

Applicant's Proposed DOSAGE AND ADMINISTRATION Section**DOSAGE AND ADMINISTRATION****Applicant's Proposed CLINICAL STUDIES Section**

The Applicant has not proposed a CLINICAL STUDIES Section for the indication of community-acquired pneumonia.

Labeling for Other fluoroquinolones Approved for the Indication of Community-Acquired Pneumonia**AVELOX (moxifloxacin tablets)****INDICATIONS AND USAGE**

- AVELOX Tablets are indicated for the treatment of adults (\geq 18 years of age) with infections caused by susceptible strains of the designated microorganisms in the conditions listed below. Please see **DOSAGE AND ADMINISTRATION** for specific recommendations.

Community Acquired Pneumonia (of mild to moderate severity) caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, or *Moraxella catarrhalis*.

TEQUIN (gatifloxacin tablets and injection)**INDICATIONS AND USAGE**

- TEQUIN (gatifloxacin) is indicated for the treatment of infections due to susceptible strains of the designated microorganisms in the conditions listed below. (See DOSAGE AND ADMINISTRATION.)

Community Acquired Pneumonia due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, or *Legionella pneumophila*.

LEVAQUIN (levofloxacin tablets and Injection)

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INDICATIONS AND USAGE

- LEVAQUIN Tablets are indicated for the treatment of adults (≥ 18 years of age) with mild, moderate, and severe infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

Community-acquired pneumonia due to *Staphylococcus aureus*, *Streptococcus pneumoniae* (including penicillin-resistant strains, MIC value for penicillin ≥ 2 mcg/mL), *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Klebsiella pneumoniae*, *Moraxella catarrhalis*, *Chlamydia pneumoniae*, *Legionella pneumophila*, or *Mycoplasma pneumoniae*. (See **CLINICAL STUDIES**.)

FLOXIN (ofloxacin tablets)**INDICATIONS AND USAGE**

- FLOXIN (ofloxacin tablets) Tablets are indicated for the treatment of adults with mild to moderate infections (unless otherwise indicated) caused by susceptible strains of the designated microorganisms in the infections listed below. Please see **DOSAGE AND ADMINISTRATION** for specific recommendations.

Community-acquired Pneumonia due to *Haemophilus influenzae* or *Streptococcus pneumoniae*.

ZAGAM (sparfloxacin tablets)**INDICATIONS AND USAGE**

- Zagam (sparfloxacin) is indicated for the treatment of adults (≥ 18 years of age) with the following infections caused by susceptible strains of the designated microorganisms:

Community-acquired pneumonia caused by *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, or *Streptococcus pneumoniae*

TROVAN (trovafloxacin mesylate tablets and alatrofloxacin mesylate injection for intravenous infusion)**INDICATIONS AND USAGE**

- TROVAN is indicated for the treatment of patients initiating therapy in in-patient health care facilities (i.e., hospitals and long term nursing care facilities) with serious, life- or limb-threatening infections caused by susceptible strains of the designated microorganisms in the conditions listed below. (See **DOSAGE AND ADMINISTRATION**.)

Community acquired pneumonia caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Mycoplasma pneumoniae*, *Moraxella catarrhalis*, *Legionella pneumophila*, or *Chlamydia pneumoniae*.

Selected Other Drugs Approved for Pneumonia or Lower Respiratory Tract Infection:**CIPRO (ciprofloxacin tablets, suspension, and injection for intravenous infusion)**
INDICATIONS AND USAGE

- CIPRO® is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below. Please see **DOSAGE AND ADMINISTRATION** for specific recommendations.

Lower Respiratory Tract Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, or *Streptococcus pneumoniae*. Also, *Moraxella catarrhalis* for the treatment of acute exacerbations of chronic bronchitis.

NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the treatment of presumed or confirmed pneumonia secondary to *Streptococcus pneumoniae*.

ZINACEF (cefuroxime for injection)**INDICATIONS AND USAGE**

- ZINACEF is indicated for the treatment of patients with infections caused by susceptible strains of the designated organisms in the following diseases:

Lower Respiratory Tract Infections, including pneumonia, caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* spp., *Staphylococcus aureus* (penicillinase- and non-penicillinase-producing strains), *Streptococcus pyogenes*, and *Escherichia coli*.

Medical Officer's Comment: ZINACEF (cefuroxime for injection) is approved for the treatment of lower respiratory tract infections however, the oral preparation of cefuroxime (cefuroxime axetil) has not received approval for community-acquired pneumonia or lower respiratory tract infections.

BIAXIN (clarithromycin tablets and oral suspension)**INDICATIONS AND USAGE**

- BIAXIN Filmtab tablets and BIAXIN Granules for oral suspension are indicated for the treatment of mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

Adults:

Pneumonia due to *Mycoplasma pneumoniae*, *Streptococcus pneumoniae*, or *Chlamydia pneumoniae* (TWAR)

AUGMENTIN (amoxicillin/clavulanate tablets)**INDICATIONS AND USAGE**

- *Augmentin* is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below:

Lower Respiratory Tract Infections --caused by (beta)-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*.

While *Augmentin* is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to *Augmentin* treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and (beta)-lactamase-producing organisms susceptible to *Augmentin* should not require the addition of another antibiotic. Because amoxicillin has greater *in vitro* activity against *Streptococcus pneumoniae* than does ampicillin or penicillin, the majority of *Streptococcus pneumoniae* strains with intermediate susceptibility to ampicillin or penicillin are fully susceptible to amoxicillin and *Augmentin*. (See Microbiology subsection.)

AMOXIL (amoxicillin capsules, tablets, chewable tablets, powder for oral suspension and pediatric drops for oral suspension)**INDICATIONS AND USAGE**

- Amoxil (amoxicillin) is indicated in the treatment of infections due to susceptible (ONLY (beta)-lactamase-negative) strains of the designated microorganisms in the conditions listed below:

Infections of the lower respiratory tract due to *Streptococcus* spp. ((alpha)- and (beta)-hemolytic strains only), *Streptococcus pneumoniae*, *Staphylococcus* spp., or *H. influenzae*

ZITHROMAX (azithromycin tablets, capsules, oral suspension)**INDICATIONS AND USAGE**

- ZITHROMAX® (azithromycin) is indicated for the treatment of patients with mild to moderate infections (pneumonia: see **WARNINGS**) caused by susceptible strains of the designated microorganisms in the specific conditions listed below. As recommended dosages, durations of therapy, and applicable patient populations vary among these infections, please see **DOSAGE AND ADMINISTRATION** for specific dosing recommendations.

Adults:

Community-acquired pneumonia due to *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, or *Streptococcus pneumoniae* in patients appropriate for oral therapy.

NOTE: Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness or risk factors such as any of the following:

patients with cystic fibrosis,
 patients with nosocomially acquired infections,
 patients with known or suspected bacteremia,
 patients requiring hospitalization,
 elderly or debilitated patients, or
 patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).

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NOTE: Penicillin by the intramuscular route is the usual drug of choice in the treatment of *Streptococcus pyogenes* infection and the prophylaxis of rheumatic fever. ZITHROMAX® is often effective in the eradication of susceptible strains of *Streptococcus pyogenes* from the nasopharynx. Because some strains are resistant to ZITHROMAX®, susceptibility tests should be performed when patients are treated with ZITHROMAX®. Data establishing efficacy of azithromycin in subsequent prevention of rheumatic fever are not available.

Children: (See Pediatric Use and CLINICAL STUDIES IN PEDIATRIC PATIENTS.)

Community-acquired pneumonia due to *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, or *Streptococcus pneumoniae* in patients appropriate for oral therapy. (For specific dosage recommendation, see **DOSAGE AND ADMINISTRATION.)**

NOTE: Azithromycin should not be used in pediatric patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness or risk factors such as any of the following:

patients with cystic fibrosis,
 patients with nosocomially acquired infections,
 patients with known or suspected bacteremia,
 patients requiring hospitalization, or
 patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).

Other approved antimicrobials with an oral formulation that are labeled for the indication of community-acquired pneumonia or lower respiratory tract infection (with a similar spectrum of pathogens listed in the indication) include the following:

- CECLOR (cefaclor)
- DYNABAC (dirithromycin)
- ERY-TAB (erythromycin)
- LORABID (loracarbef)
- OMNICEF (cefdinir)
- SPECTROBID (bacampicillin)
- VANTIN (cefprozime proxetil)

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Material reviewed:

- NDA 21-158 electronic submission dated October 4, 2002
- IND ~~_____~~ (N-219) Final Study Report Study 185, June 7, 2001
- Response to FDA requests for information formally submitted to IND ~~_____~~ (N0252, N0251) dated July 25, 2002, July 29, 2002

- Response to FDA requests for information submitted to NDA 21-158 on October 16, 2002, November 13, 2002, November 14, 2002, November 25, 2002
- Adverse event datasets for study 287 submitted October 28, 2002
- Outcome datasets for study 185 submitted October 31, 2002
- Medical Officer's Review for the indication of CAP for NDA 21-158
- Medical Officer's Review for the indication of CAP for NDA 20-759/20-760
- Medical Officer's Review for the indication of CAP for NDA 20-634/20-635
- Medical Officer's Review for the indication of CAP for NDA 21-061
- Medical Officer's addendum Review of NDA 21-277
- Approvable letter dated December 11, 2000
- Resubmission premeeting package and meeting minutes February 27, 2001

Abbreviations:

CRF = Case Report Form

AE = Adverse Event

EOT = End of Therapy

ITT = Intent to Treat

CPP = Clinical Per Protocol Population

BPP – Bacteriologic Per Protocol Population

CAP = Community acquired Pneumonia

BITT = Bacteriologic Intent to Treat

TOC- Test of Cure

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Note on fonts: This review is written in Times New Roman 12. Arial is used for direct quotes from the applicant's submission.

Regulatory Background

NDA 21-158 was originally submitted by GSK as a new drug application (NDA) on December 15, 1999. In that application, the applicant requested the indications of community-acquired pneumonia, acute exacerbation of chronic bacterial bronchitis, _____

A not approvable letter was issued on December 11, 2000 wherein the applicant was informed that "There is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended or suggested in its proposed labeling." Of particular concern is the lack of data available in your NDA to fully assess the potential risks posed by the high incidence of hypersensitivity/rash in the clinical trials in order to balance these with the efficacy profile of gemifloxacin'.

'Based on our review of the clinical trial data submitted in your NDA, we have concluded that gemifloxacin is effective in treating community-acquired pneumonia (CAP) of mild to moderate severity, acute bacterial exacerbation of chronic bronchitis (ABECB), _____

Approval of these indications is dependent on completion of the above studies with demonstration of an acceptable safety profile. You have not provided adequate information to support the efficacy of gemifloxacin for the use outlined below:

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Regulatory Guidance for the Indication of Community-Acquired Pneumonia

The information provided by the IDSA/FDA guidelines (1992), the Points-to-Consider Document, and the recent Agency Draft Guidance for CAP are briefly summarized below.

IDSA/FDA Guidelines

The IDSA/FDA guidelines recommend that the patients included in clinical trials of antimicrobial agents for the treatment of CAP should meet the following minimal diagnostic criteria. Patients must have clinical signs and symptoms of bacterial pneumonia and radiographic or other laboratory evidence that supports the diagnosis of CAP. Suitable specimens from the respiratory tract should be obtained for microbiological analysis. In addition, blood cultures should be obtained on all patients. The guidelines state that a microbiologic diagnosis should be based upon the identification of a pathogen from an appropriate microbiologic specimen. For some microbes, diagnosis by non-culture techniques is acceptable.

The IDSA/FDA Guidelines state in part the following regarding the conduct of the clinical study. Patients should be monitored while on study for signs of response to therapy. An assessment within 5-7 days after completion of therapy is recommended. In order to be evaluable, patients should have received at least 5 days of therapy and must have taken at least 80% or more of the prescribed medication. The recommended categories for clinical response are clinical cure, clinical failure, or indeterminate. The recommended microbiological response categories include eradication, presumed eradication, persistence, presumed persistence, relapse, colonization, superinfection, and indeterminate.

Points-to-Consider

The Points to Consider (PTC) document recommends one statistically adequate and well-controlled multicenter trial establishing equivalence or superiority to an approved product and one open trial corroborating the findings of the controlled trial. Preferably the trials should be conducted within the United States. The study design should incorporate rigid case definitions and specific entry criteria. The primary effectiveness endpoints should be clinical and radiographic endpoints. Microbiological evaluations should also be performed. The data analysis should evaluate outcomes in the clinically evaluable population and also in the clinically and microbiologically evaluable population. The analysis of the data should also generally confirm (by means of comparing the direction of the independent 95% confidence intervals) the successful outcome rates for the clinically evaluable and clinically and microbiologically evaluable population. The analysis should also establish a correlation between clinical cure and bacterial eradication in both of the aforementioned evaluable populations.

The PTC document also suggests a second study which may be an open trial involving at least 2 investigators. The open trial should be similar to the adequate and well-controlled trial with regards to patient demographics, disease severity, exclusion/inclusion criteria, evaluability criteria, and the effectiveness parameters that are evaluated. The results from the second study should corroborate the results of the adequate and well-controlled trial.

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Agency Draft Guidance on CAP

More recently CDER has produced a Draft Guidance Document describing the design of studies intended to evaluate the safety and efficacy of antimicrobials for the treatment of community-acquired pneumonia (CAP). This Draft Guidance states that in order to be eligible for study, patients should have a combination of clinical signs and symptoms and radiographic findings of pneumonia. A thorough microbiological evaluation should be performed on all patients in search of the microbial etiology for their pneumonia. In general, studies should exclude patients with medical or pulmonary conditions that would impair their ability to respond to antimicrobial therapy for their pneumonia.

Regarding evaluability, the Draft Guidance recommends that patients be required to receive at least 48-72 hours of therapy before the clinical assessment for failure can be made and at least 5 days of therapy with a minimum of 80% compliance before an assessment of a favorable outcome can be assigned. Patient evaluations at the following time points are described: pre-therapy, on-therapy, end-of therapy, early post-therapy, and test-of-cure (TOC) visits. The Draft Guidance document recommends that the TOC visit occur at least 7 days, and no later than 3 weeks, after the completion of treatment. The half-life of the drug under study should also be considered when specifying the timing for the TOC visit.

The Draft Guidance specifies that clinical outcome is the primary efficacy variable for the indication of CAP and classifies clinical outcome as clinical cure or clinical failure. The categories of microbiological response that are described are the following: eradication, presumed eradication, persistence, presumed persistence, superinfection, recurrence, new infection, and colonization.

Chemistry/Manufacturing and Controls

Please see Chemist's review of NDA 21-158 (original submission).

Animal Pharmacology/Toxicology

Please see Dr. Amy Ellis' Pharmacology/toxicology review (original submission).

Microbiology

Please see Dr. Peter Dionne's Microbiologist's Review.

Gemifloxacin's MIC against gram-positive organisms is lower than some of the other quinolones. However, the serum concentrations achieved with gemifloxacin are also lower – partially counter balancing the agent's lower MIC values.

The applicant studied the activity of gemifloxacin in an animal model of experimentally induced pulmonary pneumococcal infection in which the applicant included strains

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resistant to other marketed fluoroquinolones. When strains resistant to some of the other fluoroquinolones were used, gemifloxacin therapy had to be initiated earlier and the dose had to be divided and given twice daily in order to obtain outcomes similar to when "fully susceptible" pneumococcal strains were used. For further details please see Dr. Dionne's review.

Human Pharmacokinetics/Pharmacodynamics

Please see Dr. Phillip Colangelo's Biopharmaceutics Review (original submission).

Summary of the Efficacy Data for Gemifloxacin for the Treatment of Community-Acquired Pneumonia NDA 21-158 (original data copied from MOR)

Data were presented from three principal studies and one supportive study of gemifloxacin's efficacy in the treatment of CAP. Studies 012 and 049, the two "pivotal" CAP studies, were statistically adequate and well-controlled multicenter CAP studies to evaluate the safety and efficacy of gemifloxacin in the treatment of patients with CAP. Both studies were designed to demonstrate non-inferiority of gemifloxacin to an approved/scientifically acceptable comparator or comparator-regimen for the treatment of CAP. Study 011 was a randomized, double-blind, controlled, multicenter study designed to study a population of patients with CAP suspected to be due to *Streptococcus pneumoniae*. Study 061 was a non-comparative lower respiratory tract infection study (CAP or ABECB).

The two pivotal studies (studies 012 & 049) and the other principal study (Study 011) found the clinical response rates (success or failure) at the follow-up assessment in the CPP population (the primary efficacy endpoint) to demonstrate non-inferiority of gemifloxacin to its comparators within the agreed upon delta of -15%.

In Study 012, 220/251 (87.6%) gemifloxacin-treated patients achieved a clinical response of success at follow-up compared to 238/257 (92.6%) of the clarithromycin/cefuroxime-treated patients. The 95% confidence interval for the difference in the point estimates of Success [95% CI -10.1, 0.2] contained zero and is within a delta of 15% and the confidence interval includes unity.

Study 049 compared gemifloxacin to trovafloxacin in the treatment of CAP. In the CPP population, a clinical response of success was achieved in 203/216 (94.0%) of the gemifloxacin-treated patients and in 186/207 (89.9%) of the trovafloxacin-treated patients. The 95% confidence interval for the difference in the point estimates of success [95% CI -1.1, 9.3] contained zero and remained within a lower bound of -15%.

Study 011 was designed to study gemifloxacin in CAP in a group of patients with suspected pneumococcal pneumonia based upon entry criteria designed to enrich the population for cases of pneumococcal pneumonia. In the CPP population, a clinical response of success at follow-up was achieved in 102/115 (88.7%) of gemifloxacin-treated patients and 99/113 (87.6%) of amoxicillin/clavulanate-treated patients. The

confidence interval for the difference in success rates [95% CI -7.3, 9.5] remained within a delta of 15% and encompassed zero allowing non-inferiority to be declared.

The differences for the point estimates for clinical response at follow-up were -5.0% [95% CI -10.1, 0.2] (gemifloxacin - clarithromycin/cefuroxime) for Study 012 compared to +4.1% [95% CI -1.1, 9.3] (gemifloxacin - trovafloxacin) for Study 049. Review of the data did not disclose any particular reason behind these differences between studies 012 and 049. The secondary endpoint of bacteriological response at follow-up in the BPP population corroborated the finding of non-inferiority for the primary efficacy endpoint. The other secondary endpoint analyses also corroborated the findings of the primary efficacy endpoint

There was sufficient clinical evidence of the activity of gemifloxacin in the treatment of CAP at the TOC follow-up visit on the bacteriologic PP population with *Mycoplasma pneumoniae* (84/97 (86.6%)), *Streptococcus pneumoniae* (58/62 (93.5%)), *Chlamydia pneumoniae* (39/41 (95.1%)), and *Haemophilus influenzae* (33/38 (86.8%))

Table 6
Pre-Therapy Pathogens Eradicated or Presumed Eradicated at Follow-Up: CAP
Combined Principal and Supportive Studies 012, 049, 011 and 061

Follow-Up	Combined CAP studies 012, 049, 011, 061							
	Bacteriology PP**				Bacteriology ITT			
	Gemifloxacin		All Comparators		Gemifloxacin		All Comparators	
	N=272		N=211		N=371		N=273	
	n/N*	%	n/N*	%	n/N*	%	n/N*	%
All Pathogens	296/337	(87.8)	221/246	(89.8)	366/462	(79.2)	267/330	(80.9)
<i>M. pneumoniae</i>	84/97	(86.6)	80/93	(86.0)	105/128	(82.0)	94/113	(83.2)
<i>S. pneumoniae</i>	58/62	(93.5)	48/51	(94.1)	71/88	(80.7)	56/69	(81.2)
<i>C. pneumoniae</i>	39/41	(95.1)	27/30	(90.0)	47/58	(81.0)	32/41	(78.0)
<i>H. influenzae</i>	33/38	(86.8)	15/16	(93.8)	40/50	(80.0)	19/22	(86.4)

Note: failures at end of therapy are carried forward into the follow-up analysis by applying the following algorithms:

- (1) failures and 'unable to determine' at end of therapy are added to the denominator at follow-up
- (2) successes at end of therapy with missing data at follow-up are NOT added to the denominator at follow-up.

* n/N = number of pathogens eradicated or presumed eradicated / number of pathogens.

** Bacteriology PP follow-up population.

† Please see the discussions within this review regarding the weight of evidence presented by the cases where _____ was isolated.

‡ In the MO's Bacteriology Per Protocol population (evaluable population) the Eradication/Presumed Eradication rate for _____ at Follow-Up was 9/15 (60%). Please see the discussion of _____ within the Integrated Summary of Efficacy within this review for further details.

There was insufficient evidence of activity to support the inclusion of _____ (6/6, 100%) and _____ (9/9, 100%) among the indicated pathogens.

Review of the cases of CAP due to _____ found the data insufficient to support a claim for _____ in the CAP indication. (Only 7 of the evaluable cases had _____ as their only pathogen at screening. The

clinical and/or bacteriological success rate in this group of 7 was 5/7 (71%). Two of these 7 cases were bacteremic with _____ - both failed.)

Review of the cases of CAP where _____ was a pathogen at screening did not provide sufficient evidence to support a claim for _____. The cure rate in the Medical Officer's evaluable population was 60% (9/15). Many of the patients with _____ as a pathogen at screening had other common pathogens of CAP at screening and most _____ cases were diagnosed serologically. In addition, in study 011 where Augmentin® was the comparator, 5/6 (83%) of the Augmentin®-treated patients with _____ diagnosed at screening achieved clinical success. These high success rates in response to Augmentin® therapy raised the question of "assay sensitivity" for demonstrating efficacy for gemifloxacin in the treatment of CAP due to _____

[_____]

Given the characteristics of the population studied for gemifloxacin, the MO proposed that the CAP indication be limited to mild or moderate CAP for this oral agent. For patients enrolled from US study centers only 8 of 377 patients with CAP were hospitalised, 2 of these 8 patients were classified as having severe disease. Of the 22 patients classified as having severe disease from US study centers in the pivotal studies (Study 012 and Study 049) only 2 of the 22 patients were hospitalised, which raised question about the validity of the applicant's adaptation of the ATS Guidelines CAP severity index as applied to these study populations.

Most patients in the CAP studies were treated with 7 days of therapy. The number of patients receiving 14 or more days of therapy was limited. Therefore the MO proposed that the recommended duration of therapy in the label should be 7 days. Retrospective exploratory analyses using the applicant's severity index (based on the ATS Guidelines) did not provide compelling evidence that patients with "severe" disease benefited from 14 instead of 7 days of therapy.

In summary, the data presented in the CAP studies in NDA 21-158 provided sufficient evidence of the efficacy for gemifloxacin in the treatment of CAP (of mild to moderate severity) due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae* with a labeled duration of therapy of 7 days.

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Six clinical studies were presented in the resubmission to demonstrate the efficacy of gemifloxacin in CAP. Four of the studies were controlled (three of a double-blind design and one an open study) and two studies were uncontrolled. Five studies are complete and one, study 287, is ongoing; an interim analysis of Study 287 was conducted with all data from completed patients received in-house on or before August 28, 2001 included.

***Medical Officer's Comment:** Studies 011, 012, 049, and 061 were reviewed as part of the original NDA submission (see above). The MO elected to present a summary of the applicant's combined summary and analyses in this section. Also included will be determinations of approvability of requested pathogens not previously recommended for approval. Reviews of the individual studies can be found in appendices A and B.*

**Table 7
Community Acquired Pneumonia: Controlled and Uncontrolled
Studies of Gemifloxacin**

Study	Treatment Regimen	Duration	N*	Geographic Region
Controlled studies				
011	gemifloxacin 320 mg od	7 days	168	Europe, S. Africa
	amoxicillin /clavulanate 1g/125 mg tid	10 days	156	
012	gemifloxacin 320 mg od	7 or 14 days	319	U.S. Canada, Europe, S. Africa
	cefuroxime 500 mg /clarithromycin 500 mg bid	7 or 14 days	322	
049	gemifloxacin 320 mg od	7 or 14 days	290	U.S., Mexico, Spain
	trovafloxacin 200 mg od	7 or 14 days	281	
185	gemifloxacin 320 mg od	7-14 days	172	Australia, Europe, Guatemala, Lebanon, Philippines, Singapore and North America
	IV ceftriaxone 2g od +	1-7 days +	173	
	oral cefuroxime 500 mg bid**	1-13 days (IV/oral = ≤ 14)		
Uncontrolled studies				
061	gemifloxacin 320 mg od	7 days	216 [§]	World-Wide (Except N. America)
287	gemifloxacin 320 mg od	7 days	188	Asia, U.S., Mexico Philippines

* N refers to the number of randomized patients (enrolled for uncontrolled studies)

** both comparator treatments were administered with or without macrolide

§ Study 061 was conducted in patients with CAP or AECB. N= number of patients with CAP.

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The 3 previously reviewed controlled studies, Studies 011, 012 and 049, were randomized, multicenter, double-blind, double-dummy, parallel group studies designed to evaluate the clinical and antibacterial efficacy and safety of gemifloxacin in comparison with approved comparator antimicrobial agents (amoxicillin/clavulanate, cefuroxime axetil/clarithromycin and trovafloxacin)

Duration of treatment was for 7 days but in Studies 012 and 049, study medication could be extended to 14 days if the patient had a severe infection, if the pneumonia was confirmed or suspected to be due to an atypical pathogen (including _____) or at the investigators' discretion. All patients received 7 days of treatment with gemifloxacin in Study 011.

Study 185, the fourth controlled study, was an open study designed to show that oral gemifloxacin (7 – 14 days) was as effective as the comparator regimen of intravenous ceftriaxone 2g once daily for a minimum of 1 day and up to a maximum of 7 days, followed by oral cefuroxime for a minimum of 1 day and up to a maximum of 13 days (total treatment duration = 14 days). A macrolide could be prescribed concurrently at the screening visit for patients randomized to the comparator regimen.

Male and female patient at least 18 years of age were enrolled into all studies if they met the inclusion criteria that included new infiltrate on CxR as well as the signs and symptoms of CAP. In study 011 subjects had to satisfy additional criteria that suggested pneumococcal involvement (sudden onset; chills; pleuritic chest pain; localized alveolar consolidation on chest radiograph; Gram positive cocci on sputum gram stain). In studies 011, 012, and 049, patients could be either outpatients or hospitalized while entry into study 185 was limited to hospitalized patients.

The two uncontrolled studies of gemifloxacin in CAP were designed to meet specific objectives in the development plan for gemifloxacin. The first study, Study 061, was conducted in patients with either CAP or AECB and was designed to maximize the number of bacteriologically evaluable patients treated with gemifloxacin. Study 287, the second uncontrolled study remains ongoing and is being conducted in areas of the world with a high prevalence of drug-resistant respiratory pathogens.

The inclusion criteria for enrollment of CAP patients into the these studies were similar to those in the controlled studies, with the exception that in study 287, patients had to have evidence of pneumococcal infection (positive urine antigen test and/or positive Gram stain for diplococci resembling *Streptococcus pneumoniae*). In both studies, patients were either out-patients or hospitalized depending on clinical need, and received open-label treatment with gemifloxacin 320 mg once daily for 7 days.

In both the controlled and uncontrolled studies of gemifloxacin in CAP, patient assessments occurred on four occasions over four to five weeks. Following screening (Day 0) and randomization to treatment, the timing of these assessments were as follows:

- During therapy:

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Days 2 to 4 (Studies 011, 012, 049, 185 and 061)
Days 3 to 5 (Study 287)

- End of Therapy (EOT):
Days 12-14 (Study 011)
2-4 days post-therapy (Studies 012, 049 and 185)
Days 9-11 (Studies 061 and 287)

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- Follow-up (TOC):

Days 24-30 (Study 011)
14-21 days post-therapy (Studies 012 and 049)
21-28 days post-therapy (Study 185)
Days 21-28 (Study 061)
Days 28-35 (Study 287)

Note: evaluable visit windows were extended for the purpose of the per protocol analysis.

The **primary efficacy endpoint** in the four controlled clinical studies (Studies 011, 012, 049, and 185) and in uncontrolled Study 061, was clinical response at follow-up (test of cure [TOC]). In non-comparative study 287, the primary objective was to demonstrate bacteriological efficacy in the treatment of CAP of suspected pneumococcal origin and so the primary endpoint in this study was the bacteriological response at the follow-up visit.

Clinical response was also assessed at end of therapy (EOT) as a secondary endpoint. It is important to note that clinical outcome was evaluated at follow-up only if the patient was a clinical success at the EOT. Patients with a clinical outcome of clinical failure at the EOT were carried forward to the TOC as failures. Similarly patients with a clinical outcome of unable to determine (UTD) at the EOT were carried forward to the TOC as failures in the ITT analyses.

Bacteriological response was determined for each patient from the bacteriological outcome for pathogens isolated from sputum, other respiratory samples, or blood culture. Patients with a pre-therapy pathogen but without an evaluable sample at EOT or follow-up were assigned a presumed bacteriological outcome on the basis of clinical response.

Therapeutic response at follow-up was determined based on the combined clinical and bacteriological response. A patient was a therapeutic success if both the clinical and bacteriological response were success at follow-up. If the clinical and/or bacteriological response was failure, the patient was a therapeutic failure.

Radiological outcome at follow-up (i.e., improved, unchanged, worse or unable to determine) was determined by comparing the chest X-rays at follow-up with screening. In the absence of an X-ray at follow-up, improvement was presumed if the patient was a

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clinical success at follow-up. Radiological outcome was presumed as failure if clinical response at end of therapy was not clinical success.

Patients with a radiological outcome of improved or presumed improved were included in the overall radiological success response rate. With the exception of study 287, radiological response of failure included radiological outcomes of unchanged, worse, unable to determine or presumed failure. In study 287, the outcome of unchanged was included as success.

In studies 185 and 287, efficacy endpoints included the combined clinical and radiological response rate at follow-up. A combined clinical and radiological response of success at follow-up included patients who were a clinical success and who had a radiological outcome of improved, unchanged or presumed improved.

A combined clinical and radiological response of failure at follow-up included patients who were a clinical failure or with a radiological outcome of worse, presumed failure or unable to determine.

In all of the CAP clinical studies there were four patient populations in whom efficacy was determined:

- **Intent to Treat (ITT):** All randomized patients who took at least one dose of study medication. In Study 185, all randomized patients were included to reduce potential bias associated with the open design.
- **Clinical Per Protocol (CPP):** A subset of the ITT population that excluded patients who violated the protocol to an extent that could affect treatment efficacy.
- **Bacteriology ITT (BITT):** A subset of the ITT population that included patients with evidence of infection with at least one pre-therapy pathogen identified at screening.
- **Bacteriology PP (BPP):** A subset of the BITT population that excluded patients who violated the protocol to an extent that could affect treatment efficacy.

Patients were excluded from the PP populations only from the time that the violation occurred. Hence, the CPP and BPP populations may have contained different numbers of patients at the EOT and follow-up.

The protocols for Studies 011, 012, 049 and 185 identified the PP populations as the primary analysis populations, with the ITT population providing confirmatory analysis. In the two uncontrolled studies, the ITT population was of primary interest. In the ITT analyses, patients with a clinical outcome of unable to determine were assigned a clinical response of failure, representing a worst case approach (these patients were excluded from the CPP population).

Medical Officer's Comment: *The results from both the ITT and CPP populations are of equal importance to the Agency.*

The four controlled CAP studies were designed to demonstrate that gemifloxacin was at least as good as the active comparator. The estimation of sample size assumed 90% power to demonstrate that the lower bound of the two-sided 95% confidence interval (CI) for the difference in response rates (gemifloxacin minus comparator) was no less than a pre-defined non-inferiority limit. The planned sample size in Studies 012 and 049 was determined based on an underlying equivalent clinical response rate of 90% at follow-up. The non-inferiority limit for these studies was set at -10%. In contrast, in Studies 011 and 185 which recruited populations likely to have more severe CAP (patients with suspected pneumococcal involvement in Study 011 and hospitalized patients in study 185), a lower clinical response rate of 85% at follow-up was anticipated, and a non-inferiority limit of -15% was selected.

The efficacy of gemifloxacin in the treatment of CAP was demonstrated primarily by the results of each of the individual studies. The applicant provided a supportive analysis of the combined controlled studies to provide additional evidence of the clinical and bacteriological response at follow-up. As per the applicant, "Since there was some evidence of heterogeneity between the phase III studies and in addition the design of study 185 differed slightly from the others, a random effects meta-analysis technique was employed to produce a pooled treatment difference and confidence interval. The non-inferiority of gemifloxacin was concluded if the lower limit of the two-sided 95% CI for the treatment difference was greater than or equal to -10%".

Combined study datasets were used to determine response rates at follow-up in subgroups of interest, specifically: clinical response by gender, age, race for the combined controlled studies; clinical and bacteriological response by planned treatment duration and CAP characteristic (severity, hospitalized, bacteremic status and PRSP). In addition, random effects meta-analysis was also applied to assess the treatment effect in patients with severe CAP, hospitalized patients and patients taking 7 or 14 days of treatment duration. In these analyses, where formal statistical comparison between treatment groups is made, only the controlled studies were analyzed together. Otherwise, controlled and uncontrolled studies were combined.

Finally, the bacteriological efficacy of gemifloxacin was further assessed by combining data from the controlled and uncontrolled studies to determine eradication rates of pathogens isolated at screening in the CAP studies of gemifloxacin.

Medical Officer's Comment: *The sponsor is only interested in obtaining an indication for a 7-day dosing regimen. However, 3 of the 4 controlled studies allowed dosing to continue to 14 days or up to 14 days in a non-randomized fashion based on post-randomization efficacy information. The sponsor has presented data combining the fixed 7-day regimen (controlled study 11 and uncontrolled studies 061 and 287) with the patients whose post-randomization planned duration was 7 days from the 3 other controlled studies (012, 049, and 185). It is the Agency's viewpoint that these two types*

of 7-day data should not be combined. The 7-day data from the fixed 7-day regimen contain information from all patients enrolled in the studies while the 7-day data from the 7-14 day studies have patients removed who were considered by their physicians to have needed more treatment and could in general represent a more ill population. This would cause this 7-day efficacy data from these studies to be biased, most likely upwards.

In the Agency analyses of the data, these two groups of 7-day duration subjects were not combined. Since the Applicant is interested only in a 7-day regimen, we considered the data from the 7 day fixed regimen as the primary data with the 7-14 days as supportive. The data are presented individually by studies, by controlled studies and uncontrolled studies, and by duration as 7-day fixed regimen, 7-day from the 7-14 day studies, and 14 days from the 7-14 day studies. As cautioned by the Applicant, the 7-day efficacy data should not be directly compared to the 14-day efficacy data. Each group of gemifloxacin patients should only be compared to their respective controls.

Patient Disposition:

In the CAP studies 1349 patients received treatment with gemifloxacin 320 mg once daily and 927 patients received treatment with an active comparator.

In the four randomized, controlled studies (Studies 011, 012, 049 and 185), 947 patients were treated with gemifloxacin and 927 received a comparator. Four hundred two (402) patients received treatment with gemifloxacin 320 mg once daily in the uncontrolled studies.

Similar numbers of patients withdrew from the controlled and uncontrolled studies. In the combined controlled study population, the incidence of withdrawal for the combined gemifloxacin group was 16.3% compared with the combined comparator group (15.9%). A similar incidence of withdrawals (16.6%) was observed in the combined uncontrolled study population.

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Table 8
Patient Disposition: CAP Combined Controlled and Uncontrolled Studies (All Randomized Patients)

	Controlled Studies		Uncontrolled Studies	All Studies	
	Studies 011, 012, 049 and 185		Studies 061 and 287	Controlled + Uncontrolled	
	Gemifloxacin 320 mg od	Pooled Comparators	Gemifloxacin 320 mg od	Gemifloxacin 320 mg od	Pooled Comparators
	n	n	n	n	n
Randomized	949	932	404	1353	932
Received study medication (ITT)	947	927	402	1349	927
Completed study, n (%)*	794 (83.7)	784 (84.1)	337 (83.4)	1131 (83.4)	784 (84.1)
Withdrawal reason, n (%):					
Adverse event	73 (7.7)	66 (7.1)	18 (4.5)	91 (6.7)	66 (7.1)
Insufficient therapeutic effect	20 (2.1)	16 (1.7)	8 (2.0)	28 (2.1)	16 (1.7)
Protocol deviation **	23 (2.4)	16 (1.7)	12 (3.0)	35 (2.6)	16 (1.7)
Lost to follow-up	27 (2.8)	43 (4.6)	21 (5.2)	48 (3.5)	43 (4.6)
Other reason	12 (1.3)	7 (0.8)	8 (2.0)	20 (1.5)	7 (0.8)
Total withdrawn, n (%)	155 (16.3)	148 (15.9)	67 (16.6)	222 (16.4)	148 (15.9)
Populations for Analysis					
Clinical PP end of therapy	755	762	335	1090	762
Clinical PP follow-up	697	698	315	1012	698
Bacteriology ITT	381	355	171	552	355
Bacteriology PP end of therapy	305	303	142	447	303
Bacteriology PP follow-up	280	274	135	415	274

Data Source: ISE Table 11.01, Table 11.02, Table 11.03, Table 11.04, Table 11.05, Table 11.06.

* Patients were considered to have completed the study if they were not actively withdrawn from the study.

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Table 9
Patient Disposition: CAP Combined Controlled and Uncontrolled Studies (All Randomized Patients with Planned Treatment Duration of 7 Days)

	Controlled Studies Studies 011, 012, 049 and 185		Uncontrolled Studies Studies 061 and 287	All Studies Controlled + Uncontrolled			
	Gemifloxacin 320 mg od n	Pooled Comparators n	Gemifloxacin 320 mg od n	Gemifloxacin 320 mg od n	Pooled Comparators n		
Randomized	637	615	404	1041	615		
RECEIVED STUDY MEDICATION (ITT)	635	610	402	1037	610		
Completed study, n (%)*	536 (84.1)	509 (82.8)	337 (83.4)	873 (83.9)	509	(82.8)	
Withdrawal reason, n (%):							
Adverse event	49 (7.7)	43 (7.0)	18 (4.5)	67 (6.4)	43	(7.0)	
Insufficient therapeutic effect	11 (1.7)	14 (2.3)	8 (2.0)	19 (1.8)	14	(2.3)	
Protocol deviation **	17 (2.7)	14 (2.3)	12 (3.0)	29 (2.8)	14	(2.3)	
Lost to follow-up	14 (2.2)	30 (4.9)	21 (5.2)	35 (3.4)	30	(4.9)	
Other reason	10 (1.6)	5 (0.8)	8 (2.0)	18 (1.7)	5	(0.8)	
Total withdrawn, n (%)	101 (15.9)	106 (17.2)	67 (16.6)	168 (16.1)	106	(17.2)	
Populations for Analysis							
Clinical PP end of therapy	515	494	335	850	494		
Clinical PP follow-up	478	461	315	793	461		
Bacteriology ITT	238	223	171	409	223		
Bacteriology PP end of therapy	191	184	142	333	184		
Bacteriology PP follow-up	175	167	135	310	167		

Data Source: ISE Table 11.68a, Table 11.68b, Table 11.68c, Table 11.69a, Table 11.69b, Table 11.69c.

* Patients were considered to have completed the study if they were not actively withdrawn from the study.

** Including non-compliance

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For inclusion in the BITT population, patients had to have at least one respiratory pathogen identified at screening from an evaluable sample. In the ITT population of the combined controlled studies, 40.2% (381/947) of the combined gemifloxacin group and 38.3% (355/927) of the combined comparator group were in this category. In the ITT population of the combined uncontrolled studies, 42.5% (171/402) satisfied this criteria.

Demographics:

In the ITT population for the combined controlled studies, there were more male than female patients (combined gemifloxacin: 56.4%; combined comparators: 57.9%), the average age was approximately 54 years and the majority of the patients were white (combined gemifloxacin: 89.7%; combined comparators: 88.8%). The demographic profile for the combined uncontrolled studies showed a slightly higher proportion of female patients (53.2%), an average age of 51 years and the most predominant racial group was Oriental (40.5%). There were no major differences evident between the ITT population and the CPP population in any of the individual studies or the combined study datasets.

Table 10. FDA Demographics and Baseline Characteristics Controlled CAP Studies – ITT Population

Characteristic	7-Day Fixed			7 – 14 Day Studies			
	Study 011	Comparator	Uncontrolled Studies	7 Days		14 Days	
	Gemifloxacin			Gemifloxacin	Comparator	Gemifloxacin	Comparator
	N = 167	N = 153	N = 402	N = 468	N = 457	N = 312	N = 317
GENDER							
Male	107 (64.1)	96 (62.8)	188 (46.8)	272 (58.1)	256 (56.0)	155 (49.7)	185 (58.4)
Female	60 (35.9)	57 (37.2)	214 (53.2)	196 (41.9)	201 (44.0)	157 (50.3)	132 (41.6)
RACE							
White	138 (82.6)	120 (78.4)	109 (27.1)	435 (93.0)	419 (91.7)	276 (88.5)	284 (89.6)
Black	17 (10.2)	26 (17.0)	11 (2.7)	16 (3.4)	21 (4.6)	18 (5.8)	18 (5.7)
Oriental	7 (4.2)	3 (2.0)	163 (40.5)	8 (1.7)	7 (1.5)	3 (1.0)	7 (2.2)
Other	5 (3.0)	4 (2.6)	119 (29.6)	9 (1.9)	10 (2.2)	15 (4.8)	8 (2.5)
AGE							
Mean (SD)	53.3 (20.4)	55.3 (19.8)	51.1 (18.3)	53.4 (18.2)	51.9 (18.3)	55.7 (17.8)	54.9 (18.0)
Range	18-97	18-86	18 - 89	18-94	18-93	18-90	18-97
CAP SEVERITY							
Mild	120 (71.9)	93 (60.8)	320 (79.6)	345 (73.7)	342 (74.8)	211 (67.6)	218 (68.8)
Moderate	27 (16.2)	44 (28.8)	61 (15.2)	78 (16.7)	79 (17.3)	58 (18.6)	56 (17.7)
Severe	20 (12.0)	16 (10.5)	21 (5.2)	45 (9.6)	36 (7.9)	43 (13.8)	43 (13.6)
HOSPITALIZED	152 (91.0)	149 (97.4)	204 (50.7)	229 (48.9)	193 (42.2)	175 (56.1)	197 (62.2)
Bacteremic	11 (6.6)	16 (10.5)	15 (3.7)	11 (2.4)	17 (3.7)	25 (8.0)	20 (6.3)
Severe CAP, Hospitalized or Bacteremic	152 (91.0)	151 (98.7)	213 (53.0)	239 (51.1)	209 (45.7)	180 (57.8)	203 (64.0)
Patients with PRSP	4 (2.4)	0	7 (1.7)	2 (0.4)	2 (0.4)	1 (0.3)	2 (0.6)

At the Division's request, the applicant provided demographic data by duration of treatment. As can be seen in the following tables, PP subjects that received 14 days duration were somewhat older than those that received 7 days duration of treatment. Other demographic parameters were similar between the 2 groups and with the comparator group.

Table 11
Demographic Characteristics
7 day treatment group CPP

Demographic/Baseline Characteristic	Gemifloxacin 320 mg od (N=793)	Pooled Comparators (N=461)
Gender: n (%)		
Male	434 (54.7%)	265 (57.5%)
Female	359 (45.3%)	196 (42.5%)
Race: n (%)		
White	532 (67.1%)	417 (90.5%)
Black	29 (3.7%)	13 (6.7%)
Oriental	135 (17%)	5 (1.1%)
Other	97 (12.2%)	8 (1.7%)
Age		
Mean (SD)	52 (18.5)	52.8 (18.6)
Range	18 -94	18 - 93

Table 12
Demographic Characteristics
14 day treatment group CPP

Demographic/Baseline Characteristic	Gemifloxacin 320 mg od (N=219)	Pooled Comparators (N=237)
Gender: n (%)		
Male	115 (52.5%)	135 (57%)
Female	104 (47.5%)	102 (43%)
Race: n (%)		
White	199 (91%)	216 (91.1%)
Black	9 (4.1%)	9 (3.8%)
Oriental	3 (1.4%)	5 (2.1%)
Other	8 (3.6%)	7 (2.9%)
Age		
Mean (SD)	56.9 (17.4)	54.9 (17.7)
Range	18 -90	18 - 97

Severity of CAP

For the studies included in the original NDA submission (studies 011, 012, 049 and 061), the severity of CAP was originally assessed using a classification based on the

American Thoracic Society guidelines. For the purpose of this current ISE, severity was determined by categorizing patients according to the mortality risk classes published by Fine *et al* [20]. Patients were assigned to one of the five classes (I, II, III, IV, and V) with respect to risk of death within 30 days, firstly according to an algorithm (class I) and then on the basis of a total points score (classes II-V). A prediction rule assigned points based on age and the presence of co-existing disease, abnormal physical findings, and abnormal laboratory findings at presentation. Since the current classification was performed retrospectively, not all of the variable data that contribute to the total points score were available. The applicant utilized a conservative approach, with patients more likely classified to a lower risk class than if all data were available. Only in study 287 were these criteria applied prospectively.

Based on the assigned risk class, patients were classified as having mild, moderate, or severe CAP.

In the ITT population for the combined controlled studies, the majority of patients had CAP of mild severity (risk class I or II); 71.4% in the gemifloxacin group compared with 70.4% of patients in the comparator group. Approximately 10.5% of patients had severe CAP (classes IV or V) in this population. The proportions of patients with mild, moderate, and severe CAP were similar between the combined gemifloxacin group and the combined comparator group. **Of note, however,** of the 129 ITT patients with severe disease, 125 had class IV disease including 2 with PRSP. The remaining 4 had class V disease. In the PP population, the respective numbers were 89 with class IV disease and 2 with class V disease. Again there were 2 subjects with severe PRSP and both were class IV patients. The highest proportion of patients classified as having severe CAP were in Study 185 (approximately 21% overall). A slightly lower proportion of patients (5.2%) had severe CAP in the combined uncontrolled studies population.

The applicant provided demographic statistics on all subjects by degree of severity. This information was requested in order to ascertain if demographic differences could justify the varied success rates between the treatment groups. Most subjects had mild disease (996 gemifloxacin) and there were more females than males. Of note was the mean age of this category of patients, 46.6 years. Those subjects with moderate and severe disease were predominately males (68 – 72%) and older with a mean age of 69.4 for the moderately ill gemifloxacin-treated subjects and a mean age of 76.3 for the severe group of gemifloxacin-treated subjects.

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Table 13
Demographics by Severity

Severity	Gender		Age	Duration		
	Male	Female	Mean (sd) Range	7 day fixed	7 day	14 day
Mild n=996	473 (47.4)	523 (52.5)	46.6 (15.8) 18-80	440	345	211
Moderate n=224	156 (69.6)	68 (30.4)	69.4 (11.3) 28-89	88	78	58
Severe n=129	93 (72.1)	36 (27.9)	76.3 (8.8) 46-97	41	45	43

Mean Day of Assessment:

The MO requested that the applicant provide information on the mean day of the TOC assessment both by protocol and by study. As noted previously the windows of evaluability were from between 2 – 4 weeks post-treatment. As can be seen in the tables provided by the applicant, the mean day of evaluation fell within this range for all studies except for study 185 where the window was extended to days 19 – 41. The mean day of assessment was day 31 in study 287 but this was within the prespecified range.

- Days 24-30 (Study 011)
- 14-21 days post-therapy (Studies 012 and 049)
- 21-28 days post-therapy (Study 185)
- Days 21-28 (Study 061)
- Days 28-35 (Study 287)

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Table 14
Mean Day of Assessment

Gemifloxacin			Comparator	
	Mean	Median	Mean	Median
011 (gemifloxacin n = 114, comparator n = 113)	28	28	28.2	28
012 (gemifloxacin n = 249, comparator n = 257)	25.3	24	25.3	24
012 (gemifloxacin n = 214, comparator n = 205)	26.3	26	26.3	26
061 (gemifloxacin n = 166)	24.3	24	-	-
185 (gemifloxacin n = 116, comparator n = 119)	35.9	36	35.1	35
287 (gemifloxacin n = 144)	31.5	31	-	-
ITT (gemifloxacin n = 1271 comparator n = 868)	28.1	28	27.9	28
PP (gemifloxacin n = 1003 comparator n = 694)	27.8	28	27.8	28

Efficacy Analyses:

Primary Parameter of Efficacy:

An analysis of clinical success rates at follow-up for the CPP and ITT populations is presented below for each study. The results of study 011 show that the clinical efficacy of gemifloxacin at follow-up was at least as good as (non-inferior to) the comparator regimen of amoxicillin/clavulanate in both the clinical per protocol and the ITT populations since the lower limit of the 95% CI exceeded the pre-specified non-inferiority margin of -15%. The results for the 7 – 14 days comparative studies and 7-day fixed uncontrolled studies support this conclusion.

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Table 15
Summary of Clinical Response at Follow-Up

	Success Rate		
	Gemifloxacin	Comparator*	Treatment Difference
	% (n/N)	% (n/N)	% (95% CI)**
Clinical PP Population			
Controlled Studies			
Study 011	88.7% (102/115)	87.6% (99/113)	1.1 (-7.3, 9.5)
Study 012	87.6% (220/251)	92.6% (238/257)	-5.0 (-10.1, 0.2)
Study 049	94.0% (202/215)	89.9% (186/207)	4.1 (-1.1, 9.3)
Study 185	92.2% (107/116)	93.4% (113/121)	-1.15 (-7.73, 5.43)
Pooled 011/012/049/185 [§]	90.5% (631/697)	91.1% (636/698)	-0.34 (-4.70, 4.02)
Uncontrolled Studies			
Study 061	91.7% (154/168)	-	(86.1, 95.2)
Study 287	89.8% (132/147)	-	(84.9, 94.7)
Intent-to-Treat			
Controlled Studies			
Study 011	77.2% (129/167)	79.1% (121/153)	-1.8 (-10.9, 7.2)
Study 012	78.4% (250/319)	84.7% (272/321)	-6.4 (-12.4, -0.4)
Study 049	87.5% (253/289)	81.1% (227/280)	6.5 (0.5, 12.4)
Study 185	75.6% (130/172)	78.6% (136/173)	-3.03 (-11.89, 5.83)
Pooled 011/012/049/185 [§]	80.5% (762/947)	81.6 (756/927)	-1.02 (-7.44, 5.39)
Uncontrolled Studies			
Study 061	82.9% (179/216)	-	(77.0, 87.5)
Study 287	78.5% (146/186)	-	(72.6, 84.4)

* Comparators were amoxicillin/ clavulanate 1g/125 mg tid (011), clarithromycin 500 mg/cefuroxime 500 mg bid (012), trovafloxacin 200 mg od (049), and ceftriaxone/cefuroxime 2g iv od/500 mg bid (185).

* Non-inferiority limit was prospectively defined as $\geq 10\%$ for Studies 012 and 049; $\geq 15\%$ for Studies 011 and 185 $\geq 10\%$ for the combined analysis of the four studies. For uncontrolled studies, the 95% CI around the success rate is shown.

§ Note that the success rate is for the sum of the individual studies. The treatment difference and 95% CI were generated using a random effects meta-analysis technique so the pooled treatment difference will not necessarily correspond to the difference in observed Gemifloxacin and 'All Comparators' response.

Medical Officer's Comment: Gemifloxacin was non-inferior to approved comparator agents in the treatment of CAP in the individual controlled studies as well as in the pooled analysis when the lower bound of the 95% CI was $\pm 10\%$. Similar results were seen in an independent FDA analysis where clinical response was assessed by study as well as by gender, race, and age.

Table 16
Clinical Response at Follow-up PP population

	Study 011		Studies 012, 049, 185			
	Gemi N=115	Comp N=113	Gemi 7 N=363	Comp 7 N=338	Gemi 14 N=219	Comp 14 N=237
Gender						
Male	67/76 (88.2)	62/70 (88.6)	193/210 (91.9)	178/185 (96.2)	103/115 (89.6)	122/135 (90.4)
Female	35/39 (89.7)	37/43 (86.0)	136/153 (88.9)	141/153 (92.2)	97/104 (93.3)	96/102 (94.1)
Race						
White	87/98 (88.8)	75/88 (85.2)	311/344 (90.4)	304/329 (92.7)	182/199 (91.5)	198/216 (91.7)
Black	9/9 (100.0)	18/19 (94.7)	10/10 (100.0)	9/12 (75.0)	9/9 (100.0)	8/9 (88.9)
Oriental	3/4 (75.0)	2/2 (100.0)	3/4 (75.0)	3/3 (100.0)	3/3 (100.0)	5/5 (100.0)
Other	3/4 (75.0)	4/4 (100.0)	5/5 (100.0)	3/4 (75.0)	6/8 (75.5)	7/7 (100.0)
Age						
18 to <40	31/33 (93.9)	29/31 (93.5)	94/103 (91.3)	93/104 (89.4)	41/43 (95.3)	45/48 (93.8)
40 to < 65	36/44 (81.8)	28/35 (80.0)	127/142 (89.4)	125/136 (91.9)	80/90 (80.9)	97/104 (93.3)
65 to <75	15/18 (83.3)	14/18 (77.8)	68/75 (90.7)	61/65 (93.8)	37/41 (90.2)	50/54 (92.6)
>=75	20/20 (100.0)	28/29 (96.6)	40/43 (93.0)	40/43 (93.0)	42/45 (93.3)	26/31 (83.9)

Secondary Parameters of Efficacy:

Clinical Response at the EOT:

Clinical response at the EOT is presented below for the controlled and uncontrolled studies. As above, gemifloxacin was non-inferior to the comparators with a lower bound of the 95% CI of $\pm 10\%$ with the exception of the ITT analysis for study 185. However in that study the lower bound of the CI was $\pm 15\%$. Similar results were obtained for the uncontrolled studies.

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**Table 17
Clinical Response at End of Therapy
CAP Controlled Studies 011, 012, 049, and 185**

Population	Study 011				Study 012				Study 049				Study 185				
	Gemi-floxacin 320 mg od		Amoxicillin/ clavulanate 1g/ 125 mg tid		Gemi-floxacin 320 mg od		Clarithro/ Cefuroxime 500 mg/ 500 mg bid		Gemi-floxacin 320 mg od		Trova-floxacin 200 mg od		Gemi-floxacin 320 mg od		Ceftriaxone /cefuroxime 2g iv od/ 500 mg bid		
CPP EOT																	
N	128		121		267		279		237		233		123		129		
Success, n (%)	122	(95.3)	109	(90.1)	243	(91.0)	264	(94.6)	227	(95.8)	218	(93.6)	118	(95.9)	124	(96.1)	
Failure, n (%)	6	(4.7)	12	(9.9)	24	(9.0)	15	(5.4)	10	(4.2)	15	(6.4)	5	(4.1)	5	(3.9)	
Treatment diff, %*	5.2				-3.6				2.2				-0.19				
95% CI	-0.2, 11.7				-7.9, 0.7				-1.8, 6.3				-5.01, 4.64				
ITT																	
N	167		153		319		321		289		280		172		173		
Success, n (%)	143	(85.6)	128	(83.7)	274	(85.9)	287	(89.4)	268	(92.7)	249	(88.9)	141	(82.0)	149	(86.1)	
Failure, n (%)	24	(14.4)	25	(16.3)	45	(14.1)	34	(10.6)	21	(7.3)	31	(11.1)	31	(18.0)	24	(13.9)	
Known failure	12	(7.2)	17	(11.1)	24	(7.5)	21	(6.5)	12	(4.2)	1	9	(6.8)	15	(8.7)	10	(5.8)
Unable to determine	12	(7.2)	8	(5.2)	21	(6.6)	13	(4.0)	9	(3.1)	12	(4.3)	16	(9.3)	14	(8.1)	
Treatment diff, %*	2.0				-3.5				3.8				-4.15				
95% CI	-5.9, 8.5				-8.6, 1.6				-0.9, 8.5				-11.87, 3.57				

Data Source: Study 011, Section 11, Tables 11.12a, 11.12b, 11.13a, 11.13b; Appendix C, Listing C.01; Study 012, Section 11, Tables 11.12a, 11.13a, 11.13b, 11.14a, 11.14b; Appendix C, Listing C.01; Study 049, Section 11, Tables 11.12a, 11.12b, 11.13a, 11.13b; Appendix C, Listing C.01; ; Study 185, Section 12, Tables 11.09a, 11.09b, 11.10a, 11.10b; Appendix C, Listing C.01.

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Table 18
Clinical Response at End of Therapy
CAP Uncontrolled Studies (061, 287)

Population	Gemifloxacin 320 mg for 7 days			
	Study 061		Study 287	
	N=216		N=186	
ITT				
Success, n (%)	186	(86.1)	153	(82.3)
Failure, n (%)	30	(13.9)	33	(17.7)
Failure at end of therapy	12	(5.6)	18	(9.7)
Unable to determine	18	(8.3)	15	(8.1)
95% CI for Success	80.6,90.3		76.8,87.7	
Clinical PP End of Therapy	N=179		N=156	
Success, n (%)	168	(93.9)	141	(90.4)
Failure, n (%)	11	(6.1)	15	(9.6)
95% CI for Success	89.0, 96.7		85.8, 95.0	

Data Source: Study 061, Section 11, Table 11.09a, Table 11.09b, Table 10a, Table 11.10b; Study 061, SAS Datasets; Study 287, Section 11, Table 11.44a, Table 11.44b, Table 11.45a, Table 11.45b; Study 287, SAS Datasets.

Bacteriological Response at Follow-Up and End of Therapy:

Bacteriologic response (success or failure) at the follow-up visit was a secondary efficacy variable in the four controlled CAP studies (012, 049, 011, and 185) and in uncontrolled Study 061.

***Medical Officer's Comment:** In uncontrolled Study 287, bacteriological response at follow-up was the primary efficacy variable.*

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Table 19
Bacteriological Response at Follow-Up
CAP All Studies 011, 012, 049, 185, 061 and 287

	Success Rate		Treatment Difference** % (95% CI)
	Gemifloxacin % (n/N)	Comparator* % (n/N)	
Bacteriology PP Follow-Up Population			
Controlled Studies			
Study 011	87.2% (41/47)	89.1% (41/46)	-1.9 (-15.0, 11.2)
Study 012	89.9% (71/79)	88.9% (80/90)	1.0 (-8.3, 10.3)
Study 049	87.8% (79/90)	89.3% (67/75)	-1.6 (-11.3, 8.2)
Study 185	90.6% (58/64)	87.3% (55/63)	3.3 (-7.6, 14.2)
Pooled 011/012/049/185 [§]	88.9% (249/280)	88.7% (243/274)	0.33 (-4.9, 5.6)
Uncontrolled Studies			
Study 061	87.3% (48/55)	-	(74.9, 94.3)
Study 287	90.0% (72/80)	-	(83.4, 96.6)
Bacteriology Intent-to-Treat			
Controlled Studies			
Study 011	75.0% (54/72)	76.2% (54/72)	-1.2 (-15.7, 13.3)
Study 012	80.4% (82/102)	86.1% (93/108)	-5.7 (-15.8, 4.4)
Study 049	84.0% (100/119)	80.4% (82/102)	3.6 (-6.5, 13.8)
Study 185	76.1% (67/88)	79.3% (65/82)	-3.13 (-15.6, 9.4)
Pooled 011/012/049/185 [§]	79.5% (303/381)	81.1% (288/355)	-1.5 (-7.2, 4.2)
Uncontrolled Studies			
Study 061	77.9% (60/77)	-	(66.8, 86.3)
Study 287	84.0% (79/94)	-	(76.6, 91.4)

Comparators were amoxicillin/ clavulanate 1g/125 mg tid (011), clarithromycin 500 mg/cefuroxime 500 mg bid (012), trovafloxacin 200 mg od (049) and ceftriaxone/cefuroxime 2g iv od/500 mg bid (185).

For uncontrolled studies, the 95% CI around the success rate is shown.

Note that the success rate is for the sum of the individual studies. The treatment difference and 95% CI were generated using a random effects meta-analysis technique so the pooled treatment difference will not necessarily correspond to the difference in observed Gemifloxacin and 'All Comparators' response.

Medical Officer's Comment regarding other secondary parameters of efficacy: The applicant provided analyses for bacteriologic response at the EOT, radiologic response at the EOT and at follow-up, combined clinical and radiological response rates at the EOT and at follow-up, and therapeutic response at the EOT and follow-up. The prespecified 95% CI was met in all analyses and gemifloxacin was shown to have similar

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efficacy to comparators. The MO elected NOT to present these analyses in the MOR as they have been presented individually in the MORs of the individual studies.

In the BPP follow-up population, 88.5% (461/521) of initial pathogens in the combined gemifloxacin group were either eradicated or presumed eradicated as compared with 89.9% (301/335) of initial pathogens in the combined comparator group. By pathogen eradication rates can be seen in the table below.

Streptococcus pneumoniae and *Mycoplasma pneumoniae*, the most frequently isolated pathogens in this combined study population of CAP patients, had eradication rates in the gemifloxacin group of 90.7% and 88.7%, respectively (BPP population). For the pooled comparator group the corresponding rates for these pathogens were 92.9% and 87% respectively.

Table 20
Pre-Therapy Pathogens Eradicated or Presumed Eradicated at Follow-Up
CAP Combined Principal and Supportive Studies 012, 049, 011, 185 and 287, 061

Follow-Up	Combined CAP studies 012, 049, 011, 061, 185, 287							
	Bacteriology PP**				Bacteriology ITT			
	Gemifloxacin		All Comparators		Gemifloxacin		All Comparators	
	N=415		N=274		N=552		N=355	
	n/N*	%	n/N*	%	n/N*	%	n/N*	%
All Pathogens	461/521	(88.5)	301/335	(89.9)	552/702	(78.6)	361/445	(81.1)
<i>M. pneumoniae</i>	102/115	(88.7)	94/108	(87.0)	126/153	(82.4)	109/129	(84.5)
<i>S. pneumoniae</i>	117/129	(90.7)	65/70	(92.9)	136/168	(81.0)	76/94	(80.9)
<i>C. pneumoniae</i>	51/54	(94.4)	41/45	(91.1)	62/77	(80.5)	48/59	(81.4)
<i>H. influenzae</i>	51/58	(87.9)	25/28	(89.3)	60/75	(80.0)	30/37	(81.1)
<i>M. catarrhalis</i>	13/14	(92.9)	3/3	(100.0)	15/16	(93.8)	4/4	(100.0)
<i>K. pneumoniae</i>	17/19	(89.5)	4/4	(100.0)	23/29	(79.3)	4/4	(100.0)

Note: failures at end of therapy are carried forward into the follow-up analysis by applying the following algorithms:

(1) failures and 'unable to determine' at end of therapy are added to the denominator at follow-up

(2) successes at end of therapy with missing data at follow-up are NOT added to the denominator at follow-up.

* n/N = number of pathogens eradicated or presumed eradicated / number of pathogens.

** Bacteriology PP follow-up population.

Medical Officer's Comment: By pathogen eradication rates for the most frequently isolated pathogens, were similar to those seen in the initial NDA submission. Specifically for *Mycoplasma pneumoniae* initial eradication rate was 86.6% (84/97), as compared to 88.7% (102/115), in the resubmission. For *Streptococcus pneumoniae*, the initial rate was 93.5% (58/62) as compared to 90.7% (117/129) in the current submission. For *Chlamydia pneumoniae*, the initial rate was 39/41 (95.1%), and for *Haemophilus influenzae* it was (33/38 (86.8%) as compared to 51/54 (94.4%) and 51/58 (87.9%) in the current resubmission. Of note, the large number of *Klebsiella pneumoniae* isolates as compared to the initial submission.

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The eradication rates of pathogens for the combined population of patients with a planned duration of treatment of 7 days are shown in the following table. Eradication rates for *Streptococcus pneumoniae* and *Mycoplasma pneumoniae* for the gemifloxacin treated patients were 89.9% and 85.2%, respectively (BPP population). For the comparator group, the corresponding rates for these pathogens were 91.1% and 82.9%

Table 21
Follow-Up: All CAP Studies (Patients with a Planned 7 Day Treatment Duration)

Follow-Up	Combined CAP studies 011, 12, 049, 185, 061 (CAP patients only) and 287							
	Bacteriology PP**				Bacteriology ITT			
	Gemifloxacin		All Comparators		Gemifloxacin		All Comparators	
	N=310		N=167		N=409		N=223	
	n/N*	%	n/N*	%	n/N*	%	n/N*	%
All Pathogens	332/382	(86.9)	166/190	(87.4)	393/511	(76.9)	201/264	(76.1)
<i>S. pneumoniae</i>	89/99	(89.9)	41/45	(91.1)	101/130	(77.7)	47/62	(75.8)
<i>M. pneumoniae</i>	69/81	(85.2)	58/70	(82.9)	85/107	(79.4)	68/83	(81.9)
<i>H. influenzae</i>	43/49	(87.8)	10/12	(83.3)	50/62	(80.6)	12/16	(75.0)
<i>C. pneumoniae</i>	31/32	(96.9)	21/23	(91.3)	36/45	(80.0)	25/31	(80.6)
<i>K. pneumoniae</i>	16/17	(88.9)	2/2	(100)	21/27	(77.8)	2/2	(100)
<i>M. catarrhalis</i>	11/11	(100)	1/1	(100)	13/13	(100)	1/1	(100)

Data Source: ISE Table 11.70a, Table 71a.

* n/N = number of pathogens eradicated or presumed eradicated / number of pathogens.

** Bacteriology PP populations at follow-up and end of therapy.

Notes: For patients with more than one type of pathogen, each patient is included in the count for each individual micro-organism. In all studies except Study 287, if a patient had more than one

Medical Officer's Comment: In an FDA analysis, pathogen eradication rates were assessed in subjects who received 7 days of treatment by study. As can be seen in the table below, pathogen eradication rates in studies where only the 7 day treatment option was available (011, 061, and 287) were similar to those in the sponsor's analysis. In the studies where patients could have received 7 or 14 days of treatment, eradication rates were also similar.

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Table 22
Bacterial response by pathogen for patients who received 7 days of treatment
Bact PP

	Studies 011, 061, 287		Studies 012, 049, 185	
	Gemi	Comp	Gemi	Comp
All pathogens	196/225 (87.1)	51/57 (89.5)	136/157 (86.6)	115/133 (86.5)
<i>S. pneumoniae</i>	68/77 (88.3)	18/19 (94.7)	22/22 (95.5)	23/26 (88.5)
<i>M. pneumoniae</i>	21/22 (95.5)	13/16 (81.3)	48/59 (81.4)	45/54 (83.3)
<i>H. influenzae</i>	30/35 (85.7)	5/5 (100.0)	13/14 (92.9)	5/7 (71.4)
<i>C. pneumoniae</i>	13/14 (92.9)	3/3 (100.0)	18/18 (100.0)	18/20 (90.0)
<i>K. pneumoniae</i>	14/16 (87.5)	2/2 (100.0)	2/2 (100.0)	-
<i>M. catarrhalis</i>	10/10 (100.0)	-	1/1 (100.0)	1/1 (100.0)

Treatment Failures:

Forty-seven of 415 (11%) gemifloxacin CAP controlled and uncontrolled patients in the BPP population at follow-up were classified as treatment failures as compared to 31 of 274 (11%) comparator-treated patients. Most clinical isolates were sensitive to gemifloxacin at screening with the exception of 3 isolates of *Pseudomonas aeruginosa* (gemifloxacin MICs = 0.12 ug/mL, 0.25ug/mL, and 4 ug/mL), one isolate of *Serratia marcescens* (gemifloxacin MIC = 0.25ug/mL) and one isolate of *B. cepacia* (gemifloxacin MIC = 1 ug/mL).

Eleven of the 47 treatment failures in the gemifloxacin group (23%) had documented microbiological evidence of persistence at the EOT or recurrence/new infection at follow-up; in the remainder of cases bacteriological failure was presumptive based on clinical response. Pathogens that persisted at end of therapy in individual patients were *Mycoplasma pneumoniae* (2 patients), *Klebsiella pneumoniae*, *beta-hemolytic Streptococcus group G* and _____ At follow-up, the following pathogens recurred: *Streptococcus pneumoniae*, *Mycoplasma pneumoniae* (3 patients), *Klebsiella pneumoniae*, and _____

Twelve patients who failed treatment in the BPP population had *Streptococcus pneumoniae* identified at screening; ten isolates were penicillin-susceptible and 2 isolates were penicillin-intermediate. With one exception, CAP due to *Streptococcus pneumoniae* in these treatment failures was monomicrobial. Two treatment failures with *Streptococcus pneumoniae* were bacteremic, three patients had CAP of moderate severity and one patient had severe CAP.

Among the 47 gemifloxacin-treated patients who were treatment failures in the BPP population, five patients were bacteremic at screening and two patients had severe CAP.

Among the 31 comparator patients who failed treatment, four patients were bacteremic and seven patients had severe CAP. Patients who were hospitalized comprised 60% (28/47) of treatment failures in the gemifloxacin group and 68% (21/31) of treatment failures in the combined comparator group.

Special Populations:

There was no evidence that age or gender had any effect on the clinical response to gemifloxacin. As the majority of patients were white (91.7% of gemifloxacin patients). Clinical success rates for the small number of black, oriental, and other race patients did not indicate any differential responses compared with the overall study population but the numbers of subjects was too small to allow for valid comparisons.

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Table 23
Clinical Response CPP Population at Follow-up/controlled Studies

		Clinical Response	Treatment Group	
			Gemifloxacin (N=697)	Comparators (N=698)
Age Group	>=18 to <40	Success	166 (92.7%)	167 (91.3%)
		Failure	13 (7.3%)	16 (8.7%)
	>=40 to <65	Success	243 (88.0%)	250 (90.9%)
		Failure	33 (12.0%)	25 (9.1%)
	>=65 to <75	Success	120 (89.6%)	125 (91.2%)
		Failure	14 (10.4%)	12 (8.8%)
	>=75	Success	102 (94.4%)	94 (91.3%)
		Failure	6 (5.6%)	9 (8.7%)
Gender	Male	Success	363 (90.5%)	362 (90.5%)
		Failure	38 (9.5%)	38 (9.5%)
	Female	Success	268 (90.5%)	274 (91.9%)
		Failure	28 (9.5%)	24 (8.1%)
Race	White	Success	580 (90.5%)	577 (91.2%)
		Failure	61 (9.5%)	56 (8.8%)
	Black	Success	28 (100.0%)	35 (87.5%)
		Failure	0	5 (12.5%)
	Oriental	Success	9 (81.8%)	10 (100.0%)
		Failure	2 (18.2%)	0
	Other	Success	14 (82.4%)	14 (93.3%)
		Failure	3 (17.6%)	1 (6.7%)

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Table 24

Clinical Response ITT Population at Follow-up				
			Treatment Group	
		Clinical Response	Gemifloxacin (N=947)	Comparators (N=927)
Age Group	>=18 to <40	Success	204 (81.6%)	197 (79.4%)
		Failure	46 (18.4%)	51 (20.6%)
	>=40 to <65	Success	290 (78.2%)	303 (82.6%)
		Failure	81 (21.8%)	64 (17.4%)
	>=65 to <75	Success	144 (81.8%)	136 (81.9%)
		Failure	32 (18.2%)	30 (18.1%)
	>=75	Success	124 (82.7%)	120 (82.2%)
		Failure	26 (17.3%)	26 (17.8%)
Gender	Male	Success	426 (79.8%)	434 (80.8%)
		Failure	108 (20.2%)	103 (19.2%)
	Female	Success	336 (81.4%)	322 (82.6%)
		Failure	77 (18.6%)	68 (17.4%)
Race	White	Success	687 (80.9%)	677 (82.3%)
		Failure	162 (19.1%)	146 (17.7%)
	Black	Success	44 (86.3%)	45 (69.2%)
		Failure	7 (13.7%)	20 (30.8%)
	Oriental	Success	12 (66.7%)	15 (88.2%)
		Failure	6 (33.3%)	2 (11.8%)
	Other	Success	19 (65.5%)	19 (86.4%)
		Failure	10 (34.5%)	3 (13.6%)

Clinical Response by duration of treatment:

The applicant provided analyses of clinical response by duration of treatment. Subjects were divided into those that received 7 days or less of treatment and those that received between 8 and 14 days of treatment. The decision to extend the duration of treatment was not made at the time of randomisation but at the on-therapy visit. If subjects were improved, the investigator had the option of extending the treatment duration. If patients

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were failing at the on-therapy visit, they were removed from study treatment and classified as failures. Thus an element of bias was introduced as no patient failing treatment at the On-Therapy visit could have been included in the 14-day group but only in the 7-day group. As per the Applicant, only subjects doing well at the On-Therapy visit could have had their treatment extended beyond 7 days. Thus the 14-day group results were artificially inflated and the 7-day results deflated in comparison to the 14-day group. Comparisons therefore between the 7- and 14-day groups of the same treatment arm should not be made.

Medical Officer's Comment: *From the Agency's standpoint, it could only be assumed that the investigator would have more often extended the treatment of more ill patients to 14 days, while less ill patients would be given only 7 days. When looking at demographics and baseline characteristics, it was noted that patients in the 14-day group were a few years older on average and that as the severity of disease increased a larger proportion of subjects received 14 days of treatment.*

The results of the applicant's meta-analysis demonstrated that the efficacy of gemifloxacin for patients with a planned 7-day treatment duration was at least as good as the combined comparator group for both the CPP, 95% CI (-6.5%, 6.9%) and ITT populations, 95% CI (-7.3%, 12.3%) as the lower limit of the 95% CI was -10%. The same conclusion of non-inferior clinical efficacy was drawn from the meta-analysis of the 14-day groups; lower limit of the confidence interval was -10% for both the CPP, 95% CI (-6.9%, 6.1%) and ITT populations, 95% CI (-6.1%, 5.6%).

Table 25
Rates of Clinical and Bacteriological Success at Follow-Up by
Planned Treatment Duration: CAP Combined Controlled Studies

	Success Rate		
	Gemifloxacin % (n/N)	Comparator % (n/N)	Treatment Difference % (95% CI)**
CLINICAL RESPONSE			
Clinical PP Follow-Up	N=697	N=698	
7 days*	90.2% (431/478)	90.7% (418/461)	0.2 (-6.5, 6.9)
14 days	91.3% (200/219)	92.0% (218/237)	-0.4 (-6.9, 6.1)
ITT	N=947	N=927	
7 days*	79.4% (504/635)	80.7% (492/610)	2.5 (-7.3, 12.3)
14 days	82.7% (258/312)	83.3% (264/317)	-0.3 (-6.1, 5.6)
BACTERIOLOGICAL RESPONSE			
Bacteriology PP Follow-Up	N=280	N=274	
7 days*	87.4% (153/175)	90.7% (146/167)	21.3 (-13.6, 56.1)
14 days	91.4% (96/105)	90.7% (97/107)	-0.2 (-7.6, 7.2)
Bacteriology ITT	N=381	N=355	
7 days*	76.9% (183/238)	77.6% (173/223)	3.3 (-7.5, 14.0)
14 days	83.9% (120/143)	87.1% (115/132)	-3.2 (-11.5, 5.2)

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Notes: N = number of patients in the analysis population, n = number of patients who were a success, N=number of patients included in the subgroup.

Medical Officer's Comment: *The bacteriologic response of the gemifloxacin BPP population at follow-up treated for 7 days, did not meet the 10% delta specified by the applicant. This difference did not extend to the 7 day BITT population. Similarly, the delta was also not met for the analysis of bacteriologic response for the BITT gemifloxacin-treated population treated for 14 days at follow-up. The significance of these analyses is unclear, as the studies were not powered for this parameter. Additionally, the 14-day results were artificially inflated, as fewer failures were included in this group.*

An assessment of the age of the subjects by duration revealed that the mean age for 793 PP gemifloxacin-treated subjects treated for 7 days was 52 (range 18 – 94) and was 52 for the 348 comparator-treated subjects (range 18 – 93). There were 219 gemifloxacin-treated subjects that received 14 days of treatment with a mean age of 56.9 (18 - 90) and there were 237 comparator patients with a mean age of 54.8 (range 18 –97). Thus, subjects in the 14 days treatment group, or those that required longer treatment were somewhat older than those in the 7 days groups.

In the Agency analysis, when the allowed comparisons between treatment groups are made, for both the 7-day fixed and the 7 – 14 day studies gemifloxacin clinical success rates were similar to those of the respective comparators.

Table 26
FDA Analysis of Clinical Response at Follow-up by Duration of Therapy

	Treatment Group	
	Gemifloxacin n/N (%)	Comparators n/N (%)
Clinical Per Protocol Population		
7-day Fixed studies*		
Controlled (011)	102/115 (88.7)	99/113 (87.6)
Uncontrolled (061, 287)	286/315 (90.8)	
Combined (Controlled and Uncontrolled)	388/430 (90.2)	
"7 - 14" day studies**		
7 days	329/363 (90.6)	319/348 (91.7)
14 days†	200/219 (91.3)	218/237 (92.0)
All patients	529/582 (90.9)	537/585 (91.8)
Intent-to-Treat Population		
7-day Fixed studies*		
Controlled (011)	129/167 (77.2)	121/153 (79.1)
Uncontrolled (061, 287)	325/363 (90.6)	
Combined (Controlled and Uncontrolled)	454/569 (79.8)	
"7 - 14" day studies**		
7 days	375/468 (80.2)	371/457 (81.2)

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14 days†	258/312 (82.7)	264/317 (83.3)
All patients	633/780 (81.2)	636/774 (82.0)

* includes Studies 011, 061, and 287

** includes Studies 012, 049, and 185 – all were controlled studies

† note: "14-days" includes all patients who were to receive a planned duration of therapy of >7 days.

Clinical Response by Severity:

As noted previously, the applicant retrospectively applied the Fine criteria as an indicator of severity of illness. Overall, of the 1012 subjects in the CPP gemifloxacin-treated population, 91 (9.9%) were classified as having severe disease (Fine classes IV and V). Similarly, of the 1349 gemifloxacin ITT patients, 129 (9.5%) had severe disease. **Of note however, of the 129 "severe" ITT gemifloxacin subjects, only 4 had class V disease and 125 had class IV disease. Of the 91 PP subjects with severe disease, 89 had class IV disease and 2 had class V disease. The mortality risk for class IV subjects ranges from 9 – 12%, whereas for class V subjects it is in the 30% range.**

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Table 27
Clinical Response Rate at Follow-Up for the CAP Population with Severe Disease

Study	Gemifloxacin	All Comparators	Treatment Difference (%)	95% CI (%)
CPP				
	n/N (%)	n/N (%)		
Pooled CPP* (Controlled)	631/697 (90.5)	636/698 (91.1)	-0.34	[-4.70, 4.02]
All CPP (Controlled and Uncontrolled)	917/1012 (90.6)	636/698 (91.1)		
Pooled Severe Controlled CPP*	74/78 (94.9)	57/67 (85.1)	7.82	[-0.21, 15.86]
All Severe CPP (Controlled and Uncontrolled)	85/91 (93.4)	57/67 (85.1)	-	-
ITT				
Pooled ITT* (Controlled)	762/947 (80.5)	756/927 (81.6)	-1.02	[-7.44, 5.39]
All ITT (Controlled and Uncontrolled)	1087/1349 (80.6)	756/927 (81.6)		
Pooled Severe ITT* Controlled	85/108 (78.7)	69/95 (72.6)	5.73	[-5.96, 17.42]
All Severe ITT (Controlled and Uncontrolled)	101/129 (78.3)	69/95 (72.6)	-	-

* Treatment difference and 95% CI based on random effects meta analysis performed for the controlled studies, using DerSimonian & Laird method, so the pooled treatment difference will not necessarily correspond to the difference in observed Gemifloxacin and 'All Comparators' response rates.

Medical Officer's Comment: Clinical response rates of CPP patients categorized as Fine class IV and V, were numerically superior to the response rates of the all controlled and all CAP CPP populations. Additionally, the response rates of the severe CAP patients treated with gemifloxacin were numerically superior to those of the severe comparator treated patients. Similar results were seen for the ITT populations, although response rates for the ITT populations were about 10 percentage points less than those for the per protocol populations. As noted previously, the severe gemifloxacin subjects were predominantly males, white and had a mean age of 76 (74 comparator).

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Table 28
Rates of Clinical and Bacteriological Success at Follow-Up by
Severity of CAP: CAP Combined Controlled Studies

	Success Rate		Treatment Difference % (95% CI)*
	Gemifloxacin % (n/N)	Comparator % (n/N)	
CLINICAL RESPONSE			
CAP Severity[§]			
Clinical PP Follow-Up	N=697	N=698	
Mild	90.2% (449/498)	91.9% (453/493)	
Moderate	89.3% (108/121)	91.3% (126/138)	
Severe	94.9% (74/78)	85.1% (57/67)	7.8 (-0.2, 15.9)
ITT	N=947	N=927	
Mild	80.9% (547/676)	82.8% (541/653)	
Moderate	79.8% (130/163)	81.6% (146/179)	
Severe	78.7% (85/108)	72.6% (69/95)	5.7 (-6.0, 17.4)
BACTERIOLOGICAL RESPONSE			
Bacteriology PP Follow-Up	N=280	N=274	
Mild	88.9% (185/208)	89.8% (185/206)	
Moderate	84.1% (37/44)	92.1% (35/38)	
Severe	96.4% (27/28)	76.7% (23/30)	
Bacteriology ITT	N=381	N=355	
Mild	79.7% (228/286)	82.6% (219/265)	
Moderate	76.3% (45/59)	84.0% (42/50)	
Severe	83.2% (30/36)	67.5% (27/40)	

Data Source: ISE Table 11.23a, 11.23b, 11.25a, 11.25b, 11.31a, 11.31b. ISE Appendix 8.G.1. Table 13, Table 14, Table 19 and Table 20.

Notes: N = number of patients in the analysis population. n = number of patients who were a success, N = number of patients included in the subgroup.

*Treatment difference and 95% CI based on random effects meta-analysis performed for the controlled studies, using DerSimonian & Laird method, so the pooled treatment difference will not necessarily correspond to the difference in observed Gemifloxacin and 'All Comparators' response rates [34].

§ As defined in Section 8.G.3.3

Medical Officer's Comment: Clinical response rates for CPP severe CAP patients treated with gemifloxacin, were higher than those seen for patients classified as having mild to moderate disease. However, the ITT analysis was the opposite with the severely ill patients having the lower response rates.

Fifty-seven patients with severe CAP in the combined gemifloxacin group (CPP population) were categorized as receiving 7 days of treatment. The clinical and bacteriological success rates for patients with severe CAP were comparable regardless of whether patients received 7 or 14 days of gemifloxacin treatment (PP populations). This difference did not extend to the ITT analyses. The applicant pointed out the lower response rates in the 7 day ITT analysis as compared to the 14 day and stated that the

lower rates were due to the inclusion of early failures and withdrawals in the 7-day group and not in the 14-day group

Table 29
Rates of Clinical and Bacteriological Success at Follow-Up for
Patients with Severe CAP by Planned Duration of Treatment: CAP Combined
All Studies

	Gemifloxacin		Comparator	
	Success Rate % (n/N)	95% CI	Success Rate % (n/N)	95% CI
CPP Follow-Up	N=91		N=67	
7 days*	94.7% (54/57)	85.4, 98.9	86.5% (32/37)	71.2, 95.3
14 days	91.2% (31/34)	76.3, 98.1	83.3% (25/30)	65.3, 94.2
ITT	N=129		N=95	
7 days*	74.4% (64/86)	63.9, 83.0	75.0% (39/52)	61.1, 85.7
14 days	86.0% (37/43)	72.1, 94.6	69.8% (30/43)	53.9, 82.4
BPP Follow-up	N=36		N=30	
7 days*	95.2% (20/21)	76.2, 99.9	66.7% (8/12)	34.9, 88.9
14 days	93.3% (14/15)	68.1, 99.8	83.3% (15/18)	58.6, 96.2
BITT	N=48		N=40	
7 days*	74.2% (23/31)	55.4, 87.7	56.3% (9/16)	29.9, 78.5
14 days	94.1% (16/17)	71.3, 99.8	75.0% (18/24)	53.3, 89.7

Data Source: ISE Appendix 8.G.1., Table 15, Table 16, Table 17, Table 18, Table 21, Table 22, Table 23 and Table 24.

* Includes all Study 011 patients although the comparator group received 10 days of treatment.

Additional analysis by the FDA statistician, revealed that 86 of the 129 ITT patients categorized as severe (Fine classes IV and V) received 7 days of treatment. 43 subjects received 14 days.

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Table 30
CAP Severity by Duration/ITT

		Gemifloxacin	Comparators
Overall	Mild	996	653
	Moderate	224	179
	Severe	129	95
7 day only (011, 061, 287)	Mild	440	93
	Moderate	88	44
	Severe	41	16
Controlled	Mild	120	
	Moderate	27	
	Severe	20	
Uncontrolled	Mild	320	
	Moderate	61	
	Severe	21	
Others (012, 049, 185)	Mild	556	560
	Moderate	136	135
	Severe	88	79
7 days	Mild	345	342
	Moderate	78	79
	Severe	45	36
14 days	Mild	211	218
	Moderate	58	56
	Severe	43	43

Subjects in the "severe" group were on average older and received more prolonged durations of treatment. As can be seen in the following table representing the agency's analysis, although efficacy in all severely ill subjects was high, there were very few patients treated with the 7 day fixed regimen. Also as noted previously, the 7 day group of the 7-14 day studies cannot be added to the fixed 7-day patient population and additionally, comparisons cannot be made between the 7 and 14 day regimens. Thus, the data currently available on severe patients are quite limited.

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Table 31
FDA Analysis of Clinical Response at Follow-up by Severity

<u>CPP</u>	7 day fixed		7 day		14 day		
	Gemi	Comp	Gemi uncount	Gemi	Comp	Gemi	Comp
Mild	73/84 (86.9)	57/67 (85.1)	236/257 (91.8)	246/272 (90.1)	241/261 (92.3)	130/141 (92.2)	155/165 (93.9)
Moderate	16/18 (88.9)	32/35 (91.4)	39/45 (86.7)	53/58 (91.4)	56/61 (91.8)	39/44 (88.6)	38/42 (90.5)
Severe	13/13 (100.0)	10/11 (90.9)	11/13 (84.6)	30/31 (96.8)	22/26 (84.6)	31/34 (91.2)	25/30 (83.3)

In addition to the classification of subjects by the Fine criteria, the applicant also assessed clinical response in hospitalized subjects to assess the effectiveness of gemifloxacin in more severe cases of CAP.

Medical Officer's Comment: *As the decision to hospitalize or not was investigator-driven in all studies except study 185, it would not appear that the presence or absence of this factor can be used as a determinant of severity of illness. Additionally, in study 185 where all subjects were hospitalized (gemifloxacin N= 172, comparator N = 173), only 36 of the 172 gemifloxacin subjects were classified to Fine classes IV and V. Approximately 80% of the subjects in that study that were hospitalized had mild to moderate disease, thus again raising the question of the appropriateness of using hospitalization alone as a criterion for severe CAP.*

The applicant provided further details on these subjects regarding intubation status, use of pressors or respiratory treatments. None of the subjects had documented use of any of these treatments at the time of enrollment. Six subjects required at least one of these concomitant treatments during the study and all were ultimately categorized as failures.

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