Factive® (gemifloxacin)  
NDA #21-158

FDA Advisory Committee Meeting  
March 4, 2003
Gemifloxacin
A Potent Dual Targeting Fluoroquinolone

- Potent Gram-positive activity
  (MIC$_{90}$ S.pneumoniae 0.03 µg/mL)
- Effective against quinolone-resistant respiratory pathogens
Pharmacokinetics

- Rapidly absorbed, $T_{max} = 0.5-2$ h
- 70% oral bioavailability
- $T_{1/2} = 8$ hours for once daily dosing
- Plasma protein binding = 55-65%
- No cytochrome P450 interaction
- Both renal and biliary clearance
Gemifloxacin Regulatory History

- **Oct 1997**: INDs filed
- **Dec 1999**: NDA filed (CAP, AECB, ABS, uUTI, cUTI)
- **Dec 2000**: Non approvable letter
- **Apr 2000**: Additional studies at FDA request (Study 344)
- **Oct 2002**: NDA resubmitted (CAP, AECB)
- **Mar 2003**: FDA Advisory Committee Meeting
Gemifloxacin Clinical History

- Clinical trial program 9931
- Oral 320 mg dose in phase II/III trials 6775
Indications/Dose/Treatment Durations

• Indications
  – Acute Exacerbation of Chronic Bronchitis (AECB)
  – Community Acquired Pneumonia (CAP)

• Treatment dose
  – 320 mg
  – Once daily by mouth

• Treatment durations
  – 5 days for AECB
  – 7 days for CAP
Agenda

- **Introduction**
  - **Gary Patou, MD**
    - President, GeneSoft Pharmaceuticals

- **Unmet Medical Need**
  - **Donald E. Low, MD**
    - Professor, Microbiology and Medicine, University of Toronto

- **Efficacy**
  - **Lionel A. Mandell, MD**
    - Professor of Medicine, Chief of Infectious Diseases, McMaster University

- **Safety**
  - **Gary Patou, MD**
    - President, GeneSoft Pharmaceuticals
  - **Neil H. Shear, MD**
    - Professor and Chief Dermatology, Director, Drug Safety Research Group, University of Toronto

- **Benefit/Risk and Risk Management**
  - **Gary Patou, MD**
    - President, GeneSoft Pharmaceuticals
Additional Experts

- **Project Medical Director**
  - Wayne M. Dankner, MD
    Sr. Medical Director, Parexel; Assoc. Professor, Duke University Medical Center

- **Dermatology**
  - James J. Leyden, MD
    Professor Emeritus, Department of Dermatology, University of Pennsylvania
  - Mark H. Lowitt, MD
    Vice Chairman, Department of Dermatology, University of Maryland

- **Dermatopathology**
  - Wedad Hanna, MD, FRCPC
    Chief, Dept. of Pathology, Sunnybrook and Women’s College Health Sciences Center
  - Judit Zubovits, MD, FRCP
    Dept. of Anatomic Pathology, Sunnybrook and Women’s College Health Sciences Center

- **Immunology**
  - Werner Pichler, MD
    Head, Division of Allergy, University of Bern, Switzerland

- **Hepatology**
  - James Lewis, MD
    Professor of Medicine, Director of Hepatology, Georgetown University
  - Paul Watkins, MD
    Professor of Medicine, Director, General Clinical Research Center, University of N. Carolina
Additional Experts

• Cardiology
  – Jean T. Barbey, MD
    Assistant Professor, Depts of Pharmacology and Medicine, Georgetown University Hospital

• Microbiology
  – Steve Brown, PhD
    Director, The Clinical Microbiology Institute, Wilsonville, Oregon
  – Michael Jacobs, MD, PhD
    Director, Medical Microbiology, University Hospitals of Cleveland
  – Keith Klugman, MD
    Professor of Medicine, Division of Infectious Diseases, Emory University

• Toxicology
  – John Connelly, PhD
    Former Director of Toxicology, GSK
  – Gwyn Morgan, DVM, PhD
    Former Vice President of Safety Assessment, GSK

• Pharmacokinetics
  – Edmund Capparelli, PharmD
    Associate Clinical Professor of Pediatrics, Co-Director, Pediatric Pharmacology Research Unit, University of California, San Diego
Emerging Resistance In Respiratory Pathogens

Problems and Solutions

Donald E. Low, MD
Microbiologist-in-Chief, Mount Sinai Hospital
Professor of Medicine, University of Toronto
Agenda

- Define the problem
  - emerging fluoroquinolone resistance in pneumococci

- Explain the clinical consequences

- Outline a strategy to deal with fluoroquinolone resistance
  - using the most potent fluoroquinolone
Gemifloxacin Key Attributes

- Functionally dual-targeting quinolone
- Potent *in vitro* activity and PK/PD parameters against *S. pneumoniae*
- Excellent activity against other respiratory pathogens
  - *H. influenzae* MIC$_{90}$ = 0.004-0.015 µg/mL
  - *M. catarrhalis* MIC$_{90}$ = 0.015 µg/mL
  - *M. pneumoniae* MIC$_{90}$ = 0.12 µg/mL
  - *C. pneumoniae* MIC$_{90}$ = 0.25 µg/mL
  - *L. pneumophila* MIC$_{90}$ = 0.015 µg/mL
**Defining the Problem**

*Streptococcus pneumoniae*

- Most common bacterial cause of lower respiratory tract infections
- Associated with the most significant morbidity and mortality

Growing antimicrobial resistance to

- β-Lactams
- Macrolides
- Tetracyclines
- Trimethoprim/sulfa
Fluoroquinolones

Academia and Industry Response to Antimicrobial Resistance
Penicillin Non-susceptible S. pneumoniae U.S. 1941-2001

Isolates (%)

- Resistant
- Non-susceptible

Years:
- 1941
- 1965
- 1979
- 1981
- 1984
- 1985
- 1989
- 1990
- 1993
- 1995
- 1998-99
- 1999-00
- 2000-01

First Resistance Report (24 yrs)

1st Patient Treated

References:
- Farrar GE. 1941. Clin Ther. 19891(4):555-6
Quinolone Non-susceptible S. pneumoniae
U.S. 1987-2001

MMWR, Sept 2001. 50(37):800-806
Sahm DF, et al. 2000. AAC. 44:2521-4
Cipro FDA Approved (Bayer)
First Clinical Failures Reported (4 yrs)

Resistant
Non-Susceptible

Year

Sahm DF, et al. 2001. AAC. 45:1037-42
Doern, GV et al 2001. AAC. 45:1721-9
Lee et al. 1999, NEJM.325:520-521
Levofloxacin-resistant *S. pneumoniae*
*Hong Kong 1995-2000*

Increasing Levofloxacin-resistant S. pneumoniae

Isolates (%)

<table>
<thead>
<tr>
<th></th>
<th>U.S.</th>
<th>MA</th>
<th>CO</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.8</td>
<td>4.8</td>
<td>4.6</td>
<td></td>
</tr>
</tbody>
</table>

N=10,103 isolates from 44 states and 154 cities

Clinical Implications
<table>
<thead>
<tr>
<th>Disease</th>
<th># Patients Levofloxacin Resistant</th>
<th>Patient Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Bronchitis(^1)</td>
<td>1</td>
<td>Treatment Failure</td>
</tr>
<tr>
<td>Pneumococcal Meningitis(^2)</td>
<td>1</td>
<td>Treatment Failure/Death</td>
</tr>
<tr>
<td>Hospital Acquired Pneumococcal Pneumonia(^3)</td>
<td>1</td>
<td>Treatment Failure</td>
</tr>
<tr>
<td>Community Acquired Pneumonia(^4)</td>
<td>4</td>
<td>4 Treatment Failures 1 Death</td>
</tr>
<tr>
<td>CAP, Sepsis, Meningitis(^5)</td>
<td>1</td>
<td>Treatment Failure/Death</td>
</tr>
</tbody>
</table>

5) Ross et al. NEJM 2002
Mechanism of Action of Fluoroquinolones

- Topoisomerase IV (ParC, ParE)
- DNA gyrase (GyrA, GyrB)
Development of Resistance to Fluoroquinolones

- Topoisomerase IV (ParC, ParE)
- DNA gyrase (GyrA, GyrB)
Development of Resistance to Fluoroquinolones

- Topoisomerase IV (ParC, ParE)
- DNA gyrase (GyrA, GyrB)
Development of Resistance to Fluoroquinolones

- Topoisomerase IV (ParC, ParE)
- DNA gyrase (GyrA, GyrB)
| Mutation | Levofloxacin | | Gemifloxacin | |
|----------|--------------|------------------|------------------|
| None     | 0.038 (S)    | NA               | 0.016 (S)        | NA              |

### Gemifloxacin is Functionally Dual Targeting

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Levofloxacin</th>
<th>Gemifloxacin</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>MIC</td>
<td>Increase MIC</td>
</tr>
<tr>
<td>None</td>
<td>0.038 (S)</td>
<td>NA</td>
</tr>
<tr>
<td>parC</td>
<td>1.5 (S)</td>
<td>32X</td>
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<tr>
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<td>0.75 (S)</td>
<td>20X</td>
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<tr>
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<td>NA</td>
<td>0.016 (S)</td>
<td>NA</td>
</tr>
<tr>
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<td>1.5 (S)</td>
<td>32X</td>
<td>0.064 (S)</td>
<td>4X</td>
</tr>
<tr>
<td>gyrA</td>
<td>0.75 (S)</td>
<td>20X</td>
<td>0.023 (S)</td>
<td>1.4X</td>
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</table>

**Gemifloxacin is Functionally Dual Targeting**

<table>
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<tr>
<th>Mutation</th>
<th>MIC (S)</th>
<th>Increase MIC</th>
<th>MIC (S)</th>
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<tbody>
<tr>
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<td>0.038</td>
<td>NA</td>
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<td>NA</td>
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<tr>
<td><em>parC</em></td>
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<td>0.75</td>
<td>20X</td>
<td>0.023</td>
<td>1.4X</td>
</tr>
<tr>
<td><em>parC</em> <em>gyrA</em></td>
<td>&gt;32.0</td>
<td>&gt;1000X</td>
<td>N/A</td>
<td>N/A</td>
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</tbody>
</table>

### Gemifloxacin is Functionally Dual Targeting

<table>
<thead>
<tr>
<th>Mutation</th>
<th>MIC</th>
<th>Increase MIC</th>
<th>MIC</th>
<th>Increase MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0.038 (S)</td>
<td>NA</td>
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<tr>
<td>parC</td>
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<td>4X</td>
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<td>0.75 (S)</td>
<td>20X</td>
<td>0.023 (S)</td>
<td>1.4X</td>
</tr>
<tr>
<td>parC</td>
<td>&gt;32.0 (R)</td>
<td>&gt;1000X</td>
<td>0.25 (S)</td>
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</tbody>
</table>

Reservoir of 1<sup>st</sup> & 2nd Step Mutants in Untreated Patients with Pneumococcal Pneumonia

- **Frequency of 1<sup>st</sup>-step mutations**
  - $1/10^7$

- **Frequency of 2<sup>nd</sup>-step mutations**
  - $1/10^5$

- **Number of bacteria in lung in pneumococcal pneumonia**
  - $10^{12}$ to $10^{14}$

- **Number of mutated bacteria in pneumococcal pneumonia**
  - $10^5$ – $10^7$ isolates with 1<sup>st</sup>-step mutation
  - Up to a hundred isolates with 1<sup>st</sup> and 2<sup>nd</sup> step mutation

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TB Resistance
A Precedent for Quinolone Resistance

Mutations Rendered Single-Agent Antituberculosis Therapy Useless
## Mutations Rendered Single-Agent Anti-TB Therapy Useless

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Mutation Frequency</th>
<th>Wild Type</th>
<th>Mutant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Catalase-Peroxidase</td>
<td>10^{-7}</td>
<td>0.09</td>
<td>200</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Arabinosyl transferase</td>
<td>10^{-7}</td>
<td>0.25</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Ribosomal protein S12 / 16S&lt;sub&gt;RNA&lt;/sub&gt;</td>
<td>10^{-7}</td>
<td>0.25</td>
<td>&gt;500</td>
</tr>
</tbody>
</table>

In Vitro Development of Resistance
S. pneumoniae ATCC 49619

Fold increase in MIC*

- **Trovafoxacin**
  - (Baseline MIC = 0.12 µg/mL)
- **Ciprofoxacin**
  - (Baseline MIC = 0.5 µg/mL)
- **Gemifloxacin**
  - (Baseline MIC = 0.008 µg/mL)

*Increased from initial MIC

Passage (days)
Gemifloxacin: Most Active Fluoroquinolone Against 2nd Step S. pneumoniae Mutants

Data on file, GSK
Fluoroquinolone Killing of a Quinolone-Resistant S. pneumoniae Isolate Simulating Free AUC/MIC Ratios

**In Vivo Efficacy of Gemifloxacin, Moxifloxacin and Gatifloxacin Against S. pneumoniae**

- **No treatment**
- **Gemifloxacin**
- **Moxifloxacin**
- **Gatifloxacin**

<table>
<thead>
<tr>
<th>Mutation Type</th>
<th>Log$_{10}$ CFU/Lung</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No mutation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single mutation</td>
<td></td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Double mutation</td>
<td></td>
<td>P&gt;0.05</td>
</tr>
</tbody>
</table>

P-values indicate statistical significance at the 0.05 level.
Gemifloxacin Demonstrates the Lowest MIC$_{90}$ Against *S. pneumoniae*

<table>
<thead>
<tr>
<th>MIC$_{90}$ (µg/mL)</th>
<th>Gemifloxacin</th>
<th>Moxifloxacin</th>
<th>Gatifloxacin</th>
<th>Levofloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.032</td>
<td>0.25</td>
<td>0.5</td>
<td>1.0</td>
<td></td>
</tr>
</tbody>
</table>

ICAAC 2000 [Hoban et al.-N.A. (n=1450)]
Gemifloxacin Demonstrates Comparable MIC<sub>90</sub> Against Other Respiratory Pathogens

**MIC<sub>90</sub>** (µg/mL)

- **Gemifloxacin**
- **Moxifloxacin**
- **Gatifloxacin**
- **Levofloxacin**

### Pathogens
- **H. influenzae**
- **M. catarrhalis**
- **M. pneumoniae**
- **C. pneumoniae**
- **L pneumophila**

### MIC<sub>90</sub> Values

- Gemifloxacin: 0.002, 0.004, 0.015, 0.032, 0.063, 0.125, 0.25, 0.5, 1.0, 2.0
- Moxifloxacin: 0.008, 0.016, 0.032, 0.063, 0.125, 0.25, 0.5, 1.0, 2.0
- Gatifloxacin: 0.015, 0.032, 0.063, 0.125, 0.25, 0.5, 1.0, 2.0
- Levofloxacin: 0.015, 0.032, 0.063, 0.125, 0.25, 0.5, 1.0, 2.0

### Notes

- *Data on file, GSK [2000 Alexander Project-Global (n=2764)] and [2001 Jacobs Study-US (n=290)]; **Data on file, GSK [2000 Alexander Project-Global (n=250)] and [2001 Jacobs Study-US (n=205)]; +Waites et al., ASM 2001 (n=103); #Roblin et al., AAC. 1999 (n=20); ^Yu et al., ICAAC 2000 [(n=68) all strains were L. pneumophila serogroup I].

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**U33**
Predictors of Bacterial Eradication & Clinical Efficacy

**PK/PD Profile for Quinolones**

- **AUC/MIC** - target > 25-30
- **C_{max}/MIC** - target > 10

Predictors of Bacterial Eradication & Clinical Efficacy for *M. catarrhalis*

**PK/PD Profile for Ciprofloxacin**

<table>
<thead>
<tr>
<th>Target</th>
<th>Actual</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC/MIC</td>
<td>17/0.06</td>
</tr>
<tr>
<td>$C_{\text{max}}$/MIC</td>
<td>2.1/0.06</td>
</tr>
</tbody>
</table>

Predictors of Bacterial Eradication & Clinical Efficacy for *S. pneumoniae*

**PK/PD Profile for Gemifloxacin**

<table>
<thead>
<tr>
<th></th>
<th>Target</th>
<th>Actual</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AUC/MIC</strong></td>
<td>2.9-3.8/0.03</td>
<td>&gt;25</td>
</tr>
<tr>
<td><strong>C&lt;sub&gt;max&lt;/sub&gt;/MIC</strong></td>
<td>0.56-0.72/0.03</td>
<td>&gt;10</td>
</tr>
</tbody>
</table>

Gemifloxacin has the Most Favorable Quinolone PK/PD Profile

<table>
<thead>
<tr>
<th>Free Drug</th>
<th>AUC&lt;sub&gt;24&lt;/sub&gt;/MIC&lt;sub&gt;90&lt;/sub&gt;</th>
<th>Cmax/MIC&lt;sub&gt;90&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemifloxacin (320 mg)</td>
<td>97-127</td>
<td>19-24</td>
</tr>
<tr>
<td>Moxifloxacin (400 mg)</td>
<td>96</td>
<td>9.2</td>
</tr>
<tr>
<td>Gatifloxacin (400 mg)</td>
<td>82</td>
<td>6.8</td>
</tr>
<tr>
<td>Levofloxacin (500 mg)</td>
<td>30-36</td>
<td>3.5-4.3</td>
</tr>
</tbody>
</table>

AUC and Cmax data from product prescribing information
Gemifloxacin Susceptibility in Eight Levofloxacin Treatment Failures

- All isolates obtained at baseline susceptible to gemifloxacin
- 5/8 patient’s isolates susceptible to gemifloxacin following emergence of levofloxacin resistance, isolates R and I to moxifloxacin & gatifloxacin
- Isolate from patient who died was gemifloxacin sensitive

Gemifloxacin Summary

- Excellent *in vitro* activity
- Excellent *in vivo* efficacy
- Most active against quinolone resistant strains
- Help preserve fluoroquinolone class
- Most effectively treat patients
Gemifloxacin – Efficacy Review

Lionel A. Mandell, MD, FRCPC
Professor of Medicine,
Chief, Division of Infectious Diseases
McMaster University
Infectious Diseases is the only medical specialty where the implications of treatment go far beyond the individual patient.
Agenda

- Impact of AECB and CAP
- Challenges in the treatment of AECB and CAP
- Has gemifloxacine demonstrated
  - clinical effectiveness in AECB?
  - unique / differentiable features in AECB?
  - clinical effectiveness in CAP?
  - unique / differentiable features in CAP?
Impact of Acute Exacerbation of Chronic Bronchitis (AECB)

- At least 13 million cases annually in U.S.
- *H. influenzae* and *S. pneumoniae* are major bacterial pathogens; emerging resistance now a major issue
- Up to 30% mortality rate in hospitalized patients
Impact of Community–Acquired Pneumonia (CAP)

- 3-4 million annual reported cases in US
- 600,000 hospitalizations
- 64 million days of restricted activity
- 64,000 deaths annually
- Pneumonia is seventh leading cause of death overall
- #1 cause of death from infection
Challenges in Treatment of AECB and CAP

- Increasing fluoroquinolone resistance in AECB and CAP
  - Treatment Failures
  - Deaths
- Growth in vulnerable patient population
  - Co-morbidities/co-medications
  - Need to maintain mobility & reduce hospitalization
Has Gemifloxacin Demonstrated Clinical Effectiveness in AECB?
## Gemifloxacin 320mg Demonstrated Clinical Effectiveness in AECB Non-Inferiority Trials

### Principal Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 068</td>
<td>Gemifloxacin: 5 days</td>
<td>Clarithromycin: 7 days</td>
</tr>
<tr>
<td>Study 070</td>
<td>Gemifloxacin: 5 days</td>
<td>Amoxicillin/Clavulanate: 7 days</td>
</tr>
<tr>
<td>Study 212</td>
<td>Gemifloxacin: 5 days</td>
<td>Levofloxacin: 7 days</td>
</tr>
</tbody>
</table>

### Supportive Studies

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<tr>
<th>Study</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
</tr>
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<tbody>
<tr>
<td>Study 069</td>
<td>Gemifloxacin: 5 days</td>
<td>Trovafloxacin: 5 days</td>
</tr>
<tr>
<td>Study 207</td>
<td>Gemifloxacin: 5 days</td>
<td>IV Ceftriaxone: 1-3 days</td>
</tr>
</tbody>
</table>

PO Cefuroxime: 7 days

Long-term follow-up studies: 112, 139 (068 extension)
AECB Clinical Success

Treatment Difference at Follow-Up (%; 95% CI)

PP

ITT

Gemifloxacin Better

Comparator Better

Study 068  Study 070  Study 212  Study 068  Study 070  Study 212
AECB Bacteriological Success

Treatment Difference at Follow-Up (\%; 95\% CI)

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<tbody>
<tr>
<td>Study 068</td>
<td>10 (95% CI)</td>
<td>5 (95% CI)</td>
</tr>
<tr>
<td>Study 070</td>
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<td>0 (95% CI)</td>
</tr>
<tr>
<td>Study 212</td>
<td>0 (95% CI)</td>
<td>0 (95% CI)</td>
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Gemifloxacin Better

Comparator Better
Gemifloxacin Has Demonstrated Clinical Effectiveness in AECB

- 3/3 principal studies meet non-inferiority criteria
- Equivalent to comparator in primary clinical endpoints in three principal studies (068, 070, 212)
- High bacteriologic success rates
- 5 days of gemifloxacin as effective as 7-10 days of comparators
Does Gemifloxacin Have Unique / Differentiable Features in AECB?
Gemifloxacin
Unique / Differentiable Features in AECB

- Faster bacteriological eradication than clarithromycin (study 068)
- Significantly more patients relapse-free compared to clarithromycin and trend towards fewer patients hospitalized (study 139)
- Statistically superior to IV/PO cephalosporin (study 207, ITT)
- Less time spent in hospital compared to IV/PO cephalosporin (study 207)
- Statistically superior clinical success compared to potent quinolone trovafloxacin (study 069, ITT)
Faster *H. influenzae* Eradication Compared to Clarithromycin

<table>
<thead>
<tr>
<th></th>
<th>Bacterial Persistence (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gemifloxacin x 5 days N = 12</td>
<td></td>
<td>Clarithromycin x 7 days N = 12</td>
</tr>
<tr>
<td>Day 0</td>
<td>100</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>0</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Day 2</td>
<td>0</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Day 3</td>
<td>0</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Day 4</td>
<td>0</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Day 5</td>
<td>0</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Day 6</td>
<td>0</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>
More Patients Relapse-Free with Gemifloxacin

Study 068 Extension

Patients (%)

<table>
<thead>
<tr>
<th>Week 4-5</th>
<th>Week 12</th>
<th>Week 26</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemifloxacin</td>
<td>Clarithromycin</td>
<td></td>
</tr>
<tr>
<td>87.1</td>
<td>71.0</td>
<td>58.5</td>
</tr>
<tr>
<td>80.8</td>
<td>74.4</td>
<td></td>
</tr>
<tr>
<td>80.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$p = 0.016$

$p = 0.048$ Bonferroni corrected

PO Gemifloxacin 5 Days Statistically Superior to 7-10 Days IV/PO Cephalosporins in Severe Disease (ITT)

Treatment Difference at Follow-up (%; 95% CI)

![Graph showing treatment differences in clinical and bacteriological success](image)
Statistically Significant Reduction in Median Duration of Hospitalization

<table>
<thead>
<tr>
<th></th>
<th>Gemifloxacin N = 138</th>
<th>Ceftriaxone IV / Cefuroxime PO N = 136</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Patients discharged (n)</td>
<td>120 (87.0%)</td>
<td>111 (81.6%)</td>
</tr>
<tr>
<td>Median time to discharge</td>
<td>9 days</td>
<td>11 days</td>
</tr>
<tr>
<td>p value</td>
<td>0.04</td>
<td></td>
</tr>
</tbody>
</table>

Statistically Significant Reduction in Median Duration of Hospitalization
Statistically Superior Clinical Success Compared to Trovafloxacin (ITT)

Treatment Difference at Follow-up (%; 95% CI)

Clinical Success

Gemifloxacin Better

Compared to Trovafloxacin (ITT)

Bacteriological Success

Comparator Better
Has Gemifloxacin Demonstrated Clinical Effectiveness in CAP?
### Principal Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Duration</th>
<th>Comparator</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 011</td>
<td>Gemifloxacin: 7 days</td>
<td></td>
<td>vs. Amoxicillin/Clavulanate: 10 days</td>
<td></td>
</tr>
<tr>
<td>Study 012</td>
<td>Gemifloxacin: 7 or 14 days</td>
<td></td>
<td>vs. Clarithromycin/Cefuroxime: 7 or 14 days</td>
<td></td>
</tr>
<tr>
<td>Study 049</td>
<td>Gemifloxacin: 7 or 14 days</td>
<td></td>
<td>vs. Trovafloxacin: 7 or 14 days</td>
<td></td>
</tr>
<tr>
<td>Study 185</td>
<td>Gemifloxacin: 7-14 days</td>
<td></td>
<td>vs. IV Ceftriazone 1-7 days PO Cefuroxime: 1-13 days (± Macrolide)</td>
<td></td>
</tr>
</tbody>
</table>

### Supportive Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 061*</td>
<td>Gemifloxacin: 7 days</td>
<td>(*CAP and AECB)</td>
</tr>
<tr>
<td>Study 287</td>
<td>Gemifloxacin: 7 days</td>
<td></td>
</tr>
</tbody>
</table>
## Key CAP Demographics

<table>
<thead>
<tr>
<th>Demographic/Baseline Characteristic</th>
<th>Gemifloxacin N=1349</th>
<th>Pooled Comparators N=927</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Severe/Risk Class IV-V</td>
<td>129</td>
<td>9.6%</td>
</tr>
<tr>
<td>Hospitalized Patients</td>
<td>760</td>
<td>56.3%</td>
</tr>
<tr>
<td>Bacteremic Patients</td>
<td>62</td>
<td>4.6%</td>
</tr>
<tr>
<td>Severe CAP, Hospitalized or Bacteremic</td>
<td>784</td>
<td>58.1%</td>
</tr>
<tr>
<td>Patients &gt; 65 yr</td>
<td>441</td>
<td>32.7%</td>
</tr>
</tbody>
</table>
CAP Clinical Success

Treatment Difference at Follow-Up (%; 95% CI)

- PP
- ITT

Gemifloxacin Better

Comparator Better

Study 011  Study 012  Study 049  Study 185  Pooled  Study 011  Study 012  Study 049  Study 185  Pooled
Effective Pathogen Eradication
7 Days Gemifloxacin

Eradication Rate* At Follow Up (%)

- All: 86.9, 90.9, 91.1
- S. pneumoniae: 87.8, 83.3
- H. influenzae: 88.9
- K. pneumoniae: 100.0
- M. pneumoniae: 85.2, 82.9
- C. pneumoniae: 96.9, 91.3
- L. pneumophila: 71.4

*eradicated or presumed eradicated
Gemifloxacin Has Demonstrated Clinical Effectiveness in CAP

- 3/4 principal studies meet non-inferiority criteria
Does Gemifloxacin Have Unique / Differentiable Features in CAP?
Gemifloxacin
Unique / Differentiable Features in CAP

• 7 days treatment effective for all severities of CAP

• Oral gemifloxacin as effective as IV ceftriaxone/oral cefuroxime in hospitalized patients (study 185)

• Gemifloxacin superior in head to head against potent quinolone trovafloxacin (study 049, ITT)

• Effective in eradicating PRSP, MRSP, CRSP, and ciprofloxacin non-susceptible SP
7 Days Effective in Patients with CAP

Clinical Response at Follow Up (%)

- **Controlled 7-day fixed studies**
  - Gemifloxacin: 88.7%
  - Pooled Comparators: 87.6%
- **Uncontrolled**
  - Gemifloxacin: 90.8%
  - Pooled Comparators: 90.6%
- **7 days “7-14” day studies**
  - Gemifloxacin: 91.7%
  - Pooled Comparators: 91.3%
- **8-14 days**
  - Gemifloxacin: 92.0%

FDA analysis of clinical response at follow-up by duration of therapy.
Gemifloxacin 7 Days Effective in Patients with Severe CAP (Fine Criteria)

Clinical Response at Follow Up (%)

<table>
<thead>
<tr>
<th>Duration</th>
<th>Gemifloxacin</th>
<th>Pooled Comparators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled 7-day fixed</td>
<td>100</td>
<td>90.9</td>
</tr>
<tr>
<td>Uncontrolled</td>
<td>84.6</td>
<td>96.8</td>
</tr>
<tr>
<td>7 days &quot;7-14&quot; day studies</td>
<td>91.2</td>
<td>93.3</td>
</tr>
<tr>
<td>8-14 days</td>
<td>31/34</td>
<td>32/40</td>
</tr>
</tbody>
</table>

FDA analysis of clinical response at follow-up for severe patients by duration of therapy.
Gemifloxacin 7 Days Is Effective for Hospitalized Patients

FDA analysis of clinical response at follow-up for hospitalized patients by duration of therapy:

- Controlled 7-day fixed studies: 87.4% (90/103) vs 87.4% (97/111)
- Uncontrolled: 89.8% (141/157) vs 90.2% (147/163)
- 7 days “7-14” day studies: 90.8% (118/130) vs 92.8% (142/153)
Oral Gemifloxacin as Effective as IV/PO Cephalosporin in Hospitalized Patients

Treatment Difference at Follow-up (%; 95% CI)

Clinical Success

<table>
<thead>
<tr>
<th></th>
<th>Gemifloxacin Better</th>
<th>Comparator Better</th>
</tr>
</thead>
<tbody>
<tr>
<td>PP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Bacteriological Success

<table>
<thead>
<tr>
<th></th>
<th>Gemifloxacin Better</th>
<th>Comparator Better</th>
</tr>
</thead>
<tbody>
<tr>
<td>PP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Gemifloxacin Statistically Superior to Potent Quinolone Trovafloxacin (Clinical & Radiological Response, ITT)

Treatment Difference at Follow-up (%; 95% CI)

<table>
<thead>
<tr>
<th></th>
<th>Clinical Success</th>
<th>Bacteriological Success</th>
<th>Radiological Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemifloxacin Better</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comparator Better</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Clinical Success**
  - PP: [Diagram showing data]
  - ITT: [Diagram showing data]

- **Bacteriological Success**
  - PP: [Diagram showing data]
  - ITT: [Diagram showing data]

- **Radiological Success**
  - PP: [Diagram showing data]
  - ITT: [Diagram showing data]
Gemifloxacin 7 Days Effective in Eradicating PRSP, MRSP, CRSP & Ciprofloxacin Non-susceptible SP

Clinical & Bacteriological Response at Follow Up (%)

- Penicillin Resistant: 100 (11/11)
- Macrolide Resistant: 88.2 (19/22)
- Cefuroxime Resistant: 94.4 (17/18)
- Ciprofloxacin MIC 2ug/mL: 91.7 (22/24)
- Ciprofloxacin MIC 4 ug/mL: 100 (4/4)

S. pneumoniae Strains
AECB
- Demonstrated clinical effectiveness
- Faster bacteriological eradication
- Reduced relapse rate
- Reduced duration of hospitalization
- Comparable to IV regimen

CAP
- Demonstrated clinical effectiveness
  - all severities
  - hospitalized patients
- Comparable to IV regimen
- Effective against PRSP, MRSP, CRSP & ciprofloxacin non-susceptible SP
Gemifloxacin – Safety Review

Gary Patou, MD
President, Genesoft Pharmaceuticals
Safety of Gemifloxacin

- Adverse events
- Serious adverse events
- Withdrawals
- Class effects
- Cutaneous manifestations
## Gemifloxacin

### Low Rate of Adverse Events (AEs)

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Gemifloxacin N = 6775</th>
<th>Pooled Comparators N = 5248</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>343</td>
<td>5.1</td>
</tr>
<tr>
<td>Headache</td>
<td>304</td>
<td>4.5</td>
</tr>
<tr>
<td>Nausea</td>
<td>265</td>
<td>3.9</td>
</tr>
<tr>
<td>Rash</td>
<td>241</td>
<td>3.6</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>157</td>
<td>2.3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>123</td>
<td>1.8</td>
</tr>
<tr>
<td>Dizziness</td>
<td>117</td>
<td>1.7</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>105</td>
<td>1.5</td>
</tr>
</tbody>
</table>
# Gemifloxacin

*Few Serious AEs / Few Withdrawals Due to AEs*

<table>
<thead>
<tr>
<th></th>
<th>Gemifloxacin (N = 6775)</th>
<th></th>
<th>Pooled Comparators (N = 5248)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Serious adverse experiences (SAE)</td>
<td>247</td>
<td>3.6</td>
<td>228</td>
</tr>
<tr>
<td>SAE of rash</td>
<td>7</td>
<td>0.1</td>
<td>1</td>
</tr>
<tr>
<td>Withdrawal due to AE</td>
<td>264</td>
<td>3.9</td>
<td>226</td>
</tr>
<tr>
<td>Withdrawal due to treatment-related AE</td>
<td>152</td>
<td>2.2</td>
<td>109</td>
</tr>
<tr>
<td>Deaths</td>
<td>33</td>
<td>0.5</td>
<td>30</td>
</tr>
</tbody>
</table>
Quinolone Class Effects
Gemifloxacin

*Minimal Class Effects*

- Antacid and sucralfate interactions only
- Low phototoxicity
- No dysregulation of glucose homeostasis
Effects on the QTc Interval

QTc prolongation (ms ± SD)

- Moxifloxacin: 6.0 ± 26†
- Levofloxacin: 4.6 ± 23‡
- Gatifloxacin: 2.9 ± 16.5†
- Gemifloxacin: 2.6 ± 24.5

Hepatic Safety
Analyses

- Patients with pretreatment normal ALT
- Patients with pretreatment elevated ALT
- Patients reporting adverse events
  - Hepatic related AEs in patients with underlying liver disease
- Independent reviews
  - Paul Watkins, MD, University of North Carolina
  - James Lewis, MD, Georgetown University
Gemifloxacin 320 mg Elevated ALT Values on Therapy:
Patients with Pretreatment Normal ALT Values

<table>
<thead>
<tr>
<th>Range</th>
<th>Gemifloxacin N=3989</th>
<th>All Comparators N=3588</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>&lt;ULN</td>
<td>3800</td>
<td>95.3</td>
</tr>
<tr>
<td>ULN-&lt;2xULN</td>
<td>162</td>
<td>4.1</td>
</tr>
<tr>
<td>2 to &lt;4xULN</td>
<td>26</td>
<td>0.7</td>
</tr>
<tr>
<td>4 to &lt;6xULN</td>
<td>1</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>6 to &lt;8xULN</td>
<td>0</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>≥8xULN</td>
<td>0</td>
<td>&lt;0.1</td>
</tr>
</tbody>
</table>
## Gemifloxacin 640 mg Elevated ALT Values on Therapy

### Patients with Pretreatment Normal ALT Values

<table>
<thead>
<tr>
<th>Range</th>
<th>Gemifloxacin N=592</th>
<th>Ciprofloxacin N=606</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n$</td>
<td>$%$</td>
</tr>
<tr>
<td>&lt;ULN</td>
<td>569</td>
<td>96.1</td>
</tr>
<tr>
<td>ULN-&lt;2xULN</td>
<td>14</td>
<td>2.4</td>
</tr>
<tr>
<td>2 to &lt;4xULN</td>
<td>4</td>
<td>0.7</td>
</tr>
<tr>
<td>4 to &lt;6xULN</td>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td>6 to &lt;8xULN</td>
<td>3</td>
<td>0.5</td>
</tr>
<tr>
<td>$\geq$8xULN</td>
<td>1</td>
<td>0.2</td>
</tr>
</tbody>
</table>
Clinical Trial Signals Used to Predict Potential for Serious Hepatotoxicity

• Criteria for signals
  – “Hy’s rule (law)”
    • Hepatocellular jaundice (bilirubin $\geq 3.0$ mg/dL + very high serum ALT) due to drug administration
    • Eosinophilia associated with elevated ALT

• Database search parameters
  – Bilirubin $\geq 1.5$ mg/dL + ALT $\geq 2x$ ULN
  – Cases further reviewed by expert hepatologists
### No Treatment Emergent Signals for Serious Hepatotoxicity

**Signals**
- **Hy’s rule**: 0 0
- **Eosinophilia + elevated ALT**: 0 0

**Database search parameters**
- **Bilirubin ≥ 1.5 mg/dL + ALT ≥ 2x ULN**: 2 0
# Elevated ALT Values on Therapy

*Patients with Pretreatment Elevated ALT Values*

<table>
<thead>
<tr>
<th>Range</th>
<th>Gemifloxacin 320mg N=329</th>
<th>All Comparators N=255</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>&lt;ULN</td>
<td>101</td>
<td>30.7</td>
</tr>
<tr>
<td>ULN-&lt;2xULN</td>
<td>144</td>
<td>43.8</td>
</tr>
<tr>
<td>2 to &lt;4xULN</td>
<td>67</td>
<td>20.4</td>
</tr>
<tr>
<td>4 to &lt;6xULN</td>
<td>11</td>
<td>3.3</td>
</tr>
<tr>
<td>6 to &lt;8xULN</td>
<td>3</td>
<td>0.9</td>
</tr>
<tr>
<td>≥8xULN</td>
<td>3</td>
<td>0.9</td>
</tr>
</tbody>
</table>
### Change in ALT Values at Either on Therapy or End of Therapy Visit

**Patients with Pretreatment Elevated ALT Values**

<table>
<thead>
<tr>
<th>Pretreatment Abnormal ALT Values (N = 94)</th>
<th>Change from Baseline*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 to &lt;4x ULN=78</td>
<td><strong>Decrease</strong> 48%</td>
</tr>
<tr>
<td>4 to &lt;6x ULN=8</td>
<td>45%</td>
</tr>
<tr>
<td>6 to &lt;8x ULN=3</td>
<td><strong>Increase (n=6)</strong> 7%</td>
</tr>
<tr>
<td>≥ 8x ULN=5</td>
<td>4%</td>
</tr>
</tbody>
</table>

* Change to another range as shown in †

---

**On Therapy**
- Decrease: 48%
- No change: 45%
- Increase: 7%

**End of Therapy**
- Decrease: 80%
- No change: 16%
- Increase: 4%
## 6 Patients with Further Increase in ALT on Treatment

### Patients with Pretreatment Elevated ALT Values

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Lab Test</th>
<th>Pre-treatment</th>
<th>On Therapy</th>
<th>End of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>11737</td>
<td>ALT</td>
<td>149</td>
<td>262</td>
<td>236</td>
</tr>
<tr>
<td></td>
<td>Bilirubin</td>
<td>0.59</td>
<td>0.53</td>
<td>0.41</td>
</tr>
<tr>
<td>09311</td>
<td>ALT</td>
<td>122</td>
<td>151</td>
<td>279</td>
</tr>
<tr>
<td></td>
<td>Bilirubin</td>
<td>0.65</td>
<td>0.53</td>
<td>0.65</td>
</tr>
<tr>
<td>05037</td>
<td>ALT</td>
<td>125</td>
<td>315</td>
<td>107</td>
</tr>
<tr>
<td></td>
<td>Bilirubin</td>
<td>1.0</td>
<td>0.53</td>
<td>0.53</td>
</tr>
<tr>
<td>10594</td>
<td>ALT</td>
<td>185</td>
<td>211</td>
<td>342</td>
</tr>
<tr>
<td></td>
<td>Bilirubin</td>
<td>1.0</td>
<td>0.65</td>
<td>0.59</td>
</tr>
<tr>
<td>10597</td>
<td>ALT</td>
<td>127</td>
<td>193</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>Bilirubin</td>
<td>1.0</td>
<td>0.88</td>
<td>0.59</td>
</tr>
<tr>
<td>13830</td>
<td>ALT</td>
<td>110</td>
<td>501</td>
<td>132</td>
</tr>
<tr>
<td></td>
<td>Bilirubin</td>
<td>0.59</td>
<td>0.59</td>
<td>0.47</td>
</tr>
</tbody>
</table>
No Hepatic AEs of Clinical Concern In Patients with Underlying Liver Disease

- AEs related to laboratory LFT abnormalities, not clinical findings
  - Patients were reviewed in extensive biochemical analyses previously described
  - None had symptoms of treatment-emergent hepatic disease
  - Withdrawal rate lower in gemifloxacin group (8%) vs. comparators (16%)
Hepatic SAEs

- Reported in 4 gemifloxacin treated subjects
- All from unblinded study 185
- All reported as laboratory LFT abnormalities
- All asymptomatic
- All reviewed in extensive biochemical analyses previously described
- None met criteria for Hy’s rule
**Summary**

**No Hepatic Safety Concern**

- **320 mg dose** devoid of defined signals predictive of serious hepatotoxicity potential
  - No subject met criteria for treatment-emergent Hy’s rule
  - No signals of acute liver failure or irreversible injury
  - No evidence of hypersensitivity reaction

- **640 mg dose** does not raise significant safety concerns about 320 mg dose

- **No evidence** that gemifloxacin treatment in patients with preexisting liver disease represents a liver safety concern
Gemifloxacin

Cutaneous Manifestations

Neil H. Shear, MD, FRCPC, FACP
Professor and Chief Dermatology and Director,
Drug Safety Research Group, University of Toronto
Agenda

• Evaluation of drug rashes in general

• Observations of rash in gemifloxacin clinical trials

• Study 344 (done to characterize rash)
  – Landmark safety study
  – Enriched study population
  – Determined rash not an indicator of concern

• Interpretation of data
  – Higher rash rate vs. comparators
  – Observed rash is benign
  – Cross-reactivity rates are low
Rash Diagnostic Triangle

Appearance

Systemic

Histology

RASH DIAGNOSTIC TRIANGLE
Drug-related Rashes – A Primer

Amoxicillin | Aspirin | Isoniazid | Tetracycline

- Amoxicillin
- Aspirin
- Isoniazid
- Tetracycline
Rash Morphology – A Primer

- Exanthem
- Urticarial
- Pustular
- Blistering
Rash Morphology – A Primer

<table>
<thead>
<tr>
<th>Exanthem</th>
<th>Urticarial</th>
<th>Pustular</th>
<th>Blistering</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity Syndrome Reaction (HSR)</td>
<td>Serum Sickness-Like Reaction (SSLR)</td>
<td>Acute Generalized Exanthematous Pustulosis (AGEP)</td>
<td>Stevens-Johnson/Toxic Epidermal Necrolysis (SJS / TEN)</td>
</tr>
</tbody>
</table>

+ Fever with systemic involvement = 

+ Fever with systemic involvement = 

Hypersensitivity Syndrome Reaction (HSR) | Serum Sickness-Like Reaction (SSLR) | Acute Generalized Exanthematous Pustulosis (AGEP) | Stevens-Johnson/Toxic Epidermal Necrolysis (SJS / TEN) |
Important Cutaneous Drug Reactions – A Primer

- **Angioedema**
  - Swelling of face and lips
  - Hypotension
  - Wheezing

- **Hypersensitivity syndrome reaction**
  - Fever
  - Lymphadenopathy
  - Swollen face

- **Stevens-Johnson syndrome / Toxic epidermal necrolysis**
  - Cutaneous blistering
  - Hemorrhagic crusting of mucosa
Relationship of Hypersensitivity Syndrome Reaction (HSR) to SJS / TEN

- Pathogenesis for HSR and SJS / TEN
  - Shared for many drugs (cotrimoxazole, phenytoin, carbamazepine, lamotrigine)
  - Predominant CD8+ cell infiltrate in skin

- HSR for phenytoin & carbamazepine is 1/3000

- SJS / TEN incidence for phenytoin & carbamazepine is 1/10000

- HSR is a potential harbinger of SJS / TEN
Histology of Stevens-Johnson / TEN
Rash Diagnostic Triangle

Appearance

Systemic

Histology

RASH DIAGNOSTIC TRIANGLE
# Rash Characteristics in Clinical Trials

<table>
<thead>
<tr>
<th></th>
<th>Gemifloxacin N = 6775</th>
<th>Pooled Comparators N = 5248</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevalence</strong></td>
<td>3.6 %</td>
<td>1.1 %</td>
</tr>
<tr>
<td><strong>Median onset</strong></td>
<td>9 days</td>
<td>4 days</td>
</tr>
<tr>
<td><strong>Median duration</strong></td>
<td>5 days</td>
<td>4 days</td>
</tr>
<tr>
<td><strong>Longest duration</strong></td>
<td>&gt; 30 days</td>
<td>&gt; 30 days</td>
</tr>
<tr>
<td><strong>Withdrawals due to rash</strong></td>
<td>0.9 %</td>
<td>0.3 %</td>
</tr>
<tr>
<td><strong>Cutaneous SAEs</strong></td>
<td>0.1%</td>
<td>&lt; 0.1%</td>
</tr>
<tr>
<td><strong>Severity: Mild/Moderate/Severe</strong></td>
<td>1.8 / 1.3 / 0.5%</td>
<td>0.6 / 0.4 / 0.1%</td>
</tr>
</tbody>
</table>
### 7 Rash SAEs in Gemifloxacin Clinical Trials (N=6775)

<table>
<thead>
<tr>
<th>Patient Description</th>
<th>Center Location</th>
<th>Reason for Seriousness</th>
<th>Comments</th>
</tr>
</thead>
</table>
| 18 yr male  
7 days dosing  
ABS | Hungary | Hospitalization | Tested positive for mono: “Rash probably associated with underlying mononucleosis and drug.” |
| 24 yr female  
8 days dosing  
ABS | Poland | Hospitalization | Treated with steroid and antihistamine. Recovered by day three. |
| 52 yr female  
9 days dosing  
ABS | Poland | Hospitalization | Mild rash. No medical reason for hospitalization but patient required reassurance. |
| 60 yr female  
8 days after 1st dose  
UTI | Poland | Hospitalization | Treated with steroid, antihistamine and calcium. Recovered within 7 days. |

ABS = acute bacterial sinusitis, UTI = urinary tract infection
### 7 Rash SAEs in Gemifloxacin Clinical Trials (N=6775) - Cont.

<table>
<thead>
<tr>
<th>Patient Description</th>
<th>Center Location</th>
<th>Reason for seriousness</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>87 yr male 7 days dosing CAP</td>
<td>Canada</td>
<td>Investigator judgment</td>
<td>Rash 48 hours post therapy; asymptomatic, afebrile. Rash began fading in 2 days without intervention.</td>
</tr>
<tr>
<td>72 yr male 2 days dosing AECB</td>
<td>Netherlands</td>
<td>Investigator judgment</td>
<td>Allergic to gold and penicillin. Receiving 8 co-medications. Treated with antihistamin. Rash resolving at day 18.</td>
</tr>
<tr>
<td>42 yr female 4 days dosing ABS</td>
<td>USA</td>
<td>Investigator judgment</td>
<td>Serum Sickness. Onset 13 days after last dose. CXR infiltrate in RLL, serological diagnosis of acute mycoplasma pneumoniae infection. Largely resolved after 15 days.</td>
</tr>
</tbody>
</table>
## Quinolone Rechallenge Data

<table>
<thead>
<tr>
<th>Previous exposure</th>
<th>Total Exposed</th>
<th>Number Reporting Rash On Rechallenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous exposure to another quinolone</td>
<td>181</td>
<td>3</td>
</tr>
<tr>
<td>Previous exposure to gemifloxacin with no rash</td>
<td>41</td>
<td>0</td>
</tr>
<tr>
<td>Subsequent exposure to another quinolone after gemifloxacin rash</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>
## Frequency Distributions of Rash

### Gemifloxacin

<table>
<thead>
<tr>
<th>Gender</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 yrs</td>
<td>6.7%</td>
<td>4.7%</td>
</tr>
<tr>
<td>≥40 yrs</td>
<td>2.5%</td>
<td>1.1%</td>
</tr>
<tr>
<td>5 days</td>
<td>1.2%</td>
<td>0.9%</td>
</tr>
<tr>
<td>7 days</td>
<td>5.3%</td>
<td>1.1%</td>
</tr>
<tr>
<td>10 days</td>
<td>6.4%</td>
<td>1.1%</td>
</tr>
<tr>
<td>14 days</td>
<td>7.4%</td>
<td>2.9%</td>
</tr>
</tbody>
</table>

### Pooled Comparators

<table>
<thead>
<tr>
<th>Gender</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>0.8%</td>
</tr>
<tr>
<td>Females</td>
<td>1.4%</td>
</tr>
<tr>
<td>&lt;40 yrs</td>
<td>1.3%</td>
</tr>
<tr>
<td>≥40 yrs</td>
<td>1.1%</td>
</tr>
<tr>
<td>5 days</td>
<td>0.9%</td>
</tr>
<tr>
<td>7 days</td>
<td>1.1%</td>
</tr>
<tr>
<td>10 days</td>
<td>1.1%</td>
</tr>
<tr>
<td>14 days</td>
<td>2.9%</td>
</tr>
</tbody>
</table>

**N = 6775**

**N = 5248**

**CLINICAL TRIALS**
Highest Risk Group
Women <40 yr Treated for >7 Days

Rash rate in women < 40 treated for 10 days

- Gemifloxacin: 15.3%
- Comparators: 1.9%
Objectives for Phase I Dermatology Safety Study

To assess, in an enriched population, with extended dosing:

- Clinical and histological features of drug rash
- Cross-sensitization potential with ciprofloxacin
- Sub-clinical sensitization potential
- Potential relationship between plasma levels of gemifloxacin, N-acetyl gemifloxacin and rash
PART A

Females 18-40 Yrs

(5:1)

10 days gemifloxacin
320mg daily

Rash

No Rash

10 days ciprofloxacin
500mg bid

Rash

No Rash
Study Design

PART A

Females 18-40 Yrs

10 days gemifloxacin
320mg daily

Rash
No Rash

(5:1)

10 days ciprofloxacin
500mg bid

Rash
No Rash

4-6 week wash-out period

PART B

(3:1)

(1:1)

ciprofloxacin
placebo
gemifloxacin
placebo
placebo
ciprofloxacin

Cross-sensitization potential
Sub-Clinical sensitization potential
Baseline
Key Evaluation Criteria

- **Skin**
  - Board-certified dermatologist examined clinical rash within 24 hrs
  - Rash photographed
  - 3 biopsies from rash and 3 from non-rash sites

- **Blood and urine sampling**
  - Drug levels
  - Clinical chemistry including liver function tests
  - Standard hematology including eosinophils
  - EBV screen

- **12 Lead ECG** taken pre dose and 2 hrs post dose Day 1
Histology, Pharmacokinetics and Photographic Data

- **Histology review**
  - 288 subjects biopsied from parts A and B
    - 576 histology slides
  - 2,880 immunofluorescence slides
    - IgG, A, M and C3 plus negative and positive controls
  - 4,032 immunohistochemistry slides

- **Population pharmacokinetic analysis**
  - 7943 gemifloxacin plasma concentration-time data
  - 7934 N-acetyl gemifloxacin plasma concentration-time data

- **Photographic data**
  - 300 subjects with photographic records
Outcome for Part A

**PART A**

- **Females 18-40 Yrs**
  - 10 days gemifloxacin 320mg daily
  - Rash
  - No Rash

**PART B**

- ciprofloxacin
- placebo
- Cross-sensitization potential

- gemifloxacin
- placebo
- Sub-Clinical sensitization potential

- placebo
- ciprofloxacin
- Baseline

# (% with rash) for Part A:
- Rash: 260 (31.7)
- No Rash: 7 (4.3)

4-6 week wash-out period
Majority of Rashes Occur Days 8-10

% of Subjects with Rash (N = 260)

Day of onset

Treatment Period
Rash Morphology

Appearance

Average

Worst
Reported Cases of Severe Rash
Reported Cases of Severe Rash
Reported Cases of Severe Rash
Reported Cases of Severe Rash
Reported Cases of Severe Rash
# No Angioedema

<table>
<thead>
<tr>
<th>Sign Or Symptom</th>
<th>Patients</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Urticaria”</td>
<td>25</td>
<td>Time of onset and duration similar to other rashes; biopsy findings similar to non urticarial subjects</td>
</tr>
<tr>
<td>Facial edema</td>
<td>11</td>
<td>All but two had maculopapular rash on face. With 2 exceptions (one subject urticaria and another with diarrhea) none had any other symptoms indicating a type I reaction</td>
</tr>
</tbody>
</table>
### No SJS/TEN
### No Hypersensitivity Syndrome

**Systemic**

#### Diagnostic Triangle
- **Appearance**
- **Histology**

#### Study 344

<table>
<thead>
<tr>
<th>Sign Or Symptom</th>
<th>Patients</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucosal involvement</td>
<td>15</td>
<td>Dry mouth or eyes, macular erythema on lips and aphthous buccal ulcers, no hemorrhagic blistering</td>
</tr>
<tr>
<td>Wheezing</td>
<td>1</td>
<td>No other symptoms possibly indicating a Type I reaction</td>
</tr>
<tr>
<td>Fever with rash</td>
<td>6</td>
<td>One associated with lymphadenopathy; none associated with other systemic symptoms</td>
</tr>
</tbody>
</table>
No Other Markers of Systemic Involvement

- No clinically significant rise in serum transaminases and no association with rash

<table>
<thead>
<tr>
<th></th>
<th>Rash N=260</th>
<th>No Rash N=559</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Alk Phos</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AST</td>
<td>0</td>
<td>2 (0.4%)</td>
</tr>
<tr>
<td>Total Bilirubin</td>
<td>2 (0.8%)</td>
<td>4 (0.7%)</td>
</tr>
<tr>
<td>GGT</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- No significant changes in eosinophil counts
Histopathology

Slide R01 128-14:
Mild lymphocytic infiltrate
278 of 288

Slide R01 121-97:
Moderate superficial & deep infiltrate
10 of 288
Pathology Consistent with Mild Exanthematous Eruption

- Mild superficial perivascular lymphocytic infiltrate
- 10 biopsies showed a denser infiltrate
- Inflammatory infiltrate was composed of lymphocytes
- Mixed CD4 and CD8 population
- No erythema multiforme
- No epidermal necrosis
- No vasculitis
Evaluation of Sensitization Potential

**PART A**

**Females 18-40 Yrs**

- 10 days gemifloxacin 320mg daily
- 10 days ciprofloxacin 500mg bid

**PART B**

<table>
<thead>
<tr>
<th></th>
<th>ciprofloxacin</th>
<th>placebo</th>
<th>gemifloxacin</th>
<th>placebo</th>
<th>placebo</th>
<th>ciprofloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td># with rash</td>
<td>15 (8)</td>
<td>2 (1)</td>
<td>8 (6)</td>
<td>7 (5)</td>
<td>0</td>
<td>7 (5)</td>
</tr>
<tr>
<td>% with rash</td>
<td>10.4% (5.9%)</td>
<td>3.9% (2.0%)</td>
<td>3.2% (2.4%)</td>
<td>2.7% (2.0%)</td>
<td></td>
<td>4.9% (3.5%)</td>
</tr>
</tbody>
</table>

4-6 week wash-out period
Cross Sensitization Potential

**PART A**

Females 18-40 Yrs

10 days gemifloxacin
320mg daily

Rash

4-6 week wash-out period

**PART B**

(3:1)

ciprofloxacin  placebo

<table>
<thead>
<tr>
<th># with rash</th>
<th>15 (8)</th>
<th>2 (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% with rash</td>
<td>10.4% (5.9%)</td>
<td>3.9% (2.0%)</td>
</tr>
</tbody>
</table>
PART A

Females 18-40 Yrs

10 days gemifloxacin
320mg daily

No Rash

4-6 week wash-out period

PART B

(1:1)

gemifloxacin placebo

# with rash
8 (6) 7 (5)

% with rash
3.2% (2.4%) 2.7% (2.0%)
Evaluation of Sensitization Potential

**PART A**

Females 18-40 Yrs

- 10 days ciprofloxacin
  - 500mg bid

- Rash
- No Rash

4-6 week wash-out period

**PART B**

- Placebo
- Ciprofloxacin

| # with rash | 0 | 7 (5) |
| % with rash | 0% | 4.9% (3.5%) |
Part B Summary

• Low cross-sensitization

• No evidence of sub-clinical sensitization

• Rashes in Part B tended to be
  – earlier onset
  – shorter duration
  – mild
  – affecting <10% of body surface area
  – similar to ciprofloxacin associated rash in Part A
Summary Study 344

• 10 day exposure in women under age 40

• Rash rate of 31.7%

• No cases of hypersensitivity syndrome
  – 1 case of fever and lymphadenopathy

• No cases of SJS / TEN
  – 1 case of buccal aphthae

• Rash was clinically and pathologically an exanthem
Summary Patient Trial Data

- Rate of rash in 6775 subjects was 3.6% overall
- Rate of rash in women under 40, using 10 days of treatment was 15.3%
- 1 case suggestive of serum sickness-like reaction
- No angioedema
- No Stevens-Johnson / TEN
- No hypersensitivity syndrome
Interpretation

Gemifloxacin Associated Rash

- Rash Rate = 3.6% in overall patient population
- Highest risk group identified as women under 40
- The observed rash is benign by multiple measures
- Well characterized in landmark drug rash safety study
- No HSR or SJS / TEN in ~10,000 exposures at all doses
- Low sensitization potential
Gemifloxacin Safety Summary

- No liver or clinically significant QTc problems
- Rash rate in CAP (4.7%) and AECB (1.5%) greater than controls but:
  - No evidence of significant morbidity
  - Low rate of cross sensitization
  - No sub-clinical sensitization
Gemifloxacin Benefit/Risk
Current AECB & CAP
Treatment Choices

- Antibiotic resistance → dependence on newer fluoroquinolones
- Increasing fluoroquinolone resistance
- Limitations of current fluoroquinolones
  - Gatifloxacin “life threatening hyperosmolar coma” †
  - Moxifloxacin “QTc prolongation warning” †
  - Levofloxacin “pneumococcal pneumonia treatment failure” ‡
- Gemifloxacin can help fill unmet medical need

Gemifloxacin Benefit/Risk

- Potent, with favorable PK/PD
  - Shorter therapy courses
  - Less resistance pressure

- Active against resistant (including quinolone-resistant) organisms
  - Effective empiric treatment choice

- Beneficial beyond acute treatment period
  - Reduced AECB relapse rates
  - Reduced duration of hospitalization
Gemifloxacin Benefit/Risk

- High oral bioavailability
  - As effective orally as IV/oral switch comparator regimens in AECB & CAP

- No significant drug-drug interactions
  - CAP & AECB comprised of large numbers of elderly patients, many on co-medications

- Both renal and biliary clearance
  - No dosage adjustment in hepatic or mild-to-moderate renal impairment
Gemifloxacin Benefit/Risk

• Good AE profile

• Well tolerated/low withdrawal rates

• Quinolone class effects
  – No hepatic safety signal
  – Short QTc prolongation (2.6 msec)

• Overall rash rate 3.6%

• Rash characteristics
  – Typical mild drug rash
  – Rate higher in sub-population
  – No evidence of significant morbidity
  – Low sensitization potential
Gemifloxacin Risk Management

- Target label population (AECB and CAP patients) predominantly over 40 years old
- Short treatment course minimizes incidence of rash
- Fixed dosage packs: 5 or 7 days only
- Clinical program including study 344 demonstrates that rash is clinically manageable
- Adverse experiences described in package insert
- Physician education
- Active pharmacovigilance Phase IV study
Conclusions

- Gemifloxacin in AECB and CAP is a critically needed addition to physicians’ armamentarium
### Odds ratios and 95% Confidence Intervals for the Effects of OC Use in the Model Containing Planned Duration of therapy, Age and Country group as Explanatory Variables

<table>
<thead>
<tr>
<th>Explanatory Variable</th>
<th>Value</th>
<th>Odds Ratio (95% CI)</th>
<th>Likelihood Ratio Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>DF</td>
</tr>
<tr>
<td>OC use*</td>
<td>Yes</td>
<td>1.491 (0.892 – 2.492)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>1.000</td>
<td></td>
</tr>
</tbody>
</table>

*results obtained from model using only females who were younger than 40 years
### Odds ratios and 95% confidence intervals for the effects of HRT use in the model containing planned duration of therapy, age and country group as explanatory variables

<table>
<thead>
<tr>
<th>Explanatory Variable</th>
<th>Value</th>
<th>Odds Ratio (95% CI)</th>
<th>Likelihood Ratio Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>DF</td>
</tr>
<tr>
<td>HRT use*</td>
<td>Yes</td>
<td>1.900 (1.122 – 3.217)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>1.000</td>
<td></td>
</tr>
</tbody>
</table>

*results obtained from model using only females who were younger than 40 years
## Demographic Characteristics of Study Population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>Height (m)</th>
<th>Race</th>
<th>Skin Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1011</td>
<td>1011</td>
<td>1011</td>
<td>White: 929</td>
<td>I: 76</td>
</tr>
<tr>
<td>Mean</td>
<td>28</td>
<td>64.4</td>
<td>165.7</td>
<td>Black: 2</td>
<td>II: 218</td>
</tr>
<tr>
<td>SD</td>
<td>6.2</td>
<td>9.0</td>
<td>6.9</td>
<td>Other: 11</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>18–40</td>
<td>44.8–96.6</td>
<td>141.0–187.0</td>
<td>Oriental: 20</td>
<td>III: 478</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hispanic: 49</td>
<td>IV: 239</td>
</tr>
</tbody>
</table>
Rash Not Related to Drug Levels

- No relationship between serum concentrations of gemifloxacin or its N-acetyl metabolite and occurrence of rash

![AUC graph showing no relationship between rash and drug levels](image_url)
Number of Days After Therapy When Rash Started
Clinical Trial Population

% of Patients with Rash after Therapy

<table>
<thead>
<tr>
<th>No. Days After Therapy</th>
<th>Gemifloxacin</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
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</tr>
<tr>
<td>6</td>
<td>5</td>
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<td>30</td>
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</table>
## Study 139 – Clinical & Smoking History (ITT)

<table>
<thead>
<tr>
<th>Clinical/Smoking History</th>
<th>Treatment Group</th>
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<tbody>
<tr>
<td></td>
<td>Gemifloxacin 320mg od N=214</td>
</tr>
<tr>
<td></td>
<td>Clarithromycin 500mg bid N=224</td>
</tr>
<tr>
<td>Duration of Chronic Bronchitis (year)</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>213</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>12.7 (12.1)</td>
</tr>
<tr>
<td>Range</td>
<td>2.0 – 65.1</td>
</tr>
<tr>
<td></td>
<td>224</td>
</tr>
<tr>
<td></td>
<td>12.4 (11.4)</td>
</tr>
<tr>
<td></td>
<td>1.8 – 66.2</td>
</tr>
<tr>
<td>Number of Exacerbations Treated with Antibacterials in Last Year, n(%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>41 (19.2)</td>
</tr>
<tr>
<td>1 to 4</td>
<td>143 (66.8)</td>
</tr>
<tr>
<td>&gt; 4</td>
<td>29 (13.6)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (0.5)</td>
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<tr>
<td></td>
<td></td>
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<tr>
<td>Use of Supplemental Oxygen, n(%)</td>
<td></td>
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<tr>
<td>Yes</td>
<td>21 (9.8)</td>
</tr>
<tr>
<td></td>
<td>14 (6.3)</td>
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<tr>
<td>Use of Systemic Steroids in Last Year, n(%)</td>
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<tr>
<td>Yes</td>
<td>54 (25.2)</td>
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<tr>
<td></td>
<td>55 (24.6)</td>
</tr>
<tr>
<td>Number of Pack Years Patient Has Smoked</td>
<td></td>
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<tr>
<td>0</td>
<td>34 (15.9)</td>
</tr>
<tr>
<td>&gt;0 to 30</td>
<td>88 (41.1)</td>
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<tr>
<td>&gt;30</td>
<td>91 (42.5)</td>
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<tr>
<td>Unknown</td>
<td>1 (0.5)</td>
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<tr>
<td>Smoked in Last Month, n(%)</td>
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<tr>
<td>Yes</td>
<td>95 (44.4)</td>
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<tr>
<td></td>
<td>107 (47.8)</td>
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</tbody>
</table>
### Efficacy of Gemifloxacin, Moxifloxacin and Gatifloxacin Against *S. pneumoniae* in the Rat RTI Model

<table>
<thead>
<tr>
<th><em>S. pneumoniae</em> strain</th>
<th>MIC (µg/mL)</th>
<th>Log$_{10}$ CFU/lungs</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>GEMI</td>
<td>MOXI</td>
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<tr>
<td>404053</td>
<td>≤0.03</td>
<td>0.06</td>
</tr>
<tr>
<td>406081</td>
<td>≤0.03</td>
<td>0.125</td>
</tr>
<tr>
<td>205118</td>
<td>≤0.03</td>
<td>0.25</td>
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<td>305313</td>
<td>0.125</td>
<td>2.0</td>
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<tr>
<td>509063</td>
<td>0.25</td>
<td>2.0</td>
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<tr>
<td>PT 9424123</td>
<td>0.25</td>
<td>2.0</td>
</tr>
<tr>
<td>622286</td>
<td>0.125</td>
<td>1.0</td>
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<tr>
<td>402123</td>
<td>0.25</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Genetically-defined second step mutants

* significantly different compared with GATI p<0.05, ** significantly different to MOXI p<0.05
* Not significantly different to non-treated controls (NTC) p>0.05