CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-158

STATISTICAL REVIEW(S)

Statistical Reviewer's Memorandum

To: NDA 21-158

From: Cheryl Dixon, Ph.D.
Biostatistician, Division of Biometrics III

Through: Karen Higgins, Sc.D.
Statistical Team Leader, Division of Biometrics III

APPEARS THIS WAY
ON ORIGINAL

Re: Addendum to Statistical Review dated November 30, 2000

Date: March 14, 2003

General

The original NDA for Factive® (gemifloxacin mesylate) was submitted December 15, 1999 by SmithKline Beecham Pharmaceuticals. This submission contained studies that were conducted to support the following indications: community-acquired pneumonia (CAP), acute exacerbation of chronic bronchitis (AECB), [redacted] This reviewer reviewed the studies that were submitted in support of CAP, [redacted] (see Statistical Review and Evaluation dated November 30, 2000).

On December 15, 2000, a not approvable letter was sent to the applicant. This letter stated that gemifloxacin was effective in treating CAP of mild to moderate severity, AECB, [redacted] There was also insufficient information to determine whether the drug was safe for use under the conditions suggested in the proposed label. The primary concern dealt with the lack of data to fully assess the potential risks posed by the high incidence of rash in the clinical trials.

On October 7, 2002, PAREXEL International, on behalf of LG Life Sciences, Ltd. (LGLS) who resumed the rights to gemifloxacin, submitted a complete response to the FDA Action Letter. LGLS decided to only pursue the indications of CAP and AECB. Due to an unfavorable risk-benefit ratio, the new applicant decided not to pursue the indications of [redacted]

The remainder of this memorandum will discuss the issues associated with CAP included in the resubmission. The results of a new study (Study 344) that was conducted to characterize the rash associated with gemifloxacin will also be briefly discussed. A memorandum written by Karen Higgins, Sc.D. discusses the issues associated with AECB included in the resubmission.

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Community Acquired Pneumonia (CAP)

The resubmission contains 3 double blind, controlled studies (Studies 011, 012, and 049), one open-label controlled study (Study 185), and two uncontrolled studies (Studies 061 and 287) to support the claims for CAP. Studies 011, 012, 049, and 061 were submitted in the original submission and the three controlled studies were reviewed at the time of the original submission (see Statistical Review and Evaluation dated November 30, 2000). It was determined that these studies provided evidence of the efficacy of gemifloxacin in the treatment of mild to moderate CAP for 7 days.

The duration of treatment with gemifloxacin in Studies 011, 061, and 287 was 7 days. These studies will be referred to as having a fixed 7-day regimen. In Studies 012 and 049, treatment could be extended to 14 days if the patient had a severe infection, if the pneumonia was due to an atypical pathogen or at the investigator's discretion. Study 185 allowed for treatment from 7 to 14 days. These studies will be referred to as the 7-14 day studies with 7 day and 14 day planned duration groups. To maintain an acceptable risk-benefit ratio, the applicant is requesting an indication of the treatment of CAP for duration of 7 days. However, the applicant maintains that a 7-day course of gemifloxacin is effective for the treatment of all severities of CAP.

The Division of Special Pathogen and Immunologic Drug Products maintains that gemifloxacin is effective in the treatment of mild to moderate CAP for 7 days supported primarily by Study 011 and the two uncontrolled studies. The three remaining studies, which allowed 7 to 14 days of treatment, are supportive of this claim. These studies are considered supportive of a 7-day claim because the length of treatment was made in a non-randomized fashion at the investigator's discretion based on the patient's response at the on-therapy visit. The 7 day data from the fixed 7-day regimen contain information on all patients enrolled in the studies while the 7 day data from the 7-14 day studies have patients removed who were considered by their physicians to have needed more treatment and could in general represent a more ill population. This would cause the 7-day efficacy data in the 7-14 day studies to be biased, most likely upwards, in comparison to the fixed 7-day regimen. In addition, for the 7-14 day studies, early failures or withdrawals are included in the 7-day group and not in the 14-day group. This causes a bias in favor of the 14-day group. The following table summarizes the results for clinical response at follow-up by duration of treatment.

Table 1

Clinical Response at Follow-up by Duration of Treatment

Clinical PP	Gemifloxacin	Comparators
7 day fixed		
Controlled (011)	102/115 (88.7)	99/113 (87.6)
Uncontrolled (061, 287)	286/315 (90.8)	-
7-14 days (012,049, 185)		
7 days	329/363 (90.6)	319/348 (91.7)
14 days	200/219 (91.3)	218/237 (92.0)

Table 2 summarizes the results for clinical response by severity. The majority of the subjects were classified as having mild disease. The results for the mild and moderate

groups were similar to the overall results. Even though the efficacy in severe patients was high, very few were treated with the fixed 7-day regimen. Since the 7-day data from the 7-14 day studies cannot be combined and comparisons between the 7 and 14-day regimens cannot be made, the data available in severe patients is limited. It should also be noted that the mild subjects treated with gemifloxacin were on average young (46 years) and primarily female (52.5%). This is the demographic group that has the highest rate of rash. The moderate and severe subjects were primarily older males (69 and 76 years, respectively and >70% male).

Table 2
Clinical Response at Follow-up by Severity

	Fixed 7-day			7-days		14-days	
CPP	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)
Mod	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)

Rash- Study 344

Study 344 was designed to assess the following:

1. The clinical and histological characteristics of gemifloxacin associated rash.
2. The potential for cross-sensitization to ciprofloxacin in subjects who experienced an gemifloxacin-associated rash.
3. The potential for sub-clinical sensitization in subjects not developing a rash on first exposure to gemifloxacin
4. To explore the relationship between plasma levels of gemifloxacin and N-acetyl gemifloxacin and the incidence of rash.

In order to maximize the occurrence of rash, the study exposed female subjects age <40 to 10 days of gemifloxacin. Study 344 was conducted in two parts. In Part A, subjects were randomized to receive gemifloxacin or ciprofloxacin in a 5:1 ratio. Treatment duration was to be for 10 days or until a rash was reported. After a 4-6 week washout period, subjects were enrolled into Part B unless they had a rash in Part A that was classified as a Type I hypersensitivity or otherwise severe reaction. Subjects who had a gemifloxacin rash in Part A were randomized to ciprofloxacin or placebo in a 3:1 ratio. Subjects who received gemifloxacin and did not have a rash in Part A were randomized to gemifloxacin or placebo in a 1:1 ratio. Subjects who had a ciprofloxacin rash in Part A received placebo. Subjects who received ciprofloxacin and did not have a rash in Part A received a repeat course of ciprofloxacin.

A total of 1011 healthy female subjects participated in Part A and 873 subjects continued into Part B. Table 3 summarizes the incidence of rash in Study 344. The

results for Part B exclude subjects from Center 027. This center had a higher incidence of rash in comparison to the other centers including a 100% rash rate for subjects treated with placebo. The Medical Officer reviewed all cases from this center and decided that the analysis should not include these subjects. In Part A, the incidence of gemifloxacin rash was 31.7% compared to 4.3% for ciprofloxacin. In Part B following a gemifloxacin rash in part A, the rate of rash in subjects randomized to ciprofloxacin was 5.9% compared to 2.0% for subjects randomized to placebo.

Table 3
Incidence of Rash- Study 344

Part	Regimen	Rash (%)	Exact 95% CI
A	Gemifloxacin	260/819 (31.7)	(28.6, 35.1)
	Ciprofloxacin	7/164 (4.3)	(1.7, 8.6)
B*	Gemi/rash/cipro	8/136 (5.9)	(2.6, 11.3)
	Gemi/rash/placebo	1/50 (2.0)	(0.1, 10.6)
	Gemi/ no rash/gemi	6/248 (2.4)	(0.9, 5.2)
	Gemi/ no rash/placebo	5/256 (2.0)	(0.6, 4.5)
	Cipro/rash/placebo	0/4	(0.0, 60.2)
	Cipro/ no rash/ cipro	5/141 (3.5)	(1.2, 8.1)

*Excluding Center 027

In addition, the rate of rash in subjects randomized to ciprofloxacin following a gemifloxacin rash in Part A (5.9%) was slightly more than 1.5 times that for subjects rechallenged with ciprofloxacin (3.5%). The applicant claims that the results regarding cross-sensitization must be interpreted with caution. They claim that the study design included an inherent bias in the comparison of the two arms, since the Cipro/no rash/ Cipro arm excludes all subjects known to have a rash with ciprofloxacin on first exposure whereas the Gemi/Rash/Cipro arm does not. The applicant tried to assess the impact of this bias statistically using a probability model. The results of the probability model are based on the key assumption that all subjects with a ciprofloxacin rash would have a rash if they received gemifloxacin. The Division believes that this assumption cannot be inherently made. Therefore, while this approach tries to adjust for the bias, it too is flawed.

Even though this study cannot definitively establish the rate of cross-sensitization to ciprofloxacin in patients who had a gemifloxacin rash, one cannot rule out that cross-sensitization does not exist. Please see the Medical Officer review written by Maureen Tierney, M.D. for a complete review of this study including the characterization of the gemifloxacin rash.

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/s/

Cheryl Dixon
3/14/03 10:42:14 AM
BIOMETRICS

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Karen Higgins
3/14/03 12:19:29 PM
BIOMETRICS

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Statistical Reviewer's Addendum

To: NDA 21-158 Factive™ (gemifloxacin) Tablets

From: Karen Higgins, Sc.D.
Statistical Team Leader
FDA/CDER/OPaSS/OB/DBIII

APPEARS THIS WAY
ON ORIGINAL

Through: Aloka Chakravarty, Ph.D.
Deputy Division Director
FDA/CDER/OPaSS/OB/DBIII

Re: Addendum to Statistical Review dated 12/28/00

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1 Introduction

The initial NDA for gemifloxacin was submitted on December 16, 1999 and included information on five indications. This reviewer reviewed the acute exacerbation of chronic bronchitis (AECB) indication (review dated 12/18/00). A non-approval letter was sent to the sponsor on December 15, 2000 stating that though gemifloxacin was effective in treating AECB, ——————————————————————————— and mild to moderate community-acquired pneumonia (CAP), there were concerns regarding the safety of gemifloxacin. On October 7, 2002, PAREXEL International, on behalf of LG life Sciences Ltd., submitted a complete response to the non-approval letter requesting that the AECB and CAP indication be considered for approval. This NDA resubmission contains efficacy information on these two indications, as well as extensive safety data. This addendum will focus on the efficacy of gemifloxacin in AECB. Please see the addendum written by Cheryl Dixon, Ph.D., which discusses issues associated with the CAP and safety information included in the resubmission.

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In the original review of NDA 21-158, the conclusion was that efficacy in AECB was demonstrated based on pre-specified non-inferiority criteria relative to the comparators used in the controlled studies. This conclusion has not changed. For this reason a full statistical review of this indication will not be conducted for this resubmission. This document will serve as an addendum to the statistics review dated 12/18/00.

In the initial submission of this NDA dated December 16, 1999 the sponsor submitted two primary studies, studies 068 and 070, to support the approval of gemifloxacin 320 mg once daily for five days in the treatment of AECB. A third phase III study using this regimen of gemifloxacin was also submitted as supportive information (study 069). The efficacy results from both primary studies along with the supportive study suggests that gemifloxacin is effective in the treatment of AECB.

Note that in the interim between the non-approval of the original submission and this resubmission questions arose regarding the conduct of two investigators used in one of the original AECB pivotal studies, Dr. DeAbate and Dr. Sokol (study 068). For this reason the division asked the sponsor to remove the data from these two investigators. The following table gives the results from study 068 with and without the two investigators removed. Note that the exclusion of these investigators' data has no effect on the overall interpretation of the study results.

	All Data Included		**DeAbate and Sokol Removed**	
	Gemifloxacin	**Clarithromycin**	**Gemifloxacin**	**Clarithromycin**
Clinical PP at follow-up	245/287 (85.4%)	247/292 (84.6%)	239/278 (86.0%)	240/283 (84.8%)
*Treatment diff. and 95% C.I.**	*0.8 (-5.0, 6.6)*		*1.2 (-4.7, 7.0)*	
ITT	279/351 (79.5%)	280/358 (78.2%)	272/340 (80.0%)	272/348 (78.2%)
*Treatment diff. and 95% C.I.**	*1.3 (-4.7, 7.3)*		*1.8 (-4.2, 7.9)*	

Source: Sponsor's table 1 from abridged study 068 report.
*Confidence intervals calculated as gemifloxacin – comparator using normal approximation to the binomial.

The current resubmission includes five additional studies using this regimen. One study is considered primary (study 212), one is considered supportive (study 207), and three are considered additional (studies 105, 112, and 139). These five studies will be reviewed briefly below.

In addition to the general claim of efficacy in the treatment of AECB, the sponsor has included in their advisory committee background package additional efficacy claims. The sponsor states that gemifloxacin keeps more patients recurrence free, that fewer patients are hospitalized due to respiratory tract infection (RTI)-related episodes compared to clarithromycin, that gemifloxacin patients spend less time in the hospital than IV-PO cephalosporin-treated patients, and that gemifloxacin eradicated *H. influenzae* faster than clarithromycin. In general, we do not feel that these claims are adequately supported by the data submitted and each will be reviewed below. Note that sections 3 and 4 are taken almost directly from the Division's advisory committee meeting background package.

2 Brief summary of new primary and supportive studies

2.1 Study 212

Study 212 is a randomized, double-blind, double-dummy, study to assess the efficacy and safety of gemifloxacin 320 mg once daily for 5 days compared to oral levofloxacin 500 mg once daily for 7 days in the treatment of AECB. The study was conducted at 62 centers in Germany, the United Kingdom and the United States. Enrollment criteria and study design were similar to the two previously submitted primary studies. Patients were seen at screening, on therapy, end of therapy (Day 9-11), follow-up (Visit 4, Day 14-21), and long-term follow-up (Day 28-35). The primary endpoint was clinical response at follow-up. Secondary parameters included clinical response at end of therapy and long-term follow-up and bacteriological response at all post-therapy visits. Clinical response was defined as sufficient improvement or resolution of signs and symptoms of AECB such that no additional antibacterial therapy was required for AECB. The non-inferiority margin was defined to be –13% for the difference in cure rates of gemifloxacin minus levofloxacin.

The demographics and baseline characteristics were similar between the two arms. The following results were obtains for the primary endpoint.

Table 1: Clinical response at the follow-up visit

	Gemifloxacin n/N (%)	**Levofloxacin n/N (%)**	**Difference* (95% CI)**
Clinical Per protocol population	134/152 (88.2%)	126/148 (85.1%)	3.0 (-4.7, 10.7)
ITT population	155/182 (85.2%)	139/178 (78.1%)	7.1 (-0.9, 15.1)

Source: Sponsor's table 37 of the 212 study report
*Difference calculated as gemifloxacin – levofloxacin. Confidence intervals calculated using normal approximation to the binomial

These results support the results found in the review of the original primary studies. Gemifloxacin is similar to the control, in terms of the primary endpoint, clinical response at follow-up. Though the non-inferiority margin was set at –13%, this study would have been able to exclude a margin of –5%.

The secondary endpoints are in general support the primary analysis. Note that though the gemifloxacin clinical success rates are numerically higher than those of levofloxacin, the levofloxacin bacteriological response rates are numerically higher than those of gemifloxacin except at the long-term follow-up.

2.2 Study 207

Study 207 is a randomized, open-label study to compare the efficacy and safety of gemifloxacin 320 mg once daily for 5 days compared to parenteral ceftriaxone followed by oral cefuroxime axetil in the treatment of hospitalized adult patients with AECB. The

study was conducted from 11/99 to 6/00 at 46 centers in Europe, Mexico and South Africa. The study enrolled patients who were at least 40 years old, presenting with symptomatology consistent with AECB, able to tolerate both parenteral and oral treatment, and if hospitalization was clinically indicated.

The protocol stated that patients would be assessed at screening (Day 0), on-therapy (Day 2-4), at end of therapy (2-4 days post therapy) and at follow-up (21-28 days post therapy) to evaluate their clinical and bacterial response. However, the windows for the end of therapy and follow-up visits were extended for the purposes of analysis. The sponsor does not state how these extended windows were determined. The windows for gemifloxacin became days 7-9 (a 3 day window) and days 26-33 (a 7 day window). The windows for the comparator became days 4-14 (an 11 day window) and days 23-38 (a 16 day window).

The primary endpoint was defined as clinical response at Day 21-28 post-therapy. The four secondary efficacy parameters were clinical response at end of therapy, bacterial response at end of therapy, bacterial response at follow-up, and time to discharge from hospital. Other endpoints were duration of therapy, time to switch from IV to oral, patients' quality of life, medical resources used including length of hospital stay in days (including re-admissions), number of visits to physicians, care at home, cost analysis, and therapeutic response at end of therapy and at follow-up. No adjustments to the type I error rate were proposed to account for these multiple secondary and other endpoints.

Patients on gemifloxacin were discharged from the hospital at the investigator's discretion. Patients on the comparator were given IV therapy and then switched to oral therapy at the investigator's discretion. Patients who were switched to oral therapy were discharged from the hospital at the investigator's discretion.

The following results were obtains for the primary endpoint.

Table 2: Clinical response at the follow-up visit

	Gemifloxacin n/N (%)	**Comparator n/N (%)**	**Difference* (95% CI)**
Clinical Per protocol population	105/121 (86.8)	91/112 (81.3)	5.5 (-3.9, 14.9)
ITT population	114/138 (82.6)	98/136 (72.1)	10.6 (0.7, 20.4)

Source: Sponsor's table 32 of the 207 study report
*Difference calculated as gemifloxacin – control. Confidence intervals calculated using normal approximation to the binomial

The results from this supportive study support the results found in the three pivotal studies. Gemifloxacin is similar to the control, in terms of the primary endpoint, clinical response at follow-up.

Concerns regarding this study include the fact that it was open label, that hospitalized patients in the countries used for this study may differ from hospitalized patients in the United States, that the window of assessment was changed and that it was changed to

different lengths for the two treatment arms, and that no adjustments for type I error were proposed for the many additional endpoints.

3 Descriptions of three additional studies

3.1 Study 105

Study 105 was designed to investigate the pharmacokinetic and pharmacodynamic properties of 320mg oral gemifloxacin once daily for 5 days versus 500 mg clarithromycin bid for 7 days in patients with AECB at risk of early recurrence. This study was exploratory and there were no primary efficacy parameters defined. Formal statistical testing was not planned. Rather the purpose of this study was to elucidate an understanding of the pathogenesis of AECB, as well as the PKPD of antibacterials in AECB, and the safety of gemifloxacin. The following 10 efficacy parameters were listed in the protocol:

Clinical response at end of therapy and at follow-up
Bacteriological response at end of therapy and at follow-up
Time to bacterial eradication over all pathogens and by pathogens
Change in clinical signs and symptoms
Change in response to the sGRQ from screening
Change in percent predicted FEV1
Change in inflammatory parameters
Proportion of patients with eradication of NP colonizing organisms (S. pneumoniae, S. aureus, M. catarrhalis, and H. influenzae) on Day 1, Day 4, end of therapy and follow-up
Time from the follow-up visit to next episode of AECB
Change in sputum cytology

The protocol stated that this is an investigational study, that "no formal statistical testing will be carried out, and results will be for descriptive only." Therefore, the sponsor did not provide any adjustment for the type one error rate. Given that there are approximately 31 comparisons accounting for the different pathogens and different time points for analysis, there would be a very high probability of seeing a statistically significant result by chance alone.

3.2 Study 112

Study 112 was a large study conducted in 10 countries which sought to establish superiority of gemifloxacin 320 mg once daily for 5 days over clarithromycin 500 mg bid for 7 days in time to next exacerbation of chronic bronchitis. For all patients who were clinical successes at Visit 2 (1-2 weeks after end of therapy), the time to next exacerbation was measured in days. Patients who were clinical failures at Visit 2 would have a time to next exacerbation as 0 days. Survival analysis techniques were to be used to assess time to event data. No specific survival test was specified as primary. Secondary efficacy parameters included clinical response at Visit 2 and Visit 3 (16-18 weeks after Visit 2) and time to resolution of initial episode of AECB. This study also collected a number of pharmacoeconomic and health related quality of life measures.

3.3 Study 139

Study 139 was a 26 week double-blind, observational parallel/follow-on study to study 068 to assess the proportion of patients who had resolved from their initial episode and remained recurrence free. Following the first 4 to 5 weeks of study 068 in the United States and Canada, patients were recruited to attend two further visits, at Weeks 12 and 26 following the screening visit for study 068. Patients would be assessed for recurrence of AECB at Visit 2 (long-term follow-up for study 068, day 28-35), Visit 3 (week 12) and Visit 4 (week 26). Investigators telephoned patients between visits at Week 8, Week 17 and Week 21. The primary analysis would compare the proportion of patients who have not yet had a recurrence across treatments at each visit and call. This is for a total of 6 analyses. No adjustment for the type 1 error rate was proposed in the protocol. Secondary parameters included the number of recurrences, quality of life measures, use of resources measures, and indirect cost measures.

4 Additional claims

The following four claims were made by the sponsor in their advisory committee meeting (held on 3/4/03) background package based on the results from studies 105, 112, 139, 068, and 207.

Prolonged exacerbation-free intervals (Study 112, 105, 139)
Shorter time to discharge in patients requiring hospitalization (Study 207)
Fewer hospitalizations due to RTI-related episodes (Study 139)
Shorter time to eradication of *H. influenzae* (Study 105 and 068)

We do not believe that these claims are valid for numerous reasons discussed below, including lack of adjustments for multiple comparisons, that the claims are not reproducible from study to study, that similar endpoints did not support the claims, and/or that clinical benefit was not associated with the claim.

4.1 Claim 1: Prolonged exacerbation-free intervals

Three studies measured the time to recurrence of AECB. In study 139 the analysis of the proportion of patients resolved and remaining recurrence free was the primary endpoint. In study 112 comparison of gemifloxacin to clarithromycin in time to next exacerbation of chronic bronchitis was the primary efficacy endpoint. While in study 105, time to recurrence was one of many efficacy parameters.

For study 139, the sponsor states that the proportion of patients who were recurrence free was statistically significantly higher for gemifloxacin with a difference in point estimates of 12% at visit 4. The following table gives the results for each visit and call.

Table 3: Proportion of patients resolved and with no recurrence study 139 – Sponsor's ITT results

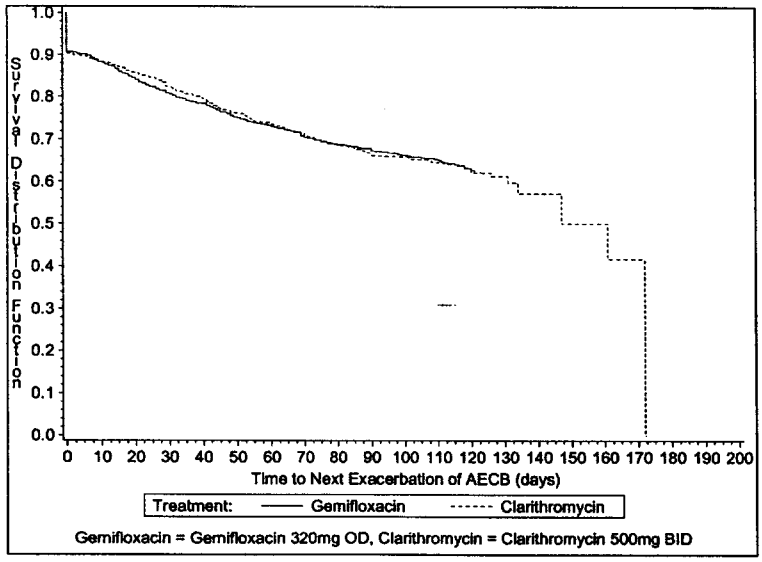
Visit/Call	Gemifloxacin	Clarithromycin	P-value
Visit 2 (week 4-5)	176/202 (87.1)	173/214 (80.8)	0.081
Call 1 (week 8)	165/195 (84.6)	159/197 (80.7)	0.039
Visit 3 (week 12)	148/183 (80.9)	131/176 (74.4)	0.143
Call 2 (week 17)	135/179 (75.4)	118/176 (67.0)	0.084
Call 3 (week 21)	117/160 (73.1)	97/156 (62.2)	0.110
Visit 4 (week 26)	120/169 (71.0)	100/171 (58.5)	0.016

However, given that there were 6 endpoints listed as primary (3 visits and 3 calls) and no adjustment for multiple comparisons, this endpoint would not be considered statistically significant using a Bonferroni adjustment (limit = 0.008 = 0.05/6). Furthermore, the protocol stated that the primary analysis would be conducted on the per protocol population. The analysis of this population did not yield any p-values less than 0.05.

Furthermore, it is difficult to reconcile the impact at 26 weeks post treatment to the 5 day treatment course with gemifloxacin for a clinical condition for which the rate of spontaneous resolution is 50% or more.

Study 112 did not find any difference in recurrence rates between gemifloxacin and clarithromycin in time to next exacerbation. The risk for recurrence was not significantly different between treatment groups (hazard ratio 0.98, 95% CI 0.84, 1.15) as can be seen in the following Kaplan Meier plot (sponsor's Figure 2 from study report for study 112).

Figure 2 Kaplan Meier Plot: Time Next Exacerbation of Chronic Bronchitis (ITT Population)



The following table gives the results of the proportion of patients remaining recurrence free. There was no statistically significant difference between the two arms.

Table 4: Proportion of patients remaining recurrence free study 112

ITT analysis	Gemifloxacin	Clarithromycin	P-value
By 17-20 weeks after end of therapy	595/903 (65.9)	586/896 (64.5)	0.827

Study 105 also looked at time to recurrence as one of its many endpoints. Recurrence rate of AECB was higher for gemifloxacin (60%, 50/83) than for clarithromycin (53%, 42/80) and occurred earlier in the gemifloxacin treatment group (median time to recurrence 22 vs. 46 days for gemifloxacin and clarithromycin, respectively). The following table gives the proportion of patients resolved and remaining recurrence-free.

Table 5: Proportion of patients resolved and with no recurrence study 105

ITT population	Gemifloxacin	Clarithromycin	P-value
Week 11 (approx.)*	33/83 (39.8)	38/80 (47.5)	0.319

Source: from Sponsor's table 43 of 105 study report.
*Patients were seen at follow-up on Day 21-25 and at four post-follow-up visits (every 2 weeks after the follow-up visit). Patients who withdrew before an exacerbation were censored.

The following figures are of the time to next episode of AECB for the ITT both including and excluding (respectively) patients who had a time to next episode of 0 days. These are the sponsor's figures 3 and 4 from study report for study 105.

Figure 3 Time to Next Episode of AECB–Kaplan Meier Plot (ITT Population)

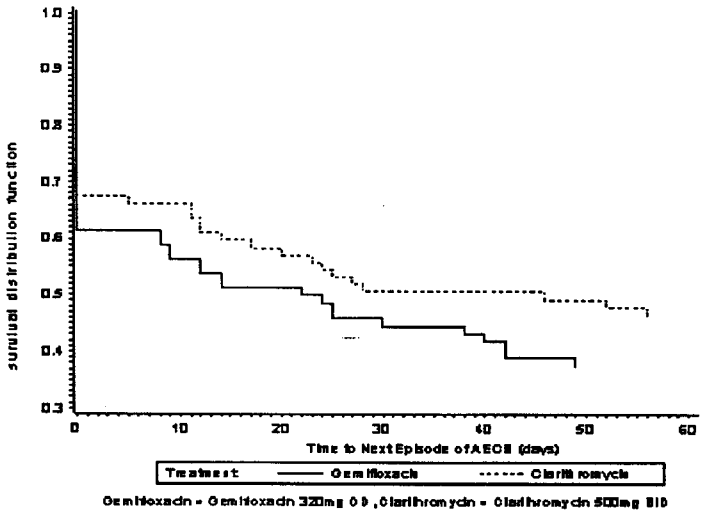


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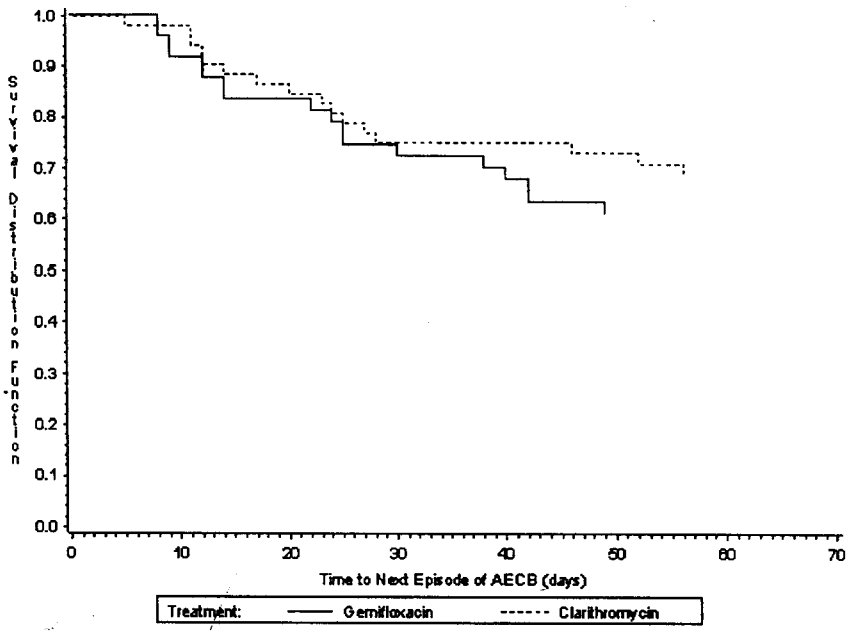
Figure 4 Time to Next Episode of AECB - Kaplan Meier Plot - Clinical Successes (Intent to Treat)



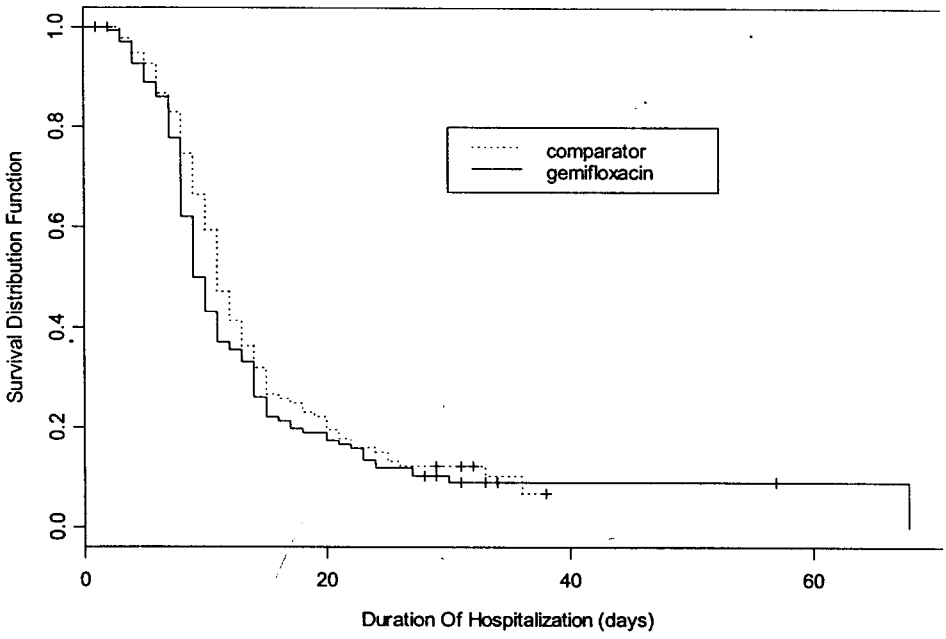
Based on the results of these three studies, we do not agree with the sponsor's claim that gemifloxacin has prolonged exacerbation free intervals. Of the 3 studies that measured this endpoint, one study favored gemifloxacin, one study favored clarithromycin and one study showed no difference.

4.2 Claim 2: Shorter time to discharge in patients requiring hospitalization

In study 207, a supportive open-label study, the sponsor also evaluated the duration of hospitalization in inpatients with AECB along with its primary endpoint of clinical response at follow-up. This endpoint was one of four secondary endpoints with no adjustment for multiple comparisons proposed. This study compared gemifloxacin 320mg for 5 days with parenteral ceftriaxone followed by oral cefuroxime axetil in the treatment of hospitalized adult patients. The sponsor's analysis shows that patients who received gemifloxacin had a median time to discharge that was 2 days shorter than that of the comparator. The sponsor determined that there was a statistically significant difference in time to discharge based on a Wilcoxon p-value of 0.04. However, the hazard ratio of 0.83 is not statistically significantly different from one (0.83, 95% C.I. 0.64, 1.07) and the log-rank test was not significant with a p-value of 0.16. Note that patients in the IV group received at least one dose of IV and this alone could explain the difference in the time to discharge.

The following figure shows the Kaplan Meier plot of this data [reproduction of Figure 13.01 of study report for study 207].

SB-265805 Study 207
Figure 13.01
Time to Discharge – Kaplan Meier Plot
Intent-To-Treat Population



As part of a pharmacoeconomics analysis, the sponsor also conducted an analysis of duration of hospitalization using a general linear model. Treatment was not a statistically significant variable in the model ($p = 0.55$).

Based on the results from this study, we do not believe that the sponsor has shown a significant decrease in days of hospitalization.

4.3 Claim 3: Fewer hospitalizations due to RTI-related episodes

The number of patients hospitalized for respiratory tract infection (RTI)-related episodes over the 26-week study period was one of many secondary endpoints under the category of use of resources in study 139.

The following table of results is from the sponsor's tables 28 and 29 of the study report for study 139. Note that there was not a significant difference between the number of patients with an RTI related hospital episode.

Table.6: Study 139 Number of patients with an RTI related hospital episode at each visit n (%)

Visit	Gemifloxacin N=214	Clarithromycin N=224	Difference (95% CI*)	P-value*
Visit 2	1/202 (0.5)	5/214 (2.3)	-1.8 (-4.1, 0.4)	0.217
Visit 3	2/183 (1.1)	4/176 (2.3)	-1.2 (-3.9, 1.5)	0.441
Visit 4	3/169 (1.8)	5/179 (2.9)	-1.1 (-4.4, 2.1)	0.723
Total	5/214 (2.3)	14/224 (6.3)	-3.91 (-7.67,-0.15)	0.059

Source: Sponsor's table 28 and 29 of 139 study report

* Confidence intervals (gemifloxacin – clarithromycin) calculated using normal approximation to the binomial. Due to the small number of events, these intervals should be interpreted with caution. P-values calculated using exact methods.

Additional secondary endpoints under the category use of resources included for each visit, length of RTI related hospital stay, number of days on antibiotic therapy, number of days on RTI related antibiotic therapy, and number of RTI related physician visits. None of these endpoints showed a difference between treatments.

Based on the results of this study, we do not believe that the result seen is significant, especially given the large number of secondary endpoints. Furthermore, additional endpoints on use of resources did not support this result.

4.4 Claim 4: Shorter time to eradication of H. influenzae

Two studies, 105 and 068, measured the time to bacterial eradication of *H. influenzae.*

In study 105 the sponsor found that bacterial pathogens were more rapidly eradicated in patients treated with gemifloxacin compared to those treated with clarithromycin. By day 6, only 2% (1/66) of gemifloxacin treated patients had persistently positive sputum cultures, compared to 28% 16/58 in the clarithromycin group. The median time to bacteriological eradication of all pathogens was 1 day for gemifloxacin and 2.5 days for clarithromycin. Results from this study for *H. influenzae* showed that on Day 1 the bacterial eradication rates of *H. influenzae* on gemifloxacin was 18/23 (78%) compared to 13/31 (42%) for clarithromycin. The median time to eradication of *H. influenzae* was 1 day for gemifloxacin and 2 days for clarithromycin. These results are based on one of many efficacy parameters analyzed in this study for descriptive purposes without an adjustment for multiple comparisons.

The following two tables show the number with continued clinical success at the six time points for this study for both the subset of patients with any pathogen and the subset of patients with *H. influenzae.* Note that there is no advantage of gemifloxacin in terms of clinical success rates.

Table 7: Study 105 Sustained clinical success in patients with pathogens at baseline

Clinical Success (ITT) n (%)	**Gemifloxacin N=66**	**Clarithromycin N=58**
EOT	55 (83.3%)	45 (77.6%)
Follow-up	38 (57.6%)	39 (67.2%)
Visit 1	30 (45.5%)	33 (56.9%)
Visit 2	25 (37.9%)	27 (46.6%)
Visit 3	20 (30.3%)	27 (46.6%)
Visit 4	19 (28.8%)	24 (41.4%)

Table 8: Study 105 Sustained clinical success in patients with *H. influenzae*

Clinical Success (ITT) n (%)	**Gemifloxacin N=23**	**Clarithromycin N=31**
EOT	19 (82.6%)	24 (77.4%)
Follow-up	16 (69.6%)	21 (67.7%)
Visit 1	12 (52.2%)	18 (58.1%)
Visit 2	8 (34.8%)	14 (45.2%)
Visit 3	7 (30.4%)	14 (45.2%)
Visit 4	6 (26.1%)	13 (41.9%)

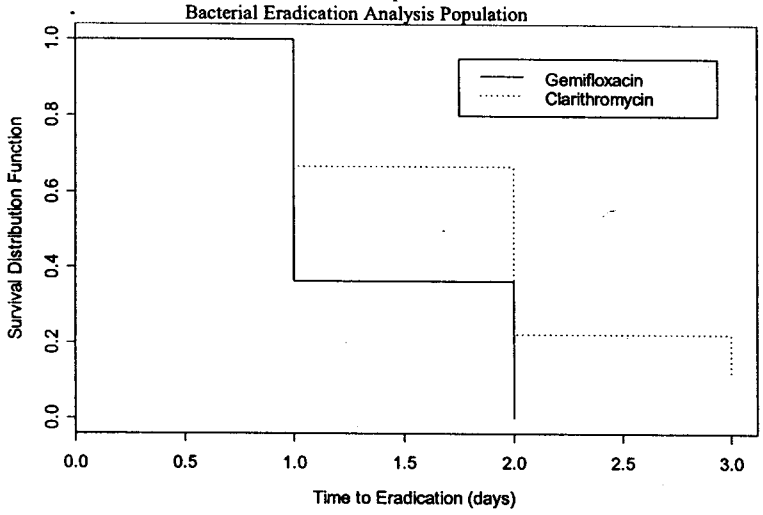
Study 068, a pivotal trial, contained a sub-study on the time to *H. influenzae* eradication which was one of 6 listed secondary analyses. This analysis was restricted to the subgroup of patients enrolled in the sub-study who had *H. influenzae* cultured at baseline (n=24). These patients had their bacteriological outcome determined daily from days 1 to 6. At each day an outcome of eradication, persistence, or unable to be determined was given. Time to bacterial eradication was defined as the time in days to the first outcome of bacterial eradication. Kaplan Meier plots of time to eradication were presented along with the comparison of time to eradication and an analysis of proportion of patients with eradication on Day 1.

The following table shows the results of this sub-study in number eradicated and percent eradicated. Though the analysis of day 1 proportion eradicated did not lead to significant results, the sponsor did report a statistically significant difference in time to bacterial eradication (p=0.02). The following figure shows the Kaplan-Meier plot for the time to eradication. It is a reproduction of figure 13.01 from the original NDA submission.

Table 9: Study 068 Sub-study number (percent) eradicated

Number Eradicated	Gemifloxacin 320 mg PO x 5 days N = 12	Clarithromycin 500 mg bid x 7 days N = 12
Day 1	7 (58%)	3 (25%)
Day 2	11(92%)	7 (58%)
Day 3	11 (92%)	8 (67%)
	1 subject was censored on day 0	1 subject was censored on day 0 1 subject was censored on day 3 2 subjects were censored on day 4

SB-265805 STUDY 068: Figure 13.01
Time to Eradication – Kaplan-Meier Plot
Bacterial Eradication Analysis Population



However, the time to eradication did not significantly impact patient clinical outcomes; gemifloxacin was less than or equal to clarithromycin in efficacy except in the per protocol analysis at follow-up. The following table gives the clinical cure rates for both the per protocol (PP) and the intent-to-treat (ITT) populations at the end of therapy (EOT), the follow-up, and the long-term follow-up visits.

Table 10: Study 068 sub-study clinical cure in patients with *H. influenzae*

Clinical Cure	Gemifloxacin	Clarithromycin
PP at EOT	8/10 (80%)	10/12 (83%)
PP at follow-up	8/10 (80%)	8/12 (67%)
ITT at EOT	8/12 (67%)	10/12 (83%)
ITT at follow-up	8/12 (67%)	8/12 (67%)
ITT at long-term follow-up	6/12 (50%)	7/12 (58%)

The sponsor showed in two studies that eradication of *H. influenzae* in the sputum occurs sooner for gemifloxacin than for clarithromycin. Though, these results were based on

analyses unadjusted for multiple comparisons, they are very consistent across the two studies. However, we do not believe that this earlier eradication of *H. influenzae* translates into a clinical benefit.

5 Conclusions

The conclusion regarding the efficacy of gemifloxacin in treating patients with acute bacterial exacerbation of chronic bronchitis has not changed from the conclusion stated in the statistical review of the original NDA submission of gemifloxacin. Based on the two pivotal trials from the original submission, 068 and 070, it was concluded that efficacy of gemifloxacin was demonstrated based on the results that gemifloxacin was shown to be non-inferior compared to the active controls. This conclusion has not changed with the removal of data from two investigators from study 068 or with the addition of a third pivotal trial, 212. Efficacy of gemifloxacin continued to be demonstrated based on the re-analysis of study 068 results and the results of study 212.

The data provided by the applicant suggest that a regimen of gemifloxacin 320mg once daily for five days is effective in the treatment of acute exacerbation of chronic bronchitis.

Although the overall efficacy of gemifloxacin in treating patients with AECB was shown, we do not believe that the additional claims made by the sponsor in the advisory committee background package are valid. The reasons why we do not believe that these claims are valid were given in section 4 of this document and include the lack of adjustments for multiple comparisons, that the claims are not reproducible from study to study, that similar endpoints did not support the claim, and/or that clinical benefit was not associated with the claim.

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/s/

Karen Higgins
3/25/03 06:55:27 PM
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Aloka Chakravarty
3/26/03 09:08:47 AM
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NDA 21-158

FACTIVE® (gemifloxacin mesylate) 320mg Tablets

Action Date: December 15, 2000

TL: Leissa

MO: Powers, Alivisatos, Cox

CHM: M. Sloan

PCL: Ellis

MIC: Dionne

BPH: Colangelo

STT: Higgins, Dixon, Silliman

RPM: Kimzey

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REASON:

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__X__ b(4) CCI

_____ b(4) TS

_____ b(5) Deliberative Process; Attorney Client and Attorney Work Product Privilege

_____ b(6) Personal Privacy

_____ b(7) Law Enforcement Records

Statistical Review and Evaluation

NOV 30 2000

NDA #: 21-158

Applicant: SmithKline Beecham Pharmaceuticals

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Name of Drug: Factive™ (gemifloxacin mesylate)

Documents Reviewed: NDA Index and Summary sections (Vols. 1.1.001, 1.2.001, 1.3.001, and 1.2.002), Statistical sections (Vols. 1.8.001-1.8.109) dated December 15, 1999, and SAS datasets of the clinical efficacy and safety data.

Indications: The treatment of infections caused by susceptible strains of various organisms in the following: community-acquired pneumonia (CAP); acute exacerbation of chronic bronchitis (AECB); [redacted] This reviewer completed the statistical review of CAP. [redacted] Karen Higgins completed the statistical review of AECB and [redacted]

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Statistical Reviewer: Cheryl Dixon, Ph.D. (HFD-725)

Medical Reviewers: Dr. Edward Cox (HFD-590)- CAP and ABS
Dr. Regina Alivisatos (HFD-590)- pyelonephritis
Dr. John Powers (HFD-590)- safety

I. INTRODUCTION

Gemifloxacin is a fluoroquinolone antibiotic agent developed by SmithKline Beecham Pharmaceuticals. The clinical program focused on five indications: community-acquired pneumonia (CAP), acute exacerbation of chronic bronchitis (AECB), [redacted]). Eleven randomized, double blind, adequately controlled principal clinical studies and four supportive clinical studies were performed to evaluate the efficacy of gemifloxacin in these indications. The Phase III clinical studies of gemifloxacin tested an oral dose of 320 mg once daily with a variable duration of dosing depending on indication. In addition, a single dose of 640 mg was tested in

This review will focus on the principal studies conducted in support of community acquired pneumonia (Studies 011, 012, and 049), [redacted]

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II. COMMUNITY-ACQUIRED PENUMONIA (CAP)

Three principal well-controlled clinical studies were conducted to investigate the efficacy of gemifloxacin in the treatment of community acquired pneumonia (CAP), Studies 012, 049, and 011. In addition, one supportive open label, uncontrolled study was conducted, Study 061. All three of the principal studies were randomized, double blind, double dummy, parallel group, active comparator studies. Study 012, conducted in Europe, the United States, Canada, and South Africa, compared gemifloxacin 320 mg once daily for 7 or 14 days and cefuroxime 500 mg/clarithromycin 500 mg bid for 7 to 14 days. Study 049, conducted in the United States, Mexico, and Spain, compared gemifloxacin 320 mg once daily for 7 or 14 days and trovafloxacin 200 mg once daily for 7 or 14 days. In Studies 012 and 049, the decision to extend treatment to 14 days was to be made at the on-therapy visit. Study 011, conducted in Europe and South Africa, compared gemifloxacin 320 mg once daily for 7 days and amoxicillin 1 g/clavulanate 125 mg tid for 10 days.

Reviewer's Comment: *Only the three controlled studies will be discussed in this review. See the Medical Officer's efficacy review written by Dr. Ed Cox for discussion of the results of Study 061.*

Patients aged ≥ 18 years with radiographic evidence of CAP, at least two other clinical signs or symptoms of CAP, and either a history of fever for the current episode of CAP and/or an elevated total peripheral WBC count were enrolled into the studies. In Study 011, patients were to have a clinical presentation that suggested pneumococcal involvement. Clinical, bacteriological, and radiological response to treatment was assessed at the on-therapy visit, at end of therapy, and at a follow-up visit. The follow-up visit, which occurred 14 to 21 days after the end of study medication, was the test of cure visit.

The primary efficacy parameter in the CAP studies was the clinical response (success or failure) at follow-up. A clinical response of success at follow-up was defined as sufficient improvement or resolution of the signs and symptoms of CAP, such that no additional antibacterial therapy was required. Clinical failures at the end of therapy were carried forward as failures to the follow-up assessment. Secondary efficacy parameters were clinical response at end of therapy and bacteriological response and radiological response at end of therapy and follow-up.

The three studies were designed to demonstrate that gemifloxacin was at least as good as the active comparator. Sample sizes were based on 90% power to show that the lower bound of the two-sided 95% confidence interval for the differences in response rates (gemifloxacin- comparator) was no less than a pre-defined non-inferiority limit. In Studies 012 and 049, 508 patients were to be enrolled in order to provide 380 evaluable patients assuming a clinical response rate of 90%. It was assumed that 25% of the population would be ineligible for the per protocol analysis. A delta of 10% was used for

these studies. In Study 011, which recruited CAP patients with suspected pneumococcal involvement, a lower clinical response rate of 85% was assumed and a delta of 15% was used. Thus, 320 patients were enrolled to provide 240 evaluable patients in Study 011.

Reviewer's Comment: *At the End of Phase IIA meeting (August 11, 1998), the sponsor was told that a delta of 15% would be acceptable for all indications other than ——— The more stringent and conservative delta of 10% was selected by the sponsor for Studies 012 and 049 due to discussions with other regulatory authorities.*

Four patient populations were defined for the analysis of clinical, radiological and bacteriological efficacy. They are:

- ITT: all randomized patients who took at least one dose of study medication.
- Clinical PP: a subset of the ITT population that excluded patients who violated the protocol to an extent that could bias efficacy results.
- Bacteriology ITT: all randomized patients who took at least one dose of study medication and had evidence of infection with at least one pre-therapy pathogen identified at screening.
- Bacteriology PP: a subset of the Bacteriology ITT population that excluded patients who violated the protocol to an extent that could bias efficacy results.

In the ITT analyses, patients with a clinical outcome of unable to determine were classed as having a clinical response of failure.

Reviewer's Comment: *The PP populations are the primary analysis populations but the ITT analyses will be used to test the robustness of the per protocol results.*

In Study 012, the protocol-specified windows for end of therapy (Day 9-11) and follow-up (Day 21-28) (Day 16-18 and Day 28-35, respectively, for 14 day treatment) were extended for the purposes of analysis to Day 8-12 and Day 19-32, respectively (Day 14-18 and Day 27-36, respectively, for 14 day treatment period) before the blind was broken. In Study 049, the protocol specified windows for end of therapy (2-4 days post therapy) and follow-up (14-21 days post therapy) were extended for the purpose of analysis to 1-4 days post therapy and 13-21 days post therapy, respectively, before the blind was broken. In Study 011, the protocol specified windows for end of therapy (Day 12-14) and follow-up (Day 24-30 days post therapy) were extended for the purpose of analysis to Day 11-16 and Day 23-37, respectively, before the blind was broken.

Reviewer's Comment: *The medical reviewer accepted the sponsor's revised windows for end of therapy and follow-up.*

The primary efficacy analysis was based on the Clinical PP follow-up population. Two-sided 95% confidence intervals, calculated using the normal approximation to the binomial distribution with continuity correction, were used to estimate the difference in the proportion of success between the treatment groups. A conclusion of non-inferior efficacy of gemifloxacin was drawn if the lower limit of the confidence interval

(gemifloxacin- comparator) was greater than or equal to the delta set in the protocol. In addition, for studies 012 and 049, in order to take into account the effect of treatment duration (7 or 14 days), a 95% confidence interval was also calculated using a Mantel-Haenszel stratified approach by this reviewer.

Study 012
Results: Efficacy

Reviewer's Comment: *A 20% random sample of the patients enrolled in this study was generated by the statistical reviewer and reviewed by the medical officer. No changes were made to either evaluability or outcome. Therefore, the sponsor's data was accepted and all analyses are based on the data as submitted by the sponsor.*

Study 012 was conducted at 109 centers in 15 countries. There were 1 to 30 centers participating from each country. Germany, which had 30 participating centers, enrolled the largest number of patients overall. A total of 641 patients were randomized to receive study treatment; 319 were randomized to receive gemifloxacin and 322 to receive cefuroxime/clarithromycin. One patient in the cefuroxime/clarithromycin withdrew from the study before receiving any study medication and was not included in the ITT population. There were 210 patients in the ITT population who had at least one pathogen identified at screening. These patients comprise the Bacteriology ITT population. Patient disposition is shown in Table 012-1.

Table 012-1
Patient Disposition

Population	Treatment Group	
	Gemifloxacin 320 mg od	Cef/Clari 500/500 mg bid
Randomized	319	322
ITT (received study medication)	319	321
Completed Study	265	278
Clinical PP End of Therapy	267	279
Clinical PP Follow-up	251	257
Bacteriology ITT	102	108
Bacteriology PP End of Therapy	85	99
Bacteriology PP Follow-up	79	90

The treatment groups were comparable with respect to reasons for withdrawal from the study prior to completion. Reasons for withdrawal include adverse experience, insufficient therapeutic effect, protocol deviation (including non-compliance), lost to follow-up, and other as determined by the investigator (withdrew consent). A total of 52 (16.3%) gemifloxacin patients and 42 (13.1%) cefuroxime/clarithromycin patients were excluded from the Clinical PP end of therapy population and 68 (21.3%) gemifloxacin patients and 64 (19.9%) cefuroxime/clarithromycin patients were excluded from the

Clinical PP follow-up population. The most frequent reasons for exclusion from the PP populations include other antibacterial treatment for reasons other than clinical failure or clinical recurrence, medication compliance, visit compliance, and unable to determine-clinical. There were no differences between the treatment groups in the incidence of exclusion for any reason.

Table 012-2 shows the demographic characteristics of the ITT population. There were no significant differences across treatment groups. At least half of the patients were male and the majority of the patients were white. The mean age was 54 years in the gemifloxacin group and 53 years in the cefuroxime/clarithromycin group.

Table 012-2
Demographic Characteristics (ITT)

	Treatment Group	
	Gemifloxacin 320 mg od	**Cef/Clari 500/500 mg bid**
# Patients	319	321
Gender N (%)		
Female	132 (41.4)	145 (45.2)
Male	187 (58.6)	176 (54.8)
Age mean (SD)	54.7 (17.5)	53.7 (17.4)
Min, max	18, 94	18, 92
Race N (%)		
White	310 (97.2)	311 (96.9)
Black	6 ((1.9)	3 (0.9)
Oriental	2 (0.6)	3 (0.9)
Other	1 (0.3)	4 (1.2)

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There were 102 patients in the gemifloxacin group and 108 patients in the cefuroxime/clarithromycin group who had at least one pathogen identified from any source (sputum/respiratory samples, blood culture, serology or urine antigen) pre-therapy. The most common pathogens identified at screening from any source were —— *C. pneumoniae, S. pneumoniae,* and *H. influenzae.* The distribution of pre-therapy pathogens was relatively similar in both treatment groups with the following exceptions. The proportion of patients with *H. influenzae* was higher in the gemifloxacin group than in the cefuroxime/clarithromycin group (14.7% vs. 7.4% Bacteriology ITT population and 16.5% vs. 5.6% in the Bacteriology PP follow-up population). In the Bacteriology PP follow-up population, the proportion of patients with —— was lower in the gemifloxacin group than in the cefuroxime/clarithromycin (44.3% vs. 51.1%).

Treatment 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 or otherwise at the investigator's discretion. In the ITT population, 78 (24.5%) patients in the gemifloxacin group and 72 (22.4%) patients in the cefuroxime/clarithromycin group had an extension of their study treatment to a total duration of 14 days. In the Clinical PP

follow-up population, there were 52 (20.7%) and 53 (20.6%) patients with a treatment extension, respectively. In most cases, the extension was because the patient had a severe infection. There were no differences between the groups in the reasons for treatment extension.

Table 012-3 summarizes the primary efficacy analysis results. The primary efficacy parameter was clinical response (success or failure) at follow-up. The results of the Clinical PP follow-up and the ITT population are both presented. The clinical success rate at follow-up in the Clinical PP follow-up population was 87.6% in the gemifloxacin group and 92.6% in the cefuroxime/clarithromycin group. Results in the ITT population were 78.4% and 84.7%, respectively. At the protocol specified non-inferiority limit (10%), the clinical efficacy of gemifloxacin was not shown to be non-inferior to cefuroxime/clarithromycin in either population.

Table 012-3
Clinical Response at Follow-up

Clinical Response	Treatment Group		Difference %(Gemi-Cef/Clari) 95% CI
	Gemifloxacin 320 mg od	Cef/Clari 500/500 mg bid	
Clinical PP follow-up	**N=251**	**N=257**	
Success n (%)	220 (87.6)	238 (92.6)	-5.0 (-10.6, 0.6)
ITT	**N=319**	**N=321**	
Success n (%)	250 (78.4)	272 (84.7)	-6.3 (-12.6, 0.004)

Reviewer's Comment: *The results stated in the above table are slightly different than those stated by the sponsor in the study report. A continuity correction was applied to the above confidence interval and will be applied in all non-exact confidence intervals presented in this review.*
For the Clinical PP follow-up population, the lower limit of the 95% CI only marginally exceeded the protocol specified delta of 10%. However, the Division usually allows a delta of 15% for CAP studies. Given the 15% delta, the lower limit of the 95% CI for both populations is well within the criterion to declare that the clinical efficacy of gemifloxacin is at least as good as that of cefuroxime/clarithromycin.

The sponsor also performed a multiple imputation analysis on the clinical ITT population to investigate the impact of missing data. There were 37 (11.6%) patients in the gemifloxacin group and 24 (7.5%) patients in the cefuroxime/clarithromycin group who were excluded from the Clinical PP follow-up population because of a clinical outcome of unable to determine. In the original ITT analysis, these patients were considered clinical failures. Five datasets were generated with imputed values of clinical response for these patients using Solas® 1.0. For each of the datasets, an estimate of treatment difference with corresponding variance was calculated. These results were then combined to give an overall estimate of the treatment difference and a corresponding 95% confidence interval was calculated. For each of the multiple imputations and the

combined multiple imputation analysis, the lower limit of the confidence interval was greater than –10%. This conclusion contrasts the results of the original ITT analysis. The sponsor explains this contrast as being due to the fact that the rate of unable to determine was slightly higher in the gemifloxacin group and the majority of the unable to determine outcomes were imputed as success because the majority of the observed cases were successes.

Reviewer's Comment: *The results of the multiple imputation analysis may contrast the results of the original ITT analysis if a delta of 10% is used for determining non-inferiority. However, if a delta of 15% is used to assess non-inferiority then the results of the multiple imputation analysis are supportive of the original ITT analysis. In this case, the multiple imputation analysis is an acceptable method for investigating the impact of missing data as a supportive analysis.*

Since treatment could be extended to 14 days, clinical response at follow-up was also analyzed by duration of dosing (7 or 14 days). Table 012-4 summarizes these results. Patients who received treatment for 14 days had slightly lower success rates in both treatment groups than those patients who received 7 days of treatment. The lower bound of the 95% confidence interval about the difference in success rates for patients who received 14 days of therapy is less than –15%. It should be noted, however, that the sample size for this subgroup is relatively small and the study was not powered to show non-inferiority for this subgroup analysis. When controlling for duration of therapy, the Mantel-Haenszel confidence interval about the difference in success rates is (-10.6, 0.7). Thus, the robustness of the primary analysis is supported.

Table 012-4
Clinical Response at Follow-up by Duration of Dosing
(Clinical PP Follow-up Population)

Duration of Dosing	Treatment Group		Difference %(Gemi-Cef/Clari) 95% CI
	Gemifloxacin 320 mg od	Cef/Clari 500/500 mg bid	
7 Days	**N=199**	**N=204**	
Success n (%)	175 (87.9)	190 (93.1)	-5.2 (-11.4, 1.0)
14 Days	**N=52**	**N=53**	
Success n (%)	45 (86.5)	48 (90.6)	-4.1 (-18.2, 10.0)

Table 012-5 summarizes the results of the analysis based on clinical response at end of therapy, a secondary endpoint. In both populations, the clinical efficacy of gemifloxacin at end of therapy was found to be at least as good as that of cefuroxime/clarithromycin.

Table 012-5
Clinical Response at End of Therapy

Clinical Response	Treatment Group		Difference %(Gemi-Cef/Clari) 95% CI
	Gemifloxacin 320 mg od	Cef/Clari 500/500 mg bid	
Clinical PP end of therapy	**N=267**	**N=279**	
Success n (%)	243 (91.0)	264 (94.6)	-3.6 (-8.3, 1.1)
ITT	**N=319**	**N=321**	
Success n (%)	274 (85.9)	287 (89.4)	-3.5 (-8.9, 1.9)

Table 012-6 summarizes the results for per patient bacteriological response at follow-up. Per patient bacteriological efficacy of gemifloxacin at follow-up in the Bacteriology PP follow-up population was at least as good as that of cefuroxime/clarithromycin. However, per patient bacteriological efficacy of gemifloxacin at follow-up in the Bacteriology ITT population was not shown to be at least as good as that of cefuroxime/clarithromycin.

Table 012-6
Per Patient Bacteriological Response at Follow-up

Bacteriological Response	Treatment Group		Difference %(Gemi-Cef/Clari) 95% CI
	Gemifloxacin 320 mg od	Cef/Clari 500/500 mg bid	
Bacteriology PP follow-up	**N=79**	**N=90**	
Success n (%)	71 (89.9)	80 (88.9)	1.0 (-9.5, 11.5)
Bacteriology ITT	**N=102**	**N=108**	
Success n (%)	82 (80.4)	93 (86.1)	-5.7 (-16.7, 5.3)

Per patient bacteriological response at end of therapy was also investigated. The success rates at end of therapy were slightly higher than the success rates seen at follow-up. The conclusions drawn for per patient bacteriology response at end of therapy were similar to the conclusions drawn for per patient bacteriology response at follow-up for both the Bacteriology PP and ITT populations.

Results: Safety

A total of 157 patients (49.2%) in the gemifloxacin group and 179 patients (55.8%) in the cefuroxime/clarithromycin group had at least one adverse event during the interval on-therapy plus 30 days post-therapy. The most common adverse event in both treatment groups was diarrhea. The incidence of diarrhea was statistically significantly higher in the cefuroxime/clarithromycin group (12.8%) than in the gemifloxacin group (6.6%) (p=0.011). The incidence of rash and related experiences associated with the skin was higher in the gemifloxacin group (4.1%) than in the cefuroxime/clarithromycin group (1.2%) (p=0.028).

Drug related (suspected or probable) adverse events occurred in 73 patients (22.9%) in the gemifloxacin group and 95 patients (29.6%) in the cefuroxime/clarithromycin group. The most commonly occurring drug related adverse event was diarrhea in both treatment groups (6.0% gemifloxacin and 11.8% cefuroxime/clarithromycin). As with adverse events overall, diarrhea related to study drug was statistically significantly higher in the cefuroxime/clarithromycin group than in the gemifloxacin group (p=0.012).

Most of the adverse events were mild to moderate in severity. Symptoms were classified as severe in 6.9% of gemifloxacin treated patients and 10.6% of cefuroxime/clarithromycin treated patients. There were 19 (6.0%) gemifloxacin patients and 26 (8.1%) cefuroxime/clarithromycin patients with serious adverse events, and seven deaths in the study, four in the gemifloxacin treatment group and three in the cefuroxime/clarithromycin treatment group. There was one additional death in the gemifloxacin group that occurred more than 30 days after the last dose of study medication. All of the deaths were reported as unrelated to study treatment. One patient in the gemifloxacin group and two patients in the cefuroxime/clarithromycin group had a serious adverse event that was reported to be related to study treatment.

Twenty-six patients (8.2%) in the gemifloxacin group and 22 patients (6.9%) in the cefuroxime/clarithromycin group discontinued study drug due to adverse events. Diarrhea, rash, tuberculosis infection, uticaria, respiratory disorder, nausea, pneumonia, vomiting, and taste perversion were the most commonly reported (at least 0.5%) reasons for discontinuation. Discontinuation due to rash occurred more often in the gemifloxacin group. Discontinuation due to tuberculosis infection and uticaria was unique to gemifloxacin treated patients. Discontinuation due to nausea, pneumonia, vomiting, and taste perversion was unique to cefuroxime/clarithromycin treated patients. More patients in the gemifloxacin group (46.2%) than in the cefuroxime/clarithromycin group (40.9%) had adverse events leading to withdrawal reported as suspected/probably related to study drug.

For a more detailed review of the safety data, please see the Medical Officer Safety review written by Dr. John Powers.

Study 049
Results: Efficacy

Reviewer's Comment: *A 20% random sample of the patients enrolled in this study was generated by the statistical reviewer and reviewed by the medical officer. No changes were made to either evaluability or outcome. Therefore, the sponsor's data was accepted and all analyses are based on the data as submitted by the sponsor.*

Study 049 was conducted at 72 centers in 3 countries. There were 2 centers in Mexico, 18 centers in Spain, and 52 centers in the United States. More than half of the patients enrolled were from the United States. A total of 573 patients were randomized to

receive study treatment; 291 were randomized to receive gemifloxacin and 282 to receive trovafloxacin. Two patients, one patient from each treatment group, withdrew from the study before receiving any study medication and were not included in the ITT population. There were 222 patients in the ITT population who had at least one pathogen identified at screening. Patient disposition is shown in Table 049-1.

Table 049-1
Patient Disposition

Population	Treatment Group	
	Gemifloxacin 320 mg od	Trovafloxacin 200 mg od
Randomized	291	282
ITT (received study medication)	290	281
Completed Study	256	242
Clinical PP End of Therapy	238	233
Clinical PP Follow-up	216	207
Bacteriology ITT	120	102
Bacteriology PP End of Therapy	100	90
Bacteriology PP Follow-up	91	75

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Reasons for withdrawal from the study prior to completion include adverse experience, insufficient therapeutic effect, protocol deviation (including non-compliance), lost to follow-up, and other as determined by the investigator (withdrew consent and refusal to take more medication). The treatment groups were comparable with respect to reasons for withdrawal. The only exception was lost to follow-up, which occurred slightly more often in the trovafloxacin treatment group (2.4% gemifloxacin vs. 6.4% trovafloxacin) (p=0.024). A total of 52 (17.9%) gemifloxacin patients and 48 (17.1%) trovafloxacin patients were excluded from the Clinical PP end of therapy population and 74 (25.5%) gemifloxacin patients and 74 (26.3%) trovafloxacin patients were excluded from the Clinical PP follow-up population. The most frequent reasons for exclusion from the PP populations include other antibacterial treatment for reasons other than clinical failure or clinical recurrence, medication compliance, visit compliance, and unable to determine-clinical. There were no differences between the treatment groups in the incidence of exclusion for any reason.

Table 049-2 shows the demographic characteristics of the ITT population. There were no significant differences across treatment groups. At least half of the patients were male and the majority of the patients were white. The mean age was 50 years in the gemifloxacin group and 49 years in the trovafloxacin group.

Table 049-2
Demographic Characteristics (ITT)

	Treatment Group	
	Gemifloxacin 320 mg od	**Trovafloxacin 200 mg od**
# Patients	290	281
Gender N (%)		
Female	138 (47.6)	121 (43.1)
Male	152 (52.4)	160 (56.9)
Age mean (SD)	50.8 (18.0)	49.3 (17.8)
Min, max	18, 92	18, 93
Race N (%)		
White	254 (87.6)	244 (86.8)
Black	20 (6.9)	25 (8.9)
Oriental	0	3 (1.1)
Other	16 (5.5)	9 (3.2)

There were 120 patients in the gemifloxacin group and 102 patients in the trovafloxacin group who had at least one pathogen identified from any source (sputum/respiratory samples, blood culture, serology or urine antigen) pre-therapy. The most common pathogens identified at screening from any source were [redacted], *S. pneumoniae,* and *C. pneumoniae.* The distribution of pre-therapy pathogens was relatively similar in both treatment groups.

Treatment 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 or otherwise at the investigator's discretion. In the ITT population, 107 (36.9%) patients in the gemifloxacin group and 95 (33.8%) patients in the trovafloxacin group had an extension of their study treatment to a total duration of 14 days. In the Clinical PP follow-up population, there were 72 (33.3%) and 67 (32.4%) patients with a treatment extension, respectively. In most cases, the extension was because the patient had a severe infection. There were no differences between the groups in the reasons for treatment extension.

Table 049-3 summarizes the primary efficacy analysis results. The primary efficacy parameter was clinical response (success or failure) at follow-up. The results of the Clinical PP follow-up and the ITT population are both presented. The clinical success rate at follow-up in the Clinical PP follow-up population was 94.0% in the gemifloxacin group and 89.9% in the trovafloxacin group. Results in the ITT population were 87.6% and 81.1%, respectively. The clinical efficacy of gemifloxacin was at least as good as that of trovafloxacin in both populations, since the lower limit of the 95% CIs were greater than –10%.

Table 049-3
Clinical Response at Follow-up

Clinical Response	Treatment Group		Difference %(Gemi-Trova) 95% CI
	Gemifloxacin 320 mg od	Trovafloxacin 200 mg od	
Clinical PP follow-up	**N=216**	**N=207**	
Success n (%)	203 (94.0)	186 (89.9)	4.1 (-1.6, 9.8)
ITT	**N=290**	**N=281**	
Success n (%)	254 (87.6)	228 (81.1)	6.5 (0.2, 12.8)

The sponsor also performed a multiple imputation analysis on the clinical ITT population to investigate the impact of missing data (see description of multiple imputation analysis under Study 012). There were 21 (7.2%) patients in the gemifloxacin group and 28 (10.0%) patients in the trovafloxacin group who were excluded from the Clinical PP follow-up population because of a clinical outcome of unable to determine. The results of the multiple imputation analysis were consistent with the results of the original ITT analysis.

Since treatment could be extended to 14 days, clinical response at follow-up was also analyzed by duration of dosing (7 or 14 days). Table 049-4 summarizes these results. When controlling for duration of therapy, the Mantel-Haenszel confidence interval about the difference in success rate is (-1.6, 9.9). Thus, the robustness of the primary analysis is supported by this stratified analysis.

Table 049-4
Clinical Response at Follow-up by Duration of Dosing
(Clinical PP Follow-up Population)

Duration of Dosing	Treatment Group		Difference %(Gemi-Trova) 95% CI
	Gemifloxacin 320 mg od	Trovafloxacin 200 mg od	
7 Days	**N=144**	**N=140**	
Success n (%)	135 (93.8)	127 (90.7)	3.1 (-3.8, 10.0)
14 Days	**N=72**	**N=67**	
Success n (%)	68 (94.4)	59 (88.1)	6.3 (-4.5, 17.1)

Clinical response at end of therapy was also investigated. The success rates at end of therapy were slightly higher than the success rates seen at follow-up. The conclusions drawn for clinical response at end of therapy were similar to the conclusions drawn for clinical response at follow-up for both the Clinical PP and ITT populations.

Table 049-5 summarizes the results for per patient bacteriological response at follow-up. Per patient bacteriological efficacy of gemifloxacin at follow-up in the Bacteriology PP follow-up population was slightly lower than that of trovafloxacin. However, per patient bacteriological efficacy of gemifloxacin at follow-up in the Bacteriology ITT population was at least as good as that of trovafloxacin.

Table 049-5
Per Patient Bacteriological Response at Follow-up

Bacteriological Response	Treatment Group		Difference %(Gemi-Trova) 95% CI
	Gemifloxacin 320 mg od	Trovafloxacin 200 mg od	
Bacteriology PP follow-up	**N=91**	**N=75**	
Success n (%)	80 (87.9)	67 (89.3)	-1.4 (-12.3, 9.5)
Bacteriology ITT	**N=120**	**N=102**	
Success n (%)	101 (84.2)	82 (80.4)	3.8 (-7.2, 14.8)

Per patient bacteriological response at end of therapy was also investigated. The success rates at end of therapy were slightly higher than the success rates seen at follow-up. At end of therapy, per patient bacteriological efficacy of gemifloxacin was similar to that of trovafloxacin in both the Bacteriology PP follow-up and Bacteriology ITT populations.

Results: Safety

A total of 179 patients (61.7%) in the gemifloxaein group and 181 patients (64.4%) in the trovafloxacin group had at least one adverse event during the interval on-therapy plus 30 days post-therapy. The most common adverse event in the gemifloxacin group was headache, which was reported by 9.3% of patients compared with 7.8% of patients in the trovafloxacin group. The most common adverse event in the trovafloxacin group was dizziness, which was reported by 8.5% of patients compared with 2.4% of patients in the gemifloxacin group. This difference was statistically significant (p=0.0003). The incidence of diarrhea was statistically significantly higher in the gemifloxacin group (6.9%) than in the trovafloxacin group (2.8%) (p=0.03). The incidence of rash was statistically significantly higher in the gemifloxacin group (6.6%) than in the trovafloxacin group (2.5%) (p=0.03).

Drug related (suspected or probable) adverse event occurred in 58 patients (20.0%) in the gemifloxacin group and 72 patients (25.6%) in the trovafloxacin group. In the gemifloxacin group, the most commonly occurring drug related adverse events were rash and headache. Rash was reported by 5.2% of patients in the gemifloxacin group and 1.8% in the trovafloxacin group and 3.4 % of patients in the gemifloxacin group and 2.5% in the trovafloxacin group reported headache. In the trovafloxacin group, the most commonly occurring drug related adverse events were dizziness and nausea. These events were reported by 5.0% and 4.6% of patients in the trovafloxacin group, respectively, compared with 0.7% of patients in the gemifloxacin group for both adverse events.

Most of the adverse events were mild to moderate in severity. Symptoms were classified as severe in 9.7% of gemifloxacin treated patients and 8.2% of trovafloxacin treated patients. There were 11 (3.8%) gemifloxacin patients and 15 (5.3%) trovafloxacin patients with serious adverse events, and two deaths in the study, one in each treatment

group. Both of the deaths were reported as unrelated to study treatment. One patient in the gemifloxacin group and three patients in the trovafloxacin group had a serious adverse event that was reported to be related to study treatment.

Sixteen patients (5.5%) in the gemifloxacin group and 13 patients (4.6%) in the trovafloxacin group discontinued study drug due to adverse events. In the gemifloxacin group, rash (2.8%) was the most commonly reported reason for discontinuation. In the trovafloxacin group, dizziness (1.1%) and rash (0.7%) were the most commonly reported reasons for discontinuation. There were no serious adverse events leading to withdrawal in the gemifloxacin group. In the trovafloxacin group, four patients had an adverse event that lead to withdrawal.

For a more detailed review of the safety data, please see the Medical Officer Safety review written by Dr. John Powers.

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Study 011

Results: Efficacy

Reviewer's Comment: *A 20% random sample of the patients enrolled in this study was generated by the statistical reviewer and reviewed by the medical officer. No changes were made to either evaluability or outcome. Therefore, the sponsor's data was accepted and all analyses are based on the data as submitted by the sponsor.*

Study 011 was conducted at 102 centers in 3 countries. There were 22 centers in France, 1 center in Poland, and 9 centers in the Republic of South Africa. The majority of the patients enrolled were from France. A total of 324 patients were randomized to receive study treatment; 168 were randomized to receive gemifloxacin and 156 to receive amoxicillin/clavulanate. Four patients, one patient from the gemifloxacin group and 3 from the amoxicillin/clavulanate group, withdrew from the study before receiving any study medication and were not included in the ITT population. There were 135 patients in the ITT population who had at least one pathogen identified at screening. Patient disposition is shown in Table 011-1.

Table 011-1
Patient Disposition

Population	Treatment Group	
	Gemifloxacin 320 mg od	Amox/Clav 1 g/ 125 mg tid
Randomized	168	156
ITT (received study medication)	167	153
Completed Study	134	120
Clinical PP End of Therapy	128	121
Clinical PP Follow-up	115	113
Bacteriology ITT	72	63
Bacteriology PP End of Therapy	54	49
Bacteriology PP Follow-up	47	46

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Reasons for withdrawal from the study prior to completion include adverse experience, insufficient therapeutic effect, protocol deviation (including non-compliance), lost to follow-up, and other as determined by the investigator (withdrew consent, incarceration, visit 3 not performed, and a mistake in the study medication dosing regimen). The proportion of patients who withdrew from the study due to insufficient therapeutic effect was statistically significantly higher in the amoxicillin/clavulanate group than in the gemifloxacin group (5.9% vs. 1.2%, respectively, p=0.03). All of the patients who withdrew due to other reasons were from the gemifloxacin group. A total of 39 (23.4%) gemifloxacin patients and 32 (20.9%) amoxicillin/clavulanate patients were excluded from the Clinical PP end of therapy population and 52 (31.1%) gemifloxacin patients and 40 (26.1%) amoxicillin/clavulanate patients were excluded from the Clinical PP follow-up population. The most frequent reasons for exclusion from the PP populations include other antibacterial treatment for reasons other than clinical failure or clinical recurrence, medication compliance, visit compliance, and unable to determine-clinical. Slightly more patients in the gemifloxacin group (14 patients, 8.4%) were excluded from the PP populations due to medication compliance than in the amoxicillin/clavulanate group (7 patients, 4.6%).

Table 011-2 shows the demographic characteristics of the ITT population. There were no significant differences across treatment groups. More than half of the patients were male and the majority of the patients were white. The mean age was 53 years in the gemifloxacin group and 55 years in the amoxicillin/clavulanate group.

Table 011-2
Demographic Characteristics (ITT)

	Treatment Group	
	Gemifloxacin 320 mg od	**Amox/Clav 1 g/ 125 mg tid**
# Patients	167	153
Gender N (%)		
Female	60 (35.9)	57 (37.3)
Male	107 (64.1)	96 (62.7)
Age mean (SD)	53.3 (20.4)	55.3 (19.8)
Min, max	18, 97	18, 86
Race N (%)		
White	138 (82.6)	120 (78.4)
Black	17 (10.2)	26 (17.0)
Oriental	7 (4.2)	3 (2.0)
Other	5 (3.0)	4 (2.6)

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There were 72 patients in the gemifloxacin group and 63 patients in the amoxicillin/clavulanate group who had at least one pathogen identified from any source (sputum/respiratory samples, blood culture, serology or urine antigen) pre-therapy. The most common pathogens identified at screening from any source were *S. pneumoniae,* [redacted] and *H. influenzae.* The distribution of pre-therapy pathogens was relatively similar in both treatment groups.

Table 011-3 summarizes the primary efficacy analysis results. The primary efficacy parameter was clinical response (success or failure) at follow-up. The results of the Clinical PP follow-up and the ITT population are both presented. The clinical success rate at follow-up in the Clinical PP follow-up population was 88.7% in the gemifloxacin group and 87.6% in the amoxicillin/clavulanate group. Results in the ITT population were 77.2% and 79.1%, respectively. The clinical efficacy of gemifloxacin at follow-up was at least as good as that of amoxicillin/clavulanate in both populations, since the lower limit of the 95% CI was greater than –15%.

Table 011-3
Clinical Response at Follow-up

Clinical Response	Treatment Group		Difference %(Gemi-Amox/Clav) 95% CI
	Gemifloxacin 320 mg od	Amox/Clav 1 g/ 125 mg tid	
Clinical PP follow-up	**N=115**	**N=113**	
Success n (%)	102 (88.7)	99 (87.6)	1.1 (-8.2, 10.4)
ITT	**N=167**	**N=153**	
Success n (%)	129 (77.2)	121 (79.1)	-1.9 (-11.6, 7.8)

The sponsor also performed a multiple imputation analysis on the clinical ITT population to investigate the impact of missing data (see description of multiple imputation analysis under Study 012). There were 19 (11.4%) patients in the gemifloxacin group and 13 (8.5%) patients in the amoxicillin/clavulanate group who were excluded from the Clinical PP follow-up population because of a clinical outcome of unable to determine. The results of the multiple imputation analysis were consistent with the results of the original ITT analysis.

Clinical response at end of therapy was also investigated. The success rates at end of therapy were slightly higher than the success rates seen at follow-up. The conclusions drawn for clinical response at end of therapy were similar to the conclusions drawn for clinical response at follow-up for both the Clinical PP and ITT populations.

Table 011-4 summarizes the results for per patient bacteriological response at follow-up. Per patient bacteriological efficacy of gemifloxacin at follow-up was not shown to be at least as good as that of amoxicillin/clavulanate for either the Bacteriology PP follow-up or the Bacteriology ITT population. The lower limits of the 95% confidence intervals were less than –15%. It should be noted that the study was not designed to demonstrate non-inferiority for secondary endpoints and the number of patients analyzed were small.

Table 011-4
Per Patient Bacteriological Response at Follow-up

Bacteriological Response	Treatment Group		Difference %(Gemi-Amox/Clav) 95% CI
	Gemifloxacin 320 mg od	Amox/Clav 1 g/ 125 mg tid	
Bacteriology PP follow-up	**N=47**	**N=46**	
Success n (%)	41 (87.2)	41 (89.1)	-1.9 (-17.2, 13.4)
Bacteriology ITT	**N=72**	**N=63**	
Success n (%)	54 (75.0)	48 (76.2)	-1.2 (-17.2, 14.8)

Per patient bacteriological response at end of therapy was also investigated. The success rates at end of therapy were slightly higher than the success rates seen at follow-up and the success rates for the gemifloxacin group were numerically higher than the success rates for the amoxicillin/clavulanate group. In both populations, the per patient bacteriological efficacy at end of therapy of gemifloxacin was at least as good as amoxicillin/clavulanate.

Results: Safety

A total of 98 patients (58.7%) in the gemifloxacin group and 95 patients (62.1%) in the amoxicillin/clavulanate group had at least one adverse event during the interval on-therapy plus 30 days post-therapy. The most common adverse events were insomnia, diarrhea, and headache for gemifloxacin treated patients (11.4%, 8.4%, and 5.4%, respectively) and diarrhea and insomnia for amoxicillin/clavulanate treated patients (13.1% and 5.2%, respectively). The incidence of insomnia was marginally statistically significantly higher in the amoxicillin/clavulanate group than in the gemifloxacin group (p=0.07).

Drug related (suspected or probable) adverse event occurred in 31 patients (18.6%) in the gemifloxacin group and 35 patients (22.9%) in the amoxicillin/clavulanate group. The most commonly occurring drug related adverse event was diarrhea in both treatment groups (6.0% of gemifloxacin and 11.1% of amoxicillin/clavulanate patients).

Most of the adverse events were mild to moderate in severity. Symptoms were classified as severe in 13.8% of gemifloxacin treated patients and 18.3% of amoxicillin/clavulanate treated patients. There were 24 (14.4%) gemifloxacin patients and 31 (20.3%) amoxicillin/clavulanate patients with serious adverse events, and seven deaths in the study, four in the gemifloxacin treatment group and three in the amoxicillin/clavulanate treatment group. There was one additional death in the gemifloxacin group that occurred more than 30 days after the last dose of study medication. All of the deaths were reported as unrelated to study treatment. Five patients in the gemifloxacin group and four patients in the amoxicillin/clavulanate group had a serious adverse event that was reported to be related to study treatment.

Fourteen patients (8.4%) in the gemifloxacin group and 15 patients (9.8%) in the amoxicillin/clavulanate group discontinued study drug due to adverse events. In the gemifloxacin group, pneumonia and pleurisy were the two adverse events that resulted in the withdrawal of more than one patient (3 and 2 patients, respectively). In the amoxicillin/clavulanate group, respiratory disorder resulted in the withdrawal of two patients. Six patients in the gemifloxacin group and five patients in the amoxicillin/clavulanate had adverse events leading to withdrawal reported as suspected/probably related to study drug.

For a more detailed review of the safety data, please see the Medical Officer Safety review written by Dr. John Powers.

Pooled Studies 012, 049, and 011

Results: Efficacy

To further investigate clinical response of patients at follow-up, data from Studies 012, 049, and 011 were pooled. Data from these studies were also pooled to explore the effect of gender, age, and treatment duration on the clinical response at follow-up. In these pooled analyses, differences (gemifloxacin – combined comparators) and the 95% CIs were stratified by study.

Table C-1 summarizes the clinical response at follow-up for each of the three CAP studies. Since there was a statistically significant treatment by study interaction (p=0.054), a random effects approach to combining the results of the three CAP studies was used [reference: DerSimonian and Laird, Controlled Clinical Trials 7:177-188 (1986)]. This approach incorporates the heterogeneity of effects in the analysis of the overall treatment efficacy. Using the random effects approach, an estimate of the difference in clinical response rates at follow-up was –0.05 and the corresponding 95% CI was (-6.1, 6.0). Therefore, the clinical efficacy of gemifloxacin at follow-up was at least as good as the combined comparator group.

Table C-1
Clinical Response at Follow-up

	Treatment Group		
Clinical Response PP follow-up	**Gemifloxacin 320 mg od**	**Comparator**	**Difference %(Gemi-Comp) 95% CI**
Study 012	87.6%	92.6%	-5.0 (-10.5, 0.6)
Study 049	94.0%	89.9%	4.1 (-1.6, 9.8)
Study 011	88.7%	87.6%	1.1 (-8.2, 10.4)
Combined			-0.05 (-6.1, 6.0)*

*Treatment difference and CI estimated using random effects approach.

The effect of gender, age (<65, ≥65), and treatment duration (7 days, 14 days) on the clinical efficacy at follow-up of gemifloxacin was investigated for Studies 012, 049, and 011 combined. Since the majority of the patients were white, a subgroup analysis was

not performed for race. The results summarized in Table C–2 are for the Clinical PP follow-up population. In all subgroups, the clinical efficacy of gemifloxacin at follow-up was at least as good as the combined comparators. The clinical success rate of each subgroup was consistent with the overall study population.

Table C-2

Clinical Response at Follow-up by Gender, Age, and Treatment Duration

	Treatment Group		
Clinical Response PP follow-up	**Gemifloxacin 320 mg od**	**Combined Comparators**	**Difference %(Gemi-Comp) 95% CI***
Gender			
Male	311/342 (90.9)	294/328 (89.6)	1.4 (-3.4, 6.2)
Female	214/240 (89.2)	229/249 (92.0)	-3.0 (-8.7, 2.8)
Age			
<65	352/394 (89.3)	356/393 (90.6)	-1.2 (-5.7, 3.3)
≥65	173/188 (92.0)	167/184 (90.8)	1.2 (-5.2, 7.6)
Treatment duration			
7 days	412/458 (90.0)	416/457 (91.0)	-1.1 (-5.1, 3.0)
14 days	113/124 (91.1)	107/120 (89.2)	1.9 (-6.6, 10.4)

*Treatment differences and CIs are stratified by study.

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_____ b(5) Deliberative Process; Attorney Client and Attorney Work Product Privilege

_____ b(6) Personal Privacy

_____ b(7) Law Enforcement Records

Reviewer's Conclusions (which may be conveyed to the sponsor in the action letter)

1. *The clinical efficacy of gemifloxacin in the treatment of community acquired pneumonia was supported by three well-controlled studies. All three studies demonstrated that the clinical efficacy of gemifloxacin at follow-up was at least as good as that of an active comparator (trovafloxacin, amoxicillin/clavulanate, or cefuroxime/clarithromycin) assuming a delta of 15%.*

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4. *Rash occurred at higher rates in the gemifloxacin group versus all comparators, was the most frequently reported adverse event leading to withdrawal, and was the most frequent serious adverse event with a suspected or probable relationship to study medication.*

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/S/ 11/30/00
Cheryl Dixon, Ph.D.
Biostatistician, DOB III

/S/ 11/30/00
Concur: Karen Higgins, Sc.D.
Team Leader, DOB III

cc:
Archival NDA 21-158 Factive
HFD-590
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HFD-725/ Dr. Dixon
Chron.

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STATISTICAL REVIEW AND EVALUATION

NDA#:	21-158
Name of Drug:	FACTIVE™ capsules (gemifloxacin mesylate)
Applicant:	SmithKline Beecham Pharmaceuticals
Indications:	Acute Exacerbation of Chronic Bronchitis
Documents Reviewed:	Volumes 1 and 23 – 46 and electronic submission
Review Type:	Clinical data
Statistical Reviewer:	Karen M. Higgins, HFD-725
Medical Officers:	Brad Leissa, HFD-590, Efficacy John Powers, HFD-590, Safety
Project Manager:	Lorene Kimzey, HFD-590
Keywords:	quinolone, fluoroquinolone

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I. INTRODUCTION

FACTIVE™ (gemifloxacin mesylate) is a new fluoroquinolone antibiotic submitted by SmithKline Beecham Pharmaceuticals on December 16, 1999. The clinical program focused on the following five indications: community-acquired pneumonia, acute exacerbation of chronic bronchitis, [redacted] There are a total of 11 multicenter, double-blind pivotal clinical trials and 5 supportive studies.

This review will focus the acute exacerbation of chronic bronchitis indication. The three controlled clinical studies submitted for the acute exacerbation of chronic bronchitis indication were studies 068, 069, and 070. The comparators used in these studies were clarithromycin, trovafloxacin, and amoxicillin/clavulanate, respectively. Studies 068 and 070 are considered the primary studies and are reviewed in section II of this review. Study 069 was conducted in Europe with a dose of the comparator, trovafloxacin, that is

not approved in the United States. The results of this study will be briefly discussed in Conclusions, Section III. Three additional studies (008, 061, and 001) were conducted in acute exacerbation of chronic bronchitis patients. However, the length of dosing of gemifloxacin used in these studies is longer than that being proposed for this indication. Therefore, these studies will not be discussed in this review.

II. PRIMARY EFFICACY STUDIES

Study Report 068 (RSD-100WPL/1) A Randomized, Double-Blind, Double-Dummy, Multicenter, Parallel Group Study to Assess the Efficacy and Safety of Oral Gemifloxacin 320mg Once Daily for Five Days Versus Oral Clarithromycin 500mg Twice Daily for Seven Days for the Treatment of Acute Exacerbation of Chronic Bronchitis

Study Report 070 (RSD-100ZW7/1) A Randomized, Double-Blind, Double-Dummy, Multicenter, Parallel Group Study to Assess the Efficacy and Safety of Oral Gemifloxacin 320mg Once Daily for Five Days Versus Oral Amoxicillin/Clavulanate 500/125mg Three Times Daily for Seven Days for the Treatment of Acute Exacerbation of Chronic Bronchitis

- Objectives and Study Design

Two primary phase III studies were conducted for the indication of acute exacerbation of chronic bronchitis (AECB): studies 068 and 070. Both studies had very similar study designs and conduct. The objective of study 068 and study 070 was to establish clinical efficacy and safety of gemifloxacin 320mg once daily for five days compared to an active control of oral clarithromycin 500mg twice daily for seven days and an active control of amoxicillin/clavulanate 500/125mg three times daily for seven days in the treatment of adults (>40 years of age) with documented acute exacerbation of chronic bronchitis.

Study 068 enrolled patients from 93 centers in seven countries: Australia (1 center), Canada (10 centers), France (5 centers), Germany (12 centers), Mexico (3 centers), United Kingdom (2 centers) and United States (60 centers). Seventy-three percent of patients enrolled in study 068 were from the United States. The study was conducted from November 20, 1998 to June 3, 1999. Study 070 enrolled patients from 112 centers in ten countries: Belgium (6 centers), Denmark (1 center), Estonia (1 center), Finland (3 centers), France (55 centers), Germany (23 centers), Ireland (15 centers), Norway (1 center), Sweden (1 center), and the United Kingdom (6 centers). This study did not contain any centers in the United States. The study was conducted from September 30, 1998 to April 7, 1999.

These studies were randomized (1:1), double-blind, multi-center, comparative studies. The primary inclusion criteria were age greater than or equal to 40 years, history of chronic bronchitis, increased purulent sputum based on appearance, and increased cough and dyspnea.

Patients were evaluated at screening (Day 0), on therapy (Day 2-4), end of therapy (Day 9-11), follow-up (Day 13-24), and long-term follow-up (Day 28-35). Signs and symptoms of AECB were recorded at each visit. Evaluation of clinical and bacteriological outcome were determined at end of therapy, follow-up and long term follow-up

Reviewer's comment: Before breaking the study blind, the evaluable follow-up visit was extended from Day 14 to 21 to include any follow-up visit between Day 13 and Day 24. The medical reviewer accepted this extension.

The primary efficacy parameter was clinical response at the follow-up visit. The clinical response at follow-up was success if the patient's clinical outcome at end of therapy and at follow-up was clinical success. The response at follow-up was failure if the response at end of therapy was a failure or unable to determine or if the response at follow-up was clinical recurrence or unable to determine. The definitions of success, failure, recurrence, and unable to determine for the end of therapy and follow-up visits given on page 47 of the study report for study 068 are shown here:

End of Therapy (Visit 3, Day 9-11)

Clinical Success	Sufficient improvement or resolution of the signs and symptoms of AECB recorded at screening such that no additional antibacterial therapy was indicated for AECB.
Clinical Failure	Insufficient improvement or deterioration of signs and symptoms of AECB recorded at screening such that additional antibacterial therapy was indicated for AECB.
Unable to Determine	An assessment of clinical outcome could not be made, eg the patient was lost to follow-up or did not consent to clinical examination.

Follow-Up (Visit 4, Day 14-21)

Follow-Up Clinical Success	Sufficient improvement or resolution of signs and symptoms of AECB for patients who were clinical successes at the end of therapy visit, such that no additional antibacterial therapy was indicated for AECB.
Clinical Recurrence	Reappearance or deterioration of signs and symptoms of AECB for patients who were clinical successes at the end of therapy, such that additional antibacterial therapy was indicated for AECB.
Unable to Determine	An assessment of clinical outcome could not be made, eg the patient was lost to follow-up or did not consent to clinical examination.

The intent to treat (ITT) analysis included all randomized patients who took at least one dose of study medication. The clinical per protocol (PP) population is the population that excludes patients who violated the protocol to an extent that could bias efficacy results. Note that the determination of eligibility into the data sets was made prior to breaking the study blind. Patients who had an outcome of unable to determine were excluded from the per protocol population.

Reviewer's comment: The sponsor's defined principle efficacy analysis was in the per protocol population. The FDA considers the analyses based on the intent to treat population as co-primary.

Subjects were tested for pre-treatment pathogens from sputum specimens. In addition to assessing each subject's clinical outcome, each pre-treatment pathogen was assigned a bacteriologic outcome at the end of therapy and at follow-up based on either a post-therapy repeat sputum culture or the subject's clinical response. The possible bacteriologic responses were bacteriological eradication, presumed bacteriological eradication, bacteriological persistence, and presumed bacteriological persistence. A presumed eradication was concluded if the subject was a clinical cure in absence of an

evaluable repeat culture. A presumed persistence was concluded if the subject was a clinical failure in absence of an evaluable repeat culture. A bacteriologic cure includes subjects who had a response of eradication or presumed eradication on all baseline pathogens. The bacteriologic intent to treat population included all subjects from the ITT population who had at least one pre-therapy pathogen identified at screening. The bacteriologic per protocol was a subset of the bacteriologic ITT that excluded subjects who violated the protocol to an extent that could bias efficacy results.

➢ Study Population and Baseline Demographics

A total of 1312 patients were enrolled in these two studies. Seven hundred twelve patients were enrolled in study 068 (351 to gemifloxacin and 361 to clarithromycin) and 600 were enrolled in study 070 (304 to gemifloxacin and 296 to amoxicillin/clavulanate). Table II.1 contains the numbers of subjects included in the different analysis populations (primary analysis populations are bolded). Note that 82% of the ITT patients in study 068 and 88% of the ITT patents in 070 were considered in the primary clinical per protocol analysis at the follow-up time point.

Table II.1 Patient Disposition (All Randomized Patients) for Studies 068 and 070
From Table 7 of Applicant's Study Reports for 068 and 070.

	Study 068		Study 070	
Population	**Gemifloxacin n**	**Clarithro. n**	**Gemifloxacin n**	**Amox/Clav n**
Randomized	351	361	304	296
ITT (Received Study Medication)	**351**	**358**	**304**	**296**
Completed Study				
Clinical PP End of Therapy	298	304	268	274
Clinical PP Follow-up	**287**	**292**	**264**	**266**
Clinical PP Long-term follow-up	279	284	250	254
Bacteriological ITT	57	66	51	49
Bacteriological PP End of Therapy	47	54	44	45
Bacteriological PP Follow-up	45	52	44	44
Bacteriological PP Long-term follow-up	44	50	42	42

Proportions of patients contained in the above populations were similar across treatment arms. Reasons for withdrawals were similar between the two study arms for 068 and 070. The most frequent reason for withdrawal was adverse events (3.1% and 4.5% in study 068 and 3.3% and 3.0% in study 070 for gemifloxacin and comparator, respectively) and protocol deviations including non-compliance (4.3% and 2.5% in study 068 and 2.0% and 2.0% in study 070 for gemifloxacin and comparator, respectively). Overall compliance with study medication was similar for the two arms in both studies.

There were not large differences in the demographic characteristics gender, race, age, height and weight between the two treatment groups in either study. In study 068, 48% were female (51% gemifloxacin and 45% clarithromycin), the majority of patents were white (83% gemifloxacin, 86% clarithromycin). The mean age was 59 years for gemifloxacin and 58 years for clarithromycin with a range of 36 to 90 years. In study 070, 44% were female (47% gemifloxacin and 40% amoxicillin/clavulanate), the vast majority of patients were white (99% gemifloxacin, 99% amoxicillin/clavulanate). The

mean age was 64 years for both gemifloxacin and amoxicillin/clavulanate with a range of 40 to 97 years. Baseline covariates were generally similar between the two treatment groups in both studies.

The most common pathogen found at screening in study 068 was *H. influenzae* (30.9%), followed by *H. parainfluenzae* (13.1%), *S. pneumoniae* (11.4%), and *M. catarrhalis* (11.4%). The percentages were very similar between the two treatment arms. The most common pathogen found at screening in study 070 was *M. catarrhalis* (29.0%), followed by *H. influenzae* (21.0%), *S. pneumoniae* (19.0%), and *H. parainfluenzae* (2.0%). The percentages were similar between the two treatments, except for *S. aureus* where there was only one patient (2.0%) on gemifloxacin and 10 patients (20.4%) on amoxicillin/clavulanate with this pathogen.

➢ Applicant's Efficacy Analyses and Results

Reviewer's comments: A 20% random sample of the sponsor's data was reviewed by the medical officer. No changes were made to this sample for either evaluability or outcome. Therefore, the applicant's defined data set was accepted and used in all analyses in this review.

It was stated in the study reports that gemifloxacin would be considered no worse than clarithromycin or amoxicillin/clavulanate if the 95% confidence interval around the difference in cure rates did not extend beyond 10% in favor of the comparator. The confidence intervals were constructed using the normal approximation to the binomial.

Study 068

Table II.2 reports study 068 results of the primary analyses, the clinical response at follow-up for the clinical per-protocol (PP) and the intent-to-treat (ITT) data sets. The cure rates for gemifloxacin are slightly higher than for clarithromycin in both data sets. The confidence intervals for the per-protocol and the intent-to-treat populations are well within the limit of –10%. Table II.3 gives the results for secondary analyses. The results of these analyses are supportive of the primary analyses.

Table II.2 Primary Efficacy Analyses for Study 068

Population	Number Cured/Number of Patients (%) Gemifloxacin 320 mg OD x 5 days	Clarithromycin 500mg BID x 7 days	95% confidence Interval*
Clinical			
ITT at follow-up	279/351 (79.5)	280/358 (78.2)	(-4.7, 7.3)
PP at follow-up	245/287 (85.4)	247/292 (84.6)	(-5.0, 6.6)

*Confidence interval for the difference of Gemifloxacin – Clarithromycin using normal approximation to the binomial without a continuity correction

Reviewer's comment: The 95% confidence intervals calculated using the normal approximation to the binomial with a continuity correction are (-5.0%, 7.6%) for the ITT population and (-5.4%, 6.9%) for the clinical per protocol population.

Table II.3 Secondary Efficacy Analyses for Study 068

Population	Number Cured/Number of Patients (%) Gemifloxacin 320 mg OD x 5 days		Clarithromycin 500mg BID x 7 days		95% confidence Interval*
Clinical					
ITT at end of therapy	304/351	(86.6)	314/358	(87.7)	(-6.0, 3.8)
PP at end of therapy	272/298	(91.3)	278/304	(91.4)	(-4.7, 4.3)
ITT at long term	262/351	(74.6)	259/358	(72.3)	(-4.2, 8.8)
PP at long term	222/279	(79.6)	223/284	(78.5)	(-5.7, 7.8)
Bacteriological					
ITT at end of therapy	49/57	(86.0)	49/66	(74.2)	(-2.2, 25.6)
PP at end of therapy	44/47	(93.6)	44/54	(81.5)	(-0.4, 24.6)
ITT at follow-up	43/57	(75.4)	42/66	(63.6)	(-4.3, 27.9)
PP at follow-up	39/45	(86.7)	38/52	(73.1)	(-2.0, 29.2)
ITT at long-term	41/57	(71.9)	37/66	(56.1)	(-0.8, 32.6)
PP at long-term	36/44	(81.8)	31/50	(62.0)	(2.2, 37.5)

*Confidence interval for the difference of Gemifloxacin – Clarithromycin using normal approximation to the binomial without a continuity correction

Reviewer's comment: The confidence intervals for both the primary and secondary analyses are all within a –10% limit.

Subgroup analyses were performed using logistic regression to determine if there were different effects between treatments across three variables, smoking, country, and severity of AECB. No significant interactions were found between these variables and treatment

Reviewer's comment: There were no significant by-treatment interactions for the covariates age, race, or gender.

A multiple imputation analysis was conducted to investigate the impact of missing data on the primary ITT analysis. In the gemifloxacin group 28 (8.5%) of patients had a follow-up clinical outcome of "unable to determine" (UTD). The clarithromycin group had 22 (6.1%) of patients with an outcome of UTD. These subjects were considered failures in the ITT analyses (they were removed from the PP analyses). The multiple imputation analysis was conducted using Solas® 1.0. Five data sets were generated with imputed values for the UTDs. These 5 data sets were then combined to obtain an overall analysis. The confidence interval obtained was contained within the limit of 10% and is supportive of the primary analysis.

Study 068 contained of sub-study of time to bacterial eradication of *H. influenzae* in a subset of 193 patients from 30 centers. Of the 193 subjects, 24 were identified as having *H. influenzae* as a pathogen in an evaluable sputum sample (12 subjects per treatment group). These patients were then monitored daily for the presence of the pathogen to determine the day of *H. influenzae* eradication. On each day each subject was given a response of bacteriologic eradication, bacteriologic persistence, or unable to determine. The results of this sub-study are given in Table II.4.

Table II.4 ***H. Influenzae*** **Eradication Results for Study 068**

Day cleared	Gemifloxacin N = 12	Clarithromycin N = 12
Day 1	7	3
Day 2	4	4
Day 3	0	1
Day 4	0	0
	1 subject was censored on day 0	1 subject was censored on day 0 1 subject was censored on day 3 2 subject was censored on day 4

The applicant's analysis of Day 1 eradication compared 7/12 on gemifloxacin versus 3/12 on clarithromycin. They did not find a significant difference, p=0.21. There was little difference in clinical cure rates between these two groups. In the intent to treat population at follow-up, both treatment groups had observed cure rates of 8/12. In the clinical per protocol population at follow-up, gemifloxacin had an observed cure rate of 8/10 while clarithromycin had an observed cure rate of 8/12.

Study 070

Table II.5 reports study 070 results of the primary analyses, the clinical response at follow-up for the clinical per-protocol (PP) and the intent-to-treat (ITT) data sets. The cure rates for gemifloxacin and amoxicillin/clavulanate are very similar. The confidence intervals for the per-protocol and the intent-to-treat populations are well within the limit of –10%. Table II.6 gives the results for secondary analyses. The results of these analyses are supportive of the primary analyses.

Table II.5 **Primary Efficacy Analyses for Study 070**

Population	Number Cured/Number of Patients (%) Gemifloxacin 320mg OD x 5 days		Amoxicillin/Clavulanate 500/125mg TID x 7 days		95% confidence Interval*
Clinical					
ITT at follow-up	269/304	88.5	263/296	88.9	(-5.4, 4.7)
PP at follow-up	247/264	93.6	248/266	93.2	(-3.9, 4.6)

*Confidence interval for the difference of Gemifloxacin – Amoxicillin/Clavulanate using normal approximation to the binomial without a continuity correction

Table II.6 **Secondary Efficacy Analyses for Study 070**

Population	Number Cured/Number of Patients (%) Gemifloxacin 320mg OD x 5 days		Amoxicillin/Clavulanate 500/125mg TID x 7 days		95% confidence Interval*
Clinical					
ITT at end of therapy	279/304	(91.8)	281/296	(94.9)	(-7.1, 0.8)
PP at end of therapy	256/268	(95.5)	265/274	(96.7)	(-4.4, 2.1)
ITT at long term	253/304	(83.2)	242/296	(81.8)	(-4.6, 7.5)
PP at long term	218/250	(87.2)	222/254	(87.4)	(-6.0, 5.6)
Bacteriological					
ITT at end of therapy	45/51	(88.2)	40/49	(81.6)	(-7.4, 20.6)
PP at end of therapy	42/44	(95.5)	38/45	(84.4)	(-1.2, 23.3)
ITT at follow-up	42/51	(82.4)	37/49	(75.5)	(-9.1, 22.8)
PP at follow-up	40/44	(90.9)	35/44	(79.5)	(-3.3, 26.0)
ITT at long-term	38/51	(74.5)	34/49	(69.4)	(-12.5, 22.7)
PP at long-term	34/42	(81.0)	32/42	(76.2)	(-12.8, 22.3)

*Confidence interval for the difference of Gemifloxacin – Amoxicillin/Clavulanate using normal approximation to the binomial without a continuity correction

Reviewer's comment: For the primary analyses (Table II.5), the 95% confidence intervals calculated using the normal approximation to the binomial with a continuity correction are (-5.8%, 5.4%) for the ITT population and (-4.3%, 4.9%) for the clinical per protocol population.

Reviewer's comment: The confidence intervals for the primary and most of the secondary analyses are all within a –10% limit. The only analyses that fall outside of this limit are the bacteriological responses at long-term follow-up.

Subgroup analyses were performed on the clinical per protocol population using logistic regression to determine if there were different effects between treatments across four variables, smoking, country, percent predicted FEV 1 and severity of AECB. No significant interactions were found between country, percent predicted FEV 1 or severity of AECB and treatment. There was a significant interaction between smoking status and treatment (p=0.04). Among heavy smokers (> 30 smoking pack years) amoxicillin/clavulanate had a higher observed cure rate, 95.9% (70/73), than gemifloxacin, 88.3% (68/77). In the moderate (0-30 smoking pack years) and non-smokers gemifloxacin had a higher observed cure rate, 95.7% (179/187), than amoxicillin/clavulanate, 92.2% (178/193).

Reviewer's comment: There were no significant by-treatment interactions for the covariates age, race, or gender.

A multiple imputation analysis was not performed due to the small number of subjects with unknown clinical outcome. In the gemifloxacin group 11 (3.6%) of patients had a follow-up clinical outcome of UTD. The clarithromycin group had 10 (3.4%) of patients with an outcome of UTD.

Study 068 and 070
Reviewer's comment: The cure rates for both treatments seen in study 068 are lower than those seen in study 070 by approximately 10%. The primary difference in patient populations between these two studies is country. Study 070 was conducted entirely in the Europe while study 068 was conducted in both Europe (11% of patients) and North America (89% of patients). The cure rates for study 068 for North America and Europe compared to study 070 are given in Table II.7. In 068, observed cure rates in Europe are higher than those seen in North America. However, the results for gemifloxacin were similar to control.

Table II.7 North America Versus Europe, Studies 068 and 070

Clinical cure rates at follow-up	Gemifloxacin	Control
068 North America (ITT)	*247/314 (78.7)*	244/317 (77.0)
068 Europe (ITT)	*32/37 (86.5)*	36/41 (87.8)
070 Europe (ITT)	*269/304 (88.5)*	263/296 (88.9)
068 North America (PP)	*218/256 (85.2)*	*214/256 (83.6)*
068 Europe (PP)	*27/31 (87.1)*	*33/31 (91.7)*
070 Europe (PP)	*247/264 (93.6)*	*248/266 (93.2)*

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➢ Reviewer's Additional Analyses

Missing Data Analysis

In the intent-to-treat analyses, missing data (unable to determines) were treated as failures. This method of "imputing" missing values may not be conservative given that this is an equivalence trial. The true difference may be diluted by a large number of missing values. To examine the robustness of the conclusions with regard to the missing data, a very conservative analysis was conducted. The analysis considered all missing data on gemifloxacin as treatment failures and all missing data on the controls as cures. The 95% confidence intervals calculated using the normal approximation to the binomial with continuity correction are given here, in Table II.8.

Table II.8 Missing Data Analysis, Studies 068 and 070

ITT - Clinical Response at follow-up	Gemifloxacin	Control	95% confidence Interval
Study 068	279/351 (79.5)	302/358 (84.4)	(-10.8%, 1.1%)
Study 070	269/304 (88.5)	273/296 (92.2)	(-8.8%, 1.3%)

The confidence interval for study 068 is just past the limit of –10%, while the confidence interval for study 070 remains above the limit of –10%, indicating robust results with regard to missing data.

By Center Analysis

Table II.9 summarizes the clinical response results stratified by center. Confidence intervals of the difference in cure rates (Gemifloxacin – comparator) are calculated using a Mantel-Haenszel stratified approach (reference: Koch GG, Carr GJ, Amara IA, Stokes ME, and Uryniak TJ (1989). Categorical Data Analysis. In Statistical Methodology in the Pharmaceutical Sciences (Berry, ed.). Marcel Dekker: New York, pp. 389-473). Results are generally consistent with those from the unstratified confidence intervals.

Table II.9 By Center Analyses, Studies 068 and 070

Analysis Population	Study 068	Study 070
Clinical ITT at follow-up	(-4.7%, 7.9%)	(-5.3%, 6.9%)
Clinical PP at follow-up	(-3.9%, 9.4%)	(-5.6%, 6.8%)

➢ Safety

Reviewer's comment: The following is a brief summary of safety. Please see the medical officer's review for a complete discussion of the safety issues.

Study 068

There were 173 (49.3%) patients on gemifloxacin and 196 (54.7%) patients on clarithromycin who experienced at least one adverse event with diarrhea, headache and nausea occurring most frequently on both arms. Most of the adverse events were mild to moderate, with only 32 subjects in each arm experiencing a severe event. There were a total of 23 serious adverse events, 9 (2.6%) on gemifloxacin and 14 (3.9%) on clarithromycin. Twelve patients experienced rash as an adverse event. Of the 7 of these patients who were on gemifloxacin, 3 experienced a mild rash while 4 experienced a moderate rash. All of the 5 rashes on clarithromycin were mild. There were 4 patient deaths (all occurred post-therapy), 3 on gemifloxacin arm and 1 on the clarithromycin arm. The gemifloxacin patients died at 22, 82 and greater than 30 days post-therapy. The one clarithromycin patient died 21 days post-therapy.

Study 070
There were 95 (31.3%) patients on gemifloxacin and 104 (35.1%) patients on amoxicillin/clavulanate who experienced at least one adverse event with diarrhea and nausea occurring most frequently on both arms. Most of the adverse events were mild to moderate, with only 11 subjects on gemifloxacin and 12 subjects on amoxicillin/clavulanate experiencing a severe event. There were a total of 15 serious adverse events, 10 (3.3%) on gemifloxacin and 5 (1.7%) on amoxicillin/clavulanate. Four patients experienced rash as an adverse event. The two patients on gemifloxacin experienced a moderate rash. Of the two patients on amoxicillin/clavulanate, one experienced a mild rash and one experienced a moderate rash. There were 3 patient deaths, all on gemifloxacin arm. The deaths were at 1, 8 and 35 days post-therapy.

Reviewer's comment: There were a larger number of deaths on gemifloxacin than the comparator. However, these deaths all occurred post-therapy. The relationship between these deaths and study drug is discussed in the medical officer's safety review.

III. CONCLUSIONS

The applicant submitted data from two primary studies, studies 068 and 070, to support the approval of gemifloxacin 320mg once daily for five days in the treatment of acute exacerbation of chronic bronchitis. A third phase III study using this regimen of gemifloxacin was also submitted as supportive information.

1. Study 068 contained a total of 709 treated subjects who were randomized to receive either gemifloxacin 320mg once daily for five days or clarithromycin 500mg twice daily for 7 days. Cure rates for gemifloxacin were found to be similar to clarithromycin. The 95% confidence intervals using a continuity correction on the difference in cure rates of gemifloxacin minus clarithromycin are (-5.0%, 7.6%) for the intent to treat analysis and (-5.4%, 6.9%) for the clinical per protocol analysis.

2. Study 070 contained a total of 600 treated subjects who were randomized to receive either gemifloxacin 320mg once daily for five days or amoxicillin/clavulanate 500/125mg three times a day for 7 days. Cure rates for gemifloxacin were found to be similar to amoxicillin/clavulanate. The 95% confidence intervals using a continuity correction on the difference in cure rates of gemifloxacin minus amoxicillin/clavulanate are (-5.8%, 5.4%) for the intent to treat analysis and (-4.3%, 4.9%) for the clinical per protocol analysis.

3. A third phase III study, study 069, was conducted for this regimen of gemifloxacin. The comparator used in this study was trovafloxacin at a dose (200mg once daily for five days) that is not approved in the United States. This study is not discussed in this review but the results are summarized here. This study contained 616 treated patients. Gemifloxacin clinical cure rates were found to be similar to the control arm for both the intent to treat (89.4% and 83.1%, respectively) and the clinical per protocol (91.5% and 87.6%, respectively) populations. The 95% confidence intervals using a continuity correction on the difference of cure rates of gemifloxacin minus trovafloxacin are (0.6%, 12.0%) for the intent to treat analysis and (-1.6%, 9.4%) for the clinical per protocol analysis.

The efficacy results from both primary studies along with the supportive study suggest that gemifloxacin is effective in the treatment of acute exacerbation of chronic bronchitis.

RECOMMENDED REGULATORY ACTION:

The data provided by the applicant in this submission suggest that a regimen of gemifloxacin 320mg once daily for five days is effective in the treatment of acute exacerbation of chronic bronchitis.

/S/ 12/6/00

Karen M. Higgins, Sc.D.
Statistical Team Leader, DB III

Concur: /S/ 12/6/00
Mohammad Huque, Ph.D.
Division Director, DB III

cc:
Orig. NDA #21-158
HFD-590/R. Albrecht
HFD-590/M. Goldberger
HFD-590/B. Leissa
HFD-590/J. Powers
HFD-590/L. Kimzey
HFD-725/M. Huque
HFD-725/K. Higgins
This review contains 11 pages.

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