

Table A32
Number (%) Patients with Clinical Chemistry Values Outside the F2F3
Range at the EOT Visit

Functional Group/ Variable	F2F3 Range	Gemifloxacin 320 mg QD N = 169		Ceftriaxone 2 GM IV QD Cefuroxime 500 mg BID N = 172	
		n/N*	(%)	n/N*	(%)
Clinical Chemistry					
ALT	High	7/159	(4.4)	5/155	(3.2)
AST	High	4/159	(2.5)	1/155	(0.6)
ALK-P	High	1/158	(0.6)	1/154	(0.6)
BUN	High	2/161	(1.2)	6/155	(3.9)
Creatinine	High	1/155	(0.6)	3/154	(1.9)
Calcium	Low	1/160	(0.6)	0/152	(0.0)
Total Bilirubin	High	0/159	(0.0)	1/153	(0.7)
Sodium	Low	0/152	(0.0)	1/162	(0.6)
Potassium	High	1/159	(0.6)	1/156	(0.6)
Potassium	Low	2/159	(1.3)	0/156	(0.0)

*n/N = number of patients with flag/number of patients evaluated for the particular parameter

Medical Officer's Comment: Overall there were no striking differences between the treatment arms although the incidence of treatment-related liver dysfunction was higher on the gemifloxacin treatment arm and seemed primarily isolated to ALT. None of the subjects with an elevation of a liver function test had symptoms or associated AEs. In 3 cases, the increases were ranked as severe and 1 as moderate. In all cases there was resolution within 21 days. One subject (305.29877) had increased ALT/AST at baseline (4xULN) and developed an increased bilirubin (2x ULN) at the on-therapy visit that resolved by the EOT. There were no cases of severe increases in LFTs on the comparator arm.

Summary and Conclusions:

Study 185 was an open, multicenter trial designed to assess the efficacy and safety of gemifloxacin 320 mg PO QD vs. IV ceftriaxone 2 gm followed by oral cefuroxime in hospitalised patients with CAP. Total duration of treatment ranged from 7 – 14 days and a minimum of 1 dose of ceftriaxone was required prior to oral switch. Subjects on the comparator arm could also receive a concurrent macrolide. Primary endpoint was clinical response at the follow-up visit (21 – 28 days post-treatment) for subjects in the clinical per protocol (CPP population).

345 (172 gemifloxacin and 173 comparator) subjects were randomized and 341 patients received treatment, 169 on the gemifloxacin arm and 172 on the comparator. Treatment groups were relatively well matched with a mean age of 60 on the gemifloxacin arm and 58 on the comparator. Severity of CAP was retrospectively categorised according to the Fine criteria into 5 risk classes with class V representing those patients at most risk of death within 30 days. 36 (21%) of the gemifloxacin and 35 (20.3%) of the comparator patients were considered high risk (i.e. risk classes IV and V).

27% (93/345) patients were excluded from the CPP EOT population. 49 (28.5%) from the gemifloxacin arm and 44 (25.4%) from the comparator arm. 108/345 (31.3%) were excluded from the CPP population at follow-up, 56 (32.6%) from the gemifloxacin arm and 52 (30.1%) from the comparator arm.

The most common reason for exclusion from the clinical follow-up population was non-compliance in 25 subjects on each arm (14.5%), followed by a clinical outcome of unable to determine in 23 (13.4%) of gemifloxacin subjects and 22 (12.7%) of comparator subjects.

The primary reason for non-compliance was the use of alternative antimicrobials in 17% of the gemifloxacin compared to 10% of the comparator patients. As and did not include subjects who received antimicrobials because of clinical failure or recurrence.

49.3 % of all subjects had a baseline pathogen and were included in the BITT population (88 gemifloxacin and 82 comparator subjects). Most commonly isolated pathogens included *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*. *Streptococcus pneumoniae* was the predominant cause of bacteremia and was isolated in 24/170 (14%) of subjects (16 gemifloxacin). In general most isolates were sensitive to gemifloxacin as well as comparators. There were 3 isolates considered to be PRSP. 2 from the sputum of a gemifloxacin-treated patient (MIC = 2 mcg/mL). This subject also had *Mycoplasma pneumoniae*. All subjects were clinical and bacteriological successes. None of the bacteremic patients had PRSP.

The result for the primary determinant of efficacy, the clinical success rate in the CPP population for the gemifloxacin arm was 92.2% (107/116) compared to 93.4% (113/121) in the comparator arm. The 95% CI for the difference in clinical success rates (gemifloxacin-comparator) was within the lower bound of the protocol-specified delta of -15%. Clinical response at follow-up was also assessed for the CITT population, all randomized patients who took at least one dose of study medication. In the ITT analysis, patients with a clinical response of unable to determine were handled as failures. In that analysis the clinical success rate for gemifloxacin was 75.6% (130/172) compared to 78.6% (136/173) for the comparator arm. The 95% CI for the difference in success rates was within the lower bound of the protocol-specified delta of -15%. These results led to the conclusion that gemifloxacin was at least as good as the ceftriaxone/cefuroxime regimen. Clinical recurrence rates were similar on both treatment arms (4 gemifloxacin (2.3%) vs. 5 comparators, 2.9%).

Similarly, the sponsor was able to meet the protocol-specified delta for the secondary analyses and thus show that gemifloxacin was as good as the comparator for clinical response at the EOT, radiological response at the EOT and at follow-up, and for combined clinical and radiological response at both timepoints.

An analysis was done of success rate according to severity. For subjects assigned to risk classes I – II, clinical success for the CPP population at follow-up was 93.5% (87/93) for the gemifloxacin treatment group and 95.95 (93/97) for the comparator arms. These

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results varied considerably from the success rates for those subjects in risk classes IV and V (20% of the population) (gemifloxacin 86.9% (20/23) vs. 83.3% (20/24) comparator).

Bacteriologic response rates were as expected and comparable between the treatment arms at follow-up with 100% eradication or presumed eradication rates for *Haemophilus parainfluenzae* and *Legionella pneumophila* on both. The numbers of isolates was however, too small for some pathogens such as *Legionella* to draw any conclusion.

Mean total duration of treatment was 10 days on both arms and mean duration of IV treatment was 4 days on the comparator arm. *Maximum duration was 17 days for the gemifloxacin-treated patients and 15 for the comparator-treated.*

69.8% (118/169) of patients in the gemifloxacin 320 mg QD group and 62.2% (107/172) of patients in the all comparators group reported at least one AE during the interval on-therapy plus 30 days post-therapy.

Most frequent AEs were from the GI tract on both treatment arms, followed by AEs from the metabolic/nutritional, and respiratory systems. The body systems in which the reporting rate of AEs in the gemifloxacin 320 mg QD group exceeded the rate in the all comparators group by at least 2% were the CNS and skin and appendages body systems. The body as a whole, platelet and clotting, and liver and biliary systems were the systems in which the rate of adverse experiences in the all comparators group exceeded the rate in the gemifloxacin 320 mg QD group by at least 2%.

Diarrhea and hypokalemia were the most common AEs by preferred term in both the gemifloxacin 320 mg QD group and the comparator groups. Other AEs reported in more than 5% of patients included hyperglycemia, insomnia, constipation, and rash on the gemifloxacin arm as compared to insomnia and increased SGPT on the comparator arm.

There were 5.3% (9/169) patients with an AE of rash in the gemifloxacin 320 mg QD group compared to 4.8% in the original NDA gemifloxacin group, and 5/172 (2.9%) in the comparator group of the study under review.

Investigators considered at least one AE to be of suspected or probable relationship to study medication for 16.6% (28/169) of patients in the gemifloxacin 320 mg QD group and 21.5% (37/172) of patients in the comparator group reported during the interval on-therapy plus 30 days post-therapy.

The most frequent AEs of suspected or probable relationship to study medication in the gemifloxacin 320 mg QD group were rash (3 %; 5/169), diarrhea (4%; 7/169) increased hepatic enzymes (3; 5/169). The most frequent AEs of suspected or probable relationship to study medication in the comparator group were diarrhea (6.4%; 11/172), hepatic enzymes increased (1.7%; 3/172), SGPT increased (4.7%; 8/169), and SGOT increased (3.5%; 6/172).

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3/169 (1.8%) gemifloxacin and 6n(3.6%) comparator treated patients died during the study. Causes of death in the gemifloxacin patients were CA, aortic stenosis, and NP. On the comparator arm the causes were cardiac in 4 and respiratory in 2. None of these events or deaths appeared related to treatment.

Of the 169 patients in the gemifloxacin 320 mg QD group, 25 patients (14.4%) reported serious AEs during the interval on-therapy to 30 days post-therapy. In the comparator group, 24 of 172 patients (14%) reported serious AEs during this interval. 5 subjects on the gemifloxacin arm and none of the subjects on the comparator arm had SAEs attributable to treatment. The SAEs included an episode of bloody diarrhea and 4 episodes of increased hepatic enzymes to 3 – 4 x ULN. The LFT abnormalities occurred between days 5 – 7 of treatment and resolved in all subjects within the study period. In no case was there evidence of a concurrently increased bilirubin.

No patients from either treatment arm sustained a change of ≥ 60 msec from baseline QTc to on therapy.

In summary, gemifloxacin was as effective as a combined IV to PO comparator regimen in hospitalised patients with CAP. Approximately 20% of the subjects were assigned to categories IV – V (Fine class) and had similar efficacy. Both regimes were well-tolerated. There was a higher incidence of rash and increased ALT on the gemifloxacin arm.

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Study 287: An Open, Non-Comparative, Multicenter Study to Assess the Efficacy and Safety of Oral Gemifloxacin 320 mg Once Daily for Seven Days for the Treatment of Community acquired Pneumonia of suspected Pneumococcal Origin in Countries with a High Prevalence of Drug-Resistant Respiratory Pathogens

Study Dates: 29 September 2000 through 28 August 2001

NOTE: The applicant submitted and interim analysis of this study that is still ongoing.

Study Centers: The study involved 28 centers in 9 countries (Indonesia, Mexico, Philippines, South Korea, Singapore, Taiwan, Thailand, Vietnam, and the USA).

Objectives

The **primary objective** was to evaluate the bacteriological efficacy of oral gemifloxacin 320 mg once daily for 7 days in patients with CAP of suspected pneumococcal origin.

Secondary objectives were:

- To evaluate the clinical efficacy of oral gemifloxacin 320 mg once daily for 7 days in patients with CAP of suspected pneumococcal origin.
- To evaluate the clinical and bacteriological efficacy and safety of oral gemifloxacin 320 mg once daily for 7 days in the treatment of penicillin-resistant pneumococcal pneumonia (PRSP) in adults.
- To evaluate the safety and tolerability of oral gemifloxacin 320 mg once daily for 7 days in the treatment of CAP of suspected pneumococcal origin in adults

MO Comment: Study 287 was performed in order to obtain at least 16 patients with PRSP and to enrich the NDA population thus the applicant utilized study centers located within regions of the world where drug-resistant respiratory pathogens are prevalent.

Study Drug

The batch numbers for the gemifloxacin tablets used in the study were batch numbers N99255 and N00145.

Compliance:

Compliance was assessed using the same methodologies as described for study 185.

Study Design:

The study design for 287 differed from that of the blinded, comparative trial 185 as well as from the three previously described blinded, comparative CAP studies (049, 012, and

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011) and the previously described study 061 (uncontrolled) because it enrolled patients with CAP that had a positive urinary pneumococcal antigen and/or a positive Gram stain for diplococci resembling *Streptococcus pneumoniae*.

The study was an open-label, multicenter, non-comparative phase III study. Patients who fulfilled the entry criteria were to receive 7 days of therapy with gemifloxacin 320 mg PO QD. Patients were evaluated at a screening assessment (Day 0) and at three subsequent visits (on-therapy, day 2-4; end of therapy (EOT), day 9-11; and follow-up, day 21-28). The assessments and procedures planned at each of the visits were essentially the same as previously described for Study 185 with one exception, only those patients with a positive urinary pneumococcal antigen test and/or a confirmed positive gram stain for diplococci resembling *Streptococcus pneumoniae*, received treatment. Thus, screening failures were discontinued at visit 1 (day 0) without receiving treatment.

Inclusion Criteria

For a patient to be eligible for enrollment in the subset of patients with CAP within Study 061, he/she was required to meet the following inclusion criteria:

- Patients, either male or female, ≥ 18 years of age
- Patients who have given written dated informed consent to participate in the study.
- Patients with a clinical and radiological diagnosis of community-acquired bacterial pneumonia, who are suitable for oral therapy, as defined below:
 - A CxR within 48 hours of enrollment in which there was evidence 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, crackles and/or evidence of pulmonary consolidation;
 - dyspnea, tachypnea or hypoxemia;
 - 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 $>39^{\circ}\text{C}$) or a history of fever for the current episode of CAP;
 - 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 .
- Patients who are willing and able to comply with the study protocol.

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- Female patients of childbearing potential must have a negative urine pregnancy test prior to enrolment (including those who are practicing birth control, those with tubal ligation and those less than 1 year post-menopausal).
- Patients with a positive urine test for pneumococcal antigen at screening and/or with the confirmed presence of Gram (+) diplococci resembling *Streptococcus pneumoniae* on direct examination of a Gram stain of a sputum or other respiratory sample smear.

Exclusion Criteria

The exclusion criteria for Study 061 were essentially the same as described for Study 185 and included the exclusion of subjects with nosocomial pneumonia, cystic fibrosis, aspiration pneumonia, disseminated infection, and septic shock.

Also excluded were subjects who had received > 24 hours of antimicrobial treatment for the current episode of CAP except for patients presenting with signs and symptoms of CPA and the confirmed presence of Gram (+) diplococci resembling streptococcus pneumoniae who had received at least 72 hours of first-line antibacterial treatment.

***MO Comment:** Patients who failed previous treatment were eligible for enrollment if they had the prerequisite sputum.*

Reasons for Withdrawal

The reasons for withdrawal from Study 287 were the same as previously described for Study 185 except for those subjects classified as screening failures. Withdrawal was defined as any case in which the subject was not a screen failure, received at least one dose of study medication, but did not complete the study.

Evaluability Criteria

The evaluability criteria used in Study 061 were essentially the same as previously described for Study 049.

Efficacy Endpoints

Primary efficacy endpoint was "per patient" bacteriologic response (success or failure) at the follow-up visit (days 21 – 28 post-therapy) for the bacteriologic ITT (BITT) population.

Secondary efficacy parameters included:

- Bacteriologic response at the EOT (2 – 4 days post-therapy)
- Clinical response at the EOT (2 – 4 days post-therapy)
- Clinical response at the follow-up visit (21 – 28 days post-therapy)

- Radiologic response at the EOT (2 – 4 days post-therapy)
- Radiologic response at the follow-up visit (21 – 28 days post-therapy)
- Clinical and radiologic response at the EOT (2 – 4 days post-therapy)
- Clinical and radiologic response at the follow-up visit (21 – 28 days post-therapy)
- Clinical and bacteriologic response (therapeutic response) at the EOT (2 – 4 days post-therapy)
- Clinical and bacteriologic response (therapeutic response) at the follow-up visit (21 – 28 days post-therapy)

The definitions of the efficacy endpoints for Study 287 were the same as previously described for Study 185.

MO comment: *the primary efficacy endpoint of this study differs from that of all previous CAP studies in that it is bacteriologic and not clinical response at the follow-up visit.*

Severity of Illness:

In this study as opposed to previous studies, the Fine criteria were applied prospectively, prior to database release of evaluation. Patient were initially assigned to Risk class I or not. If not, they were then assigned points and classified into risk classes II – V. Arterial blood gases were NOT used to assess the degree of hypoxemia. Pulse oximetry was used instead. This led to a change in the assessment method of 8 subjects, and a re-categorization of 3. One patient (287-041-49784) was reclassified from a risk class III to IV, patient 287-005-49828 from risk class II to III and patient 287-005-49971 from III to II.

MO Comment: *The MO reviewed the details of these cases and determined that the reclassifications were acceptable. Additionally, the reassessment of these patients did not affect the integrity of the overall dataset.*

Other subgroups on whom Analyses were performed:

Hospitalized patients (i.e. those who were hospitalized at the time of screening)

The subset of subjects with PRSP. Clinical and bacteriologic response at the EOT and at follow-up with 95% CIs were determined for the PRSP bacteriologic per protocol (BPP) and the bacteriologic intent-to –treat (BITT) populations.

Statistical Considerations

Study 287 is a non-comparative open-label ongoing study. At the time of the interim analysis 7 subjects with PRSP had been enrolled. As per the applicant, the study will continue until the goal of 16 subjects with PRSP is reached.

Analysis Populations

The Analysis populations for Study 287 are described below:

- **Bacteriology ITT (BITT):** The population comprised all patients who took at least one dose of study medication and who had at least one evaluable pathogen identified from culture at the screening visit.
- **Penicillin-Resistant Streptococcus pneumonia Bacteriology ITT Population (PRSP BITT):**
The subset of patient in the BITT population with documented PRSP from culture (penicillin MIC \geq 2 mcg/mL) at screening.
- **Bacteriology Per Protocol (BPP):** this population excluded patients who had protocol violations such that biased efficacy results.
- **PRSP BPP:** A subset of the BPP population who had documented PRSP from culture (penicillin MIC \geq 2 mcg/mL) at screening.
- **Intent-to Treat (ITT):** All patient who received at least one dose of study medication.
- **Clinical Per Protocol (CPP):** this population excluded patients with protocol violations such that biased efficacy results. A subset of the ITT population.

NOTE: The Medical Officer reviewed a random sample of 20% of the case report forms (CRFs). This sample was generated by the reviewing statistician. Based on this review, the MO determined that the sponsor adhered to the protocol and thus the sponsor's determinations of efficacy were accepted.

Study Results

Populations

A total of 188 patients were included in the interim analysis. Of these, 186 patients received at least one dose of study medication and comprised the ITT and safety populations. The number of patients from the CAP ITT population that completed each of the various milestones in the study are summarized below. Of the 216 patients with CAP who received at least one dose of study drug, 94 (51%) were in the BITT population.

Table B1
Patient Disposition for Patients with CAP (Study 287)

Population	Gemifloxacin 320 mg QD	
	n/N	(%)
Entered	188	100
Received Study Medication (ITT)*	186/188	99
Completed Study	156/186	84
Clinical PP end of therapy	156/186	84
Clinical PP follow-up	147/186	79
Bacteriology ITT	94/186	51
Bacteriology PP end of therapy	82/186	44
Bacteriology PP follow-up	80/186	43

Adapted and modified from the Applicant's Table 8, from NDA 21-158, Vol. 1.8.059, p. 75

* These patients comprised the safety population.

Demographic and Baseline Characteristics

The ITT population from had a mean age of 51 years with an age range of 18-89 years of age. Approximately 54% of the patients enrolled in the ITT population were males. This difference was more pronounced in the BPP population where 62% percent of the patients enrolled were males.

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Table B2
Demographic Characteristics

Demographic Characteristic ITT	Gemifloxacin 320 mg QD N=186
Gender n(%)	
Male	100 (53.8)
Female	86 (46.2)
Age (yr)	
Mean (SD)	51.3 (19.7)
Range	18-89
Race* n(%)	
White	42 (22.6)
Black	10 (5.4)
Oriental	100 (53.8)
Other**	34 (18.3)
Weight (kg)	
Mean (SD)	62.2 (18.0)
Range	30.5-155.0
Height (cm)	
Mean (SD)	163.8 (9.5)
Range	144.0 -193.0
Demographic Characteristic BPP	Gemifloxacin 320 mg QD N=94
Gender n(%)	
Male	58 (61.7)
Female	36 (38.3)
Age (yr)	
Mean (SD)	53.1 (20.1)
Range	18-89
Race* n(%)	
White	22 (23.4)
Black	8 (8.5)
Oriental	52 (55.3)
Other**	12 (12.8)
Weight (kg)	
Mean (SD)	62.3 (19.6)
Range	30.5-155.0
Height (cm)	
Mean (SD)	165.4 (9.6)
Range	145.0 -188.0

Adapted from Applicant's Table 14, from NDA 21-158, Vol. 1.8.059, p. 82

* Included Asian and Hispanic

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The clinical characteristics of patients at screening are summarized below.

Table B3**Number (%) of Patients with Clinical Characteristics of CAP at Screening**

Clinical Characteristic	Gemifloxacin 320 mg QD			
	ITT N=186		CPP Follow-Up N= 147	
	n	(%)	n	(%)
Sputum				
Purulent Sputum	165	(88.7)	130	(88.4)
Changes in Characteristics	155	(83.3)	121	(82.3)
Cough				
New or Increased Cough	186	(100)	147	(100)
None	0	(-)	0	(-)
Mild	57	(30.6)	41	(27.9)
Moderate	94	(50.5)	76	(51.7)
Severe	35	(18.8)	30	(20.4)
Pleuritic Chest Pain				
None	82	(44.1)	66	(44.9)
Mild	50	(26.9)	36	(24.5)
Moderate	39	(21.0)	30	(20.4)
Severe	15	(8.1)	15	(10.2)
Dyspnea				
None	55	(29.6)	44	(29.9)
Mild	64	(34.4)	50	(34.0)
Moderate	57	(30.6)	47	(32.0)
Severe	10	(5.4)	6	(4.1)
Tachypnea				
None	95	(51.1)	79	(53.7)
Mild	59	(31.7)	43	(29.3)
Moderate	30	(16.1)	25	(17.0)
Severe	2	(1.1)	0	(-)
Hypoxemia				
None	153	(82.3)	119	(81.0)
Mild	14	(7.5)	13	(8.8)
Moderate	9	(4.8)	8	(5.4)
Severe	9	(4.8)	7	(4.8)
Unknown	1	(0.5)		
Other Characteristics				
Fever*	158	(84.9)	124	(84.4)
Abnormal WBC Count**	100	(53.8)	81	(55.1)

Adapted from the Applicant's Table 18, from NDA 21-158, Vol. 1.8.059, p. 86

* Fever was defined as $\geq 38^{\circ}\text{C}$ oral, $\geq 38.5^{\circ}\text{C}$ tympanic, $\geq 39^{\circ}\text{C}$ rectal measured in the clinic

** an elevated total peripheral WBC count of >10000 cells/ mm^3 , or $>15\%$ immature neutrophils regardless of total peripheral WBC count, or leukopenia with total WBC count of <4500 cells/ mm^3 .

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Medical Officer's Comment: Fewer patients had evidence of severe disease as compared to study 185.

The chest X-ray findings from baseline for patients with CAP are summarized below. Most patients with a chest X-ray consistent with CAP had infiltrates suggestive of CAP or localized alveolar consolidation.

Table B4
Details of Chest X-Ray at Baseline for Patients with CAP

Chest X-Ray Details	Gemifloxacin 320 mg QD			
	ITT •		Clinical PP Follow-Up	
	N=186		N=147	
	n	(%)	n	(%)
Total Patients with Chest X-ray	186	(100.0)	147	(100.0)
Chest X-Ray Consistent with CAP	184	(84.9%)	146	(99.3)
Infiltrates Suggestive of CAP	158	(76.4)	130	(88.4)
Localised Alveolar Consolidation	42	(22.6)	32	(21.8)
Pleural Effusion	16	(8.6)	12	(8.2)
Chest X-Ray Inconsistent with CAP	2	(1.1)	1	(0.5)

Applicant's Table 15, from NDA 21-158, Vol. 1.8.059, p. 83

Severity by Fine criteria:

The severity of CAP was assessed at screening according to risk classes I – V based on age, presence or absence of co-existing disease, abnormal physical and laboratory findings. Approximately seventy-seven percent of subjects were categorized as having mild disease and eleven (5.9%) met the criteria for risk classes IV and V (severe disease).

Table B5
Severity of CAP at screening by Fine Criteria

Category	Gemifloxacin 320 mg QD			
	ITT		CPP Follow-Up	
	N=186		N= 147	
	n	(%)	n	(%)
Mild (I and II)	143	(76.9)	116	(78.9)
Moderate (III)	33	(17.2)	23	(15.6)
Severe (IV and V)*	11	(5.9)	8	(5.4)

*Subject 287.041.49784 was found to have been erroneously assigned to Fins class III because the investigator noted that the patient was not hypoxemic at baseline. However pulse oximetry was 905 and thus the patient was reassigned to category IV.

Medical Officer's Comment: As noted above, the percentage of subjects with severe disease was lower in this study as compared to that of study 185.

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Withdrawals

The reasons that patients were withdrawn from study are enumerated in the table below. Comparison of these reasons for withdrawal in Study 287 with the prior studies a higher incidence of subjects lost to follow-up. No explanation was provided for this difference.

Table B6
Number (%) of CAP Patients Who Completed the Study or Were
Withdrawn, by Reason for Withdrawal (ITT Population) (Study 287)

Study Conclusion Reason	Gemifloxacin 320 mg QD	
	N=186	
	n	(%)
COMPLETED STUDY*	156	(83.9)
Reason for Withdrawal		
Adverse Experience **	8	(4.3)
Insufficient Therapeutic Effect	4	(2.2)
Protocol Deviation (Including Non-Compliance)	3	(1.6)
Lost to Follow-Up	11	(5.9)
Other+	4	(2.2)
TOTAL WITHDRAWN	30	(16.1)

Adapted from the Applicant's Table 11, from NDA 21-158, Vol. 1.8.059, p. 77.

- * Patients were considered to have completed the study if that was the opinion of the investigator.
- ** One patient (287-091-60182) was withdrawn an AE (elevated AST) occurring at baseline
- + Other reasons for withdrawal, as determined by the investigator, included unevaluable sputum

Note: This table shows withdrawals at any time during the study.

Evaluability/Protocol Violations

As in most CAP studies, the primary reason for exclusion from the BITT population was lack of a pathogen. Primary reasons for exclusion from the BP and ultimately from the BPP at follow-up were "unable to determine clinical and bacteriological outcome".

The CITT population was compromised of 186 patients. Thirty (16%) were excluded from the CPP EOT population, and 39 (21%) from the CPP follow-up population. Primary reason for exclusion was again "unable to determine clinical outcome".

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Table B7
Number (%) of CAP Patients Excluded from CPP, by Reason (Study 287)

Protocol Violation	Gemifloxacin 320 mg QD	
	N=186	
	n	(%)
END OF THERAPY		
PV1 (inclusion criteria violated)	3	(1.6)
PV2 (exclusion criteria violated)	1	(0.5)
PV12 Other Antibacterial Therapy*	5	(2.7)
PV24 Concomitant Medication	4	(2.2)
PV19 (> 10 mg/day prednisone)	5	(2.7)
PV28 Medication Compliance	1	(0.5)
PV27 Visit Compliance	6	(3.2)
PV26 Unable to Determine (Bacteriologic)	5	(2.7)
PV25 Unable to Determine (Clinical)	15	(8.1)
Total Excluded	30	(16.1)
FOLLOW-UP		
PV1 (inclusion criteria violated)	3	(1.6)
PV2 (exclusion criteria violated)	1	(0.5)
PV12 Other Antibacterial Therapy*	5	(2.7)
PV9 Complicating infection	1	(0.5)
PV19 (> 10 mg/day prednisone)	5	(2.7)
PV24 Concomitant Medication	4	(2.2)
PV28 Medication Compliance	1	(0.5)
PV27 Visit Compliance	10	(5.4)
PV26 Unable to Determine (Bacteriologic)	6	(3.2)
PV20 Unable to Determine (Clinical)	22	(11.8)
Total Excluded	39	(21.0)

Adapted from the Applicant's Table 13, from NDA 21-158, Vol. 1.8.059, p. 80.

Note A patient could have more than one violation.

* Patients who received other antibacterial therapy for clinical failure or clinical recurrence were not excluded.

Note: 94 subjects were excluded from the BITT because they did not have pathogen.

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Table B8
Number (%) of Patients Excluded from BPP Populations, by Reason

Protocol Violation	Gemifloxacin 320 mg QD	
	N=94	
	n	(%)
END OF THERAPY		
PV1 (inclusion criteria violated)	2	(2.1)
PV2 (exclusion criteria violated)	1	(1.1)
PV12 Other Antibacterial Therapy*	1	(1.1)
PV24 Concomitant Medication	1	(1.1)
PV28 Medication Compliance	1	(1.1)
PV27 Visit Compliance	4	(4.3)
PV19 (> 10 mg/day prednisone)	3	(3.2)
PV26 Unable to Determine (Bacteriologic)	5	(5.3)
PV20 Unable to Determine (Clinical)	5	(5.3)
Total Excluded	12	(12.8)
FOLLOW-UP		
PV1 (inclusion criteria violated)	2	(2.1)
PV2 (exclusion criteria violated)	1	(1.1)
PV12 Other Antibacterial Therapy*	1	(1.1)
PV24 Concomitant Medication	3	(3.2)
PV28 Medication Compliance	1	(1.1)
PV27 Visit Compliance	5	(5.3)
PV19 (> 10 mg/day prednisone)	3	(3.2)
PV26 Unable to Determine (Bacteriologic)	6	(6.4)
PV20 Unable to Determine (Clinical)	6	(6.4)
Total Excluded	14	(14.9)

Adapted from the Applicant's Table 12, from NDA 21-158, Vol. 1.8.059, p. 79.

Note: A patient could have more than one violation.

* Patients who received other antibacterial therapy for clinical failure or clinical recurrence were not excluded.

MO Comment: Patient disposition by Study center was also reviewed.

Treatment Compliance

The patients in Study 287 achieved an Overall Compliance rate of approximately 91%. These results are somewhat lower than the 96% seen in the previously reviewed uncontrolled study 061.

Table B9
Number (%) of Patients Compliant with Receipt of Study Medication (ITT)

Compliance	Gemifloxacin 320 mg QD	
	N=186	
	n	(%)
Early Compliance		
Yes	170	(91.4)
No	1	(0.5)
Unknown	15	(8.1)
Percentage Compliance		
< 40%	3	(1.6)
40 - <80%	10	(5.4)
80 - 120%	169	(90.9)
Unknown	4	(2.2)
Overall Compliance*	168	(90.3)

Adapted from Applicant's Table 27 from NDA 21-158, Vol. 1.8.59, p. 96.

Efficacy Results

Primary Efficacy Parameter:

Bacteriologic Response at Follow-up (21 – 28 days post-treatment):

The primary parameter of bacteriologic response was assessed in the BITT population. Additionally, the BPP as well as PRSP BITT and PRSP BPP populations were also assessed,

Table B10
Per Patient Bacteriological Response at Follow-Up

Bacteriological Response	Gemifloxacin 320 mg QD
Bacteriology ITT Population	N=94
Success n (%)	79 (84.0)
Failure* n (%)	15 (16.0)
95% CI for Success	76.6, 91.4
Bacteriology PP Follow-Up Population	N= 80
Success n (%)	72 (90.0)
Failure n (%)	8 (10.0)
95% CI for Success	83.4, 96.6
PRSP Bacteriology ITT Population	N=7
Success n (%)	6 (85.7)
Failure* n (%)	1 (14.3)
95% CI for Success	42.1, 99.6
PRSP Bacteriology PP Follow-Up Population	N= 6
Success n (%)	6 (100.0)
Failure n (%)	0 (-)
95% CI for Success	54.1, 100.0

Adapted from Applicant's Table 28, from NDA 21-158, Vol. 1.8.059, p. 98.

* Included one subject who was excluded because she received 3 days of high dose steroid treatment.

Below is the secondary efficacy parameter of bacteriologic response at the EOT:

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Table B11
Per Patient Bacteriological Response at the EOT (2 – 4 days post-treatment)

Bacteriological Response	Gemifloxacin 320 mg QD
Bacteriology ITT Population	N=94
Success n (%)	80 (85.1)
Failure* n (%)	14 (14.9)
95% CI for Success	77.9, 92.3
Bacteriology PP Follow-Up Population	N= 82
Success n (%)	74 (90.2)
Failure n (%)	8 (9.8)
95% CI for Success	83.8, 96.7
PRSP Bacteriology ITT Population	N=7
Success n (%)	6 (85.7)
Failure* n (%)	1 (14.3)
95% CI for Success	42.1, 99.6
PRSP Bacteriology PP Follow-Up Population	N= 6
Success n (%)	6 (100.0)
Failure n (%)	0 (-)
95% CI for Success	54.1, 100.0

Adapted from Applicant's Table 28, from NDA 21-158, Vol. 1.8.059, p. 98.

* Included one subject who was excluded because she received 3 days of high dose steroid treatment.

The Per Pathogen Bacteriological Response rates for all and frequently isolated pathogens in the BPP Follow-Up population at Follow-Up are summarized below and were in general, similar to what was observed in the other CAP studies.

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Table B12
Bacteriological Response (Success) Rate at Follow-Up by Pre-Therapy Pathogen
for All Pathogens in the BPPFU Population:**

Follow-Up	Bacteriology PP** Gemifloxacin	
	n/N*	%
All Pathogens	84/95	88.4
<i>S. pneumoniae</i>	39/44	88.6
<i>H. influenzae</i>	12/13	92.3
<i>M. catarrhalis</i>	3/3	100.0
<i>K. pneumoniae</i>	13/13	100

Prepared from the Applicant's Tables 11.01b pp.000624-5 NDA 21-158, Vol. 1.8.059

Note: Failures at end of therapy are carried forward to Follow-Up

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

** Bacteriology PP follow-up population

Although clinical response was a secondary parameter of efficacy in this study, it is a key endpoint in a CAP study.

Clinical Response at Follow-Up

The clinical response rates were similar to what was observed in the previously described CAP studies.

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Table B13
Clinical Response at Follow-Up in Patients with CAP

Clinical Response	Gemifloxacin 320 mg QD
ITT Population	N=186
Success n (%)	146 (78.5)
Failure* n (%)	40 (21.5)
95% CI for Success	77.0, 87.5
Clinical PP Follow-Up Population	N=147
Success n (%)	132 (91.7)
Failure n (%)	15 (8.3)
95% CI for Success	84.9, 94.7
PRSP BITT Population	N=7
Success n (%)	6 (82.9)
Failure* n (%)	6 (17.1)
95% CI for Success	42.1, 99.6
PRSP BPP Follow-Up Population	N=6
Success n (%)	6 (100.0)
Failure n (%)	0 (-)
95% CI for Success	54.1, 100.0

Adapted from Applicant's Table 32, from NDA 21-158, Vol. 1.8.059, p. 105

Clinical Response at End of Therapy

Clinical success was achieved in 141/156 (90.4%) of the patients in the CPP population at EOT. The results for clinical response in the CPP and in the ITT populations are similar to the rates observed in the previously reviewed CAP studies. The EOT clinical response rates for the PRSP BITT and BPP populations were the same as those at follow-up.

Table B14
Clinical Response at End of Therapy

Clinical Response	Gemifloxacin 320 mg QD
ITT Population	N=186
Success n (%)	153 (82.3)
Failure* n (%)	33 (17.7)
95% CI for Success	76.8, 87.7
CPP End of Therapy Population	N=156
Success n (%)	141 (90.4)
Failure n (%)	15 (9.6)
95% CI for Success	85.8, 95.0

Adapted from Applicant's Table 32 from NDA 21-158, Vol. 1.8.059, p. 105.

Therapeutic Response

Therapeutic success was observed in 79/94 (84%) of patients in the BITT population and 72/80 (90%) of the patients in the BPP population at Follow-Up. As would be expected, at the earlier time point of end of therapy, the therapeutic response success rates were slightly higher than the rates observed at follow-up but the differences were minimal. For the PRSP BITT and BPP populations, therapeutic response rates were the same at the EOT and at the follow-up visit.

Table B15
Therapeutic Response at Follow-Up,

Therapeutic Response	Gemifloxacin 320 mg QD
BITT Population	N=94
Success n (%)	79 (84.0)
Failure n (%)	15 (16.0)
BPP Follow-Up Population	N=80
Success n (%)	72 (90.0)
Failure n (%)	8 (10.0)
PRSP BITT Population	N=7
Success n (%)	6 (85.7)
Failure n (%)	1 (14.3)
BPP Follow-Up Population	N=6
Success n (%)	6 (100)
Failure n (%)	0 (-)

Adapted from Applicant's Table 35, from NDA 21-158, Vol. 1.8.059, p. 108

Table B16
Therapeutic Response at End of Therapy, Patients with CAP

Therapeutic Response	Gemifloxacin 320 mg QD
BITT Population	N=94
Success n(%)	80 (85.1)
Failure n(%)	14 (14.9)
BPP End of Therapy Population	N=82
Success n(%)	74 (90.2)
Failure n(%)	8 (9.8)

Adapted from Applicant's Table 35, from NDA 21-158, Vol. 1.8.059, p. 108

Radiological Response

The results from the analysis of the secondary endpoint of radiologic response in the ITT and CPP population support the observed response rates in the primary efficacy analyses

of bacteriologic response at follow-up and of those observed in the secondary analyses including that of clinical response in the CPP population at Follow-Up.

Failures:

Of the 15 BITT treatment failures, five subjects were lost to follow-up and one was withdrawn as a treatment violation. Thus 6 of the 15 failures were assigned a clinical outcome of "unable to determine". 3 of these subjects had *Streptococcus pneumoniae* including 1 subject who also had *Serratia marcescens* isolated from the sputum. The remaining 3 had *Staphylococcus aureus*, *Haemophilus influenzae*, and *Serratia marcescens* isolated from respiratory samples. 3 of these subjects were categorized as Fine risk class I, and there was one each in classes II, III, and IV. Two subjects were hospitalized, both Fine class I, one with *Streptococcus pneumoniae* and one with *Serratia marcescens*.

Of the 9 subjects who were assessed as failures at the EOT and at follow-up, 2 had a polymicrobial infection, one with *Streptococcus pneumoniae* and *Staphylococcus aureus* and the other with MRSA, *Escherichia coli*, and *Pseudomonas aeruginosa*. 5 subjects had infections due to *Streptococcus pneumoniae*, 1 due to *Haemophilus influenzae*, and 1 due to *B. cepacia*. None of these subjects had severe disease (Fine classes IV and V) and 5 were hospitalized including 3 with *Streptococcus pneumoniae* (one each classes I, II, and III).

One subject (287-091-49306) had PRSP (penicillin MIC = 2 mcg/mL). This subject had improved clinically at the EOT and also had radiologic improvement however, the investigator prescribed a course of cefuroxime at the EOT. This patient was excluded from the analyses because she received IV hydrocortisone for 3 days.

Outcome by severity:

The Fine criteria were used to classify baseline CAP severity as mild (suitable for outpatient treatment), moderate (possible hospitalization) or severe (hospitalization recommended). Of the 11 patients classified as having severe CAP at baseline, 10 (90.9%) were clinical successes at the follow-up visit.

Table B17
Clinical Response at Follow-up by Severity of CAP at Screening
Gemifloxacin 320 mg QD

Population	ITT N=186 n/N** (%)	Clinical PP N=147 n/N** (%)
Severity*		
Mild		
Success	114/143 (79.7)	104/116 (89.7)
Failure [†]	29/143 (20.3)	12/116 (10.3)
Moderate		
Success	22/32 (68.8)	20/23 (87.0)
Failure	10/32 (31.3)	3/23 (13.0)
Severe^{††}		
Success	10/11 (90.9)	8/8 (100)
Failure	1/11 (9.1)	0/8 -

Data source: Section 11, Tables 11.38a and 11.38b; Appendix B, Listing B.10a; Appendix C, Listing C.01.

* CAP severity was assessed using criteria defined by Fine *et al* [22]

** n/N = number of successes or failures /number of patients in a particular severity category.

† Clinical PP failures with mild CAP in this table include three protocol violators (PIDs 287.009.49818, 287.009.49819, 287.009.49981) who received 14 continuous days of gemifloxacin, but were evaluated for clinical outcome prior to completing treatment. See Section 4.3.

†† Patient 287.041.49784 is categorized as having moderate CAP (risk class III) in Section 11, Tables 11.38a and 11.38b. Although the investigator indicated that this patient was not hypoxemic at study entry, pulse oximetry shows this patient to have an oxygen saturation <90% which changes the Fine risk class assignment from III to IV. Therefore, this patient is presented among patients with severe rather than moderate CAP in the table above.

In the BITT population, seven of eight (87.5%) patients with severe CAP were clinical successes, as were all six (6) patients with severe CAP in the BPP population. All patients from whom PRSP was recovered at screening presented with mild CAP (risk class I or II).

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Table B18
Clinical Response at Follow-up by Severity of CAP at Screening
(Bacteriology Populations)

Gemifloxacin 320 mg QD				
Population	Bacteriology ITT N=94	Bacteriology PP N=80		
Severity*	n/N** (%)	n/N**	(%)	
Mild				
Success	61/73 (83.6)	55/61	(90.2)	
Failure [†]	12/73 (16.4)	6/61	(9.8)	
Moderate				
Success	11/13 (84.6)	11/13	(84.6)	
Failure	2/13 (15.4)	2/13	(15.4)	
Severe^{††}				
Success	7/8 (87.5)	6/6	(100)	
Failure	1/8 (12.5)	0/6	-	

Data source: Section 11, Tables 11.38c and 11.38d; Appendix B, Listing B10a; Appendix C, Listing C.01.

* CAP severity was assessed using criteria defined by Fine *et al* [22]

** n/N = number of successes or failures /number of patients in a particular severity category.

† Bacteriology PP failures with mild CAP in this table include one protocol violator (PID 287.009.49981) who received 14 continuous days of gemifloxacin, but was evaluated for clinical outcome prior to completing treatment. See Section 4.3.

†† Patient 287.041.49784 is categorized as having moderate CAP (risk class III) in Section 11, Tables 11.38c and 11.38d. Although the investigator indicated that this patient was not hypoxemic at study entry, pulse oximetry shows this patient to have an oxygen saturation <90% which changes the Fine risk class assignment from III to IV. Therefore, this patient is presented among patients with severe rather than moderate CAP in the table above.

Subjects with *Streptococcus pneumoniae* at screening:

As stated previously, this study specifically targeted enrollment of patients with CAP of suspected pneumococcal origin. *Streptococcus pneumoniae* was isolated from 51 (54.3%) of the 94 patients in the BITT population and 44 (55%) of 80 patients in the BPP follow-up population.

Medical Officer's Comment: Bacteriologic response for the PRSP BPP population at follow-up was lower than that that seen in the levofloxacin and Augmentin XR databases.

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Table B19

Bacteriological Response for Patients with CAP due to *Streptococcus pneumoniae*
Gemifloxacin 320 mg QD

<i>Streptococcus pneumoniae</i>	Bacteriology ITT	Bacteriology PP
End of Therapy	N=51	N=46
Success, n (%)	43 (84.3)	41 (89.1)
Failure, n (%)	8 (15.7)	5 (10.9)
Follow-up	N=51	N=44
Success, n (%)	42 (82.4)	39 (88.6)
Failure, n (%)	9 (17.6)	5 (11.4)

Data Source: Section 11, Tables 11.06a, 11.06b, 11.21a, 11.21b; Appendix C, Listing C.02.

Clinical response of patients with *Streptococcus pneumoniae* was similar to the bacteriological response with 41/80 (87.2%) of subjects categorized as successes as compared to 6 (12.8%) failures at the follow-up visit.

Table B20

Bacteriological Success Rate at Follow-up by Screening *Streptococcus pneumoniae*
Susceptibility to Penicillin (Bacteriology Populations)
Gemifloxacin 320 mg QD

	Bacteriology ITT	Bacteriology PP	
	N*=51	N*=44	
Susceptibility	n/N** (%)	n/N**	(%)
Susceptible	29/34 (85.3)	27/31	(87.1)
Intermediate	9/13 (69.2)	8/10	(80.0)
Resistant	6/7 (85.7)	6/6	(100.0)

Data source: Section 11, Tables 11.13a, 11.13b; Appendix C, Listings C.02 and C.03.

*N = number of patients with *S. pneumoniae*.

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

Bacteremic Patients

Streptococcus pneumoniae was the predominant cause of bacteremia. None of the bacteremic patients had penicillin-resistant *Streptococcus pneumoniae*

Of the seven bacteremic patients with *Streptococcus pneumoniae*, six (85.7%) were clinical and bacteriological successes at end of therapy and follow-up.

The failure (PID 287.072.49535) was a 31 YO female with Fine class I disease that had *Streptococcus pneumoniae* present in sputum as well as in blood culture at screening.

Table B21
Per Patient Bacteriological Response for Bacteremic Patients with
Streptococcus pneumoniae

Bacteremic Patients with <i>Streptococcus pneumoniae</i>	Gemifloxacin 320 mg QD	
	BITT	BPP
End of Therapy	N=7	N=6
Success, n (%)	6 (85.7)	5 (83.3)
Failure, n (%)	1 (14.3)	1 (16.7)
Follow-up	N=7	N=6
Success, n (%)	6 (85.7)	5 (83.3)
Failure, n (%)	1 (14.3)	1 (16.7)

B. cepacia was isolated from the remaining bacteremic patient. This patient (PID 287.023.60084) was a 36 YO male with Fine class I disease who was a clinical and bacteriological failure at end of therapy and follow-up.

Bacteriological and Clinical Response for Macrolide-Resistant S. pneumoniae

S. pneumoniae which was resistant to clarithromycin and erythromycin was isolated from 17 patients in the Bacteriology ITT population. Bacteriological success rates for macrolide-susceptible and macrolide-resistant *S. pneumoniae* isolates were at least 85% in the Bacteriology PP population (Table 44). The eradication/presumed eradication rate for macrolide-resistant *S. pneumoniae* in the Bacteriology PP population was 86.7%. Bacteriological success in the Bacteriology ITT population was somewhat lower for erythromycin-resistant (76.5%) and clarithromycin-resistant (72.2%) isolates. At follow-up, the macrolide-resistant pathogens were eradicated in two patients and presumed to be eradicated in an additional 11 patients, for a total eradication rate of 76.5%. The lower success rate in the ITT population is due in part to the inclusion of patients with outcomes of "unable to determine" as failures.

Table B22
Bacteriological Success Rate at Follow-up by Screening *S. pneumoniae*
Susceptibility to Macrolides (Bacteriology Populations)

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

*N = number of patients with *S. pneumoniae*.

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

Summary of Efficacy Results from Study 287

Study 287 was a supportive noncomparative study of gemifloxacin in the treatment of patients with CAP. Patients with clinical signs and symptoms of CAP including a pre-therapy CXR consistent with CAP as well as a positive urinary pneumococcal antigen test and/or a confirmed positive gram stain for diplococci resembling *Streptococcus pneumoniae*, received treatment. Were eligible for enrollment. All patients received gemifloxacin 320 mg PO QD for 7 days.

The primary efficacy endpoint for this non-comparative study was Per Patient Bacteriologic Response at Follow-Up (Day 21-28). The bacteriologic response rate for the bacteriologic per protocol population was 90% (72/80) and the clinical response rate at Follow-Up in the Clinical Per Protocol population was 91.7% (132/147). The results from the secondary efficacy endpoints corroborated the findings in the primary efficacy endpoint.

This study provided 7 subjects with PRSP to the applicant's PRSP database. All per protocol subjects were clinical and bacteriological successes.

Overall, the results in Study 287 were generally similar to the other CAP studies and provide supportive evidence of the efficacy of gemifloxacin in the treatment of CAP.

Safety:

All enrolled patients who received at least one dose of study medication (i.e., the ITT population) were included in the safety population. One hundred sixty-three patients (87.6%) received seven days of active therapy. The mean duration of exposure was 6.9 days.

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Table B23
Extent of Exposure

Number of Days On Therapy	Gemifloxacin (N=186)
1	3 (1.6%)
2	1 (0.5%)
3	3 (1.6%)
4	7 (3.8%)
7	163 (87.6%)
8	2 (1.1%)
>9	4 (2.2%)
Missing	3 (1.6%)

Ninety of 186 patients (48.4%) reported at least one AE during the interval on-therapy plus 30 days post-therapy. The most frequently reported AE was maculo-papular rash, which was reported by 5.4% (10/186) patients. Anorexia, nausea and urticaria were the second most frequently reported AEs, reported by seven (3.8%) patients each.

Hepatic enzymes increased were reported by 6/186 (3.2%) of subjects and hepatic function abnormal and increased SGPT were reported by 4 (2.2%) each.

Nineteen (10.2%) of subjects reported an AE from the skin (20 AEs).

Table B24
Number (%) of Patients With the Most Frequently Reported Adverse Experiences (≥ 2 Patients)

Preferred Term	Gemifloxacin 320 mg QD	
	N=186	
	n	(%)
Patients with at least one AE	90	(48.4)
Rash Maculo-Papular*	10	(5.4)
Anorexia	7	(3.8)
Nausea	7	(3.8)
Urticaria	7	(3.8)
Asthma	6	(3.2)
Diarrhea	6	(3.2)
Headache	6	(3.2)
Hepatic Enzymes Increased	6	(3.2)
Constipation	5	(2.7)
Dizziness	5	(2.7)
Infection Tuberculosis	5	(2.7)
Insomnia	5	(2.7)
Pharyngitis	5	(2.7)
Abdominal Pain	4	(2.2)
Hepatic Function Abnormal	4	(2.2)
Hypokalemia	4	(2.2)
Rhinitis	4	(2.2)
SGPT Increased**	4	(2.2)
Creatine Phosphokinase Increased	3	(1.6)
Hemoptysis	3	(1.6)
Back Pain	2	(1.1%)
Bilirubinemia	2	(1.1%)
Bronchospasm	2	(1.1%)
Dyspepsia	2	(1.1%)
Ear Disorder NOS	2	(1.1%)
Gastritis	2	(1.1%)
HSV	2	(1.1%)
Hyperglycemia	2	(1.1%)
Hyperkalemia	2	(1.1%)
Increased alkaline phosphatase	2	(1.1%)
Pneumonia	2	(1.1%)
Respiratory Insufficiency	2	(1.1%)
SGOT Increased	2	(1.1%)
Thrombocythemia	2	(1.1%)
Vomiting	2	(1.1%)

Data Source: Section 12, Table 12.09; Appendix D, Listings D.01 and D.02

* One additional patient reported a rash of unspecified type.

Medical Officer's Comment: Thirty-two subjects reported AEs (17.2%) from the GI tract including 7 (3.8%) reporting anorexia, 6 (3.2%) with diarrhea, and 5 (2.7%) with constipation. AEs from the respiratory system were reported from 25 (13.4%) of subjects and 19 subjects (10.2%) reported skin and appendage AEs. The liver and biliary system was the source of AEs from 17 subjects (9.1%). CNS abnormalities were reported from 12 (6.5%) of subjects and included headache in 6 (3.2%) and dizziness in 5 (2.7%). The onset of GI events anorexia, nausea, and diarrhea occurred primarily during the first six days of treatment and in most cases had resolved by Days 7 to 13. Maculopapular rash, urticaria and increased hepatic enzymes generally appeared between study days 7 to 13.

Events Related to Treatment:

During the interval on-therapy plus 30 days post-therapy, 18.3% (34/186) of patients reported at least one AE of suspected or probable relationship to study medication. The most frequent AEs reported as being of suspected or probable relationship to study medication were maculo-papular rash in 3.2% (6/186), and nausea and urticaria in 2.2% or 4 each.

Table B 25
Number (%) of Patients With the Most Frequently Reported Adverse Experiences With a Suspected or Probable Relationship to Study Medication

Preferred Term	Gemifloxacin 320 mg QD	
	n	(%)
Number Of Patients With Suspected or Probably Related Adverse Experiences	34	(18.3)
Rash Maculo-Papular	6	(3.2)
Nausea	4	(2.2)
Urticaria	4	(2.2)
Diarrhea	3	(1.6)
Hepatic Enzymes Increased	3	(1.6)
Anorexia	2	(1.1)
Dizziness	2	(1.1)
Headache	2	(1.1)
Hepatic Function Abnormal	2	(1.1)
SGPT Increased*	2	(1.1)
Abdominal Pain	1	(0.5)
Bilirubinemia	1	(0.5)
Flushing	1	(0.5)
Granulocytopenia	1	(0.5)
HSV	1	(0.5)
Leukopenia	1	(0.5)
Moniliasis	1	(0.5)
Moniliasis Genital	1	(0.5)
Increased alkaline phosphatase	1	(0.5)
Photophobia	1	(0.5)
Photosensitivity Reaction	1	(0.5)
Rash	1	(0.5)
Sweating Increased	1	(0.5)
Thrombocythemia	1	(0.5)

Data Source: Section 12, Table 12.14; Appendix D, Listings D.01 and D.02

*SGPT (serum glutamic-pyruvic transferase) is the preferred term for ALT (alanine)

Severity of AEs:

Most of the AEs reported during the interval on-therapy plus 30 days post-therapy were of mild to moderate intensity. Thirteen AEs (7%) were severe and included pneumonia and respiratory insufficiency reported in 2 subjects (1.1%) each and the only severe AEs reported by more than one patient. Severe AEs reported in 1 subject each (0.5%) were hypotension, abdominal pain, constipation, diarrhea, duodenal ulcer, atrial arrhythmia, cardiac arrest, increased SGOT, increased CPK, pulmonary carcinoma, sepsis, coughing, dyspnea, pleurisy, pulmonary edema, and rash.

Table B26
Number (%) of Patients With at Least One AE by Severity

Severity of AE	Gemifloxacin 320 mg QD	
	n	(%)
Patients with at Least One AE	90	(48.4)
Mild	72	(38.7)
Moderate	40	(21.5)
Severe	13	(7.0)

Serious AEs:

Nine patients (4.8%) reported serious AEs. Each serious AE was reported by one patient, with the exception of pneumonia and respiratory insufficiency, which were each reported by two patients. None of the serious AEs were reported by the investigator to have a relationship to study medication.

Note: The MO reviewed all CRFs by the sponsor and agreed with determinations.

Table B27
Number (%) of Patients with Serious Adverse Experiences

Preferred Term	Gemifloxacin 320 mg QD	
	N	%
Patients with at Least One Serious AE	9	(4.8)
Pneumonia	2	(1.1)
Respiratory Insufficiency	2	(1.1)
Arrhythmia Atrial	1	(0.5)
Cardiac Arrest	1	(0.5)
Cerebrovascular Disorder	1	(0.5)
Constipation	1	(0.5)
Hemorrhagic Duodenal Ulcer	1	(0.5)
Dyspnea	1	(0.5)
Pulmonary Carcinoma	1	(0.5)
Pulmonary Edema	1	(0.5)
Sepsis	1	(0.5)

Data Source: Section 12, Table 12.39; Appendix D, Listing D.02.

Withdrawals:

Eight (4.3%) patients reported AEs leading to withdrawal from the study. Of the AEs leading to withdrawal, only photophobia was considered by the investigator to be of probable relationship to study medication. Two events (infection tuberculosis and pneumonia) were reported as reasons for withdrawal by more than one patient.

Table B28
Number (%) of Patients With AEs Leading to Withdrawal

Preferred Term	Gemifloxacin 320 mg QD	
	n	(%)
Patients with at least one AE leading to withdrawal	8*	(4.3)
Infection Tuberculosis	2	(1.1)
Pneumonia	2	(1.1)
Bilirubinemia*	1	(0.5)
Cardiac Arrest	1	(0.5)
Cerebrovascular Disorder	1	(0.5)
Dyspnea	1	(0.5)
Photophobia	1	(0.5)
Pulmonary Edema	1	(0.5)
Respiratory Insufficiency	1	(0.5)

Data Source: Section 12, Table 12.47 ; Appendix D, Listings D.01 and D.02

*In Section 10, Table 12.47, Patient 287.005.49827 is noted as having an AE of bilirubinemia leading to withdrawal; however, this patient was withdrawn due to a PV because bilirubinemia occurred at screening.

Deaths:

Three patients died during the study. All deaths occurred during the post-therapy period.

Patient 287.022.49638: a 60-year-old female with a history of DM had no pathogens identified from pre-therapy blood or sputum samples. She had a history of diabetes mellitus. She was classified as Fine risk class II. The patient received seven days of gemifloxacin at 320 mg per day and at end of therapy was a clinical failure. Four days after completing study medication the patient had abnormally elevated laboratory values for CPK (614 U/L), alkaline phosphatase (345 U/L), and ALT (161 U/L). The following day the patient experienced a decrease in consciousness and was diagnosed as having septicemia. The patient was treated with gentamicin and dexamethasone. The patient died five days after completing study medication. The investigator reported the patient's death as not related to treatment with study medication and was probably associated with the patient's worsening pneumonia.

Patient 287.023.60078, a 71-year-old female with a history HTN, dyslipidemia, and NIDDM had no pre-therapy pathogens identified in blood and had a positive urine for pneumococcal antigen. She was classified as Fine risk class III. The patient was a clinical success at the EOT. The patient died of pneumonia, respiratory failure, acute lung edema and cardiac arrest 17 days after the last dose of study medication. Initially the investigator reported that the pneumonia was possibly related to treatment with study medication but later amended this assessment to not related as this was a nosocomial infection. In addition, the investigator commented that the acute lung edema led to respiratory failure and cardiac arrest.

Patient 287.104.50045, a 72-year-old male with a history of COPD, HTN, rhinitis, glaucoma, cataracts, hernia and upper respiratory infection had no pre-therapy pathogens identified from blood and was classified as Fine risk class III. The patient was a clinical success at the EOT. Seven days after completing the 7-day course of gemifloxacin, the patient was admitted to the hospital with a diagnosis of worsening bilateral pneumonia. Subsequently, the patient developed respiratory distress and suffered several episodes of cardiac irregularity. He died 19 days after the last dose of study medication. Autopsy results showed interstitial pneumonitis, consistent with a prolonged pulmonary fibrotic type pattern that had been complicated by acute pneumonitis and subsequent cardiac failure with the development of ARDS and pulmonary insufficiency. The investigator reported the worsening bilateral pneumonia as not related to treatment with study medication.

Rash and skin-related AEs:

Of the 20 AEs reported for the skin body system, ten were of mild intensity, nine were of moderate intensity, and one was of severe intensity (PID 287.071.49521, maculo-papular rash). One patient (PID 287.083.49652) experienced more than one AE associated with skin.

Of the cases of urticaria all were mild except one that was of moderate severity. Th

Table B29
Number (%) of Patients Reporting Selected Adverse Experiences
Associated with the Skin Body System

Preferred Term	Gemifloxacin 320 mg od	
	N=186	
Number Of Patients With the Skin Body System Related Adverse Experiences	19	(10.2%)
Rash Maculo-Papular	10	(5.4%)
Urticaria	7	(3.8%)
Photosensitivity Reaction	1	(0.5%)
Pruritus	1	(0.5%)
Rash	1	(0.5%)

Data Source: Section 12, Table 12.05; Appendix D, Listing D.01.

Relationship to the study medication was reported as suspected or probably related in six patients with maculo-papular rash and one with rash. Maculo-papular rash generally appeared within eight days of starting study medication (study days 6 – 13) and resolved within eight days (days 14 – 21). Only three rashes lasted longer than eight days; one rash lasted 14 days; one lasted 21 days; and one was ongoing at the follow-up visit. A total of seven patients received corrective therapy for rash. No patients were withdrawn from the study for AEs associated with rash.

Laboratory Parameters:**APPEARS THIS WAY
ON ORIGINAL****Hematology:**

Of the hematology parameters, only elevated platelets were considered an F2F3 level abnormality at the EOT. Follow-up hematology samples from 5 patients showed that the platelet counts had returned to within the normal range. Two of the 19 patients with F2F3-flagged values for platelet count had a corresponding AEs of thrombocytopenia (PID 287.004.49871 and PID 287.005.49975) and both AEs resolved by the follow-up visit.

Clinical Chemistry:

At the EOT, 9 patients experienced a F2F3-flagged laboratory abnormality for elevated ALT and 8 experienced a F2F3-flagged abnormality for elevated AST. Two patients (PID 287.065.49464 and PID 287.068.49511) had a flagged value for both elevated ALT and AST and one patient (PID 287.022.49638) had flagged values for AST and bilirubin. Follow-up laboratory samples for seven of the 14 patients with flagged AST and/or ALT showed that values had returned to normal range in most cases. All AEs resolved by the end of the study with the exception of Patient 287.022.49638 who experienced sepsis.

Review of F2F3 flags for markers of renal function (BUN, serum creatinine) and serum electrolytes (sodium, potassium, calcium) did not reveal any findings of clinical significance.

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Table B30
Number (%) of Patients With Hematology/Clinical Chemistry Values of
Potential Clinical Concern (F2F3-Flagged) at the EOT

Functional Group/ Parameter	F2/F3 Flag*	Gemifloxacin 320 mg QD	
		n/N	%
Hematology			
Hemoglobin	high	1/171	(0.6)
	low	2/171	(1.2)
Hematocrit	low	2/171	(1.2)
	high	1/166	(0.6)
Red Blood Cell Count	low	1/97	(1.0)
	high	19/166	(11.4)
Platelets	low	1/166	(0.6)
	high		
Clinical Chemistry			
ALT	high	9/171	(5.3)
AST	high	8/170	(4.7)
Alkaline Phosphatase	high	1/165	(0.6)
Creatine Phosphokinase	high	1/132	(0.8)
Blood Urea Nitrogen	high	1/161	(0.6)
Calcium	high	1/164	(0.6)
Potassium	high	1/163	(0.6)
Total Bilirubin	high	1/167	(0.6)

Data Source: Section 12, Table 12.68; Appendix F, Listings F.01 and F.02.

*NRH=Normal Range High; NRL=Normal Range Low; NRS=Normal Range Span

**n/N=Number of patients with a flag/number of patients evaluated for the particular parameter

ALT=Alanine Aminotransferase;

AST=Aspartate
Aminotransferase

PID 287.005.49975: (simultaneous F2F3-flagged elevation in ALT and AST)

The patient's ongoing medical history at screening included hyperemic skin, multiple capped teeth, multiple filled teeth and multiarticular joint tenderness. Prior medications included trimethoprim, hydrocodone bitartrate/paracetamol (Lortab) and paracetamol/codeine phosphate (Tylenol #3) up until one day before the start of study medication with hydrocodone bitartrate/ paracetamol (Lortab) continuing at the start of study. The patient received 7 days of gemifloxacin from 26 January 2001 to 1 February 2001. At screening (26 January 2001), the patient had normal ALT (18 IU/L) and AST (37 IU/L) levels. Three days later, at the on-therapy visit (29 January 2001) ALT (114 IU/L) and AST (98 IU/L) were elevated. No corrective therapy was given. At the end of therapy visit, eleven days after starting study medication (6 February 2001), ALT (195 IU/L), AST (50 IU/L) remained elevated. At a follow-up assessment 31 days after starting study medication values had returned to normal levels. Bilirubin levels were normal during the study period.

This patient had an elevated platelet count of $741 \times 10^9 /L$ at the EOT eleven days after starting study medication (6 February 2001). The investigator prescribed acetylsalicylic acid for the raised platelet level and at follow-up, 31 days after starting study medication, platelets had returned to normal levels.

The elevated ALT and AST were recorded as an AE of abnormal hepatic function. The increased platelet count was recorded as an AE of thrombocytopenia. Both were reported by the investigator to be of suspected relationship to study medication.

PID 287.065.49464: 38 YO female with a simultaneous F2F3-flagged elevation in ALT and AST. PMH included epigastric discomfort. Concomitant medications included paracetamol (Tylenol), codeine, potassium chloride (K-contin), ambroxol hydrochloride (Mucopect), zipeprol dihydrochloride (Respilene syrup), streptodornase/streptokinase (Varidase), *L. acidophilus*/*L. bifidis*/*S. faecalis* (Andilac), and amylase/ dimeticone/ activated lipase/ protease (Phazyme 95).

The patient received the 7 days of gemifloxacin from 29 December 2000 to 4 January 2001. At screening (29 December 2000), the patient had a slightly elevated ALT (40 IU/L) and normal AST (31 IU/L) levels. At the EOT, eleven days after starting study medication (9 January 2001), both ALT (148 IU/L) and AST (92 IU/L) were elevated. No corrective therapy was given and at follow-up 32 days after starting study medication (30 January 2001), ALT (17 IU/L) and AST (15 IU/L) had returned to normal levels. Bilirubin levels were normal during the study. The elevated ALT and AST were recorded as an AE of increased hepatic enzymes. The AE was reported by the investigator to be of unlikely relationship to study medication.

This patient also developed an AE of maculopapular rash seven days after starting study medication (5 January 2001). And was reported as having a relationship to study medication. No corrective therapy was given.

PID 287.068.49511: 52 YO oriental female with a simultaneous F2F3-flagged elevation in ALT and AST. The patient was had a Fine Class II classification. Prior medications which stopped on the first study day included roxithromycin, paracetamol (Tylenol), almagate, ambroxol, cimetidine, clenbuterol, diazepam and ammonium chloride/ camphor/ ephedrine hydrochloride/ menthol/ plant extracts (Optipect). Concomitant medications included codeine; cough syrup and biodiastase/ dimeticone/ activated lipase/ pancellase ss/ pancreatin/ panprosin ss/ ursodesoxycholic acid (Bears).

The patient received 7 days of gemifloxacin from 6 December 2000 to 12 December 2000. At screening (6 December 2000), the patient had a normal ALT (19 IU/L) and normal AST (14 IU/L) levels. At the EOT, ten days after starting study medication (16 December 2000), both ALT (223 IU/L), AST (126 IU/L) were elevated. No corrective therapy was given and at the follow-up assessment 33 days after starting study medication (8 January 2001), ALT (32 IU/L) and AST (24 IU/L) had returned to normal levels. Bilirubin levels were normal during the study. The elevated ALT and AST were

recorded as an AE of increased hepatic enzymes reported by the investigator to be of suspected relationship to study medication.

Patient 287.022.49638: a 60-year-old female with a history of DM had no pathogens identified from pre-therapy blood or sputum samples. She had a history of diabetes mellitus. She was classified as Fine risk class II. The patient received seven days of gemifloxacin at 320 mg per day and at end of therapy was a clinical failure. Four days after completing study medication the patient had abnormally elevated laboratory values for CPK (614 U/L), alkaline phosphatase (345 U/L), and ALT (161 U/L). Total bilirubin (31.63 IU/L) and creatinine (141.44 IU/L) were also elevated. AEs were reported for increased SGPT, SGOT, alkaline phosphatase and CPK. The investigator reported the AE of elevated alkaline phosphatase as having a suspected relationship to study medication and the other AEs as unrelated to study medication. In addition, at the on-therapy visit neutrophils ($35.73 \times 10^9 /L$) were elevated and had an F2F3 flag. The following day the patient experienced a decrease in consciousness and was diagnosed as having septicemia. The patient was treated with gentamicin and dexamethasone. The patient died five days after completing study medication. The investigator reported the patient's death as not related to treatment with study medication and was probably associated with the patient's worsening pneumonia. The laboratory abnormalities were ongoing at the time of the patient's death.

Safety conclusions:

Approximately half of the patients reported at least one AE in this interim analysis of study 287. Maculopapular rash was the most frequently reported AE and did not lead to withdrawal of any patients. Eight patients withdrew from the study due to AEs, and 9 patients experienced serious AEs during the study. Three patients died during the study, all within the 30 days post-therapy period. None of the AEs associated with death were reported by the investigator as related to study medication. Five percent of patients had F2F3-flagged elevations in ALT. Overall, the safety from the interim analysis of Study 287 was consistent with the overall safety profile reported for gemifloxacin.

February 13, 2003

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this page is the manifestation of the electronic signature.**

/s/

Regina Alivisatos
3/25/03 08:21:52 AM
MEDICAL OFFICER

CAP Medical Officer's Review

Edward Cox
4/4/03 06:59:42 PM
MEDICAL OFFICER

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**Addendum to Medical Officer's Review of NDA 21-158
FACTIVE (gemifloxacin mesylate 320 mg tablets)
CAP Indication**

NDA Submission number: 21-158

Applicant: LG LifeSciences Ltd.
25th Floor, LG Twin Tower east
20 Yoido-dong, Youngdungpo-gu
Seoul 150-721, Korea

Contact person: Parexel International
195 West St.
Waltham, MA 02451

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Date of Submission: October 4, 2002
Date of Amendment to MOR: April 4, 2003

Established name: Gemifloxacin mesylate

Proposed proprietary name: Factive™

Regulatory Background

NDA 21-158 was originally submitted by GSK as a new drug application (NDA) on December 15, 1999. Although a not approvable letter was issued on December 11, 2000 because of safety considerations, the applicant was informed that based on the review of the clinical trial data submitted in the NDA, it was concluded that gemifloxacin was effective in treating community-acquired pneumonia (CAP) of mild to moderate severity caused by *Mycoplasma pneumoniae*, *Streptococcus pneumoniae*, *Chlamydia pneumoniae* and *Haemophilus influenzae*.

NDA 21-158 was resubmitted on October 4, 2002 by LG LifeSciences Ltd (LGLF) the manufacturer of the active drug substance and its US representative, Parexel International. In the current submission, the applicant again requested that the CAP indication be included in approved labeling as follows: "Factive is indicated for the treatment of community-acquired pneumonia caused by *Streptococcus pneumoniae* (including penicillin-, clarithromycin- and cefuroxime-resistant strains), *Haemophilus influenzae*; *Moraxella catarrhalis*; *Mycoplasma pneumoniae*; *Chlamydia pneumoniae*;
_____ The proposed dose was one 320-mg tablet daily for 7 days.

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Data Reviewed, Conclusions and Recommendations:

Three double-blind, randomized, actively-controlled clinical studies (studies 011, 012, and 049) and one open, actively-controlled study (study 185) were submitted in support of the efficacy of gemifloxacin in the treatment of community acquired pneumonia in adults. In addition, two uncontrolled studies (studies 061 and 287) were conducted. Three of the studies, pivotal study 011 and the uncontrolled studies, had a fixed 7-day duration of treatment for gemifloxacin. Pivotal study 011 compared a 7-day course of gemifloxacin with a 10-day treatment course of amoxicillin/clavulanate (1g/125 mg tid) and clinical success rates were similar between treatment arms. The results of comparative studies 049, 185, and 012 were supportive although treatment duration could have been 7 to 14 days. As applicant requested only a 7 day duration of treatment because of safety concerns, it was determined that in labeling, only the results of studies with a fixed 7 day duration of treatment should be utilized. This included bacteriologic eradication rates.

Review of the data revealed that there was sufficient evidence of the efficacy of gemifloxacin 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 data submitted in support of a "serious" disease claim were deemed inadequate to support an approval (see MOR of NDA 21-158/resubmission).

Multi-drug resistant *Streptococcus pneumoniae* (MDRSP):

The issue of PRSP, — and cefuroxime-resistant *Streptococcus pneumoniae* was discussed at an Anti-Infective Drug Advisory Committee meeting on March 4, 2003. At that meeting, the issue of each individual drug versus 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

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. _____
_____ After review of the data, it was determined
that an approval only for PRSP should be granted _____

Klebsiella pneumoniae:

_____ was determined however during labeling discussions that gemifloxacin has acceptable clinical and bacteriological success rates in patients with primarily mild disease treated with a fixed 7 day duration of treatment. Thus it was concluded that this pathogen should be included in labeling with the following caveat:

* In the clinical trials, there were 13 subjects with *Klebsiella pneumoniae*, primarily from non-comparative studies. 10 subjects had mild disease, 2 had moderate disease, and 1 had severe disease. There were two clinical failures in subjects with mild disease (one of these had a bacteriologic recurrence).

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CLINICAL STUDIES:**Community Acquired Pneumonia (CAP)**

The clinical program to evaluate the efficacy of gemifloxacin in the treatment of community acquired pneumonia in adults consisted of three double-blind, randomized, actively-controlled clinical studies (studies 011, 012, and 049) and one open, actively-controlled study (study 185). In addition, two uncontrolled studies (studies 061 and 287) were conducted. Three of the studies, pivotal study 011 and the uncontrolled studies, had a fixed 7-day duration of treatment for FACTIVE. Pivotal study 011 compared a 7-day course of FACTIVE with a 10-day treatment course of amoxicillin/clavulanate (1g/125 mg tid) and clinical success rates were similar between treatment arms. The results of comparative studies 049, 185, and 012 were supportive although treatment duration could have been 7 to 14 days. The results of the clinical studies with a fixed 7-day duration are shown in Table 8:

Table 8. Clinical Response at Follow-Up (Test of Cure): CAP Studies with a Fixed 7 Day Duration of Treatment

Drug Regimen	Success Rate % (n/N)	Treatment Difference (95% CI)*
Study 011		
FACTIVE 320 mg x 7 days	88.7% (102/115)	1.1 (-7.3, 9.5)
Amoxicillin/clavulanate 500 mg/125 mg tid x 10 days	87.6% (99/113)	
Study 061		
FACTIVE 320 mg x 7 days	91.7%(154/168)	(86.1, 95.2)
Study 287		
FACTIVE 320 mg x 7 days	89.8% (132/147)	(84.9, 94.7)

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

The combined bacterial eradication rates for patients treated with a fixed 7-day treatment regimen of FACTIVE are shown in Table 9:

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Table 9. Bacterial Eradication by Pathogen for Patients Treated with FACTIVE in Studies with a Fixed 7-day Duration of Treatment

Pathogen	n/N	%
<i>S. pneumoniae</i>	68/77	88.3
<i>M. pneumoniae</i>	21/22	95.5
<i>H. influenzae</i>	30/35	85.7
<i>C. pneumoniae</i>	13/14	92.9
<i>K. pneumoniae</i> *	11/13	84.6
<i>M. catarrhalis</i>	10/10	100

* Subjects with *Klebsiella pneumoniae* included in this table were from non-comparative studies 061 and 287. 10 of these subjects had mild disease, 2 had moderate disease, and 1 had severe disease. Both failures were in subjects with mild disease (one of these had a bacteriologic recurrence).

FACTIVE was also effective in the treatment of CAP due to PRSP (penicillin MIC of ≥ 2 $\mu\text{g/mL}$). Of 11 patients with PRSP treated for 7 days, 100% achieved clinical and bacteriological success at follow-up. Two of these subjects were classified as having severe disease and were bacteremic.

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/Colangelo
4/4/03

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