

Table 32
Rates of Clinical and Bacteriological Success at Follow-Up for Hospitalized Patients by Planned Duration of Treatment: All Studies

	Gemifloxacin		Comparator	
	Success Rate % (n/N)	95% CI	Success Rate % (n/N)	95% CI
Clinical PP Follow-Up	N=553		N=411	
7 days	89.4% (378/423)	86.0, 92.1	87.6% (226/258)	82.9, 91.3
14 days	90.8% (118/130)	84.4, 95.1	92.8% (142/153)	87.5, 96.3
ITT	N=760		N=539	
7 days	75.9% (444/585)	72.2, 79.3	77.2% (264/342)	72.4, 81.5
14 days	81.7% (143/175)	75.2, 87.1	82.7% (163/197)	76.7, 87.7
BPP Follow-Up	N=244		N=161	
7 days	87.1% (149/171)	81.2, 91.7	84.9% (73/86)	75.5, 91.6
14 days	91.8% (67/73)	83.0, 97.0	88.0% (66/75)	78.4, 94.3
Bacteriology ITT	N=332		N=213	
7 days	74.1% (177/239)	68.0, 79.4	72.4% (89/123)	63.6, 79.9
14 days	85.0% (79/93)	76.0, 91.4	85.6% (77/90)	76.6, 92.0

As can be seen in the following table of the Agency's analysis, the response rates of hospitalized patients were comparable between treatment arms.

Table 33
FDA Analysis of Clinical Response at Follow up in Hospitalized Patients

	Gemifloxacin n/N (%)	Comparators n/N (%)
Clinical Per Protocol Population		
7-day CAP studies		
Controlled (011)	90/103 (87.4)	97/111 (87.4)
Uncontrolled (061, 287)	141/157(89.8)	
Combined (Controlled and Uncontrolled)	231/260 (88.8)	
"7 - 14" day CAP studies		
7 days	147/163 (90.2)	129/147 (87.8)
14 days†	118/130(90.8)	142/153 (92.8)
All patients	265/293 (90.4)	271/300 (90.3)
ITT		
7-day CAP studies		
Controlled (011)	114/152 (75.0)	118/149 (79.2)
Uncontrolled (061, 287)	161/204(78.9)	
Combined (Controlled and Uncontrolled)	275/356 (77.2)	
"7 - 14" day CAP studies		
7 days	169/229 (73.8)	146/193 (75.6)
14 days†	143/175 (81.7)	163/197 (82.7)
All patients	312/404 (77.2)	309/309 (79.2)

As an additional indicator of the effectiveness of gemifloxacin in severe disease, the applicant elected to provide a separate analysis of outcome in bacteremic subjects. In the combined all studies dataset (CPP), 4.7% (48/1012 patients) of the gemifloxacin group had a positive blood culture at screening. For the combined all studies population, bacteremic patients who were treated with gemifloxacin had a clinical success rate at follow-up of 89.6% (CPP) and 89.4% for bacteriological response (BPP). The clinical and bacteriological response of bacteremic patients was examined by the planned duration of treatment for the combined all studies dataset. Of the 48 bacteremic patients in the combined gemifloxacin group (CPP), 25 patients were included in the 7-day duration group and 23 in the 14-day duration group. In the CPP population, the clinical success rate for patients who received 7 days of treatment in the combined gemifloxacin group was comparable with patients who received 7 days treatment in the combined comparator group; 84.0% vs. 82.6%.

For the ITT population of bacteremic patients, the clinical success rate was comparable between the combined gemifloxacin group (67.6%) and combined comparator group (69.7%). Bacteriological success rates were almost identical to the clinical success rates

Table 34
Rates of Clinical Success at Follow-Up for Patients with
Bacteremia by Planned Duration of Treatment:
CAP Combined All Studies

	Gemifloxacin		Comparator	
	Success Rate % (n/N)	95% CI	Success Rate % (n/N)	95% CI
Clinical PP Follow-Up	N=48		N=37	
CPP TOTAL	89.6% (43/48)		89.1% (33/37)	
7 days	84.0% (21/25)	63.9, 95.3	82.6% (19/23)	61.2, 94.8
14 days	95.7% (22/23)	78.1, 99.9	100.0% (14/14)	76.8, 100.0
ITT	N=62		N=52	
ITT TOTAL	79% (49/62)		78.8% (41/53)	
7 days	67.6% (25/37)	50.2, 81.4	69.7% (23/33)	51.3, 83.8
14 days	96.0% (24/25)	79.7, 99.9	90.0% (18/20)	68.3, 98.7

Data Source: ISE Appendix 8.G.1., Table 39, Table 40, Table 41 and Table 42.

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

In the Agency's analysis of bacteremic subjects, though clinical response rates were comparable between treatment arms, the sample size was too small to allow for valid comparisons.

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Table 35
FDA Analysis of Clinical Response at Follow up in Bacteremic Patients

	Gemifloxacin n/N (%)	Comparators n/N (%)
Clinical Per Protocol Population		
7-day Fixed studies		
Controlled (011)	8/8 (100.0)	10/11 (90.9)
Uncontrolled (061, 287)	9/13 (69.2)	
Combined (Controlled and Uncontrolled)	17/21 (81.0)	
"7 - 14" day studies		
7 days	4/4 (100.0)	9/12 (75.0)
14 days†	22/23 (95.7)	14/14 (100.0)
All patients	26/27 (96.3)	23/26 (88.5)
ITT Population		
7-day fixed studies		
Controlled (011)	9/11 (81.8)	12/16 (75.0)
Uncontrolled (061, 287)	10/15 (66.7)	
Combined (Controlled and Uncontrolled)	19/26 (73.1)	
"7 - 14" day studies		
7 days	6/11 (54.5)	11/17 (64.7)
14 days†	24/25 (96.0)	18/20 (90.0)
All patients	30/36 (83.3)	29/37 (78.4)

Thirty-seven of the 48 bacteremic gemifloxacin-treated subjects had *Streptococcus pneumoniae*. Twenty of these subjects received more than 7 days of treatment. Clinical success rates in these subjects were 35/37 PP (94.5%). In the > 7-day group the rate was 19/20 (95%).

Medical Officer's Additional Analyses:

Mortality

The clinical review team requested that the applicant provide tables of risk class specific mortality for all ITT patients and for in- and outpatients separately. Overall mortality was similar between the gemifloxacin and comparator-treated groups as well as between the gemifloxacin controlled and uncontrolled study patients with 12 deaths (1.3%) in the gemifloxacin controlled study patients, 13 deaths (1.4%) in the comparator-treated patients, and 5 deaths (1.2%) in the gemifloxacin-treated uncontrolled study patients. There were 17 deaths (1.3%) in all gemifloxacin-treated patients.

When mortality was assessed in the ITT population by in or outpatient status, it was apparent that most of the deaths occurred in the inpatients with 14 of 17 gemifloxacin deaths in inpatients (11 controlled and 3 uncontrolled) as compared to 12 of 13 deaths on the comparators arm.

When deaths were assessed by Fine class, it appeared that mortality rates for Class I, II, and III patients mortality rates were consistent with what was expected based on the publication by Fine et al.² In class IV subjects the mortality rates in the clinical studies appeared to be somewhat less than what was reported for Fine Class IV patients. There were too few class V subjects in the dataset to draw any conclusions for this class. (The mortality risk for class IV subjects ranges from 9 – 12%, whereas for class V subjects it is in the 30% range in the publication by Fine et al.)

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² Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, Coley CM, Marrie TJ, Kapoor WN. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med.* 1997 Jan 23;336(4):243-50.

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Table 36
For All Patients – Risk Class Specific Mortality Rates - CAP studies/ITT

Fine Class (score)*	Fine pneumonia Validation cohort		Comparative Studies				Non-Comparative Studies		All	
	Mortality		gemifloxacin		comparators		gemifloxacin		gemifloxacin	
	# of patients	% who died	# of patients	% who died	# of patients	% who died	# of patients	% who died	# of patients	% who died
			n	%	n	%	n	%	n	%
I	772	0.1	347	1 (0.3%)	369	3 (0.8%)	154	0	501	1 (0.2%)
II (<70)	477	0.6	330	2 (0.6%)	287	2 (0.7%)	166	3 (1.8%)	496	5 (1.0%)
III (71-90)	326	0.9	164	4 (2.4%)	181	3 (1.7%)	63	2 (3.2%)	227	6 (2.6%)
IV (91-130)	486	9.3	104	5 (4.8%)	90	4 (4.4%)	21	0	125	5 (4.0%)
V (>130)	226	27.0	4	0	5	1 (20.0%)	0	0	4	0
Total	2287	5.2	949	12 (1.3%)	932	13 (1.4%)	404	5 (1.2%)	1353	17 (1.3%)

* Inclusion in risk class I was based upon the absence of all predictors identified in step 1 of the Fine prediction rule.

Inclusion in risk classes II, III, IV, and V was determined by a patient's total risk score, which was computed according to the Fine scoring system.

Table design adapted from Table 3. in Fine MJ et al. N Engl J Med 1997;336:243-50.

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ON ORIGINAL****Regulatory History:****Ofloxacin (AP 2/95) NDA 19-735/SW-029 and NDA 20-087/S-009:**

The applicant submitted an NDA requesting the addition of _____ disease to their mild to moderate lower respiratory tract infection (CAP and NP) indication. Of note, the sponsor had both a PO and an IV formulation. The supplement consisted of 2 clinical studies, one, an open comparative trial of IV ofloxacin vs. ceftazidime in hospital acquired respiratory infection and the other a multicenter open trial of IV ofloxacin in the treatment of lower respiratory tract infections. . The protocol did not differentiate between CAP and NP. Additionally there was no guidance regarding acceptable serologies or quality of sputum specimens. The MO considered 8 subjects evaluable per arm in the first study and 84 in the second. Most subjects in both studies had severe pneumonia based on the applicant's criteria. These criteria used to define severe lower respiratory tract infection were divided into major and minor and a patients with severe disease had to have either 2 or more major criteria, 1 major and 3 minor criteria, 5 minor criteria, bacteremia, or Gram (-) or *Staphylococcus aureus* pneumonia. Major criteria included: bacteremia, temperature > 101.5F, immunosuppression, *Staphylococcus aureus* pneumonia, Gram (-) pneumonia, nosocomial pneumonia, mechanical ventilation, multilobar infiltration, abscess of empyema, ICU care, death during or after study, PT, tracheotomy, coma or cachexia. Minor criteria included a WBC < 5000 or > 15,000/mm³, bands > 40%, pulse > 110/min, RR > 28/min, systolic BP < 100 mm Hg, severe chills, malaise, chest pain, SOB, cough, sputum production, rales or raunchy, changes in percussion or a unilobar infiltrate. Of note these criteria were not based on any published literature and had not been validated. As per the MO, the best factors for predicting mortality were a RR of > 30/min, a diastolic BP of < 60 mm H, and a BUN > 19.6 mg/dL. Other than the presence of fever and increased WBC, the MO determined that the applicant had not provided an adequate severity scale. Additionally, the lack of differentiation between NP and CAP was a concern. Finally the applicant provided severity determinations only for subjects on the ofloxacin arm. The application to add severe infections to the label was denied.

Moxifloxacin: NDA 21-085 (AP 11/99)

The applicant did not distinguish among degrees of severity for CAP in their initial application. Patients with severe disease including those requiring parenteral treatment, ventilatory support, aspiration pneumonia, or underlying conditions were specifically excluded. Thus the reviewing MO determined that the INDICATIONS and USAGE section of the label should be modified to reflect the mild to moderate disease of the CAP population studied.

Levofloxacin NDA 20-634/20-635:

2 studies were submitted in support of the indication of CAP. Subjects with severe disease were defined as those with hypotension (diastolic BP < 60 mm Hg in the absence of volume depletion), subjects with mental status changes, subjects who required

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mechanical ventilation, subjects with bacteremia, and subjects with a baseline RR of > 28/min. This differentiation was utilized to determine mode of treatment (IV or PO) and duration of treatment at the time of randomization. In study K90-071, 190/226 CPP subjects (84%) treated with levofloxacin had mild to moderate disease as did 193/230 (84%) of the comparator-treated subjects. Thus 36 levofloxacin and 37 comparator CPP subjects or 16% had severe disease. 35/36 (97%) of the severe levofloxacin patients were considered cured or improved as compared to 34/37 (92%) of the comparator patients. In study M92-075, 36/163 bacteriologically evaluable levofloxacin-treated subjects (22%) had severe disease and the clinical response rate in these subjects was 35/36 (97%). Based on this data, the indication of mild, moderate, or severe CAP was granted.

PRSP:

There were 13 isolates of *Streptococcus pneumoniae*, isolated from 12 patients in the combined gemifloxacin group at screening that were resistant to penicillin (penicillin MIC of ≥ 2 mg/L) in the BPP population at follow-up and 15 isolates from 14 patients in the BITT population. Note that one patient had two isolates of PRSP isolated from sputum. There were a total of 126 PP and 165 ITT subjects with *Streptococcus pneumoniae* (12/126, 9.5%). 37 subjects were bacteremic with *Streptococcus pneumoniae*.

All 13 PRSP isolated from 12 patients in the BPP population in the combined gemifloxacin group were successfully eradicated (confirmed eradication/presumed eradication based on clinical success). The clinical and bacteriological success rates associated with PRSP were 100% (12/12 or 13/13). In the BITT population, there was one PRSP that was not eradicated in the combined gemifloxacin group; the pathogen eradication rate and the associated clinical and bacteriological response rates for this population were 13/14 (92.8%) and 14/15 (93.2%) respectively. Four patients in the combined comparator group of the gemifloxacin CAP studies had PRSP, which were successfully eradicated with corresponding 100% clinical and bacteriological success rates. Of the 14 bacteriologically evaluable ITT CAP patients (13 in the BPP follow-up population) with PRSP, 2 patients were assessed as having severe CAP and 3 patients had CAP of moderate severity. Three patients were bacteremic including 2 patients with severe CAP. In total, ten of the PRSP patients were hospitalized. All but one patient received 7 days treatment with gemifloxacin.

Of the PP subjects, there were 2 subjects with severe disease as well as 2 bacteremic subjects one of who had severe disease. 8 subjects were hospitalized. The duration of treatment in 1 subject was 14 days.

11 of the patients with PRSP also had cefuroxime and TMP-SMX-resistant isolates. 10 of these isolates were also resistant to macrolides.

Clinical success rates for all subjects with *Streptococcus pneumoniae* were 115/126 (91%) and 134/165 (81%).

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Medical Officer's Comment: In the levofloxacin SNDA 20-634 SE1-008 and NDA 20-635 SE1-007 there were 15 PP subjects identified with PRSP of 250 total subjects with CAP due to *Streptococcus pneumoniae*. 6 of the levofloxacin PRSP patients had severe disease and 6 PRSP subjects were bacteremic (total # of bacteremic subjects with *Streptococcus pneumoniae* (55). Clinical success was attained in all subjects (100%).

Telithromycin AC (January 8 2002): 27 PP subjects were identified with PRSP of 318 total subjects with CAP due to *Streptococcus pneumoniae*. 82 telithromycin-treated subjects were bacteremic with *Streptococcus pneumoniae*. Clinical success was achieved in 19/27 (70.3%) PRSP subjects and in 300/318 (94%) as well as in 5/7 bacteremic subjects. The AC voted to grant the indication of CAP due to PRSP in subjects with mild to moderate degrees of illness.

In the Augmentin XR NDA 50-785 resubmission, there were 20 ITT isolates of PRSP (15 evaluable) and 14 ITT PISP (13 PP PISP). Eradication rates were 14/15 (94%) for PRSP and 13/13 (100%) for PISP. 4 ITT subjects (20%) had severe disease (13% of the PRSP evaluable population) and 4 ITT subjects were bacteremic (2 evaluable).

Moxifloxacin NDA 21-085: The application was not approved as there were 7 cases of PRSP with a success rates of 5/7 (71%) and 15 cases of CAP due to PISP with an eradication rate of 13/15 (87%) for this oral quinolone.

Moxifloxacin IV NDA 21-277: This NDA combined information from 7 studies, 4 contributing PRSP isolates. There were 164 cases of *Streptococcus pneumoniae* related CAP with a clinical response rate of 149/164 (91%) (Uncontrolled 36/37 (97%), controlled 113/127 (90%). There were 34 cases of bacteremia and a cure rate of 30/34 (99%) and there were 13 cases of PRSP with a cure rate of 12/13 (92.3%). 2 cases (2/13 (15%) were bacteremic, 6 (46%) had severe disease determined by ATS criteria and 7/13 (54%) were hospitalized. The application was turned down on the grounds that the bar set by levofloxacin was not met.

Table 37
Penicillin Resistant *Streptococcus pneumoniae* and Regulatory Precedence

Antimicrobial	PRSP Success Rate	<i>Streptococcus pneumoniae</i> success rate	# Severe PP	#Bacteremic PP	Approval	#Bacteremic
Levofloxacin	15/15 (100%)	245/250 (98%)	6	6	YES	55
Moxifloxacin	6/8 (75%)	80/89 (90%)	None	0	NO	Unknown
Moxifloxacin IV and PO	12/13 (92.3%)	149/164 (91%)	6	2	NO	Unknown
Trovafloxacin	4/4 (100%) ITT	88/95 (93%)	Unknown	Unknown	NO	Unknown
Gatifloxacin	2/2 (100%)	59/85 (81%)	Unknown	Unknown	NO	Unknown
Augmentin XR	14/15 (94%)	Unknown	2	2	YES	Unknown
Telithromycin	19/27 (70.3%)	300/318 (94%)	3	7	YES	82
Gemifloxacin	12/12 (100%)	124/136 (91%)	2	2	?	37

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Table 38
Rates of Clinical Success, Bacteriological Eradication and Bacteriological Success at Follow-Up by
Streptococcus pneumoniae Screening Susceptibility to Penicillin: CAP

Susceptibility to Penicillin CAP	Combined Gemifloxacin 320 mg od [§]									
	Clinical Success		Bacteriology PP				Bacteriology ITT			
	n/N	(%)	Bacteriological Eradication*	Bacteriological Success**	Clinical Success	Bacteriological Eradication*	Bacteriological Success**	n/N	(%)	
	N=415					N=552				
Susceptible (≤ 0.06 ug/mL)	93/103	(90.3)	93/103 (90.3)	93/103 (90.3)	106/128 (82.8)	106/128 (82.8)	106/128 (82.8)	106/128	(82.8)	
Intermediate (0.12-1 ug/mL)	15/17	(88.2)	15/17 (88.2)	15/17 (88.2)	21/27 (77.8)	21/27 (77.8)	21/27 (77.8)	21/27	(77.8)	
Resistant (≥ 2 ug/mL)	13/13	(100)	13/13 (100)	13/13 (100)	14/15 (93.3)	14/15 (93.3)	14/15 (93.3)	14/15	(93.3)	
Missing	2/2	(100)	2/2 (100)	2/2 (100)	3/6 (50)	3/6 (50)	3/6 (50)	3/6	(50%)	
Not Done	1/1	(100)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	1/1	(100%)	
ALL	124/136	(91.2)	124/136 (91.2)	124/136 (100)	145/177 (81.9)	145/137 (81.9)	145/177 (81.9%)	145/177	(81.9%)	

Data Source: ISE Table 11.39a, Table 11.39b, Table 11.40a, Table 11.40b, Table 11.41a, Table 11.41b.

* Bacteriological eradication includes isolates that were eradicated or presumed eradicated.

** Bacteriological response is evaluated on a per patient basis and takes into account information on all initial and new pathogens.

§ Gemifloxacin treatment groups combined from the following studies: CAP studies 011, 012, 049, 185, 061 (CAP patients only), 287;

Notes:

n/N = number of successes or eradications / number of susceptible, intermediate or resistant isolates.

If a patient had more than one isolate of *S. pneumoniae* with MIC data, all of the isolates have been included in the susceptible, intermediate and resistant calculations in this table.

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Tables 39 and 40

Bacteriological Eradication and Clinical Cure for *Streptococcus pneumoniae* Pathogens by gemifloxacin MIC BPP Population

MIC (mg/ml)	n/N (%) Subjects	
	Bact. Eradication	Clinical Cure
0.002	2/2 (100)	2/2 (100)
0.008	23/25 (92)	23/25 (92)
0.015	58/64 (90.6)	58/64 (90.6)
0.03	25/27 (92.6)	25/27 (92.6)
0.06	1/1 (100)	1/1 (100)
NA*	3/4 (75)	3/4 (75)
ND**	3/3 (100)	3/3 (100)
Total	115/126 (91.3)	115/126 (91.3)

* NA = not available

**ND = not done

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MIC (mg/ml)	n/N (%) Subjects	
	Bact. Eradication	Clinical Cure
0.002	2/2 (100)	2/2 (100)
0.008	26/29 (89.7)	26/29 (89.7)
0.015	69/85 (81.2)	69/85 (81.2)
0.03	29/36 (80.6)	29/36 (80.6)
0.06	1/1 (100)	1/1 (100)
NA *	3/5 (60)	3/5 (60)
ND **	4/7 (57.1)	4/7 (57.1)
Total	134/165 (81.2)	134/165 (81.2)

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Table 41
All PRSP

PID	Severity* /Bactere- mic/ Hospital.	Clinical Response - EOT - F-U	Bacteriol. Response - EOT - F-U	Isolate Source	Pathogens (s)	Bacteriological Outcome - EOT - follow-up	Gemifloxacin MIC (ug/mL) screening/ EOT/F-U	Penicillin MIC (ug/mL) screening/ EOT/F-U	Clarithro/ Erythro MIC (ug/mL) screen/EOT/ F-U
Study 011									
011.017.05204* ^W Not included in PP because of ?	Mild/ Yes/ Yes	Success Success	Success Success	Blood	<i>S. pneumoniae</i>	Presumed eradication Presumed eradication	0.015 / - / -	2 / - / -	≤0.015 / - / - -
011.043.05283	Mild/ No/ Yes	Success Success	Success Success	Sputum	<i>S. pneumoniae</i>	Presumed eradication Presumed eradication	0.008 / - / -	2 / - / -	16 / - / -
011.052.05074	Severe/ Yes/ Yes	Success Success	Success Success	Blood	<i>S. pneumoniae</i>	Presumed eradication Presumed eradication	0.008 / - / -	2 / - / -	0.06 / - / -
011.115.05555	Moderate/ No/ Yes	Success Success	Success Success	Sputum Sputum	<i>S. pneumoniae</i> <i>M. catarrhalis</i>	Presumed eradication Presumed eradication Presumed eradication	0.015 / - / - 0.008 / - / -	2 / - / -	>16 / - / -
Study 049									
049.088.10538 > 7 days treatment	Moderate/ No/ Yes	Success Success	Success Success	Sputum	<i>S. pneumoniae</i>	Eradication Eradication	0.015 / - / -	4 / - / -	0.03 / - / -
049.088.10642	Severe/ Yes/ Yes	Success Success	Success Success	Blood Serol.	<i>S. pneumoniae</i> <i>C. pneumoniae</i>	Presumed eradication Presumed eradication Presumed eradication	0.015 / - / - - -	2 / - / - - -	>16 / - / - - -
Study 185									
185.153.29538	Moderate/ No/ Yes	Success Success	Success Success	Sputum Sputum	<i>S. pneumoniae</i> <i>S. pneumoniae</i>	Presumed eradication Presumed eradication Presumed eradication	0.015 / - / - 0.015 / - / -	2 / - / - 2 / - / -	32 / - / - >16 / - / - >32 / - / - >16 / - / -

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				Serol.	<i>M. pneumoniae</i>	Presumed eradication Presumed eradication	-	-	-
Study 287									
287.005.50002	Mild/ No/ No	Success Success	Success Success	Sputum	<i>S. pneumoniae</i>	Presumed eradication Presumed eradication	0.015 / - / -	4 / - / -	4 / - / - 8 / - / -
287.015.49893	Mild/ No/ No	Success Success	Success Success	Sputum	<i>S. pneumoniae</i>	Presumed eradication Presumed eradication	0.03 / - / -	2 / - / -	1 / - / - 2 / - / -
287.068.49520	Mild/ No/ Yes	Success Success	Success Success	Sputum	<i>S. pneumoniae</i>	Presumed eradication Presumed eradication	0.015 / - / -	2 / - / -	32 / - / - 16 / - / -
287.071.49522	Mild/ No/ No	Success Success	Success Success	Sputum	<i>S. pneumoniae</i>	Eradication Eradication	0.015 / - / -	2 / - / -	32 / - / - 16 / - / -
287.091.49306* [†] Not evaluable Received IV steroids days 5 – 8. EOT. Follow-up missing because determined failure at EOT and received 1 week additional R/x.	Mild/ No/ Yes	Failure Failure	Failure Failure	Sputum	<i>S. pneumoniae</i>	Presumed persistence Missing/EOT Failure	0.015 / - / -	2 / - / -	32 / - / - 16 / - / -
287.098.49392	Mild/ No/ Yes	Success Success	Success Success	Sputum	<i>S. pneumoniae</i>	Presumed eradication Presumed eradication	0.008 / - / -	2 / - / -	2 / - / - 2 / - / -
				Sputum	<i>K. pneumoniae</i>	Presumed eradication	0.12 / - / -		
287.104.50042	Mild/ No/	Success Success	Success Success	Sputum	<i>S. pneumoniae</i>	Presumed eradication Presumed eradication	0.06 / - / -	4 / - / -	>32 / - / - >16 / - / -

* Patients excluded from the Bacteriology Per Protocol Follow-Up population

† Patients excluded from the Clinical Per Protocol Follow-Up population

Note: Susceptibility to penicillin defined as: susceptible = ≤ 0.06 ug/mL, intermediate = 0.12-1 ug/mL, resistant = ≥ 2 ug/mLAPPEARS THIS WAY
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Macrolide-Resistant *Streptococcus pneumoniae* (MRSP):

The applicant has also submitted labeling requesting macrolide-resistant *Streptococcus pneumoniae*. This request was also made at the time of the original submission. In response to an agency request, the applicant submitted a discussion and literature to support their claim. As per the original reviewing MO:

“Among the data cited are the results from recent studies by Thornsberry et al that found a prevalence rate of 22% for macrolide-resistant *S. pneumoniae* among *S. pneumoniae* respiratory tract isolates from the 1997-1998 respiratory infections season.³ Also noted is a study by Jacobs et al from 1998 that found a prevalence rate of 30% in the US for macrolide-resistant *S. pneumoniae*.⁴ In the Jacobs study, considerable variability in prevalence rates for MRSP across geographic regions within the US was noted with rates varying from 22.5% to 44%.”

“The Applicant also notes that the amount of data on the effect of macrolide-resistance on clinical outcomes in the literature is limited at this time. The Applicant cites several case reports where patients with macrolide-resistant *S. pneumoniae* clinically deteriorated while receiving macrolide therapy for a macrolide-resistant *S. pneumoniae* isolate”.

This topic was the subjects of a discussion involving ODEIV. An agreement was reached that an out-of-class resistance claim for MRSP should not be entertained because macrolides were not considered the most important therapeutic option for the treatment of infections due to *Streptococcus pneumoniae*, macrolide resistance among *Streptococcus pneumoniae*, while a problem, did not represent a major public health problem among drug-resistant *Streptococcus pneumoniae* and the awarding an out-of-class resistance claim for MRSP, when a claim for PRSP was already available for sponsors to pursue was unlikely to provide any additional public health benefit.

Also of note was that 2 other sponsor's with fluoroquinolones with respiratory tract indications previously submitted proposed claims or plans to pursue a proposed claim for MRSP in CAP (Bayer – Avelox and RWJ/PRI – Levaquin). Following a request for scientific evidence in support of the proposed claim, both of these sponsors either withdrew or put plans on hold to pursue an MRSP claim within the indication of CAP.

At the time of the original submission, the applicant provided information about a subset of subjects with clarithromycin-resistant *Streptococcus pneumoniae*. In the BPP

³ Thornsberry C, Jones ME, Hickey ML, Mauriz Y, Kahn J, and Sahn DF. Resistance surveillance of *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* in the United States, 1997-1998. J Antimicrob Chemother 1999;44:749-759.

⁴ Jacobs MR, Bajaksouzian S, Lin G, Zilles A, Pankuch GA, and Appelbaum PC. 1999. Susceptibility of *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* to oral agents: results of a 1998 US outpatient surveillance study. 39th Interscience Conference on Antimicrobial Agents and Chemotherapy. San Francisco, California.

population 7/8 (87.5%) gemifloxacin-treated patients with MRSP achieved clinical success and bacteriological eradication at follow-up. For comparator-treated patients in the BPP population, 9/9 (100%) achieved clinical success and bacteriological eradication. In the BITT population, 9/15 (60.0%) of the gemifloxacin-treated patients with MRSP achieved clinical success and bacteriological eradication. For comparator-treated patients in the BITT population with MRSP, 11/11 (100%) achieved clinical success and bacteriological eradication.

In the current submission, with the addition of 2 studies (randomized controlled study 185 and open study 287), the applicant presented data on 36 BITT gemifloxacin-treated MRSP patients of whom 25 were included in the CPP and BPP populations. There were 14 BITT comparator-treated subjects of whom 12 were in the BPP and CPP populations.

Of the 25 BPP gemifloxacin MRSP, 10 (40%) were also PRSP (11/36 BITT, 30%). All subjects with PRSP and MRSP were clinical successes with presumed eradication at follow-up. 8 had mild disease, one had moderate disease, and 1 had severe disease. 3 PP MRSP subjects were bacteremic of whom 2 had mild disease and 1 had severe disease. All 3 were successfully treated with presumed eradication. There were an additional 2 BITT subjects who were bacteremic, both were categorized as severe and outcome was not determined in either case. Of note, there were 2 PP subjects with moderate disease and the remaining subjects were classified as mild or in the cases of the subjects from the original submission, as not severe.

Overall clinical success and bacteriologic eradication rates on the gemifloxacin arm were 22/25 (88%) for the PP population. For the MRSP ITT gemifloxacin-treated population, there were 27/36 (75%) clinical successes, 4 failures and 5 "unable to determine". Similar results were obtained for the BITT population, with 3 isolates presumed persistent and 6 "unable to determine".

Of the 12 BPP comparator-treated MRSP subjects, 4 were bacteremic. All were clinical successes with presumed eradication, 2 of these subjects had non-severe disease, and 2 were considered severe. Overall clinical and bacteriological success rate on the comparators arm was 11/12 (91.6%). 3 of the 12 BPP subjects were also PRSP.

The issue of macrolide-resistant *Streptococcus pneumoniae* was addressed at the January 8, 2002 advisory committee meeting within the context of the telithromycin approval. Although the committee did not specifically address the issue of the public health benefits associated with the recognition of MRSP as a pathogen, the committee voted to grant the indication.

At the March 4, 2003 DAIDP AC, the issue of MDRSP (multi-drug resistant *Streptococcus pneumoniae*) was discussed. It was the committee's determination that penicillin resistant, macrolide resistant, and cefuroxime-resistant *Streptococcus pneumoniae* are not separate entities but the same and that an approval should be granted for MDRSP and not for each separately.

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<u>Gemifloxacin</u> Patient #	<u>Indication</u>	<u>Isolate</u> <u>Source</u>	<u>Clari</u> <u>MIC</u> (mcg/mL)	<u>Gemi</u> <u>MIC</u> (mcg/mL)	<u>Table 42</u> <u>Clinical</u> <u>Outcome</u>	<u>Micro</u> <u>Outcome</u>	<u>Bacter-</u> <u>emic</u>	<u>Hospital-</u> <u>ized</u>	<u>Severe</u> <u>CAP</u>	<u>MRSP</u>	<u>PRSP</u>	<u>ER</u>
011.017.05408	CAP	Sputum	>16	0.015	Failure	Pres. Persist.	No	Yes	No	Yes		ND
011.043.05283	CAP	Sputum	16	0.008	Success	Pres. Erad.	No	Yes	No	Yes	Yes	ND
011.043.05285* ^ψ	CAP	Blood	>16	0.015	UTD ^a	UTD ^a	Yes	Yes	Yes	Yes		ND
011.046.05208	CAP	Sputum	2	0.015	Success	Pres. Erad	No	Yes	No	Yes		ND
011.111.05111* ^ψ	CAP	Blood	>16	0.030	UTD ^a	UTD ^a	Yes	Yes	No	Yes		ND
011.115.05555	CAP	Sputum	>16	0.015	Success	Pres. Erad.	No	Yes	No	Yes	Yes	ND
011.123.05674* ^ψ	CAP	Sputum	>16	0.015	Success	Pres. Erad.	No	Yes	Yes	Yes		ND
049.019.10812	CAP	Sputum	8	0.008	Success	Pres. Erad.	No	No	No	Yes		ND
049.037.10748	CAP	Sputum	>16	0.008	Success	Pres. Erad.	No	No	No	Yes		ND
049.085.11359	CAP	Sputum	>16	0.008	Success	Pres. Erad.	No	No	No	Yes		ND
049.088.10642	CAP	Blood	>16	0.015	Success	Pres. Erad.	Yes	Yes	Yes	Yes	Yes	ND
061.034.13831* ^ψ	CAP	Sputum	>16	0.030	Success	Pres. Erad.	No	Yes	N/A ^a	Yes		ND
061.043.13827* ^ψ	CAP	Sputum	>16	0.008	UTD ^a	UTD ^a	No	No	N/A ^a	Yes		ND
061.058.13806* ^ψ	CAP	Sputum	>16	0.015	UTD ^a	UTD ^a	No	Yes	N/A ^a	Yes		ND
061.058.13929* ^ψ	CAP	Sputum	>16	0.015	UTD ^a	UTD ^a	No	Yes	N/A ^a	Yes		ND
185.022.29339* ^ψ	CAP	Respiratory	> 32	0.03	Success	Pres. Erad	No	Yes	Severe	Yes		Yes
185.153.29538	CAP	Sputum	> 32	0.015	Success	Pres. Erad	No	Yes	Moderat	Yes	Yes	Yes
185.603.30181	CAP	Blood	4	0.015	Success	Pres. Erad	Yes	Yes	Mild	Yes		Yes
287.002.49883	CAP	Sputum	16	0.008	Success	Pres. Erad	No	Yes	Moderat	Yes		Yes
287.005.49830* ^ψ	CAP	Sputum	4	0.015	Failure	UTD	No	No	Severe	Yes		Yes
287.005.49975	CAP	Sputum	4	0.03	Success	Pres. Erad	No	No	Mild	Yes		Yes
287.005.50002	CAP	Sputum	4	0.015	Success	Pres. Erad	No	No	Mild	Yes	Yes	Yes
287.015.49893	CAP	Sputum	1	0.03	Success	Pres. Erad	No	No	Mild	Yes	Yes	Yes
287.042.29742* ^ψ	CAP	Sputum	1	0.015	Success	Pres. Erad ^a	No	No	Mild	Yes		NO
287.061.49443	CAP	Sputum	1	0.015	Success	Pres. Erad	No	Yes	Mild	Yes		Yes
287.062.49487	CAP	Blood	32	0.015	Success	Pres. Erad	Yes	Yes	Mild	Yes		Yes
287.064.49061	CAP	Sputum	2	0.008	Failure	Pres. Pers.	No	Yes	Mild	Yes		Yes
287.064.49065	CAP	Sputum	1	0.015	Success	Pres. Erad	No	Yes	Mild	Yes		Yes
287.068.49520	CAP	Sputum	32	0.015	Success	Pres. Erad	No	Yes	Mild	Yes	Yes	Yes
287.071.49521	CAP	Sputum	32	0.008	Failure	Pres. Pers.	No	No	Mild	Yes		Yes
287.071.49522	CAP	Sputum	32	0.015	Success	Pres. Erad	No	No	Mild	Yes	Yes	Yes
287.084.49201	CAP	Sputum	2	0.008	Success	Pres. Erad	No	Yes	Mild	Yes		Yes
287.091.49301	CAP	Sputum	32	0.015	Success	Pres. Erad	No	Yes	Mild	Yes		Yes
287.091.49306* ^ψ	CAP	Sputum	32	0.015	Success	Pres. Erad	No	Yes	Mild	Yes	Yes	Yes
287.098.49392	CAP	Sputum	2	0.008	Success	Pres. Erad	No	Yes	Mild	Yes	Yes	Yes
287.104.50042	CAP	Sputum	> 32	0.06	Success	Pres. Erad	No	No	Mild	Yes	Yes	Yes

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Comparator Patient #	Indication	Isolate Source	Clari MIC (mcg/mL)	Gemi MIC (mcg/mL)	Clinical Outcome	Micro Outcome	Bacter-emic	Hospital-ized	Severe CAP	MRSP	PRSP	ER
011.024.05107	CAP	Sputum	>16	0.008	Success	Pres. Erad.	No	Yes	No	Yes		
011.029.05137	CAP	Sputum	>16 ^b	0.015 ^b	Success	Pres. Erad.	No	Yes	Yes	Yes		
011.045.05189	CAP	Blood & Sputum	2 & >16 ^c	0.015 ^c	Success	Pres. Erad.	Yes	Yes	Yes	Yes		
011.152.05644	CAP	Sputum	>16	0.015	Success	Eradiated	No	No	No	Yes		
011.161.05879**	CAP	Sputum	8	0.015	Success	Pres. Erad.	No	Yes	No			
011.194.25910	CAP	Blood	8 ^d	0.015 ^d	Success	Pres. Erad.	Yes	Yes	Yes	Yes		
012.061.17855	CAP	Blood & Resp	8 ^e	0.015 & <0.001 ^e	Success	Pres. Erad.	Yes	Yes	No	Yes		
012.072.10463	CAP	Sputum	1	0.015	Success	Pres. Erad.	No	No	No	Yes		
012.301.22505	CAP	Blood	>16	<0.001	Success	Pres. Erad.	Yes	No	No	Yes		
049.038.11133**	CAP	Sputum	2	0.008	Success	Pres. Erad.	No	No	No	Yes		
049.088.10528	CAP	Sputum	8	0.015	Success	Eradiated	No	Yes	No	Yes		
185.305.29814	CAP	Respiratory	4	0.015	Success	Pres. Erad.	No	Yes	Severe	Yes	Yes	
185.305.29900	CAP	Sputum	1	0.015	Failure	Pres. Pers.	No	Yes	Severe	Yes	Yes	
185.351.29734	CAP	Sputum	1	0.015	Success	Pres. Erad.	No	Yes	Mild	Yes	Yes	

* Patients excluded from the Bacteriology Per Protocol follow-up population
 ** Patients excluded from the Clinical Per Protocol follow-up population
 † UTD = Unable to Determine NA = Not available
 ‡ This patient had two *S. pneumoniae* isolates from sputum both with the same clarithromycin and gemifloxacin MICs
 § This patient had *S. pneumoniae* isolated from blood (Clari MIC = 2 mcg/mL, Gemi MIC = 0.015 mcg/mL) and two isolates from sputum, both with Clari MIC >16 mcg/mL and Gemi MIC = 0.015 mcg/mL
 ¶ This patient had two *S. pneumoniae* isolates from blood both with the same clarithromycin and gemifloxacin MICs
 †† This patient had *S. pneumoniae* isolated from blood (Clari MIC = 8 mcg/mL, Gemi MIC = 0.015 mcg/mL) and sputum (Clari MIC = 8 mcg/mL, Gemi MIC = < 0.001 mcg/mL)

Note: Susceptibility to clarithromycin defined as:
 susceptible = ≤0.25 ug/mL, intermediate = 0.5 ug/mL, resistant = ≥1 ug/mL

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***Streptococcus pneumoniae* resistant to other antibacterials:**

The applicant provided information regarding the clinical and bacteriological efficacy of gemifloxacin at follow-up for isolates of *Streptococcus pneumoniae* from gemifloxacin-treated patients in CAP studies that were resistant to cefuroxime and quinolones (ofloxacin and levofloxacin). Since there are no NCCLS approved breakpoints for ciprofloxacin, efficacy was assessed by ciprofloxacin MIC.

In the combined CAP gemifloxacin group (BPP population) there were

- 18 patients with *Streptococcus pneumoniae* resistant to cefuroxime with an MIC of \geq 4 ug/mL.
- 12 of the 18 cefuroxime-resistant isolates were also penicillin resistant (3 with an MIC of 4 mcg/mL and 9 with an MIC of 2 mcg/mL).
- 15 of the 18 cefuroxime-resistant isolates were also clarithromycin resistant (10 with MICs of 16 mcg/mL or $>$, 1 with an MIC of 4 mcg/mL, 3 with an MIC of 3 and 1 with an MIC of 1
- 4 subjects had severe disease, 3 had moderate disease, and 11 had mild disease.
- 2 severe subjects were bacteremic. One subject with mild disease was also bacteremic.

Clinical success and bacteriological eradication/presumed eradication rates at follow-up for the BPP population with cefuroxime-resistant isolates of *Streptococcus pneumoniae* were 17/18 (94.4%). The failure was in a subject with mild disease who was not bacteremic but was hospitalized. This subject's isolate was clarithromycin-resistant (MIC 2 mcg/mL) but penicillin sensitive (MIC 1 mcg/mL).

On the comparators arm there were 7 subjects with *Streptococcus pneumoniae* isolates (PP) resistant to cefuroxime and all successfully treated (ITT 8). 4 of these isolates were also penicillin-resistant and 5 were also clarithromycin resistant. 2 subjects had severe disease, 1 had moderate disease, and 4 had mild disease. 3 subjects were bacteremic including 1 with severe disease and 2 with mild disease.

In the gemifloxacin group of the combined studies population, there were no pathogens resistant to ofloxacin and levofloxacin as identified by NCCLS breakpoints. There was 1 resistant isolate on the all comparators arm that was a clinical and bacteriological failure.

In the gemifloxacin group there were 4 isolates of *Streptococcus pneumoniae* with an MIC against ciprofloxacin of 4 ug/mL (all 4 isolates were from patients with a planned treatment duration of 7 days). The clinical and bacteriological success rate associated with these isolates was 100%. There were 2 PP and 3 ITT isolates with ciprofloxacin MIC's of 4 (2 isolates) and $>$ 16 (1 isolate). One PP isolate was successfully treated and the others were associated with clinical failure.

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PID	PP F/U?	Severity*/ Bacteremic/ Hospital	Clari MIC	Gemi MIC	Pen MIC	Cipro MIC	Table 43		Pathogens	Clinical Response F/U	Isolate Source	Bacteriol. Response F/U
							Cefurox MIC	Levo MIC				
011.017.05204	N	Mild/Yes/Yes	<=0.015	0.015	2	1	4	0.5	S pneumoniae	Success	Blood	Presum Bac Erad
011.043.05283	Y	Mild/No/Yes	16	0.008	2	1	8	0.5	S pneumoniae	Success	Sputum	Presum Bac Erad
011.052.05074	Y	Severe/Yes/Yes	0.06	0.008	2	1	8	0.5	S pneumoniae	Success	Blood	Presum Bac Erad
011.115.05555	Y	Moder/No/Yes	>16	0.015	2	1	8	1	S pneumoniae M catarrhalis	Success Success	Sputum Sputum	Presum Bac Erad Presum Bac Erad
011.123.05674	N	Severe/No/Yes	>16	0.015	1	1	4	1	S pneumoniae S aureus	Success	Sputum Sputum	Presum Bac Erad Missing
049.088.10538	Y	Moder/No/Yes	0.03	0.015	4	1	8	1	S pneumoniae	Success	Sputum	Bacteriol Erad
049.088.10642	Y	Severe/Yes/Yes	>16	0.015	2	0.5	4	0.5	S pneumoniae C pneumoniae	Success Success	Blood Serology	Presum Bac Erad Presum Bac Erad
185.153.29538	Y	Moder/No/Yes	>32	0.015	2	1	4	1	S pneumoniae M pneumoniae	Success Success	Sputum Serology	Presum Bac Erad Presum Bac Erad
287.005.50002	Y	Mild/No/No	4	0.015	4	1	8	1	S pneumoniae	Success	Sputum	Presum Bac Erad
287.015.49893	Y	Mild/No/No	1	0.03	2	2	4	1	S pneumoniae	Success	Sputum	Presum Bac Erad
287.053.60042	Y	Mild/No/No	0.03	0.015	1	2	4	0.5	S pneumoniae	Success	Sputum	Presum Bac Erad
287.062.49487	Y	Mild/Yes/Yes	32	0.015	1	0.5	2	0.5	S pneumoniae	Success	Blood	Presum Bac Erad
287.064.49061	Y	Mild/No/Yes	2	0.008	1	0.5	2	0.25	S pneumoniae	Failure	Sputum	Presum Persist
287.068.49520	Y	Mild/No/Yes	32	0.015	2	0.5	4	0.25	S pneumoniae	Success	Sputum	Presum Bac Erad
287.071.49522	Y	Mild/No/No	32	0.015	2	0.5	4	0.5	S pneumoniae	Success	Sputum	Bacteriol Erad
287.083.49659	Y	Severe/No/Yes	0.015	0.015	0.015	1	32	0.5	S pneumoniae K pneumoniae	Success Success	Sputum Sputum	Presum Bac Erad Presum Bac Erad

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287.084.49201	Y	Mild/No/Yes	2	0.008	1	0.25	4	0.25	S pneumoniae	Success	Sputum	Presum Bac Erad
287.091.49301	Y	Mild/No/Yes	32	0.015	1	1	4	0.5	S pneumoniae	Success	Sputum	Presum Bac Erad
287.098.49392	Y	Mild/No/Yes	2	0.008	2	0.5	4	0.5	S pneumoniae	Success	Sputum	Presum Bac Erad
									K pneumoniae	Success	Sputum	Presum Bac Erad
287.104.50042	Y	Mild/No/No	>32	0.06	4	4	8	1	S pneumoniae	Success	Sputum	Presum Bac Erad

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Beta-Lactamase Production by *H. influenzae* and Other Pathogens:

The clinical and bacteriological efficacy of gemifloxacin at follow-up was evaluated against beta-lactamase producing strains of *H. influenzae*, *H. parainfluenzae*, _____ and *M. catarrhalis*. In the combined dataset from controlled and uncontrolled studies (Bacteriology PP population), the proportion of strains of these pathogens isolated from gemifloxacin treated patients which were found on testing to be beta-lactamase producers were as follows:

- *Haemophilus influenzae*: 12.5% (7/56 isolates)
- *H. parainfluenzae*: 5.3% (1/19 isolates)
- _____
- *M. catarrhalis*: 92.9% (13/14 isolates)

In these subjects, clinical success rates at follow-up were 6/7 (85.7%) for beta-lactamase positive *H. influenzae*, 1/1 for beta-lactamase positive *H. parainfluenzae*, 21/23 (91.3%) for beta-lactamase positive _____ and 12/13 (92.3%) for beta-lactamase positive *M. catarrhalis*.

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Table 44 Rates of Clinical Success, Bacteriological Eradication and Bacteriological Success at Follow-Up by *S. pneumoniae* Screening Susceptibility to Other Antibacterial Agents: CAP Combined Controlled and Uncontrolled Studies

Gemifloxacin 320 mg od[§]

	Clinical Success		Bacteriology PP				Bacteriology ITT			
	n/N	(%)	Bacteriological Eradication*	Bacteriological Success**	Clinical Success		Bacteriological Eradication*	Bacteriological Success**		
			n/N (%)	n/N (%)	n/N (%)		n/N (%)	n/N (%)	n/N (%)	
Erythromycin susceptibility			N=415				N=552			
Susceptible (≤ 0.25 ug/mL)	46/52	(88.5)	46/52 (88.5)	46/52 (88.5)	51/61 (83.6)		51/61 (83.6)	51/61 (83.6)	51/61 (83.6)	
Intermediate (0.5 ug/mL)	-	-	--	-	-		-	-	-	
Resistant (≥ 1 ug/mL)	17/18	(94.4)	17/18 (94.4)	17/18 (94.4)	18/21 (85.7)		18/21 (85.7)	18/21 (85.7)	18/21 (85.7)	
Clarithromycin Susceptibility			N=415				N=552			
Susceptible (≤ 0.25 ug/mL)	96/105	(91.4)	96/105 (91.4)	96/105 (91.4)	113/131 (86.3)		113/131 (86.3)	113/131 (86.3)	113/131 (86.3)	
Intermediate (0.5 ug/mL)	1/1	(100)	1/1 (100)	1/1 (100)	1/1 (100)		1/1 (100)	1/1 (100)	1/1 (100)	
Resistant (≥ 1 ug/mL)	24/27	(88.9)	24/27 (88.9)	24/27 (88.9)	27/38 (71.1)		27/38 (71.1)	27/38 (71.1)	27/38 (71.1)	
Cefuroxime Susceptibility			N=415				N=552			
Susceptible (≤ 1 ug/mL)	103/114	(90.4)	103/114 (90.4)	103/114 (90.4)	118/141 (83.7)		118/141 (83.7)	118/141 (83.7)	118/141 (83.7)	
Intermediate (2 ug/mL)	-	-	--	-	2/4 (50.0)		2/4 (50.0)	2/4 (50.0)	2/4 (50.0)	
Resistant (≥ 4 ug/mL)	17/18	(94.4)	17/18 (94.4)	17/18 (94.4)	20/24 (83.3)		20/24 (83.3)	20/24 (83.3)	20/24 (83.3)	
Ciprofloxacin MIC			N=415				N=552			
0.25 ug/mL	1/1	(100)	1/1 (100)	1/1 (100)	1/1 (100)		1/1 (100)	1/1 (100)	1/1 (100)	
0.5 ug/mL	24/28	(85.7)	24/28 (85.7)	24/28 (85.7)	29/37 (78.4)		29/37 (78.4)	29/37 (78.4)	29/37 (78.4)	
1 ug/mL	70/76	(92.1)	70/76 (92.1)	70/76 (92.1)	82/96 (85.4)		82/96 (85.4)	82/96 (85.4)	82/96 (85.4)	
2 ug/mL	22/24	(91.7)	22/24 (91.7)	22/24 (91.7)	25/32 (78.1)		25/32 (78.1)	25/32 (78.1)	25/32 (78.1)	
4 ug/mL	4/4	(100)	4/4 (100)	4/4 (100)	4/4 (100)		4/4 (100)	4/4 (100)	4/4 (100)	

* Bacteriological eradication includes isolates that were eradicated or presumed eradicated.

** Bacteriological response is evaluated on a per patient basis and takes into account information on all initial and new pathogens.

§ Gemifloxacin treatment groups combined from the following CAP studies: 011, 012, 049, 185, 061 (CAP patients only), 287.

Notes:

n/N = number of successes or eradications / number of susceptible, intermediate or resistant isolates

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A review of the MOR of the original submission revealed that there were 10 ITT patients with *Klebsiella pneumoniae* isolated in a respiratory sample with a clinical success rate of 80% (8/10) and a bacteriologic success rate of 60% (6/10 isolates eradicated or presumed eradicated). The difference in clinical and bacteriologic success rates at the follow-up visit was accounted for by 2 subjects, the first, 061.031.13854, was a clinical success with bacteriologic persistence at the EOT and carried forward as a failure and patient 061.039.13895 was a clinical success with presumed eradication at the EOT and recurrence at the follow-up visit. Ninety percent (9/10) of these subjects were classified as having mild disease, and only 1 had moderate disease (061.058.13927, success). Five of 10 subjects were hospitalized including the one subject with moderate disease. 3 subjects had *Klebsiella pneumoniae* in conjunction with another pathogen including *Escherichia coli* from the sputum in 049.016.10678 (mild disease, not hospitalized, clinical success), *Pseudomonas* spp. in subject 049.017.10652 (mild, not hospitalized, success), and *Streptococcus pneumoniae* in subject 061.058.13806 (mild, hospitalized, classified as a failure due to missing data).

In the resubmission, there were 29 ITT subjects with *Klebsiella pneumoniae* isolated in a respiratory sample. Included were an additional 4 subjects from study 185 (ITT) with *Klebsiella pneumoniae* isolated from the sputum in 3 subjects, and from the blood and the sputum in 1. One case where the *Klebsiella pneumoniae* was isolated from the sputum only (185.022.29338) was classified as having severe disease and was a clinical failure and bacteriologic success at the EOT but was reclassified as a clinical failure and bacteriologic recurrence at follow-up (i.e. failure). Of note, this patient also had *Acinetobacter calcoaceticus*, *Staphylococcus aureus*, and *Chlamydia pneumoniae* isolated from the sputum or by serology. The other patients with *Klebsiella pneumoniae* from the sputum only, (185.441.29782 and 185.542.30107) were clinical and bacteriological successes at the EOT and follow-up visits. Both of these patients were classified as having moderate disease and the former had other pathogens isolated (185.441.29782: *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*). The final patient from study 185 with *Klebsiella pneumoniae* (185.542.30102) was classified as having moderate disease and had sputum and blood cultures positive for *Klebsiella pneumoniae*, *Escherichia coli*, and *Acinetobacter calcoaceticus*. This patient was classified as a clinical success with bacteriologic failure at the follow-up visit. This patient had a recurrence of the *Klebsiella pneumoniae* in the sputum and the blood. The *Escherichia coli* was eradicated, and the *Acinetobacter calcoaceticus* was persistent at the EOT. (NOTE: all patients were hospitalized in study 185)

From study 287, there were an additional 15 patients (ITT) with *Klebsiella pneumoniae* isolated from the sputum only. 12 subjects had mild disease and all were clinical and bacteriological successes. 2 patients had severe disease and one (287.083.49695) also had *Streptococcus pneumoniae* isolated from the sputum, was hospitalized, and was a clinical and bacteriological success. The other (287.083.49680) was also hospitalized and was also a clinical and bacteriological success. Similarly one patient (287.096.49357) was

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classified as having moderate disease, was also hospitalized and was also a clinical and bacteriological success. Of the 12 subjects with mild disease, 5 were hospitalized including 2 who also had *Streptococcus pneumoniae* isolated. There were 4 subjects with both *Klebsiella pneumoniae* and *Streptococcus pneumoniae* as well as 1 subject with *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Serratia marcescens*.

In summary, there were 29 subjects with *Klebsiella pneumoniae* in the gemifloxacin ITT dataset. Of these, 27 had *Klebsiella pneumoniae* isolated from the sputum alone, one was of unknown source, and one patient had *Klebsiella pneumoniae* from the blood and sputum. 17 ITT subjects had *Klebsiella pneumoniae* alone, 5 ITT subjects had *Klebsiella pneumoniae* in association with *Streptococcus pneumoniae*, 5 had *Klebsiella pneumoniae* associated with other Gram (-) rods, 5 also had or only had *Klebsiella pneumoniae* associated with *Chlamydia* or *Mycoplasma pneumoniae*, and 1 had *Klebsiella pneumoniae* with *Staphylococcus aureus*. Twenty-six of 29 (90%) subjects were classified as clinical successes at the follow-up visit and 23/29 (79%) were classified as bacteriologic successes at the follow-up visit. **16/17 ITT subjects with *Klebsiella pneumoniae* only were clinical successes and 14/17 were bacteriologic successes.** There were 2 subjects with clinical success and bacteriologic failure including one subject (061.031.13854) who had persistence at the EOT and 061.039.13895 who had a recurrence. Both of these subjects had mild disease and the former was hospitalized. The final patient, 061.058.13811 was a clinical and bacteriologic failure who apparently was lost to follow-up prior to the EOT. This patient also had mild disease and was hospitalized. 13 of the subjects with *Klebsiella pneumoniae* only had mild disease, 3 had moderate disease, and 1 had severe disease.

Of the subjects with *Klebsiella pneumoniae* and *Streptococcus pneumoniae*, 4 were clinical and bacteriological successes and 1 was a failure due to missing data. Of the subjects with Gram (-) pneumonia, 2 were failures including the subject who was bacteremic. The patient with *Staphylococcus aureus* and *Klebsiella pneumoniae* was also a clinical success.

5 of these subjects had moderate disease, 3 had severe disease, and the remaining 21 had mild disease. 19 subjects were hospitalized included all 8 with moderate or severe disease. 6 of these subjects were successes and 2 were failures. Both failures (1 moderate, 1 severe) had mixed Gram (-) disease.

There were 22 subjects with *Klebsiella pneumoniae* included in the BPP population. Of these patients, 2 had severe disease, 4 had moderate disease, and the remaining 16 had mild disease. 22/22 (100%) were clinical successes at the EOT and 20/22 (90.9%) were bacteriologic successes. Both failures were in subjects with mild disease, one hospitalized one not and *Klebsiella pneumoniae* was the only pathogen isolated in both. 4 subjects had *Klebsiella pneumoniae* and *Streptococcus pneumoniae* (all successes, 3 mild, 1 severe), and 3 had other Gram (-) pathogens isolated concurrently in the sputum (all mild, all successes). All moderately and severely ill subjects were hospitalized, as were 7 of the mild subjects of whom only 1 was a failure. **There were 14 BPP subjects with *Klebsiella pneumoniae* alone with a clinical success rate of 100% and a**

bacteriologic success rate of 12/14 (85.7%). 10 of the PP subjects had mild disease, 3 had moderate disease, and 1 had severe disease.

14 of the patients including 9 with *Klebsiella pneumoniae* alone were from study 287, albeit mostly from different centers.

Of note, there were only 4 comparator patients with *Klebsiella pneumoniae* in the ITT and PP datasets. None of these subjects were from studies 185 or 287. 3 had moderate disease and had mild disease. All were clinical and bacteriologic successes. Two subjects had *Klebsiella pneumoniae* in conjunction with other respiratory pathogens and 1 had concurrent *Pseudomonas aeruginosa*. Thus only 1 comparator PP subject had *Klebsiella pneumoniae* alone.

Previous Regulatory Experience

Levofloxacin NDA 20-634/20-635:

There was an insufficient number of isolates in the original submission (N = 6) with a 100% clinical and bacteriological success rate, to justify the inclusion of *Klebsiella pneumoniae* in the labeling. There were an additional 5 cases that were considered unevaluable that were reviewed again by the medical team leader and it was determined that 4 of those cases could be recategorized as evaluable. Thus the final evaluable population consisted of 10 cases with an overall success rate of 100%. This number was considered adequate for an approval.

Table 45
***Klebsiella pneumoniae* and Regulatory Precedence:**

Antimicrobial	Number Eradicated/ Number evaluable (success rate)	Total Bacteriologically Evaluable for NDA	Approval
Levofloxacin	10/10 (100%)	370	YES
Moxifloxacin	13/15 (87%)	474	NO
Moxifloxacin ALL	14/17 (82%)	Unknown	YES*
Trovafloxacin	13/19 (82%) (included 4/8 NP)	280	YES
Gatifloxacin	3/3 (100%)	400	NO
Gemifloxacin	12/14 (85.7%)	521	?

*AECB caused by *Klebsiella pneumoniae* previously approved

Trovafloxacin NDA 20-759/20-760 (AP 12/96):

The initial NDA submission included 11 evaluable cases of CAP due to *Klebsiella pneumoniae* with a bacteriologic success rate at the EOS of 9/11 or 82% and a clinical success rate of 8/9 (89%). The reviewing MO pointed out that based on the 10% rule, the applicant needed at least 28 cases to attain an approval as opposed to 2.5%. A reanalysis of the data revealed that there were an additional 8 cases of nosocomial pneumonia due to *Klebsiella pneumoniae*, with an eradication rate of 4/8 (50%). This rate was an acceptable rate for NP but not for CAP. However the total number of isolates was adjusted to 19

with and eradication rate of 70% (13/19). This was deemed adequate for an approval as one-third of the patients had a more serious disease (NP).

Comment: There were 2 trovafloxacin formulations, the PO and the IV. The nosocomial pneumonia patients were treated with the IV formulation.

Gatifloxacin NDA 21-061 (AP 11/99):

There were 3 evaluable cases of CAP due to *Klebsiella pneumoniae* with an eradication rate of 100%. Of note, the total number of bacteriologically evaluable cases in the NDA was 403 and if the 10% rule was applied, 40 cases would have been required. The MO did not recommend an approval for this pathogen.

Moxifloxacin: NDA 21-085 (AP 11/99)

Five studies were submitted in support of the application for this orally administered quinolone. A total pathogen number was not provided in the MOR. A review of the MOR of each study found that there were 15 evaluable cases of CAP due to *Klebsiella pneumoniae* with an eradication rate of 97% (13/15). There were 474 bacteriologically evaluable cases. The MO recommended against the approval for this isolate because it was unlikely that CAP due to *Klebsiella pneumoniae* could be managed on an outpatient basis. Additionally the MO stated that most patients with this pathogen were co-infected with two or more organisms.

Moxifloxacin IV NDA 21-277: In addition to the 15 cases referenced in the PO moxifloxacin NDA, an additional 2 cases were provided with a total of 17 cases and a cure rate of 14/17 (82%). An approval was granted despite the lack of adequate data because an approval had been granted for AECB due to *Klebsiella pneumoniae*.

The MO elected to recommend an approval for *Klebsiella pneumoniae* in mild to moderate CAP but not in severe CAP because of the small number of patients with severe disease that were studied as well as ongoing concerns regarding the approvability of an oral agent for severely ill subjects. Finally the MIC90 for *Klebsiella pneumoniae* is 0.5 mcg/mL and is indicative of the fact that some strains of this organism might be only moderately susceptible.

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Client and Attorney Work Product Privilege

_____ b(6) Personal Privacy

_____ b(7) Law Enforcement Records

Moraxella catarrhalis and Haemophilus parainfluenzae:

Included in the resubmission were efficacy data on 14 isolates of *Moraxella catarrhalis* and 19 isolates of _____ 13/14 isolates of *Moraxella* were presumed eradicated (92.9%) as were 15/19 (78.9%) of _____ Similar efficacy was found on the comparators arm with and eradication rate of 15/16 for *Moraxella catarrhalis*, and 16/23 (69.6%) for _____

The gatifloxacin approval was issued based on a clinical response rate for _____ of 31/35 (89%) and of 26/28 (93%) for *Moraxella catarrhalis* in microbiologically evaluable subjects. The trovafloxacin NDA included 16 subjects with *Moraxella catarrhalis* and a success rate of 100%. There were no subjects with _____ included in that submission. Clinical success rates for subjects with _____ and *Moraxella catarrhalis* in the levofloxacin NDA were 19/20 (95%) and 16/18 (89%) respectively.

Based on the above, the MO elected to include only *Moraxella catarrhalis* in the CAP indication and not _____

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Conclusions:

The clinical and bacteriological efficacy of gemifloxacin 320 mg once daily for either 7 or up to 14 days was assessed in four active controlled and two uncontrolled studies in CAP.

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.

Table 50
Clinical Success at Follow-Up
CAP Controlled and Uncontrolled Studies 011, 012, 049, 185, 061 and 287

	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)

In an independent FDA analysis where clinical response at TOC was assessed by age, race, and gender as well as by study and duration of treatment, similar results were obtained.

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The clinical efficacy of gemifloxacin was supported by similar bacteriological success rates for gemifloxacin treated patients in all studies.

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 be non-inferior to comparators.

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. Eradication rates at follow-up for these pathogens in the BITT population were slightly lower in both combined treatment groups.

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 51
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 N=415		All Comparators N=274		Gemifloxacin N=552		All Comparators 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.

An independent FDA analysis of pathogen eradication rates in subjects treated for 7 days by study revealed similar rates to those above, independent if patients were enrolled in the 7 day studies (011, 061, and 287) or if they received 7 days of treatment in the studies where a 7 or 14 day treatment regimen could have been utilized.

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In summary, the data presented in the CAP studies in both the original NDA 21-158 submission and the currently under review resubmission provide 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.

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.

Specific to the resubmission, the applicant reassessed response to treatment by duration of treatment, by severity of disease, by hospitalization studies and by the presence or not of bacteremia.

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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 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 fewer patients 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

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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%).

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.

Severity of Disease:

The Fine criteria were retrospectively applied as an indicator of severity of illness in all studies except study 287 where they were applied prospectively. 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.**

In the applicant’s analysis, 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.

In the FDA 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.

Table 52
FDA Analysis of Clinical Response at Follow-up by Severity

<u>CPP</u>	7 day fixed			7 day		14 day	
	Gemi	Comp	Gemi uncont	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. However, 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.

As can be seen in the following table of the Agency's analysis, the response rates of hospitalized patients were comparable between treatment arms.

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Table 53
FDA Analysis of Clinical Response at Follow up in Hospitalized Patients

	<i>Treatment Group</i>	
	Gemifloxacin n/N (%)	Comparators n/N (%)
Clinical Per Protocol Population		
7-day CAP studies*		
Controlled (011)	90/103 (87.4)	97/111 (87.4)
Uncontrolled (061, 287)	141/157(89.8)	
Combined (Controlled and Uncontrolled)	231/260 (88.8)	
"7 - 14" day CAP studies**		
7 days	147/163 (90.2)	129/147 (87.8)
14 days†	118/130(90.8)	142/153 (92.8)
All patients	265/293 (90.4)	271/300 (90.3)
ITT		
7-day CAP studies*		
Controlled (011)	114/152 (75.0)	118/149 (79.2)
Uncontrolled (061, 287)	161/204(78.9)	
Combined (Controlled and Uncontrolled)	275/356 (77.2)	
"7 - 14" day CAP studies**		
7 days	169/229 (73.8)	146/193 (75.6)
14 days†	143/175 (81.7)	163/197 (82.7)
All patients	312/404 (77.2)	309/309 (79.2)

* 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.

As an additional indicator of the effectiveness of gemifloxacin in severe disease, the applicant provided a separate analysis of outcome in bacteremic subjects. In the combined all studies dataset (CPP), **4.7% (48/1012 patients)** of the gemifloxacin group had a positive blood culture at screening. For the combined all studies population, bacteremic patients who were treated with gemifloxacin had a clinical success rate at follow-up of 89.6% (CPP) and 89.4% for bacteriological response (BPP). The clinical and bacteriological response of bacteremic patients was examined by the planned duration of treatment for the combined all studies dataset. Of the 48 bacteremic patients in the combined gemifloxacin group (CPP), 25 patients were included in the 7-day duration group and 23 in the 14-day duration group. In the CPP population, the clinical success rate for patients who received 7 days of treatment in the combined gemifloxacin group was comparable with patients who received 7 days treatment in the combined comparator group; 84.0% vs. 82.6%. For the ITT population of bacteremic patients, the clinical success rate was comparable between the combined gemifloxacin group (67.6%) and combined comparator group (69.7%). Bacteriological success rates were almost identical to the clinical success rates

In the Agency's analysis of bacteremic subjects, though clinical response rates were comparable between treatment arms, the sample size was too small to allow for valid comparisons.

Table 54
FDA Analysis of Clinical Response at Follow up in Bacteremic Patients

	<i>Treatment Group</i>	
	Gemifloxacin n/N (%)	Comparators n/N (%)
Clinical Per Protocol Population		
7-day Fixed studies*		
Controlled (011)	8/8 (100.0)	10/11 (90.9)
Uncontrolled (061, 287)	9/13 (69.2)	
Combined (Controlled and Uncontrolled)	17/21 (81.0)	
"7 - 14" day studies**		
7 days	4/4 (100.0)	9/12 (75.0)
14 days†	22/23 (95.7)	14/14 (100.0)
All patients	26/27 (96.3)	23/26 (88.5)
ITT Population		
7-day fixed studies*		
Controlled (011)	9/11 (81.8)	12/16 (75.0)
Uncontrolled (061, 287)	10/15 (66.7)	
Combined (Controlled and Uncontrolled)	19/26 (73.1)	
"7 - 14" day studies**		
7 days	6/11 (54.5)	11/17 (64.7)
14 days†	24/25 (96.0)	18/20 (90.0)
All patients	30/36 (83.3)	29/37 (78.4)

* 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.

Thirty-seven of the 48 bacteremic gemifloxacin-treated subjects had *Streptococcus pneumoniae*. Twenty of these subjects received more than 7 days of treatment. Clinical success rates in these subjects were 35/37 PP (94.5%). In the > 7-day group the rate was 19/20 (95%).

The clinical review team requested that the applicant provide tables of risk class specific mortality for all ITT patients and for in- and outpatients separately. Overall mortality was similar between the gemifloxacin and comparator-treated groups as well as between the gemifloxacin controlled and uncontrolled study patients with 12 deaths (1.3%) in the gemifloxacin controlled study patients, 13 deaths (1.4%) in the comparator-treated patients, and 5 deaths (1.2%) in the gemifloxacin-treated uncontrolled study patients. There were 17 deaths (1.3%) in all gemifloxacin-treated patients.

When mortality was assessed in the ITT population by in or outpatient status, it was apparent that most of the deaths occurred in the inpatients with 14 of 17 gemifloxacin

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deaths in inpatients (11 controlled and 3 uncontrolled) as compared to 12 of 13 deaths on the comparators arm.

When deaths were assessed by Fine class, it appeared that mortality rates for Class I, II, and III patients mortality rates were consistent with what was expected based on the publication by Fine *et al.*⁶ In class IV subjects the mortality rates in the clinical studies appeared to be somewhat less than what was reported for Fine Class IV patients. There were too few class V subjects in the dataset to draw any conclusions for this class (Table). (The mortality risk for class IV subjects ranges from 9 – 12%, whereas for class V subjects it is in the 30% range in the publication by Fine *et al.*)

The MO concluded that severe disease should not be added to the label for the following reasons:

- The small number of patients with Fine classes IV and V disease (9.9%).
- The lack of additional indicators of the effectiveness of gemifloxacin in severe disease.
- The quality of the data in this submission as compared to those in previous NDAs. Most notably, in NDAs 20-634/20-635 (Levofloxacin), 25.8% of the patients (72/279) studies in to controlled trials had severe disease where severe disease was defined as those subjects with hypotension (diastolic BP < 60 mm Hg in the absence of volume depletion), subjects with mental status changes, subjects who required mechanical ventilation, subjects with bacteremia, and subjects with a baseline RR of > 28/min.
- The lack of an adequate number of cases of CAP etiologically associated with pathogens that would qualify as severe disease.

PRSP:

Regarding penicillin-resistant *Streptococcus pneumoniae* (PRSP), there were 12 evaluable patients with 13 isolates of PRSP treated with gemifloxacin in the combined CPP population of the all studies dataset. All 12 patients with PRSP were both clinical and bacteriological successes at follow-up: i.e. 100% success. All but one of the PRSP patients received treatment for 7 days. There were 2 subjects in this group with severe disease as well as 2 with bacteremia (one with severe disease). 8 of the PRSP subjects were hospitalized. 37 subjects were bacteremic with *Streptococcus pneumoniae*.

The MO determined that the data gathered by the applicant regarding PRSP was impressive and although it did not meet the standard set by the data that formed the basis

⁶ Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, Coley CM, Marrie TJ, Kapoor WN. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med.* 1997 Jan 23;336(4):243-50.

for approval for levofloxacin and PRSP, it was adequate to allow for the recommendation of an approval in mild to moderate disease.

MRSP:

The applicant presented data on 36 BITT gemifloxacin-treated MRSP patients of whom 25 in the BPP populations. There were 14 BITT comparator-treated subjects of whom 12 were in the BPP and CPP populations.

Of the 25 BPP gemifloxacin MRSP, 10 (40%) were also PRSP (11/36 BITT, 30%). All subjects with PRSP and MRSP were clinical successes with presumed eradication at follow-up. 8 had mild disease, one had moderate disease and 1 had severe disease. Overall clinical success and bacteriologic success rates on the gemifloxacin arm were 22/25 (88%) for the PP population. For the MRSP ITT gemifloxacin-treated population, there were 27/36 (78%) clinical successes, 4 failures and 5 "unable to determine". Similar results were obtained for the BITT population, with 3 isolates presumed persistent and 6 "unable to determine". Overall clinical and bacteriological success rate on the comparators arm was 11/12 (91.6%). 3 of the 12 BPP subjects were also PRSP.

The MO elected to defer a recommendation for or against an approval for MRSP pending presentation of the application to an Advisory Committee. Issues to be discussed include the fact that typically, approximately 60% of PRSP are also MRSP and approximately 40% of MRSP isolates are also PRSP and the non-issuance of an approval for one isolate should lead to a similar decision for the other. Beyond this however, is the issue of whether an approval should be issued for MRSP. This claim has not been previously granted and scientific issues regarding CAP caused by MRSP as a separate entity remain in question.

At the March 4, 2003 DAIDP AC, the issue of MDRSP (multi-drug resistant *Streptococcus pneumoniae*) was discussed. It was the committee's determination that penicillin resistant, macrolide resistant, and cefuroxime-resistant *Streptococcus pneumoniae* are not separate entities but the same and that an approval could be granted for MDRSP and not for each separately.

Cefuroxime-resistant *Streptococcus pneumoniae*:

In the combined CAP gemifloxacin group (BPP population) there were

- 18 patients with *Streptococcus pneumoniae* resistant to cefuroxime with an MIC of ≥ 4 ug/mL.
- 12 of the 18 cefuroxime-resistant isolates were also penicillin resistant (3 with an MIC of 4 mcg/mL and 9 with an MIC of 2 mcg/mL).

- 15 of the 18 cefuroxime-resistant isolates were also clarithromycin resistant (10 with MICs of 16 mcg/mL or >, 1 with an MIC of 4 mcg/mL, 3 with an MIC of 3 and 1 with an MIC of 1)
- 4 subjects had severe disease, 3 had moderate disease, and 11 had mild disease.
- 2 severe subjects were bacteremic. One subject with mild disease was also bacteremic.

Clinical success and bacteriological eradication/presumed eradication rates at follow-up for the BPP population with cefuroxime-resistant isolates of *Streptococcus pneumoniae* were 17/18 (94.4%). The failure was in a subject with mild disease who was not bacteremic but was hospitalized. This subject's isolate was clarithromycin-resistant (MIC 2 mcg/mL) but penicillin sensitive (MIC 1 mcg/mL).

A final recommendation regarding approvability for the requested indication cannot be made pending an advisory committee discussion of the merits of approving antimicrobials for *Streptococcus pneumoniae* resistant to various antimicrobials as opposed to "drug-resistant *Streptococcus pneumoniae*."

MDRSP (Multidrug resistant *Streptococcus pneumoniae*):

The applicant submitted additional line listings for review on 3/20/03. A review of the listings revealed that there were 9 patients with *Streptococcus pneumoniae* isolates resistant to 4 drugs (penicillin, cefuroxime, macrolides, and TMP-SMX. There were 5 subjects with isolates resistant to 3 drugs including 3 subjects with isolates resistant to penicillin. Two of these 3 were also cefuroxime and TMP-SMX resistant and 1 was also cefuroxime and macrolide resistant. There were 2 subjects with MDR isolates but both of these had isolates that were penicillin sensitive but cefuroxime, clarithromycin and TMP-SMX resistant. Finally there were 5 subjects with Isolates resistant to 2 drugs. 3 of these were resistant to clarithromycin and TMP-SMX, 1 was resistant to cefuroxime and TMP-SMX, and 1 was resistant to cefuroxime and clarithromycin. Data regarding tetracycline-resistant isolates was not submitted.

***Klebsiella pneumoniae*:**

There were 29 subjects with *Klebsiella pneumoniae* in the gemifloxacin ITT dataset. Twenty-six of 29 (90%) subjects were classified as clinical successes at the follow-up visit and 23/29 (79%) were classified as bacteriologic successes at the follow-up visit. **16/17 (94%) ITT subjects with *Klebsiella pneumoniae* only were clinical successes and 14/17 (82%) were bacteriologic successes.**

There were 22 subjects with *Klebsiella pneumoniae* included in the BPP population. Of these patients, 2 had severe disease, 4 had moderate disease, and the remaining 16 had mild disease. 22/22 (100%) were clinical successes and 20/22 (90.9%) were bacteriologic successes. **There were 14 BPP subjects with *Klebsiella pneumoniae* alone with a clinical success rate of 100% and a bacteriologic success rate of 12/14 (85.7%).** 10 of the PP subjects had mild diseases, 3 had moderate disease, and 1 had severe disease.

The MO elected to not recommend an approval for _____ in CAP because of the small number of patients with severe disease that were studied as well as ongoing concerns regarding the approvability of an oral agent for severely ill subjects. Finally the MIC90 for *Klebsiella pneumoniae* is 0.5 mcg/mL and is indicative of the fact that some strains of this organism might be only moderately susceptible.

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Moraxella catarrhalis and _____

Included in the resubmission were efficacy data on 14 isolates of *Moraxella catarrhalis* and 19 isolates of _____ 13/14 isolates of *Moraxella* were presumed eradicated (92.9%) as were 15/19 (78.9%) of _____
The MO elected to include only *Moraxella catarrhalis* in the CAP indication.

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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*, *Chlamydia pneumoniae*, *Moraxella catarrhalis*, and *Haemophilus parainfluenzae*, with a labeled duration of therapy of 7 days.

B. Recommendations

The MO recommends that gemifloxacin be considered approvable in the treatment of CAP (of mild to moderate severity) due to *Streptococcus pneumoniae* (including penicillin-resistant strains), *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Moraxella catarrhalis*, with a labeled duration of therapy of 7 days.

The issuance of an approval is dependent upon the establishment of an acceptable safety profile.

Regina Alivisatos, MD
DSPIDP, HFD-590

Concurrence only:
HFD-590/DIVDir/AlbrechtR

Cc:
Orig. NDA 21-158
HFD-590
HFD-590/MTL/CoxE
HFD-590/CSO/YUY
HFD-590/TLMicro/Bala
HFD-725/Biostat/HigginsK
HFD-725/DixonC
HFD-520/Biopharm/
3/25/03

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**APPEARS THIS WAY
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Study 185: A Randomised, Open, Multicenter, Study to Assess the Efficacy and Safety of Oral Gemifloxacin 320 mg Once Daily Versus IV Ceftriaxone (with or without macrolide) followed by Oral Cefuroxime (with or without macrolide) for 7 or 14 Days in the Treatment of Hospitalised Adult Patients with Bacterial Community-Acquired Pneumonia (CAP).

Summary: Study 185, was an open-label, non-comparative study that enrolled hospitalized adult patients with clinical signs and symptoms of CAP and a CxR with findings consistent with CAP. Enrolled patients were evaluated at an initial screening assessment (Day 0) and then at 3 subsequent visits to monitor response to treatment and any adverse events that may have occurred (on-therapy, Day 2-4; EOT Day, 2 to 4 days post-therapy; and follow-up, 21 to 28 days post-therapy). Patients were to receive either 7 or 14 days of therapy with gemifloxacin; the investigator determined the duration of therapy at the on-therapy visit.

Patients underwent clinical, microbiological, and radiological evaluations at screening, EOT, and at follow-up. Patients who withdrew from study prior to the EOT or follow-up were to undergo an evaluation at the time of withdrawal from study. The standard microbiological evaluation included cultures of blood and respiratory secretions, serologic evaluations, and other diagnostic evaluations for the etiologies of CAP (e.g., Legionella urine antigen).

All patients who received at least one dose of study medication were included in the Intent-to-Treat (ITT) population. Patients in the ITT population with a pathogen diagnosed by the microbiological evaluation performed at screening were included in the BITT population.

In order to be included in the CPP population (i.e. the clinically evaluable population), patients needed to be compliant with study therapy, attend the designated follow-up assessments, and remain free of other medications or conditions that would interfere with the assessment of the patient's response to study therapy. Patients that required other antibiotic therapy because of a failure of their CAP to respond to study therapy were to be scored as failures and remained within the PP populations. In order for a patient to be included in the BPP population the patient needed to be in the CPP population and have a microbial etiology for his/her CAP determined at screening, and comply with the microbiological assessments at EOT and follow-up.

Clinical and bacteriological responses were categorized as either success or failure. The primary efficacy endpoint for the studies was clinical response in the CPP population at the follow-up visit. The secondary efficacy variables included clinical response at EOT, bacteriologic response at follow-up and EOT, radiologic response at follow-up and EOT, and therapeutic response (a composite of clinical and microbiologic response) at follow-up and EOT.

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This open comparative CAP study was designed to demonstrate non-inferiority to the comparator regimen. The sample-size for these studies was estimated using a delta for non-inferiority of 15%. In discussions with the Division during the End-of-Phase II meeting (August 11, 1998), it was agreed that the demonstration of non-inferiority within a delta of 15% would be acceptable.

Study Dates: 7 December 1999 through 15 June 2000

Objective

To demonstrate that oral gemifloxacin 320 mg once daily was at least as good as IV ceftriaxone followed by oral cefuroxime (both with or without a macrolide) for 7 or 14 days for the treatment of CAP in hospitalized adults.

Compliance was assessed by monitoring the number of IV infusions or counting the unused tablets and capsules at the EOT visit. A pill count was also performed at the on therapy visit. Patients were considered compliant overall if they had taken 80-120% of the intended total regimen.

Adequacy of Comparator(s): The comparators are the most frequently used IV and oral antimicrobial agents for the treatment of CAP.

Study Design

This was an open, randomized, multicenter, parallel group Phase III study to assess the safety and efficacy of oral gemifloxacin in comparison to IV ceftriaxone followed by oral cefuroxime 500 mg BID (both with or without a macrolide) for treatment of CAP. Patients were randomized on a 1:1 ratio to receive either gemifloxacin 320 mg PO QD for a minimum of 7 days and up to a maximum of 14 days or IV ceftriaxone for a minimum of 1 day and a maximum of 7 days followed by oral cefuroxime for a minimum of 1 day and a maximum of 14 days. Treatment was administered routinely for 7 days, but this could be extended to 14 days if the patient had a severe infection, a probable or confirmed diagnosis of pneumonia due to an atypical pathogen (including *Legionella pneumophila*), or otherwise at the investigator's discretion. Patients were evaluated 4 times over a duration of approximately 6 weeks (Day 0, screening; Day 2-4, on therapy; 2-4 days post-therapy, EOT; and 21 - 28 days post-therapy, follow-up) to evaluate their clinical, radiological, and bacteriological response to treatment. The follow-up visit (21 - 28 days post-therapy) was the TOC visit (the time point for the primary efficacy analysis).

Sample Size

The applicant's sample size calculation was based upon the assumption of an equivalent clinical response rate of 85% at follow-up. The applicant calculated that 240 evaluable patients (120 per treatment arm) would be required to give a power of 90% to detect that the lower bound of the two-sided 95% confidence interval for the difference in rates

(gemifloxacin group minus trovafloxacin group) is no less than -15%. The applicant estimated that 30 % of randomised patients would be ineligible for the CPP population. Therefore 344 patients needed to be enrolled to provide 240 PP evaluable patients.

Protocol amendments:

13 December 1999: Austrian and German centers received study medication from a local source; US datasheet for ceftriaxone/cefuroxime arm modified.

10 January 2000: Period of oral dosing was increased to a maximum of 13 days with a total maximum dosing period of 14 days; patients who had received > 24 hours of dosing with an IV or IM antimicrobial for the current CAP episode were excluded; ECG monitoring was added

Protocol Overview

Patients were required to meet the following inclusion and exclusion criteria for study participation.

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Hospitalized male or female patients aged ≥ 18 years who had given written dated informed consent to participate in the study with a clinical and radiological diagnosis of bacterial CAP defined as:

a CxR within the 48-hour period prior to randomization that shows the presence of new or progressive infiltrate(s), consolidation or pleural effusion consistent with pneumonia and at least **two** of the following signs and symptoms:

- New or increased cough;
- Purulent sputum or a change in sputum characteristics;
- Auscultatory findings on pulmonary examination of rales and/or evidence of pulmonary consolidation;
- Dyspnea, tachypnea or hypoxemia;
- Pleuritic chest pain
- Fever defined as an oral temperature of $>38^{\circ}\text{C}$, tympanic temperature of $>38.5^{\circ}\text{C}$, or rectal temperature of $>39^{\circ}\text{C}$.)
- An elevated total peripheral WBC count of $>10,000$ cells/ mm^3 , or $>15\%$ immature neutrophils regardless of total peripheral WBC count, or leukopenia with total WBC count of $<4,500$ cells/ mm^3 .
- Hypoxemia with a $\text{PO}_2 < 60$ mm Hg (RA)

Exclusion criteria:

Patients meeting any of the following criteria were excluded from the study:

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- Female patients who are pregnant, lactating (breast feeding) or planning a pregnancy during the course of the study, or are of childbearing potential and are not using an accepted method of birth control (i.e. surgically sterile, intra-uterine contraceptive device, oral contraceptive plus barrier contraceptive, hormonal delivery system plus barrier contraceptive, diaphragm or condom in combination with contraceptive cream, jelly or foam).
- Patients with known or suspected hypersensitivity to the quinolones.
- Patients with a history of tendonitis while taking fluoroquinolones.
- Patients with hospital-acquired pneumonia diagnosed more than 48 hours after admission or who have been hospitalized within 2 weeks preceding entry into the study.
- Patients with known bronchial obstruction or a history of post-obstructive pneumonia (this does not exclude patients who have chronic obstructive pulmonary disease).
- Patients with aspiration pneumonia.
- Patients with cystic fibrosis, active tuberculosis, bronchiectasis (with clinical signs and symptoms), or active pulmonary malignancies.
- Patients who have received more than 24 hours treatment with any other antibacterial agent for this episode of CAP within 7 days prior to enrollment.
- Patients who have a complicating infection or disease that would compromise treatment evaluation of the study medication.
- Patients with known or suspected renal impairment and/or known creatinine clearance of < 30 mL/min.
- Patients with known or suspected ALT, AST or alkaline phosphatase levels greater than 3 times the upper limit of normal.
- Patients with a history of epilepsy, convulsions or myasthenia gravis.
- Patients with a clinical history of hemolytic crisis or known G6PD deficiency.
- Patients who are immunocompromised.
- Patients who are HIV positive with a CD4 count of <500 cells/mm³.
- Patients with a life threatening or serious unstable underlying disease.
- Patients who are concurrently receiving sucralfate or probenecid.
- Treatment with an investigational drug/vaccine or device within 30 days or 5 half-lives (whichever is longer) preceding entry into the study.
- Patients with active alcohol or drug abuse.
- Patients who have been previously enrolled in this or any other study involving gemifloxacin.

Medical Officer's Comment: *The applicant's inclusion and exclusion criteria were acceptable and in general in accordance with the criteria described in the Agency's Draft Guidance on developing antimicrobial drugs for the treatment of community-acquired pneumonia.*

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Study Procedures

Eligible patients were enrolled and randomized (1:1) to either treatment group A (gemifloxacin 320 mg (one tablet) for 7 or 14 days or treatment group B (IV ceftriaxone 2 gm QD followed by PO cefuroxime 500 mg PO BID for 7 or 14 days total. Randomization was accomplished using ClinPhone[®]. The procedures and evaluations scheduled for each of the four visits in Study 185 are listed below

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