and North America/Europe combined. Antimicrobial susceptibility testing was conducted on these isolates using NCCLS microbroth and disk diffusion methodology. Microbroth dilution

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methodology was performed using commercially prepared microtitre panels manufactured by Trek Diagnostics Systems, Inc. and Dade Microscan. In addition to gemifloxacin, fourteen other comparator agents were included in the panels. Five and ten microgram gemifloxacin disks were tested in most of the North American and European laboratories. International Health Management Associates, Inc., IHMA, conducted data collection and management.

Gemifloxacin was also included in another large surveillance study, the **Alexander Project**, which is an ongoing, multicenter, international surveillance study of community-acquired respiratory tract pathogens (29). Approximately 4,012 *S. pneumoniae* and 4,188 *H. influenzae* recently collected isolates (1998-1999) were collected from 23 countries and sent to one of three testing laboratories. Susceptibility testing was conducted following NCCLS guidelines. Microbroth dilution was performed using commercially prepared microtitre panels manufactured by Trek Diagnostics Systems, Inc. In addition to gemifloxacin, 22 other comparator agents were also tested. Data management was conducted by Micron research, Marmont Priory Farm, UK.

Additional susceptibility data on gemifloxacin and other quinolones for *S. pneumoniae* (n = 897), *H. influenzae* (n = 847), *M. catarrhalis* (n= 322), and approximately 4,900 other organisms was obtained from Dr. Ronald N. Jones, **Consultants in Anti-Infectives Surveillance and Testing, Inc. (CAST)** (30). The isolates were collected in 1999 from 8 sites in Europe and more than 30 sites in the U.S. All results were processed by Dr. Jones' laboratory (Iowa City, USA and selected sites in Europe) using reference NCCLS methods or by participants applying reference quality methods.

A multi-laboratory U.S. study was also conducted to determine the *in vitro* activity of gemifloxacin and five other comparators against recently collected bacterial isolates. Eleven clinical microbiology laboratories in major teaching hospitals throughout the U.S. were requested to collect approximately 320 consecutive isolates (1998-1999) to be sent to The **Clinical Microbiology Institute (CMI, Arthur L. Barry, Ph.D., Wilsonville, OR)** for central testing (31). At least 100 isolates of each of the more common species were included. A total of 5,499 isolates were tested. Broth microdilution and disk diffusion susceptibility methods were performed following NCCLS guidelines.

The data are presented using the following groups of organisms: Gram-positives, with a focus on *S. pneumoniae*; Gram-negatives, with a focus on *Haemophilus influenzae*, *H. parainfluenzae*, and *M. catarrhalis*; anaerobic organisms; and atypicals, including *Legionella pneumophila*, *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*. For *S. pneumoniae*, other Gram-positives, *H. influenzae/H. parainfluenzae/M. catarrhalis*, and other Gram-negatives, a summary of the *in vitro* profile studies, surveillance studies, and data on the isolates from the phase III clinical studies are presented.

Only *in vitro* profile study data are available for the anaerobes and the atypical isolates. These organisms were not included in the surveillance studies and they were not tested for antimicrobial susceptibility during the phase III clinical studies.

The NDA Holders letter issued January 26, 1993, states that in order to be included in the label a microorganism should be a significant (not anecdotal) pathogen at

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*Moraxella catarrhalis*

Two hundred and five *Moraxella catarrhalis* isolates were tested against gemifloxacin and comparators in an U.S. study that collected isolates from sixteen hospitals between 1999-2000 (7). Gemifloxacin had an MIC<sub>90</sub> value of 0.015 µg/mL in this study. The other quinolones had MIC<sub>90</sub>s 2 to 4 times higher. All the quinolones tested showed good activity. These data are shown in TABLE 11.

TABLE 11  
*In vitro* activity of gemifloxacin and comparators against 205  
*M. catarrhalis* isolates from U.S. hospitals (reference 7)

| Compound      | MIC range (µg/mL) | MIC <sub>50</sub> (µg/mL) | MIC <sub>90</sub> (µg/mL) |
|---------------|-------------------|---------------------------|---------------------------|
| Gemifloxacin  | 0.004-0.03        | 0.015                     | 0.015                     |
| Ciprofloxacin | 0.03-0.12         | 0.03                      | 0.06                      |
| Levofloxacin  | 0.03-0.25         | 0.03                      | 0.06                      |
| Gatifloxacin  | 0.015-0.12        | 0.03                      | 0.03                      |
| Moxifloxacin  | 0.03-0.25         | 0.06                      | 0.06                      |

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*In vitro* Activity against Resistant Strains

This section focus on the activity of gemifloxacin and other comparator quinolones against isolates of *Streptococcus pneumoniae* that are non-susceptible or resistant to one or more of the following: penicillin, erythromycin, clarithromycin, ciprofloxacin, and levofloxacin. The activity of gemifloxacin and other comparators will be discussed for *Haemophilus influenzae* strains that have two to four mutations within the quinolone resistance determining region.

*Streptococcus pneumoniae*

Penicillin non-susceptible *S. pneumoniae*

The results of three studies, two conducted in the U.S. (6,7) and one in Canada (10) are summarized in TABLE 12. These studies show that each of the tested fluoroquinolones had basically the same MIC values independent of whether the isolate is penicillin-resistant or -susceptible.

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the body site(s) or in the infection(s) for which clinical effectiveness for other pathogens has been established. Since the applicant is requesting indications of community acquired pneumonia (CAP), acute exacerbation of chronic bronchitis (AECB), \_\_\_\_\_

\_\_\_\_\_ only microorganisms usually found at these sites that may be a pathogen for these diseases will be included in the label. If the clinical picture reveals that some species are not clinically cured, they will be deleted even though the *in vitro* results demonstrate otherwise.

The proposed susceptibility breakpoint for gemifloxacin is 0.25 µg/mL, therefore, in order to be allowed in the *in vitro* list in the label the MIC<sub>90</sub> value for an organism must be ≤ 0.25 µg/mL.

The labeling submitted by the applicant includes the following organisms in the efficacy list (list #1)

**Aerobic gram-positive microorganisms**

\_\_\_\_\_  
\_\_\_\_\_

**Aerobic gram-negative microorganisms**

*Haemophilus influenzae* \_\_\_\_\_  
*Haemophilus parainfluenzae*  
*Klebsiella pneumoniae*

*Moraxella catarrhalis*

**Other microorganisms**

*Chlamydia pneumoniae*

\_\_\_\_\_  
*Mycoplasma pneumoniae*

The *in vitro* activity list with MIC<sub>90</sub> values of ≤0.25 µg/mL includes:

**Aerobic gram-positive microorganisms**

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

*Streptococcus pyogenes*

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Aerobic gram-negative microorganisms

*Acinetobacter lwoffii*  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

*Klebsiella oxytoca*  
\_\_\_\_\_  
\_\_\_\_\_

*Proteus vulgaris*  
\_\_\_\_\_  
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Anaerobic microorganisms  
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† gemifloxacin exhibits *in vitro* minimum inhibitory concentrations (MICs) of 0.5 µg/mL or less against most strains.

Each of these organisms will be discussed below along with the reason for including or excluding it from the label.

**GRAM-POSITIVE AEROBES**

This section contains an overview of the *in vitro* activity of gemifloxacin against Gram-positive aerobes. A primary indication for gemifloxacin is respiratory tract infections, therefore, there is a particular focus on *Streptococcus pneumoniae*.

*Streptococcus pneumoniae*

Gemifloxacin has very low MIC values against *Streptococcus pneumoniae*. *In vitro* studies demonstrated that the MICs of gemifloxacin were at least four-fold lower than those of comparator quinolones. *Streptococcus pneumoniae* isolates that were resistant to other quinolones had elevated gemifloxacin MICs, however, some isolates with low level resistance to other fluoroquinolones may still be susceptible to

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gemifloxacin. The following section summarizes these studies and presents the *Streptococcus pneumoniae* data from the international surveillance studies, in addition to susceptibility data from the Phase III clinical studies.

In vitro profile studies

Nine studies were conducted to determine the activity of gemifloxacin against collections of clinical isolates of *S. pneumoniae* (32,33,34,35,36,37,38,39,40). NCCLS recommended procedures were used. All studies demonstrated that gemifloxacin had the lowest MIC values. The range of MIC<sub>90</sub> values for gemifloxacin in these studies was 0.03 to 0.12 µg/mL, including penicillin-resistant isolates. Gemifloxacin also retained activity against isolates resistant to macrolides (33, 40). The gemifloxacin MIC<sub>90</sub>s were between 4 and 32-fold lower than most of the other quinolones, including trovafloxacin and levofloxacin. Only one study (32) included clinafloxacin as a comparator. Against 182 levofloxacin susceptible strains the MIC<sub>90</sub> for gemifloxacin was 0.06 µg/mL and the MIC<sub>90</sub> for clinafloxacin was 0.12 µg/mL. A summary of these results is shown in TABLE 2.

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