# Efficacy of Garenoxacin in the Treatment of Community-Acquired Pneumonia Caused by Multidrug-Resistant *Streptococcus pneumoniae*

**G. Dien,[1] J. Gaillat,[2] L. Dunbar,[3] L. Vives,[4] H. Waskin[5]**

*[1]Centre Hospitalier, Hyeres, France; [2]Centre Hospitalier, Annecy, France; [3]Louisiana State University Health Sciences Center, New Orleans, LA, USA; [4]Centre Hospitalier, Saint-Gaudens, France; [5]Schering-Plough Research Institute, Kenilworth, NJ, USA*

## Abstract

**Objectives**: Garenoxacin (GRN), a novel, broad-spectrum des-F(6)-quinolone, is active against many clinically important respiratory pathogens, including penicillin-resistant strains of *Streptococcus pneumoniae*. There is a growing problem of resistance in strains of *S pneumoniae*, with multidrug-resistant *S pneumoniae* (MDRSP) becoming increasingly more common. The objective of this study was to evaluate the clinical and microbiologic efficacy of GRN in the treatment of community-acquired pneumonia (CAP) caused by MDRSP.

**Methods**: This was a multinational, open-label, noncomparative study. Subjects were adults (≥18 and <75 y) with clinical (clinical signs, sputum production), radiologic (new infiltrates on chest radiograph), or microbiologic (predominance of Gram-positive cocci in pairs on sputum Gram stain or a positive blood culture for *S pneumoniae*) evidence of CAP caused by *S pneumoniae*. Subjects received GRN 400 mg PO QD or GRN 400 mg IV with transition to 400 mg PO QD for 7–14 days. Clinical and microbiologic responses were determined at a test-of-cure visit 7–14 days posttherapy.

**Results**: A total of 121 subjects were enrolled. Of these, 47 (17 PO only, 30 IV/PO) were clinically and microbiologically evaluable. Clinical and microbiologic success rates were 91% (43/47) and 89% (42/47), respectively. Clinical success rates were 94% (16/17) and 90% (27/30) for PO and IV/PO, respectively. Documented *S pneumoniae* bacteremia was present in 28% (n=13) of subjects with a clinical success rate of 92%. Among evaluable subjects, resistance rates for *S pneumoniae* were penicillin 13%, second-generation cephalosporin 17%, macrolides 21%, tetracyclines 21%, and trimethoprim/sulfamethoxazole 17%. Twelve evaluable subjects had pneumonia caused by MDRSP. Clinical success rate was 92% (11/12) in subjects with MDRSP and 91% (32/35) in non-MDRSP subjects. Clinical success rates with GRN for strains resistant to 2, 3, 4, or 5 antimicrobial drug classes were 100% (5/5), 100% (1/1), 100% (2/2), and 75% (3/4), respectively. Microbiologic success was 83% (10/12) and 91% (32/35) for MDRSP and non-MDRSP (susceptible or resistant to 0 or one class) strains, respectively. GRN was generally well tolerated, with drug-related adverse events reported in 14% (8/58; PO) and 21% (13/63; IV/PO) of subjects.

**Conclusions**: GRN (PO or IV/PO) is an effective treatment for CAP caused by MDRSP and non-MDRSP. GRN is well tolerated.

## Introduction and Purpose

- In many countries, multidrug-resistant *Streptococcus pneumoniae* (MDRSP) in community-acquired pneumonia is a growing problem.[1,2]
  - Worldwide surveillance from the Alexander Project (1998–2000) found that 24% of *S pneumoniae* isolates were resistant to at least three classes of antibiotics, including penicillin.[1]
- Quinolones inhibit the bacterial DNA gyrase complex and thereby interfere with bacterial DNA replication.[3]
  - Modification of the chemical structure of quinolones has led to the development of agents with improved activity against a variety of pathogens.[4]
- Garenoxacin, a novel des-F(6)-quinolone, lacks the fluorine atom found at the C-6 position of currently marketed fluoroquinolones and is being investigated for the treatment of a variety of bacterial infections, including community-acquired pneumonia.
  - Garenoxacin has a broad spectrum of activity against clinically important pathogens, including enhanced potency against Gram-positive cocci such as MDRSP.[5-7]
  - Garenoxacin also has potent activity against other pulmonary pathogens such as *Legionella pneumophila, Mycoplasma pneumoniae, Chlamydia pneumoniae,* and *Haemophilus influenzae*.[5]

### Objective

- The purpose of this study was to evaluate the clinical and microbiologic efficacy of garenoxacin 400 mg given intravenously (IV) with or without oral transition or orally (PO) in the treatment of community-acquired pneumonia caused by MDRSP.

## Methods

### Study Design

- This was a multinational, multicenter, open-label noncomparative study.
- Subjects were treated with garenoxacin 400 mg once daily administered PO or IV with or without transition to PO garenoxacin for 7–14 days.
- Subjects were enrolled at 20 sites: six in France, five in South Africa, three in Spain, three in the United States, two in Korea, and one in Taiwan.

### Inclusion Criteria

- Hospitalized or nonhospitalized subjects ≥18 and <75 years
- Subjects had clinical, radiologic, or microbiologic evidence of *S pneumoniae*–associated community-acquired pneumonia indicated by
  - At least two clinical signs and symptoms of pneumonia
  - New infiltrate on chest radiograph
  - Sputum isolate of *S pneumoniae*, purulent sputum production (>25 polymorphonuclear/low power field) with a predominance of Gram-positive cocci in pairs, or blood culture of *S pneumoniae*

### Exclusion Criteria

- Subjects with a modified Fine Risk Class[8] score >100

### Sample Collection and Susceptibility Testing

- Pretreatment sputum or blood samples were obtained for culture.
  - Two blood samples were obtained before treatment and also during and after treatment if previous blood cultures were positive.
  - Pathogens were tested according to procedures approved by the National Committee for Clinical Laboratory Standards.[9]
- Susceptibility of *S pneumoniae* was determined for garenoxacin and for five additional classes of antibiotics: 1) penicillin, 2) second-generation cephalosporins, 3) macrolides, 4) tetracyclines, and 5) trimethoprim/sulfamethoxazole.
  - Susceptibility break points for *S pneumoniae* isolates are ≤1 µg/mL for garenoxacin, ≤0.06 µg/mL for penicillin, ≤1 µg/mL for cefuroxime, ≤0.25 µg/mL for macrolides other than azithromycin (≤0.5 µg/mL), and ≤0.5 µg/mL for trimethoprim/sulfamethoxazole.

### Assessments

- Clinical and microbiologic success rates were assessed at a test-of-cure visit 7–14 days posttherapy.
- The primary efficacy analyses were based on clinically evaluable subjects, defined as those who met the following criteria:
  - Received at least 5 days of garenoxacin (at least 3 d if subject classified as a treatment failure)
  - Received no concomitant systemic antibiotics other than garenoxacin with documented activity against *S pneumoniae,* unless to treat a clinical failure
  - Received a posttreatment assessment between Day 7–14 or at the end of treatment in the case of treatment failure
- Safety was assessed based on data collected from the first day of garenoxacin therapy through 30 days following completion of study therapy.
  - Variables included adverse events and clinical laboratory tests.
  - Safety analysis was based on all subjects who received at least one dose of garenoxacin.

## Results

### Demographics

- Of the 121 subjects randomized and treated with garenoxacin (PO, n=58; IV/PO, n=63), 47 subjects were clinically evaluable (PO, n=17; IV/PO, n=30).
  - 64 subjects were clinically unevaluable because they did not have *S pneumoniae* cultured for pretreatment blood or sputum samples. An additional six subjects who had pretreatment cultures and were clinically eligible were clinically unevaluable because of inadequate dosing **(Table 1)**.

**Table 1. Subject Disposition and Reasons for Exclusion**

| | Number of Subjects (%) | | |
|---|---|---|---|
| | PO Only (N=58) | IV/PO (N=63) | Total (N=121) |
| **Clinically eligible** | 22 (38) | 32 (51) | 54 (45) |
| **Clinically ineligible (no *Streptococcus pneumoniae* culture)** | 36 (62) | 31 (49) | 67 (55) |
| **Clinically evaluable** | 17 (29) | 30 (48) | 47 (39) |
| **Clinically unevaluable** | 41 (71) | 33 (52) | 74 (61) |
| **Reason clinically unevaluable** | | | |
| Subject is clinically ineligible | 35 (60) | 29 (46) | 64 (53) |
| Inadequate dosing | 4 (7) | 2 (3) | 6 (5) |
| Investigator unable to determine clinical response | 1 (2) | 0 (0) | 1 (1) |
| Other antibiotic given | 0 (0) | 1 (2) | 1 (1) |
| Test-of-cure visit out of window | 1 (2) | 1 (2) | 2 (2) |

IV=intravenous; PO=oral.

- The median age for all subjects was 52 years.
- 78 (64%) treated subjects were men and 43 (36%) were women. 80 (66%) treated subjects were white, 29 (24%) were black, and 12 (10%) were Asian/Pacific Islander.
- The median weight was 70.0 kg.

### Subject Disposition

- Two thirds of subjects in both treatment groups had pathogens identified in pretreatment cultures **(Table 2)**.

**Table 2. Pathogens Identified in Pretreatment Cultures**

| | PO Only (n=58) | IV/PO (n=63) |
|---|---|---|
| **Number of subjects with pathogen (%)** | 38 (66) | 42 (67) |
| Single pathogen | 29 (50) | 29 (46) |
| Multiple pathogens | 9 (16) | 13 (21) |
| **Pathogens/subtypes, n [number with blood isolates]** | | |
| *Streptococcus pneumoniae* | 22 [7] | 32 [9] |
| *Haemophilus influenzae* | 11 | 5 |
| β-lactamase negative | 1 | 4 |
| β-lactamase positive | 6 | 0 |
| Unknown | 4 | 1 |
| *Moraxella catarrhalis* (β-lactamase positive) | 1 | 1 |
| *Staphylococcus aureus* | 1 | 5 [1] |
| Methicillin sensitive | 0 | 4 [1] |
| Unknown | 1 | 1 |
| *Streptococcus* (alpha hemolytic) | 4 | 4 |
| *Escherichia coli* | 1 | 2 |
| *Haemophilus parainfluenzae* | 2 | 2 |
| *Candida albicans* | 0 | 2 |

IV=intravenous; PO=oral.

- 9/58 (16%) subjects in the garenoxacin PO group and 23/63 (37%) subjects in the garenoxacin IV/PO group received pretreatment systemic antimicrobial therapy (most commonly β-lactam antibacterials) for the infection under study before treatment was given.
- 52/58 (90%) subjects in the garenoxacin PO group and 55/63 (87%) subjects in the garenoxacin IV/PO group completed treatment.
  - The most common reason for discontinuation in both treatment groups was adverse events, which was given as the reason by 5/121 (4%) subjects.

### Susceptibility Tests

- All *S pneumoniae* isolates were susceptible to garenoxacin (minimum inhibitory concentration [MIC] <1 µg/mL).
- Among isolates recovered from evaluable subjects, resistance rates for the five antibiotic classes tested were 13% for penicillin, 17% for second-generation cephalosporins, 21% for macrolides, 21% for tetracyclines, and 17% for trimethoprim/sulfamethoxazole.
- Based on $MIC_{90}$ values, >10% of isolates were resistant to each drug class except garenoxacin and levofloxacin **(Table 3)**.

**Table 3. MICs for *Streptococcus pneumoniae* Isolates**

| Resistance Drug | Number of Isolates | $MIC_{50}$ (µg/mL) | $MIC_{90}$ (µg/mL) | MIC Range |
|---|---|---|---|---|
| Penicillin | 70 | 0.03 | 2 | 0.016–4 |
| Cefuroxime | 61 | 0.12 | 4 | 0.01–16 |
| Erythromycin | 60 | 0.12 | 16 | 0.12–16 |
| Tetracycline | 60 | 0.12 | 16 | 0.12–16 |
| Trimethoprim/ sulfamethoxazole | 60 | 0.25 | 8 | 0.12–8 |
| Levofloxacin | 62 | 1 | 1 | 0.5–1 |
| Garenoxacin | 62 | 0.03 | 0.06 | 0.004–0.12 |

MIC=minimum inhibitory concentration.

- *S pneumoniae* isolates from 35 clinically evaluable subjects were either susceptible to all tested drugs or resistant to only one drug class, while 12 evaluable subjects had MDRSP isolates at baseline.
  - The prevalence of MDRSP was higher in Europe (28%) and the rest of the world (27%) than in North America (20%).

### Clinical and Microbiologic Success Rates

- Clinical success rates in clinically evaluable subjects were 94% in the garenoxacin PO group and 90% in the garenoxacin IV/PO group **(Table 4)**.

**Table 4. Clinical Response at Test-of-Cure Visit**

| Subject Group | Clinical Response | PO Only | IV/PO |
|---|---|---|---|
| Clinically evaluable | n | 17 | 30 |
| | Success, n (%) | 16 (94) | 27 (90) |
| | Failure, n (%) | 1 (6) | 3 (10) |
| | Unable to determine, n (%) | 0 | 0 |
| Clinically eligible | n | 22 | 32 |
| | Success, n (%) | 17 (77) | 29 (91) |
| | Failure, n (%) | 1 (5) | 3 (9) |
| | Unable to determine, n (%) | 4 (18) | 0 |
| All treated | n | 58 | 63 |
| | Success, n (%) | 50 (86) | 52 (83) |
| | Failure, n (%) | 3 (5) | 8 (13) |
| | Unable to determine, n (%) | 5 (9) | 3 (5) |

IV=intravenous; PO=oral.

- One subject in the garenoxacin PO group and three subjects in the garenoxacin IV/PO group were clinical failures.
  - Clinical failures were due to use of additional/alternative antibiotics (two subjects), persistence or progression of symptoms (one subject), and death due to pneumonia (one subject).
- In the garenoxacin PO group, no prognostic factor had an unequivocal effect on the clinical success rate; in the garenoxacin IV/PO group, neither age nor history of comorbid disease affected the clinical success rate **(Table 5)**.

**Table 5. Clinical Success Rates by Prognostic Factor**

| | Number Cured/Number of Subjects (%) | |
|---|---|---|
| Prognostic Factor | PO Only | IV/PO |
| **All clinically evaluable subjects** | 16/17 (94) | 27/30 (90) |
| **Subject age, y** | | |
| ≤65 | 14/15 (93) | 15/16 (94) |
| >65 | 2/2 (100) | 12/14 (86) |
| **Previous episode of pneumonia within past 12 mo (not including the current episode)** | | |
| No | 14/15 (93) | 27/30 (90) |
| Yes | 2/2 (100) | – |
| **History of comorbid disease*** | | |
| No | 14/15 (93) | 17/19 (89) |
| Yes | 2/2 (100) | 10/11 (91) |
| **Pretreatment chest radiograph reading** | | |
| Single lobe | 13/14 (93) | 18/19 (95) |
| Multiple lobes, unilateral | 1/1 (100) | 5/7 (71) |
| Bilateral | 2/2 (100) | 4/4 (100) |
| **Long-term care resident** | | |
| No | 16/17 (94) | 27/29 (93) |
| Yes | – | 0/1 (0) |

*Included at least one of the following: chronic obstructive pulmonary disorder, diabetes mellitus, congestive heart failure, or human immunodeficiency virus infection.

- 28% (n=13) of clinically evaluable subjects had documented *S pneumoniae* bacteremia, with a clinical success rate of 92% and a microbiologic success rate of 100%.
- Clinical and microbiologic success rates in evaluable subjects were ≥80% for isolates resistant to any antibiotic class **(Table 6)**.

**Table 6. Clinical and Microbiologic Success for *Streptococcus pneumoniae* by Resistance Class in Evaluable Subjects**

| Resistance Class | Clinical Success, n/N (%) | Microbiologic Success, n/N (%) |
|---|---|---|
| Penicillin | 5/6 (83) | 5/6 (83) |
| Second-generation cephalosporins | 7/8 (88) | 7/8 (88) |
| Macrolides* | 9/10 (90) | 8/10 (80) |
| Tetracyclines | 9/10 (90) | 8/10 (80) |
| Trimethoprim/sulfamethoxazole | 7/8 (88) | 7/8 (88) |

n/N=number of subjects with clinical or microbiologic success/number of evaluable subjects.
*All subjects had MDRSP with the exception of one subject with a macrolide-only–resistant pathogen.

- MDRSP caused pneumonia in 12/47 (25%) evaluable subjects. Clinical success rates for garenoxacin were generally >90% in evaluable subjects with or without MDRSP, and microbiologic success rates were >75% **(Table 7)**.

**Table 7. Clinical and Microbiologic Success for MDRSP and Non-MDRSP Isolates**

| | Clinical Success, n/N (%) | Microbiologic Success, n/N (%) |
|---|---|---|
| **MDRSP** | 11/12 (92) | 10/12 (83) |
| Resistant to 5 classes | 3/4 (75) | 3/4 (75) |
| Resistant to 4 classes | 2/2 (100) | 2/2 (100) |
| Resistant to 3 classes | 1/1 (100) | 1/1 (100) |
| Resistant to 2 classes | 5/5 (100) | 4/5 (80) |
| **Non-MDRSP** | 32/35 (91) | 32/35 (91) |
| Resistant to 1 class | 1/1 (100) | 1/1 (100) |
| Resistant to 0 classes | 31/34 (91) | 31/34 (91) |

MDRSP=multidrug-resistant *Streptococcus pneumoniae.*
n/N=number eradicated/number of pathogens.

- Clinical and microbiologic success rates were similar for the PO and IV formulations of garenoxacin in subjects with MDRSP and non-MDRSP infections **(Table 8)**.

**Table 8. Clinical and Microbiologic Success by Route of Therapy in Evaluable Subjects**

| Resistance/Formulation | Clinical Success, n/N (%) | Microbiologic Success, n/N (%) |
|---|---|---|
| **MDRSP** | | |
| PO | 6/7 (86) | 6/7 (86) |
| IV | 5/5 (100) | 4/5 (80) |
| **Non-MDRSP** | | |
| PO | 10/10 (100) | 10/10 (100) |
| IV | 22/25 (88) | 22/25 (88) |

IV=intravenous; MDRSP=multidrug-resistant *Streptococcus pneumoniae*.
n/N=number of subjects with clinical or microbiologic success/number of evaluable subjects; PO=oral.

### Safety

- Adverse events were reported in 43% (25/58) of subjects treated with PO garenoxacin and 64% (40/63) of subjects treated with IV/PO garenoxacin.
  - The most common adverse event was headache in the PO group and abnormal breath sounds in the IV/PO group **(Table 9)**.
  - Among the 58 subjects treated only with PO garenoxacin, 8 (14%) had drug-related adverse events. Among the 63 subjects treated with IV garenoxacin (with or without oral transition), 13 (21%) had drug-related adverse events.
- Hypotension was reported in 5 subjects (PO, n=1; IV/PO, n=4). Events were considered drug-related and/or serious in 3 subjects, and only 1 subject (PO group) withdrew from the study because of the event.

**Table 9. Adverse Events Occurring in ≥5% of Subjects Treated With Garenoxacin**

| Event, n (%) | PO Only (n=58) | IV/PO (n=63) |
|---|---|---|
| Headache | 4 (6.9) | 3 (4.8) |
| Abnormal breath sounds | 3 (5.2) | 8 (12.7) |
| Pneumonia worsened or led to hospitalization | 3 (5.2) | 0 |
| Sputum increased | 3 (5.2) | 4 (6.3) |
| Hypotension | 1 (1.7) | 4 (6.3) |
| Coughing | 0 | 4 (6.3) |

IV=intravenous; PO=oral.

## Conclusions

- Once-daily administration of garenoxacin 400 mg PO or IV/PO was highly effective in the treatment of community-acquired pneumonia caused by either susceptible strains of *S pneumoniae* or MDRSP.
- Isolates of MDRSP were effectively eradicated with garenoxacin.
- Garenoxacin was well tolerated in this study.

## References

1. Jacobs MR, et al. *J Antimicrob Chemother.* 2003;52(2):229-246.
2. Jones RN, et al. *J Clin Microbiol.* 2000;38(11):4298-4299.
3. Hendershot EF. *Infect Dis Clin North Am.* 1995;9(3):715-730.
4. Andersson MI, et al. *J Antimicrob Chemother.* 2003;51(suppl 1):1-11.
5. Fung-Tomc JC, et al. *Antimicrob Agents Chemother.* 2000;44(12):3351-3356.
6. Gales A, et al. *Antimicrob Agents Chemother.* 2001;45(5):1463-1466.
7. Takahata M, et al. *Antimicrob Agents Chemother.* 1999;43(5):1077-1084.
8. Fine MJ. *Int J Clin Pract Suppl.* 2000(115):14-17.
9. Performance standards for antimicrobial susceptibility testing. National Committee for Clinical and Laboratory Standards, Wayne, PA. 2005;M100-S115.

This presentation was supported by Schering-Plough Research Institute.

16th European Congress of Clinical Microbiology and Infectious Diseases
April 1–4, 2006
Nice, France